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(54) **NOVEL NON-STEROIDAL COMPOUNDS AS ANDROGEN RECEPTOR MODULATORS**

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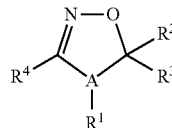
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(57) **ABSTRACT**
This invention relates to novel 4,5-dihydroisoxazoles and 4,5-dihydro[1,2,4]-oxadiazoles of formula (I), to their use as androgenic or antiandrogenic agents or androgen receptor modulators, and to methods of their preparation.

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(I)

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FIG. 1

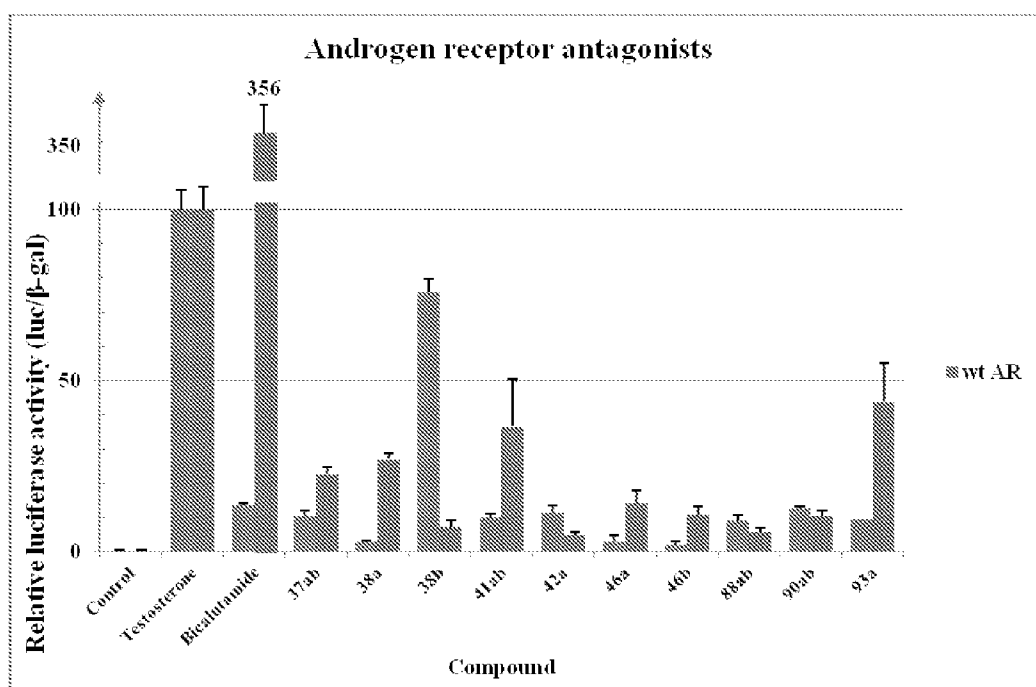


FIG. 2A

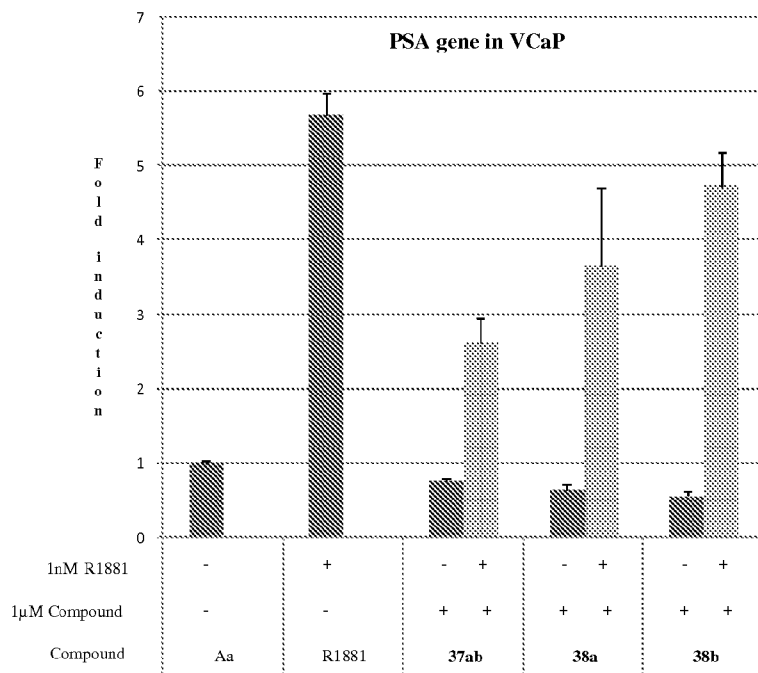


FIG. 2B

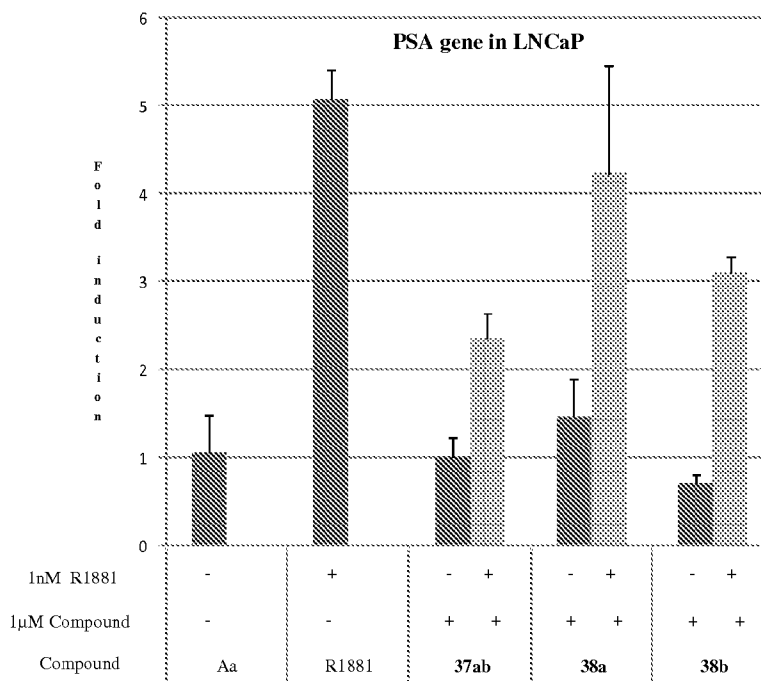


FIG. 3A

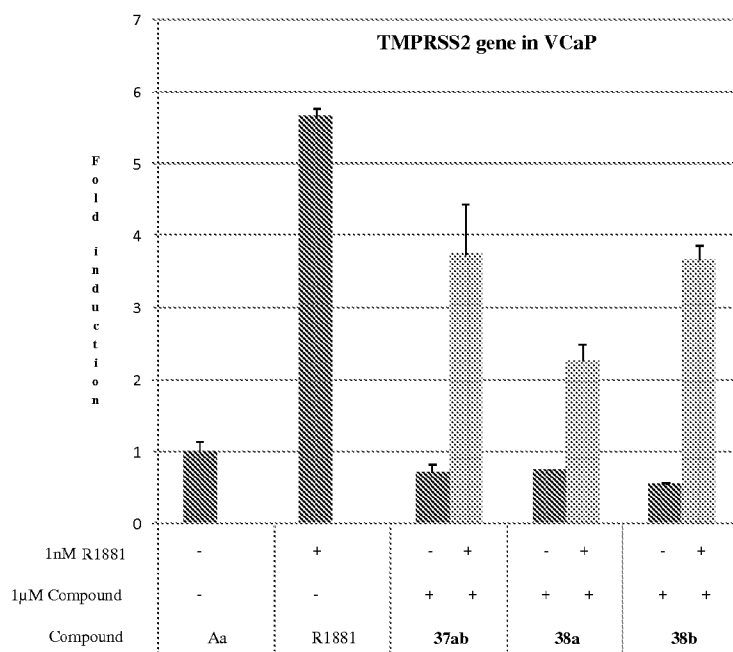


FIG. 3B

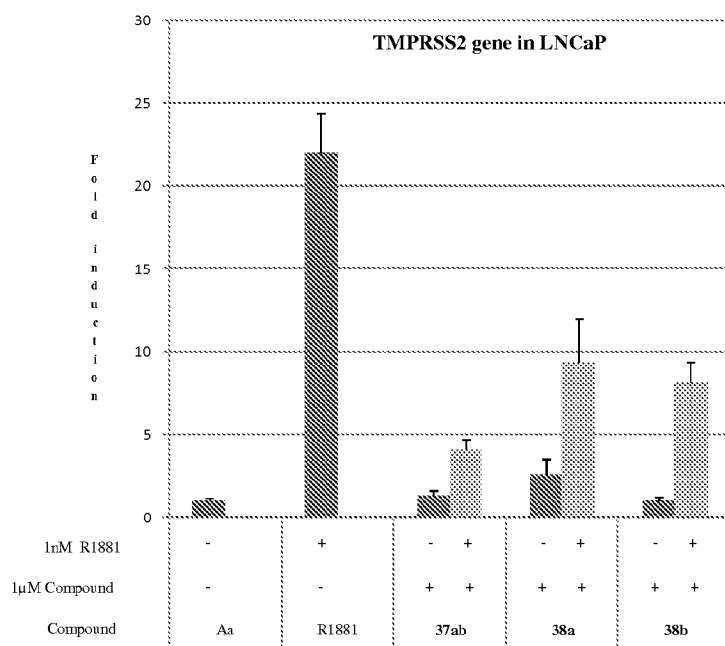


FIG. 4A

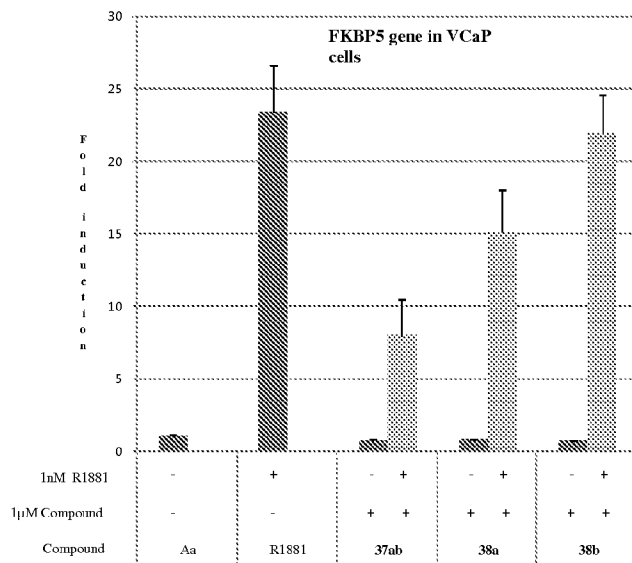
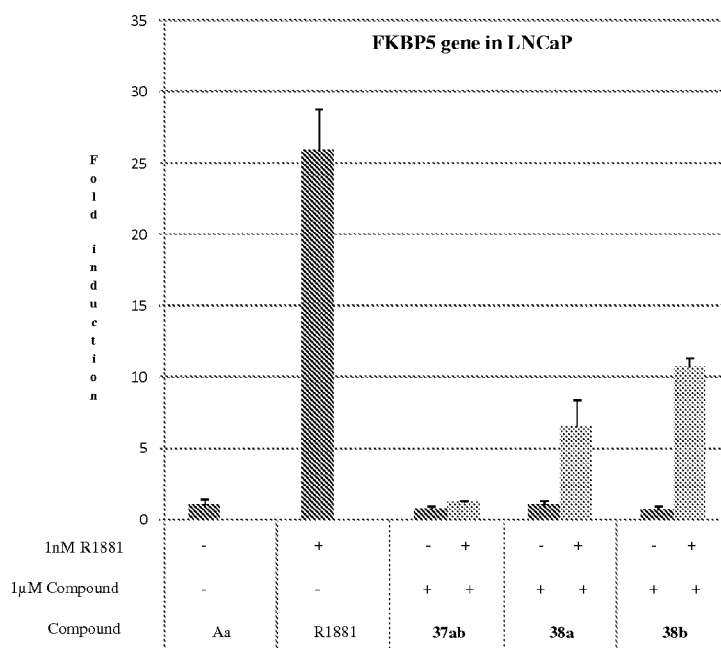


FIG 4B



NOVEL NON-STEROIDAL COMPOUNDS AS ANDROGEN RECEPTOR MODULATORS

FIELD OF THE INVENTION

[0001] This invention relates to certain 4,5-dihydroisoxazole and 4,5-dihydro-[1,2,4]oxadiazol derivatives, to their use as androgenic or antiandrogenic agents or androgen receptor modulators, and to methods of their preparation.

BACKGROUND OF THE INVENTION

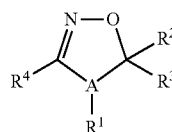
[0002] The nuclear hormone receptor superfamily is a very important target for drug development. Members of this group include androgen, estrogen, progesterone, and glucocorticoid receptors, the activity of which is controlled by ligand binding, as well as constitutive androstane and pregnane X receptors which have an essential role in drug metabolism. Nuclear hormone receptors regulate expression of their target genes, which control the essential metabolic reactions and differentiation processes of cells. Thus, disorders linked to nuclear receptors are of great clinical importance.

[0003] Androgens play an essential role in many physiological processes such as controlling the development and maintenance of muscle and skeletal mass as well as fertility in the male [Singh, S. M.; Gauthier, S.; Labrie, F. *Curr. Med. Chem.* 2000, 7211-7247]. Although non-steroidal AR agonists and antagonists are useful in the treatment of many disorders and diseases, there are no tissue specific selective androgen receptor modulators (SARMs) yet in clinical use. In particular, agonistic SARMs could be employed in the treatment of medical conditions such as hypogonadism caused by the deficiency of androgens and, especially, in the longterm hormone replacement therapy of aging people for the treatment of osteoporosis, loss of muscle mass or muscular power and sexual function disorders of both sexes. On the other hand, antiandrogenic compounds can be utilized against prostate cancer and hyperplasia, acne, cachexia and hirsutism, for example [Gao, W.; Bohl, C. E.; Dalton, J. T. *Chem. Rev.* 2005, 105, 3352-3370. Gao, W.; Reiser, P. J.; Coss, C. C.; Phelps, M. A.; Kaerby, J. D.; Miller, D. D.; Dalton, J. T. *Endocrinology* 2005, 146, 4887-4897. Gao, W.; Kim, J.; Dalton, J. T. *Pharmaceut. Res.* 2006, 23, 1641-1658].

[0004] In conclusion, there is a need for small non-steroidal molecules which can act as agonists or antagonists for nuclear hormone receptors such as AR. We now describe a novel set of compounds which bind to AR, and inhibit its activity as assessed by the function of recombinant AR in reporter gene assays as well as by the analysis of endogenous AR target gene expression in human prostate cancer VCaP and LNCaP cells [Horoszewicz, J. S.; Leong, S. S.; Kawinski, E.; Karr, J. P.; Rosenthal, H.; Chu, M.; Mirand, E. A.; Murphy, G. P. *Cancer Res.*, 1983, 43, 1809-1818]. A further group of such compounds is for the first time disclosed to also inhibit the transcriptional activation by W741L-mutated AR in COS1-cells. The W741L mutation has been reported in prostate cancer patients and shown to render clinically most commonly used antiandrogen bicalutamide to an agonist [Hara, T.; Miyazaki, J.; Araki, H.; Yamaoka, M. Kanzaki, N.; Kusaka, M.; Miyamoto, M. *Cancer Res.* 2003, 63, 149-153].

DESCRIPTION OF THE INVENTION

[0005] This invention provides a novel compound of the formula (I)



(I)

or a stereoisomer, pharmaceutically acceptable salt or a pro-drug form thereof, wherein

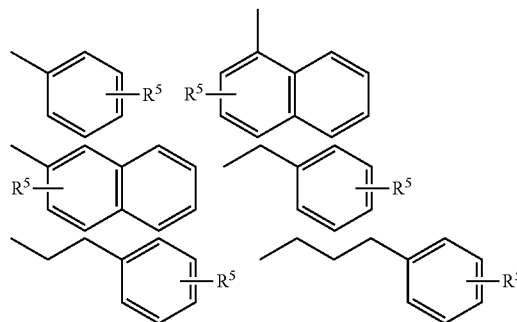
A is carbon or nitrogen;

R¹ is hydrogen or alkyl;

R² is hydrogen, alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen;

R³ is alkyl or benzyl and may form with R¹ a monocyclic aliphatic structure, which may be substituted with a side chain of the formula

[0006] wherein n is an integer from 0 to 4, and R⁶ is hydroxyl, acyloxy, carboxyl or carboxylate; provided that R² and R³ cannot simultaneously be alkyl; R⁴ is phenyl which is substituted with 1-5 R⁵, or naphthalen-1-yl, naphthalen-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵;



R⁵ is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl and lower alkoxy, provided that when R⁴ is phenyl there can not be more than one hydroxyl or lower alkoxy simultaneously present as R⁵ [WO2006085212] and that alkyl or alkoxy groups may be further substituted by the above mentioned groups; provided that

[0007] when A is carbon, R¹ is hydrogen, R² is phenyl, and R³ is methyl, then R⁴ cannot be 3-nitrophenyl or 4-chlorophenyl [Nagarajan, A.; Pillay, M. K. *Indian J. Chem., Sect. B.* 1993, 32, 471-474.]

[0008] when A is carbon, R¹ is methyl, R² is hydrogen, and R³ is methyl, then R⁴ cannot be 3-nitrophenyl, 4-nitrophenyl or 4-methoxyphenyl [Shvekhgheimer, G. A.; Baranski, A. *Tez. uses. Soveshch. Nitros.* 1974, 5, 64-65.]

[0009] when A is carbon, R¹ is methyl, R² is hydrogen, and R³ is isopropyl, then R⁴ cannot be 4-methoxyphenyl or 2,4,6-trimethylphenyl [Martin, S. F.; Dupre, B. *Tetrahedron Lett.* 1983, 24, 1337-1340.]

[0010] when A is carbon, R¹ is isopropyl, R² is hydrogen, and R³ is methyl, then R⁴ cannot be 4-methoxyphenyl or 2,4,6-trimethylphenyl [Martin, S. F.; Dupre, B. *Tetrahedron Lett.* 1983, 24, 1337-1340.]

[0011] when A is carbon, R² is hydrogen, and R¹ and R³ form together a cyclopentane ring, then R⁴ cannot be

- 3-nitrophenyl, 4-nitrophenyl, 4-chlorophenyl, 4-hydroxyphenyl or phenethyl [Nagarajan, A.; Pillay, M. K. *Indian J. Chem., Sect. B* 1993, 32, 471-474. Barbulescu, N.; Lazar, R. *Rom. Rev. Chim.* 1971, 22, 133-136. Shankar, B. B.; Yang, D. Y.; Girton, S.; Ganguly, A. K. *Tetrahedron Lett.* 1998, 39, 2447-2448. Curran, D. P.; Chao, J.-C. *J. Am. Chem. Soc.* 1987, 109, 3036-3040. Sun, R.; Li, Y.; Xiong, L.; Liu, Y.; Wang, Q. *J. Agric. Food Chem.* 2011, 59, 4851-4859.]
- [0012] when A is carbon, R² is hydrogen, and R¹ and R³ form together a cyclohexane then R⁴ cannot be 4-nitrophenyl [Giurg, M.; Mlochowski, J. *Polish J. Chem.* 1997, 71, 1093-1101.]
- [0013] when A is carbon, R² is hydrogen, and R¹ and R³ form together a cycloheptane or cyclooctane ring then R⁴ cannot be 4-chlorophenyl [Hathaway, B. A.; Mueller, R. A. *Molecules* 1999, 4, M122-M123.]
- [0014] when A is carbon, R² is methyl or phenyl, and R¹ and R³ form together a cyclopentane ring, then R⁴ cannot be 4-nitrophenyl or 4-chlorophenyl [Barbulescu, N.; Lazar, R. *Rom. Rev. Chim.* 1971, 22, 133-136.]
- [0015] when A is carbon, R² is methyl, and R¹ and R³ form together a cyclopentane or cyclooctane ring then R⁴ cannot be 2,4,6-trimethylphenyl [Becker, K. B.; Hohermuth, M. K. *Helv. Chim. Acta* 1979, 62, 2025-2036.]
- [0016] when A is nitrogen, R¹ is hydrogen, R² is phenyl, and R³ is n-butyl, then R⁴ cannot be 2-chlorophenyl [Srivastava, R. M.; Rosa, M. F.; Eduardo, C.; Carvalho, M.; Portugal, S. da G. M.; Brinn, I. M.; Da Conceicao Pereira, M.; Antunes, O. A. C. *Heterocycles* 2000, 53, 191-195.]
- [0017] when A is nitrogen, R¹ is n-butyl, R² is hydrogen, and R³ is methyl, then R⁴ cannot be 4-nitrophenyl or 4-chlorophenyl [Lauria, F.; Vecchiotti, V.; Tosolini, G. *Gazz. Chim. It.* 1964, 94, 478-484.]
- [0018] when A is nitrogen, R² is phenyl, and R¹ and R³ form together a cyclopentane ring, then R⁴ cannot be 2,4,6-dimethylphenyl or 2,6-dichlorophenyl [Danhardt, G.; Mayer, K. K.; Sommer, I. *Sci Pharm.* 1984, 52, 280-290.]
- [0019] when A is carbon, R¹ is hydrogen, R² is methyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-benzonitrile, or naphthalen-2-yl [WO2009066009]-when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl or 4-nitrophenyl [WO2009066009]
- [0020] when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is methyl, then R⁴ cannot be phenethyl, 3-phenylpropyl, 2-(2-, 3- or 4-hydroxyphenyl)-ethyl or 3-(4-hydroxyphenyl)propyl [WO2009066009].
- [0021] This invention also provides a novel compound of the formula (II)

(II)

②

② indicates text missing or illegible when filed

or a stereoisomer, pharmaceutically acceptable salt or a prodrug form thereof,

wherein

[0022] m is an integer from 1 to 4;

[0023] n is an integer from 0 to 4;

[0024] R⁶ is hydroxyl, acyloxy, carboxyl or carboxylate;

[0025] R⁴ and A are as defined above for compounds of formula (I)

provided that

[0026] when A is carbon, m is 1, n is 0, and R⁶ is hydroxyl occupying site 4 of ring X, then R⁴ cannot be 4-methoxyphenyl, 4-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl or benzyl [Kim, H. R.; Shin, S. I.; Park, H. J.; Jeon, D. J.; Ryu, E. K. *Bull. Korean Chem. Soc.* 1999, 20, 122-124. Adembri, G.; Giorgi, G.; Lampariello, R. L.; Paoli, M. L.; Sega, A. *J. Chem. Soc., Perkin Trans. 1* 2000, 2649-2656., Lakhvich, F. A.; Khripach, V. A.; Pyrko, A. N.; Antonevich, I. P.; Yankova, T. V.; Koroleva, E. V.; Akhrem, A. A. *Khim. Geterotsikl. Soed.* 1988, 972-976.]

