(19) DANMARK

(10) DK/EP 1781640 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 403/12 (2006.01)* *A 61 K 31/505 (2006.01)* *A 61 K 31/506 (2006.01)*
A 61 K 31/5513 (2006.01) *A 61 K 31/553 (2006.01)* *A 61 P 29/00 (2006.01)*
A 61 P 35/00 (2006.01) *A 61 P 37/00 (2006.01)* *C 07 D 239/48 (2006.01)*
C 07 D 401/12 (2006.01) *C 07 D 403/14 (2006.01)* *C 07 D 405/12 (2006.01)*
C 07 D 413/12 (2006.01)

(45) Oversættelsen bekendtgjort den: **2015-04-20**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2015-01-07**

(86) Europæisk ansøgning nr.: **05777896.1**

(86) Europæisk indleveringsdag: **2005-08-18**

(87) Den europæiske ansøgnings publiceringsdag: **2007-05-09**

(86) International ansøgning nr.: **EP2005054089**

(87) Internationalt publikationsnr.: **WO2006021544**

(30) Prioritet: **2004-08-20 EP 04019775**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR**

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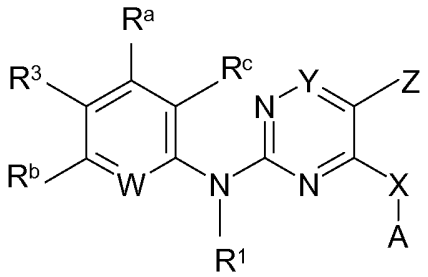
(54) Benævnelse: **2,4-DI(AMINOPHENYL)PYRIMIDINER SOM PLK-INHIBITORER.**

(56) Fremdragne publikationer:
WO-A1-00/12485
WO-A1-00/39101
WO-A1-02/04429

Fortsættes ...

WO-A1-2004/080980
WO-A2-2004/074244

The present invention relates to new pyrimidines of general formula (1),



(1)

wherein the groups A, W, X, Y, Z, R^a, R^b, R^c, R^1 and R^3 have the meanings given in the claims and description, the isomers thereof, processes for preparing these pyrimidines and their use as pharmaceutical compositions.

Background to the invention

Tumour cells wholly or partly elude regulation and control by the body and are characterised by uncontrolled growth. This is due on the one hand to the loss of control proteins such as for example Rb, p16, p21 and p53 and also to the activation of so-called accelerators of the cell cycle, the cyclin-dependent kinases.

Studies in model organisms such as *Schizosaccharomyces pombe, Drosophila melanogaster* or *Xenopus laevis* as well as investigations in human cells have shown that the transition from the G2 phase to mitosis is regulated by the CDK1/cyclin B kinase (Nurse 1990, *Nature* **344**: 503-508). This kinase, which is also known as "mitosis promoting factor" (MPF), phosphorylates and regulates a plurality of proteins, such as e.g. nuclear lamina, kinesin-like motor proteins, condensins and Golgi Matrix Proteins, which play an important part in the breakdown of the nuclear coat, in centrosome separation, the structure of the mitotic spindle apparatus, chromosome condensation and breakdown of the Golgi apparatus (Nigg. E. 2001, *Nat Rev Mol Cell Biol*. **2(1)**:21-32). A murine cell line with a temperature-sensitive CDK-1 kinase mutant shows a rapid breakdown in CDK-1 kinase after temperature increase and a subsequent arrest in the G2/M phase (Th´ng et al. 1990, *Cell*. **63(2)**:313-24). The treatment of human tumour cells with inhibitors against CDK1/cyclin B, such as e.g. butyrolactone, leads to an arrest in the G2/M phase and subsequent apoptosis (Nishio, et al. 1996, *Anticancer Res*.**16(6B)**:3387-95).

Moreover, the protein kinase Aurora B has also been described as having an essential function during entry into mitosis. Aurora B phosphorylates histone H3 on Ser10 and thereby initiates chromosome condensation (Hsu et al. 2000, *Cell*

102:279-91). A specific cell cycle arrest in the G2/M phase may, however, also be initiated e.g. by inhibition of specific phosphatases such as e.g. Cdc25C (Russell and Nurse 1986, *Cell* **45**:145-53) . Yeasts with a defective Cdc25 gene arrest in the G2 phase, whereas overexpression of Cdc25 leads to premature entry into the mitosis phase (Russell and Nurse, 1987, *Cell* **49**:559-67). Moreover, an arrest in the G2/M phase may also be initiated by inhibition of specific motor proteins, the so-called kinesins such as for example Eg5 (Mayer et al. 1999, *Science* **286**:971-4), or by microtubuli stabilising or destabilising agents (e.g. colchicin, taxol, etoposide, vinblastine, vincristine) (Schiff and Horwitz 1980, *Proc Natl Acad Sci* U S A **77**:1561-5).

In addition to the cyclin-dependent and Aurora kinases the so-called polo-like kinases, a small family of serine/threonine kinases, also play an important role in the regulation of the eukaryotic cell cycle. Up till now the polo-like kinases PLK-1, PLK-2, PLK-3 and PLK-4 have been described in the literature. PLK-1 in particular has been found to play a central role in the regulation of the mitosis phase. PLK-1 is responsible for the maturation of the centrosomes, for the activation of phosphatase Cdc25C, as well as for the activation of the Anaphase Promoting Complex (Glover et al. 1998, *Genes Dev.* **12**:3777-87; Qian et al. 2001, *Mol Biol Cell.* **12**:1791-9). The injection of PLK-1 antibodies leads to a G2 arrest in untransformed cells, whereas tumour cells arrest during the mitosis phase (Lane and Nigg 1996, *J Cell Biol.* **135**:1701-13). Overexpression of PLK-1 has been demonstrated in various types of tumour, such as non-small-cell carcinoma of the lung, plate epithelial carcinoma, breast and colorectal carcinoma (Wolf et al. 1997, *Oncogene* **14**:543-549; Knecht etal. 1999, *Cancer Res.* **59**:2794-2797; Wolf et al. 2000, *Pathol. Res. Pract.* **196**:753-759; Takahashi et al. 2003, *Cancer Sci.* **94**:148-52). Therefore, this category of proteins also presents an interesting point of attack for therapeutic intervention in proliferative diseases (Liu and Erikson 2003, *Proc Natl Acad Sci U S A* **100**:5789-5794).

Pyrimidines are generally known as inhibitors of kinases. Thus, for example, pyrimidines are described as an active component with an anticancer activity in International Patent Application WO 00/53595, which describes the use of 2,4,5-substituted pyrimidines with a heterocyclic group in the 4-position and an anilino group in the 2 position, which in turn comprises a side chain with the length of at least one n-propyl group.

Moreover, International Patent Application WO 00/39101 describes the use of 2,4,5-substituted pyrimidines as compounds with an anticancer activity which are linked in the 2- and 4-position with an aromatic or heteroaromatic ring, at least one of which comprises a side chain with the length of at least one n-propyl group.

International Patent Application WO 97/19065 further proposes the use of 2,4,5-substituted pyrimidines with a 3,4-dialkoxyanilino group in position 2 as kinase inhibitors.

International Patent Application WO 02/04429 describes 2,4,5-substituted pyrimidines with a cyano group in position 5 and their cell cycle inhibiting effect.

International Patent Application WO 03/063794 describes the use of 2,4-pyrimidinediamines as inhibitors of the IgE and/or IgG receptor signal cascade.

Antiviral 2,4,5-substituted pyrimidines, wherein the groups R^c and R^d form a heteroaromatic five-membered ring at the nitrogen of the 4- position, are known from International Patent Application WO 99/41253.

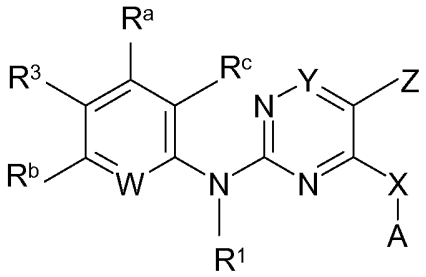
2,4,5-substituted pyrimidines which carry (hetero)aryls in position 2 and 4 (WO00/27825) and also 2, 4, 5-substituted pyrimidines which carry a (hetero)aryl group functionalised with a nitrile group in position 2 or 4 (EP 0 945 443 A1) are described as having an antiviral activity.

The resistance of many types of tumour demands that new drugs be developed to fight the tumours. The aim of the present invention is therefore to indicate new active substances which may be used for the prevention and/or treatment of diseases characterised by excessive or anomalous cell proliferation.

Detailed description of the invention

It has now been found that, surprisingly, compounds of general formula (1), wherein the groups A, W, X, Y, R^a, R^b, R^c, R^1, R^2 and R^3 are defined as hereinafter, act as inhibitors of specific cell cycle kinases. Thus, the compounds according to the invention may be used for example for the treatment of diseases associated with the activity of specific cell cycle kinases and characterised by excessive or anomalous cell proliferation.

The present invention relates to compounds of general formula (1)



(1)

wherein

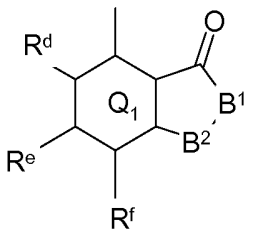
W denotes N or C-R^2,

X denotes -NR^{1a}, O or S,

Y denotes CH or N,

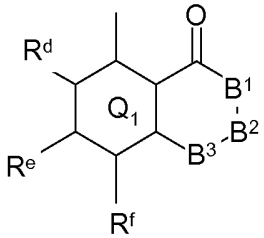
Z denotes halogen-C_{1-3}alkyl, -COH, -C(=O)-C_{1-3}alkyl, -C(=O)-C_{2-3}alkenyl, -C(=O)-C_{2-3}alkynyl, -C(=O)C_{1-3}alkyl-halogen and pseudohalogen;

A is selected from the formulae (i), (ii) or (iii)



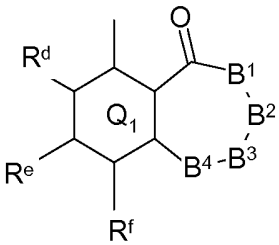
(i)

or



(ii)

or



(iii)

Q_1 denotes mono- or bicyclic aryl compounds;

B^1, B^2, B^3 and B^4 each independently of one another denote C-R^gR^h, N-R^i, O or S, while adjacent B^1 – B^4 do not each denote -O-;

R^1 and R^{1a} each independently of one another denote hydrogen or methyl,

R^2 denotes a group selected from among hydrogen, halogen, -OR^4, -C(=O)R^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5,

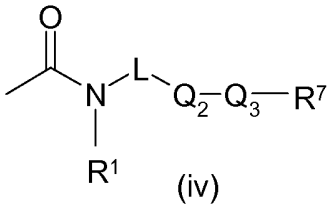
$-NR^4SO_2R^5$, $-N=CR^4R^5$, $-C=NR^i$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$ and pseudohalogen, or an optionally mono- or polysubstituted group selected from among C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen;

R^a, R^b, R^c, R^d, R^e, R^f, R^g and **R^h** each independently of one another denote a group selected from among hydrogen, halogen, =O, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-C=NR^i$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen; or an optionally mono- or polysubstituted group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl , C_{3-6}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, R^8, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen; and optionally the **R^g** and **R^h** located at the same or at adjacent C atoms may be attached in any combination to a common saturated or partially unsaturated 3-5-membered alkyl bridge which may optionally contain one to two heteroatoms;

R^i denotes a group selected from among hydrogen, =O, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen; or an optionally mono- or polysubstituted group selected from among C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl and

heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, R^8, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen; and optionally the $\mathbf{R^i}$ groups located at adjacent N atoms may be joined together or $\mathbf{R^i}$ with $\mathbf{R^g}$ or $\mathbf{R^h}$ located at adjacent C atoms may be attached in any combination to a common saturated or partially unsaturated 3-5-membered alkyl bridge which may optionally contain one to two heteroatoms;

$\mathbf{R^3}$ is selected from the formulae (iv) – (x),



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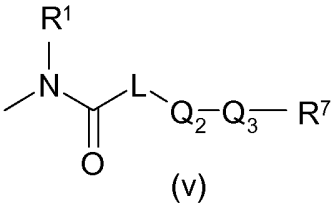

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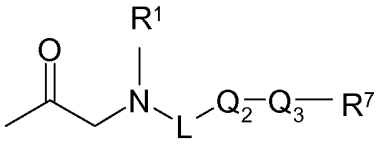

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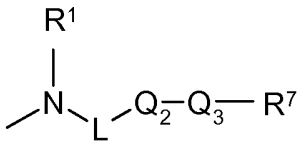

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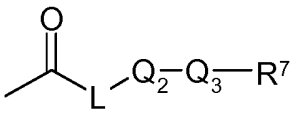

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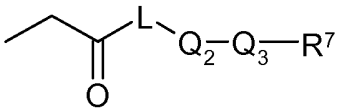

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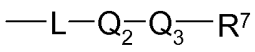


(x)

$\mathbf{R^4}$, $\mathbf{R^5}$ and $\mathbf{R^6}$ each independently of one another denote hydrogen or a group selected from among optionally mono- or polysubstituted C_{1-5}-alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among C_{3-10}-cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

L denotes a bond or a group selected from among optionally mono- or polysubstituted C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

Q_2 and **Q_3** independently of one another denote a bond or a group selected from among optionally mono- or polysubstituted C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

R^7 denotes hydrogen or a group selected from among optionally mono- or polysubstituted C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, NO_2, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8COR^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

R^8, **R^9** and **R^{10}** each independently of one another denote hydrogen or a group selected from among optionally substituted C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, methyl, ethyl, amino, methylamino, dimethylamino, -OH and pseudohalogen;

optionally in the form of the tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

In one aspect the invention relates to compounds of general formula (1) wherein

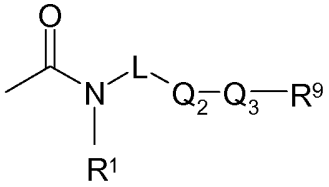
W denotes C-R^2 and the other groups are as hereinbefore defined.

In another aspect the invention relates to compounds of general formula (1), wherein

X denotes -NR^{1a} or oxygen,

R^1 and **R^{1a}** denote hydrogen;

R^3 denotes formula (iv) or (x),



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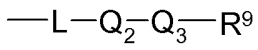


(x)

and the other groups are as hereinbefore defined.

In another aspect the invention relates to compounds of general formula (1), wherein

Y denotes CH and

Q_1 denotes monocyclic aryl compounds

and the other groups are as hereinbefore defined.

In one aspect the invention relates to compounds of general formula (1), wherein

R^c denotes a group selected from among hydrogen, -F, -Cl, methyl and ethyl

and the other groups are as hereinbefore defined.

In another aspect the invention relates to compounds of general formula (1), wherein

R^a and **R^b** each independently of one another denote hydrogen or fluorine;

or an optionally mono- or polysubstituted group selected from among C_{1-2}-alkyl, C_2-alkenyl, C_2-alkynyl, C_{3-6}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among hydrogen, halogen, -NO_2, -OR^4, -$C(=O)R^4$, -$C(=O)OR^4$, -$C(=O)NR^4R^5$, -NR^4R^5, -$NR^4C(=O)R^5$, -$NR^4C(=O)OR^5$, -$NR^4C(=O)NR^5R^6$, -$NR^4SO_2R^5$, -$N=CR^4R^5$, -SR^4, -SOR^5, -SO_2R^4, -$SO_2NR^4R^5$, -NR^4, -$SO_2NR^4R^5$, -$OSO_2NR^4R^5$ and pseudohalogen

and the other groups are as hereinbefore defined.

In another aspect the invention also relates to compounds of general formula (1), wherein
R^a and R^b each independently denote hydrogen or fluorine and the other groups are as hereinbefore defined.

In one aspect the invention relates to compounds of general formula (1), or the pharmaceutically active salts thereof, as medicaments.

In an essential aspect the invention relates to compounds of general formula (1), or the pharmaceutically active salts thereof, for use as medicaments with an antiproliferative activity.

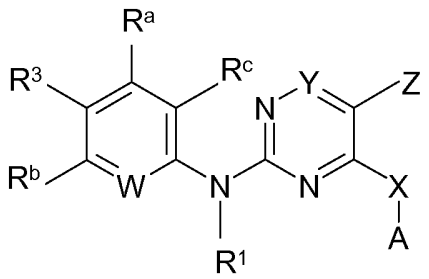
Moreover the invention includes compounds of general formula (1), or the pharmaceutically active salts thereof, for use as medicaments with an antiproliferative activity with a selective kinase-inhibiting mechanism of activity.

In one aspect the invention relates to the use of compounds of general formula (1), or the pharmaceutically active salts thereof, for preparing a medicament with an antiproliferative activity with a PLK inhibiting mechanism of activity.

In another aspect the invention relates to pharmaceutical preparations, containing as active substance one or more compounds of general formula (I), or the physiologically acceptable salts thereof, optionally in conjunction with conventional excipients and/or carriers.

In another aspect the invention relates to the use of one or more compounds of general formula (1) for preparing a medicament for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.

In another aspect the invention relates to a pharmaceutical preparation containing at least one compound of general formula (**1**)



(1)

wherein

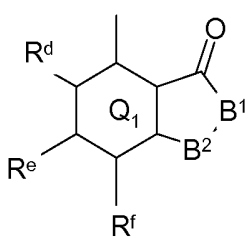
W denotes N or C-R^2,

X denotes -NR^{1a}, O or S,

Y denotes CH or N,

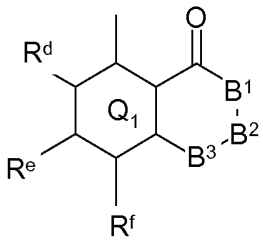
Z denotes halogen-C_{1-3}alkyl, -COH, -C(=O)-C_{1-3}alkyl, -C(=O)-C_{2-3}alkenyl, -C(=O)-C_{2-3}alkynyl, -C(=O)C_{1-3}alkyl-halogen and pseudohalogen;

A is selected from the formulae (i), (ii) or (iii)



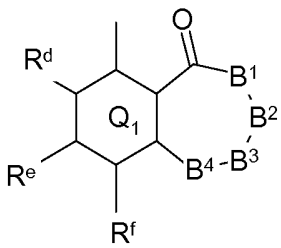
(i)

or



(ii)

or



(iii)

Q_1 denotes mono- or bicyclic aryl compounds;

B^1, B^2, B^3 and **B^4** each independently of one another denote C-R^gR^h, N-R^i, O or S, while adjacent **B^1 – B^4** do not each denote –O-;

R^1 and **R^{1a}** each independently of one another denote hydrogen or methyl,

R^2 denotes a group selected from among hydrogen, halogen, -OR^4, -C(=O)R^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5,

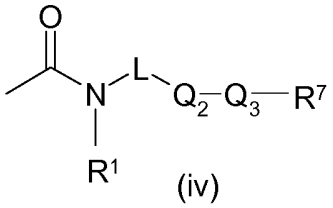
$-NR^4SO_2R^5$, $-N=CR^4R^5$, $-C=NR^i$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$ and pseudohalogen, or an optionally mono- or polysubstituted group selected from among C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen;

R^a, R^b, R^c, R^d, R^e, R^f, R^g and **R^h** each independently of one another denote a group selected from among hydrogen, halogen, =O, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-C=NR^i$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen; or an optionally mono- or polysubstituted group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl , C_{3-6}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, R^8, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen; and optionally the **R^g** and **R^h** located at the same or at adjacent C atoms may be attached in any combination to a common saturated or partially unsaturated 3-5-membered alkyl bridge which may contain one to two heteroatoms;

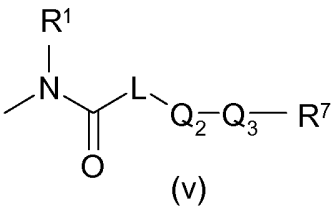
R^i denotes a group selected from among hydrogen, =O, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ or an optionally mono- or polysubstituted group selected from among C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, R^8, $-NO_2$,

$-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$,
$-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR4C(=O)NR^5R^6$, $-NR^4SO_2R^5$,
$-N=CR^4R^5$, $-SR^4$, $-SOR^4$,
$-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ and pseudohalogen; and optionally the $\mathbf{R^i}$ groups located at adjacent N atoms may be joined together or $\mathbf{R^i}$ with $\mathbf{R^g}$ or $\mathbf{R^h}$ located at adjacent C atoms may be attached in any combination to a common saturated or partially unsaturated 3-5-membered alkyl bridge which may optionally contain one to two heteroatoms;

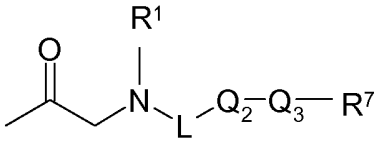
$\mathbf{R^3}$ is selected from the formulae (iv) – (x),



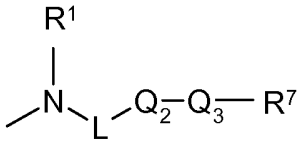
(iv)



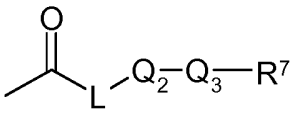
(v)



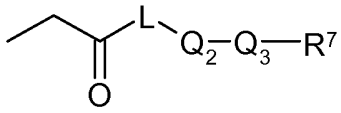
(vi)



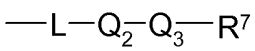
(vii)



(viii)



(ix)



(x)

$\mathbf{R^4}$, $\mathbf{R^5}$ and $\mathbf{R^6}$ each independently of one another denote hydrogen or a group selected from among optionally mono- or polysubstituted C_{1-5}-alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among C_{3-10}-cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

L denotes a bond or a group selected from among optionally mono- or polysubstituted C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or

different and are selected from among halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

Q_2 and **Q_3** independently of one another denote a bond or a group selected from among optionally mono- or polysubstituted C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

R^7 denotes hydrogen or a group selected from among optionally mono- or polysubstituted C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, NO_2, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8COR^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ and pseudohalogen;

R^8, **R^9** and **R^{10}** each independently of one another denote hydrogen or a group selected from among optionally substituted C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-10}-cycloalkyl, aryl, heterocyclyl and heteroaryl, while the substituent(s) may be identical or different and are selected from among halogen, NH_2, -OH and pseudohalogen;

optionally in the form of the tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof, and

at least one other cytostatic or cytotoxic active substance, optionally in the form of the tautomers, racemates, enantiomers, diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

DEFINITIONS

As used herein, the following definitions apply, unless stated otherwise.

By alkyl substituents are meant in each case saturated, straight-chain or branched aliphatic hydrocarbon groups (alkyl group).

The alkenyl substituents are in each case straight-chain or branched, unsaturated alkyl groups which have at least one double bond.

By alkynyl substituents are meant in each case straight-chain or branched, unsaturated alkyl groups which have at least one triple bond.

Haloalkyl refers to alkyl groups wherein one or more hydrogen atoms are replaced by halogen atoms. Haloalkyl includes both saturated alkyl groups and unsaturated alkenyl and alkynyl groups, such as for example $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$,-$CHFCF_3$, $-CH_2CF_3$, $-CF_2CH_3$, $-CHFCH_3$, $-CF_2CF_2CF_3$, $-CF_2CH_2CH_3$, $-CHFCH_2CH_3$ and $-CHFCH_2CF_3$.

Halogen relates to fluorine, chlorine, bromine and/or iodine atoms.

By pseudohalogen are meant the following groups: -OCN, -SCN, $-CF_3$ and –CN.

By cycloalkyl is meant a mono- or bicyclic ring, while the ring system may be a saturated ring or an unsaturated, non-aromatic ring, which may optionally also contain double bonds, such as for example cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, norbornyl, norbornenyl, spiro[5.5]undecane, spiro[5.4]decane and spiro[4.4]nonane.

Aryl relates to monocyclic or bicyclic rings with 6 – 12 carbon atoms such as for example phenyl and naphthyl.

By heteroaryl are meant mono- or bicyclic rings which contain instead of one or more carbon atoms one or more identical or different heteroatoms, such as e.g. nitrogen, sulphur or oxygen atoms. Examples include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl and triazinyl. Examples of bicyclic heteroaryl groups are indolyl, isoindolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, indazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl and benzotriazinyl, indolizinyl, oxazolopyridinyl, imidazopyridinyl, naphthyridinyl, indolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, cumarinyl, isocumarinyl, chromonyl, chromanonyl, pyridinyl-*N*-oxid, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocumarinyl, dihydroisocumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl-*N*-oxide, pyrimidinyl-*N*-oxide, pyridazinyl-*N*-oxide, pyrazinyl-*N*-oxide, quinolinyl-*N*-oxide, indolyl-*N*-oxide, indolinyl-*N*-oxide, isoquinolyl-*N*-oxide, quinazolinyl-*N*-oxide, quinoxalinyl-*N*-oxide, phthalazinyl-*N*-oxide, imidazolyl-*N*-oxide, isoxazolyl-*N*-oxide, oxazolyl-*N*-oxide, thiazolyl-*N*-oxide, indolizinyl-*N*-oxide, indazolyl-*N*-oxide, benzothiazolyl-*N*-oxide, benzimidazolyl-*N*-oxide, pyrrolyl-*N*-oxide, oxadiazolyl-*N*-oxide, thiadiazolyl-*N*-oxide, triazolyl-*N*-oxide, tetrazolyl-*N*-oxide, benzothiopyranyl-*S*-oxide and benzothiopyranyl-*S,S*-dioxide.

Heterocyclyl relates to saturated or unsaturated, non-aromatic mono-, bicyclic or bridged bicyclic rings comprising 5 – 12 carbon atoms, which carry heteroatoms, such as nitrogen, oxygen or sulphur, instead of one or more carbon atoms. Examples of such heterocylyl groups are tetrahydrofuranyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, isoindoliny, morpholinyl, thiomorpholinyl, homomorpholinyl, homopiperidyl, homopiperazinyl, thiomorpholinyl-*S*-oxide, thiomorpholinyl-*S,S*-dioxide, tetrahydropyranyl, piperidinyl, tetrahydrothienyl, homopiperidinyl, homothiomorpholinyl-*S,S*-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, tetrahydrothienyl-*S*-oxide, tetrahydrothienyl-*S,S*-dioxide, homothiomorpholinyl-*S*-

oxide, 2-oxa-5-azabicyclo[2.2.1]heptane, 8-oxa-3-aza-bicyclo[3.2.1]octane, 3,8-diaza-bicyclo[3.2.1]octane, 2,5-diaza-bicyclo[2.2.1]heptane, 3,8-diaza-bicyclo[3.2.1]octane, 3,9-diaza-bicyclo[4.2.1]nonane, 2,6-diaza-bicyclo[3.2.2]nonane, 2,7-diaza-spiro[3.5]nonane, 2,7-diaza-spiro[4.4]nonane, 2,8-diaza-spiro[4.5]decane, 3,9-diaza-spiro[5.5]undecane.

The Examples that follow illustrate the present invention without restricting its scope:

Preparation of the compounds according to the invention:

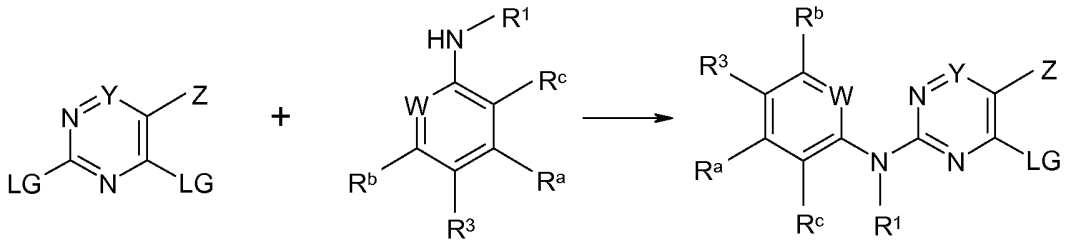
The compounds according to the invention may be prepared according to methods of synthesis A to C described hereinafter, wherein the substituents of general formulae (**I** to **XVI**) have the meanings given hereinbefore.

Method A

Step 1A

The intermediate compound **III** is prepared by substitution of a leaving group LG, for example halogen, SCN or methoxy, preferably chlorine, in a heteroaromatic system **I** by a nucleophile **II**.

Diagram 1A



I II III

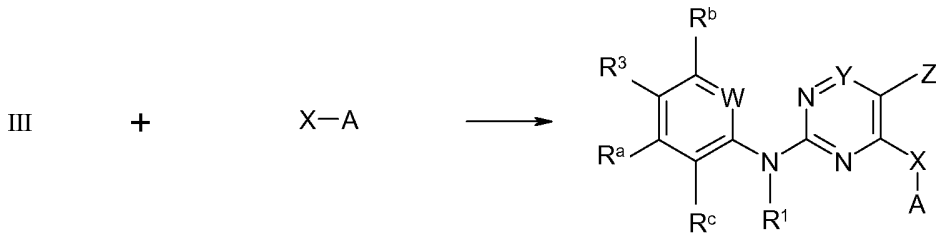
1 equivalent of compound **I** and 1 to 1.5 equivalents of compound **II** are stirred in a solvent, for example 1,4-dioxane, tetrahydrofuran, ethanol, isopropanal, *N,N*-dimethylformamide or *N,N*-dimethylacetamide. At a temperature of 15 to 25°C, 2 to 2.5 equivalents of a base, for example potassium carbonate, sodium carbonate, caesium carbonate, *N*-ethyl-*N,N*-diisopropylamine or triethylamine, are added. The reaction mixture is stirred for 6 to 72 h at a temperature of 20 to 100°C. Then the solvent is distilled off and the residue is combined with water which has been adjusted to a pH of between 1 - 4 with an inorganic acid, for example hydrochloric acid or sulphuric acid. This mixture is extracted two to three times with an organic

solvent, for example diethyl ether, ethyl acetate or dichloromethane. The combined organic extracts are dried and the solvent is distilled off. The residue is purified by chromatography.

Step 2A

The end compound **V** is prepared by substitution of a leaving group LG, for example halogen, SCN or methoxy, preferably chlorine, in a heteroaromatic system **III** by a nucleophile **IV**.

Diagram 2A



IV V

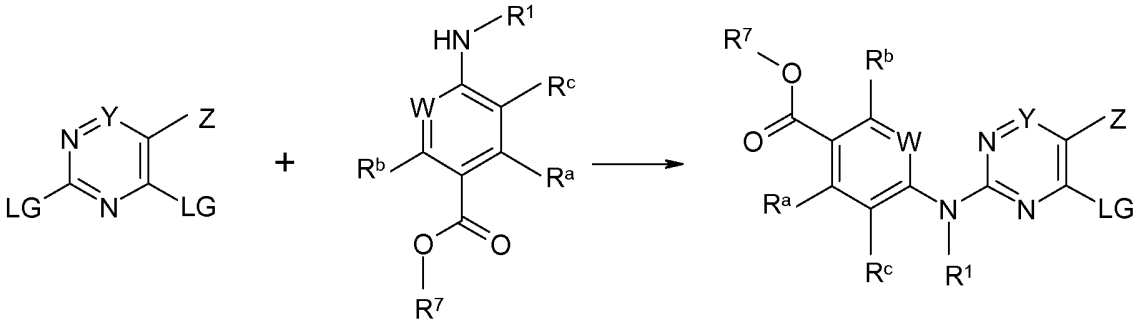
1 equivalent of the compound **III** and 1 to 3 equivalents of the compound **IV** are stirred in a solvent, for example 1,4-dioxane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methyl-2-pyrrolidinone. At a temperature of 15 to 40 °C, 1 to 2 equivalents of an inorganic acid, for example sulphuric acid or hydrochloric acid, are added. The reaction mixture is stirred for another 12 to 72 h at a temperature of 20 to 100 °C. Then the solvent is distilled off and the residue is purified by chromatography.

Method B

Step 1B

The intermediate compound **VII** is prepared by substitution of a leaving group LG, for example halogen, SCN, methoxy, preferably chlorine, in a heteroaromatic system **I** by a nucleophile **VI**.

Diagram 1B



I VI VII

1 equivalent of the compound **I** and 1 to 1.5 equivalents of the compound **VI** are stirred in a solvent, for example 1,4-dioxane, tetrahydrofuran, ethanol, isopropanol, *N,N*-dimethylformamide or *N,N*-dimethylacetamide.

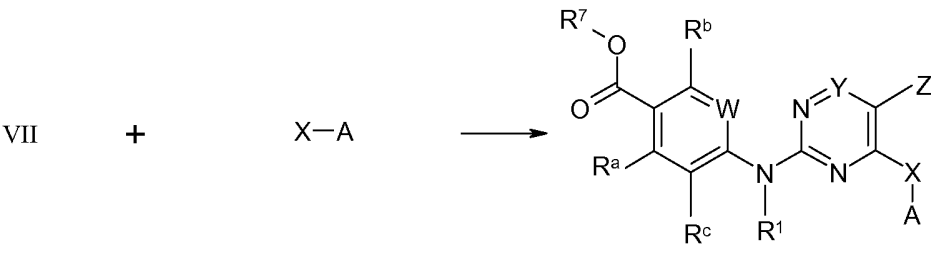
At a temperature of 15 to 25°C, 2 to 2.5 equivalents of a base, for example potassium carbonate, sodium carbonate, caesium carbonate, potassium hydrogen phosphate, *N*-ethyl-*N,N*-diisopropylamine or triethylamine are added. The reaction mixture is stirred for 6 to 72 h more at a temperature of 20 to 120 °C. The reaction mixture is combined with water, which has been adjusted to a pH of 8 to 9 with an inorganic base, for example sodium hydrogen carbonate or potassium carbonate. This mixture is extracted two to three times with an organic solvent, for example diethyl ether or ethyl acetate.

The combined organic extracts are dried and the solvent is distilled off. The residue is purified by chromatography or repeated crystallisation.

Step 2B

The intermediate compound **VIII** is prepared by substituting a leaving group LG, for example halogen, SCN, methoxy, preferably chlorine, in a heteroaromatic system **VII** by a nucleophile **IV**.

Diagram 2B



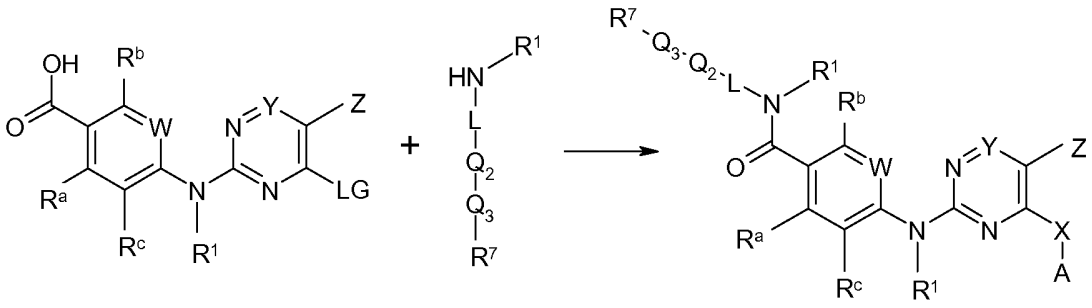
IV VIII

1 equivalent of the compound **VII** and 1 to 1.5 equivalents of the compound **IV** are stirred in a solvent, for example 1,4-dioxane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methyl-2-pyrrolidinone. At a temperature of 15 to 40°C, 0.2 to 1 equivalent of an acid, for example sulphuric acid or hydrochloric acid, is added. The reaction mixture is stirred for another 12 to 72 h at a temperature of 20 to 100°C. The reaction mixture is stirred into water and the resulting precipitate is filtered off and dried. The precipitate may be purified by chromatography or crystallisation or used as the crude product in the next step.

Step 3B

Compounds **VIII** whose group R^7 denotes hydrogen may be used directly for preparing the end compounds **X**, while a compound **VIII** is reacted with a compound **IX**. Compounds **VIII** whose group R^7 does not denote hydrogen are converted beforehand by hydrolysis or similar methods known to the skilled man into the compounds wherein the group R^7 denotes hydrogen.

Diagram 3B



VIII IX X

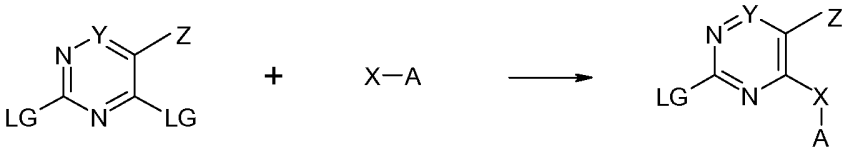
1 equivalent of the compound **VIII**, 1 to 1.5 equivalents of the compound **IX** and 1 to 3 equivalents of a base, for example triethylamine or ethyldiisopropylamine, are stirred in a solvent, for example 1,4-dioxane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methyl-2-pyrrolidinone. At a temperature of 15 to 25 °C, 1 to 1.5 equivalents of a coupling reagent, for example *N,N*-dicyclohexylcarbodiimide, *N,N*-diisopropyl-carbodiimide, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate or 1-(3-*N,N*-dimethylaminopropyl)-3-ethylcarbodiimide are added. The reaction mixture is stirred for another 4 to 24 h at a temperature of 15 to 25 °C. Then the solvent is distilled off and the residue is purified by chromatography.

Method C

Step 1C

The intermediate compound **XI** is prepared by substituting a leaving group LG, for example halogen, SCN, methoxy, preferably chlorine, at a heteroaromatic system **I** with a nucleophilic group **IV**.

Diagram 1C



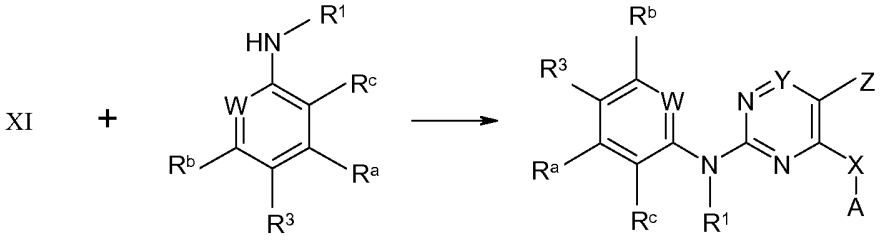
I IV XI

1 equivalent of the compound **I** and 1 to 3 equivalents of a base, for example triethylamine or ethyldiisopropylamine, are stirred in a solvent, for example 1,4-dioxane, tetrahydrofuran, *N,N*-dimethylformamide or *N,N*-dimethylacetamide. At a temperature of -60 to 0 °C, 0.8 to 1.5 equivalents of a compound **IV** are added. The reaction mixture is stirred for 6 to 72 h at a temperature of 15 to 75°C. Then the solvent is distilled off and the residue is purified by chromatography.

Step 2C

The end compound **V** is prepared by substitution of a leaving group LG, for example halogen, SCN, methoxy, preferably chlorine, at a heteroaromatic system **XI** by a nucleophile **II**.

Diagram 2C



II V

1 equivalent of the compound **XI** and 1 to 1.5 equivalents of the compound **II** are stirred in a solvent, for example 1,4-dioxane, *N,N*-dimethyl-formamide, *N,N*-dimethylacetamide or *N*-methyl-2-pyrrolidinone. At a temperature of 15 to 40 °C 1 to 2 equivalents of an acid, for example sulphuric acid or hydrochloric acid, are added.

The reaction mixture is stirred for another 6 to 72 h at a temperature of 20 to 100°C. Then the solvent is distilled off and the residue is purified by chromatography.

Chromatography:

For medium pressure chromatography (MPLC) silica gel made by Millipore (name: Granula Silica Si-60A 35-70µm) or C-18 RP-silica gel made by Macherey Nagel (name: Polygoprep 100-50 C18) is used.
For high pressure chromatography columns made by Waters (name: XTerra Prep. MS C18, 5 µM, 30*100 mm or Symmetrie C18, 5 µm, 19*100) are used.

Nuclear Magnetic Resonance (NMR) Spectroscopy:

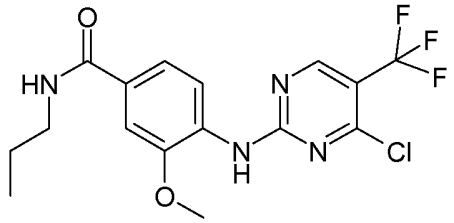
The measurement is carried out in deuterised dimethylsulphoxide-d6. If other solvents are used they are explicitly mentioned in the Examples or in the methods. The measurements are given on a delta scale in ppm. Tetramethylsilane is taken as the standard. The measurements are carried out on an Avance 400 (400MHz NMR spectrometer) made by Messrs Bruker Biospin GmbH.
The NMR spectra are given purely in a descriptive capacity. Basically, only the visible molecular signals are listed. If for example molecular signals are partly or completely masked by foreign signals such as for example water signals, DMSO signals or $CDCl_3$ signals they are not mentioned.

Mass spectroscopy / UV spectrometer:

These data are generated using an HPLC-MS apparatus (high performance liquid chromatography with mass detector) made by Agilent.
The apparatus is constructed so that a diode array detector (G1315B made by Agilent) and a mass detector (1100 LS-MSD SL; G1946D; Agilent) are connected in series downstream of the chromatography apparatus (column: Zorbax SB-C8, 3.5 µm, 2,1*50, Messrs. Agilent). The apparatus is operated with a flow of 0.6 ml/min. For a separation process a gradient is run through within 3.5 min (start of gradient: 95% water and 5% acetonitrile; end of gradient: 5% water and 95% acetonitrile; in each case 0.1% formic acid is added to the two solvents).

Method 1

2-(2-methoxy-4-propylcarbamoyl-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine



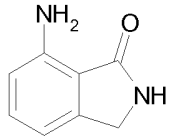
5 g (21.9 mmol) 2,4-dichloro-5-trifluoromethyl-pyrimidine are dissolved in 50 ml 1,4-dioxane and combined with 5.5 g (21.9 mmol) 4-amino-3-methoxybenzoic acid-propylamide hydrochloride (Zhuangyu Zhang, et al. 1989, *J Pharml Sci.* **78(10)**:829-32). 7.5 ml (43.8 mmol) ethyldiisopropylamine are added to this reaction mixture and the mixture is stirred for 2 days at ambient temperature. Then the reaction mixture is diluted with 250 ml of ethyl acetate and washed first with 300 ml aqueous 10% $KHSO_4$ solution, then with 300 ml saturated aqueous NaCl solution. The organic phase is dried with $MgSO_4$ and the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant is a mixture of cyclohexane:ethyl acetate (75:25).

Yield: 2.30 g (5.9 mmol; 27 %)

^{1}H-NMR: 0.91 (t, 3H), 1.50 - 1.61 (m, 2H), 3.20 - 3.28 (m, 2H), 3.87 (s, 3H), 7.46 - 7.51 (m, 1H), 7.52 - 7.56 (m, 1H), 7.70 - 7.75 (m, 1H), 8.44 (t, 1H), 8.75 (s, 1H), 9.73 (s, 1H)

Method 2

7-amino-2,3-dihydro-isoindol-1-one



a) 7-nitro-2,3-dihydro-isoindol-1-one

1.5 g (5.473 mmol) methyl 2-bromomethyl-6-nitro-benzoate are dissolved in 20 ml *N,N*-dimethylformamide and combined with 15 ml of methanolic ammonia (7 mmol/ml). After 20 h at 25°C the mixture is diluted with 100 ml of ethyl acetate and extracted 3 times with saturated sodium hydrogen carbonate solution. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*.

Yield: 960 mg (5.389 mmol, 99 %)

MS-ESI+: m/z = 179 $[M+H]^+$

b) 7-amino-2,3-dihydro-isoindol-1-one

960 mg (5.389 mmol) 7-nitro-2,3-dihydro-isoindol-1-one are dissolved in 100 ml of tetrahydrofuran and combined with 100 mg palladium on charcoal. Then the mixture is stirred for 20 h at 25°C and 4 bar hydrogen pressure (H_2 pressure). The catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 734 mg (4.958 mmol, 92 %)

MS-ESI+: m/z = 149 $[M+H]^+$

The following 7-amino-2,3-dihydro-isoindol-1-one derivatives are prepared analogously to this method. A corresponding amine is used instead of ammonia:

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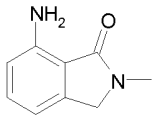
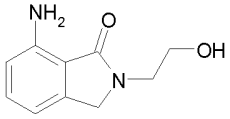
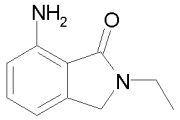
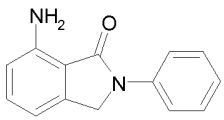
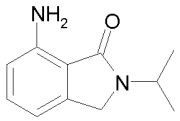
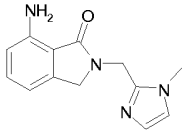
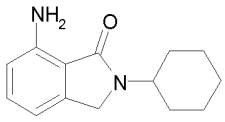
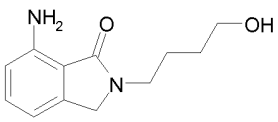
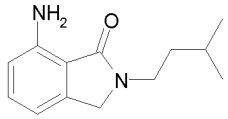
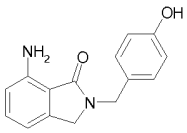
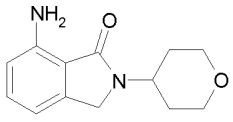
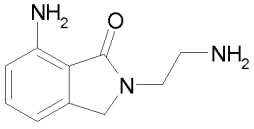
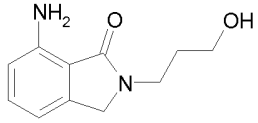
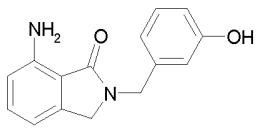
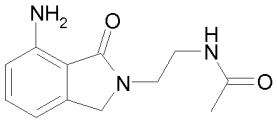
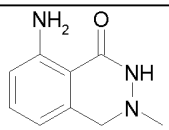
	163		193
	177		225
	191		243
	231		221
	219		255
	233		192
	207		255
	234		178

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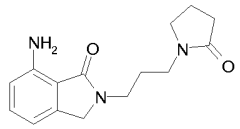
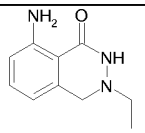
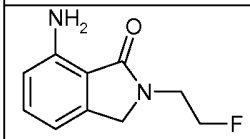
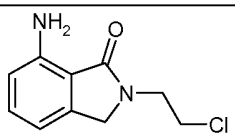
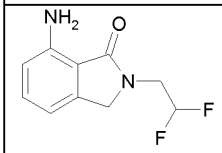
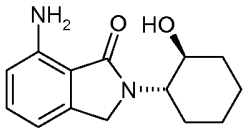
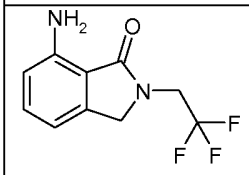
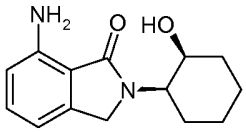
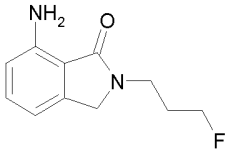
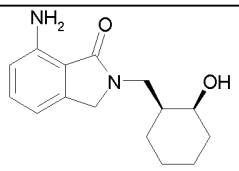
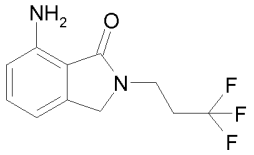
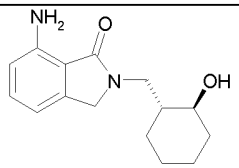
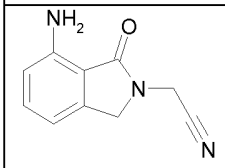
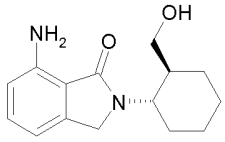
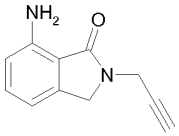
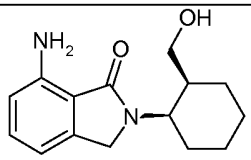
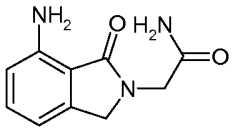
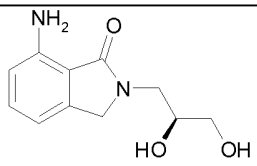
	274		192
	195		211 / 213
	213		247
	231		247
	209		261
	245		261
	188		261
	187		261
	206		223

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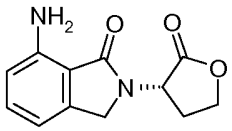
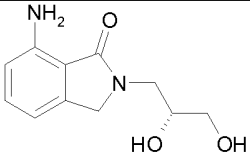
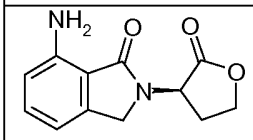
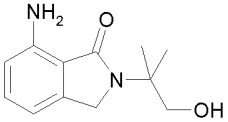
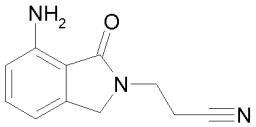
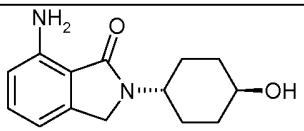
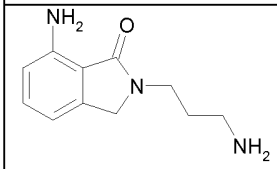
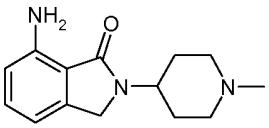
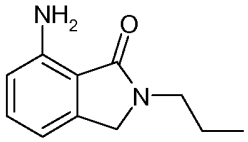
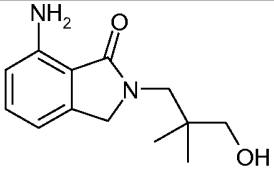
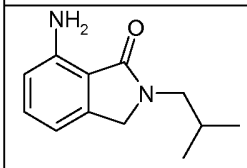
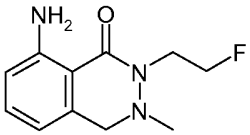
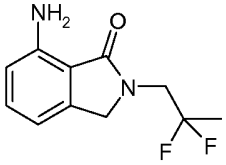
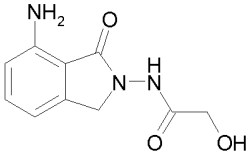
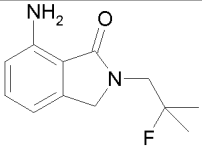
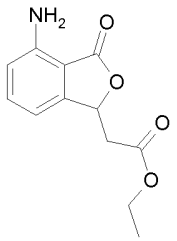
	233		223
	233		221
	202		247
	206		246
	191		235
	205		224
	227		222
	223		

Method 3

Ethyl (4-amino-3-oxo-1.3-dihydro-isobenzofuran-1-yl)-acetate



a) ethyl (4-amino-3-oxo-3*H*-isobenzofuran-1-ylidene)-acetate

500 mg (3.1 mmol) 4-amino-isobenzofuran-1,3-dione and 1.13 g (3.1 mmol) (ethoxy-carbonylmethylene)-triphenylphosphorane are dissolved in 5 ml of tetrahydrofuran (THF) and refluxed for 3 h. Then the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is a mixture of cyclohexane:ethyl acetate (75:25).

