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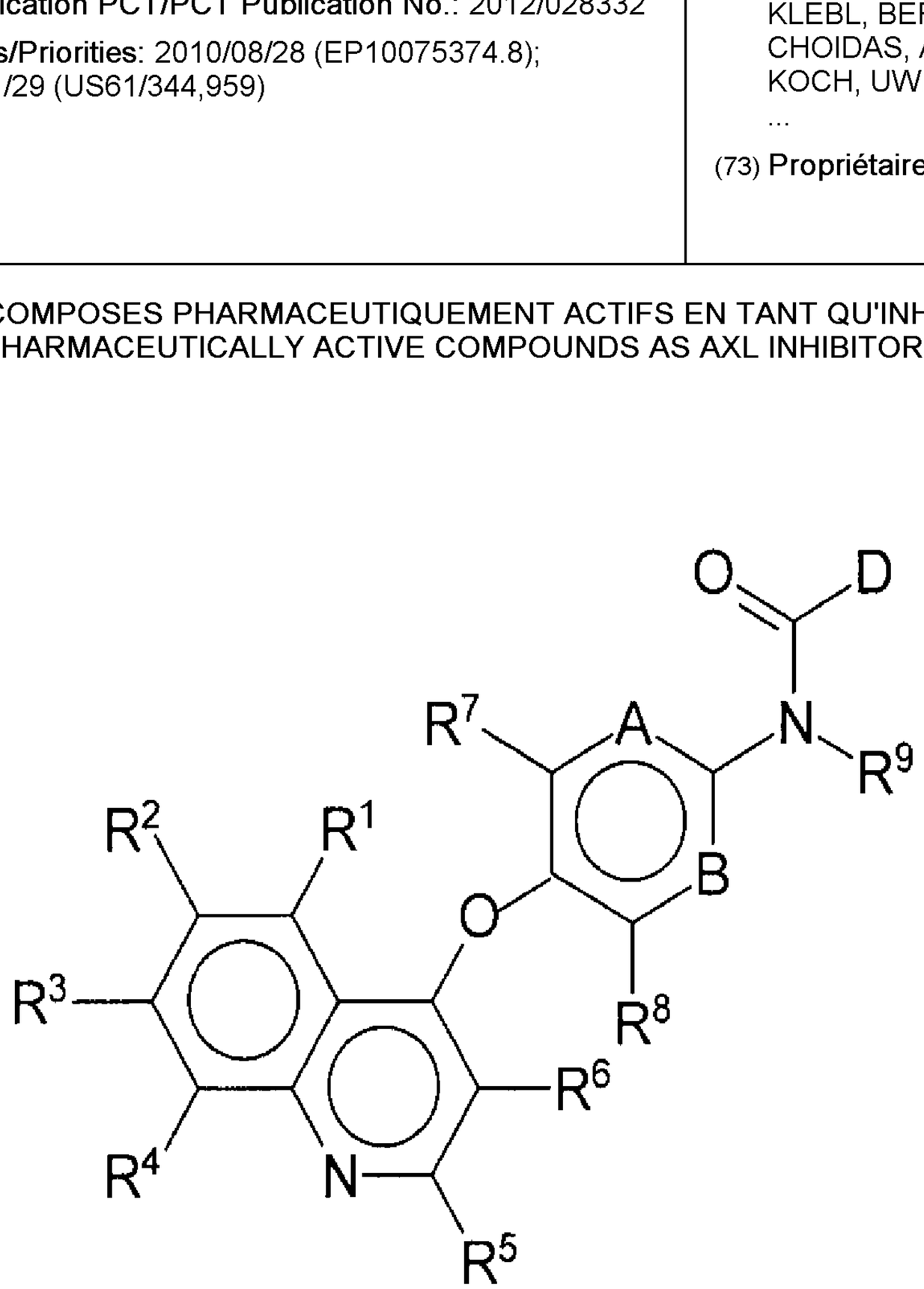
(73) Propriétaires/Owners:

(54) Titre : COMPOSES PHARMACEUTIQUEMENT ACTIFS EN TANT QU'INHIBITEURS DE AXL
(54) Title: PHARMACEUTICALLY ACTIVE COMPOUNDS AS AXL INHIBITORS



formula (I)

(57) Abrégé/Abstract:
The present invention relates to 1-nitrogen-heterocyclic-2-carboxamides of general formula (I): and/or pharmaceutically acceptable salts thereof, the use of these derivatives as pharmaceutically active agents, especially for the treatment and/or prevention of Axl receptor tyrosine kinase subfamily induced disorders, including cancer and primary tumor metastases, and pharmaceutical compositions containing at least one of said 1-nitrogen-heterocyclic-2-carboxamide derivatives and/or pharmaceutically acceptable salts thereof.

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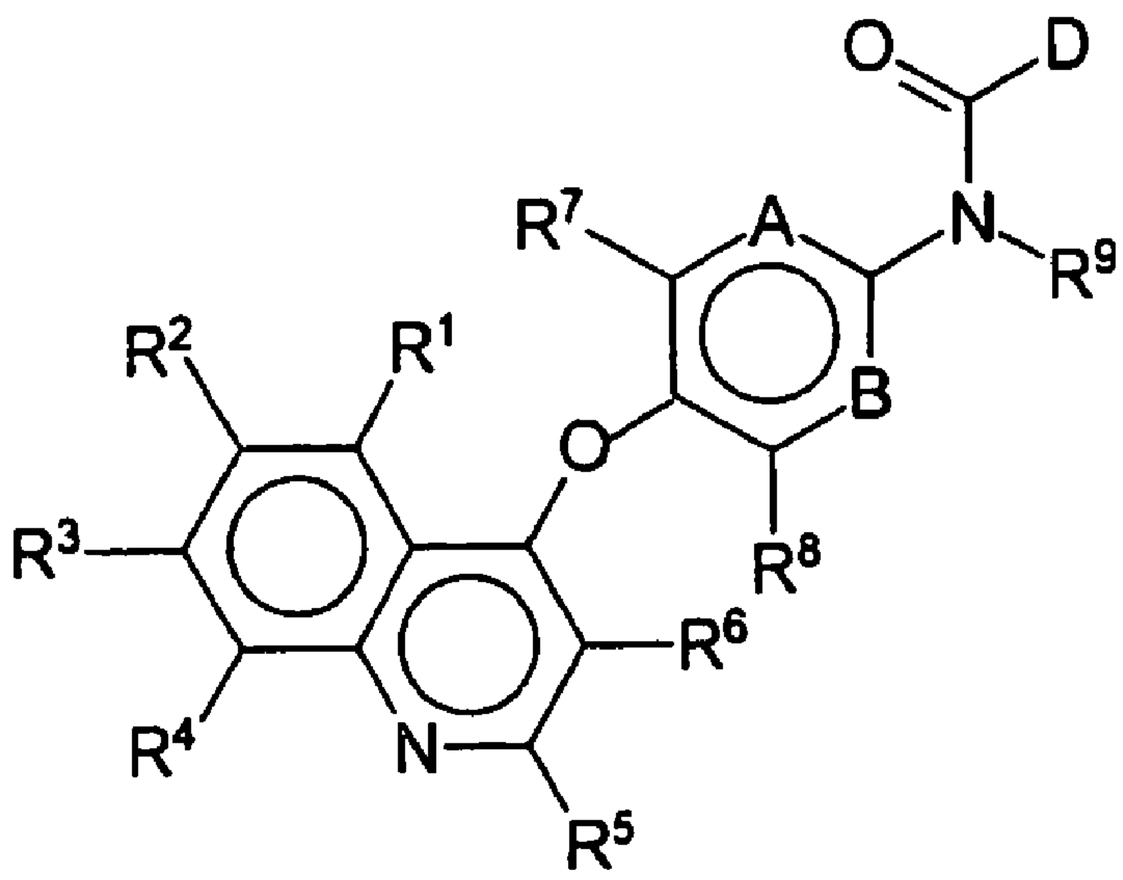
(54) Title: PHARMACEUTICALLY ACTIVE COMPOUNDS AS AXL INHIBITORS



(I)

(57) Abstract: The present invention relates to 1-nitrogen-heterocyclic-2-carboxamides of general formula (I): and/or pharmaceutically acceptable salts thereof, the use of these derivatives as pharmaceutically active agents, especially for the treatment and/or prevention of Axl receptor tyrosine kinase subfamily induced disorders, including cancer and primary tumor metastases, and pharmaceutical compositions containing at least one of said 1-nitrogen-heterocyclic-2-carboxamide derivatives and/or pharmaceutically acceptable salts thereof.

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Pharmaceutically active compounds as Axl inhibitors

The present invention relates to novel compounds which are inhibitors of Axl receptor tyrosine kinase subfamily which comprises Axl, Mer and Tyro3. These compounds are suitable for the treatment or prevention of disorders associated with, accompanied by or caused by hyperfunction of a receptor of the Axl family. The compounds are suitable for the treatment of hyperproliferative disorders, such as cancer, particularly cancer metastases.

Receptor tyrosine kinases (RTKs) are cell surface receptors that transmit signals from the extracellular environment to control growth, differentiation and survival of cells. Deregulated expression of protein kinases by gene deletion, -mutation or –amplification has been found to be important for tumor initiation and –progression, involving cancer cell proliferation, -survival, -motility and -invasivity as well tumor angiogenesis and chemotherapy resistance. Because of the advanced understanding of their critical role, protein kinases are important targets for novel therapies, especially for cancer (Hananhan et al., 2000; Blume-Jensen et al., 2001).

Axl is a member of the TAM (Tyro-Axl-Mer) receptor tyrosine kinases. This family is characterised by an extracellular domain, consisting of two immunoglobulin-like domains followed by two fibronectin type 3-like domains. The activation of the Axl RTK subfamily occurs by its cognate protein ligand, growth arrest specific 6 (Gas6). The affinity of Gas6 is highest for Axl, followed by Tyro3, and finally Mer, and thereby activates the three proteins to varying degrees. Gas6 is a member of the vitamin K-dependent family and shows a 43% sequence identity to and the same domain organisation as the protein S, a serum protein (Hafizi et al., 2006).

Axl is ubiquitously expressed at low levels and is detectable in a variety of organs. Expression patterns of the other two family members differ from that of Axl. Expression of Tyro3 is predominantly in the brain and CNS (central nervous system), while expression of Mer is almost exclusively in the monocyte cell lineage (Rescigno et al. 1991, Mark et al., 1994, Graham et al., 1994).

TAM family RTKs regulate a diverse range of cellular responses, including cell survival, proliferation, migration and adhesion (Hafizi et al., 2006). TAM receptor signalling has been shown to regulate vascular smooth muscle homeostasis (Korshunov et al., 2007), platelet function, thrombus stabilization (Angelillo-Scherrer et al., 2001; Gould et al., 2005), and erythropoiesis (Angelillo-Scherrer et al., 2008). Furthermore TAM receptors

are implicated in the control of oligodendrocyte cell survival (Shankar et al., 2006) and the regulation of osteoclast function (Katagiri et al., 2001). The TAM receptors play pivotal roles in innate immunity (Lemke et al., 2008) and in inflammation (Sharif et al., 2006; Rothlin et al., 2007). The TAM family promotes the phagocytosis of apoptotic cells (Prasas et al., 2006) and stimulates the differentiation of natural killer cells (Park et al., 2009; Caraux et al., 2006). Axl activation is linked to several signal transduction pathways, including Akt, MAP kinases, NF-κB, STAT signal transduction pathways and others (Hafizi et al., 2006).

High Axl expression is observed in many human tumors (Berclaz et al., 2001; Craven et al., 1995; Shieh et al., 2005; Sun et al., 2004; Green et al., 2006; Ito et al., 1999) and it is associated with tumor stage and -progression in cancer patients (Gjerdrum et al., 2010; Sawabu et al., 2007; Green et al., 2006; Shieh et al., 2005; Sun et al., 2003).

It is object of the present invention to provide compounds and/or pharmaceutically acceptable salts thereof which can be used as pharmaceutically active agents, especially for treatment of cell proliferative diseases like cancer, as well as compositions comprising at least one of those compounds and/or pharmaceutically acceptable salts thereof as pharmaceutically active ingredients.

The compounds of the present invention are efficient inhibitors of TAM family RTKs and thus, are suitable for the treatment of disorders associated with, accompanied by and/or caused by TAM family RTKs hyperfunction, and thereby having an effect on cell survival, proliferation, autophagy, vascular smooth muscle homeostasis, migration, adhesion, angiogenesis, platelet aggregation, thrombus stabilization, erythropoiesis, oligodendrocyte cell survival, osteoclast function, innate immunity, inflammation, phagocytosis of apoptotic cells and/or natural killer cell differentiation.

The invention provides efficient inhibitors of Axl receptor tyrosine kinase which are suitable for the treatment of hyperproliferative disorders associated with, accompanied by and/or caused by Axl hyperfunction, particularly Axl receptor tyrosine kinase induced hyperproliferative disorders. The compounds of the invention are capable of inhibiting cell proliferation and thus, are suitable for the treatment and/or prevention of Axl receptor tyrosine kinase induced hyperproliferative disorders, particularly selected from the group comprising cancer and primary tumor metastases. In a preferred embodiment of the invention, the Axl receptor tyrosine kinase induced disorders are associated with Axl receptor tyrosine kinase receptor overexpression and/or hyperactivity, e.g. an increased degree of autophosphorylation compared to normal

tissue. The disorders may be selected from breast cancer, colon cancer, prostate cancer, lung cancer, gastric cancer, ovarian cancer, endometrial cancer, renal cancer, hepatocellular cancer, thyroid cancer, uterine cancer, esophagus cancer, squamous cell cancer, leukemia, osteosarcoma, melanoma, glioblastoma and neuroblastoma. In an especially preferred embodiment, the disorders are selected from breast cancer, glioblastoma, renal cancer, non-small cell lung cancer (NSCLC), and melanoma. The compounds are also suitable for the prevention and/or treatment of other hyperproliferative disorders, particulary benign hyperproliferative disorders such as benign prostate hyperplasia.

Examples for disorders associated with, accompanied by and/or caused by Axl hyperfunction are acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, aids-related cancers, aids-related lymphoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, osteosarcoma and malignant fibrous histiocytoma, brain stem glioma, brain tumor, central nervous system atypical teratoid/rhabdoid tumor, astrocytomas, craniopharyngioma, ependymoblastoma, ependymoma, medulloblastoma, medulloepithelioma, pineal parenchymal tumors of intermediate differentiation, supratentorial primitive neuroectodermal tumors and pineoblastoma, brain and spinal cord tumors, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, gastrointestinal cancer, central nervous system (CNS) lymphoma, cervical cancer, chordoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous t-cell lymphoma, mycosis fungoides, sézary syndrome, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, esthesioneuroblastoma, ewing sarcoma family of tumors, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (gist), gastrointestinal stromal cell tumor, extracranial germ cell tumor, extragonadal germ cell tumor, ovarian germ cell tumor, gestational trophoblastic tumor, glioma, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular (liver) cancer, histiocytosis, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), kaposi sarcoma, renal cell cancer, kidney cancer, langerhans cell histiocytosis, laryngeal cancer, acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, aids-related lymphoma, burkitt lymphoma, (cutaneous t-cell lymphoma, hodgkin

lymphoma, non-hodgkin lymphoma, primary central nervous system lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone and osteosarcoma, medulloblastoma, medulloepithelioma, melanoma, melanoma intraocular (eye), merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer with occult primary, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, myelogenous leukemia, myeloid leukemia, myeloma (multiple), myeloproliferative disorders, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-hodgkin lymphoma, non-small cell lung cancer, oral cancer, oral cavity cancer, oropharyngeal cancer, osteosarcoma and malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, pregnancy and breast cancer, prostate cancer, rectal cancer, renal cell (kidney) cancer, transitional cell cancer, respiratory tract cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, ewing sarcoma, kaposi sarcoma, uterine sarcoma, nonmelanoma skin cancer, melanoma skin cancer, skin carcinoma, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, t-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, gestational cancer, ureter and renal pelvis cancer, transitional cell cancer, urethral cancer, uterine cancer, endometrial cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia and Wilms tumor.

The preferred Axl receptor tyrosine kinase induced disorders are selected from adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome (carcinoma of unknown primary origin), colorectal cancer, small intestine cancer, small intestinal tumors, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumors, gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, cervix, glioblastomas, gynecologic tumors, ear tumors, nose tumors and throat tumors, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumors (gliomas), brain metastases,

testicle cancer, hypophysis tumor, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head and neck tumors (tumors of the ear, nose and throat area), colon carcinoma, craniopharyngiomas, oral cancer (cancer in the mouth area and on lips), cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer (Hodgkin's/Non-Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumors of the gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma (mycosis fungoides), thymoma, tube carcinoma, eye tumors, urethral cancer, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma and tongue cancer.

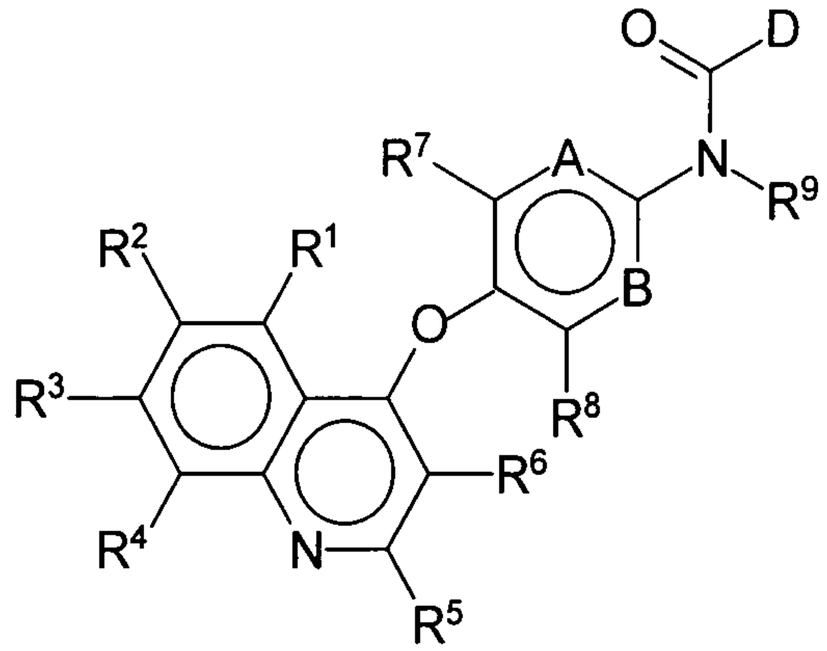
The compounds of the present invention are efficient inhibitors of TAM family RTKs. The inventive compounds are suitable for the use as a pharmaceutically active agent. The inventive compounds are suitable for the treatment of disorders associated with, accompanied by and/or caused by TAM family RTKs hyperfunction. The inventive compounds are suitable for the treatment and/or prevention of Axl receptor tyrosine induced disorders.

The inventive compounds are used in the manufacture of a medicament or of a pharmaceutical composition for the treatment of disorders associated with, accompanied by and/or caused by TAM family RTKs hyperfunction. The inventive compounds are further used in the manufacture of a medicament or of a pharmaceutical composition for the treatment and/or prevention of Axl receptor tyrosine induced disorders.

The Axl receptor tyrosine kinase induced disorders are disorders caused by, associated with and/or accomplied by Axl kinase hyperfunction. The Axl receptor tyrosine kinase induced disorders are selected from a group comprising hyperproliferative disorders. The Axl receptor tyrosine kinase induced disorders are selected from the group comprising cancer and primary tumor metastases.

Further advantageous features, aspects and details of the invention are evident from the dependent claims, the description, the examples and the drawings.

It has now surprisingly been discovered that 1-nitrogen-heterocyclic-2-carboxamides of the present invention exhibit particularly high levels of inhibition of the activity of the Axl kinase. The novel compounds according to the present invention are defined by the general formula (I):



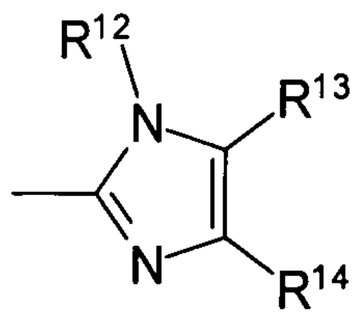
formula (I)

wherein

A represents C–R^{10}, N;

B represents C–R^{11}, N;

D represents one of the following heterocycles: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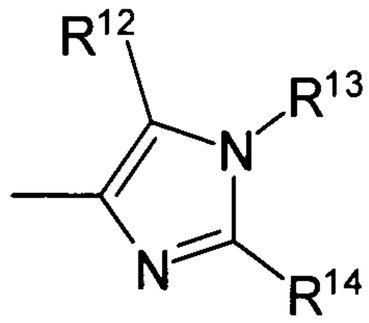
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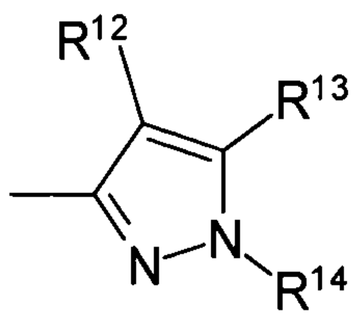
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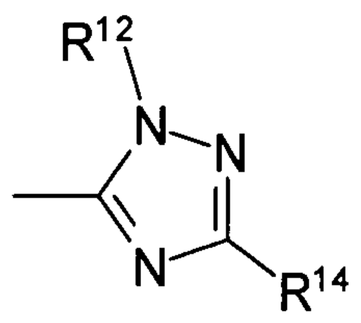
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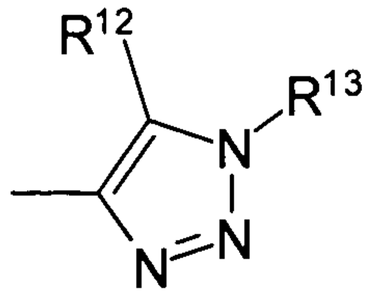
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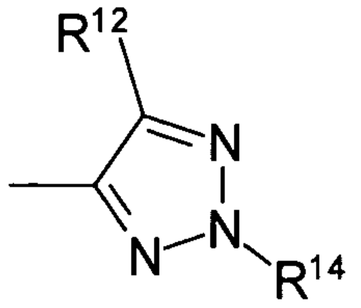
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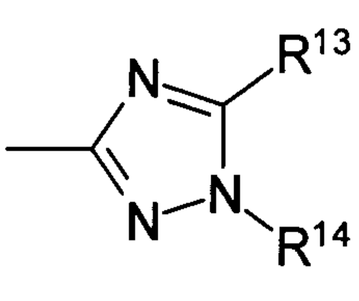
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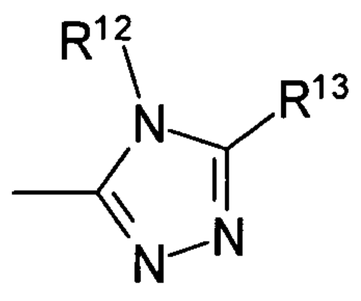
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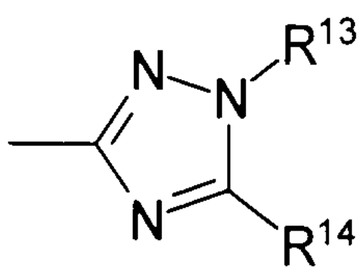
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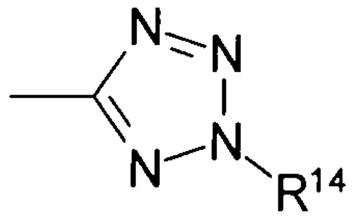
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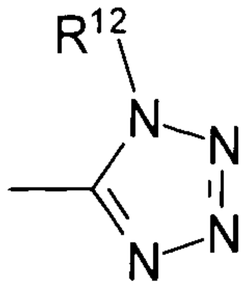
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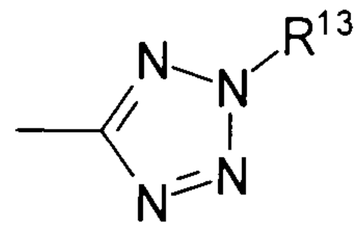
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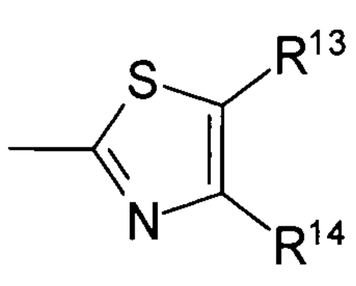
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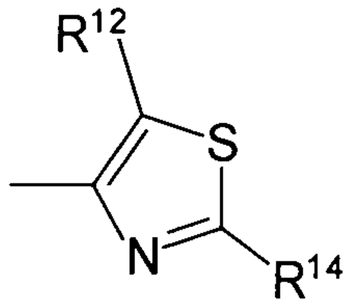
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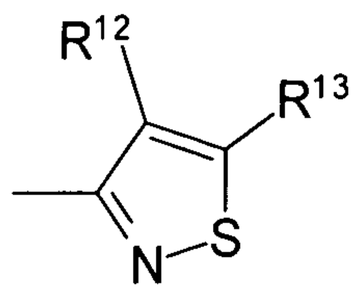
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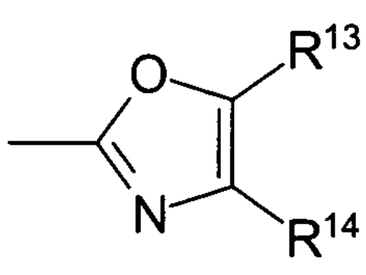
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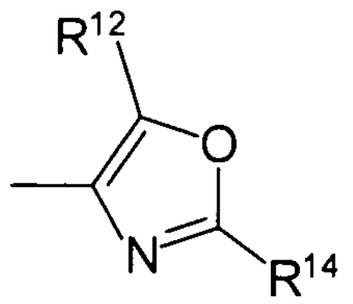
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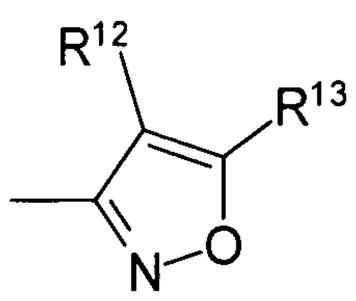
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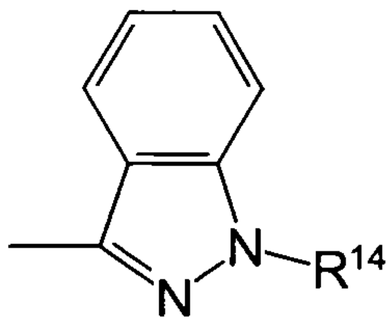

;

R^1, R^4, R^{88}, R^{92}, R^{100} are selected independently of each other from –H, –F, –Cl, –Br, –I, –OH, $–NH_2$, $–NHR^{19}$, $–NR^{19}R^{20}$, $–OCH_3$, $–OC_2H_5$, $–OC_3H_7$, $–OCH(CH_3)_2$, $–OC(CH_3)_3$, $–OC_4H_9$, $–NO_2$, –CHO, $–COCH_3$, $–COC_2H_5$, $–COC_3H_7$, –O-cyclo-C_3H_5, $–OCH_2$-cyclo-C_3H_5, $–O–C_2H_4$-cyclo-C_3H_5, –OPh, $–COCH(CH_3)_2$, $–COC(CH_3)_3$, –COOH, $–COOCH_3$, $–COOC_2H_5$, $–COOC_3H_7$, $–COOCH(CH_3)_2$, $–COOC(CH_3)_3$, $–OOC–CH_3$, $–OOC–C_2H_5$, $–OOC–C_3H_7$, $–OOC–CH(CH_3)_2$, $–OOC–C(CH_3)_3$, $–NHCH_3$, $–NHC_2H_5$, $–NHC_3H_7$, $–NHCH(CH_3)_2$, $–NHC(CH_3)_3$, $–N(CH_3)_2$, $–N(C_2H_5)_2$, $–N(C_3H_7)_2$, $–N[CH(CH_3)_2]_2$, $–N[C(CH_3)_3]_2$, $–OCF_3$, $–OC_2F_5$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2Cl$, $–CH_2Br$, $–CH_2I$, $–CH_2–CH_2F$, $–CH_2–CHF_2$, $–CH_2–CF_3$, $–CH_2–CH_2Cl$, $–CH_2–CH_2Br$, $–CH_2–CH_2I$, cyclo-C_3H_5, $–CH_2–$cyclo$–C_3H_5$, $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–CH(CH_3)_2$, $–C_4H_9$, $–CH_2–CH(CH_3)_2$, $–CH(CH_3)–C_2H_5$, $–C(CH_3)_3$, $–C_5H_{11}$, $–CH(CH_3)–C_3H_7$, $–CH_2–CH(CH_3)–C_2H_5$, $–CH(CH_3)–CH(CH_3)_2$, $–C(CH_3)_2–C_2H_5$, $–CH_2–C(CH_3)_3$, $–CH(C_2H_5)_2$, $–C_2H_4–CH(CH_3)_2$, $–C_6H_{13}$, $–C_3H_6–CH(CH_3)_2$, $–C_2H_4–CH(CH_3)–C_2H_5$, $–CH(CH_3)–C_4H_9$, $–CH_2–CH(CH_3)–C_3H_7$, $–CH(CH_3)–CH_2–CH(CH_3)_2$, $–CH(CH_3)–CH(CH_3)–C_2H_5$, $–CH_2–CH(CH_3)–CH(CH_3)_2$, $–CH_2–C(CH_3)_2–C_2H_5$, $–C(CH_3)_2–C_3H_7$, $–C(CH_3)_2–CH(CH_3)_2$, $–C_2H_4–C(CH_3)_3$, $–CH(CH_3)–C(CH_3)_3$, $–CH=CH_2$, $–CH_2–CH=CH_2$, $–C(CH_3)=CH_2$, $–CH=CH–CH_3$, $–C_2H_4–CH=CH_2$, $–CH_2–CH=CH–CH_3$, $–CH=CH–C_2H_5$, $–CH_2–C(CH_3)=CH_2$, $–CH(CH_3)–CH=CH$, $–CH=C(CH_3)_2$, $–C(CH_3)=CH–CH_3$, $–CH=CH–CH=CH_2$, $–C_3H_6–CH=CH_2$, $–C_2H_4–CH=CH–CH_3$, $–CH_2–CH=CH–C_2H_5$, $–CH=CH–C_3H_7$, $–CH_2–CH=CH–CH=CH_2$, $–CH=CH–CH=CH–CH_3$, $–CH=CH–CH_2–CH=CH_2$, $–C(CH_3)=CH–CH=CH_2$, $–CH=C(CH_3)–CH=CH_2$, $–CH=CH–C(CH_3)=CH_2$, $–C_2H_4–C(CH_3)=CH_2$, $–CH_2–CH(CH_3)–CH=CH_2$, $–CH(CH_3)–CH_2–CH=CH_2$,

$-CH_2-CH=C(CH_3)_2$, $-CH_2-C(CH_3)=CH-CH_3$, $-CH(CH_3)-CH=CH-CH_3$, $-CH=CH-CH(CH_3)_2$, $-CH=C(CH_3)-C_2H_5$, $-C(CH_3)=CH-C_2H_5$, $-C(CH_3)=C(CH_3)_2$, $-C(CH_3)_2-CH=CH_2$, $-CH(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_4H_8-CH=CH_2$, $-C_3H_6-CH=CH-CH_3$, $-C_2H_4-CH=CH-C_2H_5$, $-CH_2-CH=CH-C_3H_7$, $-CH=CH-C_4H_9$, $-C_3H_6-C(CH_3)=CH_2$, $-C_2H_4-CH(CH_3)-CH=CH_2$, $-CH_2-CH(CH_3)-CH_2-CH=CH_2$, $-CH(CH_3)-C_2H_4-CH=CH_2$, $-C_2H_4-CH=C(CH_3)_2$, $-C_2H_4-C(CH_3)=CH-CH_3$, $-CH_2-CH(CH_3)-CH=CH-CH_3$, $-CH(CH_3)-CH_2-CH=CH-CH_3$, $-CH_2-CH=CH-CH(CH_3)_2$, $-CH_2-CH=C(CH_3)-C_2H_5$, $-CH_2-C(CH_3)=CH-C_2H_5$, $-CH(CH_3)-CH=CH-C_2H_5$, $-CH=CH-CH_2-CH(CH_3)_2$, $-CH=CH-CH(CH_3)-C_2H_5$, $-CH=C(CH_3)-C_3H_7$, $-C(CH_3)=CH-C_3H_7$, $-CH_2-CH(CH_3)-C(CH_3)=CH_2$, $-CH(CH_3)-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)_2-CH=CH_2$, $-C(CH_3)_2-CH_2-CH=CH_2$, $-CH_2-C(CH_3)=C(CH_3)_2$, $-CH(CH_3)-CH=C(CH_3)_2$, $-C(CH_3)_2-CH=CH-CH_3$, $-CH(CH_3)-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH(CH_3)_2$, $-C(CH_3)=CH-CH(CH_3)_2$, $-C(CH_3)=C(CH_3)-C_2H_5$, $-CH=CH-C(CH_3)_3$, $-C(CH_3)_2-C(CH_3)=CH_2$, $-CH(C_2H_5)-C(CH_3)=CH_2$, $-C(CH_3)(C_2H_5)-CH=CH_2$, $-CH(CH_3)-C(C_2H_5)=CH_2$, $-CH_2-C(C_3H_7)=CH_2$, $-CH_2-C(C_2H_5)=CH-CH_3$, $-CH(C_2H_5)-CH=CH-CH_3$, $-C(C_4H_9)=CH_2$, $-C(C_3H_7)=CH-CH_3$, $-C(C_2H_5)=CH-C_2H_5$, $-C(C_2H_5)=C(CH_3)_2$, $-C[C(CH_3)_3]=CH_2$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$, $-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$, $-CH=CH-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH-C_2H_5$, $-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$, $-CH=CH-CH_2-C(CH_3)=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$, $-CH=C(CH_3)-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH_2-CH=CH_2$, $-CH=CH-CH=C(CH_3)_2$, $-CH=CH-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$, $-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$, $-C(CH_3)=C(CH_3)-CH=CH_2$, $-CH=CH-CH=CH-CH=CH_2$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2$-$C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$, $-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C\equiv C-CH_3$, $-C_4H_8-C\equiv CH$, $-C_3H_6-C\equiv C-CH_3$, $-C_2H_4-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$, $-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$, $-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$, $-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$, $-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$, $-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-$

CH_2–C≡CH, –C≡C–C_2H_4–C≡CH, –CH_2–C≡C–C≡C–CH_3, –C≡C–CH_2–C≡C–CH_3, –C≡C–C≡C–C_2H_5, –C≡C–$CH(CH_3)$–C≡CH, –$CH(CH_3)$–C≡C–C≡CH, –CH(C≡CH)–CH_2–C≡CH, –$C(C{\equiv}CH)_2$–CH_3, –CH_2–$CH(C{\equiv}CH)_2$, –CH(C≡CH)–C≡C–CH_3, –R^{21}, –R^{35}, –R^{36};

R^2 and R^3 are selected independently of each other from –R^{88}, –R^{37}, –R^{38}, –R^{54}, –O–R^{54}, –R^{55}, –O–R^{55}, R^{56}, –O–R^{56}, –R^{57}, –O–R^{57}, wherein the $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl or $C_{1\text{-}6}$alkoxy groups represented by R^{88} are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, –I, –O–R^{71}, –R^{72}, –R^{138}, –COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –(C=O)–$NR^{16}R^{17}$, –SO_2–$NR^{16}R^{17}$, –SO_m–$R^{16}R^{17}$, –$CR^{16}R^{17}H$, –$NR^{16}R^{17}$;

or R^2 and/or R^3 are selected independently of each other from –O–R^{18}, –O–$CR^{73}R^{74}$–R^{18}, –O–$CR^{73}R^{74}$–$CR^{75}R^{76}$–R^{18}, –O–$CR^{73}R^{74}$–$CR^{75}R^{76}$–$CR^{77}R^{78}$–R^{18}, –O–$CR^{73}R^{74}$–$CR^{75}R^{76}$–$CR^{77}R^{78}$–$CR^{79}R^{80}$–R^{18}, –O–$CR^{73}R^{74}$–$CR^{75}R^{76}$–$CR^{77}R^{78}$–$CR^{79}R^{80}$–$CR^{81}R^{82}$–R^{18}, –O–$CR^{73}R^{74}$–$CR^{75}R^{76}$–$CR^{77}R^{78}$–$CR^{79}R^{80}$–$CR^{81}R^{82}$–$CR^{83}R^{84}$–R^{18},

R^{73} – R^{84} independently of each other represent –H, –OH, –F, –Cl, –Br, –I, –R^{85};

R^{18} represents –H, –OH, –F, –Cl, –Br, –I, –O–R^{86}, –R^{87}, –COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –(C=O)–$NR^{16}R^{17}$, –SO_2–$NR^{16}R^{17}$, –SO_m–$R^{16}R^{17}$, –$CR^{16}R^{17}H$, –$NR^{16}R^{17}$;
m = 0, 1, 2;

R^5 and R^6, which may be the same or different, represent –H, –OH, –F, –Cl, –Br, –I, –CN, –NO_2, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, cyclo-C_3H_5, –CH_2–cyclo–C_3H_5, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_3H_6–$CH(CH_3)_2$, –C_2H_4–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–C_4H_9, –CH_2–$CH(CH_3)$–C_3H_7, –$CH(CH_3)$–CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–$CH(CH_3)$–C_2H_5, –CH_2–$CH(CH_3)$–$CH(CH_3)_2$, –CH_2–$C(CH_3)_2$–C_2H_5, –$C(CH_3)_2$–C_3H_7, –$C(CH_3)_2$–$CH(CH_3)_2$, –C_2H_4–$C(CH_3)_3$, –$CH(CH_3)$–$C(CH_3)_3$, –CH=CH_2, –CH_2–CH=CH_2, –$C(CH_3)$=CH_2, –CH=CH–CH_3, –C_2H_4–CH=CH_2, –CH_2–CH=CH–CH_3, –CH=CH–C_2H_5, –CH_2–$C(CH_3)$=CH_2, –$CH(CH_3)$–CH=CH, –CH=$C(CH_3)_2$, –$C(CH_3)$=CH–CH_3, –CH=CH–CH=CH_2, –C_3H_6–CH=CH_2, –C_2H_4–CH=CH–CH_3, –CH_2–CH=CH–C_2H_5, –CH=CH–C_3H_7, –CH_2–CH=CH–CH=CH_2, –CH=CH–CH=CH–CH_3, –CH=CH–CH_2–CH=CH_2, –$C(CH_3)$=CH–CH=CH_2, –CH=$C(CH_3)$–CH=CH_2, –CH=CH–$C(CH_3)$=CH_2, –C_2H_4–$C(CH_3)$=CH_2, –CH_2–$CH(CH_3)$–CH=CH_2, –$CH(CH_3)$–CH_2–CH=CH_2, –CH_2–CH=$C(CH_3)_2$, –CH_2–

$C(CH_3)=CH–CH_3$, $–CH(CH_3)–CH=CH–CH_3$, $–CH=CH–CH(CH_3)_2$, $–CH=C(CH_3)–C_2H_5$, $–C(CH_3)=CH–C_2H_5$, $–C(CH_3)=C(CH_3)_2$, $–C(CH_3)_2–CH=CH_2$, $–CH(CH_3)–C(CH_3)=CH_2$, $–C(CH_3)=CH–CH=CH_2$, $–CH=C(CH_3)–CH=CH_2$, $–CH=CH–C(CH_3)=CH_2$, $–C_4H_8–CH=CH_2$, $–C_3H_6–CH=CH–CH_3$, $–C_2H_4–CH=CH–C_2H_5$, $–CH_2–CH=CH–C_3H_7$, $–CH=CH–C_4H_9$, $–C_3H_6–C(CH_3)=CH_2$, $–C_2H_4–CH(CH_3)–CH=CH_2$, $–CH_2–CH(CH_3)–CH_2–CH=CH_2$, $–CH(CH_3)–C_2H_4–CH=CH_2$, $–C_2H_4–CH=C(CH_3)_2$, $–C_2H_4–C(CH_3)=CH–CH_3$, $–CH_2–CH(CH_3)–CH=CH–CH_3$, $–CH(CH_3)–CH_2–CH=CH–CH_3$, $–CH_2–CH=CH–CH(CH_3)_2$, $–CH_2–CH=C(CH_3)–C_2H_5$, $–CH_2–C(CH_3)=CH–C_2H_5$, $–CH(CH_3)–CH=CH–C_2H_5$, $–CH=CH–CH_2–CH(CH_3)_2$, $–CH=CH–CH(CH_3)–C_2H_5$, $–CH=C(CH_3)–C_3H_7$, $–C(CH_3)=CH–C_3H_7$, $–CH_2–CH(CH_3)–C(CH_3)=CH_2$, $–CH(CH_3)–CH_2–C(CH_3)=CH_2$, $–CH(CH_3)–CH(CH_3)–CH=CH_2$, $–CH_2–C(CH_3)_2–CH=CH_2$, $–C(CH_3)_2–CH_2–CH=CH_2$, $–CH_2–C(CH_3)=C(CH_3)_2$, $–CH(CH_3)–CH=C(CH_3)_2$, $–C(CH_3)_2–CH=CH–CH_3$, $–CH(CH_3)–C(CH_3)=CH–CH_3$, $–CH=C(CH_3)–CH(CH_3)_2$, $–C(CH_3)=CH–CH(CH_3)_2$, $–C(CH_3)=C(CH_3)–C_2H_5$, $–CH=CH–C(CH_3)_3$, $–C(CH_3)_2–C(CH_3)=CH_2$, $–CH(C_2H_5)–C(CH_3)=CH_2$, $–C(CH_3)(C_2H_5)–CH=CH_2$, $–CH(CH_3)–C(C_2H_5)=CH_2$, $–CH_2–C(C_3H_7)=CH_2$, $–CH_2–C(C_2H_5)=CH–CH_3$, $–CH(C_2H_5)–CH=CH–CH_3$, $–C(C_4H_9)=CH_2$, $–C(C_3H_7)=CH–CH_3$, $–C(C_2H_5)=CH–C_2H_5$, $–C(C_2H_5)=C(CH_3)_2$, $–C[C(CH_3)_3]=CH_2$, $–C[CH(CH_3)(C_2H_5)]=CH_2$, $–C[CH_2–CH(CH_3)_2]=CH_2$, $–C_2H_4–CH=CH–CH=CH_2$, $–CH_2–CH=CH–CH_2–CH=CH_2$, $–CH=CH–C_2H_4–CH=CH_2$, $–CH_2–CH=CH–CH=CH–CH_3$, $–CH=CH–CH_2–CH=CH–CH_3$, $–CH=CH–CH=CH–C_2H_5$, $–CH_2–CH=CH–C(CH_3)=CH_2$, $–CH_2–CH=C(CH_3)–CH=CH_2$, $–CH_2–C(CH_3)=CH–CH=CH_2$, $–CH(CH_3)–CH=CH–CH=CH_2$, $–CH=CH–CH_2–C(CH_3)=CH_2$, $–CH=CH–CH(CH_3)–CH=CH_2$, $–CH=C(CH_3)–CH_2–CH=CH_2$, $–C(CH_3)=CH–CH_2–CH=CH_2$, $–CH=CH–CH=C(CH_3)_2$, $–CH=CH–C(CH_3)=CH–CH_3$, $–CH=C(CH_3)–CH=CH–CH_3$, $–C(CH_3)=CH–CH=CH–CH_3$, $–CH=C(CH_3)–C(CH_3)=CH_2$, $–C(CH_3)=CH–C(CH_3)=CH_2$, $–C(CH_3)=C(CH_3)–CH=CH_2$, $–CH=CH–CH=CH–CH=CH_2$, $–C\equiv CH$, $–C\equiv C–CH_3$, $–CH_2$-$C\equiv CH$, $–C_2H_4–C\equiv CH$, $–CH_2–C\equiv C–CH_3$, $–C\equiv C–C_2H_5$, $–C_3H_6–C\equiv CH$, $–C_2H_4–C\equiv C–CH_3$, $–CH_2–C\equiv C–C_2H_5$, $–C\equiv C–C_3H_7$, $–CH(CH_3)–C\equiv CH$, $–CH_2–CH(CH_3)–C\equiv CH$, $–CH(CH_3)–CH_2–C\equiv CH$, $–CH(CH_3)–C\equiv C–CH_3$, $–C\equiv C–C_4H_9$, $–C_2H_4–CH(CH_3)–C\equiv CH$, $–CH_2–CH(CH_3)–CH_2–C\equiv CH$, $–CH(CH_3)–C_2H_4–C\equiv CH$, $–CH_2–CH(CH_3)–C\equiv C–CH_3$, $–CH(CH_3)–CH_2–C\equiv C–CH_3$, $–CH(CH_3)–C\equiv C–C_2H_5$, $–CH_2–C\equiv C–CH(CH_3)_2$, $–C\equiv C–CH(CH_3)–C_2H_5$, $–C\equiv C–CH_2–CH(CH_3)_2$, $–C\equiv C–C(CH_3)_3$, $–CH(C_2H_5)–C\equiv C–CH_3$, $–C(CH_3)_2–C\equiv C–CH_3$, $–CH(C_2H_5)–CH_2–C\equiv CH$, $–CH_2–CH(C_2H_5)–C\equiv CH$, $–C(CH_3)_2–CH_2–C\equiv CH$, $–CH_2–C(CH_3)_2–C\equiv CH$, $–CH(CH_3)–CH(CH_3)–C\equiv CH$, $–CH(C_3H_7)–C\equiv CH$, $–C(CH_3)(C_2H_5)–C\equiv CH$, $–C\equiv C–C\equiv CH$, $–CH_2–C\equiv C–C\equiv CH$, $–C\equiv C–C\equiv C–CH_3$, $–CH(C\equiv CH)_2$, $–C_2H_4–C\equiv C–C\equiv CH$, $–CH_2–C\equiv C–CH_2–C\equiv CH$, $–C\equiv C–C_2H_4–$

$C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$, $-CH_2-CH(C\equiv CH)_2$, $-CH(C\equiv CH)-C\equiv C-CH_3$, $-O-R^{89}$;

R^7, R^8, $R^{10}$and R^{11}, which may be the same or different, represent $-H$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, cyclo-C_3H_5, $-CH_2-$cyclo$-C_3H_5$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$, $-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$, $-CH=CH-C_3H_7$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$, $-CH(CH_3)-CH_2-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C(CH_3)=CH-CH_3$, $-CH(CH_3)-CH=CH-CH_3$, $-CH=CH-CH(CH_3)_2$, $-CH=C(CH_3)-C_2H_5$, $-C(CH_3)=CH-C_2H_5$, $-C(CH_3)=C(CH_3)_2$, $-C(CH_3)_2-CH=CH_2$, $-CH(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_4H_8-CH=CH_2$, $-C_3H_6-CH=CH-CH_3$, $-C_2H_4-CH=CH-C_2H_5$, $-CH_2-CH=CH-C_3H_7$, $-CH=CH-C_4H_9$, $-C_3H_6-C(CH_3)=CH_2$, $-C_2H_4-CH(CH_3)-CH=CH_2$, $-CH_2-CH(CH_3)-CH_2-CH=CH_2$, $-CH(CH_3)-C_2H_4-CH=CH_2$, $-C_2H_4-CH=C(CH_3)_2$, $-C_2H_4-C(CH_3)=CH-CH_3$, $-CH_2-CH(CH_3)-CH=CH-CH_3$, $-CH(CH_3)-CH_2-CH=CH-CH_3$, $-CH_2-CH=CH-CH(CH_3)_2$, $-CH_2-CH=C(CH_3)-C_2H_5$, $-CH_2-C(CH_3)=CH-C_2H_5$, $-CH(CH_3)-CH=CH-C_2H_5$, $-CH=CH-CH_2-CH(CH_3)_2$, $-CH=CH-CH(CH_3)-C_2H_5$, $-CH=C(CH_3)-C_3H_7$, $-C(CH_3)=CH-C_3H_7$, $-CH_2-CH(CH_3)-C(CH_3)=CH_2$, $-CH(CH_3)-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)_2-CH=CH_2$, $-C(CH_3)_2-CH_2-CH=CH_2$, $-CH_2-C(CH_3)=C(CH_3)_2$, $-CH(CH_3)-CH=C(CH_3)_2$, $-C(CH_3)_2-CH=CH-CH_3$, $-CH(CH_3)-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH(CH_3)_2$, $-C(CH_3)=CH-CH(CH_3)_2$, $-C(CH_3)=C(CH_3)-C_2H_5$, $-CH=CH-C(CH_3)_3$, $-C(CH_3)_2-C(CH_3)=CH_2$, $-CH(C_2H_5)-C(CH_3)=CH_2$, $-C(CH_3)(C_2H_5)-CH=CH_2$, $-CH(CH_3)-C(C_2H_5)=CH_2$, $-CH_2-C(C_3H_7)=CH_2$, $-CH_2-C(C_2H_5)=CH-CH_3$, $-CH(C_2H_5)-CH=CH-CH_3$, $-C(C_4H_9)=CH_2$, $-C(C_3H_7)=CH-CH_3$, $-C(C_2H_5)=CH-C_2H_5$, $-C(C_2H_5)=C(CH_3)_2$, $-C[C(CH_3)_3]=CH_2$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$, $-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$,

$-CH=CH-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH-C_2H_5$, $-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$, $-CH=CH-CH_2-C(CH_3)=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$, $-CH=C(CH_3)-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH_2-CH=CH_2$, $-CH=CH-CH=C(CH_3)_2$, $-CH=CH-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$, $-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$, $-C(CH_3)=C(CH_3)-CH=CH_2$, $-CH=CH-CH=CH_2$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$, $-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C\equiv C-CH_3$, $-C_4H_8-C\equiv CH$, $-C_3H_6-C\equiv C-CH_3$, $-C_2H_4-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$, $-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$, $-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$, $-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$, $-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$, $-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$, $-CH_2-CH(C\equiv CH)_2$, $-CH(C\equiv CH)-C\equiv C-CH_3$, $-O-R^{90}$, $-O-R^{110}$, $-O-R^{111}$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}alkoxy groups are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, –I;

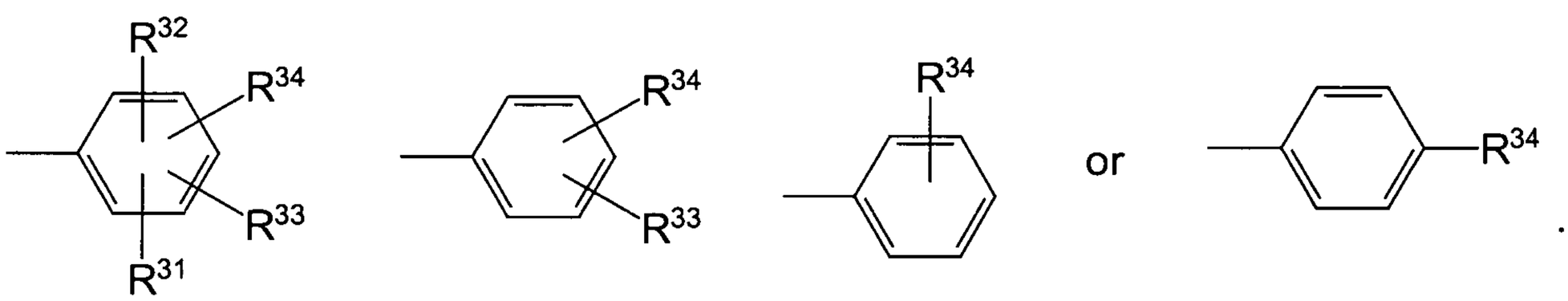
R^9 represents –H, $-R^{91}$;

R^{12} represent $-R^{92}$, –CN, $-R^{93}$, $-R^{94}$, $-OR^{94}$, phenyl, naphtalinyl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-6}alkoxy groups represented by R^{92} are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, –I, $-O-R^{95}$, $-R^{96}$, $-R^{137}$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-(C=O)-NR^{16}R^{17}$, $-SO_2-NR^{16}R^{17}$, $-SO_m-R^{16}R^{17}$, $-CR^{16}R^{17}H$, $-NR^{16}R^{17}$; and wherein the saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring systems represented by R^{137} are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, –I, $-R^{96}$;

R^{13} is selected from –H, –OH, –F, –Cl, –Br, –I, $-NO_2$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$,

$-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$, $-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$, $-CH=CH-C_3H_7$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$, $-CH(CH_3)-CH_2-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C(CH_3)=CH-CH_3$, $-CH(CH_3)-CH=CH-CH_3$, $-CH=CH-CH(CH_3)_2$, $-CH=C(CH_3)-C_2H_5$, $-C(CH_3)=CH-C_2H_5$, $-C(CH_3)=C(CH_3)_2$, $-C(CH_3)_2-CH=CH_2$, $-CH(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_4H_8-CH=CH_2$, $-C_3H_6-CH=CH-CH_3$, $-C_2H_4-CH=CH-C_2H_5$, $-CH_2-CH=CH-C_3H_7$, $-CH=CH-C_4H_9$, $-C_3H_6-C(CH_3)=CH_2$, $-C_2H_4-CH(CH_3)-CH=CH_2$, $-CH_2-CH(CH_3)-CH_2-CH=CH_2$, $-CH(CH_3)-C_2H_4-CH=CH_2$, $-C_2H_4-CH=C(CH_3)_2$, $-C_2H_4-C(CH_3)=CH-CH_3$, $-CH_2-CH(CH_3)-CH=CH-CH_3$, $-CH(CH_3)-CH_2-CH=CH-CH_3$, $-CH_2-CH=CH-CH(CH_3)_2$, $-CH_2-CH=C(CH_3)-C_2H_5$, $-CH_2-C(CH_3)=CH-C_2H_5$, $-CH(CH_3)-CH=CH-C_2H_5$, $-CH=CH-CH_2-CH(CH_3)_2$, $-CH=CH-CH(CH_3)-C_2H_5$, $-CH=C(CH_3)-C_3H_7$, $-C(CH_3)=CH-C_3H_7$, $-CH_2-CH(CH_3)-C(CH_3)=CH_2$, $-CH(CH_3)-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)_2-CH=CH_2$, $-C(CH_3)_2-CH_2-CH=CH_2$, $-CH_2-C(CH_3)=C(CH_3)_2$, $-CH(CH_3)-CH=C(CH_3)_2$, $-C(CH_3)_2-CH=CH-CH_3$, $-CH(CH_3)-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH(CH_3)_2$, $-C(CH_3)=CH-CH(CH_3)_2$, $-C(CH_3)=C(CH_3)-C_2H_5$, $-CH=CH-C(CH_3)_3$, $-C(CH_3)_2-C(CH_3)=CH_2$, $-CH(C_2H_5)-C(CH_3)=CH_2$, $-C(CH_3)(C_2H_5)-CH=CH_2$, $-CH(CH_3)-C(C_2H_5)=CH_2$, $-CH_2-C(C_3H_7)=CH_2$, $-CH_2-C(C_2H_5)=CH-CH_3$, $-CH(C_2H_5)-CH=CH-CH_3$, $-C(C_4H_9)=CH_2$, $-C(C_3H_7)=CH-CH_3$, $-C(C_2H_5)=CH-C_2H_5$, $-C(C_2H_5)=C(CH_3)_2$, $-C[C(CH_3)_3]=CH_2$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$, $-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$, $-CH=CH-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH-C_2H_5$, $-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$, $-CH=CH-CH_2-C(CH_3)=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$, $-CH=C(CH_3)-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH_2-CH=CH_2$, $-CH=CH-CH=C(CH_3)_2$, $-CH=CH-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$, $-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$, $-C(CH_3)=C(CH_3)-CH=CH_2$, $-CH=CH-$

$CH=CH–CH=CH_2$, $–C\equiv CH$, $–C\equiv C–CH_3$, $–CH_2-C\equiv CH$, $–C_2H_4–C\equiv CH$, $–CH_2–C\equiv C–CH_3$, $–C\equiv C–C_2H_5$, $–C_3H_6–C\equiv CH$, $–C_2H_4–C\equiv C–CH_3$, $–CH_2–C\equiv C–C_2H_5$, $–C\equiv C–C_3H_7$, $–CH(CH_3)–C\equiv CH$, $–CH_2–CH(CH_3)–C\equiv CH$, $–CH(CH_3)–CH_2–C\equiv CH$, $–CH(CH_3)–C\equiv C–CH_3$, $–C_4H_8–C\equiv CH$, $–C_3H_6–C\equiv C–CH_3$, $–C_2H_4–C\equiv C–C_2H_5$, $–CH_2–C\equiv C–C_3H_7$, $–C\equiv C–C_4H_9$, $–C_2H_4–CH(CH_3)–C\equiv CH$, $–CH_2–CH(CH_3)–CH_2–C\equiv CH$, $–CH(CH_3)–C_2H_4–C\equiv CH$, $–CH_2–CH(CH_3)–C\equiv C–CH_3$, $–CH(CH_3)–CH_2–C\equiv C–CH_3$, $–CH(CH_3)–C\equiv C–C_2H_5$, $–CH_2–C\equiv C–CH(CH_3)_2$, $–C\equiv C–CH(CH_3)–C_2H_5$, $–C\equiv C–CH_2–CH(CH_3)_2$, $–C\equiv C–C(CH_3)_3$, $–CH(C_2H_5)–C\equiv C–CH_3$, $–C(CH_3)_2–C\equiv C–CH_3$, $–CH(C_2H_5)–CH_2–C\equiv CH$, $–CH_2–CH(C_2H_5)–C\equiv CH$, $–C(CH_3)_2–CH_2–C\equiv CH$, $–CH_2–C(CH_3)_2–C\equiv CH$, $–CH(CH_3)–CH(CH_3)–C\equiv CH$, $–CH(C_3H_7)–C\equiv CH$, $–C(CH_3)(C_2H_5)–C\equiv CH$, $–C\equiv C–C\equiv CH$, $–CH_2–C\equiv C–C\equiv CH$, $–C\equiv C–C\equiv C–CH_3$, $–CH(C\equiv CH)_2$, $–C_2H_4–C\equiv C–C\equiv CH$, $–CH_2–C\equiv C–CH_2–C\equiv CH$, $–C\equiv C–C_2H_4–C\equiv CH$, $–CH_2–C\equiv C–C\equiv C–CH_3$, $–C\equiv C–CH_2–C\equiv C–CH_3$, $–C\equiv C–C\equiv C–C_2H_5$, $–C\equiv C–CH(CH_3)–C\equiv CH$, $–CH(CH_3)–C\equiv C–C\equiv CH$, $–CH(C\equiv CH)–CH_2–C\equiv CH$, $–C(C\equiv CH)_2–CH_3$, $–CH_2–CH(C\equiv CH)_2$, $–CH(C\equiv CH)–C\equiv C–CH_3$, cyclo-$C_3H_5$, –Ph, $–O–R^{97}$, $–R^{98}$, $–R^{99}$,



when R^{12} and R^{13} represent alkenylene groups, R^{12} and R^{13} may combine to form a condensed aromatic ring together with the atoms of residue D to which R^{12} and R^{13} are attached in order to form a bicyclic group with residue D;

R^{14} represents

(i) –H, –OH, –F, –Cl, –Br, –I, $–NO_2$, –CN, NH_2;

(ii) $–R^{100}$, $–R^{101}$, $–R^{102}$, $–O–R^{102}$, $–R^{103}$, $–O–R^{103}$, $–R^{136}$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}alkoxy groups represented by R^{100} and the ether groups represented by $–R^{136}$ are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, –I, $–O–R^{104}$, $–R^{105}$, –COOH, $–COOCH_3$, $–COOC_2H_5$, $–COOC_3H_7$, $–COOCH(CH_3)_2$, $–COOC(CH_3)_3$, $–(C=O)–NR^{16}R^{17}$, $–SO_2–NR^{16}R^{17}$, $–SO_m–R^{16}R^{17}$, $–CR^{16}R^{17}H$, $–NR^{16}R^{17}$;

(iii) $–R^{113}$, wherein the saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system represented by $–R^{113}$ is optionally mono- or polysubstituted by –F, –Cl, –Br, –I, –OH, $–NO_2$, $–NH_2$, $–C_2H_4–N(CH_3)_2$, –CN, $–CF_3$, =O, $–R^{16}$, $–R^{17}$, $–R^{106}$, $–O–R^{107}$, $–R^{108}$, $–R^{109}$, a saturated or unsaturated three- to eight-membered carbocyclic or heterocyclic group, wherein the

C_{1-6}alkyl groups represented by R^{106}, the C_{1-6}alkenyl groups represented by R^{108}, the C_{2-6}alkynyl groups represented by R^{109}, the C_{1-6}alkoxy groups represented by $-O-R^{107}$ are optionally mono- or polysubstituted by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-O-R^{104}$, $-R^{105}$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-(C=O)-NR^{16}R^{17}$, $-SO_2-NR^{16}R^{17}$, $-SO_m-R^{16}R^{17}$, $-CR^{16}R^{17}H$, $-NR^{16}R^{17}$;

R^{16} and R^{17}, which may be the same or different, represent $-H$, $-R^{112}$, optionally substituted by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-CN$;

or alternatively R^{16} and R^{17} may combine with the nitrogen atom attached thereto to form a saturated or unsaturated five to eight-membered heterocyclic group selected from $-R^{114}$; which is optionally mono- or poysubstituted by $-OH$, $=O$, $-R^{116}$, $-R^{117}$, $-R^{118}$, $-O-R^{119}$, $-R^{120}$, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system selected from $-R^{115}$; wherein the C_{1-6}alkyl group represented by R^{116}, C_{2-6}alkenyl group represented by R^{117}, C_{2-6}alkynyl group represented by R^{118} are optionally substituted by $-OH$, $-R^{122}$, or a saturated or unsaturated three- to twelve-membered carbocylic or heterocyclicring system selected from $-R^{121}$;

amino group in which one or two hydrogen atoms on the amino group are optionally substituted by $-R^{123}$, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system selected from $-R^{124}$, and the C_{1-6}alkyl group represented by R^{123} is optionally substituted by $-OH$, $-R^{125}$, or a saturated or unsaturated three- to twelve-membered carbocylic or heterocyclic ring system selected from $-R^{126}$;

or a saturated or unsaturated three- to twelve-membered carbocyclic ring system selected from $-R^{127}$; optionally substituted by $-OH$, $=O$, $-R^{128}$, $-R^{129}$, $-R^{130}$, $-O-R^{131}$, $-R^{132}$, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system selected from $-R^{133}$, wherein the C_{1-6}alkyl group represented by R^{128}, C_{2-6}alkenyl group represented by R^{129} and C_{2-6}alkynyl group represented by R^{130} are optionally substituted by $-OH$, $-R^{134}$, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system selected from $-R^{135}$;

when the carbocyclic or heterocyclic group is substituted by C_{1-6}alkyl groups, two alkyl groups may combine together to form an alkylene chain; and the carbocyclic or heterocyclic group may be condensed with another saturated or unsaturated five to seven-membered carbocyclic or heterocyclic group to form a bicyclic group;

R^{19}, R^{20}, R^{71}, R^{85}, R^{86}, R^{89}, R^{90}, R^{91}, R^{95}, R^{97}, R^{104}, R^{106}, R^{107}, R^{110}, R^{111}, R^{112}, R^{116}, R^{119}, R^{122}, R^{123}, R^{125}, R^{128}, R^{131} and R^{134} independently of each other represent $-CH_3$, $-H$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CF_3$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$,

$-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-Ph$, $-CH_2-Ph$;

R^{21} and R^{98} represent independently of each other $-CR^{22}R^{23}R^{24}$, $-CR^{23}R^{24}-CR^{25}R^{26}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$;

R^{22} – R^{34} independently of each other represent $-H$, $-F$, $-Cl$, $-Br$, $-I$, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-C_2H_5$, $-C_3H_7$;

R^{35} and R^{99} represent independently of each other $-O-CR^{22}R^{23}R^{24}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}R^{22}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$;

R^{36}, R^{72}, R^{87}, R^{96}, R^{105}, R^{120}, R^{132} and R^{136} represent independently of each other $-CR^{23}R^{24}-XH$, $-X-CR^{22}R^{23}R^{24}$, $-X-CR^{23}R^{24}-CR^{25}R^{26}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}$ $-X-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-X-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-X-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-X-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-X-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-X-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-X-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-X-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-X-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}-XH$;

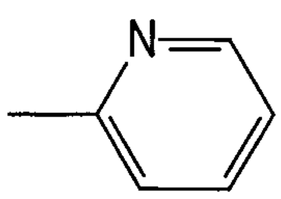
X represents $-O-$, $-CO-$, $-O-CO-$

R^{37}, R^{38}, R^{93} and R^{101} represent independently of each other $-CR^{40}R^{41}-YH$, $-Y-CR^{39}R^{40}R^{41}$, $-Y-CR^{40}R^{41}-CR^{42}R^{43}R^{39}$, $-CR^{40}R^{41}-Y-CR^{42}R^{43}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-YH$, $-Y-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}R^{39}$, $-CR^{40}R^{41}-Y-CR^{42}R^{43}-CR^{44}R^{45}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-Y-CR^{44}R^{45}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-YH$, $-Y-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}R^{39}$, $-CR^{40}R^{41}-Y-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-Y-CR^{44}R^{45}-CR^{46}R^{47}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{46}R^{39}$, $-CR^{40}R^{42}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-YH$, $-Y-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-CR^{48}R^{49}R^{39}$, $-CR^{40}R^{41}-Y-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-CR^{48}R^{49}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-Y-CR^{44}R^{45}-CR^{46}R^{47}-CR^{48}R^{49}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-CR^{48}R^{49}-YH$, $-Y-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-CR^{48}R^{49}-CR^{50}R^{51}R^{39}$, $-CR^{40}R^{41}-Y-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-CR^{48}R^{49}-CR^{50}R^{51}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-Y-CR^{46}R^{47}-CR^{48}R^{49}-CR^{50}R^{51}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-Y-CR^{48}R^{49}-CR^{50}R^{51}R^{39}$, $-CR^{40}R^{41}-CR^{42}R^{43}-CR^{44}R^{45}-CR^{46}R^{47}-CR^{48}R^{49}-CR^{50}R^{51}-YH$;

R^{39} – R^{53} represent independently of each other $-H$, $-CH_3$, $-C_2H_5$, $-C_3H_7$;

Y represents $-NR^{52}-CO-$, $-CO-NR^{53}-$;

R^{54}, R^{55} and R^{102} represent independently of each other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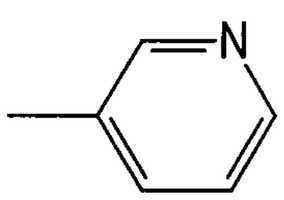
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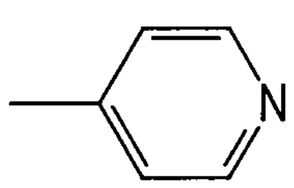
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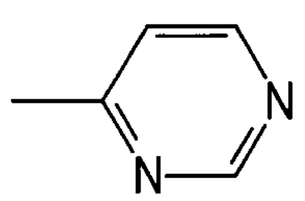
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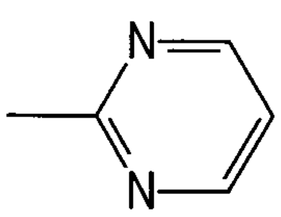
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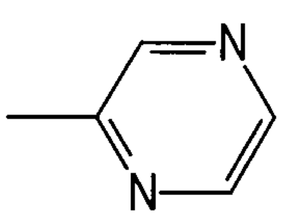
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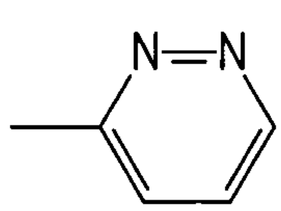
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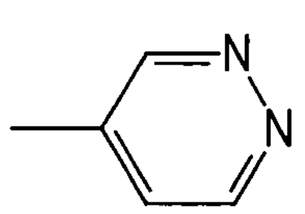
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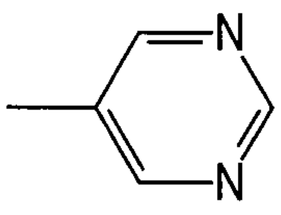
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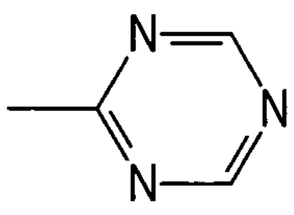
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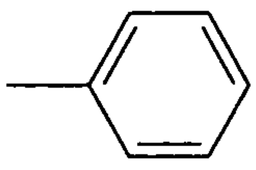
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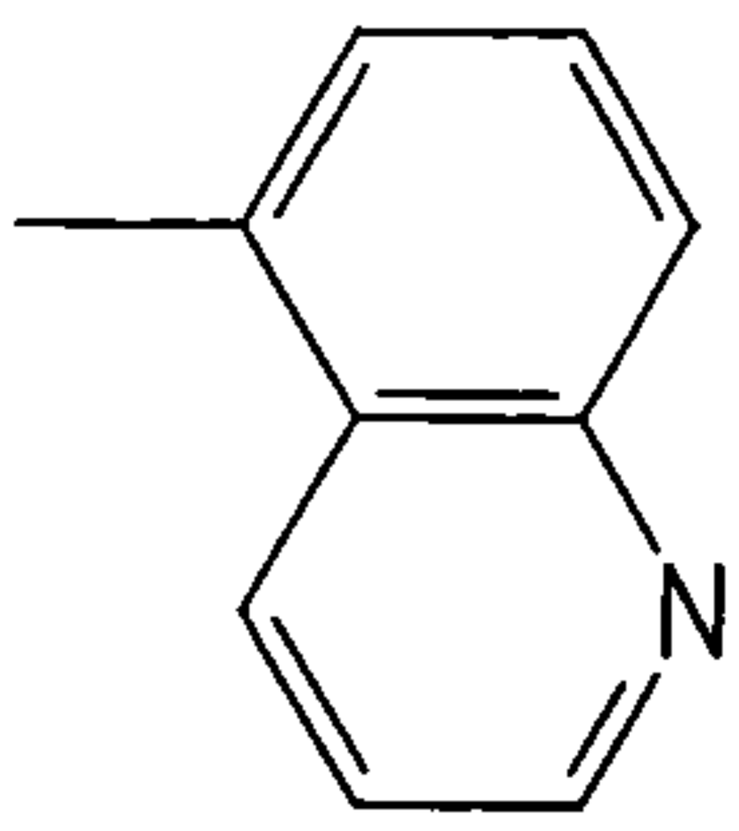
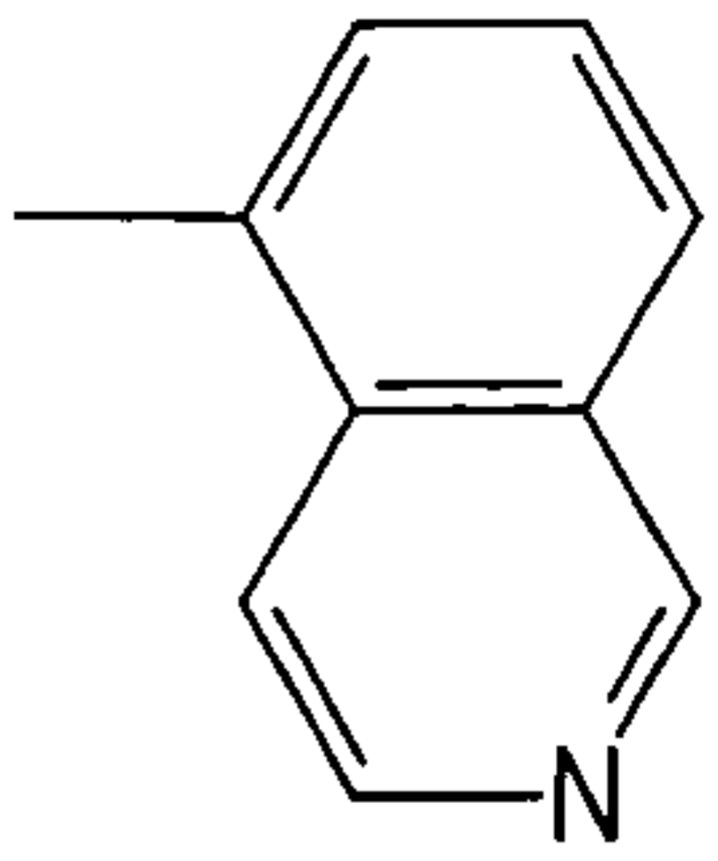
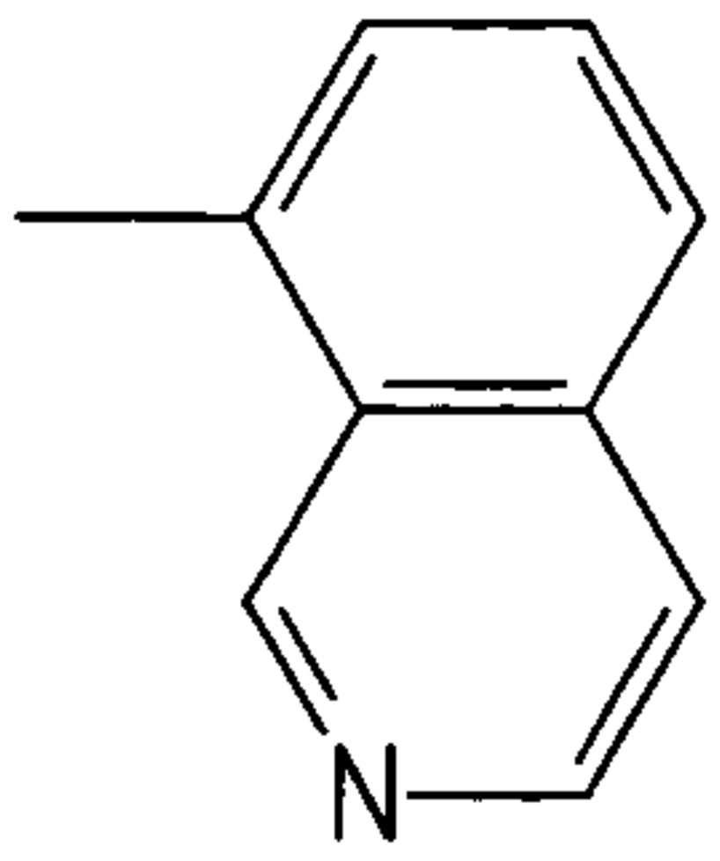
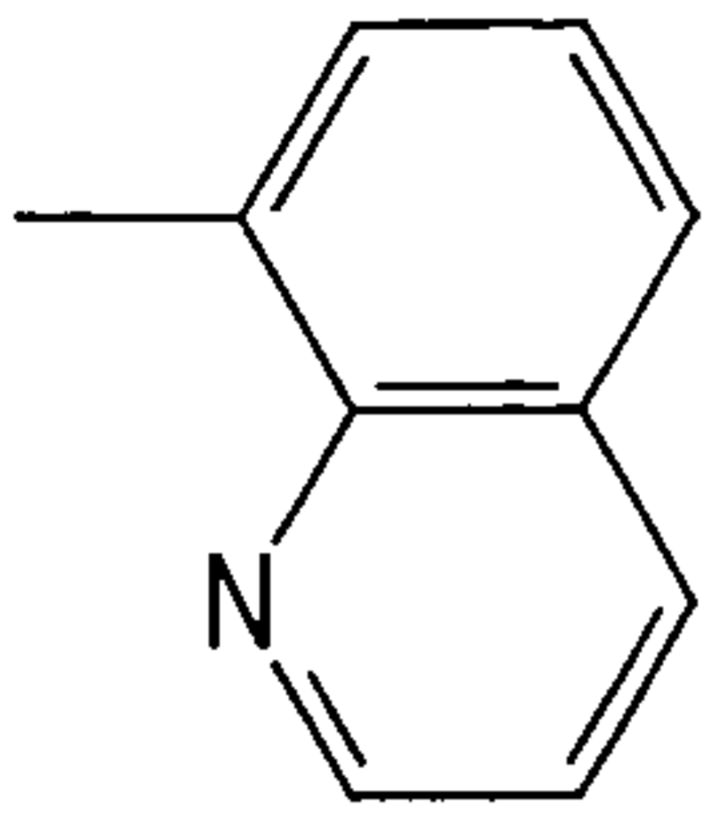
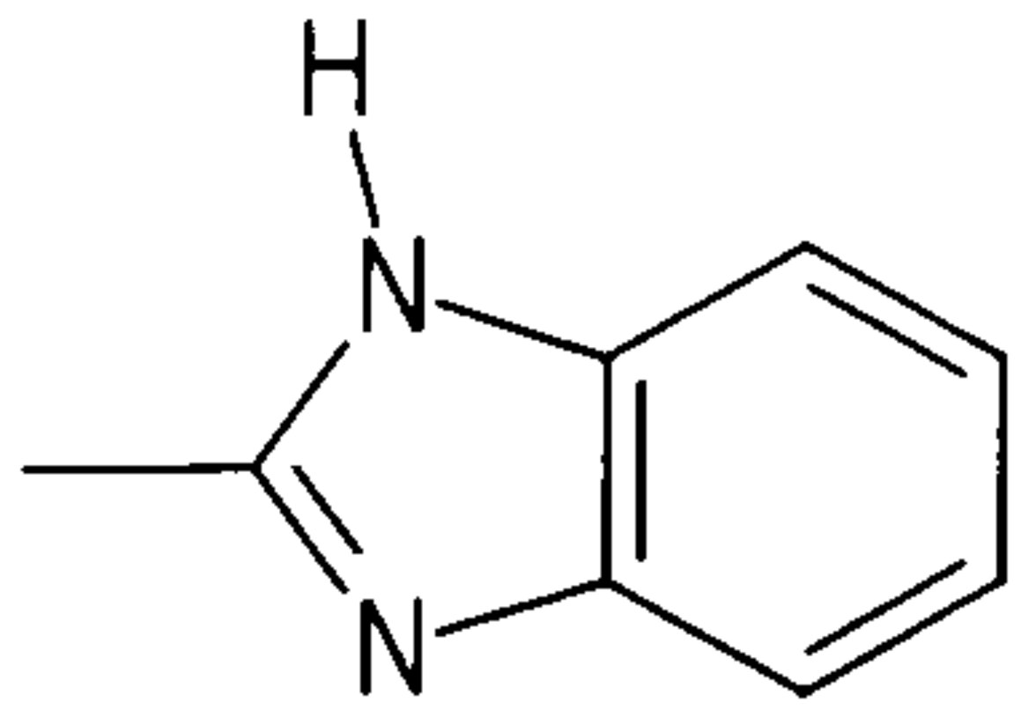
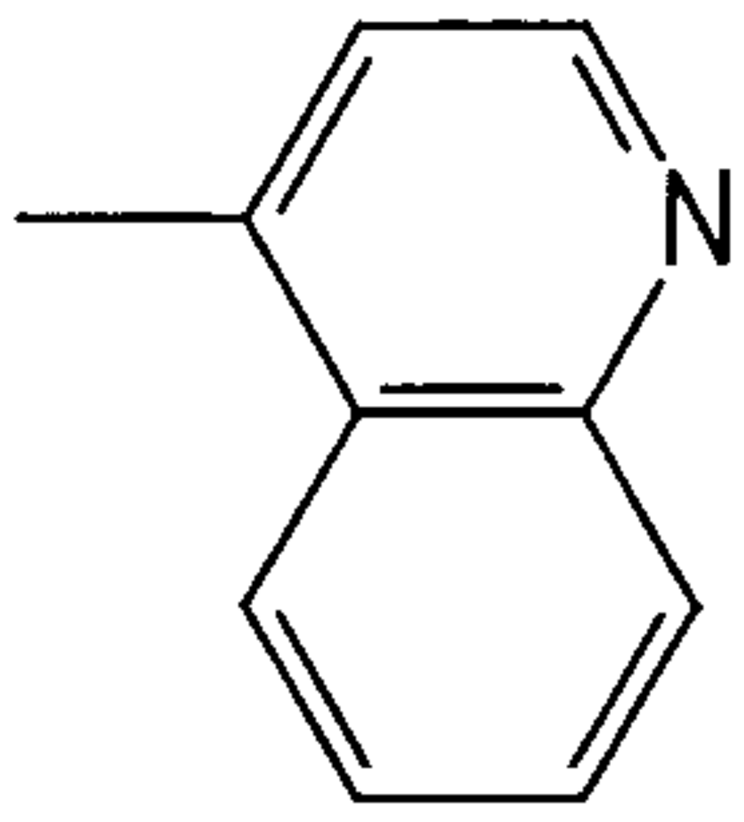
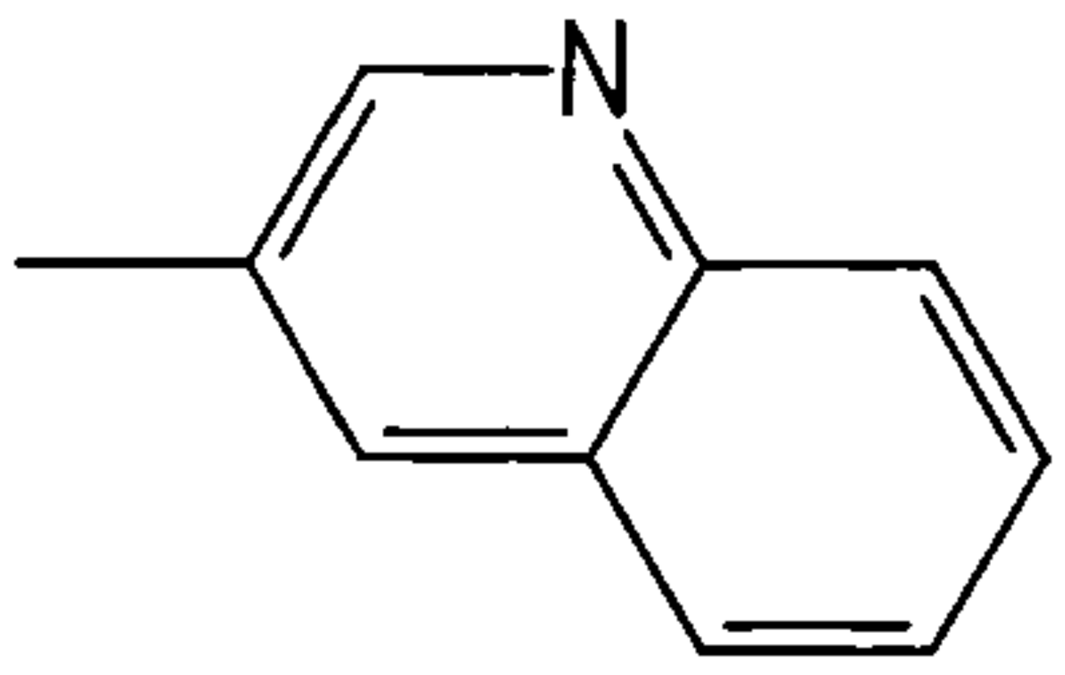
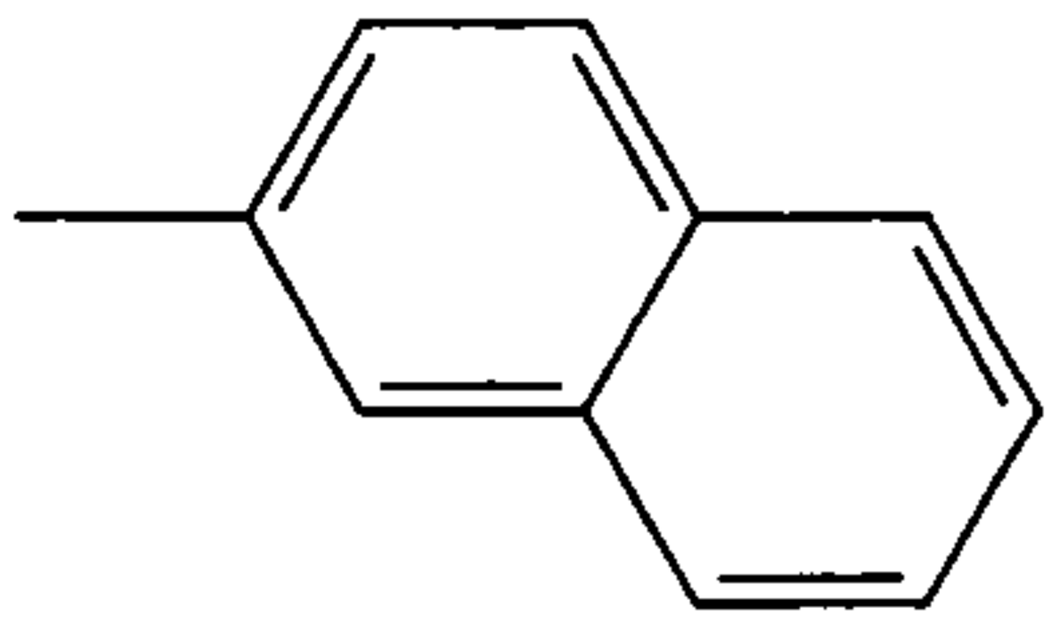
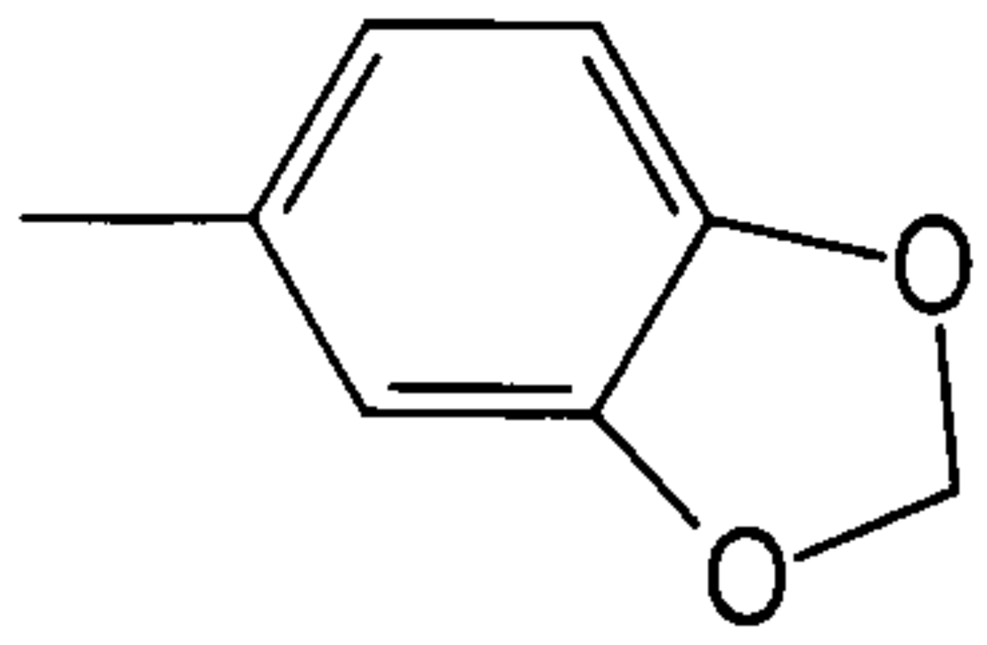
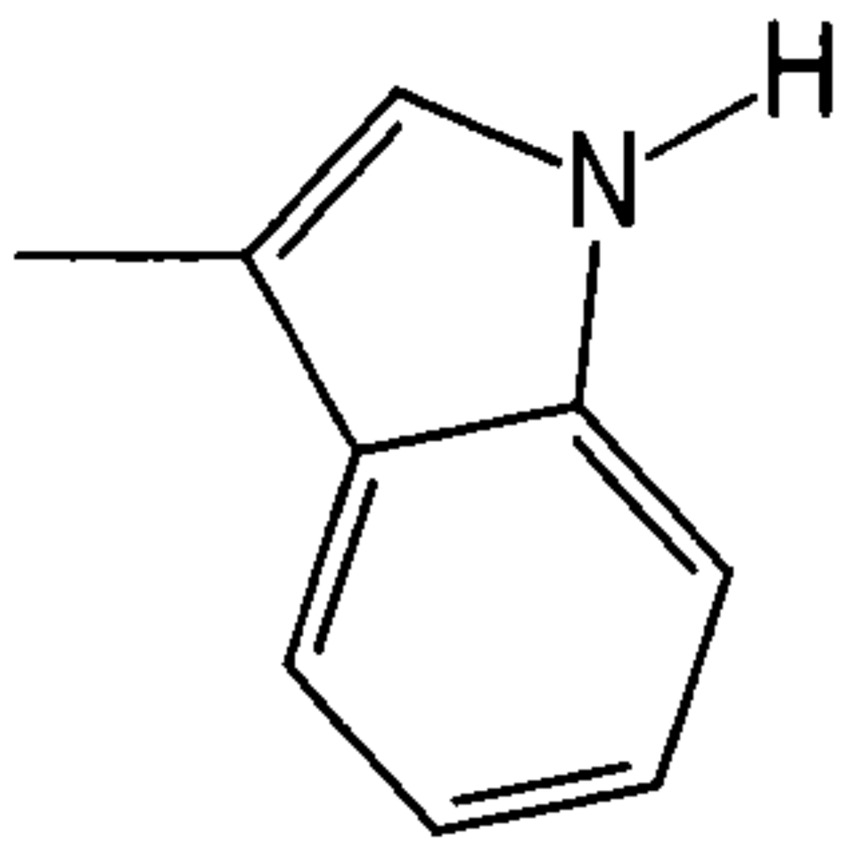
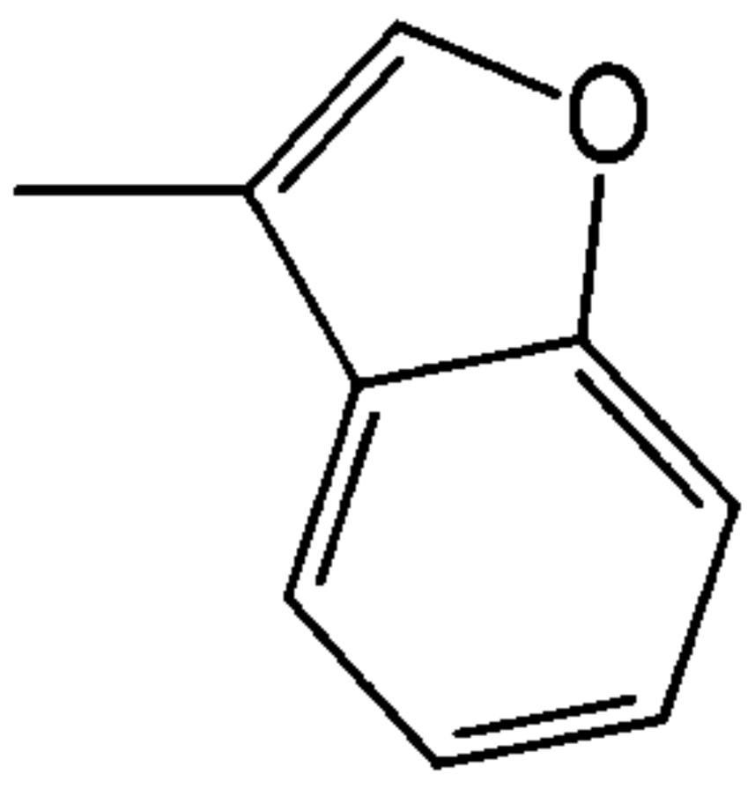
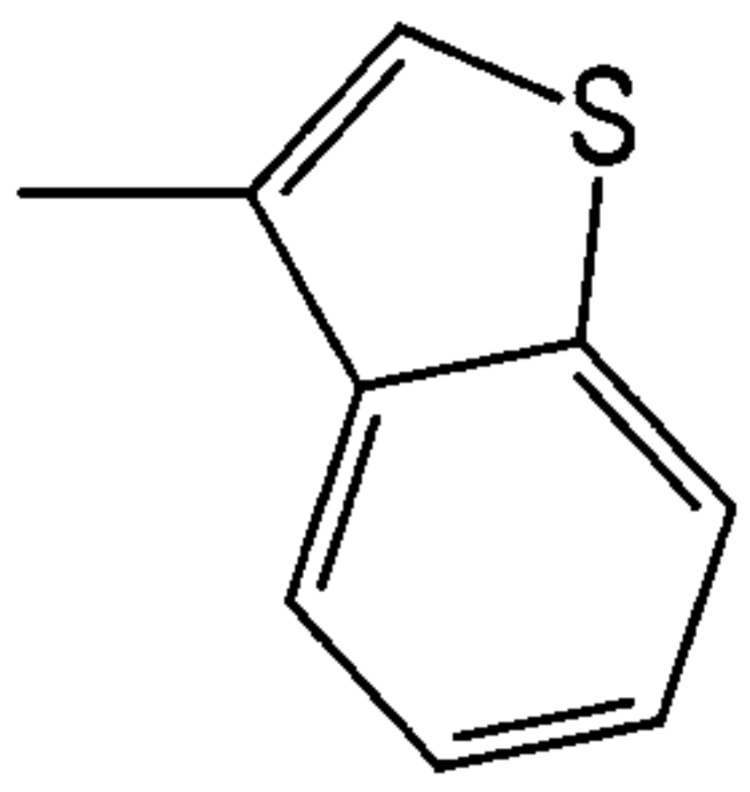
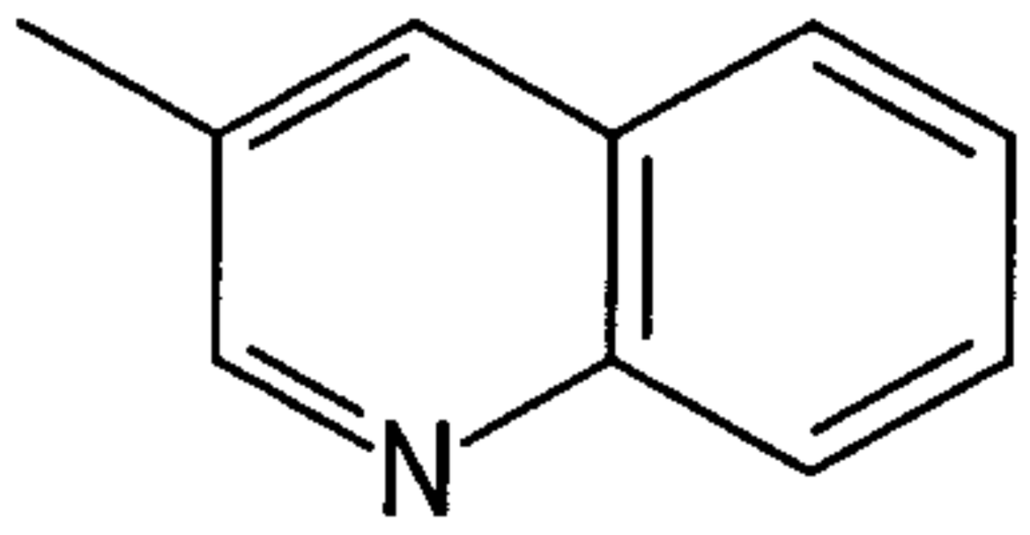
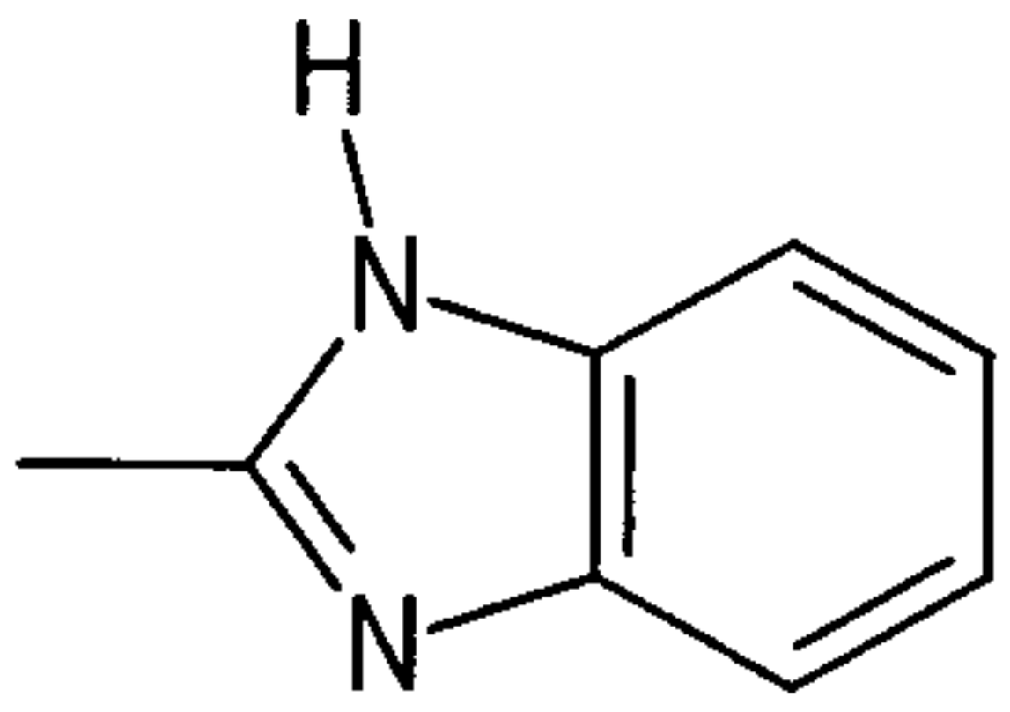
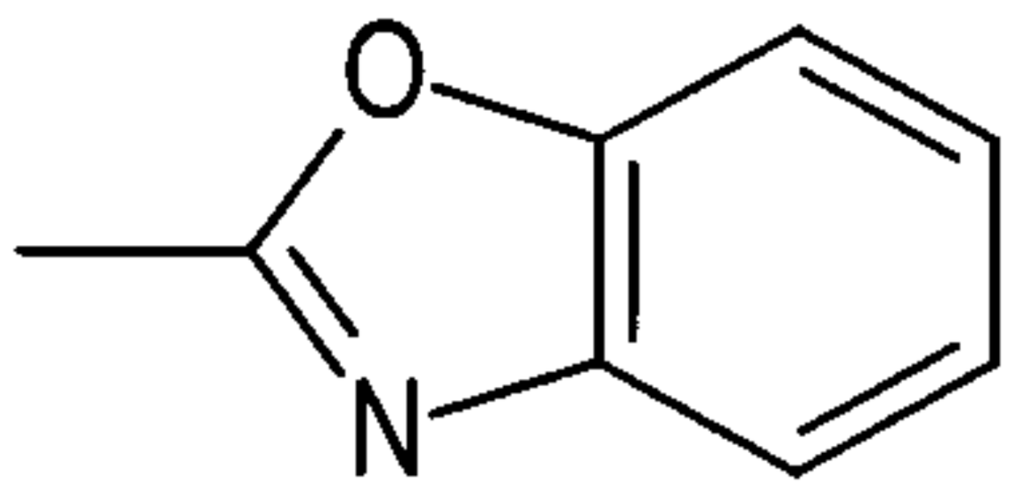
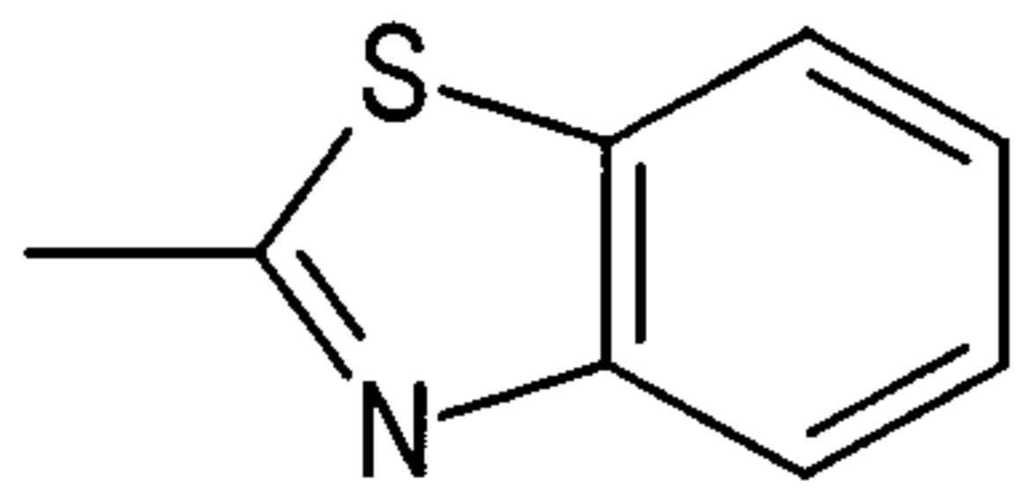
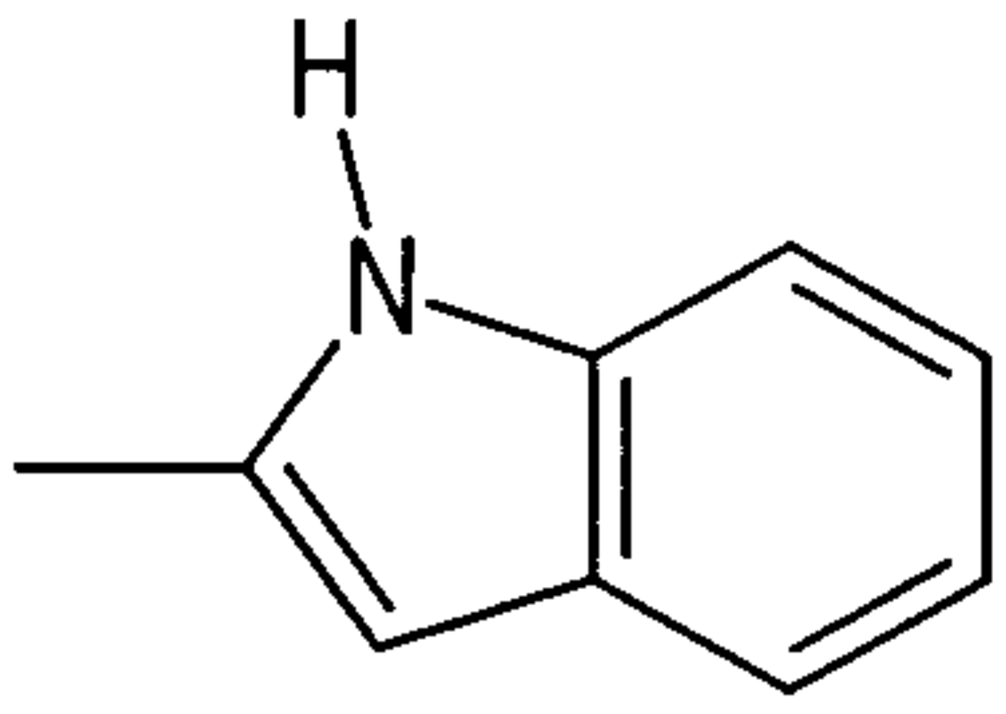
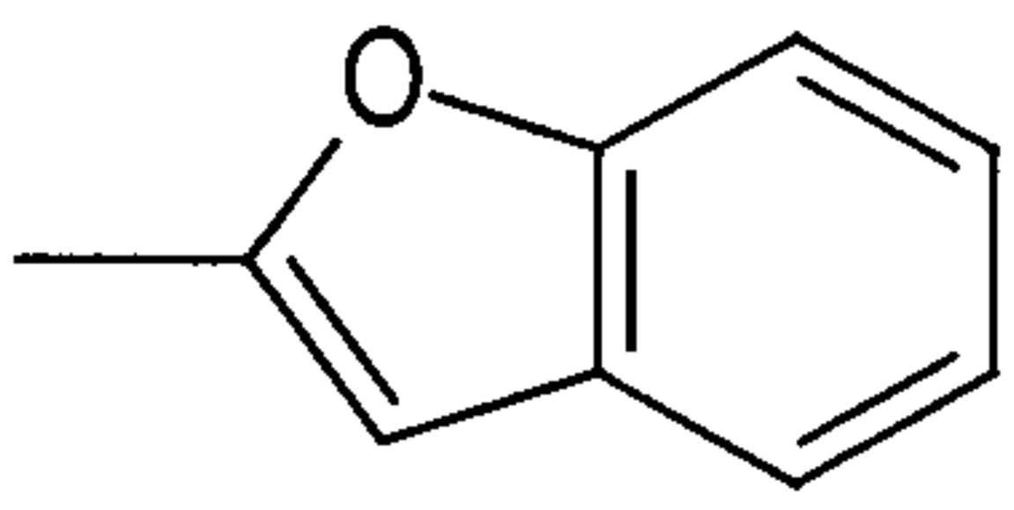
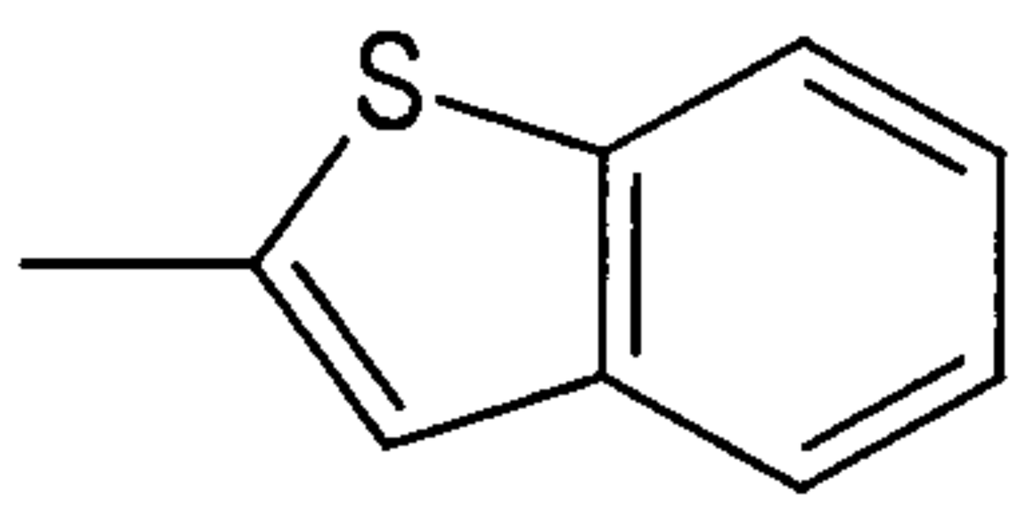
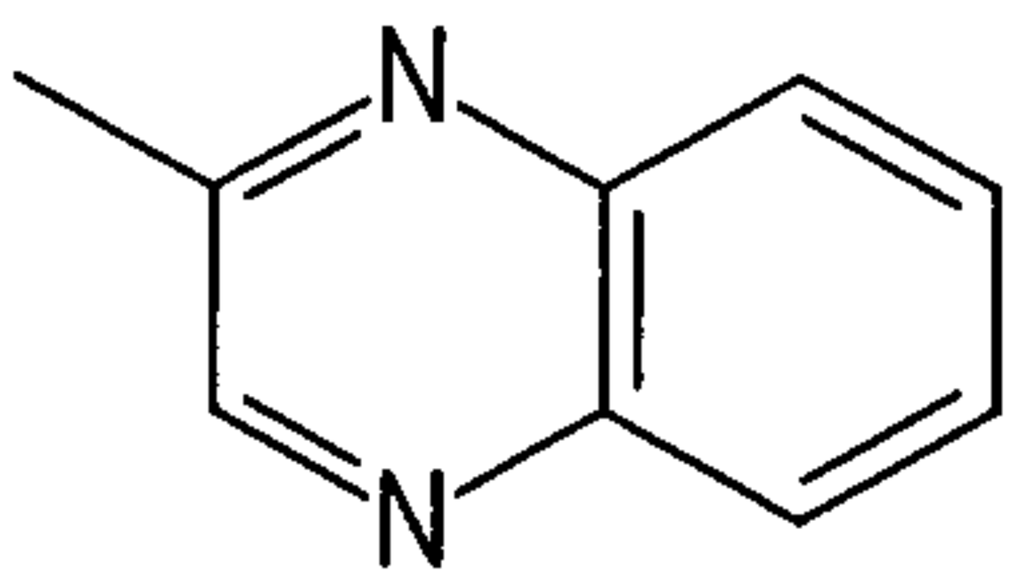
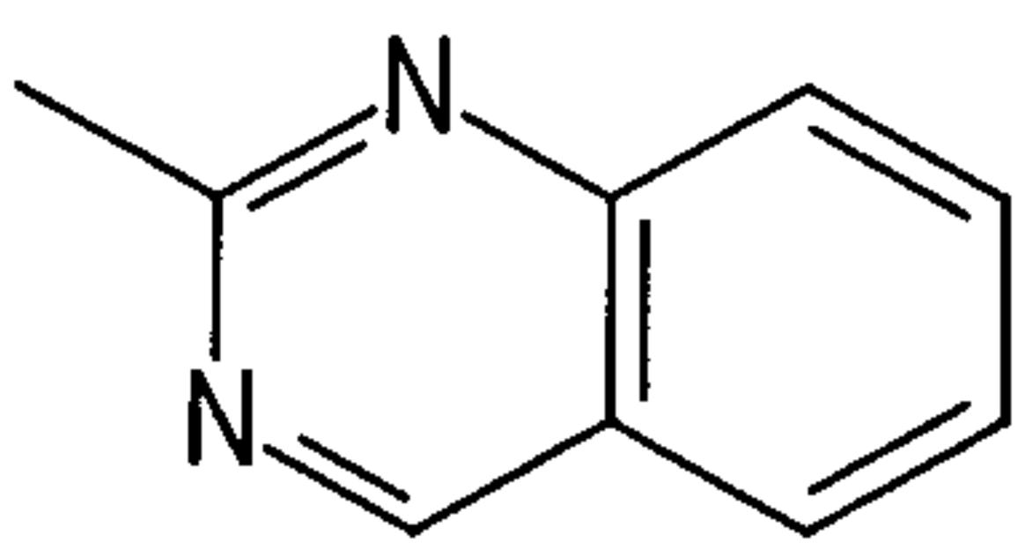
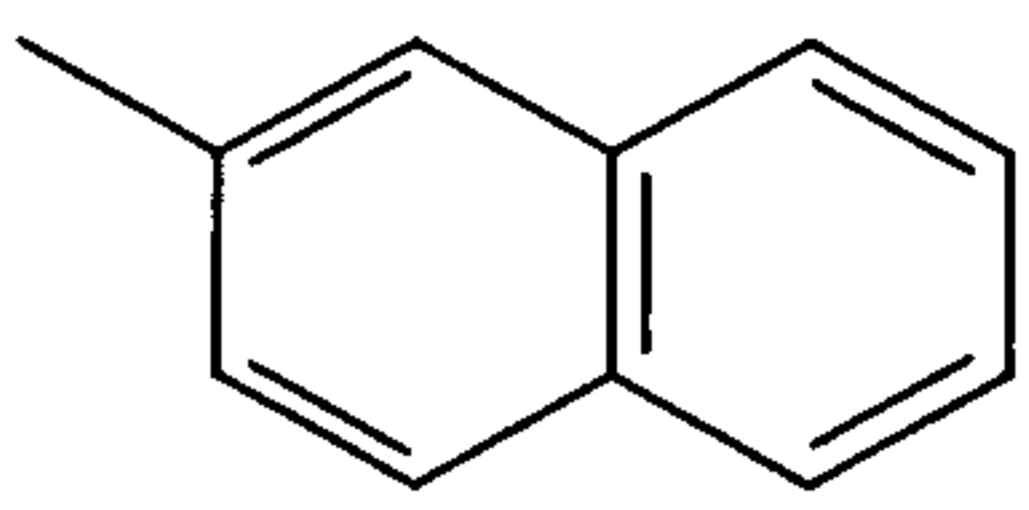
 ,  ,  ,  , 