[0027] when A is carbon, m is 3, n is 0, and R⁶ is carboxylic acid methyl ester occupying site 6 of ring X, then R⁴ cannot be 4-chlorophenyl or 4-(1-methylethyl)phenyl [Lawton, G.; Osbond, J. M.; Self, C. R., *Eur. Pat. Appl.* 1991, EP409273A2]

[0028] when A is carbon, m is 4, n is 0, and R⁶ is carboxylic acid methyl ester occupying site 6 or 7 of ring X, then R⁴ cannot be 4-chlorophenyl [Lawton, G.; Osbond, J. M.; Self, C. R., *Eur. Pat. Appl.* 1991, EP409273A2]

[0029] In the compounds of formula (I), R¹ is preferably hydrogen or lower alkyl.

[0030] R² is preferably hydrogen, lower alkyl or phenyl.

[0031] R³ is preferably benzyl or alkyl which forms an alicyclic structure with R¹.

[0032] In the compounds of formulae (I) and (II), R⁴ may be selected from phenyl which is substituted with 1-5 R⁵, or from naphthalen-1-yl, naphthalen-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵. Preferably R⁴ is a phenyl substituted by 1-2 substituents R⁵.

[0033] In the preferred compounds of formula (I), substituents R⁵ are selected from the group consisting of halogen, nitro, cyano, lower alkyl, hydroxyl and lower alkoxy. Alkyl or alkoxy groups may be further substituted by the above mentioned groups.

[0034] Even more preferably substituents R⁵ are halogen, nitro, cyano, lower alkyl or lower haloalkyl groups.

[0035] In the preferred compounds of formula (I), R⁴ is an unsubstituted naphthalen-1-yl, naphthalen-2-yl or benzyl or a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups.

[0036] In the context of the present application, the general terms used above and below preferably have the following meanings:

[0037] A prodrug is a drug which is administered in an inactive or significantly less active form but once administered, it is metabolised in vivo into the active compound.

[0038] Alkyl is a saturated hydrocarbon radical containing 1-20, preferably 1-8 carbon atoms. It is for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl or octyl.

[0039] Lower alkyl contains 1-6, preferably 1-4 carbon atoms. It is for example ethyl, methyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl or hexyl, preferably methyl, ethyl, n-propyl or isopropyl.

[0040] Haloalkyl group is a saturated hydrocarbon radical containing 1-5 carbon atoms, each substituted with 0-3 fluorine, chlorine, bromine or iodine atoms. Preferably it is a trifluoromethyl group.

[0041] In this description lower alkoxy contains 1-6, preferably 1-2 carbon atoms. It is for example methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, secbutoxy, tert-butoxy, pentyloxy or ethyloxy, preferably methoxy.

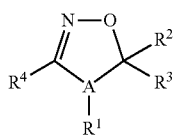
[0042] Monocyclic aliphatic unsubstituted structure contains 3-10, preferably 5-8 carbon atoms. It is for example cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl ring.

[0043] Halogen is fluorine, chlorine, bromine, or iodine, preferably fluorine or chlorine.

[0044] The compounds of the invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of the invention.

[0045] The present invention also includes isotopically labeled compounds, which are identical to those recited in formula (I) but for the fact that one or more atoms may be replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{18}F , and ^{36}Cl , respectively. Certain isotopically labelled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Further, substitution with heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements. Isotopically labelled compounds of the present invention can generally be prepared by carrying out the procedures disclosed in the Schemes and Examples, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

[0046] The invention relates particularly to the compounds of formula (I)



(I)

or stereoisomers, pharmaceutically acceptable salts or prodrug forms thereof, wherein A is carbon or nitrogen, R¹ is hydrogen or lower alkyl, R² is hydrogen, lower alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen, R³ is selected from alkyl or benzyl and may form a monocyclic aliphatic structure with R¹, provided that R² and R³ cannot simultaneously be alkyl, and R⁴ is an unsubstituted naphthalen-1-yl, naphthalen-2-yl or benzyl or a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups.

[0047] More preferably, the compounds of formula (I) or stereoisomers, pharmaceutically acceptable salts or prodrug forms thereof are those having formula (I) wherein

A is carbon,

R¹ forms with R³ a monocyclic aliphatic structure,

R² is hydrogen, and

R⁴ is a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups.

[0048] Preferred examples of the compounds of the invention are selected from the group consisting of 5-benzyl-3-(3-methoxyphenyl)-5-methyl-4,5-dihydro-isoxazole (2), 5-benzyl-3-(2-fluorophenyl)-5-methyl-4,5-dihydro-isoxazole (4), 5-benzyl-3-naphthalen-2-yl-5-methyl-4,5-dihydro-isoxazole (9), 5-benzyl-3-(2-methoxy-phenyl)-5-phenyl-4,5-dihydro-isoxazole (12), 5-benzyl-3-(4-nitrophenyl)-5-phenyl-4,5-dihydro-isoxazole (17), 4-(5-benzyl-5-phenyl-4,5-dihydro-isoxazol-3-yl)-benzotrile (18), 3-(4-fluoro-2-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole (20), 3-(4-nitro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole (21), 3-(4-fluoro-3-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo-[d]-isoxazole (35), 3-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]-isoxazole (36), 3-(4-nitro-3-trifluoro-methyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (37), 3-(4-nitro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (38), 3-(4-fluoro-2-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta-[d]-isoxazole (40), 3-(4-nitro-3-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (41), 3-(4-nitro-2-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (42), 3-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (44), 3-(4-nitro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (46), 3-Benzyl-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (47), 5-benzyl-4-butyl-3-(3-chloro-phenyl)-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (50), 5-benzyl-4-butyl-5-methyl-3-(4-nitro-phenyl)-4,5-dihydro-[1,2,4]oxadiazole (51), 4-(5-benzyl-4-butyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzotrile (52), 3,5-dibenzyl-4-butyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (55), 4-(5-benzyl-4-isobutyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzotrile (62), 4-(4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-3-yl)-2-trifluoromethyl-benzotrile (85), 4-(4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-3-yl)-3-trifluoromethyl-benzotrile (86), 4-(3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazol-3-yl)-3-trifluoromethyl-benzotrile (88), 4-(3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazol-3-yl)-2-trifluoromethyl-benzotrile (89), 4-(4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazol-3-yl)-3-trifluoro-methyl-benzotrile (90), 4-(4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazol-3-yl)-2-trifluoro-methyl-benzotrile (91), 4-(3a,4,5,6,7,8,9,9a-octahydro-cyclo-octa-[d]isoxazol-3-yl)-3-trifluoromethyl-benzotrile (92), 4-(3a,4,5,6,7,8,9,9a-octa-hydro-cycloocta[d]isoxazol-3-yl)-3-trifluoromethyl-benzotrile (93).

[0049] The invention also relates to pharmaceutical compositions which contain a compound of the formula (I) or (II) or a pharmaceutically acceptable salt thereof as active ingredient. These pharmaceutical compositions are for example those for enteral, such as in particular oral, those for parenteral administration, and those for local administration to warm-blooded animals, in particular to humans.

[0050] The pharmaceutical compositions according to the invention usually contain the pharmacologically active ingredient according to formula (I) or (II) together with known

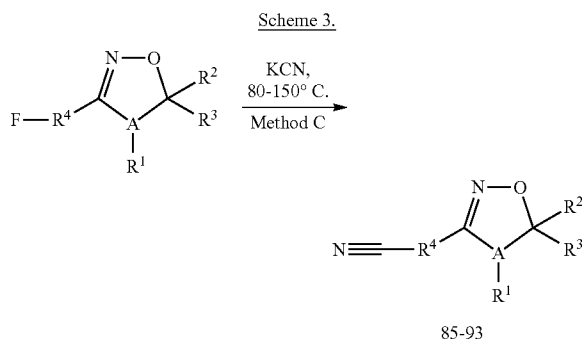
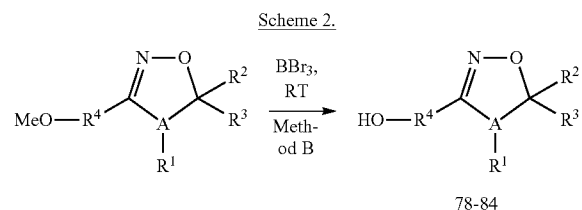
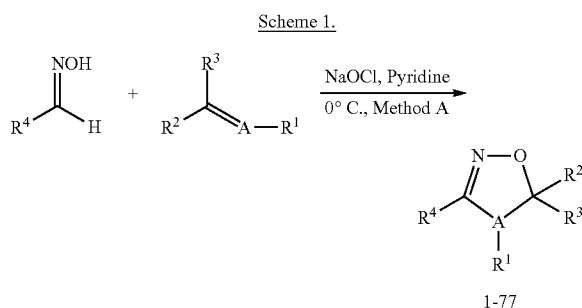
pharmaceutical excipients. The amount of the active ingredient in the pharmaceutical compositions according to the invention is, for example, from about 0.001% to 100% by weight, preferably from about 0.1% to about 50% by weight. The dose of the active ingredient can depend on various factors, such as the efficacy of the active ingredient, severity of the disease to be treated or its symptoms, administration procedure, sex, age, weight and/or individual condition of the subject in need of the treatment. In a normal case, for a human adult of about 75 kg in weight, one daily dose of about 1 mg to about 1000 mg, in particular from about 10 mg to about 500 mg, is to be estimated. This can be administered as a single dose or in several sub-doses.

[0051] The invention also relates to the compounds of the formula (I) for use in a method for treating disease states, disorders and conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity. Among such conditions may be mentioned prostate cancer, including primary and hormone refractory prostate cancer, benign prostate hyperplasia, ovarian cancer, breast cancer, hepatocellular carcinoma, alopecia, hirsutism, acne vulgaris, endometriosis, acanthosis nigricans, hypertrichosis, precocious puberty, polycystic ovary syndrome, hypersexuality/paraphilia, sarcopenia, osteoporosis, muscle wasting, wasting disease, cancer cachexia, frailty, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, male contraception and impotence. In addition, the compounds of the formula (I) and (II) may be used as female and male hormone replacement therapy, as stimulant of hematopoiesis, and as an anabolic agent.

[0052] The invention also provides a method for the therapeutic or prophylactic treatment of disease states, disorders and conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity, said method comprising administering an effective amount of a compound of formula (I) or (II) as defined above to a subject in need of such treatment.

[0053] A still further object of the invention is a method for the therapeutic or prophylactic treatment of prostate cancer, benign prostate hyperplasia, ovarian cancer, breast cancer, hepatocellular carcinoma, alopecia, hirsutism, acne vulgaris, endometriosis, acanthosis nigricans, hypertrichosis, precocious puberty, polycystic ovary syndrome, hypersexuality/paraphilia, sarcopenia, osteoporosis, muscle wasting, wasting disease, cancer cachexia, frailty, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, male contraception and impotence, said method comprising administering an effective amount of a compound of formula (I) or (II) as defined above to a subject in need of such treatment.

[0054] The compounds of the formula (I) and (II) can be prepared as described below. The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature.



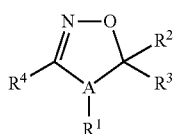
[0055] A process for preparing the compounds of the invention thus comprises

[0056] Scheme 1 (examples 1-77): nitrile oxide—dipolarophile cycloaddition reaction of an aldoxime comprising R^4 , wherein R^4 is as defined above, with an olefin or imine comprising R^1 , R^2 and R^3 , wherein R^1 , R^2 and R^3 are as defined above, in the presence of sodium hypochlorite and pyridine to afford the desired heterocycles; or

[0057] Scheme 2 (examples 78-84): demethylation reaction of the appropriate methoxy-substituted compounds in the presence of boron tribromide to afford the desired phenolic products; or

[0058] Scheme 3 (examples 85-95): cyano-dehalogenation reaction of the appropriate fluoro compounds in the presence of potassium cyanide to afford the desired benzonitrile products.

[0059] The invention also relates to the compounds of formula (I)



(I)

or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof,

wherein

A is carbon or nitrogen;

R¹ is hydrogen or alkyl;

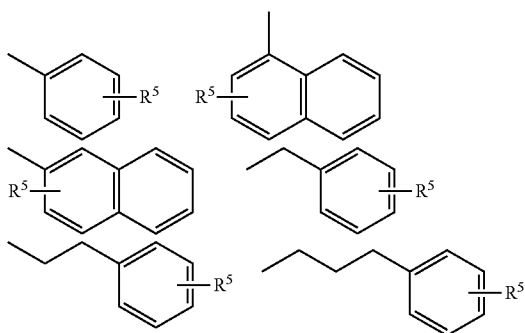
R² is hydrogen, alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen;

R³ is alkyl or benzyl and may form with R¹ a monocyclic aliphatic structure, which may be substituted with a side chain of the formula

[0060] wherein n is an integer from 0 to 4, and R⁶ is hydroxyl, acyloxyl, carboxyl or carboxylate;

provided that R² and R³ cannot simultaneously be alkyl;

R⁴ is phenyl which is substituted with 1-5 R⁵, or naphthalen-1-yl, naphthalen-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵;



R⁵ is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl and lower alkoxy, provided that when R⁴ is phenyl there can not be more than one hydroxyl or lower alkoxy simultaneously present as R⁵, provided that

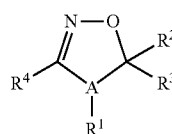
[0061] when A is carbon, R¹ is hydrogen, R² is methyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-benzonitrile, or naphthalene-2-yl [WO2009066009]

[0062] when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl or 4-nitrophenyl [WO2009066009]

[0063] when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is methyl, then R⁴ cannot be phenethyl, 3-phenylpropyl, 2-(2-, 3- or 4-hydroxyphenyl)-ethyl or 3-(4-hydroxy-phenyl)propyl [WO2009066009],

for use as pharmaceuticals, and for use in a method for treating disease states, disorders or conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity.

[0064] A further object of the invention is a pharmaceutical composition comprising a compound of the formula (I)



(I)

or a stereoisomer, pharmaceutically acceptable salt or a pro-drug form thereof,

wherein

A is carbon or nitrogen;

R¹ is hydrogen or alkyl;

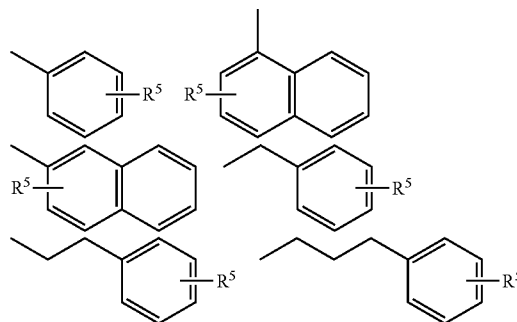
R² is hydrogen, alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen;

R³ is alkyl or benzyl and may form with R¹ a monocyclic aliphatic structure, which may be substituted with a side chain of the formula

[0065] wherein n is an integer from 0 to 4, and R⁶ is hydroxyl, acyloxyl, carboxyl or carboxylate;

provided that R² and R³ cannot simultaneously be alkyl;

R⁴ is phenyl which is substituted with 1-5 R⁵, or naphthalen-1-yl, naphthalen-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵;



R⁵ is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl and lower alkoxy, provided that when R⁴ is phenyl there can not be more than one hydroxyl or lower alkoxy simultaneously present as R⁵ and that alkyl or alkoxy groups may be further substituted by the above mentioned groups, provided that

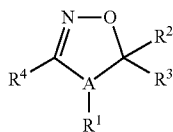
[0066] when A is carbon, R¹ is hydrogen, R² is methyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-benzonitrile, or naphthalen-2-yl [WO2009066009]

[0067] when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl or 4-nitrophenyl [WO2009066009]

[0068] when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is methyl, then R⁴ cannot be phenethyl, 3-phenylpropyl, 2-(2-, 3- or 4-hydroxyphenyl)-ethyl or 3-(4-hydroxy-phenyl)propyl [WO2009066009]

in association with a pharmaceutically acceptable carrier.

[0069] The invention also provides a method for treating disease states, disorders or conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity, said method comprising administering an effective amount of a compound of formula (I)



or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof,

wherein

A is carbon or nitrogen;

R¹ is hydrogen or alkyl;

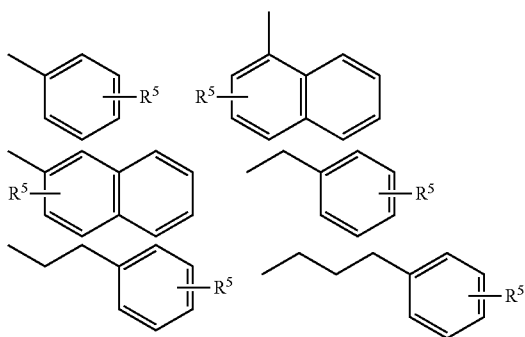
R² is hydrogen, alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen;

R³ is alkyl or benzyl and may form with R¹ a monocyclic aliphatic structure, which may be substituted with a side chain of the formula

[0070] wherein n is an integer from 0 to 4, and R⁶ is hydroxyl, acyloxyl, carboxyl or carboxylate;

provided that R² and R³ cannot simultaneously be alkyl;

R⁴ is phenyl which is substituted with 1-5 R⁵, or naphthalene-1-yl, naphthalene-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵;



R⁵ is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl and lower alkoxy, provided that when R⁴ is phenyl there can not be more than one hydroxyl or lower alkoxy simultaneously present as R⁵ and that alkyl or alkoxy groups may be further substituted by the above mentioned groups;

to a subject in need of such treatment.

BRIEF DESCRIPTION OF THE FIGURES

[0071] FIG. 1 shows inhibition of transcriptional activation of wild type and W741L-mutated AR in COS-1 cells in the presence of the ten most efficient compounds of the present invention. (W741L is common in patients with hormone responsive prostate cancer. It turns bicalutamide to an AR-agonist).

[0072] FIG. 2 illustrates the relative levels of prostate specific antigen (PSA) mRNA in VCaP (expressing wild-type AR) and LNCaP (containing an AR mutation, which turns hydroxyflutamide to an agonist) prostate cancer cells in the

(I)

presence of vehicle (Aa, ethanol), R1881 (synthetic AR agonist), novel non-steroidal compound alone or together with R1881 as indicated.

[0073] FIG. 3 shows the relative levels of TMPRSS2 mRNA in VCaP and LNCaP prostate cancer cells in the presence of different compounds. See FIG. 2 for the interpretation of the graph.

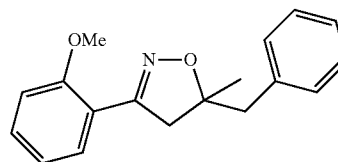
[0074] FIG. 4 shows the relative levels of FKBP5 mRNA in VCaP and LNCaP prostate cancer cells in the presence of different compounds. See FIG. 2 for the interpretation of the graph.

[0075] The following examples further illustrate the invention described above. Compounds 1-4, 7-13, 15-16 and 81-84 have been disclosed in WO 2009/066009 and are not claimed as such in the present application.

Examples 1-77

5-Benzyl-3-(2-methoxyphenyl)-5-methyl-4,5-dihydro-isoxazole (1)

[0076]



[0077] Method A:

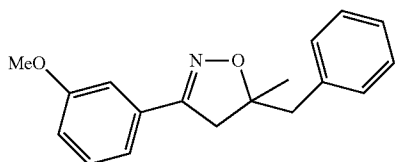
[0078] 2-Methoxybenzaldehyde oxime (1.95 g, 0.0129 mol) is dissolved into 100 ml of chloroform. (2-Methyl-allyl)-benzene (2.56 g, 0.0194 mol) and pyridine (0.31 g, 0.0039 mol) are then added and the solution is cooled to 0° C. After that, 5% NaOCl solution (58 ml, 0.039 mol) is added dropwise to the vigorously stirred reaction mixture keeping the temperature of the solution at 0-5° C. for 1.5 h. Then the mixture is allowed to warm to the room temperature. The organic layer is separated and the water phase extracted with dichloromethane. The combined organic phase is then washed with 2 M HCl, saturated NaHCO₃ and water, dried with MgSO₄ and evaporated to dryness. The residue is purified by column chromatography using dichloromethane as an eluent.

[0079] Yield 45%, a brown viscous, ¹H NMR δ 7.58 (dd, 1H, J=7.7, 1.8), 7.31 (m, 1H), 7.28-7.25 (m, 4H), 7.20 (m, 1H), 6.91 (ddd, 1H, J=7.6, 7.6, 1.0), 6.87 (d, 1H, J=8.4), 3.78 (s, 3H), 3.33 (d, 1H, J=17.2), 3.09 (d, 1H, J=17.2), 2.97 (s, 2H), 1.42 (s, 3H); ¹³C NMR δ 157.4, 156.2, 137.0 (3 s), 130.9, 130.4, 129.2, 128.1, 126.5, 120.7 (6 d), 119.4 (s), 111.3, 87.0 (2 d), 55.4 (q), 47.3, 45.7 (2 t), 25.4 (q). [WO2009066009, compound 51]

[0080] The following compounds were prepared by Method A using appropriate starting materials:

5-Benzyl-3-(3-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole (2)

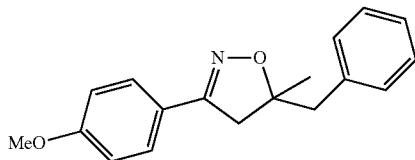
[0081]



[0082] Yield 56%, a brown viscous oil, $^1\text{H NMR}$ δ 7.28-7.19 (m, 7H), 7.09 (d, 1H, $J=7.7$), 6.90 (dd, 1H, $J=8.2, 2.1$), 3.78 (s, 3H), 3.18 (d, 1H, $J=16.5$), 2.99 (s, 2H), 2.91 (d, 1H, $J=16.5$), 1.43 (s, 3H); $^{13}\text{C NMR}$ δ 159.6, 156.4, 136.7, 131.4 (4 s), 130.3, 129.6, 128.2, 126.7, 119.1, 116.1, 111.0, 87.5 (8 d), 55.3 (q), 45.6, 44.5 (2 t), 25.8 (q). [WO2009066009, compound 52]

5-Benzyl-3-(4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole (3)

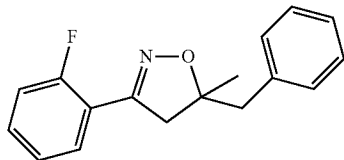
[0083]



[0084] Yield 37%, mp=97.8-98.6° C.; $^1\text{H NMR}$ δ 7.53 (m, 2H), 7.29-7.27 (m, 4H), 7.22 (m, 1H), 6.88 (m, 2H), 3.80 (s, 3H), 3.20 (d, 1H, $J=16.4$), 2.94 (s, 2H), 2.92 (d, 1H, $J=16.4$), 1.43 (s, 3H); $^{13}\text{C NMR}$ δ 160.6, 156.0, 136.9 (3 s), 130.4, 128.2, 127.9, 126.7 (4 d), 122.7 (s), 114.0, 87.0 (2 d), 55.3 (q), 45.7, 44.8 (2 t), 25.7 (q). [WO2009066009, compound 53]

5-Benzyl-3-(2-fluorophenyl)-5-methyl-4,5-dihydroisoxazole (4)

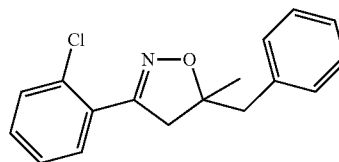
[0085]



[0086] Yield 42%, a pale yellow wax, $^1\text{H NMR}$ δ 7.74 (ddd, $J=7.7, 7.7, 1.7$), 7.33 (m, 1H), 7.29-7.27 (m, 4H), 7.23 (m, 1H), 7.12 (ddd, $J=7.6, 7.6, 1.1$), 7.04 (ddd, $J=11.3, 8.4, 0.9$), 3.32 (dd, 1H, $J=17.2, 2.4$), 3.07 (dd, 1H, $J=17.2, 2.6$), 3.01 (d, 1H, $J=14.3$), 3.00 (d, 1H, $J=14.3$), 1.45 (s, 3H); $^{13}\text{C NMR}$ δ 160.2, 153.2 (2 d), 136.7 (s), 131.4 (dd), 130.4 (d), 128.8 (dd), 128.2, 126.7 (2 d), 124.3 (dd), 118.2 (d), 116.3 (dd), 87.6 (d), 46.4 (td), 45.7 (t), 25.7 (q). [WO2009066009, compound 54]

5-Benzyl-3-(2-chlorophenyl)-5-methyl-4,5-dihydroisoxazole (5)

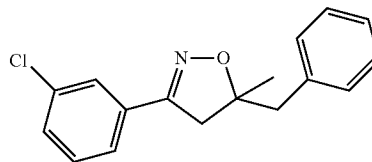
[0087]



[0088] Yield 50%, a yellow viscous oil, $^1\text{H NMR}$ δ 7.37 (dd, 1H, $J=7.6, 1.7$), 7.34 (dd, 1H, $J=7.9, 1.3$), 7.30-7.17 (m, 7H), 3.33 (d, 1H, $J=17.0$), 3.15 (d, 1H, $J=17.0$), 3.02 (dd, 1H, $J=13.8$), 2.97 (d, 1H, $J=13.8$), 1.46 (s, 3H); $^{13}\text{C NMR}$ δ 156.3, 136.7, 132.7 (3 s), 130.5, 130.4, 130.4, 130.2 (4 d), 129.7 (s), 128.2, 126.8, 126.7 (3d), 88.1 (s), 47.0, 45.7 (2 t), 25.7 (q).