Yield: 221 mg (0.95 mmol, 31 %)

MS-ESI+: m/z = 234 $[M+H]^+$

b) ethyl (4-amino-3-oxo-1,3-dihydro-isobenzofuran-1-yl)-acetate

120 mg (0.51 mmol) ethyl (4-amino-3-oxo-3*H*-isobenzofuran-1-ylidene)-acetate are dissolved in 50 ml of methanol and combined with 50 mg palladium on activated charcoal (10% Pd). The reaction mixture is hydrogenated for 3 h at 2 bar H_2 pressure and 25°C. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*.

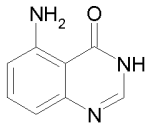
Yield: 116 mg (0.49 mmol, 97 %)

MS (ESI): m/z = 236 $(M+H)^+$

^{1}H-NMR: 1.17 (t, 3H), 2.68 – 2.78 (m, 1H), 3.08 – 3.16 (m, 1H), 4.10 (q, 2H), 5.67 – 5.74 (m, 1H), 6.28 (bs, 2H), 6.61 – 6.70 (m, 2H), 7.30 – 7.38 (m, 1H)

Method 4

5-amino-3*H*-quinazolin-4-one



a) 2,6-diaminobenzamide

5 g (25.373 mmol) 2,6-dinitro-benzonitrile is combined with 20 ml of an aqueous 80% sulphuric acid and stirred for 2 h at 80°C. The reaction mixture is combined with 100 ml of tetrahydrofuran and neutralised with 10% aqueous sodium hydroxide solution. The organic phase is separated off, combined with another 100 ml of tetrahydrofuran

and 200 mg palladium on charcoal and stirred for 20 h at 8 bar H_2 pressure and 25°C. The solids are filtered off. The filtrate is combined with 300 ml of ethyl acetate and extracted with saturated potassium hydrogen carbonate solution. The organic phase is separated off, dried and the solvent is eliminated *in vacuo*. The residue is purified by chromatography . The carrier used is silica gel and the eluant used is dichloromethane, to which 7% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution are added.

Yield: 900 mg (5.958 mmol; 23 %)

MS (ESI): 152 $(M+H)^+$

b) 5-amino-3*H*-quinazolin-4-one

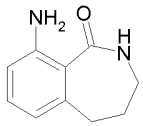
900 mg (5.958 mmol) 2,6-diaminobenzamide are dissolved in 3.6 ml *N,N*-dimethylacetamide and combined with 6.3 ml (57.01 mmol) trimethylorthoformate and 792 µl (8.865 mmol) 98% sulphuric acid. After 16 h at 25°C the reaction mixture is taken up with 20 ml of methanol and the solvent is eliminated *in vacuo*. The residue is again taken up in 20 ml of methanol, neutralised with concentrated ammonia. The solvent is eliminated *in vacuo* and the residue purified by chromatography . The carrier used is silica gel and the eluant used is dichloromethane, to which 7% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution are added.

Yield: 782 mg (4.852 mmol; 81 %)

MS (ESI): 162 $(M+H)^+$

Method 5

9-amino-2,3,4,5-tetrahydro-2-benzazepin-1-one



500 mg (1.825 mmol) 2-bromomethyl-6-nitro-methylbenzoate are heated to 100°C in 2 ml trimethyl phosphate for 5 h. 2-(dimethylphosphonomethyl)-6-nitromethylbenzoate is obtained by evaporation under a high vacuum and used further directly. The crude product is dissolved in 24 ml of tetrahydrofuran at -70°C under N_2, 2.7 ml (2.7 mmol) of a 1 M lithium hexamethyldisilazide solution in tetrahydrofuran is added dropwise and then 430 mg (2.70 mmol) *tert.*-butyl-*N*-(2-oxoethyl)-carbamate in 5 ml of tetrahydrofuran are added. The reaction mixture is slowly heated to ambient temperature, combined with 5 ml of 1 M HCl and extracted with ethyl acetate. The combined organic phases are concentrated by

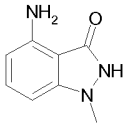
evaporation and, by chromatography on silica gel with a mixture of cyclohexane-ethyl acetate in the ratio 95:5 to 75:25, 338 mg (1.006 mmol, 55 %) of the *E*-/*Z* mixture of 2-(3-*tert.*-butoxycarbonylamino-prop-1-en-1-yl)-6-nitro-methylbenzoate are obtained. This *E*-/*Z*-mixture is treated for 12 h with 10 ml of a saturated methanolic potassium hydroxide solution. After acidification with aqueous 1 M HCl and extraction with ethyl acetate 302 mg (0.938 mmol, 93%) of the *E*-/*Z* mixture of 2-(3-*tert.*-butoxy-carbonylamino-prop-1-en-1-yl)-6-nitro-methylbenzoic acid are obtained. To this are added 20 mg Raney nickel in 100 ml of methanol and the mixture is hydrogenated at 5 bar H_2 pressure. The catalyst is filtered off, the filtrate concentrated by evaporation and stirred overnight with a 1:1 mixture of trifluoroacetic acid and dichloromethane at ambient temperature. After elimination of the solvent 133 mg (0.686 mmol, 73%) 2-amino-6-(3-amino-propyl)-benzoic acid are obtained. The further reaction is carried out by dissolving in 10 ml THF and 10 ml DCM with the addition of 300 mg (1.570 mmol) *N*-(3-dimethylaminopropyl)-N^4-ethylcarbodiimide hydrochloride and 134 µl (0.830 mmol) *N,N*-diisopropyl-ethylamine and 48 h stirring at ambient temperature. The solvent is eliminated *in vacuo* and the crude product is purified by chromatography with C18-RP silica gel and an eluant mixture of acetonitrile and water in the ratio 5:95 to 95:5, to which 0.1 % formic acid has been added.

Yield: 28 mg (0.160 mmol, 23 %)

MS (ESI): m/z = 177 $(M+H)^+$

Method 6

4-amino-1-methyl-1.2-dihydro-indazol-3-one



a) 4-nitro-1,2-dihydro-indazol-3-one

5 g (27.5 mmol) 2-amino-6-nitro-benzoic acid are combined with 22.2 ml (225.3 mmol) concentrated HCl and 45 ml (30.0 mmol) 5 % aqueous sodium nitrite solution and stirred for 1 h at ambient temperature. Then the suspension is diluted with 150 ml dist. H_2O and added dropwise to 350 ml destilliertes water which has been saturated with sulphur dioxide. Sulphur dioxide is piped through the reaction mixture for a further 30 min. Then the reaction mixture is refluxed for 30 min and then left to cool slowly to 20°C. The resulting precipitate is filtered off.

Yield: 1.7 g (9.5 mmol, 35 %)

MS (ESI): m/z = 180 $(M+H)^+$

b) 1-methyl-4-nitro-1,2-dihydro-indazol-3-one

306 mg (1.7 mmol) 4-nitro-1,2-dihydro-indazol-3-one are dissolved in 1 ml *N,N*-dimethyl-acetamide, combined with 150 µl (2.4 mmol) methyl iodide and 500 µl (2.32 mmol) of *N*-ethyldiisopropylamide and stirred for 2 h at ambient temperature. Then the reaction mixture is combined with 40 ml of a 1 N aqueous hydrochloric acid and extracted twice with 50 ml dichloromethane. Then the organic phase is dried with $MgSO_4$, the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and 5% water and 95% acetonitrileat the finishing point.

Yield: 144 mg (0.7 mmol, 44 %)

MS (ESI): m/z = 194 $(M+H)^+$

^{1}H-NMR: 3.90 (s, 3H), 7.47–7.52 (m, 1H), 7.68–7.73 (m, 1H), 7.88–7.93 (m, 1H), 10.53 (s, 1H)

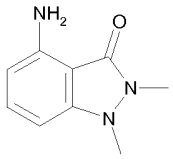
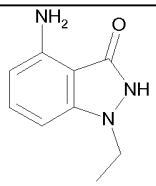
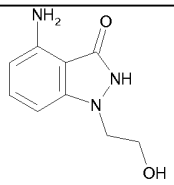
c) 4-amino-1-methyl-1,2-dihydro-indazol-3-one

140 mg (0.7 mmol) 1-methyl-4-nitro-1,2-dihydro-indazol-3-one are suspended in 6 ml of ethanol and combined with 600 mg (4.4 eq, 2.9 mmol) sodium dithionite, dissolved in 2 ml distilled water, and stirred for 15 min at 25 °C. Then the reaction mixture is combined with distilled water and extracted twice with ethyl acetate. Then the organic phase is dried with $MgSO_4$ and the solvent is eliminated *in vacuo*.

Yield: 33 mg (0.2 mmol, 28 %)

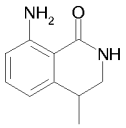
MS (ESI): m/z = 164 $(M+H)^+$

4-amino-1,2-dihydro-indazol-3-one and the following compounds are prepared analogously to this method.

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	178		178
	194		

Method 7

8-amino-4-methyl-3,4-dihydro-2*H*-isoquinolin-1-one



a) methyl 2-(cyanomethyl-2-methyl)-6-nitro-benzoate

400 mg (1.8 mmol) methyl 2-cyanomethyl-6-nitro-benzoate are dissolved in 13 ml THF, combined with 114 µl (1.8 mmol) methyl iodide and the mixture is cooled to -20 °C under a nitrogen atmosphere. Then at this temperature 250 mg (2.2 mmol) potassium-*tert*-butoxide are added. After 1 h the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and 5% water and 95% acetonitrile at the finishing point.

Yield: 289 mg (1.2 mmol, 68 %)

MS (ESI): 233 $(M-H)^-$

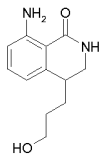
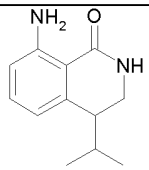
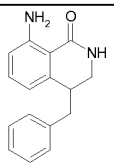
b) 8-amino-4-methyl-3,4-dihydro-2*H*-isoquinolin-1-one

400 mg (1.8 mmol) methyl 2-(cyanomethyl-2-methyl)-6-nitro-benzoate are dissolved in 13 ml of methanol and combined with 50 mg Raney nickel. The reaction mixture is hydrogenated for 16 h at 4 bar H_2 pressure and 25 °C. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 170 mg (0.8 mmol, 46 %)

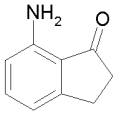
MS (ESI): 177 $(M+H)^+$

8-amino-3,4-dihydro-2*H*-isoquinolin-1-one and 8-amino-4,4-dimethyl-3,4-dihydro-2*H*-isoquinolin-1-one and the following compounds are prepared analogously to this method.

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	221		205
	253		

Method 8

7-amino-indan-1-one



a) indan-4-ylamine

24 ml (349 mmol) 65 % nitric acid are cooled to 0-5°C. 28 ml (518.5 mmol) of concentrated sulphuric acid are slowly added dropwise while cooling with ice. This solution is cooled to 5°C and slowly added dropwise to 30 ml (232 mmol) indane cooled to 0-5°C, with vigorous stirring and further cooling with ice. The reaction mixture is stirred for 30 min at 0-5°C, and then heated to 25°C for 1 h with stirring. Then the solution is added dropwise to 150 ml ice/water and stirred for 30 min. The aqueous phase is extracted three times with 200 ml diethyl ether. The combined organic phases are washed twice with 200 ml saturated sodium hydrogen carbonate solution and once with 150 ml distilled water. Then the organic phase is dried with $MgSO_4$ and the solvent is eliminated *in vacuo*. The crude product is dissolved in 250 ml of methanol and combined with 4.5 g Raney nickel. The reaction mixture is hydrogenated for 16 h at 3 bar H_2 pressure and 25° C. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is a mixture of cyclohexane:ethyl acetate (75:25).

Yield: 3.81 g (28.6 mmol, 12 %)

MS (ESI): 134 $(M+H)^+$

^{1}H-NMR: 1.90–2.00 (m, 2H), 2.61 (t, 2H), 2.76 (t, 2H), 4.73 (s, 2H), 6.33–6.38 (m, 1H), 6.39–6.45 (m, 1H), 6.76–6.83 (m, 1H)

b) *N*-indan-4-yl-acetamide

226 mg (1.7 mmol) indan-4-ylamine are combined with 5 ml acetic anhydride. The suspension is stirred for 16 h at 70 °C. The resulting solution is stirred into 40 ml distilled water, adjusted to pH 7 with sodium carbonate and extracted three times with 30 ml of ethyl acetate. Then the organic phase is dried with $MgSO_4$, the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is a mixture of cyclohexane:ethyl acetate (70:30).

Yield: 152 mg (0.9 mmol, 51 %)

MS (ESI): 176 $(M+H)^+$

^{1}H-NMR: 1.93–2.03 (m, 2H), 2.04 (s, 3H), 2.79 (t, 2H), 2.86 (t, 2H), 6.94–7.01 (m, 1H), 7.02–7.10 (m, 1H), 7.36–7.44 (m, 1H), 9.25 (s, 1H)

c) *N*-(3-oxo-indan-4-yl)-acetamide

147 mg (0.84 mmol) *N*-indan-4-yl-acetamide are dissolved in 10 ml acetone and combined with 770 µl of a 15% aqueous magnesium sulphate solution. The solution is cooled to 0°C and 397 mg (2.490 mmol) potassium permanganate are added batchwise. After 2 h the mixture is diluted with 50 ml of water, and extracted three times with 20 ml chloroform. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is a mixture of cyclohexane:ethyl acetate (85:15).

Yield: 95 mg (0.500 mmol, 60%)

MS (ESI): 190 $(M+H)^+$

d) 7-amino-indan-1-on

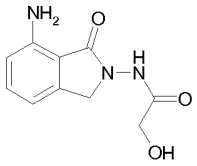
500 mg (2.6 mmol) *N*-(3-oxo-indan-4-yl)-acetamide are dissolved in 5 ml of ethanol, combined with 5 ml 18% hydrochloric acid and stirred for 3 h at 70 °C. Then the reaction mixture is stirred into 100 ml distilled water, adjusted to pH 7 with sodium carbonate and extracted three times with 30 ml of ethyl acetate. Then the organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*.

Yield: 388 mg (2.6 mmol, 100 %)

8-amino-3,4-dihydro-2*H*-naphthalen-1-one is prepared analogously to this method. 1,2,3,4-tetrahydronaphthalene is used as starting material instead of indane.

Method 9

N-(7-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-acetamide



a) 2-benzyloxy-*N*-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-acetamide

870 mg (4.5 mmol) 2-amino-7-nitro-2,3-dihydro-isoindol-1-one (prepared analogously to method 2) are dissolved in 82 ml dichloromethane and 64 ml THF. The solution is combined with 2.8 ml (3.3 eq, 20 mmol) benzyloxyacetyl chloride, 4.8 ml (28.0 mmol) *N*-ethyldiisopropyl-amine and 10 mg *N,N*-dimethylaminopyridine and stirred for 3 h at 25°C. Then the reaction mixture is combined with 100 ml aqueous 0.1 N hydrochloric acid and extracted three times with 50 ml of ethyl acetate. The organic phase is dried with magnesium sulphate, the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is a mixture of dichloromethane:methanol (95:5).

Yield: 910 mg (2.7 mmol, 59 %)

b) *N*-(7-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-acetamide

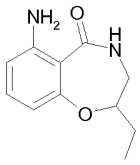
790 mg (2.3 mmol) 2-benzyloxy-*N*-(7-nitro-1-oxo-1,3-dihydro-isoindol-2-yl)-acetamide are dissolved in 100 ml of methanol and combined with 80 mg palladium hydroxide. The reaction mixture is hydrogenated for 48 h at 4 bar H_2 pressure and 25°C. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*. The crude product is purified by chromatography . The carrier used is silica gel and the eluant used is a mixture of dichloromethane:methanol (90:10).

Yield: 210 mg (0.1 mmol, 41 %)

MS (ESI): 222 $(M+H)^+$

Method 10

6-amino-2-ethyl-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one



a) 2-amino-6-(1-aminomethyl-propoxy)-benzonitrile

2.01 g (22 mmol) 1-amino-2-butanol are dissolved in 6.5 ml 1,4-dioxane, combined with 880 mg (7.8 mmol) sodium hydride and stirred for 30 min at ambient temperature. 2 g (14.7 mmol) of 2-amino-6-fluorobenzonitrile are added to this reaction mixture and it is stirred for 24 h at 50°C. Then the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is dichloromethane, to which 5% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution has been added.

Yield: 1.15 g (5.6 mmol, 38 %)

MS (ESI): 206 $(M+H)^+$

b) 2-amino-6-(1-aminomethyl-propoxy)-benzoic acid

1.15 g (5.6 mmol) 2-amino-6-(1-aminomethyl-propoxy)-benzonitrile are dissolved in 10 ml 20% ethanolic KOH and stirred for 24 h at 80°C. Then the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is dichloromethane, to which 12% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

Yield: 262 mg (1.2 mmol, 21 %)

MS (ESI): 225 $(M+H)^+$

c) 6-amino-2-ethyl-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one

262 mg (1.2 mmol) 2-amino-6-(1-aminomethyl-propoxy)-benzoic acid are dissolved in 26 ml THF, combined with 680 mg (3.5 mmol) 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride and 0.6 ml (3.5 mmol) diisopropyl-ethylamine and stirred for 3 h at 50°C. Then the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is dichloromethane, to which 4% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

Yield: 50 mg (0.2 mmol, 21 %)

MS (ESI): 207 $(M+H)^+$

The following compounds are prepared analogously to this method. 1-amino-2-butanol was replaced by a corresponding aminoalcohol or by a corresponding 1,2-diaminoethylene.

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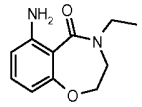
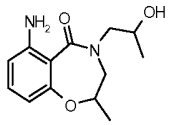
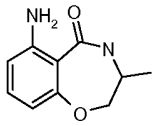
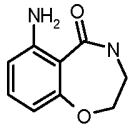
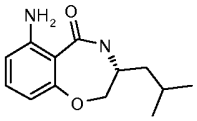
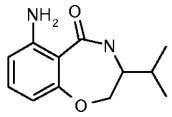
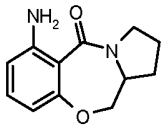
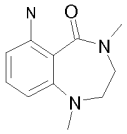
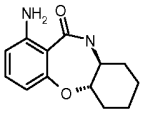
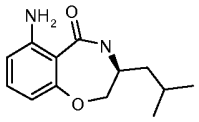
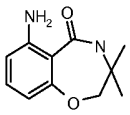
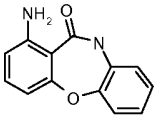
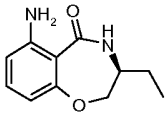
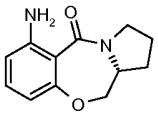
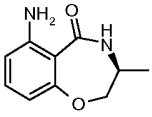
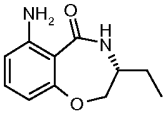
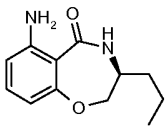
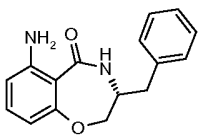
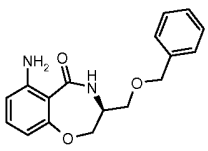
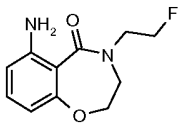
	207		251
	193		179
	235		221
	219		206
	233		235
	207		227
	207		219
	193		207
	221		269
	299		225

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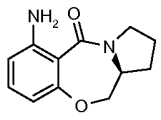
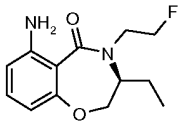
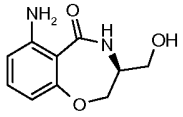
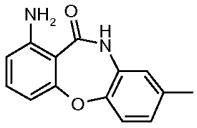
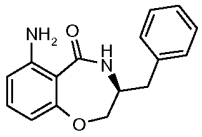
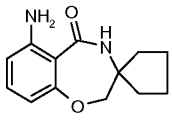
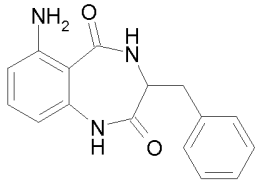
	219		253
	209		241
	269		233

Method 11

6-amino-3-benzyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione



a) methyl 2-(2-amino-6-nitro-benzoylamino)-3-phenyl-propionate

1.18 g (6.5 mmol) 2-amino-6-nitrobenzoic acid, 1.0 g (4.6 mmol) D,L-phenylalanine-methylester hydrochloride, 4.05 ml (23.2 mmol) *N*-ethyldiisopropylamine are combined with 2.5 ml of tetrahydrofuran. 1.71 g (5.1 mmol) *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate are added to this reaction mixture and it is heated for 12 h to 50°C. Then the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is a mixture of cyclohexane:ethyl acetate (50:50).

Yield: 1.04 g (3.03 mmol, 65 %)

MS (ESI): 344 $(M+H)^+$

b) 2-(2-amino-6-nitro-benzoylamino)-3-phenyl-propionic acid

1.04 g (3.03 mmol) methyl 2-(2-amino-6-nitro-benzoylamino)-3-phenyl-propionate are dissolved in 3 ml 20% ethanolic KOH and stirred for 1.5 h at 50°C. Then the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is dichloromethane, to which 15% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution has been added.

Yield: 636 mg (1.9 mmol, 64 %)

MS(ESI): 329 $(M+H)^+$

^{1}H-NMR: 2.86 – 2.94 (m, 1H), 3.17 (s, 1H), 3.22 – 3.29 (m, 1H), 4.30 – 4.38 (m, 1H),

6.63 (s, 2H), 6.89 – 6.96 (m, 1H), 6.97 – 7.02 (m, 1H), 7.12 – 7.21 (m, 2H), 7.21 – 7.27 (m, 2H), 7.28 – 7.35 (m, 2H), 8.33 – 8.43 (m, 1H)

c) 2-(2,6-diamino-benzoylamino)-3-phenyl-propionic acid

410 mg (1.25 mmol) 2-(2-amino-6-nitro-benzoylamino)-3-phenyl-propionic acid are dissolved in 50 ml of methanol and combined with 40 mg palladium on charcoal (10% Pd). The reaction mixture is hydrogenated for 9 h at 5 bar H_2 pressure and 25°C. Then the catalyst is filtered off, the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 5% water and 95% acetonitrile at the finishing point.

Yield: 88 mg (0.29 mmol, 24 %)

MS (ESI): 300 $(M+H)^+$

d) 6-amino-3-benzyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione

88 mg (0.3 mmol) 2-(2,6-diamino-benzoylamino)-3-phenyl-propionic acid are dissolved in 2 ml THF, combined with 143 mg (0.9 mmol) 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride and 103 µl (0.6 mmol) diisopropyl-ethylamine and stirred for 17 h at 50°C. Then the solvent is eliminated *in vacuo* and the crude product is purified by chromatography . The carrier used is silica gel and the eluant used is dichloromethane, to which 5% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

Yield: 22 mg (0.08 mmol, 27 %)

MS (ESI): 282 $(M+H)^+$

The following compounds are prepared analogously to method 11.

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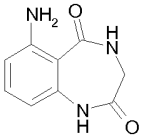
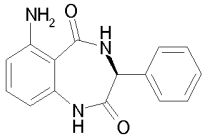
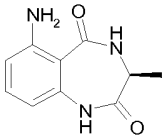
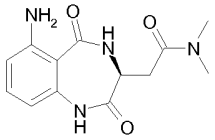
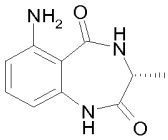
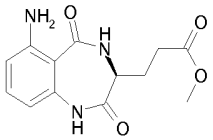
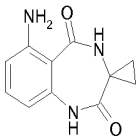
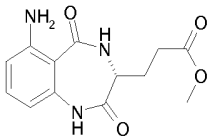
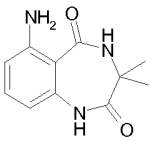
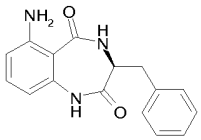
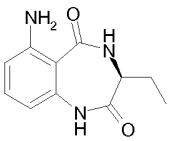
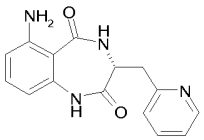
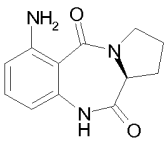
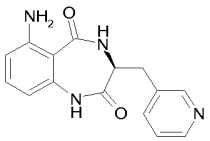
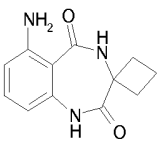
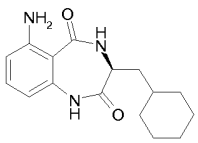
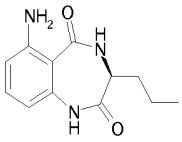
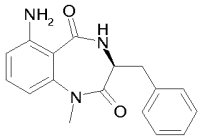
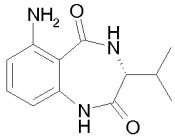
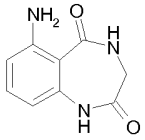
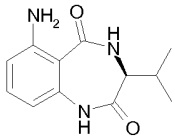
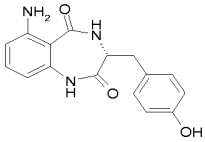
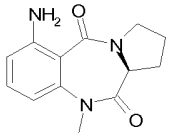
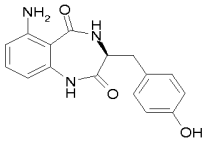
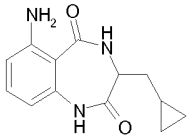
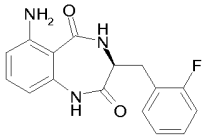
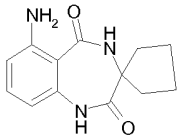
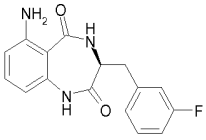
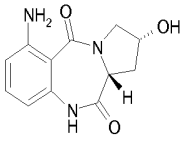
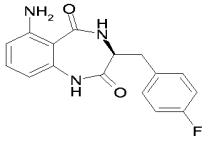
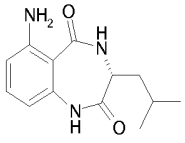
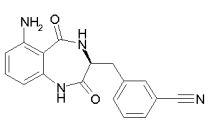
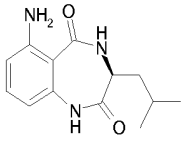
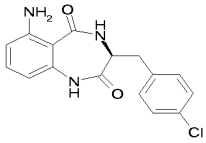
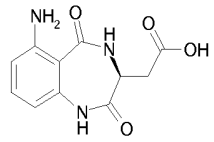
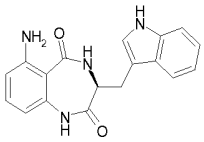
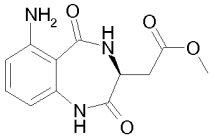
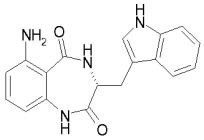
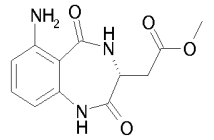
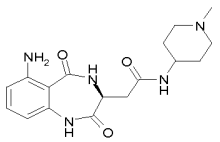
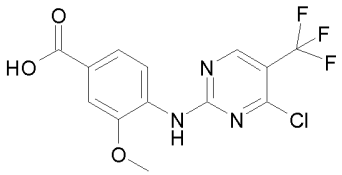
	192		268
	206		277
	206		278
	218		278
	220		282
	220		283
	232		283
	232		288

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	234		296
	234		192
	234		298
	246		298
	246		300
	246		300
	248		300
	248		307
	248		316 / 318

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	250		321
	265		321
	265		346

Method 12

2-(4-carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine



7.36 g (44 mmol) 4-amino-3-methoxybenzoic acid are suspended in 80 ml of an aqueous phosphate buffer solution (pH 6.3) and combined with 9.5 g (44 mmol) 2,4-dichloro-5-trifluoro-methyl-pyrimidine, which is dissolved in 240 ml 1,4-dioxane. After 4 h at 100°C the reaction mixture is crystallised at 0°C. The precipitate is filtered off, the filtrate is combined with 150 ml of ethyl acetate and washed twice with 200 ml of a saturated aqueous sodium hydrogen carbonate solution. The organic phase is dried with $MgSO_4$ and the solvent is eliminated *in vacuo*. The crude product is suspended in 10 ml n-hexane and refluxed. The precipitate is filtered off, suspended in 48 ml of a saturated aqueous sodium hydrogen carbonate solution and heated to 65°C for 1 h. Then the solution is crystallised at 0° C. The precipitate is filtered off, the filtrate is acidified with 1 N aqueous hydrochloric acid and combined with 100 ml of ethyl acetate. The organic phase is separated off, dried with magnesium sulphate and the solvent is eliminated *in vacuo*. The residue is recrystallised from ethyl acetate.

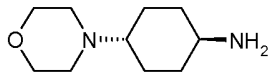
Yield: 330 mg (0.95 mmol, 2 %)

MS (ESI): 348 $(M+H)^+$

^{1}H-NMR: 1.55 (s, 1H), 4.01 (s, 3H), 7.61 – 7.64 (m, 1H), 7.79 – 7.85 (m, 1H), 8.34
(s, 1H), 8.59 – 8.63 (m, 1H), 8.66 (s, 1H)

Method 13

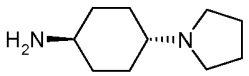
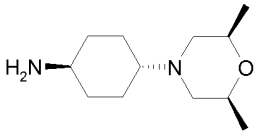
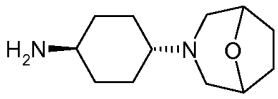
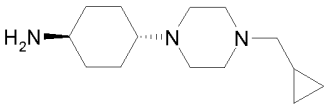
4-(4-amino-cyclohexyl)-morpholine



a) dibenzyl-(4-morpholino-4-yl-cyclohexyl)-amine
3.9 g (30 mmol) 4-dibenzylamino-cyclohexanone are dissolved in 100 ml dichloromethane and stirred with 3.9 g (45 mmol) morpholine and 9.5 g (45 mmol) sodium triacetoxyborohydride for 12 h at ambient temperature. Then water and potassium carbonate are added, the organic phase is separated off, dried and the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is ethyl acetate, to which 10% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added. The suitable fractions are evaporated down *in vacuo*.
Yield: 6.6 g (18 mmol, 60%) cis-isomer
2 g (5.4 mmol, 18%) trans-isomer.

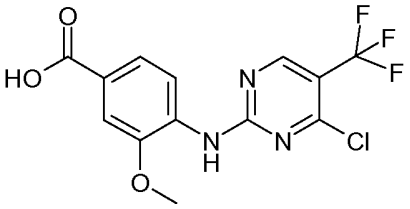
b) trans-4-morpholino-4-yl-cyclohexylamine
7.2 g (16.4 mmol) trans-dibenzyl-4-morpholino-cyclohexylamine are dissolved in 100 ml of methanol and hydrogenated on 1.4 g palladium on charcoal (10%Pd) at 30-50°C. The solvent is eliminated *in vacuo* and the residue is crystallised from ethanol and concentrated hydrochloric acid.
Yield: 3.9 g (15.2 mmol, 93%)
melting point: 312°C

The following compounds are prepared analogously to Method 13:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	169		213
	211		238

Method 14

2-(4-carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine



a) 2-(4-benzyloxycarbonyl -2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine

2 g (9.217 mmol) 2,4-dichloro-5-trifluoromethylpyrimidine are dissolved in 4 ml dioxane and combined with 6.01 g (18.430 mmol) caesium carbonate and 2.16 g (7.363 mmol) benzyl 4-amino-3-methoxybenzoate (WO 9825901). This suspension is stirred for 30 h at 100 °C. The suspension is combined with 50 ml dichloromethane and methanol and filtered to remove the insoluble constituents. The solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is silica gel and the eluant used is a mixture of 85% cyclohexane and 15% ethyl acetate.

Yield: 1.03 g (2.360 mmol; 26 %)

UV max: 320 nm

MS (ESI): 438 / 440 $(M+H)^+$ Cl distribution

436 / 438 $(M-H)^-$ Cl distribution

b) 2-(4-carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine

1 g (2.284 mmol) 2-(4-benzyloxycarbonyl -2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine are dissolved in 50 ml THF and combined with 100 mg palladium hydroxide. The reaction mixture is stirred for 16 h at ambient temperature

and 4 bar hydrogen pressure. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 0.76 g (2.192 mmol; 96 %)

UV max: 288 nm

MS (ESI): 346 / 348 $(M-H)^-$ Cl distribution

The following compounds are prepared analogously to this process:

2-(4-carboxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine

MS (ESI): 316 / 318 $(M-H)^-$ Cl distribution

2-[4-(4-benzyloxycarbonyl-piperazin-1-yl)-phenylamino]-4-chloro-5-trifluoromethyl-pyrimidine

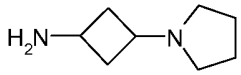
MS (ESI): 492/494 $(M+H)^+$ Cl distribution

2-[4-(4-benzyloxycarbonyl-piperazin-1-yl)-2-methoxy-phenylamino]-4-chloro-5-trifluoromethyl-pyrimidine

MS (ESI): 522/524 $(M+H)^+$ Cl distribution

Method 15

3-pyrrolidin-1-yl-cyclobutylamine



a) tert. butyl (3-benzyloxy-cyclobutyl)-carbamate

9.28 g (45 mmol) 3-benzyloxy-cyclobutancarboxylic acid (Org. Lett. 6(11), 1853-1856, 2004) are suspended in 80 ml dry *tert*-butanol and combined with 5.1 g (50 mmol) triethylamine and 13.8 g (50 mmol) phosphoric acid diphenylester azide. The reaction mixture is stirred for 20 h under reflux conditions. The solvent is eliminated *in vacuo* and the residue is taken up in dichloromethane. The organic phase is washed three times with 2 N sodium hydroxide solution, dried with sodium sulphate and the dichloromethane is eliminated *in vacuo*. The crude product is recrystallised from acetonitrile (1g crude product:5 ml acetonitrile).

Yield: 5.98 g (22 mmol; 48 %)

MS (ESI): 178 $(M+H-boc)^+$ Boc cleaving in the mass detector

b) tert. butyl (3-hydroxy-cyclobutyl)-carbamate

2.77 g (10 mmol) tert. butyl (3-benzyloxy-cyclobutyl)-carbamate are suspended in 100 ml of methanol and combined with 200 mg palladium hydroxide. The reaction mixture is stirred for 5 h at 45°C and 45 bar H_2 pressure. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*. The residue is taken up in chloroform and

washed three times with aqueous sodium hydrogen carbonate solution. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*.

Yield: 1.53 g (8.2 mmol; 82 %)

MS (ESI): 188 $(M+H)^+$

c) tert. butyl (3-tosyl-cyclobutyl)-carbamate

18.7 g (100 mmol) tert. butyl (3-hydroxy-cyclobutyl)-carbamate and 12.1 g (120 mmol) triethylamine are placed in 500 ml chloroform. 20.5 g (105 mmol) tosyl chloride, dissolved in 150 ml chloroform, is added dropwise to this solution at 0°C with stirring. Then the mixture is left to come up to ambient temperature and stirred for 2 h. The organic phase is washed successively with water, dilute hydrochloric acid, sodium hydrogen carbonate solution and water. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*.

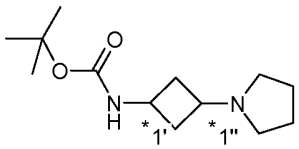
Yield: 28.30 g (83 mmol; 83 %)

MS (ESI): 342 $(M+H)^+$

d) tert. butyl (3-pyrrolidine-cyclobutyl)-carbamate

34.1 g (100 mmol) tert. butyl (3-tosyl-cyclobutyl)-carbamate are dissolved in 750 ml pyrrolidine, and combined with a catalytic amount of DMAP. The reaction mixture is refluxed for 20 h with stirring. The pyrrolidine is eliminated *in vacuo*, the residue is taken up in 500 ml of ethyl acetate and washed twice with saturated sodium hydrogen carbonate solution. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*. The crude product consists – as in all the analogous reactions – of a mixture of 2 isomeric compounds which are separated by column chromatography. The stationary phase used is silica gel and the eluant used is dichloromethane, to which 9% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

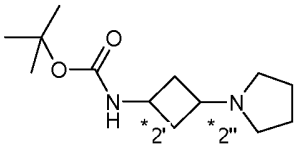
The substances that elute first are designated as follows:



Yield product A: 1 g (4.17 mmol; 4 %)

RF value (silica gel; dichloromethane:methanol:conc. aqueous ammonia = 90:9:1)= 0.62

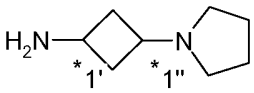
The substances that elute second are designated as follows:



Yield product C: 2.00 g (8.33 mmol; 8 %)

RF value (silica gel; dichloromethane:methanol:conc. aqueous ammonia = 90:9:1)= 0.53

e) (*1', *1'')-3-pyrrolidin-1-yl-cyclobutylamine

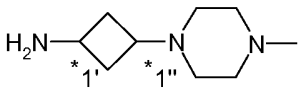
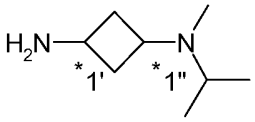
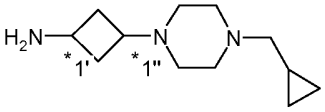
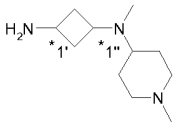
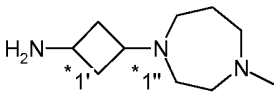
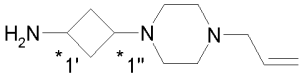
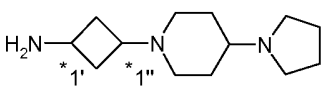
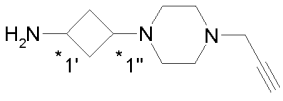
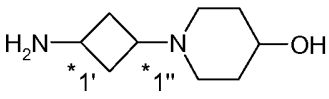
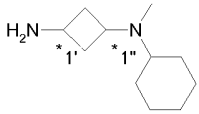


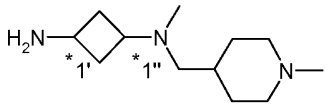
1 g (4.17 mmol) tert. butyl (3-pyrrolidine-cyclobutyl)-carbamate (product A from precursor) are stirred in 20 ml of a 2 N aqueous hydrochloric acid solution for 2 h at 40°C. Then the solvent is eliminated *in vacuo* and the residue is recrystallised from ethanol.

Yield: 0.43 g (2.786 mmol; 67 %)

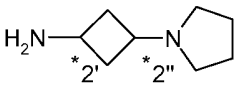
MS (ESI): 141 $(M+H)^+$

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	170		143
	210		198
	184		196
	224		194
	171		183

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	212		

(*2', *2'')-3-pyrrolidin-1-yl-cyclobutylamine

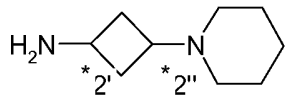
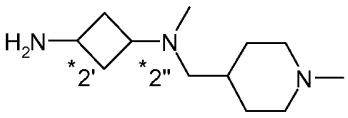
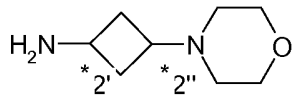
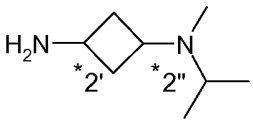
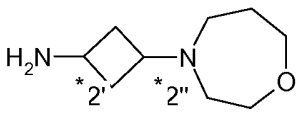
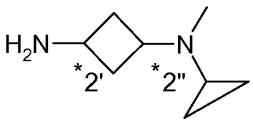
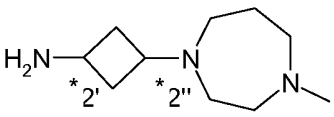
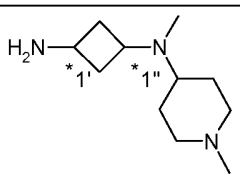


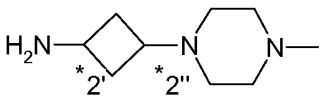
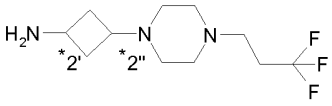
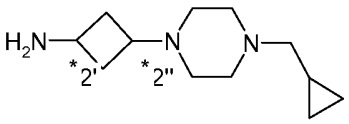
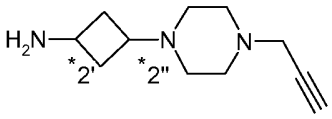
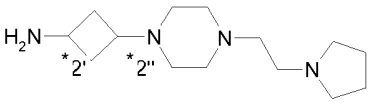
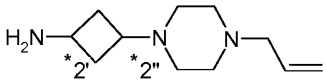
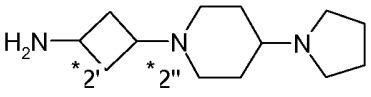
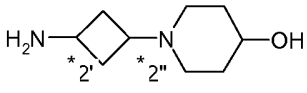
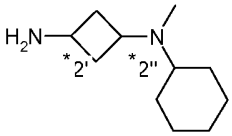
1 g (4.17 mmol) tert. butyl (3-pyrrolidine-cyclobutyl)-carbamate (product C from precursor) are stirred in 20 ml of a 2 N aqueous hydrochloric acid solution for 2 h at 40°C. Then the solvent is eliminated *in vacuo* and the residue is recrystallised from ethanol.

Yield: 0.43 g (3.09 mmol; 74 %)

MS (ESI): 141 $(M+H)^+$

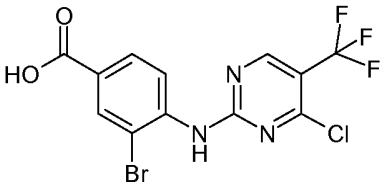
The following compounds are prepared analogously to this method:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	155		212
	157		143
	171		141
	184		198

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	170		251
	210		194
	253		196
	224		171
	183		

Method 16

2-(4-carboxy-2-bromo-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine



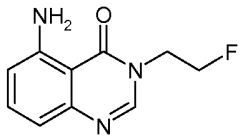
1 g (3.15 mmol) 2-(4-carboxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine are dissolved in 5 ml DMF and combined batchwise with 3.36 g (18.89 mmol) *N*-bromosuccinimide. The reaction mixture is stirred for 16 h at ambient temperature. The solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 2% water and 98% acetonitrile at the finishing point. 0.1% formic acid is added in each case to both the water and to the acetonitrile.

Yield: 0.57 g (1.44 mmol; 46 %)

MS (ESI): 396 / 398 $(M-H)^+$ Cl/Br distribution

Method 17

5-amino-3-(2-fluoro-ethyl)-3*H*-quinazolin-4-one



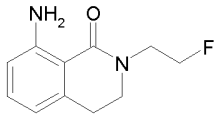
500 mg (3.102 mmol) 5-amino-3*H*-quinazolin-4-one are combined with 2 ml (15.596 mmol) 1-bromo-2-fluoroethane. 125 mg (3.125 mmol) sodium hydride are added thereto and the mixture is stirred for 5 days at ambient temperature. The reaction mixture is diluted with 100 ml of ethyl acetate and washed with 100 ml saturated aqueous sodium chloride solution. The aqueous phase is combined with 50 ml 1 N sodium hydroxide solution and extracted 5 times with ethyl acetate. The combined organic phases are dried and the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid is added in each case to both the water and to the acetonitrile.

Yield: 67 mg (0.323 mmol; 10 %)

MS (ESI): 208 $(M+H)^+$

Method 18

8-amino-2-(2-fluoro-ethyl)-3,4-dihydro-2*H*-isoquinolin-1-one



a) 8-dibenzylamino-3,4-dihydro-2*H*-isoquinolin-1-one

1.466 g (9.039 mmol) 8-amino-3,4-dihydro-2*H*-isoquinolin-1-one are dissolved in 15 ml DMF and combined with 3.226 g (23.340 mmol) potassium carbonate and with 3.808 ml (31.420 mmol) benzylbromide. This reaction mixture is stirred for 16 h at 50°C. The reaction mixture is diluted with ethyl acetate and extracted with sodium hydrogen carbonate solution. The organic phases are dried and the solvent is eliminated *in vacuo*.