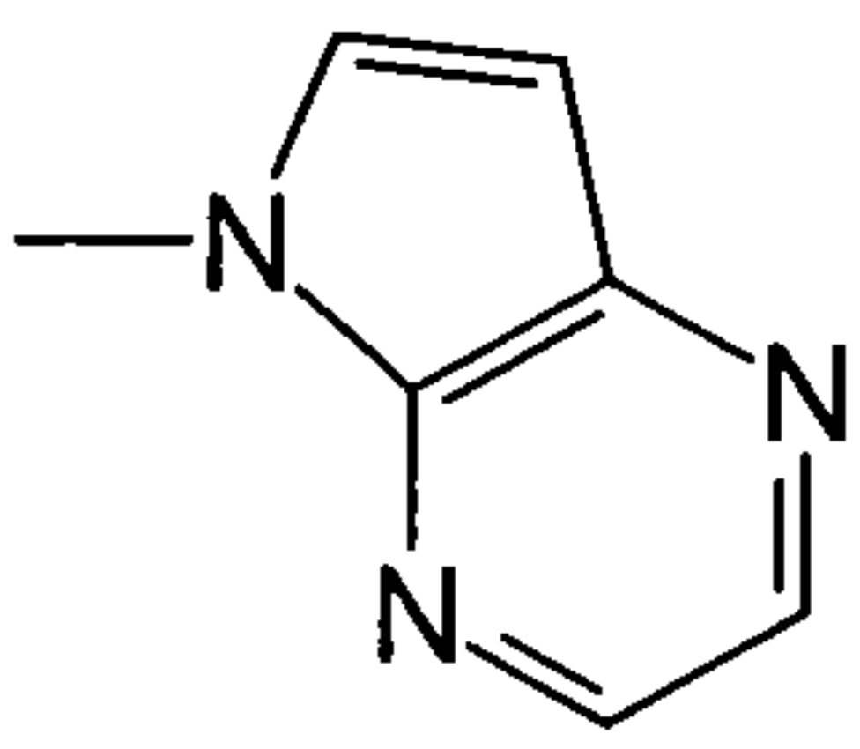
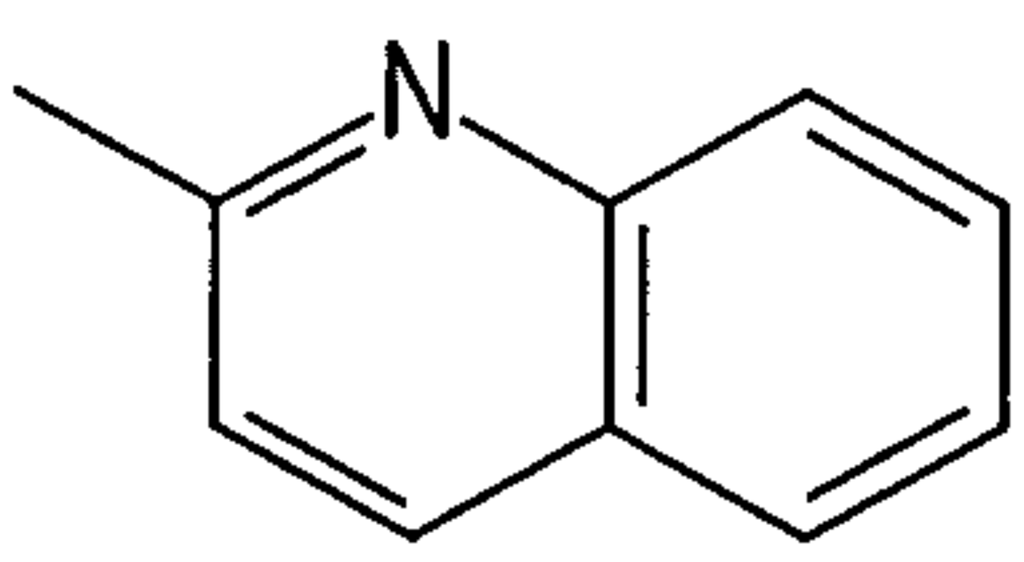
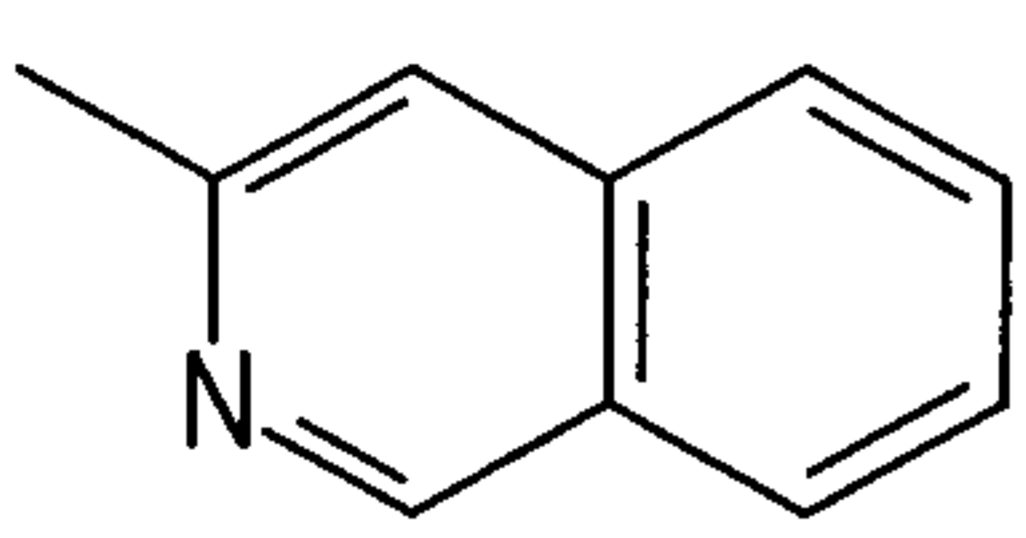
 .   , 

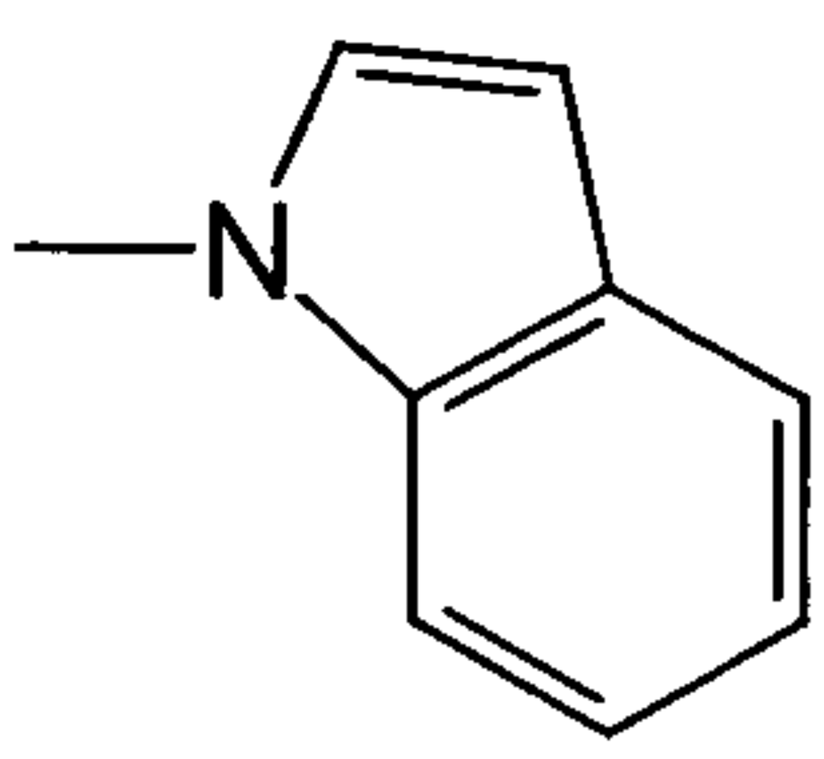
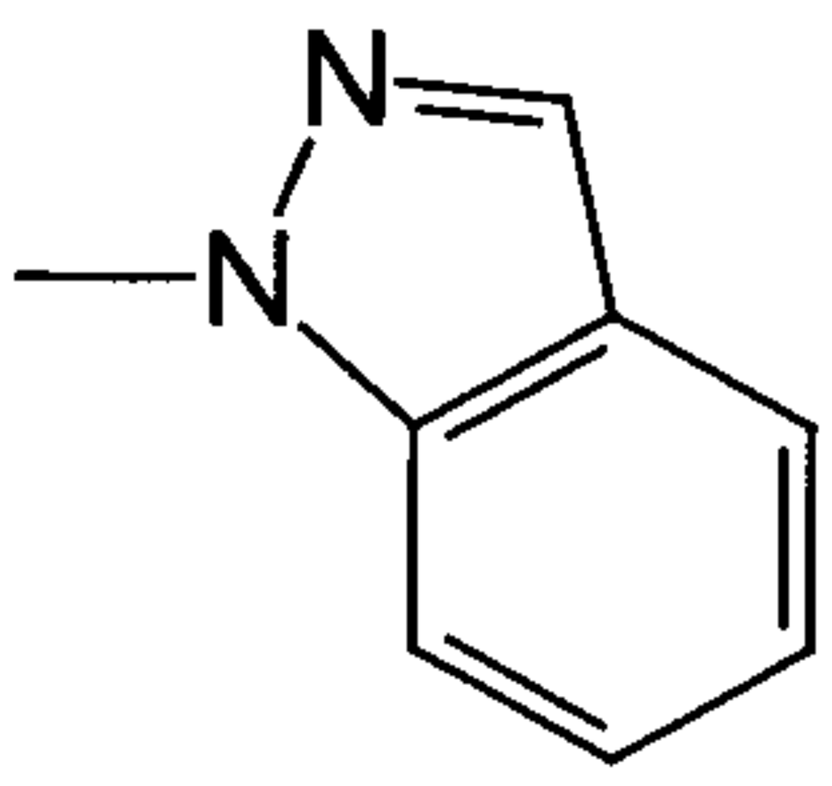
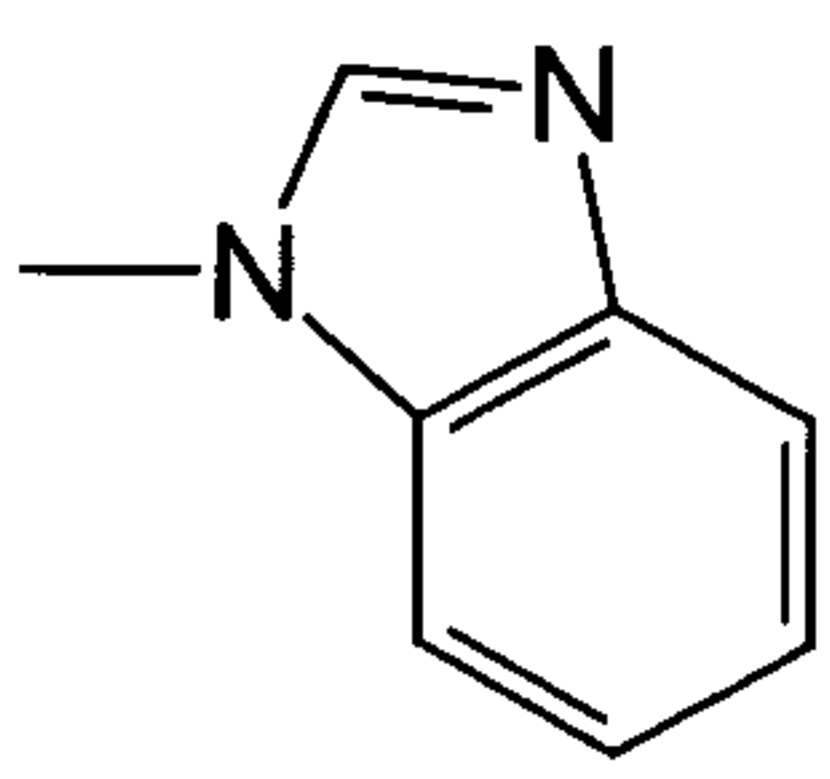
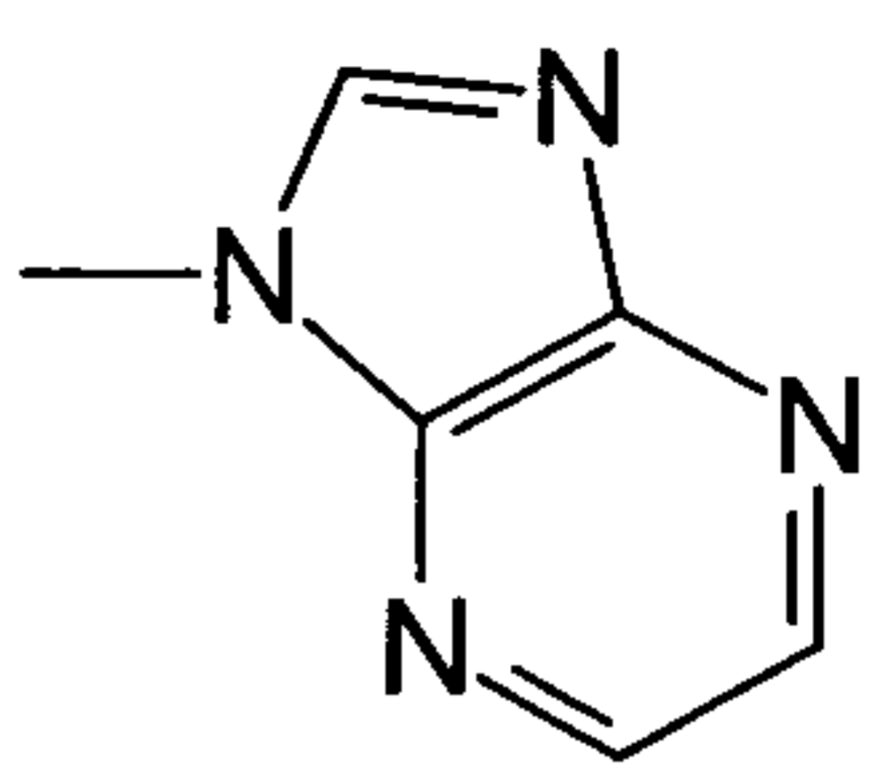
 ,  ,  ,  ,

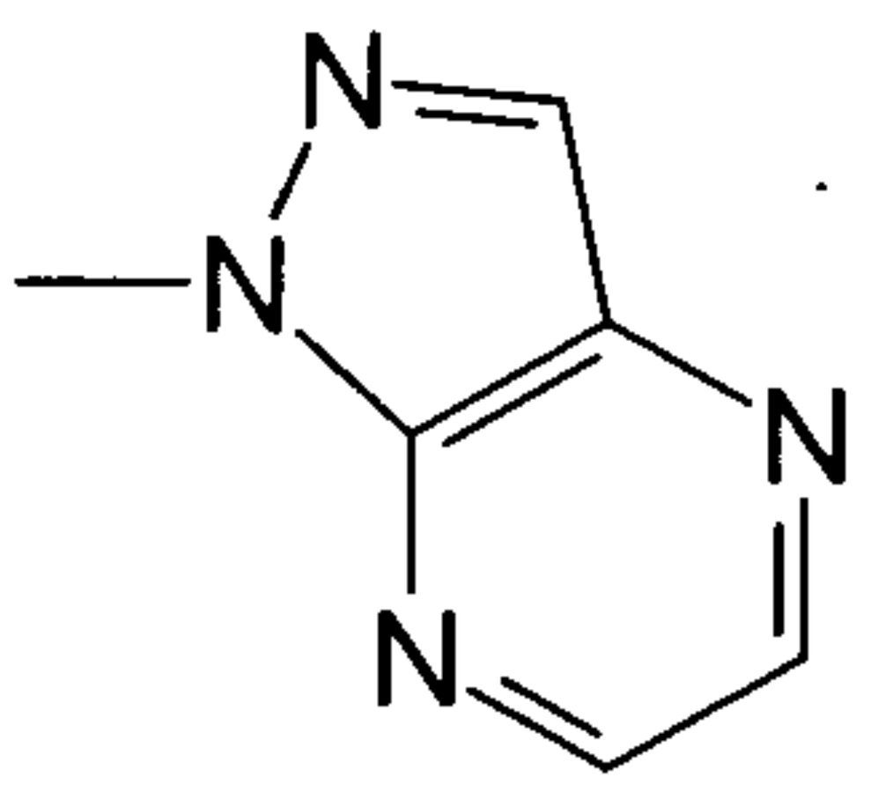
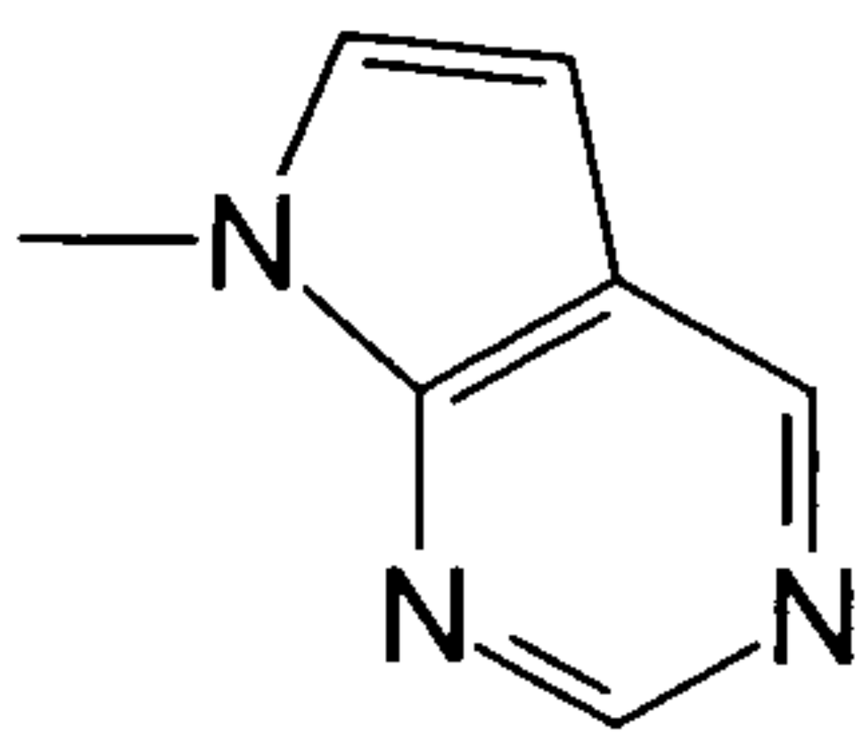
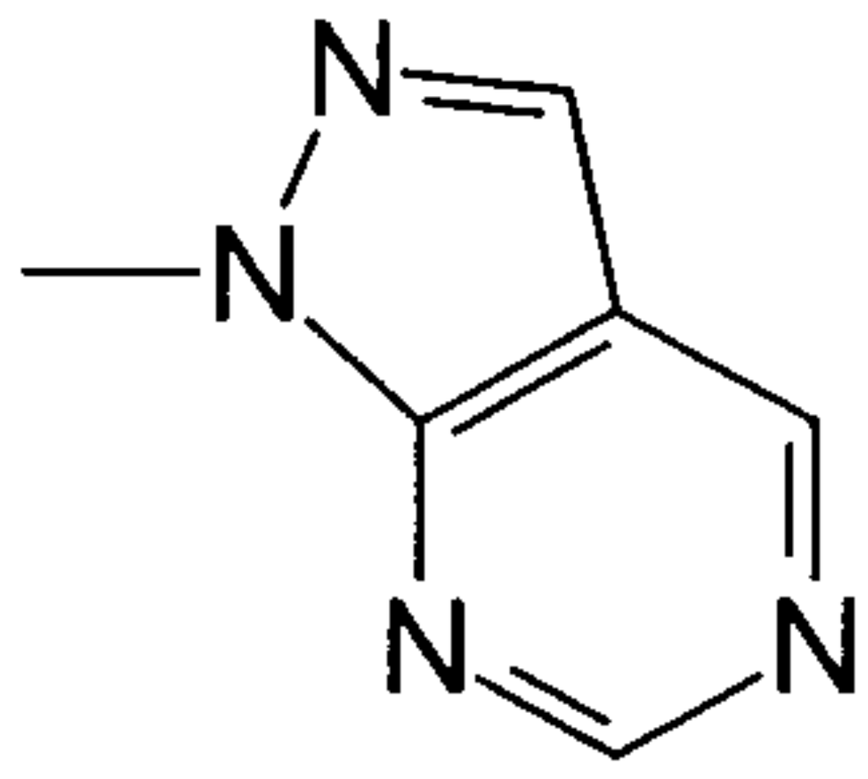
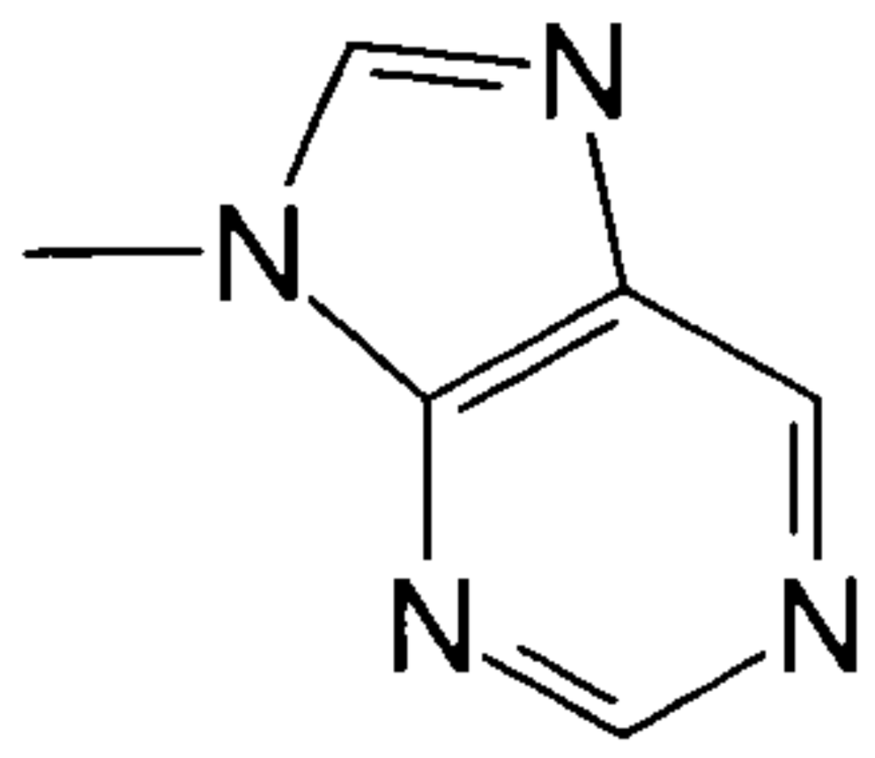
 ,  ,  ,

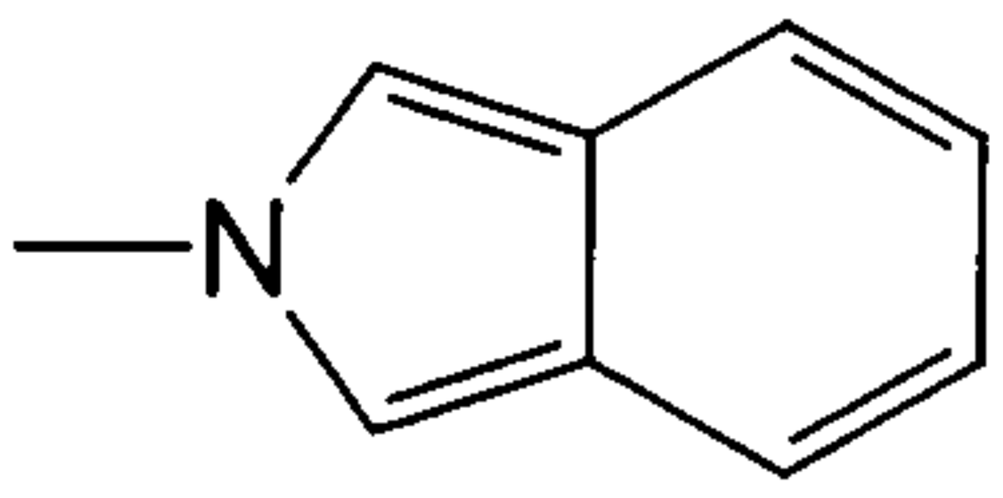
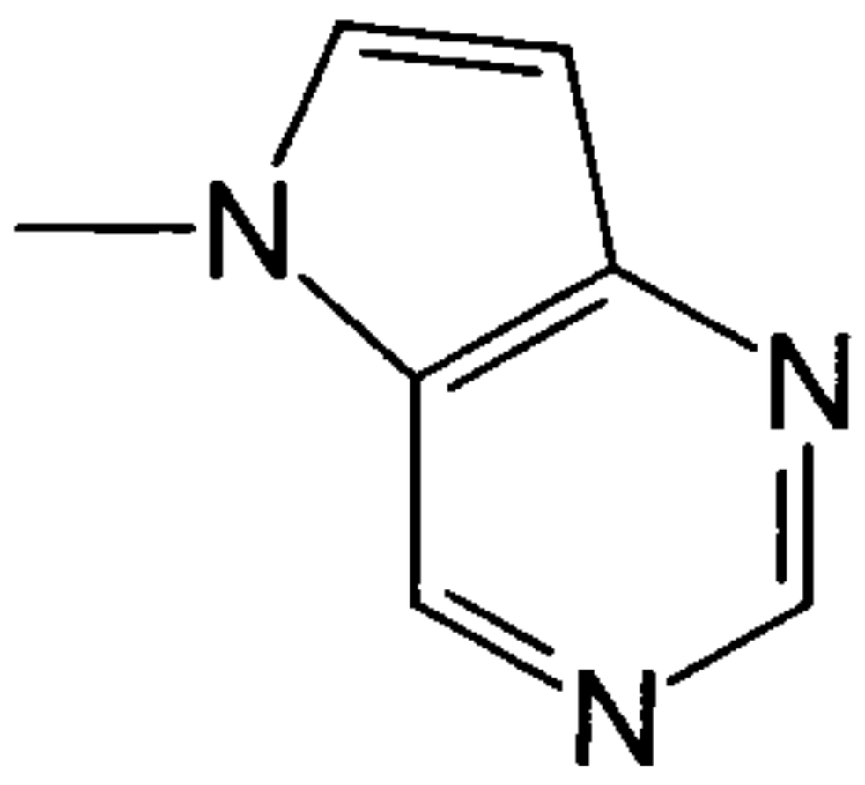
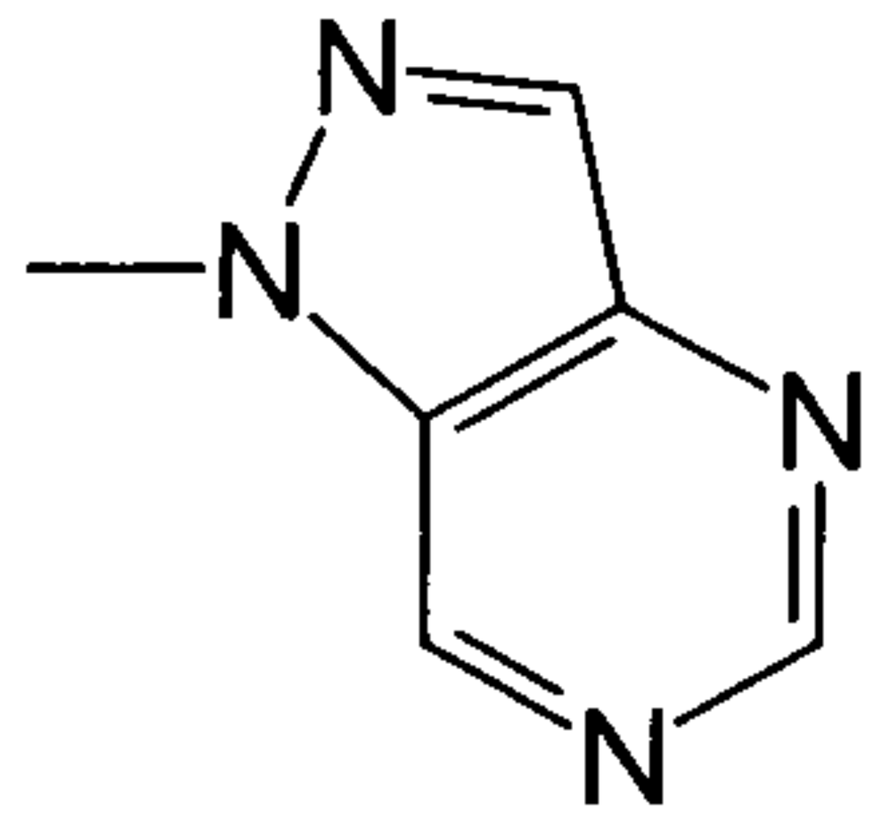
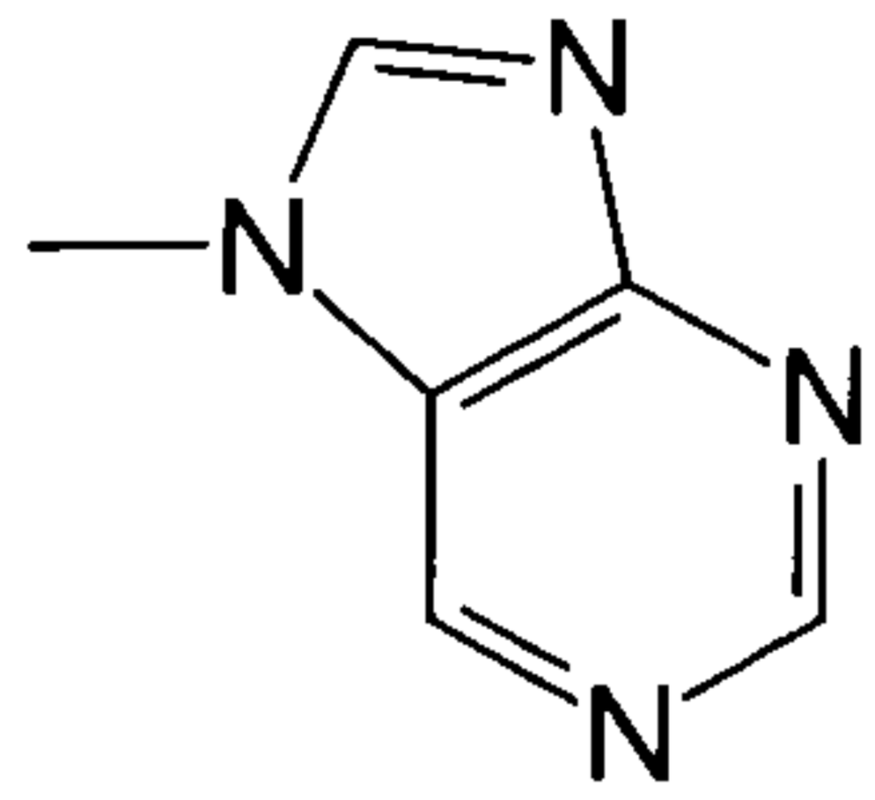
 ,  ,  ,

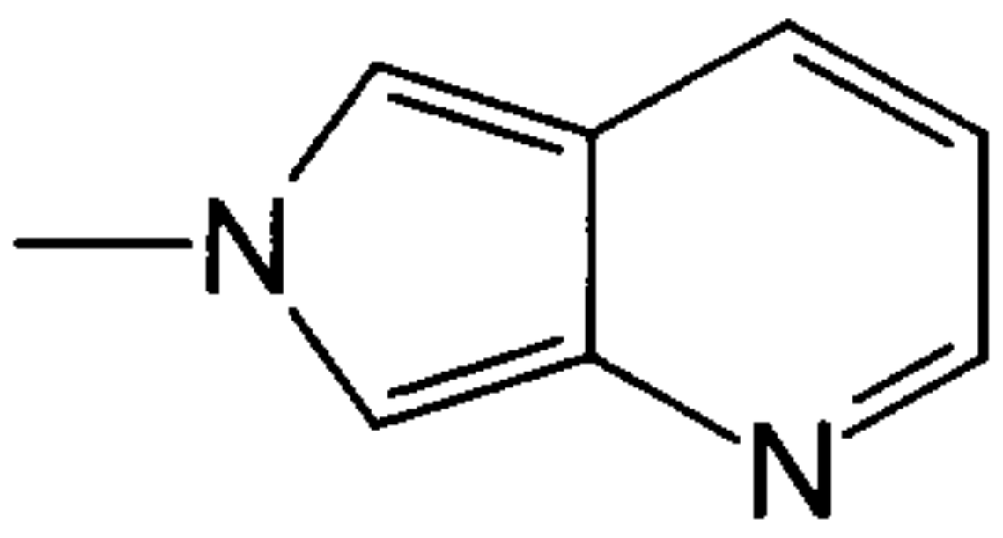
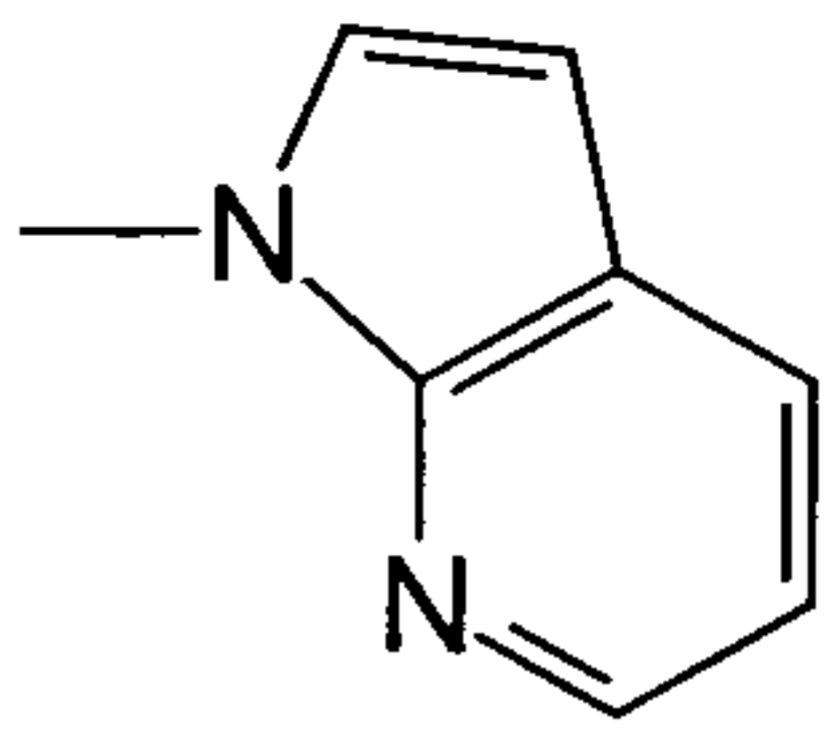
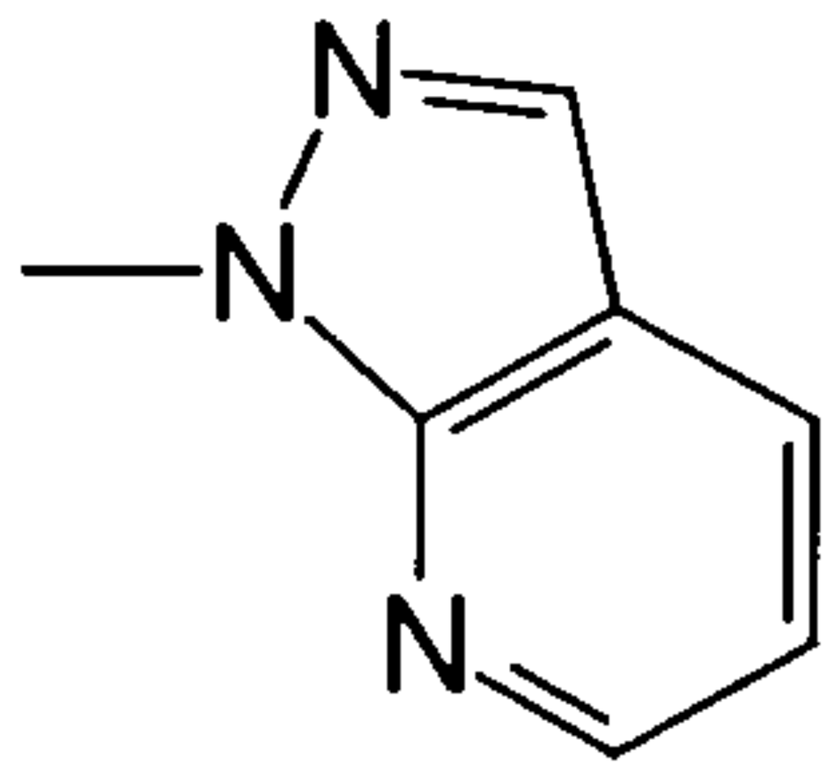
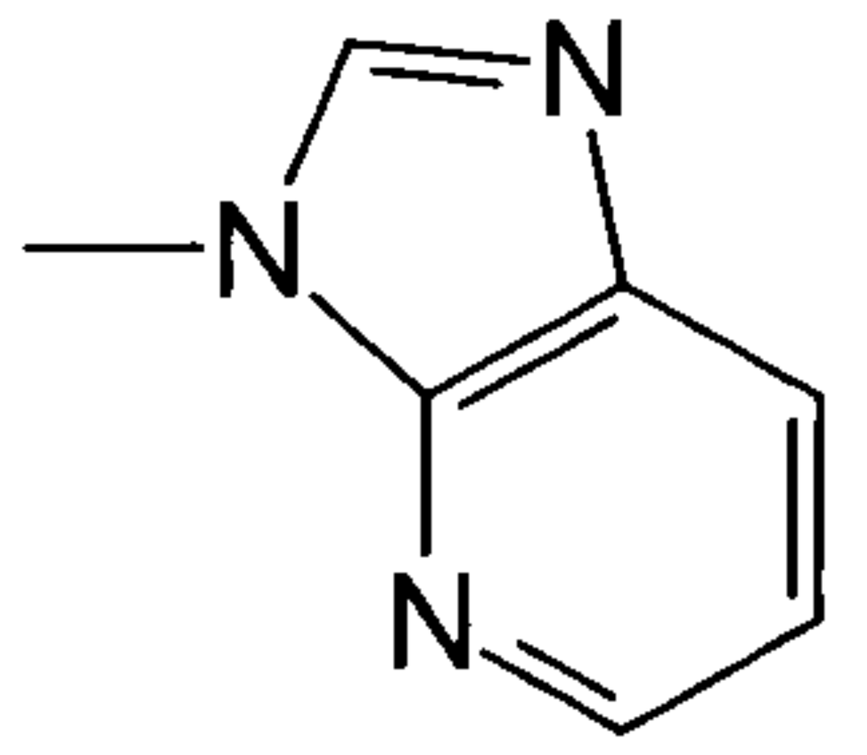
 ,  ,  ,

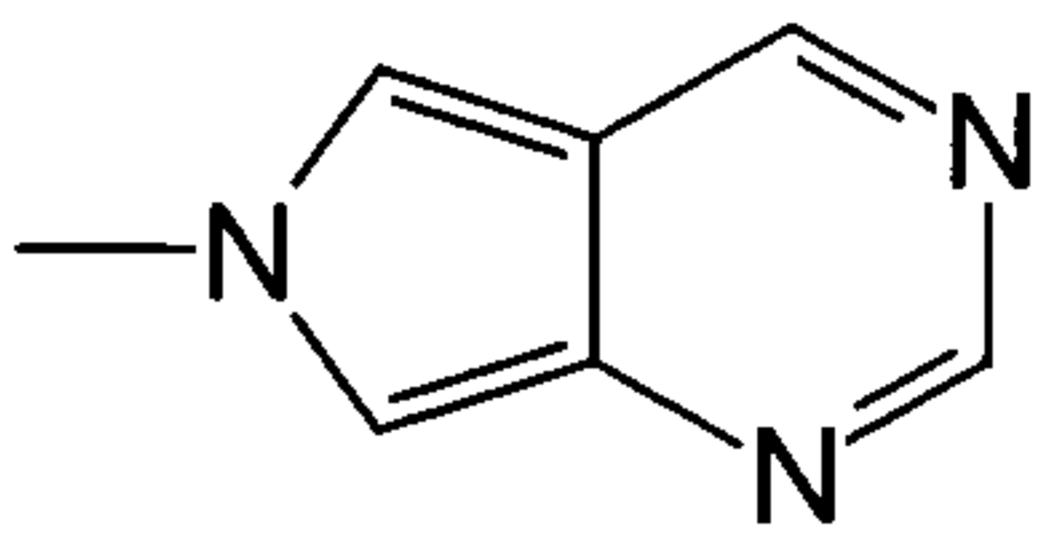
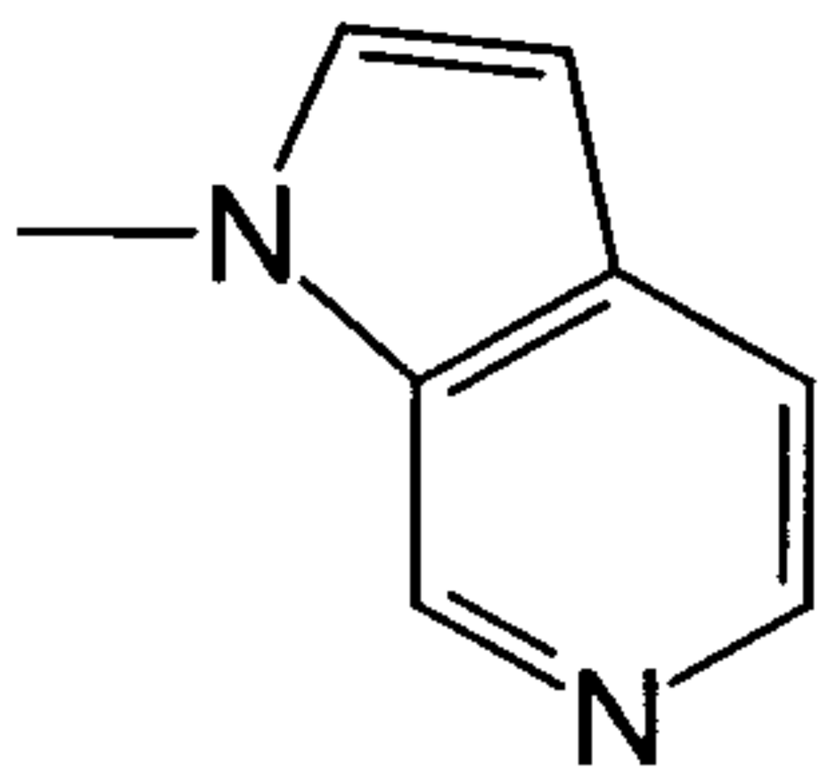
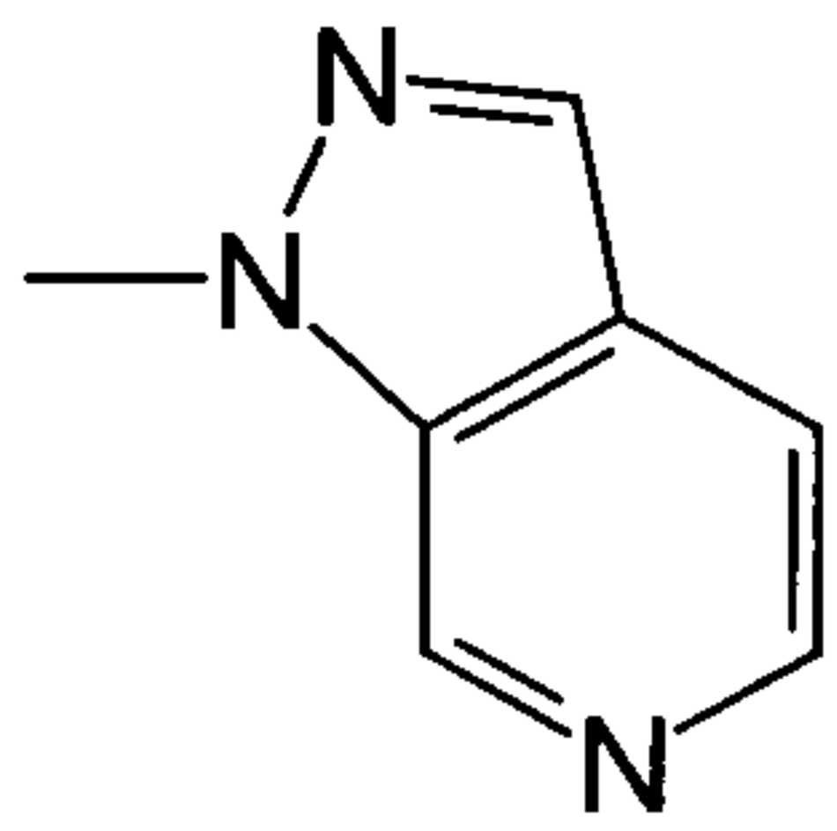
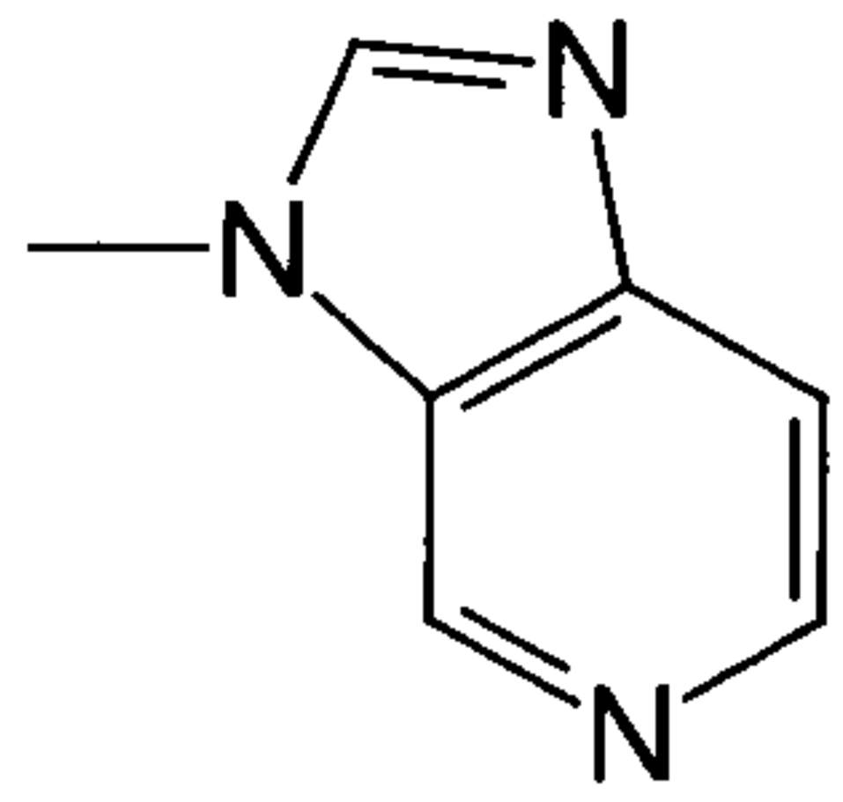
  ,  ,

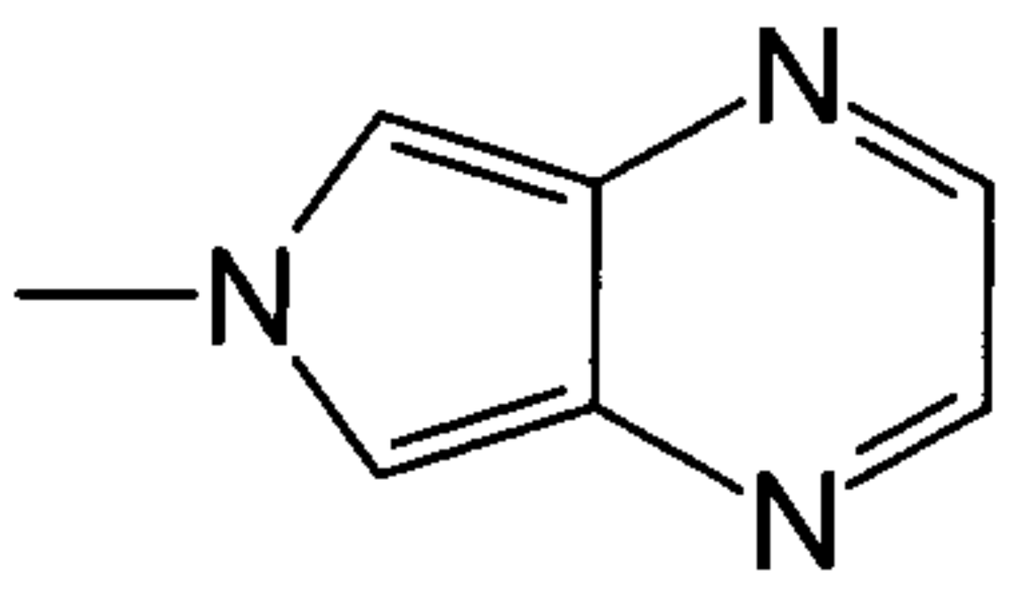
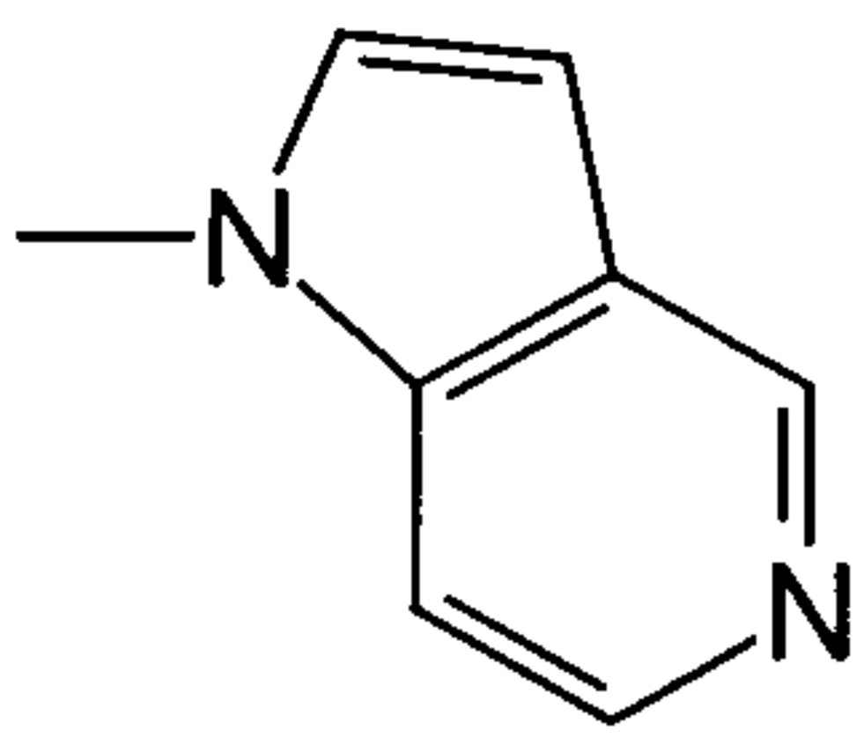
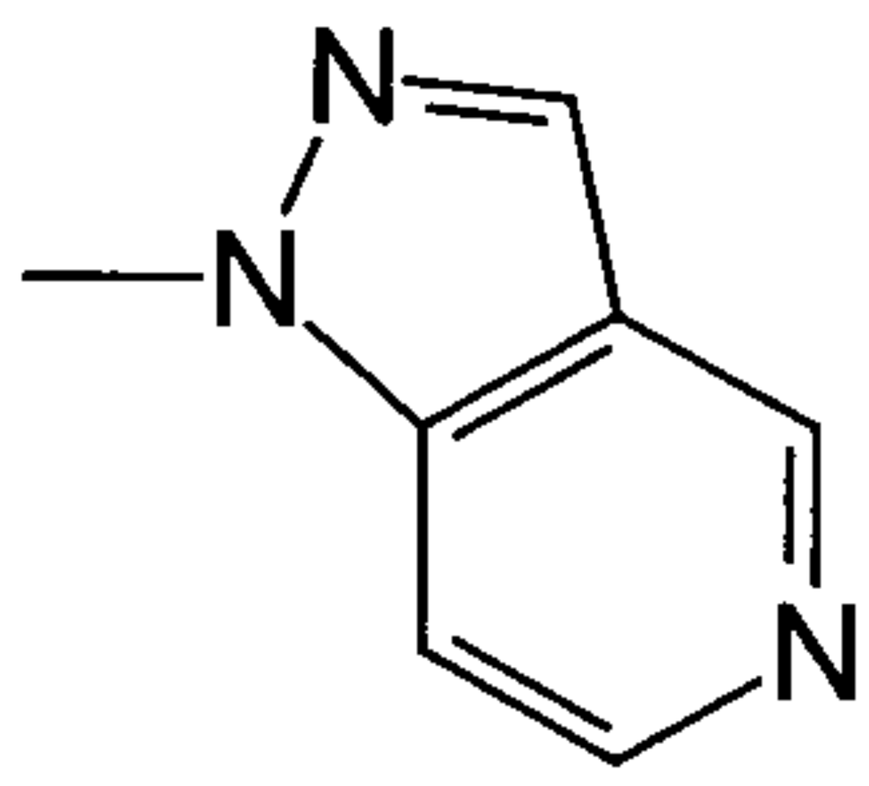
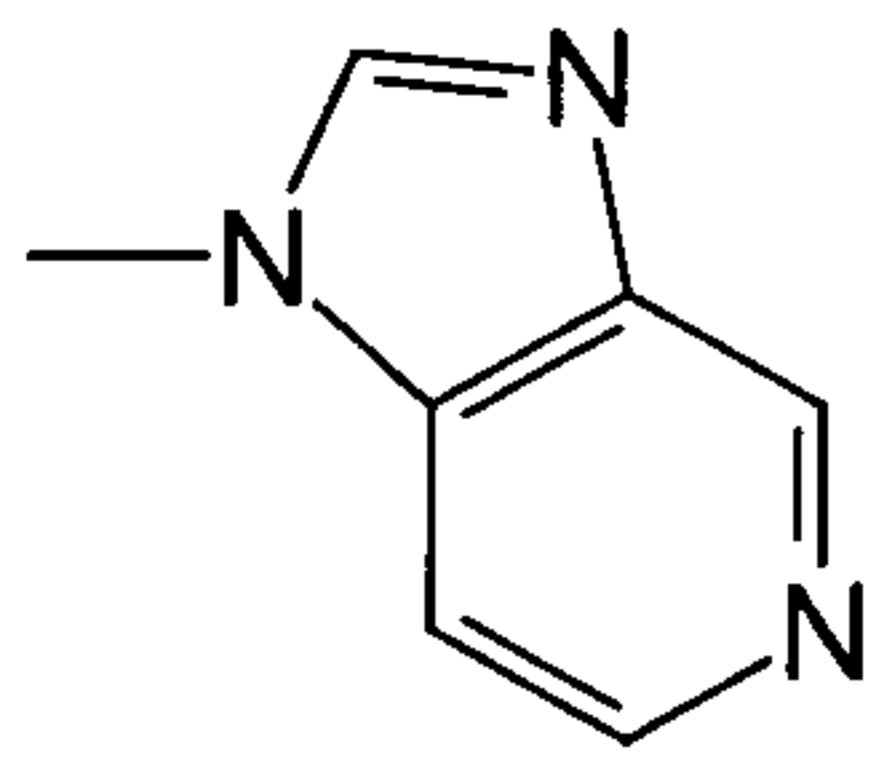
 ,  ,  ,  ,

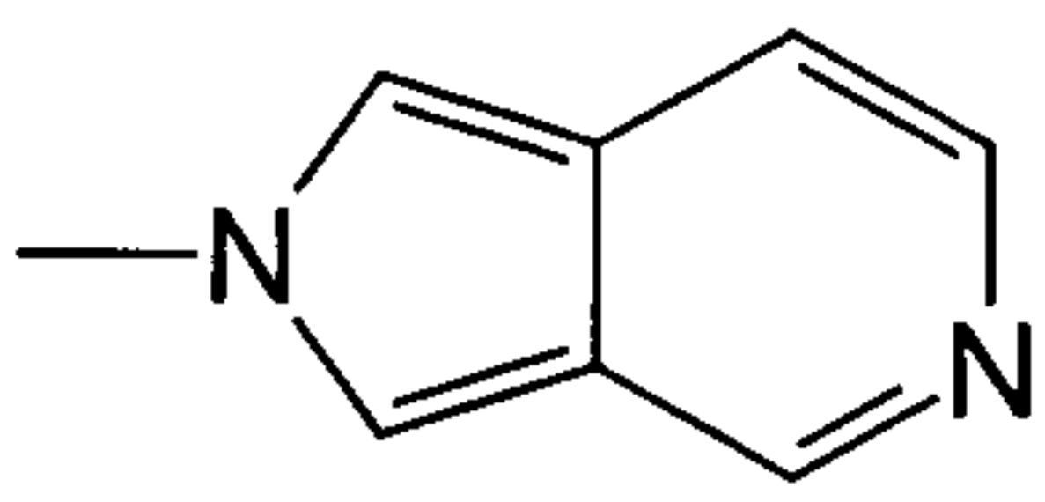
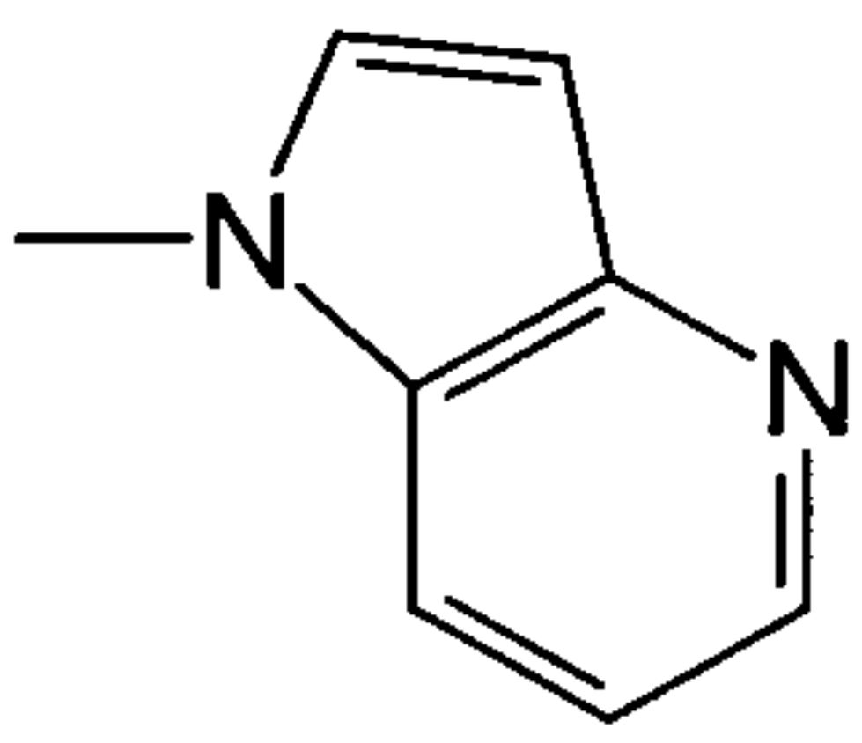
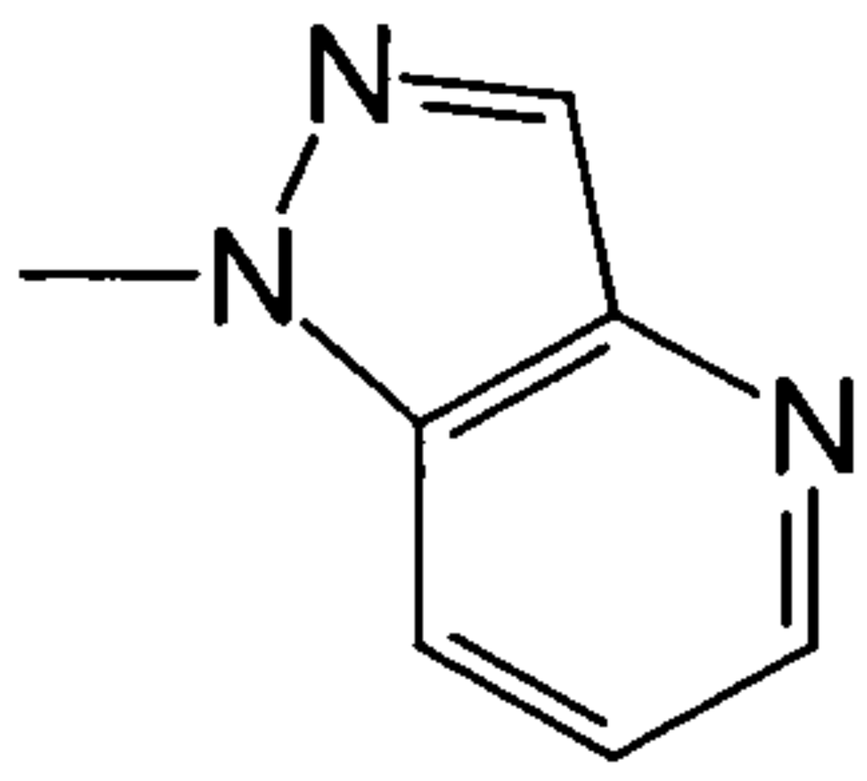
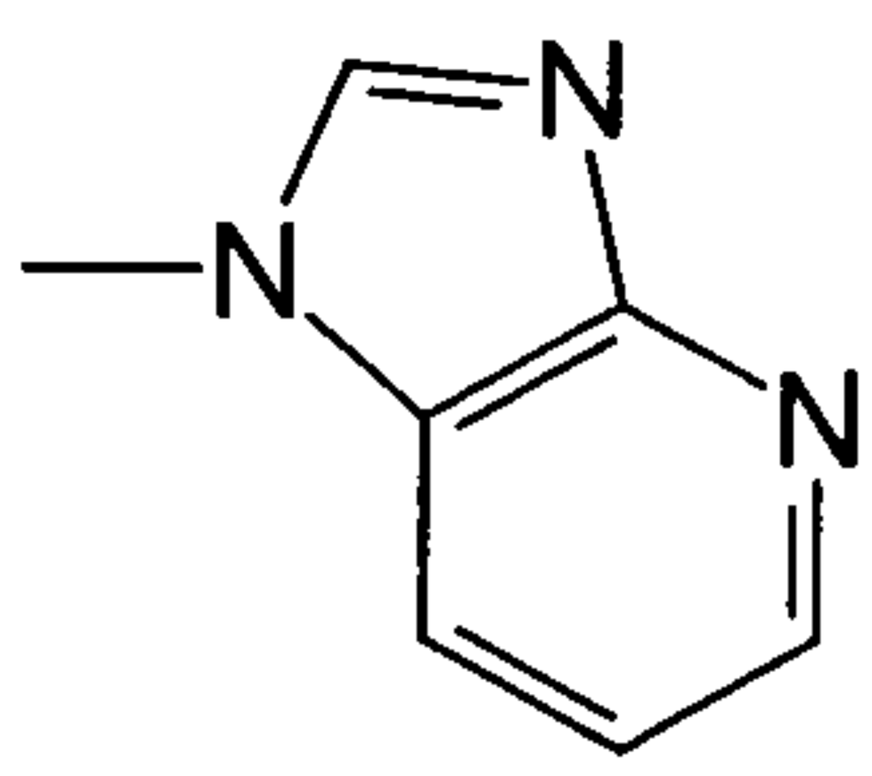
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ;

R^{56}, R^{57}, R^{94} and R^{103} represent independently of each other $-CR^{58}R^{16}R^{17}$, $-CR^{58}R^{59}R^{60}$, $-CR^{16}R^{17}-CR^{61}R^{62}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}R^{58}$, $-CR^{16}R^{17}-CR^{61}R^{62}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}R^{58}$, $-CR^{16}R^{17}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}-CR^{63}R^{64}-CR^{66}R^{67}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{16}R^{17}R^{58}$, $-CR^{16}R^{17}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}-CR^{65}R^{66}-CR^{67}R^{68}R^{69}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{16}R^{17}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-$

$CR^{65}R^{66}$–$CR^{16}R^{17}R^{58}$, –$CR^{16}R^{17}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{67}R^{68}$–$CR^{69}R^{70}R^{58}$, –$CR^{59}R^{60}$–$CR^{16}R^{17}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{67}R^{68}$–$CR^{69}R^{70}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{16}R^{17}$–$CR^{65}R^{66}$–$CR^{67}R^{68}$–$CR^{69}R^{70}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{16}R^{17}$–$CR^{67}R^{68}$–$CR^{69}R^{70}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{16}R^{17}$–$CR^{69}R^{70}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{67}R^{68}$–$CR^{16}R^{17}R^{58}$;

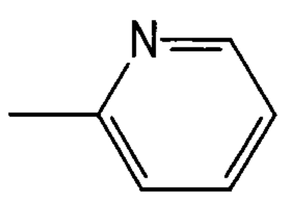
R^{58} – R^{70} represent independently of each other –H, –NH_2, –OH, –F, –Cl, –Br, –I, –R^{71}, –O–R^{71}, –R^{72}, –O–R^{95}, –R^{96}, –O–R^{104}, –R^{105}, –COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –(C=O)–$NR^{16}R^{17}$, –SO_2–$NR^{16}R^{17}$, –SO_m–$R^{16}R^{17}$, –$CR^{16}R^{17}H$, –$NR^{16}R^{17}$;

R^{108}, R^{117} and R^{129} represent independently of each other –$CH=CH_2$, –CH_2–$CH=CH_2$, –H, –$C(CH_3)=CH_2$, –CH=CH–CH_3, –C_2H_4–$CH=CH_2$, –CH_2–CH=CH–CH_3, –CH=CH–C_2H_5, –CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–CH=CH, –$CH=C(CH_3)_2$, –$C(CH_3)$=CH–CH_3, –CH=CH–CH=CH_2, –C_3H_6–$CH=CH_2$, –C_2H_4–CH=CH–CH_3, –CH_2–CH=CH–C_2H_5, –CH=CH–C_3H_7, –CH_2–CH=CH–CH=CH_2, –CH=CH–CH=CH–CH_3, –CH=CH–CH_2–$CH=CH_2$, –$C(CH_3)$=CH–CH=CH_2, –$CH=C(CH_3)$–$CH=CH_2$, –CH=CH–$C(CH_3)=CH_2$, –C_2H_4–$C(CH_3)=CH_2$, –CH_2–$CH(CH_3)$–$CH=CH_2$, –$CH(CH_3)$–CH_2–$CH=CH_2$, –CH_2–$CH=C(CH_3)_2$, –CH_2–$C(CH_3)$=CH–CH_3, –$CH(CH_3)$–CH=CH–CH_3, –CH=CH–$CH(CH_3)_2$, –$CH=C(CH_3)$–C_2H_5, –$C(CH_3)$=CH–C_2H_5, –$C(CH_3)$=$C(CH_3)_2$, –$C(CH_3)_2$–$CH=CH_2$, –$CH(CH_3)$–$C(CH_3)=CH_2$, –$C(CH_3)$=CH–CH=CH_2, –CH=$C(CH_3)$–$CH=CH_2$, –CH=CH–$C(CH_3)=CH_2$, –C_4H_8–$CH=CH_2$, –C_3H_6–CH=CH–CH_3, –C_2H_4–CH=CH–C_2H_5, –CH_2–CH=CH–C_3H_7, –CH=CH–C_4H_9, –C_3H_6–$C(CH_3)=CH_2$, –C_2H_4–$CH(CH_3)$–$CH=CH_2$, –CH_2–$CH(CH_3)$–CH_2–$CH=CH_2$, –$CH(CH_3)$–C_2H_4–$CH=CH_2$, –C_2H_4–$CH=C(CH_3)_2$, –C_2H_4–$C(CH_3)$=CH–CH_3, –CH_2–$CH(CH_3)$–CH=CH–CH_3, –$CH(CH_3)$–CH_2–CH=CH–$CH(CH_3)_2$, –CH_2–CH=$C(CH_3)$–C_2H_5, –CH_2–$C(CH_3)$=CH–C_2H_5, –$CH(CH_3)$–CH=CH–C_2H_5, –CH=CH–CH_2–$CH(CH_3)_2$, –CH=CH–$CH(CH_3)$–C_2H_5, –$CH=C(CH_3)$–C_3H_7, –$C(CH_3)$=CH–C_3H_7, –CH_2–$CH(CH_3)$–$C(CH_3)=CH_2$, –$CH(CH_3)$–CH_2–$C(CH_3)=CH_2$, –$CH(CH_3)$–$CH(CH_3)$–$CH=CH_2$, –CH_2–$C(CH_3)_2$–$CH=CH_2$, –$C(CH_3)_2$–CH_2–$CH=CH_2$, –CH_2–$C(CH_3)=C(CH_3)_2$, –$CH(CH_3)$–$CH=C(CH_3)_2$, –$C(CH_3)_2$–CH=CH–CH_3, –$CH(CH_3)$–$C(CH_3)$=CH–CH_3, –CH=$C(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)$=CH–$CH(CH_3)_2$, –$C(CH_3)$=$C(CH_3)$–C_2H_5, –CH=CH–$C(CH_3)_3$, –$C(CH_3)_2$–$C(CH_3)=CH_2$, –$CH(C_2H_5)$–$C(CH_3)=CH_2$, –$C(CH_3)(C_2H_5)$–$CH=CH_2$, –$CH(CH_3)$–$C(C_2H_5)=CH_2$, –CH_2–$C(C_3H_7)=CH_2$, –CH_2–$C(C_2H_5)$=CH–CH_3, –$CH(C_2H_5)$–CH=CH–CH_3, –$C(C_4H_9)=CH_2$, –$C(C_3H_7)$=CH–CH_3, –$C(C_2H_5)$=CH–C_2H_5, –$C(C_2H_5)$=$C(CH_3)_2$, –$C[C(CH_3)_3]=CH_2$, –$C[CH(CH_3)(C_2H_5)]=CH_2$, –$C[CH_2$–$CH(CH_3)_2]=CH_2$, –C_2H_4–CH=CH–CH=CH_2, –CH_2–CH=CH–CH_2–$CH=CH_2$, –CH=CH–CH_2–CH=CH_2, –CH_2–CH=CH–CH=CH–

CH_3, –CH=CH–CH_2–CH=CH–CH_3, –CH=CH–CH=CH–C_2H_5, –CH_2–CH=CH–$C(CH_3)=CH_2$, –CH_2–CH=$C(CH_3)$–CH=CH_2, –CH_2–$C(CH_3)$=CH–CH=CH_2, –$CH(CH_3)$–CH=CH–CH=CH_2, –CH=CH–CH_2–$C(CH_3)=CH_2$, –CH=CH–$CH(CH_3)$–$CH=CH_2$, –CH=$C(CH_3)$–CH_2–CH=CH_2, –$C(CH_3)$=CH–CH_2–CH=CH_2, –CH=CH–$CH=C(CH_3)_2$, –CH=CH–$C(CH_3)$=CH–CH_3, –CH=$C(CH_3)$–CH=CH–CH_3, –$C(CH_3)$=CH–CH=CH–CH_3, –CH=$C(CH_3)$–$C(CH_3)=CH_2$, –$C(CH_3)$=CH–$C(CH_3)=CH_2$, –$C(CH_3)$=$C(CH_3)$–CH=CH_2, –CH=CH–CH=CH–CH=CH_2;

R^{109}, R^{118} and R^{130} represent independently of each other –H, –C≡CH, –C≡C–CH_3, –CH_2-C≡CH, –C_2H_4–C≡CH, –CH_2–C≡C–CH_3, –C≡C–C_2H_5, –C_3H_6–C≡CH, –C_2H_4–C≡C–CH_3, –CH_2–C≡C–C_2H_5, –C≡C–C_3H_7, –$CH(CH_3)$–C≡CH, –CH_2–$CH(CH_3)$–C≡CH, –$CH(CH_3)$–CH_2–C≡CH, –$CH(CH_3)$–C≡C–CH_3, –C_4H_8–C≡CH, –C_3H_6–C≡C–CH_3, –C_2H_4–C≡C–C_2H_5, –CH_2–C≡C–C_3H_7, –C≡C–C_4H_9, –C_2H_4–$CH(CH_3)$–C≡CH, –CH_2–$CH(CH_3)$–CH_2–C≡CH, –$CH(CH_3)$–C_2H_4–C≡CH, –CH_2–$CH(CH_3)$–C≡C–CH_3, –$CH(CH_3)$–CH_2–C≡C–CH_3, –$CH(CH_3)$–C≡C–C_2H_5, –CH_2–C≡C–$CH(CH_3)_2$, –C≡C–$CH(CH_3)$–C_2H_5, –C≡C–CH_2–$CH(CH_3)_2$, –C≡C–$C(CH_3)_3$, –$CH(C_2H_5)$–C≡C–CH_3, –$C(CH_3)_2$–C≡C–CH_3, –$CH(C_2H_5)$–CH_2–C≡CH, –CH_2–$CH(C_2H_5)$–C≡CH, –$C(CH_3)_2$–CH_2–C≡CH, –CH_2–$C(CH_3)_2$–C≡CH, –$CH(CH_3)$–$CH(CH_3)$–C≡CH, –$CH(C_3H_7)$–C≡CH, –$C(CH_3)(C_2H_5)$–C≡CH, –C≡C–C≡CH, –CH_2–C≡C–C≡CH, –C≡C–C≡C–CH_3, –$CH(C≡CH)_2$, –C_2H_4–C≡C–C≡CH, –CH_2–C≡C–CH_2–C≡CH, –C≡C–C_2H_4–C≡CH, –CH_2–C≡C–C≡C–CH_3, –C≡C–CH_2–C≡C–CH_3, –C≡C–C≡C–C_2H_5, –C≡C–$CH(CH_3)$–C≡CH, –$CH(CH_3)$–C≡C–C≡CH, –$CH(C≡CH)$–CH_2–C≡CH, –$C(C≡CH)_2$–CH_3, –CH_2–$CH(C≡CH)_2$, –$CH(C≡CH)$–C≡C–CH_3;

R^{113}, R^{115}, R^{121}, R^{124}, R^{126}, R^{127}, R^{133}, R^{135}, R^{137} and R^{138} independently of each other represent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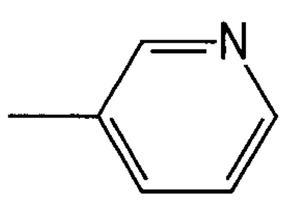
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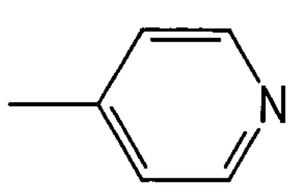
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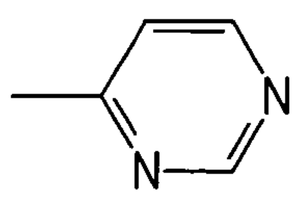
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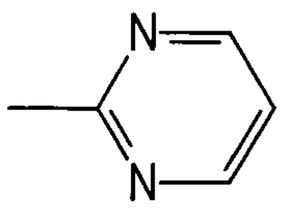
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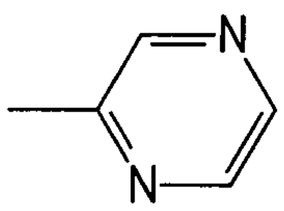
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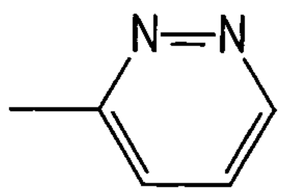
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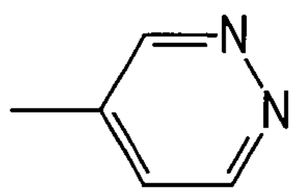
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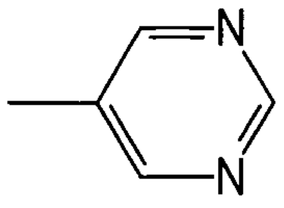
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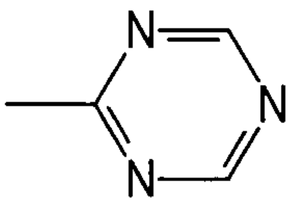
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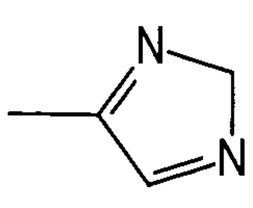
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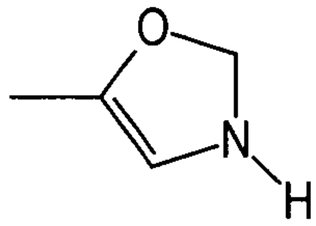
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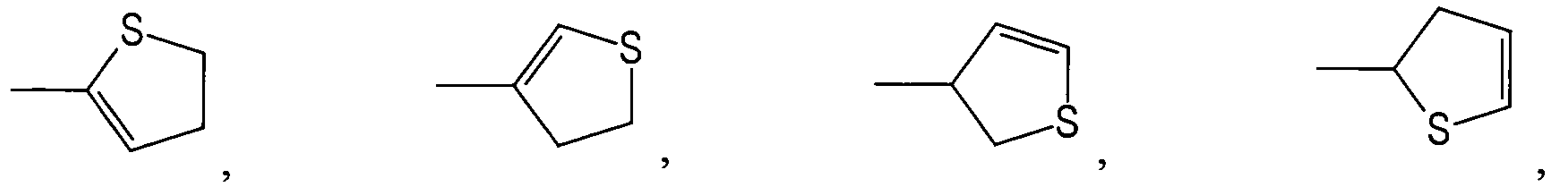