5-Benzyl-3-(3-chlorophenyl)-5-methyl-4,5-dihydroisoxazole (6)

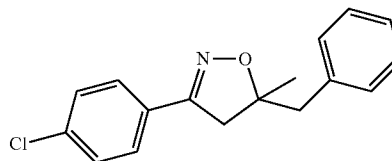
[0089]



[0090] Yield 52%, a yellow viscous oil, $^1\text{H NMR}$ δ 7.55 (dd, 1H, $J=1.7, 1.6$), 7.45 (ddd, 1H, $J=7.5, 1.7, 1.6$), 7.31-7.23 (m, 6H), 7.21 (m, 1H), 3.17 (d, 1H, $J=16.5$), 3.00 (d, 1H, $J=14.1$), 3.00 (d, 1H, $J=14.1$), 2.89 (dd, 1H, $J=14.1$), 1.44 (s, 3H); $^{13}\text{C NMR}$ δ 155.3, 136.5, 134.6, 131.9 (4 s), 131.9, 129.8, 129.6, 128.3, 126.8, 126.4, 124.4 (7 d), 87.9 (s), 45.7, 44.2 (2 t), 25.9 (q).

5-Benzyl-3-(4-chlorophenyl)-5-methyl-4,5-dihydroisoxazole (7)

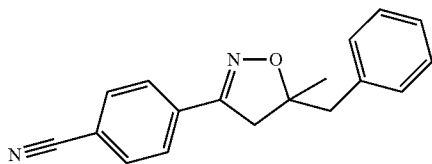
[0091]



[0092] Yield 35%, a pale brown viscous oil, $^1\text{H NMR}$ δ 7.50 (m, 2H), 7.32 (m, 2H), 7.29-7.26 (m, 4H), 7.23 (m, 1H), 3.18 (d, 1H, $J=16.5$), 3.01 (d, 1H, $J=13.9$), 3.00 (d, 1H, $J=13.9$), 2.91 (d, 1H, $J=16.5$), 1.45 (s, 3H); $^{13}\text{C NMR}$ δ 155.4, 136.6, 135.7 (3 s), 130.3, 128.8 (2 d), 128.6 (s), 128.3, 127.6, 126.8, 87.8 (4 d), 45.7, 44.3 (2 t), 25.9 (q). [WO2009066009, compound 55]

4-(5-Benzyl-5-methyl-4,5-dihydro-isoxazol-3-yl)-benzonitrile (8)

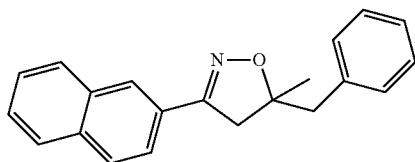
[0093]



[0094] Yield 35%, a pale yellow wax, $^1\text{H NMR}$ δ 7.67 (m, 2H), 7.63 (m, 2H), 7.29-7.25 (m, 4 OH), 7.22 (m, 1H), 3.20 (d, 1H, $J=16.5$), 3.05 (d, 1H, $J=13.9$), 3.00 (d, 1H, $J=13.9$), 2.94 (d, 1H, $J=16.5$), 1.48 (s, 3H); $^{13}\text{C NMR}$ δ 155.0, 136.3, 134.4 (3 s), 132.4, 130.3, 128.3 (3 d), 127.8 (s), 126.9, 126.8 (2 d), 118.4 (s), 88.8 (d), 45.7, 43.7 (2 t), 26.0 (q). [WO2009066009, compound 56]

5-Benzyl-3-naphthalen-2-yl-5-methyl-4,5-dihydro-isoxazole (9)

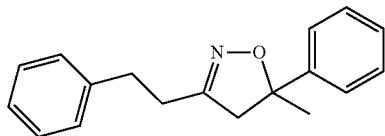
[0095]



[0096] Yield 40%, mp=144.8-146.3° C.; $^1\text{H NMR}$ δ 7.92 (dd, 1H, $J=8.7, 1.5$), 7.82-7.78 (m, 4H), 7.49 (m, 2H), 7.38-7.27 (m, 4H), 7.22 (m, 1H), 3.35 (d, 1H, $J=16.3$), 3.07 (d, 1H, $J=16.3$), 3.06 (s, 2H), 1.49 (s, 3H); $^{13}\text{C NMR}$ δ 156.6, 136.8, 133.9, 133.0 (4 s), 130.4, 128.4, 128.3, 127.8 (5 d), 127.8 (s), 126.9, 126.8, 126.6, 126.5, 123.4, 87.7 (6 d), 45.8, 44.4 (2 t), 25.9 (q). [WO2009066009, compound 57]

5-Methyl-3-phenethyl-5-phenyl-4,5-dihydroisoxazole (10)

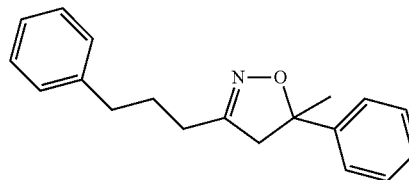
[0097]



[0098] Yield 65%, yellow viscous oil, $^1\text{H NMR}$ δ 7.39-7.36 (m, 2H), 7.33 (m, 2H), 7.24 (m, 3H), 7.19-7.16 (1H), 7.15-7.12 (2H), 3.01 (d, 1H, $J=16.8$), 2.96 (d, 1H, $J=16.8$), 2.87 (t, 2H, $J=8.0$), 2.62 (t, 2H, $J=8.0$), 1.65 (s, 3H); $^{13}\text{C NMR}$ δ 158.0, 145.8, 140.5 (3 s), 128.5, 128.4, 128.3, 127.2, 126.3, 124.7 (6 d), 86.8 (s), 51.0, 32.7, 29.7 (3 t), 28.1 (q). [WO2009066009, compound 71]

5-Methyl-5-phenyl-3-(3-phenyl-propyl)-4,5-dihydro-isoxazole (11)

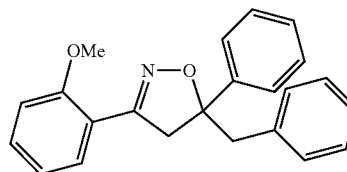
[0099]



[0100] Yield 34%, yellow viscous oil, $^1\text{H NMR}$ δ 7.40 (m, 2H), 7.32 (m, 2H), 7.24 (m, 3H), 7.17 (m, 1H), 7.10 (m, 2H), 3.03 (d, 1H, $J=16.7$), 2.99 (d, 1H, $J=16.7$), 2.58 (m, 2H), 2.31 (t, 2H, $J=7.5$), 1.84 (m, 2H), 1.68 (s, 3H); $^{13}\text{C NMR}$ δ 158.5, 145.8, 141.4 (3 s), 128.4, 128.4, 128.4, 127.2, 125.9, 124.6 (6 d), 86.6 (s), 50.7, 35.1 (2 t), 28.1 (q), 27.9, 27.4 (2 t). [Arai, N.; Iwakoshi, M.; Tanabe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* 1999, 72, 2277-2285], [WO2009066009, compound 115].

5-Benzyl-3-(2-methoxyphenyl)-5-phenyl-4,5-dihydro-isoxazole (12)

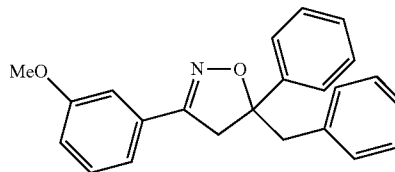
[0101]



[0102] Yield 72%, mp=109.3-110.2° C., $^1\text{H NMR}$ δ 7.54 (dd, 1H, $J=7.7, 1.7$), 7.37 (m, 2H), 7.32-7.29 (m, 3H), 7.24 (m, 1H), 7.20-7.15 (m, 3H), 7.08 (m, 2H), 6.90 (ddd, 1H, $J=7.5, 7.5, 1.0$), 6.86 (d, 1H, $J=8.4$), 3.78 (s, 3H), 3.69 (d, 1H, $J=17.1$), 3.59 (d, 1H, $J=17.1$), 3.27 (d, 1H, $J=13.8$), 3.23 (d, 1H, $J=13.8$); $^{13}\text{C NMR}$ δ 157.4, 156.2, 144.6, 136.2 (4 s), 131.1, 130.7, 129.3, 128.1, 127.8, 127.1, 126.5, 125.5, 120.7 (8 d), 119.1 (s), 111.3 (d), 90.6 (s), 55.5 (q), 48.0, 47.4 (2 t). [WO2009066009, compound 74]

5-Benzyl-5-phenyl-3-(3-methoxyphenyl)-4,5-dihydro-isoxazole (13)

[0103]

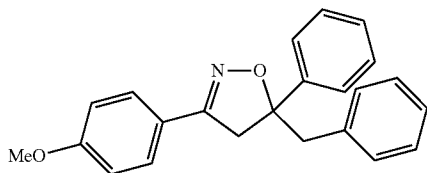


[0104] Yield 66%, mp=94.4-95.2° C., $^1\text{H NMR}$ δ 7.37 (m, 2H), 7.28 (m, 2H), 7.23-7.12 (m, 6H), 7.09-7.03 (m, 3H), 6.85 (d, 1H, $J=7.5$), 3.72 (s, 3H), 3.52 (d, 1H, $J=16.4$), 3.43 (d, 1H, $J=16.4$), 3.28 (d, 1H, $J=13.9$), 3.23 (d, 1H, $J=13.9$); $^{13}\text{C NMR}$ δ 159.6, 156.5, 144.3, 135.8, 130.9 (5 s), 130.6, 129.5, 128.2,

127.9, 127.3, 126.7, 125.3, 119.1, 116.2, 111.0 (10 d), 90.9 (s), 55.4 (q), 47.3, 45.4 (2 t). [WO2009066009, compound 77]

5-Benzyl-3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-isoxazole (14)

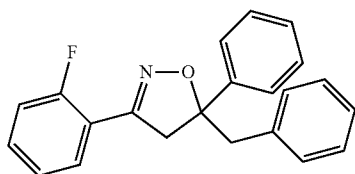
[0105]



[0106] Yield 63%, mp=139.3-141.0° C., ¹H NMR δ 7.50 (m, 2H), 7.37 (m, 2H), 7.30 (m, 2H), 7.22 (m, 1H), 7.19-7.12 (m, 3H), 7.08 (m, 2H), 6.83 (m, 2H), 3.75 (s, 3H), 3.53 (d, 1H, J=16.3), 3.42 (d, 1H, J=16.3), 3.29 (d, 1H, J=14.0), 3.23 (d, 1H, J=14.0); ¹³C NMR δ 160.9, 156.1, 144.5, 136.0 (4 s), 130.7, 128.2, 128.0, 127.9, 127.4, 126.6, 125.4 (7 d), 122.3 (s), 114.4 (d), 90.5 (s), 55.3 (q), 47.3, 45.6 (2 t).

5-Benzyl-3-(2-fluorophenyl)-5-phenyl-4,5-dihydro-isoxazole (15)

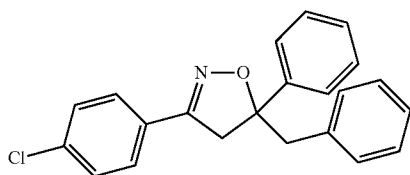
[0107]



[0108] Yield 56%, mp=134.3-135.2° C., ¹H NMR δ 7.72 (ddd, 1H, J=7.7, 7.6, 1.7), 7.38 (m, 2H), 7.35-7.29 (m, 3H), 7.26 (dd, 1H, J=7.3, 7.1), 7.21-7.15 (m, 3H), 7.10 (m, 2H), 7.09 (dd, J=7.3, 1.0), 7.03 (ddd, 1H, J=10.6, 8.4, 0.8), 3.67 (dd, 1H, J=17.1, 2.4), 3.58 (dd, 1H, J=17.1, 2.5), 3.31 (d, 1H, J=13.9), 3.24 (d, 1H, J=13.9); ¹³C NMR δ 160.2, 153.3 (2 d), 144.3, 135.8 (2 s), 131.6 (dd), 130.7 (d), 128.8 (dd), 128.3, 127.9, 127.4, 126.7, 125.4, 124.3 (6 d), 117.8 (d), 116.3 (dd), 91.1 (s), 47.4 (t), 47.1 (td). [WO2009066009, compound 75]

5-Benzyl-3-(4-chlorophenyl)-5-phenyl-4,5-dihydro-isoxazole (16)

[0109]

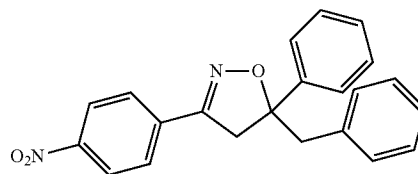


[0110] Yield 40%, mp=120.3-122.1° C., ¹H NMR δ 7.49 (m, 2H), 7.39 (m, 2H), 7.33 (m, 2H), 7.27 (m, 1H), 7.21-7.15

(m, 3H), 7.10 (m, 2H), 3.54 (d, 1H, J=16.4), 3.45 (d, 1H, J=16.4), 3.32 (d, 1H, J=14.0), 3.25 (d, 1H, J=14.0); ¹³C NMR δ 155.5, 144.2, 135.8, 135.7 (4 s), 130.6, 128.8, 128.3 (3 d), 128.2 (s), 128.0, 127.7, 127.4, 126.8, 125.3 (5 d), 91.2 (s), 47.4, 45.2 (2 t). [WO2009066009, compound 76]

5-Benzyl-3-(4-nitrophenyl)-5-phenyl-4,5-dihydro-isoxazole (17)

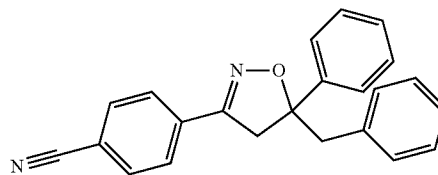
[0111]



[0112] Yield 13%, mp=158.0-159.2° C.; ¹H NMR δ 8.15 (m, 2H), 7.70 (m, 2H), 7.39 (m, 2H), 7.35 (m, 2H), 7.28 (m, 1H), 7.23-7.15 (m, 3H), 7.12 (m, 2H), 3.59 (d, 1H, J=16.5), 3.49 (d, 1H, J=16.5), 3.35 (d, 1H, J=14.1), 3.26 (d, 1H, J=14.1); ¹³C NMR δ 155.4, 148.8, 144.4, 136.2, 135.9 (5 s), 131.1, 128.9, 128.6, 128.1, 127.6, 127.4, 125.6, 124.3 (8 d), 92.8 (s), 48.0, 45.2 (2 t).

4-(5-Benzyl-5-phenyl-4,5-dihydro-isoxazol-3-yl)-benzotrile (18)

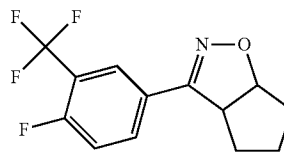
[0113]



[0114] Yield 33%, mp=104.5-107.0° C.; ¹H NMR δ 7.63 (m, 2H), 7.59 (m, 2H), 7.38 (m, 2H), 7.34 (m, 2H), 7.26 (m, 1H), 7.22-7.16 (m, 3H), 7.11 (m, 2H), 3.55 (d, 1H, J=16.5), 3.45 (d, 1H, J=16.5), 3.34 (d, 1H, J=14.1), 3.24 (d, 1H, J=14.1); ¹³C NMR δ 155.6, 144.4, 135.9, 134.4, 133.2 (5 s), 132.8, 131.1, 128.9, 128.5, 128.1, 127.3, 125.6 (7 d), 118.8 (s), 113.6 (d), 92.5 (s), 47.9, 45.1 (2 t).

3-(4-Fluoro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]-isoxazole (19)

[0115]

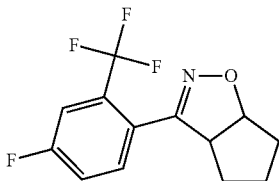


[0116] Yield 70%, a yellow wax; ¹H NMR δ 7.94 (d, 1H, J=7.0), 7.88 (m, 1H), 7.24 (m, 1H), 4.28 (dd, 1H, J=8.5, 5.0), 4.03 (m, 1H), 2.19 (m, 1H), 1.95-1.87 (m, 2H), 1.85-1.73 (m,

2H), 1.53 (m, 1H); ^{13}C NMR δ 160.7 (dd), 157.0 (s), 132.6 (dd), 126.6 (d), 126.0 (qd), 122.6 (q), 119.1 (qd), 117.8 (dd), 88.9, 52.1 (2 d), 36.1, 31.7, 23.8 (3 t).

SL-060709-2: 3-(4-Fluoro-2-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole (20)

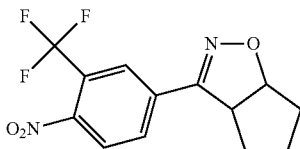
[0117]



[0118] Yield 75%, a yellow wax; ^1H NMR δ 7.43-7.38 (m, 2H), 7.24 (m, 1H), 5.20 (m, 1H), 4.02 (m, 1H), 2.11 (m, 1H), 1.72-1.65 (m, 2H), 1.64-1.57 (m, 2H), 1.47 (m, 1H); ^{13}C NMR δ 163.0 (dd), 157.2 (s), 133.9 (dd), 131.3 (qd), 125.3 (d), 123.3 (qd), 119.4 (dd), 115.0 (ddq), 87.9, 55.7 (2 d), 36.2, 30.7, 23.4 (3 t).

SL-210709-1: 3-(4-Nitro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole (21)

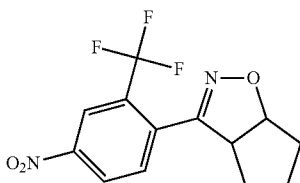
[0119]



[0120] Yield 16%, a yellow wax; ^1H NMR δ 8.13 (d, 1H, $J=1.6$), 7.95 (dd, 1H, $J=8.5, 1.6$), 7.90 (d, 1H, $J=8.5$), 5.32 (m, 1H), 4.01 (m, 1H), 2.19 (m, 1H), 1.97-1.83 (m, 2H), 1.82-1.75 (m, 2H), 1.50 (m, 1H); ^{13}C NMR δ 156.5, 148.2, 134.8 (3 s), 131.0 (d), 126.5 (q), 126.1 (d), 124.8 (dq), 122.1 (q), 90.0, 51.4 (2 d), 36.1, 31.8, 23.9 (3 t).

SL-170809-1: 3-(4-Nitro-2-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole (22)

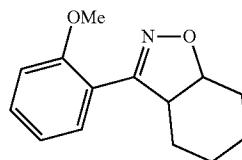
[0121]



[0122] Yield 13%, yellow viscous oil ^1H NMR δ 8.61 (d, 1H, $J=2.2$), 8.41 (dd, 1H, $J=8.5, 2.2$), 7.70 (d, 1H, $J=8.5$), 5.31 (dd, 1H, $J=8.9, 5.6$), 4.13 (dd, 1H, $J=8.9, 8.4$), 2.19 (dd, 1H, $J=12.2, 6.8$), 1.70-1.45 (m, 5H).

3-(2-Methoxy-phenyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (23)

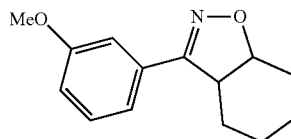
[0123]



[0124] Yield 21%, a yellow wax; ^1H NMR δ 7.61 (dd, 1H, $J=7.6, 1.6$), 7.34 (ddd, 1H, $J=8.4, 7.5, 1.8$), 6.94 (ddd, 1H, $J=7.6, 7.5, 1.0$), 6.90 (dd, 1H, $J=8.4$), 4.52 (m, 1H), 3.81 (s, 3H), 3.58 (m, 1H), 2.02 (m, 1H), 1.77 (m, 1H), 1.72 (m, 1H), 1.53-1.41 (m, 3H), 1.29-1.18 (m, 2H); ^{13}C NMR δ 163.5, 157.9 (2 s), 131.6, 130.5, 121.2 (3 d), 119.1 (s), 111.7, 80.3 (2 d), 55.9 (q), 47.1 (d), 26.2, 25.5, 22.6, 20.8 (4 t).

3-(3-Methoxy-phenyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (24)

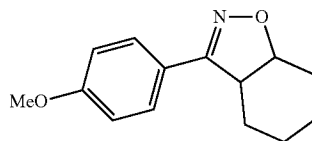
[0125]



[0126] Yield 77%, a yellow wax; ^1H NMR δ 7.29 (m, 1H), 7.27 (d, 1H, $J=7.9$), 7.20 (d, 1H, $J=7.7$), 6.92 (d, 1H, $J=8.2$), 4.47 (m, 1H), 3.81 (s, 3H), 3.21 (m, 1H), 2.24 (m, 1H), 1.96 (m, 1H), 1.73 (m, 1H), 1.65 (m, 1H), 1.59 (m, 1H), 1.51 (m, 1H), 1.30-1.18 (m, 2H); ^{13}C NMR δ 164.3, 160.2, 131.1 (3 s), 130.1, 120.0, 116.7, 111.9, 80.9 (5 d), 55.8 (q), 45.0 (d), 26.9, 25.5, 22.8, 20.6 (4 t).