Yield: 1.670 g (4.877 mmol; 54 %)

MS (ESI): 343 $(M+H)^+$

b) 8-dibenzylamino-2-(2-fluoro-ethyl)-3,4-dihydro-2*H*-isoquinolin-1-one

1.06 g (3.095 mmol) 8-dibenzylamino-3,4-dihydro-2*H*-isoquinolin-1-one are combined with 1.5 ml (12 mmol) 1-bromo-2-fluoro-ethane and at ambient temperature 780 mg (19.50 mmol) sodium hydride are added batchwise over a period of 30 h. The reaction mixture is diluted with ethyl acetate and extracted with sodium hydrogen carbonate solution. The organic phases are dried and the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is dichloromethane, to which 5% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

Yield: 0.83 g (2.136 mmol; 69 %)

MS (ESI): 389 $(M+H)^+$

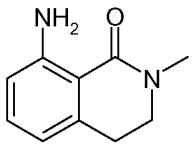
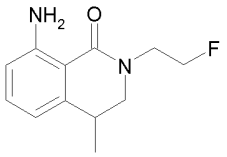
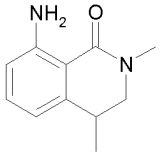
c) 8-amino-2-(2-fluoro-ethyl)-3,4-dihydro-2*H*-isoquinolin-1-one

830 mg (2.136 mmol) 8-dibenzylamino-2-(2-fluoro-ethyl)-3,4-dihydro-2*H*-isoquinolin-1-one are dissolved in 50 ml of methanol and combined with 80 mg palladium hydroxide. The reaction mixture is stirred for 48 h at ambient temperature and 4.5 bar H_2 pressure. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 0.403 g (1.935 mmol; 91 %)

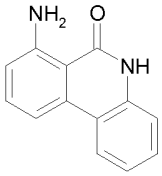
MS (ESI): 209 $(M+H)^+$

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		**MS (ESI) $(M+H)^+$**
	177		223
	191		

Method 19

7-amino-5*H*-phenanthridin-6-one



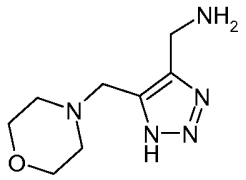
250 mg (1.16 mmol) methyl 2-chloro-6-nitro-benzoate, 458 mg (1.392 mmol) caesium carbonate, 211 mg (1.218 mmol) 2-nitrophenylboric acid and 18 mg (0.035 mmol) bis(tri-*tert*-butylphosphin)palladium(0) are placed under argon and combined with 0.8 ml dioxane. This reaction mixture is stirred for 48 h at 80°C. The reaction mixture is diluted with ethyl acetate and extracted with 1 N hydrochloric acid. The organic phase is dried and the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid is added to both the water and the acetonitrile. The suitable fractions are freeze-dried. 71 mg of the intermediate product thus obtained are dissolved in 50 ml of methanol and combined with 10 mg palladium on charcoal. The reaction mixture is stirred for 48 h at ambient temperature and 4.5 bar H_2 pressure. 50 ml dichloromethane are added to the reaction solution, the mixture is treated for 5 min in the ultrasound bath and then the catalyst is filtered off. The solvent is eliminated *in vacuo*.

Yield: 46 mg (0.221 mmol; 94 %)

MS (ESI): 211 $(M+H)^+$

Method 20

C-(5-morpholin-4-ylmethyl-1*H*-[1,2,3]triazol-4-yl)-methylamine



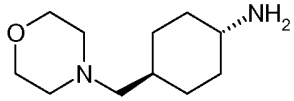
18.021 g (100 mmol) 1-azido-4-morpholino-2-butyne and 19.728 g (100 mmol) dibenzylamine are dissolved in 100 ml dioxane and heated to 80 °C with stirring. After stirring for 20 h at this temperature the solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is silica gel and the eluant used is dichloromethane, to which 5% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added. The suitable fractions are combined and the solvent is eliminated *in vacuo*. The residue is dissolved in 480 ml of methanol and combined with 30 ml concentrated aqueous hydrochloric acid and 1 g palladium on charcoal. This reaction mixture is stirred for 5 h at 50°C and 50 bar H_2 pressure. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 8.588 g (28.00 mmol; 28%)

MS (ESI): 198 $(M+H)^+$

Method 21

4-morpholin-4-ylmethyl-cyclohexylamine

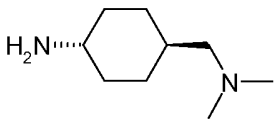
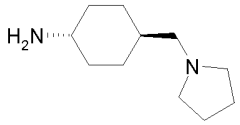
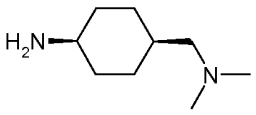
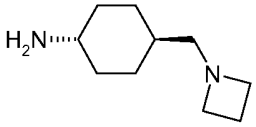


2.5 g (11 mmol) tert. butyl trans-(4-formyl-cyclohexyl)-carbamate dissolved in 25 ml dimethylacetamide are combined with 1 ml (11 mmol) morpholine and 0.7 ml acetic acid. 2.4 g (11.3 mmol) sodium triacetoxyborohydride dissolved in 12.5 ml dimethylacetamide is added to this mixture. The reaction mixture is stirred for 16 h at ambient temperature. Then the reaction mixture is added to 250 ml 10% potassium hydrogen carbonate solution and this mixture is extracted three times with 100 ml of ethyl acetate. The organic phases are combined, dried and then the solvent is eliminated *in vacuo*. The residue is taken up in 20 ml dichloromethane and 20 ml trifluoroacetic acid and stirred for 1 h at ambient temperature. The solvents are eliminated *in vacuo*.

Yield: 4.22 g (9.9 mmol; 90 %) (double trifluoroacetic acid salt)

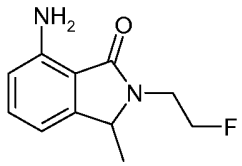
MS (ESI): 199 $(M+H)^+$

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		
	157		183
	157		169

Method 22

7-amino-2-(2-fluoro-ethyl)-3-methyl-2,3-dihydro-isoindol-1-one



10 g (42.157 mmol) methyl 2-acetyl-6-nitro-benzoate (J. Org. Chem. (1952), 17, 164-76), 6.06 g (54.804 mmol) 2-fluoroethylamine and 9.32 ml (54.804 mmol) of

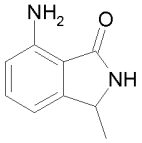
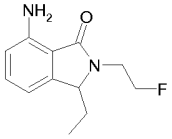
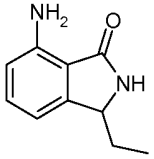
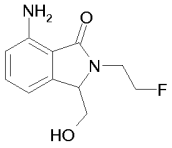
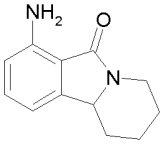
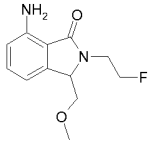
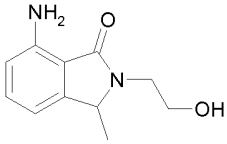
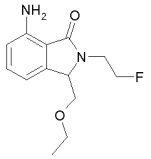
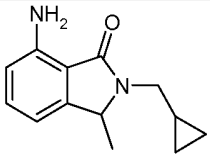
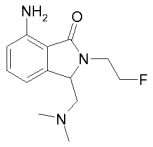
N-ethyldiisopropylamine are suspended in 25 ml of toluene and refluxed for 40 h with stirring. The reaction mixture is diluted with 400 ml of methanol and combined with 2.5 g palladium on charcoal. Then the mixture is stirred for 48 h at ambient temperature and 5 bar H_2 pressure. The catalyst is filtered off and the solvent is eliminated *in vacuo*. The residue is taken up in dichloromethane and washed with water. The organic phase is dried with magnesium sulphate, the solvent is eliminated *in vacuo* and the crude product is purified by chromatography. The carrier used is silica gel and the eluant used is a mixture of cyclohexane:ethyl acetate (70:30).

Yield: 3.83 g (18.404 mmol, 43 %)

MS (ESI): 209 $(M+H)^+$

UV max: 318 nm

The following compounds are prepared analogously to this process, using the corresponding methyl 6-nitro-benzoate derivative:

	MS (ESI) $(M+H)^+$		**MS (ESI) $(M+H)^+$**
	163		223
	177		225
	203		239
	207		253
	217		252

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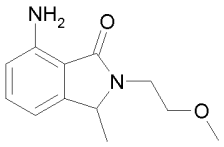
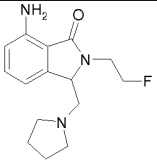
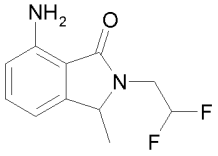
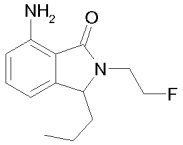
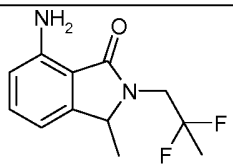
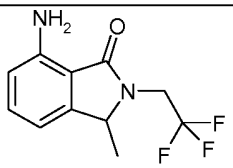
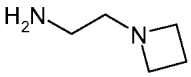
	221		278
	227		237
	241		245

Method 23

2-azetidin-1-yl-ethylamine

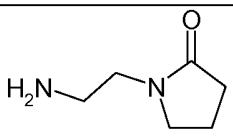
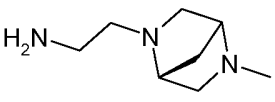


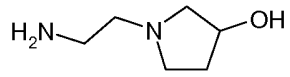
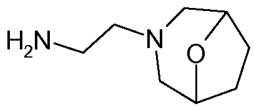
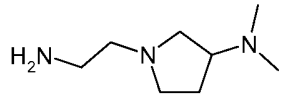
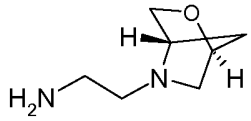
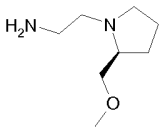
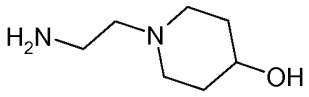
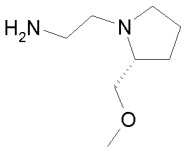
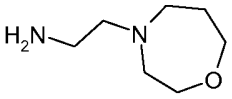
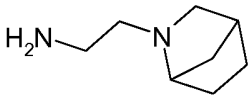
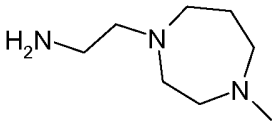
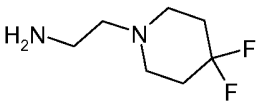
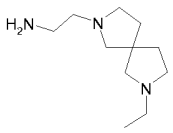
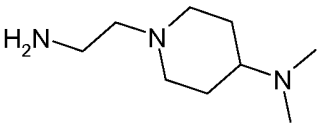
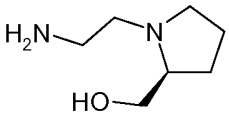
500 µl (7.49 mmol) azetidin are dissolved in 15 ml acetonitrile, combined with 4.831 g (34.822 mmol) potassium carbonate and 445 µl (7.038 mmol) chloroacetonitrile. This reaction mixture is stirred for 20 h at ambient temperature. To this reaction mixture are added 20 ml diethyl ether, the suspension is stirred for 10 min and filtered to separate the solid constituents. The filtrate is freed from solvents *in vacuo*. 463 mg (4.816 mmol) of this intermediate product are dissolved in 50 ml 7 N methanolic ammonia and Raney nickel is added. The reaction mixture is stirred for 2 h at 60°C and 20 bar H_2 pressure. The catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 365 mg (3.664 mmol, 48 %)

MS (ESI): 101 $(M+H)^+$

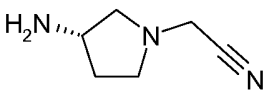
The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	129		156

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	131		157
	158		143
	159		145
	159		145
	141		158
	165		198
	172		145

Method 24

((S)-3-amino-pyrrolidin-1-yl)-acetonitrile



1 g (5.369 mmol) (S)-3-(Boc-amino)-pyrrolidine are dissolved in 20 ml acetonitrile and combined with 4.831 g (34.822 mmol) potassium carbonate and 322 µl (5.101 mmol) chloroacetonitrile. This reaction mixture is stirred for 20 h at ambient temperature. 20 ml diethyl ether are added to this reaction mixture, the suspension is stirred for 10 min and filtered to separate off the solid constituents. The filtrate is freed from the solvents *in vacuo*. The intermediate product is dissolved in 2 ml

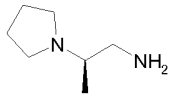
dioxane and combined with 13 ml of 4 N dioxanic hydrochloric acid and stirred overnight at RT. Then the solvent is eliminated *in vacuo*.

Yield: 500 mg (3.995 mmol, 74 %)

MS (ESI): 126 $(M+H)^+$

Method 25

(R)-2-pyrrolidin-1-yl-propylamine



a) (R)-2-pyrrolidin-1-yl-propionamide

2 g (16.055 mmol) R-alaninamide hydrochloride, 6.67 g (16.083 mmol) potassium carbonate and 8 mg (0.048 mmol) potassium iodide are suspended in 50 ml acetonitrile and then combined with 1.921 ml (16.083 mmol) 1,4-dibromobutane. This reaction mixture is refluxed for 14 h with stirring. 100 ml 1 N hydrochloric acid and 100 ml dichloromethane are added to the reaction mixture. The organic phase is separated off and discarded. The aqueous phase is made basic with sodium hydroxide solution and extracted three times with dichloromethane. The organic phases are combined, dried and freed from the solvent *in vacuo*.

Yield: 1.305 g (9.177 mmol, 57 %)

MS (ESI): 143 $(M+H)^+$

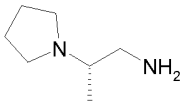
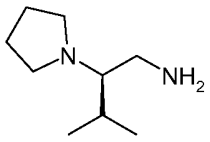
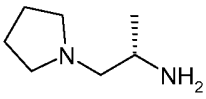
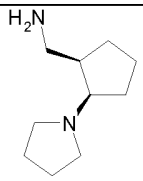
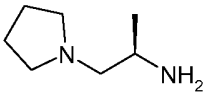
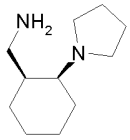
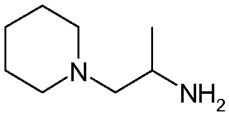
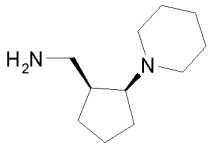
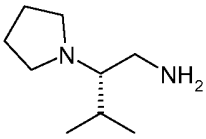
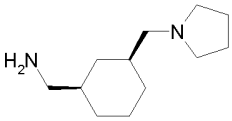
b) (R)-2-pyrrolidin-1-yl-propylamine

Under a nitrogen atmosphere 31.65 ml 1 M lithium aluminium hydride solution (THF) are taken and combined with 1 g (7.032 mmol) (R)-2-pyrrolidin-1-yl-propionamide, dissolved in 2 ml THF, at 0 °C. The reaction mixture is stirred for 48 h at 50 °C. The reaction mixture is combined with 100 ml of methanol and then with the same amount of dichloromethane while cooling with ice. Approx. 25 g silica gel are added to this mixture and the solvent is eliminated *in vacuo*. This silica gel applied to a suction filter which has previously been charged with approx. 75 g silica gel. The suction filter is washed batchwise with a total of 500 ml of a mixture of dichloromethane, methanol and aqueous conc. ammonia (90:9:1). The majority of the solvent is eliminated at a vacuum of 200 mbar and a sump temperature of approx. 50 °C. The product is distilled at 69-71 °C and 10 mbar.

Yield: 160 mg (1.248 mmol, 18 %)

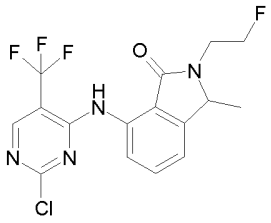
MS (ESI): 129 $(M+H)^+$

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	129		157
	129		169
	129		183
	143		183
	157		197

Method 26

2-chloro-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



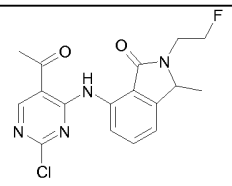
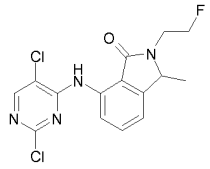
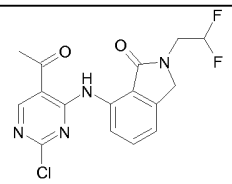
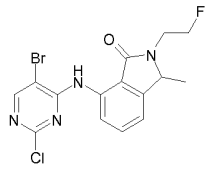
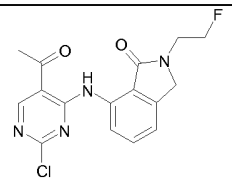
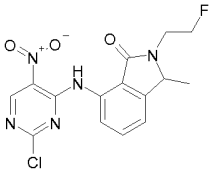
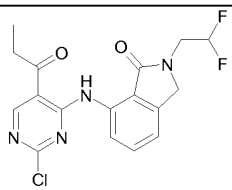
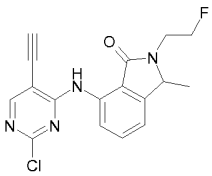
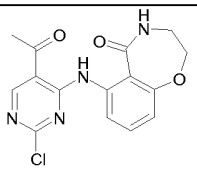
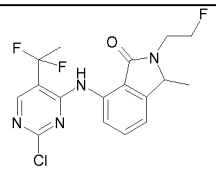
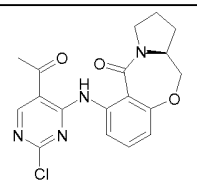
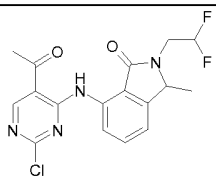
1.1 g (5.07 mmol) 2,4-dichloro-5-trifluoromethylpyrimidin are dissolved in 1 ml dioxane and combined with 0.9 g (4.322 mmol) 7-amino-2-(2-fluoro-ethyl)-3-methyl-2,3-dihydro-isoindol-1-one (method 22) and 0.9 ml (5.257 mmol) diisopropyethylamine. This mixture is stirred for 1 h at 80 °C. Then the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 20% water and 80%

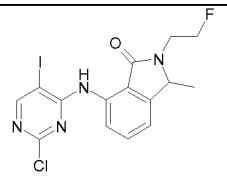
acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are combined with dichloromethane, the organic phase is separated off, dried and the solvent is eliminated *in vacuo*.

Yield: 485 mg (1.250 mmol, 25 %)

MS (ESI): 389/391 $(M+H)^+$; Cl distribution

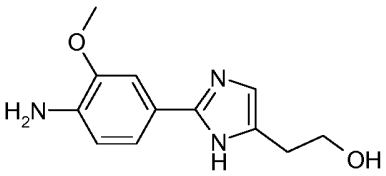
The following compounds are prepared analogously to this process. The aniline derivatives used are described in the supplements to method 2, in method 10 and in the supplements to method 10. The preparation of the 2,4-dichloropyrimidine derivatives is known from the literature or may be carried out by methods known from the literature.

	MS (ESI) $(M+H)^+$		**MS (ESI) $(M+H)^+$**
	363/365		355/357
	367/369		399/401
	349/351		366/368
	381/383		345/347
	333/335		385/387
	373/375		381/383

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	447/449		

Method 27

2-[2-(4-amino-3-methoxy-phenyl)-1*H*-imidazol-4-yl]-ethanol



a) 3-methoxy-4-nitro-benzonitrile

25 g (150.504 mmol) 3-fluoro-4-nitrobenzonitrile and 25 g (462.757 mmol) sodium methoxide are dissolved in 125 ml THF at 0°C. This reaction mixture is stirred for 30 min. The reaction mixture is extracted with ethyl acetate and 1 N hydrochloric acid. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*.

Yield: 25.092g (140.852 mmol, 94%)

UV max: 334 nm

b) 3-methoxy-4-nitro-benzamidine

99 ml (99mmol) lithium-bis-trimethylsilylamide solution (1 mol/l in THF) are diluted with 640 ml THF, cooled to 10°C and combined with 8.3 g (46.591 mmol) 3-methoxy-4-nitro-benzonitrile. The reaction mixture is stirred for 10 min at 20°C. The mixture is cooled to 0°C and combined with 80 ml 3 N hydrochloric acid. The reaction mixture is evaporated down *in vacuo* and extracted with water and ethyl acetate. The aqueous phase is adjusted to pH 14 with 3 N sodium hydroxide solution. The product is then suction filtered.

Yield: 14.30 g (crude product: 60% purity)

MS (ESI): 196 $(M+H)^+$

UV max: 334 nm

c) [2-(3-methoxy-4-nitro-phenyl)-1*H*-imidazol-4-yl]-acetic acid

7 g (60% purity, 21.519 mmol) 3-methoxy-4-nitro-benzamidine are dissolved in methanol and combined with 11 ml (44 mmol) 4 N dioxanic hydrochloric acid, the

solvents are eliminated *in vacuo*. The residue and 6.13 g (44.384 mmol) potassium carbonate are suspended in 350 ml acetonitrile and combined with 3.24 ml (22.764 mmol) ethyl 4-chloracetoacetate and 880 mg (5.301 mmol) potassium iodide. The reaction mixture is stirred for 16 h at 45 °C. The reaction mixture is diluted with water and combined with 1 N sodium hydroxide solution, and extracted with ethyl acetate. The aqueous phase is adjusted to pH 1 with 1 N HCL and saturated with sodium chloride. The product is then suction filtered.

Yield: 1.45 g (5.230 mmol, 24%)

MS (ESI): 278 $(M+H)^+$

UV max: 294 nm

d) 2-[2-(3-methoxy-4-nitro-phenyl)-1*H*-imidazol-4-yl]-ethanol

1.45 g (5.23 mmol) [2-(3-methoxy-4-nitro-phenyl)-1*H*-imidazol-4-yl]-acetic acid are dissolved in 36 ml THF and cooled to 0 °C and combined with 10 ml (18 mmol) borane-THF complex (1.8 mol/l). After 1 h the mixture is heated to 20°C and stirred for 16 h. Water is added until the development of gas has ended. Then the mixture is extracted twice with saturated aqueous sodium hydrogen carbonate solution and ethyl acetate. The organic phases are combined, dried and freed from the solvent *in vacuo*.

Yield: 0.65 g (2.465 mmol, 47%)

MS (ESI): 264 $(M+H)^+$

UV max: 298 nm

e) 2-[2-(4-amino-3-methoxy-phenyl)-1*H*-imidazol-4-yl]-ethanol

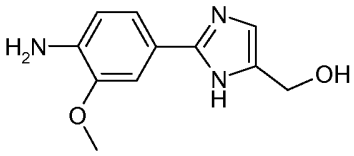
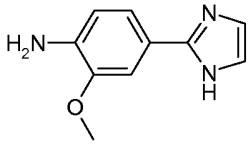
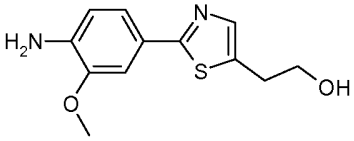
0.144 g (0.547 mmol) 2-[2-(3-methoxy-4-nitro-phenyl)-1*H*-imidazol-4-yl]-ethanol are dissolved in 100 ml of methanol and combined with 0.08 g (5%) palladium on charcoal. The reaction mixture is hydrogenated for 16 h at 20 °C and 4 bar H_2 pressure. The palladium on charcoal is suction filtered and the methanol is eliminated *in vacuo*.

Yield: 87 mg (0.373 mmol, 68%)

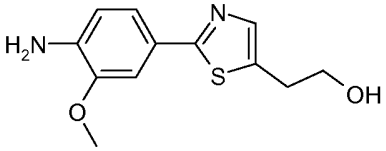
MS (APCI): 234 $(M+H)^+$

UV max: 314 nm

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	220		190
	251		

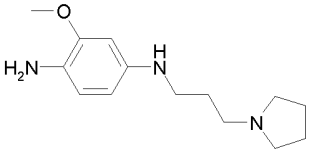
2-[2-(4-amino-3-methoxy-phenyl)-thiazole-5-yl]-ethanol is prepared analogously to the processes described above. For the cyclisation, 4-amino-3-methoxy-thiobenzamide is used (analogously to J. Am. Soc. 82, 2656, **1960**) instead of 3-methoxy-4-nitro-benzamidine.



MS (ESI): 251 $(M+H)^+$

Method 28

2-methoxy-N^4-(3-pyrrolidin-1-yl-propyl)-benzene-1,4-diamine



a) (3-methoxy-4-nitro-phenyl)-(3-pyrrolidin-1-yl-propyl)-amine

1 g (5.884 mmol) 4-fluoro-2-methoxy-1-nitro-benzene, 975 mg (7.369 mmol) 1-(3-aminopropyl)pyrrolidine and 1.5 ml (8.765 mmol) diisopropyethylamine are dissolved in 5 ml dioxane and stirred for 24 h at 95 °C. The solvents are eliminated *in vacuo* and the crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is dichloromethane, to which 15% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution has been added.

Yield: 1.07 g (3.827 mmol; 65 %)

MS (ESI): 280 $(M+H)^+$

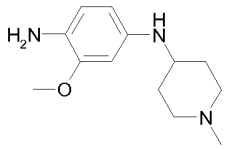
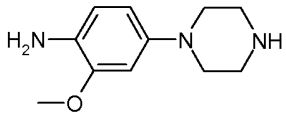
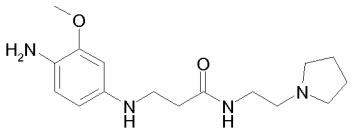
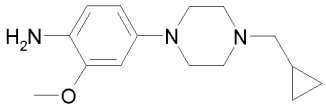
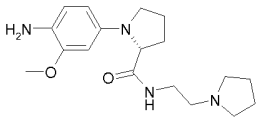
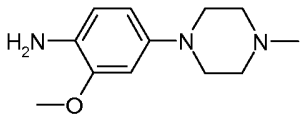
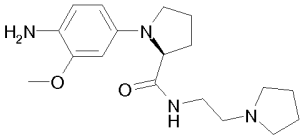
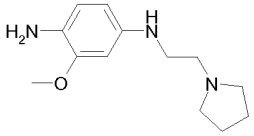
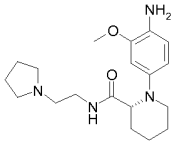
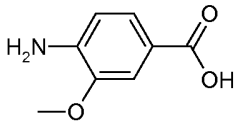
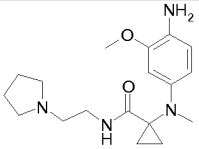
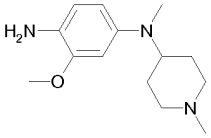
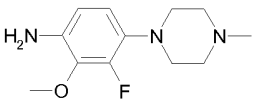
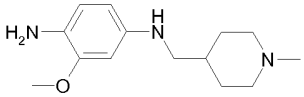
b) 2-methoxy-N^4-(3-pyrrolidin-1-yl-propyl)-benzene-1,4-diamine

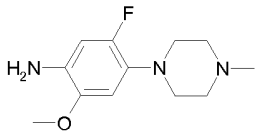
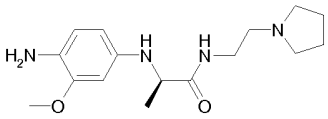
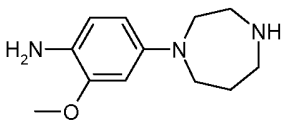
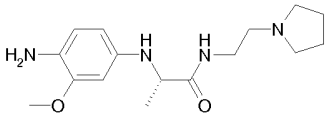
200 mg (0.716 mmol) (3-methoxy-4-nitro-phenyl)-(3-pyrrolidin-1-yl-propyl)-amine are dissolved in 10 ml of methanol and combined with 537 µl (2.148 mmol) dioxanic hydrochloric acid and 20 mg palladium on charcoal. The reaction mixture is stirred for 1 h at ambient temperature and 5 bar H_2 pressure. The catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 213 mg (0.661 mmol, 92 %)

MS (ESI): 250 $(M+H)^+$

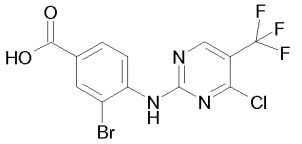
The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		**MS (ESI) $(M+H)^+$**
	236		208
	307		262
	333		222
	333		236
	347		168
	333		250
	240		250

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	240		307
	222		307

Method 29

2-(4-carboxy-2-bromo-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine



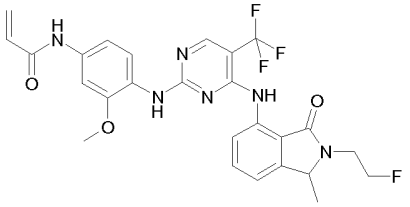
1 g (3.148 mmol) 2-(4-carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine (method 12 or 14) are dissolved in 5 ml DMF and combined batchwise with 3.36 g (18.889 mmol) *N*-bromosuccinimide. This reaction mixture is stirred for 16 h at ambient temperature. Then the solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 2% water and 98% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile.

Yield: 571 mg (1.440 mmol, 46 %)

MS (ESI): 396 / 398 $(M+H)^+$

Method 30

2-(4-Acryloylamino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



a) 4-amino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine

1 g (1.925 mmol) 2-(4-carboxy-2-methoxy-phenylamino)-4-[2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino]-5-trifluoromethyl-pyrimidine (prepared analogously to Example 53) are dissolved in 2 ml of toluene and combined successively with 0.43 ml (2.503 mmol) diisopropylethylamine, with 1.8 ml *tert*-butanol and with 0.49 ml (2.310 mmol) diphenylphosphorylazide and heated to 80 °C for 18 h. The reaction mixture is cooled, diluted with 100 ml of ethyl acetate and washed twice with 0.5 N sodium hydroxide solution. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*. The residue is taken up in dichloromethane and combined with 4 M dioxanic hydrochloric acid. The mixture is stirred for 72 h at ambient temperature. It is diluted with ethyl acetate and extracted 4 times with 1 N hydrochloric acid. The aqueous phases are combined and extracted once with ethyl acetate. The aqueous phase is made basic with sodium hydroxide solution and extracted three times with ethyl acetate. The organic phases are combined, dried and the solvent is eliminated *in vacuo*.

Yield: 606 mg (1.236 mmol, 64 %)

MS (ESI): 491 $(M+H)^+$

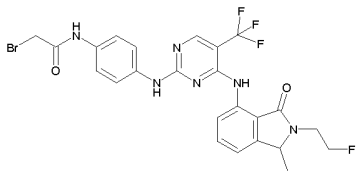
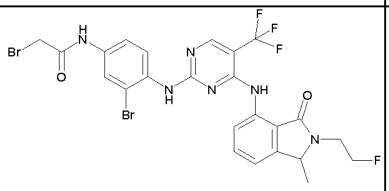
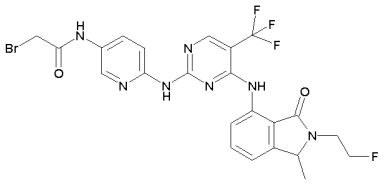
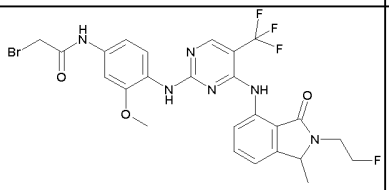
b) 2-(4-Acryloylamino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine

311 mg (0.634 mmol) 2-(4-amino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine are dissolved in 10 ml THF and combined with 115 µl (0.824 mmol) triethylamine and 62 µl (0.761 mmol) acrylic chloride. This mixture is stirred for 1 h at ambient temperature. Then it is diluted with ethyl acetate and extracted three times with water. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*.

Yield: 340 mg (0.625 mmol, 98 %)

MS (ESI): 545 $(M+H)^+$

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	581		659
	582		611

Method 31

Separation of the racemic 7-amino-2-(2-fluoro-ethyl)-3-methyl-2,3-dihydro-isoindol-1-one (method 22) into the two enantiomers

The separation is carried out by preparative chromatography under the following conditions:

column: 280 x 110 mm CHIRALPAK® AD 20 µm

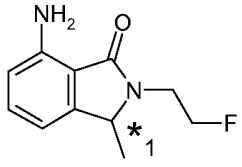
Eluant: 95% acetonitrile/5% isopropanol (v/v)

Flow rate: 570 ml/min

Temperature: ambient temperature

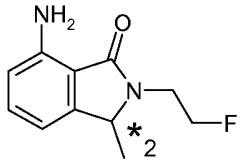
The enantiomer that elutes first is known as enantiomer 1 and in the chemical formula bears the symbol *1:

Enantiomer 1



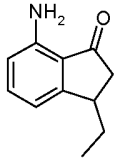
The enantiomer that elutes second is known as enantiomer 2 and in the chemical formula bears the symbol *2:

Enantiomer 2



Method 32

7-amino-3-ethyl-indan-1-one

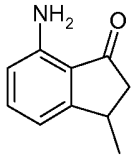
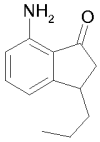


262 mg (1.364 mmol) copper iodide are taken and heated in an argon current. Then the copper iodide is suspended in ether and cooled to -78 °C. At this temperature 0.8 ml of a 3 M ethylmagnesium bromide solution (in ether) are added and the mixture is stirred for 10 min and then left to thaw to 0 °C. After 15 min stirring at this temperature the mixture is cooled to -78 °C again and 200 mg (0.802 mmol) *N*-(3-oxo-3*H*-inden-4-yl)-benzamide, dissolved in 9 ml THF, are added dropwise and the mixture is stirred for 1 h at 0 °C. The reaction mixture is diluted with dichloromethane and washed three times with concentrated aqueous ammonia solution. The organic phase is dried with magnesium sulphate and the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 98% water and 2% acetonitrile at the starting point and 2% water and 98% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are freeze-dried. This intermediate product is dissolved in 2 ml dioxane and combined with 5 ml concentrated hydrochloric acid. The reaction mixture is refluxed for 24 h with stirring. Then it is diluted with water and extracted three times with dichloromethane. The combined organic phases are again washed with water, dried and the solvent is removed. The residue is purified by column chromatography. The carrier used is silica gel and the eluant used is dichloromethane, to which 5% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

Yield: 70 mg (0.399 mmol; 29 %)

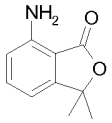
MS (ESI): 176 $(M+H)^+$

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	162		190

Method 33

7-amino-3,3-dimethyl-3*H*-isobenzofuran-1-one

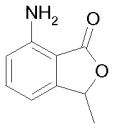
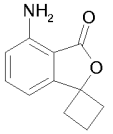
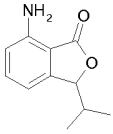
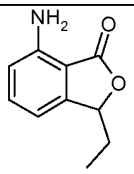
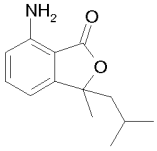


250 mg (0.609 mmol) methyl 2-dibenzylamino-benzoate are combined under argon with 0.609 ml of a 1 M lithium chloride solution (THF). This solution is cooled to ambient temperature and slowly 0.914 ml (1.827 mmol) of a 2 M isopropyl-magnesium chloride solution are metered in. After stirring for 16 h at this temperature, 45 µl (0.609 mmol) acetone are added dropwise and the mixture is stirred for 4 h at ambient temperature. The reaction solution is combined with sodium hydrogen carbonate solution and extracted three times with dichloromethane. The combined organic phases are dried and the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are freeze-dried. This intermediate product is dissolved in 50 ml of methanol combined with 10 mg palladium on charcoal and hydrogenated for 20 h at 5 bar hydrogen pressure and ambient temperature. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are freeze-dried.

Yield: 34 mg (0.192 mmol; 32 %)

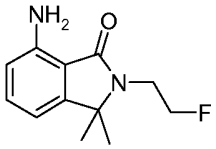
MS (ESI): 178 $(M+H)^+$

The following compounds are prepared analogously to this process:

	MS (ESI) $(M+H)^+$		MS (ESI) $(M+H)^+$
	164		190
	192		178
	220		

Method 34

7-amino-2-(2-fluoro-ethyl)-3,3-dimethyl-2,3-dihydro-isoindol-1-one



a) methyl 2-(cyano-dimethyl-methyl)-6-nitro-benzoate

3 g (13.625 mmol) methyl 2-cyanomethyl-6-nitro-benzoate (WO 9518097) are dissolved in 20 ml THF combined with 4.33 ml (68.788 mmol) iodomethane and cooled to 0 °C. At this temperature 40.87 ml of a 1 M potassium-*tert*-butoxide solution is slowly added dropwise. The mixture is heated to ambient temperature and stirred for 16 h at this temperature. The reaction mixture is diluted with ethyl acetate and extracted three times with 1 M hydrochloric acid. The combined organic phases are dried and the solvent is eliminated *in vacuo*.

Yield: 3.11 g (12.535 mmol; 92 %)

b) 3,3-dimethyl-7-nitro-2,3-dihydro-isoindol-1-one

Reaction mixture 1

1 g (4.028 mmol) methyl 2-(cyano-dimethyl-methyl)-6-nitro-benzoate are suspended in 20% ethanolic potassium hydroxide solution and stirred for 24 h at ambient temperature.

Reaction mixture 2

1.9 g (47.577 mmol) sodium hydroxide are dissolved in 40 ml of water cooled to 0 °C and combined with 0.5 ml (28.899 mmol) bromine. reaction mixture 1 is slowly added dropwise to this solution. After 8 h the same amount of reaction mixture 1 is added again. The mixture is stirred for a further 48 h at RT. Then sodium sulphite solution is added, the mixture is stirred for 20 min and then acidified with potassium hydrogen sulphate solution. It is extracted three times with ethyl acetate. The combined organic phases are dried and the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is silica gel and the eluant used is a mixture of cyclohexane:ethyl acetate (3:1).

Yield: 67 mg (0.325 mmol, 8 %)

MS (ESI): 207 $(M+H)^+$

c) 3,3-dimethyl-7-amino-2,3-dihydro-isoindol-1-one

67 mg (0.325 mmol) 3,3-dimethyl-7-nitro-2,3-dihydro-isoindol-1-one are dissolved in 50 ml of methanol and combined with 10 mg palladium on charcoal. The mixture is hydrogenated for 16 h at 4 bar H_2 pressure and ambient temperature. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 50 mg (0.284 mmol, 93 %)

MS (ESI): 177 $(M+H)^+$

d) 7-dibenzylamino-3,3-dimethyl-2,3-dihydro-isoindol-1-one

50 mg (0.284 mmol) 3,3-dimethyl-7-amino-2,3-dihydro-isoindol-1-one are dissolved in 0.5 ml DMF and combined with 141 mg (1.021 mmol) potassium carbonate and 10 mg (0.028 mmol) tetrabutylammonium iodide. The mixture is heated to 50 °C and 155 µl (1.277 mmol) benzylbromide are added dropwise thereto. After stirring for 16 h at this temperature the mixture is diluted with ethyl acetate and extracted three times with 1 M hydrochloric acid. The combined organic phases are dried and the solvent is eliminated *in vacuo*.

Yield: 67 mg (0.188 mmol; 66 %)

MS (ESI): 357 $(M+H)^+$

e) 7-dibenzylamino-2-(2-fluoro-ethyl)-3,3-dimethyl-2,3-dihydro-isoindol-1-one

67 mg (0.188 mmol) 7-dibenzylamino-3,3-dimethyl-2,3-dihydro-isoindol-1-one are dissolved in 1 ml (7.877 mmol) 1-bromo-2-fluoroethane and combined with 52 mg (0.376 mmol) sodium hydride. After 4 h stirring at ambient temperature the mixture is

diluted with ethyl acetate and extracted three times with 1 M hydrochloric acid. The combined organic phases are dried and the solvent is eliminated *in vacuo*.

Yield: 75 mg (0.188 mmol; 100 %)

MS (ESI): 403 $(M+H)^+$

f) 7-amino-2-(2-fluoro-ethyl)-3,3-dimethyl-2,3-dihydro-isoindol-1-one

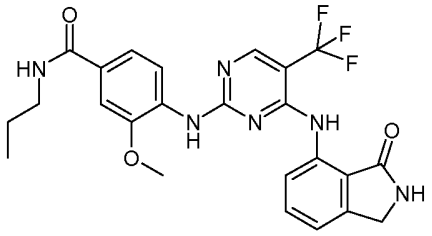
75 mg (0.188 mmol) 7-dibenzylamino-2-(2-fluoro-ethyl)-3,3-dimethyl-2,3-dihydro-isoindol-1-one are dissolved in 50 ml of methanol and combined with 10 mg palladium on charcoal. The mixture is hydrogenated for 16 h at 5 bar H_2 pressure and ambient temperature. Then the catalyst is filtered off and the solvent is eliminated *in vacuo*.

Yield: 36 mg (0.162 mmol, 87 %)

MS (ESI): 223 $(M+H)^+$

Example 1

2-(2-methoxy-4-*N*-propylcarbamoyl-phenylamino)-4-(3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



100 mg (0.257 mmol) 2-(2-methoxy-4-propylcarbamoyl-phenylamino)-4-chloro-5-trifluoro-methyl-pyrimidine (method 1) are dissolved in 1 ml *N,N*-dimethylacetamide and combined with 83 mg (0.565 mmol) 7-amino-2,3-dihydro-isoindol-1-one (method 2). 48 µl of a 4 molar solution of HCl (0.193 mmol) in 1,4-dioxane are metered into this reaction mixture. After two days at 50°C the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is dichloromethane, to which 5% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added. The concentrated crude product is again purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 80% water and 20% acetonitrile at the starting point and 60% water and 40% acetonitrile aat the finishing point.

Yield: 42 mg (0.084 mmol; 33 %)

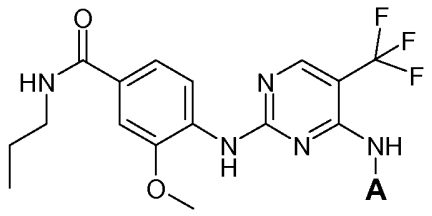
UV max: 318 nm

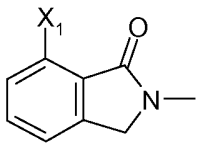
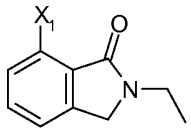
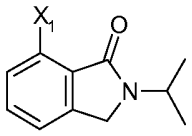
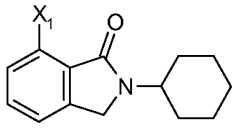
MS (ESI): 501 $(M+H)^+$

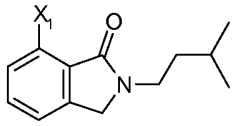
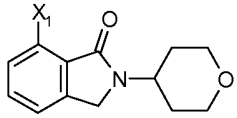
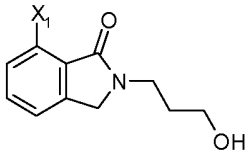
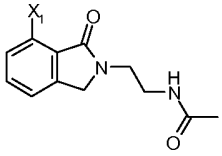
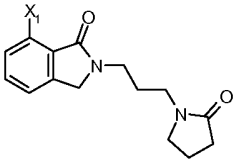
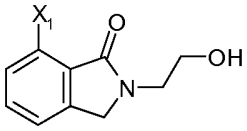
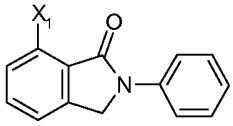
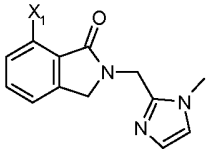
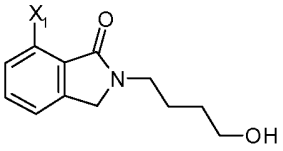
^{1}H-NMR: 0.92 (t, 3H), 1.51 - 1.63 (m, 2H), 3.21 - 3.29 (m, 2H), 3.86 (s, 3H), 4.37 (s, 2H), 7.14 - 7.21 (m, 1H), 7.33 (t, 1H), 7.47 - 7.54 (m, 1H), 7.55 - 7.60 (m, 1H), 7.73 - 7.82 (m, 1H), 8.35 - 8.50 (m, 3H), 8.75 (s, 1H), 9.09 (s, 1H), 10.66 (s, 1H)

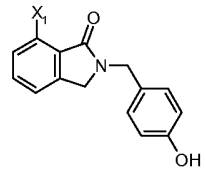
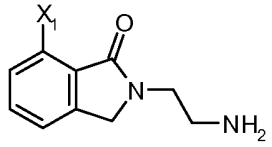
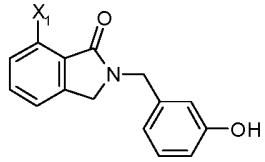
Examples 2-17

The following compounds are prepared by an analogous method as described in Example 1. 2-(2-Methoxy-4-propylcarbamoyl-phenylamino)-4-chloro-5-trifluoromethylpyrimidine and a corresponding 7-amino-2,3-dihydro-isoindol-1-one derivative (method 2) are used. *N*-methyl-2-pyrrolidinone or *N,N*-dimethylacetamide is used as solvent.



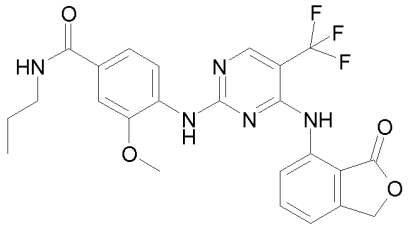
#	A	UV max [nm]	MS (ESI) $(M+H)^+$
2		322	515
3		314	529
4		285	543
5		286 / 310	583

#	A	UV max [nm]	MS (ESI) $(M+H)^+$
6		322	571
7		285 / 321	585
8		285 / 318	559
9		285 / 318	586
10		281 / 316	626
11		284 / 316	545
12		325	577
13		282 / 318	595
14		284 / 322	573

#	A	UV max [nm]	MS (ESI) $(M+H)^+$
15		286, 306	607
16		325	
17		318/282	607

Example 18

2-(2-methoxy-4-*N*-propylcarbamoyl-phenylamino)-4-(3-oxo-1,3-dihydro-isobenzofuran-4-ylamino)-5-trifluoromethyl-pyrimidine



100 mg (0.257 mmol) 2-(2-methoxy-4-propylcarbamoyl-phenylamino)-4-chloro-5-trifluoro-methyl-pyrimidine (method 1) are dissolved in 1 ml *N,N*-dimethylacetamide and combined with 46 mg (0.308 mmol) 7-amino-3*H*-isobenzofuran-1-one (Safdar Hayat et al., *Tetrahedron Lett* 2001, **42(9)**:1647-1649). 48 µl of a 4 molar solution of HCl (0.193 mmol) in 1,4-dioxane are metered into this reaction mixture. After 4 days at 50°C the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is dichloromethane, to which 4% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

Yield: 26 mg (0.051 mmol; 20 %)

UV max: 322 nm

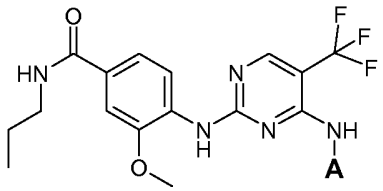
MS (ESI): 502 $(M+H)^+$

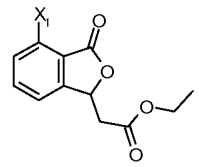
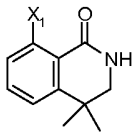
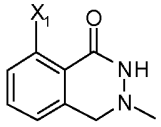
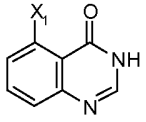
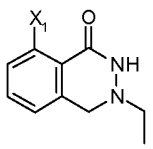
^{1}H-NMR: 0.92 (t, 3H), 1.51 - 1.63 (m, 2H), 3.22 - 3.28 (m, 2H), 3.86 (s, 3H), 5.42 (s, 2H), 7.24 - 7.30 (m, 1H), 7.44 - 7.55 (m, 2H), 7.55 - 7.60 (m, 1H),

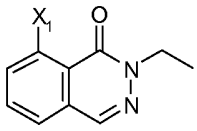
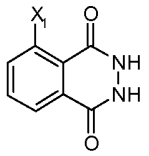
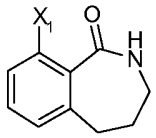
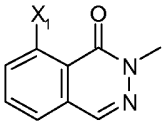
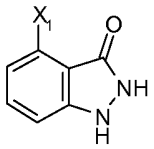
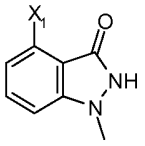
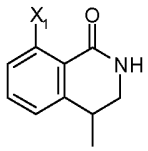
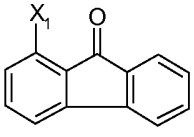
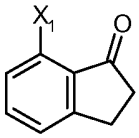
7.67 - 7.78 (m, 1H), 8.38 - 8.48 (m, 2H), 8.50 (s, 1H), 9.21 (s, 1H), 9.64 (s, 1H)

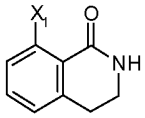
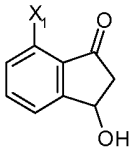
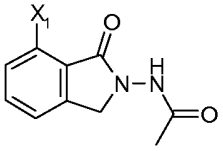
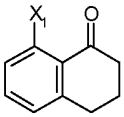
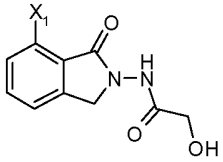
Examples 19-37

The following compounds are prepared by analogous methods to those described in Example 1 and Example 18. 2-(2-methoxy-4-propylcarbamoyl-phenylamino)-4-chloro-5-trifluoromethylpyrimidine (method 1) is used. The corresponding aniline derivative is commercially obtainable, known from the literature or is prepared by the processes described in method 2 and 4 to 9. *N*-methyl-2-pyrrolidinone or *N,N*-dimethylacetamide is used as solvent.