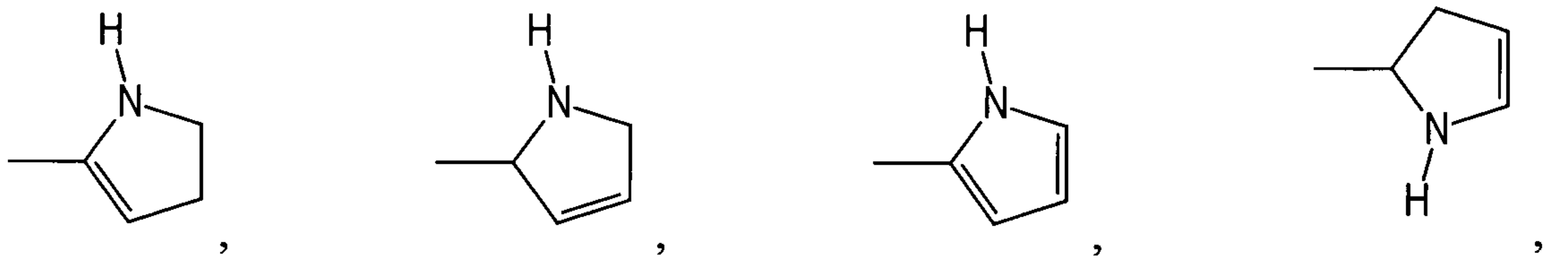

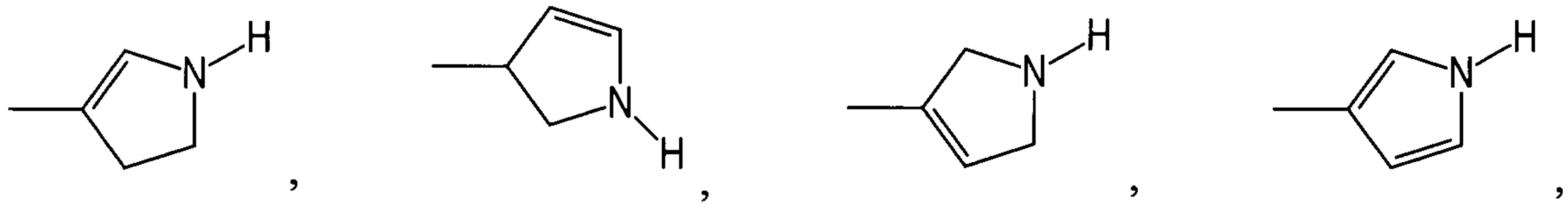

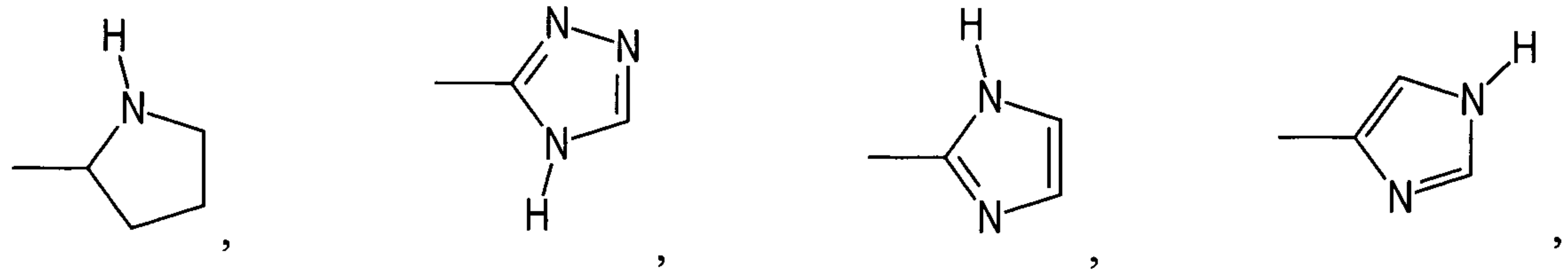

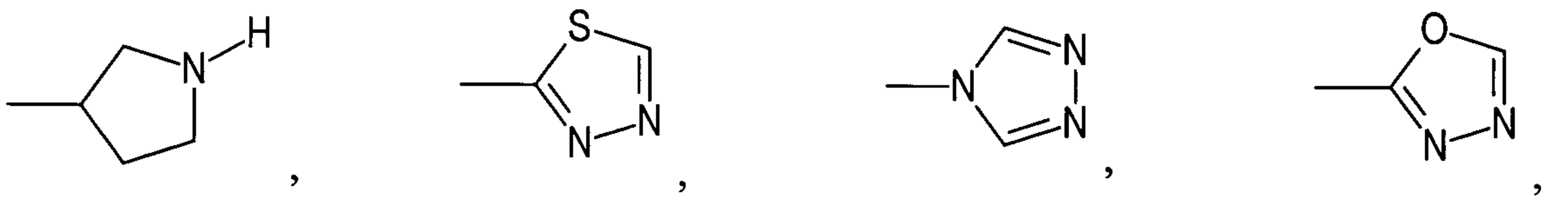

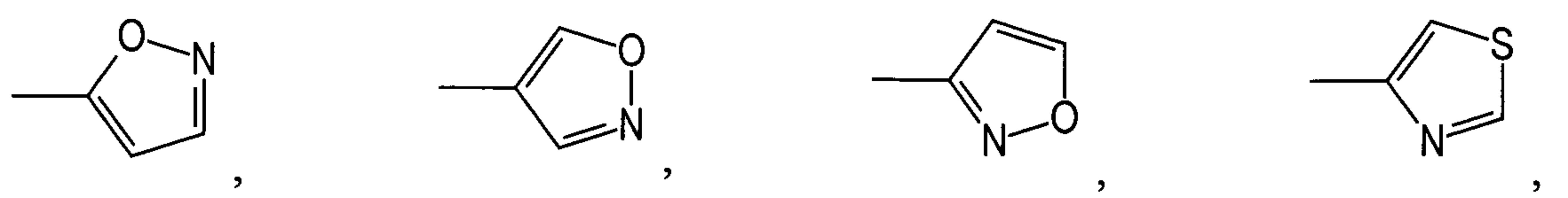

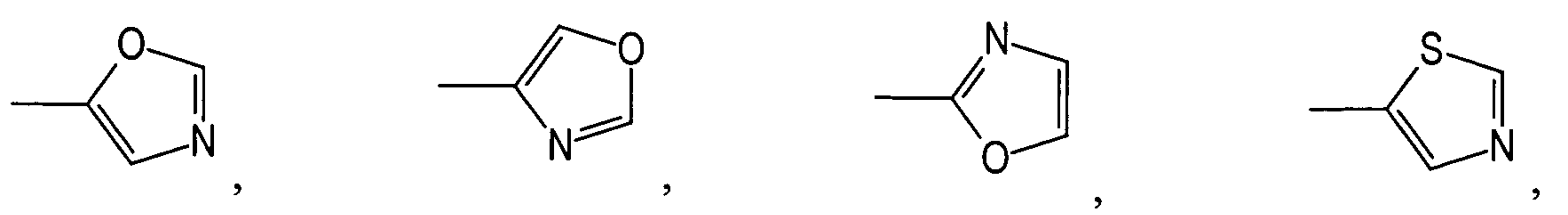

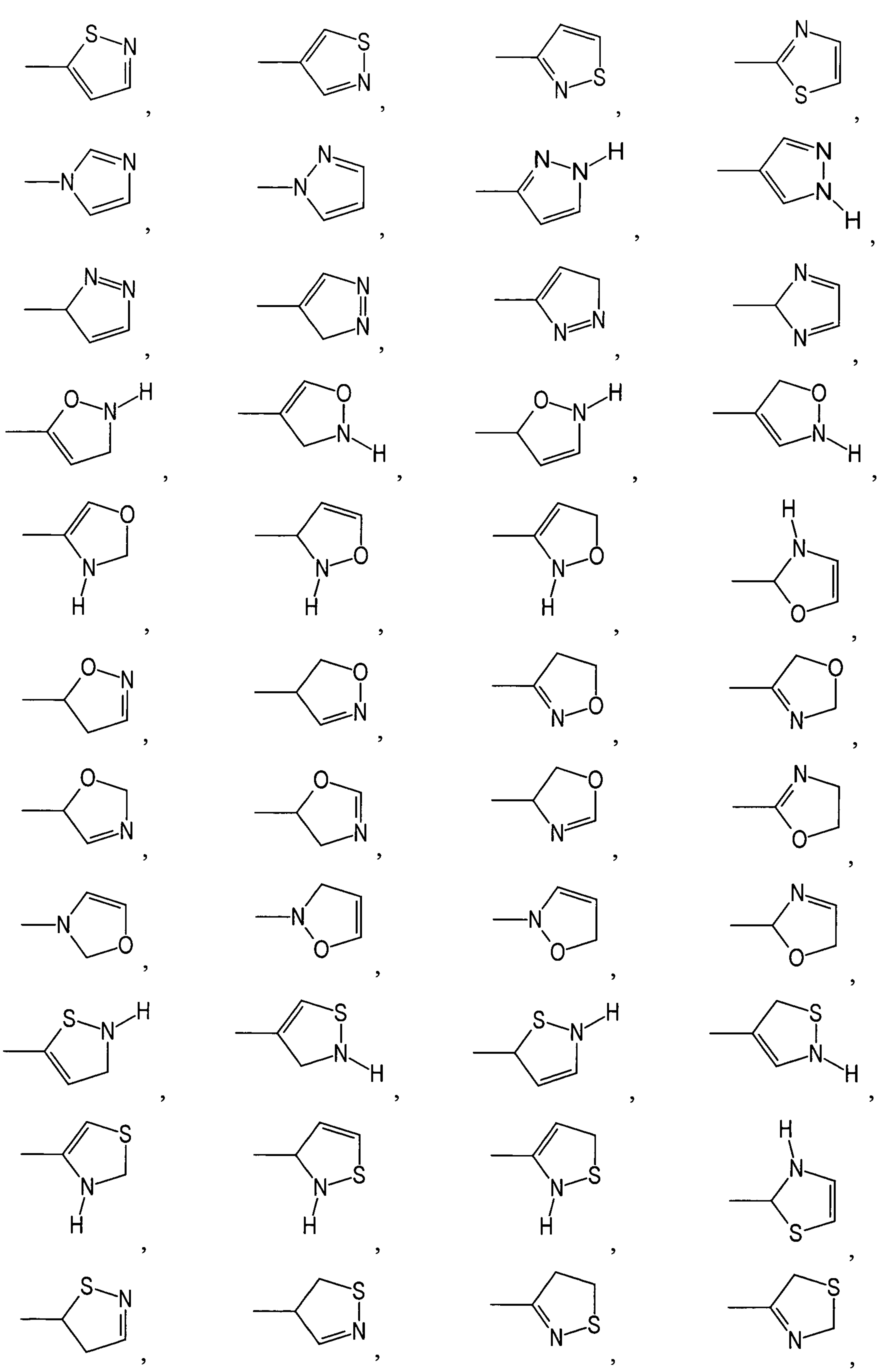
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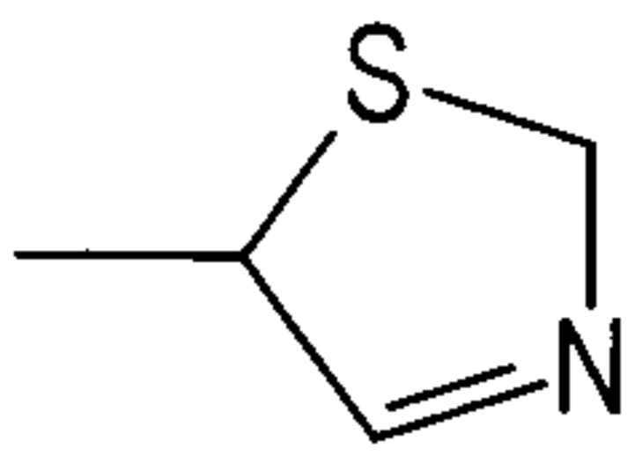
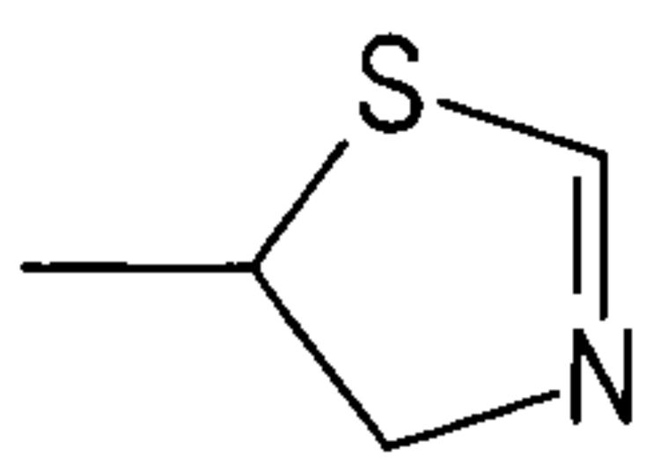
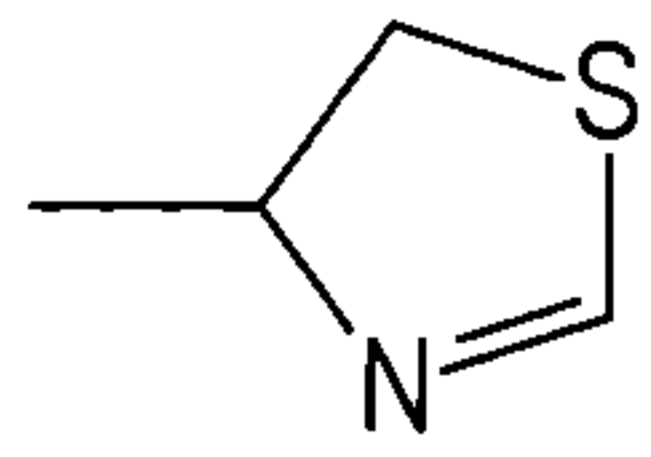
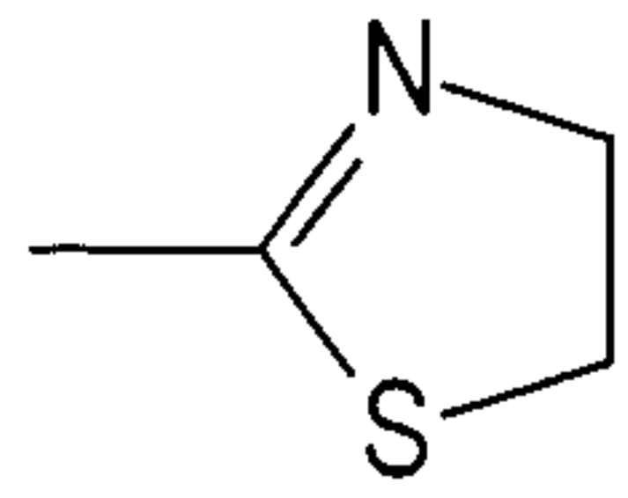
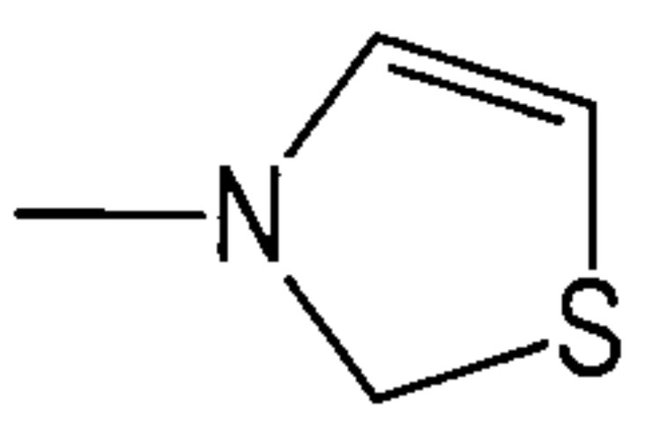
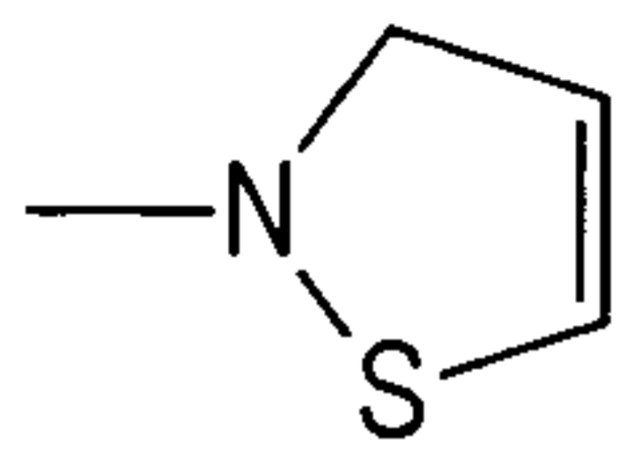
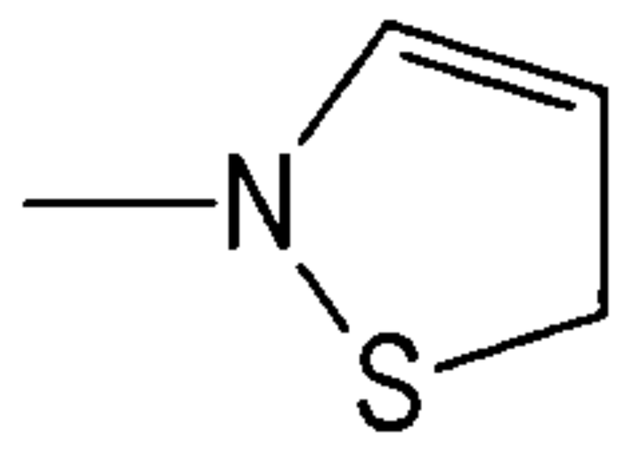
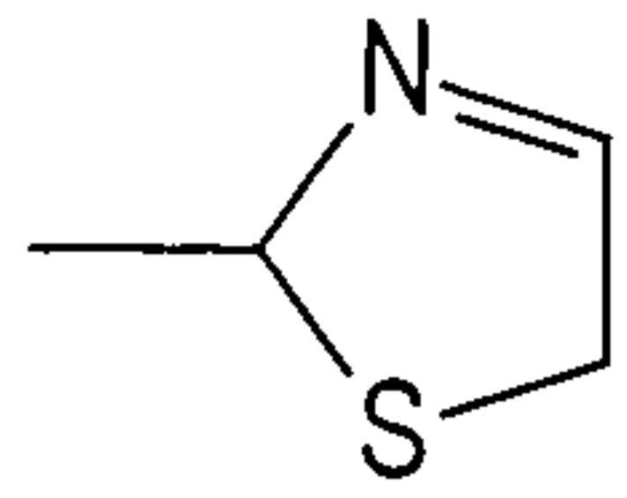
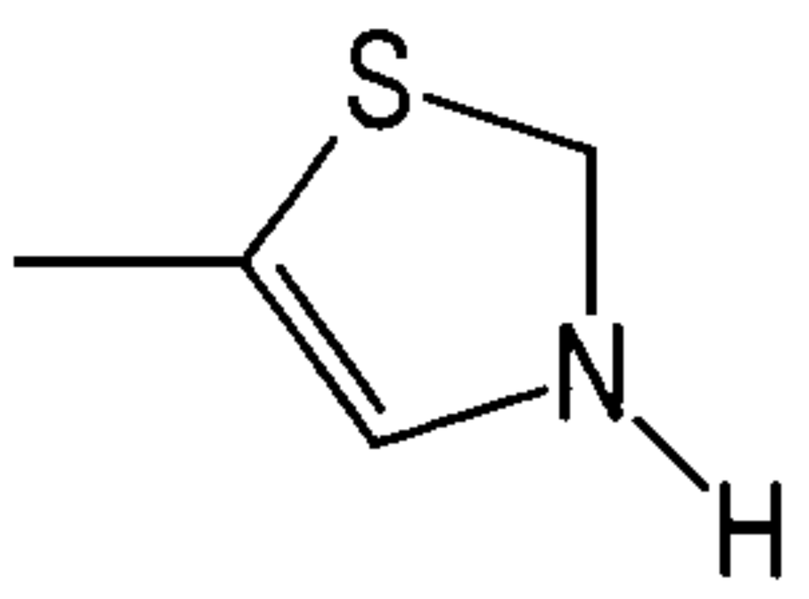
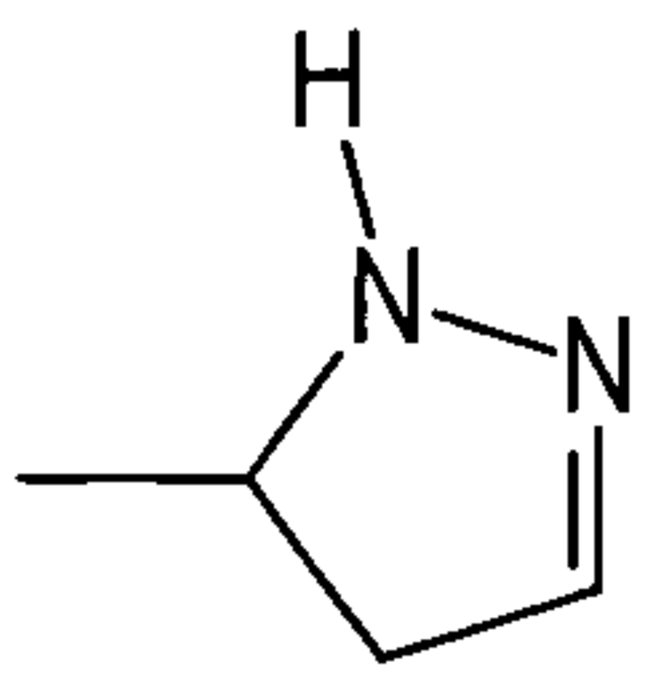
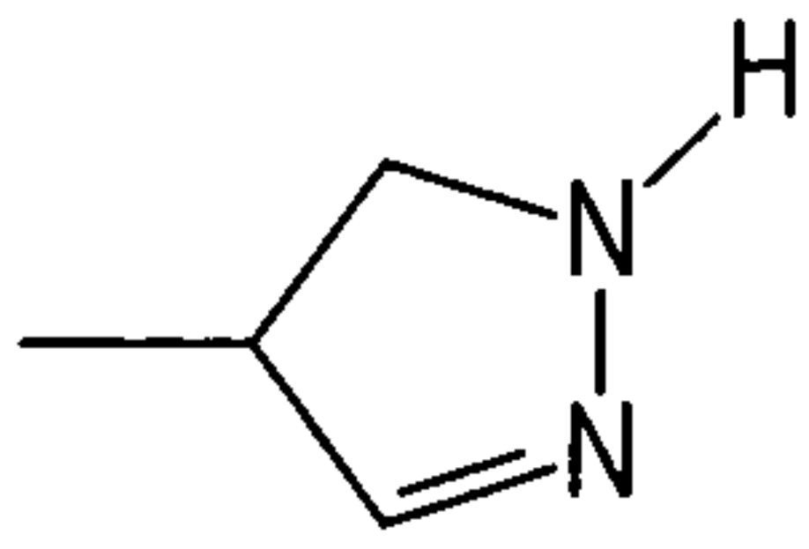
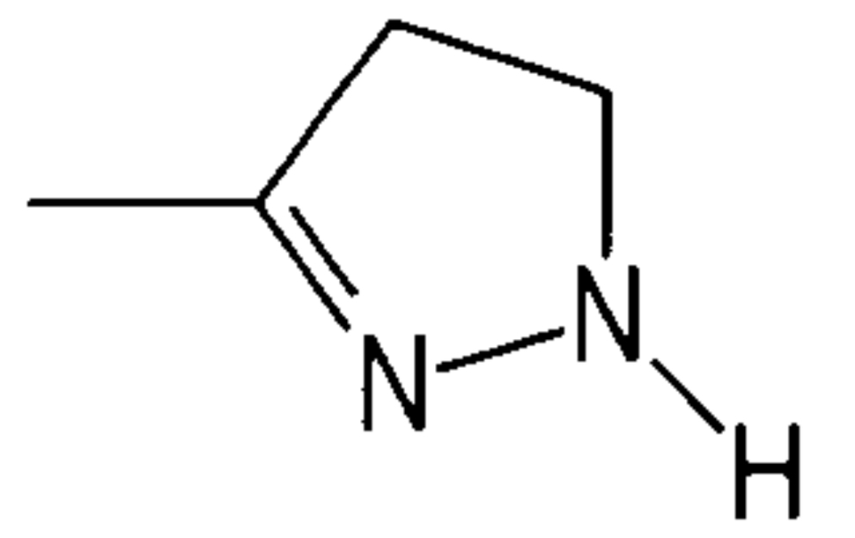
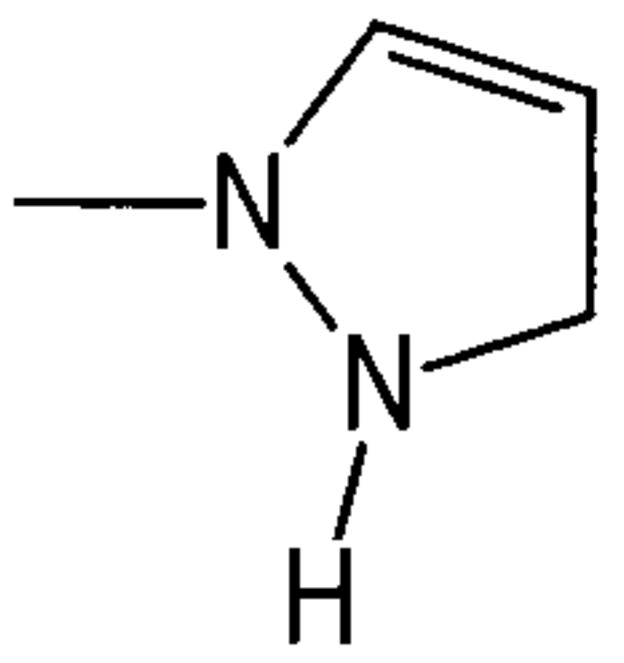
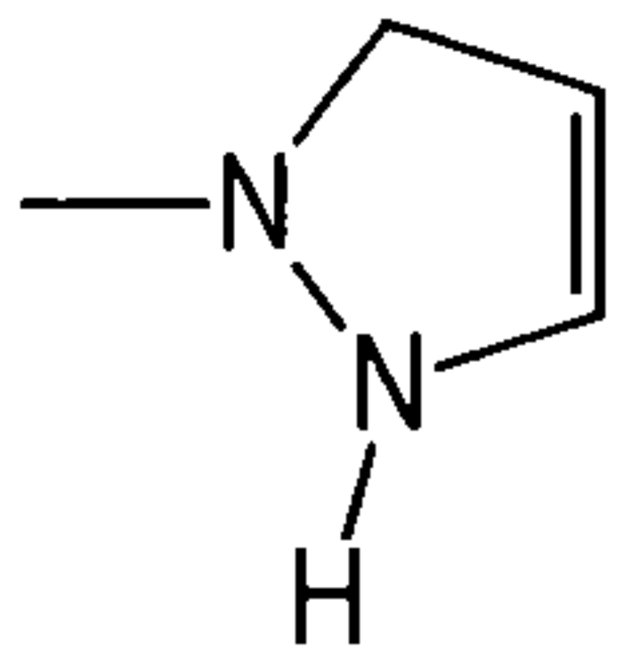
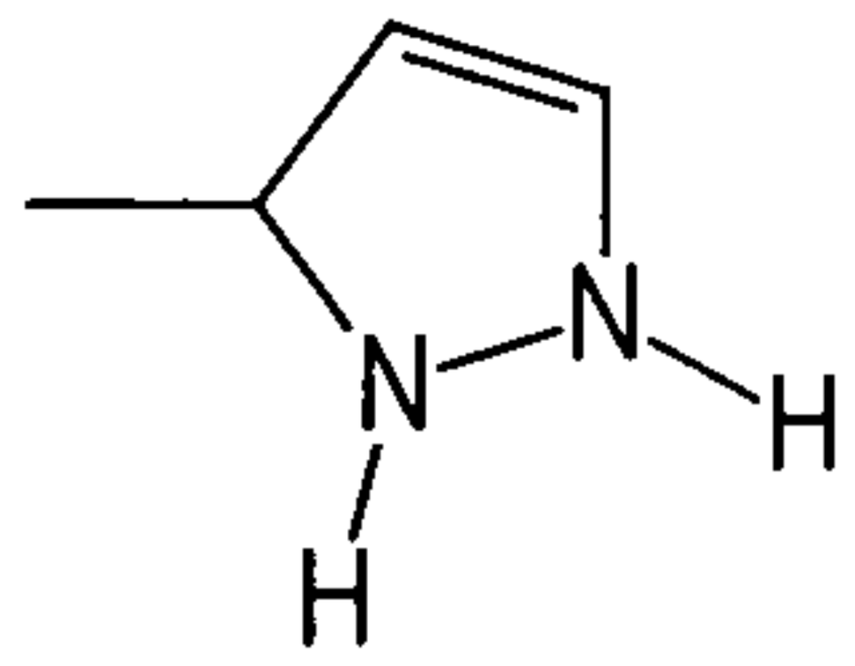
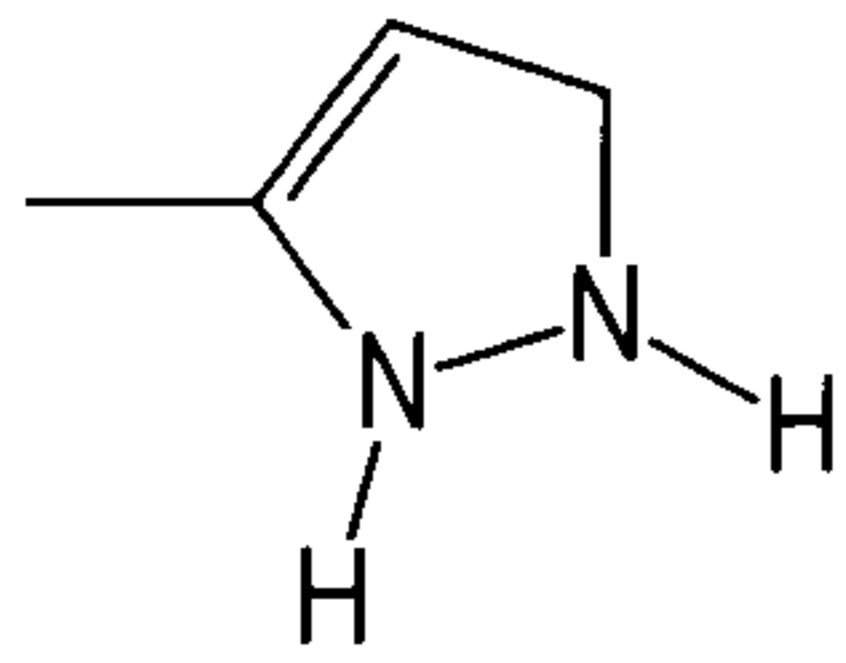
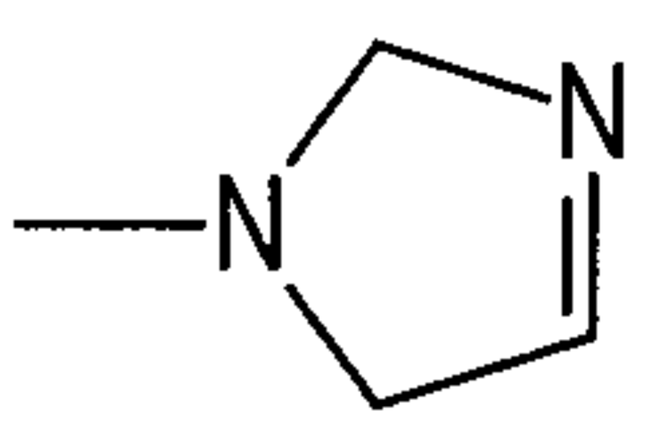
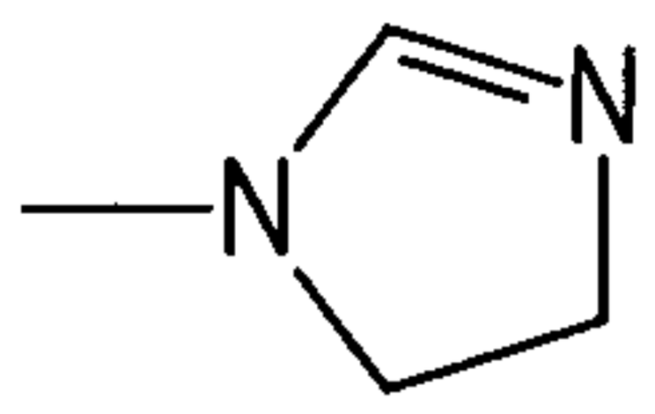
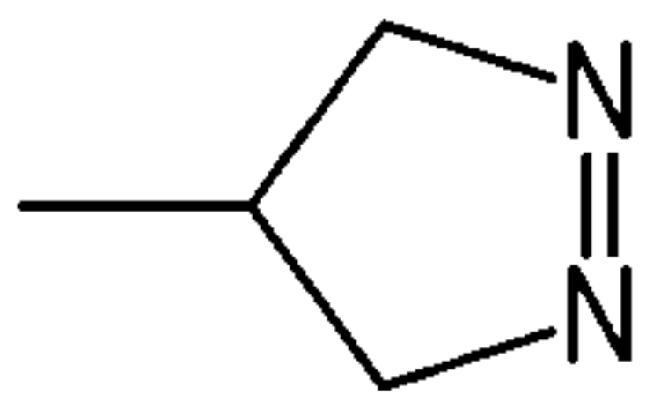
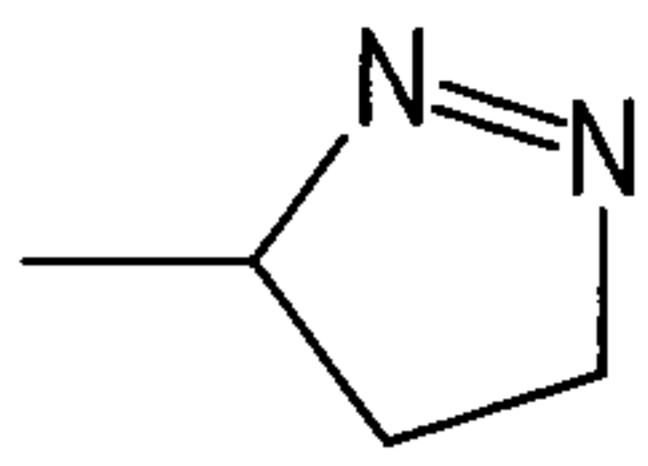
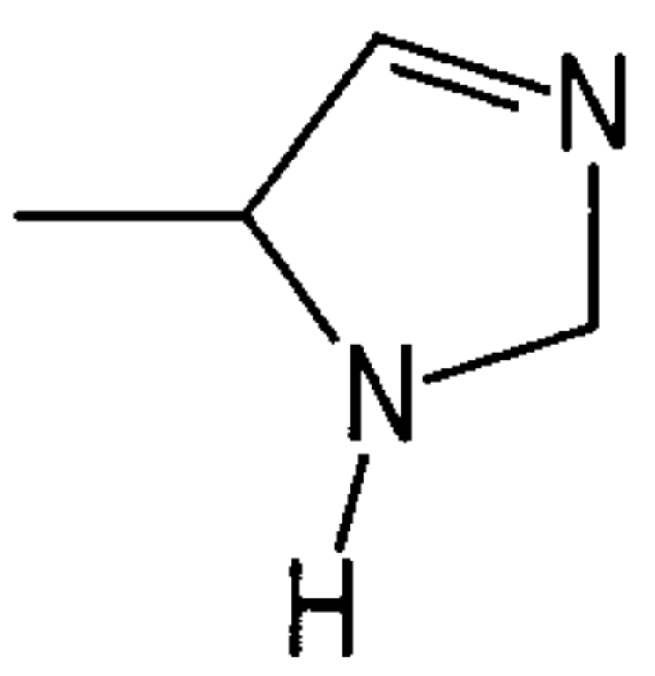
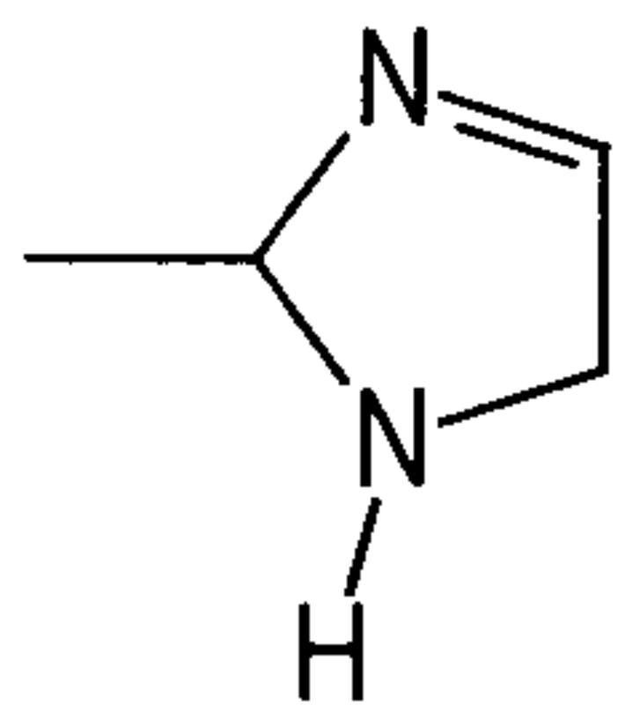
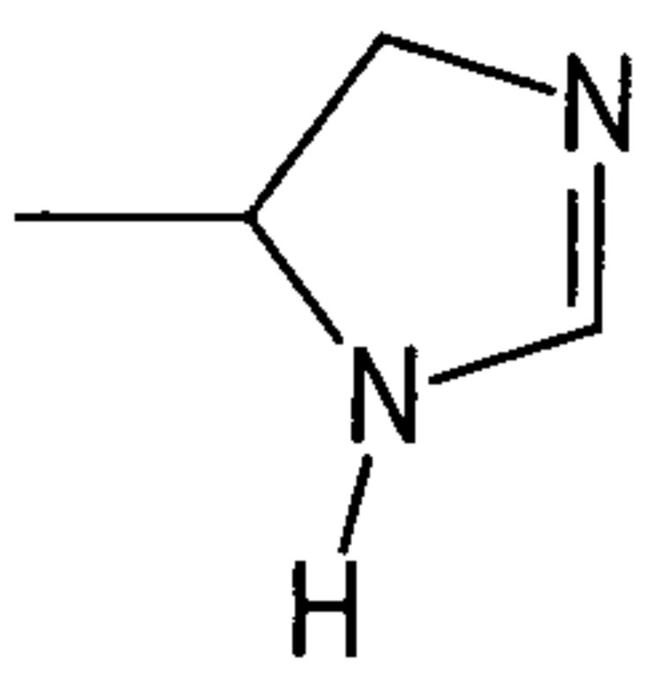
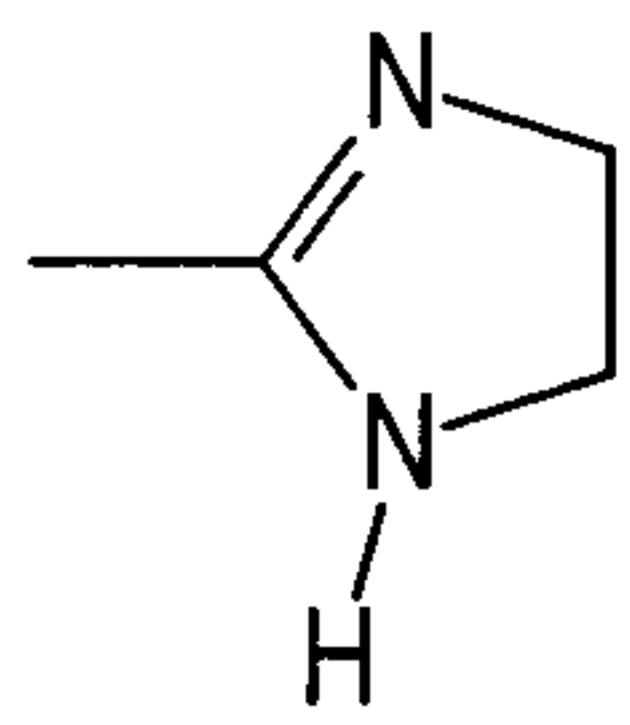
 ,  ,  ,  ,

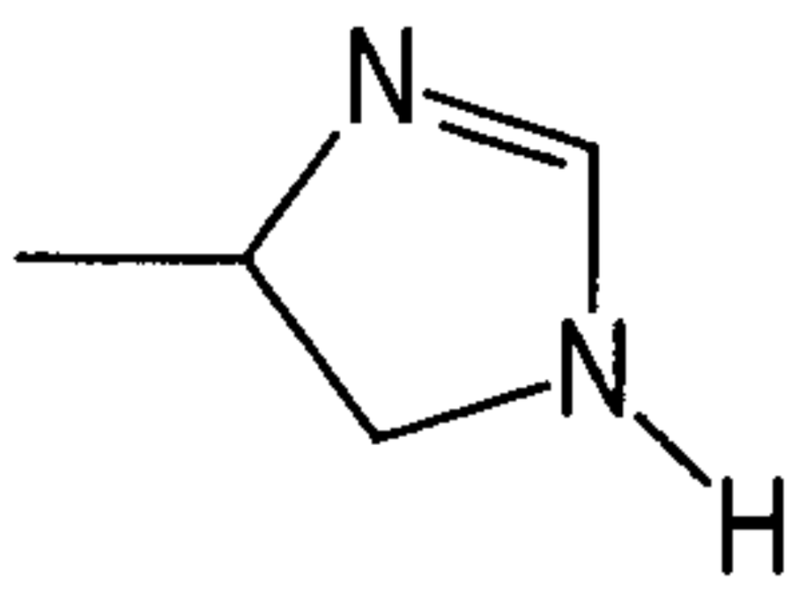
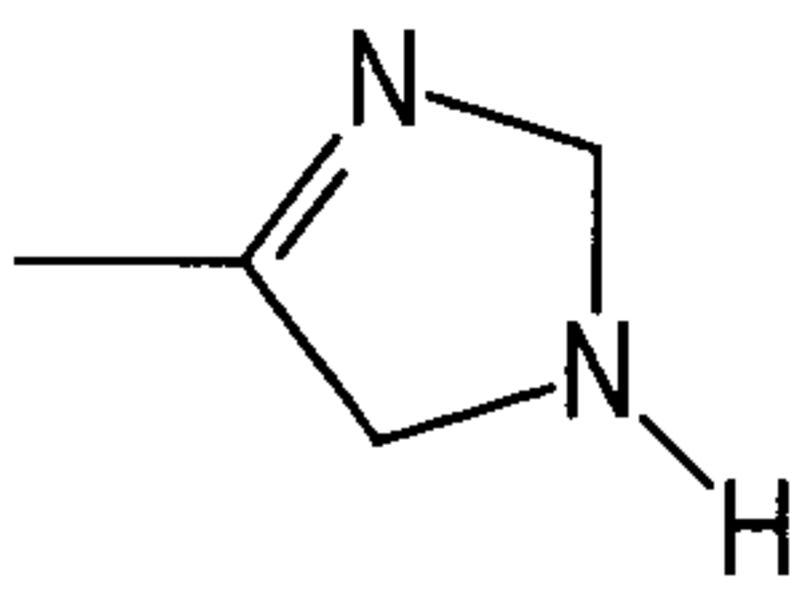
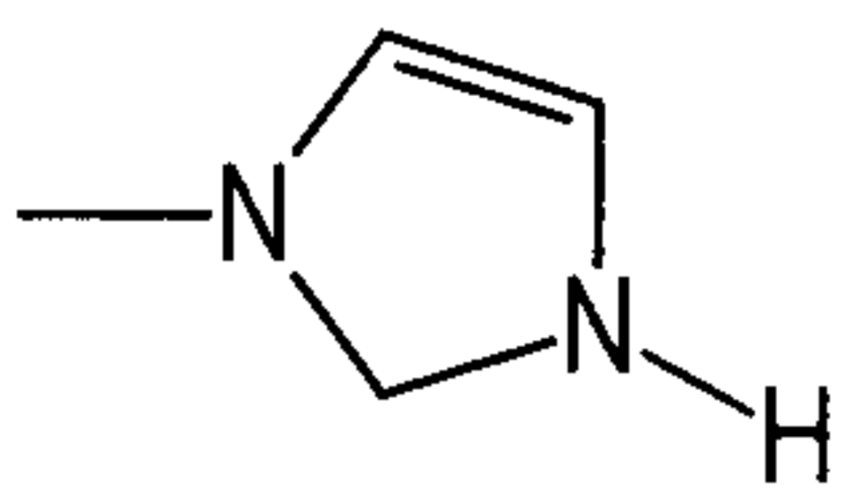
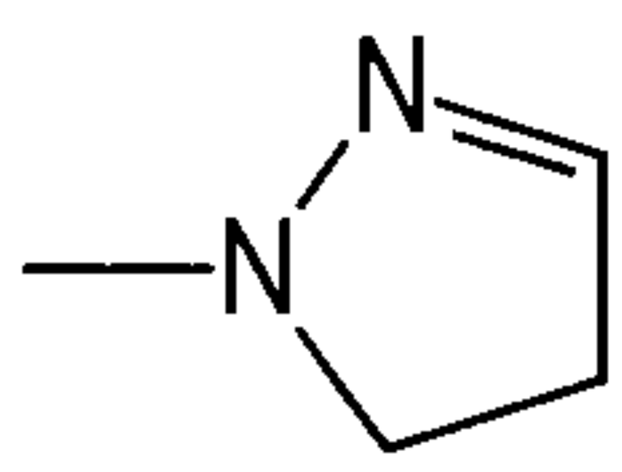
 ,  ,  ,  ,

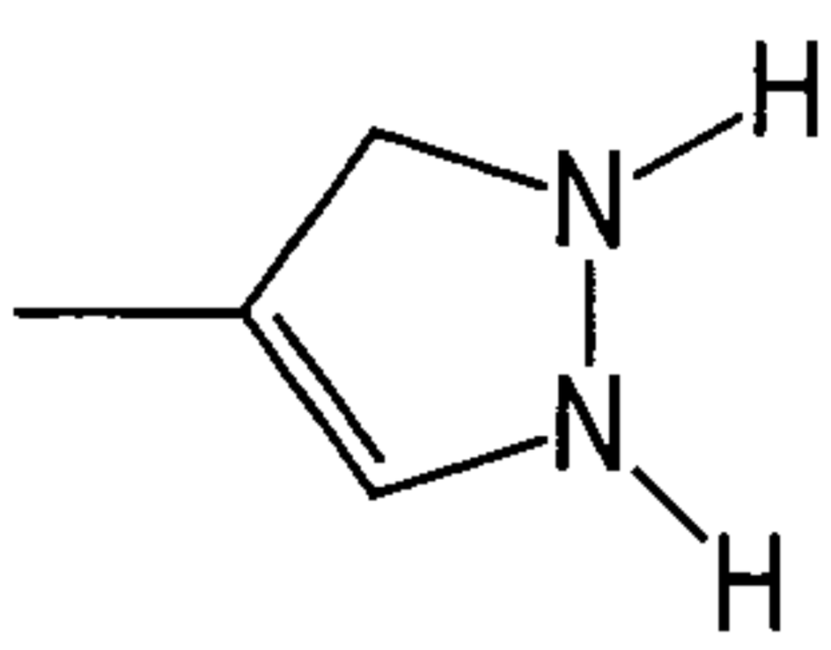
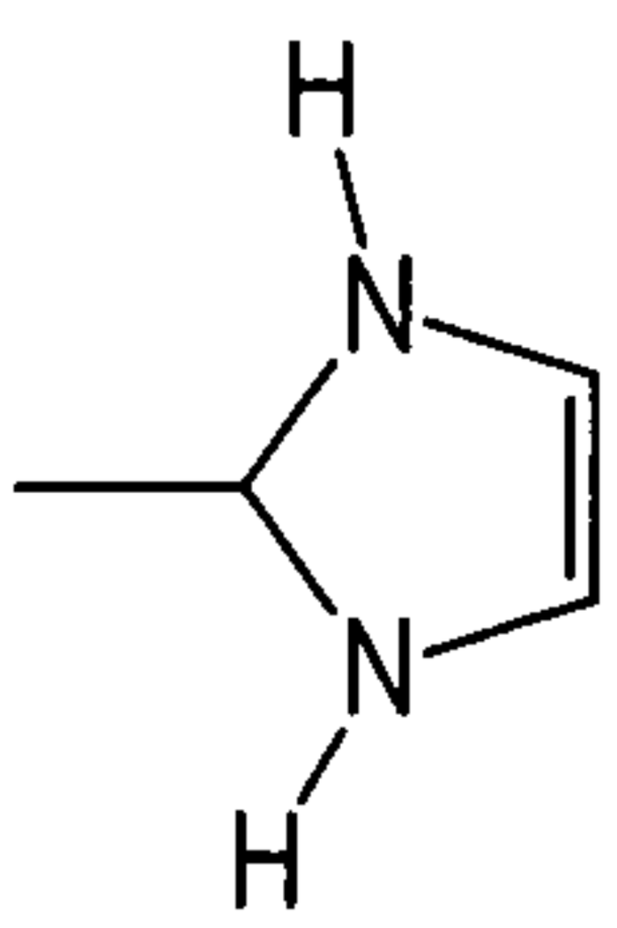
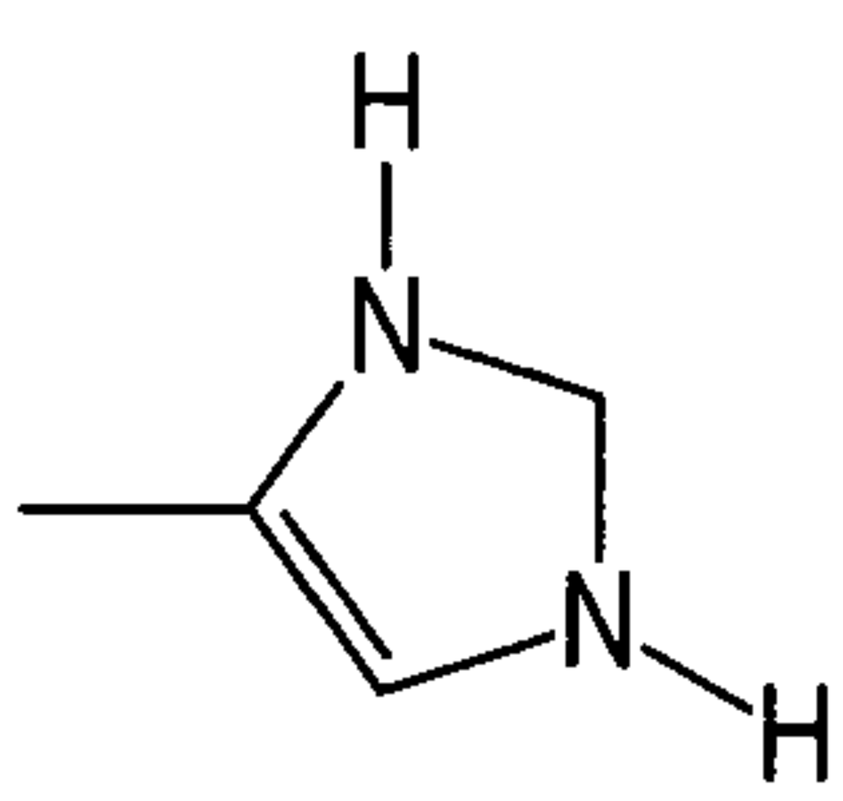
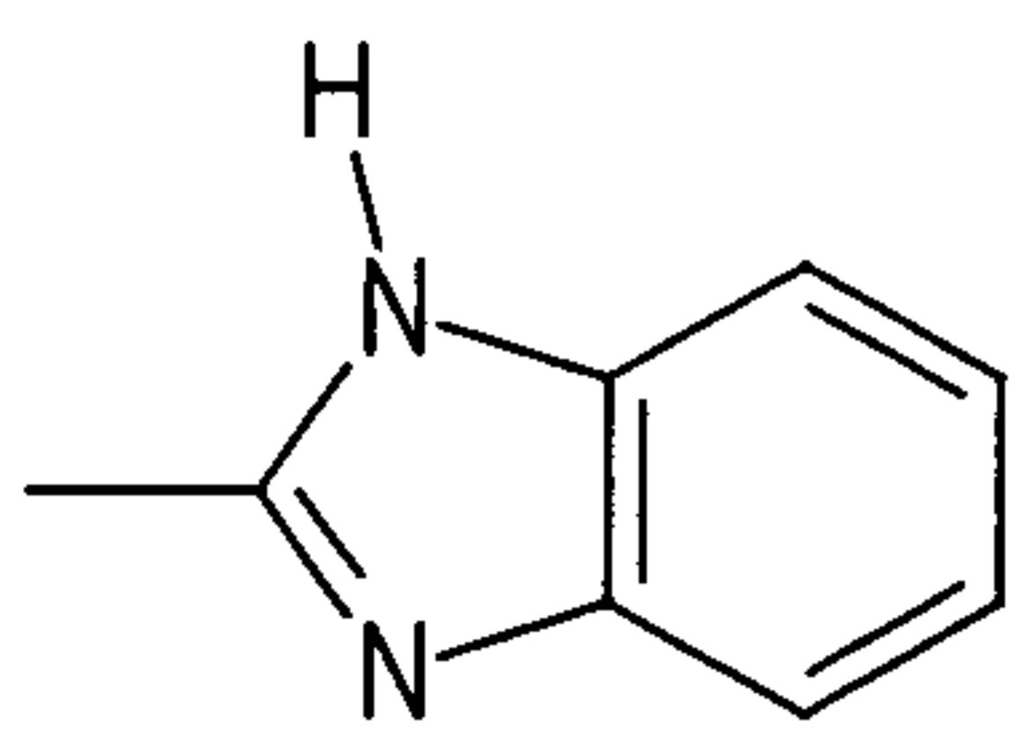
 ,  ,  ,  ,

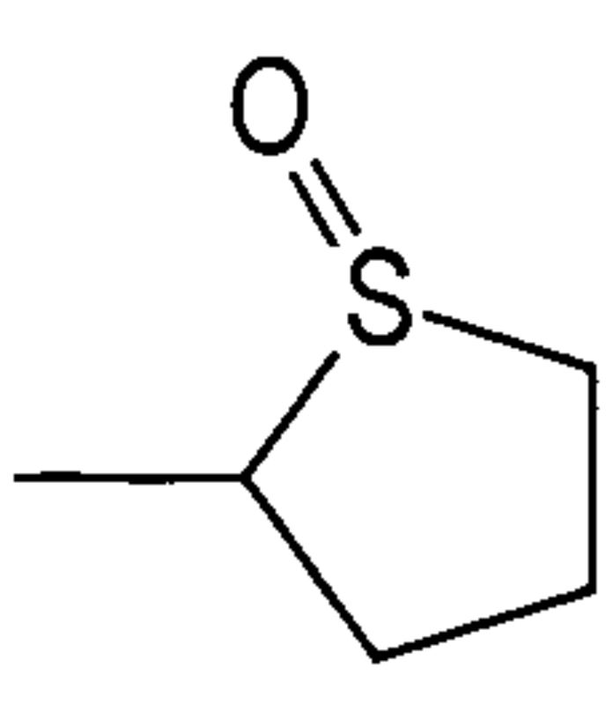
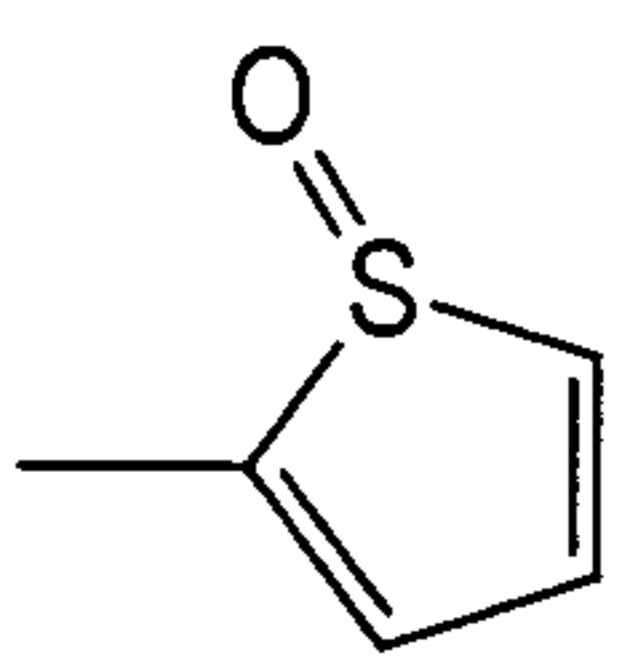
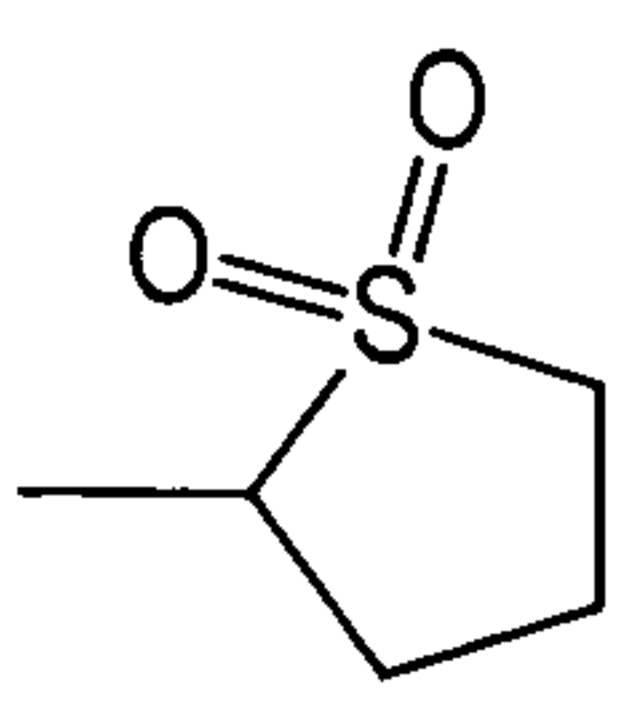
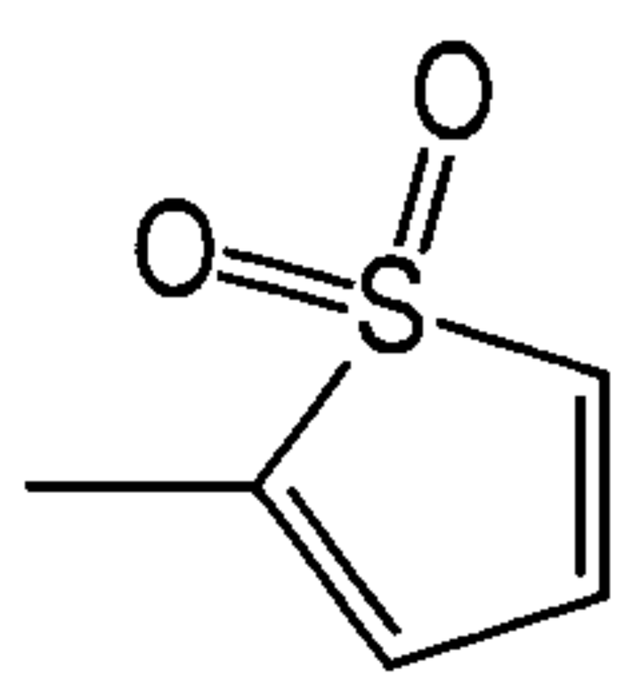
 ,  ,  ,  ,

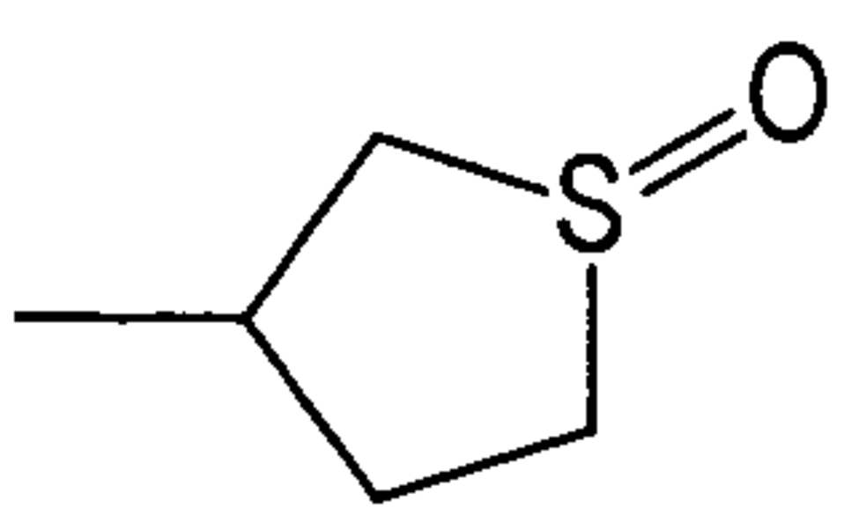
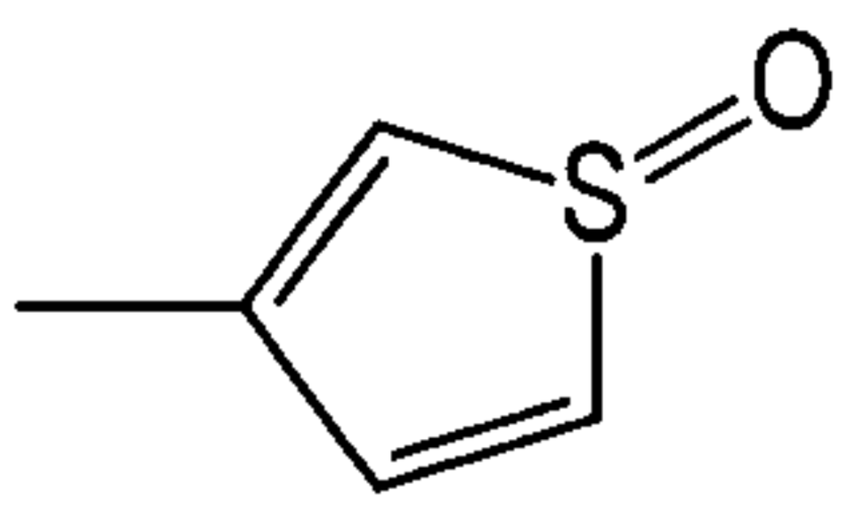
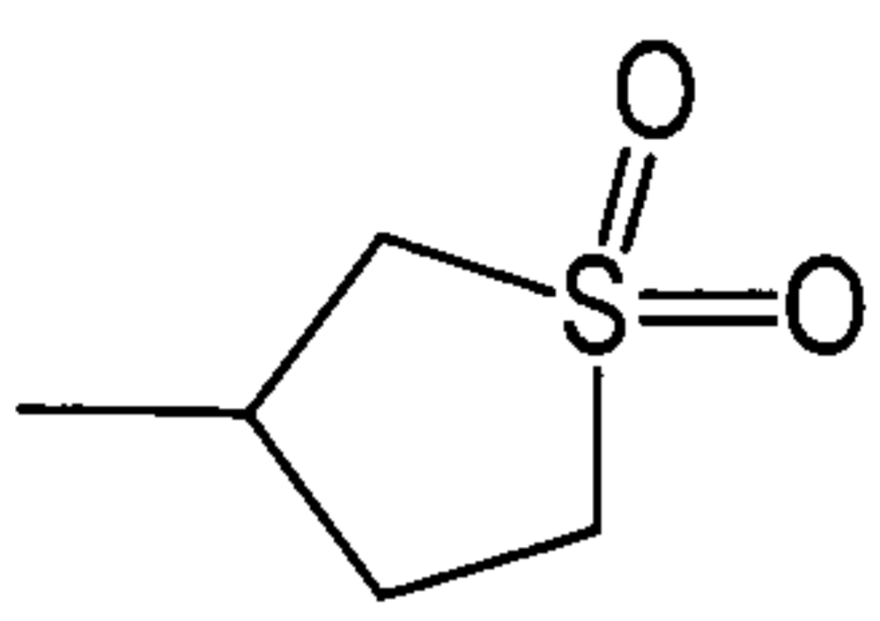
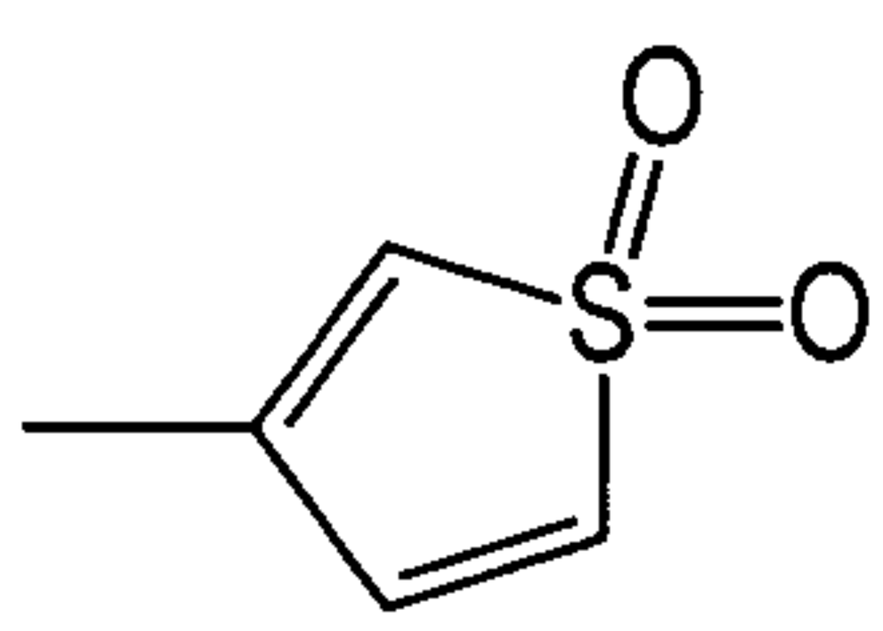
 ,  ,  ,  ,

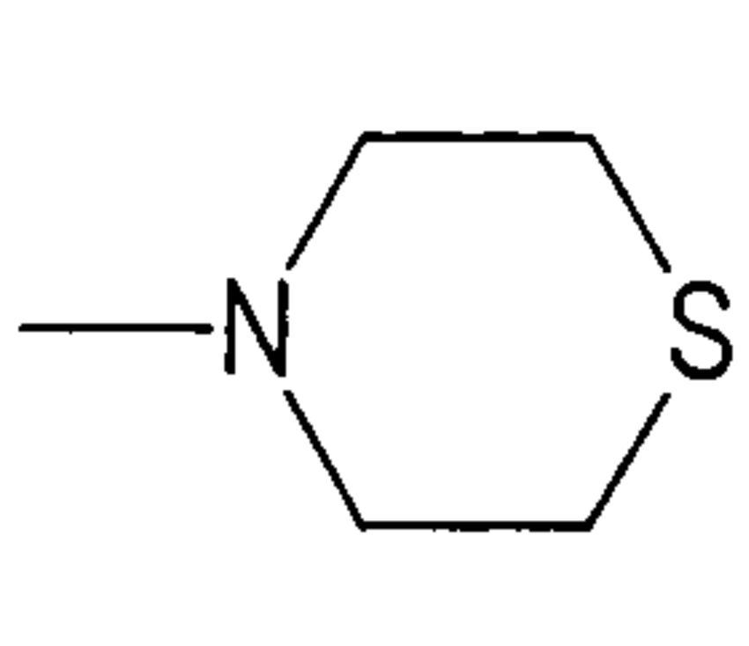
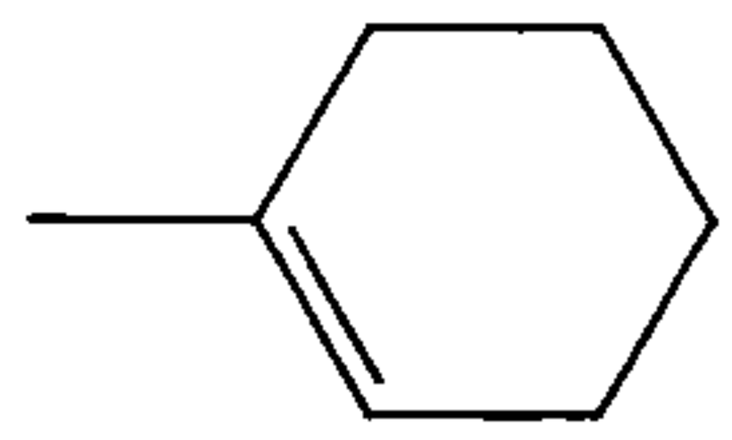
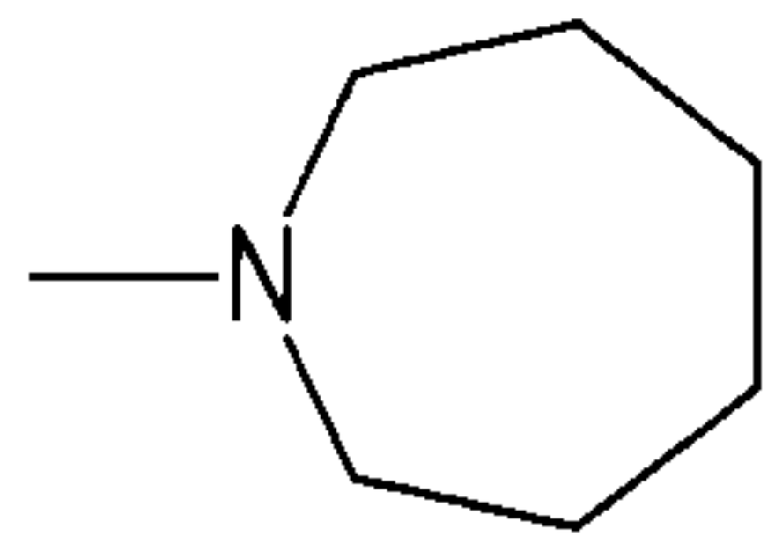
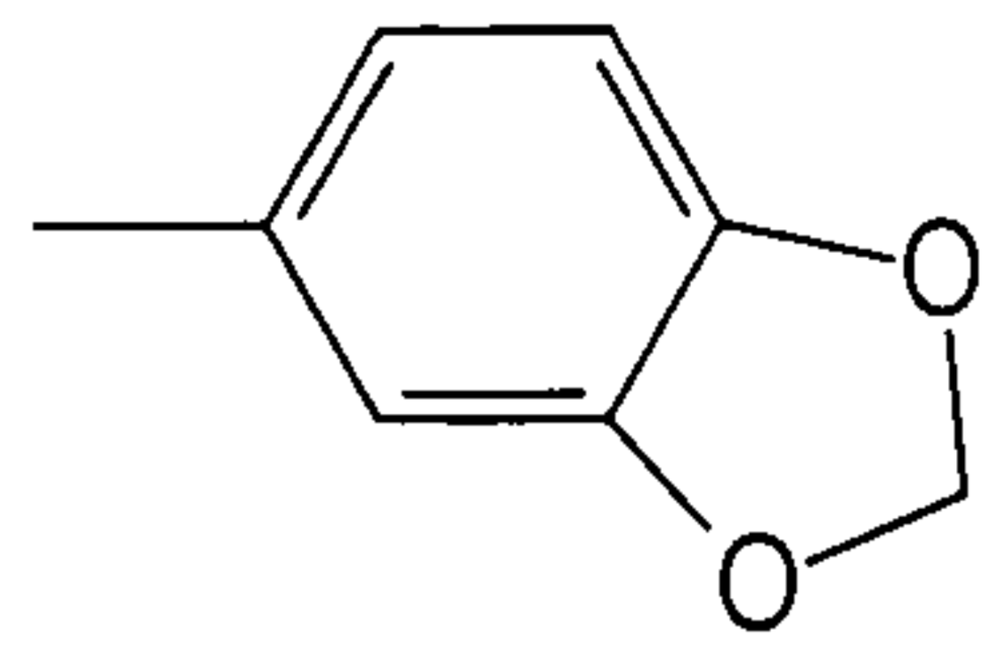
 ,  ,  ,  ,

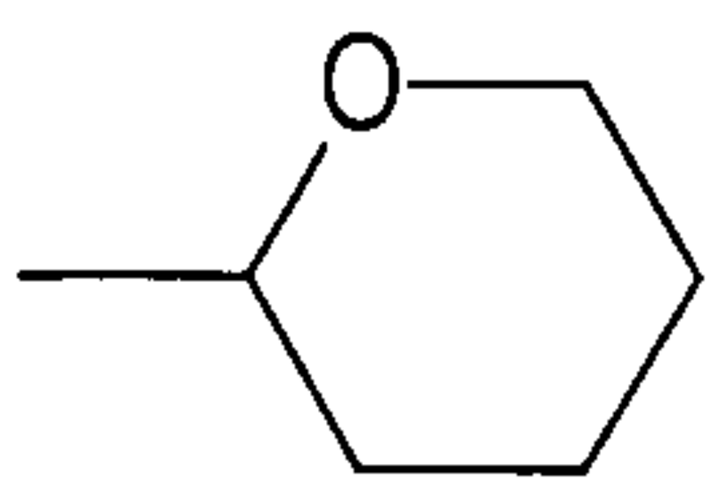
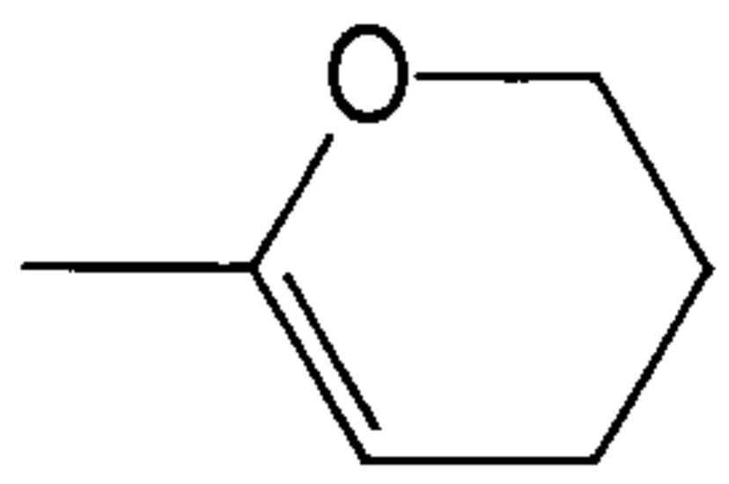
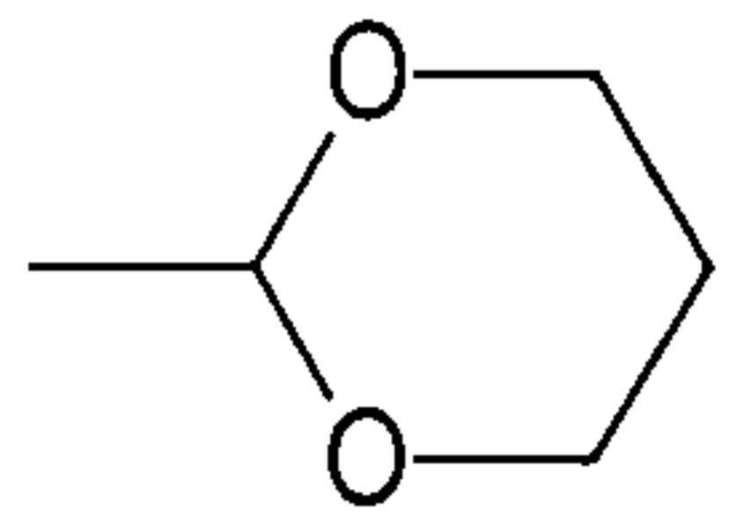
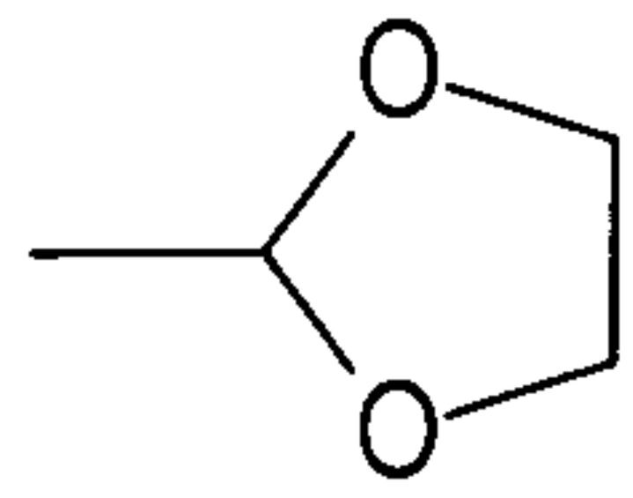
 ,  ,  ,  ,

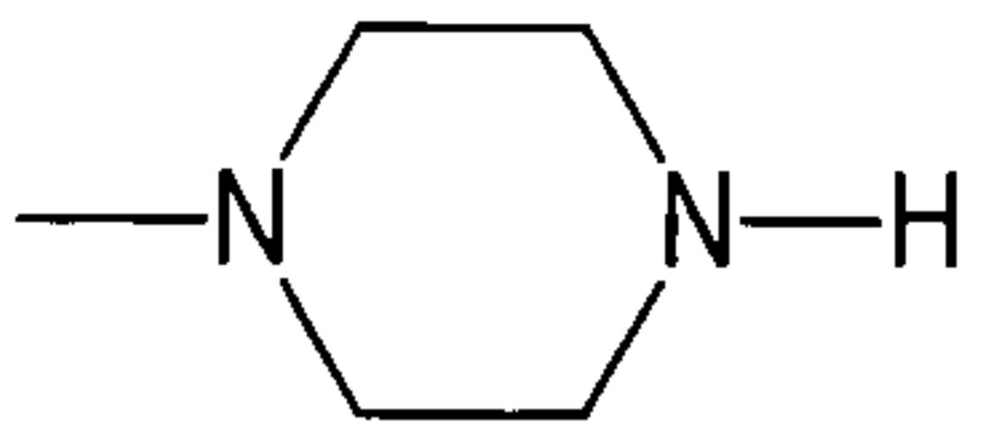
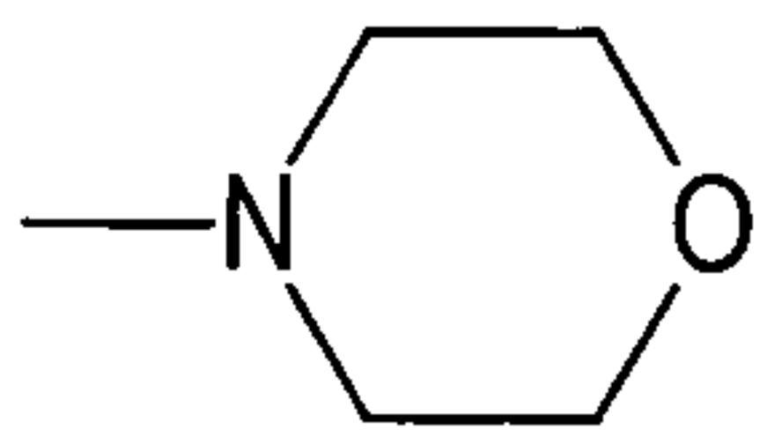
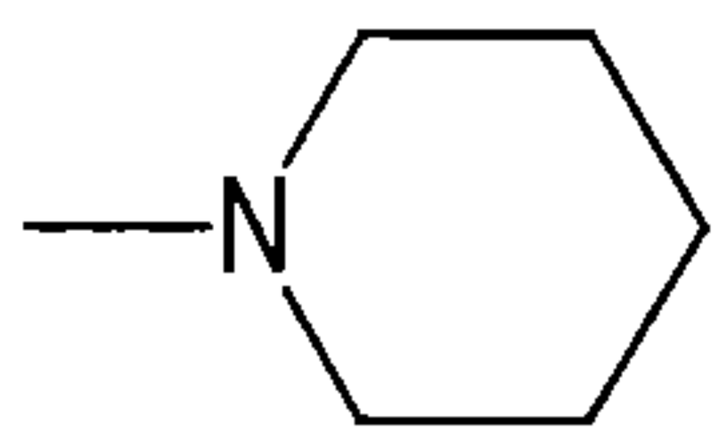
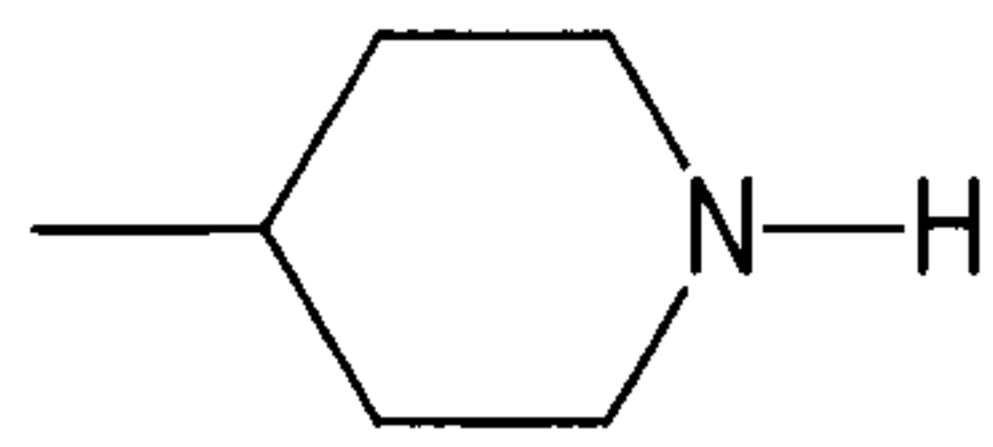
 ,  ,  ,  ,

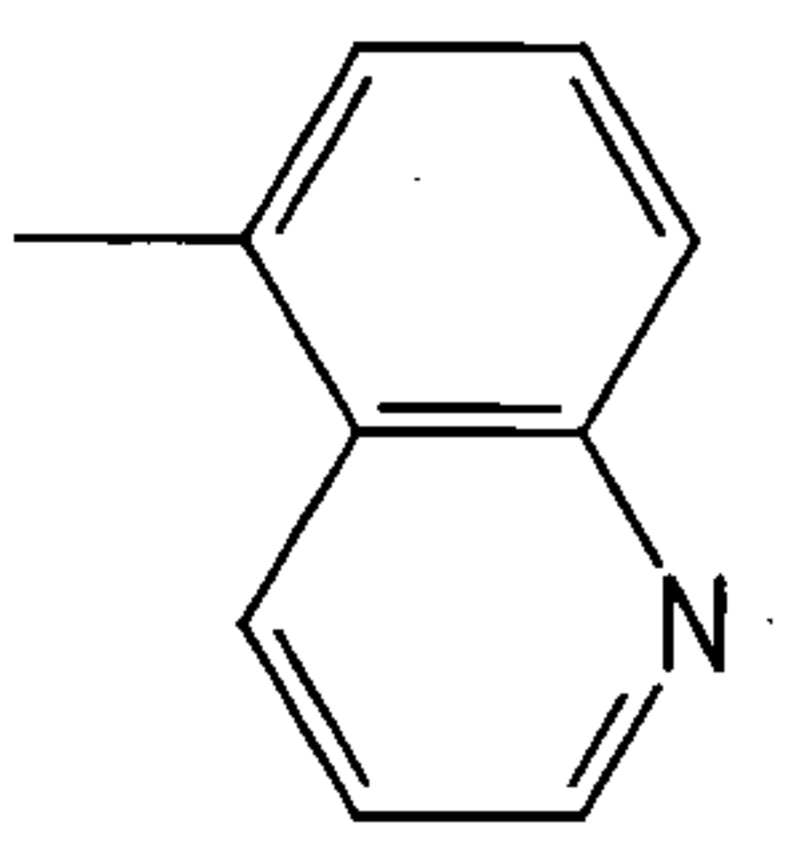
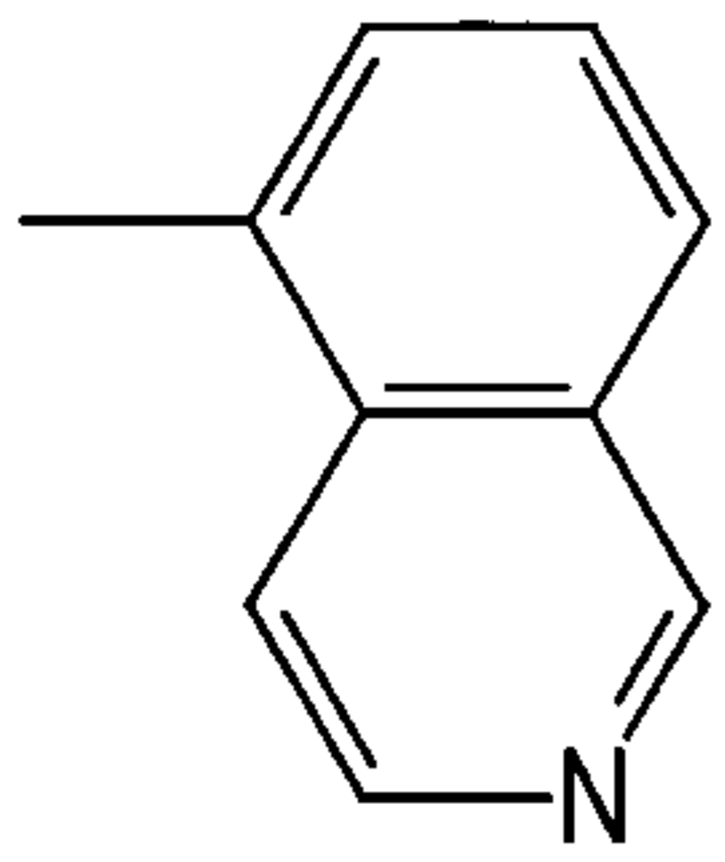
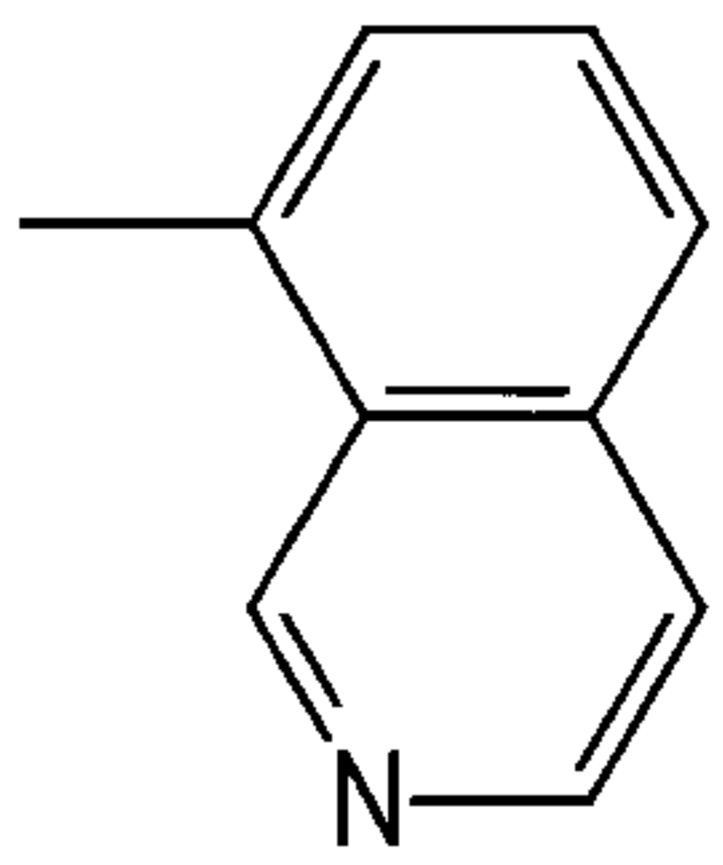
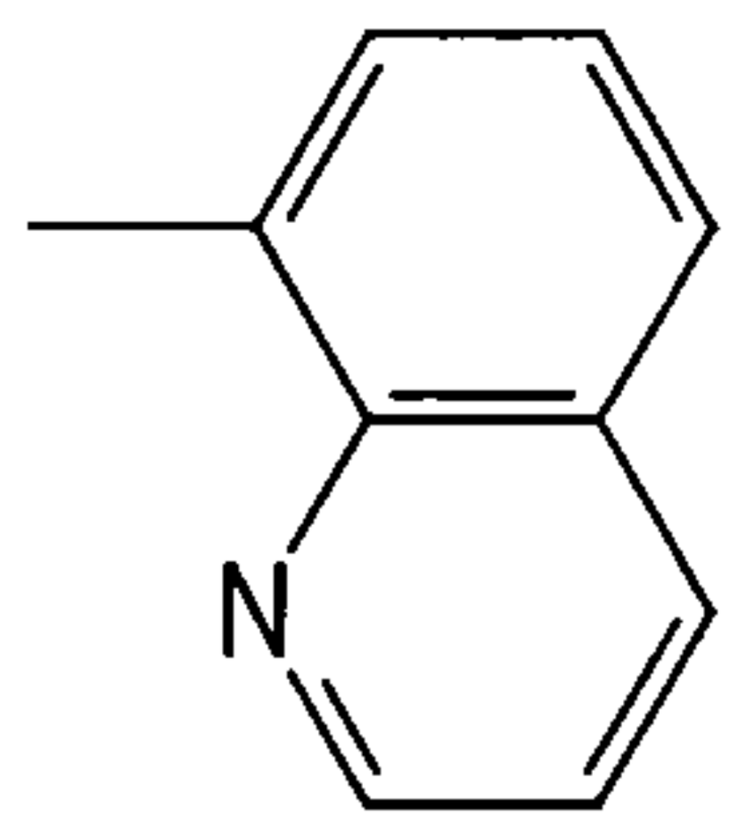
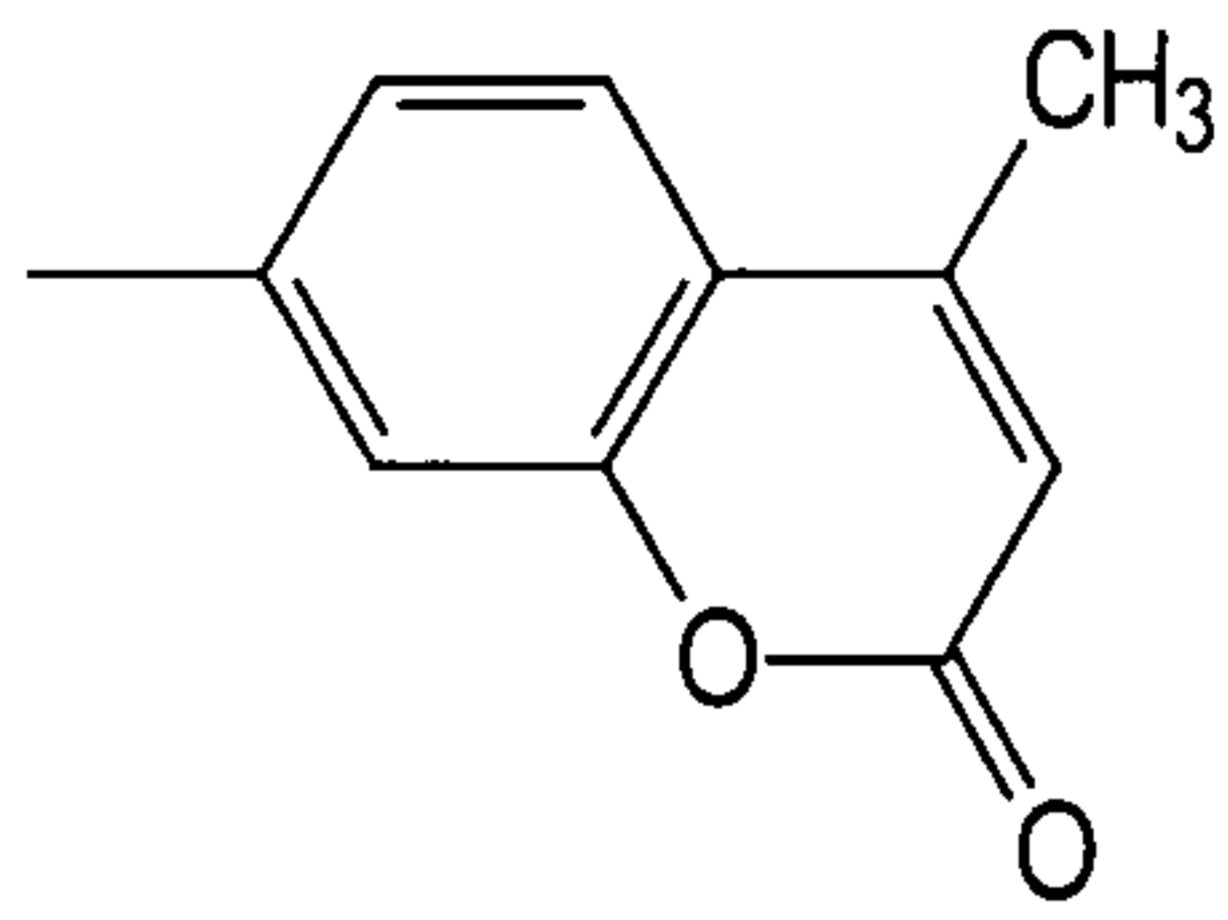
 ,  ,  ,  ,

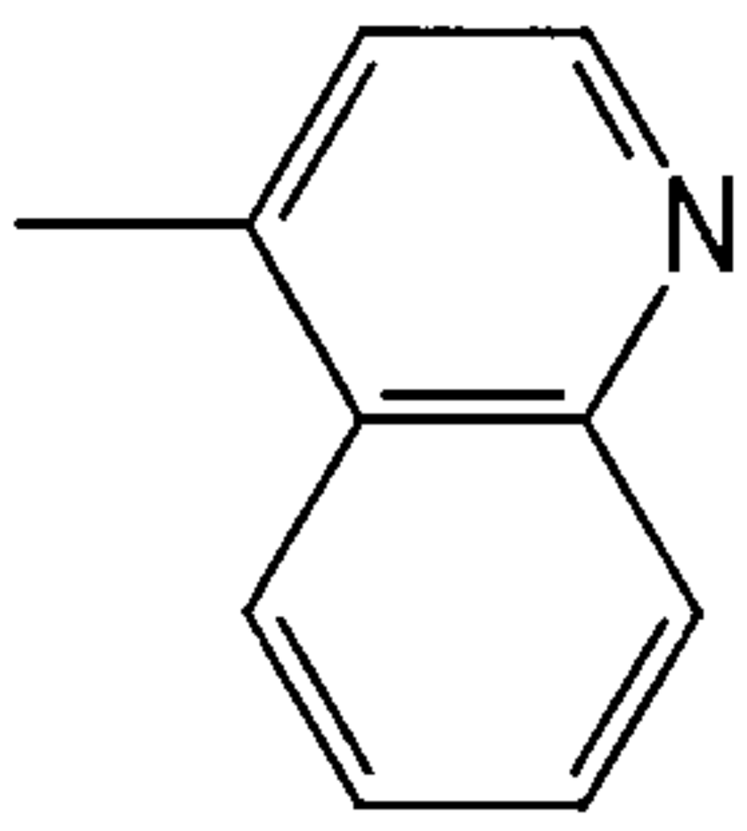
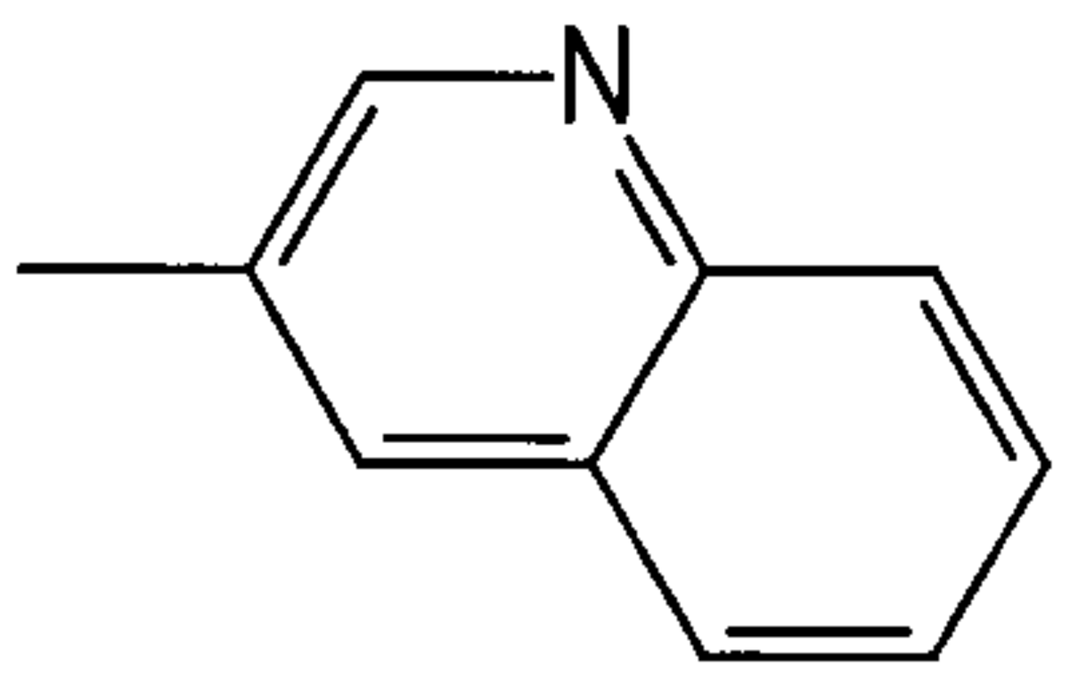
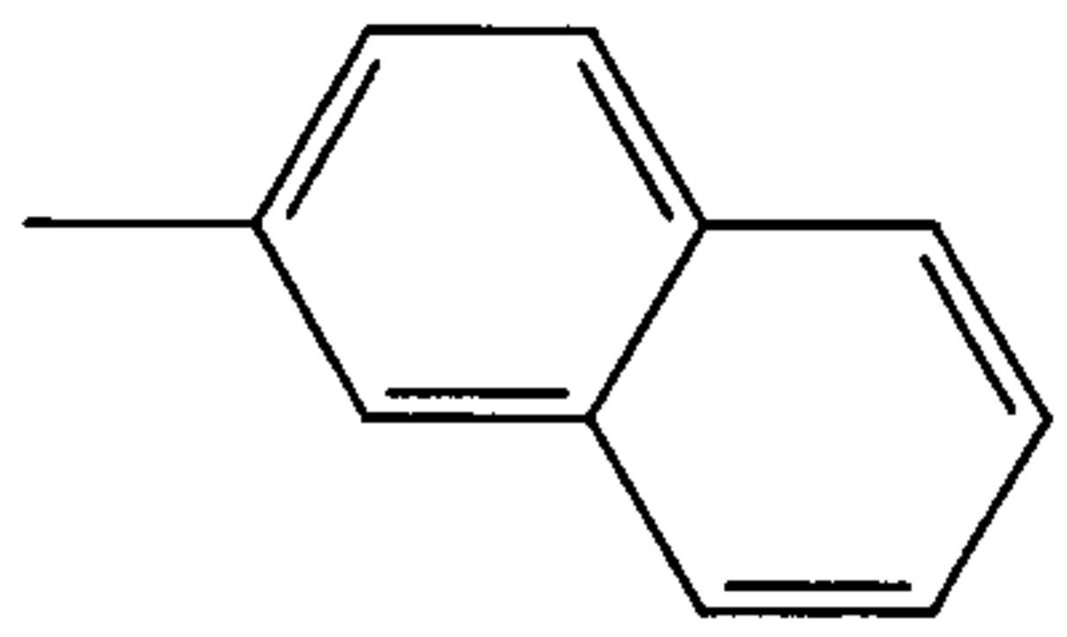
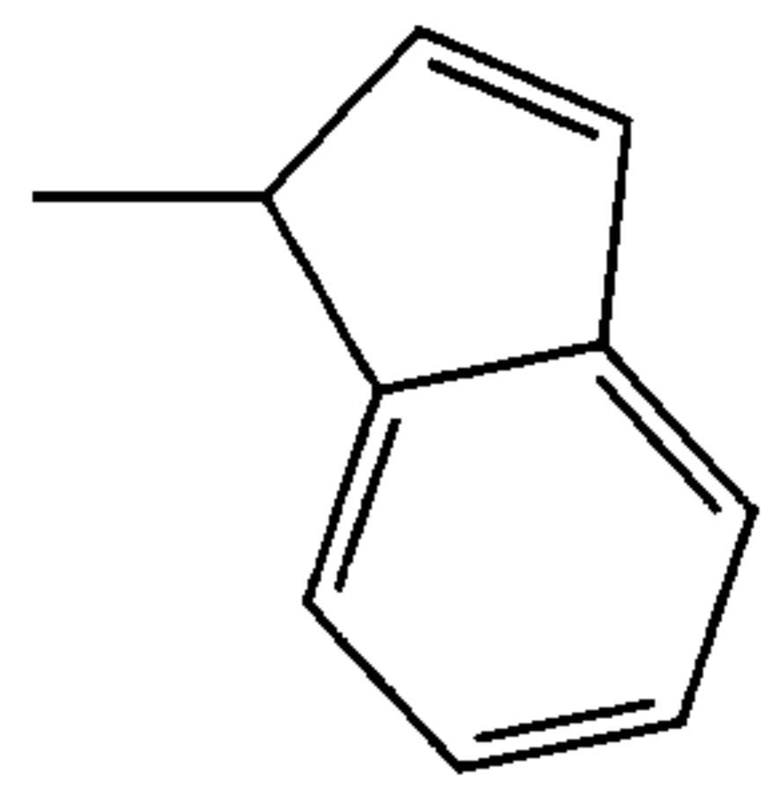
 ,  ,  , 