3-(4-Methoxy-phenyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (25)

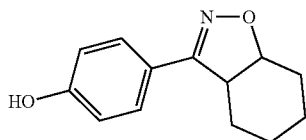
[0127]



[0128] Yield 22%, a yellow wax; ^1H NMR δ 7.61 (m, 2H), 6.89 (m, 2H), 4.43 (m, 1H), 3.80 (s, 3H), 3.19 (m, 1H), 2.23 (m, 1H), 1.93 (m, 1H), 1.72 (m, 1H), 1.67 (m, 1H), 1.58 (m, 1H), 1.51 (m, 1H), 1.25-1.18 (m, 2H); ^{13}C NMR δ 164.0, 161.4 (2 s), 128.8 (d), 122.4 (s), 114.6, 80.5 (2 d), 55.7 (q), 45.1 (d), 26.9, 25.5, 22.9, 20.7 (4 t).

4-(3a,4,5,6,7,7a-Hexahydro-benzo[d]isoxazol-3-yl)-phenol (26)

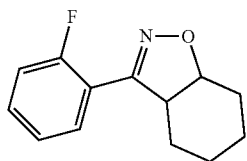
[0129]



[0130] Yield 22%, a yellow wax; $^1\text{H NMR}$ δ 7.58 (m, 2H), 6.83 (m, 2H), 4.44 (m, 1H), 3.19 (m, 1H), 2.22 (m, 1H), 1.93 (m, 1H), 1.71 (m, 1H), 1.66 (m, 1H), 1.58 (m, 1H), 1.51 (m, 1H), 1.25-1.18 (m, 2H); $^{13}\text{C NMR}$ δ 164.0, 161.2 (2 s), 129.1 (d), 122.4 (s), 116.1, 80.5 (2 d), 45.1 (d), 26.9, 25.5, 22.9, 20.7 (4 t).

3-(2-Fluoro-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (27)

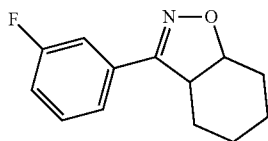
[0131]



[0132] Yield 25%, a yellow viscous oil; $^1\text{H NMR}$ δ 7.85 (ddd, 1H, $J=7.6, 7.5, 1.7$), 7.38 (m, 1H), 7.17 (ddd, 1H, $J=7.6, 7.5, 0.9$), 7.11 (dd, 1H, $J=11.3, 8.4$), 4.54 (m, 1H), 3.44 (m, 1H), 2.19 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.64-1.55 (m, 2H), 1.54 (m, 1H), 1.30-1.20 (m, 2H); $^{13}\text{C NMR}$ δ 160.9, 160.7 (2 d), 132.0, 129.9, 124.9 (3 dd), 118.0 (d), 116.8 (dd), 80.9, 46.3 (2 d), 25.9, 25.6, 22.5, 20.6 (4 t).

3-(3-Fluoro-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (28)

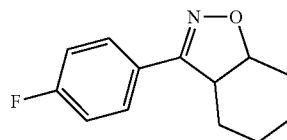
[0133]



[0134] Yield 11%, a yellow wax; $^1\text{H NMR}$ δ 7.47 (d, 1H, $J=7.9$), 7.43 (m, 1H), 7.37 (m, 1H), 7.09 (m, 1H), 4.52 (m, 1H), 3.23 (m, 1H), 2.27 (m, 1H), 1.98 (m, 1H), 1.77 (m, 1H), 1.72-1.61 (m, 2H), 1.55 (m, 1H), 1.30-1.20 (m, 2H); $^{13}\text{C NMR}$ δ 163.5, 163.3, 132.0 (3 d), 130.6, 123.0, 117.2, 114.1 (4 dd), 81.1, 44.8 (2 d), 26.8, 25.4, 22.6, 20.5 (4 t).

3-(4-Fluoro-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (29)

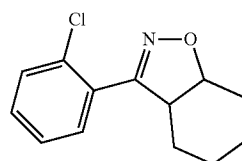
[0135]



[0136] Yield 11%, a yellow wax; $^1\text{H NMR}$ δ 7.70 (m, 2H), 7.09 (m, 2H), 4.50 (m, 1H), 3.23 (m, 1H), 2.26 (m, 1H), 1.96 (m, 1H), 1.77 (m, 1H), 1.71-1.60 (m, 2H), 1.54 (m, 1H), 1.30-1.20 (m, 2H); $^{13}\text{C NMR}$ δ 164.1 (d), 163.1 (s), 129.2 (dd), 126.1 (d), 116.3 (dd), 80.9, 45.0 (2 d), 26.8, 25.4, 22.7, 20.6 (4 t).

3-(2-Chloro-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (30)

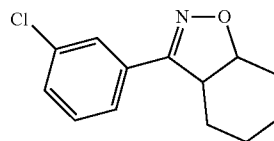
[0137]



[0138] Yield 24%, a colorless wax; $^1\text{H NMR}$ δ 7.53 (dd, 1H, $J=7.6, 1.8$), 7.43 (dd, 1H, $J=8.1, 1.2$), 7.35 (ddd, 1H, $J=8.1, 7.5, 1.8$), 7.30 (dd, 1H, $J=7.6, 7.5, 1.2$), 4.67 (m, 1H), 3.70 (m, 1H), 2.04 (m, 1H), 1.83 (m, 1H), 1.71 (m, 1H), 1.57 (m, 1H), 1.59-1.43 (m, 2H), 1.35 (m, 1H), 1.26 (m, 1H); $^{13}\text{C NMR}$ δ 163.6, 133.5 (2 s), 131.5, 131.2, 130.6 (3 d), 129.5 (s), 127.3 (d), 80.6, 47.2 (2 d), 26.2, 25.2, 22.4, 20.7 (4 t).

3-(3-Chloro-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (31)

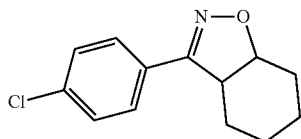
[0139]



[0140] Yield 11%, a colorless wax; $^1\text{H NMR}$ δ 7.68 (m, 1H), 7.59 (m, 1H), 7.37-7.31 (m, 2H), 4.51 (m, 1H), 3.23 (m, 1H), 2.27 (m, 1H), 1.97 (m, 1H), 1.77 (m, 1H), 1.71-1.60 (m, 2H), 1.54 (m, 1H), 1.27-1.22 (m, 2H); $^{13}\text{C NMR}$ δ 163.3, 135.2 (2 s), 130.4, 130.3 (2 d), 128.3 (s), 127.3, 125.4, 81.1, 44.7 (4 d), 26.7, 25.4, 22.6, 20.5 (4 t).

3-(4-Chloro-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo
[d]-isoxazole (32)

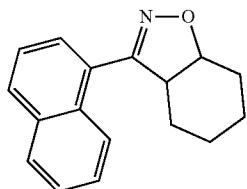
[0141]



[0142] Yield 25%, a colorless wax; $^1\text{H NMR}$ δ 7.64 (m, 2H), 7.37 (m, 2H), 4.50 (m, 1H), 3.22 (m, 1H), 2.27 (m, 1H), 1.95 (m, 1H), 1.77 (m, 1H), 1.72-1.60 (m, 2H), 1.54 (m, 1H), 1.28-1.20 (m, 2H); $^{13}\text{C NMR}$ δ 163.4, 136.3 (2 s), 129.5, 128.5 (2 d), 128.3 (s), 81.0, 44.7 (2 d), 26.8, 25.4, 22.7, 20.6 (4 t).

3-Naphthalen-1-yl-3a,4,5,6,7,7a-hexahydro-benzo
[d]-isoxazole (33)

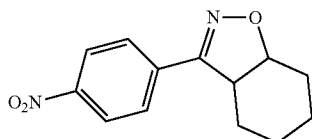
[0143]



[0144] Yield 14%, a colorless wax; $^1\text{H NMR}$ δ 8.78 (d, 1H, $J=8.5$), 7.86 (m, 2H), 7.57 (m, 2H), 7.52 (dd, 1H, $J=7.0, 6.9$), 7.48 (dd, 1H, $J=7.9, 7.5$), 4.65 (m, 1H), 3.53 (m, 1H), 2.20 (m, 1H), 1.84 (m, 1H), 1.61 (m, 1H), 1.60-1.52 (m, 2H), 1.40 (m, 1H), 1.30-1.20 (m, 2H); $^{13}\text{C NMR}$ δ 164.5, 134.5, 131.7 (3 s), 130.8 (d), 130.2 (s), 128.9, 128.1, 127.7, 127.1, 126.7, 125.3, 79.8, 48.1 (8 d), 26.1, 26.0, 22.7, 20.7 (4 t); MS(EI) obs. 251.10.

3-(4-Nitro-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo
[d]-isoxazole (34)

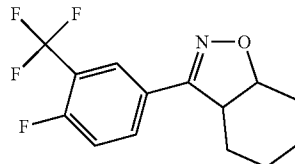
[0145]



[0146] Yield 6%, a yellow viscous oil; $^1\text{H NMR}$ δ 8.25 (m, 2H), 7.88 (m, 2H), 4.58 (m, 1H), 3.30 (m, 1H), 2.30 (m, 1H), 2.00 (m, 1H), 1.81 (m, 1H), 1.75-1.64 (m, 2H), 1.55 (m, 1H), 1.33-1.21 (m, 2H). MS(EI) obs. 246.05. [Giurg, M.; Mlochowski, J.; *Polish J. Chem.* 1997, 71, 1093-1101].

3-(4-Fluoro-3-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-
hexahydro-benzo-[d]-isoxazole (35)

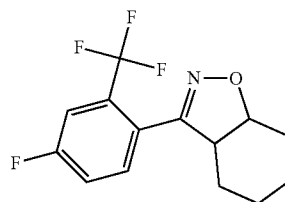
[0147]



[0148] Yield 55%, a yellow wax; $^1\text{H NMR}$ δ 7.94-7.88 (m, 2H), 7.25 (dd, 1H, $J=9.3, 9.2$), 4.54 (m, 1H), 3.72 (m, 1H), 2.26 (m, 1H), 1.97 (m, 1H), 1.78 (m, 1H), 1.77-1.59 (m, 2H), 1.54 (m, 1H), 1.38-1.15 (m, 2H); $^{13}\text{C NMR}$ δ 162.3 (s), 160.8, 138.7 (2 d), 132.6, 126.6 (2 dd), 126.1 (qd), 122.6 (q), 116.3 (dd), 81.4, 45.0 (2 d), 26.7, 25.3, 22.5, 20.4 (4 t).

3-(4-Fluoro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-
hexahydro-benzo[d]-isoxazole (36)

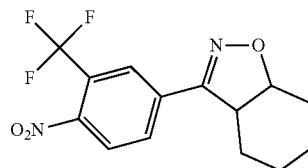
[0149]



[0150] Yield 51%, a yellow wax; $^1\text{H NMR}$ δ 7.52 (m, 1H), 7.47 (m, 1H), 7.30 (m, 1H), 4.63 (m, 1H), 3.31 (m, 1H), 2.10 (m, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.59-1.52 (m, 3H), 1.38-1.20 (m, 2H); $^{13}\text{C NMR}$ δ 163.1 (dd), 162.7 (s), 133.8 (dd), 131.4 (qd), 125.3 (d), 123.4 (qd), 119.3 (dd), 115.0 (ddq), 80.8, 48.4 (2 d), 25.8, 25.4, 22.3, 20.5 (4 t).

3-(4-Nitro-3-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-
hexahydro-benzo-[d]-isoxazole (37)

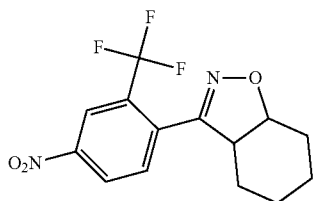
[0151]



[0152] Yield 1%, a yellow wax; $^1\text{H NMR}$ δ 8.15 (d, 1H, $J=1.7$), 8.02 (dd, 1H, $J=8.5, 1.7$), 7.93 (d, 1H, $J=8.5$), 4.61 (m, 1H), 3.31 (m, 1H), 2.33 (m, 1H), 2.00 (m, 1H), 1.80 (m, 1H), 1.78-1.63 (m, 2H), 1.54 (m, 1H), 1.32-1.21 (m, 2H); MS(EI) obs. 314.10.

3-(4-Nitro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo-[d]-isoxazole (38)

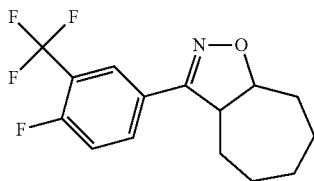
[0153]



[0154] Yield 4%, yellow viscous oil ^1H NMR: δ 8.62 (d, 1H, $J=2.1$), 8.45 (dd, 1H, $J=8.3, 2.1$), 7.76 (d, 1H, $J=8.3$), 4.69 (m, 1H), 3.40 (m, 1H), 2.15 (m, 1H), 1.82 (m, 1H), 1.72-1.62 (m, 2H), 1.58 (m, 1H), 1.34-1.22 (m, 2H); MS(EI) obs. 314.10.

3-(4-Fluoro-3-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (39)

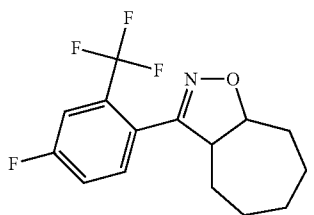
[0155]



[0156] Yield 70%, a yellow wax; ^1H NMR δ 7.90 (m, 1H), 7.83 (m, 1H), 7.24 (m, 1H), 4.91 (m, 1H), 3.72 (m, 1H), 2.05 (m, 1H), 1.98 (m, 1H), 1.83-1.47 (m, 6H), 1.45-1.36 (m, 2H); ^{13}C NMR δ 160.7 (dd), 157.0 (s), 132.7 (dd), 126.6 (d), 126.2 (qd), 122.7 (q), 119.3 (qd), 117.9 (dd), 85.9, 51.5 (2 d), 31.4, 30.5, 28.4, 27.4, 24.1 (5 t).

3-(4-Fluoro-2-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (40)

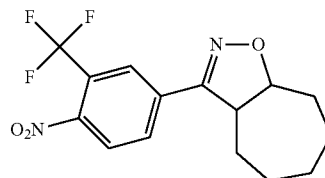
[0157]



[0158] Yield 73%, a yellow wax; ^1H NMR δ 7.49-7.43 (m, 2H), 7.29 (m, 1H), 4.92 (m, 1H), 3.71 (m, 1H), 2.07 (m, 1H), 1.94 (m, 1H), 1.85 (m, 1H), 1.73-1.62 (m, 2H), 1.59-1.45 (m, 3H), 1.38 (m, 1H), 1.27 (m, 1H); ^{13}C NMR δ 163.0 (dd), 158.9 (s), 134.0 (dd), 131.5 (qd), 125.7 (d), 123.7 (qd), 119.4 (dd), 114.7 (ddq), 85.6, 55.0 (2 d), 31.6, 30.7, 28.6, 27.5, 24.6 (5 t).

3-(4-Nitro-3-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (41)

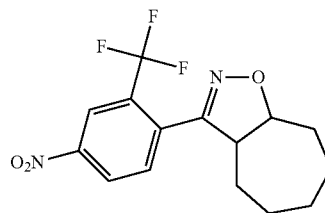
[0159]



[0160] Yield 58%, a yellow wax; ^1H NMR δ 8.14 (d, 1H, $J=1.5$), 7.95 (dd, 1H, $J=8.5, 1.5$), 7.94 (d, 1H, $J=8.5$), 4.99 (m, 1H), 3.77 (m, 1H), 2.09 (m, 1H), 2.01 (m, 1H), 1.81 (m, 1H), 1.79-1.60 (m, 2H), 1.60-1.52 (m, 3H), 1.51-1.42 (m, 2H); ^{13}C NMR δ 157.9, 148.2, 134.8 (3 s), 131.2 (d), 126.6 (q), 126.2 (d), 124.5 (dq), 122.1 (q), 86.9, 50.9 (2 d), 31.3, 30.4, 28.3, 27.4, 24.0 (5 t).

3-(4-Nitro-2-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (42)

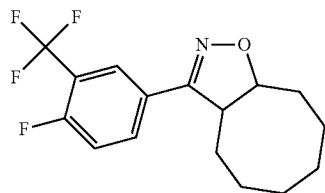
[0161]



[0162] Yield 24%, yellow viscous oil ^1H NMR: δ 8.62 (d, 1H, $J=2.1$), 8.44 (dd, 1H, $J=8.3, 2.1$), 7.72 (d, 1H, $J=8.3$), 4.99 (m, 1H), 3.80 (m, 1H), 2.81 (m, 1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.87 (m, 1H), 1.34-1.22 (m, 2H).

3-(4-Fluoro-3-trifluoromethyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (43)

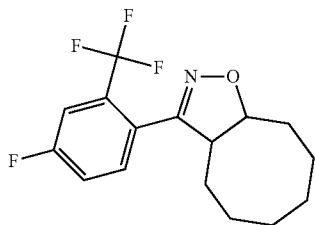
[0163]



[0164] Yield 63%, a yellow wax; ^1H NMR δ 7.92 (d, 1H, $J=7.0$), 7.84 (m, 1H), 7.26 (m, 1H), 4.54 (m, 1H), 3.42 (m, 1H), 2.06 (m, 1H), 1.88-1.73 (m, 4H), 1.68 (m, 1H), 1.60-1.50 (m, 2H), 1.42-1.25 (m, 3H); ^{13}C NMR δ 160.6 (dd), 160.8 (s), 132.7 (dd), 126.6 (d), 126.2 (qd), 122.6 (q), 119.3 (qd), 117.9 (dd), 86.6, 50.3 (2 d), 30.4, 25.8, 25.7, 25.6, 25.2, 24.8 (6 t).

3-(4-Fluoro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (44)

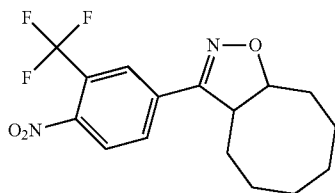
[0165]



[0166] Yield 30%, a yellow wax; $^1\text{H NMR}$ δ 7.44 (dd, 1H, $J=8.5, 5.5$), 7.42 (dd, 1H, $J=9.1, 2.7$), 7.26 (m, 1H), 4.63 (m, 1H), 3.41 (m, 1H), 2.00-1.91 (m, 2H), 1.70-1.41 (m, 6H), 1.40-1.10 (m, 4H); $^{13}\text{C NMR}$ δ 163.1 (dd), 160.5 (s), 134.4 (dd), 131.5 (qd), 125.4 (d), 123.3 (qd), 119.3 (dd), 115.0 (ddq), 86.1, 53.7 (2 d), 30.1, 26.7, 26.4, 25.7, 25.6, 24.2 (6 t).

3-(4-Nitro-3-trifluoromethyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (45)

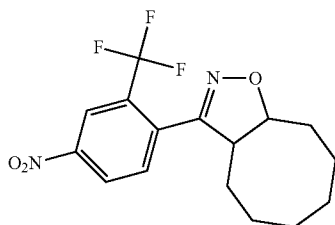
[0167]



[0168] Yield 17%, a yellow wax; $^1\text{H NMR}$ δ 8.10 (s, 1H), 7.91-7.89 (m, 2H), 4.58 (m, 1H), 3.42 (m, 1H), 2.12 (m, 1H), 2.01 (m, 1H), 1.82-1.70 (m, 4H), 1.66 (m, 1H), 1.55-1.44 (m, 2H), 1.40-1.25 (m, 3H); $^{13}\text{C NMR}$ δ 160.1, 148.3, 134.7 (3 s), 131.1 (d), 126.6 (q), 126.2 (d), 124.9 (dq), 122.1 (q), 87.6, 49.7 (2 d), 30.3, 25.8, 25.6, 25.6, 25.2, 24.9 (6 t).

3-(4-Nitro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (46)

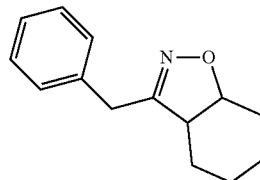
[0169]



[0170] Yield 16%, yellow viscous oil $^1\text{H NMR}$ δ 8.60 (d, 1H, $J=2.2$), 8.42 (dd, 1H, $J=8.4, 2.2$), 7.70 (d, 1H, $J=8.4$), 4.70 (dd, 1H, $J=10.4, 10.3$), 3.51 (t, 1H, $J=10.4$), 2.08-1.94 (m, 2H), 1.75-1.43 (m, 6H), 1.43-1.20 (m, 3H), 1.13 (m, 1H).

3-Benzyl-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (47)

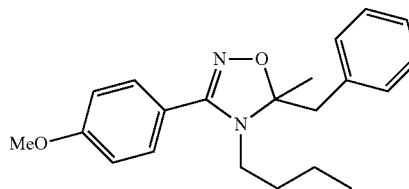
[0171]



[0172] Yield 16%, a colorless wax; $^1\text{H NMR}$ δ 7.31 (m, 2H), 7.28-7.24 (m, 3H), 4.34 (m, 1H), 3.82 (d, 1H, $J=15.0$), 3.53 (d, 1H, $J=15.0$), 2.73 (m, 1H), 1.94 (m, 1H), 1.73-1.61 (m, 2H), 1.51-1.40 (m, 3H), 1.29 (m, 1H), 1.18 (m, 1H); $^{13}\text{C NMR}$ δ 164.6, 136.4 (2 s), 129.3, 129.2, 127.4, 79.7, 46.0 (5 d), 33.6, 26.0, 25.1, 22.5, 20.7 (4 t).

5-Benzyl-4-butyl-3-(4-methoxy-phenyl)-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (48)

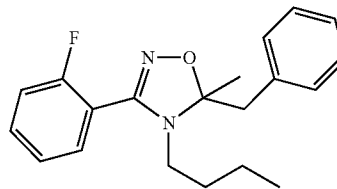
[0173]



[0174] Yield 23%, pale brown viscous oil, $^1\text{H NMR}$ δ 7.35 (m, 2H), 7.32-7.24 (m, 4H), 7.22 (m, 1H), 6.89 (m, 2H), 3.81 (s, 3H), 3.10 (m, 1H), 3.03 (d, 1H, $J=13.7$), 2.96 (d, 1H, $J=13.7$), 2.91 (m, 1H), 1.59 (s, 3H), 1.41 (m, 1H), 1.29 (m, 1H), 1.14 (m, 2H), 0.79 (t, 1H, $J=7.3$); $^{13}\text{C NMR}$ δ 161.1, 157.4, 136.1 (3 s), 130.7, 129.7, 127.9, 126.6 (4 d), 118.5 (s), 114.1 (d), 100.1 (s), 55.3 (q), 45.8, 43.6, 33.0 (3 t), 22.6 (q), 20.0 (t), 13.6 (q).