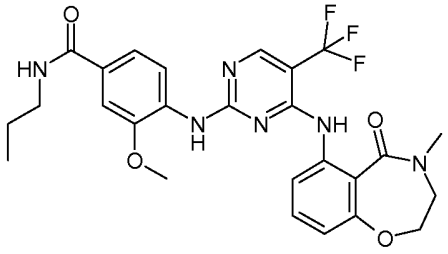
#	A	UV max [nm]	MS (ESI) $(M+H)^+$
19		235	586
20		323 / 226	543
21		325	530
22		262	514
23		320	544

#	A	UV max [nm]	MS (ESI) $(M+H)^+$
24		318	542
25		312	530
26		315	529
27		314	528
28		317	502
29		316	516
30		322	529
31		255	548
32		320	500

#	A	UV max [nm]	MS (ESI) $(M+H)^+$
33		325	515
34		250 / 286 / 318	516
35		320	558
36		316	514
37		321	

Example 38

2-(2-methoxy-4-*N*-propylcarbamoyl-phenylamino)-4-(4-methyl-5-oxo-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepin-6-ylamino)-5-trifluoromethyl-pyrimidine



50 mg (0.129 mmol) 2-(2-methoxy-4-propylcarbamoyl-phenylamino)-4-chloro-5-trifluoro-methyl-pyrimidine (method 1) are dissolved in 200 µl 1,4-dioxane and combined with 25 mg (0.13 mmol) 6-amino-4-methyl-3,4-dihydro-2*H*-benzo[f][1,4]oxazepin-5-one (method 10). 36 µl of a 4 molar solution of HCl (0.144 mmol) in 1,4-dioxane are metered into this reaction mixture. After 4 days at 50 °C the solvent is eliminated *in vacuo*. The crude product is purified by column

chromatography. The carrier used is silica gel and the eluant used is a mixture of dichloromethane and ethyl acetate (1:1).

Yield: 23 mg (0.042 mmol; 33 %)

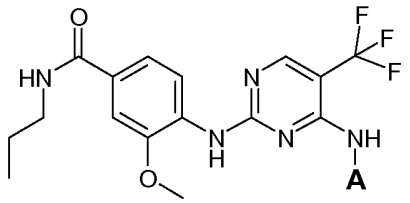
UV max: 318 nm

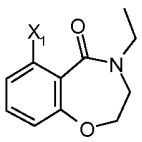
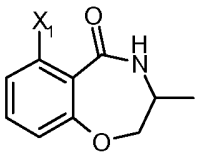
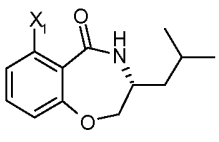
MS (ESI): 545 $(M+H)^+$

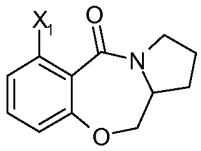
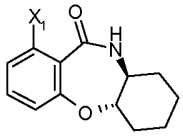
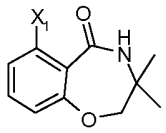
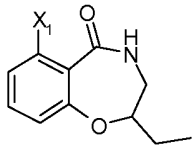
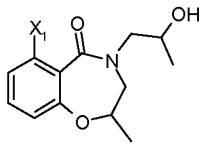
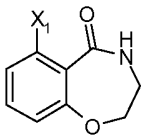
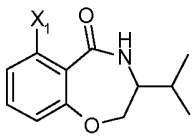
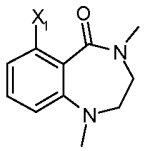
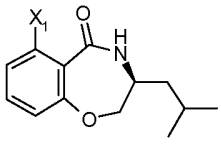
^{1}H-NMR: 0.91 (t, 3H), 1.49 - 1.61 (m, 2H), 3.09 (s, 3H), 3.20 - 3.28 (m, 2H), 3.49 (t, 2H), 3.88 (s, 3H), 4.31 (t, 2H), 6.83 - 6.88 (m, 1H), 7.34 - 7.45 (m, 2H), 7.50 - 7.54 (m, 1H), 7.88 - 8.00 (m, 2H), 8.37 - 8.44 (m, 2H), 8.62 (s, 1H), 9.97 (s, 1H)

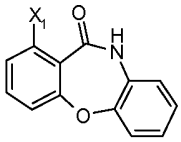
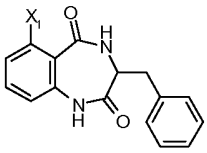
Examples 39-52

The following compounds are prepared by analogous methods to those described in Example 1 and 18. 2-(2-methoxy-4-propylcarbamoyl-phenylamino)-4-chloro-5-trifluoromethylpyrimidine (method 1) is used. The corresponding aniline derivative is commercially obtainable, known from the literature or is prepared by the processes described in method 10 and 11. *N*-methyl-2-pyrrolidinone or *N,N*-dimethylacetamide is used as solvent.



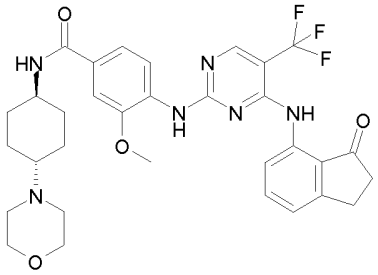
#	A	UV max [nm]	MS (ESI) $(M+H)^+$
39		229 / 279 / 315	559
40		282 / 314	545
41		282 / 318	587

#	A	UV max [nm]	MS (ESI) $(M+H)^+$
42		282 / 314	571
43		282 / 318	585
44		318	559
45		234 / 320	559
46		282 / 218	603
47		278 / 318	531
48		286/314	573
49		274/314	558
50		318	587

#	A	UV max [nm]	MS (ESI) $(M+H)^+$
51		223/282/318	579
52		318	634

Example 53

2-[2-methoxy-4-(4-morpholin-4-yl-(1,4-trans-cyclohexyl)carbamoyl)-phenylamino]-4-(2-carbamoyl-3-fluoro-phenylamino)-5-trifluoromethyl-pyrimidine



102 mg (0.29 mmol) 2-(4-carboxyamino-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine (method 12) are dissolved in 250 µl *N*-methyl-2-pyrrolidinone and combined with 47 mg (0.319 mmol) 7-amino-indan-1-one (method 8). 15 µl of a 4 M solution of HCl (0.058 mmol) in 1,4-dioxane are metered into this reaction mixture. After 16 h at 90°C the reaction mixture is stirred into 150 ml of a aqueous 1 N hydrochloric acid. The precipitate is filtered off and dried *in vacuo*. 100 mg (0.174 mmol) of this precipitate, 150 µl (0.875 mmol) *N*-ethyldiisopropyl-amine, 68 mg (0.210 mmol) *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate and 30 mg (0.163 mmol) trans-4-morpholin-4-yl-cyclohexylamine (method 13) are dissolved in 5 ml *N,N*-dimethylformamide. After 15 h at ambient temperature the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier used is silica gel and the eluant used is dichloromethane, to which 7% of a mixture of 90% methanol and 10% saturated aqueous ammonia solution have been added.

Yield: 55 mg (0.100 mmol; 57 %)

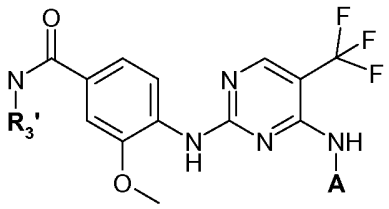
UV max: 318 nm

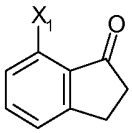
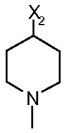
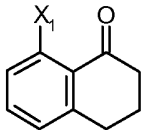
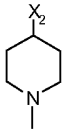
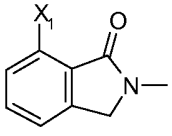
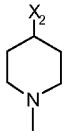
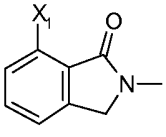
MS (ESI): 555 $(M+H)^+$

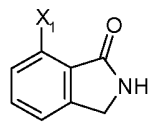
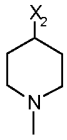
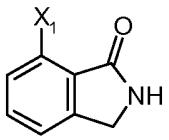
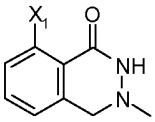
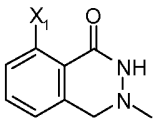
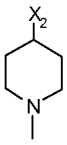
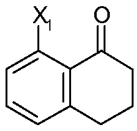
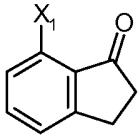
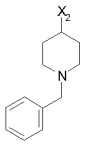
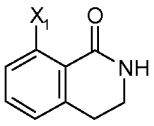
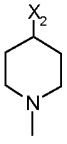
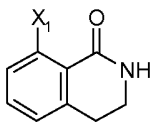
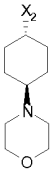
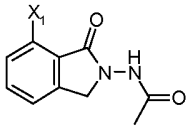
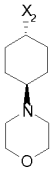
^{1}H-NMR: 1.55 - 1.69 (m, 2H), 1.74 - 1.84 (m, 2H), 1.91 - 2.02 (m, 2H), 2.18 (s, 3H), 2.69 - 2.75 (m, 2H), 2.75 - 2.84 (m, 2H), 3.03 - 3.10 (m, 2H), 3.70 - 3.83 (m, 1H), 3.86 (s, 3H), 7.15 - 7.21 (m, 1H), 7.36 - 7.46 (m, 1H), 7.48 - 7.54 (m, 1H), 7.54 - 7.58 (m, 1H), 7.71 - 7.79 (m, 1H), 8.18 - 8.25 (m, 1H), 8.30 - 8.45 (m, 1H), 8.48 (s, 1H), 9.16 (s, 1H), 10.59 (s, 1H)

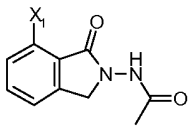
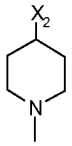
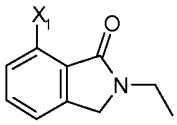
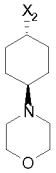
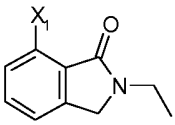
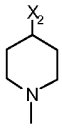
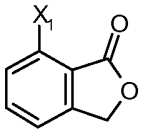
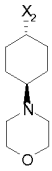
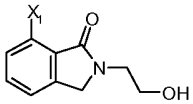
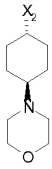
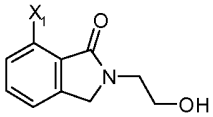
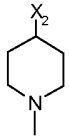
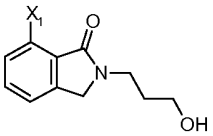
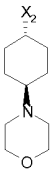
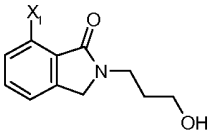
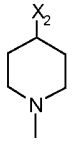
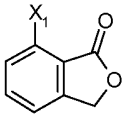
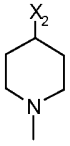
Examples 54-77

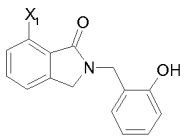
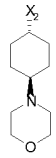
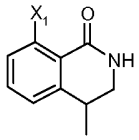
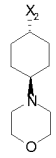
The following compounds are prepared by an analogous method to that described in Example 53. The corresponding aniline is described in method 2, 7, 8, or 9 or known from the literature. The amine used to prepare the amide is commercially obtainable or is described in method 13.



#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
54			318	555
55			318	569
56			322	570
57			320	640

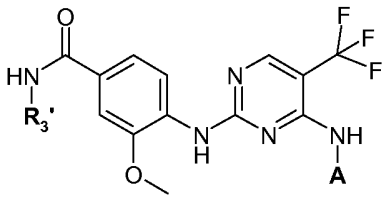
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
58			284, 322	556
59			282, 318	626
60			325	655
61			325	585
62			254, 286, 318	639
63			321	631
64			322	570
65			322	640
66			322	683

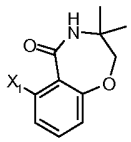
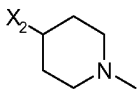
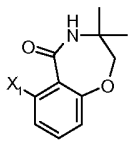
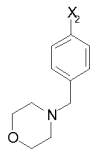
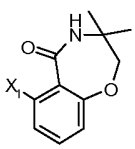
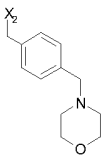
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
67			322	613
68			286, 322	654
69			286, 322	584
70			282, 322	627
71			322	670
72			286, 322	600
73			322	684
74			286, 322	614
75			322	557

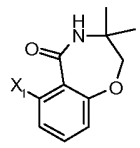
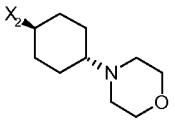
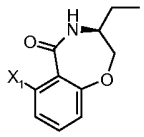
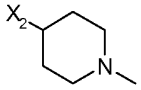
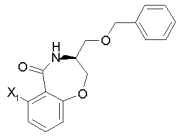
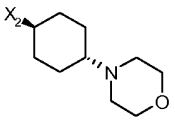
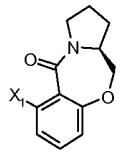
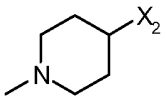
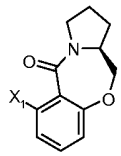
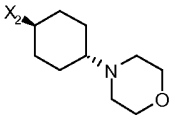
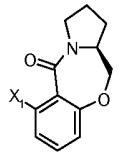
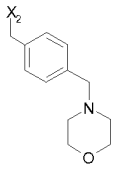
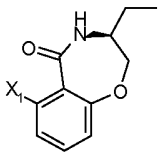
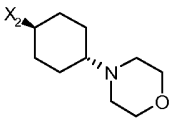
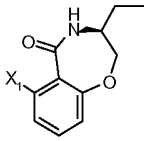
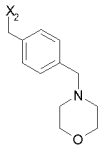
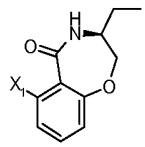
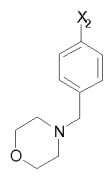
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
76			330	732
77			325	654

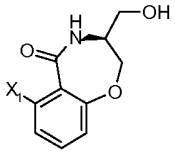
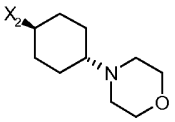
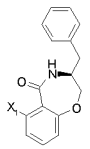
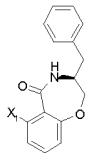
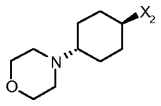
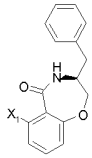
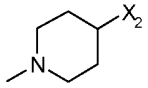
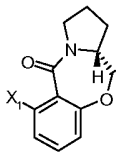
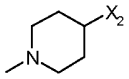
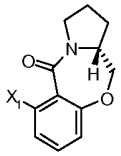
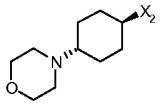
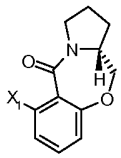
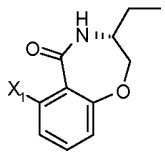
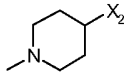
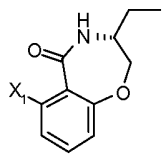
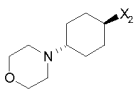
Examples 78-140

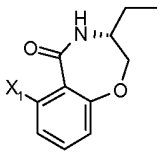
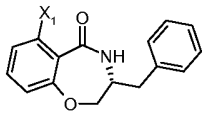
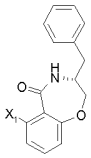
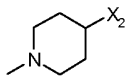
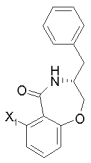
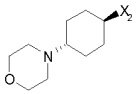
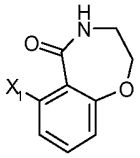
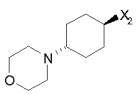
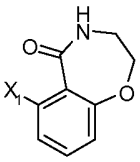
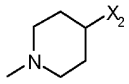
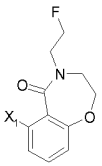
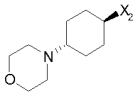
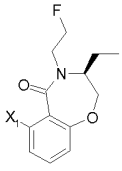
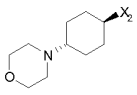
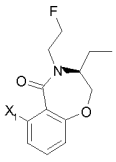
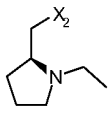
The following compounds are prepared by an analogous method to that described in Example 53. 2-(4-Carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be prepared according to method 12 or 14. The corresponding aniline is described in the supplements to method 10. The amine used to prepare the amide is commercially obtainable or is described in method 13, in the supplements to method 13, 15 or 25.

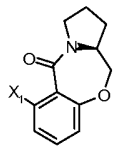
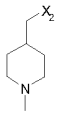
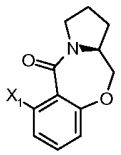
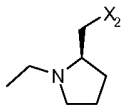
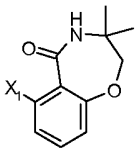
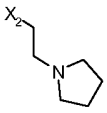
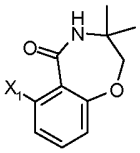
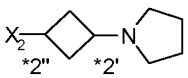
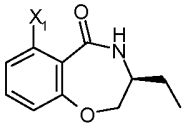
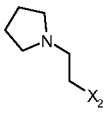
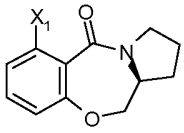
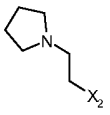
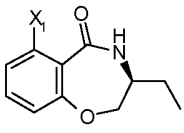
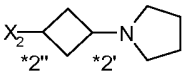
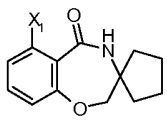
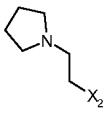
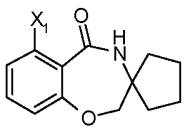
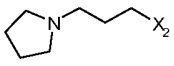


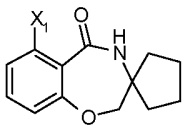
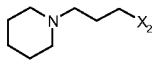
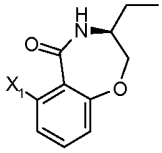
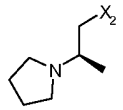
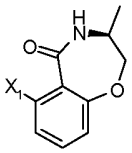
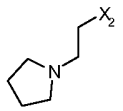
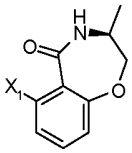
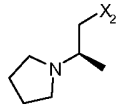
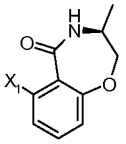
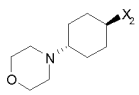
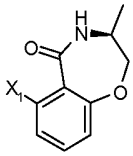
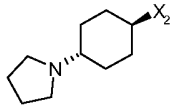
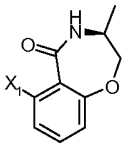
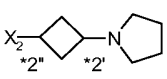
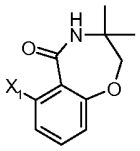
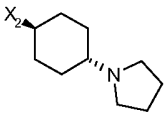
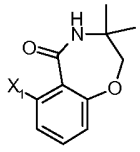
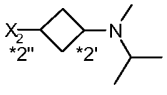
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
78			318	308
79			326	346
80			318	706

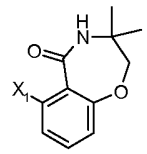
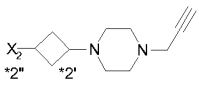
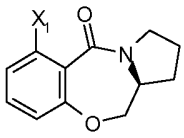
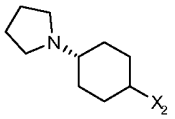
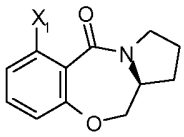
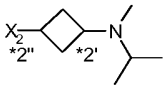
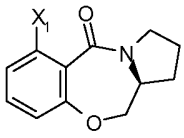
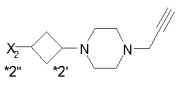
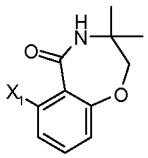
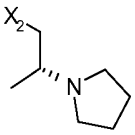
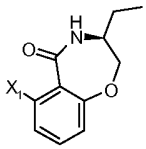
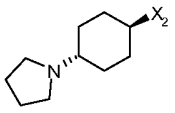
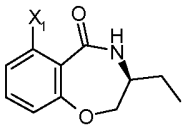
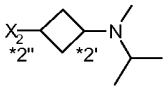
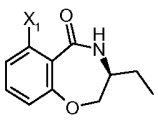
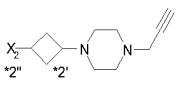
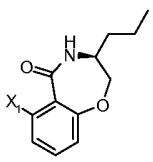
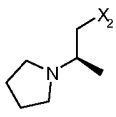
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
81			318	584
82			318	614
83			318	776
84			318	626
85			318	348
86			318	718
87			318	684
88			318	353
89			322	346

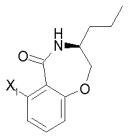
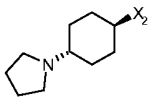
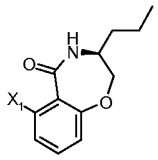
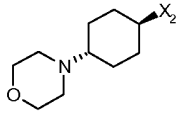
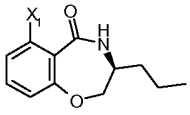
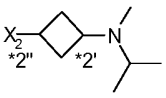
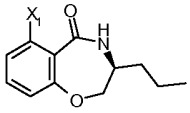
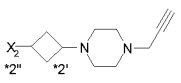
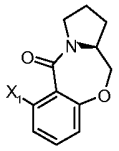
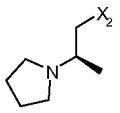
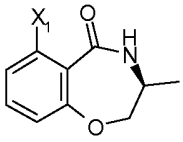
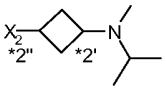
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
90			318	686
91			310	621
92			318	746
93			318	676
94			318	316
95			318	696
96			282; 310	571
97			318	614
98			318	684

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
99			315	559
100			314	621
101			314	676
102			318	747
103			318	656
104			318	586
105			318	(M
106			318	730
107			322	674

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
108			318	640
109			322	640
110			282, 318	614
111			226, 282, 318	640
112			318	614
113				626
114			318	640
115			318	640
116			318	654

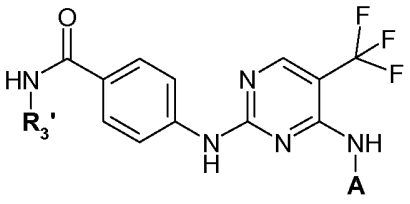
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
117			318	668
118			318	628
119			318	600
120			318-322	614
121			318	670
122			318	654
123			318	626
124			282, 318	668
125			282, 318	642

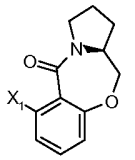
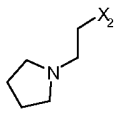
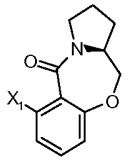
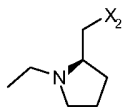
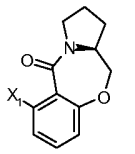
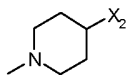
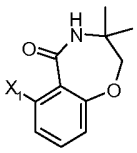
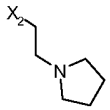
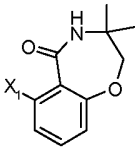
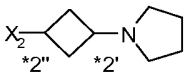
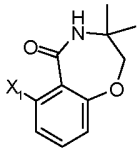
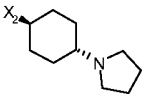
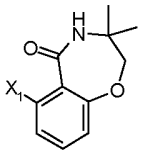
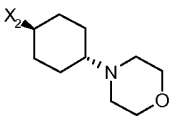
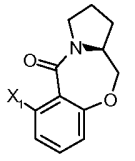
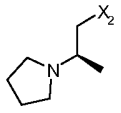
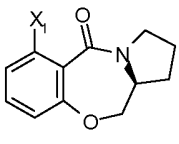
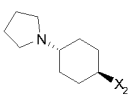
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
126			282, 318	693
127			318	680
128			318	654
129			318	705
130			226, 282, 318	628
131			318	668
132			318-322	642
133			318	693
134			318-322	642

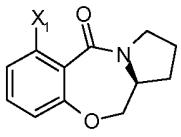
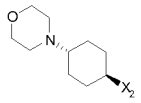
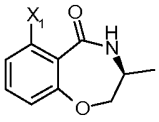
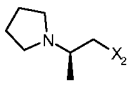
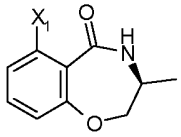
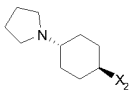
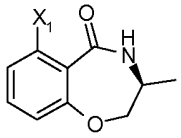
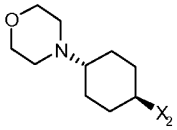
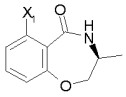
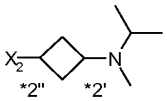
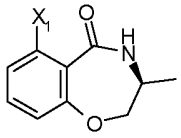
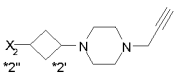
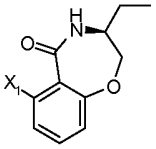
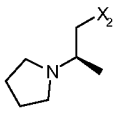
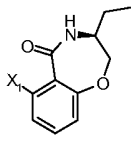
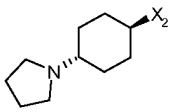
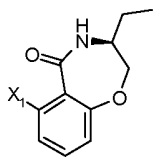
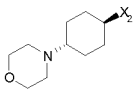
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
135			318	682
136			318	698
137			318-322	656
138			318-322	707
139			318-322	640
140			318-322	628

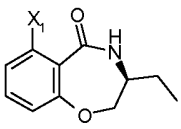
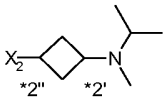
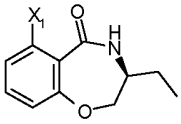
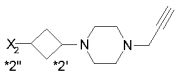
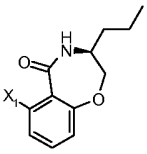
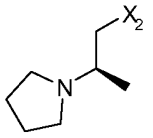
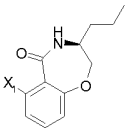
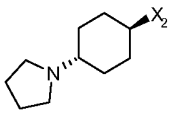
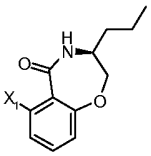
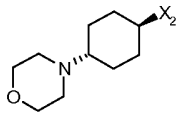
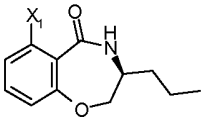
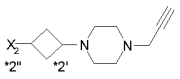
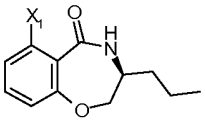
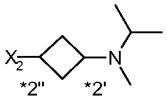
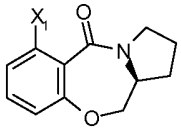
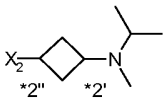
Examples 141-166

The following compounds are prepared by an analogous method to that described in Example 53. The preparation of 2-(4-carboxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine is described in method 14. The corresponding aniline is described in method 10. The amine used to prepare the amide is commercially obtainable or is described in method 13, 15 or 25.



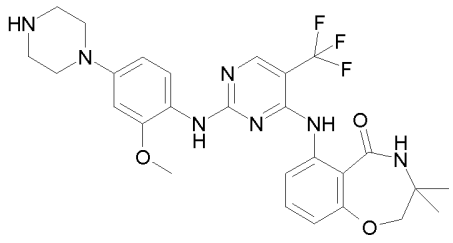
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
141			302	596
142			302	610
143			302	596
144			302	584
145			302	610
146			302	638
147			298	654
148			302	610
149			302	650

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
150			298-302	666
151			302	584
152			302	624
153			298-302	640
154			302	598
155			298-302	649
156			302	598
157			302	638
158			298-302	654

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
159			302	612
160			302	663
161			302	612
162			302	652
163			298-302	668
164			302	677
165			302	626
166			302	624

Example 167

2-(2-methoxy-4-piperazin-1-yl-phenylamino)-4-(3,3-dimethyl-5-oxo-2,3,4,5-tetrahydro-benzo[*f*][1,4]oxazepin-6-ylamino)-5-trifluoromethyl-pyrimidine



500 mg (0.958 mmol) 2-[4-(4-benzyloxycarbonyl-piperazin-1-yl)-phenylamino]-4-chloro-5-trifluoromethyl-pyrimidine (method 14) are dissolved in 0.5 ml NMP, combined with 198 mg (0.960 mmol) 6-amino-3,3-dimethyl-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one (method 10) and with 25 µl (0.1 mmol) dioxanic hydrochloric acid. This reaction mixture is stirred for 1.5 h at 100 °C. The solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile.

Yield: 0.59 g (0.86 mmol; 90 %)

0.59 g (0.86 mmol) of the above-mentioned intermediate products are dissolved in 50 ml of dimethylformamide and combined with a quantity of distilled water such that there is no precipitation. To this solution are added 60 mg palladium on charcoal and the mixture is hydrogenated at 7 bar H_2 pressure and 20 °C for 6 h. The catalyst is filtered off and the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists at the starting point of 60% water and 40% acetonitrile and at the finishing point of 15% water and 85% acetonitrile. 10 mmol/l ammonium hydrogen carbonate and 20 mmol/l ammonia are dissolved in the water. The suitable fractions are freeze-dried. The residue is dissolved in acetonitrile and combined with 2 ml of a 1 M hydrochloric acid solution. Then the solvent is eliminated *in vacuo*. The substance is obtained as the dihydrochloride.

Yield: 0.46 g (0.73 mmol; 85 %)

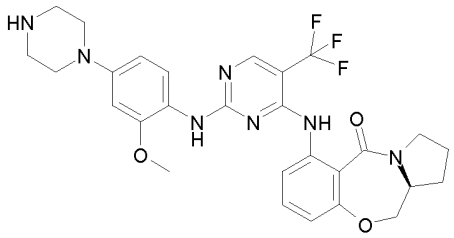
UV max: 284 nm

MS (ESI): 558 $(M+H)^+$

^{1}H-NMR: 1.19 (s, 6H), 3.19 - 3.28 (m, 4H), 3.41 - 3.49 (m, 4H), 3.80 (s, 3H), 4.07 (s, 1H), 6.54 - 6.60 (m, 1H), 6.72 - 6.76 (m, 1H), 6.83 - 6.89 (m, 1H), 7.21 - 7.42 (m, 2H), 7.85 - 8.20 (m, 1H), 8.33 - 8.60 (m, 1H), 8.74 (s, 1H), 9.30 - 9.71 (m, 3H), 12.84 (s, 1H)

Example 168

2-(2-methoxy-4-piperazin-1-yl-phenylamino)-4-((S)-4-oxo-2,3,10,10a-tetrahydro-1*H*.4*H*-9-oxa-3a-aza-benzo[*f*]azulen-5-ylamino-5-trifluoromethyl-pyrimidine



This compound is prepared analogously to Example 167. The aniline used is described in method 10.

Yield: 0.23 g (0.41 mmol; 91 %)

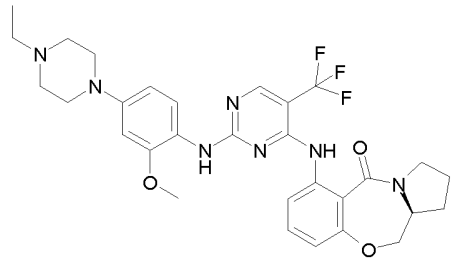
UV max: 282 nm

MS (ESI): 570 $(M+H)^+$

^{1}H-NMR: 1.53-1.71 (m, 1H), 1.79-2.06 (m, 3H), 3.15-3.32 (m, 4H), 3.32-3.55 (m, 5H), 3.58-3.72 (m, 1H), 3.72-3.94 (m, 4H), 4.00-4.23 (m, 2H), 6.48-6.61 (m, 1H), 6.68-6.77 (m, 1H), 6.83-7.00 (m, 1H), 7.19-7.50 (m, 2H), 7.78-8.10 (m, 1H), 8.23-8.60 (m, 1H), 9.18-9.64 (m, 3H), 10.54-10.86 (m, 1H)

Example 169

2-[4-(4-ethyl-piperazin-1-yl)-2-methoxy-phenylamino]-4-((S)-4-oxo-2,3,10,10a-tetrahydro-1*H*.4*H*-9-oxa-3a-aza-benzo[*f*]azulen-5-ylamino-5-trifluoromethyl-pyrimidine



60 mg (0.11 mmol) 2-(2-methoxy-4-piperazin-1-yl-phenylamino)-4-((S)-4-oxo-2,3,10,10a-tetrahydro-1*H*.4*H*-9-oxa-3a-aza-benzo[*f*]azulen-5-ylamino-5-

trifluoromethyl-pyrimidine (Example 168) are dissolved in 300 µl dimethylformamide and combined with 12 µl (0.21 mmol) acetaldehyde and 47 mg (0.21 mmol) sodium triacetoxyborohydride. This reaction mixture is stirred at 20°C for 20 h. The solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and 50% water and 50% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are combined with 500 µl of a 1 N hydrochloric acid and freeze-dried. The product is obtained as the dihydrochloride.

Yield: 49 mg (0.074 mmol; 71 %)

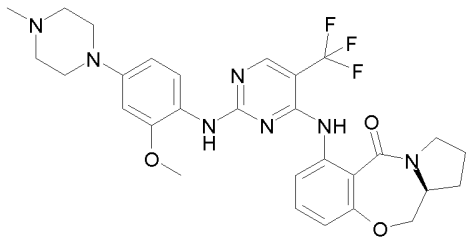
UV max: 282 nm

MS (ESI): 598 $(M+H)^+$

^{1}H-NMR: 1.23-1.37 (m, 3H), 1.57-1.72 (m, 1H), 1.80-2.06 (m, 3H), 3.02-3.27 (m, 6H), 3.34-3.48 (m, 1H), 3.48-3.71 (m, 3H), 3.71-3.94 (m, 7H), 6.48-6.61 (m, 1H), 6.68-6.79 (m, 1H), 6.84-6.97 (m, 1H), 7.18-7.43 (m, 2H), 7.78-8.08 (m, 1H), 8.26-8.53 (m, 1H), 9.14-9.44 (m, 1H), 10.49-10.74 (m, 1H), 10.80-11.08 (m, 1H)

Example 170

2-[4-(4-methyl-piperazin-1-yl)-2-methoxy-phenylamino]-4-((S)-4-oxo-2,3,10,10a-tetrahydro-1*H*.4*H*-9-oxa-3a-aza-benzo[*f*]azulen-5-ylamino-5-trifluoromethyl-pyrimidine



To prepare this compound formaldehyde is used instead of acetaldehyde. Otherwise the method is as in Example 169.

Yield: 16 mg (0.024 mmol; 28 %)

UV max: 278 nm

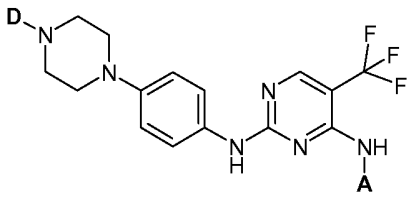
MS (ESI): 584 $(M+H)^+$

^{1}H-NMR: 1.58-1.71 (m, 1H), 1.81-2.06 (m, 3H), 2.78-2.88 (m, 3H), 3.00-3.23 (m, 4H), 4.03-4.21 (m, 2H), 6.48-6.59 (m, 1H), 6.69-6.78 (m, 1H), 6.80-6.91 (m, 1H), 7.17-7.44 (m, 2H), 7.92-8.15 (m, 1H), 8.34 (s, 1H), 8.86-9.04 (m, 1H), 10.38-10.64 (m, 2H)

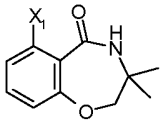
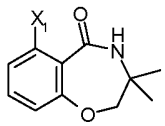
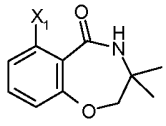
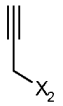
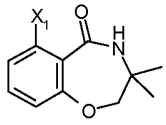
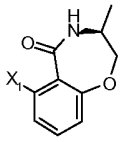
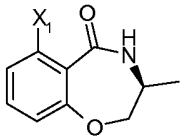
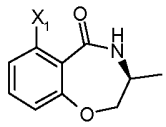
Examples 171-180

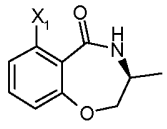
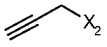
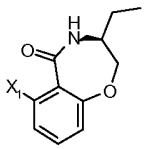
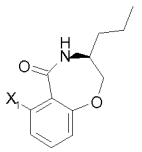
The following Examples are prepared analogously to Example 169 and 170.

The corresponding aniline is described in the supplements to method 10.



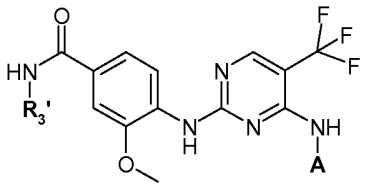
5

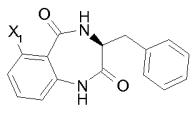
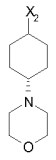
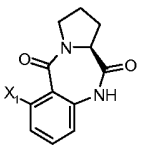
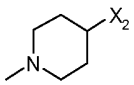
#	A	D	UV max [nm]	MS (ESI) $(M+H)^+$
171			226, 282	572
172			250, 282	586
173			250, 282	596
174			250, 282	600
175			282	544
176			282	558
177			218; 282	586

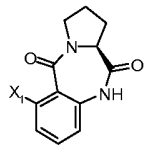
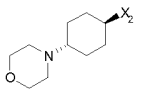
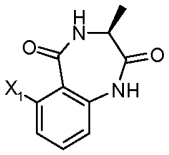
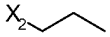
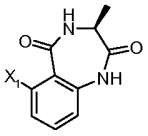
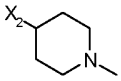
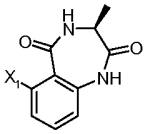
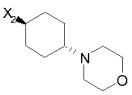
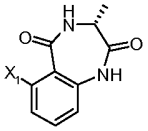
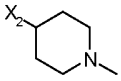
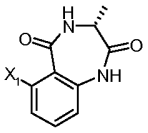
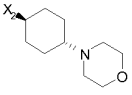
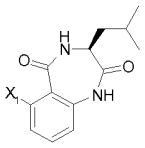
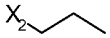
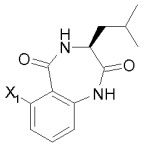
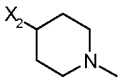
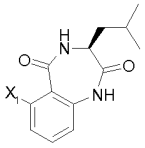
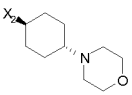
#	A	D	UV max [nm]	MS (ESI) $(M+H)^+$
178			282	582
179			226	558
180			226	572

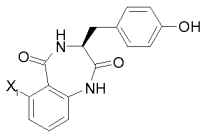
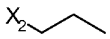
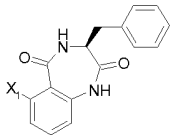
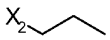
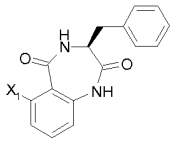
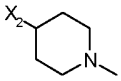
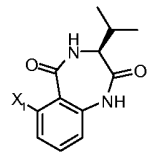
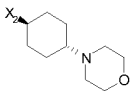
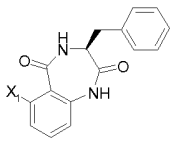
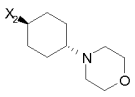
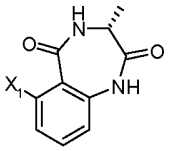
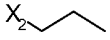
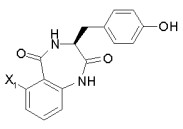
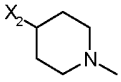
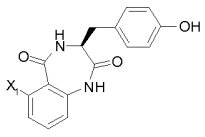
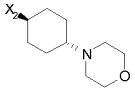
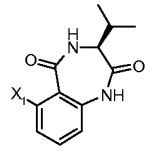
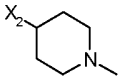
Examples 181-332

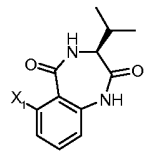
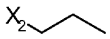
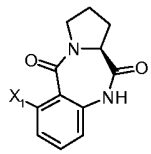
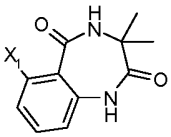
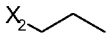
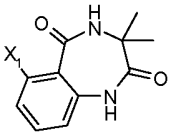
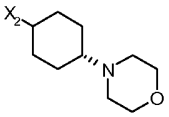
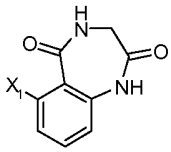
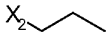
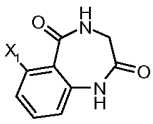
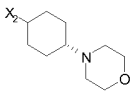
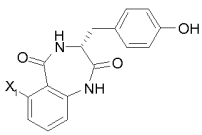
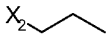
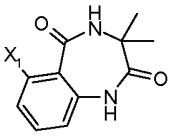
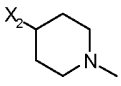
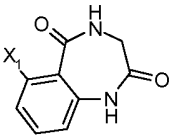
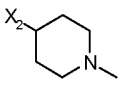
The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-Carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be obtained according to method 12 or 14. The corresponding aniline is described in method 11. The amine used to prepare the amide is commercially obtainable or described in method 13, 15 and 25.

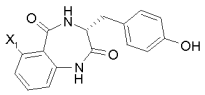
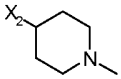
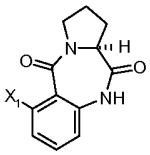
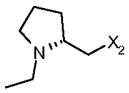
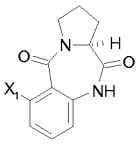
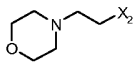
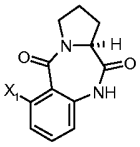
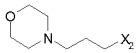
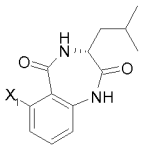
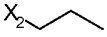
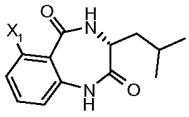
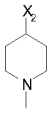
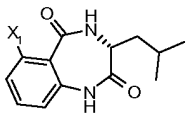
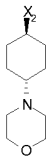
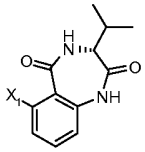
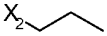
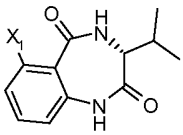
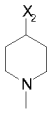


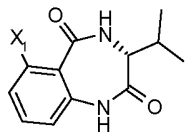
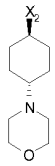
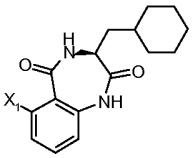
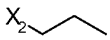
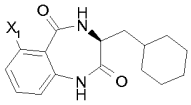
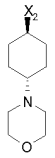
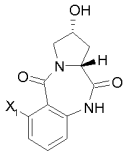
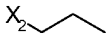
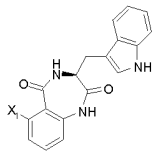
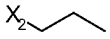
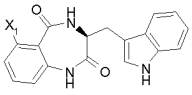
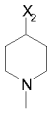
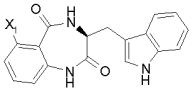
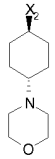
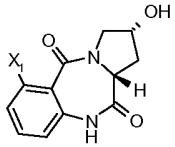
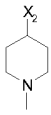
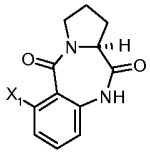
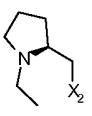
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
181			318, 282, 234	380
182			238	639

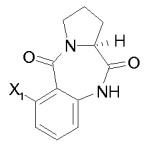
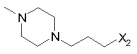
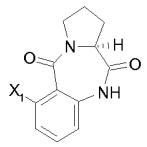
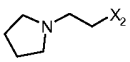
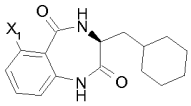
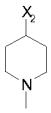
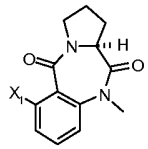
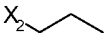
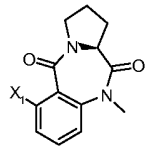
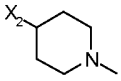
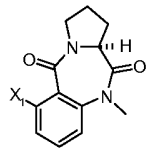
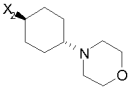
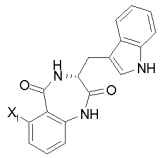
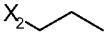
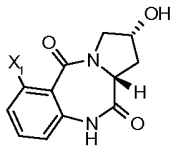
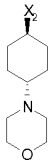
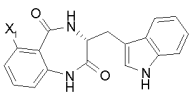
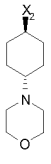
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
183			234; 318	709
184			318, 282, 248	558
185			318, 280	613
186			316, 282, 234	342
187			318, 284, 238	307
188			318, 282, 242	342
189			314, 282, 242	600
190			318, 282, 234	328
191			318	363

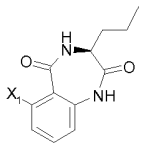
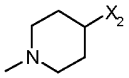
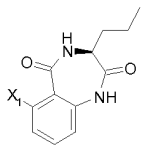
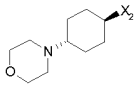
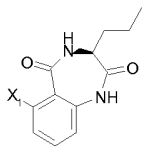
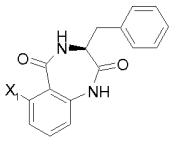
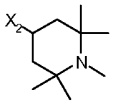
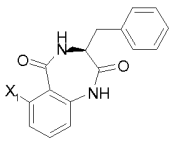
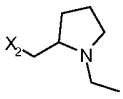
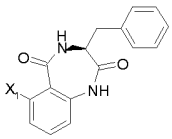
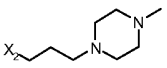
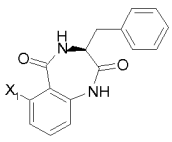
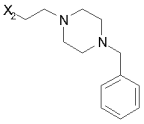
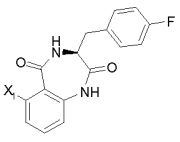
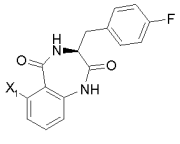
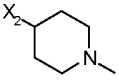
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
192			318, 230	650
193			314	634
194			318	634
195			318	671
196			318, 230	380
197			314, 282, 250	558
198			319	705
199			318, 226	775
200			318	634

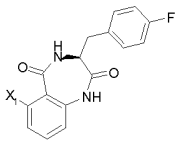
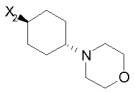
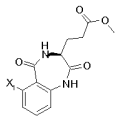
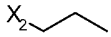
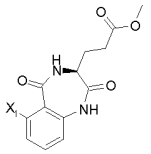
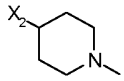
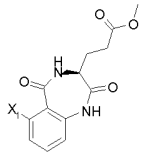
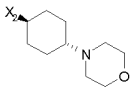
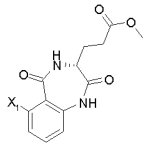
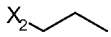
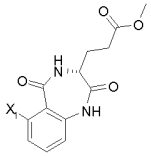
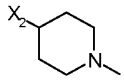
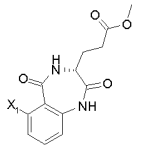
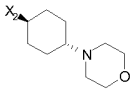
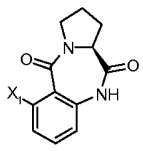
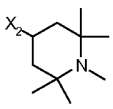
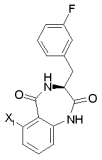
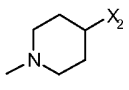
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
201			314	634
202			230; 318	584
203			317	572
204			318, 230	697
205			318, 234	544
206			318	669
207			318, 230	650
208			317	627
209			318, 230	599

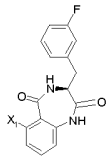
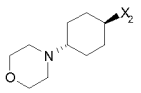
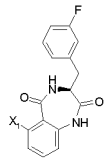
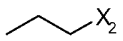
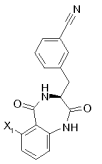
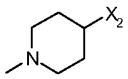
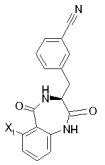
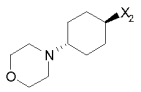
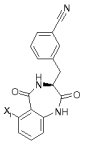
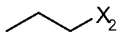
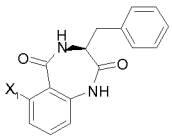
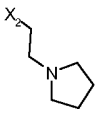
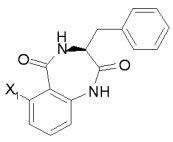
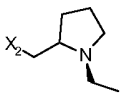
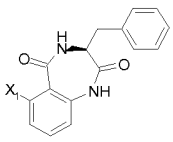
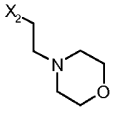
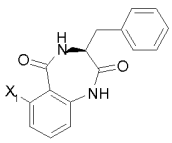
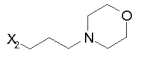
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
210			318, 230	705
211			230; 322	653
212			230; 322	655
213			230; 318	669
214			230, 282, 314	634
215			318	655
216			318, 234	725
217			314, 235	586
218			318, 230	641