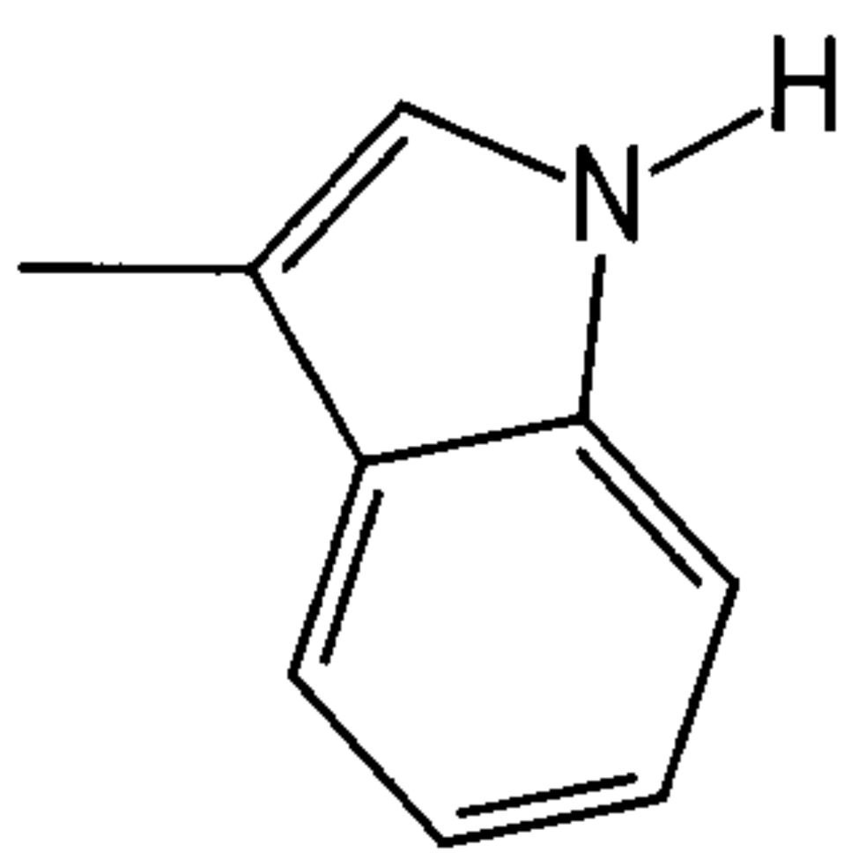
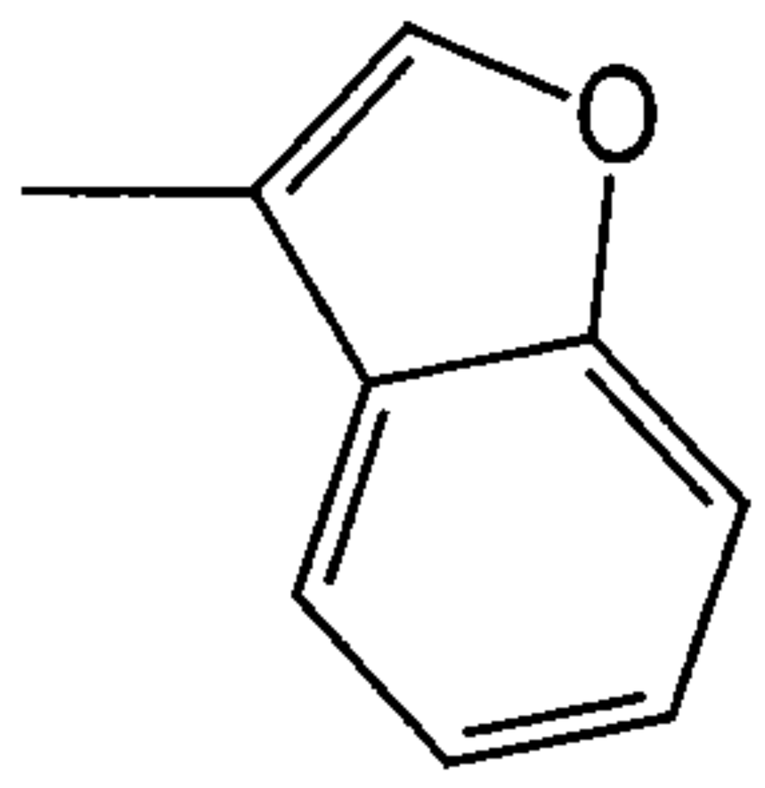
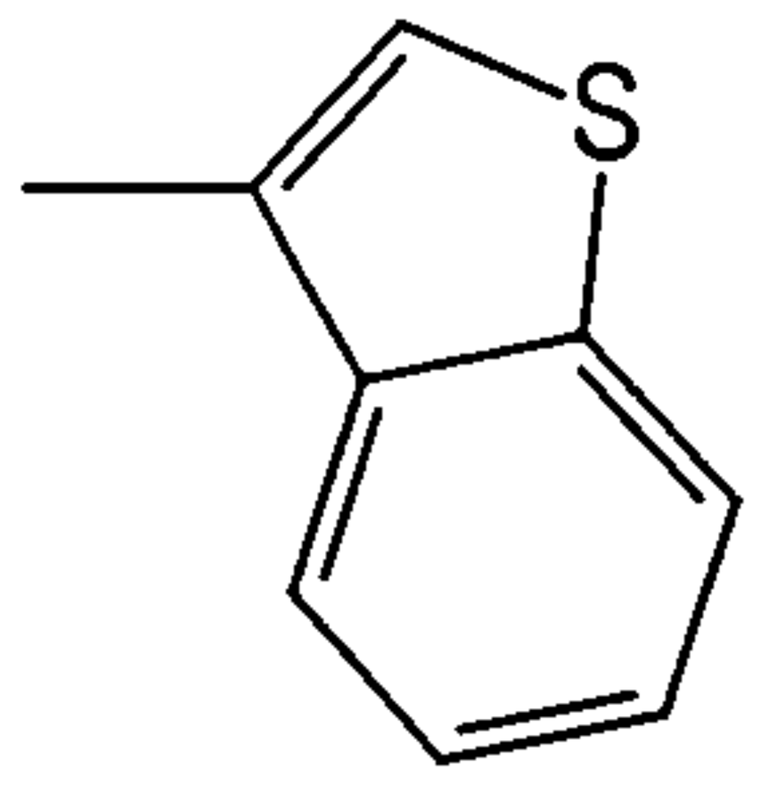
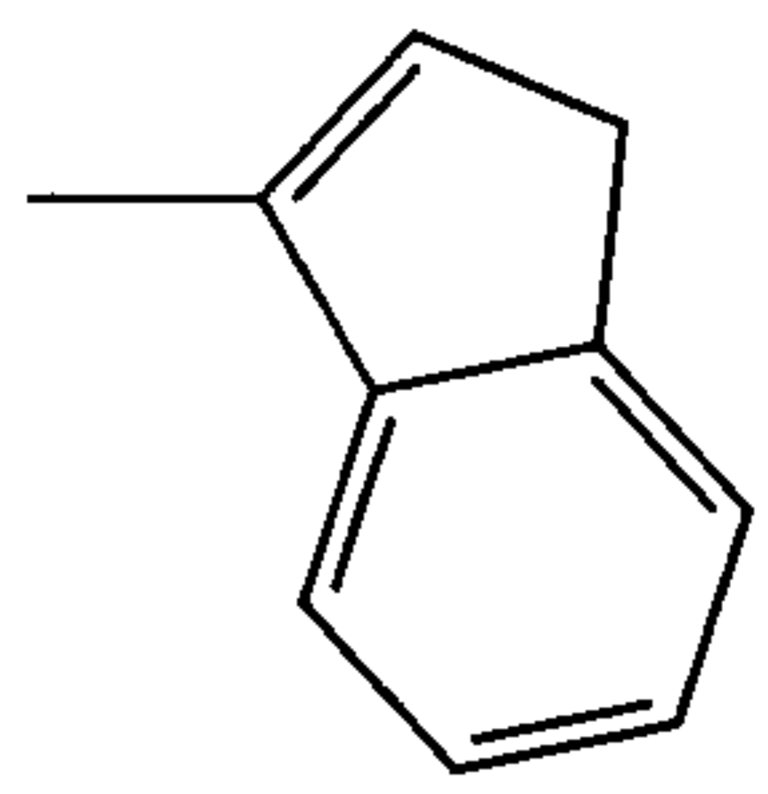
 ,
 ,
 ,
 ,

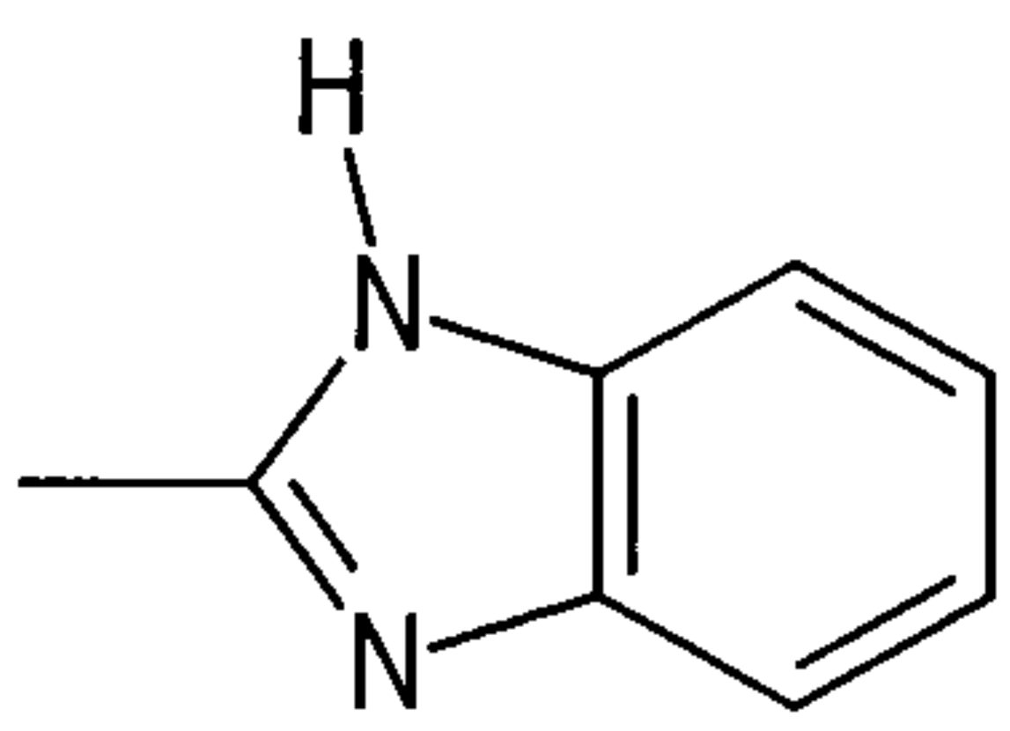
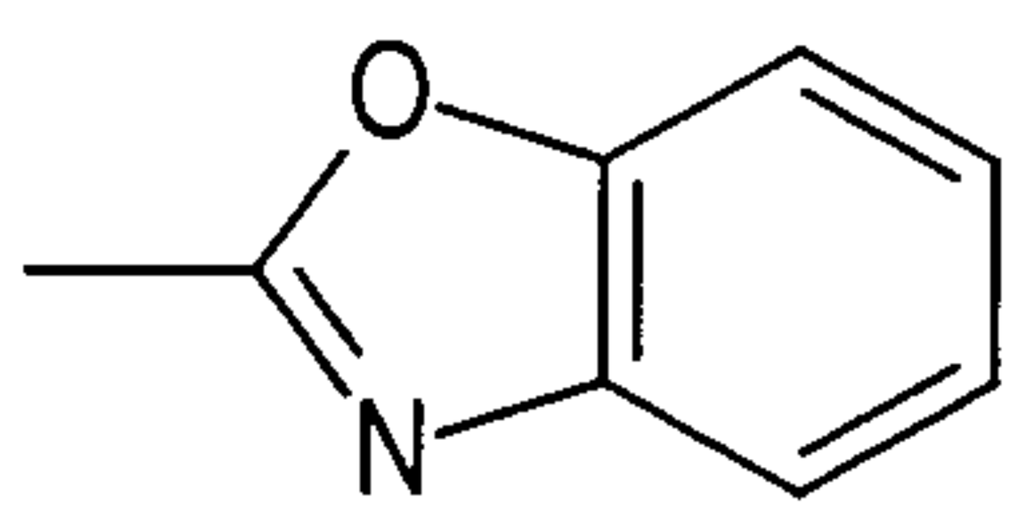
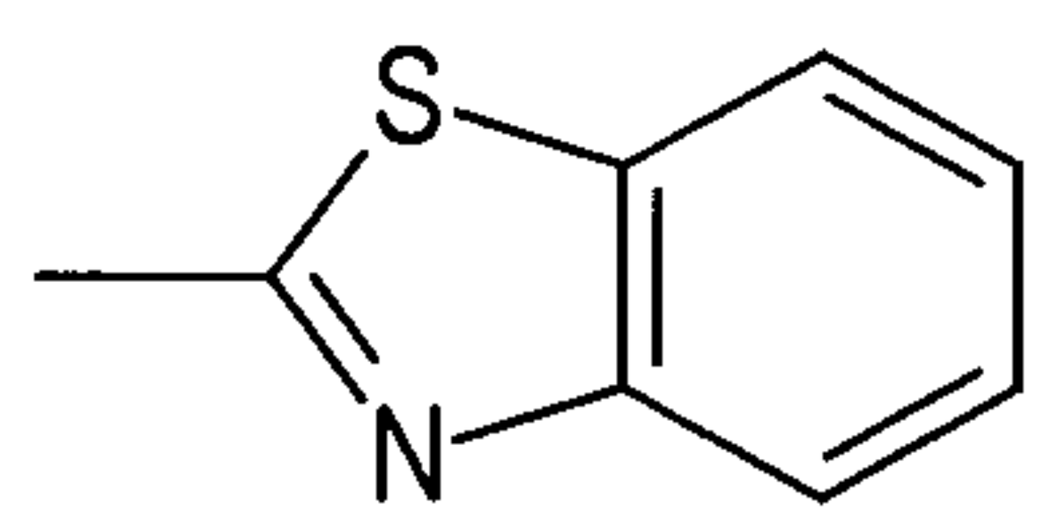
 ,
 ,
 ,
 ,

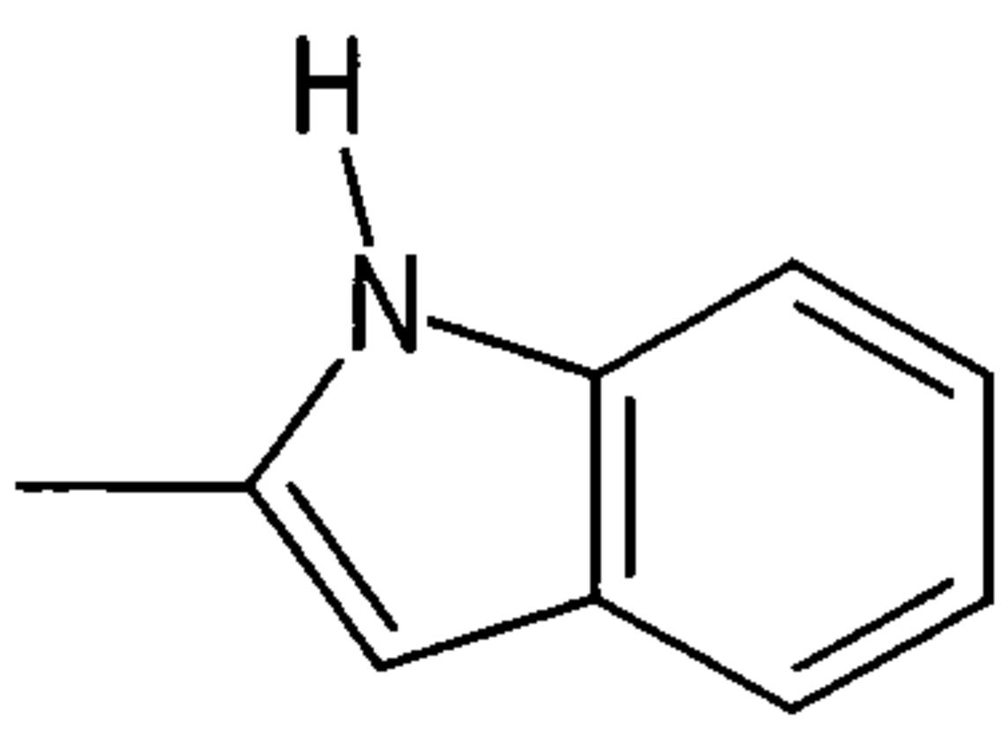
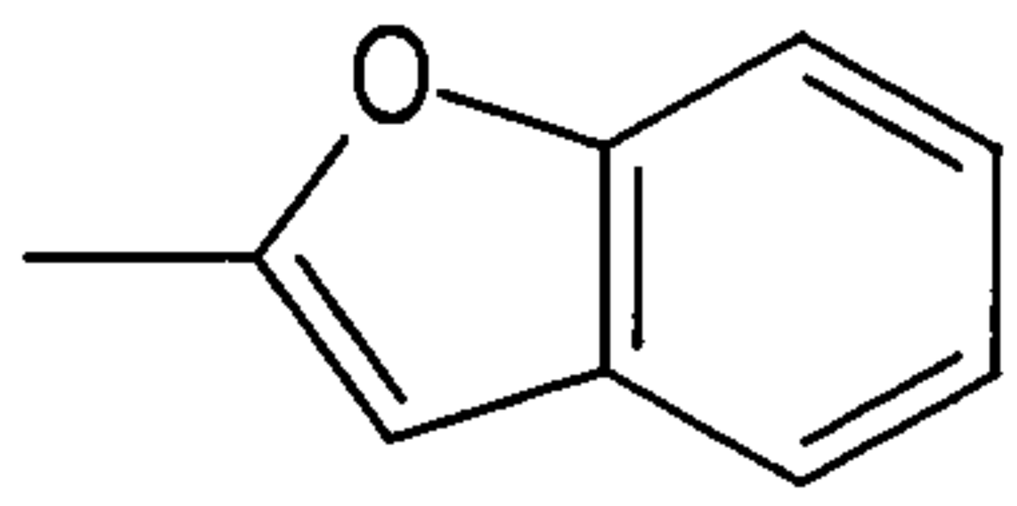
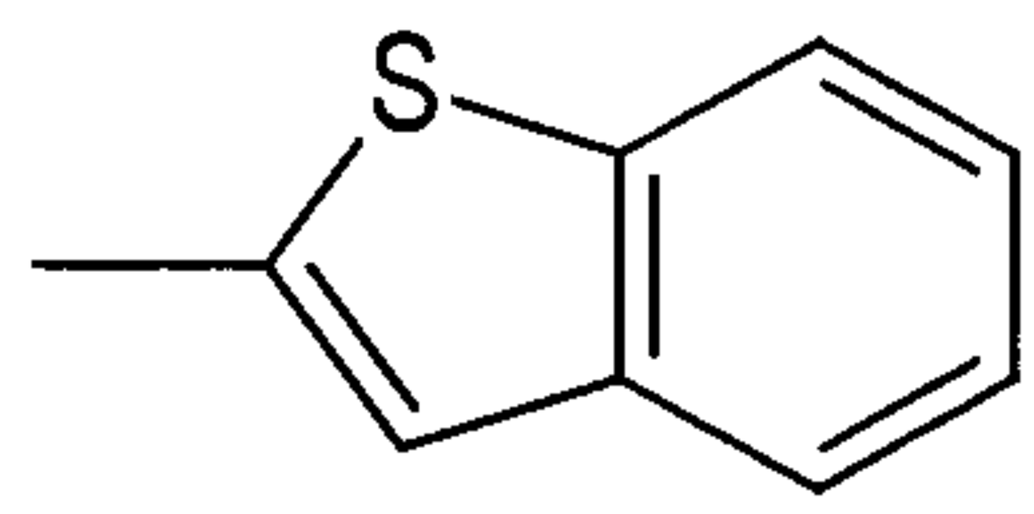
 ,
 ,
 ,
 ,

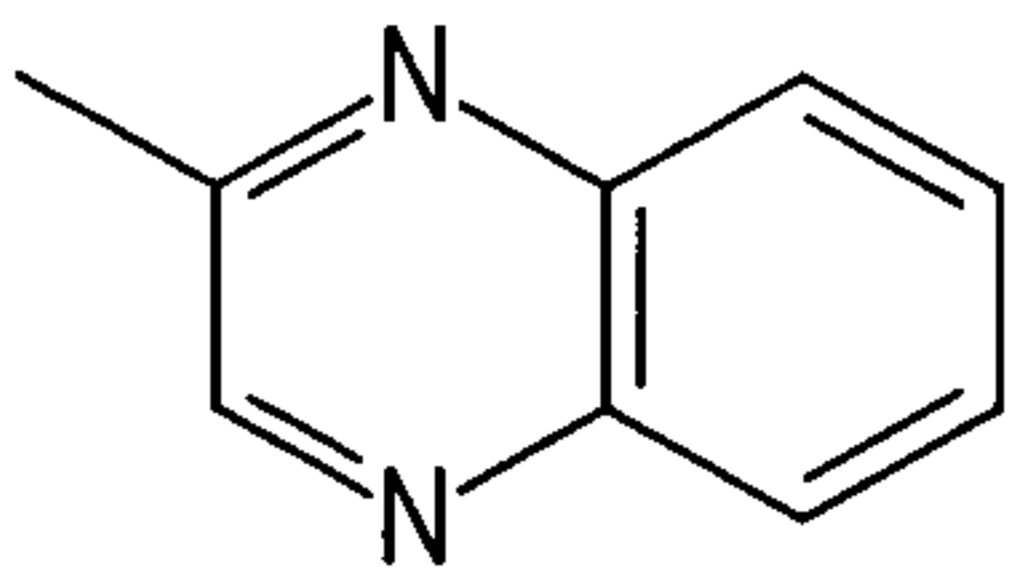
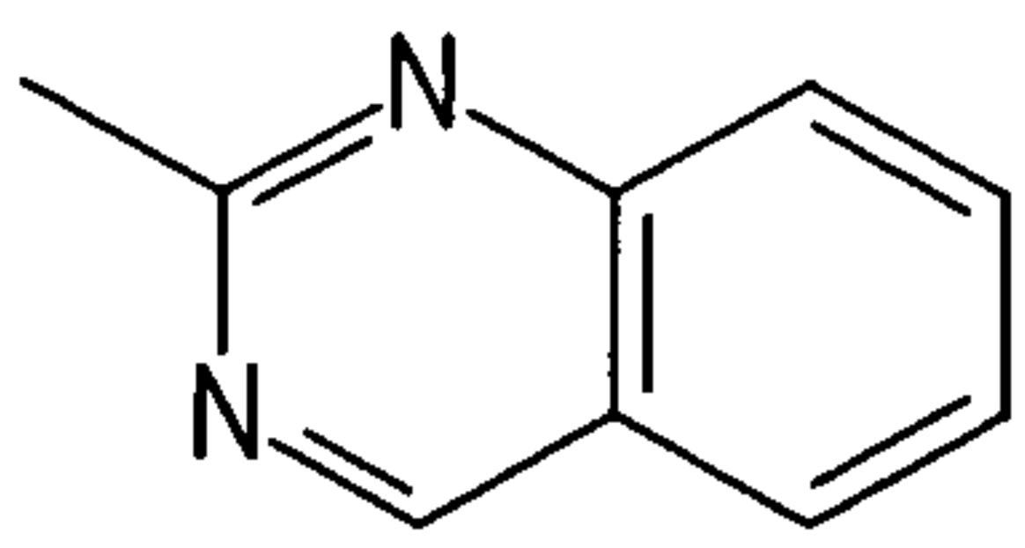
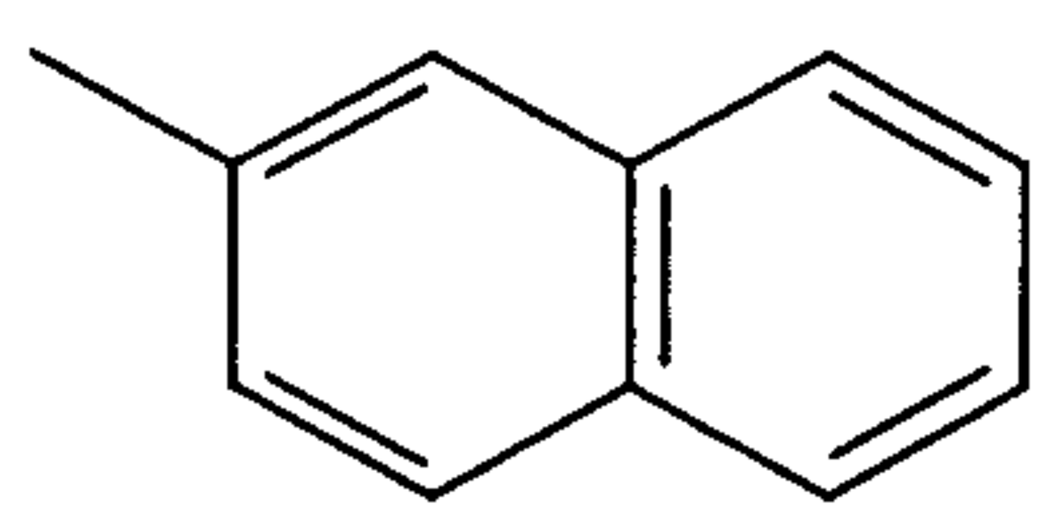
 ,
 ,
 ,
 ,
 ,

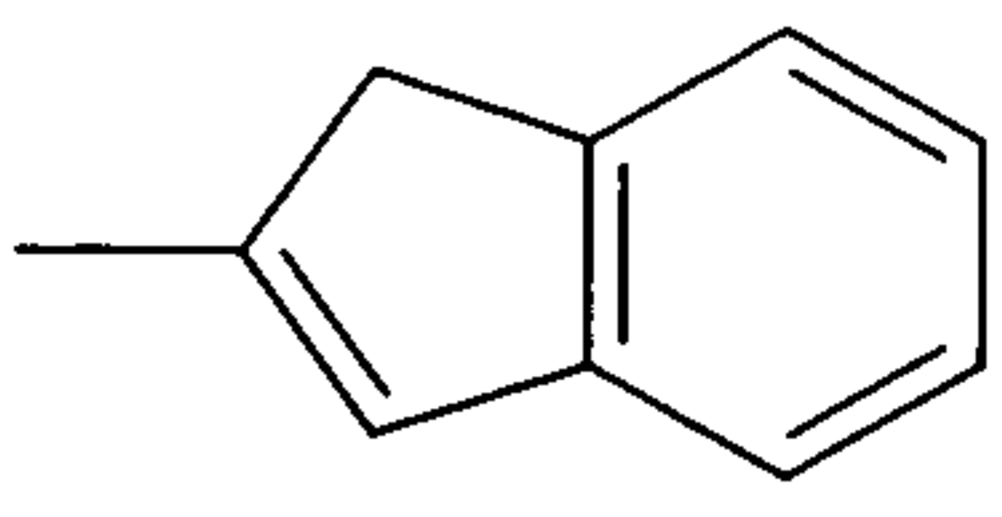
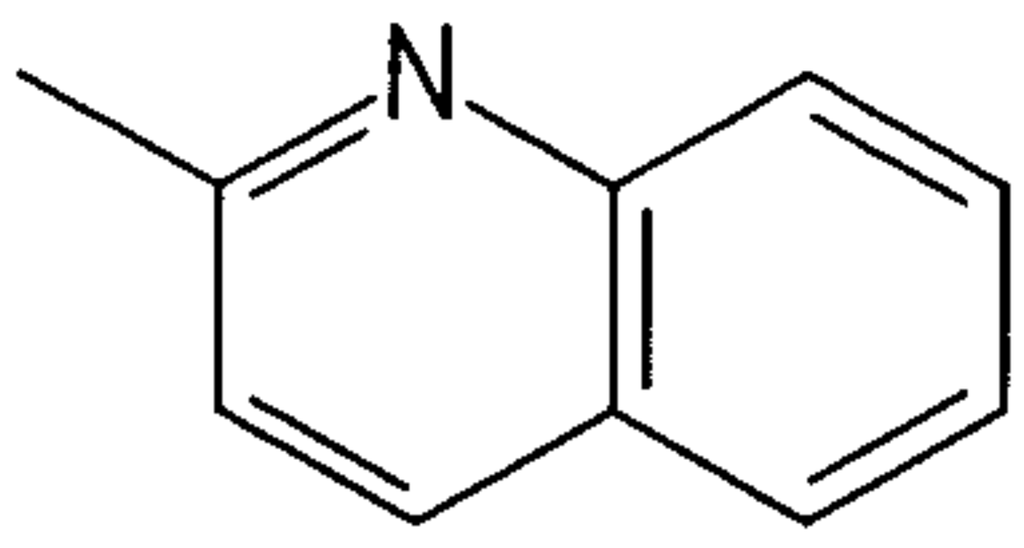
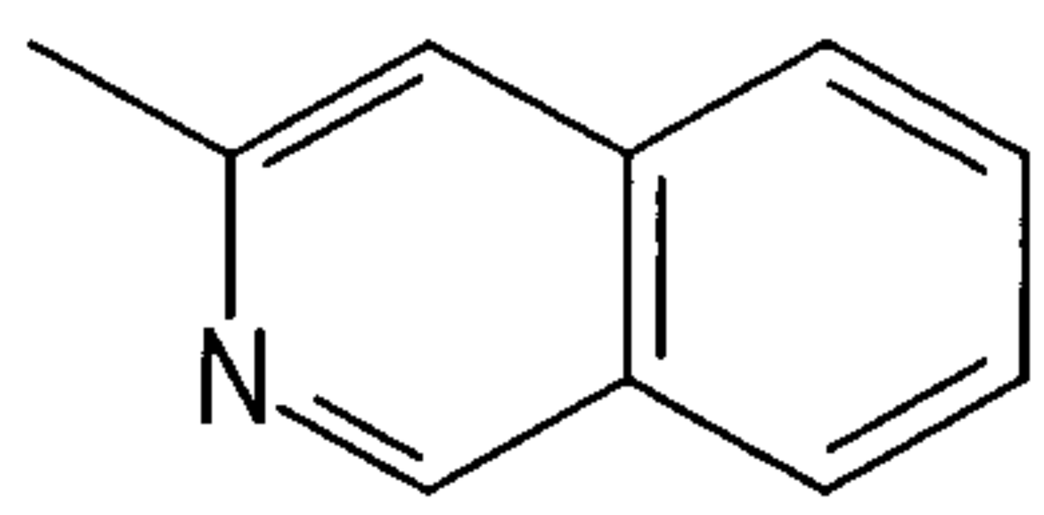
 .
 ,
 ,
 ,

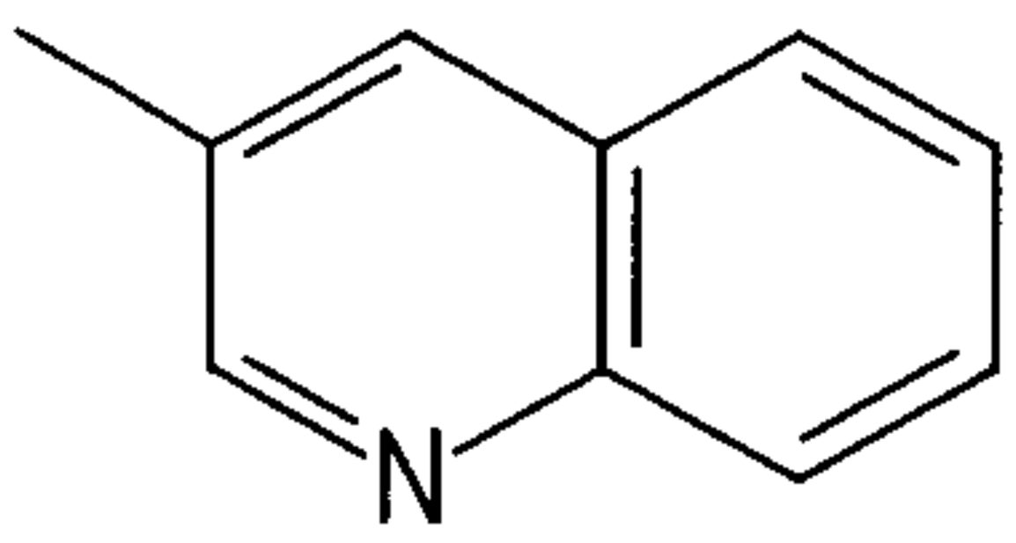
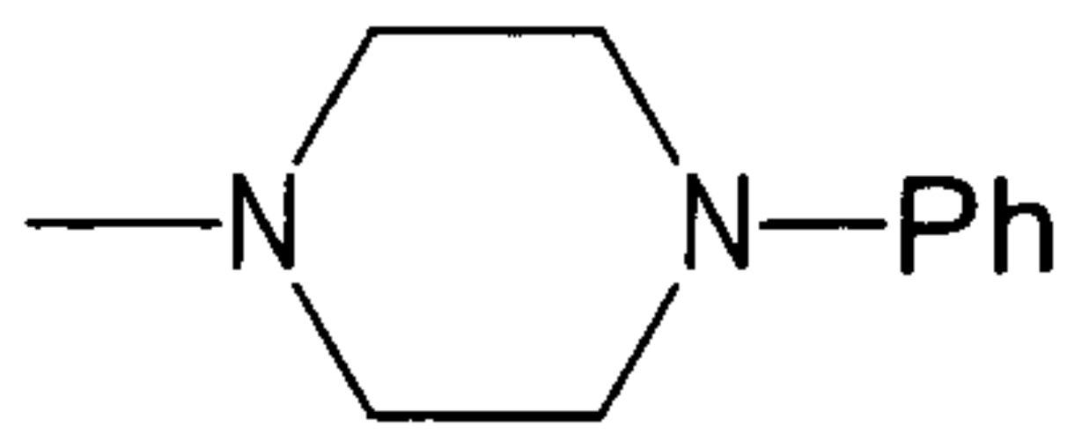
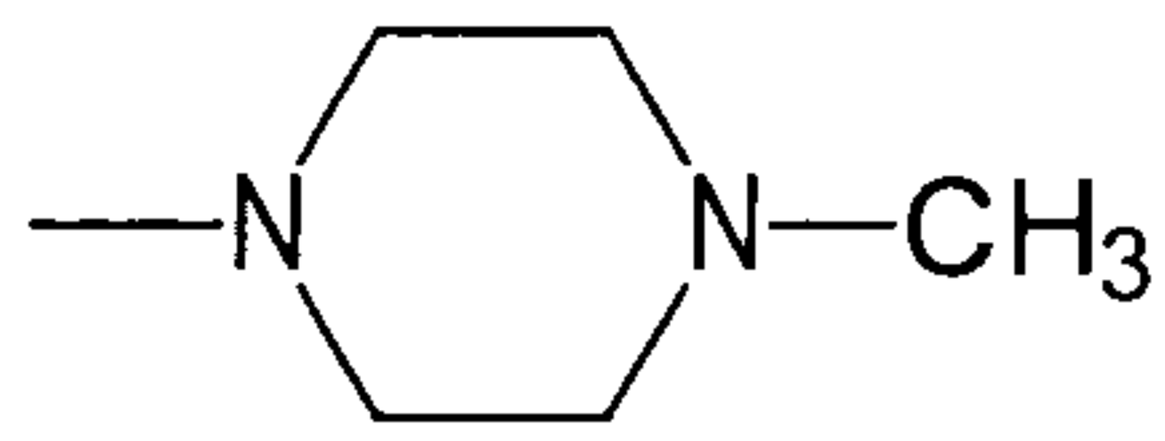
 ,
 ,
 ,
 ,

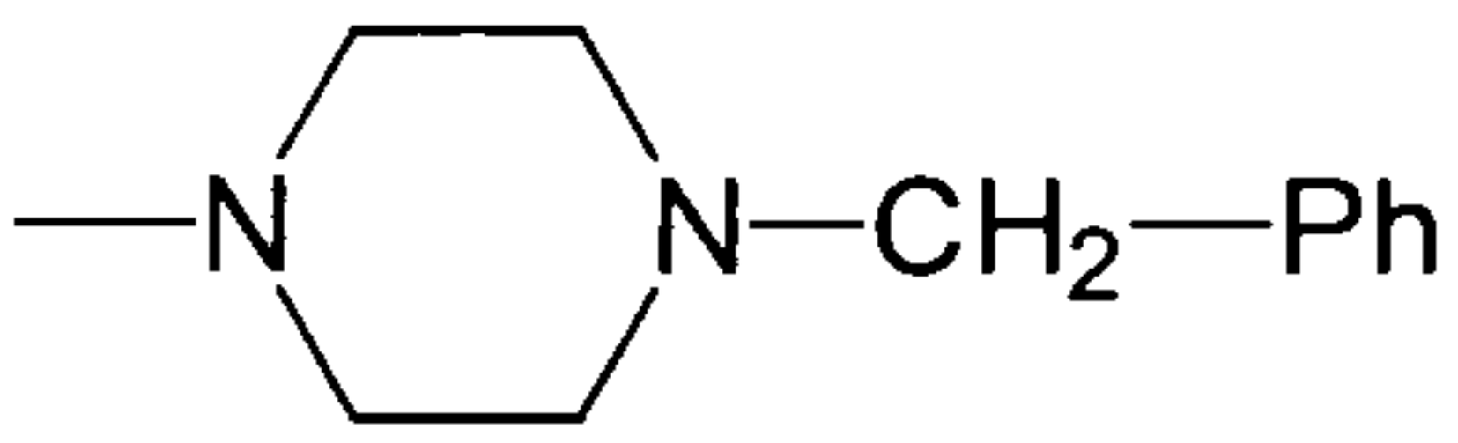
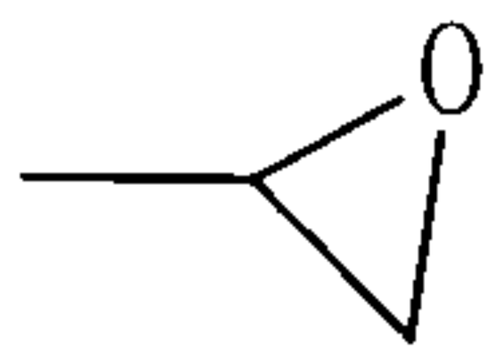
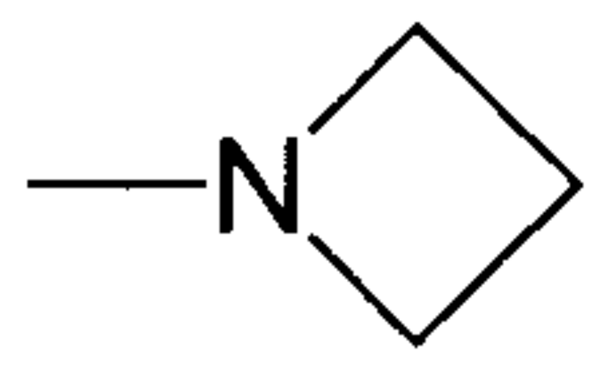
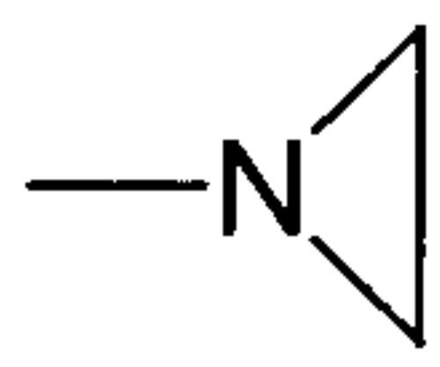
 ,
 ,
 ,

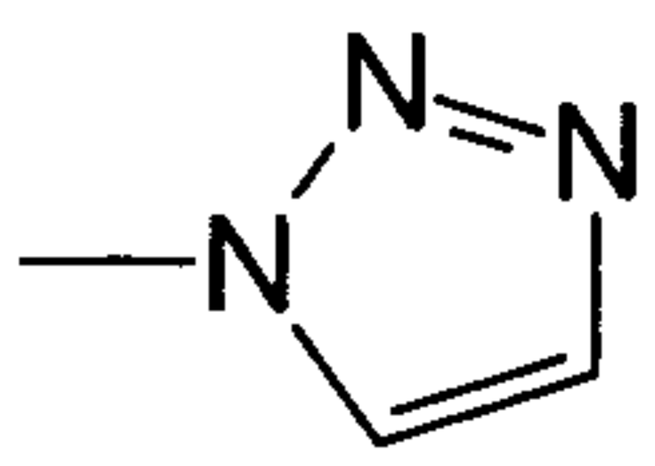
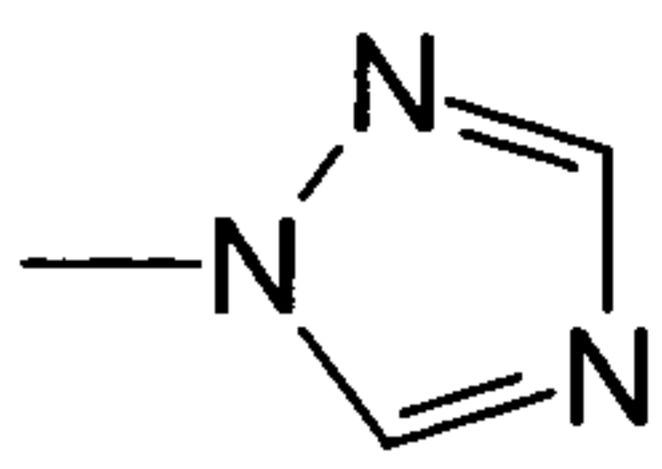
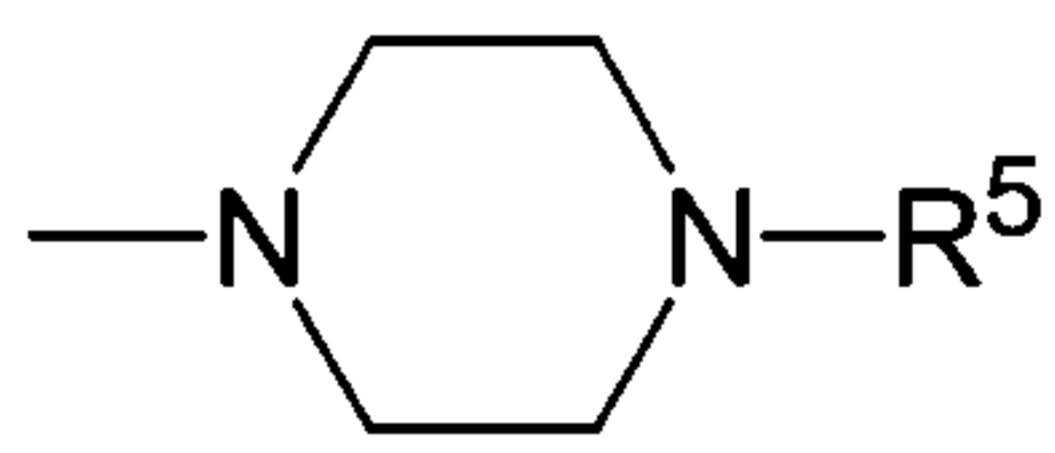
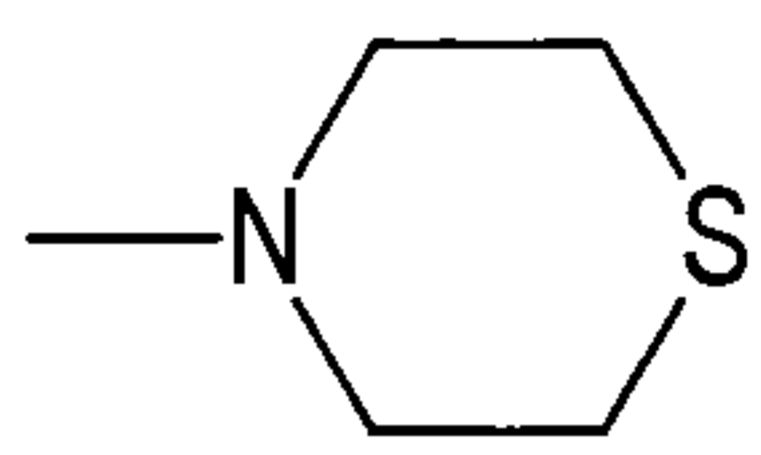
 ,
 ,
 ,

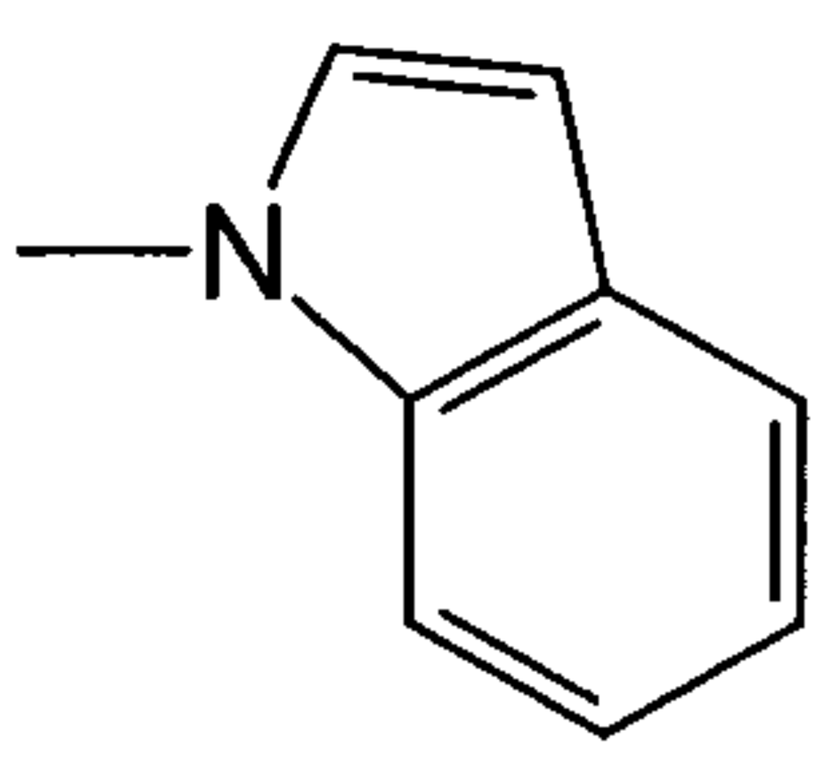
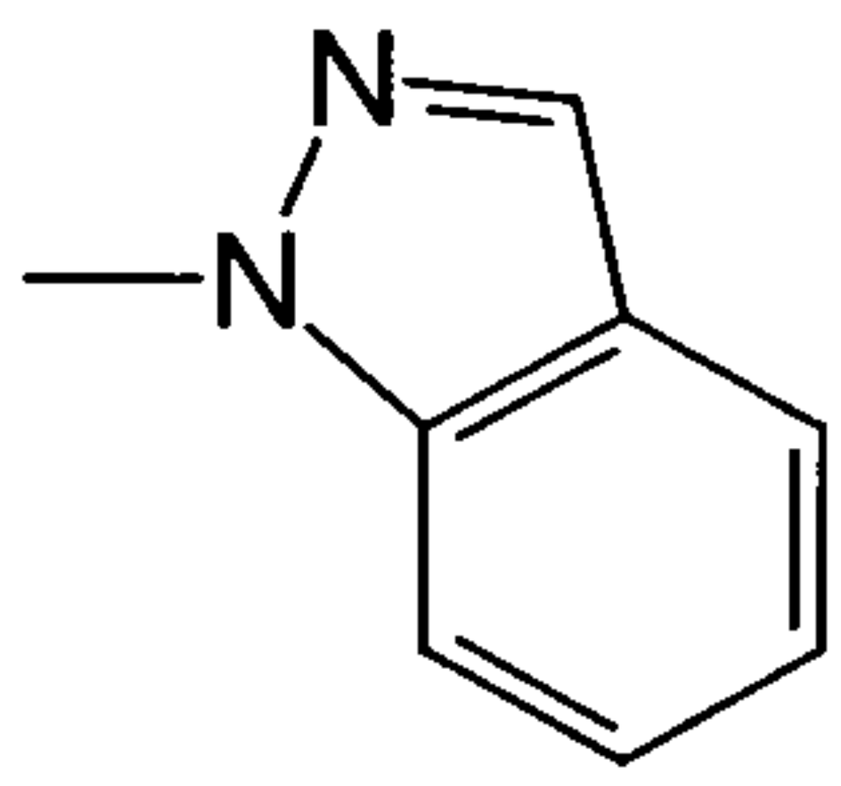
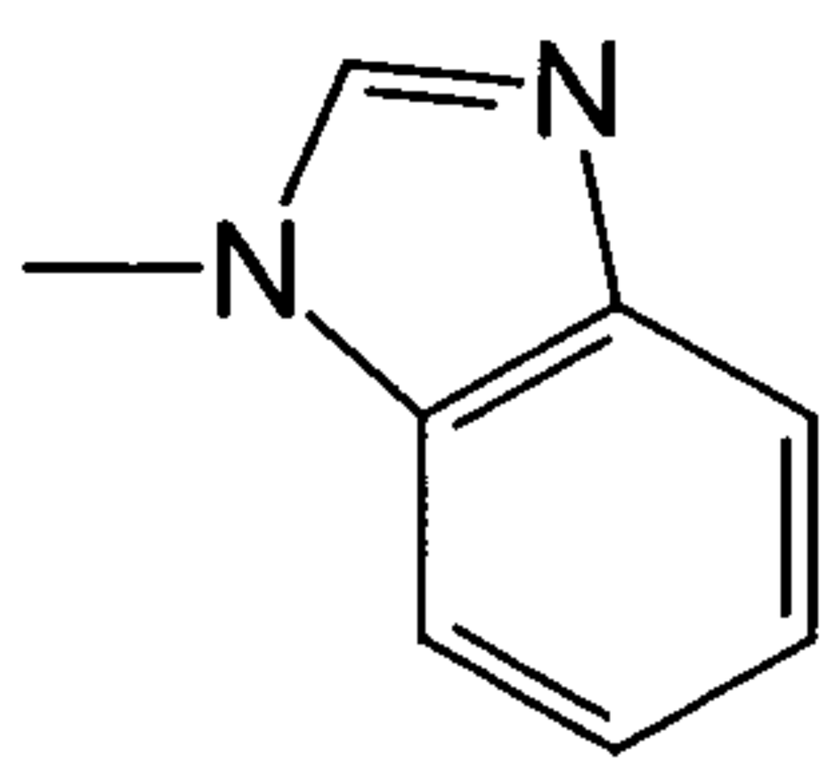
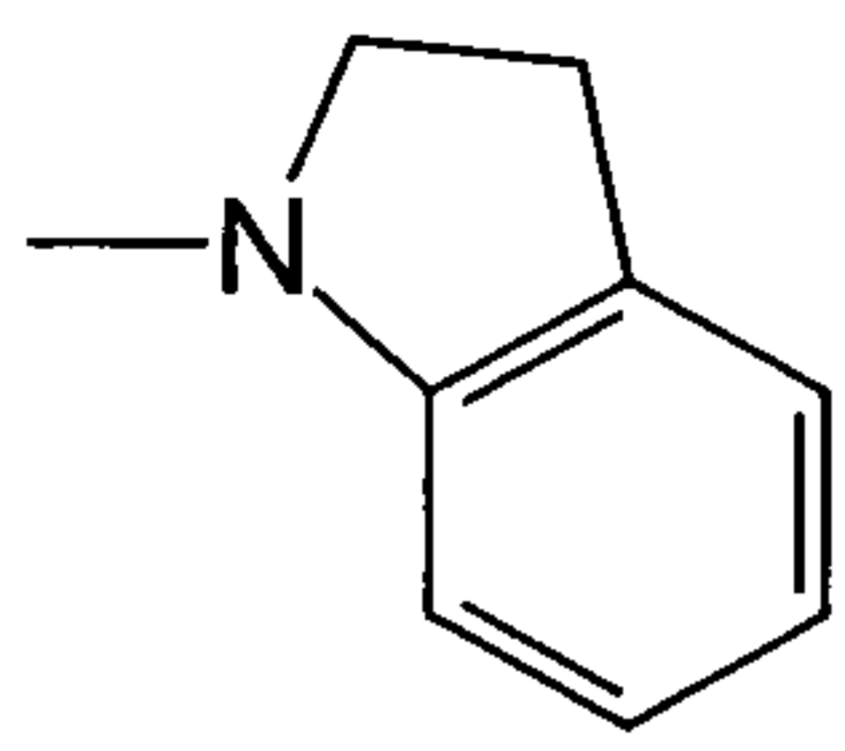
 ,
 ,
 ,

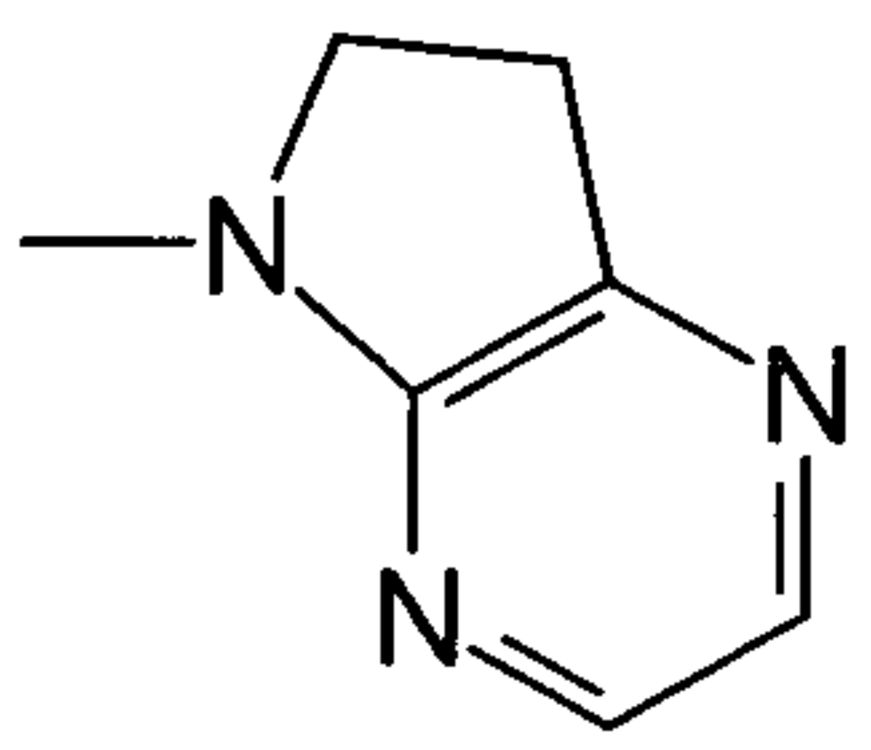
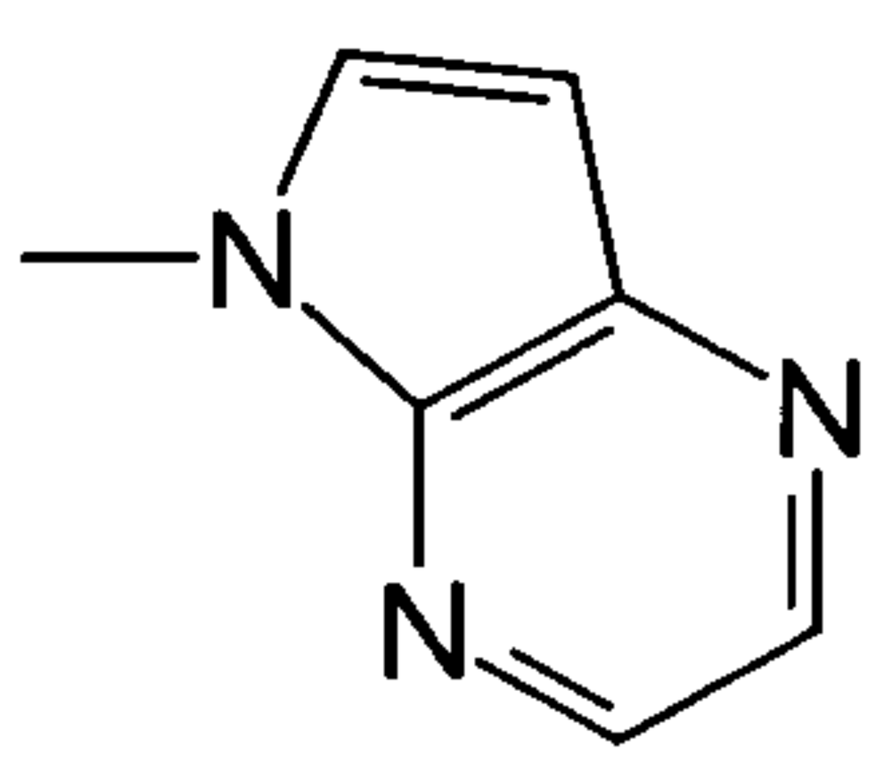
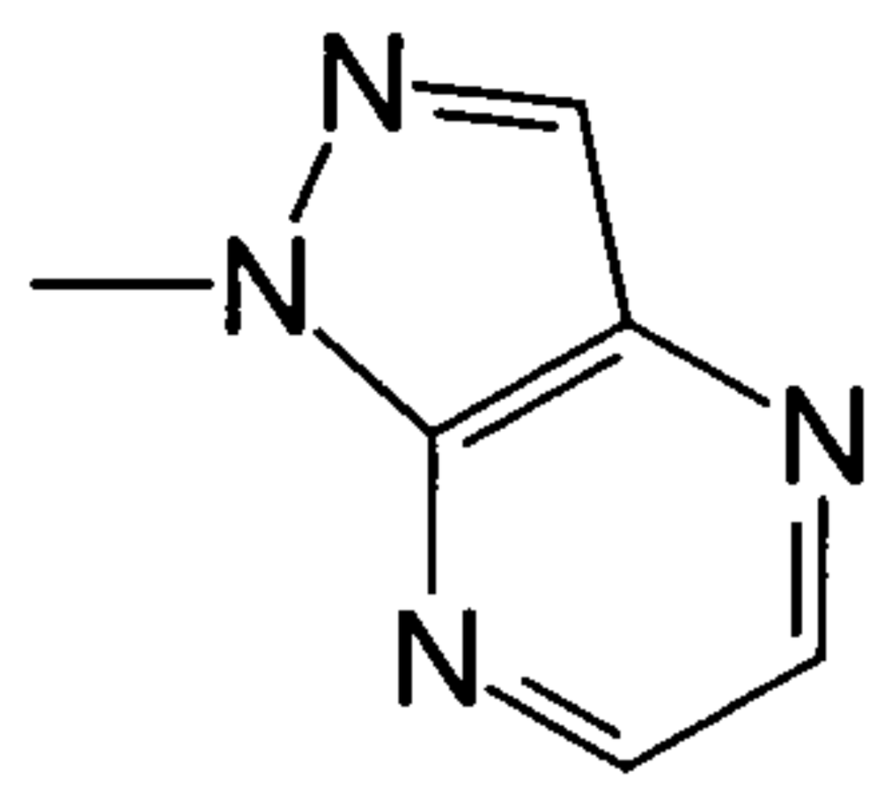
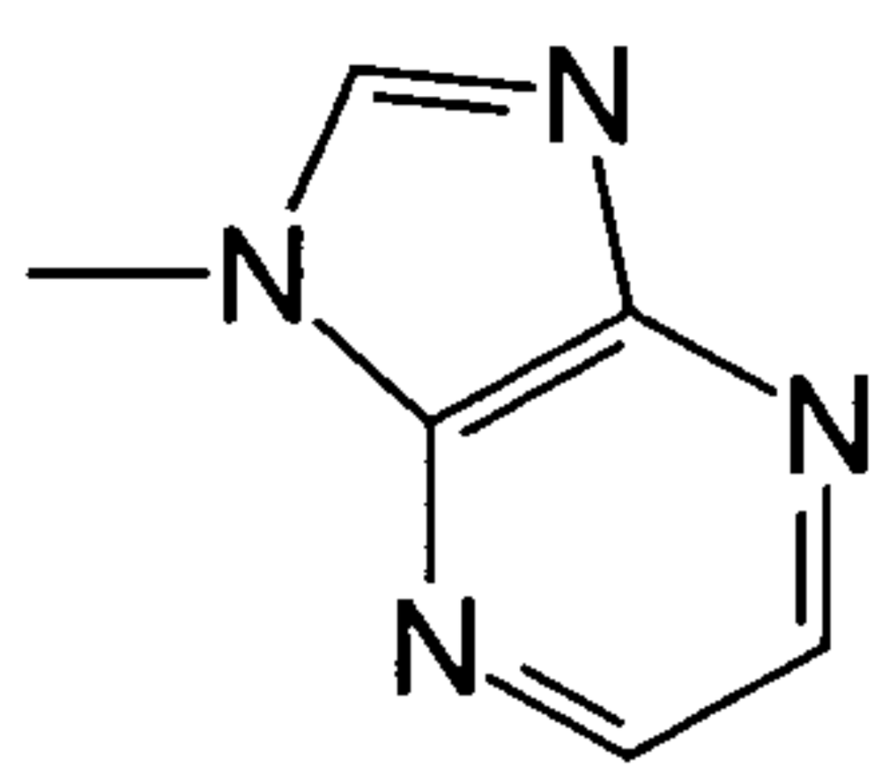
 ,  ,  ,

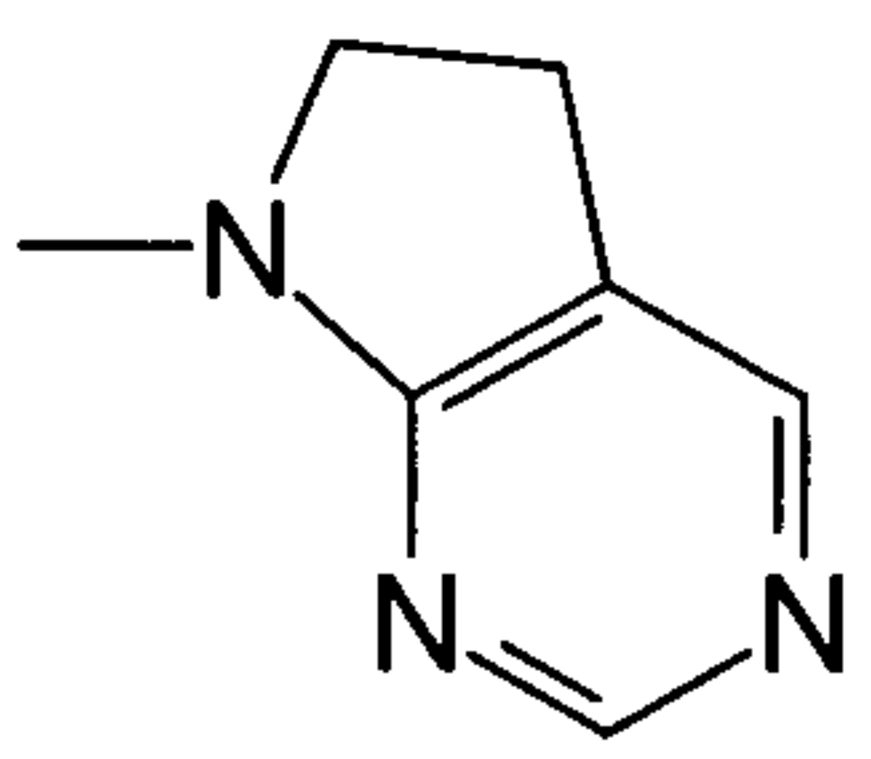
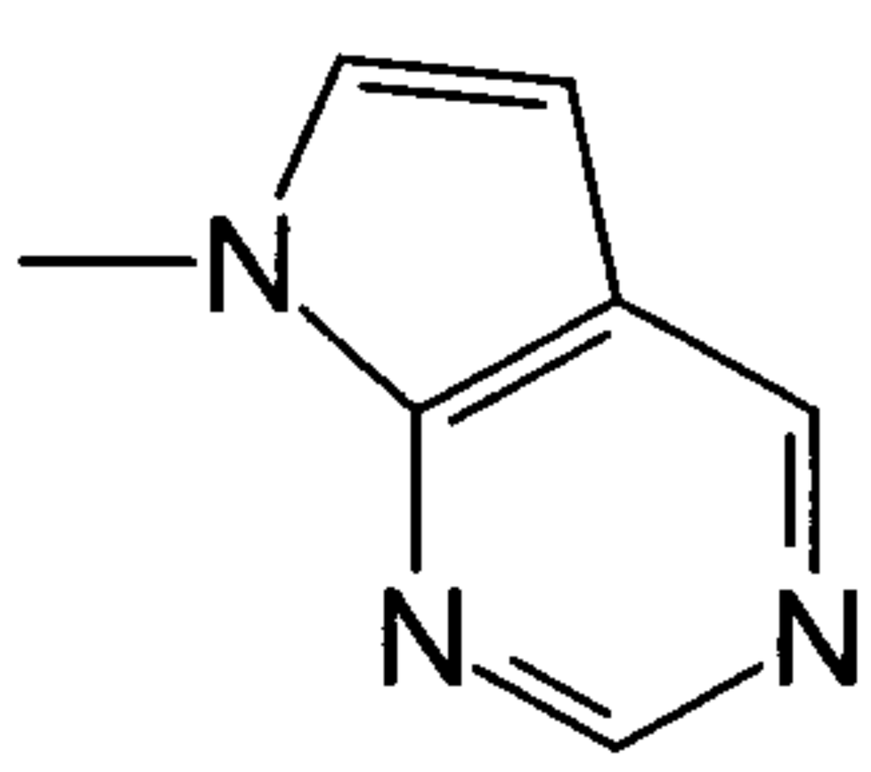
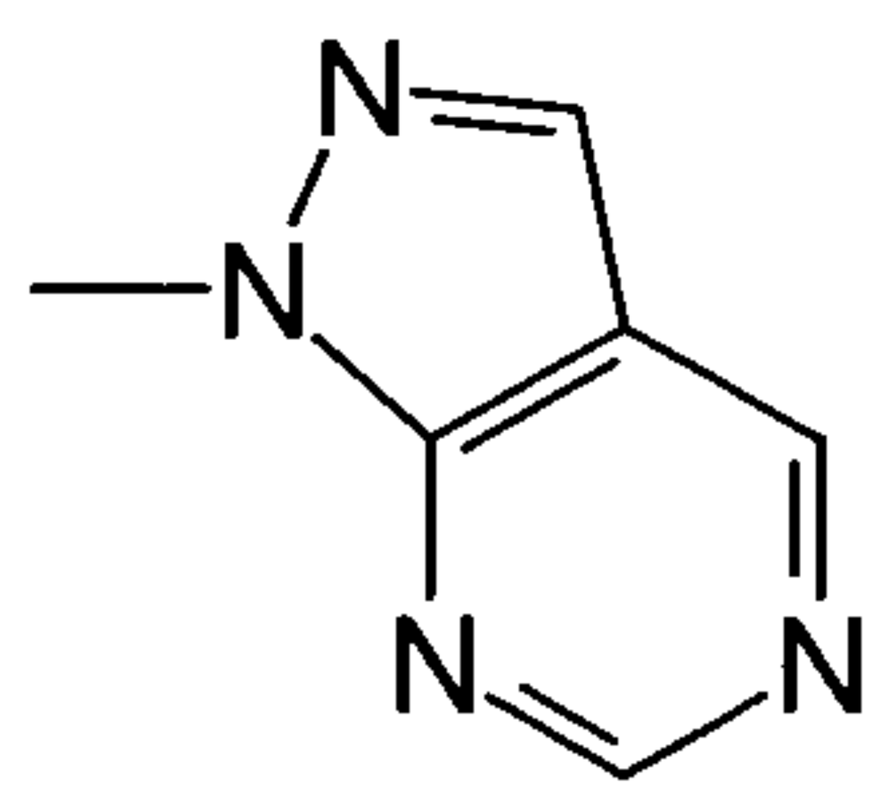
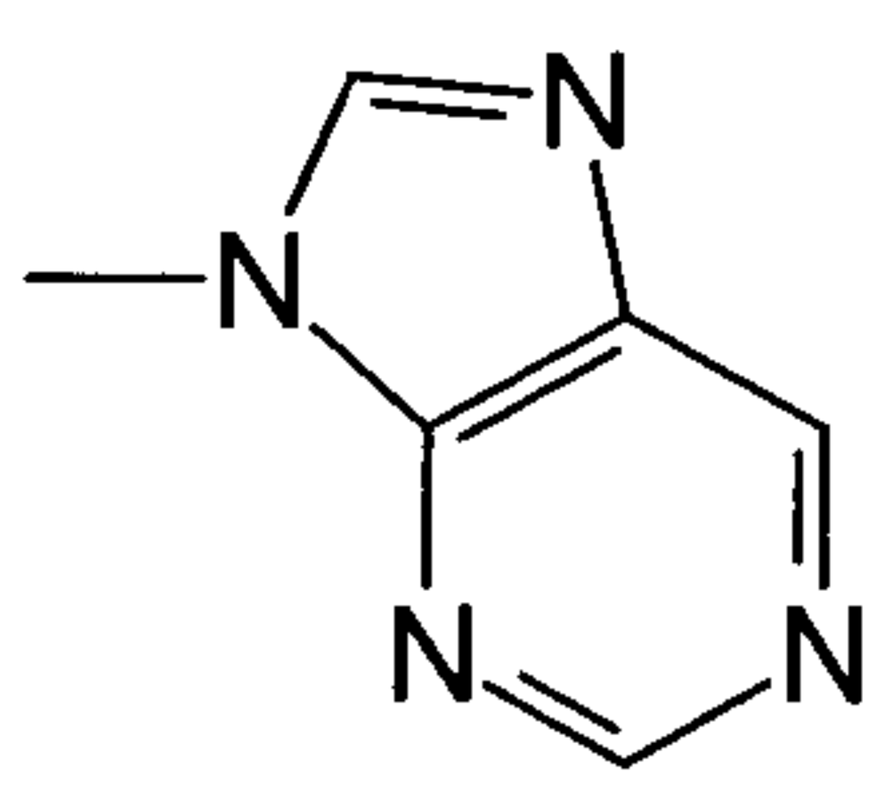
 ,  ,  ,

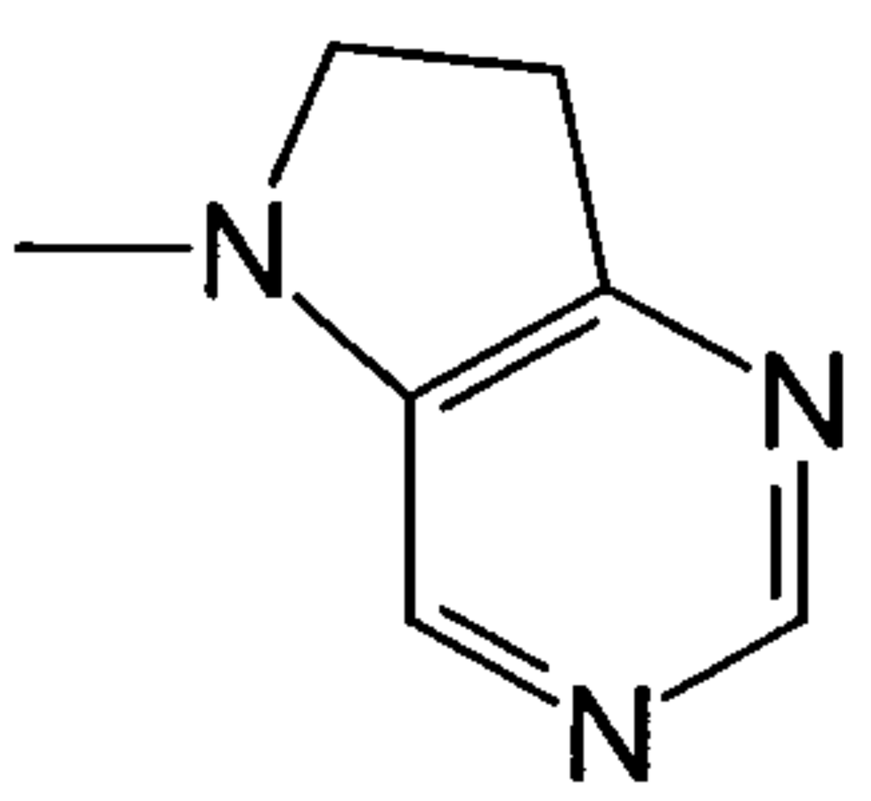
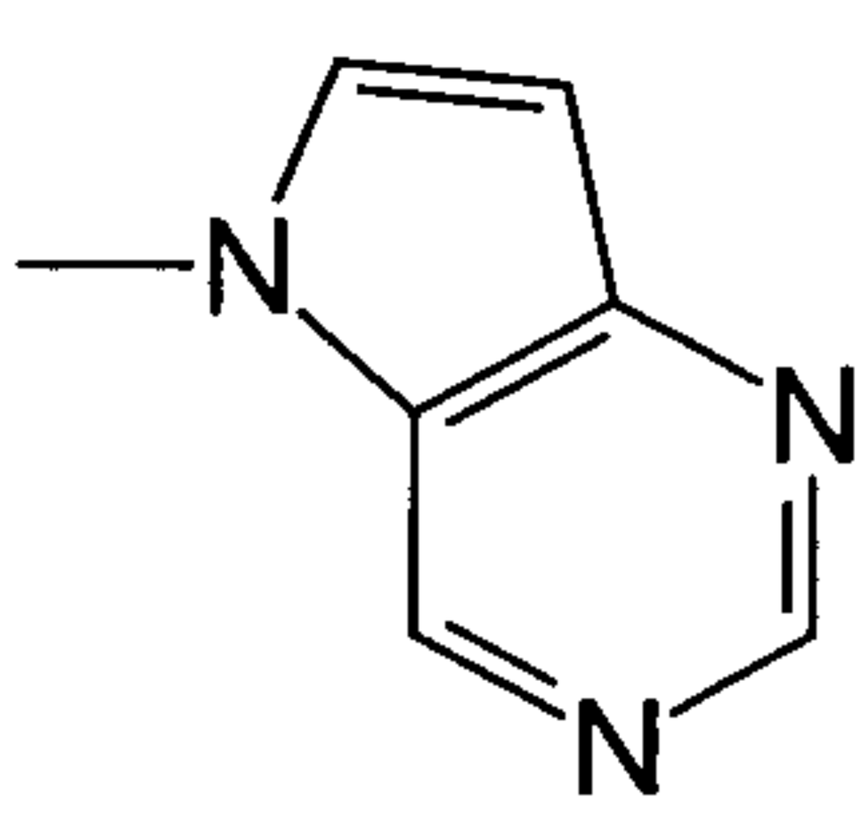
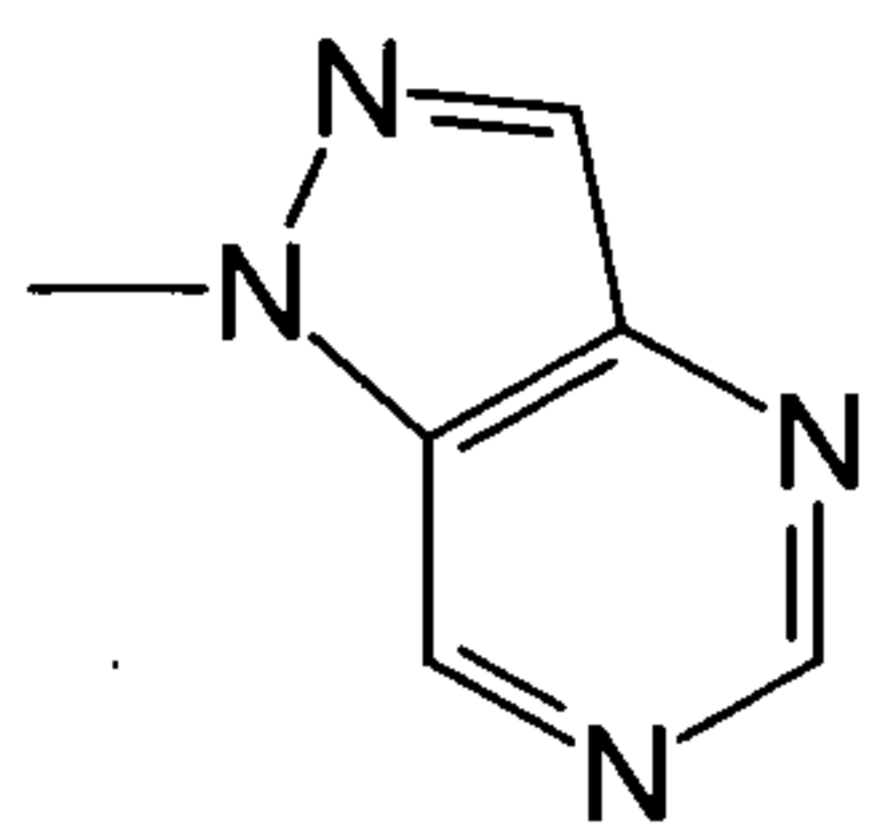
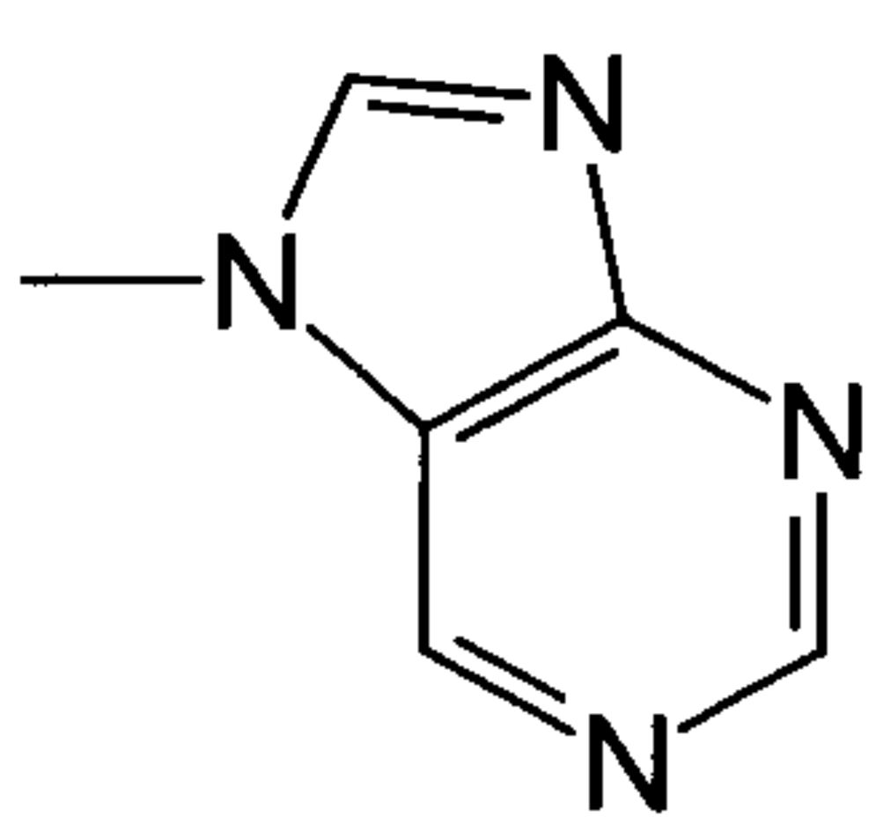
 ,  ,  ,  ,

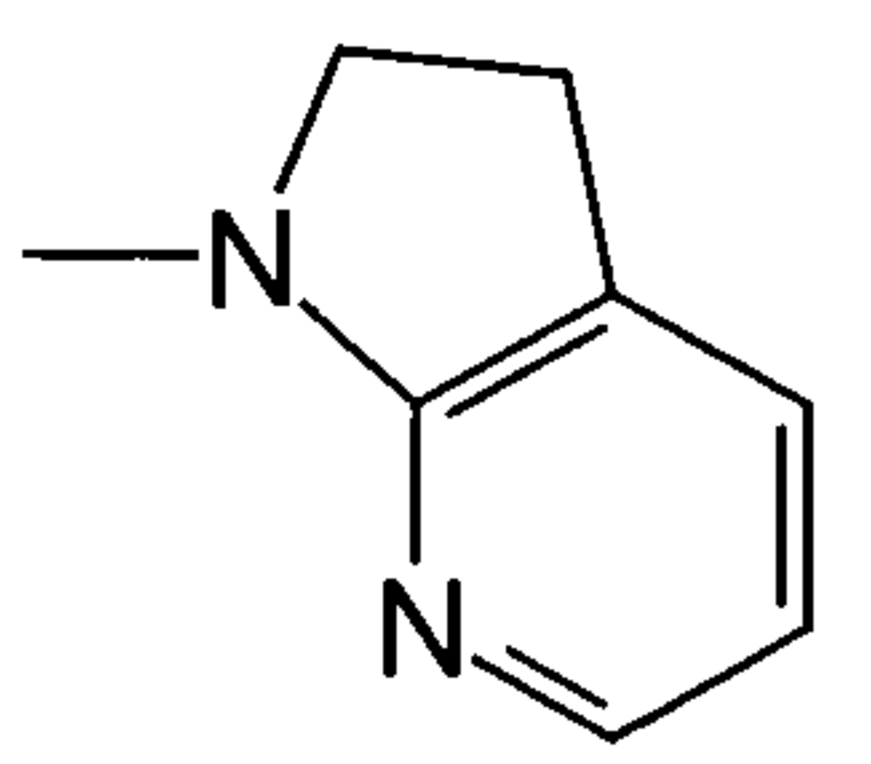
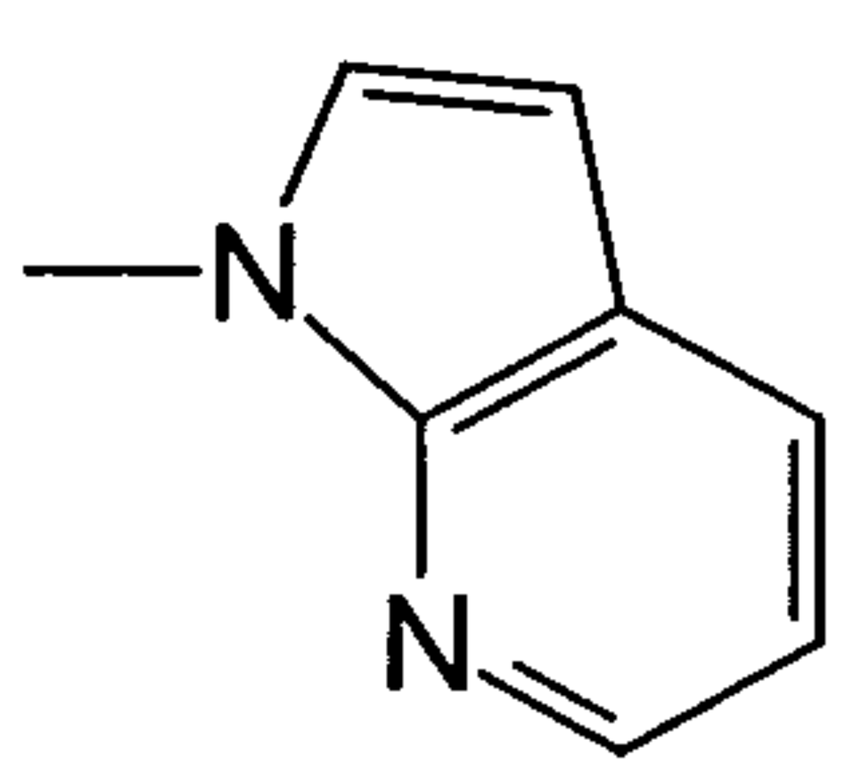
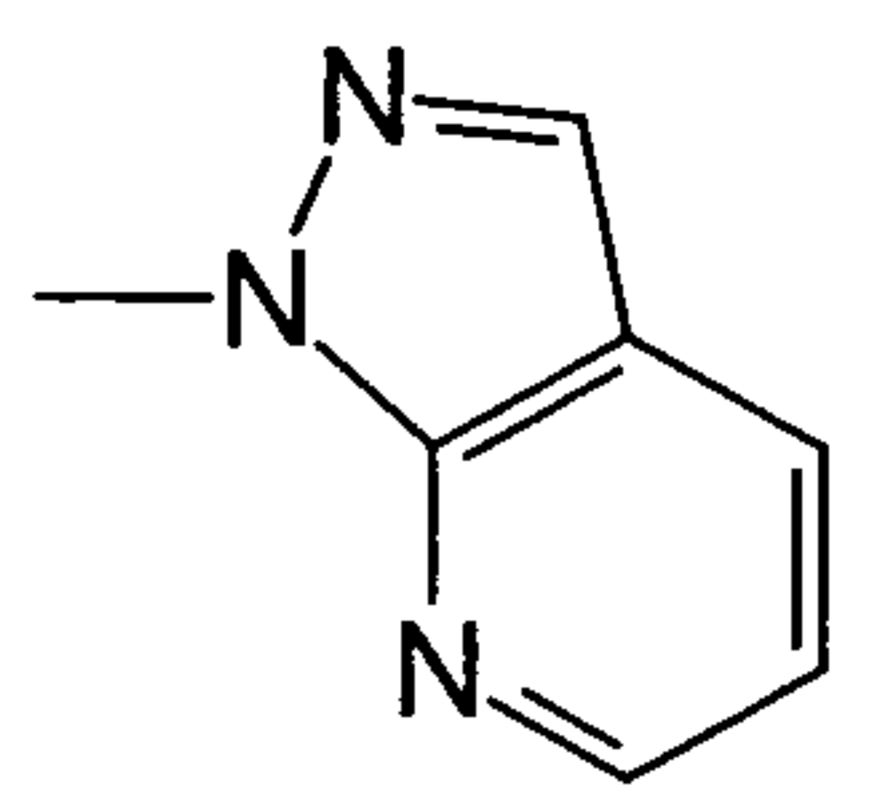
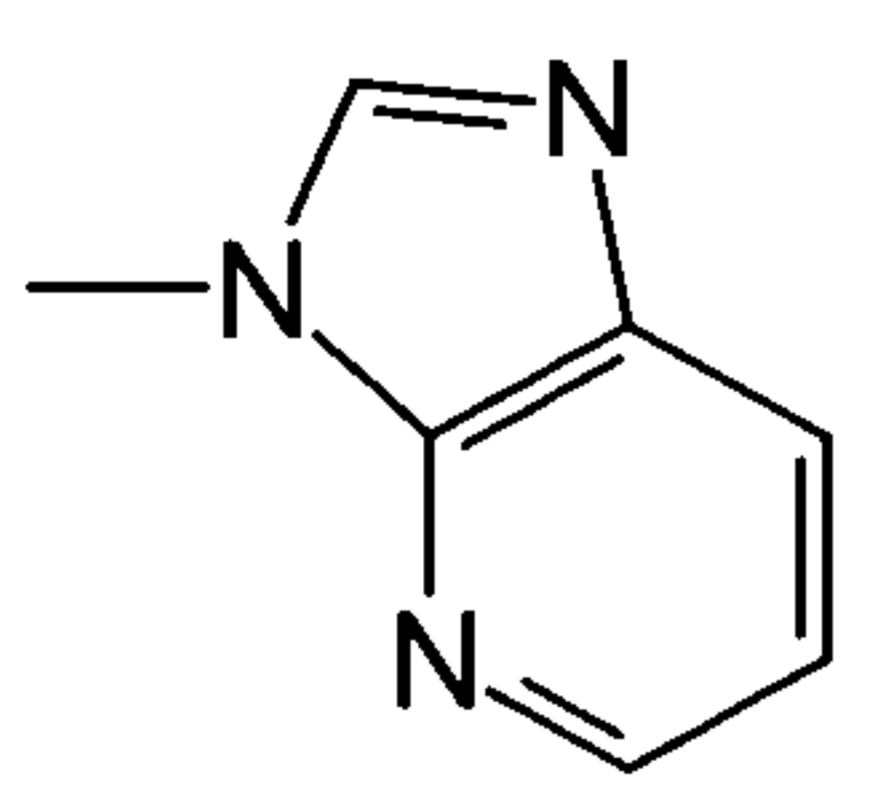
 ,  ,  ,  ,

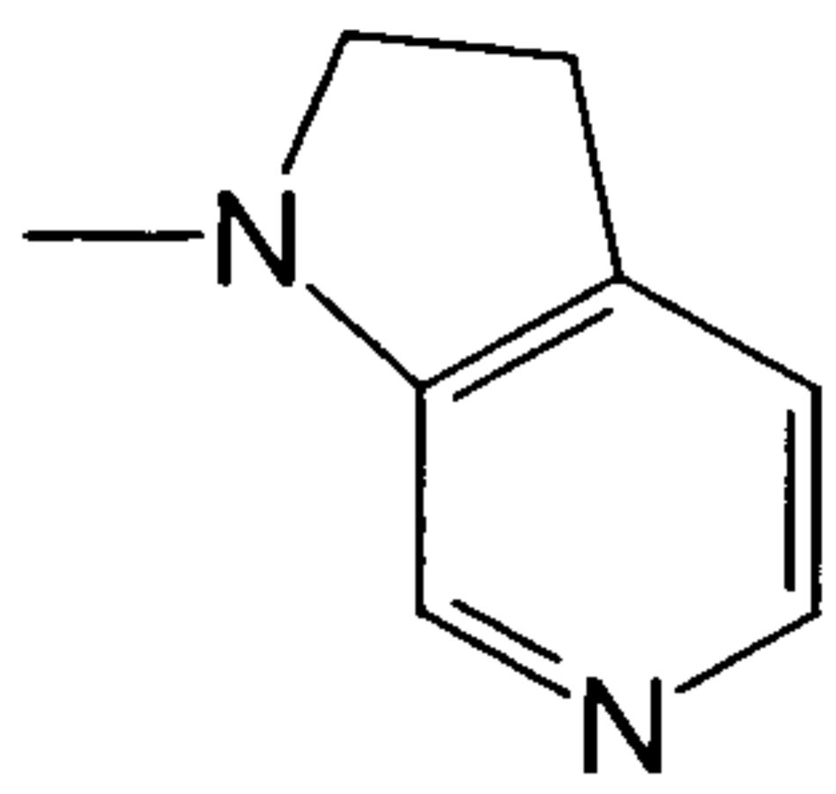
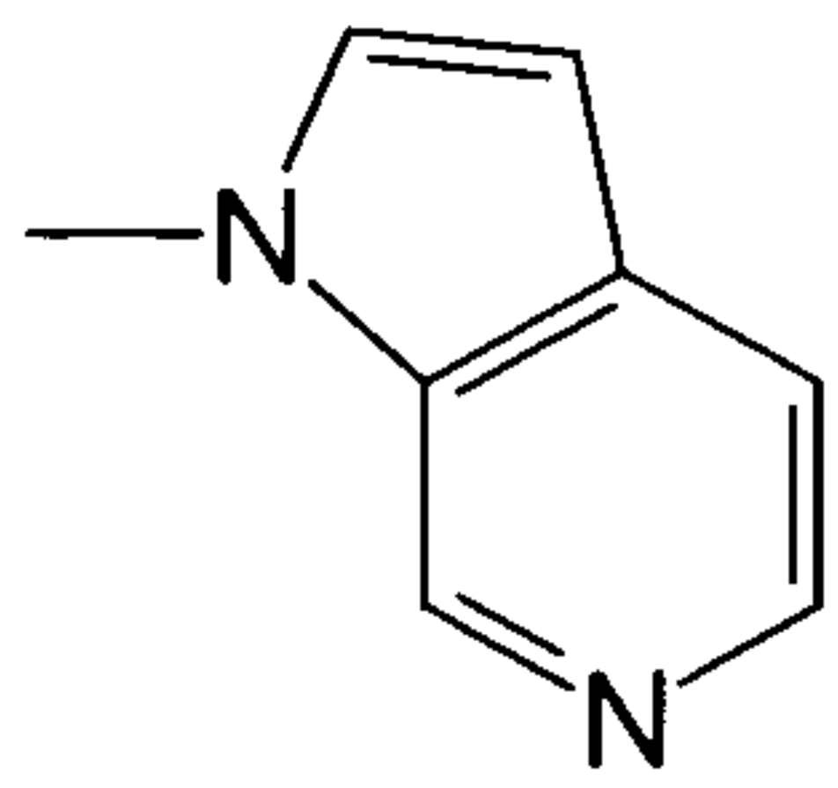
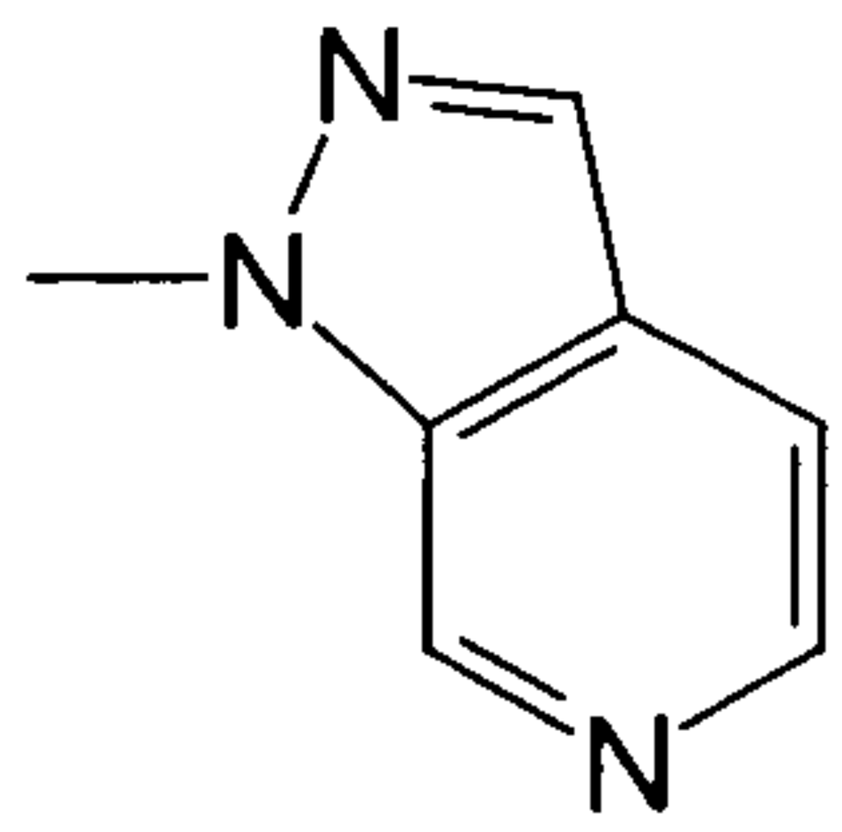
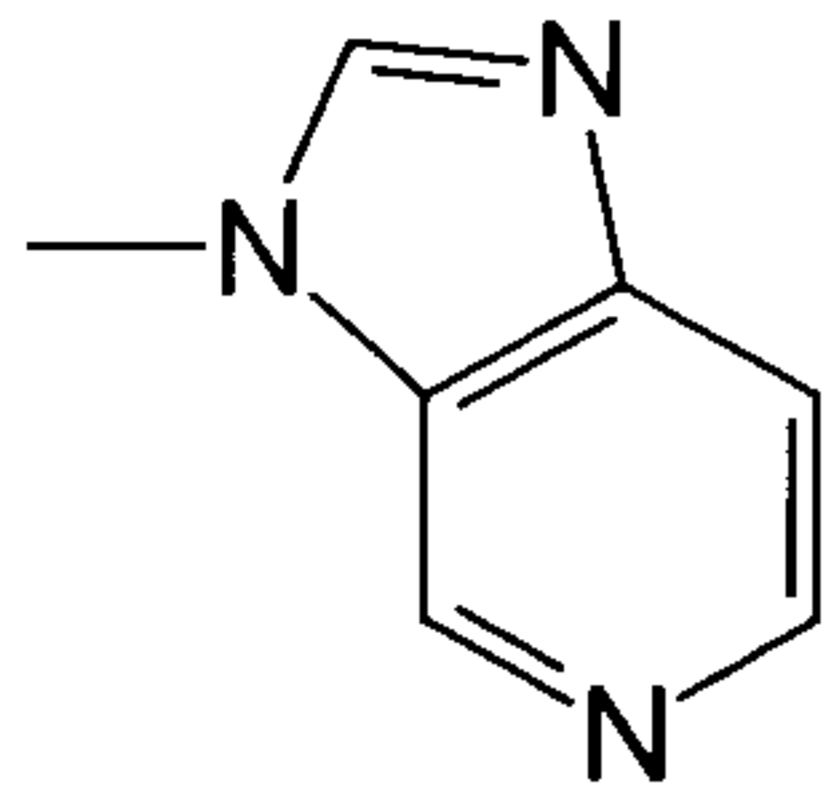
 ,  ,  ,  ,