5-Benzyl-4-butyl-3-(2-fluoro-phenyl)-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (49)

[0175]

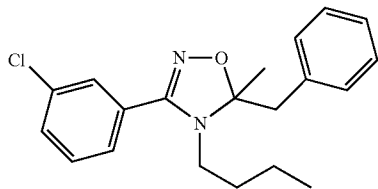


[0176] Yield 11%, brown viscous oil, $^1\text{H NMR}$ δ 7.42 (m, 1H), 7.38 (m, 2H), 7.30 (m, 2H), 7.28-7.23 (m, 2H), 7.16 (t, 1H, $J=7.5$), 7.12 (t, 1H, $J=9.1$), 3.12 (d, 1H, $J=13.8$), 3.00 (m, 1H), 2.99 (d, 1H, $J=13.8$), 2.87 (ddd, 1H, $J=15.4, 10.1, 5.8$), 1.58 (s, 3H), 1.35 (m, 1H), 1.26 (m, 1H), 1.10 (m, 2H), 0.73 (t, 1H, $J=7.3$); $^{13}\text{C NMR}$ δ 160.2 (d), 153.3, 135.8 (2 s), 132.4,

131.5 (2 dd), 130.7, 128.0, 126.6 (3 d), 124.4, 116.0 (2 dd), 114.4 (d), 100.9 (s), 44.7, 43.0, 32.8 (3 t), 23.0 (q), 19.9 (t), 13.5 (q).

5-Benzyl-4-butyl-3-(3-chloro-phenyl)-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (50)

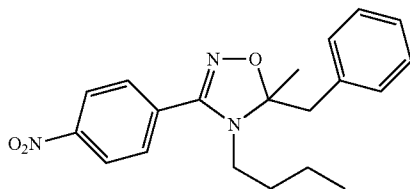
[0177]



[0178] Yield 54%, pale brown viscous oil, $^1\text{H NMR}$ δ 7.39 (d, 1H, $J=7.5$), 7.35 (m, 2H), 7.33-7.28 (m, 4H), 7.27-7.21 (m, 2H), 3.08 (m, 1H), 3.03 (d, 1H, $J=13.8$), 2.98 (d, 1H, $J=13.8$), 2.92 (m, 1H), 1.62 (s, 3H), 1.46 (m, 1H), 1.31 (m, 1H), 1.17 (m, 2H), 0.80 (t, 1H, $J=7.4$); $^{13}\text{C NMR}$ δ 155.4, 135.7, 134.6 (3 s), 130.7, 130.4, 129.9, 128.4 (4 d), 128.1 (s), 128.0, 126.8, 126.4 (3 d), 100.9 (s), 45.9, 43.5, 33.0 (3 t), 22.9 (q), 19.9 (t), 13.6 (q).

5-Benzyl-4-butyl-5-methyl-3-(4-nitro-phenyl)-4,5-dihydro-[1,2,4]oxadiazole (51)

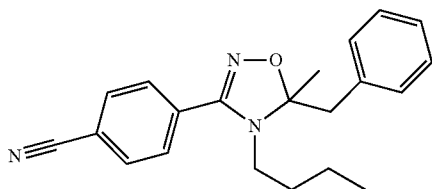
[0179]



[0180] Yield 29%, brown viscous oil, $^1\text{H NMR}$ δ 8.23 (m, 2H), 7.50 (m, 2H), 7.35 (m, 2H), 7.30 (m, 2H), 7.25 (m, 1H), 3.10 (ddd, 1H, $J=15.6, 10.5, 5.2$), 3.02 (d, 1H, $J=14.0$), 3.01 (d, 1H, $J=14.0$), 2.95 (ddd, 1H, $J=15.6, 10.9, 5.6$), 1.66 (s, 3H), 1.46 (m, 1H), 1.29 (m, 1H), 1.17 (m, 2H), 0.81 (t, 1H, $J=7.3$); $^{13}\text{C NMR}$ δ 155.8, 148.8, 135.6, 132.8 (4 s), 130.7, 129.1, 128.0, 126.8, 123.9 (5 d), 101.8 (s), 46.1, 43.7, 33.1 (3 t), 22.9 (q), 20.0 (t), 13.6 (q).

4-(5-Benzyl-4-butyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzotrile (52)

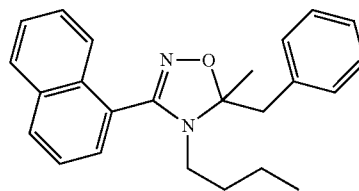
[0181]



[0182] Yield 23%, brown viscous oil, $^1\text{H NMR}$ δ 7.67 (m, 2H), 7.44 (m, 2H), 7.34 (m, 2H), 7.29 (m, 2H), 7.23 (m, 1H), 3.09 (ddd, 1H, $J=15.4, 10.6, 5.1$), 3.01 (d, 1H, $J=14.0$), 3.00 (d, 1H, $J=14.0$), 2.92 (ddd, 1H, $J=15.4, 10.9, 5.7$), 1.64 (s, 3H), 1.43 (m, 1H), 1.27 (m, 1H), 1.16 (m, 2H), 0.80 (t, 1H, $J=7.3$); $^{13}\text{C NMR}$ δ 156.1, 135.6 (2 s), 132.4 (d), 131.0 (s), 130.7, 128.8, 128.0, 126.8 (4 d), 118.1, 114.0, 101.5 (3 s), 46.1, 43.7, 33.0 (3 t), 22.9 (q), 19.9 (t), 13.6 (q).

5-Benzyl-4-butyl-5-methyl-3-naphthalen-1-yl-4,5-dihydro-[1,2,4]oxadiazole (53)

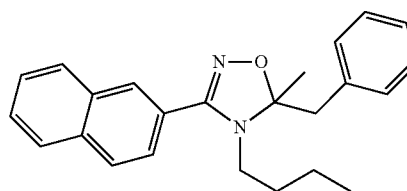
[0183]



[0184] Yield 14%, brown viscous oil, $^1\text{H NMR}$ δ 7.87 (d, 1H, $J=7.7$), 7.80 (d, 1H, $J=8.2$), 7.49 (m, 2H), 7.47-7.41 (m, 2H), 7.39-7.32 (m, 6H), 3.19 (d, 1H, 14.2), 3.17 (d, 1H, 14.2), 2.84 (m, 2H), 1.68 (s, 3H), 1.26 (m, 1H), 1.15 (m, 1H), 0.92 (m, 2H), 0.54 (t, 3H, $J=7.4$); $^{13}\text{C NMR}$ δ 155.9, 136.2, 133.3, 131.6 (4 s), 130.9, 130.4, 128.2, 128.2, 128.1, 127.0, 126.8, 126.3, 125.1, 124.9 (10 d), 123.5, 101.0 (2 s), 45.0, 42.9, 32.8 (3 t), 24.9 (q), 19.8 (t), 13.3 (q).

5-Benzyl-4-butyl-5-methyl-3-naphthalen-2-yl-4,5-dihydro-[1,2,4]oxadiazole (54)

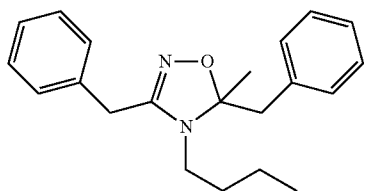
[0185]



[0186] Yield 26%, brown viscous oil, $^1\text{H NMR}$ δ 7.87 (s, 1H), 7.85-7.81 (m, 3H), 7.51 (m, 2H), 7.44-7.39 (m, 3H), 7.31 (m, 2H), 7.25 (m, 1H), 3.16 (ddd, 1H, $J=15.4, 10.5, 5.3$), 3.09 (d, 1H, 13.8), 3.03 (d, 1H, 13.8), 2.85 (ddd, 1H, $J=15.4, 10.7, 5.6$), 1.64 (s, 3H), 1.46 (m, 1H), 1.34 (m, 1H), 1.13 (m, 2H), 0.76 (t, 3H, $J=7.4$); $^{13}\text{C NMR}$ δ 157.7, 136.0, 134.0, 132.8 (4 s), 130.8, 128.4, 128.4, 128.4, 128.0, 127.8, 127.0, 126.6, 126.6 (10 d), 123.6, 100.6 (2 s), 45.8, 43.6, 33.0 (3 t), 22.8 (q), 19.9 (t), 13.6 (q).

3,5-Dibenzyl-4-butyl-5-methyl-4,5-dihydro-[1,2,4]
oxadiazole (55)

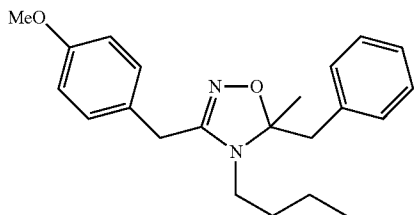
[0187]



[0188] Yield 34%, brown viscous oil, $^1\text{H NMR}$ δ 7.27-7.20 (m, 8H), 7.08 (m, 2H), 3.61 (d, 1H, $J=15.9$), 3.43 (d, 1H, $J=15.9$), 2.96 (d, 1H, $J=14.0$), 2.86 (d, 1H, $J=14.0$), 2.86 (m, 1H), 2.74 (m, 1H), 1.44 (s, 3H), 1.48-1.22 (m, 2H), 1.14 (m, 2H), 0.81 (t, 1H, $J=7.3$); $^{13}\text{C NMR}$ δ 155.0, 135.9, 134.6 (3 s), 130.6, 128.7, 128.3, 128.1, 127.0, 126.5 (6 d), 100.1 (s), 43.9, 42.1, 33.2, 30.2 (4 t), 23.6 (q), 20.1 (t), 13.7 (2 q).

5-Benzyl-4-butyl-3-(4-methoxy-phenyl)-5-methyl-4,
5-dihydro-[1,2,4]oxadiazole (56)

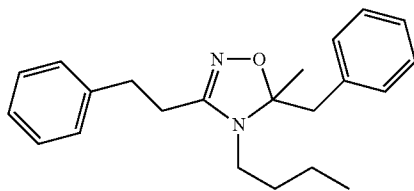
[0189]



[0190] Yield 23%, brown viscous oil, $^1\text{H NMR}$ δ 7.28-7.22 (m, 5H), 6.97 (m, 2H), 6.78 (m, 2H), 3.78 (s, 3H), 3.54 (d, 1H, $J=15.9$), 3.36 (d, 1H, $J=15.9$), 2.95 (d, 1H, $J=14.0$), 2.85 (d, 1H, $J=14.0$), 2.85 (m, 1H), 2.75 (m, 1H), 1.43 (s, 3H), 1.38-1.24 (m, 2H), 1.16 (m, 2H), 0.83 (t, 1H, $J=7.3$); $^{13}\text{C NMR}$ δ 158.6, 155.2, 135.9 (3 s), 130.6, 129.4, 128.1 (3 d), 126.5 (s), 126.5, 114.2 (2 d), 100.0 (s), 55.3 (q), 43.9, 42.0, 33.3, 29.3 (4 t), 23.9 (q), 20.1 (t), 13.7 (q).

5-Benzyl-4-butyl-5-methyl-3-phenethyl-4,5-dihydro-
[1,2,4]oxadiazole (57)

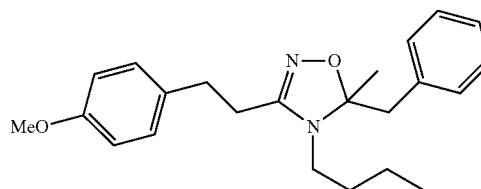
[0191]



[0192] Yield 31%, brown viscous oil, $^1\text{H NMR}$ δ 7.31-7.27 (m, 4H), 7.27-7.25 (m, 2H), 7.21 (m, 1H), 7.19 (m, 1H), 7.15 (m, 2H), 3.04 (ddd, 1H, $J=15.4, 9.9, 5.9$), 2.95 (d, 1H, $J=13.9$), 2.94 (ddd, 1H, $J=15.4, 10.0, 6.0$), 2.83 (d, 1H, $J=13.9$), 2.74-2.67 (m, 2H), 2.42 (ddd, 1H, $J=16.1, 10.5, 6.3$), 2.28 (ddd, 1H, $J=16.1, 10.7, 5.8$), 1.47 (m, 2H), 1.46 (s, 3H), 1.29 (m, 2H), 0.92 (t, 3H, $J=7.4$); $^{13}\text{C NMR}$ δ 156.0, 140.8, 135.9 (3 s), 130.6, 128.5, 128.3, 127.9, 126.5, 126.2 (6 d), 99.9 (s), 44.2, 42.1, 33.5, 32.0, 26.1 (5 t), 23.8 (q), 20.2 (t), 13.8 (q).

5-Benzyl-4-butyl-3-[2-(4-methoxy-phenyl)-ethyl]-5-
methyl-4,5-dihydro-[1,2,4]oxadiazole (58)

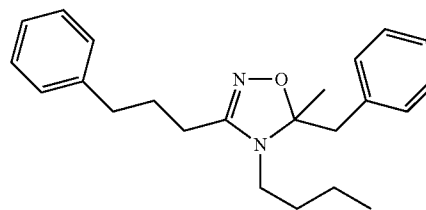
[0193]



[0194] Yield 22%, brown viscous oil, $^1\text{H NMR}$ δ 7.30-7.25 (m, 4H), 7.22 (m, 1H), 7.07 (m, 2H), 6.82 (m, 2H), 3.77 (s, 3H), 3.04 (ddd, 1H, $J=15.4, 9.8, 6.0$), 2.95 (d, 1H, $J=13.9$), 2.94 (ddd, 1H, $J=15.4, 10.0, 5.9$), 2.83 (d, 1H, $J=13.9$), 2.70-2.67 (m, 2H), 2.39 (ddd, 1H, $J=15.5, 10.1, 6.5$), 2.26 (ddd, 1H, $J=15.5, 10.7, 5.8$), 1.47 (m, 2H), 1.46 (s, 3H), 1.29 (m, 2H), 0.92 (t, 3H, $J=7.3$); $^{13}\text{C NMR}$ δ 158.1, 156.0, 136.0, 132.9 (4 s), 130.6, 129.3, 129.2, 126.5, 114.0 (5 d), 99.9 (s), 55.3 (q), 44.2, 42.1, 33.6, 31.2, 26.4 (5 t), 23.7 (q), 20.2 (t), 13.7 (q).

5-Benzyl-4-butyl-5-methyl-3-(3-phenyl-propyl)-4,5-
dihydro-[1,2,4]oxadiazole (59)

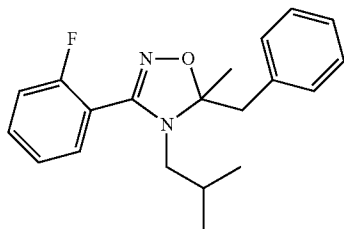
[0195]



[0196] Yield 13%, brown viscous oil, $^1\text{H NMR}$ δ 7.28 (m, 2H), 7.27-7.23 (m, 4H), 7.18 (m, 2H), 7.12 (m, 2H), 2.95 (m, 1H), 2.94 (d, 1H, $J=13.9$), 2.91 (m, 1H), 2.83 (d, 1H, $J=13.9$), 2.66-2.55 (m, 2H), 2.12 (m, 1H), 2.01 (m, 1H), 1.70 (m, 2H), 1.61 (m, 2H), 1.45 (s, 3H), 1.24 (m, 2H), 0.89 (t, 3H, $J=7.3$); $^{13}\text{C NMR}$ δ 156.2, 141.3, 135.9 (3 s), 130.6, 128.5, 128.3, 128.3, 126.5, 126.0 (6 d), 99.7 (s), 44.2, 42.1, 33.5, 32.3, 27.6, 27.2 (6 t), 23.8 (q), 20.1 (t), 13.7 (q).

5-Benzyl-3-(2-fluoro-phenyl)-4-isobutyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (60)

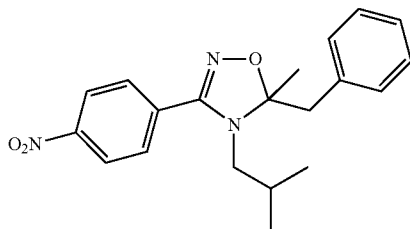
[0197]



[0198] Yield 5%, pale brown viscous oil, $^1\text{H NMR}$ δ 7.43 (m, 1H), 7.38 (m, 2H), 7.31 (m, 2H), 7.28-7.23 (m, 2H), 7.176 (m, 1H), 7.13 (m, 1H), 3.21 (d, 1H, $J=13.7$), 2.95 (d, 1H, $J=13.7$), 2.87 (dd, 1H, $J=15.3, 7.7$), 2.87 (dd, 1H, $J=15.3, 7.6$), 1.55 (s, 3H), 1.55 (m, 1H), 0.76 (d, 1H, $J=6.6$), 0.69 (d, 1H, $J=6.6$); $^{13}\text{C NMR}$ δ 160.8 (d), 153.7, 135.8 (2 s), 132.4, 131.5 (2 dd), 130.8, 128.1, 126.6 (3 d), 124.4, 116.0 (2 dd), 114.5 (d), 101.2 (s), 50.6, 43.5 (2 t), 29.5 (d), 22.8, 20.1, 20.0 (3 q).

5-Benzyl-4-isobutyl-5-methyl-3-(4-nitro-phenyl)-4,5-dihydro-[1,2,4]oxadiazole (61)

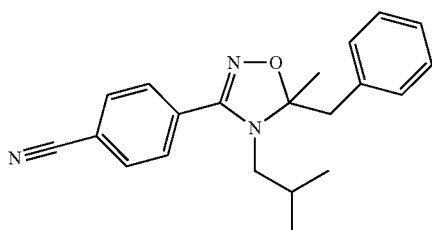
[0199]



[0200] Yield 29%, yellow wax, $^1\text{H NMR}$ δ 8.21 (m, 2H), 7.44 (m, 2H), 7.38 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 3.10 (d, 1H, $J=14.0$), 2.98 (dd, 1H, $J=14.9, 7.7$), 2.98 (d, 1H, $J=14.0$), 2.79 (dd, 1H, $J=14.9, 8.2$), 1.65 (s, 3H), 1.63 (m, 1H), 0.87 (d, 1H, $J=6.6$), 0.73 (d, 1H, $J=6.6$); $^{13}\text{C NMR}$ δ 156.0, 148.8, 135.5, 132.9 (4 s), 130.7, 129.6, 128.1, 126.9, 123.7 (5 d), 101.9 (s), 51.2, 45.5 (2 t), 28.6 (d), 23.3, 20.2, 20.1 (3 q).

4-(5-Benzyl-4-isobutyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzonitrile (62)

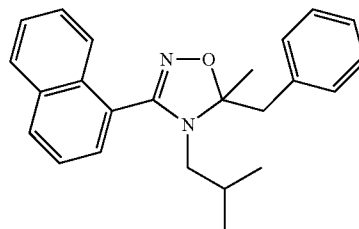
[0201]



[0202] Yield 5%, yellow wax, $^1\text{H NMR}$ δ 7.67 (m, 2H), 7.66 (m, 2H), 7.38 (m, 2H), 7.30 (m, 2H), 7.25 (m, 1H), 3.09 (d, 1H, $J=14.0$), 2.97 (d, 1H, $J=14.0$), 2.96 (dd, 1H, $J=14.9, 7.0$), 2.76 (dd, 1H, $J=14.9, 8.2$), 1.63 (s, 3H), 1.63 (m, 1H), 0.86 (d, 1H, $J=6.6$), 0.73 (d, 1H, $J=6.6$); $^{13}\text{C NMR}$ δ 157.1, 135.9 (2 s), 132.9 (d), 131.4 (s), 131.1, 129.7, 128.5, 127.8 (4 d), 118.4, 113.6, 102.2 (3 s), 51.2, 45.5 (2 t), 29.0 (d), 23.7, 20.6, 20.5 (3 q).

5-Benzyl-4-isobutyl-5-methyl-3-naphthalen-1-yl-4,5-dihydro-[1,2,4]oxadiazole (63)

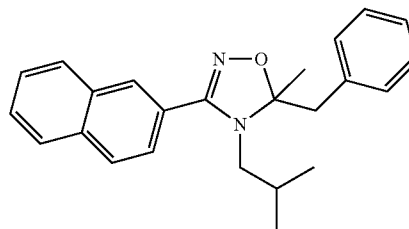
[0203]



[0204] Yield 8%, brown viscous oil, $^1\text{H NMR}$ δ 7.88 (d, 1H, $J=8.3$), 7.81 (d, 1H, $J=8.1$), 7.51 (m, 2H), 7.48-7.30 (m, 8H), 3.28 (d, 1H, 14.1), 3.10 (d, 1H, 14.1), 2.74 (m, 2H), 1.66 (s, 3H), 1.38 (m, 1H), 0.64 (d, 3H, $J=6.7$), 0.54 (d, 3H, $J=6.7$); $^{13}\text{C NMR}$ δ 156.2, 136.0, 133.3, 131.8 (4 s), 131.0, 130.4, 128.3, 128.3, 128.1, 127.0, 126.8, 126.3, 125.2, 124.8 (10 d), 123.5, 101.1 (2 s), 50.6, 44.3 (2 t), 27.9 (d), 24.5, 20.1, 20.0 (3 q).

5-Benzyl-4-isobutyl-5-methyl-3-naphthalen-2-yl-4,5-dihydro-[1,2,4]oxadiazole (64)

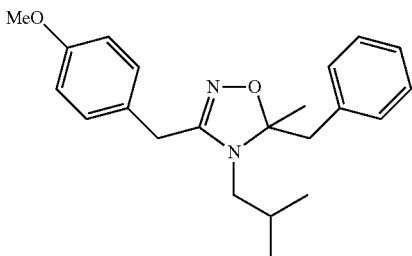
[0205]



[0206] Yield 25%, pale brown viscous oil, $^1\text{H NMR}$ δ 7.86-7.81 (m, 3H), 7.83 (s, 1H), 7.51 (m, 1H), 7.50 (m, 1H), 7.43 (m, 2H), 7.38 (m, 1H), 7.33 (m, 2H), 7.26 (m, 1H), 3.18 (d, 1H, 13.8), 3.06 (dd, 1H, $J=14.8, 7.0$), 3.2.99 (d, 1H, 13.8), 2.85 (dd, 1H, $J=14.8, 8.2$), 1.65 (m, 1H), 1.63 (s, 3H), 0.86 (d, 1H, $J=6.6$), 0.72 (d, 1H, $J=6.6$); $^{13}\text{C NMR}$ δ 157.9, 136.0, 133.9, 132.8 (4 s), 130.8, 128.9, 128.4, 128.3, 128.1, 127.8, 127.2, 126.7, 126.6, 125.3 (10 d), 123.7, 100.9 (2 s), 51.2, 45.2 (2 t), 28.5 (d), 23.0, 20.2, 20.1 (3 q).