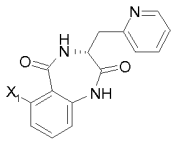
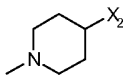
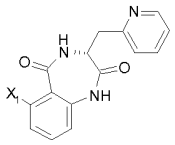
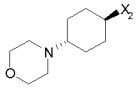
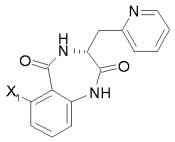
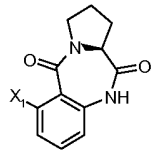
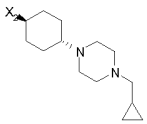
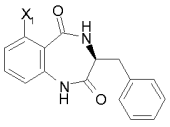
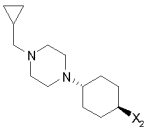
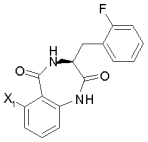
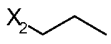
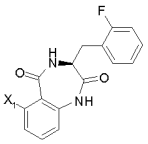
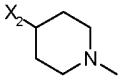
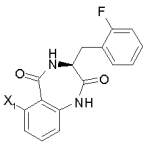
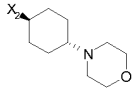
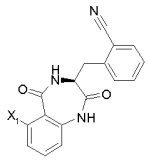
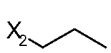
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
219			318, 226	711
220			318, 230	640
221			318	765
222			318	600
223			315	673
224			319, 226	728
225			318, 226	798
226			318, 234	655
227			230; 322	653

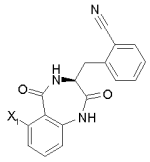
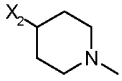
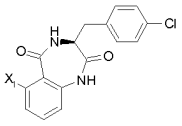
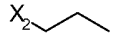
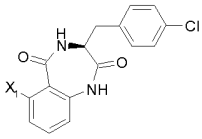
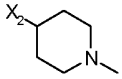
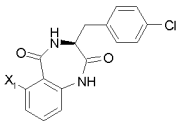
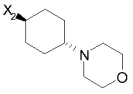
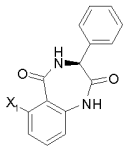
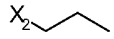
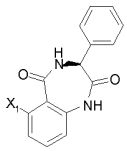
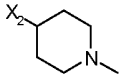
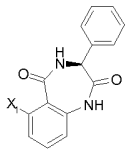
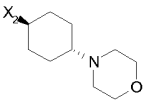
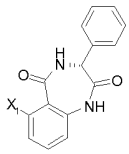
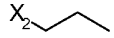
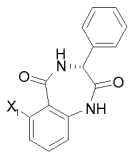
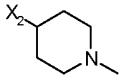
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
228			230; 318	682
229			234; 318	639
230			318, 226	695
231			234, 282, 318	598
232			230, 282, 318	653
233			234, 282, 318	723
234			318, 222	673
235			318	725
236			318, 282, 226	798

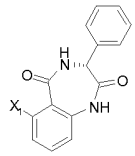
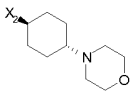
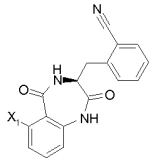
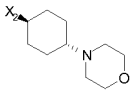
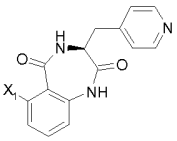
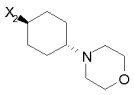
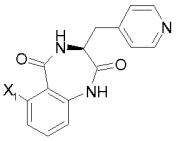
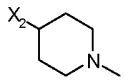
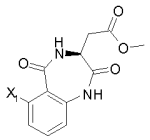
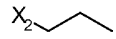
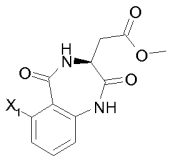
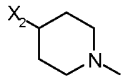
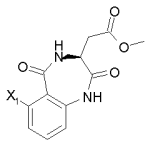
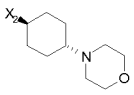
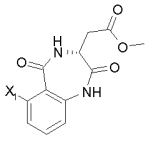
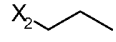
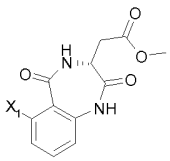
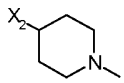
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
237			230; 318	641
238			230; 318	711
239			234; 318	586
240			318, 226	745
241			322	703
242			320, 226	732
243			321, 221	694
244			230, 282, 318	652
245			234, 282, 318	707

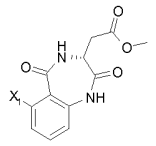
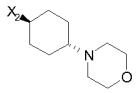
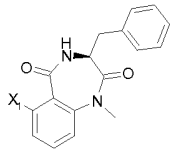
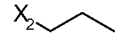
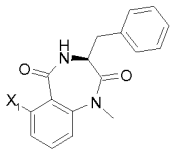
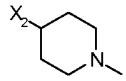
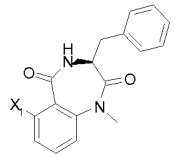
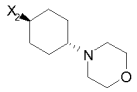
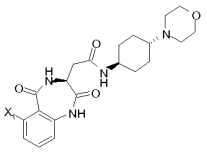
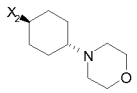
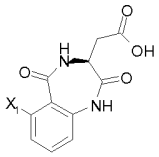
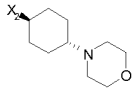
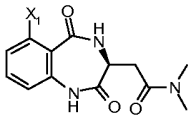
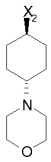
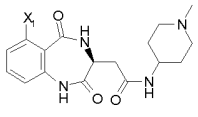
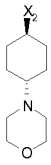
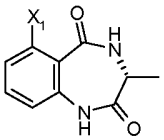
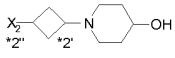
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
246			230, 282, 318	777
247			230, 282, 318	630
248			234, 282, 318	685
249			234, 282, 318	755
250			230, 282, 318	630
251			230, 282, 318	685
252			230, 282, 318	755
253			230; 318	695
254			230; 318	70

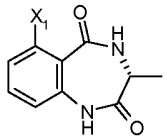
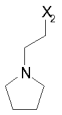
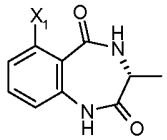
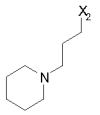
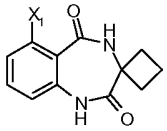
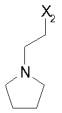
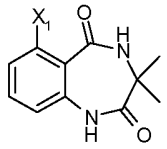
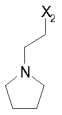
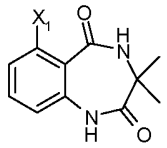
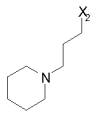
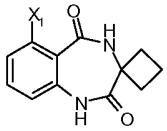
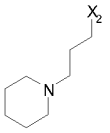
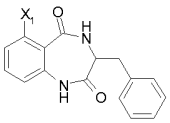
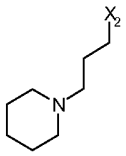
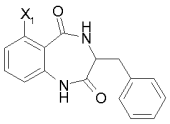
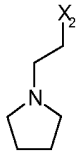
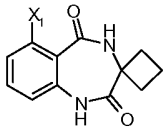
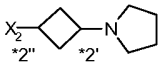
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
255			230; 318	389
256			230; 318	652
257			230	357
258			230	784
259			230	659
260			319, 230	689
261			322	703
262			322	705
263			320	719

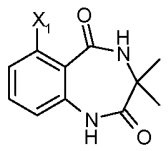
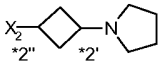
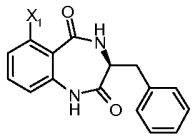
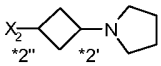
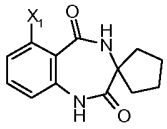
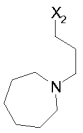
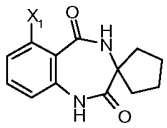
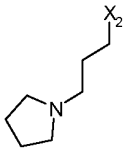
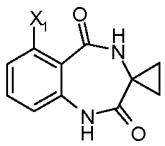
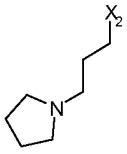
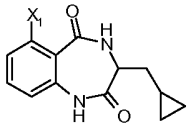
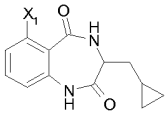
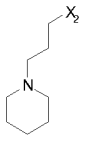
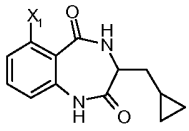
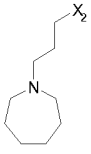
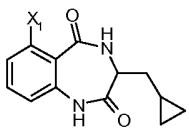
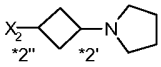
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
264			226	690
265			226; 318	760
266			230	635
267			230; 318	381
268			318	812
269			318	652
270			318	707
271			318, 226	777
272			318	659

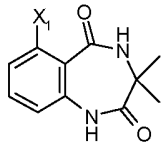
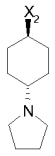
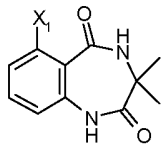
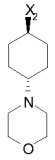
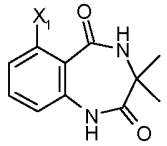
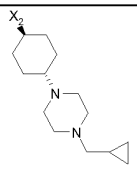
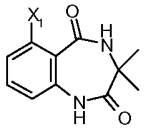
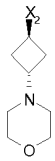
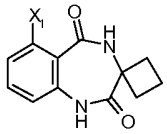
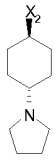
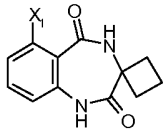
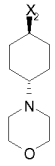
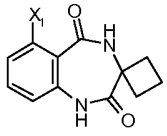
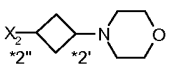
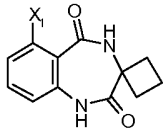
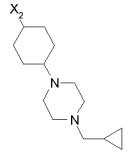
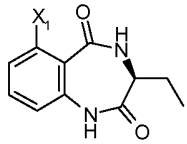
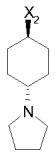
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
273			318	714
274			315, 239	669
275			319, 222	723
276			318, 226	793
277			316	620
278			318	675
279			318, 226	745
280			317, 226	620
281			318	675

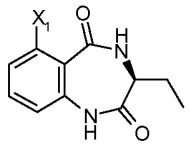
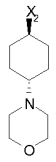
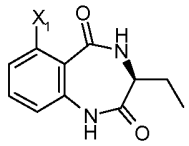
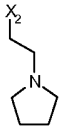
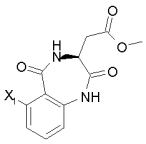
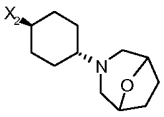
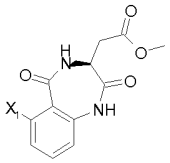
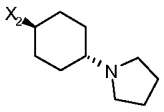
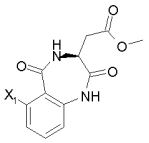
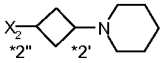
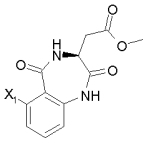
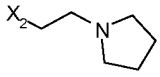
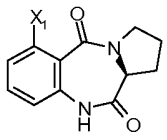
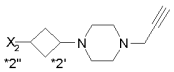
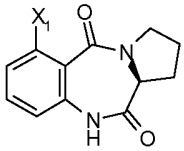
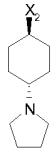
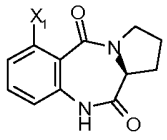
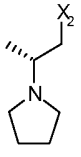
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
282			318, 230	745
283			318	784
284			318	758
285			318	688
286			238, 282, 314	616
287			230, 282, 318	671
288			230, 282, 318	741
289			234, 282, 318	616
290			226, 282, 318	671

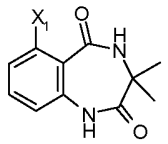
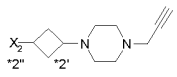
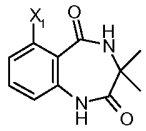
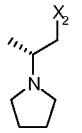
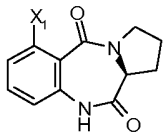
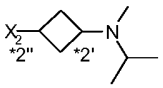
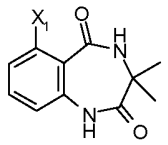
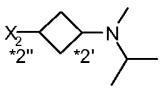
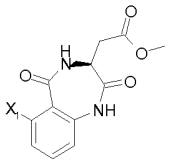
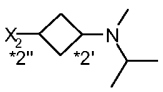
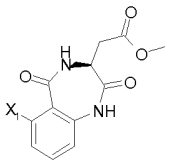
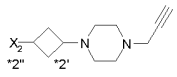
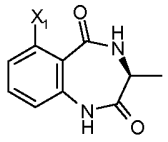
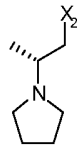
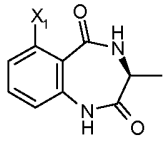
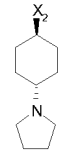
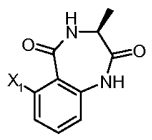
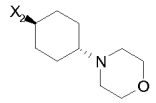
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
291			234, 282, 318	741
292			234, 282, 318	648
293			230, 282, 318	703
294			226, 282, 318	773
295			226, 282, 318	893
296			226, 282, 318	727
297			226, 282, 318	754
298			230, 282, 318	823
299			282, 318	669

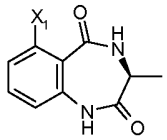
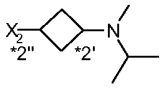
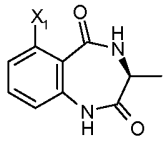
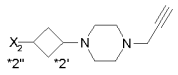
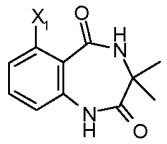
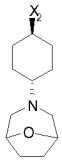
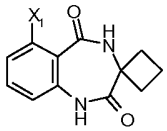
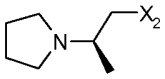
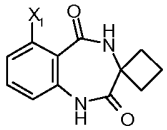
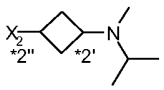
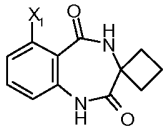
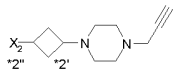
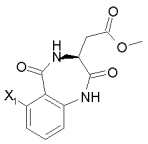
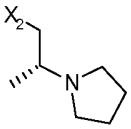
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
300			282, 318	613
301			282, 318	641
302			286, 318	639
303			286, 318	627
304			286, 318	655
305			286, 318	667
306			286, 318	717
307			286, 318	689
308			286, 318	665

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
309			230, 286, 318	653
310			230, 282, 318	715
311			286, 322	695
312			234, 286, 318	667
313			230, 282, 318	639
314			230, 282, 318	667
315			230, 282, 318	681
316			230, 282, 318	695
317				679

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
318			226, 284, 318	681
319			230, 284, 318	697
320			226, 284, 314	750
321			230, 286, 318	669
322			230, 282, 318	693
323			230, 282, 314	709
324			230, 286, 314	681
325			226, 286, 314	762
326			230, 282, 318	681

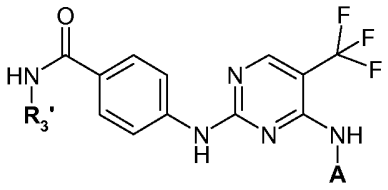
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
327			230, 282, 314	697
328			234, 282, 318	627
329			226, 282, 318	767
330			226, 282, 318	725
331			230, 286, 318	711
332			226, 282, 318	671
333			234, 282, 314	718
334			234, 282, 318	693
335			234, 286, 318	653

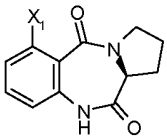
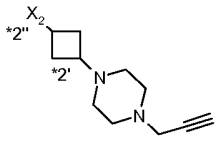
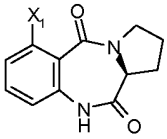
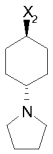
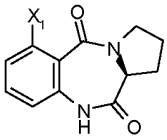
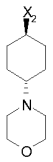
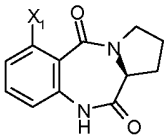
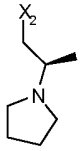
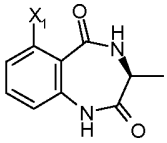
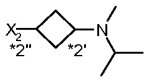
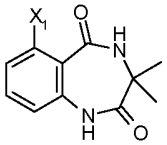
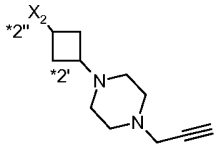
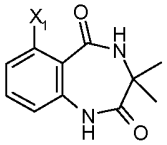
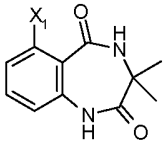
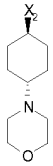
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
336			284, 318	706
337			230, 282, 318	641
338			230, 282, 314	667
339			283, 318	655
340			230, 286, 318	699
341			230, 282, 318	750
342			230, 282, 318	627
343			250, 282, 318	667
344			230, 282, 318	683

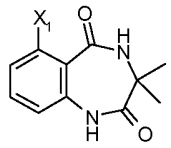
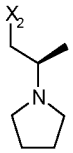
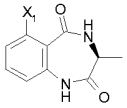
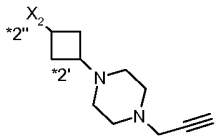
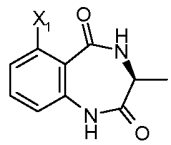
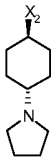
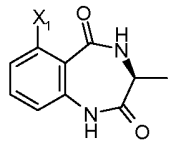
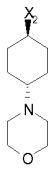
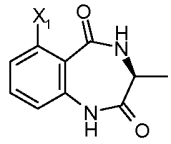
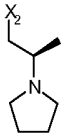
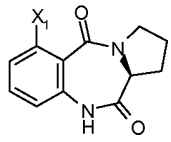
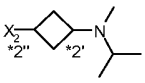
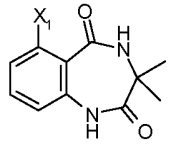
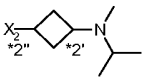
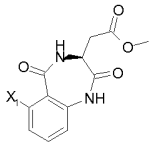
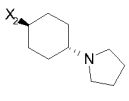
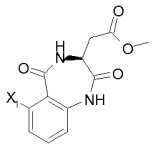
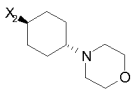
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
345			238, 282, 314	641
346			230, 314	692
347			282, 318	723
348			234, 286, 314	653
349			286, 318	667
350			234, 286, 314	718
351			230, 286, 318	685

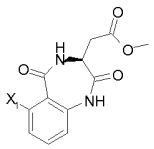
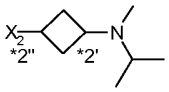
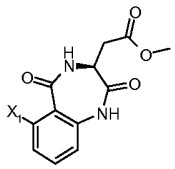
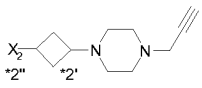
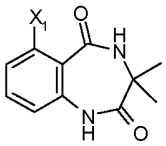
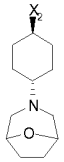
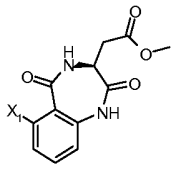
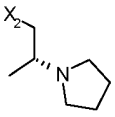
Examples 352-372

The following compounds are prepared by an analogous process to that described in Example 53 described, prepared. 2-(4-carboxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may after method 14 prepared are. The corresponding aniline is in method 11 described. The amine used to prepare the amide is commercially obtainable or is described in method 13, 15 or 25.



#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
352			222, 302	688
353			246, 298	663
354			234, 298	679
355			234, 302	623
356			298	611
357			246, 302	676
358				651
359				667

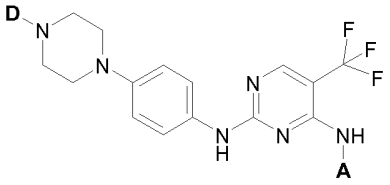
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
360			246, 302	611
361			298	662
362				637
363			234, 298	653
364			226, 302	597
365			302	637
366			246, 302	625
367			302	695
368			302	711

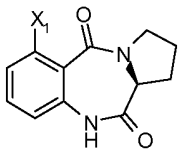
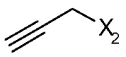
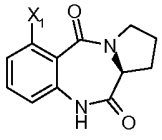
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
369			302	669
370			302	720
371			300	693
372			242, 302	655

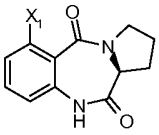
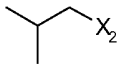
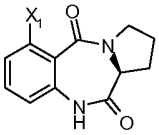
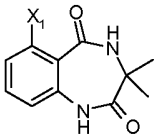
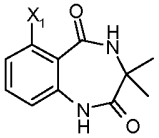
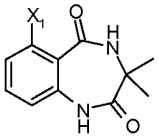
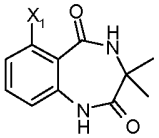
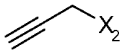
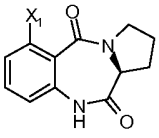
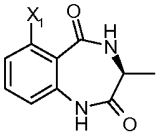
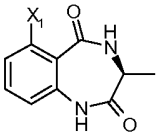
Examples 373-386

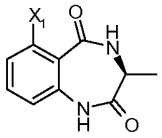
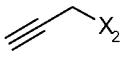
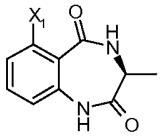
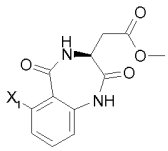
The following Examples are prepared analogously to Example 169 and 170.

The corresponding aniline is described in method 11.



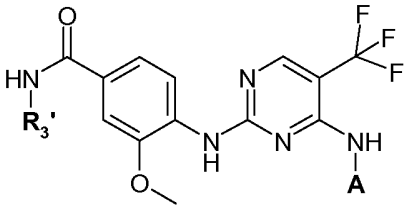
#	A	D	UV max [nm]	MS (ESI) $(M+H)^+$
373			246	621
374			246	611

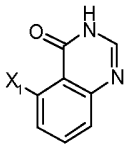
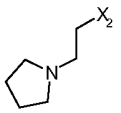
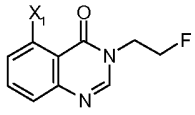
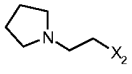
#	A	D	UV max [nm]	MS (ESI) $(M+H)^+$
375			234	639
376			238	597
377			250	599
378			250	585
379			250	613
380			250	609
381			246	625
382			250	599
383			230	571

#	A	D	UV max [nm]	MS (ESI) $(M+H)^+$
384			246	595
385			250	585
386			246, 286	615

Examples 387-388

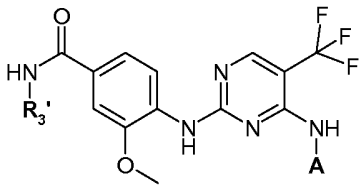
The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-Carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be prepared according to method 12 or 14. The corresponding aniline is described in method 4 or method 17. The amine used to prepare the amide is commercially obtainable.

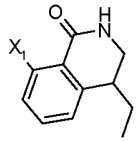
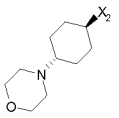
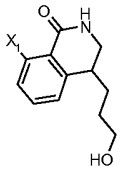
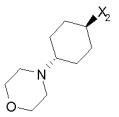
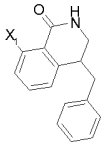
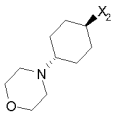
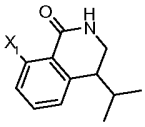
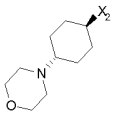
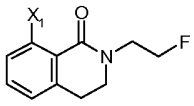
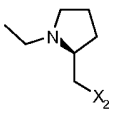
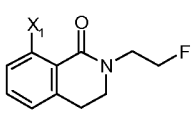
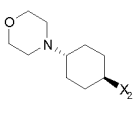


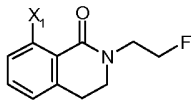
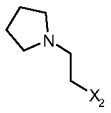
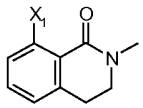
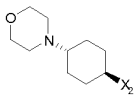
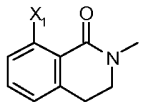
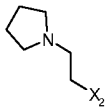
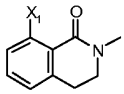
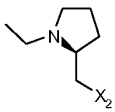
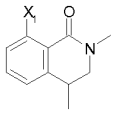
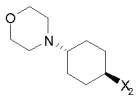
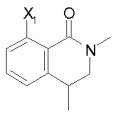
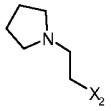
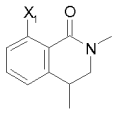
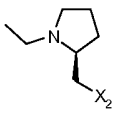
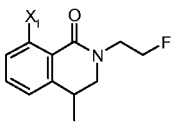
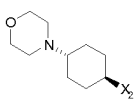
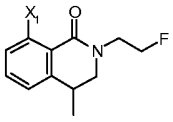
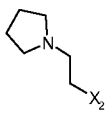
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
387			262, 318	569
388			278, 318	615

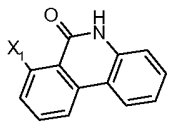
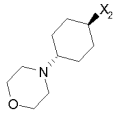
Examples 389-404

The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-Carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be prepared according to method 12 or 14. The corresponding aniline is described in method 7, in method 18 or 19. The amine used to prepare the amide is commercially obtainable or is described in method 13.



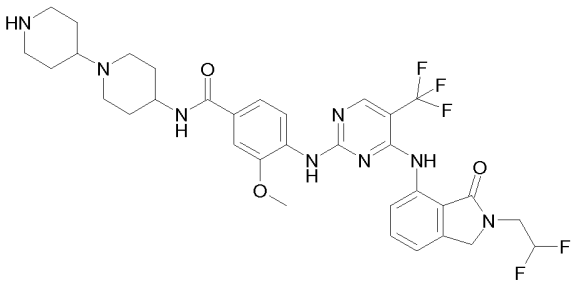
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
389			284, 322	668
390			230, 285, 325	698
391			280, 325	730
392			230, 285, 325	682
393			285, 325	630
394			284, 322	686

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
395			285, 325	616
396			285, 322	654
397			285, 325	584
398			285, 325	598
399			285, 325	668
400			285, 325	598
401			285, 325	612
402			285, 322	700
403			285, 322	630

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
404			262	688

Example 405

2-[4-([1,4']bipiperidinyl-4-ylcarbamoyl)-2-methoxy-phenylamino]-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



1150 mg (3.308 mmol) 2-(4-carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine (method 12 or 14) are dissolved in 2,5 ml *N*-methyl-2-pyrrolidinone and combined with 883 mg (4.161 mmol) 7-amino-2-(2,2-difluoro-ethyl)-2,3-dihydro-isoindol-1-one (method 2). 115 µl of a 4 M solution of HCl (0.460 mmol) in 1,4-dioxane are metered into this reaction mixture. After 16 h at 90 °C the reaction mixture is stirred into 150 ml of an aqueous 1 N hydrochloric acid. The precipitate is filtered off and dried *in vacuo*.

Yield: 1626 mg (3.110 mmol; 94 %)

MS (ESI): 524 $(M+H)^+$

100 mg (0.191 mmol) of this precipitate, 240 µl (1.402 mmol) *N*-ethyldiisopropyl-amine, 89 mg (0.279 mmol) O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate and 76 mg (0.267 mmol) *tert*-butyl 4-amino-[1,4']bipiperidinyl-1'-carboxylate are dissolved in 3 ml *N,N*-dimethylformamide. After 15 h at 20 °C the solvent is eliminated *in vacuo*. The residue is taken up in 20 ml dichloromethane and 5 ml of methanol and filtered through aluminium oxide. The aluminium oxide is washed several times with a mixture of dichloromethane and methanol (4:1). The solvent of the combined fractions is eliminated *in vacuo*. The residue is dissolved in 5 ml dichloromethane and combined with 5 ml trifluoroacetic acid. This mixture is stirred for 3 h at 20 °C and then the solvent is eliminated *in vacuo*. The crude product is purified by column chromatography. The carrier material used is C18-RP-silica gel and a gradient is run through which consists of 90% water and 10% acetonitrile at the

starting point and 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid are added both to the water and to the acetonitrile. The suitable fractions are combined with 500 µl of a 1 N hydrochloric acid and freeze-dried. The product is obtained as the trihydrochloride.

Yield: 42 mg (0.053 mmol; 28 %)

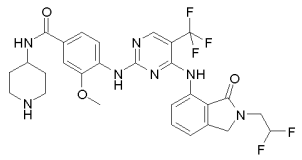
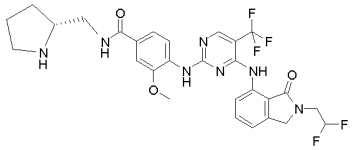
UV max: 322 nm

MS (ESI): 689 $(M+H)^+$

^{1}H-NMR: 1.92 - 2.19 (m, 6H), 2.28 - 2.37 (m, 2H), 2.86 - 3.00 (m, 2H), 3.07 - 3.19 (m, 3H), 3.84 - 4.18 (m, 7H), 4.59 (s, 2H), 6.15 - 6.47 (m, 1H), 7.23 - 7.28 (m, 1H), 7.35 - 7.43 (m, 1H), 7.54 - 7.64 (m, 2H), 7.75 - 7.82 (m, 1H), 8.40 - 8.64 (m, 3H), 8.90 - 9.01 (m, 1H), 9.10 - 9.25 (m, 2H), 10.40 - 10.47 (m, 1H), 10.91 - 11.27 (m, 1H)

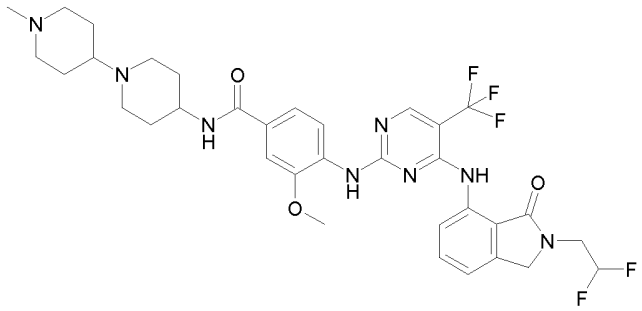
Examples 406-407

The following compounds are prepared by an analogous process to that described in Example 405.

#		UV max [nm]	MS (ESI) $(M+H)^+$
406		318	606
407		322, 286	606

Example 408

2-[2-methoxy-4-(1'-methyl-[1,4']bipiperidinyl-4-ylcarbamoyl)-phenylamino]-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



70 mg (0.087 mmol) 2-[4-([1,4']bipiperidinyl-4-ylcarbamoyl)-2-methoxy-phenylamino]-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine (Example 405) are dissolved in 3 ml of methanol, and combined with 8.5 µl (0.508 mmol) acetic acid and with 8 µl (0.107 mmol) of a 37% aqueous formaldehyde solution. Then at 20 °C 7.0 mg (0.112 mmol) sodium cyanoborohydride are added. This mixture is stirred for 16 h at 20 °C. The solvent is eliminated *in vacuo* and the crude product is purified by column chromatography. The carrier material used is C18-RP-silica gel and a gradient is run through which consists at the starting point of 95% water and 5% acetonitrile and at the finishing point of 5% water and 95% acetonitrile. 0.1% formic acid are added both to the water and to the acetonitrile.. The suitable fractions are combined with 500 µl of a 1 N hydrochloric acid and freeze-dried. The product is obtained as the trihydrochloride.

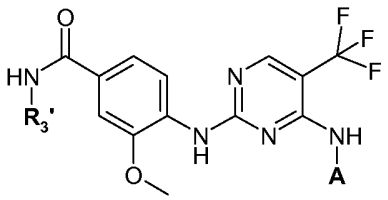
Yield: 18 mg (0.022 mmol; 25 %)

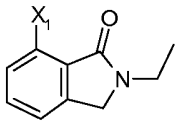
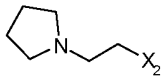
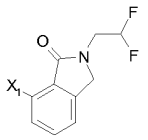
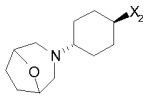
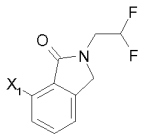
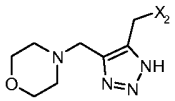
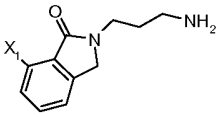
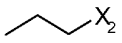
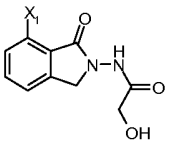
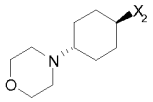
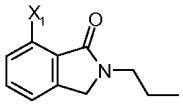
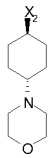
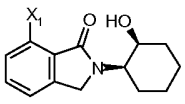
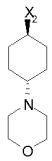
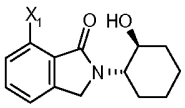
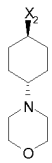
UV max: 322 nm

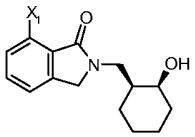
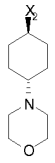
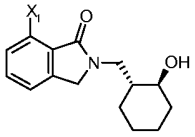
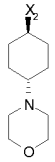
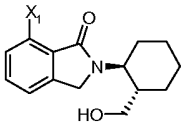
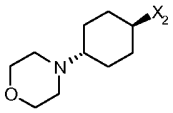
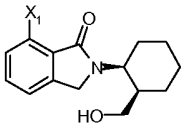
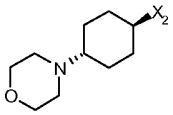
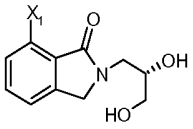
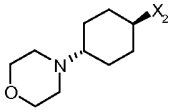
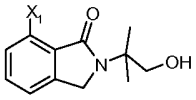
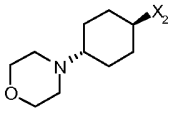
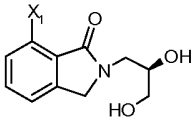
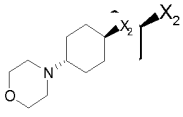
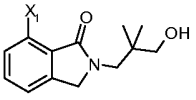
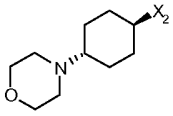
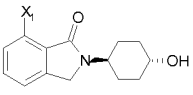
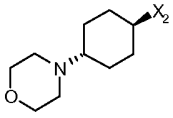
MS (ESI): 703 $(M+H)^+$

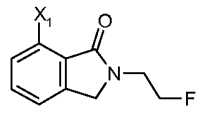
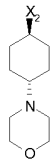
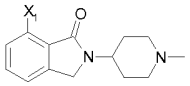
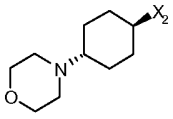
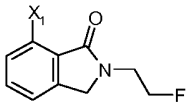
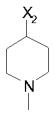
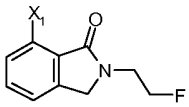
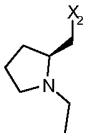
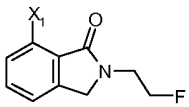
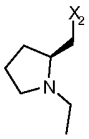
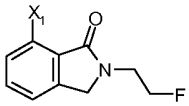
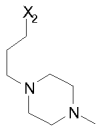
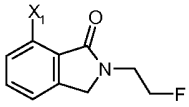
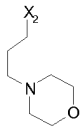
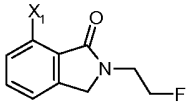
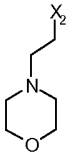
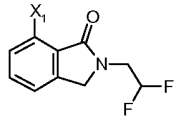
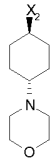
Examples 409-491

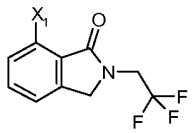
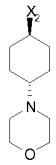
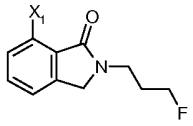
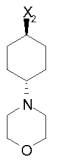
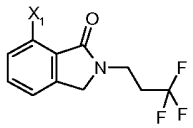
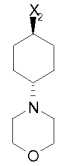
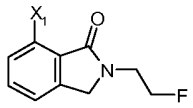
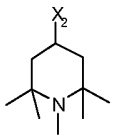
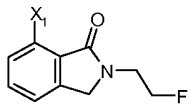
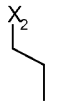
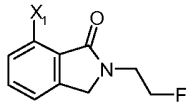
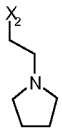
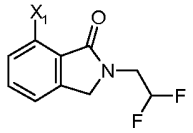
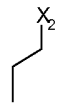
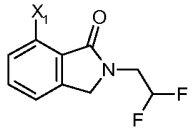
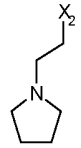
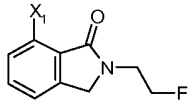
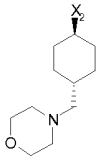
The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-Carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be prepared according to method 12 or 14. The corresponding aniline is described in method 2. The amine used to prepare the amide is commercially obtainable or is described in method 13, 20 or 21.

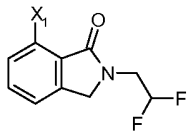
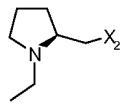
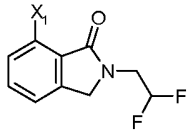
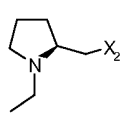
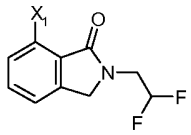
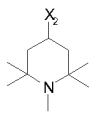
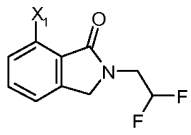
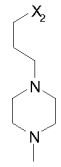
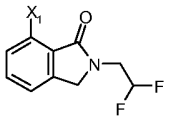
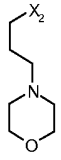
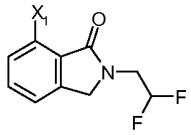
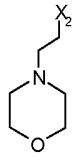
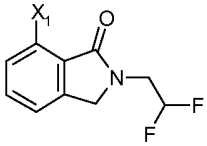
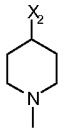
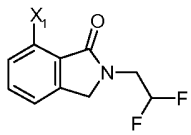
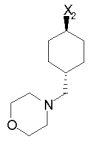
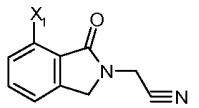
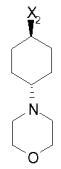


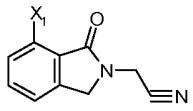
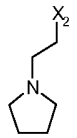
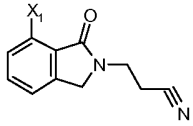
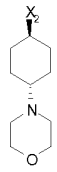
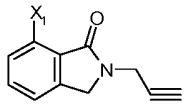
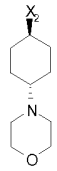
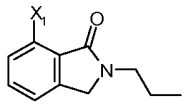
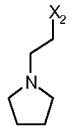
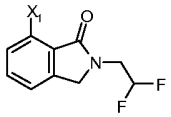
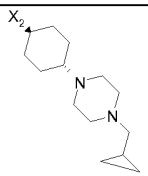
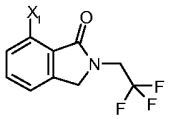
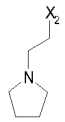
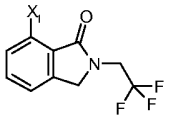
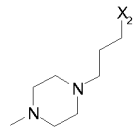
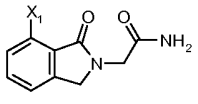
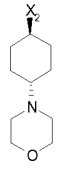
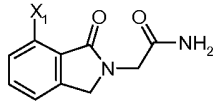
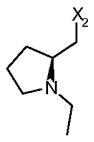
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
409			285, 320	584
410			322	716
411			326	703
412				558
413			282, 318	699
414			322, 286	668
415			322.3	724
416			322.3	362

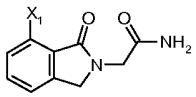
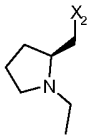
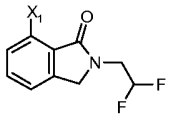
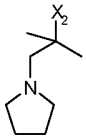
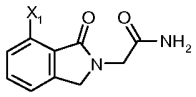
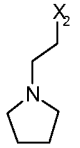
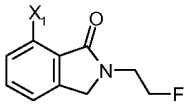
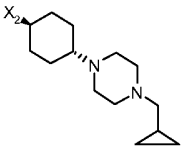
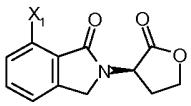
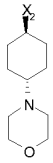
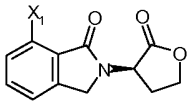
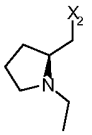
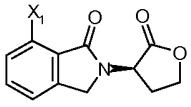
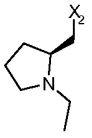
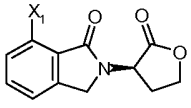
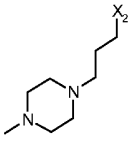
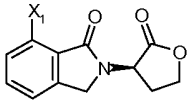
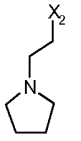
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
417			322, 286	738
418			322, 286	738
419			282, 314	738
420			286, 314	738
421			286, 318	700
422			286, 322	698
423			286, 318	700
424			286, 322	712
425			286, 322	724

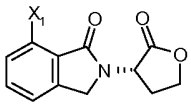
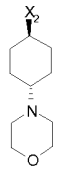
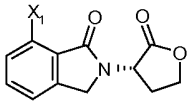
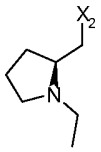
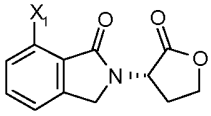
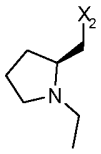
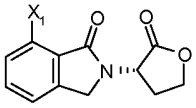
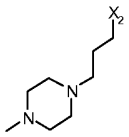
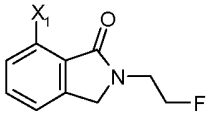
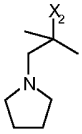
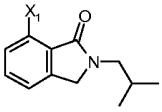
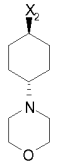
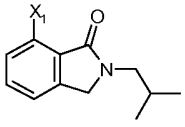
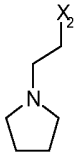
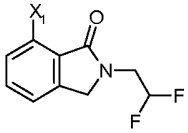
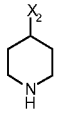
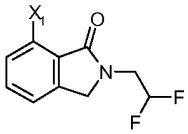
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
426			322, 286	672
427			282, 322	723
428			322, 285	602
429			326.3	616
430			322, 286	616
431			318, 286	645
432			321, 284	632
433			322, 286	618
434			318, 282	690

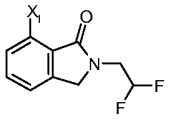
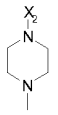
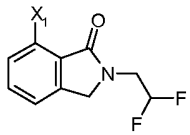
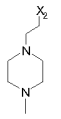
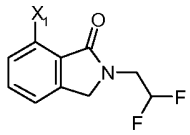
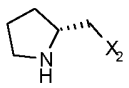
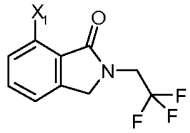
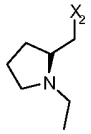
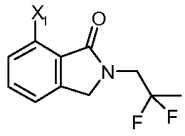
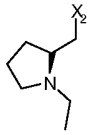
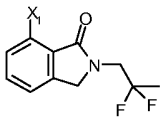
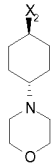
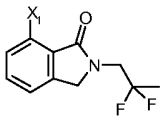
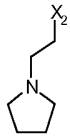
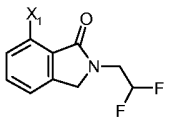
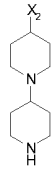
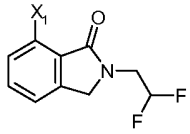
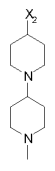
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
435			322, 282	708
436			322, 286	686
437			322, 284	722
438			322, 282	658
439			322, 285	547
440			322, 286	602
441			286.3	565
442			322, 286	620
443			322, 284	686

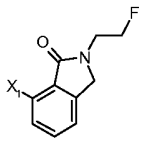
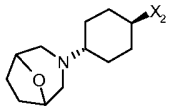
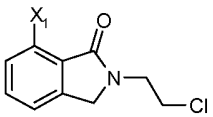
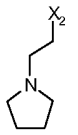
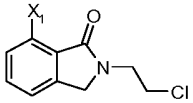
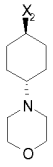
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
444			326.3	634
445			326, 286	634
446			322, 284	676
447			322.3	663
448			325.3	650
449			325.3	635
450			322, 282	620
451			322, 282	704
452			322, 282	665

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
453			326, 282	595
454			322, 284	677
455			322.3	664
456			326, 286	594
457			322, 282	743
458			326, 286	638
459			326, 283	681
460			318, 284	681
461			318, 286	627

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
462			322, 286	627
463			326, 286	648
464			322, 286	611
465			322, 286	723
466			322, 282	710
467			326, 286	654
468			326, 286	654
469			322, 284	683
470			326, 286	640

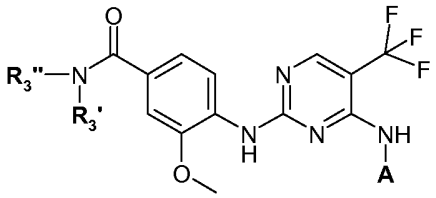
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
471			318, 283	710
472			326, 286	654
473			326, 286	654
474			321, 285	683
475			326, 286	630
476			322, 286	682
477			318, 286	612
478			318.3	606
479			322, 286	566

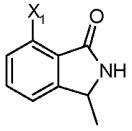
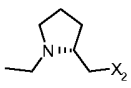
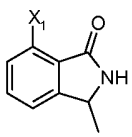
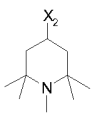
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
480			322, 286	621
481			318, 286	649
482			322, 286	606
483			326, 286	652
484			326, 286	648
485			322, 284	704
486			326, 286	634
487			322, 285	689
488			322, 285	703

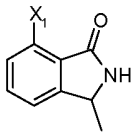
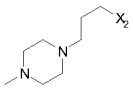
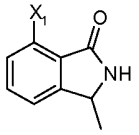
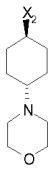
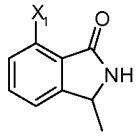
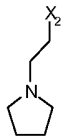
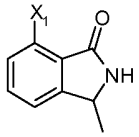
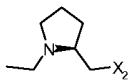
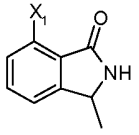
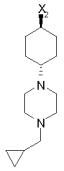
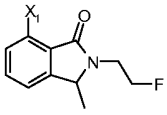
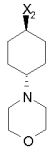
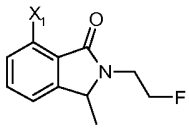
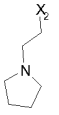
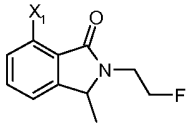
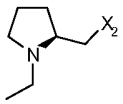
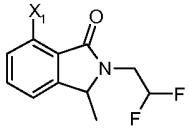
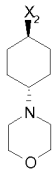
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
489			322	698
490			322, 286	619
491			322, 286	689

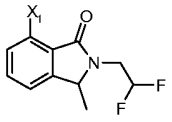
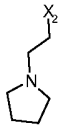
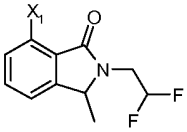
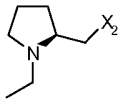
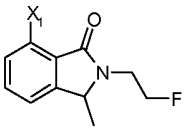
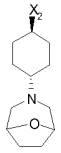
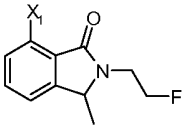
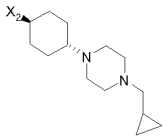
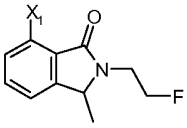
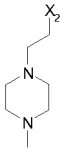
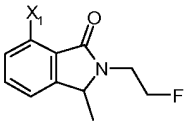
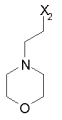
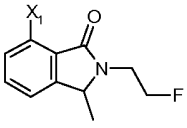
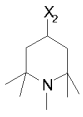
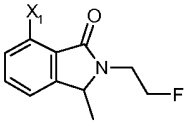
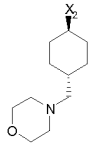
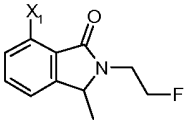
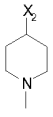
Examples 492-621

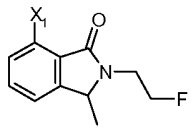
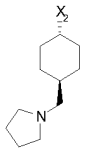
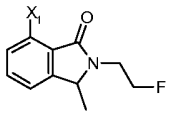
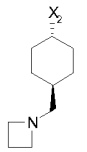
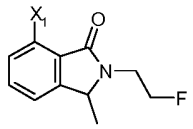
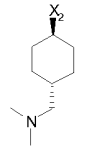
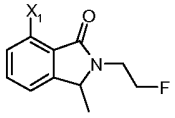
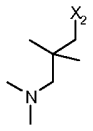
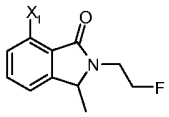
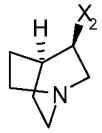
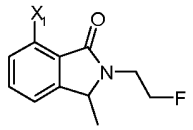
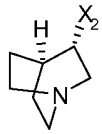
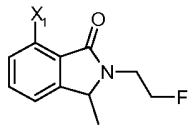
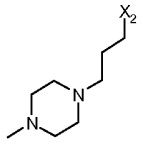
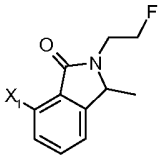
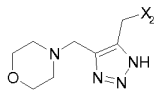
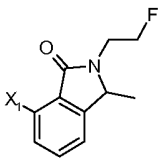
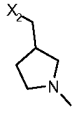
The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-carboxy-2-methoxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be prepared according to method 12 or 14. The corresponding aniline is described in method 22. The amine used to prepare the amide is commercially obtainable, described in method 13, 15, 20, 21, 23, 24 and 25 or in J. Med. Chem. **2003**, 46(5), 702-715.