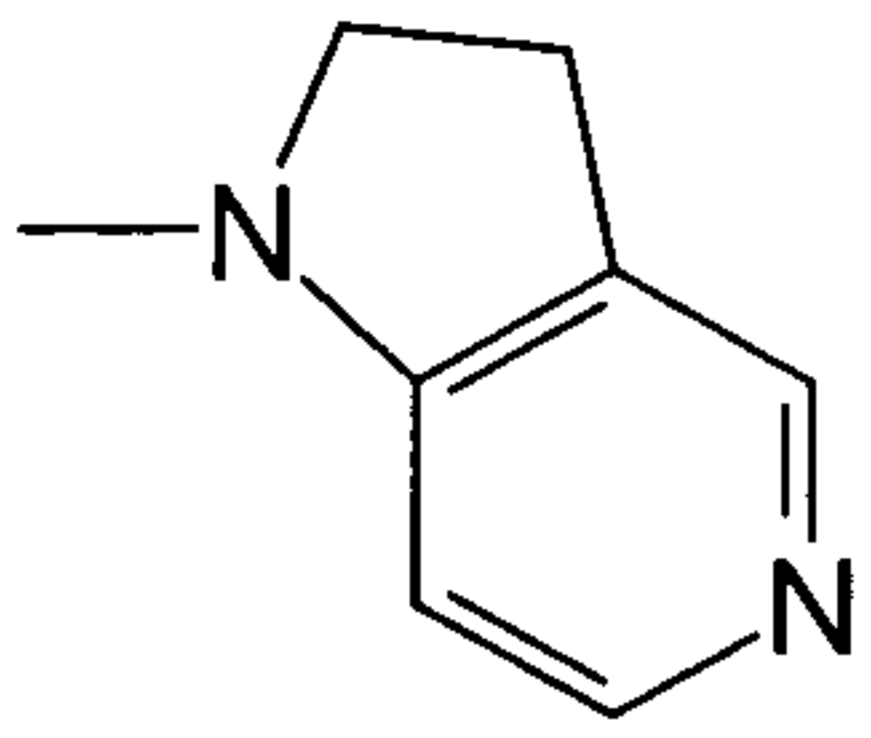
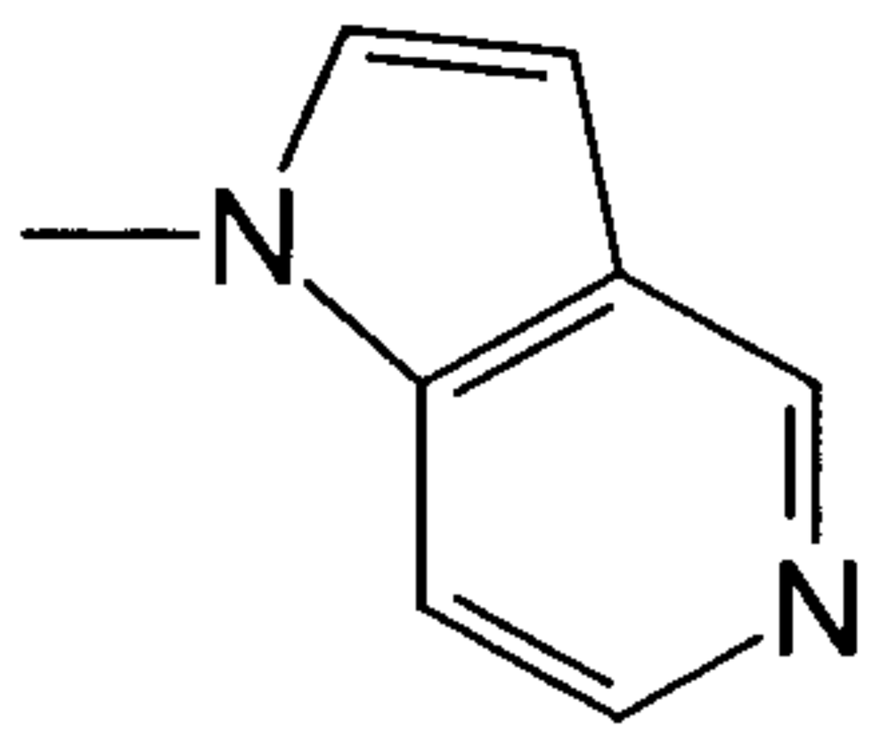
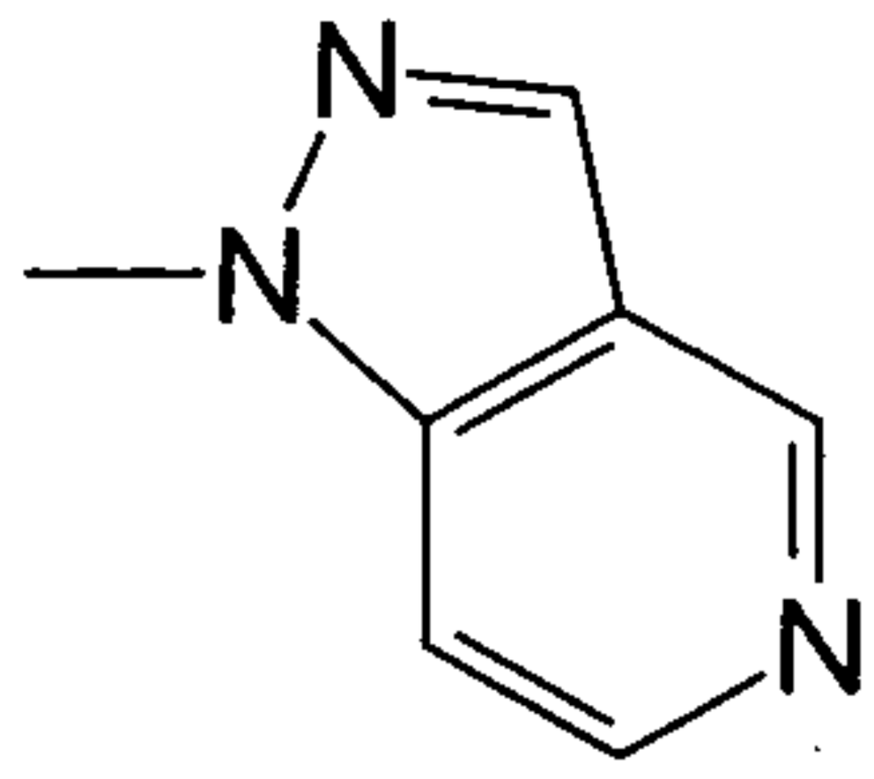
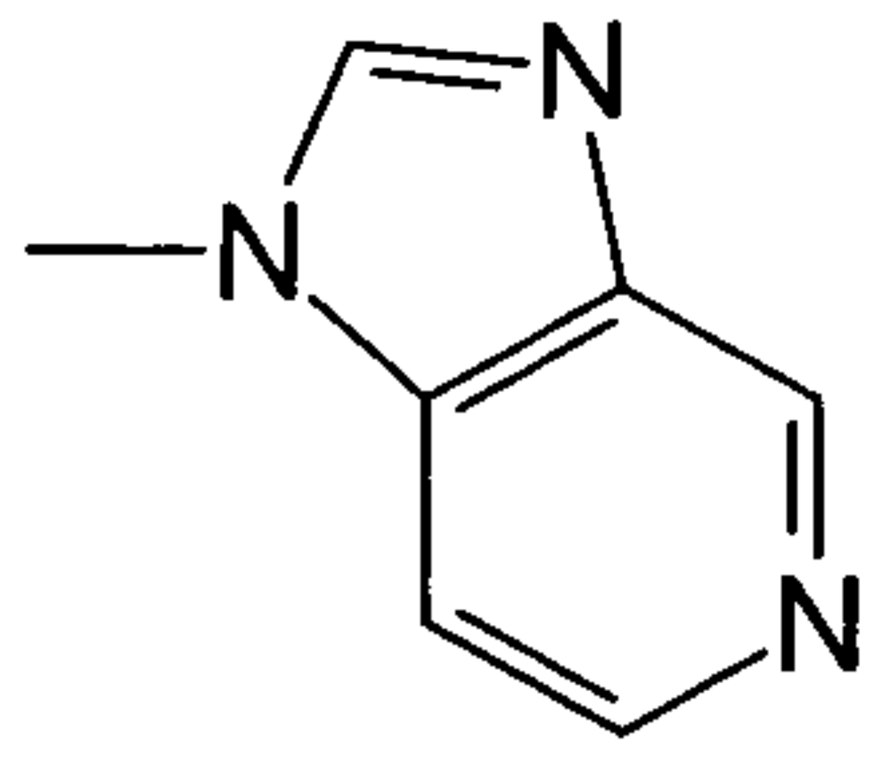
 ,  ,  ,  ,

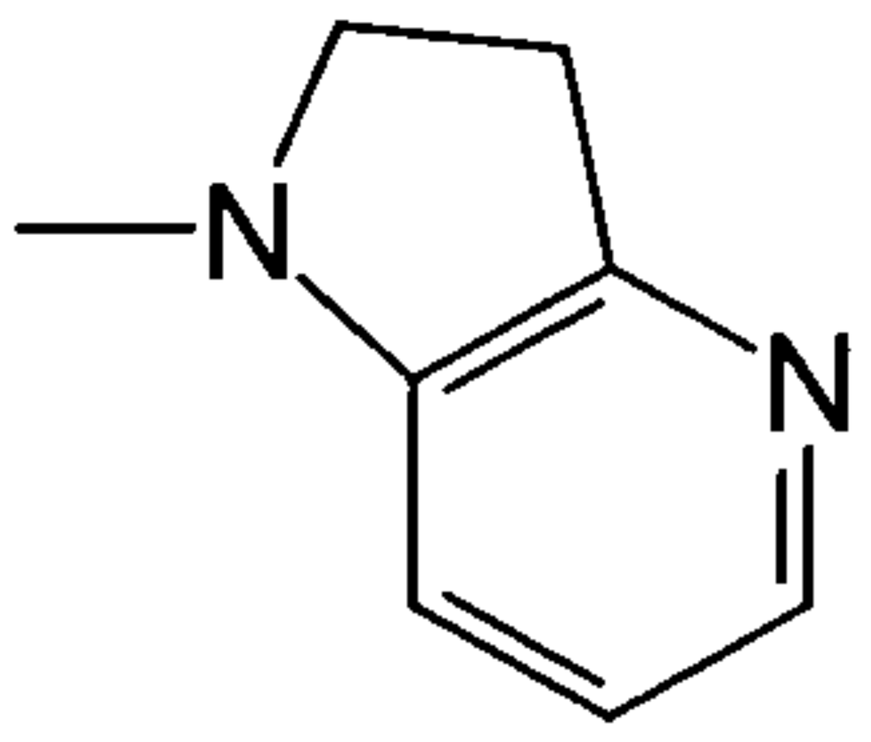
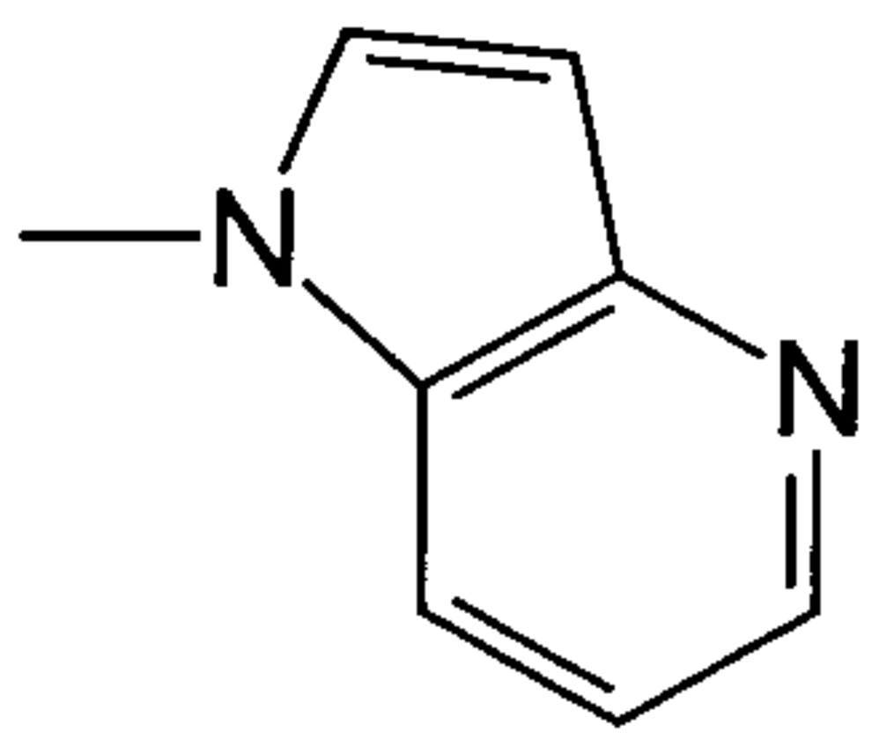
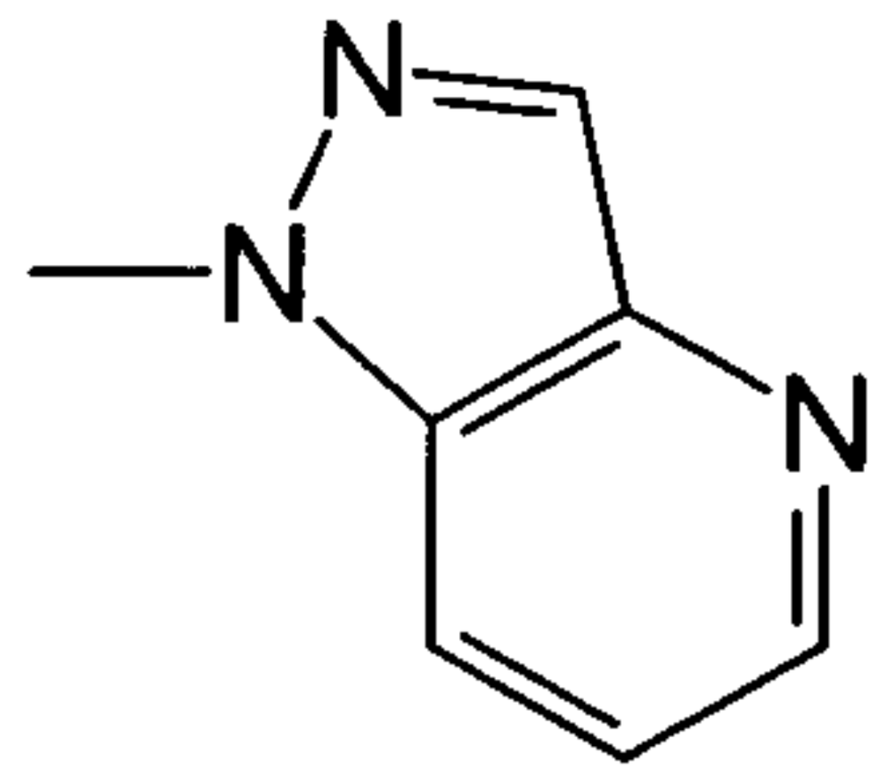
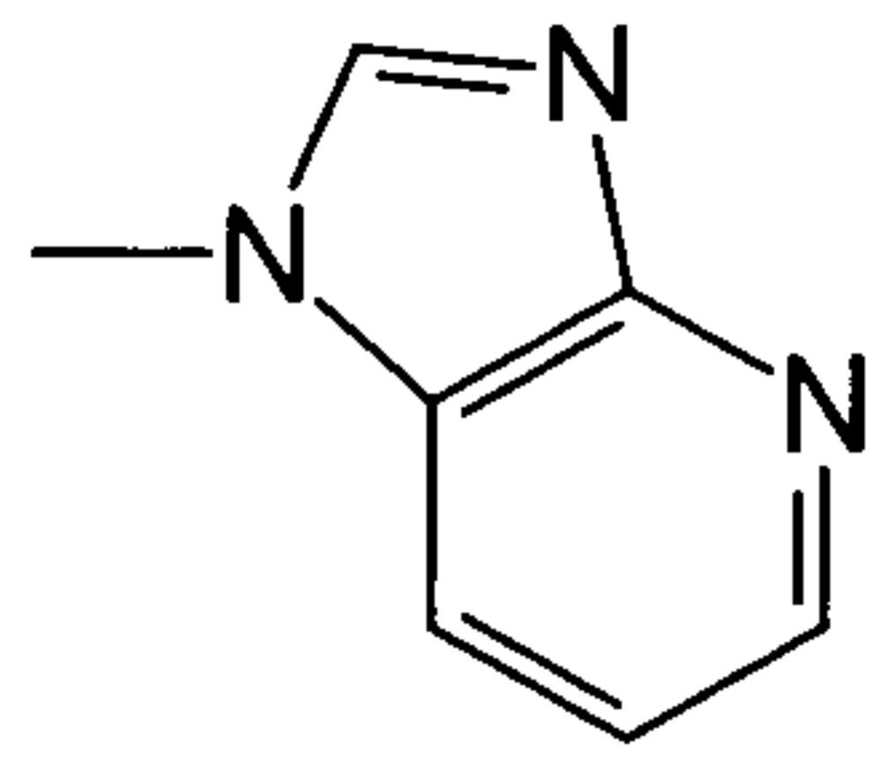
 ,  ,  ,  ,

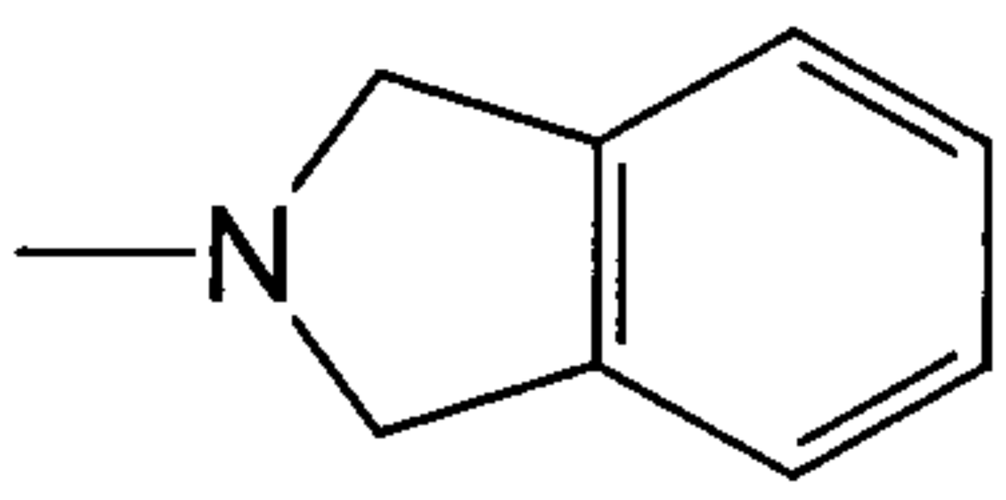
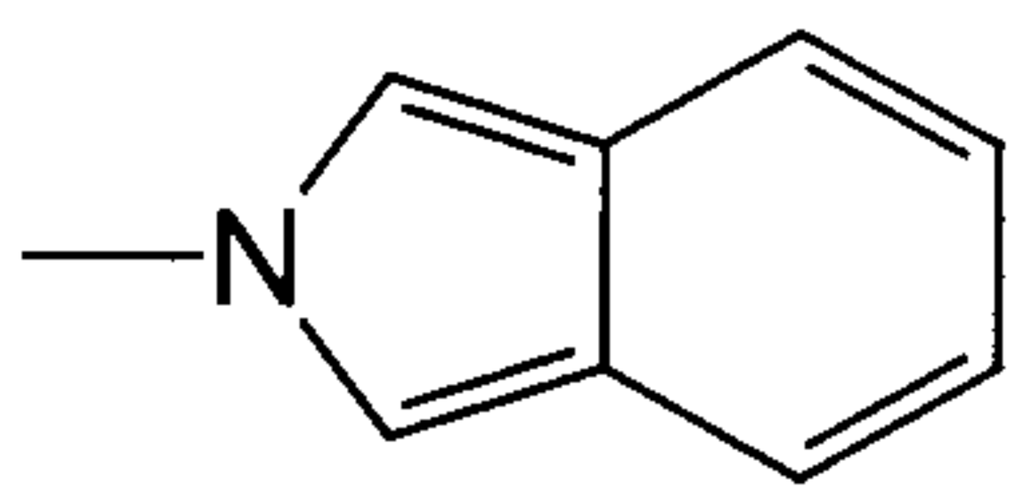
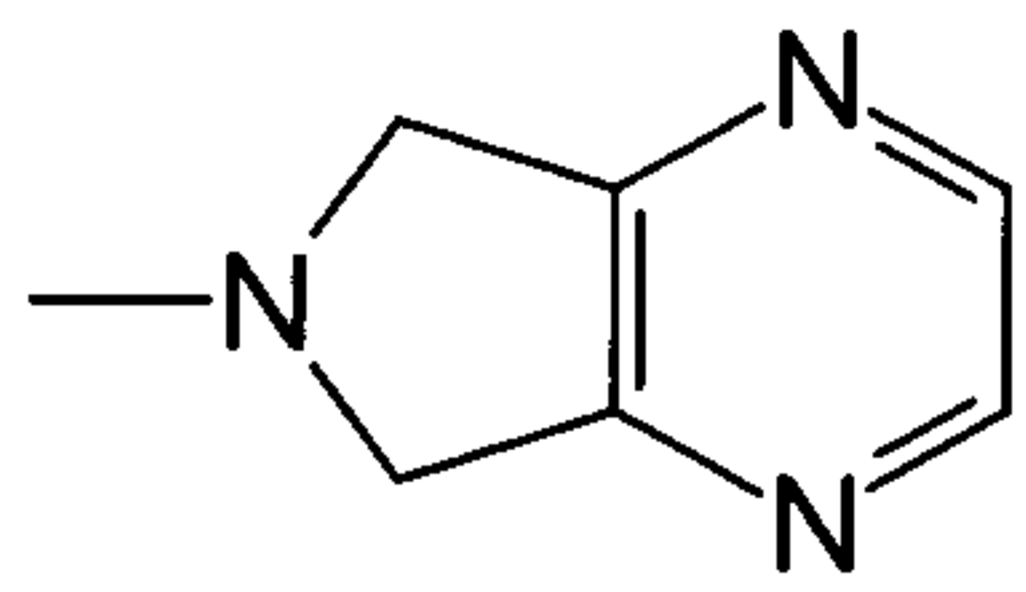
 ,  ,  ,  ,

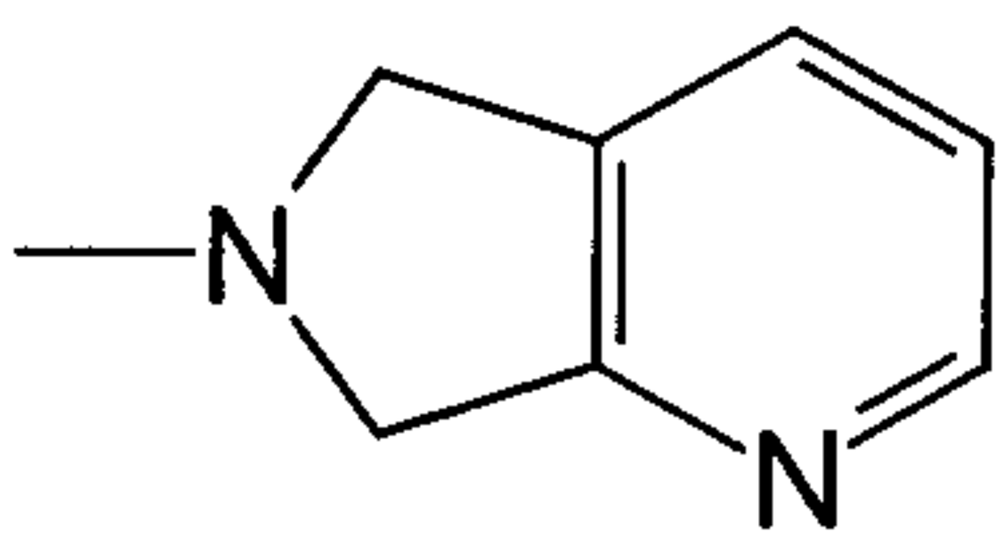
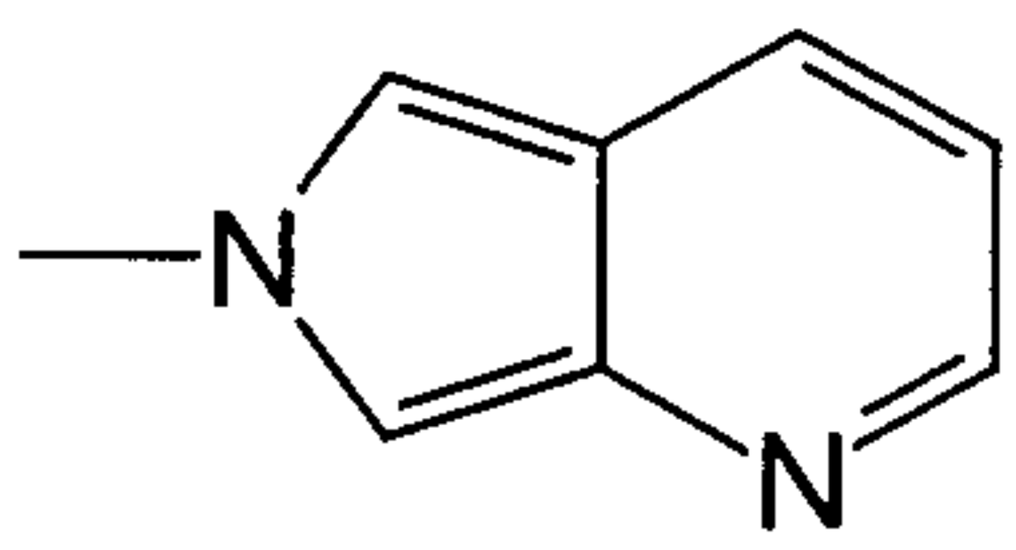
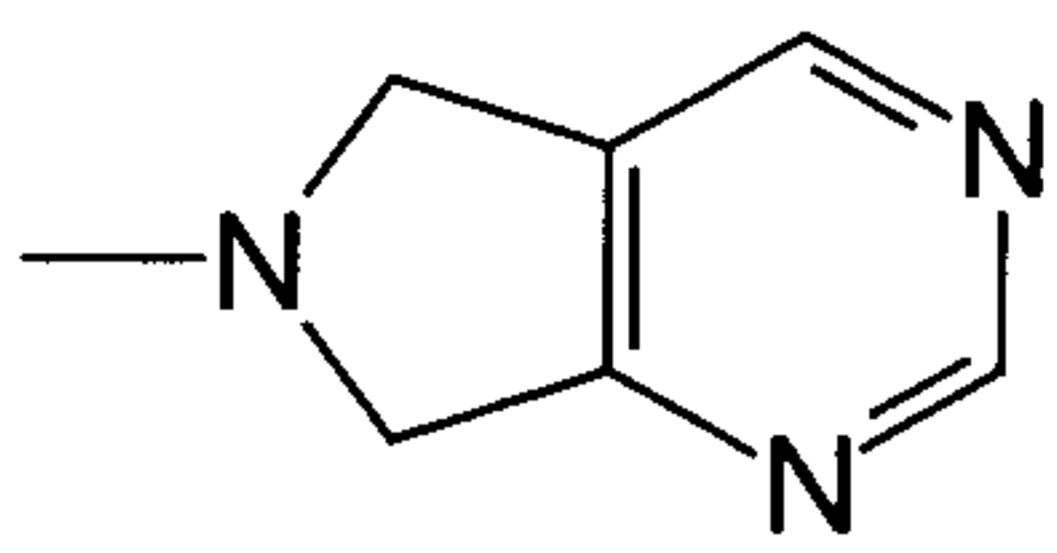
 ,  ,  ,  ,

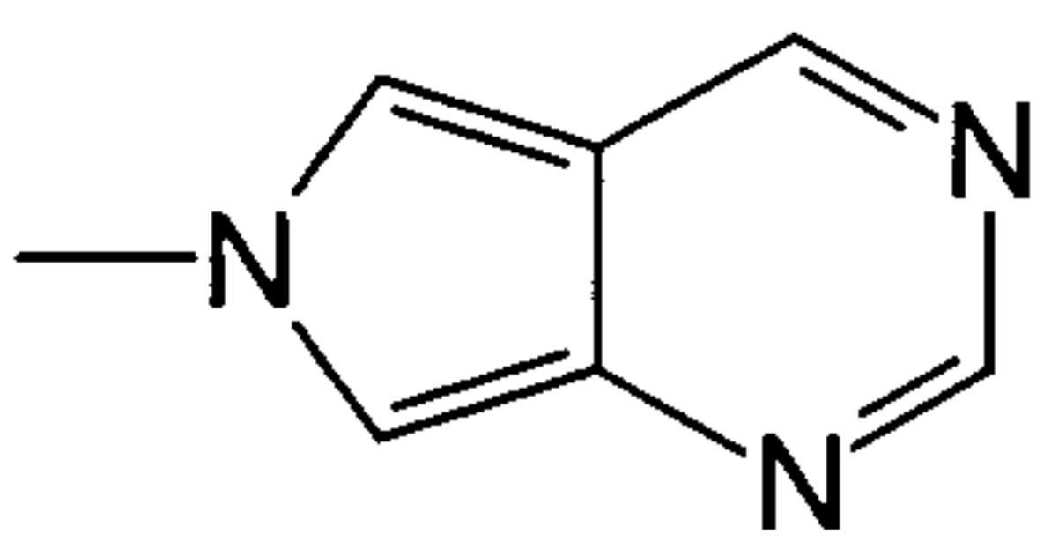
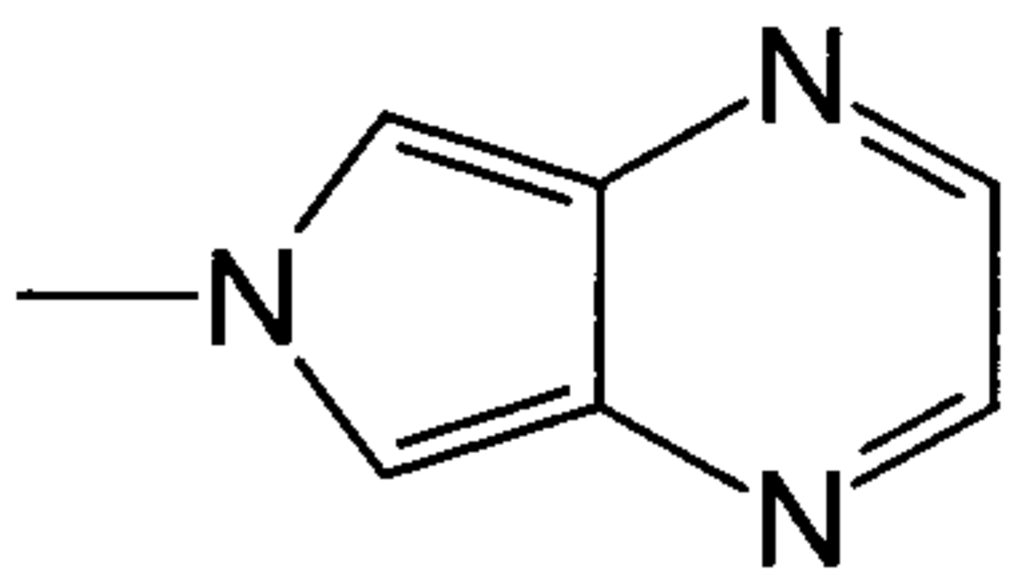
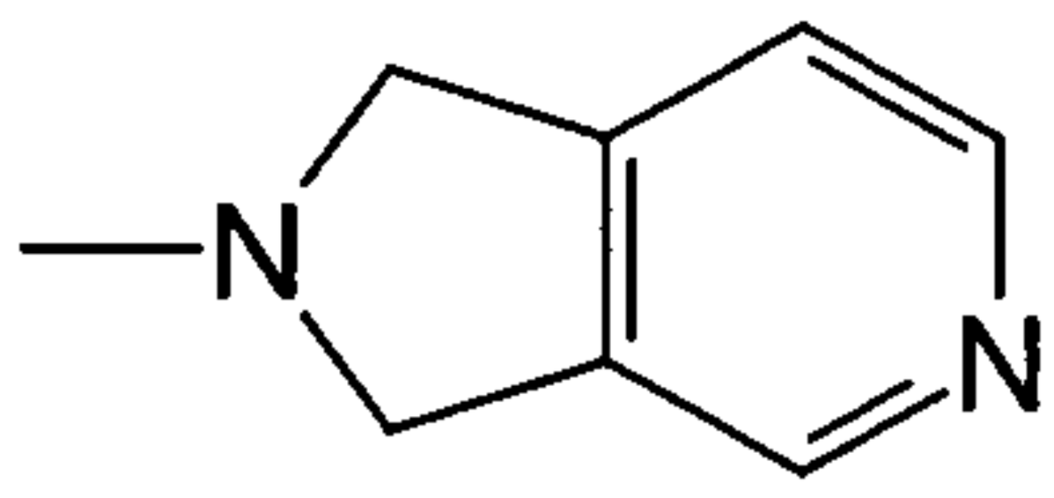
 ,  ,  ,  ,

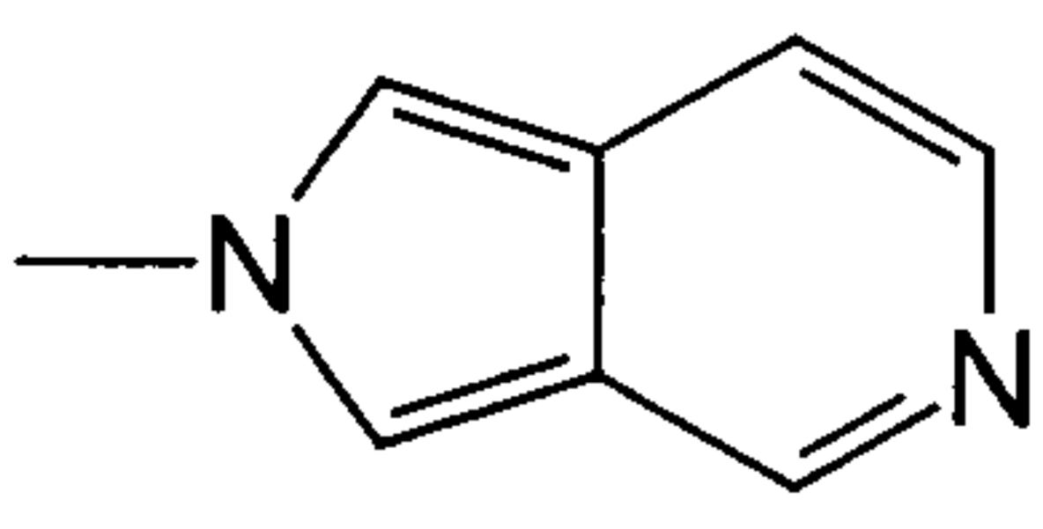
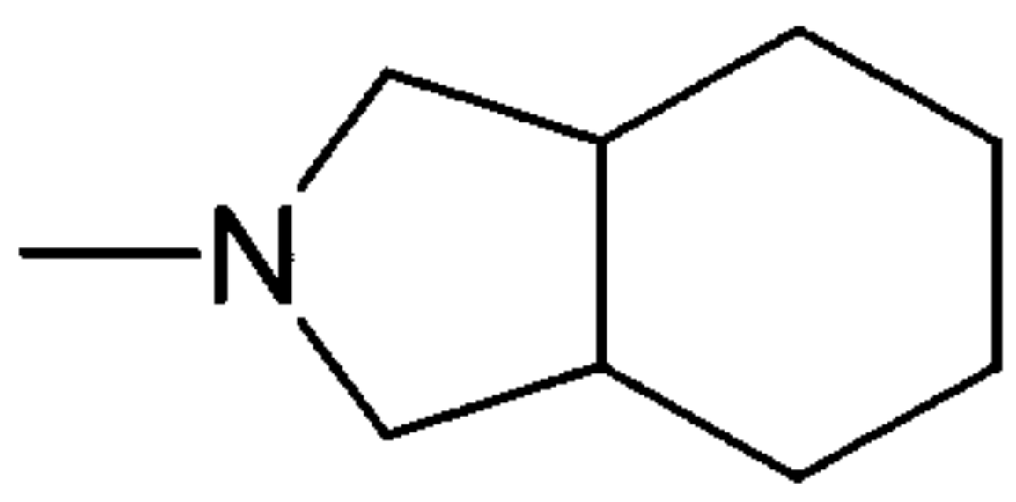
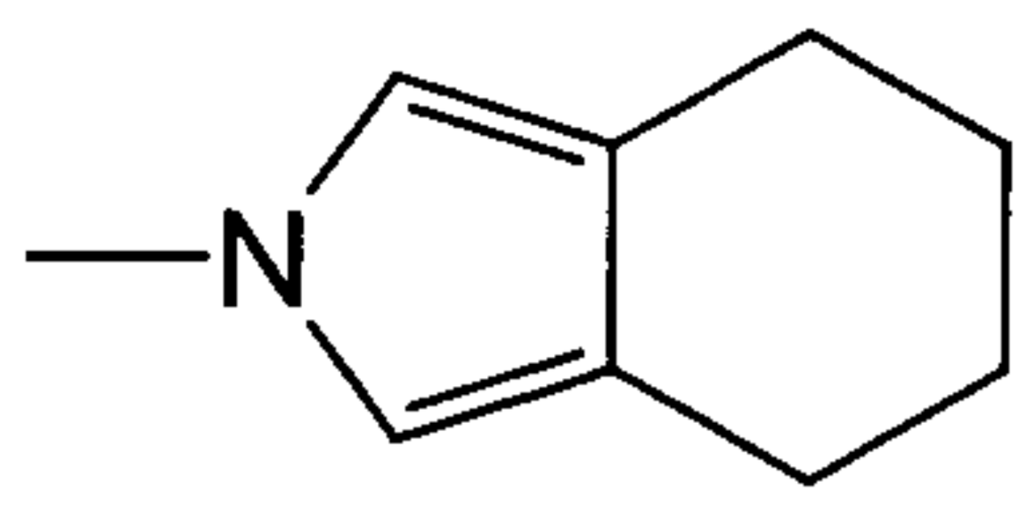
 ,  ,  ,  ,

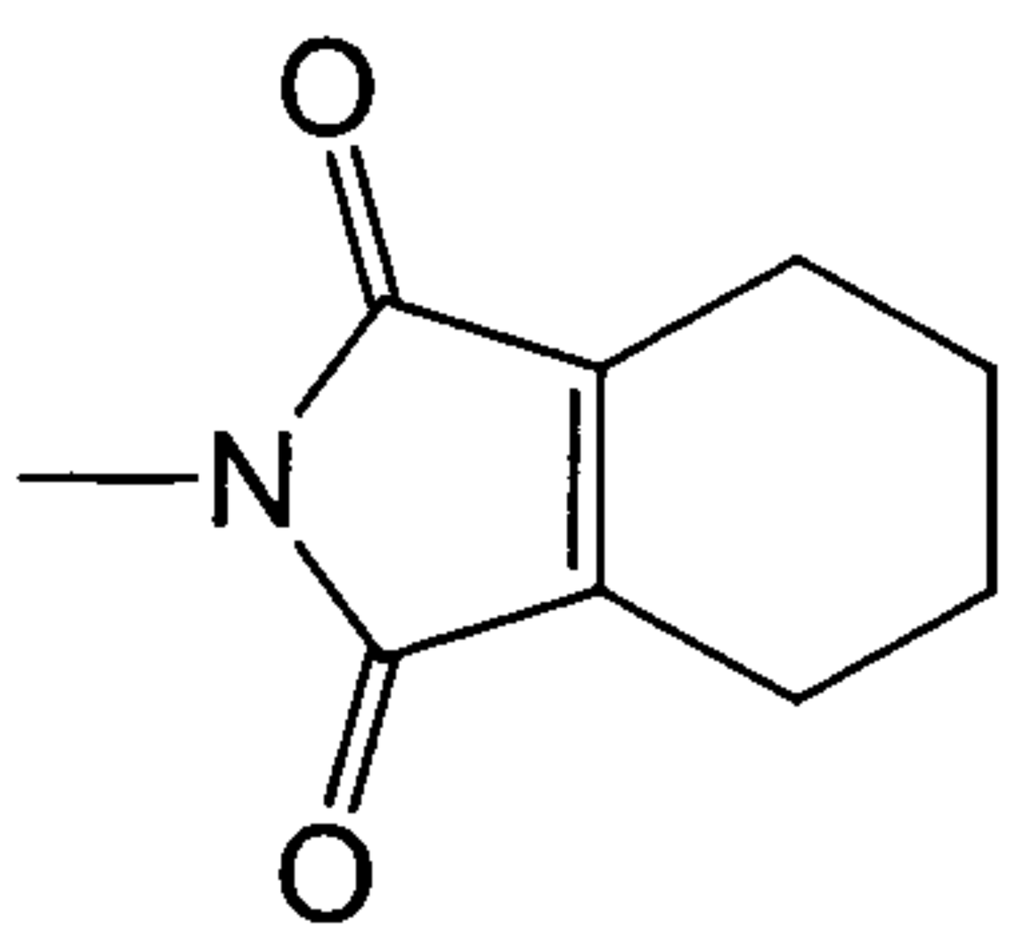
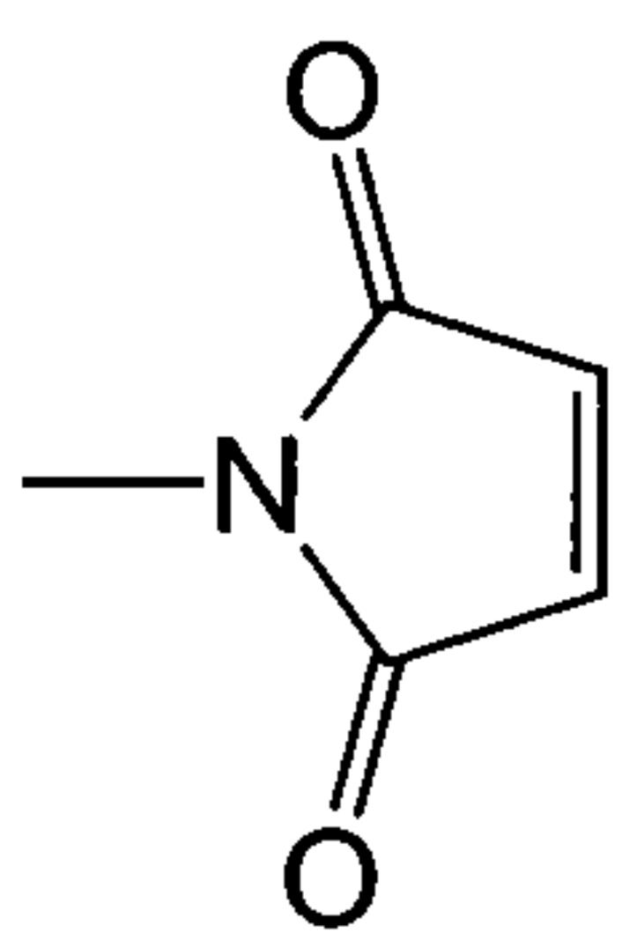
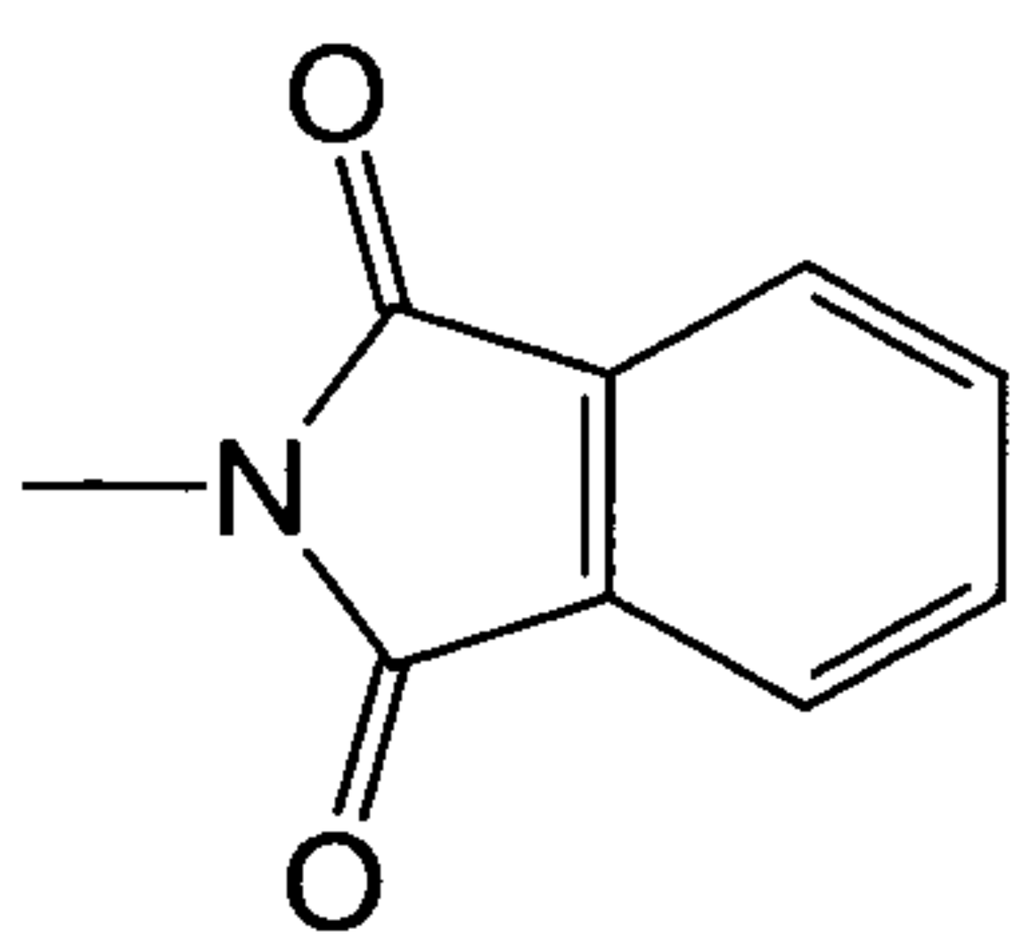
 ,  ,  ,  ,

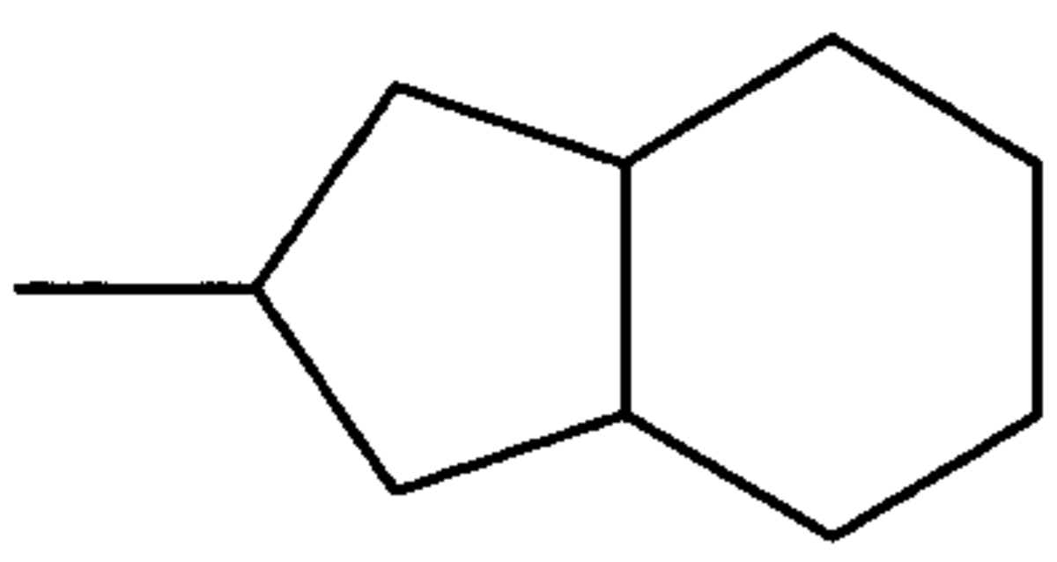
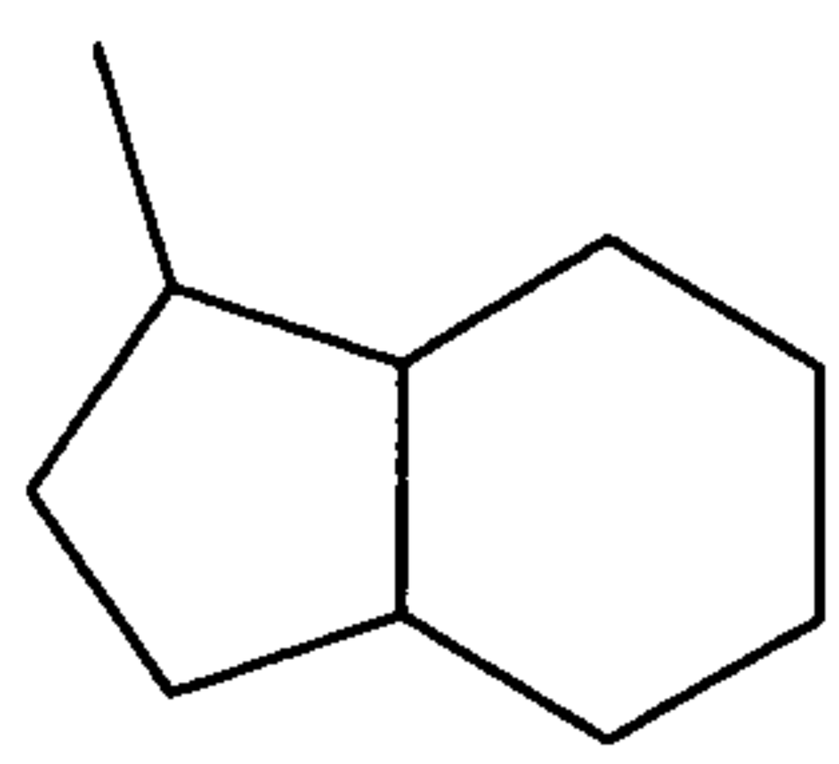
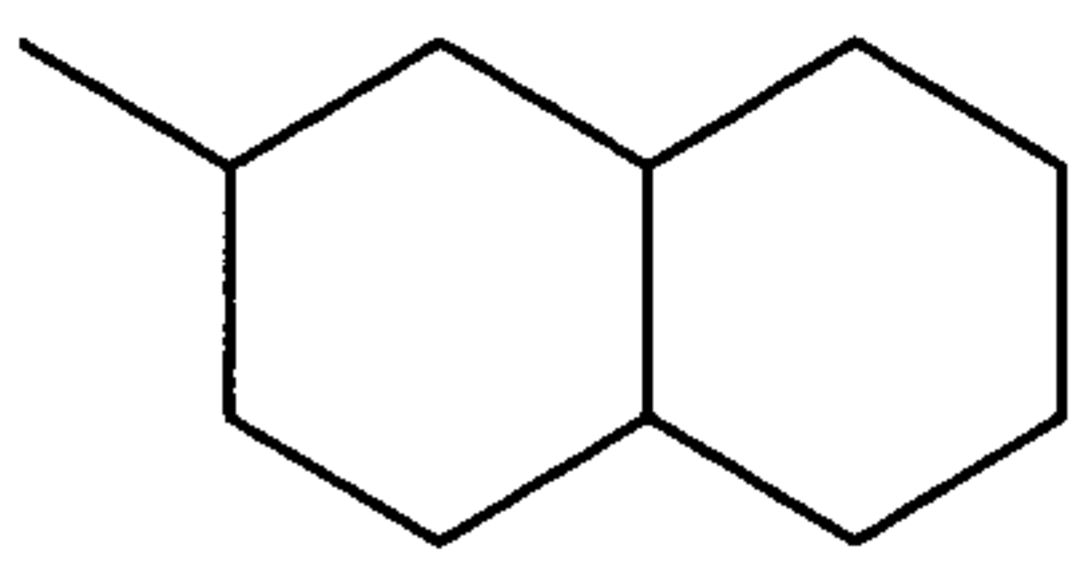
 ,  ,  ,

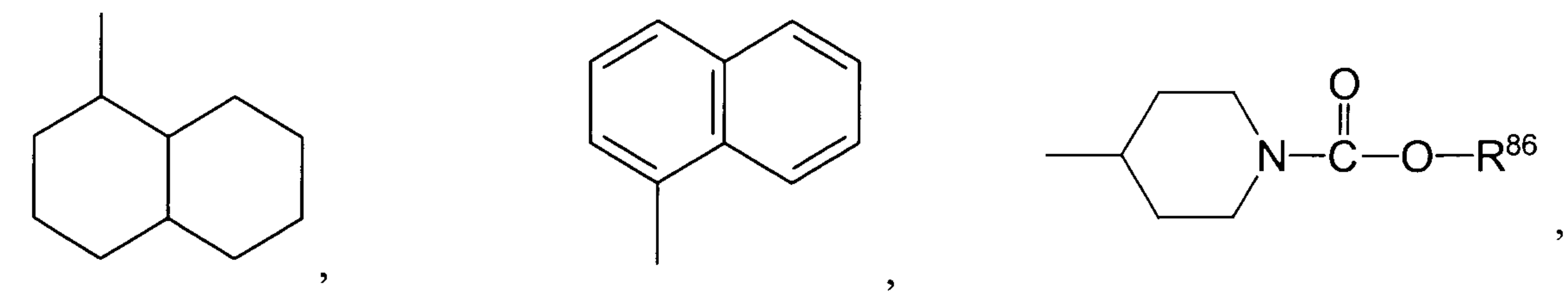
 ,  ,  ,

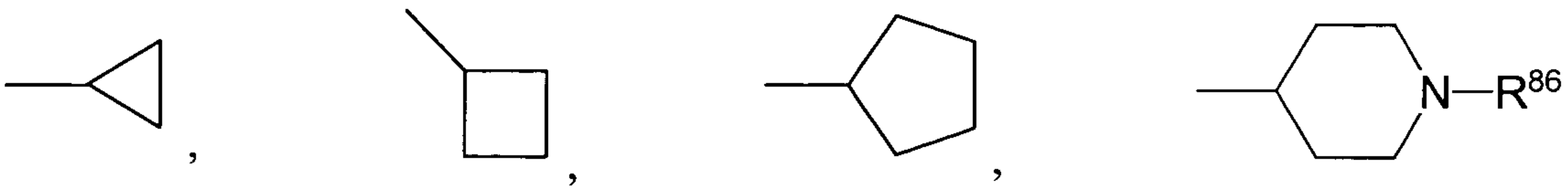
 ,  ,  ,

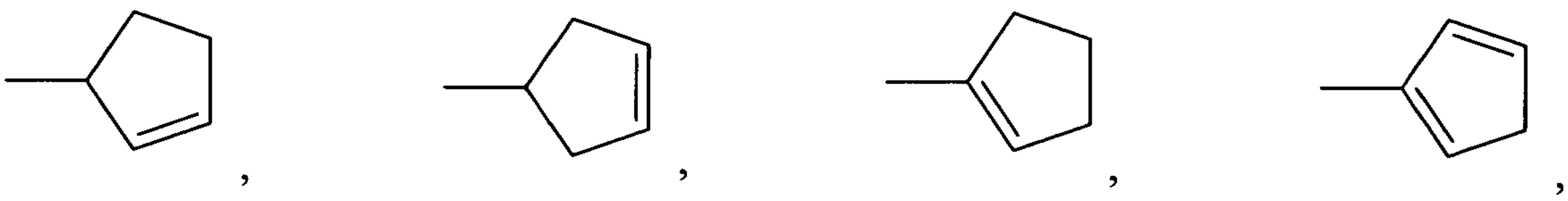
 ,  ,  ,

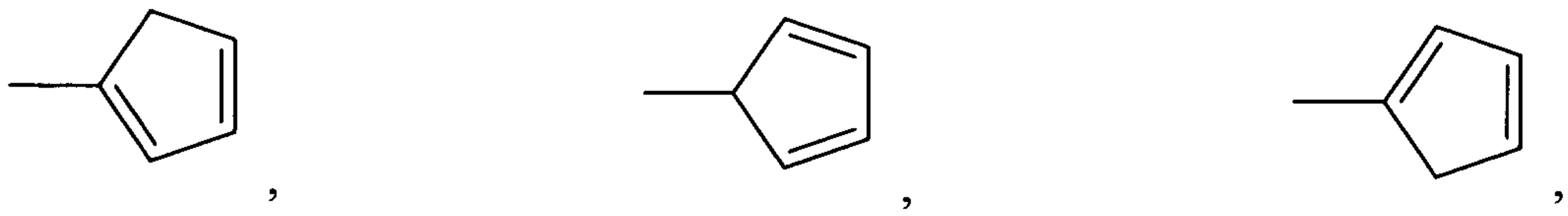
 ,  ,  ,

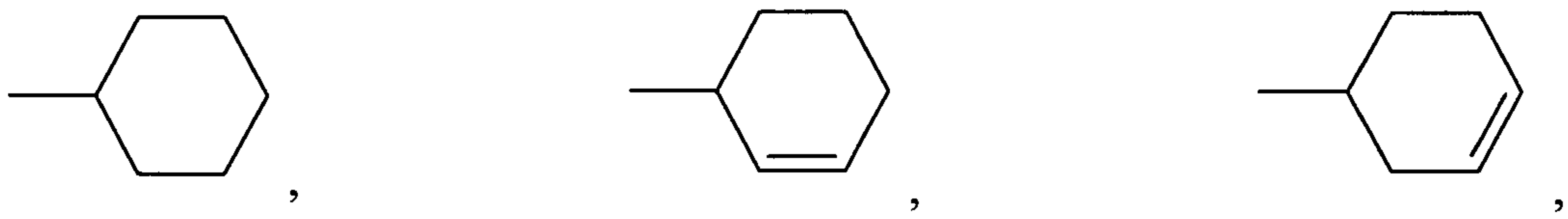
 ,  ,  ,

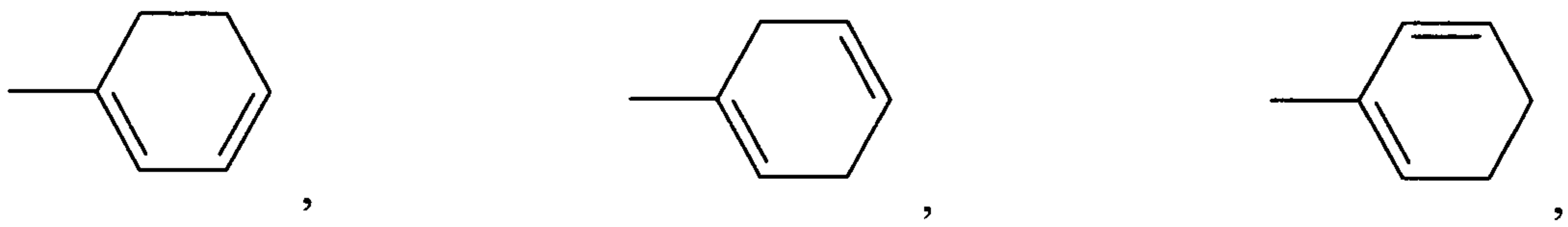


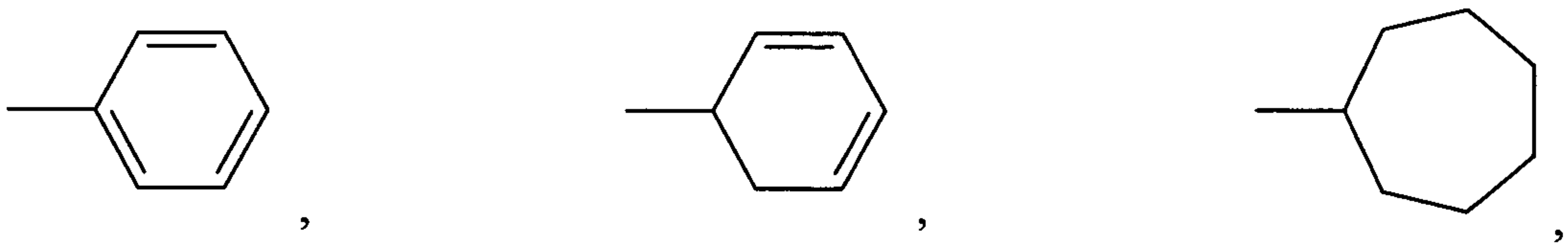


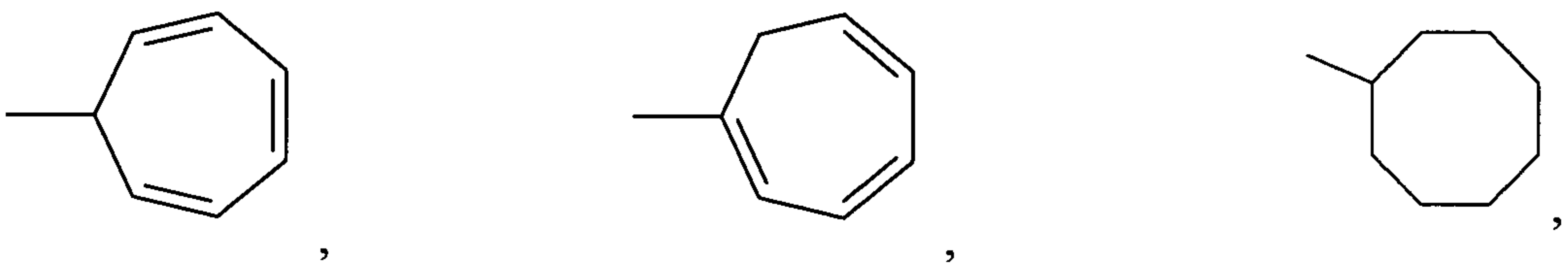


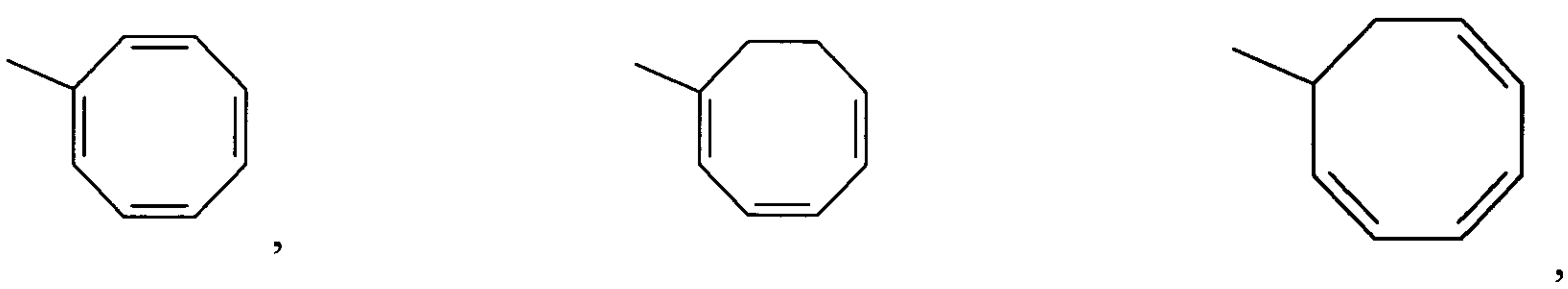




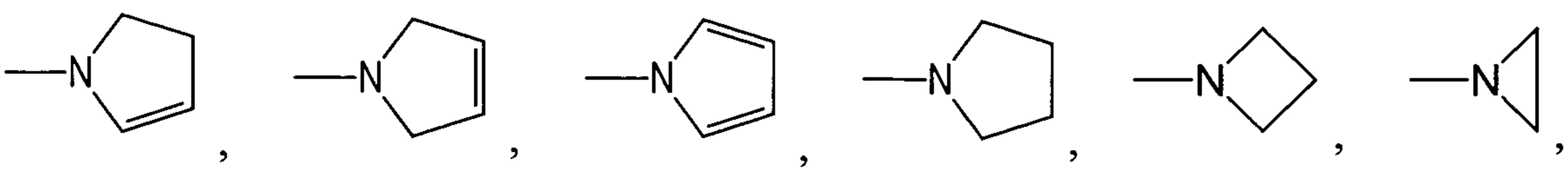


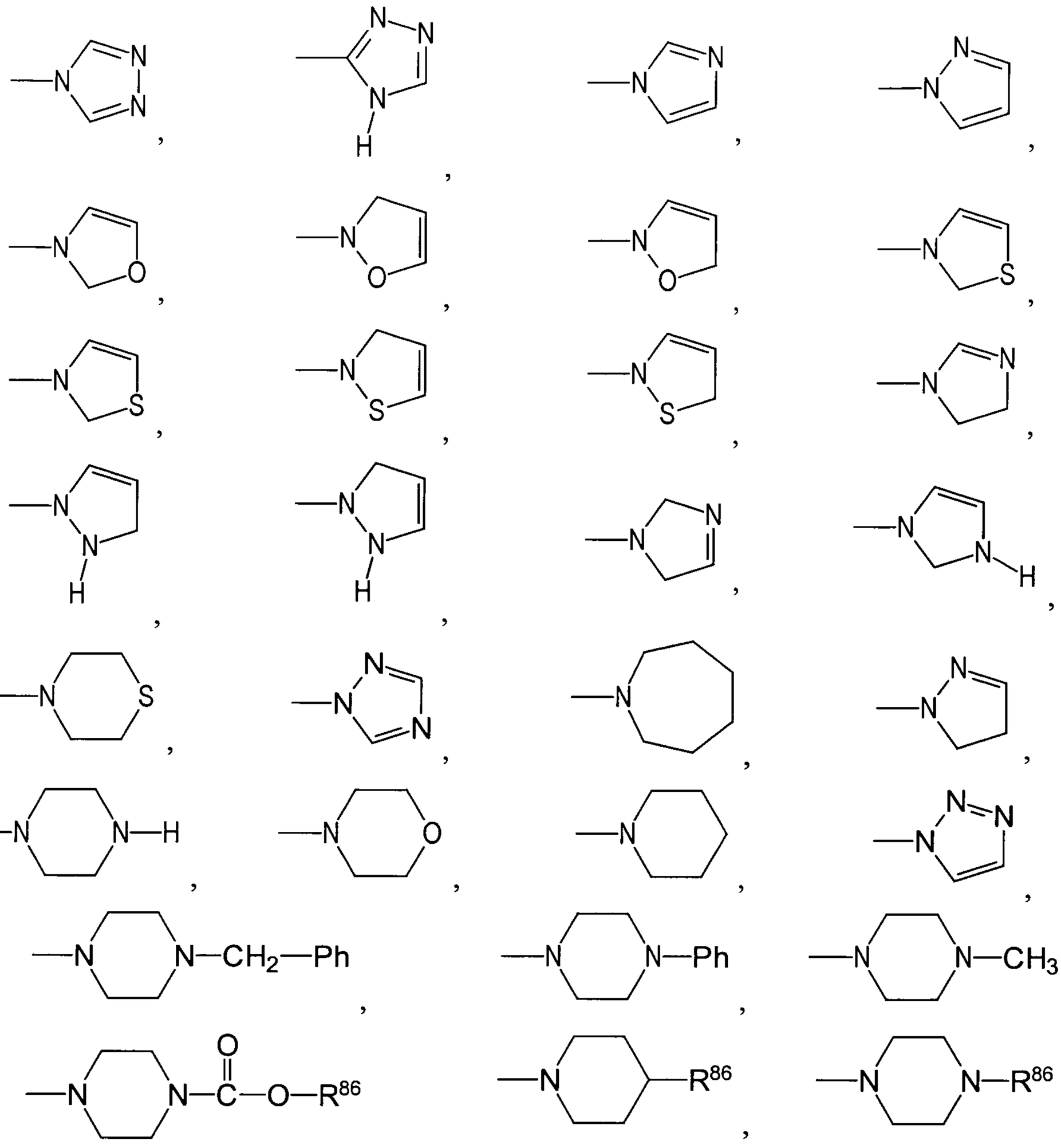






R^{114} represents





and enantiomers, stereoisomeric forms, mixtures of enantiomers, diastereomers, mixtures of diastereomers, prodrugs, hydrates, solvates, acid salt forms, tautomers, and racemates of the above mentioned compounds and pharmaceutically acceptable salts thereof.

The expression prodrug is defined as a substance, which is applied in an inactive or significantly less active form. Once applied and incorporated, the prodrug is metabolized in the body in vivo into the active compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example in "Design of Prodrugs", ed. H. B. Bundgaard, Elsevier, 1985.

The residue D contains at least one nitrogen atom. Said residue may contain one oxygen atom or one sulfur atom in addition to said one nitrogen atom. If no oxygen

and no sulfur atom is present, said residue may contain one, two or three additional nitrogen atoms so that said residue contains in total one, two, three or four nitrogen atoms. The position of the nitrogen atom in residue D is essential to the activity of the compound. It is important that this nitrogen atom is in ß position to the carbonyl group and that the ring D which is most preferably aromatic forms a conjugated system with the attached carbonyl group or that at least the ring nitrogen in ß position together with the alpha carbon atom and the attached carbonyl group form a conjugated system.

Thus, as residues D pyrazoles, imidazoles, oxazoles, isoxazoles, thiazoles, isothiazoles, triazoles, and tetrazoles are preferred. In order to obtain a high anti-cancer activity is seems to be important that the heterocyclic ring D contains a nitrogen atom next to the carbon atom through which the ring D is connected to the amid bond. Moreover pyrazoles, imidazoles, triazoles, and tetrazoles are more preferred than oxazoles, isoxazoles, thiazoles, and isothiazoles and pyrazoles are more preferred than triazoles, and tetrazoles which are again more preferred than imidazoles. Furthermore isoxazoles and isothiazoles are more preferred than oxazoles and thiazoles.

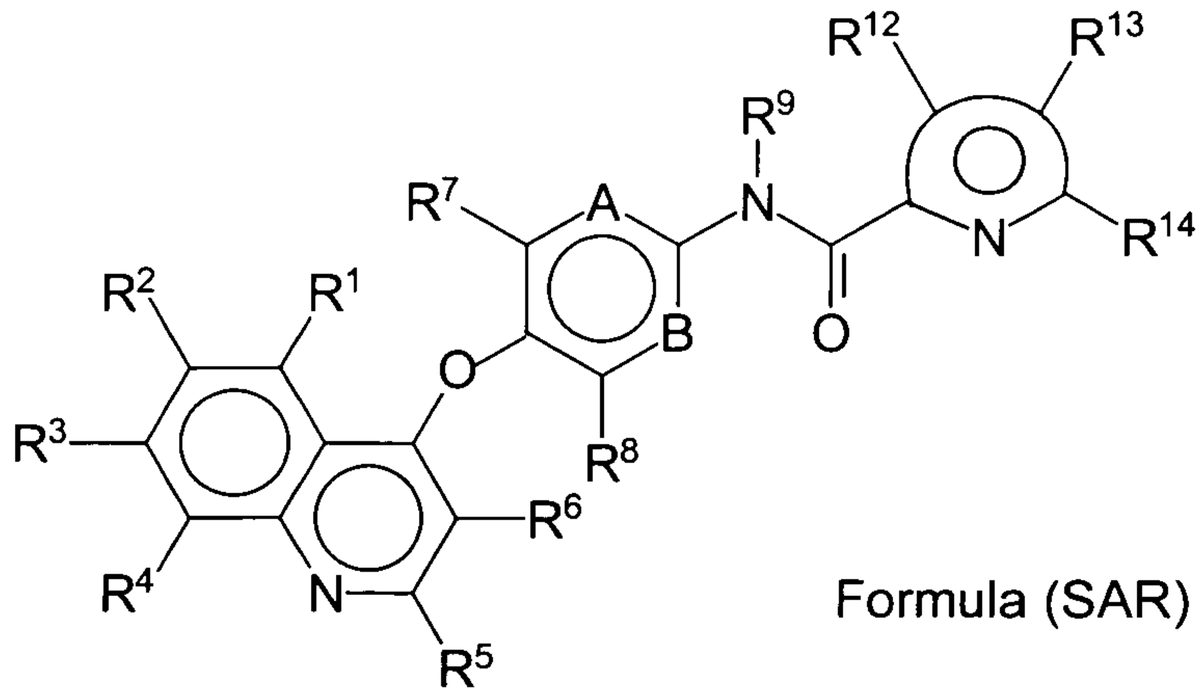
Concerning isoxazole residues as substituent D it is important that the isoxazole residue is linked through the 3-yl-carbon atom to the amide group and not through the 4-yl-carbon atom or the 5-yl-carbon atom. In case of an oxazole group as substituent D it is important that the oxazole group is linked to the amide group through 2-yl-carbon atom or the 4-yl-carbon atom but not through the 5-yl-carbon atom. A pyrazole residue should be linked to the amide group through the 3-yl-carbon atom and not through the 4-yl-carbon atom or the through the 5-yl-carbon atom.

Thiazole residues as substituent D are linked to the amide group through the 2-yl-carbon atom or the 4-yl-carbon atom, but not through the 5-yl-carbon atom. Similiar, isothiazoles are linked through the 3-yl carbon atom, but not through the 4-yl-carbon atom or 5-yl-carbon atom. Imidazoles are linked through the 2-yl-carbon or 4-yl-carbon atom, but not through the 5-yl-carbon position.

Moreover it is important that the residue D is directly connected to the amide group and not through a linker such as a methylene or ethylene linker so that the carbonyl function of the amide group can be in conjugation with the preferably aromatic ring D.

SAR

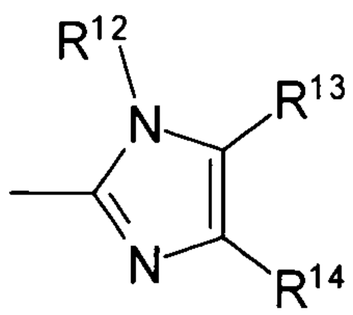
The structure activity relationship (SAR) of the compounds of the present invention as represented by the Formula (SAR)



Formula (SAR)

shows that ring D need to be an aromatic 5-membered heterocyclic ring with at least one nitrogen atom attached to the carbon atom of the aromatic ring which is attached to the amide group. Moreover it seems advantageous that the ring D is linked through a carbon atom to the amide group. The nitrogen atom of the amide group may be substituted by alkyl and substituted alkyl residues. Moreover the aromatic 5-membered ring D has to have a specific substitution pattern in order to provide active compounds for the uses disclosed herein. Said specific substitution pattern requires that substituent R^{13} is only a small group such as hydrogen, methyl, trifluoromethyl, fluoro, ethyl, otherwise the activity drops. Furthermore it seems to be advantageous that a larger group such as a substituted phenyl group is attached as R^{14} to the atom next to the ring nitrogen atom as shown in Formula (SAR). In addition a substituent R^{12} in position next to the ring carbon atom of ring D which is attached to the amide group seems to increase the activity. As substituent R^{12} short carbon chains as well as longer carbon chains, short or long alkoxy groups, ether or polyether residues or amines seem to be suitable. Thus compounds with an aromatic nitrogen containing 5-membered ring as substituent D with a small substituent R^{13} and a cyclic substituent R^{14} and a smaller or longer carbon chain as substituent R^{12} containing optionally oxygen (ethers) and/or nitrogen (amines) and/or cyclic structures such as saturated or unsaturated carbocyclic or heterocyclic rings seem to perfectly fit into the active side of the enzyme. In addition it is not important for the activity if A and B are carbon or nitrogen atoms. It seems also not important if substituents R^7, R^8, R^5, R^6, R^2, and R^1 are smaller groups such as nitro, halogen, lower alkyl, lower alkoxy, hydroxy etc. and substituents R^2 and R^3 can be modified in a broard range. The sort of residue R^2 and R^3 is not important for the activity so that R^2 and R^3 can be hydrogen, smaller groups such as methyl or methoxy as well as longer residues with a carbon chain containing optionally oxygen, nitrogen or saturated, unsaturated carbocyclic or heterocyclic rings.

Preferred is the formula (I), wherein the residue D represents one of the following heterocycles: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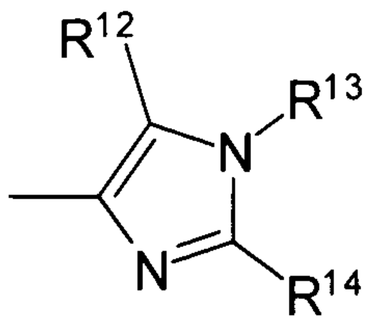
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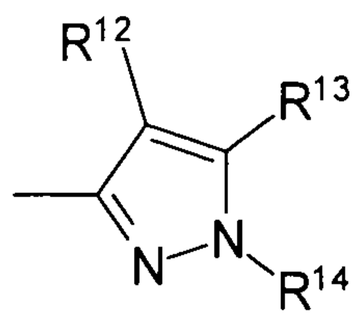
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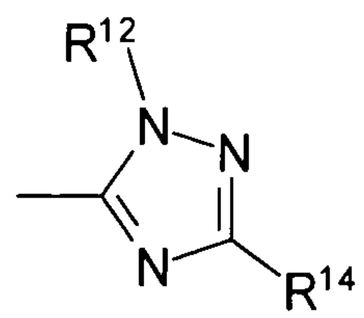
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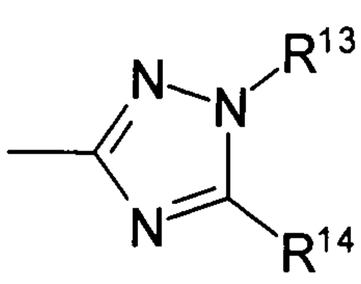
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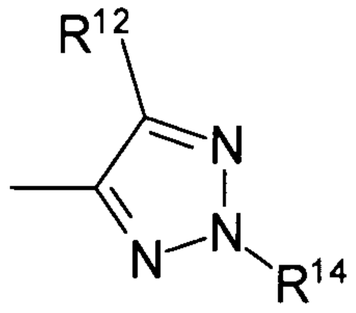
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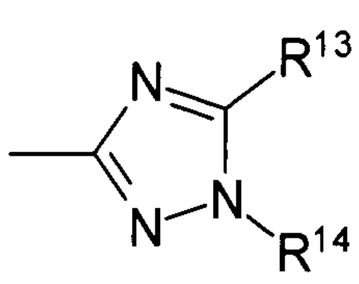
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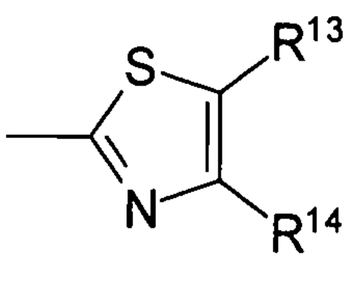
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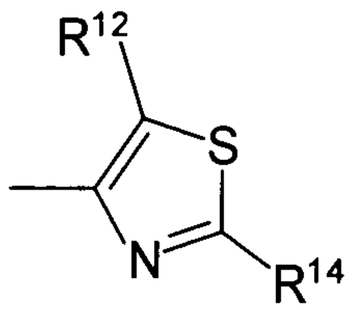
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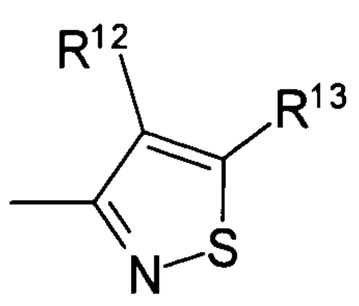
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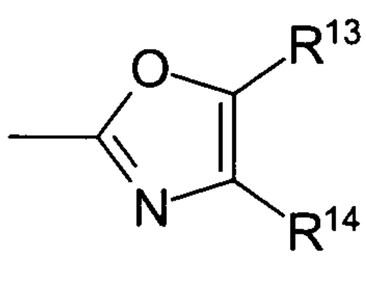
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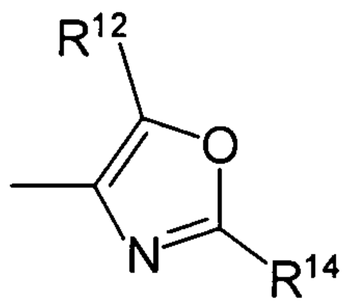
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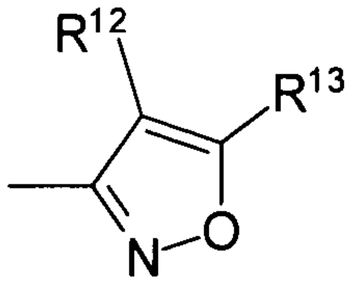
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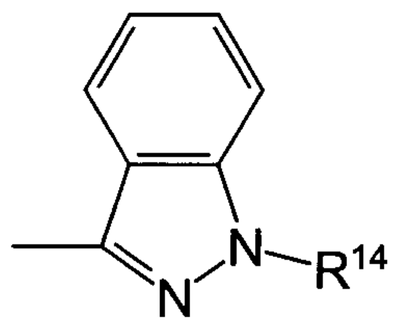
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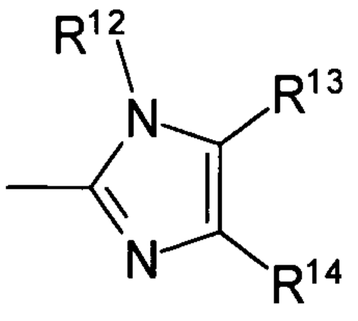
The substituents R^{12} – R^{14} have the meanings as defined in formula (I) above.

Still more preferred are the following D residues: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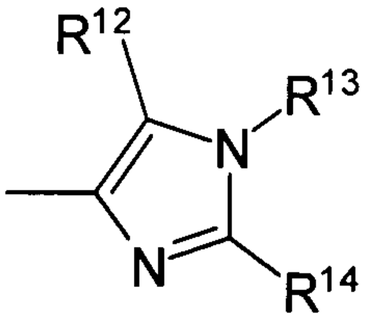
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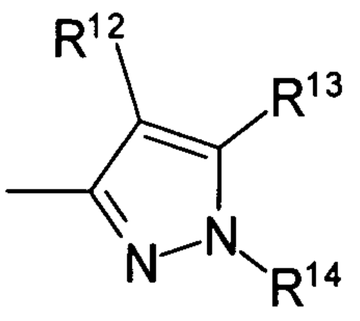
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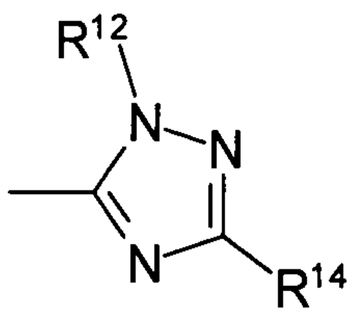
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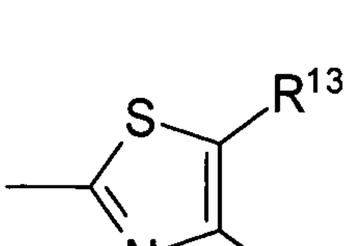
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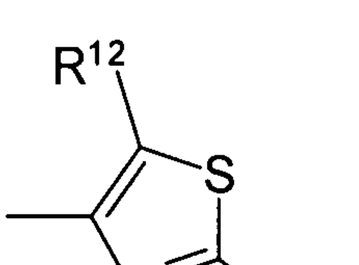
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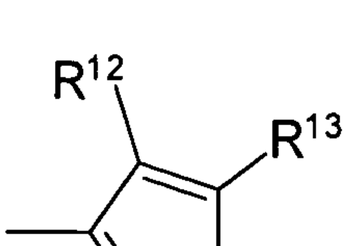
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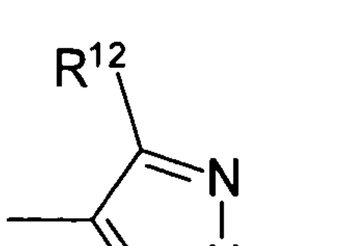
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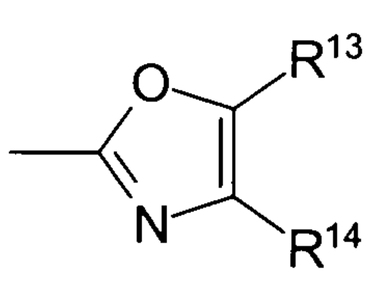
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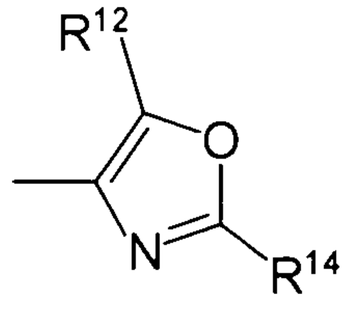
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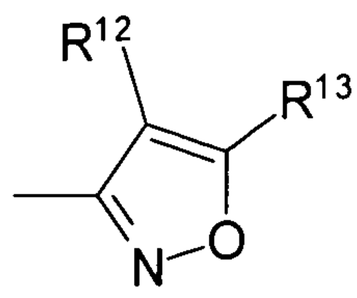
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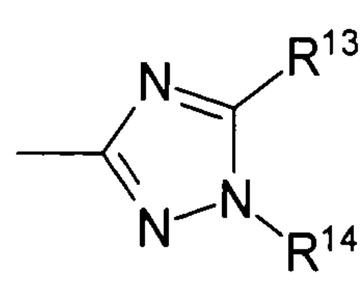
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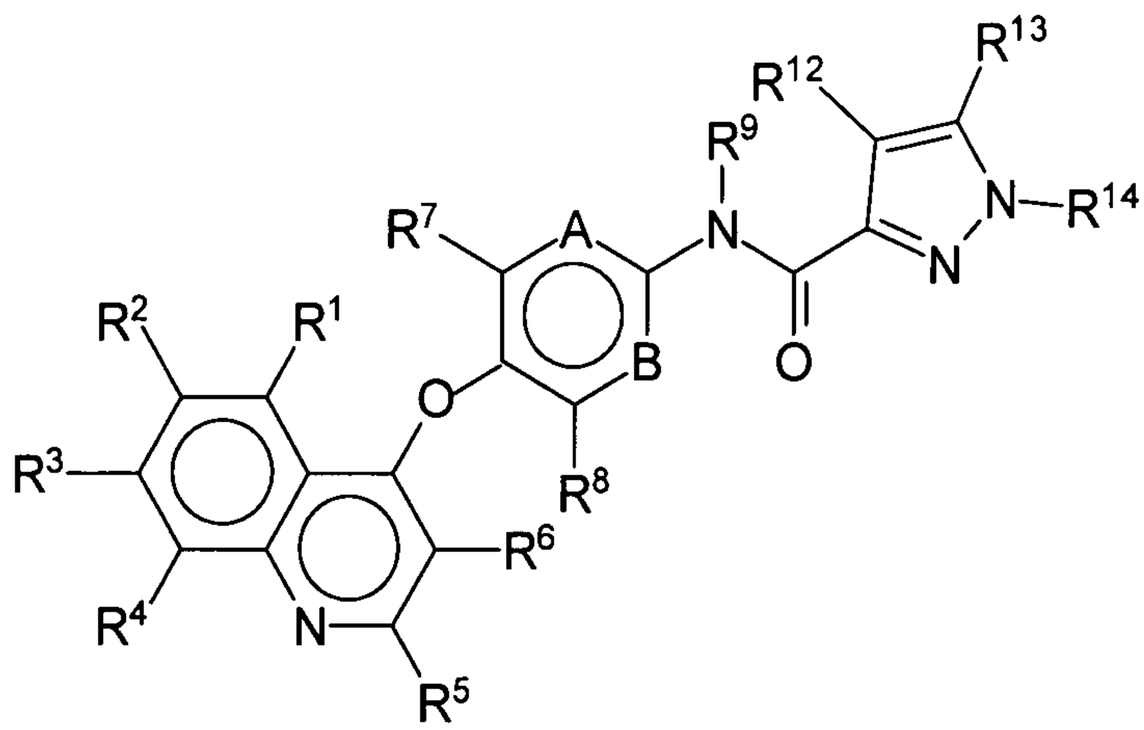
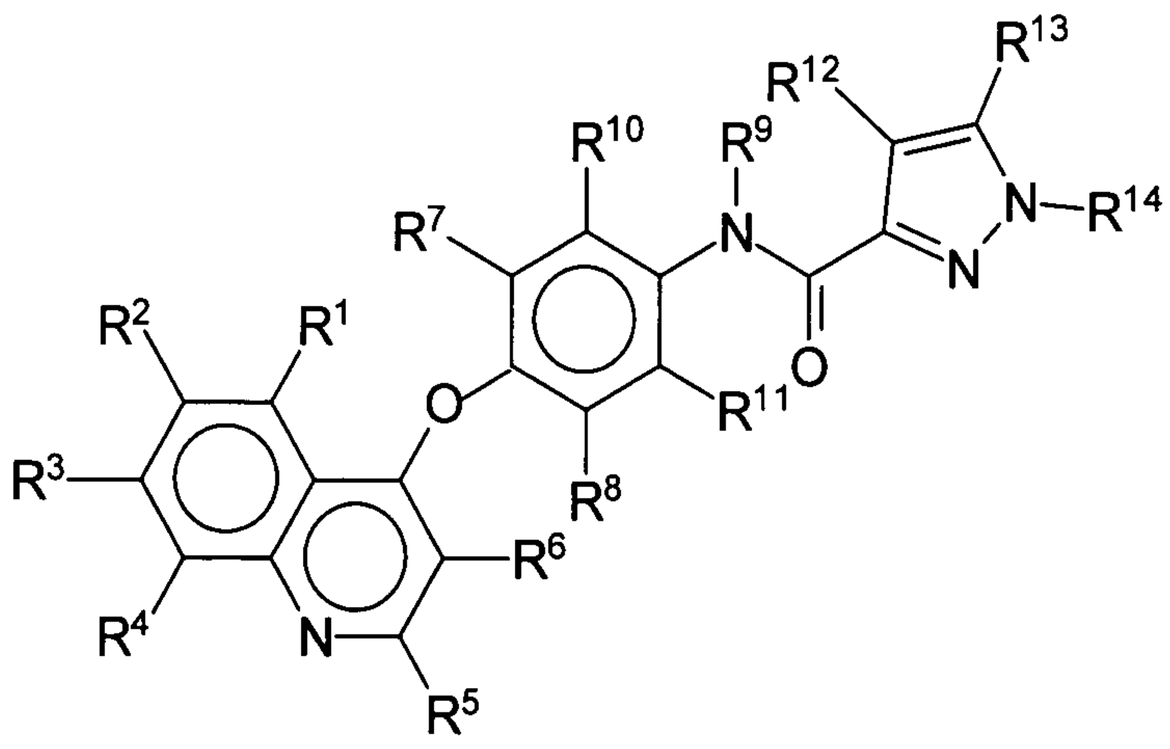
Particularly preferred are compounds of the general formula (Ia),



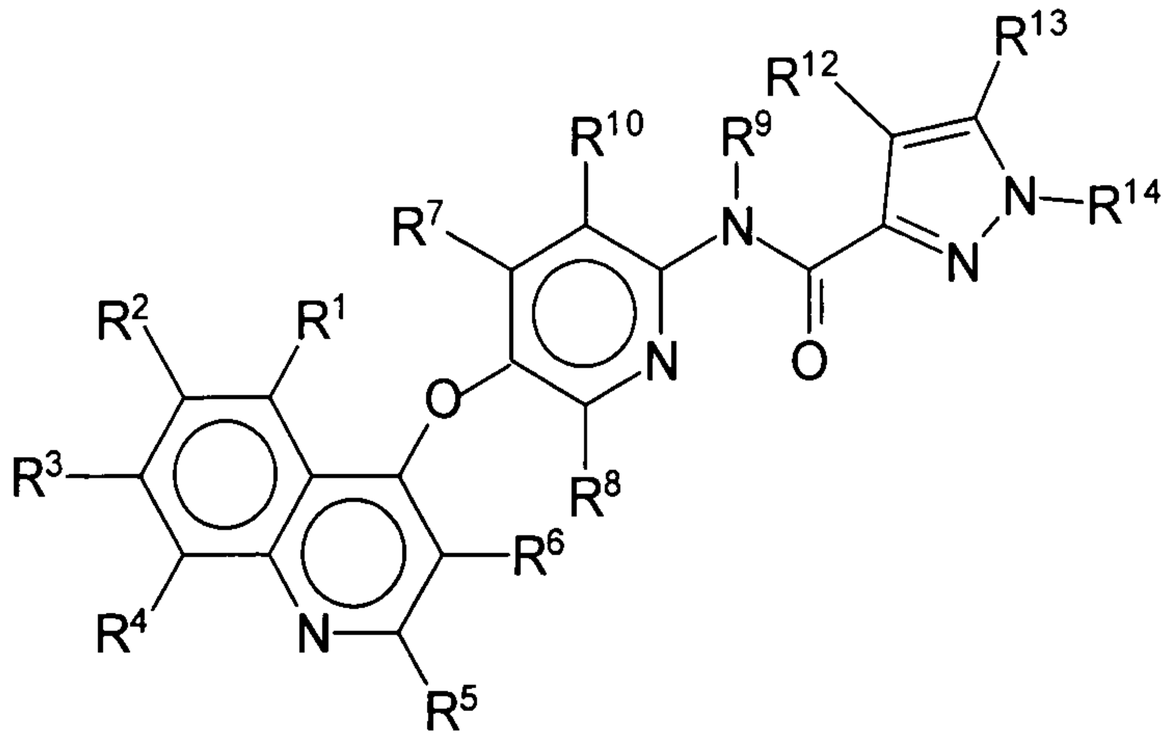
Formula (Ia)

wherein residue D is a substituted or unsubstituted pyrazole ring.

Especially preferred are compounds of the general formula (Ib) or the general formula (Ic),



Formula (Ib)



Formula (Ic)

wherein both, group A and group B are carbon atoms or wherein group A is a carbon atom and group B is a nitrogen atom, respectively.

Further preferred are compounds of the general formulas (I), (Ia), (Ib), or (Ic), wherein R^1, R^4, R^5 and R^6 are selected from hydrogen or $C_{1\text{-}6}$alkyl, particularly from hydrogen.

Furthermore preferred are compounds of the general formulas (I), (Ia), (Ib), or (Ic), wherein R^9 is a hydrogen atom.

In regard to A and B it is preferred that non of both or only one of both represents N.

Substituents R^1, R^4, R^5, and R^6 are preferably hydrogen.

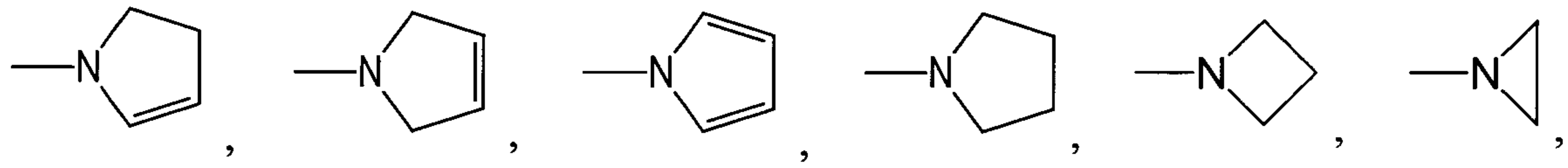
Substituents R^2 and R^3 are preferably selected independently of each other from:
$-O-R^{18}$, $-O-CR^{73}R^{74}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-CR^{79}R^{80}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-CR^{79}R^{80}-CR^{81}R^{82}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-CR^{79}R^{80}-CR^{81}R^{82}-CR^{83}R^{84}-R^{18}$,
wherein R^{73} – R^{84} independently of each other represent –H, –OH, –F, –Cl, –Br, –I, $-CH_3$, $-CF_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$;

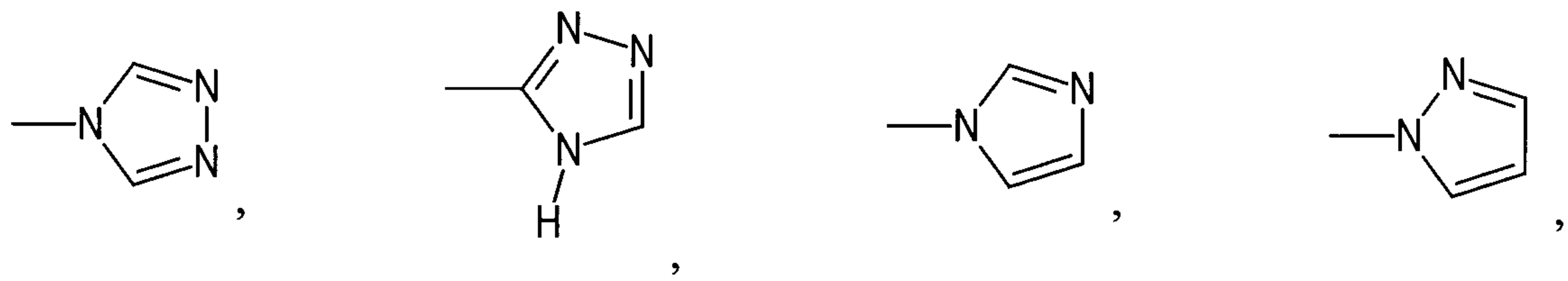
and R^{18} represents –H, –OH, –F, –Cl, –Br, –I, –O–R^{86}, –COOH, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, –(C=O)–$NR^{16}R^{17}$, $-CR^{16}R^{17}H$, $-NR^{16}R^{17}$;

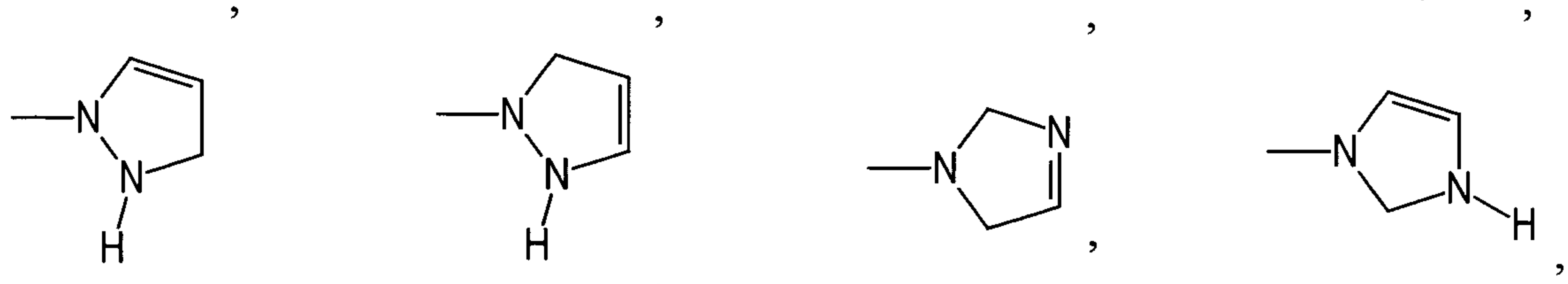
R^{86} represents $-CH_3$, $-CF_3$, –H, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$;

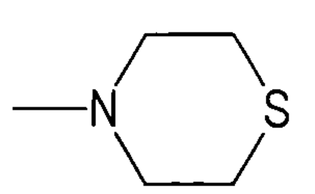
R^{16} and R^{17} represent independently of each other $-CH_3$, $-CF_3$, –H, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, –OH, –F, –Cl, –Br, –I, $-NH_2$, –CN,

the residue $-NR^{16}R^{17}$ may represent a nitrogen heterocyclic group selected from





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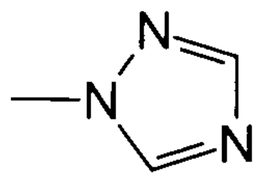
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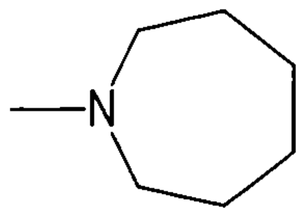
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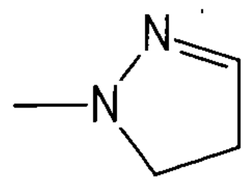
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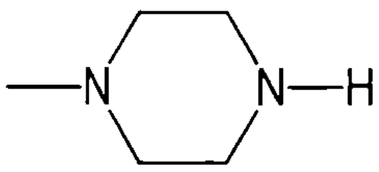
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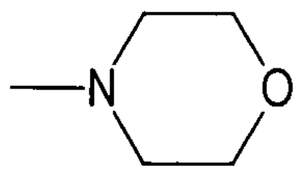
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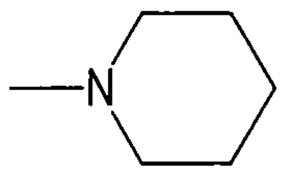
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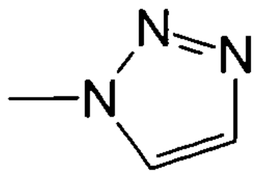
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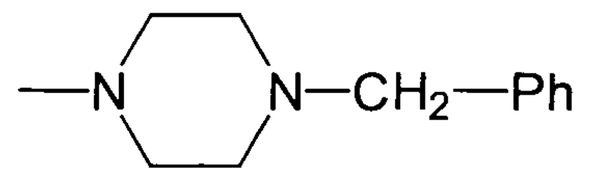
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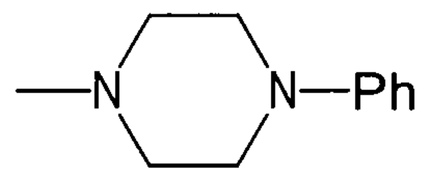
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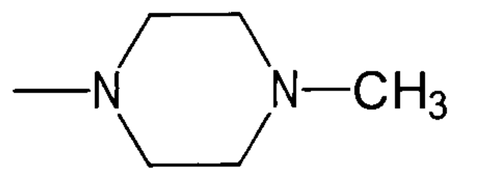
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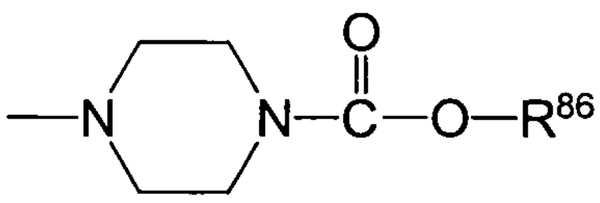
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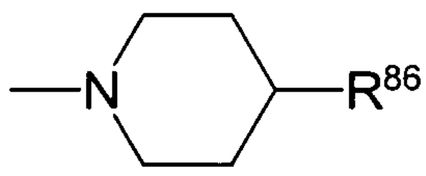
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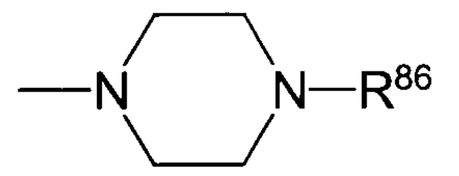
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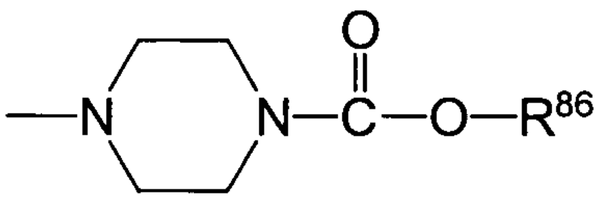
and more preferably selected from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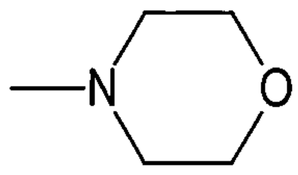
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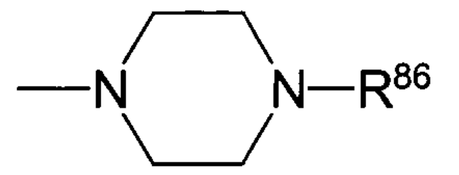
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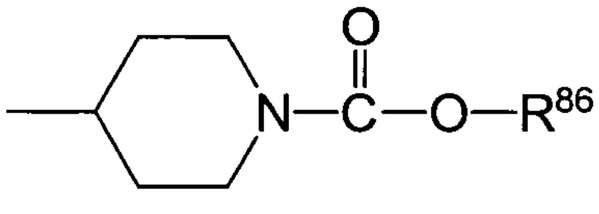
the residue $-CR^{16}R^{17}H$ may represent a carbocyclic or heterocyclic group selected from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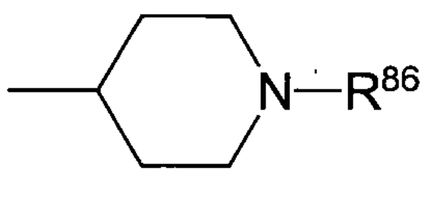
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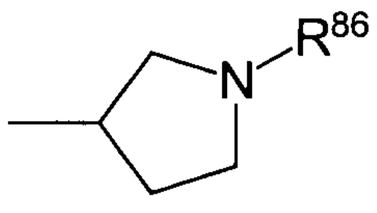
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Substituents R^7 and R^8 are preferably selected independently of each other from: –H, –F, –Cl, –Br, –I, –CN, $-NO_2$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, cyclo-C_3H_5, $-CH_2$–cyclo–C_3H_5, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2$-$C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$; and are more preferably selected from –H, –F, –Cl, –Br, –CN, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, cyclo-C_3H_5, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2$-$C\equiv CH$; and are still more preferably selected from –H, –F, –Cl, –Br, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, cyclo-C_3H_5, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C\equiv CH$, $-CH_2$-$C\equiv CH$; and R^7 and R^8 are most preferably selected independently of each other from –H, –F, –Cl, $-CH_3$.