5-Benzyl-4-isobutyl-3-(4-methoxy-benzyl)-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (65)

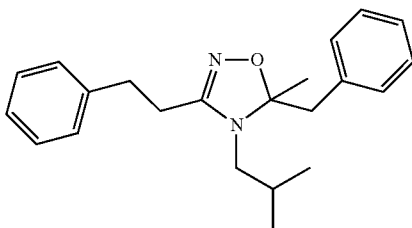
[0207]



[0208] Yield 25%, brown viscous oil, $^1\text{H NMR}$ δ 7.28-7.22 (m, 5H), 7.03 (m, 2H), 6.80 (m, 2H), 3.77 (s, 3H), 3.60 (d, 1H, $J=15.9$), 3.40 (d, 1H, $J=15.9$), 3.01 (d, 1H, $J=13.8$), 2.75 (d, 1H, $J=13.8$), 2.68 (dd, 1H, $J=14.8$, 7.7), 2.57 (dd, 1H, $J=14.8$, 7.8), 1.78 (m, 1H), 1.40 (s, 3H), 0.82 (d, 1H, $J=6.7$), 0.80 (d, 1H, $J=6.7$); $^{13}\text{C NMR}$ δ 158.6, 155.9, 135.9 (3 s), 130.7, 129.5, 128.1, 126.5 (4 d), 126.3 (s), 114.2 (d), 100.0 (s), 55.2 (q), 49.9, 43.0, 29.5 (3 t), 28.7 (d), 23.2, 20.1, 20.1.7 (3 q).

5-Benzyl-4-isobutyl-5-methyl-3-phenethyl-4,5-dihydro-[1,2,4]oxadiazole (66)

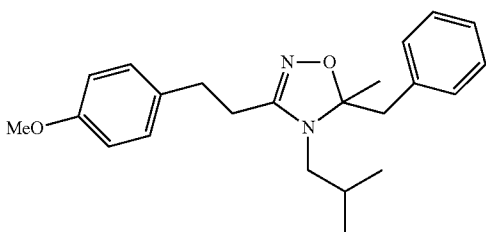
[0209]



[0210] Yield 6%, pale brown viscous oil, $^1\text{H NMR}$ δ 7.31-7.27 (m, 4H), 7.27-7.25 (m, 2H), 7.21 (m, 1H), 7.19 (m, 1H), 7.16 (m, 2H), 3.00 (d, 1H, $J=13.8$), 3.04 (dd, 1H, $J=14.9$, 7.8), 2.82-2.69 (m, 4H), 2.44 (ddd, 1H, $J=16.6$, 11.0, 5.6), 2.29 (ddd, 1H, $J=16.6$, 11.1, 5.3), 1.82 (m, 1H), 1.45 (s, 3H), 0.91 (d, 1H, $J=6.7$), 0.91 (d, 1H, $J=6.7$); $^{13}\text{C NMR}$ δ 156.8, 140.9, 135.9 (3 s), 130.7, 128.6, 128.3, 128.0, 126.5, 126.3 (6 d), 100.2 (s), 50.1, 43.4, 31.7 (3 t), 29.0 (d), 26.4 (t), 23.5, 20.3, 20.2 (3 q).

5-Benzyl-4-isobutyl-3-[2-(4-methoxy-phenyl)-ethyl]-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (67)

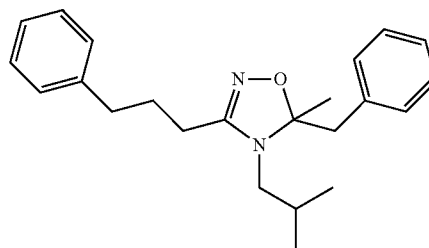
[0211]



[0212] Yield 23%, brown viscous oil, $^1\text{H NMR}$ δ 7.32-7.24 (m, 4H), 7.22 (m, 1H), 7.08 (m, 2H), 6.83 (m, 2H), 3.77 (s, 3H), 3.00 (d, 1H, $J=13.8$), 2.83 (dd, 1H, $J=14.9$, 7.8), 2.79 (dd, 1H, $J=14.9$, 7.7), 2.78 (d, 1H, $J=13.8$), 2.67 (m, 2H), 2.40 (ddd, 1H, $J=15.7$, 10.8, 5.9), 2.26 (ddd, 1H, $J=15.7$, 11.1, 5.5), 1.82 (m, 1H), 1.44 (s, 3H), 0.92 (d, 3H, $J=6.5$), 0.91 (d, 3H, $J=6.5$); $^{13}\text{C NMR}$ δ 158.1, 156.8, 135.9, 133.0 (4 s), 130.7, 129.3, 128.0, 126.5, 114.0 (5 d), 100.1 (s), 55.3 (q), 50.1, 43.4, 30.9 (3 t), 29.0 (d), 26.7 (t), 23.4, 20.3, 20.2 (3 q).

5-Benzyl-4-isobutyl-5-methyl-3-(3-phenyl-propyl)-4,5-dihydro-[1,2,4]oxadiazole (68)

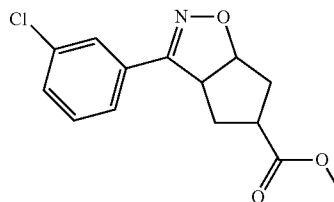
[0213]



[0214] Yield 13%, pale brown viscous oil, $^1\text{H NMR}$ δ 7.32-7.24 (m, 6H), 7.21-7.17 (m, 2H), 7.13 (m, 2H), 2.99 (d, 1H, $J=13.8$), 2.82-2.72 (m, 3H), 2.66-2.57 (m, 2H), 2.14 (m, 1H), 2.02 (m, 1H), 1.76 (m, 3H), 1.42 (s, 3H), 0.86 (d, 3H, $J=6.7$), 0.84 (d, 3H, $J=6.7$); $^{13}\text{C NMR}$ δ 156.0, 141.3, 135.9 (3 s), 130.6, 128.5, 128.3, 128.0, 126.5, 126.0 (6 d), 99.9 (s), 50.0, 43.3, 35.1 (3 t), 29.0 (d), 27.1 (t), 23.5 (q), 23.2 (t), 20.2, 20.1 (2 q).

Methyl 3-(3-chloro-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (69)

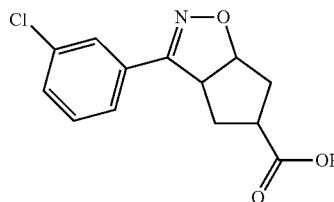
[0215]



[0216] Yield 89%, colourless viscous oil, $^1\text{H NMR}$ δ 7.65 (m, 1H), 7.55 (d, 1H, $J=7.5$), 7.39 (d, 1H, $J=8.5$), 7.32 (dd, 1H, $J=7.9$, 7.7), 5.28 (dd, 1H, $J=8.7$, 5.2), 4.11 (m, 1H), 3.68 (s, 3H), 2.85 (m, 1H), 2.46 (dd, 1H, $J=14.2$, 6.3), 2.22-2.17 (m, 2H), 2.14 (ddd, 1H, 14.2, 11.9, 5.2); $^{13}\text{C NMR}$ δ 174.4, 157.2, 134.9, 130.7 (4 s), 130.1, 130.0, 126.9, 125.0, 87.1 (5 d), 52.0 (q), 51.3, 41.6 (2 d), 39.1, 34.9 (2 t).

3-(3-Chloro-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylic acid (70)

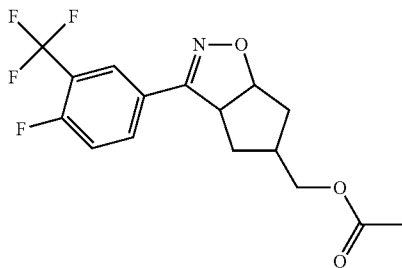
[0217]



[0218] Yield 38%, colourless viscous oil, ^1H NMR δ 7.65 (m, 1H), 7.55 (d, 1H, $J=7.6$), 7.38 (d, 1H, $J=8.5$), 7.33 (dd, 1H, $J=7.8, 7.6$), 5.29 (dd, 1H, $J=8.7, 5.1$), 4.13 (m, 1H), 2.88 (m, 1H), 2.49 (dd, 1H, $J=13.9, 5.9$), 2.25-2.29 (m, 2H), 2.14 (m, 1H); ^{13}C NMR δ 179.1, 157.2, 134.9, 130.5 (4 s), 130.1, 130.0, 126.9, 125.0, 87.1 (5 d), 51.3, 41.5 (2 d), 39.0, 34.7 (2 t).

3-(4-Fluoro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-5-ylmethyl acetate (71)

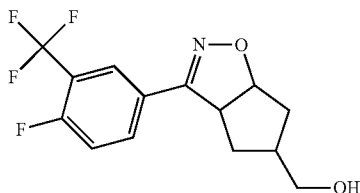
[0219]



[0220] Yield 90%, colourless viscous oil, ^1H NMR δ 7.89 (d, 1H, $J=6.7$), 7.87 (m, 1H), 7.25 (m, 1H), 5.28 (dd, 1H, $J=8.8, 5.6$), 4.11-4.05 (m, 3H), 2.33 (m, 2H), 2.04 (s, 3H), 1.99 (m, 1H), 1.75 (m, 1H), 1.66 (m, 1H); ^{13}C NMR δ 170.9 (s), 160.3 (dd), 156.5 (s), 132.2 (dd), 125.8 (d), 125.7 (qd), 122.2 (q), 119.1 (qd), 117.6 (dd), 87.8 (d), 66.0 (t), 51.3, 38.8 (2 d), 36.7, 34.4 (2 t), 20.8 (q).

[3-(4-Fluoro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-5-yl]-methanol (72)

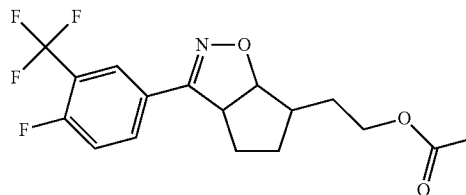
[0221]



[0222] Yield 25%, colourless viscous oil; ^1H NMR δ 7.90 (d, 1H, $J=7.3$), 7.87 (m, 1H), 7.24 (d, 1H, $J=9.3$), 5.28 (dd, 1H, $J=8.9, 5.6$), 4.08 (dd, 1H, $J=9.2, 8.7$), 3.70 (m, 1H), 3.62 (m, 1H), 2.30 (m, 1H), 2.22 (m, 1H), 2.02, (dd, 1H, $J=13.1, 6.2$), 1.78 (ddd, 1H, $J=20.9, 11.6, 9.4$), 1.67 (ddd, 1H, $J=13.3, 8.05, 1.9$), 1.34 (br s, 1H, OH); ^{13}C NMR δ 160.3 (dd), 156.6 (s), 132.2 (dd), 125.7 (d), 125.6 (qd), 122.2 (q), 119.1 (qd), 117.5 (dd), 88.0 (d), 64.9 (t), 51.4, 39.9 (2 d), 38.4, 34.2 (2 t).

2-[3-(4-Fluoro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-6-yl]-ethyl acetate (73)

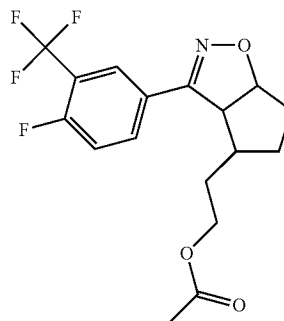
[0223]



[0224] Yield 66%, colourless viscous oil, ^1H NMR δ 7.91 (d, 1H, $J=6.8$), 7.87 (m, 1H), 7.24 (m, 1H), 5.12 (dd, 1H, $J=8.6, 4.4$), 4.19 (m, 2H), 4.05 (dd, 1H, $J=8.6, 8.5$), 2.07 (m, 2H), 2.07 (s, 3H), 2.02-1.82 (m, 4H), 1.27 (m, 1H); ^{13}C NMR δ 171.1 (s), 160.3 (dd), 156.9 (s), 132.2 (dd), 125.8 (d), 125.7 (qd), 122.3 (q), 119.2 (qd), 117.6 (dd), 88.8 (d), 63.4 (t), 51.5, 45.1 (2 d), 30.2, 28.9, 27.9 (3 t), 21.0 (q).

2-[3-(4-Fluoro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-4-yl]-ethyl acetate (74)

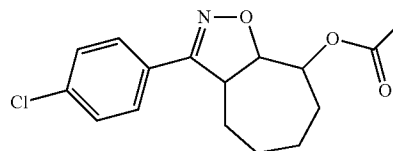
[0225]



[0226] Yield 26%, colourless viscous oil, ^1H NMR δ 7.90 (d, 1H, $J=6.9$), 7.88 (m, 1H), 7.24 (m, 1H), 5.16 (dd, 1H, $J=8.6, 4.7$), 4.04 (dd, 1H, $J=8.6, 8.5$), 3.80 (m, 1H), 2.21 (m, 1H), 1.99 (m, 1H), 1.97-1.80 (m, 4H), 1.35-1.22 (m, 2H).

3-(4-Chloro-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazol-8-yl acetate (75)

[0227]

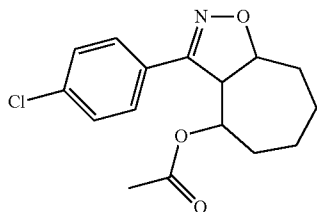


[0228] Yield 4%, colourless viscous oil, ^1H NMR δ 7.58 (m, 2H), 7.37 (m, 2H), 5.21 (dd, 1H, $J=10.3, 10.0$), 4.81 (ddd, 1H, $J=10.0, 8.8, 0.5$), 3.90 (ddd, 1H, $J=11.3, 10.3, 2.3$), 2.11 (s, 3H), 1.92 (m, 1H), 1.89-1.77 (m, 3H), 1.76-1.55 (m, 3H).

1.32 (m, 1H); ^{13}C NMR δ 170.2, 159.3, 136.0 (3 s), 129.2, 128.3 (2 d), 127.1 (s), 86.7, 75.3, 50.2 (3 d), 32.2, 28.5, 26.9, 26.7 (4 t), 21.3 (q).

3-(4-Chloro-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazol-4-yl acetate (76)

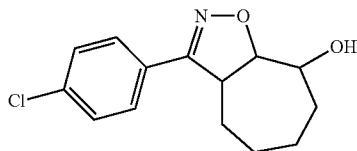
[0229]



[0230] Yield 3%, colourless viscous oil, ^1H NMR δ 7.54 (m, 2H), 7.36 (m, 2H), 5.17 (ddd, 1H, $J=7.1$, 3.0, 0.5), 4.92 (ddd, 1H, $J=11.4$, 9.3, 5.1), 3.90 (dd, 1H, $J=11.4$, 3.0), 2.23-2.10 (m, 2H), 2.03 (m, 1H), 1.90 (s, 3H), 1.84 (m, 1H), 1.63 (m, 2H), 1.53 (m, 1H), 1.42 (m, 1H); ^{13}C NMR δ 169.8, 156.9, 135.8 (3 s), 129.0, 128.3 (2 d), 128.2 (s), 83.8, 71.7, 54.3 (3 d), 32.2, 30.1, 25.5, 23.3 (4 t), 20.9 (q).

3-(4-Chloro-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazol-8-ol (77)

[0231]

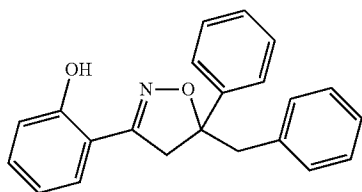


[0232] Yield 10%, colourless viscous oil, ^1H NMR δ 7.56 (m, 2H), 7.38 (m, 2H), 4.65 (dd, 1H, $J=10.6$, 8.8), 4.06 (m, 1H), 3.68 (m, 1H), 2.31 (br s, 1H, OH), 1.98 (m, 1H), 1.92-1.83 (m, 3H), 1.66 (m, 1H), 1.49-1.40 (m, 2H), 1.27 (m, 1H); ^{13}C NMR δ 159.6, 136.0 (2 s), 129.1, 128.4 (2 d), 127.2 (s), 90.0, 73.2, 50.0 (3 d), 34.0, 29.7, 28.7, 27.2 (4 t).

Examples 78-84

5-Benzyl-3-(2-hydroxy-phenyl)-5-phenyl-4,5-dihydro-isoxazole (78)

[0233]



[0234] Method B:

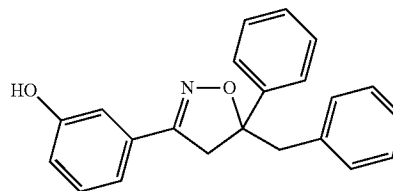
[0235] To a solution of 5-Benzyl-3-(2-methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (compound 12, 0.463 g, 2 mmol, synthesized using the general method described in Example 1) in 2 ml of dichloromethane was added 2.2 ml of 1M BBr_3 in dichloromethane (2.2 mmol; for compounds having two or three aromatic methoxyl groups, 4.2 mmol and 6.2 mmol was used, respectively) and the solution was stirred under argon at room temperature overnight. The organic layer was evaporated to give the oily product, which was purified by column chromatography using dichloromethane as an eluent.

[0236] Yield 83%, $\text{mp}=107.5\text{-}108.9^\circ\text{C}$., ^1H NMR δ 8.30 (br s, 1H, OH), 7.36 (m, 2H), 7.31 (m, 2H), 7.28-7.22 (m, 3H), 7.21-7.14 (m, 3H), 7.10-7.04 (m, 3H), 6.98 (d, 1H, $J=7.4$), 6.84 (dd, 1H, $J=7.3$, 7.2), 3.63 (d, 1H, $J=16.4$), 3.56 (d, 1H, $J=16.4$), 3.33 (d, 1H, $J=14.0$), 3.27 (d, 1H, $J=14.0$); ^{13}C NMR δ 158.7, 157.3, 143.6, 135.4 (4 s), 131.6, 130.6, 128.4, 128.2, 128.1, 127.6, 126.9, 125.3, 119.3, 116.9 (10 d), 114.0 (s), 90.0 (s), 47.0, 45.5 (2 t).

[0237] The following compounds included in the invention were prepared by Method B using appropriate starting materials:

5-Benzyl-3-(3-hydroxyphenyl)-5-phenyl-4,5-dihydro-isoxazole (79)

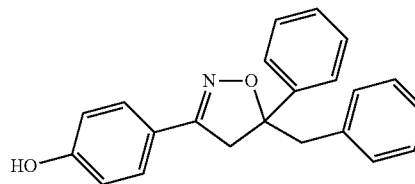
[0238]



[0239] Yield 45%, colorless viscous oil $^\circ\text{C}$., ^1H NMR δ 7.34 (m, 2H), 7.30 (m, 2H), 7.24 (m, 1H), 7.18-7.13 (m, 5H), 7.06-7.03 (m, 3H), 6.88 (dd, 1H, $J=8.2$, 1.9), 6.65 (br s, 1H, OH), 3.53 (d, 1H, $J=16.5$), 3.43 (d, 1H, $J=16.5$), 3.28 (d, 1H, $J=14.0$), 3.23 (d, 1H, $J=14.0$); ^{13}C NMR δ 156.9, 156.1, 144.1, 135.7 (4 s), 130.6 (d), 130.6 (s), 129.9, 128.3, 128.0, 127.4, 126.8, 125.3, 119.0, 117.0, 113.3 (9 d), 91.0 (s), 47.3, 45.5 (2 t).

5-Benzyl-3-(4-hydroxyphenyl)-5-phenyl-4,5-dihydro-isoxazole (80)

[0240]

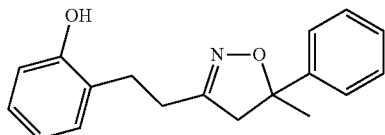


[0241] Yield 48%, $\text{mp}=151.3\text{-}153.9^\circ\text{C}$., ^1H NMR δ 7.42 (m, 2H), 7.36 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 7.19-7.15 (m, 3H), 7.07 (m, 2H), 6.79 (m, 2H), 6.34 (br s, 1H, OH), 3.55 (d, 1H, $J=16.4$), 3.44 (d, 1H, $J=16.4$), 3.29 (d, 1H, $J=14.0$),

3.24 (d, 1H, J=14.0); ^{13}C NMR δ 158.8, 156.8, 144.4, 135.9 (4 s), 130.7, 128.3, 128.3, 128.0, 127.4, 126.7, 125.4 (7 d), 121.0 (s), 115.6 (d), 90.5 (s), 47.3, 45.8 (2 t).

3-[2-(2-Hydroxy-phenyl)-ethyl]-5-methyl-5-phenyl-4,5-dihydro-isoxazole (81)

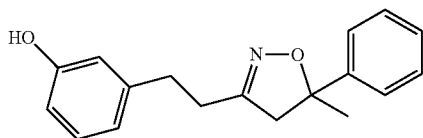
[0242]



[0243] Yield 22%, brown viscous oil, ^1H NMR δ 7.39-7.32 (m, 4H), 7.26 (m, 1H), 7.09 (m, 1H), 6.70 (m, 2H), 6.60 (m, 1H), 5.56 (br s, 1H, OH), 3.03 (d, 1H, J=16.9), 2.99 (d, 1H, J=16.9), 2.81 (t, 2H, J=7.5), 2.62 (t, 2H, J=7.5), 1.66 (s, 3H); ^{13}C NMR δ 158.5, 156.0, 145.6, 142.0 (4 s), 129.7, 128.5, 127.3, 124.7, 120.5, 115.3, 113.5 (7d), 87.0 (s), 51.0, 32.5, 29.4 (3 t), 28.0 (q). [WO2009066009, compound 85]

3-[2-(3-Hydroxy-phenyl)-ethyl]-5-methyl-5-phenyl-4,5-dihydro-isoxazole (82)

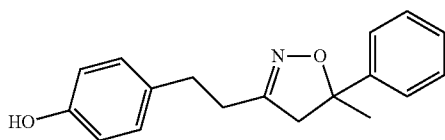
[0244]



[0245] Yield 97%, brown viscous oil, ^1H NMR δ 7.37-7.31 (m, 4H), 7.25 (t, 1H, J=6.9), 7.04 (t, 1H, J=7.6), 7.00 (d, 1H, J=7.5), 6.81 (d, 1H, J=7.9), 6.75 (t, 1H, J=7.4), 4.68 (br s, 1H, OH), 3.08 (d, 1H, J=17.1), 3.06 (d, 1H, J=17.1), 2.86 (t, 2H, J=7.5), 2.65 (t, 2H, J=7.3), 1.64 (s, 3H); ^{13}C NMR δ 159.8, 154.9, 145.6, (3 s), 130.2, 128.5, 127.7, 127.4 (4 d), 127.0 (s), 124.7, 120.0, 115.7 (3 d), 87.1 (s), 51.0 (t), 28.3 (q), 28.0, 27.4 (2 t). [WO2009066009, compound 86]

3-[2-(4-Hydroxy-phenyl)-ethyl]-5-methyl-5-phenyl-4,5-dihydro-isoxazole (83)

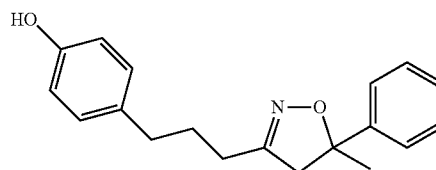
[0246]



[0247] Yield 19%, brown viscous oil, ^1H NMR δ 7.38-7.32 (m, 4H), 7.26 (m, 1H), 6.96 (m, 2H), 6.69 (m, 2H), 3.03 (d, 1H, J=16.8), 2.99 (d, 1H, J=16.8), 2.79 (t, 2H, J=7.6), 2.61 (t, 2H, J=7.6), 1.65 (s, 3H); ^{13}C NMR δ 158.4, 154.3, 145.6, 132.1 (4 s), 129.4, 128.5, 127.2, 124.7, 115.4 (5 d), 86.9 (s), 50.9, 31.8, 29.8 (3 t), 28.0 (q). [WO2009066009, compound 87]

3-[3-(4-Hydroxy-phenyl)-propyl]-5-methyl-5-phenyl-4,5-dihydro-isoxazole (84)

[0248]

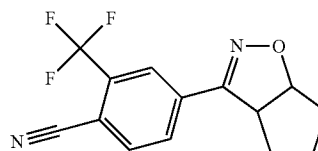


[0249] Yield 99%, a brown viscous oil, ^1H NMR δ 7.40 (m, 2H), 7.33 (m, 2H), 7.24 (m, 2H), 6.92 (m, 2H), 6.75 (m, 2H), 6.54 (br s, 1H, OH), 3.06 (d, 1H, J=16.9), 3.02 (d, 1H, J=16.9), 2.49 (m, 2H), 2.31 (t, 2H, J=7.6), 1.79 (m, 2H), 1.69 (s, 3H); ^{13}C NMR δ 159.3, 154.3, 145.5, 132.9 (4 s), 129.4, 128.5, 127.3, 124.6, 115.4 (5 d), 86.7 (s), 50.7, 34.2, 28.1 (3 t), 28.0 (q), 27.3 (t). [WO2009066009, compound 90]

Examples 85-95

4-(4,5,6,6a-Tetrahydro-3aH-cyclopenta[d]isoxazol-3-yl)-2-trifluoromethyl-benzonitrile (85)

[0250]



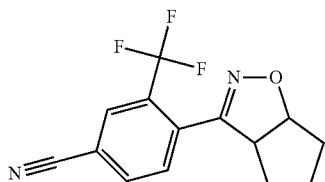
[0251] Method C:

[0252] In an oven-dried flask equipped with a condenser and stirrer, 3-(4-fluoro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole (compound 18, 0.287 g, 1 mmol, synthesized using the general method described in Example 1) and potassium cyanide (0.160 g, 4 mmol) were dissolved in 10 ml of anhydrous dimethyl sulfoxide. The solution was stirred at 150-160° C. in argon atmosphere for 16 h, poured into 10 ml of 2M HCl, and extracted three times with 10 ml of dichloromethane. The organic extracts were combined and washed once with 10 ml of H₂O, dried with MgSO₄, evaporated to dryness, and purified by preparative TLC using dichloromethane as eluent (rf 0.8).