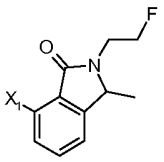
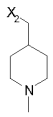
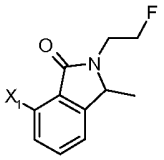
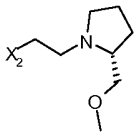
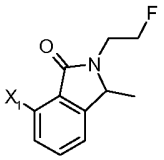
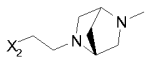
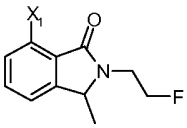
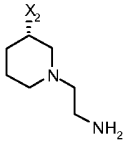
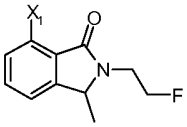
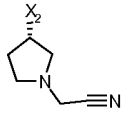
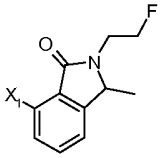
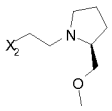
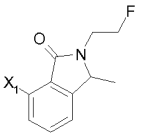
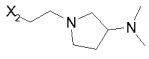
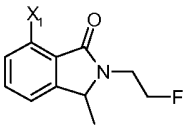
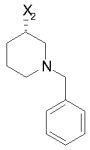
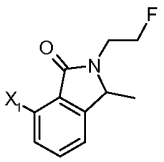
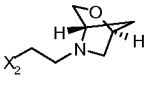


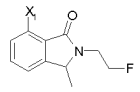
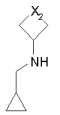
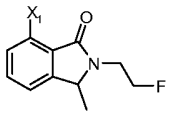
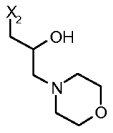
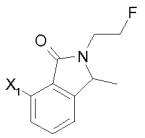
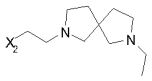
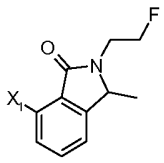
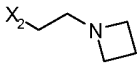
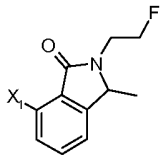
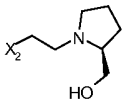
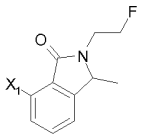
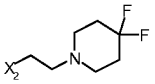
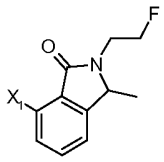
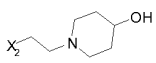
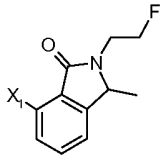
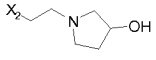
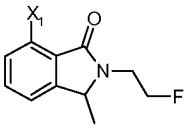
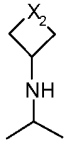
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
492			H	286, 322	584
493			H	286, 322	826

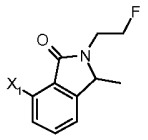
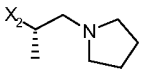
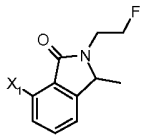
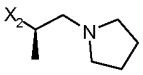
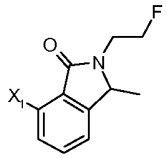
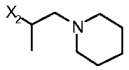
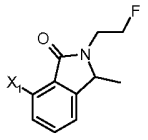
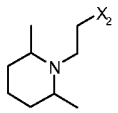
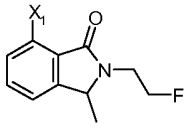
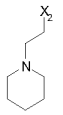
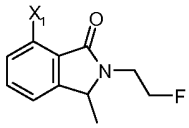
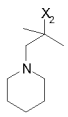
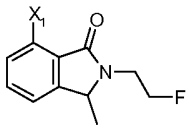
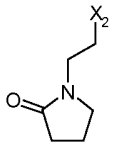
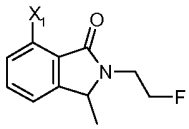
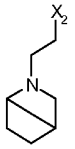
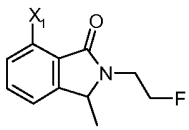
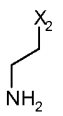
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
494			H	284, 322	613
495			H	282, 322	640
496			H	286, 320	570
497			H	286, 322	584
498			H	282, 322	693
499			H	286, 322	686
500			H	286, 326	616
501			H	286, 326	630
502			H	282, 325	704

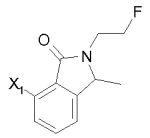
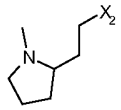
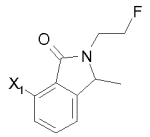
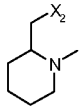
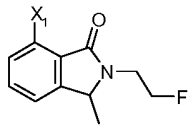
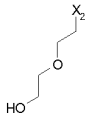
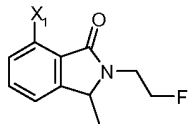
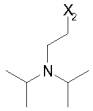
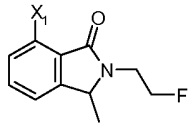
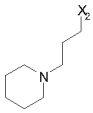
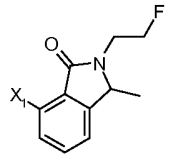
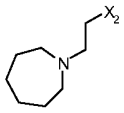
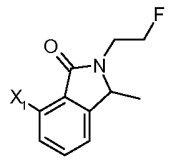
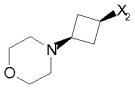
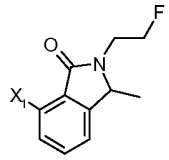
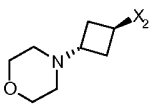
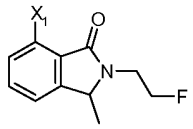
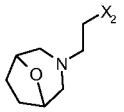
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
503			H	286, 326	634
504			H	286, 326	648
505			H	286, 322	712
506			H	322, 286	739
507			H	322, 286	645
508			H	326, 286	632
509			H	322, 286	672
510			H	322, 284	700
511			H	314, 286	616

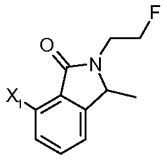
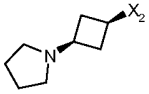
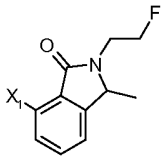
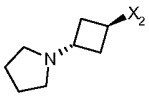
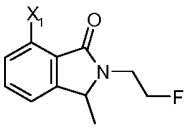
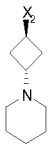
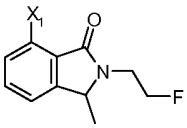
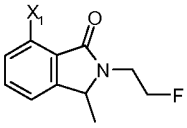
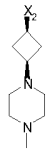
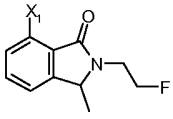
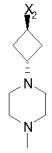
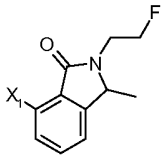
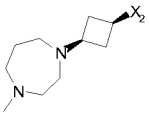
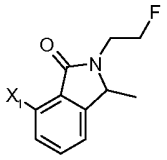
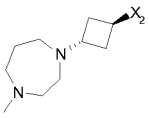
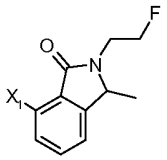
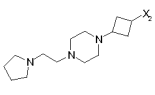
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
512			H	286, 322	684
513			H	286, 322	670
514			H	282, 322	658
515			H	322, 286	632
516			H	326, 286	628
517			H	325, 286	628
518			H	326, 286	659
519			H	326	699
520			H	284, 326	616

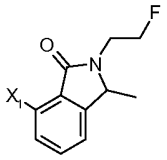
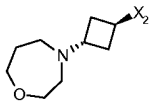
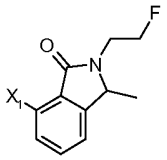
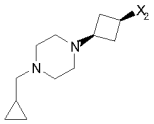
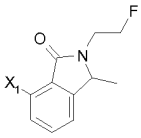
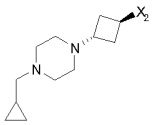
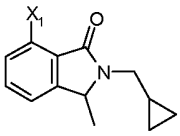
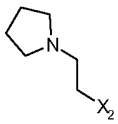
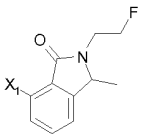
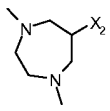
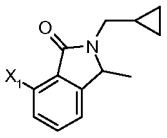
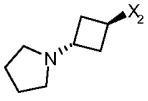
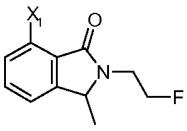
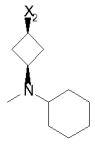
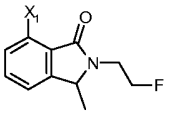
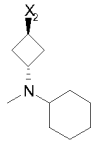
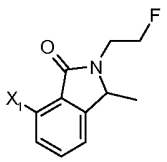
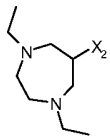
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
521			H	234, 282, 314	630
522			H	326	660
523			H	326	657
524			H		645
525			H	326	627
526			H	326	660
527			H	326	659
528			H	326	692
529			H	326	644

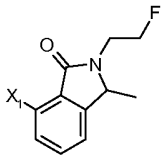
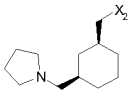
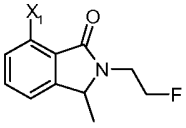
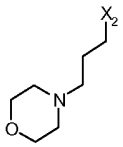
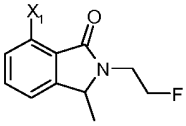
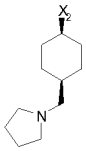
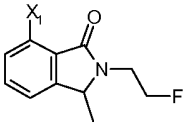
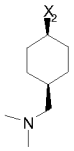
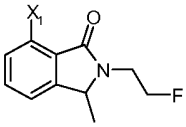
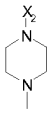
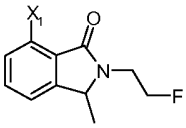
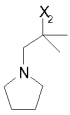
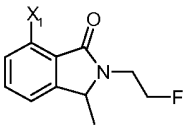
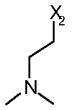
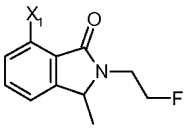
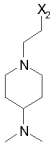
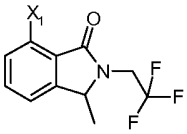
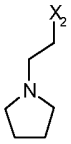
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
530			H	326	628
531			H	322	662
532			H	326	699
533			H	326	602
534			H		646
535			H	326	666
536			H	326	646
537			H	326	-
538			H	322	616

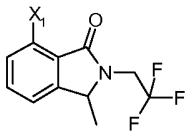
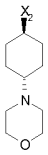
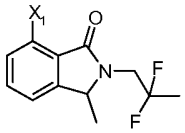
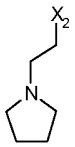
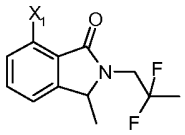
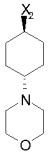
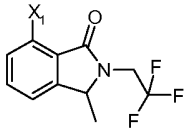
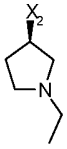
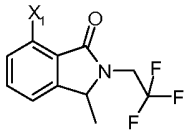
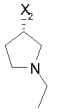
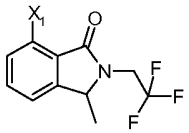
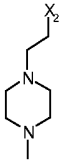
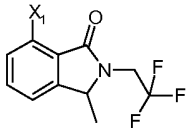
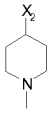
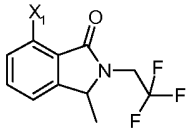
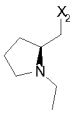
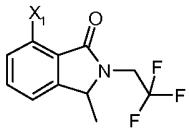
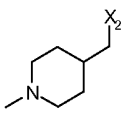
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
539			H	318	630
540			H	318	630
541			H	274	644
542			H	326	658
543			H	286, 324	630
544			H	286, 326	658
545			H	286, 322	630
546			H	286, 326	642
547			H	286, 322	562

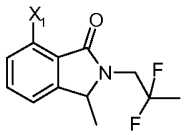
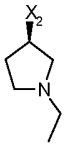
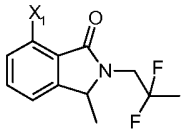
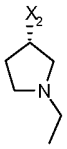
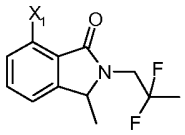
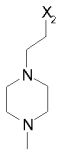
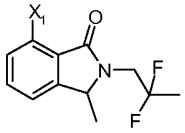
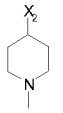
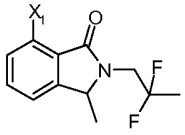
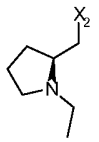
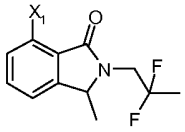
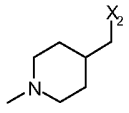
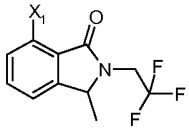
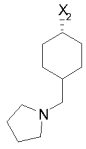
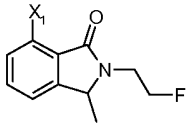
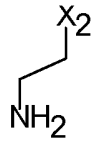
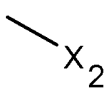
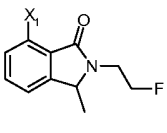
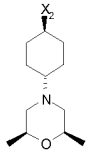
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
548			H	322-326	630
549			H	326	630
550			H	286, 322	607
551			H		646
552			H		644
553			H	326	644
554			H	322-326	658
555			H	322-326	658
556			H	286, 326	658

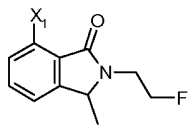
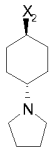
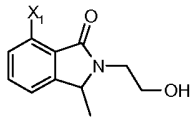
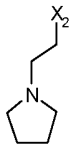
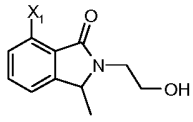
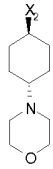
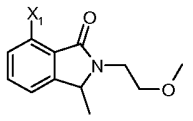
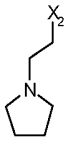
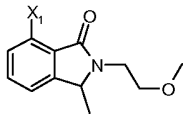
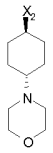
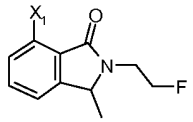
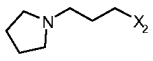
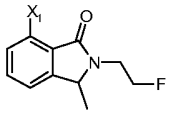
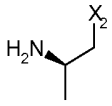
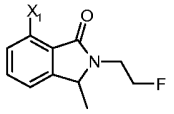
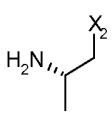
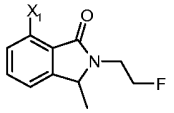
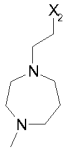
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
557			H	322-326	642
558			H	322-326	642
559			H	286, 322	656
560			H	286, 322	656
561			H	286, 322	671
562			H	286, 322	671
563			H	318	685
564			H	322-326	685
565			H	322-326	754

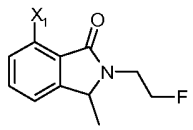
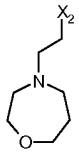
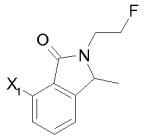
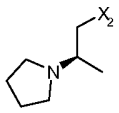
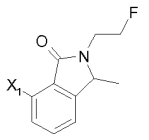
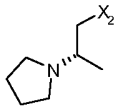
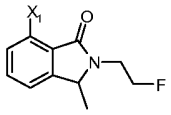
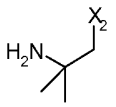
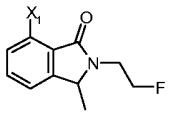
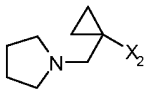
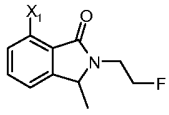
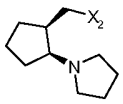
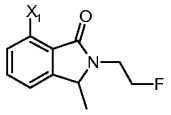
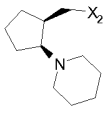
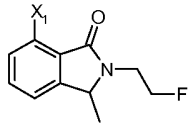
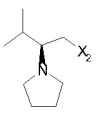
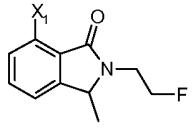
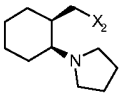
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
566			H	322-326	672
567			H	322	711
568			H	322-326	711
569			H	326	624
570			H	326	645
571			H	322-326	650
572			H	286, 326	684
573			H	286, 326	684
574			H	326	673

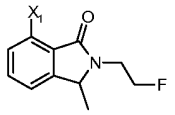
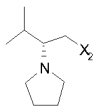
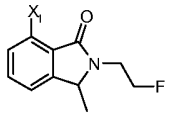
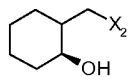
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
575			H	322	698
576			H	326, 286	646
577			H	286, 322	684
578			H	282, 322	658
579			H	322, 286	617
580			H	326, 286	644
581			H	326, 286	590
582			H	286, 326	673
583			H	326, 285	652

#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
584			H	326, 282	722
585			H	326, 286	648
586			H	326, 285	718
587			H	326, 286	652
588			H	326, 284	652
589			H	325, 283	681
590			H	325.3	652
591			H	326.3	666
592			H	325, 283	666

#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
593			H	325.3	648
594			H	325, 284	648
595			H	325, 284	677
596			H	325, 284	648
597			H	326, 285	662
598			H	325, 284	662
599			H	326, 282	720
600				314, 283	576
601			H	322, 286	714

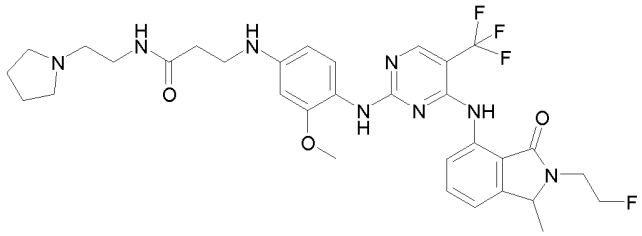
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
602			H	286, 322	670
603			H	324, 285	614
604			H	324, 284	684
605			H	324, 285	628
606			H	324, 284	698
607			H	285, 322	630
608			H	325, 284	576
609			H	325, 284	576
610			H	326, 286	659

#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
611			H	326, 286	646
612			H	325, 285	630
613			H	325, 284	630
614			H	325, 285	590
615			H	285, 325	642
616			H	325, 285	670
617			H	326, 286	684
618			H	326, 286	658
619			H	285, 324	684

#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
620			H	326, 286	658
621			H	280, 320	631

Example 622

2-(2-methoxy-4-[2-(2-pyrrolidin-1-yl-ethylcarbamoyl)-ethylamino]-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



73 mg (0.193 mmol) 3-(4-amino-3-methoxy-phenylamino)-*N*-(2-pyrrolidin-1-yl-ethyl)-propionamide hydrochloride (method 28) are dissolved in 3 ml 2-butanol and combined with 50 mg (0.129 mmol) 2-chloro-4-(2-(2-fluorethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine (method 26). This reaction mixture is stirred for 16 h at 100°C. The solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier material used is C18-RP-silica gel and a gradient is run through which consists at the starting point of 90% water and 10% acetonitrile and at the finishing point of 55% water and 45% acetonitrile. 0.1% formic acid are added both to the water and to the acetonitrile.. The suitable fractions are combined with 500 µl of a 1 M aqueous hydrochloric acid and freeze-dried. The product is obtained as the dihydrochloride.

Yield: 33 mg (0.045 mmol; 35 %)

UV max: 314 nm

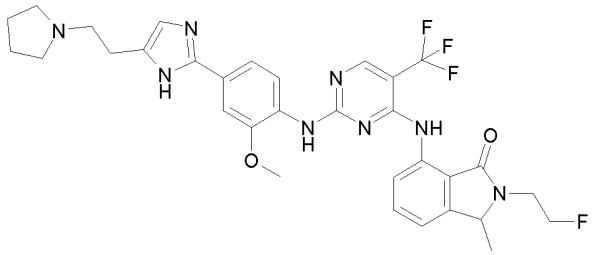
MS (ESI): 659 $(M+H)^+$

^{1}H-NMR: 1.35 - 1.48 (m, 3H), 1.64 - 1.78 (m, 4H), 2.37 - 2.46 (m, 2H), 3.48 - 3.75 (m, 4H), 3.97 - 4.14 (m, 1H), 4.50 - 4.78 (m, 3H), 5.55 - 5.71 (m,

1H), 6.14 - 6.42 (m, 2H), 6.96 - 7.32 (m, 3H), 7.86 - 7.98 (m, 1H), 8.32 (s, 1H), 8.84 (s, 1H), 10.41 (s, 1H)

Example 623

2-(2-fluoro-ethyl)-7-(2-{4-[4-(2-hydroxy-ethyl)-1*H*-imidazol-2-yl]-2-methoxy-phenylamine}-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



0.07 g (0.3 mmol) 2-[2-(4-amino-3-methoxy-phenyl)-1*H*-imidazol-4-yl]-ethanol (method 27) are suspended in 2 ml dioxane and brought into solution in the ultrasound bath at 50 °C. 0.8 ml (3.20 mmol) 4 N dioxanic hydrochloric acid are added. The dioxane is eliminated *in vacuo*, combined with 0.096 g (0,247 mmol) 7-(2-chloro-5-trifluoromethyl-pyrimidine-4-ylamine)-2-(2-fluoro-ethyl)-3-methyl-2,3-dihydro-isoindol-1-one and suspended in butanol. The mixture is stirred for 16 h at 100 °C. The crude product is purified by column chromatography. The carrier material used is C18-RP-silica gel. A gradient is run through which consists at the starting point of 75% water and 25 % acetonitrile and at the finishing point of 30% water and 70% acetonitrile. 0.1% ammonia is added to the water. 23 mg of this intermediate product and 0.018g (0.094 mmol) p-toluenesulphonyl chloride are suspended in 0.9 ml of tetrahydrofuran and 0.02 ml (0.139 mmol) triethylamine and combined with 0.007g (0.057 mmol) 4-dimethylamino-pyridine. This reaction mixture is stirred for 16 h at 20 °C. Then it is combined with 0.36 ml (5.064 mmol) pyrrolidine and stirred for 16 h at 60 °C. The crude product is purified by column chromatography. The carrier material used is C18-RP-silica gel. A gradient is run through which consists of 90% water and 10% acetonitrile at the starting point and of 60% water and 40% acetonitrile at the finishing point. 0.1% formic acid is added to the water.

Yield: 7 mg (0.011 mmol, 28%)

MS (ESI): 639 $(M+H)^+$

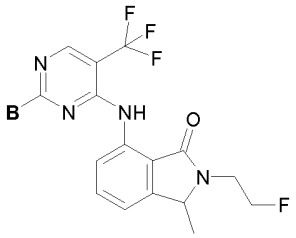
UV max: 330 nm

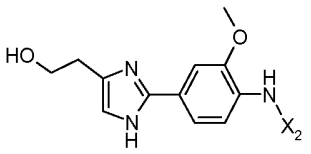
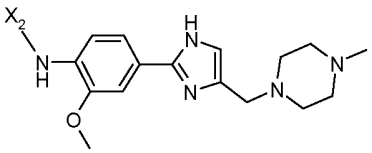
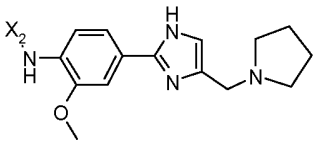
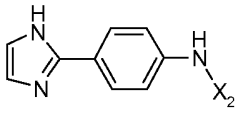
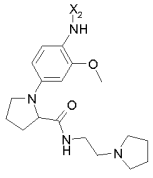
NMR: 1.42 - 1.46 (m, 3H), 1.78 - 2.08 (m, 6H), 2.29 (s, 1H), 3.95 - 4.16 (m, 4H), 4.52 - 4.78 (m, 3H), 7.09 - 7.13 (m, 1H), 7.24 - 7.28 (m, 1H), 7.46

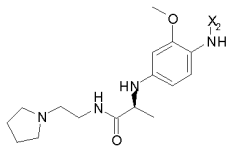
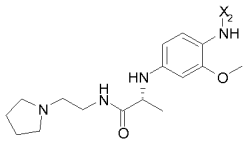
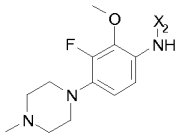
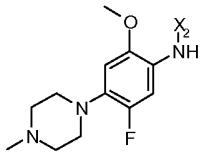
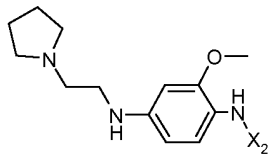
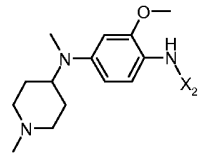
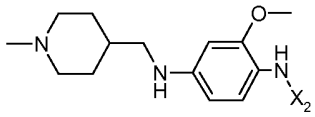
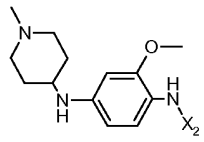
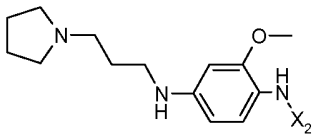
- 7.50 (m, 1H), 7.52 - 7.58 (m, 2H), 7.64 - 7.67 (m, 1H), 7.82 - 7.88 (m, 1H), 8.02 - 8.13 (m, 2H), 8.50 - 8.60 (m, 2H), 9.20 - 9.23 (m, 1H), 10.52 - 10,82 (m, 2H).

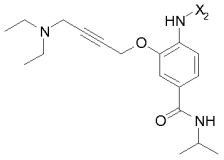
Examples 624-638

The following compounds are prepared by an analogous process to that described in Example 622 or 623. The corresponding aniline is described in method 27 and 28.



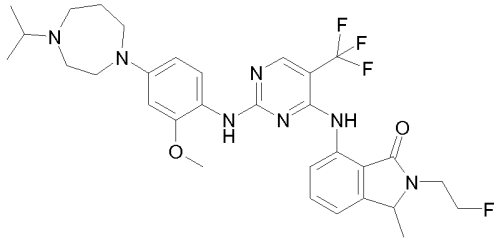
#	B	UV max [nm]	MS (ESI) $(M+H)^+$
624		290, 326	586
625		290, 330	654
626		290, 326	625
627		326	512
628		314	685

#	B	UV max [nm]	MS (ESI) $(M+H)^+$
629		290, 314	659
630			659
631		278	592
632		314	592
633		314	588
634		314	602
635		314	602
636		314	588
637		314	602

#	B	UV max [nm]	MS (ESI) $(M+H)^+$
638			670

Example 639

2-(4-(4-isopropyl-[1,4]diazepin-1-yl)-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



50 mg (0.087 mmol) 2-(4-(4-[1,4]diazepan-1-yl)-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine (method from Example 622, aniline from method 28) are dissolved in 0.5 ml dimethylacetamide and combined with 13 µl (0.174 mmol) acetone. 37 mg (0.175 mmol) sodium triacetoxyborohydride are added to this reaction mixture. After 16 h at 20 °C the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier material used is C18-RP-silica gel and within 15 min a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid are added both to the water and to the acetonitrile.. The suitable fractions are combined with 500 µl of a 1 M aqueous hydrochloric acid and freeze-dried. The product is obtained as the dihydrochloride.

Yield: 51 mg (0.074 mmol; 85 %)

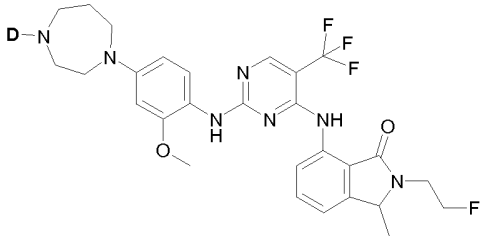
UV max: 314 nm

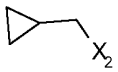
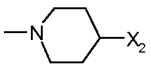
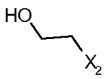
MS (ESI): 616 $(M+H)^+$

^{1}H-NMR: 1.23-1.35 (m, 6H), 1.35-1.51 (m, 3H), 2.16-2.29 (m, 1H), 2.95-3.05 (m, 1H), 3.12-3.23 (m, 1H), 3.42-3.66 (m, 6H), 3.78 (s, 3H), 3.83-4.00 (m, 2H), 4.00-4.16 (m, 1H), 4.50-4.79 (m, 3H), 6.32-6.63 (m, 2H), 7.08-8.59 (m, 4H), 9.24-9.76 (m, 1H), 10.67 (s, 2H)

Examples 640-648

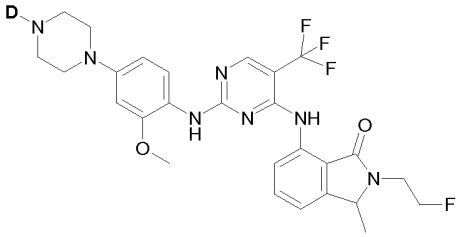
The following compounds are prepared by an analogous process to that described in Example 639.

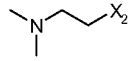
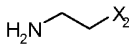
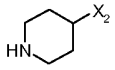
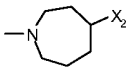
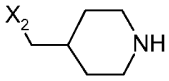
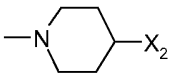
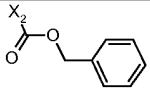


#	D	UV max [nm]	MS (ESI) $(M+H)^+$
640		314	574
641		310-314	628
642		310-314	602
643		310-314	630
644		314	671
645		310-314	618
646		314	658
647		314	588

Examples 648-659

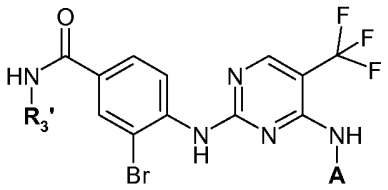
The following compounds are prepared by an analogous process to that described in Example 639. For the reductive amination 2-(2-methoxy-4-piperazin-1-yl-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine is used. The aniline for preparing this compound is described in method 28.

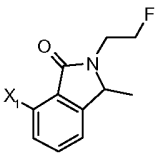
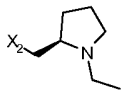
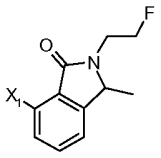
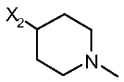
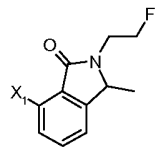
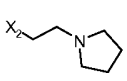
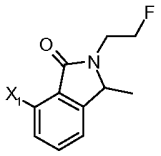
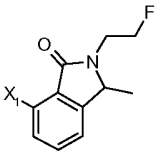
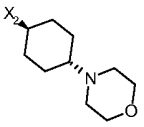
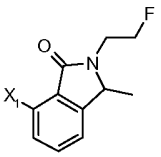
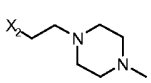


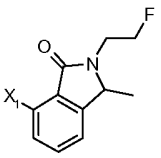
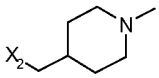
#	D	UV max [nm]	MS (ESI) $(M+H)^+$
648		286, 314	631
649		286, 314	603
650		282, 314	643
651		282, 314	671
652		286, 314	657
653		282, 314	628
654		286, 314	657
655		286, 314	671
656		282, 314	614
657		282, 314	560
658		234, 283, 314	694
659		286, 314	574

Examples 660-666

The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-Carboxy-2-bromo-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be prepared according to method 29. The corresponding aniline is described in method 22. The amine used to prepare the amide is commercially obtainable or described in method 13.

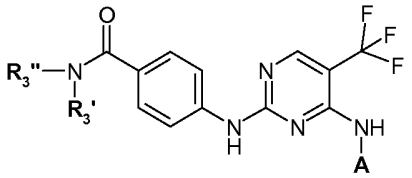


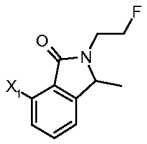
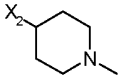
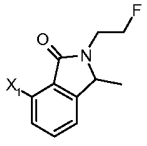
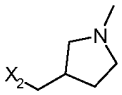
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
660			314	678 / 680
661			314	626 / 628
662			314	626 / 628
663			286	609 / 611
664			314	734 / 736
665			314	693 / 695

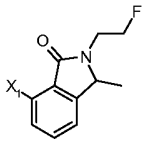
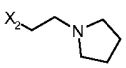
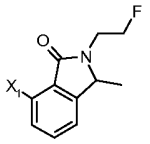
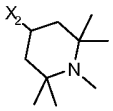
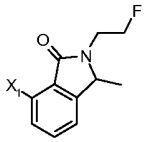
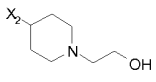
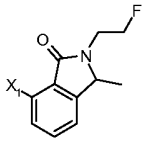
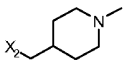
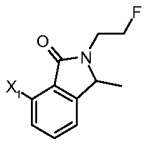
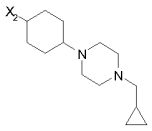
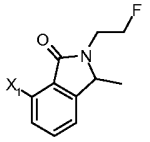
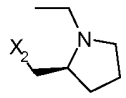
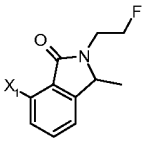
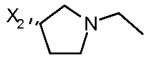
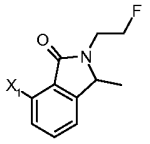
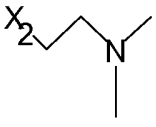
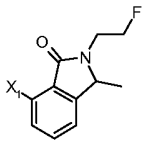
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
666			286	678 / 680

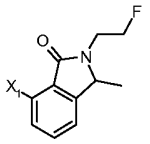
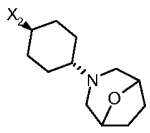
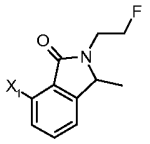
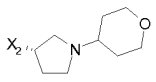
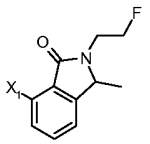
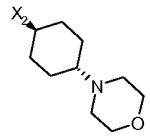
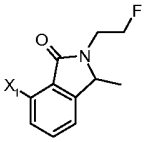
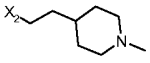
Examples 667-681

The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-Carboxy-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine may be prepared according to method 14. The corresponding aniline is described in method 22. The amine used to prepare the amide is commercially obtainable or described in method 13. In addition, the group R_3' may be synthesised analogously to Example 639 by reductive amination. An amine is used which has another protected amino function in the side chain. The protective group used may be a *tert*-butoxycarbonyl, benzyloxycarbonyl or benzyl group. This protective group is cleaved by a procedure familiar to the skilled man and reductive amination (analogously to Example 639) or alkylation (analogously to method 34 or WO2004052857) are the last steps in this sequence.



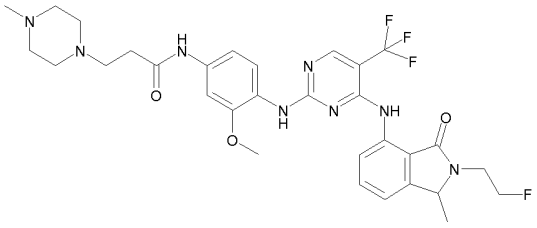
#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
667			H	314	586
668			H	314	586

#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
669			H	314	586
670			H	314	642
671			H	314	616
672			H	290	600
673			H	290	709
674			H	314	600
675			H	314	586
676				286	574
677			H	286	572

#	A	R_3'	R_3''	UV max [nm]	MS (ESI) $(M+H)^+$
678			H	290	682
679			H	314	642
680			H	290	656
681			H	314	615

Example 682

2-(2-methoxy-4-[3-(4-methyl-piperazin-1-yl)-propionylamino]-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



63 mg (0.116 mmol) 2-(4-acryloylamino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine (method 30) are dissolved in 1 ml of methanol and combined with 70 mg (0.699 mmol) N-methyl-piperazine. After stirring for 48 h at 20 °C the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier material used is C18-RP-silica gel and a gradient is run through within 20 min which consists of 95% water and 5% acetonitrile at the starting point and of 2% water and 98% acetonitrile at the finishing point. 0.1% formic acid are added both to the water and to

the acetonitrile. The suitable fractions are combined with 500 µl of a 1 M aqueous hydrochloric acid and freeze-dried. The product is obtained as the dihydrochloride.

Yield: 58 mg (0.081 mmol; 70 %)

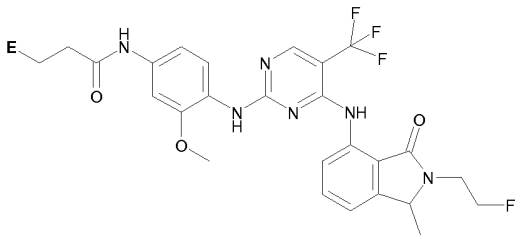
UV max: 282 nm

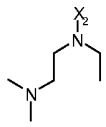
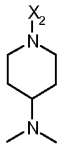
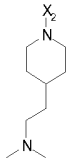
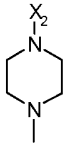
MS (ESI): 645 $(M+H)^+$

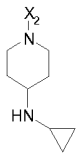
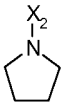
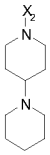
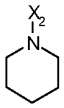
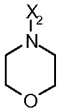
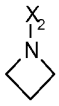
^{1}H-NMR: 1.42 (d, 3H), 2.18 (s, 3H), 2.29 - 2.43 (m, 4H), 2.65 - 2.70 (m, 2H), 3.50 - 3.62 (m, 1H), 3.72 (s, 3H), 4.00 - 4.12 (m, 1H), 4.52 - 4.76 (m, 3H), 7.12 - 7.17 (m, 1H), 7.12 - 7.42 (m 4H), 7.51 (s, 1H), 8.17 (s, 1H), 8.38 (s, 1H), 9.08 (s, 1H), 10.18 (s, 1H), 10.46 (s, 1H)

Examples 683-692

The following compounds are prepared by an analogous process to that described in Example 682.

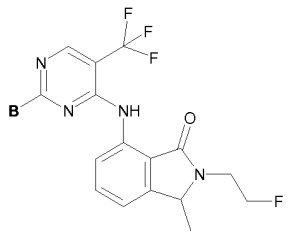


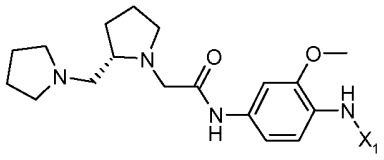
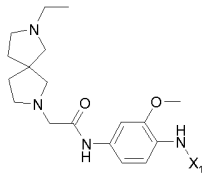
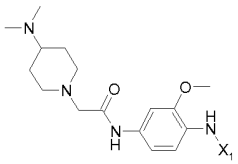
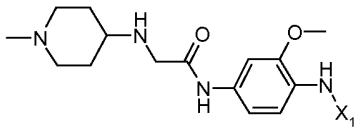
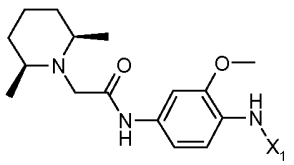
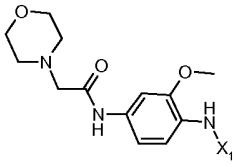
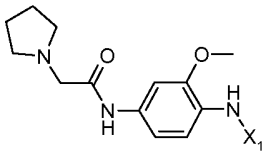
#	E	UV max [nm]	MS (ESI) $(M+H)^+$
683		282	661
684		282	673
685		282	701
686		282	645

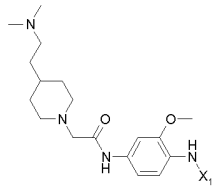
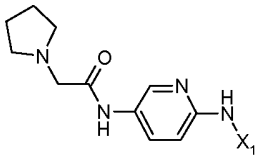
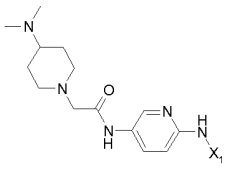
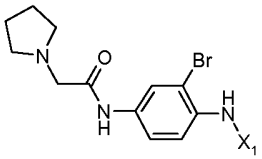
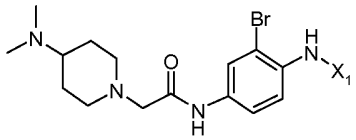
#	E	UV max [nm]	MS (ESI) $(M+H)^+$
687		282	685
688		282	616
689		282	713
690		282	630
691		282	632
692		282	602

Examples 693-704

The following compounds are prepared by an analogous process to that described in Example 682. 2-(4-(2-Bromo-acetylamino)-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine or 2-(4-(2-bromo-acetylamino)-2-bromo-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine or 2-[5-(2-bromo-acetylamino)-pyridin-2-ylamino]-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine, which are described in method 30, are used as educt for the nucleophilic substitution.

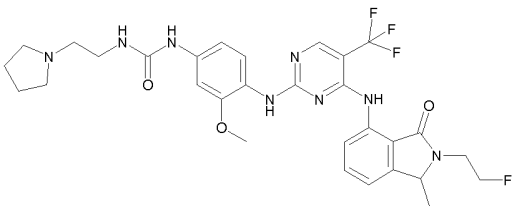


#	B	UV max [nm]:	MS (ESI) $(M+H)^+$:
693		282	685
694		282	685
695		314	659
696		282	645
697		282	644
698		282	618
699		282	602

#	B	UV max [nm]:	MS (ESI) $(M+H)^+$:
700		282	687
701		322	573
702		322	630
703		222	650
704		278	707

Example 705

2-(2-methoxy-4-[3-(3-pyrrolidin-1-yl-ethyl)-ureido]-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



70 mg (0.135 mmol) 2-(4-carboxy-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine (analogously to Example 53) are dissolved in 2 ml of toluene and combined with 190 µl (1.348 mmol) triethylamine and 60 µl (0.270 mmol) diphenylphosphorylazide. This reaction mixture is stirred for 48 h at 20 °C. Then the temperature of the suspension is adjusted to 95 °C for 2 h, whereupon a clear brown solution is formed. Then 31 mg (0.270 mmol) 1-(2-aminoethyl)-pyrrolidine are added and the mixture is again stirred

for 1 h at 95°C. The solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is C18-RP-silica gel and within 15 min a gradient is run through which consists of 95% water and 5% acetonitrile at the starting point and consists of 2% water and 98% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are made basic with 5 M sodium hydroxide solution and extracted 4 times with 50 ml dichloromethane. The combined organic phases are dried and the solvent is eliminated *in vacuo*.

Yield: 42 mg (0.067 mmol; 50 %)

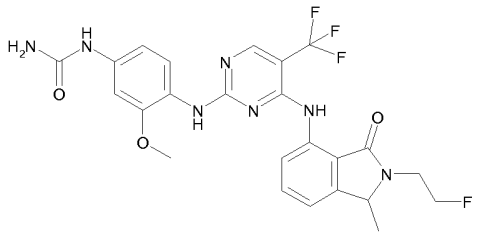
UV max: 282 nm

MS (ESI): 631 $(M+H)^+$

^{1}H-NMR: 1.42 - 1.48 (m, 3H), 1.69 - 1.79 (m, 4H), 3.22 - 3.28 (m, 2H), 3.49 - 3.62 (m, 1H), 3.70 (s, 3H), 3.99 - 4.12 (m, 1H), 4.53 - 4.76 (m, 3H), 6.17 (s, 1H), 6.84 - 6.91 (m, 1H), 7.15 - 7.33 (m, 3H), 7.40 (s, 1H), 8.36 (s, 1H), 8.76 (s, 1H), 9.01 (s, 1H), 10.44 (s, 1H)

Example 706

2-(2-methoxy-4-ureido-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



This compound is prepared analogously to Example 705.

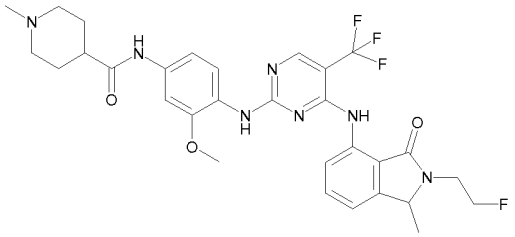
UV max: 282 / 314 nm

MS (ESI): 534 $(M+H)^+$

^{1}H-NMR: 1.42 (d, 3H), 3.48 - 3.64 (m, 1H), 3.69 (s, 3H), 3.98 - 4.13 (m, 1H), 4.50 - 4.77 (m, 3H), 5.89 (s, 2 H), 6.94 (d, 1H), 7.16 - 7.30 (m, 2H), 7.36 (s, 1H), 8.33 - 8.41 (m, 2H), 8.38 (s, 1H), 8.73 (s, 1H), 9.00 (s, 1H), 10.44 (s, 1H)

Example 707

2-(2-methoxy-4-[(1-methyl-piperidin-4-carbonyl)-amino]-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



Starting from 2-(4-amino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine (method 30) the above-mentioned product is prepared using an amide linking method familiar to the skilled man (cf. also Example 53 or 1032). The substance is obtained as a free base.

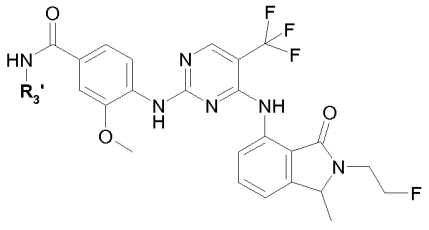
UV max: 282 nm

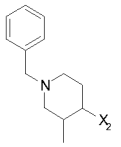
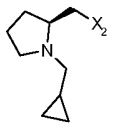
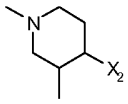
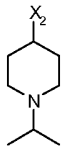
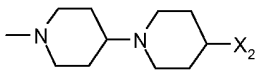
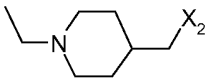
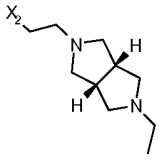
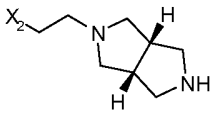
MS (ESI): 616 $(M+H)^+$

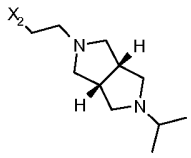
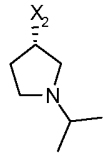
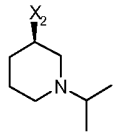
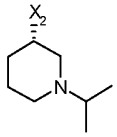
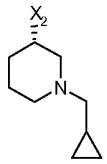
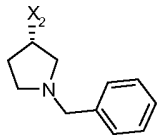
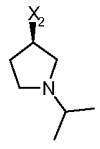
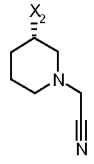
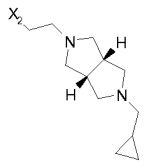
^{1}H-NMR (400 MHz, $CDCl_3$): 1.51 (d, 3H), 2.25 - 2.32 (m, 1H), 2.36 (s, 3H), 3.00 - 3.07 (m, 2H), 3.53 - 3.65 (m, 1H), 3.92 (s, 3H), 4.13 - 4.27 (m, 1H), 4.56 - 4.77 (m, 3H), 6.84 (d, 1H), 7.07 (d, 1H), 7.44 (s, 1H), 7.47 - 7.54 (m, 1H), 7.57 (s, 1H), 7.62 (s, 1H), 8.16 - 8.24 (m, 1H), 8.39 (s, 1H), 8.60 - 8.68 (m, 1H), 10.42 (s, 1H)

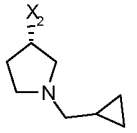
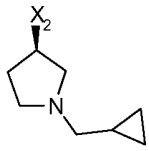
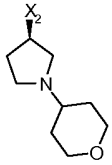
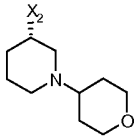
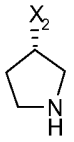
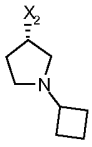
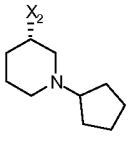
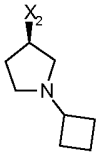
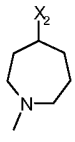
Examples 708-795

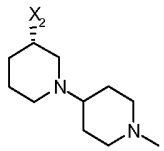
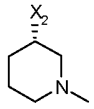
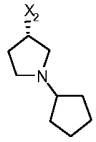
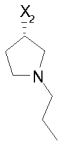
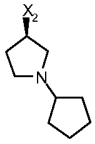
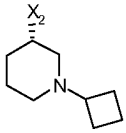
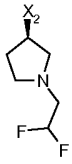
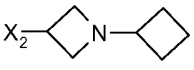
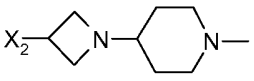
Using an analogous method to that described in Example 53 a primary amine which has another protected amino function in the side chain is coupled to 2-(4-carboxy-2-methoxy-phenylamino)-4-[2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino]-5-trifluoromethyl-pyrimidine. The protective group used may be a *tert*-butoxycarbonyl, benzyloxycarbonyl or benzyl group. This protective group is cleaved using a procedure familiar to the skilled man and reductive amination (analogously to Example 639) or alkylation (analogously to method 34 or WO2004052857) are the final steps in this sequence.