Moreover it is preferred that one of R^7 and R^8 represents hydrogen.

A and B represent preferably independently of each other C–H, C–F, C–Cl, C–Br, C–CN, C–CH_3, C–C_2H_5, C–C_3H_7, C–$CH(CH_3)_2$, C–cyclo-C_3H_5, C–$CH=CH_2$, C–CH_2–$CH=CH_2$, C–$CH=CH-CH_3$, C–$C\equiv CH$, C–$C\equiv C-CH_3$, C–CH_2-$C\equiv CH$, C–OCH_3, C–OH, C–OC_2H_5, C–OC_3H_7, C–$OCH(CH_3)_2$, C–OC_4H_9, C–$OCH_2-CH(CH_3)_2$, C–$OCH(CH_3)-C_2H_5$, C–$OC(CH_3)_3$, C–OC_5H_{11}, N. Moreover it is preferred that one of A and B

represents C–H. In addition it is preferred that only one of A and B represents N. More preferably A and B represent independently of each other C–H, C–F, C–Cl, C–Br, C–CH_3, C–C_2H_5, C–C_3H_7, C–$CH(CH_3)_2$, C–cyclo-C_3H_5, C–$CH=CH_2$, C–CH_2–$CH=CH_2$, C–C≡CH, C–OCH_3, C–OH, C–OC_2H_5, C–OC_3H_7, C–$OCH(CH_3)_2$, N; still more preferably C–H, C–F, C–Cl, C–CH_3, C–C_2H_5, C–C_3H_7, C–CH_2–$CH=CH_2$, C–OCH_3, C–OH, C–OC_2H_5, C–OC_3H_7, N; and most preferably A and B represent independently of each other C–H, C–F, C–CH_3, C–OCH_3, and N.

R^9 represents preferably hydrogen.

R^{14} represents preferably –H, –OH, –F, –Cl, –Br, –I, –NO_2, –CN, –NH_2, –R^{100}, –R^{101}, –R^{102}, –O–R^{102}, –R^{103}, –O–R^{103}, –R^{136}, or –R^{113}, wherein the saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system represented by –R^{113} is optionally mono- or polysubstituted by –F, –Cl, –Br, –I, –OH, –NO_2, –NH_2, –C_2H_4–$N(CH_3)_2$, –CN, –CF_3, =O, –R^{16}, –R^{17}, –R^{106}, –O–R^{107}, –R^{108}, –R^{109}, wherein the substituents R^{16}, R^{17}, R^{100}, R^{101}, R^{102}, R^{103}, R^{106}, R^{107}, R^{108}, R^{109}, R^{113}, and R^{136} have the meanings as disclosed herein.

More preferably R^{14} represents –H, –Cl, –Br, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –R^{103}, –R^{136}, and –R^{113}, wherein the saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system represented by –R^{113} is optionally mono- or polysubstituted by –F, –Cl, –Br, –OH, –NO_2, –NH_2, –C_2H_4–$N(CH_3)_2$, –R^{16}, –R^{106}, –O–R^{107}, –R^{108}, –R^{109};

Preferably R^{103} represents preferably –$CR^{58}R^{16}R^{17}$, –$CR^{59}R^{60}$–$CR^{16}R^{17}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{16}R^{17}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{16}R^{17}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{16}R^{17}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{67}R^{68}$–$CR^{16}R^{17}R^{58}$, –$CR^{58}R^{59}R^{60}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{67}R^{68}R^{58}$, and

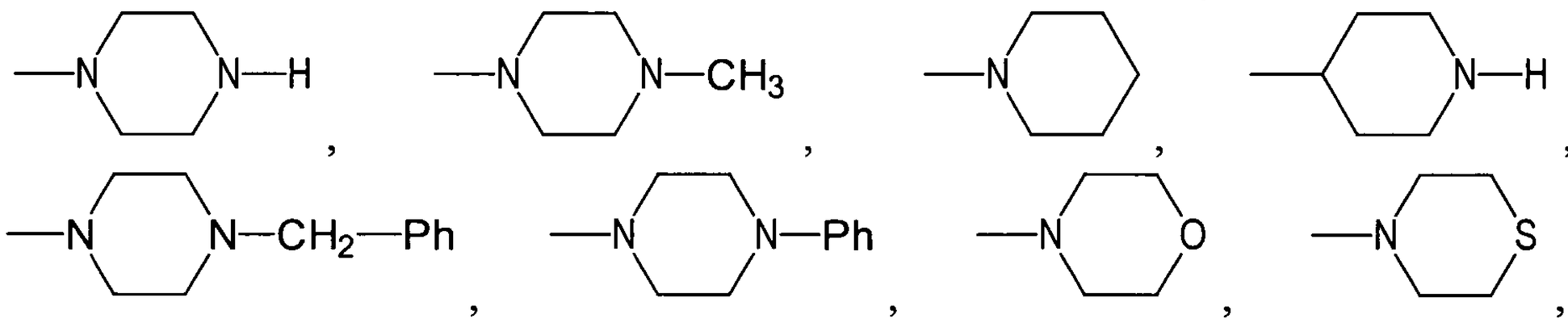
R^{58} – R^{68} represent independently of each other –H, –NH_2, –OH, –F, –Cl, –Br, –I, –OCH_3, –OCF_3, –OC_2H_5, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –C_4H_9, –CF_3, –$C(CH_3)_3$, –$CR^{16}R^{17}H$, –$NR^{16}R^{17}$; wherein R^{16} and R^{17} have the meanings as disclosed herein.

More preferably R^{103} represents –$CR^{58}R^{59}R^{60}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}R^{58}$, –$CR^{59}R^{60}$–

$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{67}R^{68}R^{58}$, and R^{58} represents –$CR^{16}R^{17}H$ or –$NR^{16}R^{17}$; and

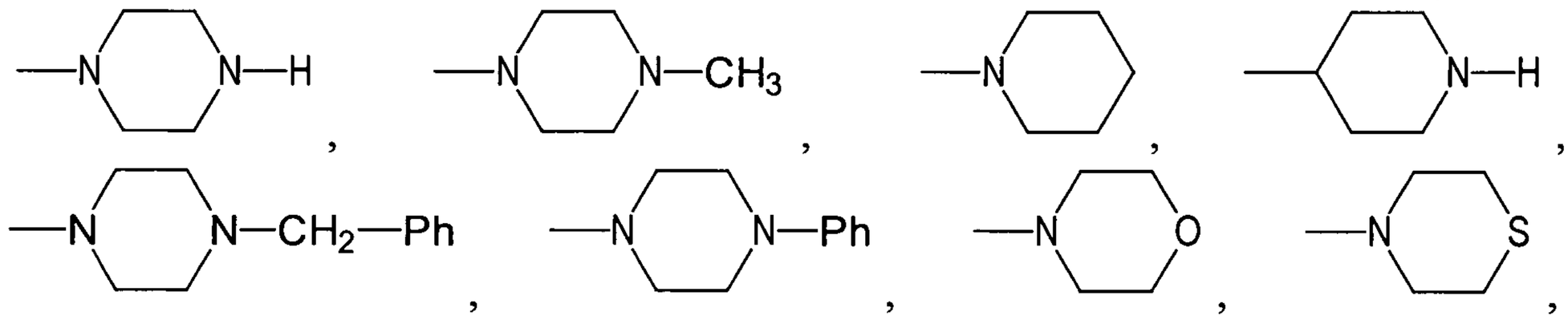
R^{59} – R^{68} represent independently of each other –H, –NH_2, –OH, –F, –Cl, –Br, –I, –OCH_3, –OCF_3, –OC_2H_5, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –C_4H_9, –CF_3, –$C(CH_3)_3$; and R^{16} and R^{17} represent independently of each other –H, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –C_5H_{11}, –CF_3, –Ph, –CH_2–Ph, or represent together with the atom to which they are attached a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system selected from –R^{133}, wherein R^{133} has the meanings as disclosed herein.

Still more preferably R^{103} represents –$CR^{58}R^{59}R^{60}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}R^{58}$, –$CR^{59}R^{60}$–$CR^{61}R^{62}$–$CR^{63}R^{64}$–$CR^{65}R^{66}$–$CR^{67}R^{68}R^{58}$, and R^{58} represents

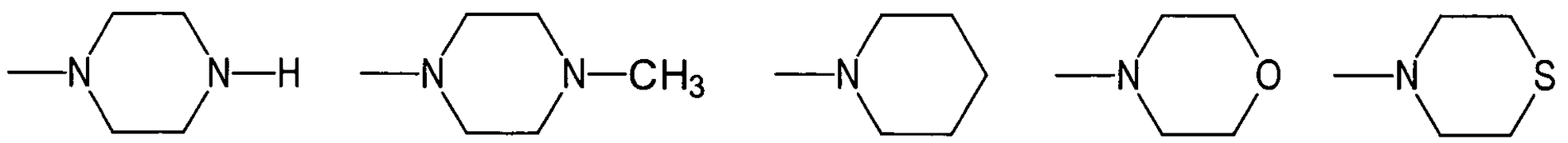


and R^{59} – R^{68} represent independently of each other –H, –CH_3, –C_2H_5, –CF_3.

Still even more preferably R^{103} represents –CH_2R^{58}, –CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2–CH_2–CH_2R^{58}, and R^{58} represents



Most preferably R^{103} represents –CH_2R^{58}, –CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2–CH_2R^{58}, and R^{58} represents



Preferably R^{136} represents –$CR^{23}R^{24}$–X–$CR^{25}R^{26}R^{22}$, –$CR^{23}R^{24}$–X–$CR^{25}R^{26}$–$CR^{27}R^{28}R^{22}$, –$CR^{23}R^{24}$–$CR^{25}R^{26}$ –X–$CR^{27}R^{28}R^{22}$, –$CR^{23}R^{24}$–X–$CR^{25}R^{26}$–$CR^{27}R^{28}$–$CR^{29}R^{30}R^{22}$, –$CR^{23}R^{24}$–$CR^{25}R^{26}$–X–$CR^{27}R^{28}$–$CR^{29}R^{30}R^{22}$, –$CR^{23}R^{24}$–$CR^{25}R^{26}$–$CR^{27}R^{28}$–X–$CR^{29}R^{30}R^{22}$, –$CR^{23}R^{24}$–X–$CR^{25}R^{26}$–$CR^{27}R^{28}$–$CR^{29}R^{30}$–$CR^{31}R^{32}R^{22}$, –$CR^{23}R^{24}$–$CR^{25}R^{26}$–X–$CR^{27}R^{28}$–$CR^{29}R^{30}$–$CR^{31}R^{32}R^{22}$, –$CR^{23}R^{24}$–$CR^{25}R^{26}$–$CR^{27}R^{28}$–

$X–CR^{29}R^{30}–CR^{31}R^{32}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–CR^{27}R^{28}–CR^{29}R^{30}–X–CR^{31}R^{32}R^{22}$, $–CR^{23}R^{24}–X–CR^{25}R^{26}–CR^{27}R^{28}–CR^{29}R^{30}–CR^{31}R^{32}–CR^{33}R^{34}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–X–CR^{27}R^{28}–CR^{29}R^{30}–CR^{31}R^{32}–CR^{33}R^{34}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–CR^{27}R^{28}–X–CR^{29}R^{30}–CR^{31}R^{32}–CR^{33}R^{34}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–CR^{27}R^{28}–CR^{29}R^{30}–X–CR^{31}R^{32}–CR^{33}R^{34}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–CR^{27}R^{28}–CR^{29}R^{30}–CR^{31}R^{32}–X–CR^{33}R^{34}R^{22}$; and X represents –O–, –CO–, –O–CO– and R^{22} – R^{34} represent independently of each other –H, –F, –Cl, $–CH_3$, $–CF_3$, $–C_2H_5$, $–C_3H_7$.

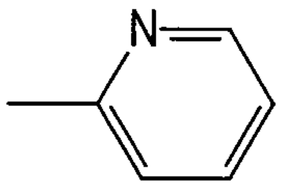
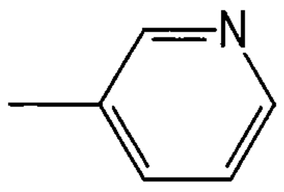
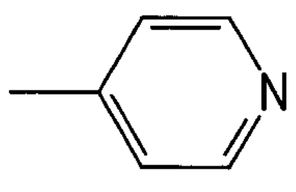
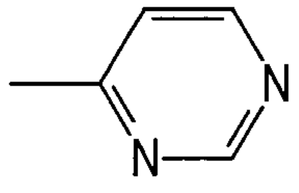
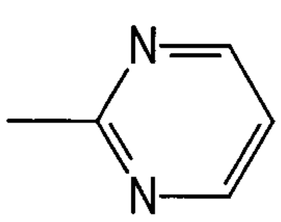
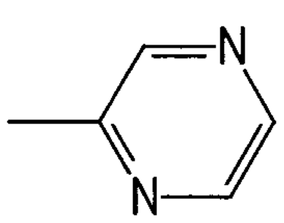
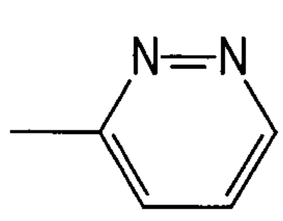
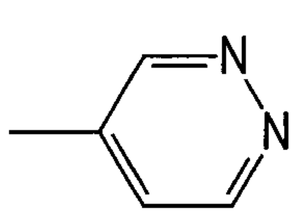
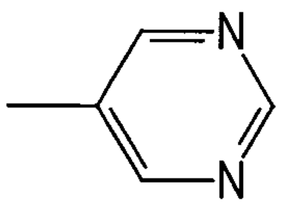
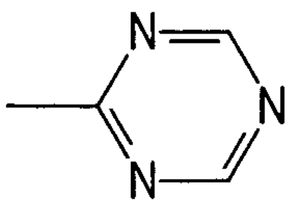
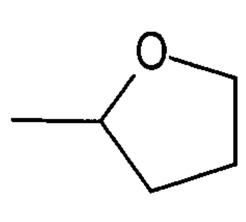
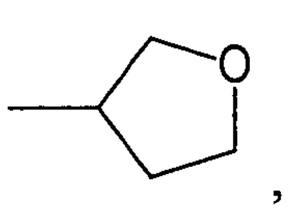
More preferably R^{136} represents $–CR^{23}R^{24}–X–CR^{25}R^{26}R^{22}$, $–CR^{23}R^{24}–X–CR^{25}R^{26}–CR^{27}R^{28}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–X–CR^{27}R^{28}R^{22}$, $–CR^{23}R^{24}–X–CR^{25}R^{26}–CR^{27}R^{28}–CR^{29}R^{30}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–X–CR^{27}R^{28}–CR^{29}R^{30}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–CR^{27}R^{28}–X–CR^{29}R^{30}R^{22}$, $–CR^{23}R^{24}–X–CR^{25}R^{26}–CR^{27}R^{28}–CR^{29}R^{30}–CR^{31}R^{32}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–X–CR^{27}R^{28}–CR^{29}R^{30}–CR^{31}R^{32}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–CR^{27}R^{28}–X–CR^{29}R^{30}–CR^{31}R^{32}R^{22}$, $–CR^{23}R^{24}–CR^{25}R^{26}–CR^{27}R^{28}–CR^{29}R^{30}–X–CR^{31}R^{32}R^{22}$; and X represents –O–, and R^{22} – R^{32} represent independently of each other –H, $–CH_3$, $–CF_3$, $–C_2H_5$, $–C_3H_7$.

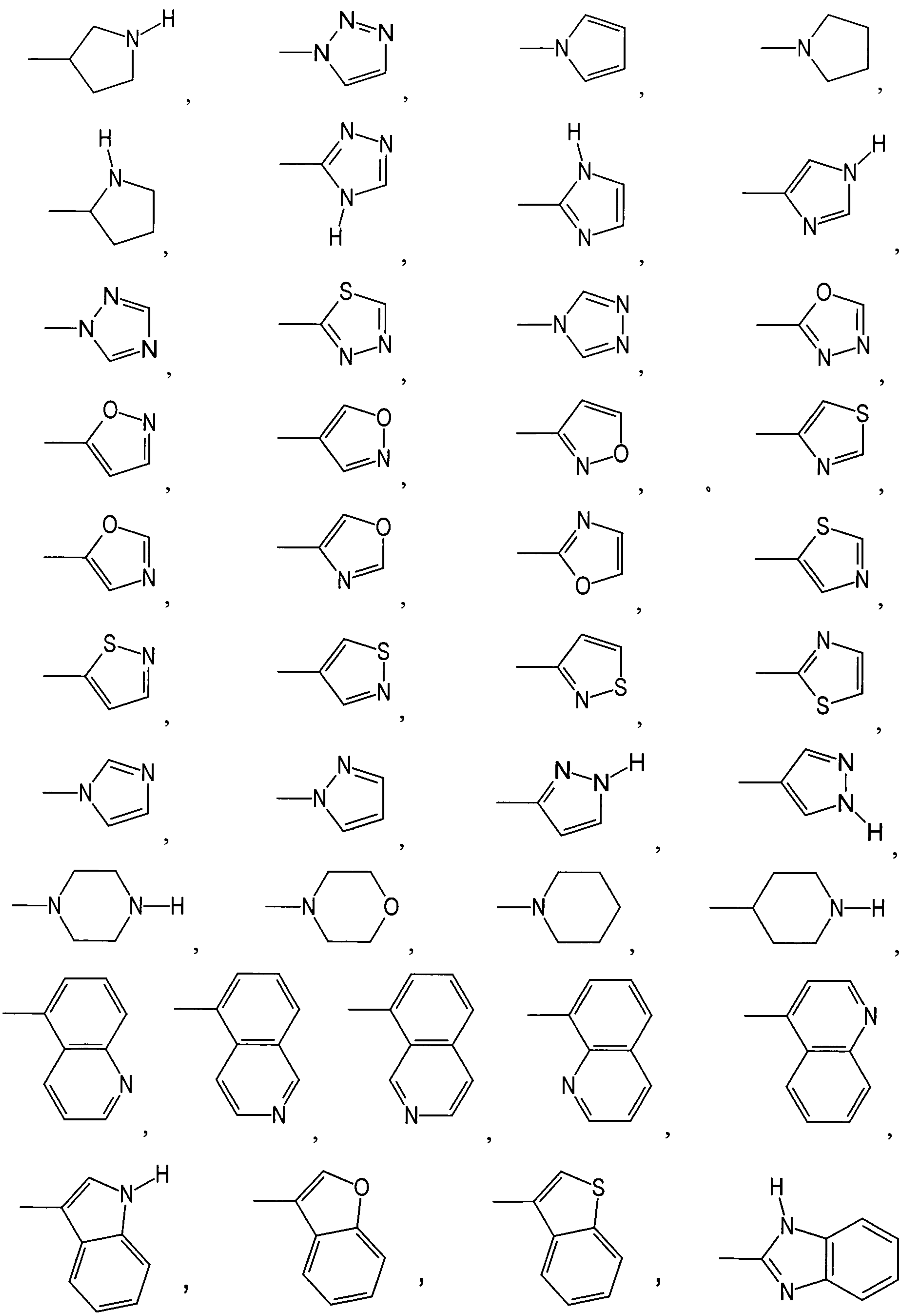
Still more preferably R^{136} represents $–CH_2–O–CH_2R^{22}$, $–CH_2–O–CH_2–CH_2R^{22}$, $–CH_2–CH_2–O–CH_2R^{22}$, $–CH_2–O–CH_2–CH_2–CH_2R^{22}$, $–CH_2–CH_2–O–CH_2–CH_2R^{22}$, $–CH_2–CH_2–CH_2–O–CH_2R^{22}$, $–CH_2–O–CH_2–CH_2–CH_2–CH_2R^{22}$, $–CH_2–CH_2–O–CH_2–CH_2R^{22}$, $–CH_2–CH_2–CH_2–O–CH_2–CH_2R^{22}$, $–CH_2–CH_2–CH_2–CH_2–O–CH_2R^{22}$; and R^{22} represents –H, $–CH_3$, $–CF_3$, $–C_2H_5$, $–C_3H_7$.

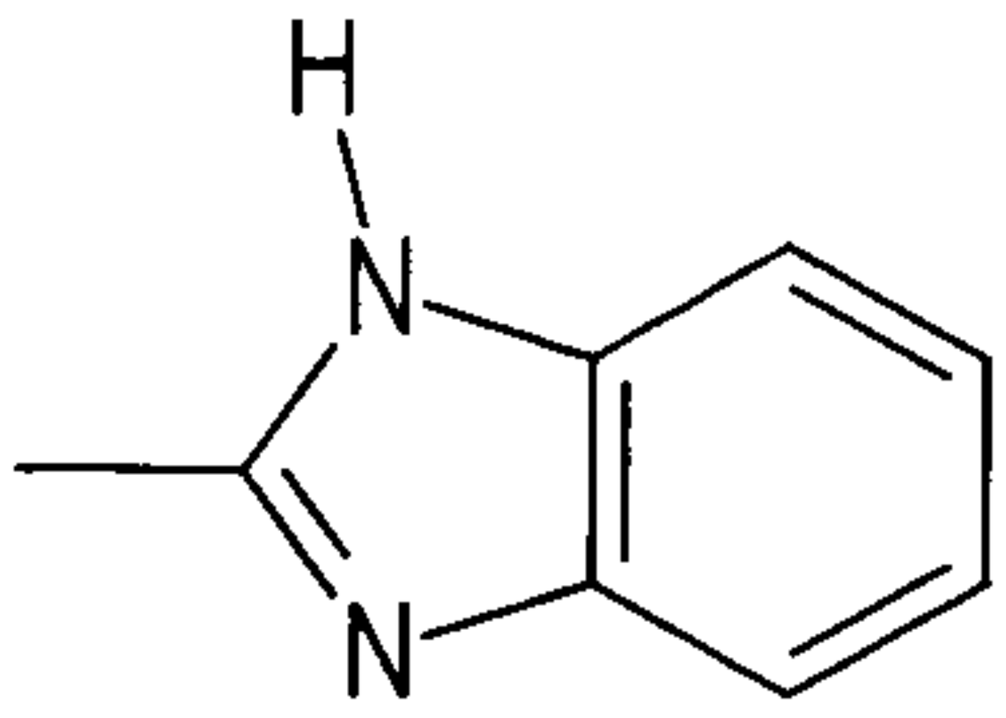
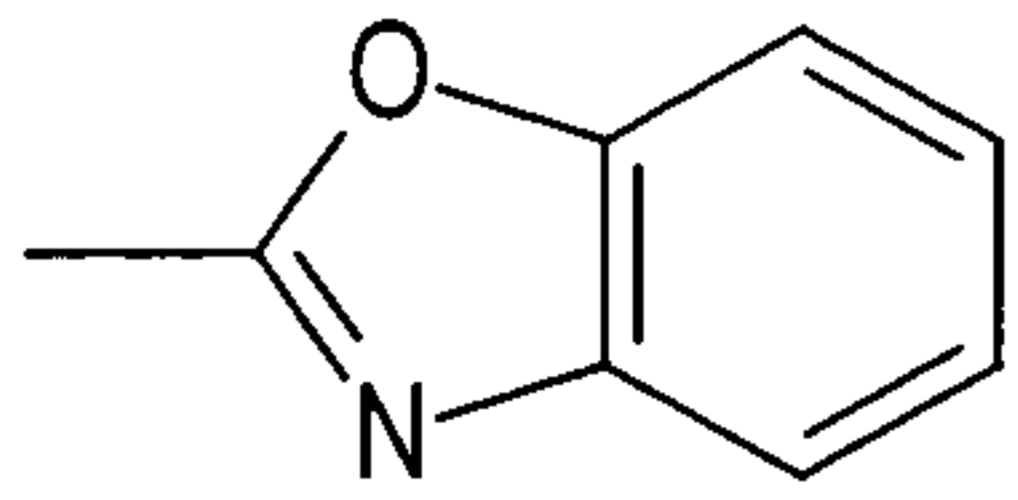
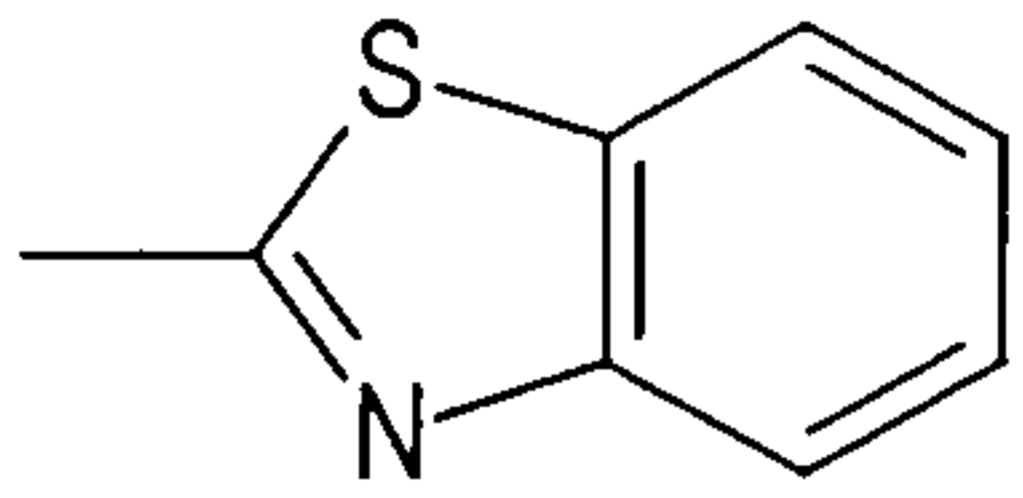
Still even more preferably R^{136} represents $–CH_2–O–CH_2R^{22}$, $–CH_2–O–CH_2–CH_2R^{22}$, $–CH_2–CH_2–O–CH_2R^{22}$, $–CH_2–O–CH_2–CH_2–CH_2R^{22}$, $–CH_2–CH_2–O–CH_2–CH_2R^{22}$, $–CH_2–CH_2–CH_2–O–CH_2R^{22}$; and R^{22} represents –H, $–CH_3$, $–CF_3$, $–C_2H_5$.

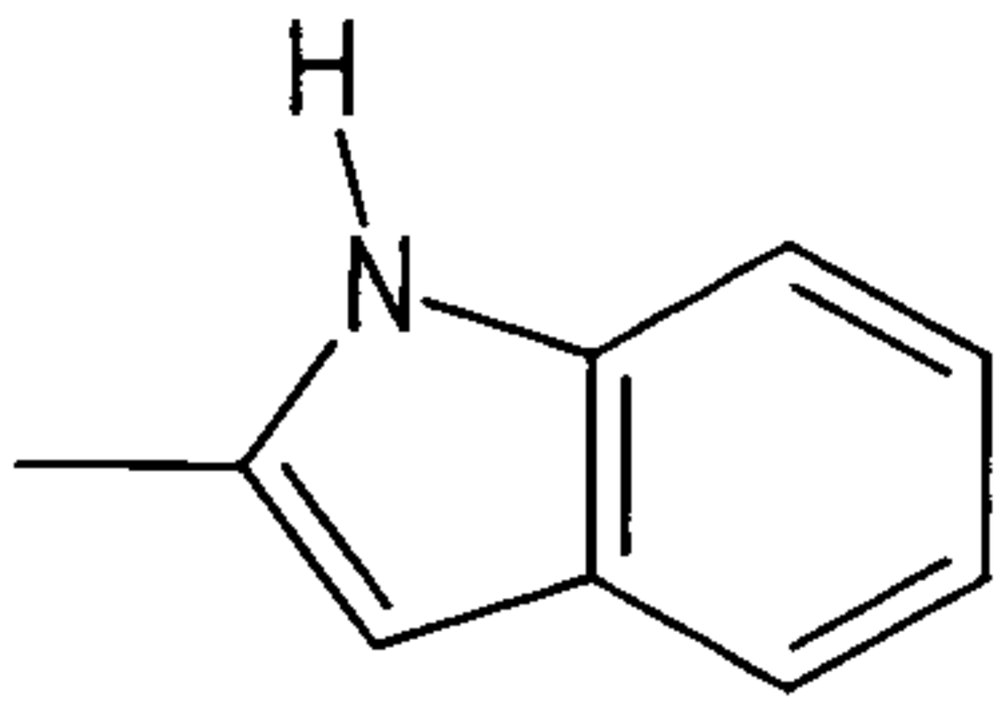
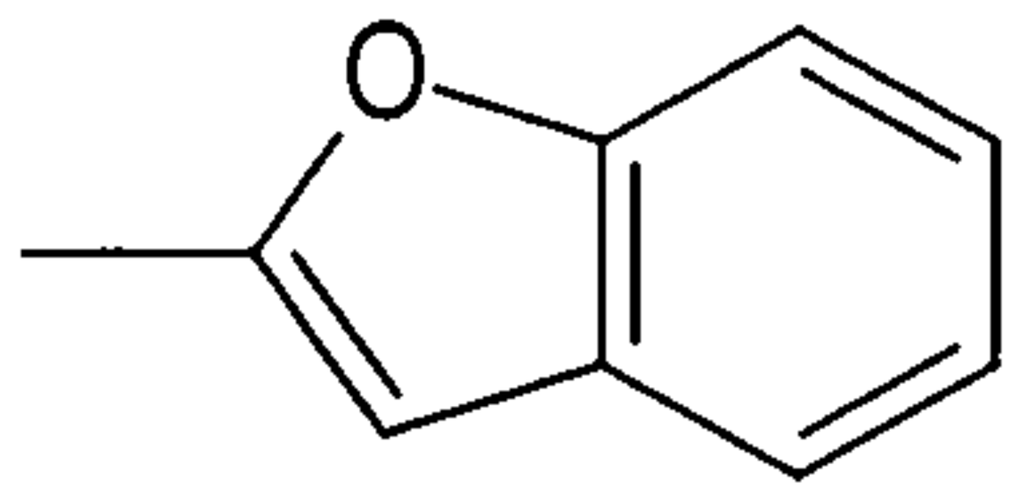
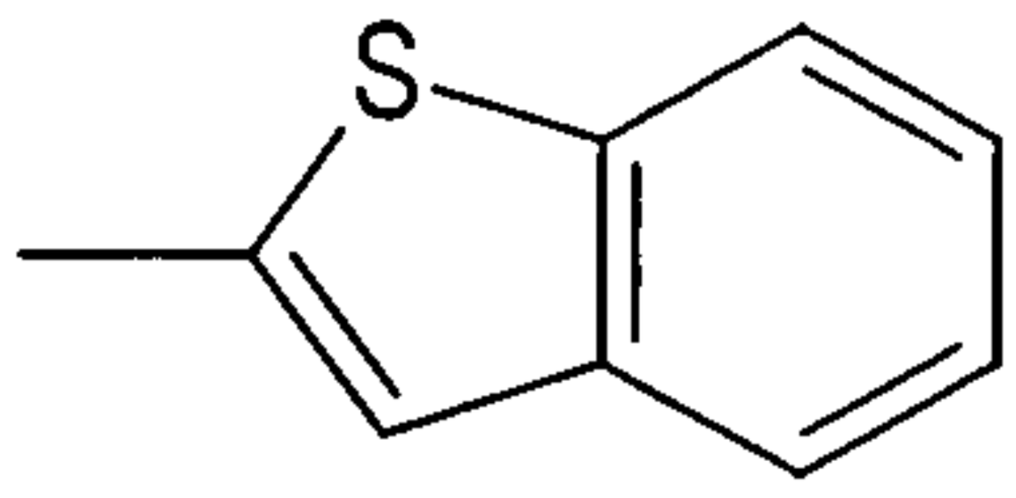
Most preferably R^{136} represents $–CH_2–O–CH_2CF_3$, $–CH_2–O–CH_2–CH_2CF_3$, $–CH_2–CH_2–O–CH_2CF_3$.

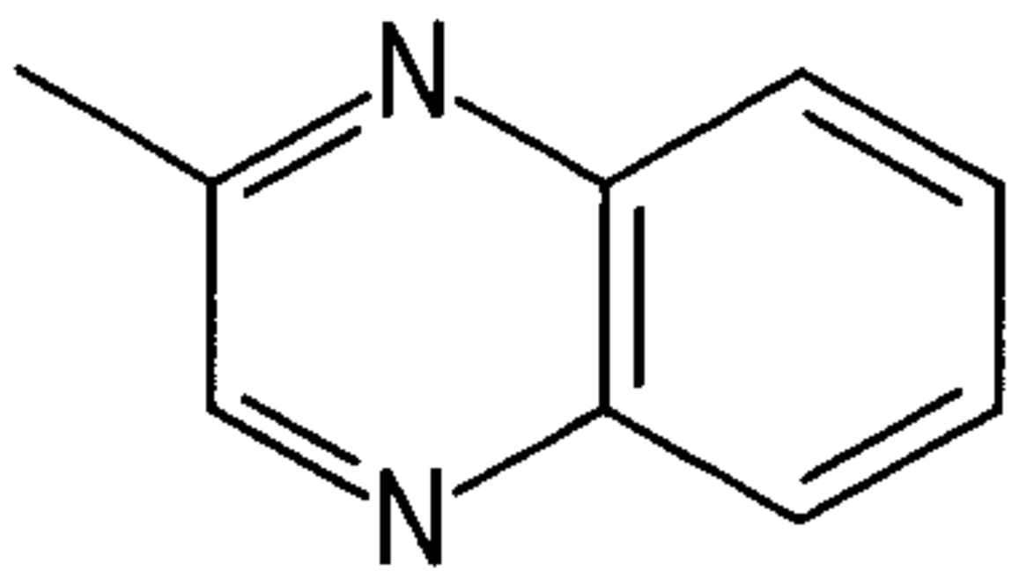
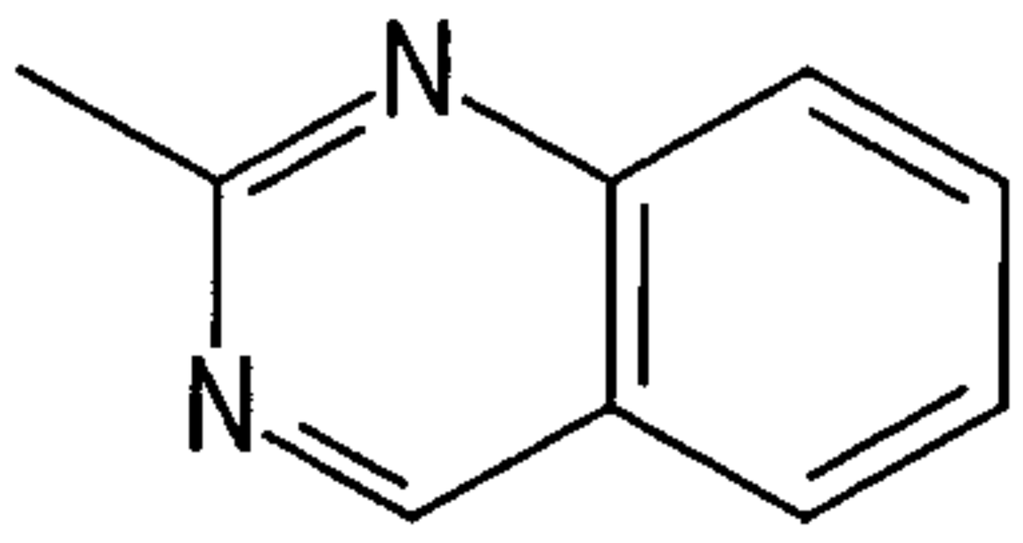
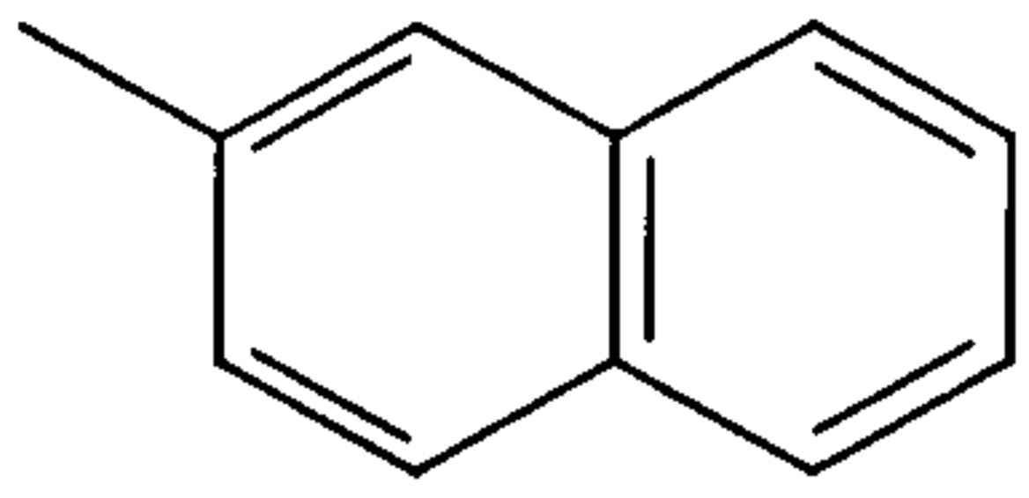
R^{113} represents preferably

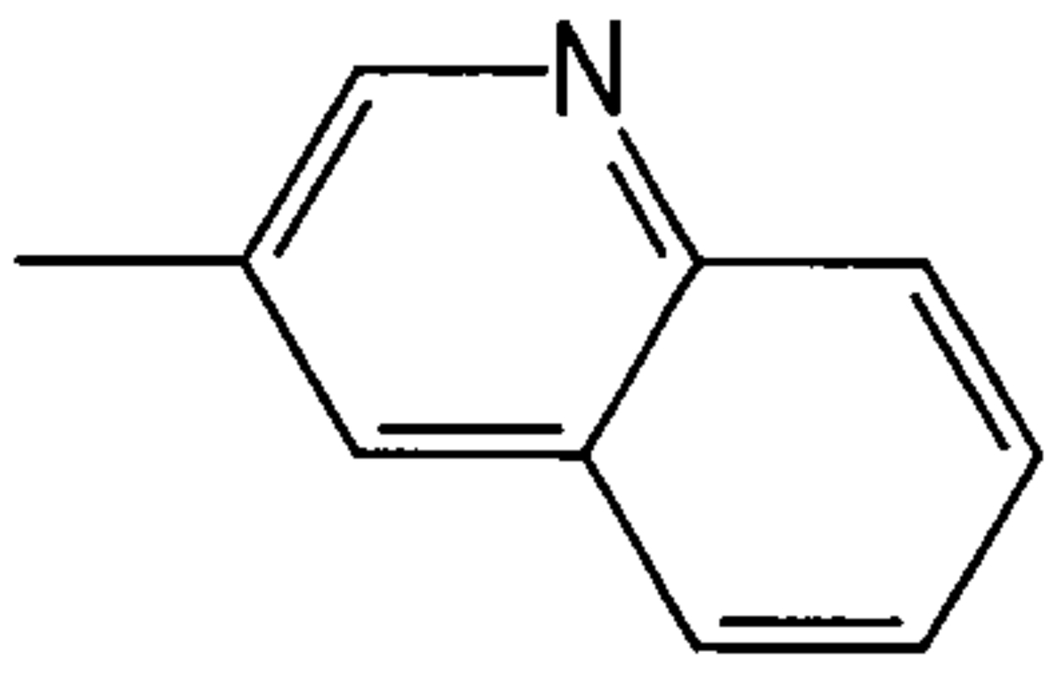
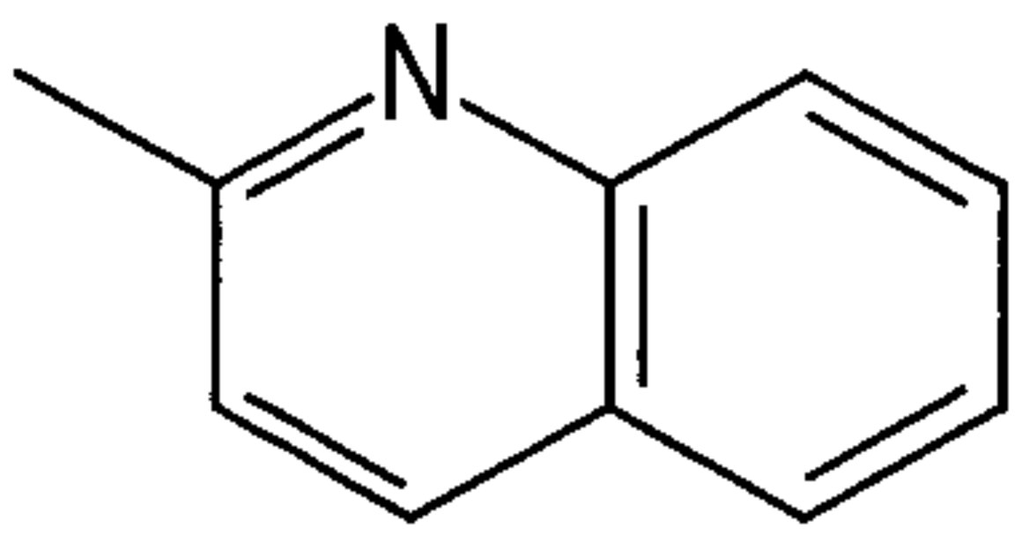
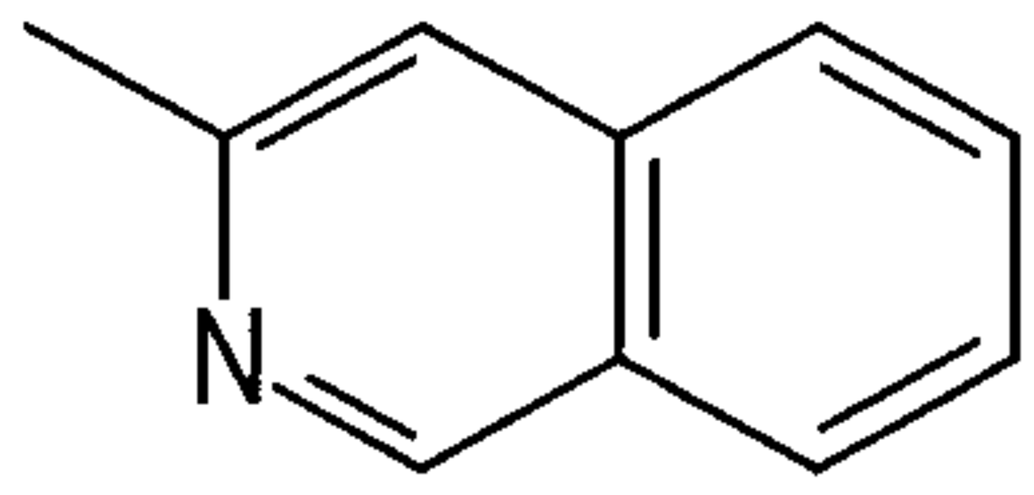
 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 

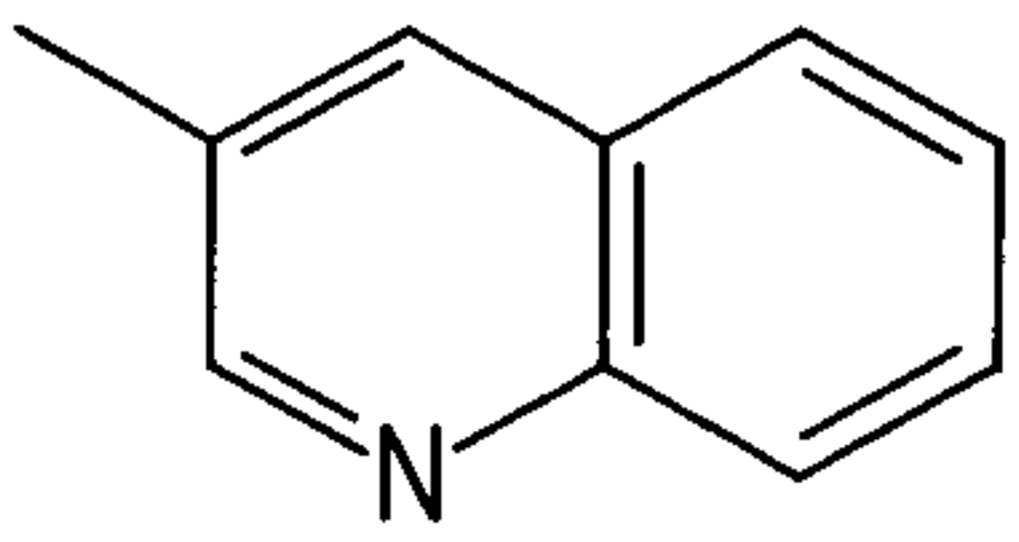
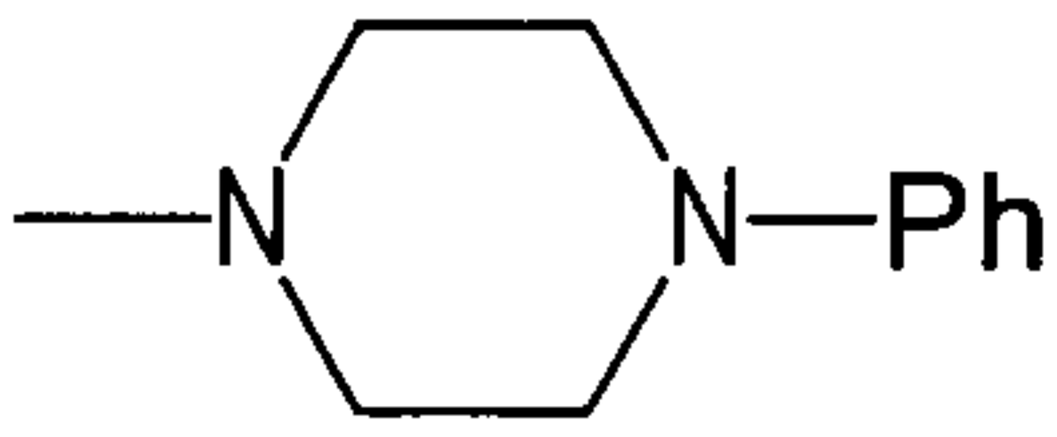
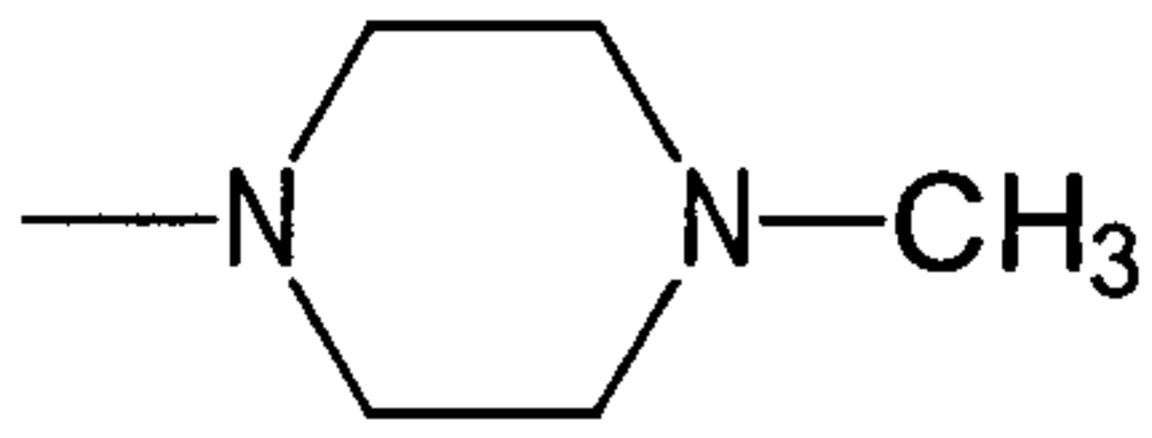


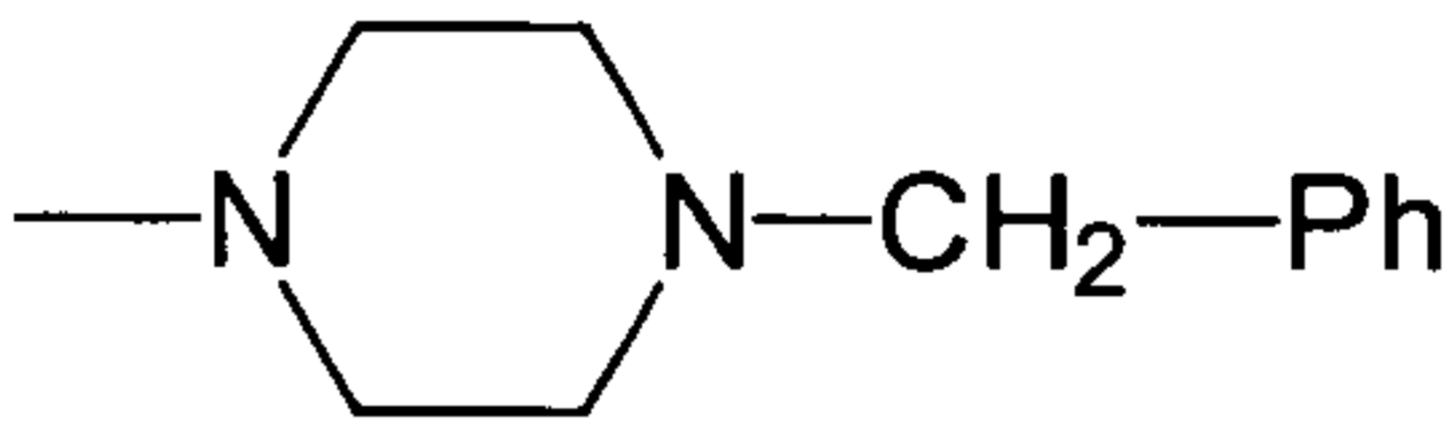
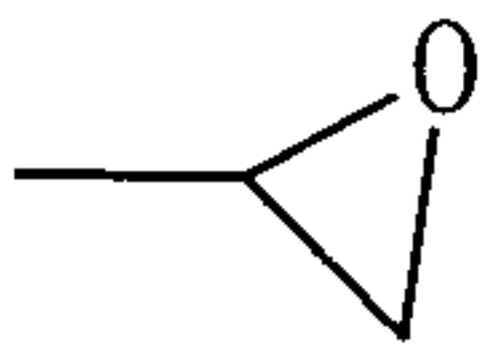
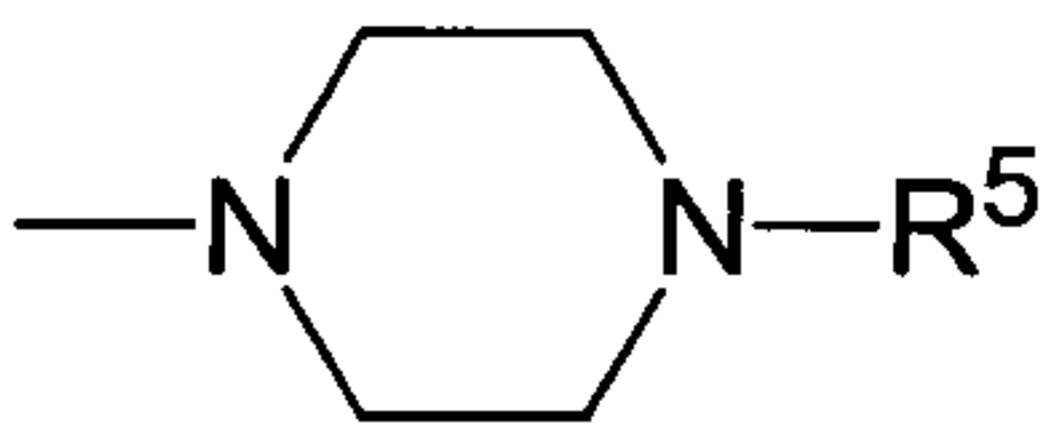
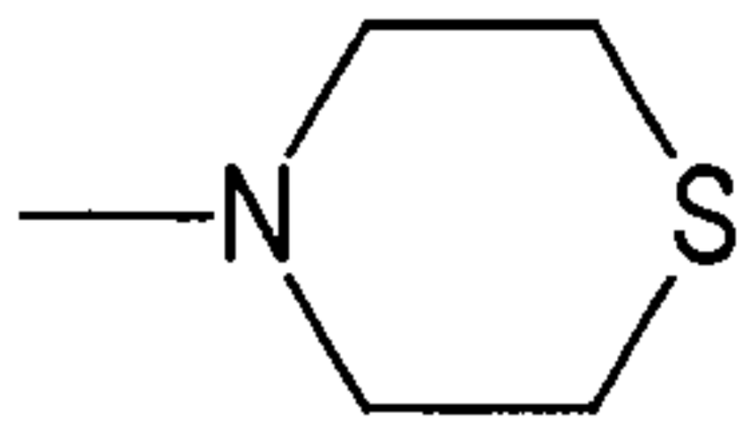
 ,  ,  ,

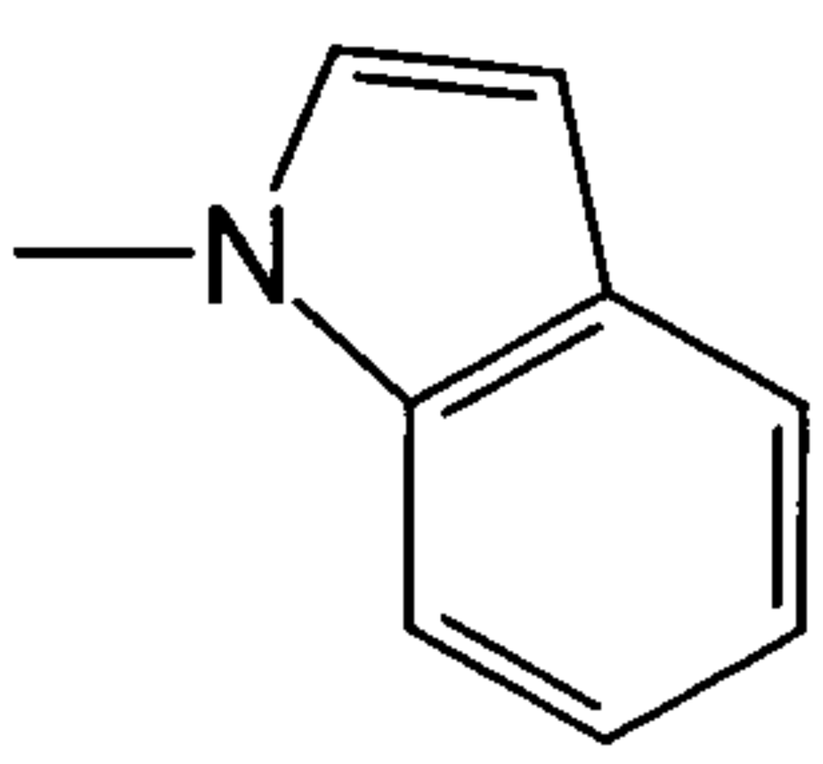
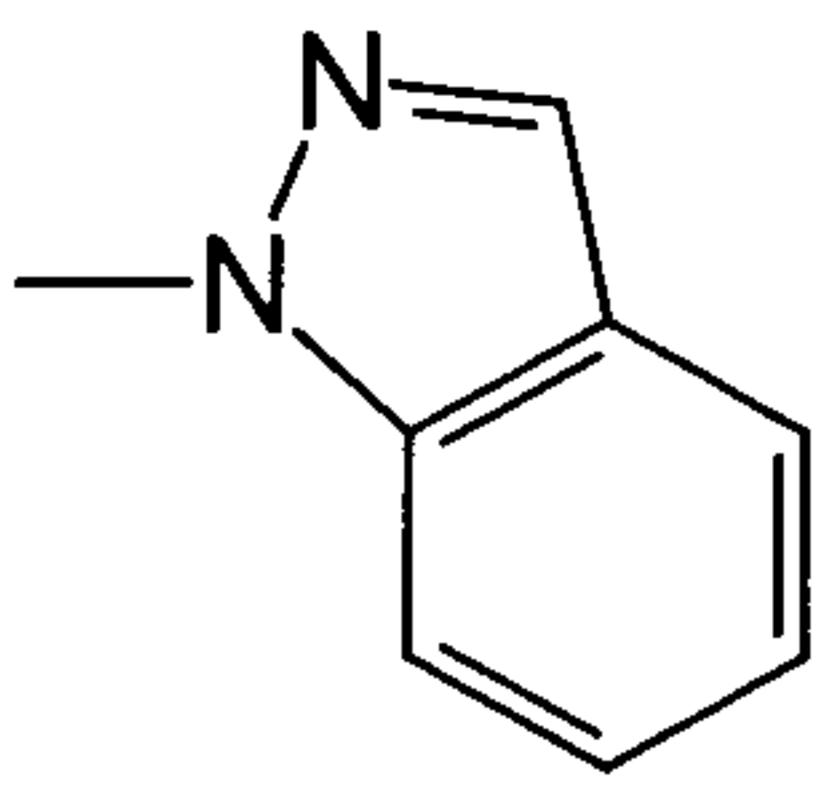
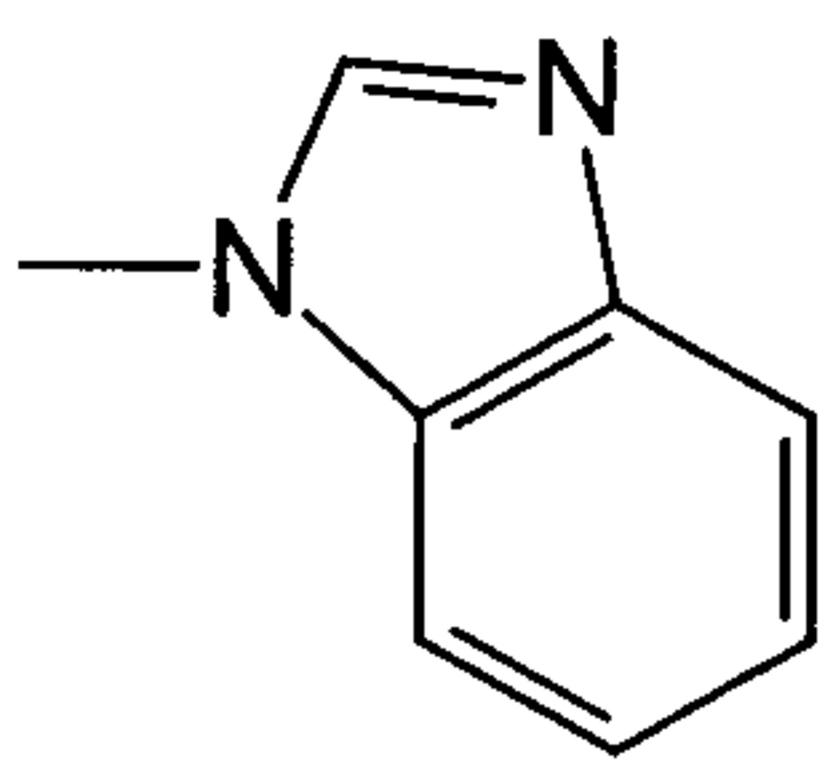
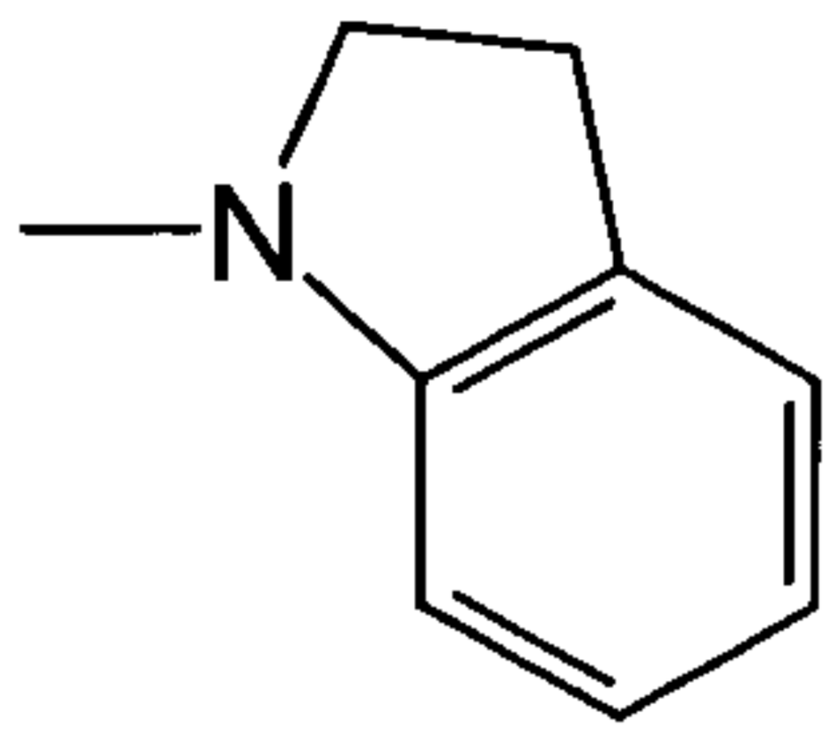
 ,  ,  ,

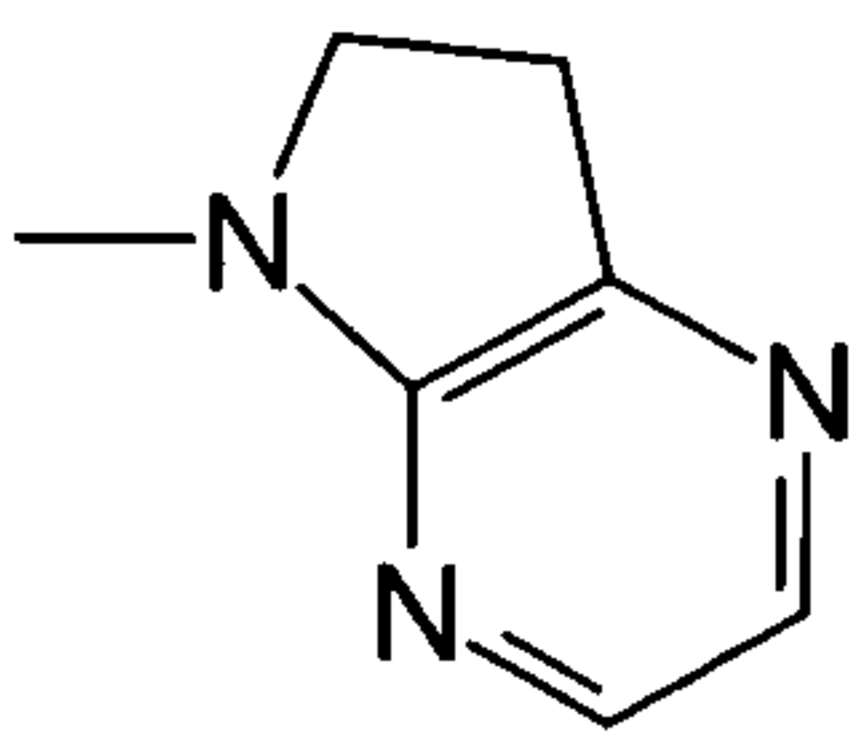
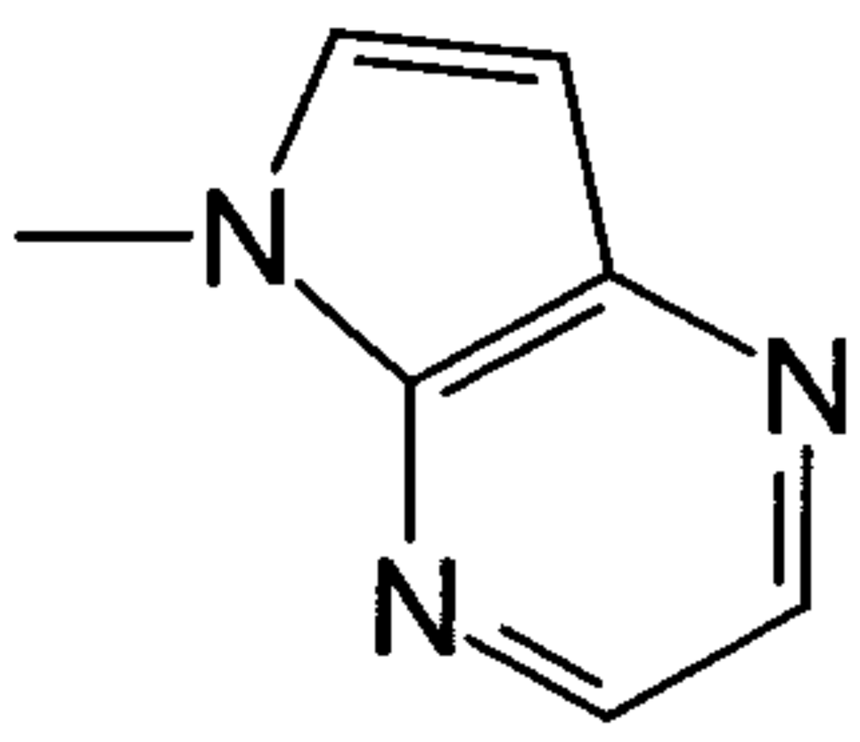
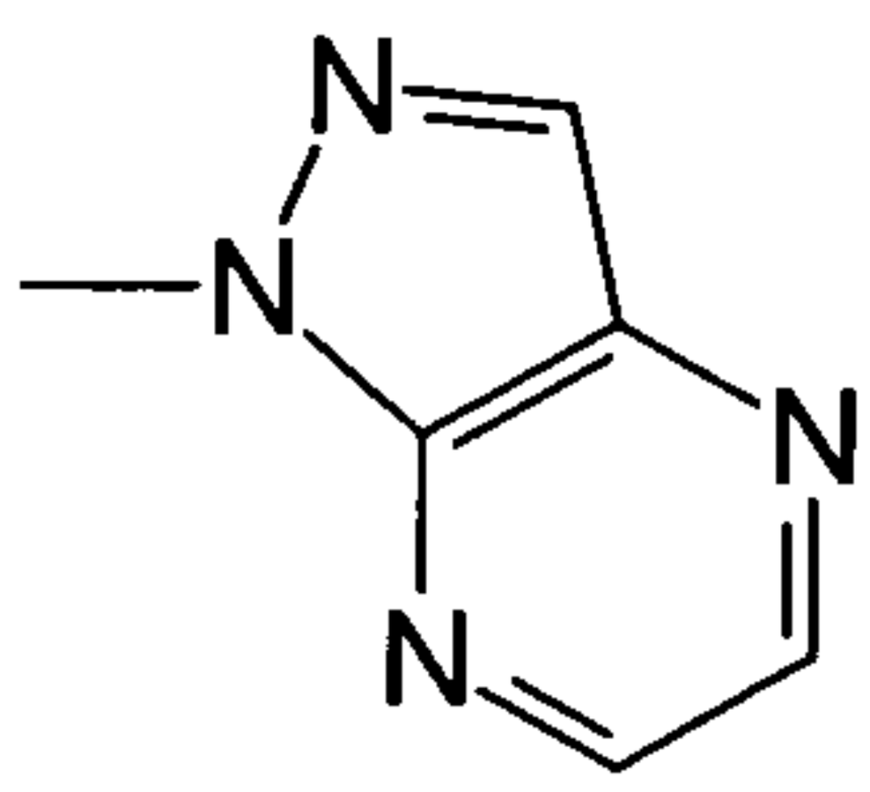
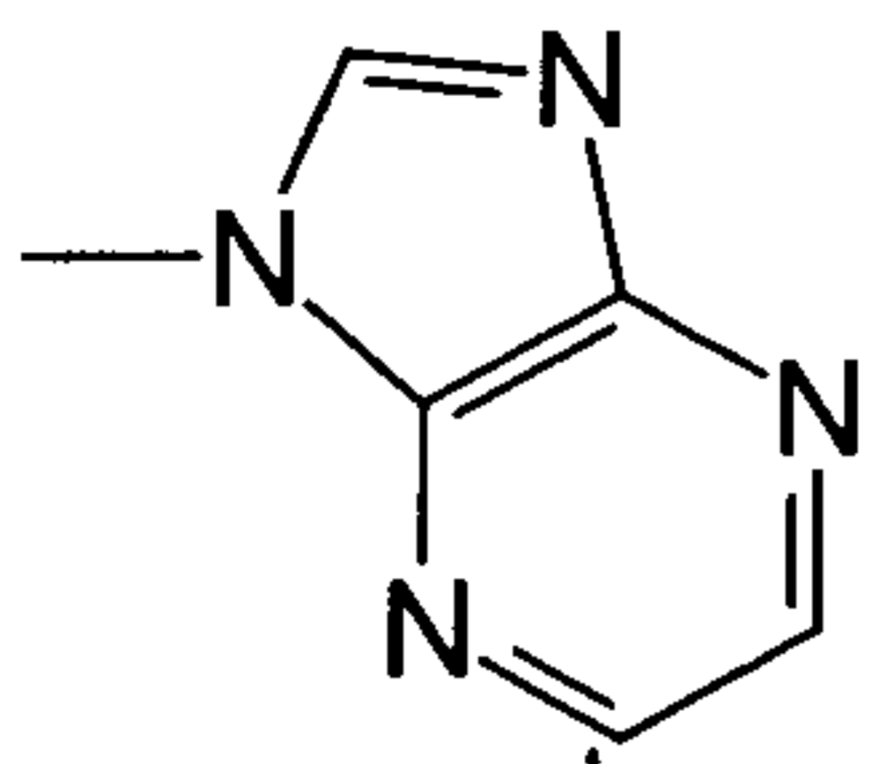
 ,  ,  ,

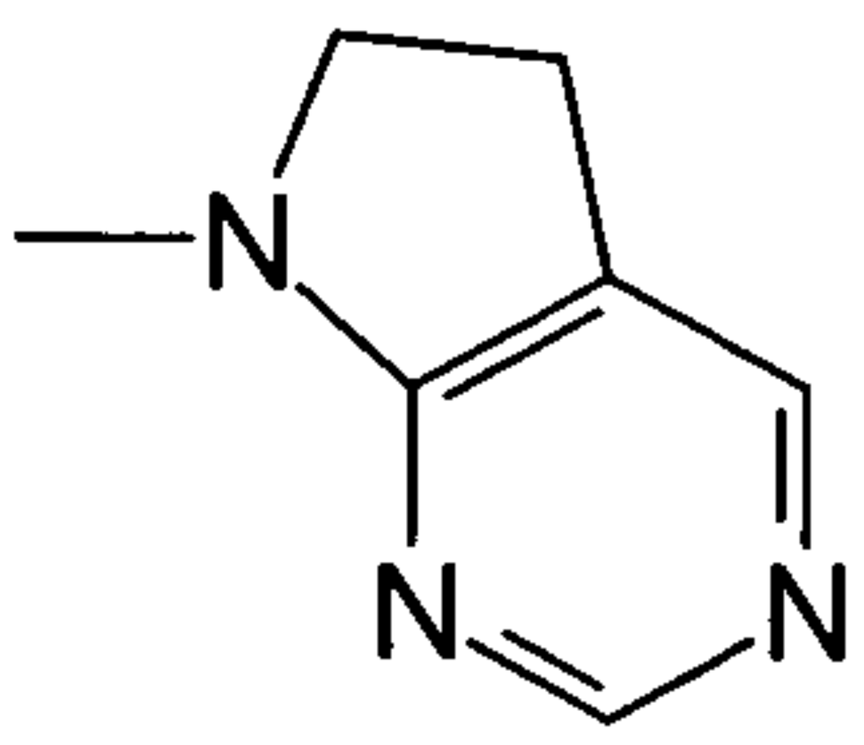
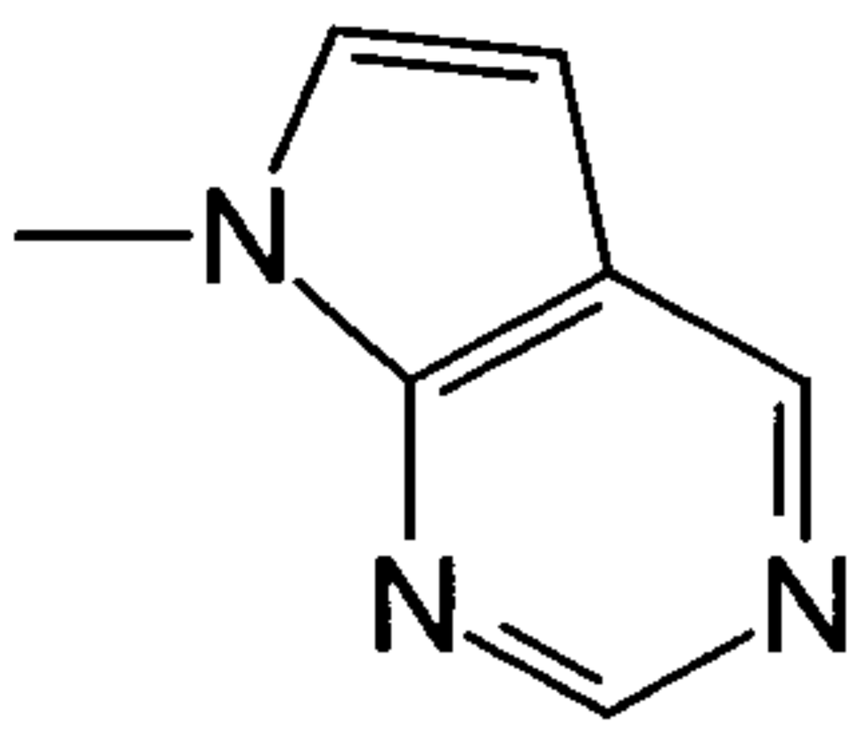
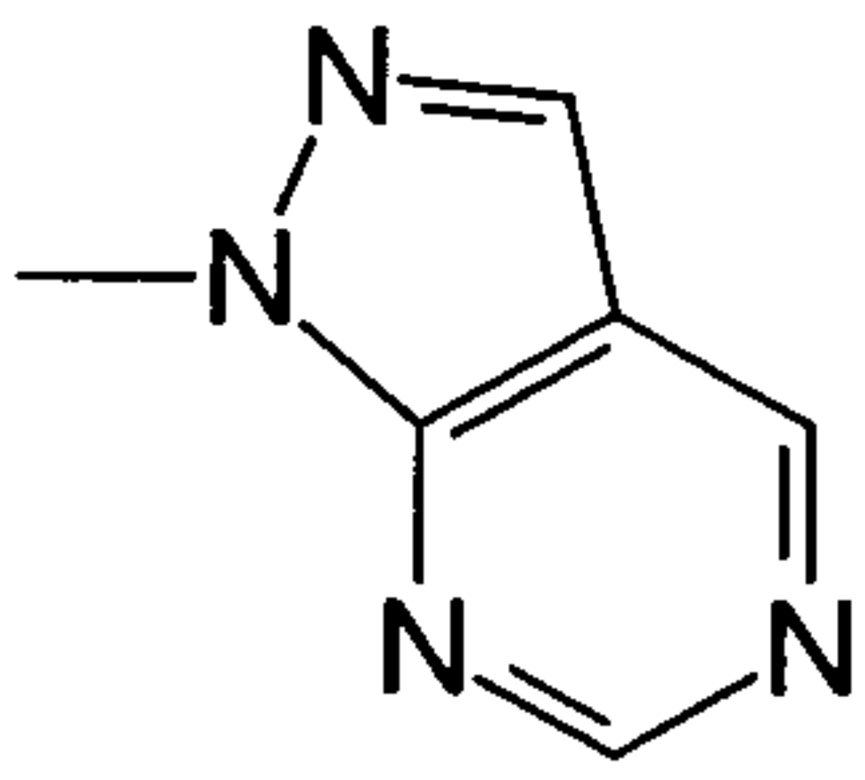
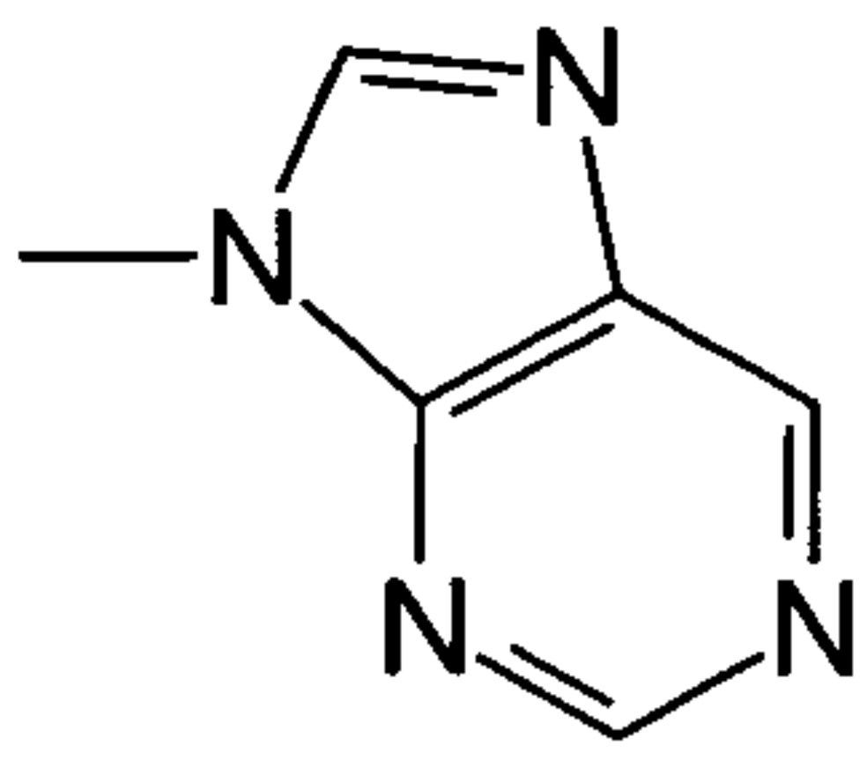
  ,  ,

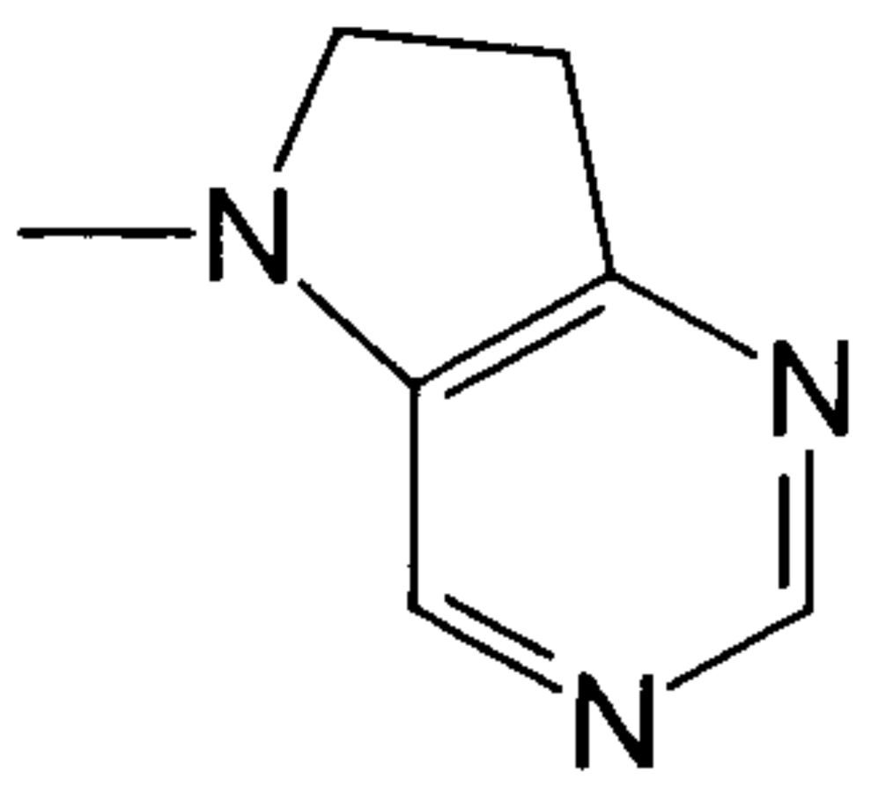
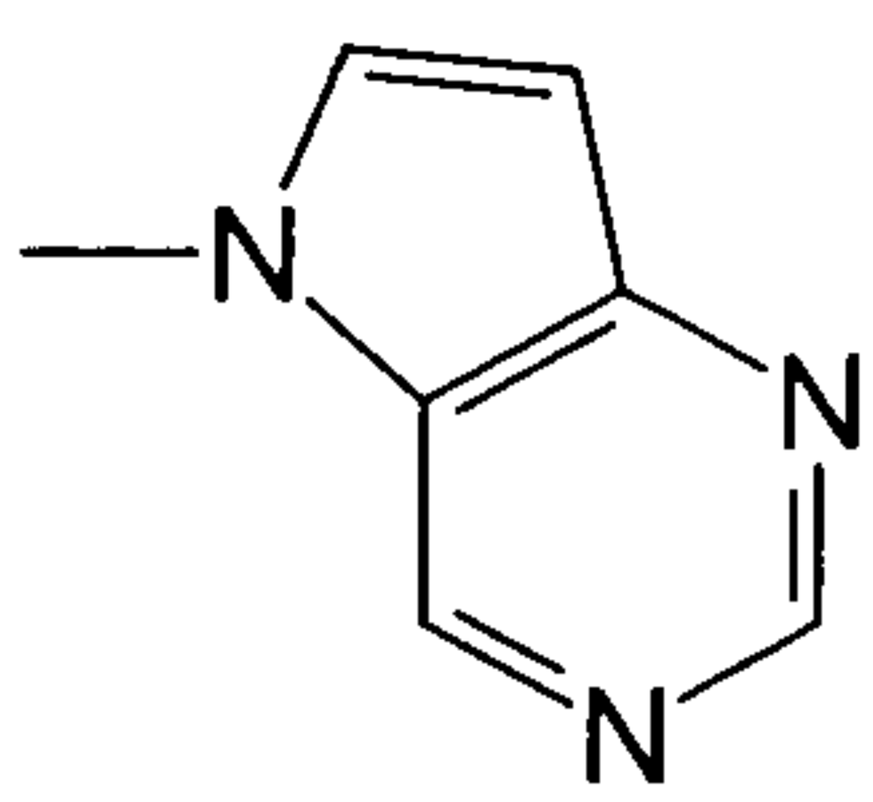
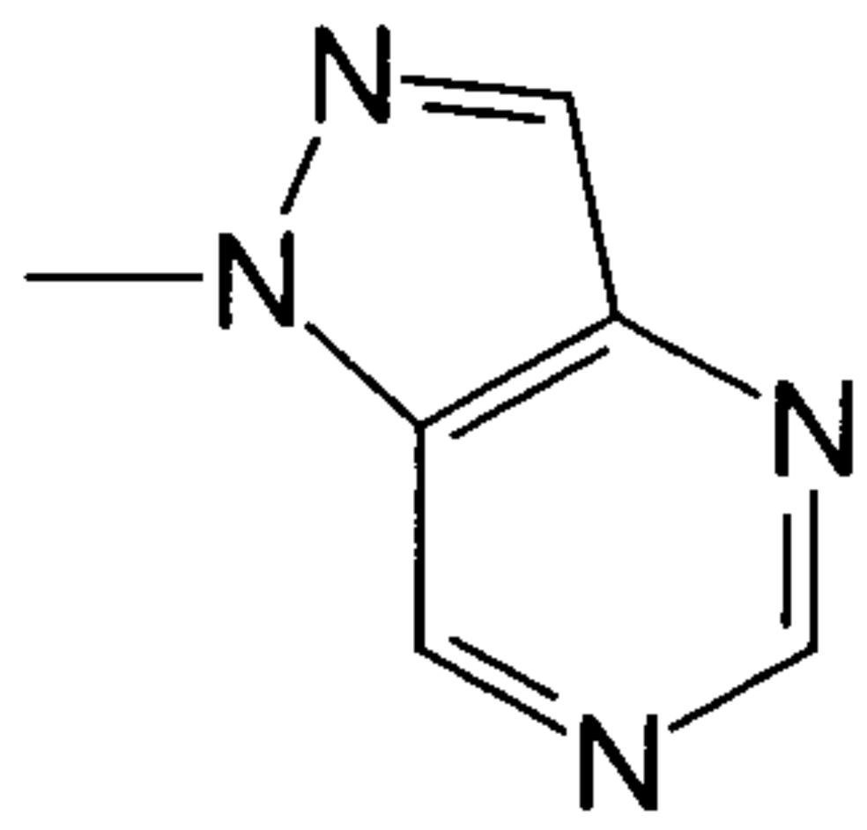
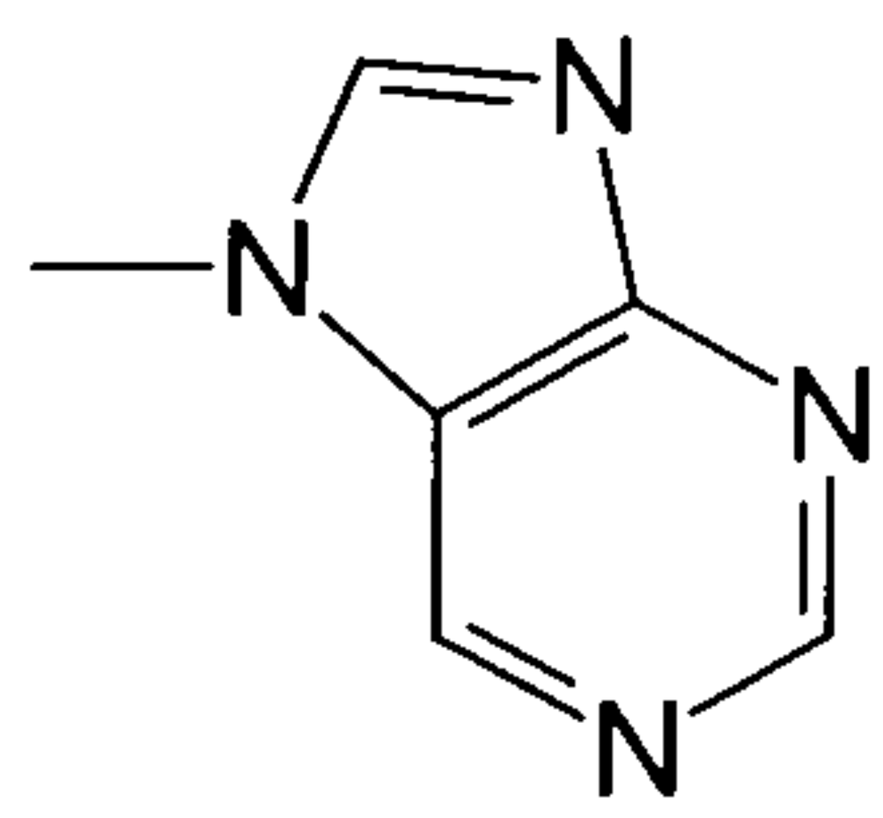
 ,  ,  ,

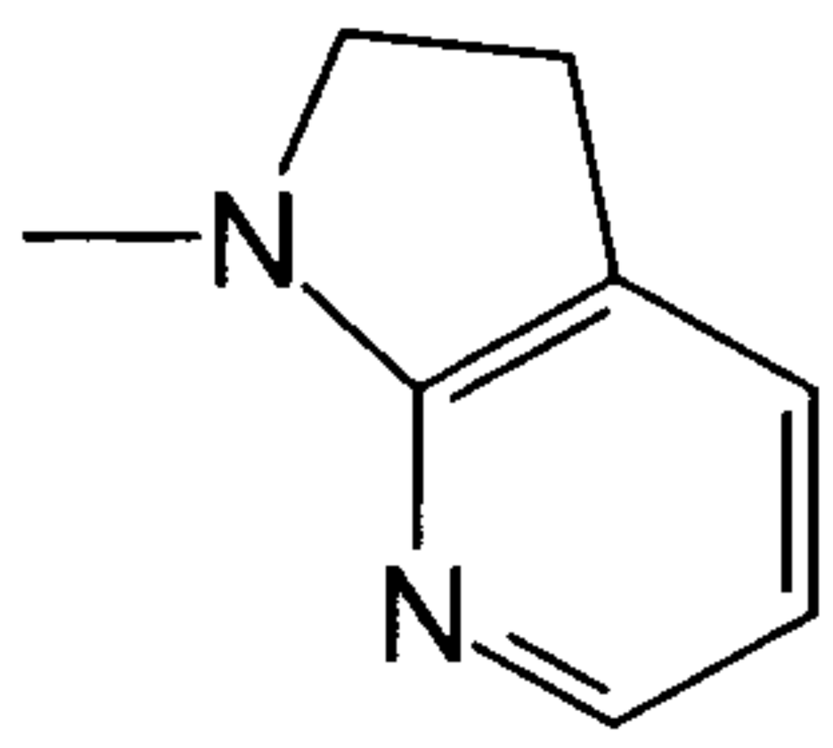
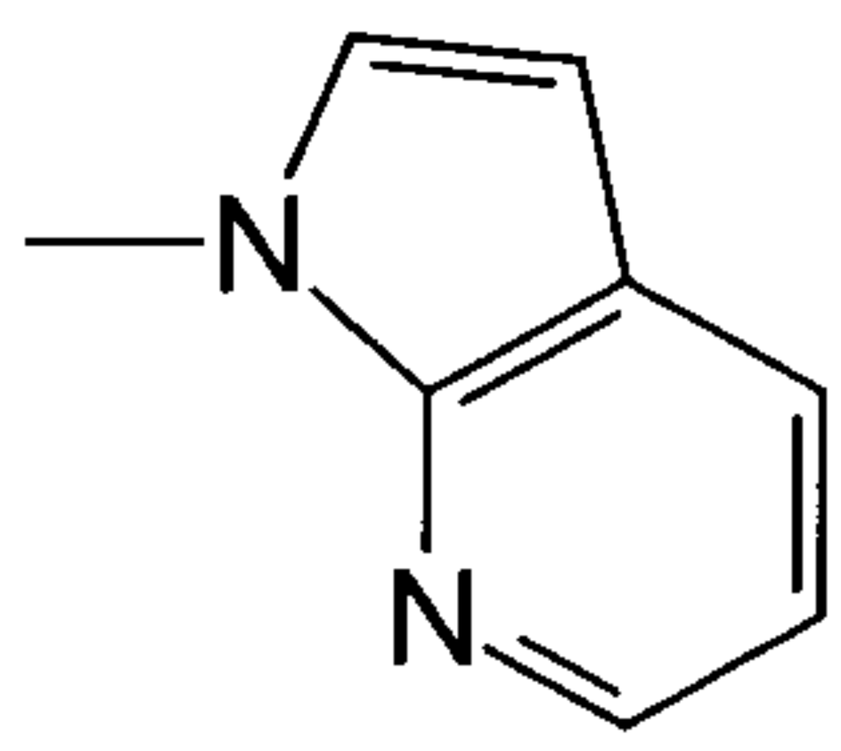
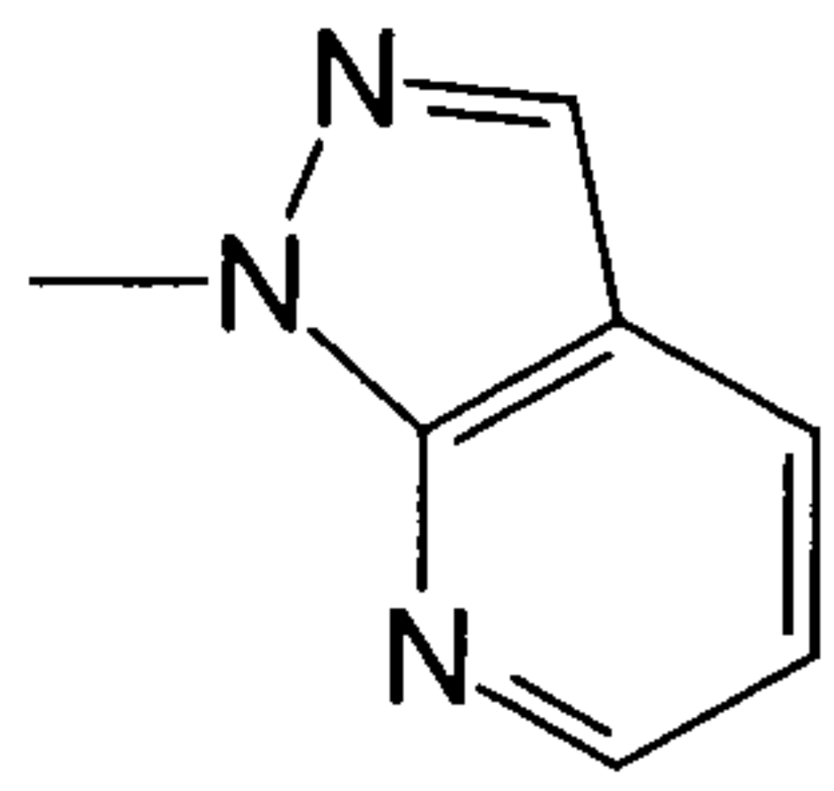
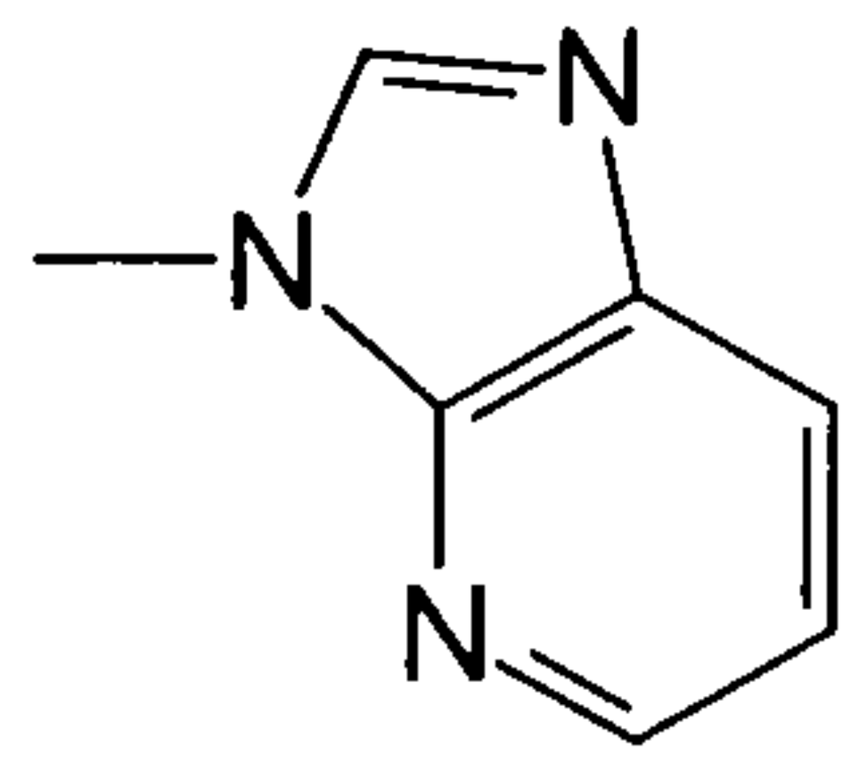
 ,  ,  ,  ,