[0253] Yield 93%, a white wax; ^1H NMR δ 8.14 (s, 1H), 7.95 (d, 1H, J=8.5), 7.87 (d, 1H, J=8.5), 5.35 (dd, 1H, J=9.0, 4.5), 4.03 (td, 1H, J=9.0, 2.0), 2.23 (m, 1H), 2.00-1.78 (m, 4H), 1.52 (m, 1H); ^{13}C NMR δ 156.9 (s), 135.5, 134.9 (2 d), 133.7 (q), 130.2 (d), 125.1, 122.6 (2 q), 115.6 (d), 110.6 (s), 90.0, 51.3 (2 d), 36.0, 31.8, 23.9 (3 t).

4-(4,5,6,6a-Tetrahydro-3aH-cyclopenta[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (86)

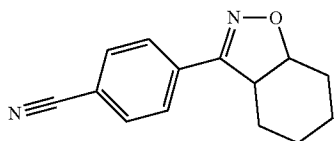
[0254]



[0255] Yield 37%, a yellow wax; $^1\text{H NMR}$ δ 8.00 (s, 1H), 7.85 (d, 1H, $J=8.0$), 7.60 (d, 1H, $J=8.0$), 5.27 (m, 1H), 4.08 (m, 1H), 2.15 (m, 1H), 1.77-1.69 (m, 2H), 1.69-1.57 (m, 2H), 1.48 (m, 1H); $^{13}\text{C NMR}$ δ 157.8 (s), 135.6 (d), 134.0 (s), 132.8 (d), 131.0, 130.6, 123.1 (3 q), 117.3 (d), 114.3 (s), 88.7, 55.3 (2 d), 36.1, 30.9, 23.5 (3 t).

4-(3a,4,5,6,7,7a-Hexahydro-benzo[d]isoxazol-3-yl)-benzo-nitrile (87)

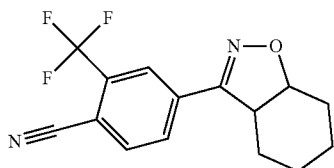
[0256]



[0257] Yield 67%, a colorless viscous oil; $^1\text{H NMR}$ δ 7.81 (m, 2H), 7.69 (m, 2H), 4.56 (m, 1H), 3.26 (m, 1H), 2.30 (m, 1H), 1.97 (m, 1H), 1.79 (m, 1H), 1.75-1.64 (m, 2H), 1.55 (m, 1H), 1.32-1.21 (m, 2H). MS(EI) obs. 226.10.

4-(3a,4,5,6,7,7a-Hexahydro-benzo[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (88)

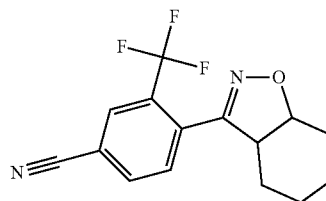
[0258]



[0259] Yield 93%, a yellow wax; $^1\text{H NMR}$ δ 8.12 (d, 1H, $J=0.8$), 7.97 (dd, 1H, $J=8.1, 0.8$), 7.88 (d, 1H, $J=8.1$), 4.59 (m, 1H), 3.29 (m, 1H), 2.31 (m, 1H), 1.98 (m, 1H), 1.81 (m, 1H), 1.75-1.62 (m, 2H), 1.55 (m, 1H), 1.35-1.18 (m, 2H); $^{13}\text{C NMR}$ δ 162.0 (s), 135.6, 134.8 (2 d), 133.8 (q), 130.2 (d), 125.1, 122.5 (2 q), 115.5 (d), 110.9 (s), 82.3, 43.9 (2 d), 26.6, 25.2, 22.3, 20.3 (4 t).

4-(3a,4,5,6,7,7a-Hexahydro-benzo[d]isoxazol-3-yl)-2-trifluoromethyl-benzonitrile (89)

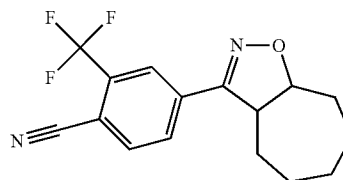
[0260]



[0261] Yield 67%, a yellow wax; $^1\text{H NMR}$ δ 8.05 (s, 1H), 7.89 (d, 1H, $J=8.0$), 7.69 (d, 1H, $J=8.0$), 4.67 (m, 1H), 3.37 (m, 1H), 2.13 (m, 1H), 1.83 (m, 1H), 1.69 (m, 1H), 1.59-1.45 (m, 3H), 1.32-1.24 (m, 2H); $^{13}\text{C NMR}$ δ 162.1 (s), 135.6 (d), 134.0 (s), 132.6 (d), 130.9, 130.7, 123.1 (3 q), 117.4 (d), 114.5 (s), 81.3, 48.1 (2 d), 25.7, 25.5, 22.2, 20.4 (4 t).

4-(4,5,6,7,8,8a-Hexahydro-3aH-cyclohepta[d]isoxazol-3-yl)-3-trifluoro-methyl-benzonitrile (90)

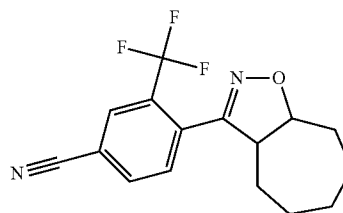
[0262]



[0263] Yield 81%, a yellow wax; $^1\text{H NMR}$ δ 8.07 (d, 1H, $J=0.8$), 7.87 (dd, 1H, $J=8.1, 0.8$), 7.88 (d, 1H, $J=8.1$), 4.94 (m, 1H), 3.71 (m, 1H), 2.05 (m, 1H), 1.98 (m, 1H), 1.83-1.47 (m, 6H), 1.45-1.36 (m, 2H); $^{13}\text{C NMR}$ δ 158.2 (s), 135.6, 134.9 (2 d), 133.8 (q), 130.4 (d), 125.3, 122.5 (2 q), 115.6 (d), 110.7 (s), 86.9, 50.8 (2 d), 31.3, 30.4, 28.4, 27.4, 24.0 (5 t).

4-(4,5,6,7,8,8a-Hexahydro-3aH-cyclohepta[d]isoxazol-3-yl)-2-trifluoro-methyl-benzonitrile (91)

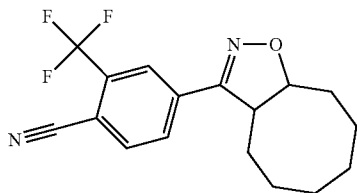
[0264]



[0265] Yield 78%, a yellow wax; $^1\text{H NMR}$ δ 8.04 (s, 1H), 7.88 (d, 1H, $J=8.0$), 7.64 (d, 1H, $J=8.0$), 4.97 (m, 1H), 3.77 (m, 1H), 2.07 (m, 1H), 1.94 (m, 1H), 1.85 (m, 1H), 1.74-1.25 (m, 5H); $^{13}\text{C NMR}$ δ 158.3 (s), 135.5 (d), 134.0 (s), 132.9 (d), 131.3, 130.9, 123.0 (3 q), 117.3 (d), 114.3 (s), 86.2, 54.6 (2 d), 31.5, 30.7, 28.5, 27.5, 24.5 (5 t).

4-(3a,4,5,6,7,8,9,9a-Octahydro-cycloocta[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (92)

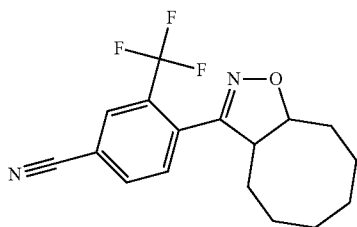
[0266]



[0267] Yield 98%, a yellow wax; $^1\text{H NMR}$ δ 8.07 (s, 1H), 7.86-7.82 (m, 2H), 4.56 (m, 1H), 3.40 (m, 1H), 2.15-2.08 (m, 1H), 2.01 (m, 1H), 1.81-1.70 (m, 4H), 1.65 (m, 1H), 1.55-1.43 (m, 2H), 1.35-1.21 (m, 3H); $^{13}\text{C NMR}$ δ 160.4 (s), 135.6, 134.8 (2 d), 133.8 (q), 130.3 (d), 125.3, 122.5 (2 q), 115.5 (d), 110.7 (s), 87.6, 49.6 (2 d), 30.3, 25.8, 25.6, 25.6, 25.2, 24.9 (6 t).

4-(3a,4,5,6,7,8,9,9a-Octahydro-cycloocta[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (93)

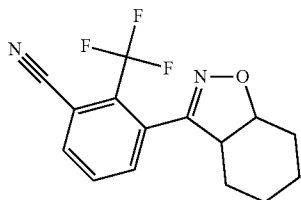
[0268]



[0269] Yield 18%, a yellow wax; $^1\text{H NMR}$ δ 8.01 (s, 1H), 7.86 (d, 1H, $J=8.0$), 7.62 (d, 1H, $J=8.0$), 4.68 (m, 1H), 3.48 (m, 1H), 2.05-1.93 (m, 2H), 1.75-1.44 (m, 6H), 1.43-1.07 (m, 4H); $^{13}\text{C NMR}$ δ 159.9 (s), 135.5 (d), 134.2 (s), 133.2 (d), 130.9, 130.7, 123.0 (3 q), 117.3 (d), 114.4 (s), 86.7, 53.8 (2 d), 30.0, 26.6, 26.3, 25.7, 25.6, 24.4 (6 t).

3-(3a,4,5,6,7,7a-Hexahydro-benzo[d]isoxazol-3-yl)-2-trifluoromethyl-benzonitrile (94)

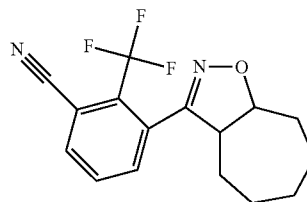
[0270]



[0271] Yield 17%, yellow viscous oil $^1\text{H NMR}$ δ 7.92 (d, 1H, $J=7.5$), 7.73 (dd, 1H, $J=8.3, 7.5$), 7.71 (d, 1H, $J=8.3$), 4.66 (m, 1H), 3.25 (m, 1H), 2.16 (m, 1H), 2.01 (m, 1H), 1.71 (m, 1H), 1.66 (m, 1H), 1.58 (m, 1H), 1.51 (m, 1H), 1.25-1.18 (m, 2H).

3-(4,5,6,7,8,8a-Hexahydro-3aH-cyclohepta[d]isoxazol-3-yl)-2-trifluoromethyl-benzonitrile (95)

[0272]



[0273] Yield 34%, yellow viscous oil $^1\text{H NMR}$ δ 7.91 (d, 1H, $J=7.5$), 7.72 (dd, 1H, $J=8.3, 7.5$), 7.66 (d, 1H, $J=8.3$), 4.95 (m, 1H), 3.66 (m, 1H), 2.10 (m, 1H), 1.94 (m, 1H), 1.87 (m, 1H), 1.75-1.43 (m, 6H), 1.13 (m, 1H).

Chiral Separations of the Racemic Mixtures.

[0274] The enantiomers were separated by semi preparative HPLC using a Regis Technologies (R,R)-Whelk-O 1 (25 cm \times 10 mm i.d.) chiral stationary phase in Hexane/*i*-PrOH/AcOH 90/10/0.5 at flow rate 5 mL/min.

Competitive AR Binding Assay.

[0275] AR binding was measured by a competitive assay against [^3H]-R1881 (PerkinElmer) in transiently transfected COS-1 cells. One day before transfection, COS-1 cells were seeded into 2 ml of DMEM (Dulbecco's modified Eagle medium, Gipro) with 10% dextran-charcoal-treated fetal bovine serum and 0.25% (vol/vol) Penicillin-Streptomycin (Euroclone) at a density of 140×10^3 cells/well. After medium change to DMEM 2.5% FBS, the cells were transfected for 24 hours with 10 ng/well of human AR expression vector pSG5 hAR by using the TransIT method (Mirus Bio TransIT LT1, Transfection Reagent). After 36 hours, the cells were treated with tested compounds using 10000 fold molarities compared to labelled R1881 (1.34 nM). After 2 hours of incubation at 37° C., the medium was removed. The cells were removed from the wells to 150 μl of 1 \times phosphate buffered saline (PBS), transferred to Eppendorf tubes and centrifuged at 4° C. using 4000 \times g for 5 min, and then washed twice with 150 μl of PBS. The cell pellets were dissolved to 50 μl of 0.5M NaOH and incubated for 15 min at 56° C., after which the samples (three replicates for each sample compound) were transferred to liquid twinkle tubes with 3 ml of OptiPhase HiSafe 3 twinkle solution (PerkinElmer) and radioactivity of AR-bound [^3H]-R1881 determined. The results were measured with LKB WALLAC 1214 racbeta equipment. The ability of test compounds to bind AR is reported as reduction in bound radioactivity obtained with 1.34 nM [^3H]-R1881.

[0276] The results (% inhibition) were calculated as:

$$\% \text{ inhibition} = 100 - [100 \times (\text{average}_{\text{compound}} / \text{average}_{[\text{3H}]\text{-R1881}})]$$

The results are shown in Tables 1-3.

TABLE 1

AR binding assay. Inhibition (%) of [³ H]-R1881 binding. Complete inhibition equals to 100%.			
Compound of Example No. (13.4 μM)	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.	Compound of Example No.	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.
Hydroxy-flutamide ^a	91.1 ± 2.2	32a	30.5 ± 5.4
2ab ^b	64.2 ± 2.2	32b	0
3ab	49.6 ± 2.0	33a	68.4 ± 1.9
4ab	69.9 ± 3.3	33b	56.9 ± 4.4
5a ^c	42.7 ± 6.6	34a	34.7 ± 2.7
5b ^d	59.7 ± 2.7	34b	0
6ab	31.4 ± 1.9	37ab	93.5 ± 0.9
7ab	51.0 ± 2.4	38a	94.5 ± 0.5
8ab	30.4 ± 2.9	38b	90.7 ± 0.5
9ab	63.7 ± 1.5	50a	63.8 ± 1.8
12a	55.9 ± 1.1	50b	55.7 ± 1.9
12b	30.2 ± 6.0	53ab	29.8 ± 10.8
13a	31.1 ± 5.6	54ab	28.2 ± 3.0
13b	1.6 ± 6.6	55a	35.1 ± 5.8
14a	29.6 ± 3.4	55b	32.7 ± 3.5
14b	0	57ab	48.7 ± 3.3
15ab	49.5 ± 4.3	58ab	8.2 ± 1.3
27a	17.0 ± 7.0	59ab	39.1 ± 2.6
27b	0	61a	14.9 ± 1.8
30a	30.2 ± 3.8	61b	0
30b	66.3 ± 6.5	65a	0
31a	20.3 ± 9.9	65b	13.5 ± 1.6
31b	0	66ab	17.8 ± 2.4
		68ab	14.7 ± 1.0

^aHydroxyflutamide (active form of flutamide, which is an oral antiandrogen drug primarily used to treat prostate cancer) was used as a reference compound.

^bab = enantiomers not separated, racemic mixture tested.

^ca = enantiomer with a shorter retention time in the chiral separation.

^db = enantiomer with a longer retention time in the chiral separation.

TABLE 2

AR binding assay. Inhibition (%) of [³ H]-R1881 binding. Complete inhibition equals to 100%.			
Compound of Example No. (13.4 μM)	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.	Compound of Example No.	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.
Hydroxy-flutamide ^a	94.8 ± 0.8	43a	66.3 ± 9.8
19ab ^b	84.6 ± 4.9	43b	76.0 ± 0.3
35ab	88.5 ± 4.2	85a	87.6 ± 0.3
36a ^c	84.6 ± 0.7	85b	91.8 ± 1.7
36b ^d	87.7 ± 3.0	88ab	99.2 ± 0.5
39ab	55.7 ± 5.8	89a	78.8 ± 0.6
40a	88.8 ± 3.1	89b	83.6 ± 0.9
40b	92.2 ± 0.7	90ab	98.7 ± 0.6
41ab	97.8 ± 0.5	91a	85.4 ± 1.5
42a	90.5 ± 3.1	91b	87.4 ± 2.7
42b	89.5 ± 2.0	92ab	85.8 ± 1.3

^{a-d}See Table 1.

TABLE 3

AR binding assay. Inhibition (%) of [³ H]-R1881 binding. Complete inhibition equals to 100%.			
Compound of Example No. (13.4 μM)	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.	Compound of Example No.	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.
Hydroxy-flutamide ^a	95.2 ± 2.9	45ab	85.7 ± 3.8

TABLE 3-continued

AR binding assay. Inhibition (%) of [³ H]-R1881 binding. Complete inhibition equals to 100%.			
Compound of Example No. (13.4 μM)	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.	Compound of Example No.	Inhibition of [³ H]-R1881 binding at 1.34 nM ± S.D.
20a	89.3 ± 3.8	46a	86.4 ± 1.8
20b	85.3 ± 2.8	46b	90.4 ± 3.8
21a	69.7 ± 4.5	86ab	91.7 ± 1.7
21b	90.9 ± 0.9	93a	87.2 ± 2.9
22ab ^b	89.3 ± 4.7	93b	76.0 ± 4.8
42a ^c	91.4 ± 3.8	94a	97.4 ± 0.4
42b ^d	89.3 ± 4.8	94b	97.6 ± 0.2
44a	90.3 ± 2.7	95a	96.2 ± 0.8
44b	85.2 ± 3.8	95b	98.1 ± 0.3

^{a-d}See Table 1.

Determination of the Antiandrogen Activity.

[0277] Testosterone was bought from Sigma Chemical Co. (St. Louis, Mo.) and hydroxyflutamide from Chemos GmbH. One day before transfection, COS-1 cells (from ATCC) were seeded into 1 ml of DMEM (Dulbecco's modified Eagle medium, Gibco) with 10% dextran-charcoal-treated fetal bovine serum and 0.25% (vol/vol) Penicillin-Streptomycin (Euroclone) at a density of 70×10³ cells/well. After medium change to DMEM 2.5% FBS, the cells were transfected for 24 hours with 10 ng/well of human AR expression vector pSG5-hAR, 100 ng/well of reporter plasmid Probasin-luc, and 10 ng/well of control plasmid pCMV-β-gal by using the TransIT method (Mirus Bio TransIT LT1, Transfection Reagent). After the transfection, the cells received treatment of test compounds giving final concentration of 10 μM for each compound. In the antagonist test the wells were also treated with 100 nM final concentration of testosterone. After 18 hours, the cells were washed, lysed and assayed for luciferase and normalization for β-galactosidase activities and protein concentrations. The cells were washed with 100 μl of cold phosphate buffered saline (PBS) and lysed with 35 μl 1× Reporter lysis Buffer (Promega) and frozen (-70° C.) for 30 minutes. Cell lysates were placed in 1.5-ml polypropylene tubes and centrifuged at 13200×g for 5 minutes at room temperature. For β-galactosidase assay 10 μl of supernatant from each cell extract was transferred to a 96-well plate (96 well Elisa Microplates, PS, Microcon) and incubated for 10 minutes at 37° C. with 65 μl of reaction mixture consisting 0.76 μl 100×Mg-buffer, 12.5 μl ONPG (4 mg/ml), and 54.3 μl of sodium-phosphate buffer (pH 7). The reaction was stopped with treatment of 125 μl Na₂CO₃. For luciferase assay 10 μl of the supernatant was transferred to a 96-well plate (Greiner Microlon lumitrac 200) and treated with 30 μl of luciferase assay substrate solution (Promega Luciferase Assay System E1501). For the study of protein concentrations 5 μl of the supernatant was transferred to a 96-well plate (Elisa Microplates, PS, Microcon) and mixed with 200 μl of Bio-rad protein assay reagent. The luciferase activities were measured with Thermo Luminoscan Ascent scanner and the protein concentrations and β-galactosidase activities with Thermo LabSystem Multiscan Ex scanner. Also blank and control samples were measured. During the maintenance, transfection, and treatment with tested compounds the cells were incubated in humidified atmosphere with 5% carbon dioxide at 37° C. The results are shown in Table 4 and FIG. 1.