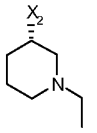
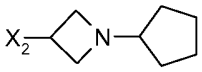
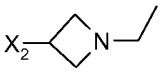
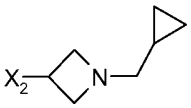
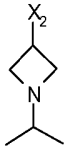
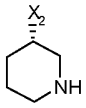
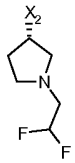
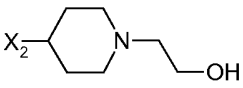
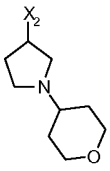


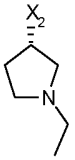
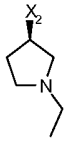
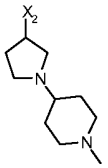
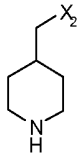
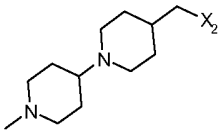
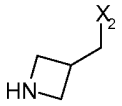
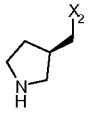
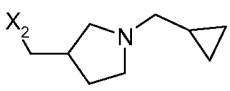
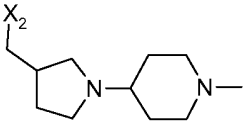
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
708		285, 322	706
709		285, 322	656
710		285, 322	630
711		322, 286	644
712		325, 286	699
713		282, 318	644
714		326	685
715		326	658

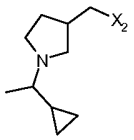
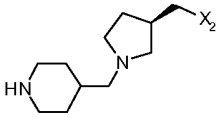
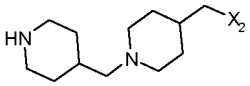
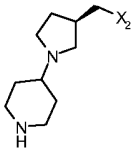
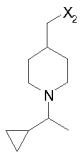
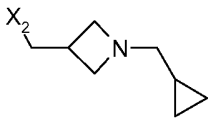
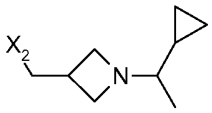
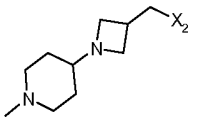
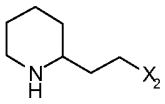
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
716		326	699
717		326	630
718		326	644
719		322	644
720		326	656
721		326	678
722		314	630
723		322	641
724		326	712

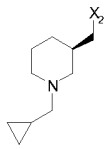
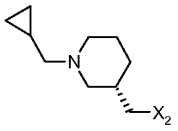
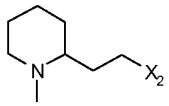
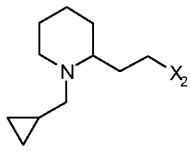
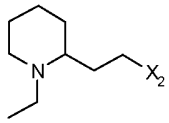
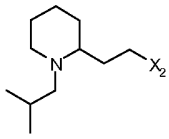
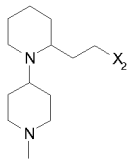
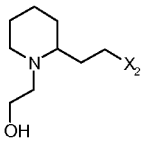
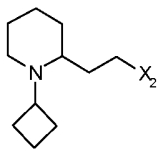
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
725		326	642
726		322	642
727		318	672
728		301	686
729		326	588
730		326	642
731		326	670
732		326	642
733		326	630

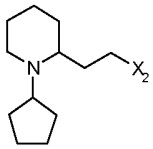
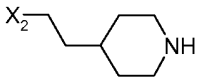
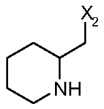
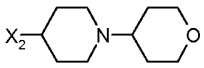
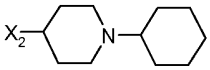
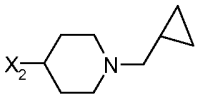
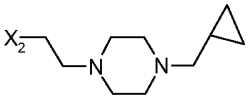
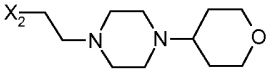
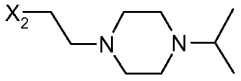
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
734		326	699
735		310	616
736		326	656
737		322	630
738		326	656
739		326	656
740		266	652
741		326	629
742		326	671

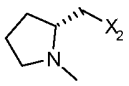
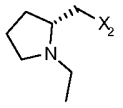
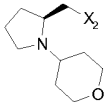
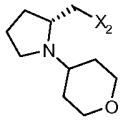
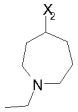
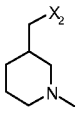
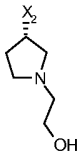
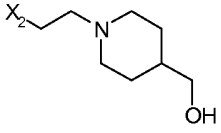
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
743		326	630
744		326	642
745		326	602
746		326	628
747		326	616
748		326	602
749		322	652
750		326	646
751		326	672

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
752		326	616
753		326	616
754		326	685
755		322	616
756		318	713
757		286, 322	588
758		226, 286, 322	602
759		322-326	656
760		322-326	699

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
761		322-326	670
762		322-326	699
763		322	713
764		326	685
765		322	684
766		326	642
767		322-326	656
768		322-326	685
769		322-326	630

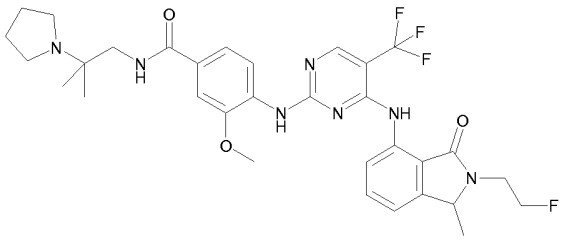
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
770		286, 322	670
771		286, 322	670
772		322-326	644
773		322	684
774		322-326	658
775		322	686
776		322-326	727
777		322-326	674
778		322-326	684

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
796		322-326	698
780		286, 322	630
781		282, 314	616
782		322, 286	686
783		326	684
784		324, 286	656
785		326, 286	685
786		322, 286	715
787		322, 286	673

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
788		285, 322	616
789		285, 322	630
790		285, 322	686
791		285, 322	686
792		326	644
793		322	630
794		326	631
795		326	660

Example 796

2-[2-methoxy-4-(2-methyl-2-pyrrolidin-1-yl-propylcarbamoyl)-phenylamino]-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



200 mg (0.385 mmol) 2-(4-carboxy-2-methoxy-phenylamino)-4-[2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino]-5-trifluoromethyl-pyrimidine (analogously to Example 53) are dissolved in 1 ml of dimethylformamide cooled to 0 °C and combined with 520 µl (3.038 mmol) diisopropylethylamine and 160 mg (0.498 mmol) *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate. This solution is slowly added dropwise after 10 min to 56 µl (0.539 mmol) 1,2-diamino-2-methylpropane, which is dissolved in 300 µl dimethylformamide. The reaction mixture is stirred for 24 h at 20°C and then the solvent is eliminated *in vacuo*. The residue is purified by column chromatography. The carrier used is C18-RP-silica gel and within 15 min a gradient is run through which consists at the starting point of 90% water and 10% acetonitrile and at the finishing point of 50% water and 50% acetonitrile. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are freeze-dried. This intermediate product is combined with 70 mg (0.515 mmol) potassium carbonate and with 84 mg (0.506 mmol) potassium iodide and suspended in 2 ml acetonitrile. 20 µl (0.170 mmol)1,4-dibromobutane are added to this mixture and it is stirred under reflux conditions for 16 h. Then the solvents are solvent eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is C18-RP-silica gel and within 15 min a gradient is run through which consists at the starting point of 90% water and 10% acetonitrile and at the finishing point of 50% water and 50% acetonitrile. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are combined with 0.5 ml 1 N hydrochloric acid and freeze-dried. The product is obtained as the dihydrochloride.

Yield: 20 mg (0.032 mmol, 8%)

UV max: 325 nm

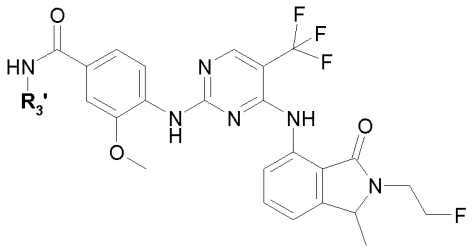
MS (ESI): 644 $(M+H)^+$

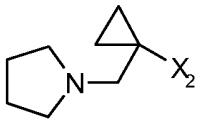
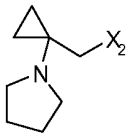
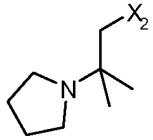
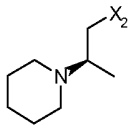
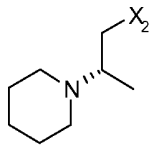
^{1}H-NMR (400 MHz): 1.30 - 1.47 (m, 9H), 1.85 - 2.01 (m, 4H), 3.20 - 3.31 (m, 2H), 3.91 (s, 3H), 3.99 - 4.15 (m, 1H), 4.51 - 4.78 (m, 3H), 7.23 - 7.29 (m,

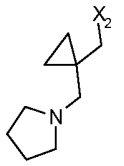
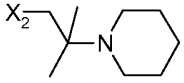
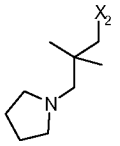
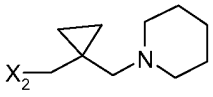
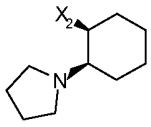
1H), 7.39 - 7.47 (m, 1H), 7.63 - 7.69 (m, 1H), 7.73 - 7.77 (m, 1H), 7.79 - 7.87 (m, 1H), 8.40 - 8.59 (m, 2H), 8.75 - 8.82 (m, 1H), 9.16 - 9.21 (m, 1H), 10.50 - 10.63 (m, 2H)

Examples 797-806

The following compounds are prepared by an analogous method to that described in Example 796:

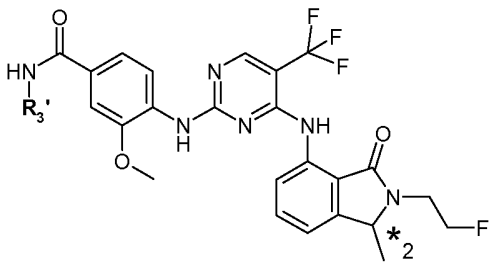


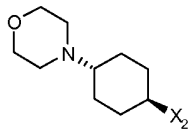
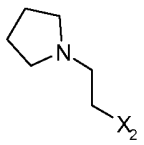
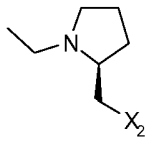
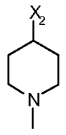
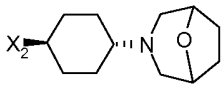
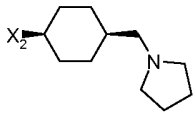
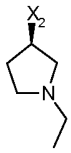
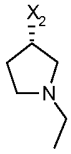
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
797		285, 325	642
798		284, 325	642
799		325, 285	644
800		325, 285	644
801		325, 285	644

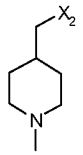
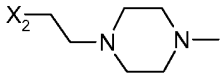
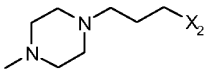
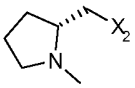
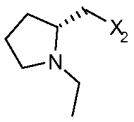
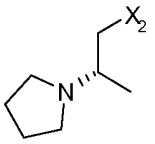
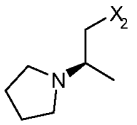
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
802		325, 285	656
803		325, 285	658
804		325, 284	658
805		326, 286	670
806		324, 285	670

Examples 807-821

The following compounds are prepared by an analogous process to that described in Example 53. The corresponding aniline is described in method 31. The amine used to prepare the amide is commercially obtainable or is described in method 13, 21 or in method 25.

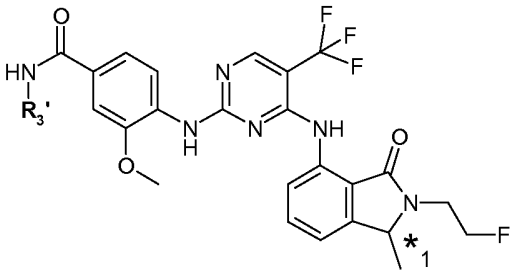


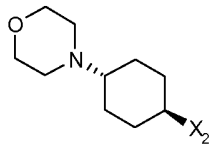
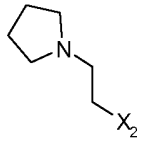
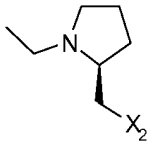
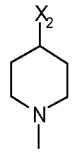
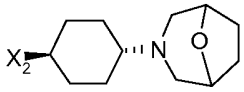
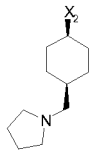
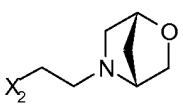
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
807		286, 322	686
808		286, 322	616
809		286, 322	630
810		286, 322	616
811		286, 322	712
812		322, 286	684
813			689
814		278	689

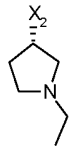
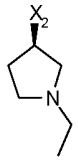
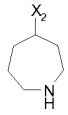
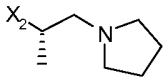
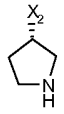
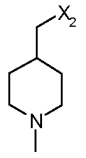
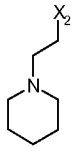
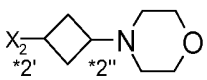
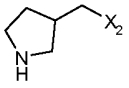
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
815		322	630
816		286, 326	645
817		285, 322	659
818		285, 322	616
819		285, 322	630
820			630
821		322, 286	630

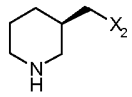
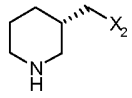
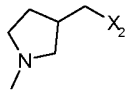
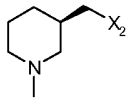
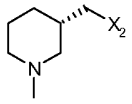
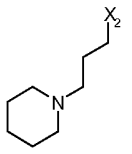
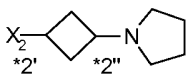
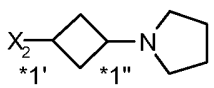
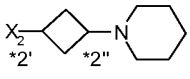
Examples 822-885

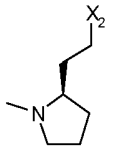
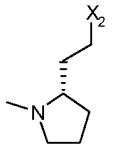
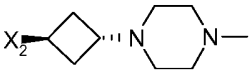
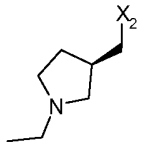
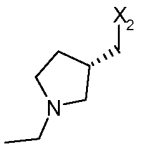
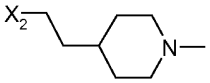
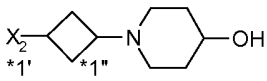
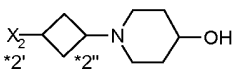
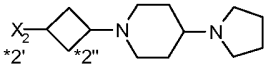
The following compounds are prepared by an analogous process to that described in Example 53. The corresponding aniline is described in method 31. The amine used to prepare the amide is commercially obtainable, described in method 13, 15, 20, 21, 23, 24 and 25 or in J. Med. Chem. **2003**, 46(5), 702-715.

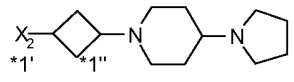
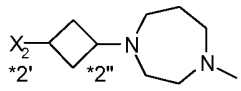
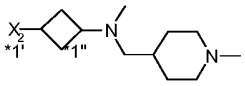
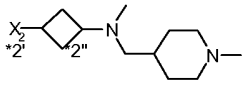
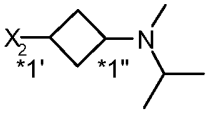
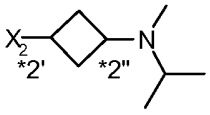
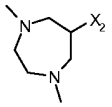
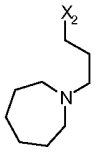
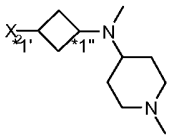


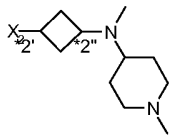
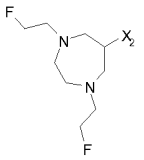
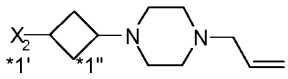
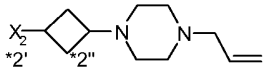
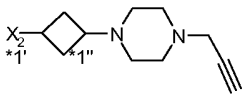
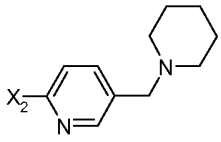
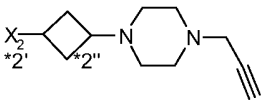
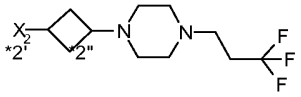
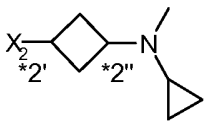
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
822		286, 322	686
823		325, 284	616
824		286, 326	630
825		286, 322	616
826		286, 318	712
827		286, 322	684
828		326	645

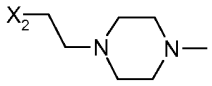
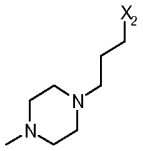
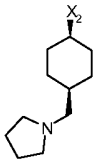
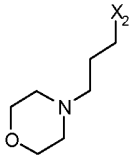
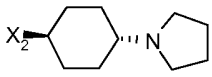
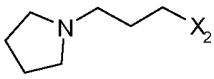
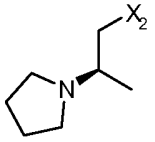
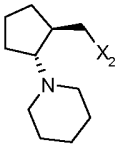
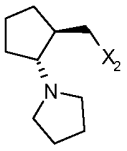
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
829		316	689
830		322	689
831			616
832		318	630
833		326	588
834		322	630
835		286, 322	630
836			658
837		322-326	602

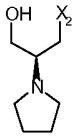
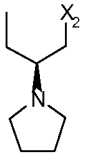
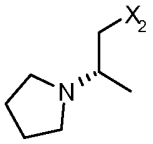
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
838		322-326	616
839		322	616
840		322-326	616
841		322-326	630
842		322-326	630
843		286, 322	644
844		286, 322	642
845		286, 322	642
846		286, 322	656

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
847		282, 318	630
848		282, 322	630
849		286, 318	671
850		286, 322	630
851		286, 322	630
852		286, 322	644
853		322-326	672
854		322	672
855		286, 322	725

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
856		286, 322	725
857		322-326	685
858		286, 322	713
859		286, 322	713
860		286, 322	644
861		286, 322	644
862		318-322	645
863		286, 322	658
864		286, 322	699

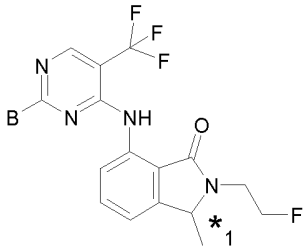
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
865		286, 322	699
866		326	709
867		322	697
868		322	697
869		318	695
870		290.3	693
871		322	695
872		286, 322	753
873		286, 326	642

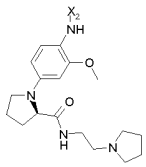
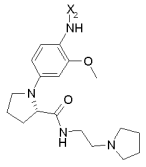
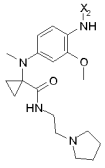
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
874		286, 322	645
875		322, 286	659
876		282, 322	684
877		324, 284	646
878		286, 322	670
879		325, 284	630
880		322, 286	630
881		322, 286	684
882		325, 286	670

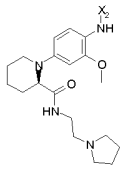
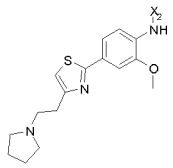
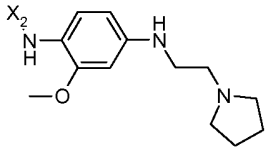
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
883		322, 286	646
884		326, 286	644
885		325, 285	630

Examples 886-891

The following compounds are prepared by an analogous process to that described in Example 622 or 623. The corresponding aniline is described in method 27 or 28.

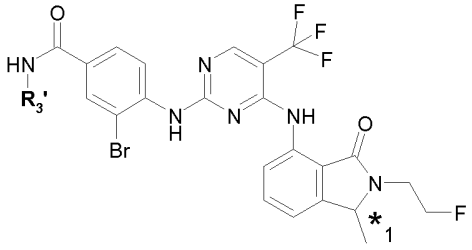


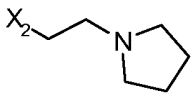
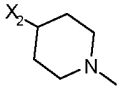
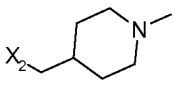
#	B	UV max [nm]	MS (ESI) $(M+H)^+$
886		314	685
887		314	685
888		286, 310	685

#	B	UV max [nm]	MS (ESI) $(M+H)^+$
889		282, 314	699
890		338	656
891		314	588

Examples 892-894

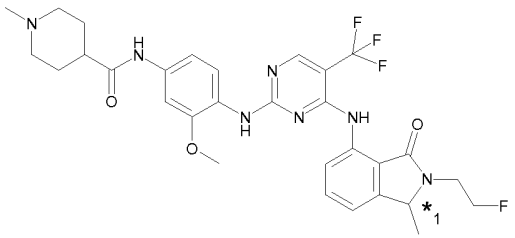
The following compounds are prepared by an analogous process to that described in Example 53. 2-(4-carboxy-2-bromo-phenylamino)-4-chloro-5-trifluoromethyl-pyrimidine is described in method 29. The corresponding aniline is described in method 31. The amine used to prepare the amide is commercially obtainable.



#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
892		314	665
893		270	665
894		270	680

Example 895

2-(2-methoxy-4-[(1-methyl-piperidin-4-carbonyl)-amino]-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine Enantiomer 1



Starting from 2-(4-amino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine enantiomer 1 (analogously to method 30) the above-mentioned product is prepared by an amide linking method familiar to the skilled man (cf. also Example 1032). It is obtained as the dihydrochloride.

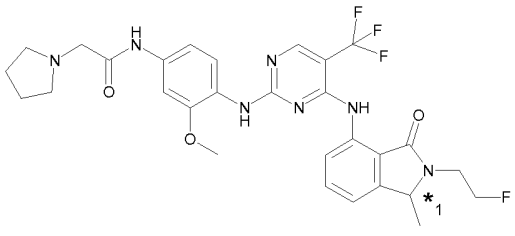
UV max: 310 nm

MS (ESI): 616 $(M+H)^+$

^{1}H-NMR (500MHz): 1.42 (d, 3H), 1.69 - 1.77 (m, 2H), 1.77 - 1.84 (m, 2H), 1.94 - 2.03 (m, 2H), 2.23 (s, 3H), 2.29 - 2.38 (m, 1H), 2.86 - 2.93 (m, 2H), 3.72 (s, 3H), 4.00 - 4.12 (m, 1H), 4.52 - 4.75 (m, 3H), 7.16 (d, 3H), 7.18 - 7.24 (m, 1H), 7.32 - 7.41 (m, 1H), 7.57 (s, 1H), 8.18 (s, 1H), 8.38 (s, 1H), 9.07 (s, 1H), 9.95 (s, 1H), 10.46 (s, 1H)

Example 896

2-(2-methoxy-4-(2-pyrrolidin-1-yl-acetylamino)-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine Enantiomer 1



Starting from 2-(4-amino-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine Enantiomer 1 (analogously to method 30) the above-mentioned product is prepared by an amide linking method familiar to the skilled man (cf. also Example 1032). It is obtained as the dihydrochloride.

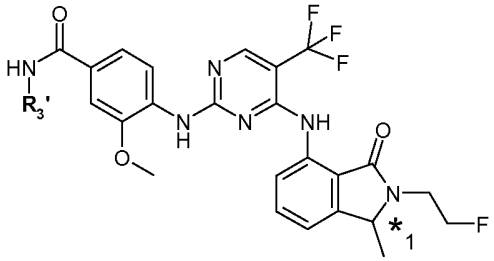
UV max: 282 nm

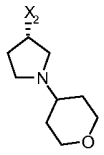
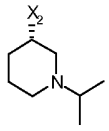
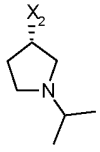
MS (ESI): 602 $(M+H)^+$

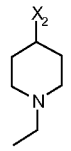
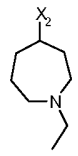
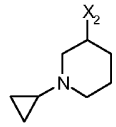
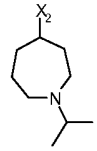
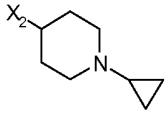
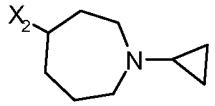
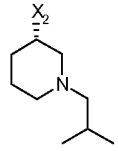
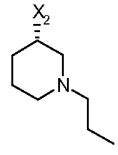
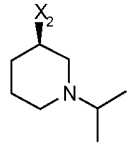
^{1}H-NMR (500MHz): 1.43 (d, 3H), 1.87 - 2.00 (m, 2H), 2.00 - 2.10 (m, 2H), 3.12 - 3.22 (m, 2H), 3.74 (s, 3H), 4.00 - 4.13 (m, 1H), 4.28 - 4.32 (m, 2H), 4.53 - 4.76 (m, 3H), 7.19 - 7.49 (m, 4H), 7.51 (s, 1H), 8.41 (s, 1H), 9.26 (s, 1H), 10.20 - 10.31 (m, 1H), 10.54 (s, 1H), 10.86 (s, 1H)

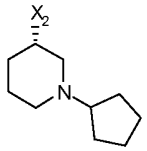
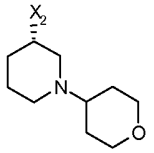
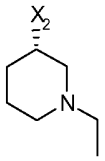
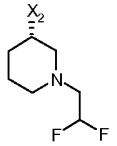
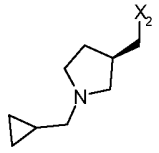
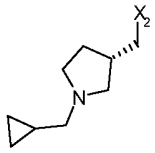
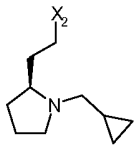
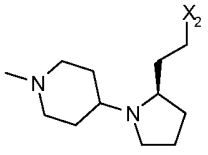
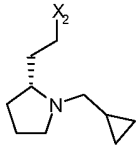
Examples 897-952

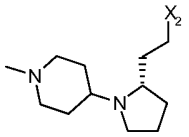
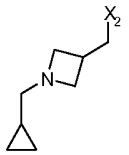
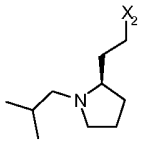
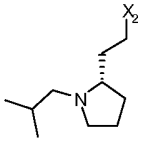
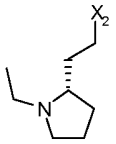
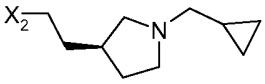
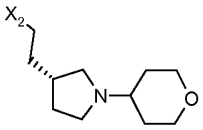
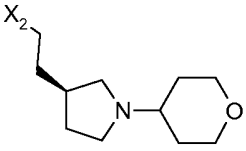
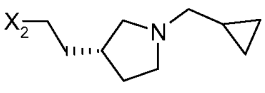
Using a method analogous to that described in Example 53 a primary amine which has another protected amino function in the side chain is coupled to 2-(4-carboxy-2-methoxy-phenylamino)-4-[2-(2-fluoro-ethyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino]-5-trifluoromethyl-pyrimidine Enantiomer 1. The protective group used may be a *tert*-butoxycarbonyl, benzyloxycarbonyl or benzyl group. This protective group is cleaved using a procedure familiar to the skilled man and reductive amination (analogously to Example 639) or alkylation (analogously to method 34 or WO2004052857) are the final steps in this sequence.

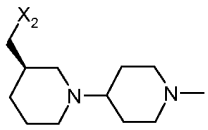
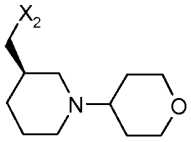
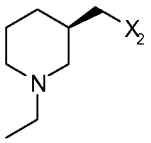
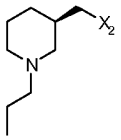
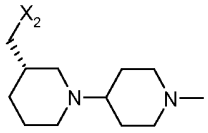
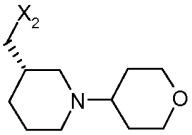
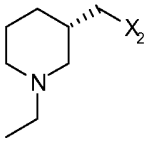
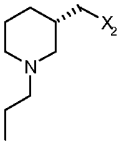
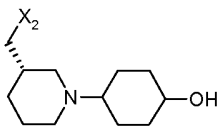


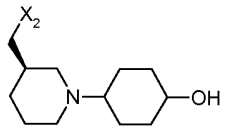
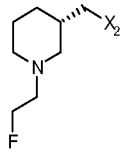
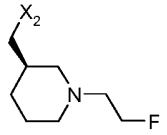
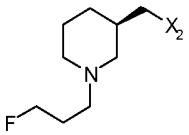
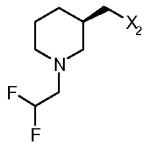
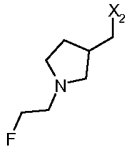
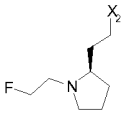
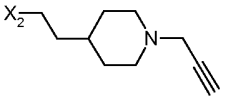
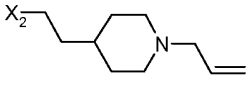
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
897			672
898		322	644
899		326	630

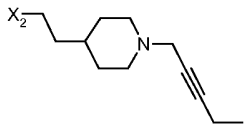
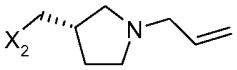
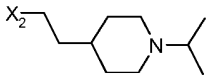
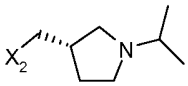
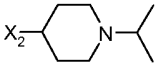
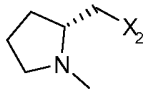
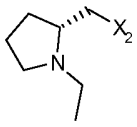
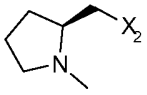
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
900		326	630
901		322	644
902		322	642
903		322	658
904		326	615
905		322	656
906		326	658
907		326	644
908		322	644

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
909		322	670
910		306	686
911		326	630
912			666
913		286, 322	656
914		286, 322	656
915		286, 318	670
916		286, 322	713
917		286, 322	670

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
918		286.3	713
919		286, 322	642
920		286, 322	672
921		286, 322	672
922		286, 322	644
923		286, 322	670
924		286, 322	700
925		286, 322	700
926		286, 322	670

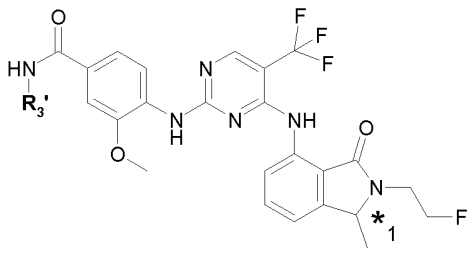
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
927		326	713
928		322-326	700
929		322-326	644
930		322	658
931		322-326	713
932		322	700
933		322-326	644
934		322	658
935		322-326	714

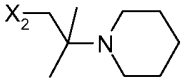
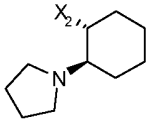
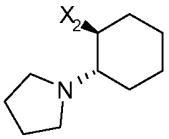
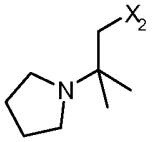
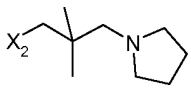
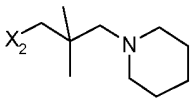
#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
936		322	714
937		322	662
938		322-326	662
939			676
940		322-326	680
941		286, 322	648
942		230, 286, 318	662
943		284, 324	668
944		282, 322	670

#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
945		282, 322	696
946		228, 284, 322	642
947		226, 286, 322	672
948		286, 322	644
949		324, 284	644
950		285, 322	616
951		285, 325	630
952		285, 325	616

Examples 953-958

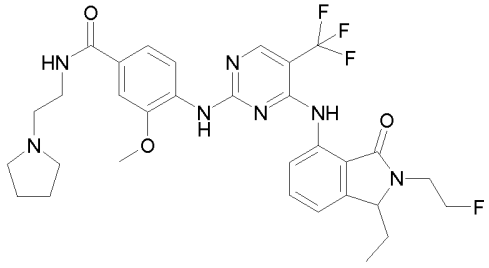
The following compounds are prepared by a method analogous to that described in Example 796:



#	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
953		326, 286	658
954		325, 285	670
955		325, 285	670
956		325, 284	644
957		325, 284	658
958		325, 285	672

Example 959

2-(2-methoxy-4-(2-pyrrolidin-1-yl-ethylcarbamoyl)-phenylamino)-4-(2-(2-fluoro-ethyl)-1-ethyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



The racemic synthesis of the above-mentioned compound is carried out using by a method analogous to that described in Example 53. The corresponding aniline is described in method 22. The two enantiomers are isolated by preparative chromatography:

column: 250 x 4.6 mm CHIRALPAKADH®

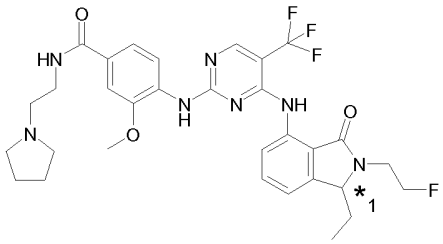
eluant: 25 ethanol / 75 methanol (v/v) (0.03% triethylamine is added to each solvent)

flow rate: 0.5 ml/min

temperature: 20°C

The enantiomer that elutes first is referred to as Enantiomer 1 and bears the symbol *1 in the chemical formula.

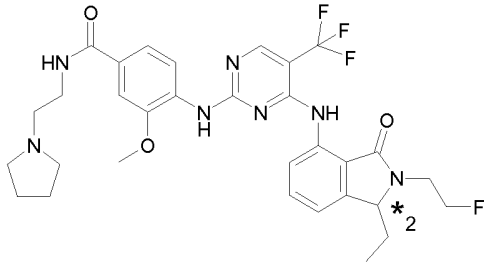
Enantiomer 1



retention time: 9.96 min

The enantiomer that elutes second is referred to as Enantiomer 2 and bears the symbol *2 in the chemical formula.

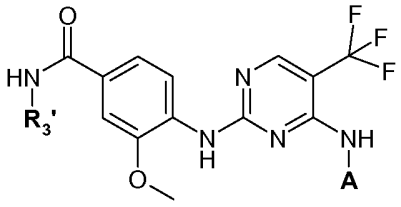
Enantiomer 2

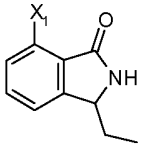
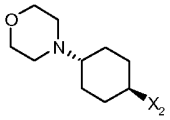
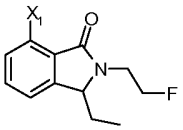
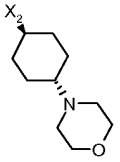
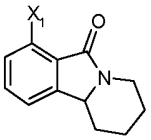
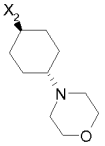
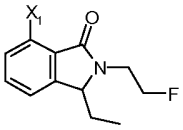
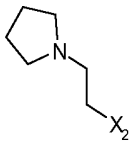
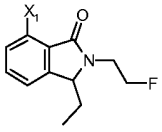
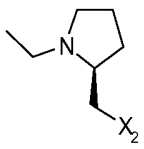
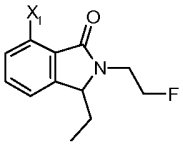
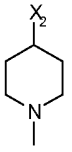


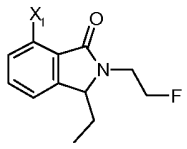
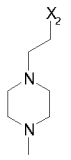
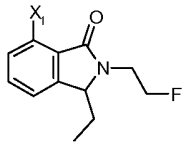
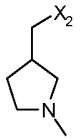
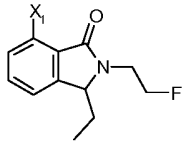
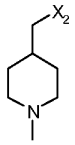
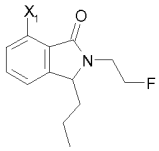
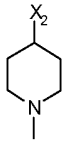
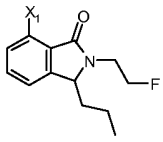
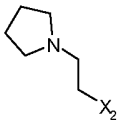
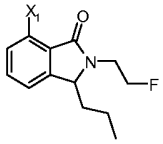
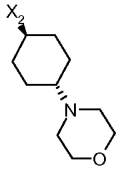
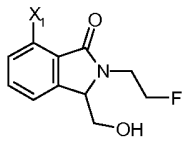
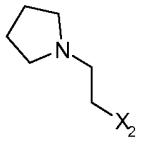
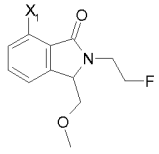
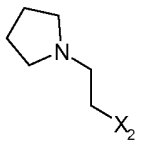
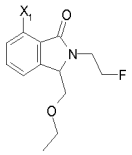
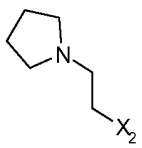
retention time: 12.60 min

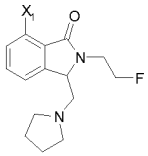
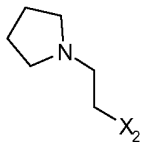
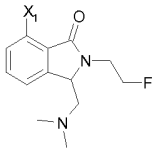
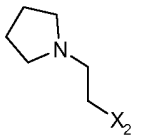
Examples 960-976

The following compounds are prepared by an analogous method to that described in Example 53. The corresponding aniline is described in method 22. The amine used to prepare the amide is commercially obtainable or is described in method 13.



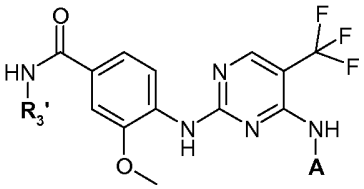
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
960			280, 320	654
961			282, 318	
962			286, 322	680
963			286, 326	630
964			286, 326	644
965			286, 326	630

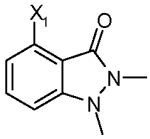
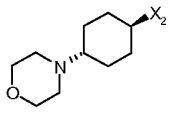
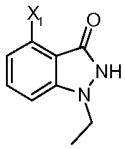
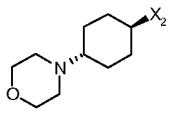
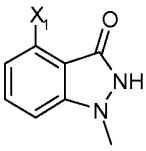
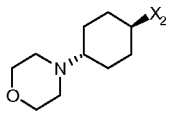
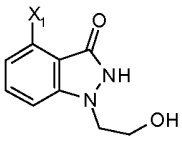
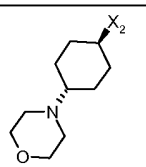
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
966			286, 326	659
967			286, 326	630
968			286, 322	644
969			286, 326	644
970			286, 326	644
971			286, 326	714
972			286, 322	632
973			286, 326	646
974			286, 326	660

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
975			282, 326	685
976			282, 326	659

Examples 977-980

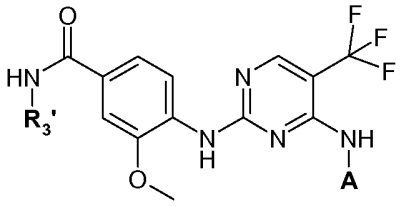
The following compounds are prepared by an analogous method to that described in Example 53. The corresponding aniline is described in method 6. The amine used to prepare the amide is described in method 13.

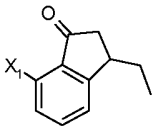
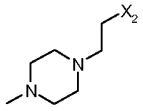
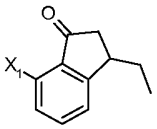
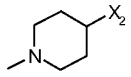
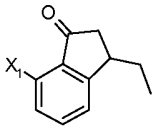
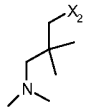
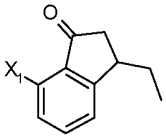
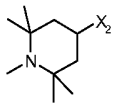
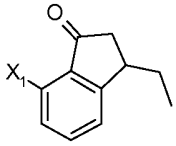
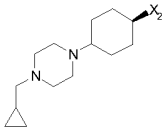
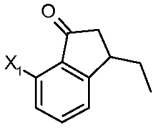
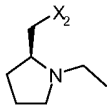


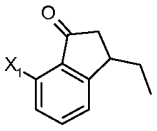
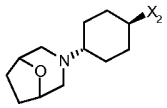
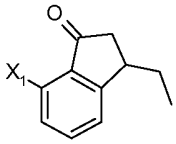
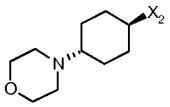
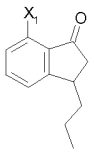
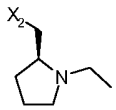
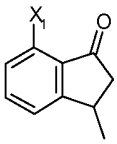
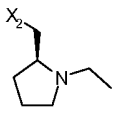
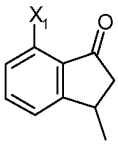
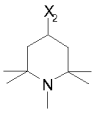
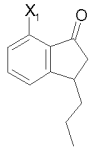
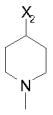
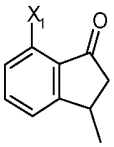
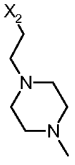
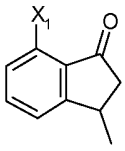
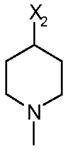
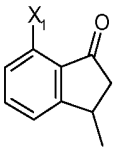
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
977			234, 282, 318	655
978			226, 282, 318	655
979			222, 282, 318	641
980			230, 282, 314	671

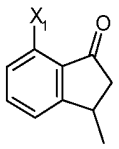
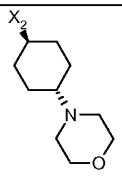
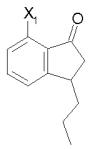
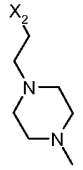
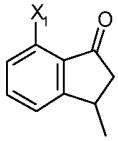
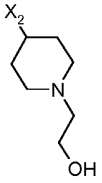
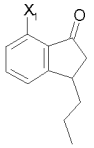
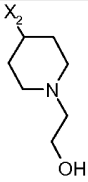
Examples 981-999

The following compounds are prepared by an analogous method to that described in Example 53. The corresponding aniline is described in method 32. The amine used to prepare the amide is commercially obtainable or described in method 13.



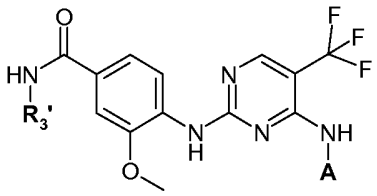
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
981			318	612
982			318	583
983			322	599
984				639
985			286	706
986			322	597

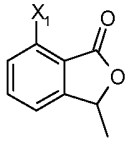
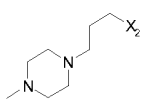
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
987			318	679
988			286	653
989			322	611
990			322	583
991			318	625
992			318	597
993			318	598
994			318	569
995			322	585

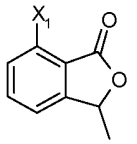
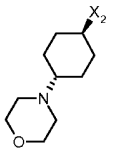
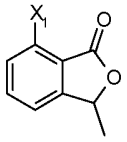
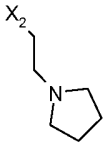
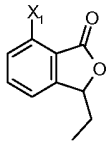
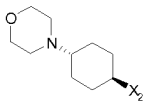
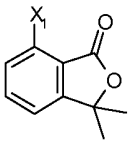
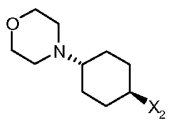
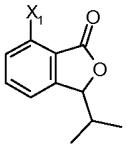
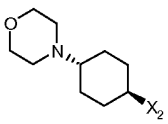
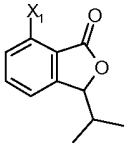
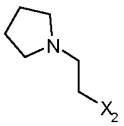
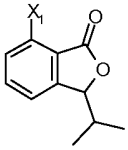
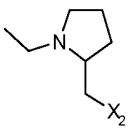
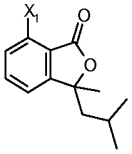
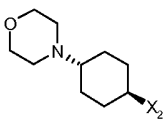
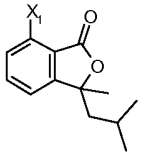
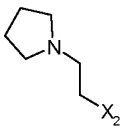
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
996			286	639
997			318	626
998			318	599
999			318	318

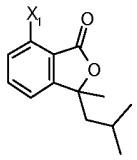
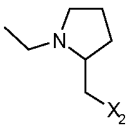
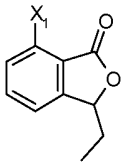
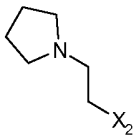
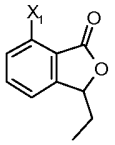
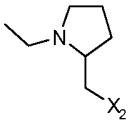
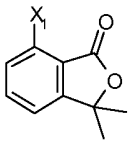
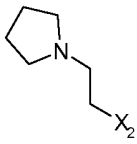
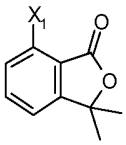
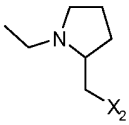
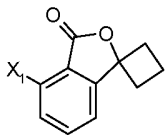
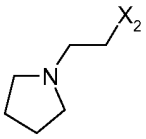
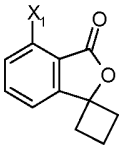
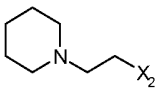
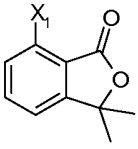
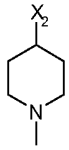
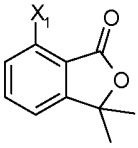
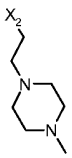
Examples 1000-1024

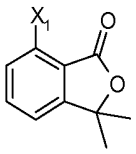
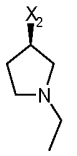
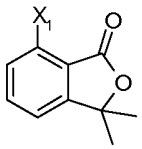
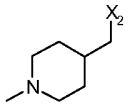
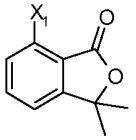
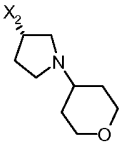
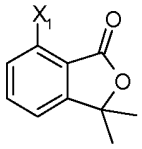
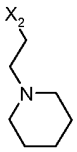
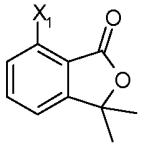
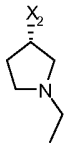
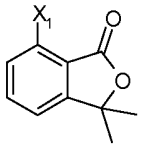
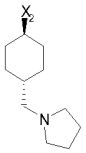
The following compounds are prepared by an analogous method to that described in Example 53. The corresponding aniline is described in method 33. The amine used to prepare the amide is commercially obtainable or described in method 13 or 21.