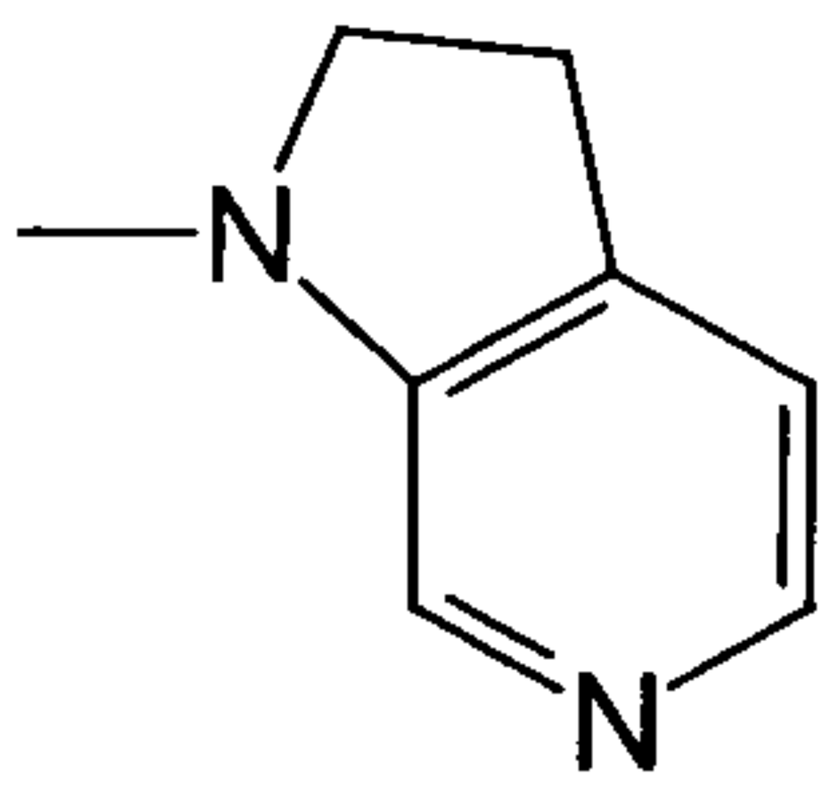
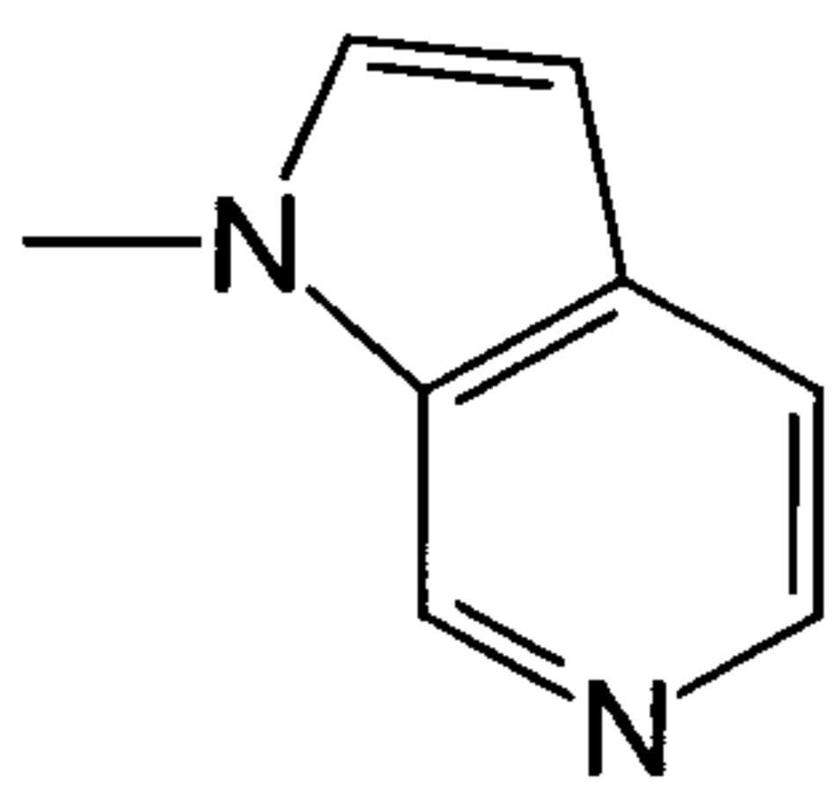
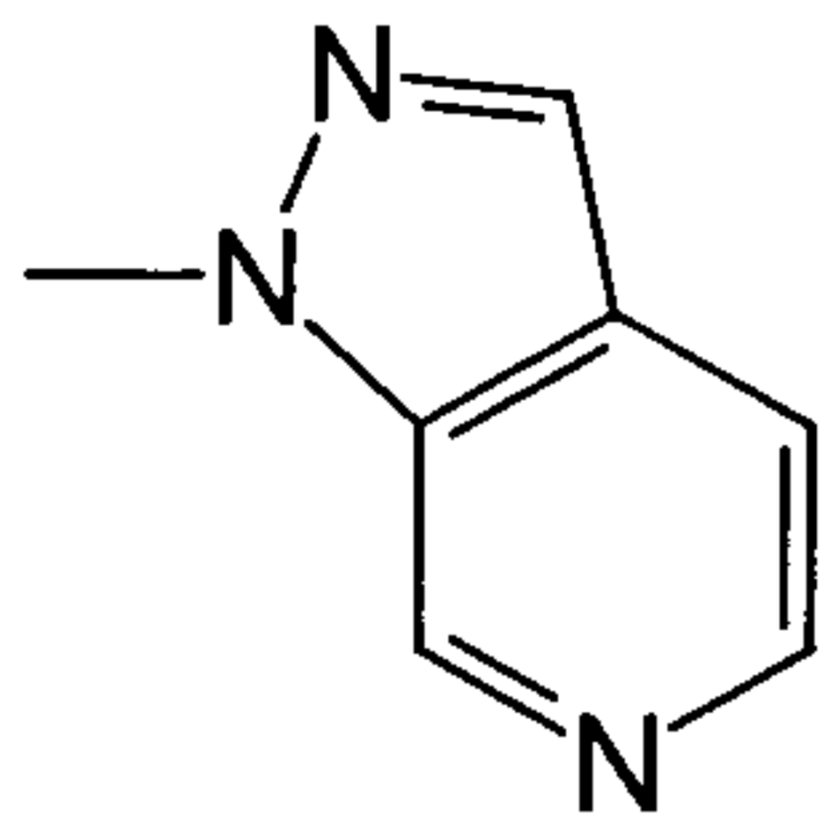
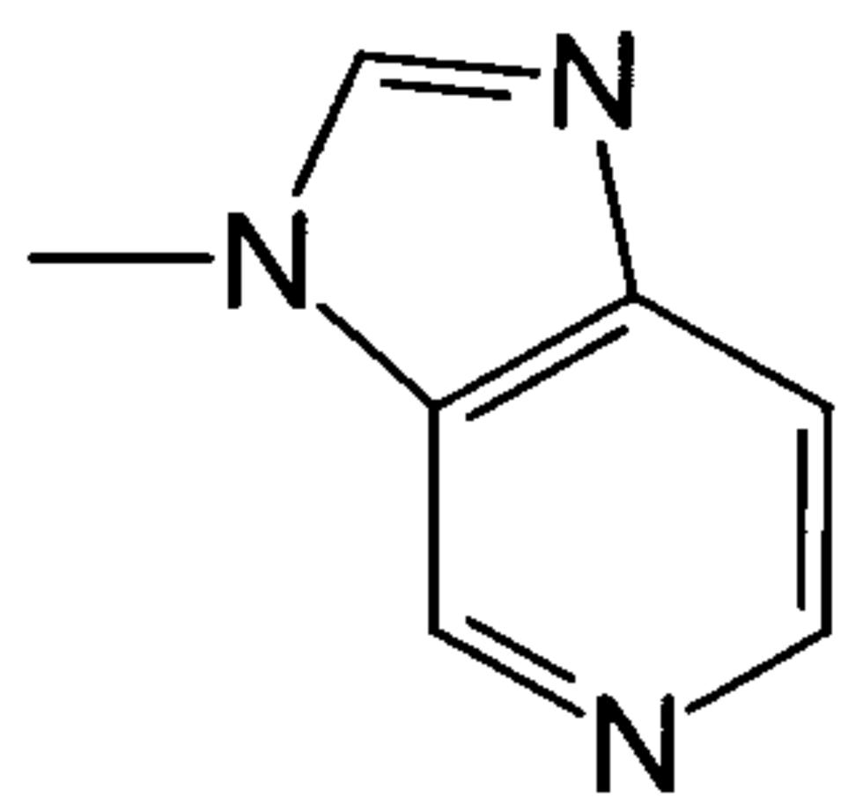
 ,  ,  ,  ,

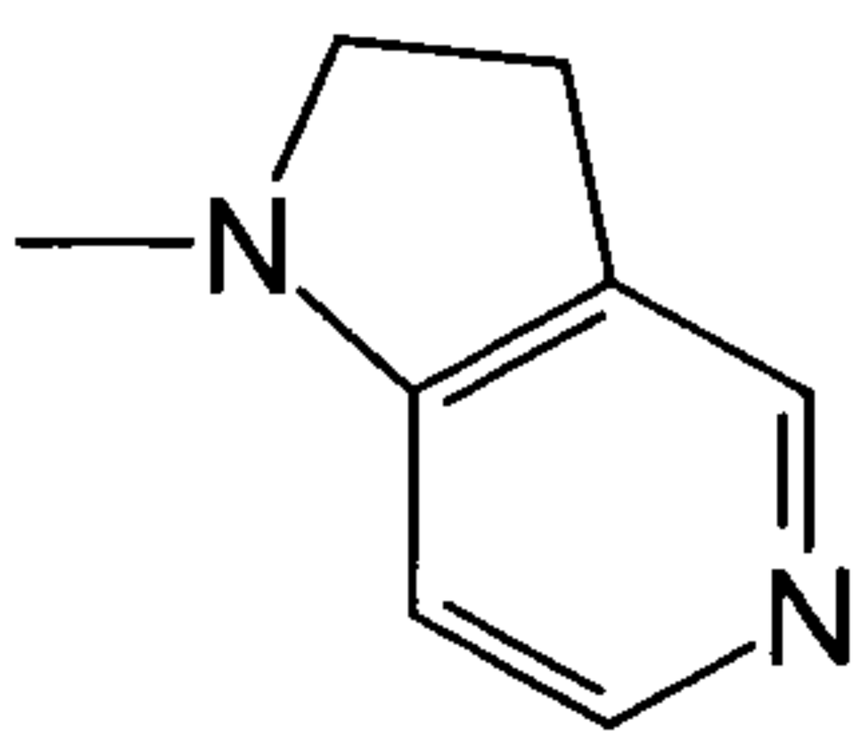
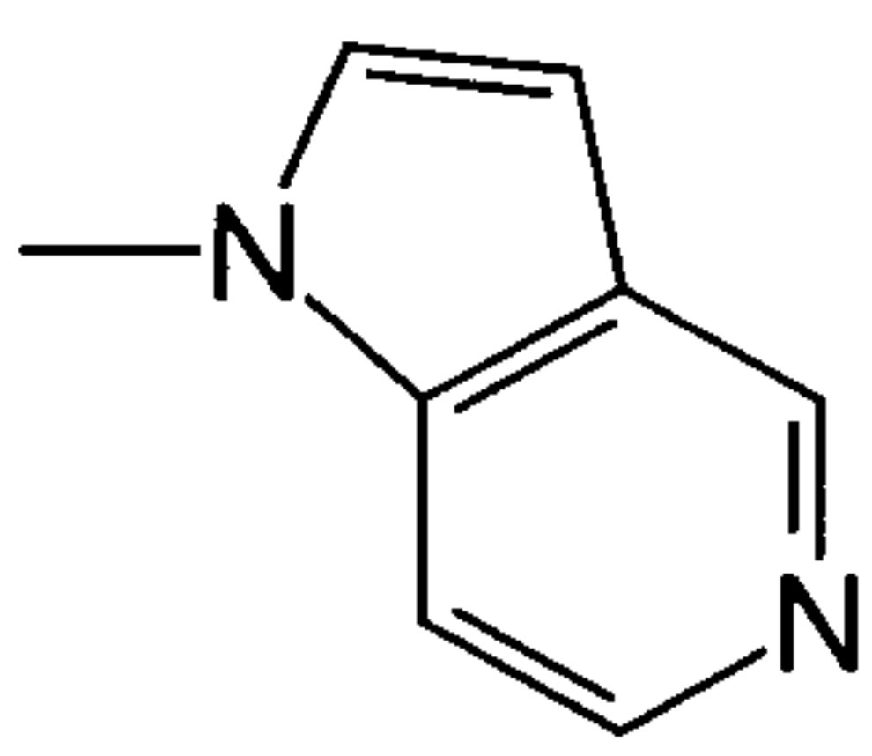
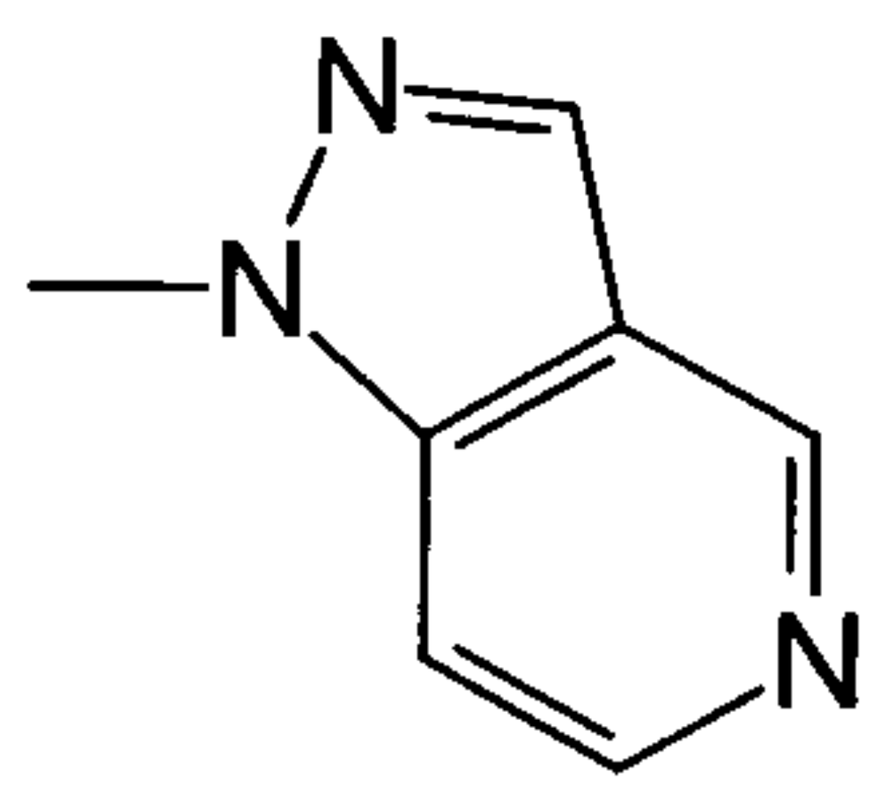
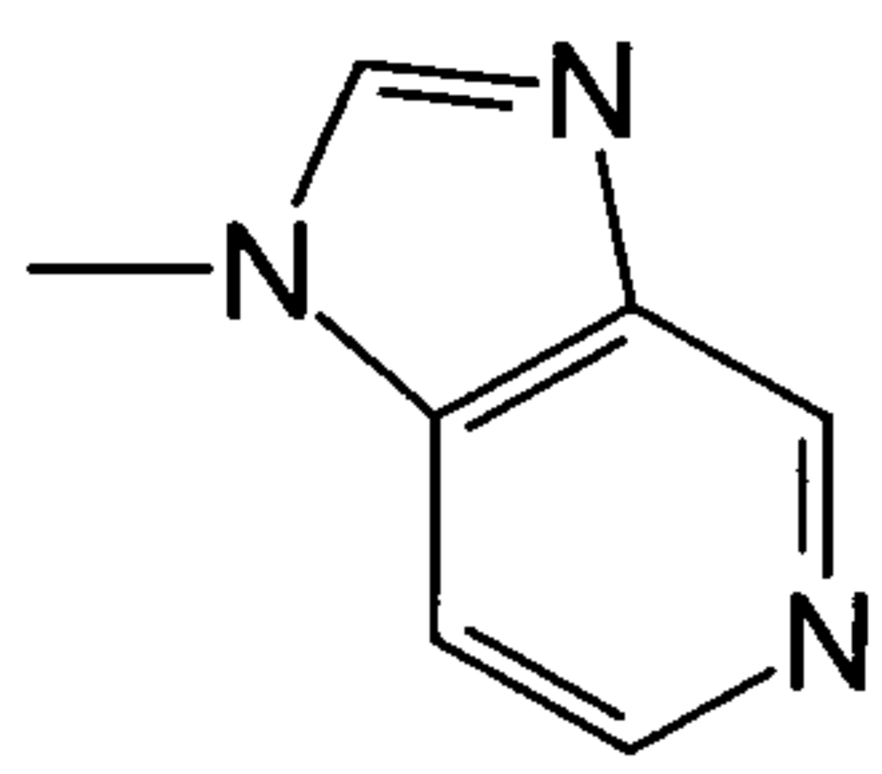
 ,  ,  ,  ,

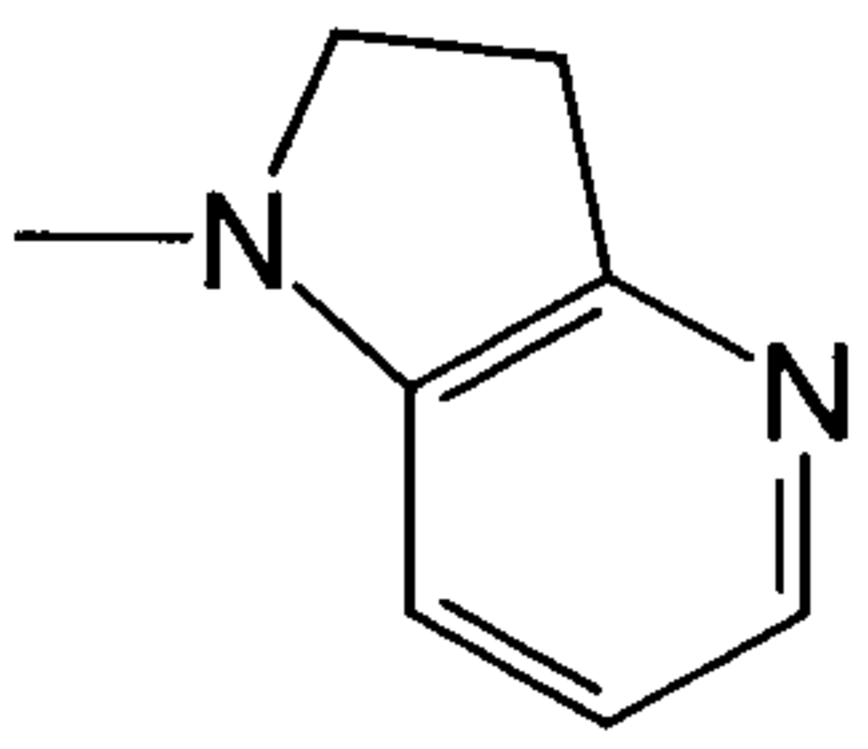
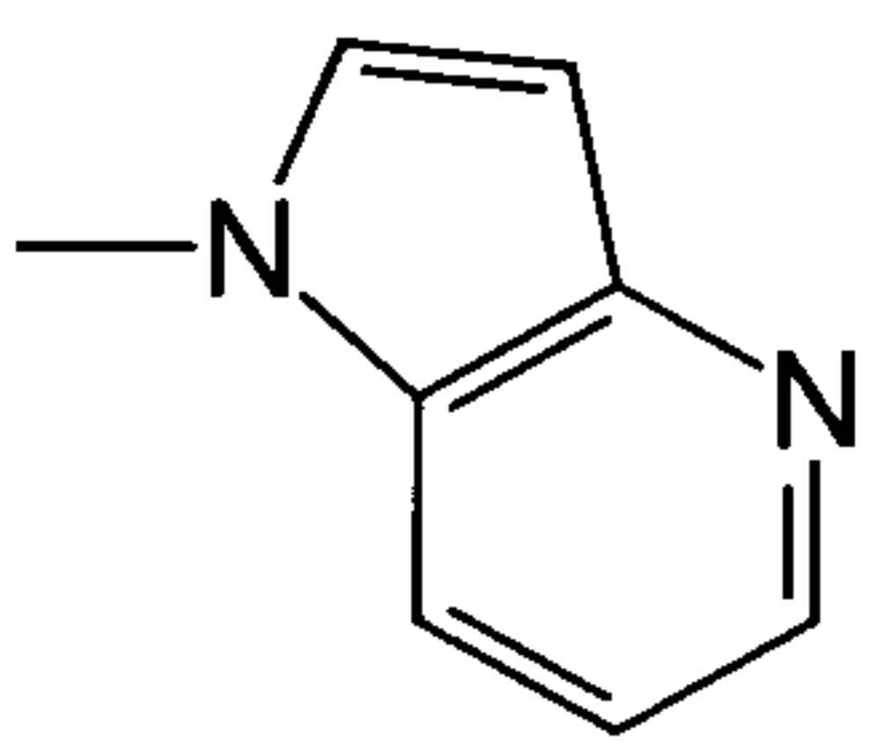
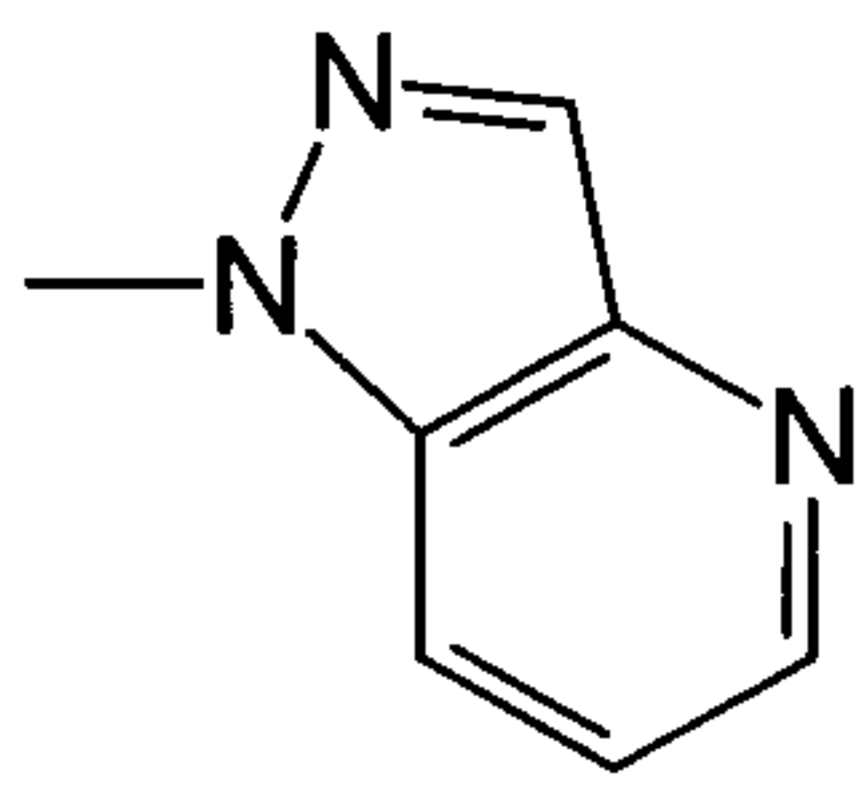
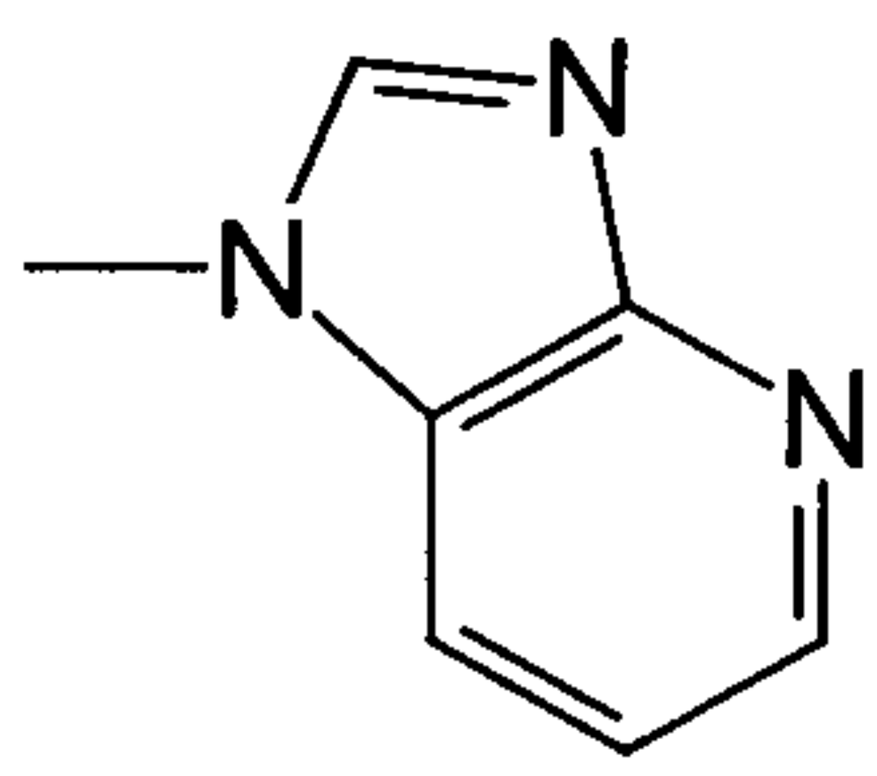
 ,  ,  ,  ,

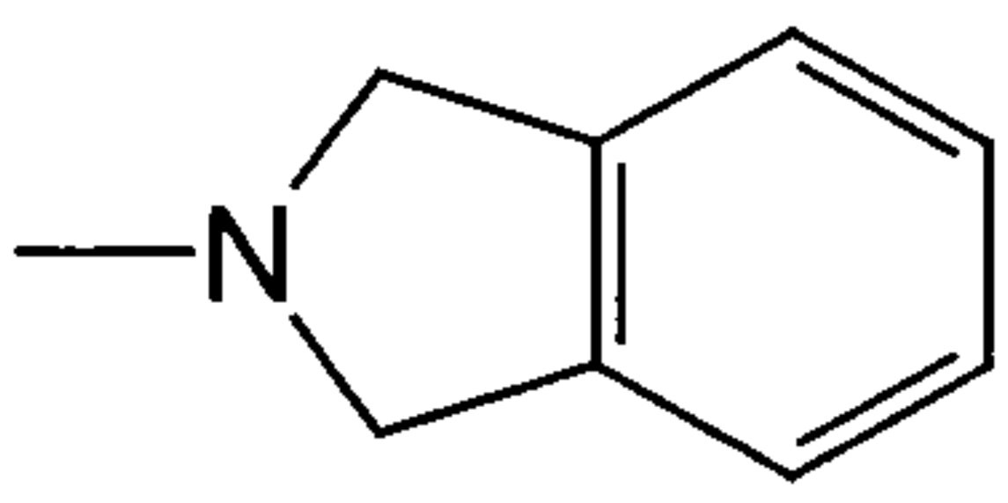
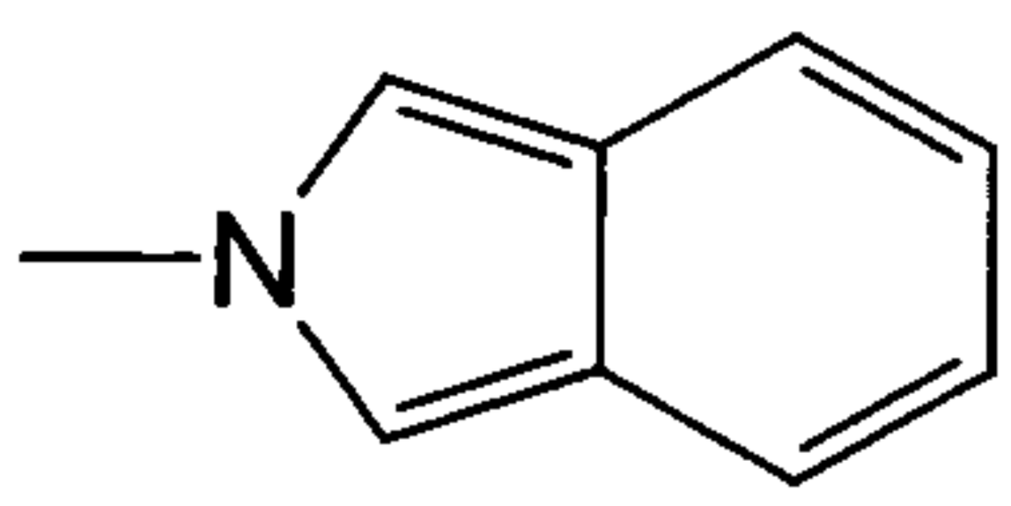
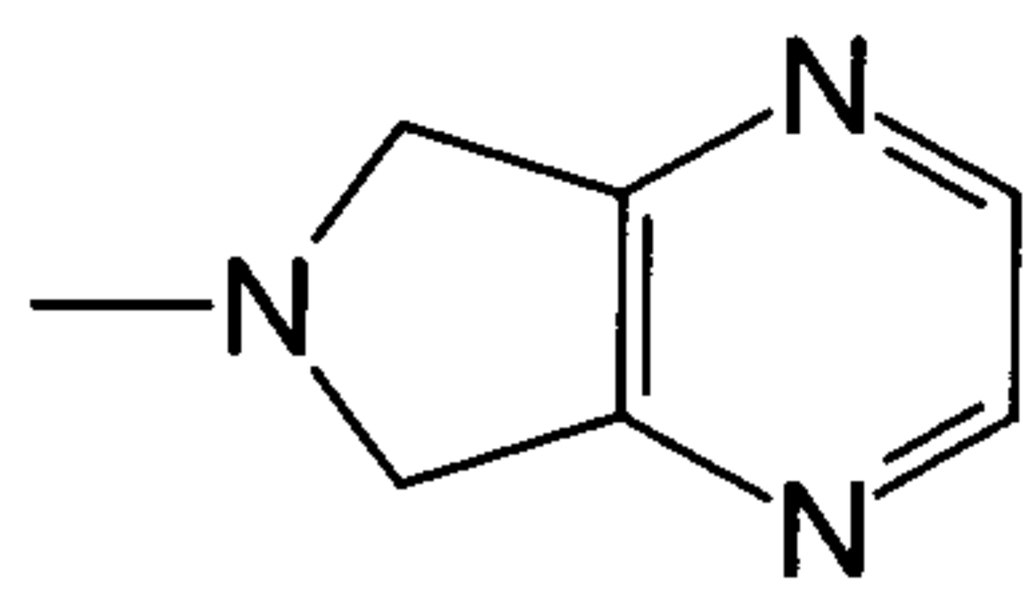
 ,  ,  ,  ,

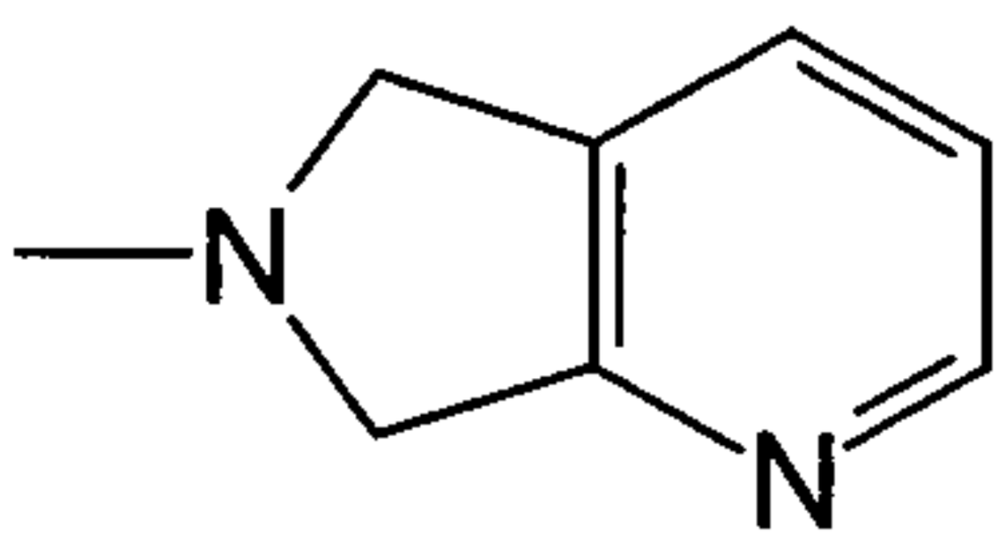
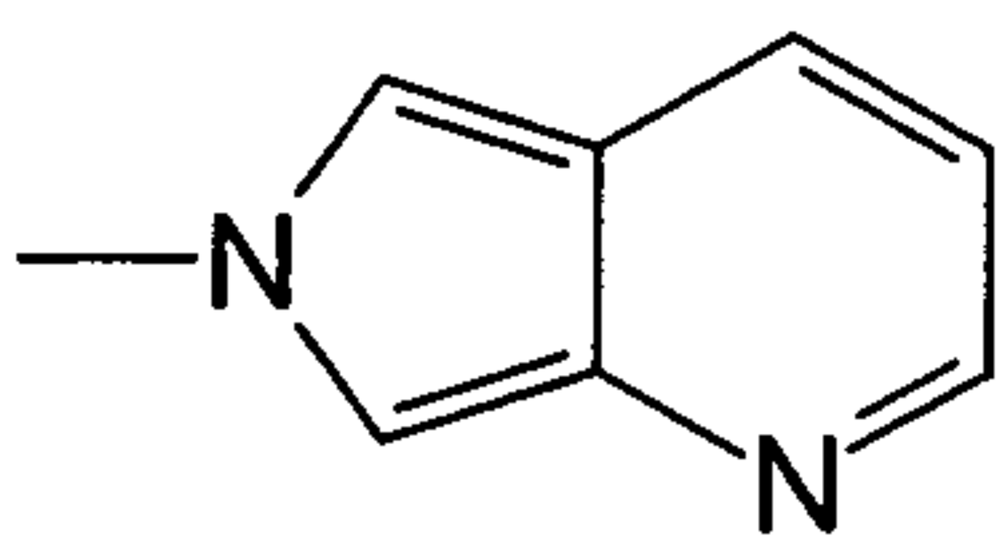
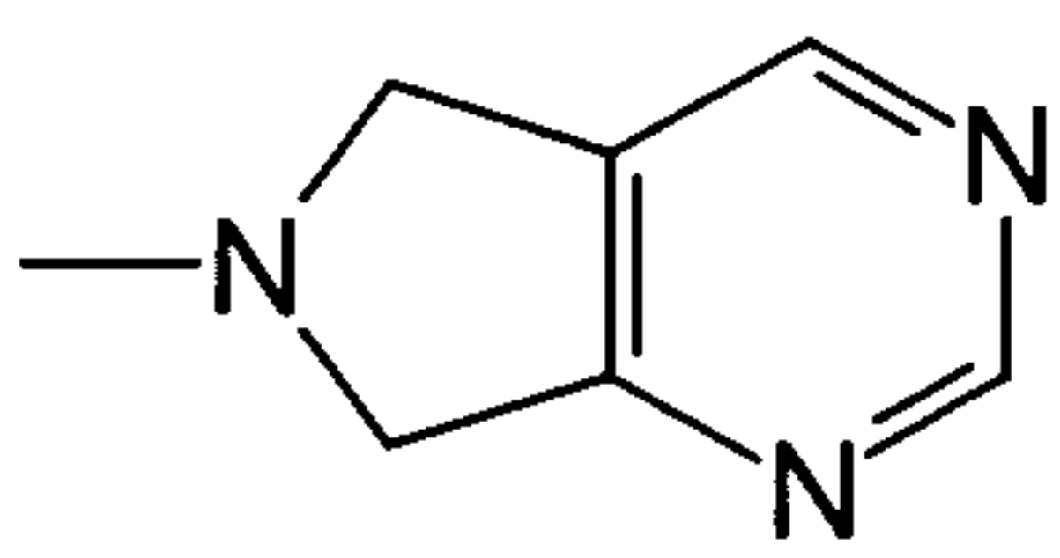
 ,  ,  ,  ,

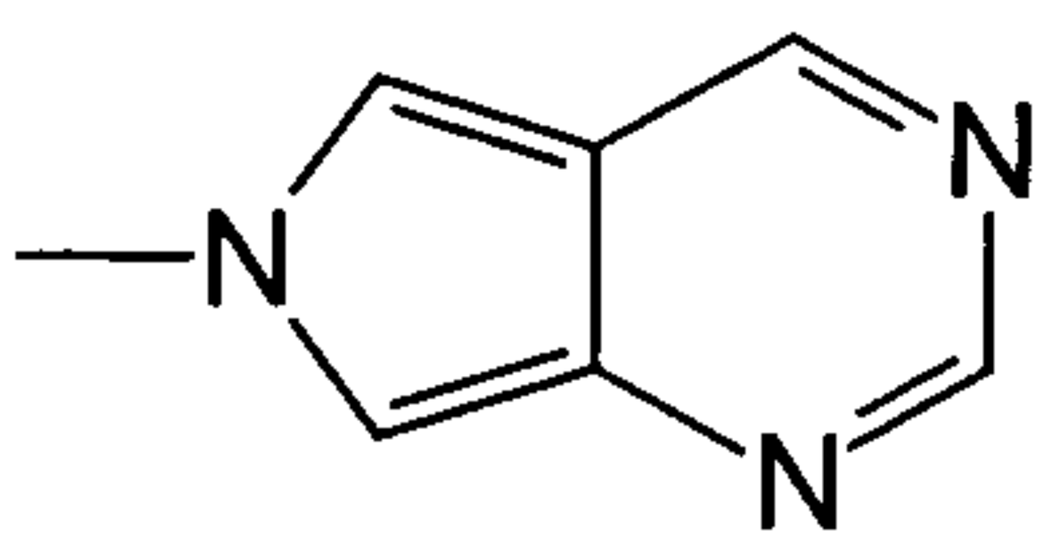
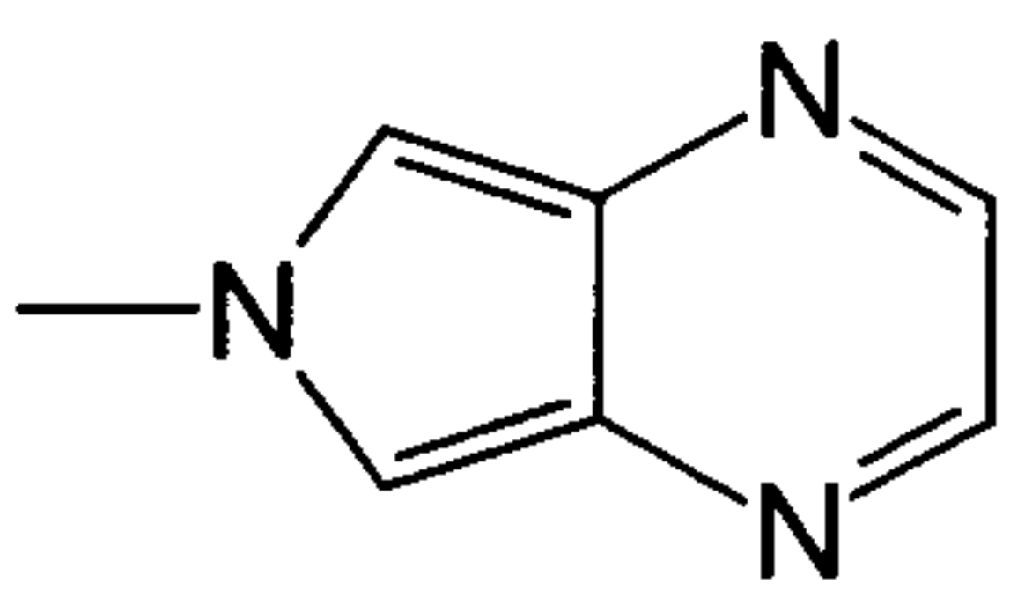
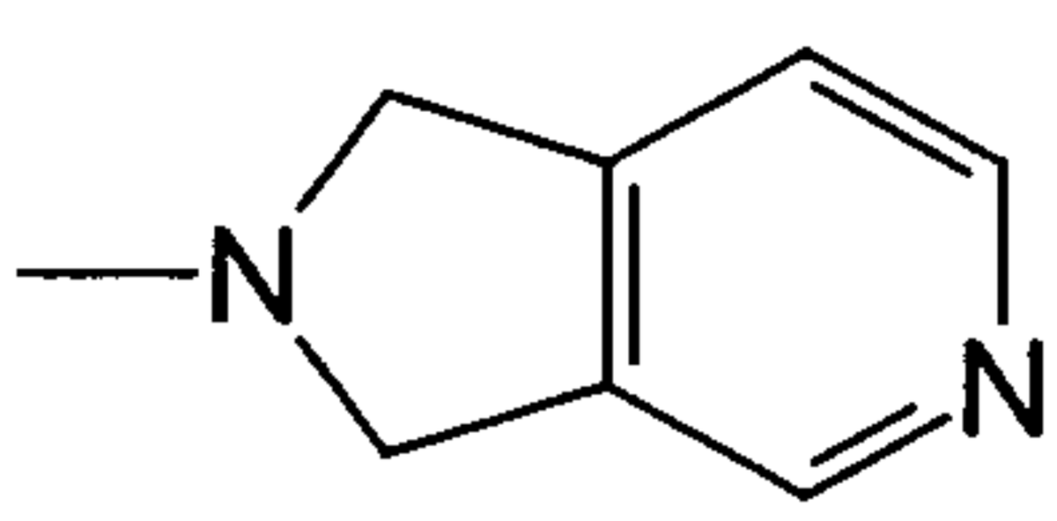
 ,  ,  ,  ,

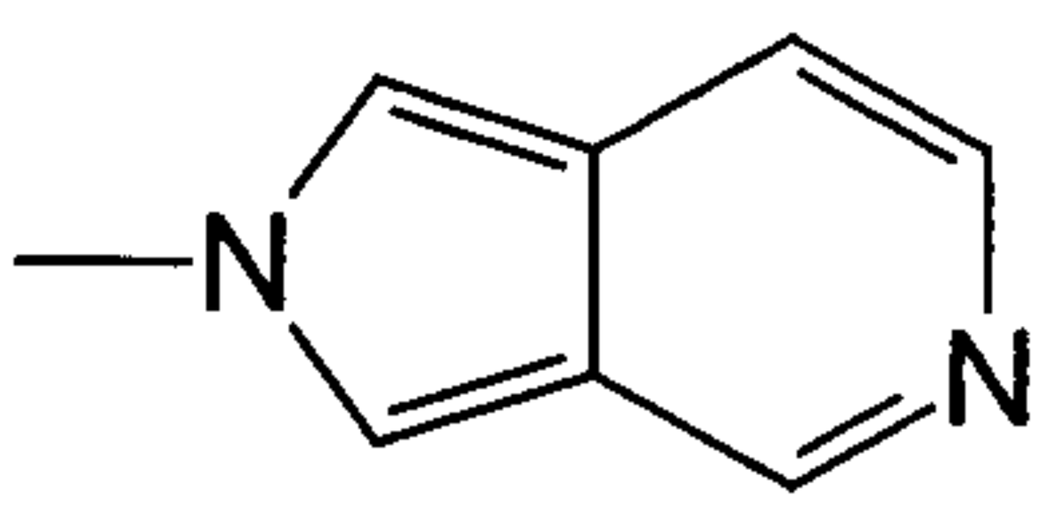
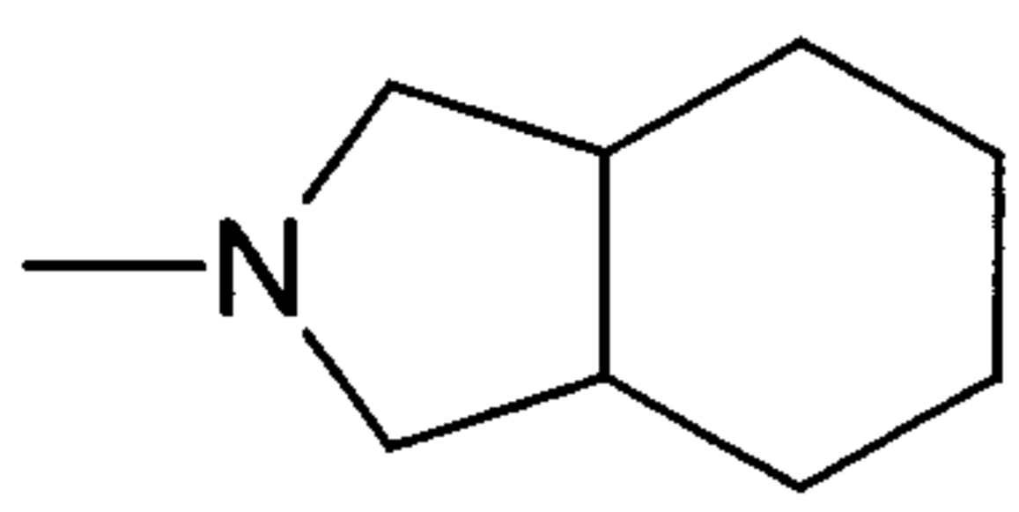
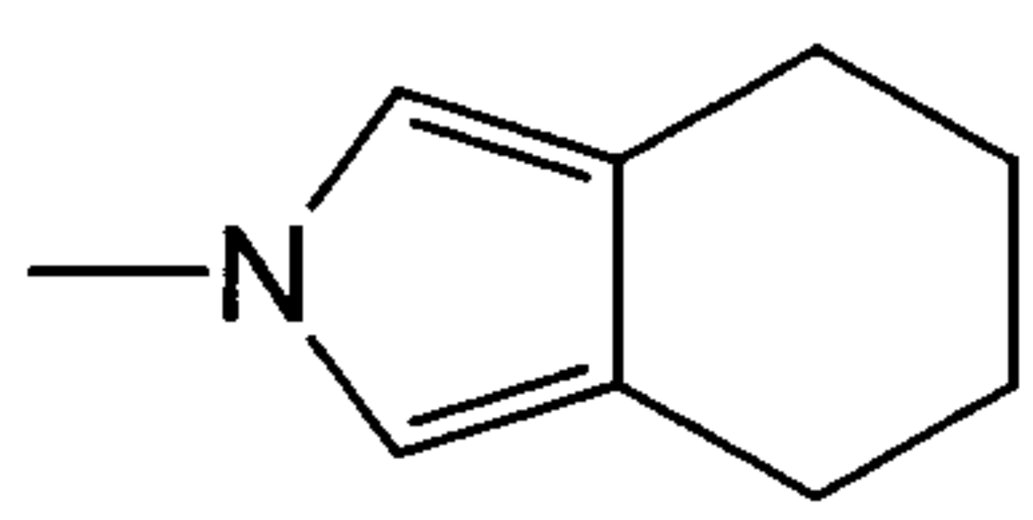
 ,  ,  ,  ,

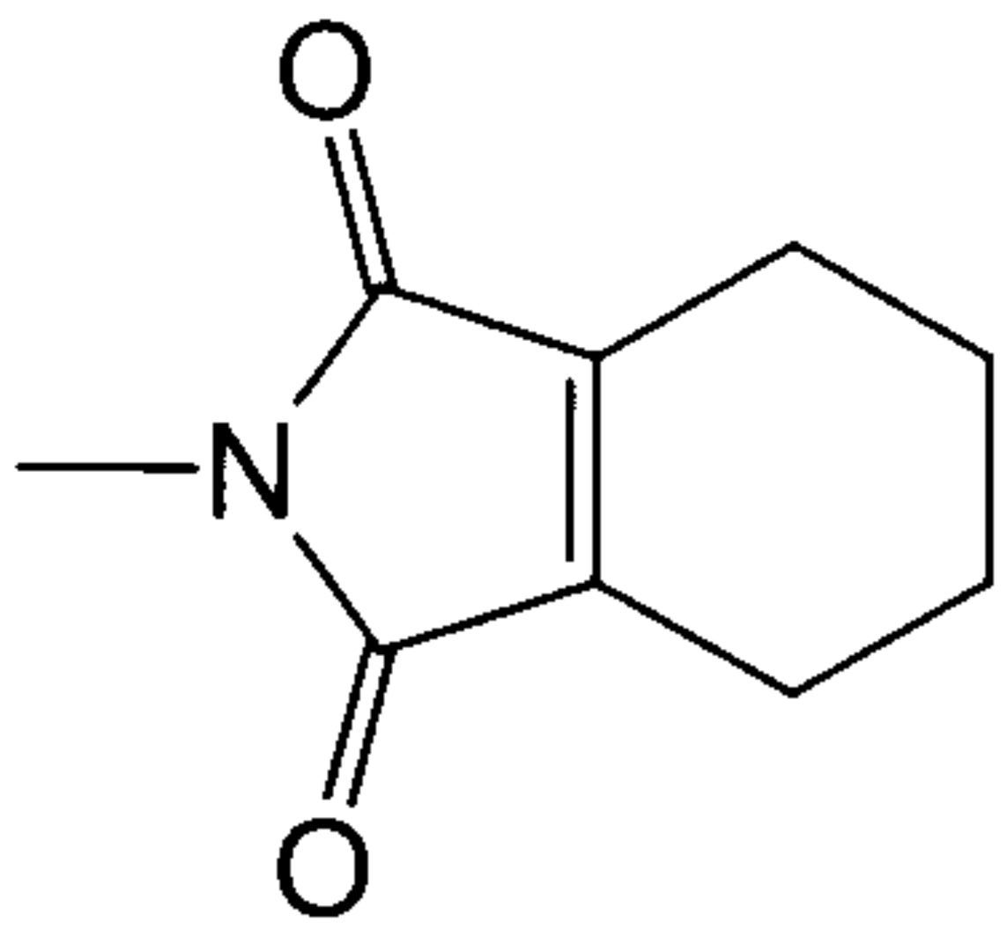
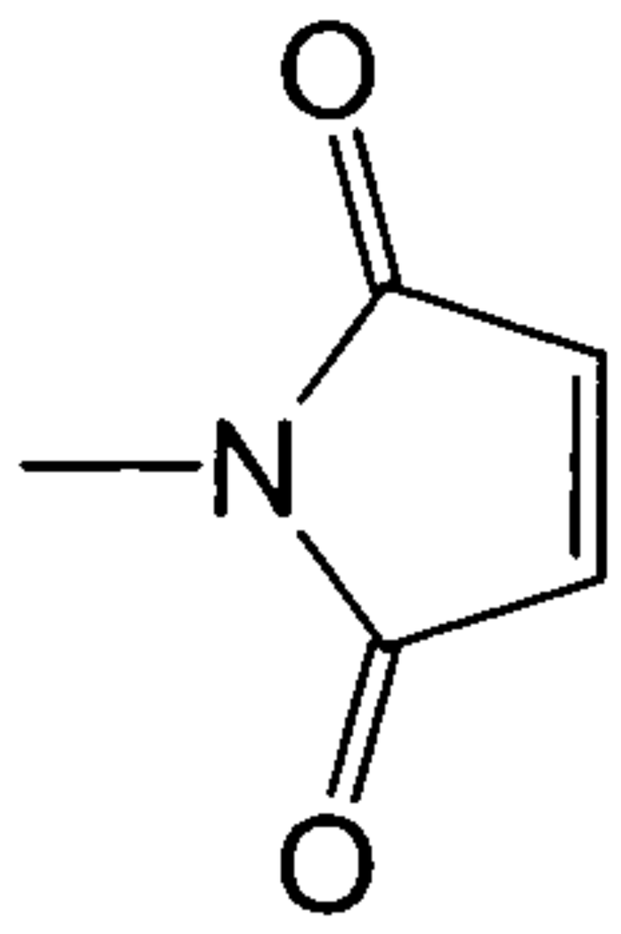
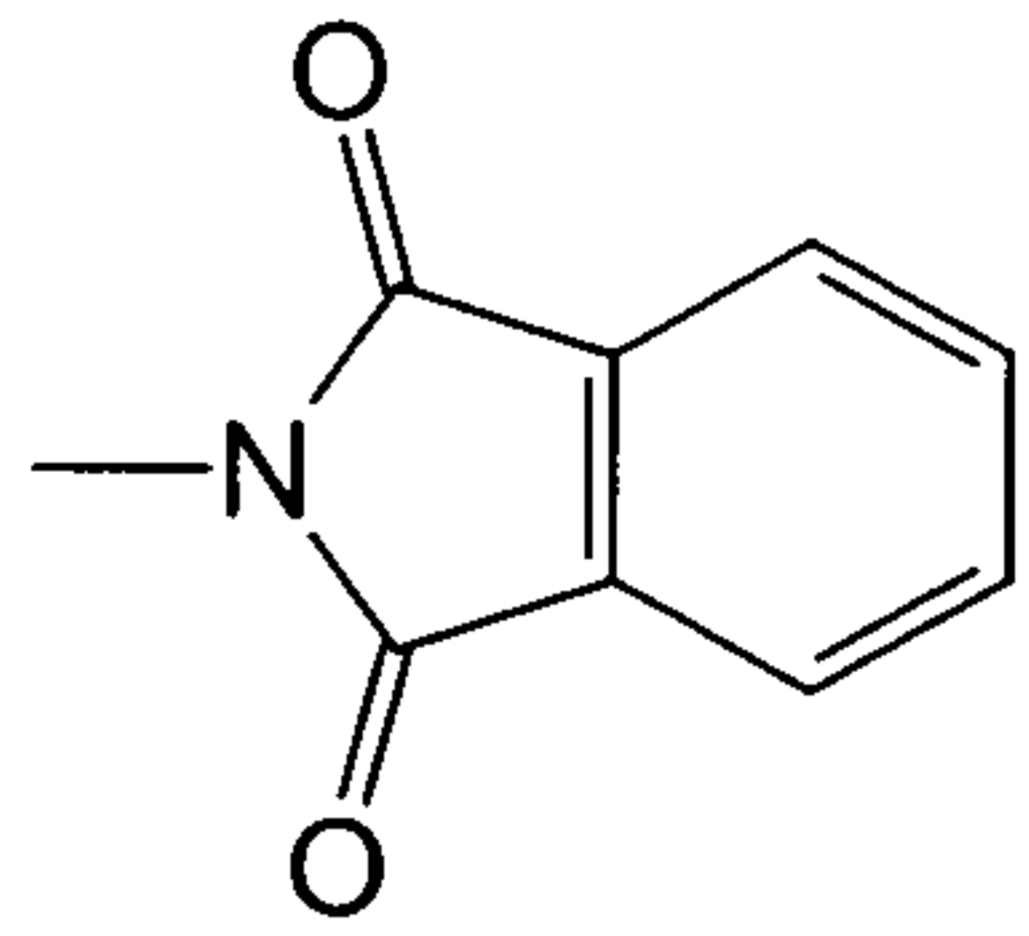
 ,  ,  ,  ,

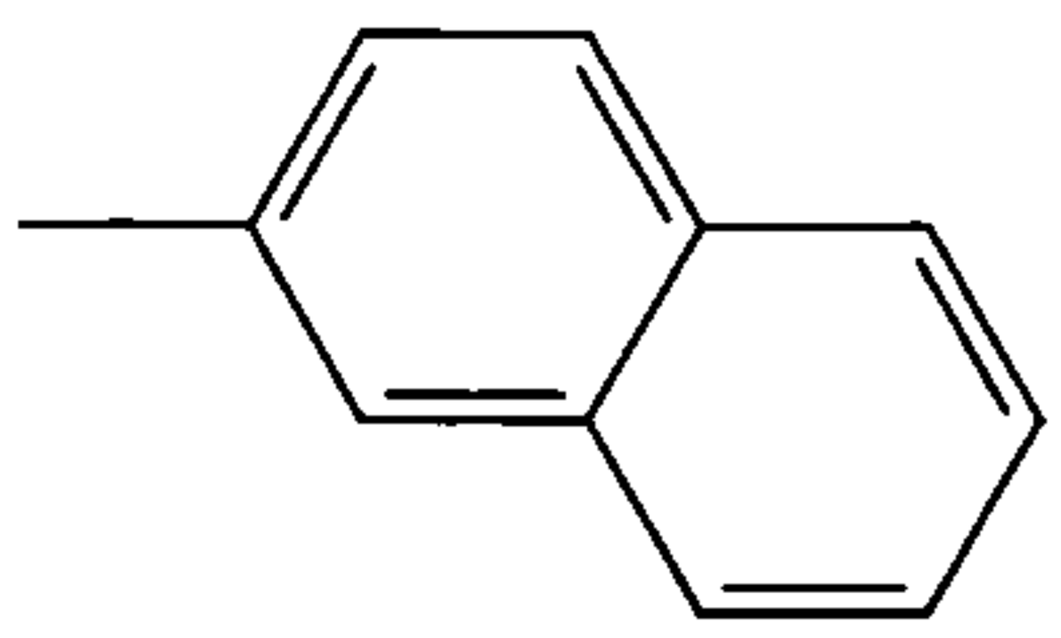
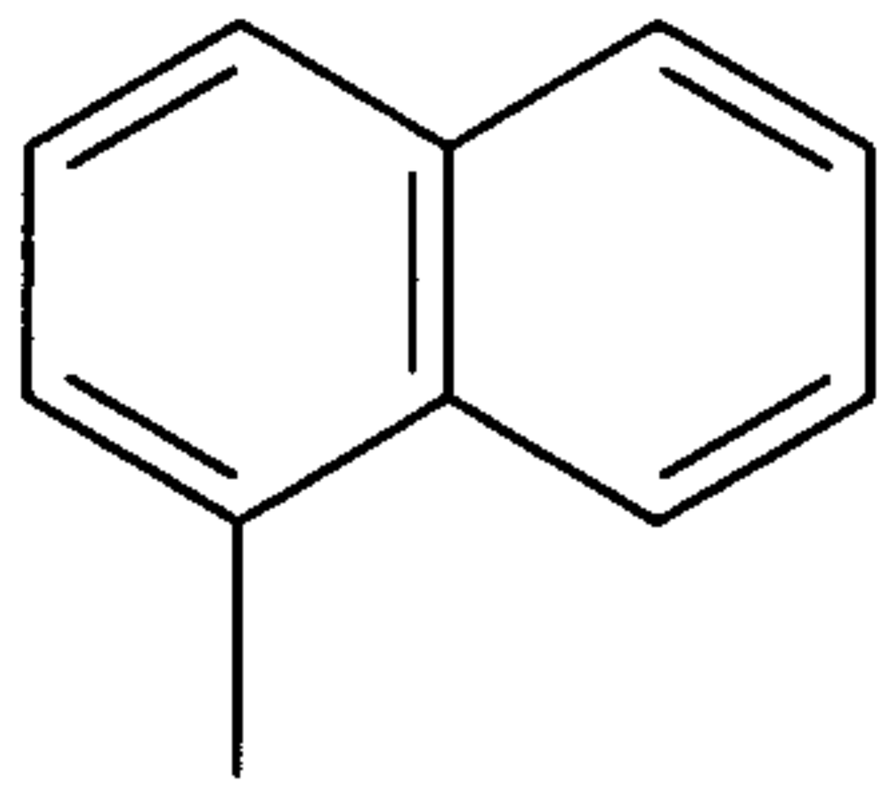
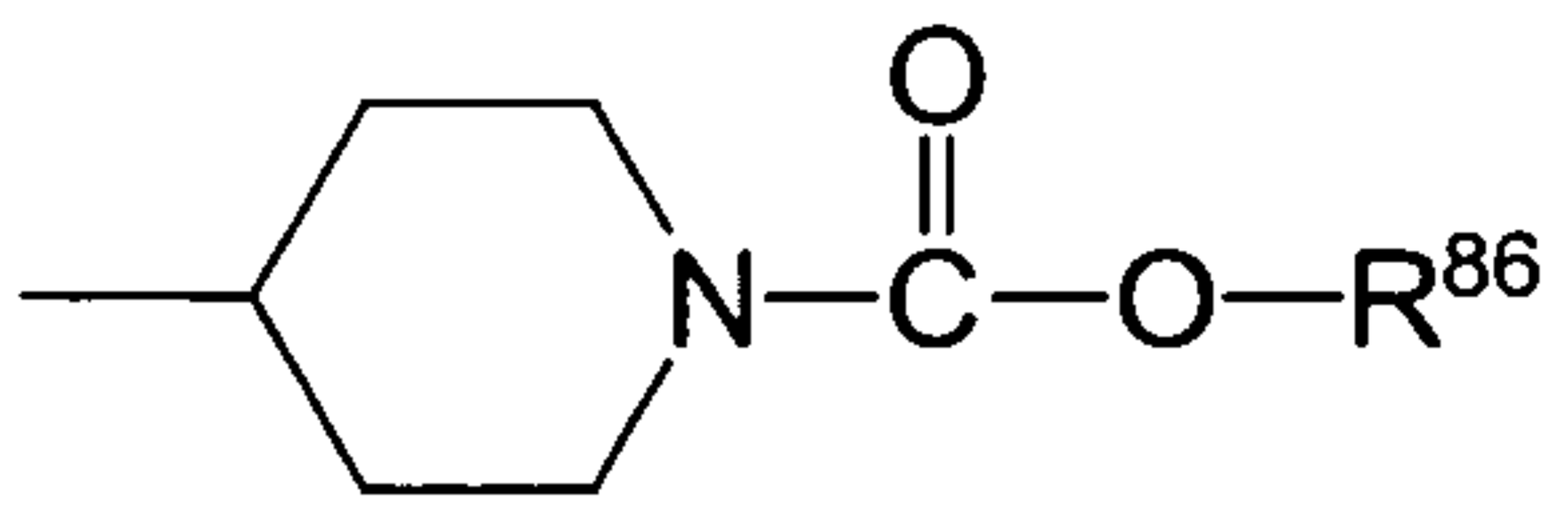
 ,  ,  ,

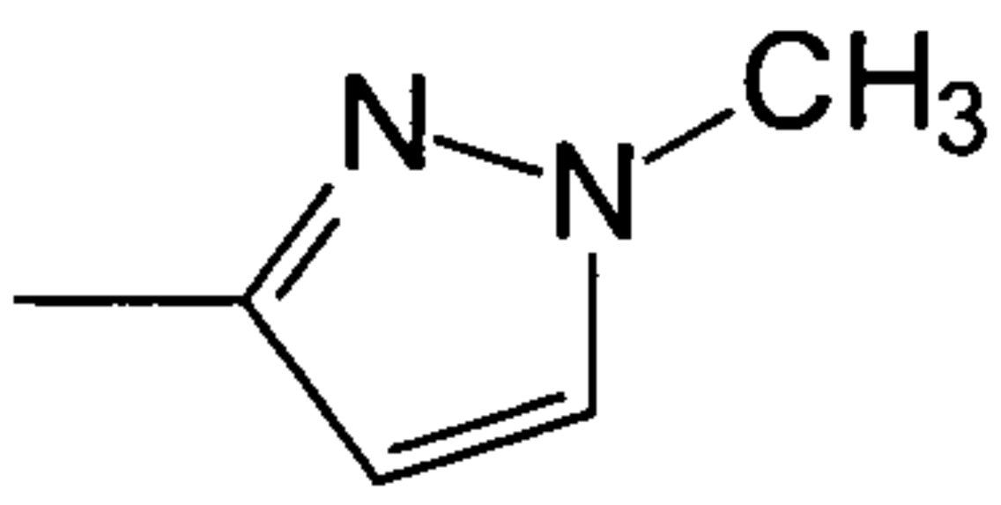
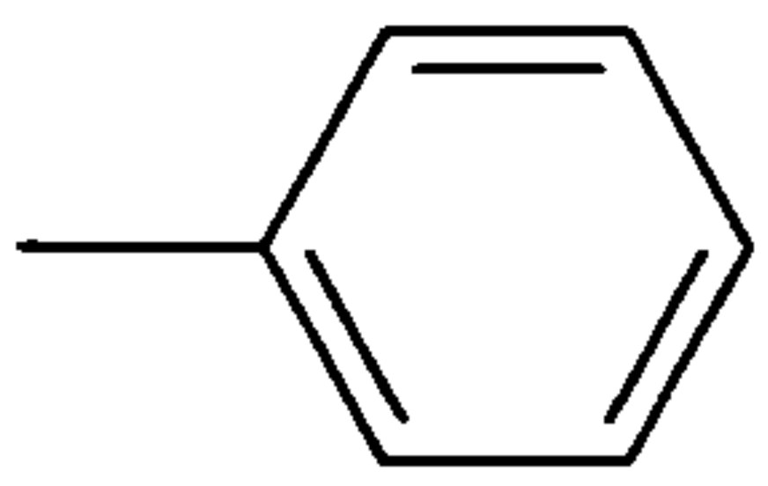
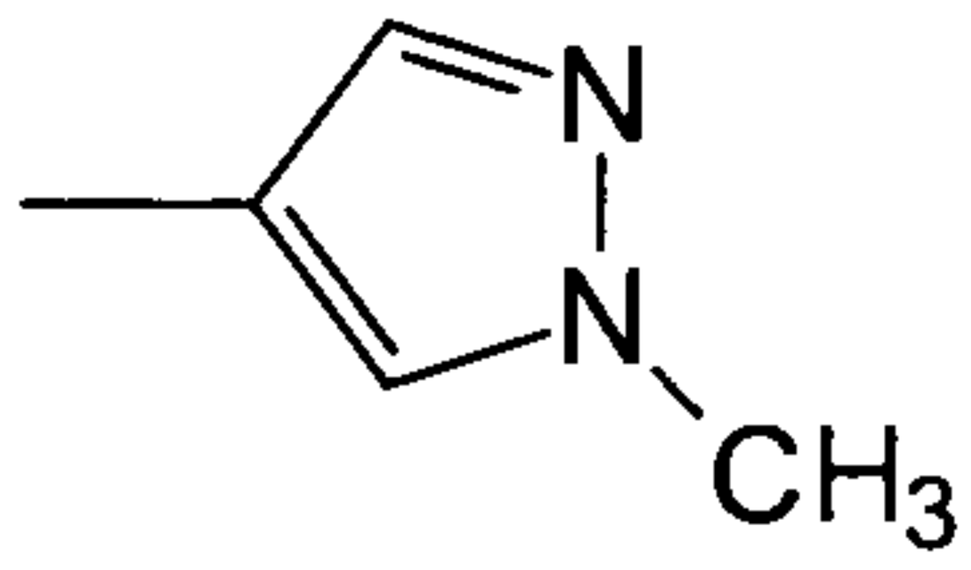
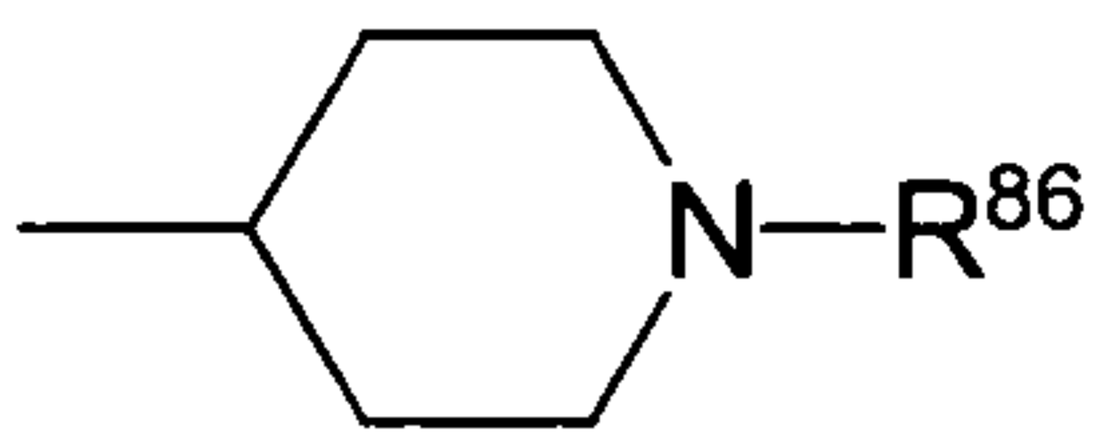
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

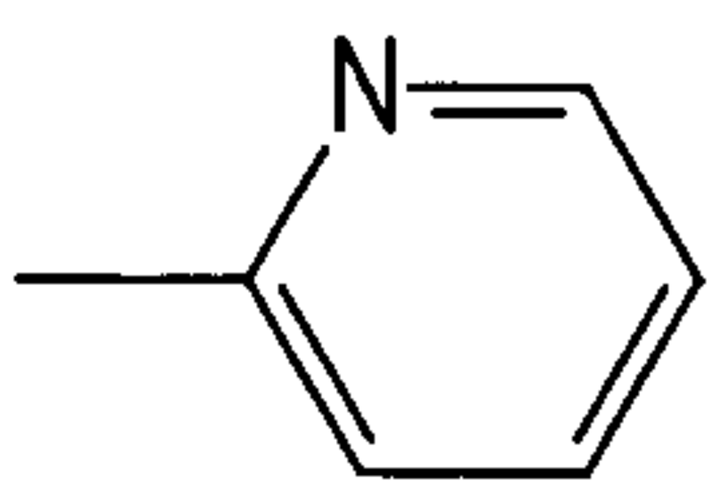
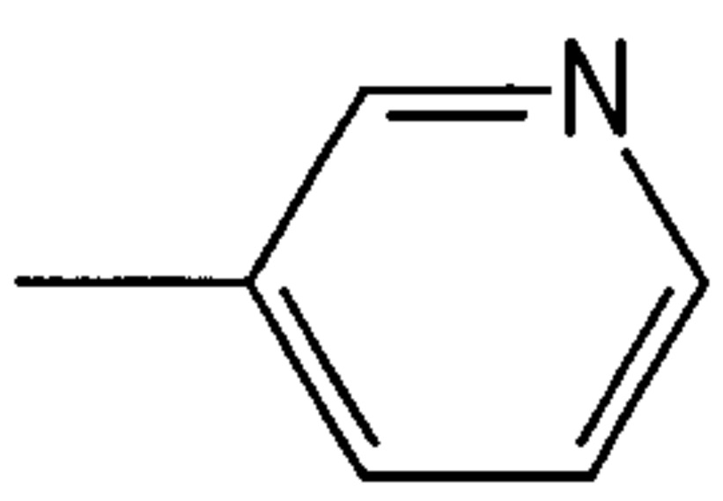
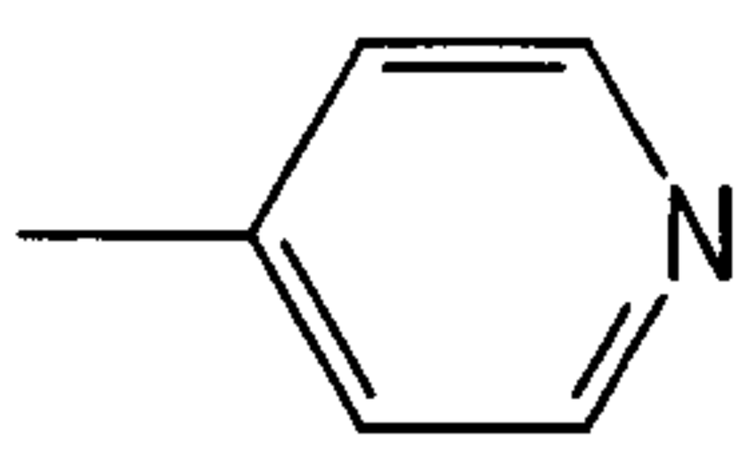
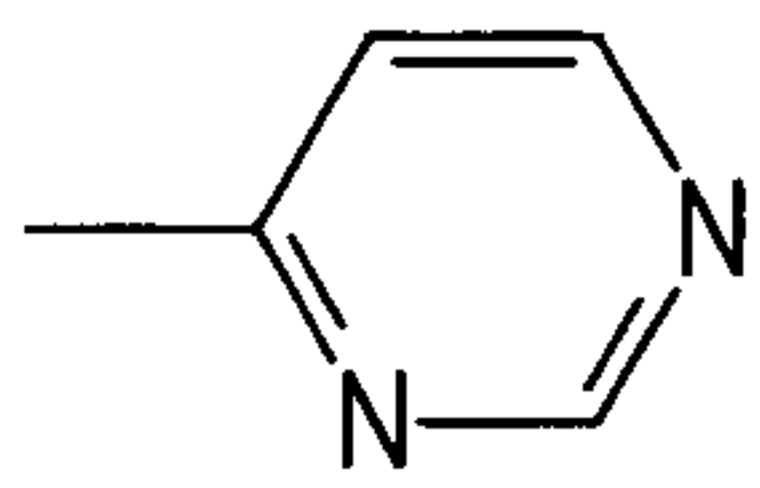
 ,  ,  ,

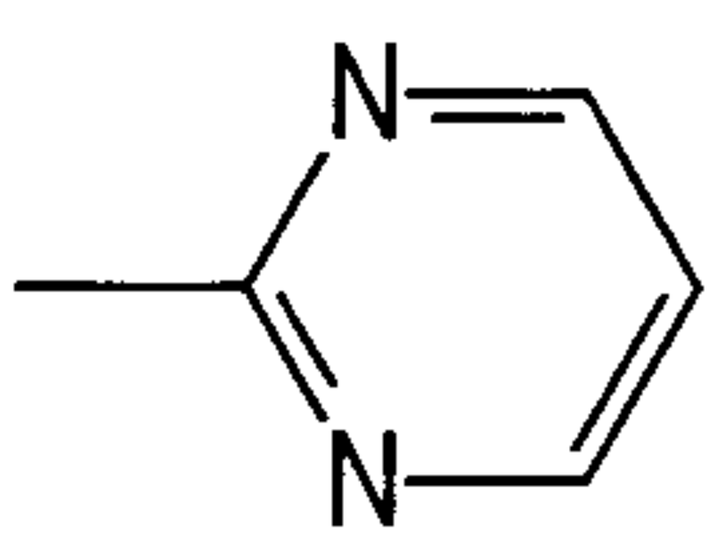
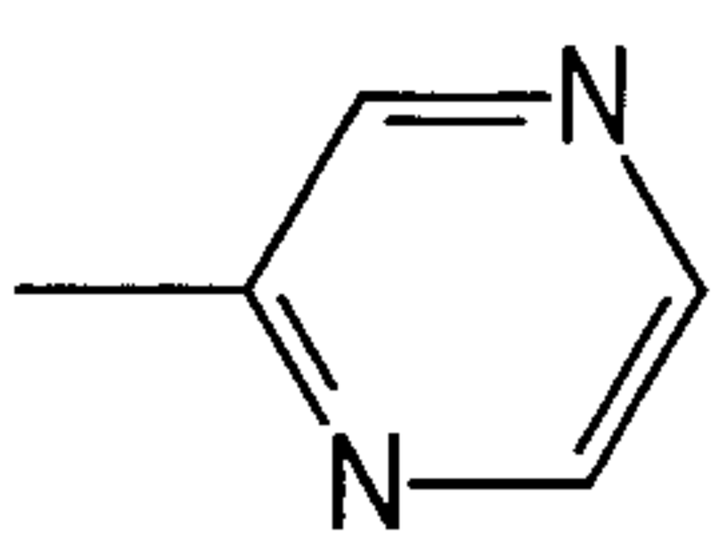
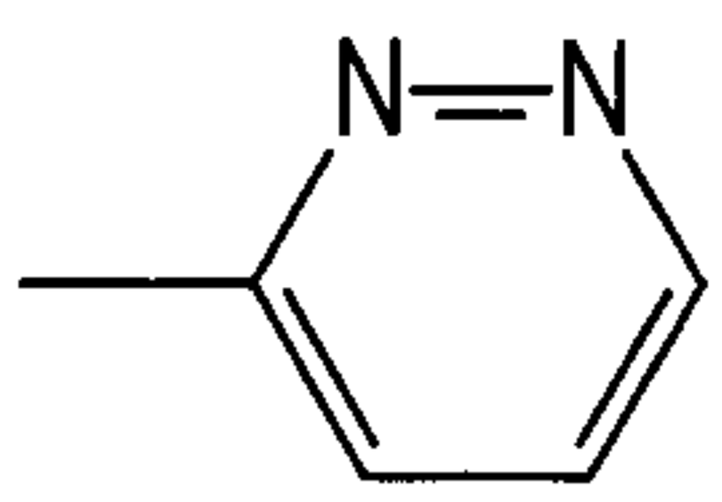
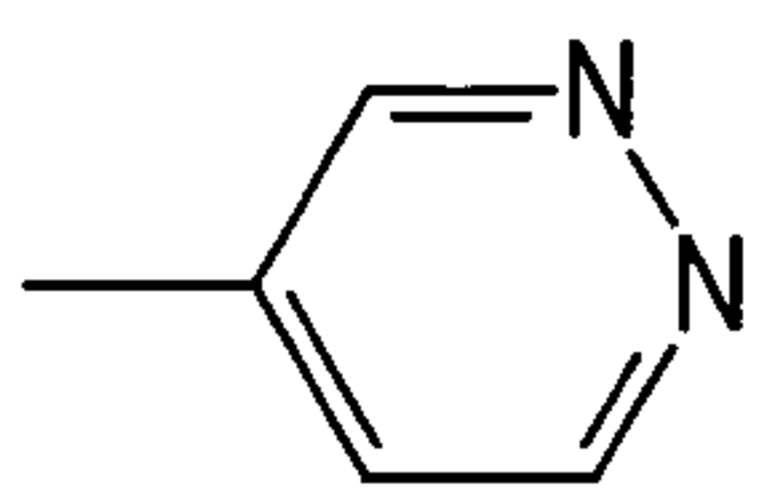
 ,  ,  ,

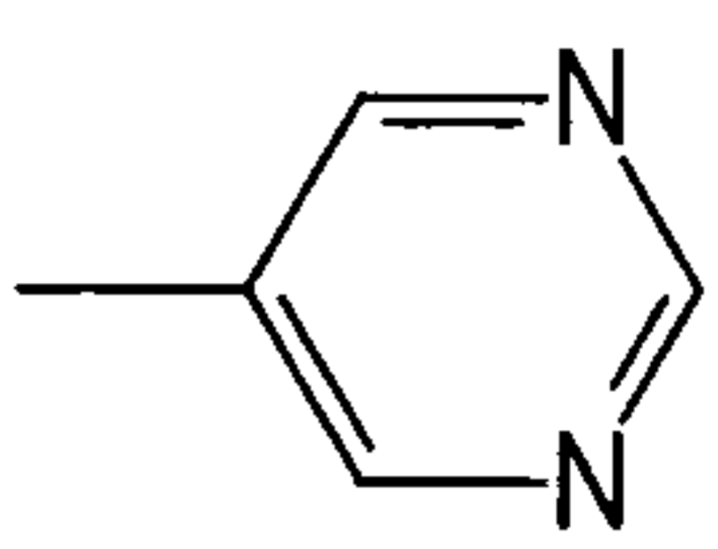
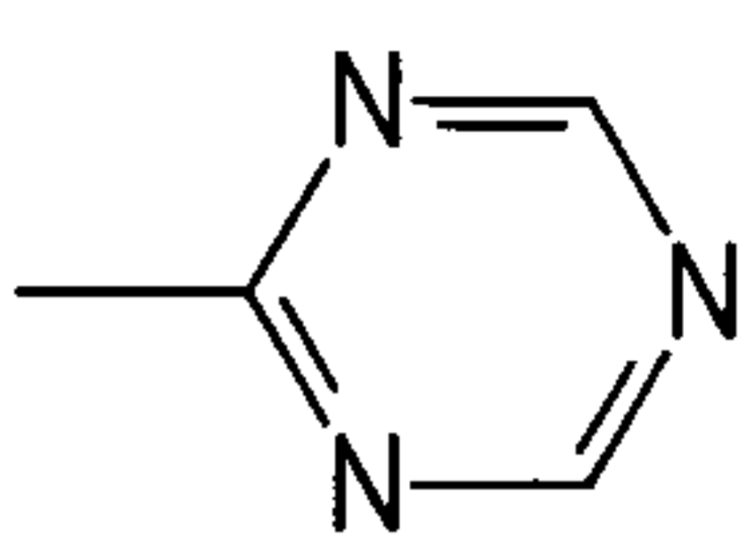
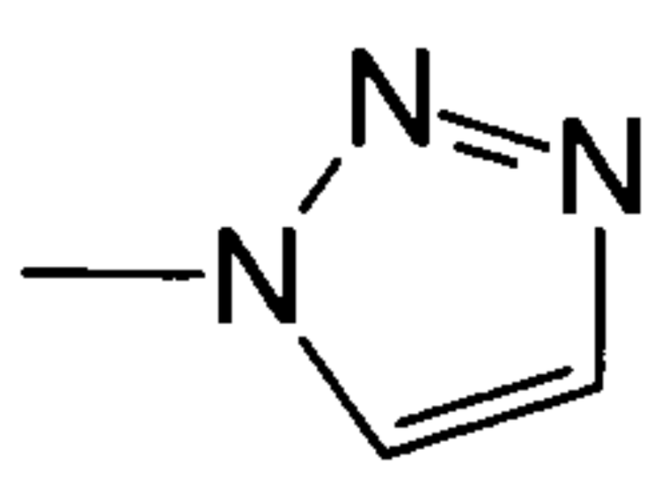
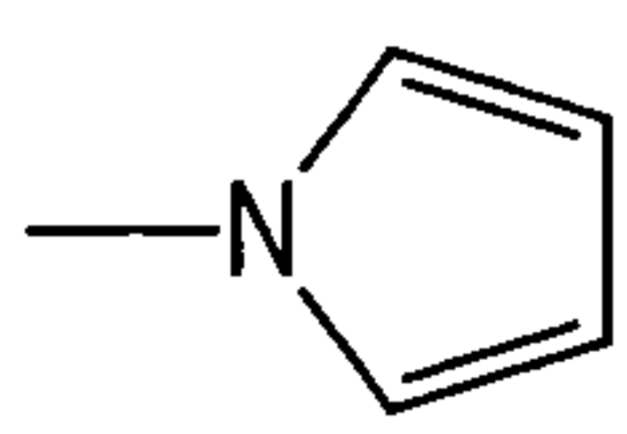
 ,  ,  ,  ;

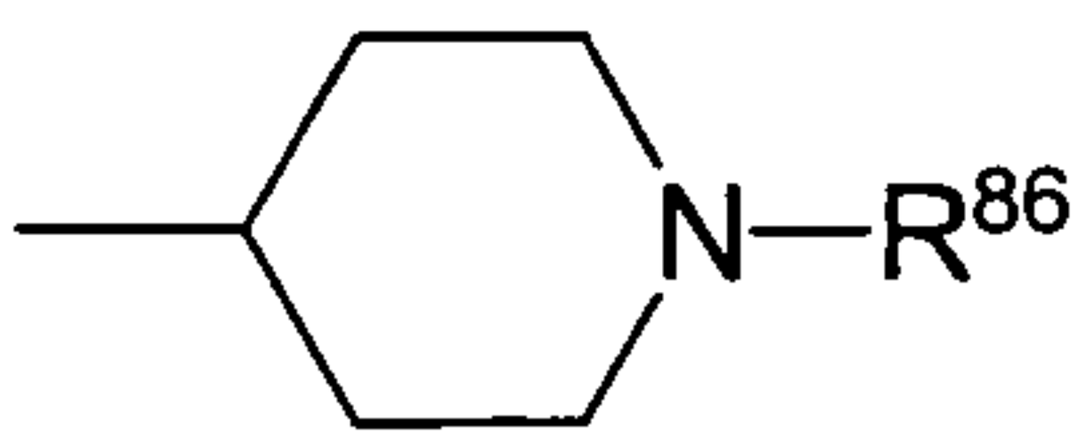
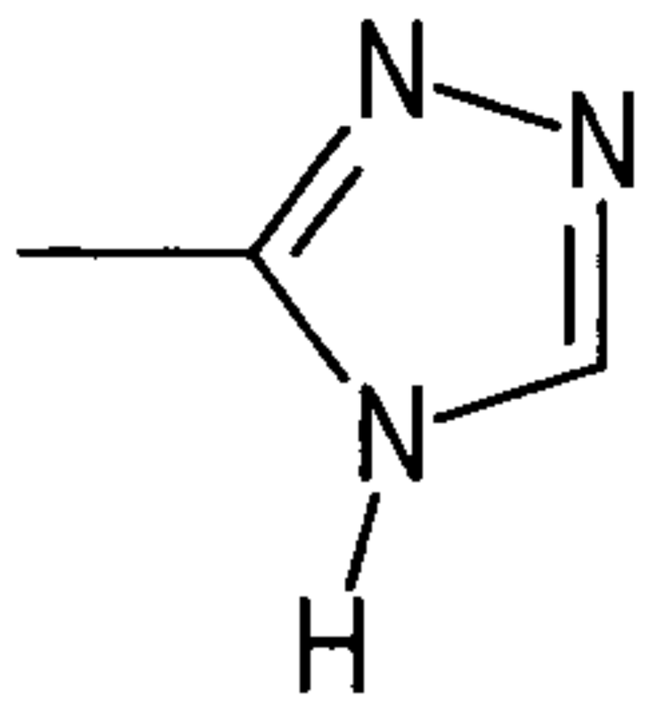
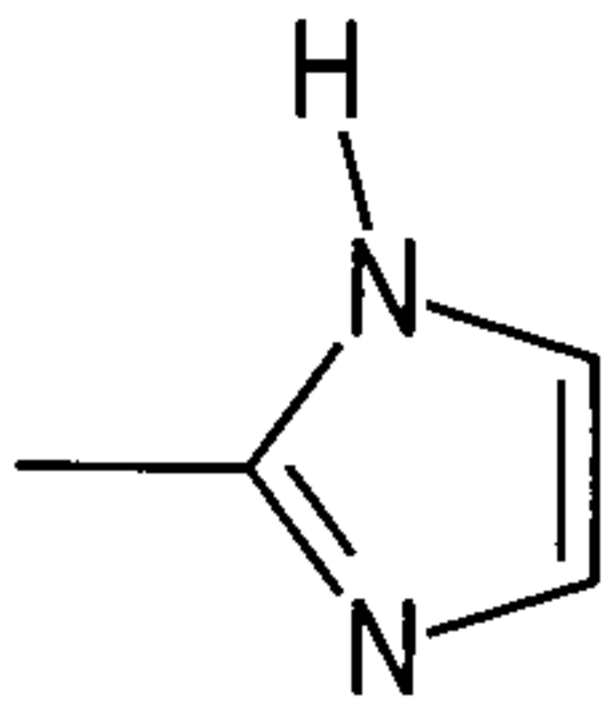
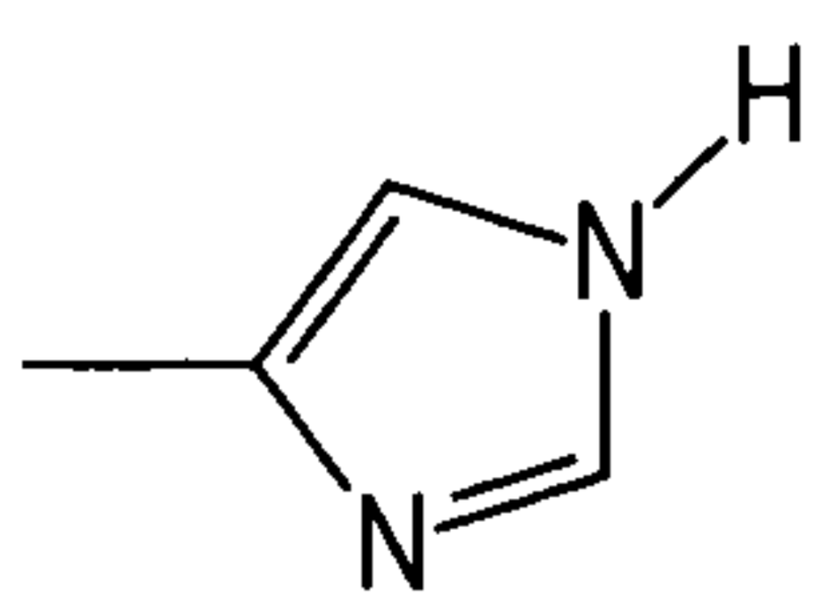
wherein the afore-mentioned residues R^{113} can be substituted by one or more substituents selected from –F, –Cl, –Br, –I, –OH, $–NO_2$, $–NH_2$, $–C_2H_4–N(CH_3)_2$, –CN, $–CF_3$, =O, $–R^{16}$, $–R^{17}$, $–R^{106}$, $–O–R^{107}$, $–R^{108}$, $–R^{109}$, and wherein R^{16}, R^{17}, R^{100}, R^{101}, R^{102}, R^{103}, R^{106}, R^{107}, R^{108}, R^{109}, R^{113}, and R^{136} have the meanings as disclosed herein.