TABLE 4

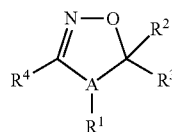
AR antagonism assay. Inhibition of transcriptional activation of AR by the novel non-steroidal compounds. Values are percentages of the relative luciferase response, which equals to 100% for testosterone (no antiandrogenic effect) and 0% for complete antagonism.			
Compound of Example No. (10.0 μM)	AR antagonism against 100 nM testosterone ± S.D.	Compound of Example No.	AR antagonism against 100 nM testosterone ± S.D.
Hydroxy-flutamide	13.0 ± 1.1	42a	17.4 ± 1.5
19ab ^b	54.6 ± 2.3	42b	25.5 ± 1.5
20a ^c	23.2 ± 0.5	43a	57.7 ± 9.9
20b ^d	37.4 ± 7.3	43b	56.6 ± 1.4
21a	19.2 ± 6.8	44a	19.8 ± 0.5
21b	22.9 ± 4.9	44b	35.6 ± 7.8
22ab	21.8 ± 4.1	45ab	27.8 ± 1.0
23ab	40.9 ± 2.4	46a	3.1 ± 1.7
26a	25.7 ± 5.5	46b	2.2 ± 0.8
26b	41.0 ± 1.6	85a	44.9 ± 3.6
32a	40.9 ± 2.4	85b	18.9 ± 0.5
32b	91.4 ± 7.7	86ab	29.3 ± 3.7
33a	40.2 ± 7.1	88ab	9.2 ± 1.7
33b	100	89a	27.5 ± 4.1
34ab	48.0 ± 6.7	89b	20.3 ± 1.7
35ab	53.4 ± 5.4	90ab	12.6 ± 0.7
36a	49.7 ± 5.1	91a	29.8 ± 3.6
36b	30.0 ± 6.1	91b	27.2 ± 4.8
37ab	10.6 ± 1.6	92ab	24.0 ± 1.7
38a	2.9 ± 0.5	93a	9.4 ± 0.3
38b	75.9 ± 3.7	93b	65.5 ± 9.0
39ab	43.8 ± 2.4	94a	17.8 ± 3.9
40a	28.8 ± 2.0	94b	5.4 ± 1.7
40b	15.6 ± 0.8	95a	14.4 ± 1.9
41ab	10.1 ± 0.9	95b	19.2 ± 2.9

^{a-d}, see Table 1.

Determination of AR-Dependent Gene Expression in Prostate Cancer Cells by Quantitative Real-Time RT-PCR.

[0278] LNCaP or VCaP prostate cancer cells (from ATCC) were splitted on day 1 on 12-well plates (140 000 cells/well). After 24 hours the cells were treated with the test compounds. Total RNA was prepared after 17-18 hours of the treatment using Trizol reagent (Invitrogen) according to the manufacturer's instructions; amounts of solutions used for 12-well format were 500 μl Trizol, 100 μl chloroform, 250 μl isopropanol, 500 μl 75% (v/v) ethanol and the RNA pellets were suspended on 15 μl sterile H₂O. RNA concentrations were determined with Nanodrop using 1 μl of RNA. All samples were diluted into equal concentration with sterile H₂O. The cDNA syntheses were done using 1 μg of RNA with Roche Transcriptor First Strand cDNA Synthesis Kit according to the manufacturer's instructions. The cDNA was diluted to 1:5 by adding 80 μl sterile H₂O into each sample. Five μl of diluted cDNA, 1 μl primer mix (containing 4 μM of each primer for PSA, TMPRSS2, FKBP51, or GAPDH), 12.5 μl of 2×SYBR-master mix (Roche), and 6.5 μl of H₂O were used for real-time PCR with Mx3000P Real-Time PCR System (Stratagene). Analyzed GAPDH mRNA levels were used to normalize the amounts of total RNA between the samples. Fold changes were calculated using the formula $2^{-\Delta\Delta Ct}$, where $\Delta\Delta Ct$ is $\Delta Ct_{(R1881)} - \Delta Ct_{(EtOH)}$, ΔCt is $Ct_{(gene X)} - Ct_{(GAPDH)}$ and Ct is the cycle at which the threshold is crossed. The results are shown in FIGS. 2-4.

1. Compounds of the formula (I)



(I)

or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof,

wherein

A is carbon or nitrogen;

R¹ is hydrogen or alkyl;

R² is hydrogen, alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen;

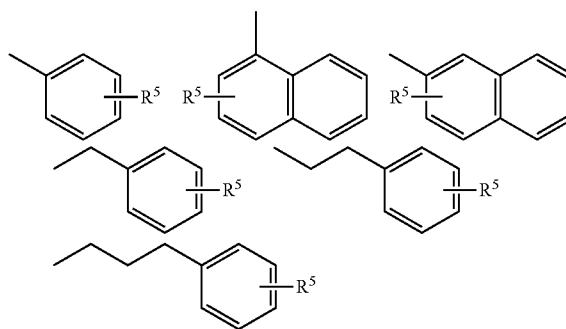
R³ is alkyl or benzyl and may form with R¹ a monocyclic aliphatic structure, which may be substituted with a side chain of the formula



wherein n is an integer from 0 to 4 and R⁶ is hydroxyl, acyloxy, carboxyl or carboxylate,

provided that R² and R³ cannot simultaneously be alkyl;

R⁴ is phenyl which is substituted with 1-5 R⁵, or naphthalene-1-yl, naphthalene-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵;



R⁵ is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl and lower alkoxy, provided that when R⁴ is phenyl there can not be more than one hydroxyl or lower alkoxy simultaneously present as R⁵ and that alkyl or alkoxy groups may be further substituted by the above mentioned groups;

provided that

when A is carbon, R¹ is hydrogen, R² is phenyl, and R³ is methyl, then R⁴ cannot be 3-nitrophenyl or 4-chlorophenyl;

when A is carbon, R¹ is methyl, R² is hydrogen, and R³ is methyl, then R⁴ cannot be 3-nitrophenyl, 4-nitrophenyl or 4-methoxyphenyl;

when A is carbon, R¹ is methyl, R² is hydrogen, and R³ is isopropyl, then R⁴ cannot be 4-methoxyphenyl or 2,4,6-trimethylphenyl;

when A is carbon, R¹ is isopropyl, R² is hydrogen, and R³ is methyl, then R⁴ cannot be 4-methoxyphenyl or 2,4,6-trimethylphenyl;

when A is carbon, R² is hydrogen, and R¹ and R³ form together a cyclopentane ring, then R⁴ cannot be 3-nitrophenyl, 4-nitrophenyl, 4-chlorophenyl, 4-hydroxyphenyl or phenethyl;

when A is carbon, R² is hydrogen, and R¹ and R³ form together a cyclohexane ring, then R⁴ cannot be 4-nitrophenyl;

when A is carbon, R² is hydrogen, and R¹ and R³ form together a cycloheptane or cyclooctane ring then R⁴ cannot be 4-chlorophenyl;

when A is carbon, R² is methyl or phenyl, and R¹ and R³ form together a cyclopentane ring, then R⁴ cannot be 4-nitrophenyl or 4-chlorophenyl;

when A is carbon, R² is methyl, and R¹ and R³ form together a cyclopentane or cyclooctane ring then R⁴ cannot be 2,4,6-trimethylphenyl;

when A is nitrogen, R¹ is hydrogen, R² is phenyl, and R³ is n-butyl, then R⁴ cannot be 2-chlorophenyl;

when A is nitrogen, R¹ is n-butyl, R² is hydrogen, and R³ is methyl, then R⁴ cannot be 4-nitrophenyl or 4-chlorophenyl;

when A is nitrogen, R² is phenyl, and R¹ and R³ form together a cyclopentane ring, then R⁴ cannot be 2,4,6-dimethylphenyl or 2,6-dichlorophenyl;

when A is carbon, R¹ is hydrogen, R² is methyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-benzonitrile, or naphthalene-2-yl;

when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl or 4-nitrophenyl;

when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is methyl, then R⁴ cannot be phenethyl, 3-phenyl-propyl, 2-(2-, 3- or 4-hydroxyphenyl)-ethyl or 3-(4-hydroxy-phenyl)propyl.

2. The compounds according to claim 1 having formula (I) or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof, wherein

A is carbon or nitrogen,

R¹ is hydrogen or lower alkyl,

R² is hydrogen, lower alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen,

R³ is selected from alkyl or benzyl and may form a monocyclic aliphatic structure with R¹, provided that R² and R³ cannot simultaneously be alkyl, and

R⁴ is an unsubstituted naphthalen-1-yl, naphthalen-2-yl or benzyl or a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups.

3. The compounds according to claim 1 having formula (I) or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof, wherein

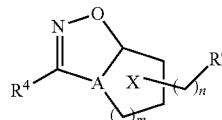
A is carbon,

R¹ forms with R³ a monocyclic aliphatic structure,

R² is hydrogen, and

R⁴ is a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups.

4. Compounds of the formula (II)



(II)

or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof,

wherein

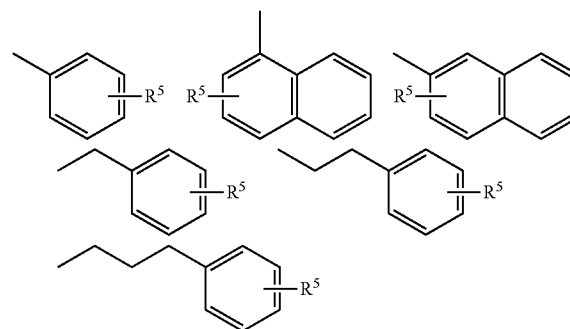
m is an integer from 1 to 4;

n is an integer from 0 to 4;

A is carbon or nitrogen;

R⁶ is hydroxyl, acyloxy, carboxyl or carboxylate;

R⁴ is phenyl which is substituted with 1-5 R⁵, or naphthalene-1-yl, naphthalene-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵;



provided that

when A is carbon, m is 1, n is 0, and R⁶ is hydroxyl occupying site 4 of ring X, then R⁴ cannot be 4-methoxyphenyl, 4-chlorophenyl, 2-fluorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl or;

when A is carbon, m is 3, n is 0, and R⁶ is carboxylic acid methyl ester occupying site 6 of ring X, then R⁴ cannot be 4-chlorophenyl or 4-(1-methylethyl)phenyl;

when A is carbon, m is 4, n is 0, and R⁶ is carboxylic acid methyl ester occupying site 6 or 7 of ring X, then R⁴ cannot be 4-chlorophenyl;

5. The compounds according to claim 4 having formula (II) or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof, wherein R⁴ is an unsubstituted naphthalen-1-yl, naphthalen-2-yl or benzyl or a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups.

6. The compound according to claim 1 selected from the group consisting of 5-benzyl-3-(4-nitrophenyl)-5-phenyl-4,5-dihydro-isoxazole (17), 4-(5-benzyl-5-phenyl-4,5-dihydro-isoxazol-3-yl)-benzotrile (18), 3-(4-fluoro-2-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]-isoxazole (20), 3-(4-nitro-3-trifluoromethyl-phenyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]-isoxazole (21), 3-(4-fluoro-3-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]-isoxazole (35), 3-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]-isoxazole (36), 3-(4-nitro-3-trifluoromethyl-phenyl)-3a,4,5,6,7,7a-hexahy-

dro-benzo[d]isoxazole (37), 3-(4-nitro-2-trifluoro-methyl-phenyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]-isoxazole (38), 3-(4-fluoro-2-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (40), 3-(4-nitro-3-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]-isoxazole (41), 3-(4-nitro-2-trifluoromethyl-phenyl)-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazole (42), 3-(4-fluoro-2-trifluoromethyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (44), 3-(4-nitro-2-trifluoro-methyl-phenyl)-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazole (46), 3-Benzyl-3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazole (47), 5-benzyl-4-butyl-3-(3-chloro-phenyl)-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (50), 5-benzyl-4-butyl-5-methyl-3-(4-nitro-phenyl)-4,5-dihydro-[1,2,4]oxadiazole (51), 4-(5-benzyl-4-butyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzonitrile (52), 3,5-dibenzyl-4-butyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazole (55), 4-(5-benzyl-4-isobutyl-5-methyl-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-benzonitrile (62), 4-(4,5,6,6a-tetrahydro-3aH-cyclo-penta[d]isoxazol-3-yl)-2-trifluoromethyl-benzonitrile (85), 4-(4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (86), 4-(3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (88), 4-(3a,4,5,6,7,7a-hexahydro-benzo[d]isoxazol-3-yl)-2-trifluoromethyl-benzo-nitrile (89), 4-(4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazol-3-yl)-3-trifluoro-methyl-benzonitrile (90), 4-(4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[d]isoxazol-3-yl)-2-trifluoro-methyl-benzonitrile (91), 4-(3a,4,5,6,7,8,9,9a-octahydro-cycloocta[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (92), 4-(3a,4,5,6,7,8,9,9a-octa-hydro-cycloocta[d]isoxazol-3-yl)-3-trifluoromethyl-benzonitrile (93).

7. The compounds according to claim 1 for use as pharmaceuticals.

8. A process for preparing the compounds of claim 1, comprising:

nitride oxide—dipolarophile cycloaddition reaction of an aldoxime comprising R^4 , wherein R^4 is as defined above, with an olefin or imine comprising R^1 , R^2 and R^3 , wherein R^1 , R^2 and R^3 are as defined above, in the presence of sodium hypochlorite and pyridine to afford the desired heterocycles; or

demethylation reaction of the appropriate methoxy-substituted compounds in the presence of boron tribromide to afford the desired phenolic products; or

cyano-dehalogenation reaction of the appropriate fluoro compounds in the presence of potassium cyanide to afford the desired benzonitrile products.

9. A pharmaceutical composition comprising a compound according to claim 1 in association with a pharmaceutically acceptable carrier.

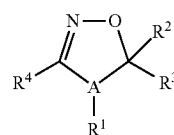
10. Compounds of formula (I) according to claim 1 or stereoisomers, pharmaceutically acceptable salts or prodrug forms thereof for use in a method for treating disease states, disorders or conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity.

11. (canceled)

12. A method for therapeutic or prophylactic treatment of disease states, disorders or conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity, said method comprising administering an effective amount of a compound according to claim 1 having formula (I) to a subject in need of such treatment.

13. The method according to claim 12 for the therapeutic or prophylactic treatment of prostate cancer, benign prostate hyperplasia, ovarian cancer, breast cancer, hepatocellular carcinoma, alopecia, hirsutism, acne vulgaris, endometriosis, acanthosis nigricans, hypertrichosis, precocious puberty, polycystic ovary syndrome, hypersexuality/paraphilia, sarcopenia, osteoporosis, muscle wasting, wasting disease, cancer cachexia, frailty, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, male contraception or impotence.

14. Compounds of the formula (I)



(I)

or stereoisomers, pharmaceutically acceptable salts or prodrug forms thereof,

wherein

A is carbon or nitrogen;

R^1 is hydrogen or alkyl;

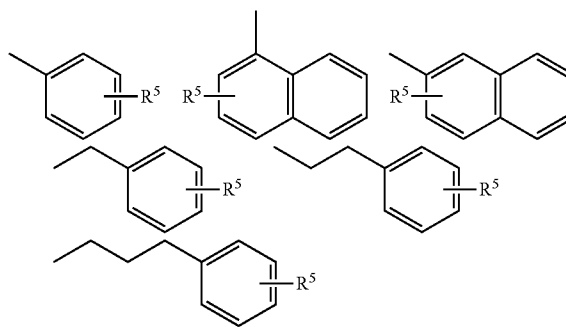
R^2 is hydrogen, alkyl or phenyl, provided that R^1 and R^2 cannot simultaneously be hydrogen;

R^3 is alkyl or benzyl and may form with R^1 a monocyclic aliphatic structure, which may be substituted with a side chain of the formula



wherein n is an integer from 0 to 4 and R^6 is hydroxyl, acyloxyl, carboxyl or carboxylate,

provided that R^2 and R^3 cannot simultaneously be alkyl; R^4 is phenyl which is substituted with 1-5 R^5 , or naphthalene-1-yl, naphthalene-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R^5 ;



R^5 is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl or lower alkoxy, provided that when R^4 is phenyl there can be no more than one hydroxyl or lower alkoxy simultaneously present as R^5 and that alkyl or alkoxy groups may be further substituted by the above mentioned groups provided that

when A is carbon, R¹ is hydrogen, R² is methyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-benzonitrile, or naphthalene-2-yl;

when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl or 4-nitrophenyl;

when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is methyl, then R⁴ cannot be phenethyl, 3-phenyl-propyl, 2-(2-, 3- or 4-hydroxyphenyl)-ethyl or 3-(4-hydroxy-phenyl)propyl;

for use as pharmaceuticals.

15. The compounds according to claim **14** wherein in the formula (I)

A is carbon or nitrogen,

R¹ is hydrogen or lower alkyl,

R² is hydrogen, lower alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen,

R³ is selected from alkyl or benzyl and may form a monocyclic aliphatic structure with R¹, provided that R² and R³ cannot simultaneously be alkyl, and

R⁴ is an unsubstituted naphthalen-1-yl, naphthalen-2-yl or benzyl or a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups,

for use as pharmaceuticals.

16. The compounds according to claim **14** wherein in the formula (I)

A is carbon,

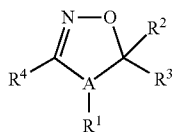
R¹ forms with R³ a monocyclic aliphatic structure,

R² is hydrogen, and

R⁴ is a phenyl mono- or disubstituted with halogen, nitro, cyano, lower alkyl or haloalkyl groups,

for use as pharmaceuticals.

17. A pharmaceutical composition comprising a compound of the formula (I)



(I)

or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof,

wherein

A is carbon or nitrogen;

R¹ is hydrogen or alkyl;

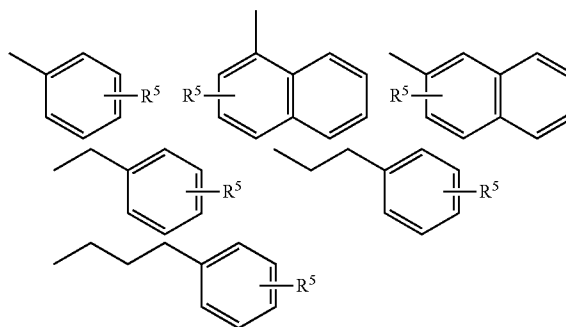
R² is hydrogen, alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen;

R³ is alkyl or benzyl and may form with R¹ a monocyclic aliphatic structure, which may be substituted with a side chain of the formula



wherein n is an integer from 0 to 4 and R⁶ is hydroxyl, acyloxy, carboxyl or carboxylate,

provided that R² and R³ cannot simultaneously be alkyl; R⁴ is phenyl which is substituted with 1-5 R⁵, or naphthalene-1-yl, naphthalene-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R⁵;



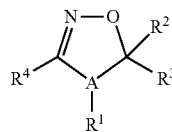
R⁵ is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl and lower alkoxy, provided that when R⁴ is phenyl there can not be more than one hydroxyl or lower alkoxy simultaneously present as R⁵ and that alkyl or alkoxy groups may be further substituted by the above mentioned groups provided that when A is carbon, R¹ is hydrogen, R² is methyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-benzonitrile, or naphthalene-2-yl;

when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is benzyl, then R⁴ cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl or 4-nitrophenyl;

when A is carbon, R¹ is hydrogen, R² is phenyl and R³ is methyl, then R⁴ cannot be phenethyl, 3-phenyl-propyl, 2-(2-, 3- or 4-hydroxyphenyl)-ethyl or 3-(4-hydroxy-phenyl)propyl;

in association with a pharmaceutically acceptable carrier.

18. Compounds of the formula (I)



(I)

or stereoisomers, pharmaceutically acceptable salts or pro-drug forms thereof,

wherein

A is carbon or nitrogen;

R¹ is hydrogen or alkyl;

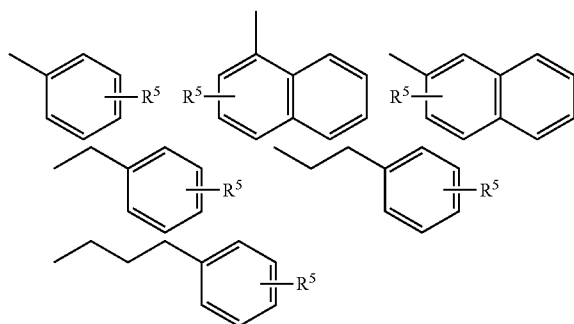
R² is hydrogen, alkyl or phenyl, provided that R¹ and R² cannot simultaneously be hydrogen;

R³ is alkyl or benzyl and may form with R¹ a monocyclic aliphatic structure, which may be substituted with a side chain of the formula



wherein n is an integer from 0 to 4 and R⁶ is hydroxyl, acyloxy, carboxyl or carboxylate,

provided that R^2 and R^3 cannot simultaneously be alkyl; R^4 is phenyl which is substituted with 1-5 R^5 , or naphthalene-1-yl, naphthalene-2-yl, benzyl, phenethyl or 3-phenylpropyl which is substituted with 0-5 R^5 ;



R^5 is selected from the group consisting of halogen, nitro, cyano, alkyl, hydroxyl and lower alkoxy, provided that when R^4 is phenyl there can not be more than one hydroxyl or lower alkoxy simultaneously present as R^5 and that alkyl or alkoxy groups may be further substituted by the above mentioned groups, provided that when A is carbon, R^1 is hydrogen, R^2 is methyl and R^3 is benzyl, then R^4 cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-benzonitrile, or naphthalene-2-yl; when A is carbon, R^1 is hydrogen, R^2 is phenyl and R^3 is benzyl, then R^4 cannot be 2-, 3- or 4-methoxyphenyl, 2-fluorophenyl, 4-chlorophenyl or 4-nitrophenyl; when A is carbon, R^1 is hydrogen, R^2 is phenyl and R^3 is methyl, then R^4 cannot be phenethyl, 3-phenyl-propyl, 2-(2-, 3- or 4-hydroxyphenyl)-ethyl or 3-(4-hydroxy-phenyl)propyl;

for use in a method for treating disease states, disorders or conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity.

19. Compounds according to claim **18** for use in a method of treating prostate cancer, including primary and hormone refractory prostate cancer, benign prostate hyperplasia, ovarian cancer, breast cancer, hepatocellular carcinoma, alopecia, hirsutism, acne vulgaris, endometriosis, acanthosis nigricans, hypertrichosis, precocious puberty, polycystic ovary syndrome, hypersexuality/paraphilia, sarcopenia, osteoporosis, muscle wasting, wasting disease, cancer cachexia, frailty, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, male contraception and impotence.

20. A method for the therapeutic or prophylactic treatment of disease states, disorders or conditions alleviated by compounds having androgen, antiandrogen or androgen receptor modulator activity, said method comprising administering an effective amount of a compound having formula I as defined in claim **18** to a subject in need of such treatment.

21. The method according to claim **20** for the therapeutic or prophylactic treatment of prostate cancer, benign prostate hyperplasia, ovarian cancer, breast cancer, hepatocellular carcinoma, alopecia, hirsutism, acne vulgaris, endometriosis, acanthosis nigricans, hypertrichosis, precocious puberty, polycystic ovary syndrome, hypersexuality/paraphilia, sarcopenia, osteoporosis, muscle wasting, wasting disease, cancer cachexia, frailty, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, male contraception and impotence.

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