#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1000			282, 322	614

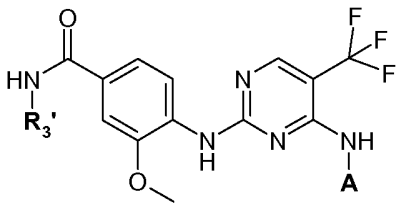
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1001			282, 322	841
1002			282, 326	571
1003			280, 322	655
1004			280, 325	655
1005			280, 322	669
1006			280, 325	599
1007			282, 327	613
1008			280, 322	697
1009			282, 325	627

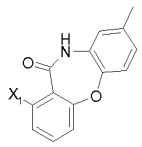
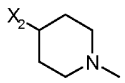
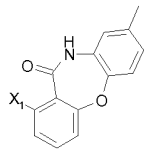
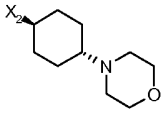
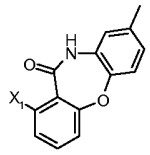
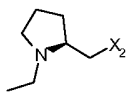
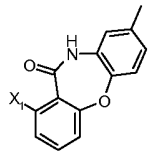
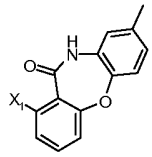
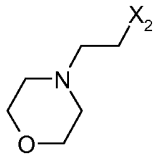
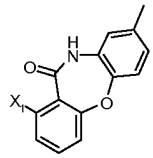
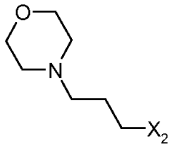
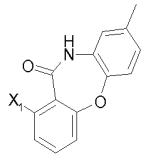
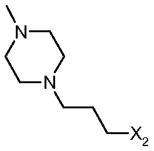
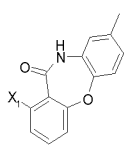
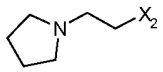
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1010			283, 328	641
1011			280, 325	585
1012			280, 325	599
1013			326, 283	585
1014			282, 327	599
1015			322-326	597
1016			326	611
1017			280, 325	585
1018			280, 325	614

#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1019			280, 325	585
1020			280, 322	599
1021			280, 325	641
1022			280, 325	599
1023			280, 325	585
1024			280, 322	653

Examples 1025-1032

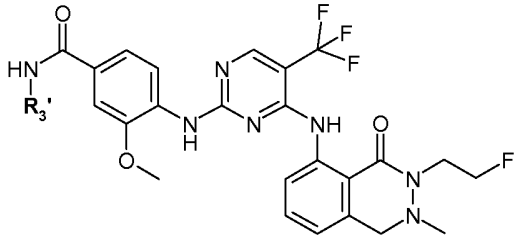
The following compounds are prepared by an analogous method to that described in Example 53. The corresponding aniline is described in method 10. The amine used to prepare the amide is commercially obtainable or described in method 13.

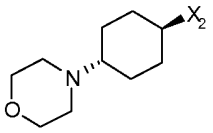
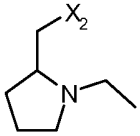
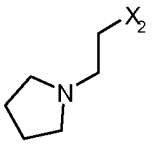


#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1025			318	648
1026			318	359
1027			322	662
1028			322	662
1029			322	664
1030			226, 318	678
1031			226, 318	691
1032			322	648

Examples 1033-1035

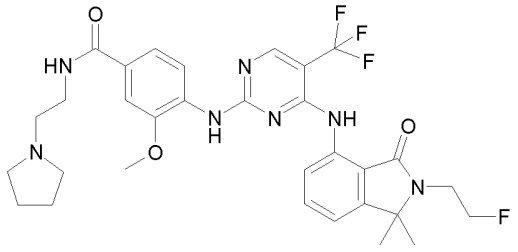
The following compounds are prepared by an analogous method to that described in Example 53. The corresponding aniline is described in method 2. The amine used to prepare the amide is described in method 13.



#	R_3'	MS (ESI) $(M+H)^+$	salt form
1033		701	base
1034		645	formate
1035		631	formate

Example 1036

2-(2-methoxy-4-(2-pyrrolidin-1-yl-ethylcarbamoyl)-phenylamino)-4-(2-(2-fluoro-ethyl)-1,1-dimethyl-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-trifluoromethyl-pyrimidine



The above-mentioned compound is prepared by a method analogous to that described in Example 53. The corresponding aniline is described in method 34. The amine used to prepare the amide is commercially obtainable. The substance is obtained as the dihydrochloride.

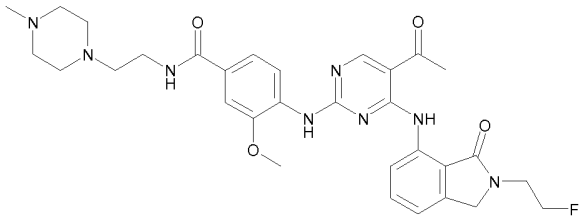
UV max: 326, 286 nm

MS (ESI): 630 $(M+H)^+$

^{1}H-NMR (400MHz): 1.44 - 1.50 (m, 6H), 1.84 - 1.95 (m, 2H), 1.98 - 2.07 (m, 2H), 3.02 - 3.12 (m, 2H), 3.62 - 3.70 (m, 4H), 3.71 - 3.76 (m, 1H), 3.77 - 3.81 (m, 1H), 3.89 (s, 3H), 4.57 - 4.61 (m, 1H), 4.69 - 4.73 (m, 1H), 7.27 - 7.31 (m, 1H), 7.39 - 7.45 (m, 1H), 7.55 - 7.59 (m, 1H), 7.63 - 7.66 (m, 1H), 7.84 - 7.88 (m, 1H), 8.44 - 8.55 (m, 2H), 8.77 - 8.82 (m, 1H), 9.11 - 9.15 (m, 1H), 9.91 - 10.03 (m, 1H), 10.51 - 10.55 (m, 1H)

Example 1037

2-(2-methoxy-4-[2-(4-methyl-piperazin-1-yl)-ethylcarbamoyl]-phenylamino)-4-(2-(2-fluoro-ethyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-acetyl-pyrimidine



50 mg (0.104 mmol) 2-(4-carboxy-2-methoxy-phenylamino)-4-(2-(2-fluoro-ethyl)-3-oxo-2,3-dihydro-1*H*-isoindol-4-ylamino)-5-acetyl-pyrimidine (prepared by an analogous process to that described in Example 622 or 623) are dissolved in 0.5 ml of dimethylformamide and combined with 72 µl (0.520 mmol) and 34 mg (0.104 mmol) *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate. After stirring for 20 min at 20 °C, 23 mg (0.156 mmol) 2-(4-methylpiperazin-1-yl)-ethylamine are added. The reaction is completed after 2 h at 20 °C. Then the solvent is eliminated *in vacuo* and the residue is purified by column chromatography. The carrier used is C18-RP-silica gel and a gradient is run through within 20 min which consists of 95% water and 5% acetonitrile at the starting point and consists of 5% water and 95% acetonitrile at the finishing point. 0.1% formic acid are added to both the water and to the acetonitrile. The suitable fractions are combined with 500 µl of a 1 M aqueous hydrochloric acid and freeze-dried. The product is obtained as the trihydrochloride.

UV max: 326 nm

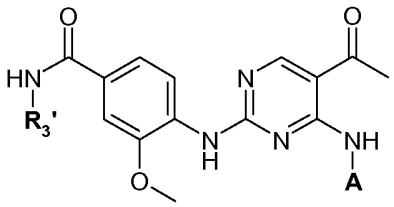
MS (ESI): 605 $(M+H)^+$

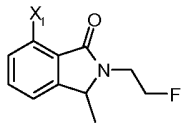
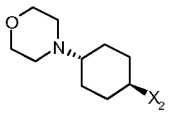
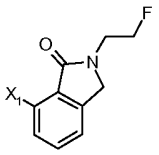
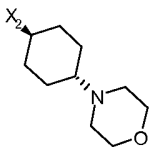
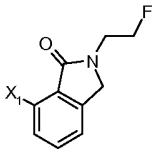
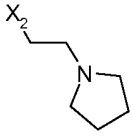
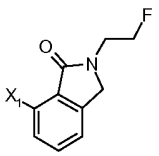
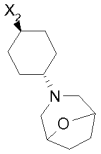
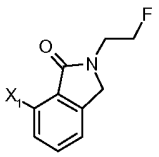
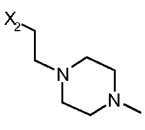
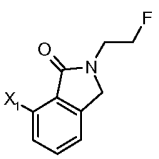
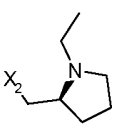
^{1}H-NMR (500MHz): 2.53-2.58 (m, 3H), 2.80-2.92 (m, 3H), 3.62-3.88 (m, 9H), 3.88-4.01 (m, 4H), 4.54 (s, 2H), 4.58-4.66 (m, 1H), 4.69-4.77 (m, 1H), 7.14-7.32 (m, 1H), 7.32-7.50 (m, 1H), 7.50-7.59 (m, 1H), 7.63-7.75 (m, 1H), 7.78-8.01 (m, 1H), 8.29-8.60 (m, 1H), 8.73-8.99 (m, 2H), 9.03-9.18 (m, 1H), 12.31-12.41 (m, 1H)

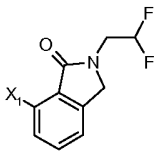
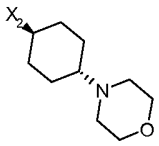
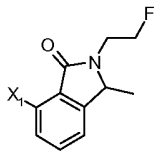
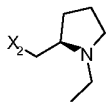
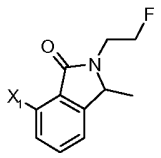
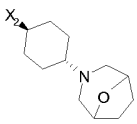
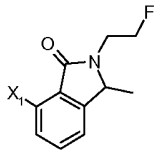
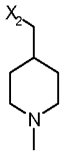
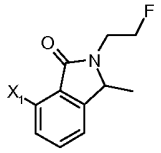
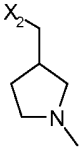
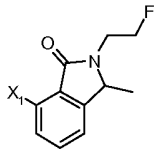
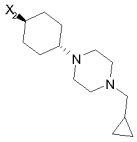
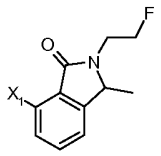
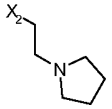
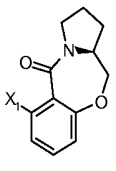
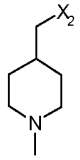
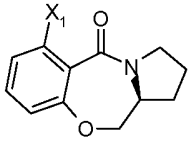
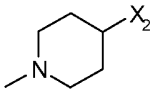
Examples 1038-1060

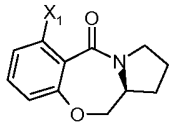
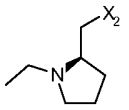
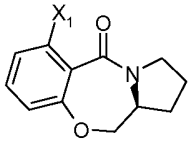
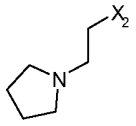
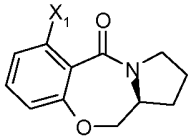
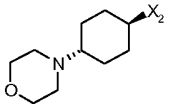
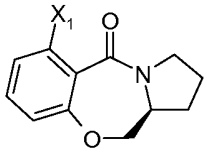
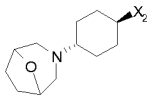
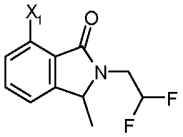
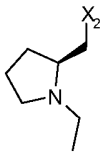
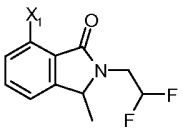
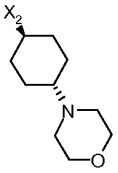
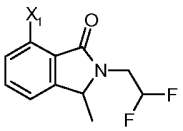
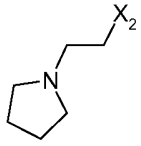
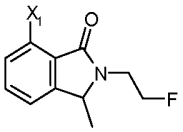
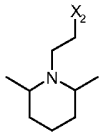
The following compounds are prepared by an analogous method to that described in Example 1037. The aniline used is described in method 28.

The amine used to prepare the amide is commercially obtainable or described in method 13.



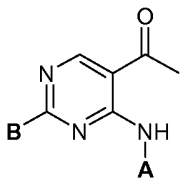
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1038			326	660
1039			326	646
1040			328	576
1041			318	672
1042			326	605
1043			330	590

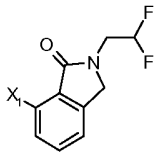
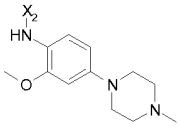
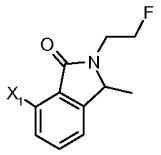
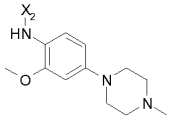
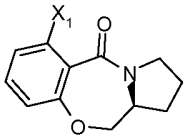
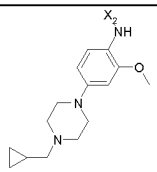
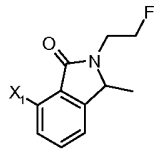
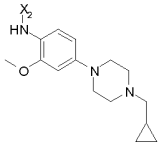
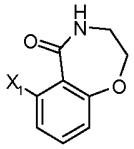
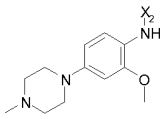
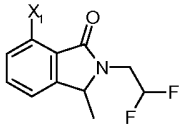
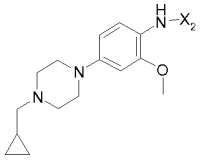
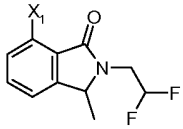
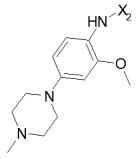
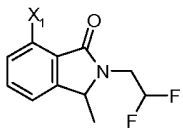
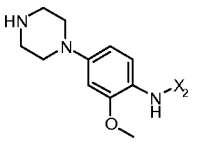
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1044			318	663
1045			330	604
1046			326	686
1047			326	604
1048			330	590
1049			326	713
1050			330	590
1051			250	614
1052			334-338	600

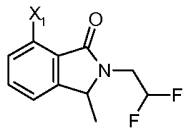
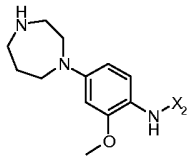
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1053			334-338	614
1054			338	600
1055			338	670
1056			334	696
1057			330	622
1058			327	340
1059			330	608
1060			330	632

Examples 1061-1069

The following compounds are prepared by an analogous method to that described in Example 622 or 623. The corresponding aniline is described in method 28.

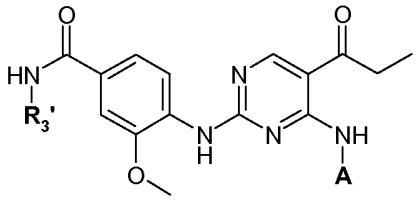


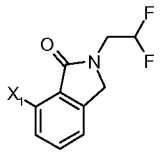
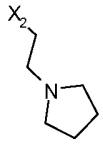
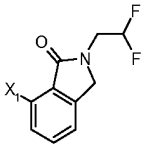
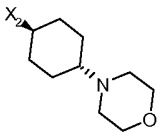
#	A	B	UV max [nm]	MS (ESI) $(M+H)^+$
1061			254, 316	552
1062			254, 314	548
1063			250	598
1064			254, 318	588
1065			250	518
1066			252, 318	606
1067			250, 310	566
1068			254, 318	552

#	A	B	UV max [nm]	MS (ESI) $(M+H)^+$
1069			262; 314-318	566

Examples 1070-1071

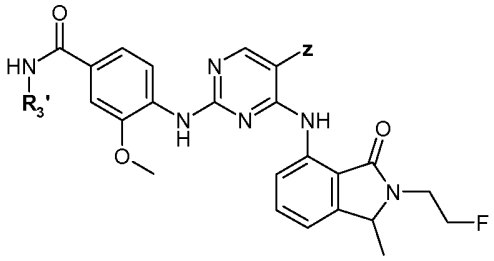
The following compounds are prepared by an analogous method to that described in Example 622 or 623 and 53. The corresponding aniline is described in method 28. The amine used to prepare the amide is commercially obtainable or described in method 13.

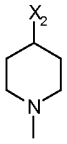
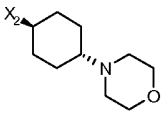
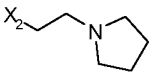
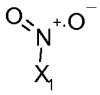
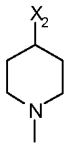
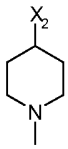
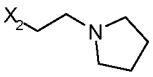
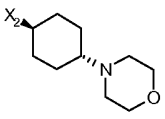
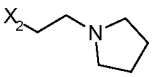
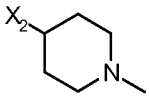


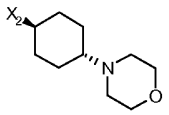
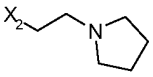
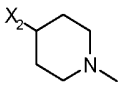
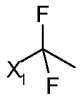
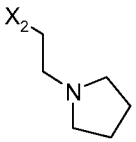
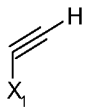
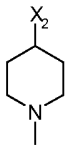
#	A	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1070			330	608
1071			330	678

Examples 1072-1085

The following compounds are prepared by an analogous method to that described in Example 1037. The corresponding aniline is described in method 28. The amine used to prepare the amide is commercially obtainable or described in method 13.



#	Z	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1072			285, 320	674
1073			326	663
1074			306	596
1075			326	593
1076			262	596
1077			326	593
1078			318	652
1079			325	582
1080			319	582

#	Z	R_3'	UV max [nm]	MS (ESI) $(M+H)^+$
1081			302	666
1082			322	626
1083			318	626
1084			286, 318	612
1085			280, 325	572

Biological properties

As demonstrated by DNA staining followed by FACS analysis, the inhibition of proliferation brought about by the compounds according to the invention is mediated above all by the arrest of the cells in the G2/M phase of the cell cycle. The cells arrest, depending on the type of cell used, for a specific length of time in this cell cycle phase before programmed cell death is initiated. An arrest in the G2/M phase of the cell cycle may be initiated e.g. by the inhibition of specific cell cycle kinases. On the basis of their biological properties the compounds of general formula I according to the invention, their isomers and the physiologically acceptable salts thereof are suitable for treating diseases characterised by excessive or anomalous cell proliferation.

Such diseases include for example: viral infections (e.g. HIV and Kaposi's sarcoma); inflammatory and autoimmune diseases (e.g. colitis, arthritis, Alzheimer's disease, glomerulonephritis and wound healing); bacterial, fungal and/or parasitic infections;

leukaemias, lymphomas and solid tumours; skin diseases (e.g. psoriasis); bone diseases; cardiovascular diseases (e.g. restenosis and hypertrophy). They are also useful for protecting proliferating cells (e.g. hair, intestinal, blood and progenitor cells) from DNA damage caused by radiation, UV treatment and/or cytostatic treatment (Davis et al., 2001). The new compounds may be used for the prevention, short- or long-term treatment of the above-mentioned diseases, also in combination with other active substances used for the same indications, e.g. cytostatics, steroids or antibodies.

The activity of the compounds according to the invention on various kinases, for example on serine-threonine kinase PLK-1, was determined by in vitro kinase assays with recombinantly produced protein. In this assay the compounds exhibit a good to very good effect on PLK1, i.e. for example an IC50 value of less than 1 µmol/L, usually less than 0.1 µmol/L.

Example PLK-1 Kinaseassay

Recombinant human PLK1 enzyme linked to GST at its N-terminal end is isolated from insect cells infected with baculovirus (Sf21). Purification is carried out by affinity chromatography on glutathione sepharose columns.

$4x10^7$ Sf21 cells (*Spodoptera frugiperda*) in 200 ml of Sf-900 II Serum free insect cell medium (Life Technologies) are seeded in a spinner flask. After 72 hours' incubation at 27°C and 70 rpm, $1x10^8$ Sf21 cells are seeded in a total of 180 ml medium in a new spinner flask. After another 24 hours, 20 ml of recombinant Baculovirus stock suspension are added and the cells are cultivated for 72 hours at 27°C at 70 rpm. 3 hours before harvesting, okadaic acid is added (Calbiochem, final concentration 0.1 µM) and the suspension is incubated further. The cell number is determined, the cells are removed by centrifuging (5 minutes, 4°C, 800 rpm) and washed 1x with PBS (8 g NaCl/l, 0.2 g KCl/l, 1.44 g Na_2HPO_4/l, 0.24 g KH_2PO4/l). After centrifuging again the pellet is flash-frozen in liquid nitrogen. Then the pellet is quickly thawed and resuspended in ice-cold lysing buffer (50 mM HEPES pH 7.5, 10 mM $MgCl_2$, 1 mM DTT, 5 µg/ml leupeptin, 5 µg/ml aprotinin, 100 µM NaF, 100 µM PMSF, 10 mM ß-glycerolphosphate, 0.1 mM Na_3VO_4, 30 mM 4-nitrophenylphosphate) to give $1x10^8$ cells/ 17.5 ml. The cells are lysed for 30 minutes on ice. After removal of the cell debris by centrifugation (4000 rpm, 5 minutes) the clear supernatant is combined with glutathione sepharose beads (1 ml resuspended and washed beads per 50 ml of supernatant) and the mixture is incubated for 30 minutes at 4°C on a rotating board.

Then the beads are washed with lysing buffer and the recombinant protein is eluted from the beads with 1 ml eluting buffer/ ml resuspended beads (eluting buffer: 100 mM Tris/HCl pH=8.0, 120 mM NaCl, 20 mM reduced glutathione (Sigma G-4251), 10 mM $MgCl_2$, 1 mM DTT). The protein concentration is determined by Bradford Assay.

Assay

The following components are combined in a well of a 96-well round-bottomed dish (Greiner bio-one, PS Microtitre plate No.650101):

- 10 µl of the compound to be tested in variable concentrations (e.g. beginning at 300 µM, and dilution to 1:3) in 6% DMSO, 0.5 mg/ml casein (Sigma C-5890), 60 mM ß-glycerophosphate, 25 mM MOPS pH=7.0, 5 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT
- 20 µl substrate solution (25 mM MOPS pH=7.0, 15 mM $MgCl_2$, 1 mM DTT, 2.5 mM EGTA, 30 mM ß-glycerophosphate, 0.25 mg/ml casein)
- 20 µl enzyme dilution (1:100 dilution of the enzyme stock in 25 mM MOPS pH=7.0, 15 mM $MgCl_2$, 1 mM DTT)
-10 µl ATP solution (45 µM ATP with $1.11x10^6$ Bq/ml gamma-P33-ATP).

The reaction is started by adding the ATP solution and continued for 45 minutes at 30 °C with gentle shaking (650 rpm on an IKA Schüttler MTS2). The reaction is stopped by the addition of 125 µl of ice-cold 5% TCA per well and incubated on ice for at least 30 minutes. The precipitate is transferred by harvesting onto filter plates (96-well microtitre filter plate: UniFilter-96, GF/B; Packard; No.6005177), then washed four times with 1% TCA and dried at 60°C. After the addition of 35µl scintillation solution (Ready-Safe; Beckmann) per well the plate is sealed shut with sealing tape and the amount of P33 precipitated is measured with the Wallac Betacounter. The measured data are evaluated using the standard Graphpad software (Levenburg-Marquard Algorhythmus).

The anti-proliferative activity of the compounds according to the invention is determined in the cytotoxicity test on cultivated human tumour cells and/or in a FACS analysis, for example on HeLa S3 cells. In both test methods the compounds exhibit good to very good activity, i.e. for example an EC50 value in the HeLa S3 cytotoxicity test of less than 5 µmol/L, generally less than 1 µmol/L.

Measurement of cytotoxicity on cultivated human tumour cells

To measure cytotoxicity on cultivated human tumour cells, cells of cervical carcinoma tumour cell line HeLa S3 (obtained from American Type Culture Collection (ATCC)) are cultivated in Ham´s F12 Medium (Life Technologies) and 10% foetal calf serum

(Life Technologies) and harvested in the log growth phase. Then the HeLa S3 cells are placed in 96-well plates (Costar) at a density of 1000 cells per well and incubated overnight in an incubator (at 37°C and 5 % CO2), while on each plate 6 wells are filled with medium alone (3 wells as the medium control, 3 wells for incubation with reduced AlamarBlue reagent). The active substances are added to the cells in various concentrations (dissolved in DMSO; DMSO final concentration: 0.1%) (in each case as a triple measurement). After 72 hours incubation 20 µl AlamarBlue reagent (AccuMed International) are added to each well, and the cells are incubated for a further 5-7 hours. As a control, 20 µl reduced AlamarBlue reagent is added to each of 3 wells (AlamarBlue reagent, which is autoclaved for 30 min). After incubation the colour change of the AlamarBlue reagent in the individual wells is determined in a Perkin Elmer fluorescence spectrophotometer (excitation 530 nm, emission 590 nm, slits 15, integrate time 0.1). The amount of AlamarBlue reagent reacted represents the metabolic activity of the cells. The relative cell activity is calculated as a percentage of the control (HeLa S3 cells without inhibitor) and the active substance concentration which inhibits the cell activity by 50% (IC50) is derived. The values are calculated from the average of three individual measurements - with correction of the dummy value (medium control).

FACS Analysis

Propidium iodide (PI) binds stoichiometrically to double-stranded DNA, and is thus suitable for determining the proportion of cells in the G1, S, and G2/M phase of the cell cycle on the basis of the cellular DNA content. Cells in the G0 and G1 phase have a diploid DNA content (2N), whereas cells in the G2 or mitosis phase have a 4N DNA content.

For PI staining, for example, $1x10^6$ HeLa S3 cells are seeded onto a 75 cm2 cell culture flask, and after 24 h either 0.1 % DMSO is added as control or the substance is added in various concentrations (in 0.1% DMSO). The cells are incubated for 24 h with the substance or with DMSO before the cells are washed 2 x with PBS and then detached with trypsin /EDTA. The cells are centrifuged (1000 rpm, 5 min, 4°C), and the cell pellet is washed 2 x with PBS before the cells are resuspended in 0.1 ml PBS. Then the cells are fixed with 80% ethanol for 16 hours at 4°C or alternatively for 2 hours at –20°C. The fixed cells are centrifuged (1000 rpm, 5min, 4°C), washed with PBS and then centrifuged again. The cell pellet is resuspended in 2 ml 0.25% Triton X-100 in PBS, and incubated on ice for 5 min before 5 ml PBS are added and the mixture is centrifuged again. The cell pellet is resuspended in 350 µl PI staining solution (0.1 mg/ml RNase A (Sigma, No. R-4875), 10 µg/ml prodium iodide (Sigma,

No. P-4864) in 1 x PBS). The cells are incubated for 20 min in the dark with the staining buffer before being transferred into sample measuring containers for the FACS scan. The DNA measurement is carried out in a Becton Dickinson FACS Analyzer, with an argon laser (500 mW, emission 488 nm), and the DNA Cell Quest Programme (BD). The logarithmic PI fluorescence is determined with a band-pass filter (BP 585/42). The cell populations in the individual cell cycle phases are quantified using the ModFit LT Programme made by Becton Dickinson.

The compounds according to the invention are also tested accordingly on other tumour cells. For example, these compounds are effective on carcinomas of all kinds of tissue (e.g. breast (MCF7); colon (HCT116), head and neck (FaDu), lung (NCI-H460), pancreas (BxPC-3), prostate (DU145)), sarcomas (e.g. SK-UT-1B), leukaemias and lymphomas (e.g. HL-60; Jurkat, THP-1) and other tumours (e.g. melanomas (BRO), gliomas (U-87MG)) and could be used for such indications. This is evidence of the broad applicability of the compounds according to the invention for the treatment of all kinds of tumour types.

The compounds of general formula (I) may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances.

Suitable preparations include for example tablets, capsules, suppositories, solutions, particularly solutions for injection (s.c., i.v., i.m.) and infusion, elixirs, emulsions or dispersible powders. The content of the pharmaceutically active compound(s) should be in the range from 0.1 to 90 wt.-%, preferably 0.5 to 50 wt.-% of the composition as a whole, i.e. in amounts which are sufficient to achieve the dosage range specified below. The doses specified may, if necessary, be given several times a day.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example

collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection and infusion are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, organic solvents may optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules. Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof. Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose) emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

The preparations are administered by the usual methods, preferably by oral or transdermal route, most preferably by oral route. For oral administration the tablets may, of course contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various

additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

For parenteral use, solutions of the active substances with suitable liquid carriers may be used.
The dosage for intravenous use is from 1 - 1000 mg per hour, preferably between 5 and 500 mg per hour.

However, it may sometimes be necessary to depart from the amounts specified, depending on the body weight, the route of administration, the individual response to the drug, the nature of its formulation and the time or interval over which the drug is administered. Thus, in some cases it may be sufficient to use less than the minimum dose given above, whereas in other cases the upper limit may have to be exceeded. When administering large amounts it may be advisable to divide them up into a number of smaller doses spread over the day.

The formulation examples which follow illustrate the present invention without restricting its scope:

Examples of pharmaceutical formulations

A) Tablets	per tablet
active substance	100 mg
lactose	140 mg
corn starch	240 mg
polyvinylpyrrolidone	15 mg
magnesium stearate	5 mg
	500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B) Tablets	per tablet
active substance	80 mg
lactose	55 mg
corn starch	190 mg
microcrystalline cellulose	35 mg
polyvinylpyrrolidone	15 mg
sodium-carboxymethyl starch	23 mg
magnesium stearate	2 mg
	400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodiumcarboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

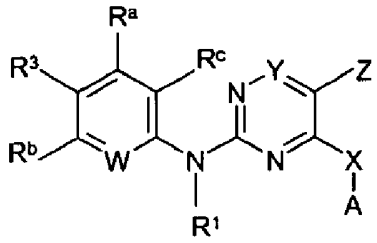
C) Ampoule solution

active substance	50 mg
sodium chloride	50 mg
water for inj.	5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

P A T E N T K R A V

1. Forbindelse ifølge den generelle formel (1),



(1)

hvor

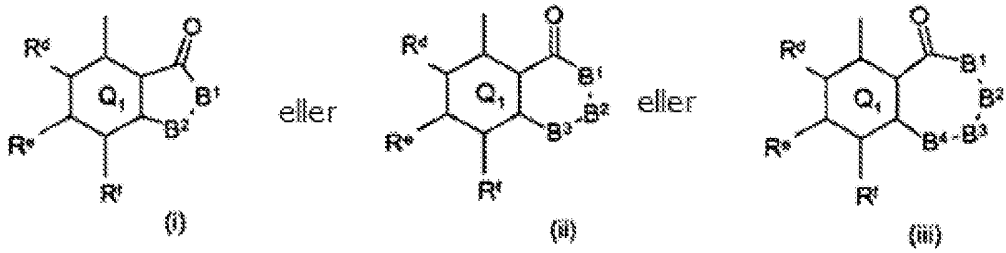
W betyder N eller C-R^2,

X betyder -NR^{1a}, O eller S,

Y betyder CH eller N,

Z betyder halogen-C_{1-3}alkyl-, -COH, -C(=O)-C_{1-3}alkyl, -C(=O)-C_{2-3}alkenyl, -C(=O)-C_{2-3}alkynyl, -C(=O)C_{1-3}alkyl-halogen og pseudohalogen;

A er valgt blandt formlerne (i), (ii) eller (iii)



Q_1 betyder mono- eller bicykliske arylforbindelser;

B^1, B^2, B^3 og B^4 betyder hhv. uafhængigt af hinanden C-R^gR^h, N-R^i, O eller S, hvor tilstødende B^1 - B^4 hhv. ikke betyder -O-;

R^1 og R^{1a} betyder hhv. uafhængigt af hinanden hydrogen eller methyl,

R^2 betyder en rest valgt fra gruppen bestående af hydrogen, halogen, -OR^4, -C(=O)R^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5, -$NR^4SO_2R^5$, -N=CR^4R^5, -C=NR^i, -SR^4, -SOR^4, -SO_2R^4, -$SO_2NR^4R^5$ og pseudohalogen eller en eventuelt mono- eller polysubstitueret rest valgt fra gruppen bestående af C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af halogen, -NO_2, -OR^4, -C(=O)R^4, -C(=O)OR^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5, -NR^4C(=O)OR^5, -NR^4C(=O)NR^5R^6, -$NR^4SO_2R^5$, -N=CR^4R^5, -SR^4, -SOR^4, -SO_2R^4, -$SO_2NR^4R^5$, -$NR^4SO_2NR^5R^6$, -$OSO_2NR^5R^6$ og pseudohalogen;

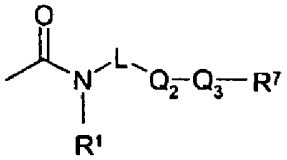
R^a, R^b, R^c, R^d, R^e, R^f, R^g og R^h hhv. uafhængigt af hinanden betyder en rest valgt fra gruppen bestående af hydrogen, halogen, =O, -NO_2, -OR^4, -C(=O)R^4, -C(=O)OR^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5, -NR^4C(=O)OR^5, -NR^4C(=O)NR^5R^6, -$NR^4SO_2R^5$, -N=CR^4R^5, -C=NR^i, -SR^4, -SOR^4, -SO_2R^4, -$SO_2NR^4R^5$, -$NR^4SO_2NR^5R^6$, -$OSO_2NR^5R^6$ og pseudohalogen; eller en eventuelt mono- eller polysubstitueret rest valgt fra gruppen bestående af C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af halo-

gen, R^8, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ og pseudohalogen; og eventuelt kan R^g og R^h, der er placeret på det samme eller tilstødende C-atomer, være forbundet i en hvilken som helst kombination med en fælles mættet eller delvist umættet 3-5-leddet alkylbro, som eventuelt kan indeholde én til to heteroatomer;

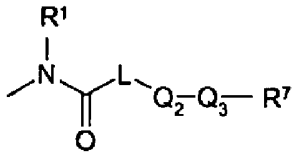
R^i betyder en rest valgt fra gruppen bestående af hydrogen, =O, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ og pseudohalogen; eller en eventuelt mono- eller polysubstitueret rest valgt fra gruppen bestående af C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af halogen, R^8,$-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, -NR4C(=O)NR^5R^6, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ og pseudohalogen;

og eventuelt kan R^i, der er placeret på tilstødende N-atomer, være forbundet med hinanden eller R^i kan, sammen med R^g eller R^h, der er placeret på tilstødende C-atomer, være forbundet i en hvilken som helst kombination med en fælles mættet eller delvist umættet 3-5-leddet alkylbro, der eventuelt kan indeholde en til to heteroatomer;

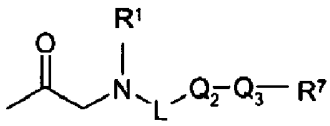
R^3 er valgt blandt formlerne (iv) - (x),



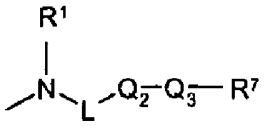
(iv)



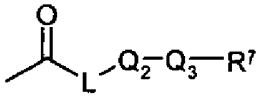
(v)



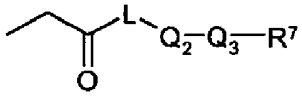
(vi)



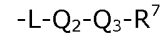
(vii)



(viii)



(ix)



(x)

R^4, R^5 og R^6 hhv. uafhængigt af hinanden betyder hydrogen eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af C_{3-10}cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

L en binding eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-16}alkyl, C_{2-16}alkenyl, C_{2-16}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og hete-

roaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af halogen, $-NO_2$, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

Q_2 og Q_3 hhv. uafhængigt af hinanden betyder en binding eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-16}alkyl, C_{2-16}alkenyl, C_{2-16}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og heteroaryl hvor substituenten(erne) kan være ens eller forskellig og valgt fra gruppen bestående af halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

R^7 betyder hydrogen eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-16}alkyl, C_{2-16}alkenyl, C_{2-16}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten(erne) kan være ens eller forskellig og valgt fra gruppen bestående af halogen-, NO_2, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8COR^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NRC(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

R^8, R^9 og R^{10} betyder hhv. uafhængigt af hinanden hydrogen eller en rest valgt fra gruppen bestående af eventuelt substitueret C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten(erne) kan være ens eller forskellig og valgt fra gruppen bestående af halogen, methyl, ethyl, amino, methylamino, dimethylamino, -OH og pseudohalogen;

hvor

aryl er monocykliske eller bicykliske ringe med 6-12 kulstofatomer;

heteroaryl er monocykliske eller bicykliske ringe, hvilke i stedet for et eller flere kulstofatomer indeholder en eller flere ens eller forskellige heteroatomer;

heterocyclyl er mættede eller umættede, ikke aromatiske mono-, bicykliske, forbundne eller spirocykliske bicykliske ringe omfattende 5-12 kulstofatomer,

hvilke i stedet for en eller flere kulstofatomer bærer heteroatomer som nitrogen, oxygen eller svovl;

eventuelt i form af tautomerer, racemater, enantiomerer, diastereomerer og blandinger, såvel som eventuelt farmakologisk acceptable syreadditionssalte deraf.

2. Forbindelse ifølge krav 1 ifølge den generelle formel (1), hvor

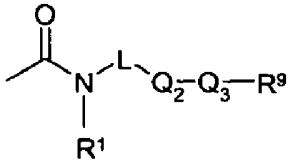
W betyder C-R^2 og de øvrige rester er som defineret i ovenstående.

3. Forbindelse ifølge krav 1 eller 2, hvor

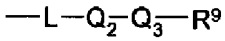
X betyder $-NR^{1a}$ eller oxygen,

R^1 og R^{1a} betyder hydrogen;

R^3 betyder formel (iv) eller (x),



(iv)



(x)

og de øvrige rester er som defineret i ovenstående.

4. Forbindelse ifølge krav 1-3, hvor

Y betyder CH og

Q_1 betyder monocykliske arylforbindelser

og de øvrige rester er som defineret i ovenstående.

5. Forbindelse ifølge krav 1-4, hvor

R^c betyder en rest valgt fra gruppen bestående af hydrogen, -F, -Cl, methyl og ethyl

og de øvrige rester er som defineret i ovenstående.

6. Forbindelse ifølge krav 1-5, hvor

R^a og R^b betyder hhv. uafhængigt af hinanden hydrogen eller fluor;

eller en eventuelt mono- eller polysubstitueret rest valgt fra gruppen bestående af C_{1-2}alkyl, C_2alkenyl, C_2alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af hydrogen, halogen, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^5$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4$, $-SO_2NR^4R^5$, $-OSO_2NR^4R^5$ og pseudohalogen

og de øvrige rester er som defineret i ovenstående.

7. Forbindelse ifølge krav 1-6, hvor

R^a og R^b betyder hhv. uafhængigt af hinanden hydrogen eller fluor og de

øvrige rester er som defineret i ovenstående.

8. Forbindelse - eller farmaceutisk virksomme salte deraf - ifølge krav 1 - 7 som lægemiddel.

9. Forbindelse - eller farmaceutisk virksomme salte deraf - ifølge 1-7 til fremstilling af et lægemiddel med antiproliferativ virkning.

10. Forbindelse - eller farmaceutisk virksomme salte deraf – ifølge krav 1-7 til fremstilling af et lægemiddel med antiproliferativ virkning med en selektiv, kinaseinhiberende virkningsmekanisme.

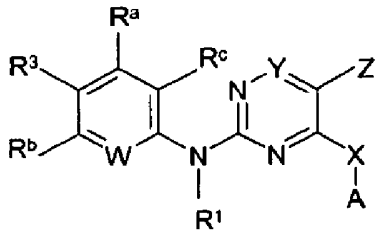
11. Forbindelse - eller farmaceutisk virksomme salte deraf - ifølge krav 1-7 til fremstilling af et lægemiddel med antiproliferativ virkning med en PLK-inhiberende virkningsmekanisme.

12. Farmaceutisk præparat indeholdende som virkestof én eller flere forbindelser ifølge den generelle formel (1) ifølge et hvilket som helst af krav 1-7 eller fysiologisk acceptable salte deraf eventuelt i kombination med sædvanlige hjælpe- og/eller bærestoffer.

13. Anvendelse af en forbindelse ifølge krav 1 - 7 til fremstilling af et lægemiddel til behandling og/eller forbyggelse af kræft, infektioner, inflammatoriske- og autoimmune

sygdomme.

14. Farmaceutisk fremstilling omfattende en forbindelse ifølge den generelle formel (1)



(1)

hvor

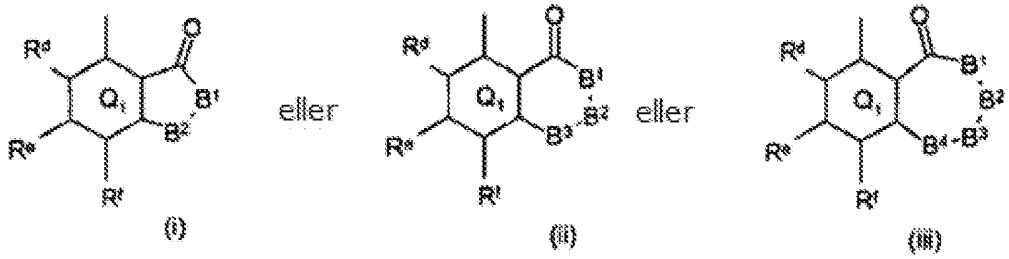
W betyder N eller C-R^2,

X betyder -NR^{1a}, O eller S,

Y betyder CH eller N,

Z betyder halogen-C_{1-3}alkyl-, -COH, -C(=O)-C_{1-3}alkyl, -C(=O)-C_{2-3}alkenyl, -C(=O)-C_{2-3}alkynyl, -C(=O)C_{1-3}alkyl-halogen og pseudohalogen;

A er valgt blandt formlerne (i), (ii) eller (iii)



Q_1 betyder mono- eller bicykliske arylforbindelser;

B^1, B^2, B^3 og B^4 hhv. uafhængigt af hinanden betyder C-R^gR^h, N-R^i, O eller S, hvor tilstødende B^1 - B^4 ikke alle betyder -O-;

R^1 og R^{1a} hhv. uafhængigt af hinanden betyder hydrogen eller methyl,

R^2 betyder en rest valgt fra gruppen bestående af hydrogen, halogen, -OR^4, -C(=O)R^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5, -$NR^4SO_2R^5$, -N=CR^4R^5, -C=NR^i, -SR^4, -SOR^4, -SO_2R^4, -$SO_2NR^4R^5$ og pseudohalogen eller en eventuelt mono- eller polysubstitueret rest valgt fra gruppen bestående af C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og er valgt fra gruppen bestående af halogen, -NO_2, -OR^4, -C(=O)R^4, -C(=O)OR^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5, -NR^4C(=O)OR^5, -NR^4C(=O)NR^5R^6, -$NR^4SO_2R^5$, -N=CR^4R^5, -SR^4, -SOR^4, -SO_2R^4, -$SO_2NR^4R^5$, -$NR^4SO_2NR^5R^6$, -$OSO_2NR^5R^6$ og pseudohalogen;

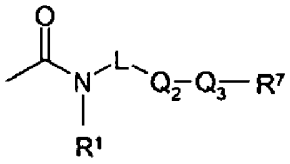
R^a, R^b, R^c, R^d, R^e, R^f, R^g og R^h hhv. uafhængigt af hinanden betyder en rest valgt fra gruppen bestående af hydrogen, halogen, =O, -NO_2, -OR^4, -C(=O)R^4, -C(=O)OR^4, -C(=O)NR^4R^5, -NR^4R^5, -NR^4C(=O)R^5, -NR^4C(=O)OR^5, -NR^4C(=O)NR^5R^6, -$NR^4SO_2R^5$, -N=CR^4R^5, -C=NR^i, -SR^4, -SOR^4, -SO_2R^4, -$SO_2NR^4R^5$, -$NR^4SO_2NR^5R^6$, -$OSO_2NR^5R^6$ og pseudohalogen;

eller en eventuelt mono- eller polysubstitueret rest valgt fra gruppen bestående af

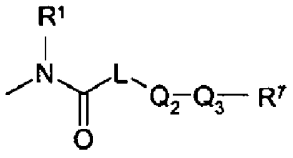
C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af halogen, R, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ og pseudohalogen; og eventuelt kan R^g og R^b placeret ved det samme eller tilstødende C-atomer være forbundet i en hvilken som helst kombination med en fælles mættet eller delvist umættet 3-5-leddet alkylbro, der kan indeholde en til to heteroatomer;

R^i betyder en rest valgt fra gruppen bestående af hydrogen, =O, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR^4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ eller en eventuelt mono- eller polysubstitueret rest valgt fra gruppen bestående af C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten kan være ens eller forskellig og valgt fra gruppen bestående af halogen, R^8, $-NO_2$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$, $-C(=O)NR^4R^5$, $-NR^4R^5$, $-NR^4C(=O)R^5$, $-NR^4C(=O)OR^5$, $-NR4C(=O)NR^5R^6$, $-NR^4SO_2R^5$, $-N=CR^4R^5$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^4SO_2NR^5R^6$, $-OSO_2NR^5R^6$ og pseudohalogen; og eventuelt kan R^i, der er placeret på tilstødende N-atomer, være forbundet med hinanden eller R^i kan, sammen med R^g eller R^h, der er placeret på tilstødende C-atomer, være forbundet i en hvilken som helst kombination med en fælles mættet eller delvist umættet 3-5-leddet alkylbro, der eventuelt kan indeholde en til to heteroatomer;

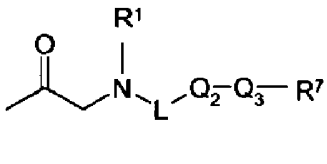
R^3 er valgt blandt formlerne (iv) - (x),



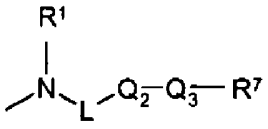
(iv)



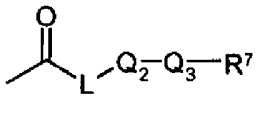
(v)



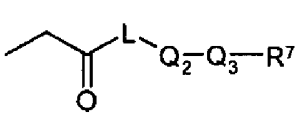
(vi)



(vii)



(viii)



(ix)

-L-Q_2-Q_3-R_7 (x)

R^4, R^5 og R^6 hhv. uafhængigt af hinanden betyder hydrogen eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten/-erne kan være ens eller forskellig og valgt fra gruppen bestående af C_{3-10}cycloalkyl, aryl, heterocyclyl, heteroaryl, halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

L betyder en binding eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cykloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten(erne) kan være ens eller forskellig og valgt fra gruppen bestående af halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

Q_2 og Q_3 hhv. uafhængigt af hinanden betyder en binding eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-16}-alkyl, C_{2-16}-alkenyl, C_{2-16}-alkynyl, C_{3-10}-cykloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten(erne) kan være ens eller forskellig og valgt fra gruppen bestående af halogen, $-NO_2$, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8C(=O)R^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

R^7 betyder hydrogen eller en rest valgt fra gruppen bestående af eventuelt mono- eller polysubstitueret C_{1-16}alkyl, C_{2-16}alkenyl, C_{2-16}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten(erne) kan være ens eller forskellig og valgt fra gruppen bestående af halogen-, NO_2, $-OR^8$, $-C(=O)R^8$, $-C(=O)OR^8$, $-C(=O)NR^8R^9$, $-NR^8R^9$, $-NR^8COR^9$, $-NR^8C(=O)OR^9$, $-NR^8C(=O)NR^9R^{10}$, $-NR^8C(=O)ONR^9R^{10}$, $-NR^8SO_2R^9$, $-N=CR^8R^9$, $-SR^8$, $-SOR^8$, $-SO_2R^8$, $-SO_2NR^8R^9$, $-NR^8SO_2NR^9R^{10}$, $-OSO_2NR^8R^9$ og pseudohalogen;

R^8, R^9 og R^{10} betyder hhv. uafhængigt af hinanden hydrogen eller en rest valgt fra gruppen bestående af eventuelt substitueret C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-10}cycloalkyl, aryl, heterocyclyl og heteroaryl, hvor substituenten(erne) kan være ens eller forskellig og valgt fra gruppen bestående af halogen, $-NH_2$, -OH og pseudohalogen;

hvor

aryl er monocykliske eller bicykliske ringe med 6-12 kulstofatomer;

heteroaryl er monocykliske eller bicykliske ringe, hvilke i stedet for en eller flere kulstofatomer indeholder en eller flere, ens eller forskellige heteroatomer;

heterocyclyl er mættede eller umættede, ikke-aromatiske mono-, bicyckliske, forbundne eller spirocykliske bicykliske ringe omfattende 5-12 kulstofatomer,

hvilke i stedet for en eller flere kulstofatomer bærer heteroatomer som nitrogen, oxygen eller svovl;

eventuelt i form af tautomerer, racemater, enantiomerer, diastereomerer og blandinger deraf, såvel som eventuelt farmakologisk acceptable syreadditionssalte deraf og

mindst et yderligere cytostatisk eller cytotoksisk aktivt stof, eventuelt i form af tautomerer, racemater, enantiomerer, diastereomerer og blandinger deraf, såvel som eventuelt farmakologisk acceptable syreadditionssalte deraf.