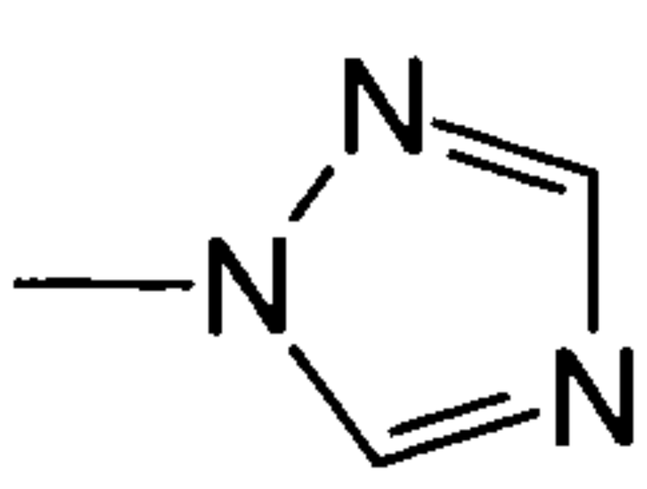
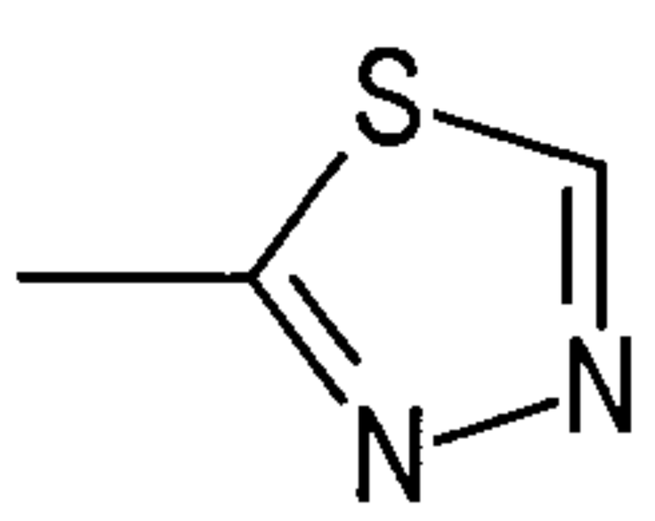
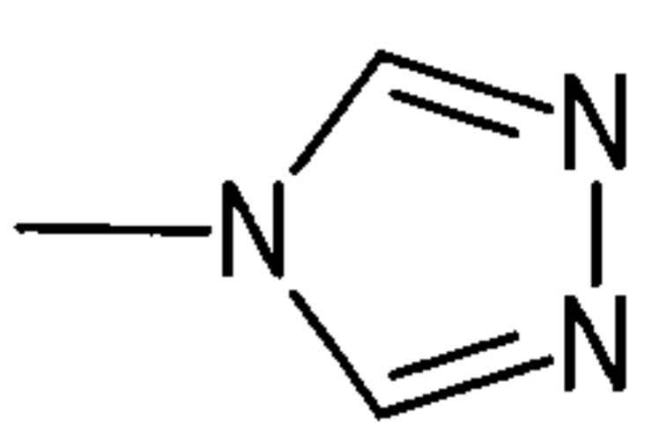
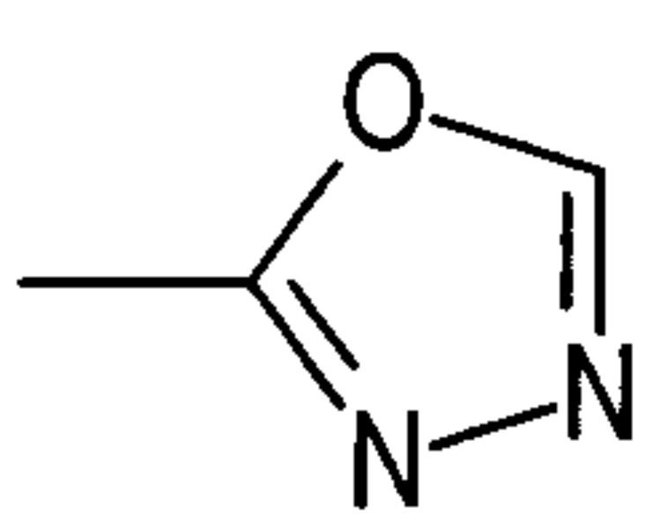
Still more preferably R^{113} represents

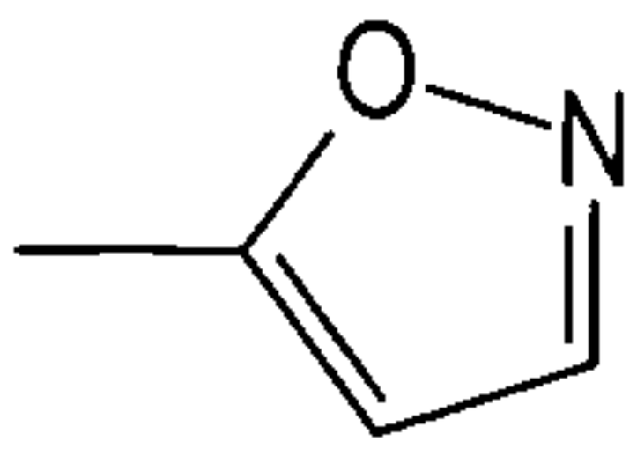
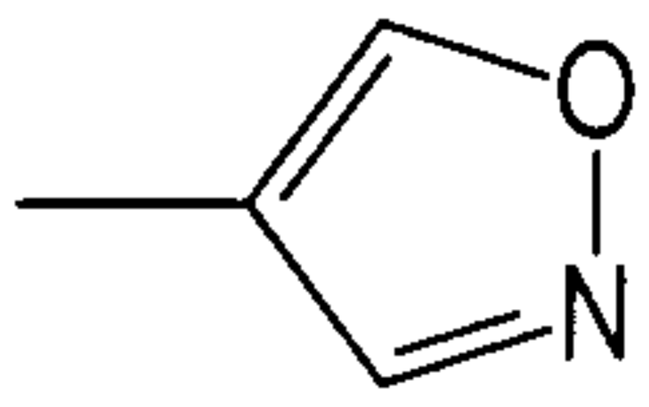
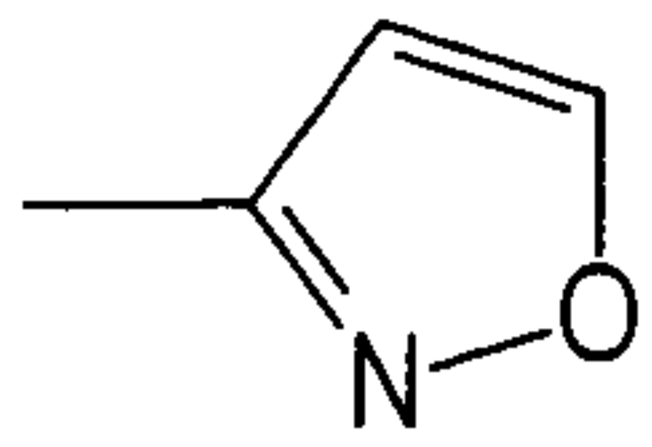
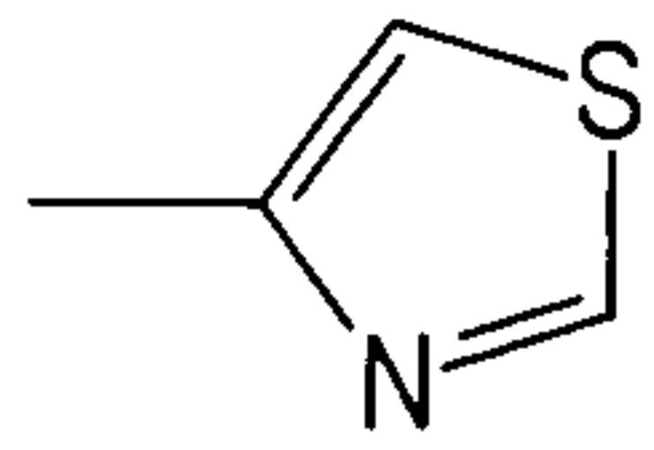
 ,  ,  ,  ,

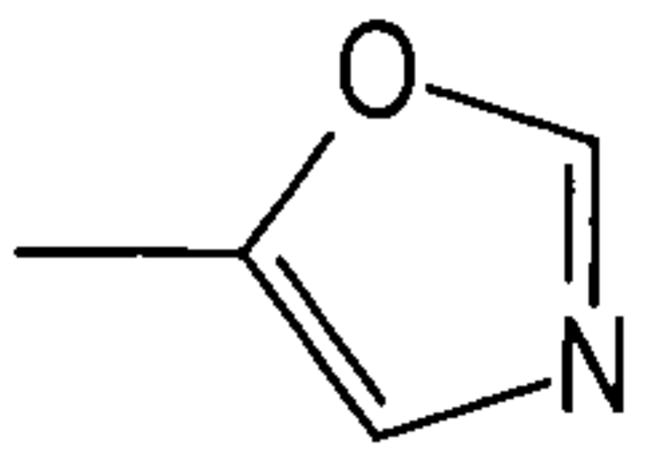
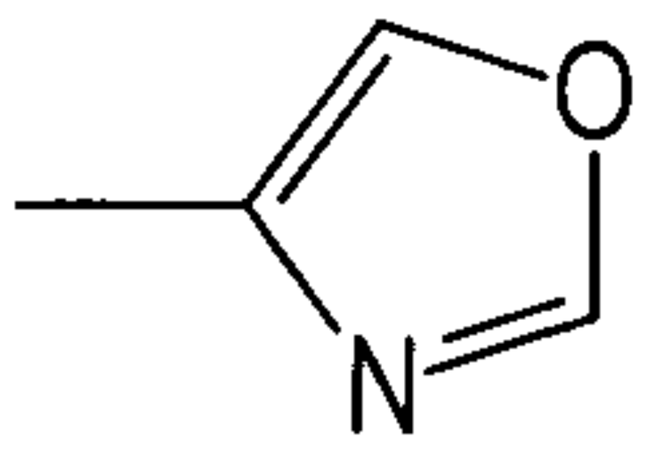
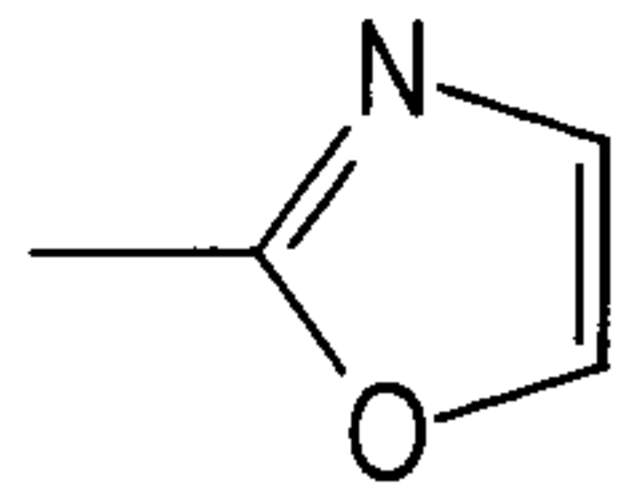
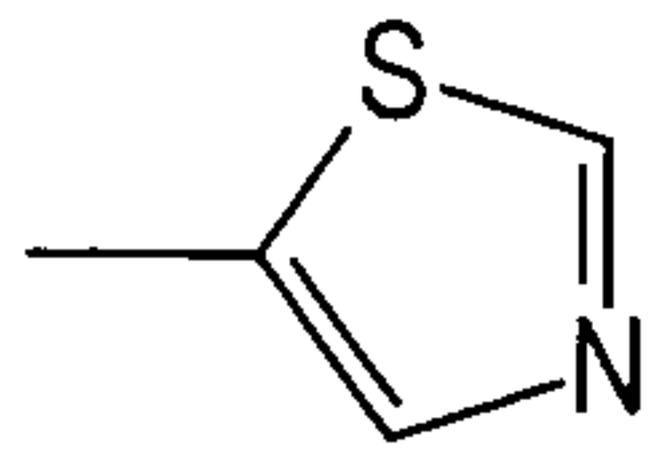
 ,  ,  ,  ,

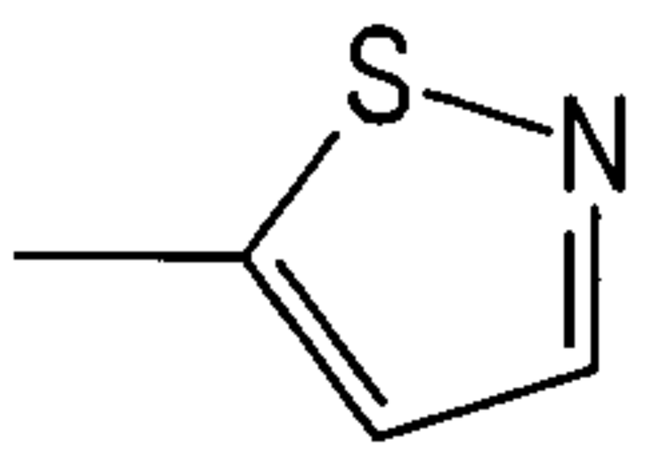
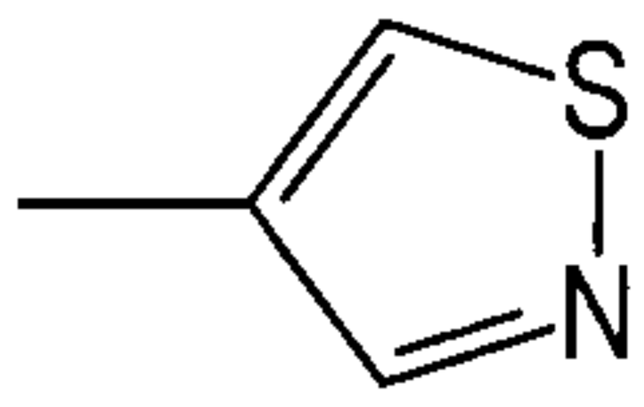
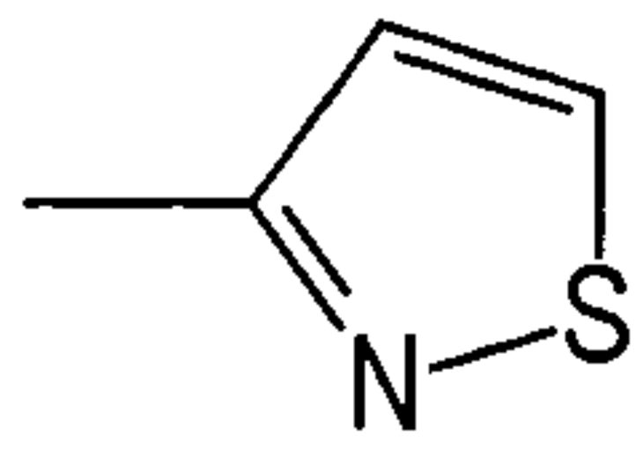
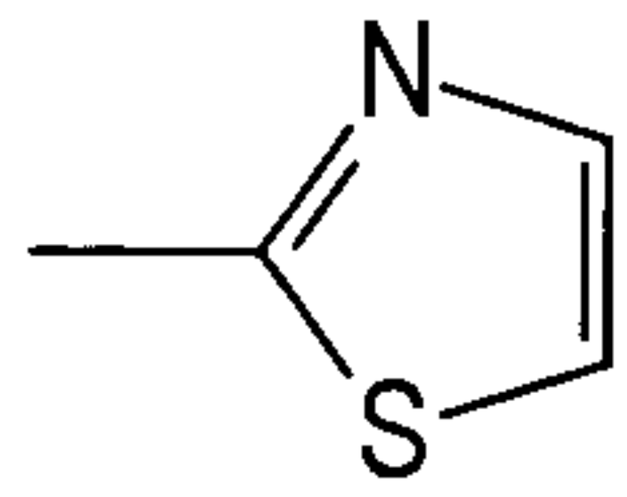
 ,  ,  ,  ,

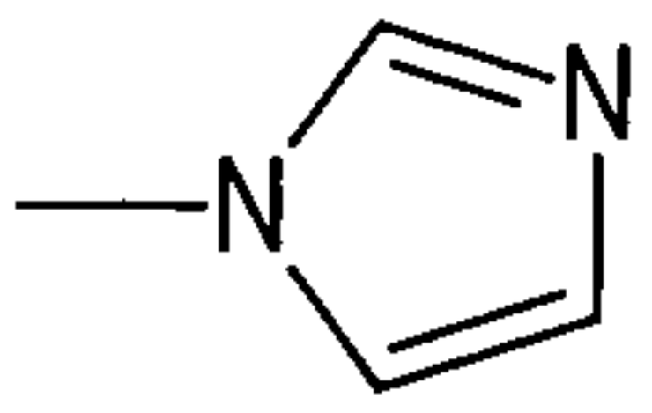
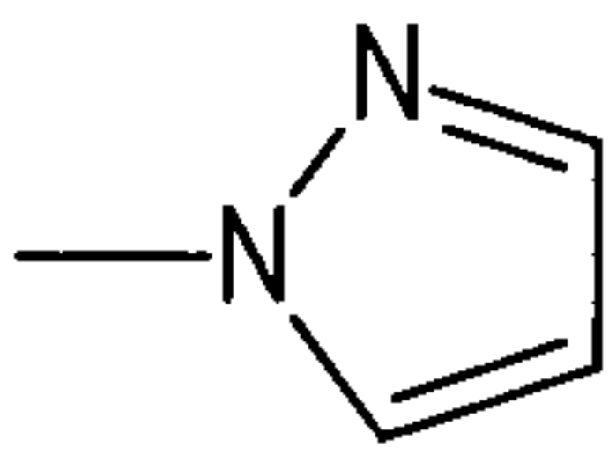
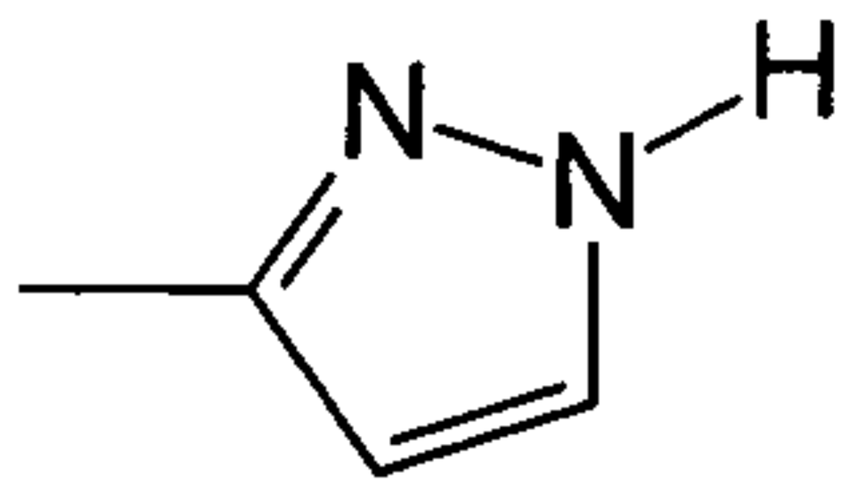
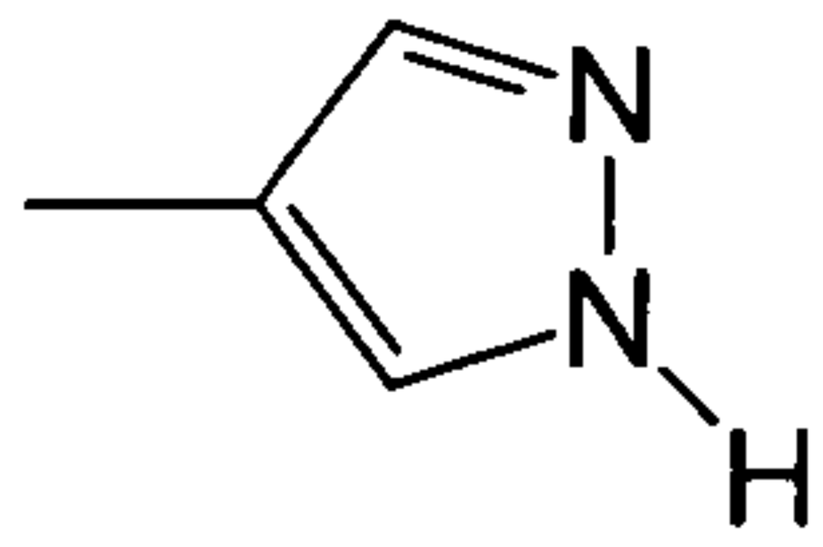
 ,  ,  ,  ,

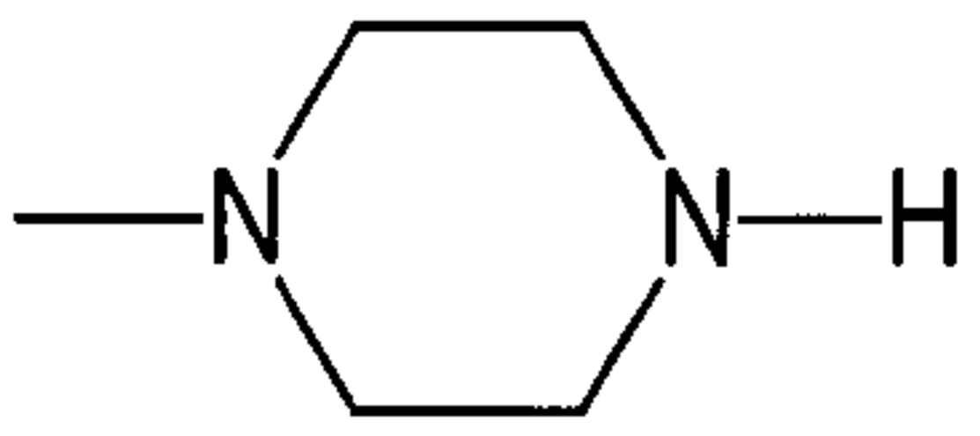
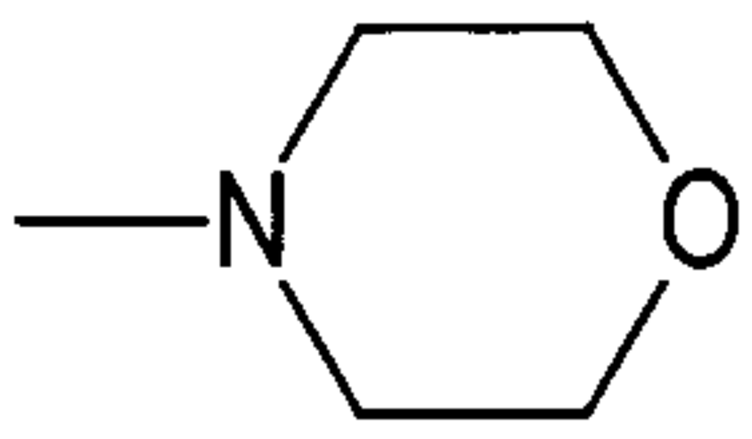
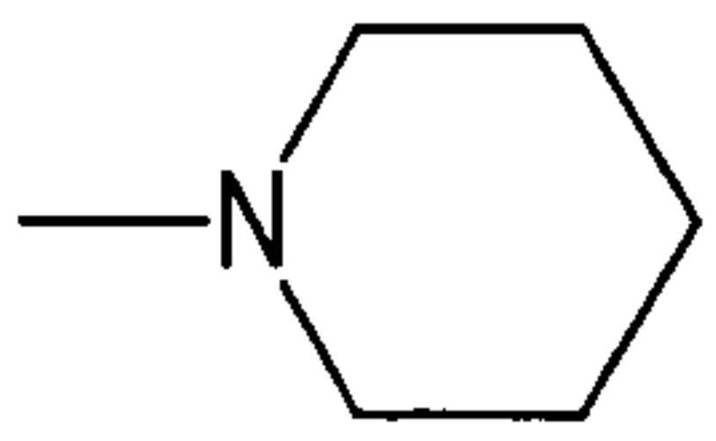
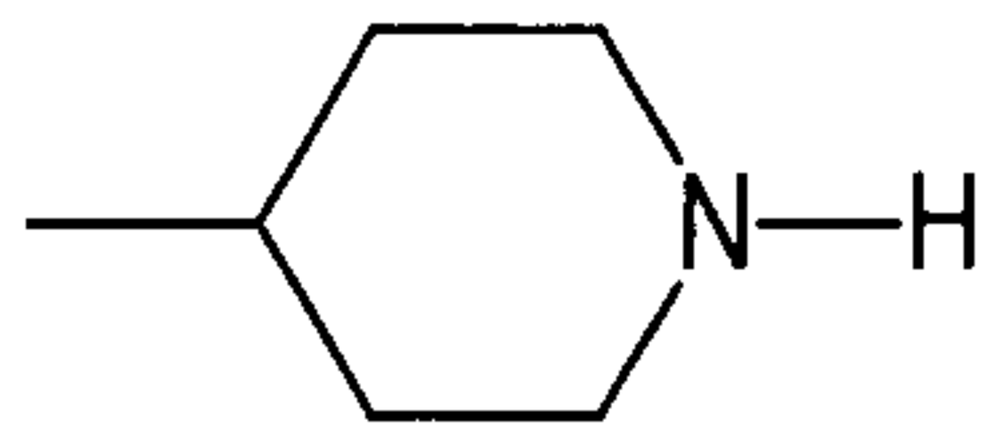
 ,  ,  ,  ,

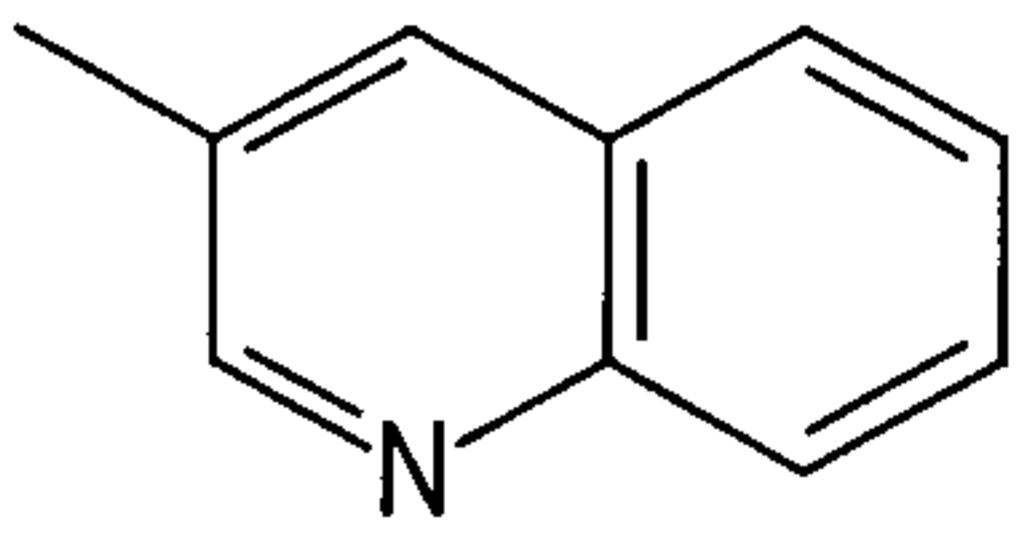
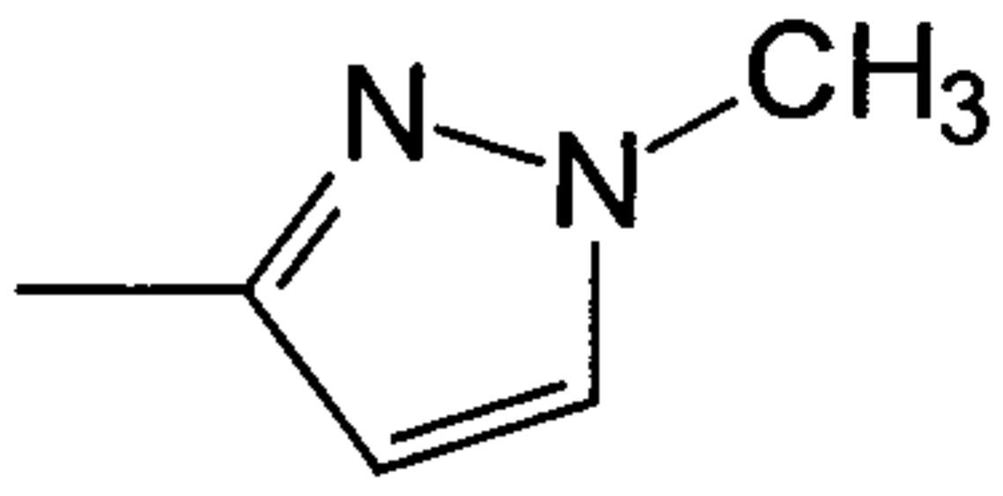
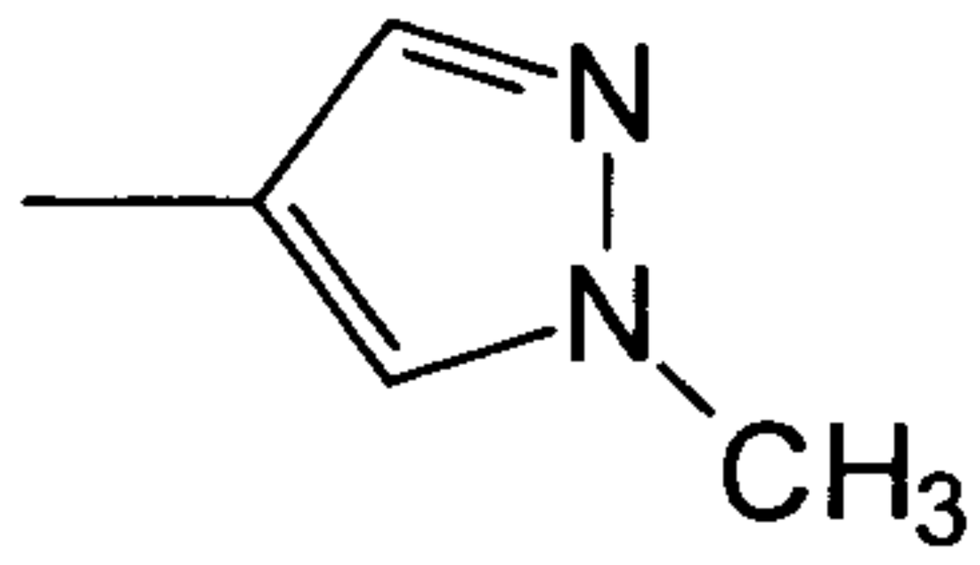
 ,  ,  ,  ,

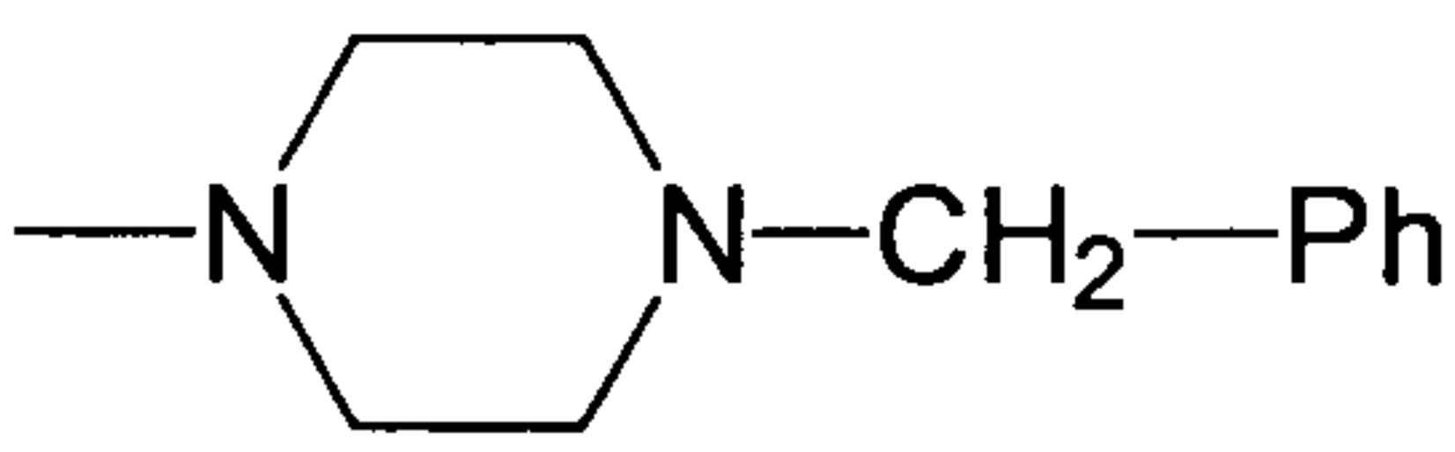
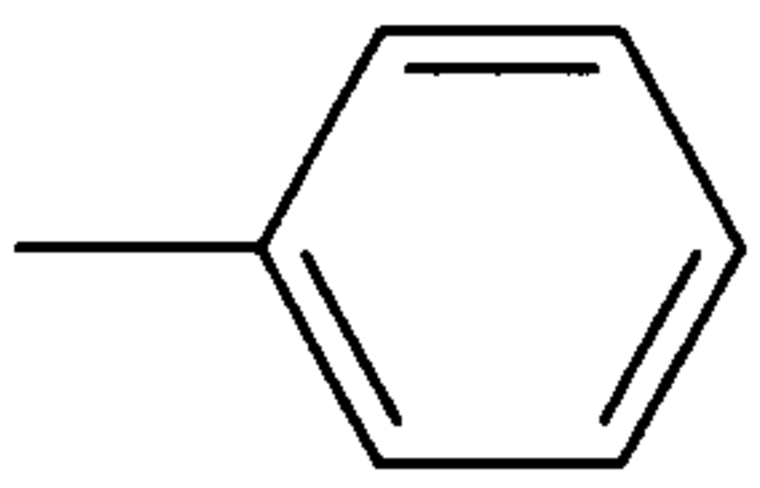
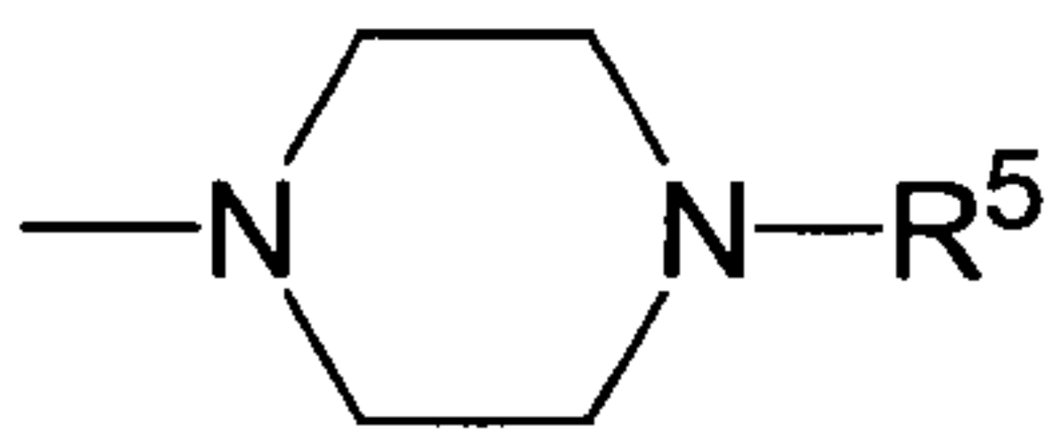
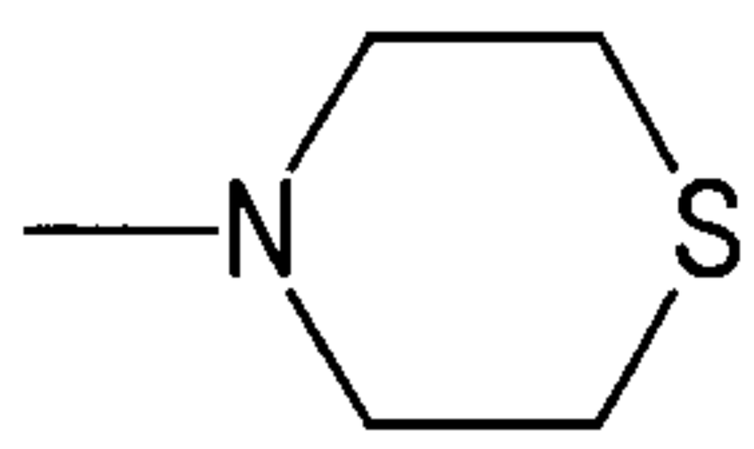
 ,  ,  ,  ,

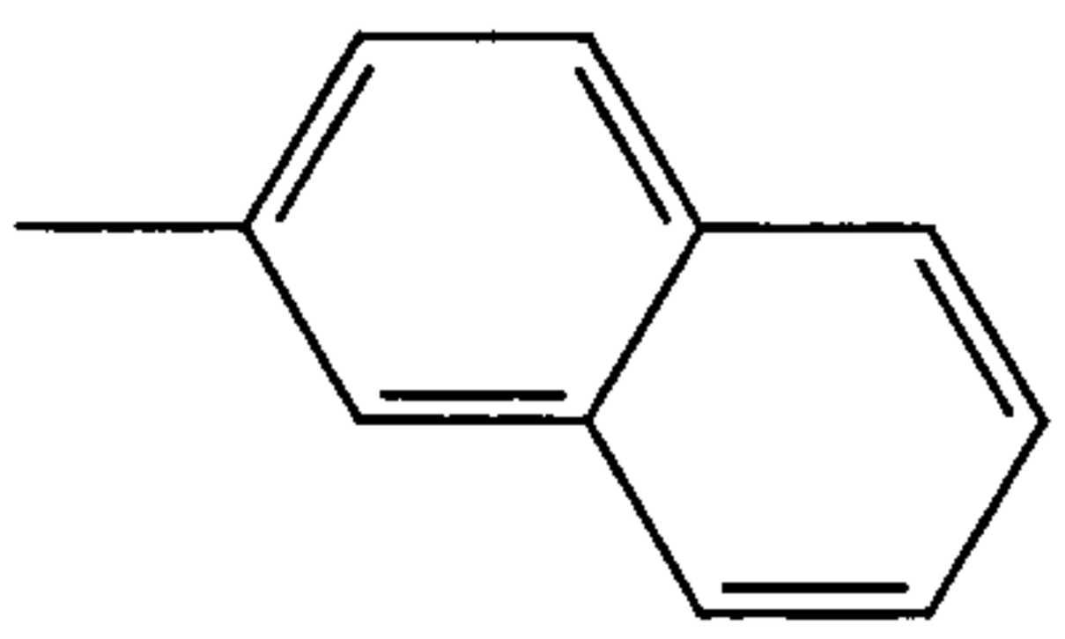
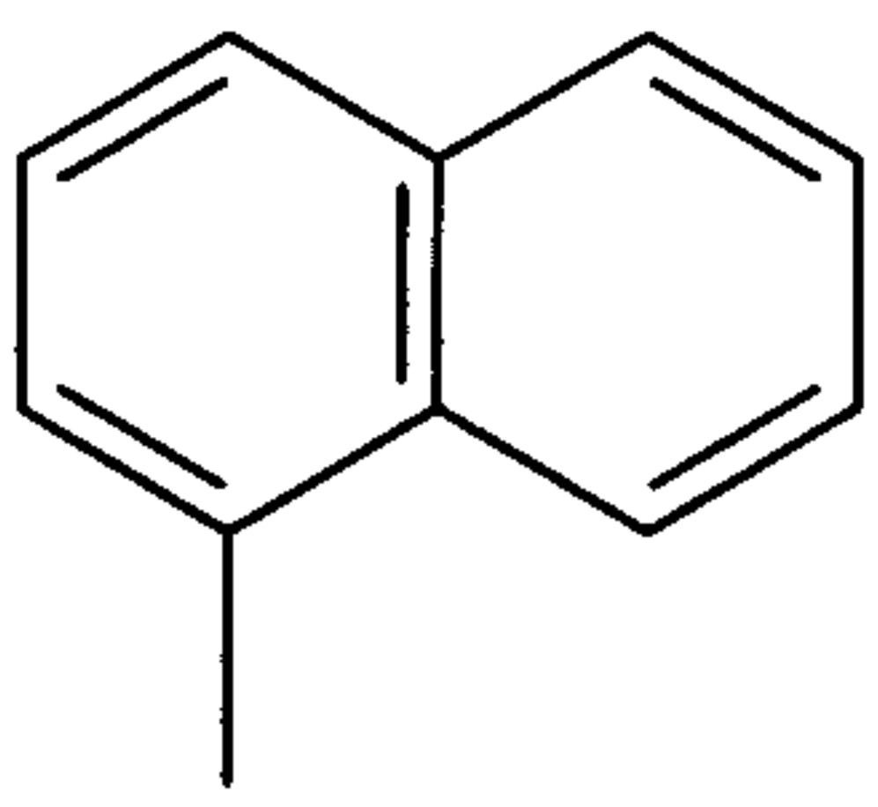
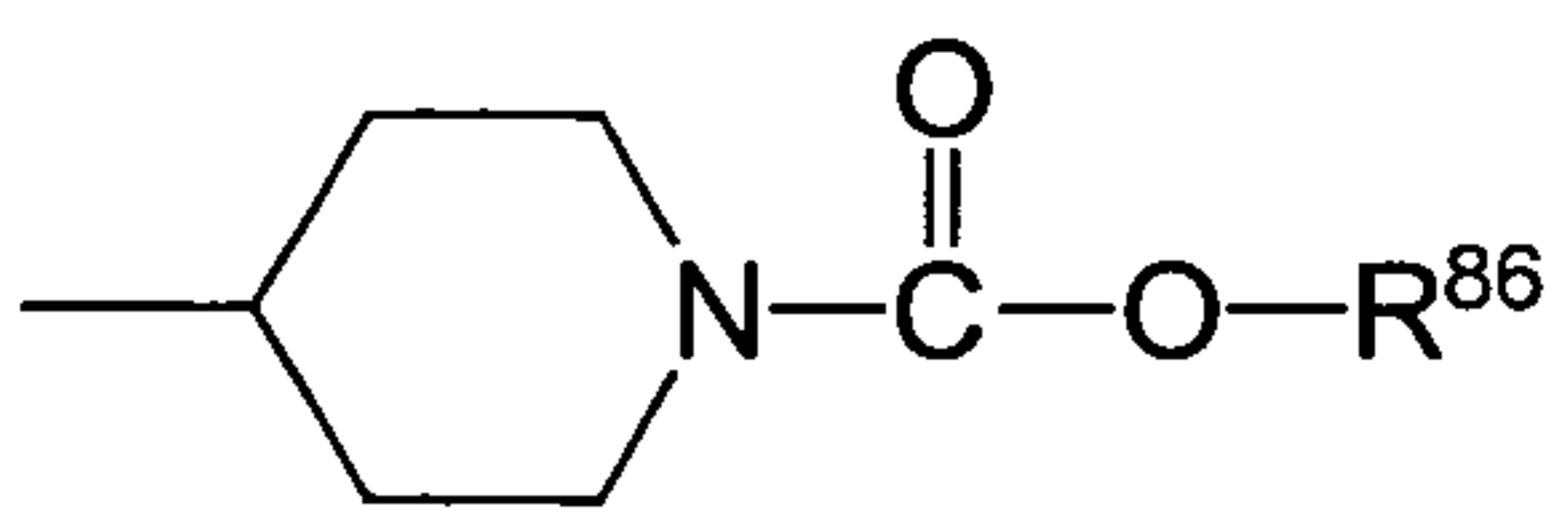
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

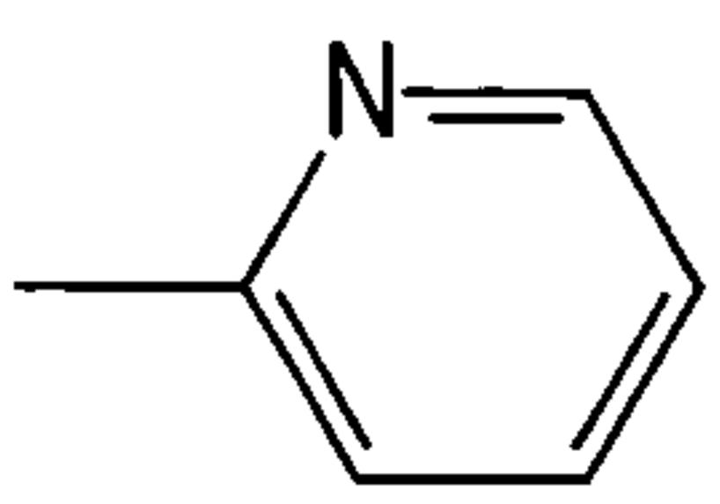
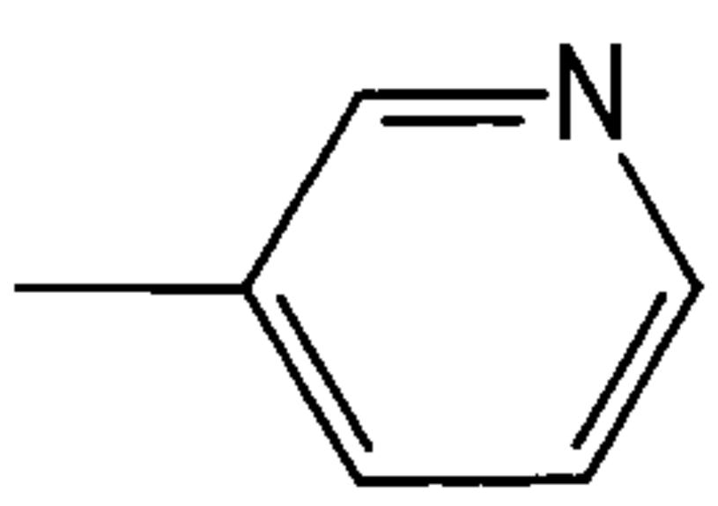
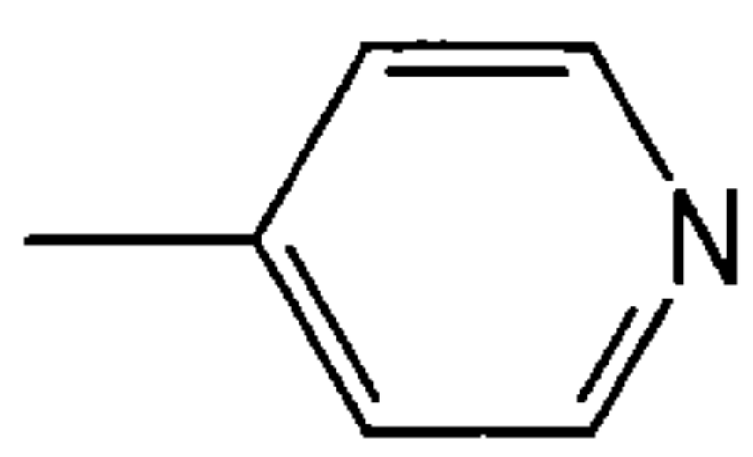
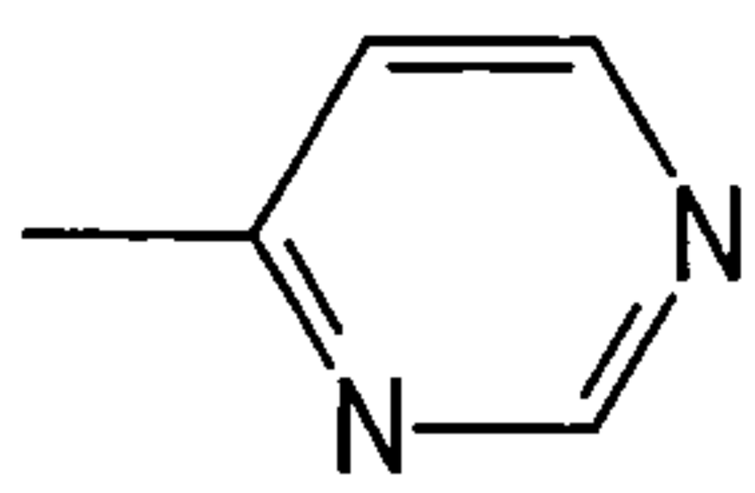
 ,  ,  ,

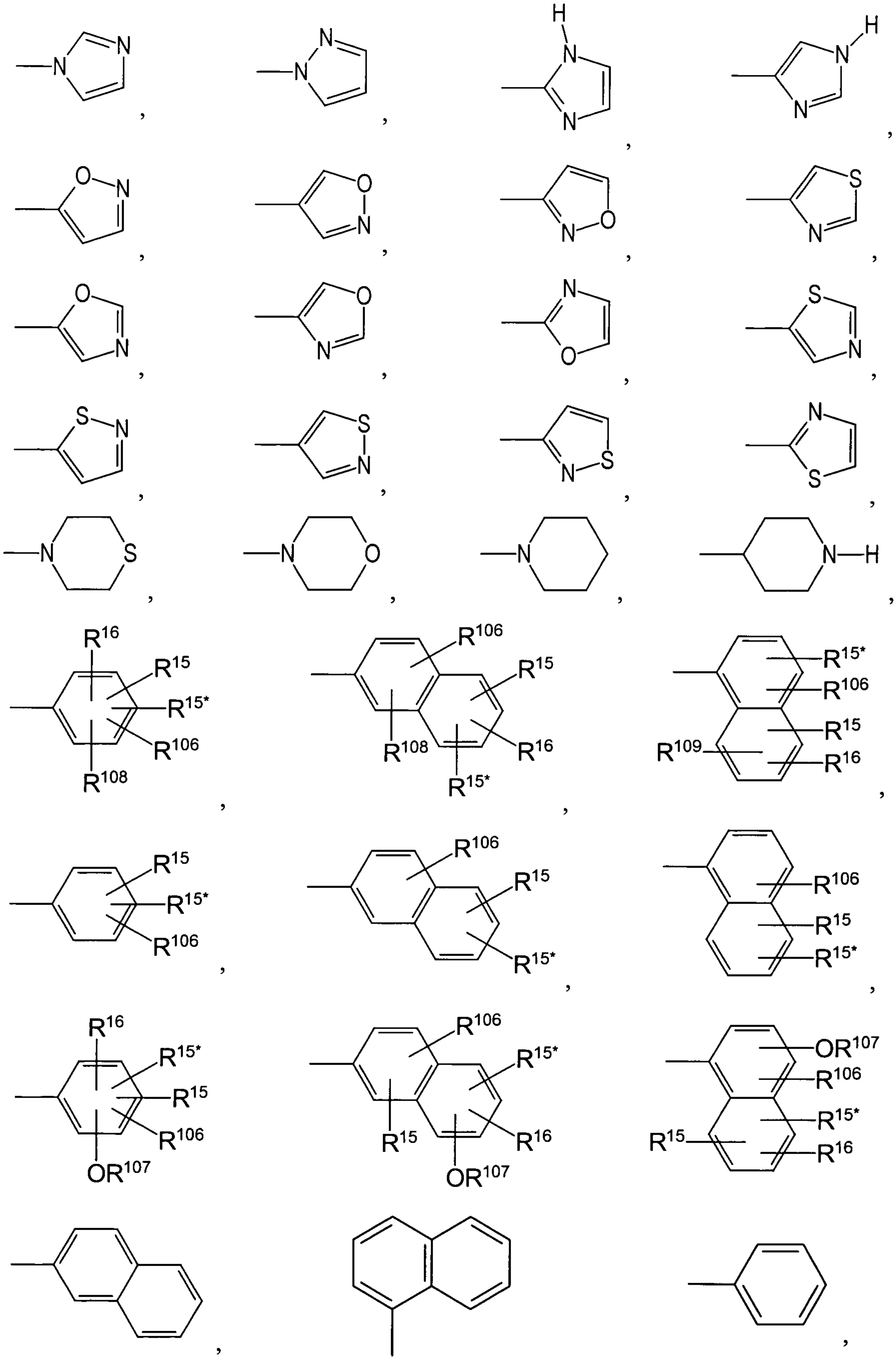
 ,  ,  ,  ,

 ,  ,  ,

wherein the afore-mentioned residues R^{113} can be substituted by one or more substituents selected from –F, –Cl, –Br, –I, –OH, $–NO_2$, $–NH_2$, $–C_2H_4–N(CH_3)_2$, –CN, $–CF_3$, =O, $–R^{16}$, $–R^{17}$, $–R^{106}$, $–O–R^{107}$, $–R^{108}$, $–R^{109}$, and wherein R^{16}, R^{17}, R^{100}, R^{101}, R^{102}, R^{103}, R^{106}, R^{107}, R^{108}, R^{109}, R^{113}, and R^{136} have the meanings as disclosed herein.

Still more preferably R^{113} represents

 ,  ,  ,  ,


R16
R15
R15*
R106
R108
R109
OR107

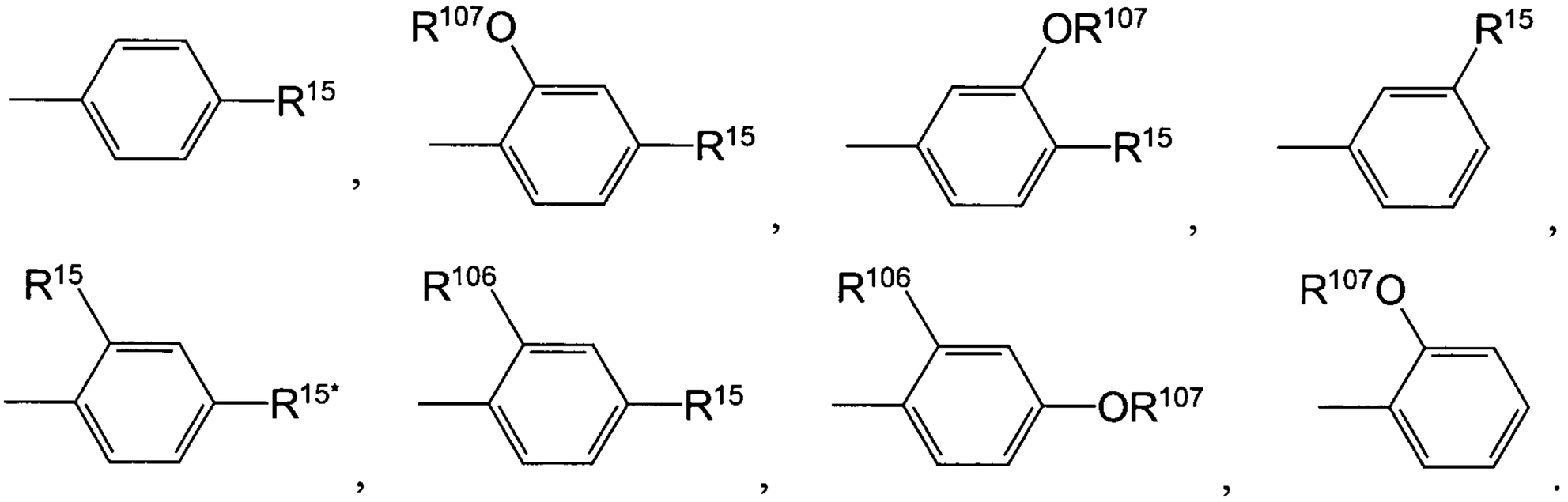
wherein R^{15}, R^{15*}, R^{16}, R^{106}, R^{107}, R^{108}, and R^{109} have the meanings as disclosed herein and more preferably R^{109} represent –H, –C≡CH, or $–CH_2$-C≡CH; and R^{108} represent –H, $–CH=CH_2$, or $–CH_2–CH=CH_2$; and

R^{16}, R^{106} and R^{107} represent independently of each other –H, $–CH_3$, $–CF_3$, –Ph, $–CH_2–Ph$, $–C_2H_5$, $–C_3H_7$, $–CH(CH_3)_2$, $–C_4H_9$, $–CH_2–CH(CH_3)_2$, $–CH(CH_3)–C_2H_5$, $–C(CH_3)_3$, $–C_5H_{11}$, $–CH(CH_3)–C_3H_7$, $–CH_2–CH(CH_3)–C_2H_5$, $–CH(CH_3)–CH(CH_3)_2$, $–C(CH_3)_2–C_2H_5$, $–CH_2–C(CH_3)_3$, $–CH(C_2H_5)_2$, $–C_2H_4–CH(CH_3)_2$, $–C_6H_{13}$, $–C_3H_6–CH(CH_3)_2$, $–C_2H_4–CH(CH_3)–C_2H_5$, $–CH(CH_3)–C_4H_9$, $–CH_2–CH(CH_3)–C_3H_7$, $–CH(CH_3)–CH_2–CH(CH_3)_2$, $–CH(CH_3)–CH(CH_3)–C_2H_5$, $–CH_2–CH(CH_3)–CH(CH_3)_2$, $–CH_2–C(CH_3)_2–C_2H_5$, $–C(CH_3)_2–C_3H_7$, $–C(CH_3)_2–CH(CH_3)_2$, $–C_2H_4–C(CH_3)_3$, $–CH(CH_3)–C(CH_3)_3$;

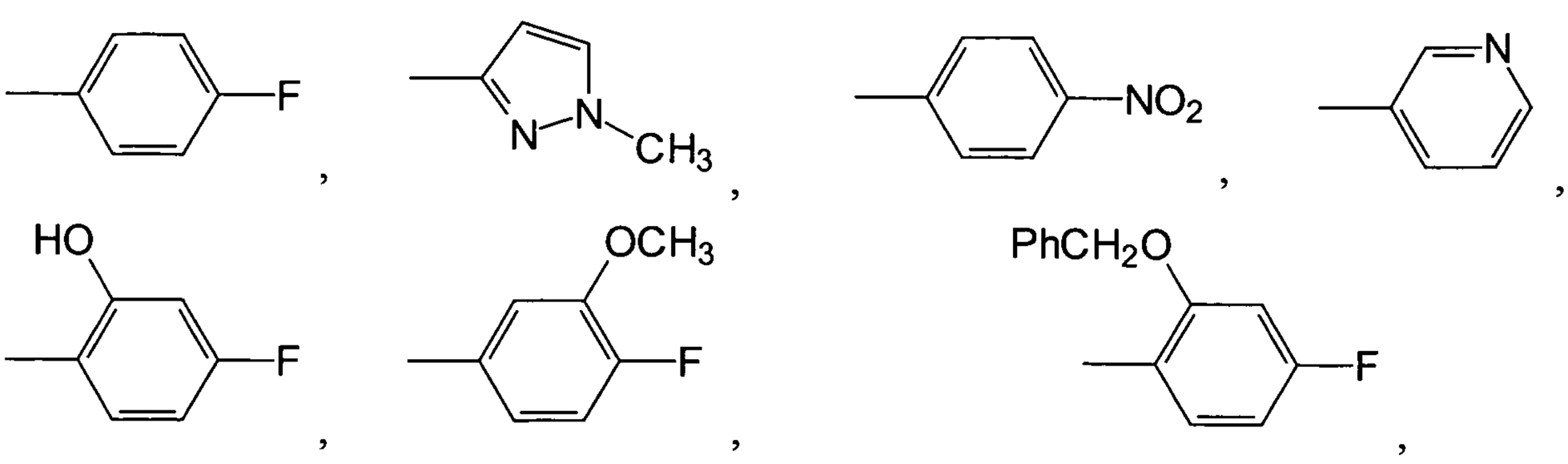
and R^{15} and R^{15*} represent independently of each other –H, –F, –Cl, –Br, –I, –OH, $–NO_2$, $–NH_2$, $–C_2H_4–N(CH_3)_2$, –CN, $–CF_3$, =O;

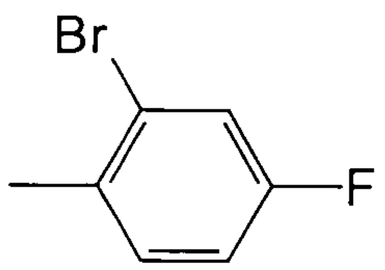
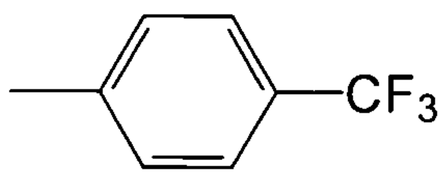
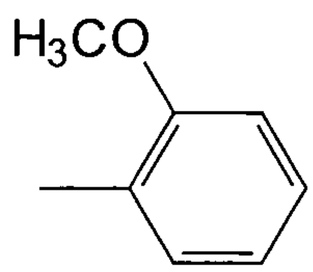
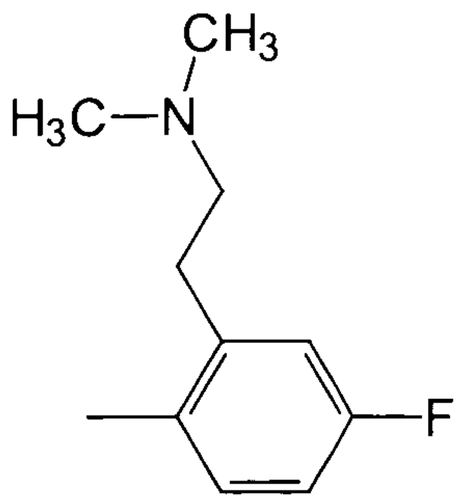
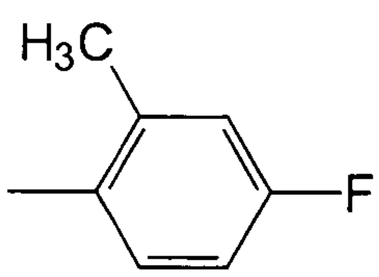
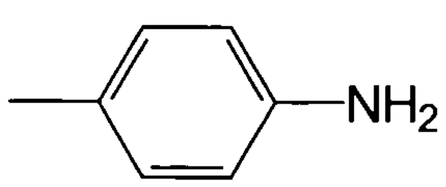
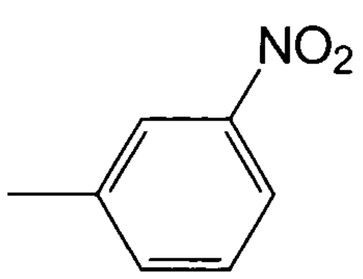
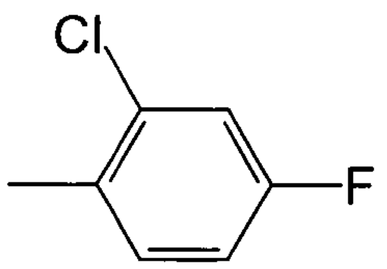
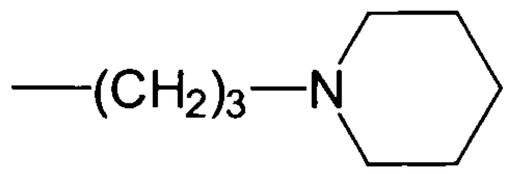
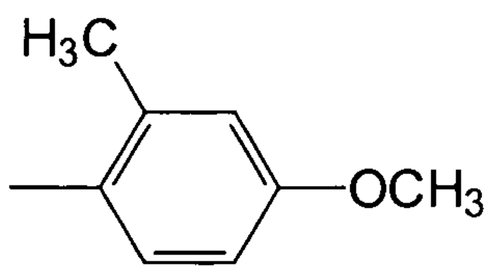
Still more preferably R^{15} and R^{15*} represent independently of each other –H, –F, –Cl, –Br, –OH, $–NO_2$, $–NH_2$, $–C_2H_4–N(CH_3)_2$, and still more preferably R^{16} represents –H, $–CH_3$, $–CF_3$, $–C_2H_5$; R^{106} represents more preferably –H, $–CH_3$, $–CF_3$, $–C_2H_5$; and R^{107} represents more preferably –H, $–CH_3$, $–CF_3$, –Ph, $–CH_2–Ph$, $–C_2H_5$, $–C_3H_7$, $–CH(CH_3)_2$, $–C_4H_9$;

Most preferably R^{113} represents



Residues for R^{14} proved by examples and thus preferred resudes are: –H, –Br, $–CH_3$, $–C_3H_7$, $–C(CH_3)_3$, –Ph, $–CH_2–O–CH_2–CF_3$



In case R^{14} is attached to a nitrogen atom, R^{14} does not represent –Br.

Preferably R^{13} represents –H, –OH, –F, –Cl, –Br, $-NO_2$, $-CH_3$, $-CF_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-CH=CH-CH_3$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, cyclo-C_3H_5, $-OCH_3$, $-OCF_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, or $-OC_4H_9$;

More preferably R^{13} represents –H, –OH, –F, –Cl, $-NO_2$, $-CH_3$, $-CF_3$, $-C_2H_5$, $-C_3H_7$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C\equiv CH$, $-CH_2-C\equiv CH$, cyclo-C_3H_5, $-OCH_3$, $-OCF_3$, $-OC_2H_5$, or $-OC_3H_7$.

Still more preferably R^{13} represents –H, –OH, –F, $-CH_3$, $-CF_3$, $-C_2H_5$, $-CH=CH_2$, $-C\equiv CH$, $-OCH_3$, $-OCF_3$, or $-OC_2H_5$.

Most preferably R^{13} represents –H, –F, $-CH_3$, $-CF_3$, or $-C_2H_5$.

Preferably R^{12} represents –H, –F, –Cl, –Br, –I, –OH, $-NH_2$, $-NHR^{19}$, $-NR^{19}R^{20}$, $-OCH_3$, $-OCF_3$, $-OC_2F_5$, $-OC_2H_5$, $-OC_3H_7$, –O-cyclo-C_3H_5, $-OCH_2$-cyclo-C_3H_5, $-O-C_2H_4$-cyclo-C_3H_5, $-O-C_3H_6$-cyclo-C_3H_5, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, –OPh, $-NO_2$, $-R^{94}$, $-OR^{94}$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N[CH(CH_3)_2]_2$, $-N[C(CH_3)_3]_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-CH_2-CH_2F$, $-CH_2-CHF_2$, $-CH_2-CF_3$, $-CH_2-CH_2Cl$, $-CH_2-CH_2Br$, $-CH_2-CH_2I$, cyclo-C_3H_5, $-CH_2-$cyclo-C_3H_5, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$,

$-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2\text{-}C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$;

and R^{94} represents preferably $-CR^{58}R^{16}R^{17}$, $-CR^{59}R^{60}-CR^{16}R^{17}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{16}R^{17}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{16}R^{17}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}-CR^{16}R^{17}R^{58}$, $-CR^{58}R^{59}R^{60}$, $-CR^{59}R^{60}-CR^{61}R^{62}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$,

and R^{58} – R^{68} preferably represent preferably independently of each other –H, $-NH_2$, –OH, –F, –Cl, –Br, –I, $-R^{71}$, $-O-R^{71}$, $-R^{72}$, $-O-R^{95}$, $-R^{96}$, $-O-R^{104}$, $-R^{105}$, $-CR^{16}R^{17}H$, $-NR^{16}R^{17}$;

wherein R^{16}, R^{17}, R^{19}, R^{20}, R^{71}, R^{72}, R^{95}, R^{96}, R^{104}, and R^{105} have the meanings as disclosed herein.

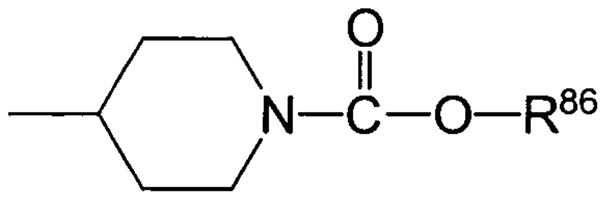
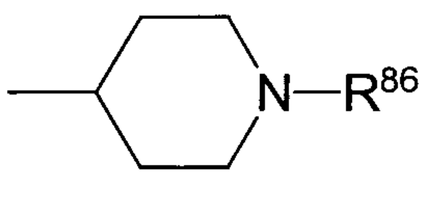
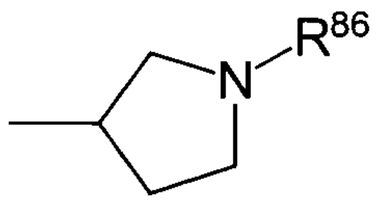
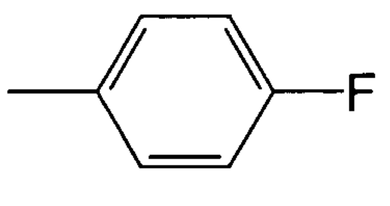
More preferably R^{12} represents –H, –F, –Cl, –Br, –I, –OH, $-NH_2$, $-CH_2F$, $-CF_3$, $-CH_2-CH_2F$, $-CH_2-CF_3$, cyclo-C_3H_5, $-CH_2$–cyclo–C_3H_5, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-C_6H_{13}$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2\text{-}C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-OCH_3$, $-OCF_3$, $-OC_2F_5$, $-OC_2H_5$, $-OC_3H_7$, –O-cyclo-C_3H_5, $-OCH_2$-cyclo-C_3H_5, $-O-C_2H_4$-cyclo-C_3H_5, $-O-C_3H_6$-cyclo-C_3H_5, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, –OPh, $-NO_2$, $-R^{94}$, $-OR^{94}$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N[CH(CH_3)_2]_2$, $-N[C(CH_3)_3]_2$;

and R^{94} represents preferably $-CR^{58}R^{59}R^{60}$, $-CR^{59}R^{60}-CR^{61}R^{62}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$,

and R^{59} – R^{68} represent independently of each other –H, $-NH_2$, –OH, –F, –Cl, –Br, –I, $-OCH_3$, $-OCF_3$, $-OC_2H_5$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CF_3$, $-C(CH_3)_3$;

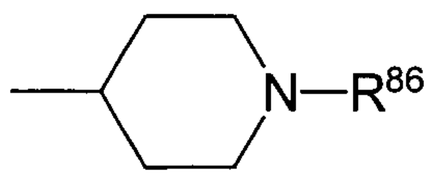
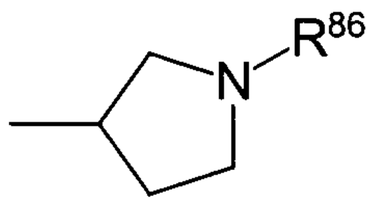
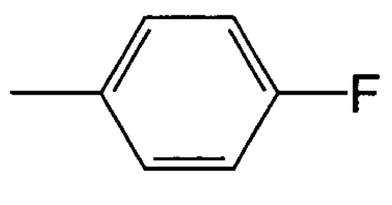
and R^{58} represents preferably $-CH_3$, $-CF_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$,

$-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-Ph$, $-CH_2-Ph$, $-OCH_3$, $-OCF_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-OC_4H_9$, $-OCH_2-CH(CH_3)_2$, $-OCH(CH_3)-C_2H_5$, $-OC(CH_3)_3$, $-OC_5H_{11}$, $-OCH_2-C(CH_3)_3$, $-OCH(C_2H_5)_2$, $-OC_2H_4-CH(CH_3)_2$, $-OC_6H_{13}$, $-OPh$, $-OCH_2-Ph$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N[CH(CH_3)_2]_2$, $-N[C(CH_3)_3]_2$,

wherein R^{86} has the meanings as disclosed herein.

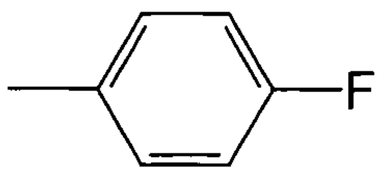
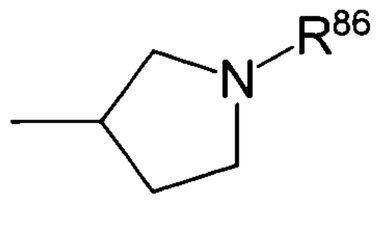
Still more preferably R^{12} represents $-H$, $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-NH_2$, $-CH_2F$, $-CF_3$, $-CH_2-CH_2F$, $-CH_2-CF_3$, cyclo-C_3H_5, $-CH_2$–cyclo–C_3H_5, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-C_6H_{13}$, $-OCH_3$, $-OCF_3$, $-OC_2F_5$, $-OC_2H_5$, $-OC_3H_7$, $-O$-cyclo-C_3H_5, $-OCH_2$-cyclo-C_3H_5, $-O-C_2H_4$-cyclo-C_3H_5, $-O-C_3H_6$-cyclo-C_3H_5, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, $-OPh$, $-NO_2$, $-R^{94}$, $-OR^{94}$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-N[CH(CH_3)_2]_2$, $-N[C(CH_3)_3]_2$;
and R^{94} represents preferably $-CH_2R^{58}$, $-CH_2-CH_2R^{58}$, $-CH_2-CH_2-CH_2R^{58}$, $-CH_2-CH_2-CH_2-CH_2R^{58}$, $-CH_2-CH_2-CH_2-CH_2-CH_2R^{58}$,
and R^{58} represents preferably $-CH_3$, $-CF_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-Ph$, $-CH_2-Ph$, $-OCH_3$, $-OCF_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-OC_4H_9$, $-OCH_2-CH(CH_3)_2$, $-OCH(CH_3)-C_2H_5$, $-OC(CH_3)_3$, $-OC_5H_{11}$, $-OC_6H_{13}$, $-OPh$, $-OCH_2-Ph$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-NHC(CH_3)_3$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$,

and R^{86} represents preferably $-H$, $-CH_3$, $-CF_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-Ph$, $-CH_2-Ph$.

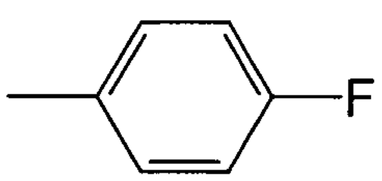
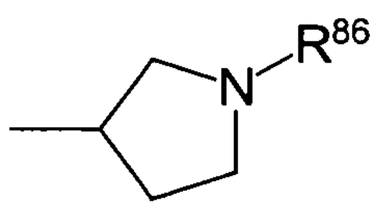
Even still more preferably R^{12} represents $-H$, $-F$, $-Cl$, $-Br$, $-CF_3$, cyclo-C_3H_5, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-OH$, $-NH_2$, $-OCH_3$, $-OCF_3$, $-OC_2H_5$, $-OC_3H_7$, $-O$-cyclo-C_3H_5, $-OCH_2$-cyclo-C_3H_5, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, $-OC_4H_9$, $-NO_2$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-N(C_3H_7)_2$, $-OCH_2R^{58}$, $-OCH_2-CH_2R^{58}$, $-OCH_2-$

CH_2–CH_2R^{58}, –OCH_2–CH_2–CH_2–CH_2R^{58}, –CH_2R^{58}, –CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2–CH_2R^{58},
and R^{58} represents preferably –CH_3, –CF_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –Ph, –OCH_3, –OCF_3, –OC_2H_5, –OC_3H_7, –$OCH(CH_3)_2$, –$N(CH_3)_2$, –$N(C_2H_5)_2$, –$N(C_3H_7)_2$,

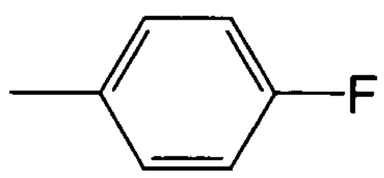
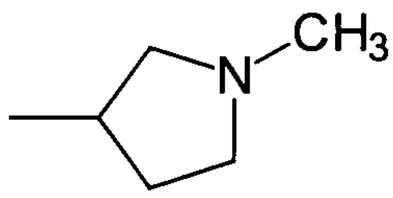

,


and R^{86} represents preferably –H, –CH_3, –CF_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$.

Most preferably R^{12} represents –H, –F, –Cl, –Br, –CF_3, cyclo-C_3H_5, –CH_3, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –OH, –NH_2, –OCH_3, –OCF_3, –OC_2H_5, –OC_3H_7, –O-cyclo-C_3H_5, –OCH_2-cyclo-C_3H_5, –$OCH(CH_3)_2$, –$OC(CH_3)_3$, –OC_4H_9, –NO_2, –OCH_2R^{58}, –OCH_2–CH_2R^{58}, –OCH_2–CH_2–CH_2R^{58}, –OCH_2–CH_2–CH_2–CH_2R^{58}, –CH_2R^{58}, –CH_2–CH_2R^{58}, –CH_2–CH_2–CH_2R^{58},
and R^{58} represents preferably –Ph, –OCH_3, –OCF_3, –OC_2H_5, –$N(CH_3)_2$, –$N(C_2H_5)_2$,


,

,

and R^{86} represents preferably –H, –CH_3, –CF_3, –C_2H_5.

Residues for R^{12} proved by examples and thus preferred resudes are:
–H, –Br, –CH_3, –NH_2, –OCH_3, –OC_2H_5, –OCH_2-cyclo-C_3H_5, –$OCH(CH_3)_2$, –NO_2, –OCH_2R^{58}, –OCH_2–CH_2R^{58}, –OCH_2–CH_2–CH_2R^{58}, –CH_2–CH_2R^{58}, and R^{58} represents preferably –Ph, –OCH_3, –$N(CH_3)_2$, 
,

.

In case R^{12} is attached to a nitrogen atom, R^{12} does preferably not represent an alkoxy group and not a halogen and represents preferably the groups and the preferred groups mentioned herein which are linked through a carbon atom to the ring nitrogen atom.

The present invention also includes within its scope N-oxides of the compounds of formula (I) above. In general, such N-oxides may be formed by conventional means, such as reacting the compound of formula I with oxone in the presence of wet alumina.

The expression tautomer is defined as an organic compound that is interconvertible by a chemical reaction called tautomerization. Tautomerization can be catalyzed preferably by bases or acids or other suitable compounds.

The compounds of the present invention may form salts with organic or inorganic acids or bases. Examples of suitable acids for such acid addition salt formation are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, citric acid, oxalic acid, malonic acid, salicylic acid, p-aminosalicylic acid, malic acid, fumaric acid, succinic acid, ascorbic acid, maleic acid, sulfonic acid, phosphonic acid, perchloric acid, nitric acid, formic acid, propionic acid, gluconic acid, lactic acid, tartaric acid, hydroxymaleic acid, pyruvic acid, phenylacetic acid, benzoic acid, p-aminobenzoic acid, p-hydroxybenzoic acid, methanesulfonic acid, ethanesulfonic acid, nitrous acid, hydroxyethanesulfonic acid, ethylenesulfonic acid, p-toluenesulfonic acid, naphthylsulfonic acid, sulfanilic acid, camphorsulfonic acid, china acid, mandelic acid, o-methylmandelic acid, hydrogen-benzenesulfonic acid, picric acid, adipic acid, D-o-tolyltartaric acid, tartronic acid, (o, m, p)-toluic acid, naphthylamine sulfonic acid, trifluoroacetic acid, and other mineral or carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form of the compounds of formula (I) with a sufficient amount of the desired acid to produce a salt in the conventional manner well known to those skilled in the art.

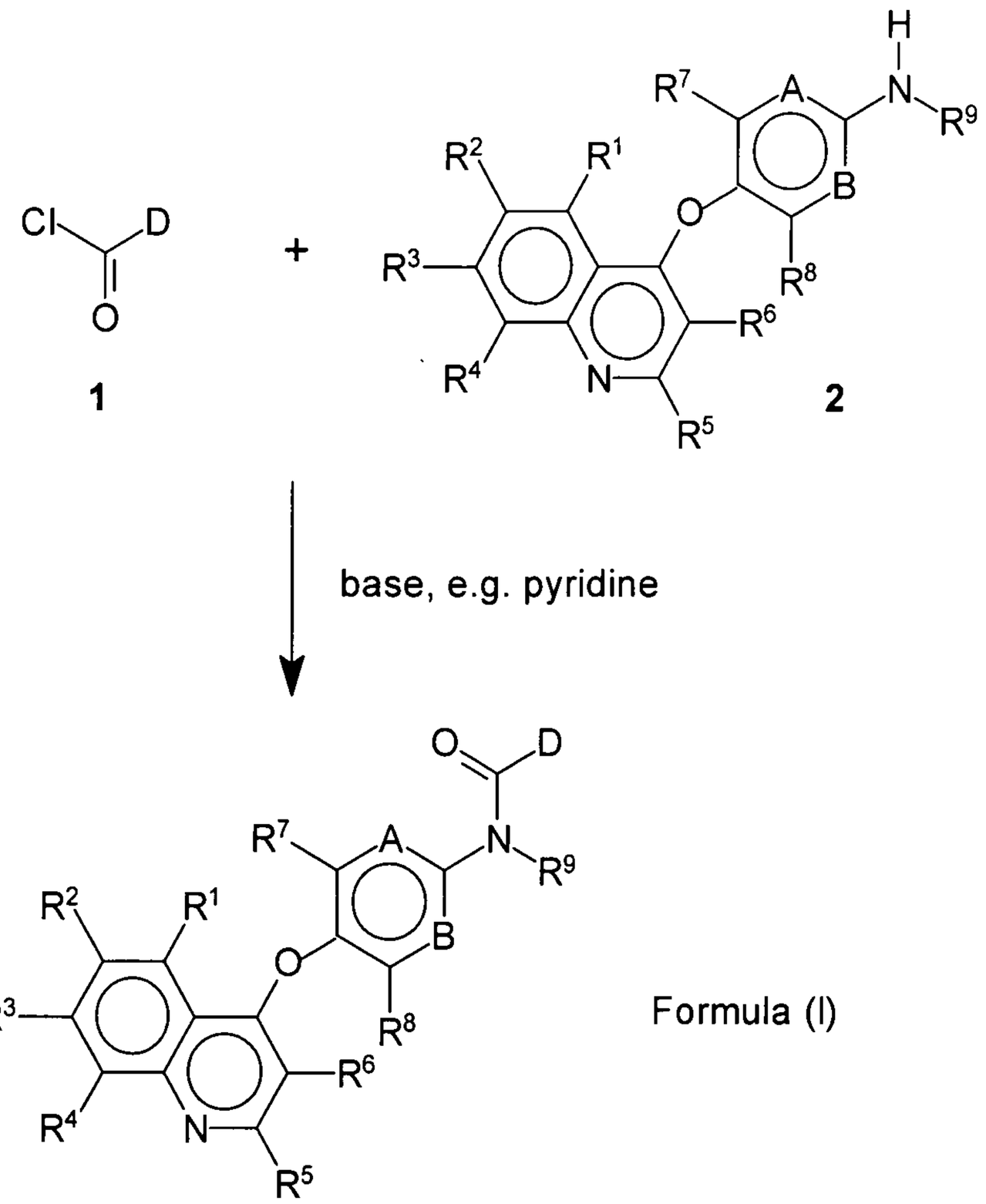
The inventive compounds may exist in a number of different polymorphic forms.

In the case the inventive compounds bear acidic groups, salts could also be formed with inorganic or organic bases. Examples for suitable inorganic or organic bases are, for example, NaOH, KOH, NH_4OH, tetraalkylammonium hydroxide, lysine or arginine and the like. Salts may be prepared in a conventional manner using methods well known in the art, for example by treatment of a solution of the compound of the general formula (I) with a solution of an acid, selected out of the group mentioned above.

Syntheses of compounds

A method to prepare compounds of formula (I) is shown in **Scheme 1**. The reaction of acid chloride **1** and aniline **2** is carried out in the presence of a base like pyridine and optionally in an inert solvent like DCM (dichloromethane). Many of the acid chlorides **1** are commercially available. The acid chlorides **1** can also be prepared from commercially available carboxylic acids via standard procedures, using thionyl chloride or oxalyl chloride as reagents. Alternatively, carboxylic acids can be directly coupled with anilines **2** under standard procedures, such as using HBTU (N,N,N′,N′-

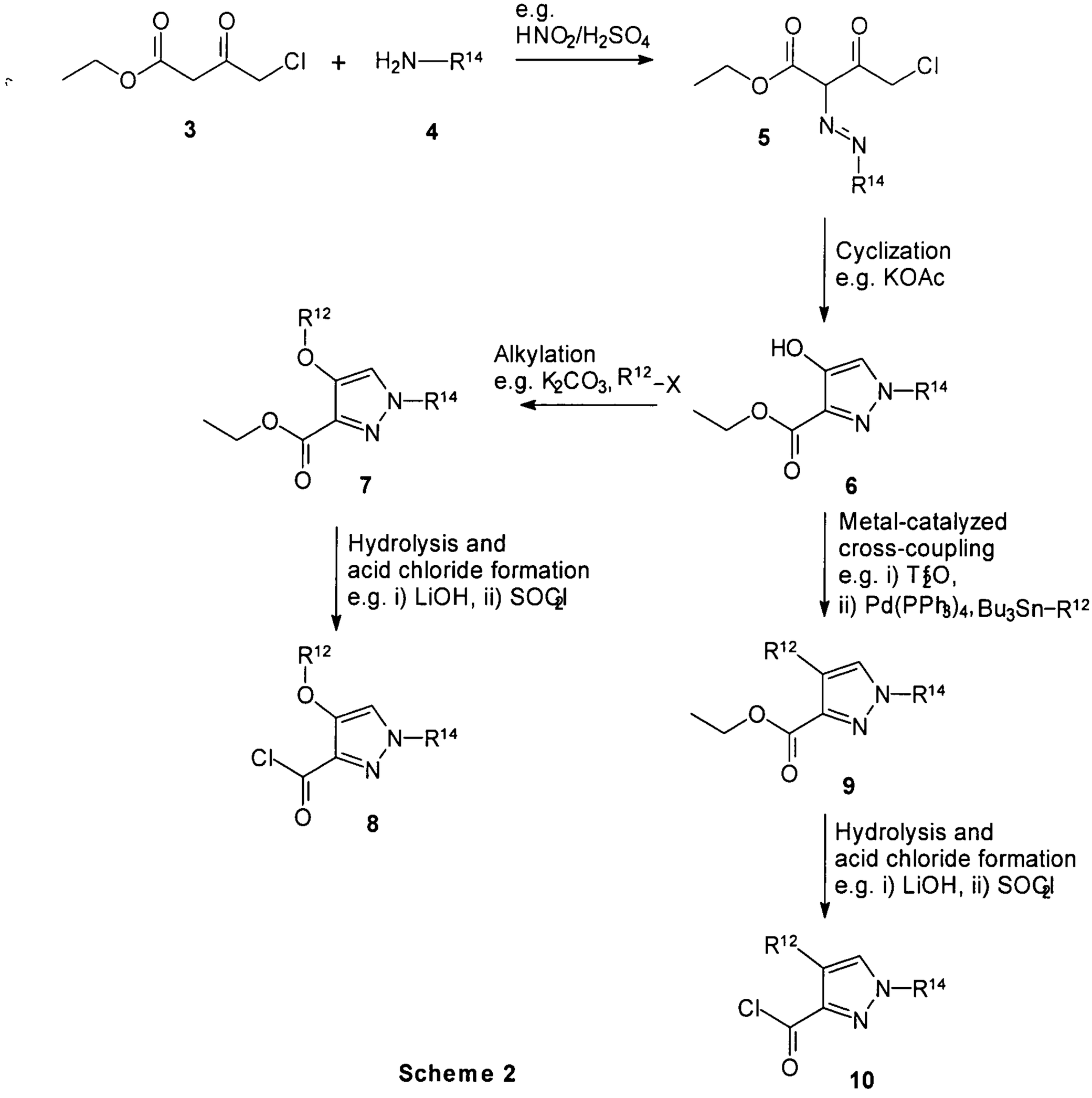
Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate) or HATU (O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate) to give compounds of formula (I).



Formula (I)

Scheme 1

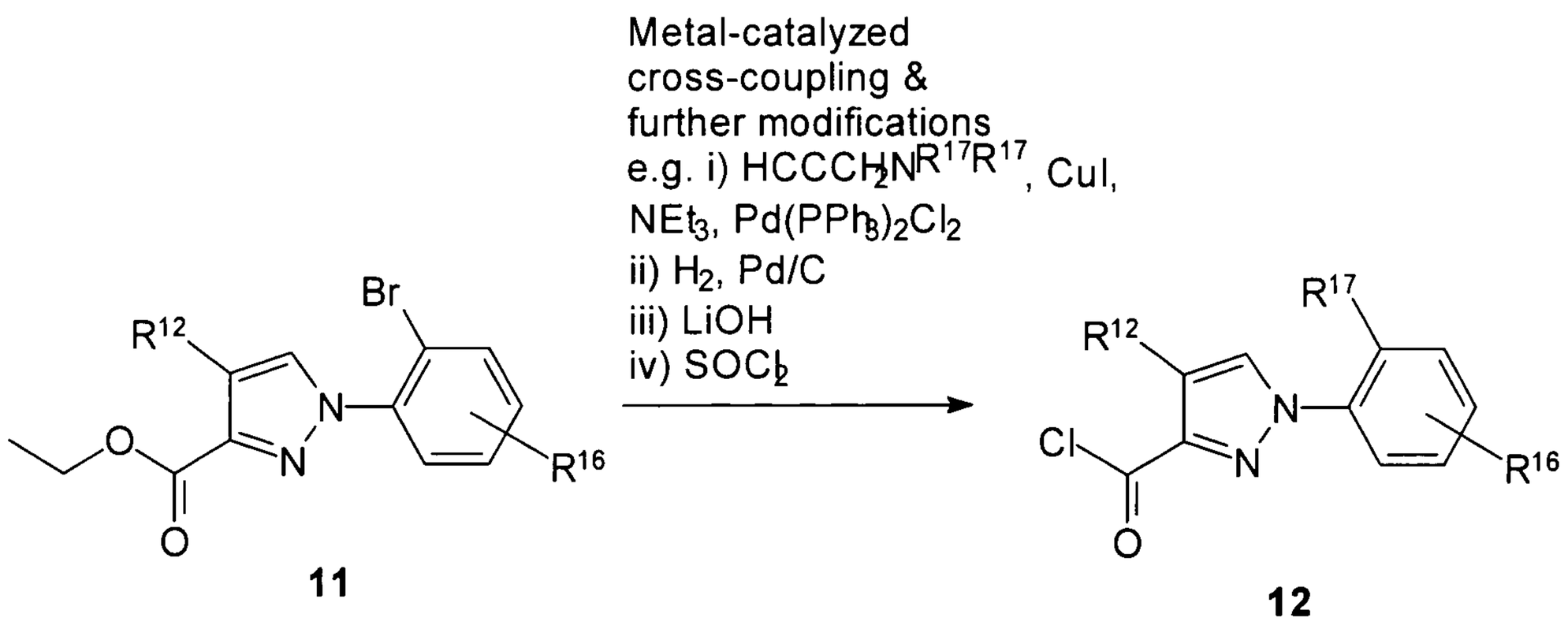
The synthesis of substituted pyrazoles **8/10** is shown in **Scheme 2**. Diazonium derivatives **5** are obtained by the reaction of ethyl 4-chloro-3-oxo-butanoate **3** with different anilines **4.** Subsequent cyclization of **5** to the corresponding pyrazoles **6** can be achieved using a base such as KOAc (potassium acetate), as described in literature (Chattaway, F.D.; Ashworth, D.R.; Grimwalde, M. *Journal of the Chemical Society* **1935**, 117-120). The hydroxyl-group of **6** can be modified by alkylation, for instance using ethyl iodide and K_2CO_3 in DMF (dimethylformamide) to give pyrazole **7**. Alternatively, the hydroxyl-moiety of **6** can be converted into the corresponding triflate which than can be used for metal-catalyzed cross-couplings to obtain derivatives **9**. Finally, hydrolysis of **7/9** and subsequent acid chloride formation yields **8/10**.



Scheme 2

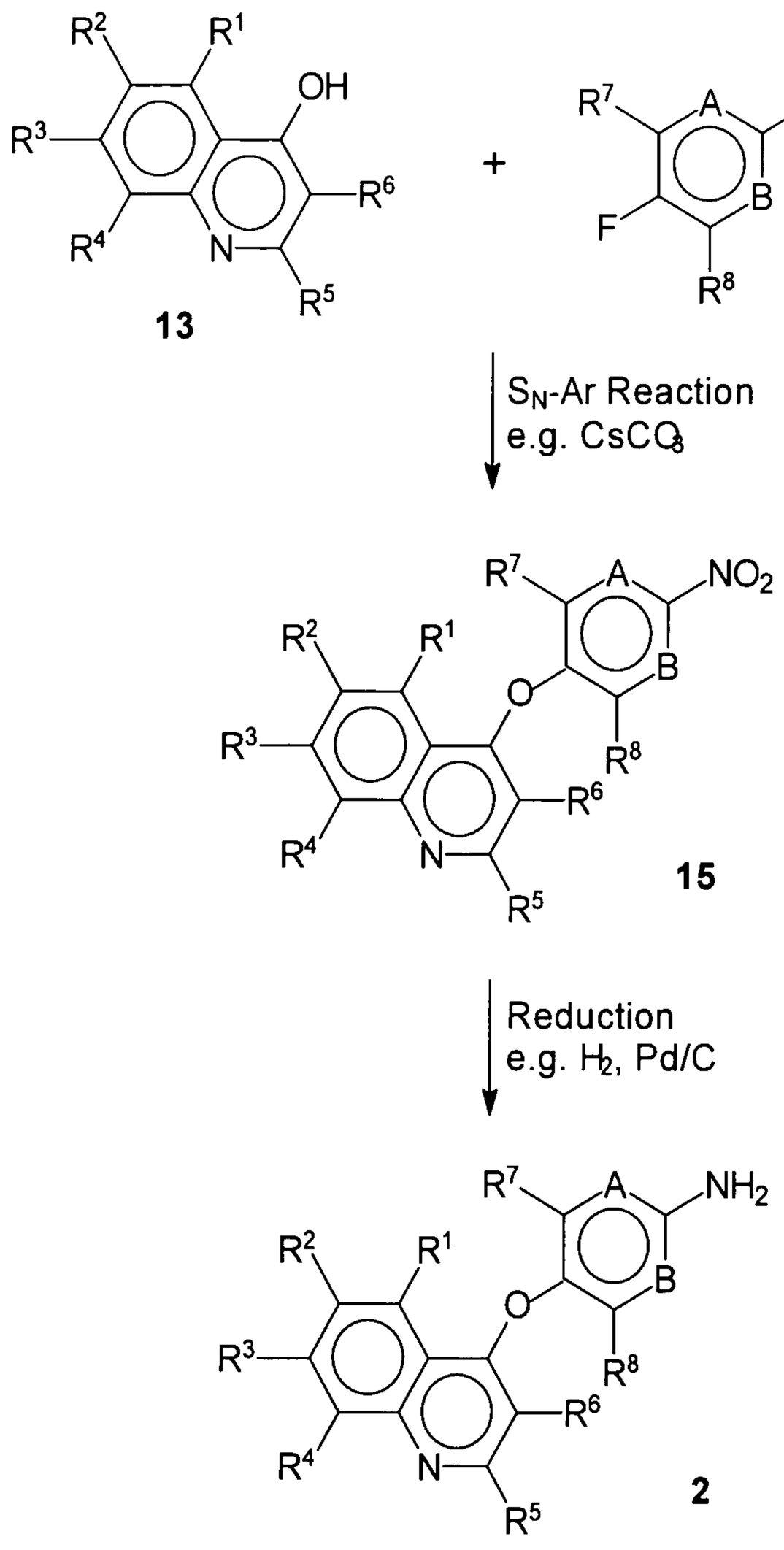
Scheme 2

A modification of the substituents of the pyrazole **11** is shown below in **Scheme 3**. The bromide derivative **11** can be used in metal-catalyzed cross-couplings, for instance under Sonogashira conditions using an alkyne, copper iodide and dichloro-bis (triphenylphosphine)palladium in the presence of a base like NEt_3 (triethylamine). Subsequent modifications yield the pyrazole derivative **12**.



Scheme 3

The synthesis of anilines **2** is shown in **Scheme 4**. Here the quinoline derivative **13** is subjected to nucleophilic aromatic substitution of the appropriate fluoro(hetero)aromatic derivative **14**. Subsequent reduction of the nitro derivative **15** yields the anilines **2**.



Scheme 4

The pharmaceutical compositions according to the present invention comprise at least one compound according to the present invention as an active ingredient together with at least one pharmaceutically acceptable (i.e. non-toxic) carrier, excipient and/or diluent. The pharmaceutical compositions of the present invention can be prepared in a conventional solid or liquid carrier or diluent and a conventional pharmaceutically made adjuvant at suitable dosage level in a known way. The preferred preparations are adapted for oral application. These administration forms include, for example, pills, tablets, film tablets, coated tablets, capsules, powders and deposits.

Furthermore, the present invention also includes pharmaceutical preparations for parenteral application, including dermal, intradermal, intragastral, intracutaneous, intravasal, intravenous, intramuscular, intraperitoneal, intranasal, intravaginal, intrabuccal, percutan, rectal, subcutaneous, sublingual, topical, or transdermal application, which preparations in addition to typical vehicles and/or diluents contain at least one compound according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient.

The pharmaceutical compositions according to the present invention containing at least one compound according to the present invention and/or a pharmaceutical acceptable salt thereof as active ingredient will typically be administered together with suitable carrier materials selected with respect to the intended form of administration, i.e. for oral administration in the form of tablets, capsules (either solid filled, semi-solid filled or liquid filled), powders for constitution, gels, elixirs, dispersable granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable carrier, preferably with an inert carrier like lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid filled capsules) and the like. Moreover, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated into the tablet or capsule. Powders and tablets may contain about 5 to about 95-weight % of the derivatives according to the general formula (I) or analogues compound thereof or the respective pharmaceutically active salt as active ingredient.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among suitable lubricants there may be mentioned boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Suitable disintegrants include starch, methylcellulose, guar gum, and the like. Sweetening and flavoring agents as well as preservatives may also be included, where appropriate. The disintegrants, diluents, lubricants, binders etc. are discussed in more detail below.

Moreover, the pharmaceutical compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimise the therapeutic effect(s), e.g. anti-cancer activity or activity against cancer metastases and the like. Suitable dosage

forms for sustained release include tablets having layers of varying disintegration rates or controlled release, polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions, and emulsions. As an example, there may be mentioned water or water/propylene glycol solutions for parenteral injections or addition of sweeteners and opacifiers for oral solutions, suspensions, and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be present in combination with a pharmaceutically acceptable carrier such as an inert, compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides like cocoa butter is melted first, and the active ingredient is then dispersed homogeneously therein e.g. by stirring. The molten, homogeneous mixture is then poured into conveniently sized moulds, allowed to cool, and thereby solidified.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions, and emulsions.

The compounds according to the present invention may also be delivered transdermally. The transdermal compositions may have the form of a cream, a lotion, an aerosol and/or an emulsion and may be included in a transdermal patch of the matrix or reservoir type as is known in the art for this purpose.

The term capsule as recited herein refers to a specific container or enclosure made e.g. of methylcellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredient(s). Capsules with hard shells are typically made of blended of relatively high gel strength gelatins from bones or pork skin. The capsule itself may contain small amounts of dyes, opaquing agents, plasticisers and/or preservatives.

Under tablet a compressed or moulded solid dosage form is understood which comprises the active ingredients with suitable diluents. The tablet may be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation, or by compaction well known to a person of ordinary skill in the art.

Oral gels refer to the active ingredients dispersed or solubilised in a hydrophilic semi-solid matrix.

Powders for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended e.g. in water or in juice.

Suitable diluents are substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol, and sorbitol, starches derived from wheat, corn, rice, and potato, and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 5 to about 95 % by weight of the total composition, preferably from about 25 to about 75 weight %, and more preferably from about 30 to about 60 weight %.

The term disintegrants refers to materials added to the composition to support break apart (disintegrate) and release the pharmaceutically active ingredients of a medicament. Suitable disintegrants include starches, “cold water soluble” modified starches such as sodium carboxymethyl starch, natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar, cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose, microcrystalline celluloses, and cross-linked microcrystalline celluloses such as sodium croscaramellose, alginates such as alginic acid and sodium alginate, clays such as bentonites, and effervescent mixtures. The amount of disintegrant in the composition may range from about 2 to about 20 weight % of the composition, more preferably from about 5 to about 10 weight %.

Binders are substances which bind or “glue” together powder particles and make them cohesive by forming granules, thus serving as the “adhesive” in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose, starches derived from wheat, corn, rice and potato, natural gums such as acacia, gelatin and tragacanth, derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate, cellulose materials such as methylcellulose, sodium carboxymethylcellulose and hydroxypropylmethylcellulose, polyvinylpyrrolidone, and inorganic compounds such as magnesium aluminum silicate. The amount of binder in the composition may range from about 2 to about 20 weight % of the composition, preferably from about 3 to about 10 weight %, and more preferably from about 3 to about 6 weight %.

Lubricants refer to a class of substances which are added to the dosage form to enable the tablet granules etc. after being compressed to release from the mould by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate, or potassium stearate, stearic acid, high melting point waxes, and other water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and D,L-leucine. Lubricants are usually added at the very last step before compression, since they must be present at the surface of the granules. The amount of lubricant in the composition may range from about 0.2 to about 5 weight % of the composition, preferably from about 0.5 to about 2 weight %, and more preferably from about 0.3 to about 1.5 weight % of the composition.

Glidents are materials that prevent caking of the components of the pharmaceutical composition and improve the flow characteristics of granulate so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition may range from about 0.1 to about 5 weight % of the final composition, preferably from about 0.5 to about 2 weight %.

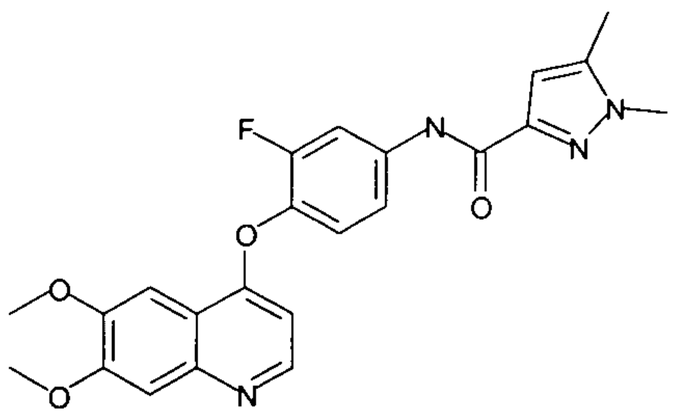
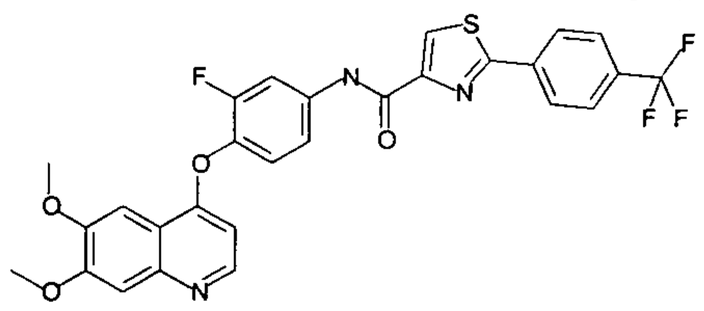
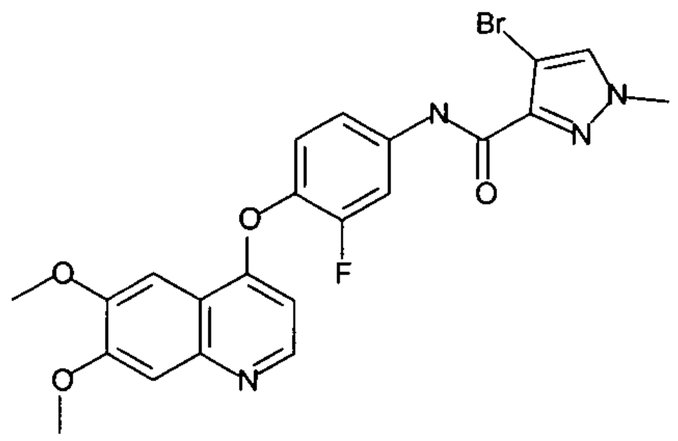
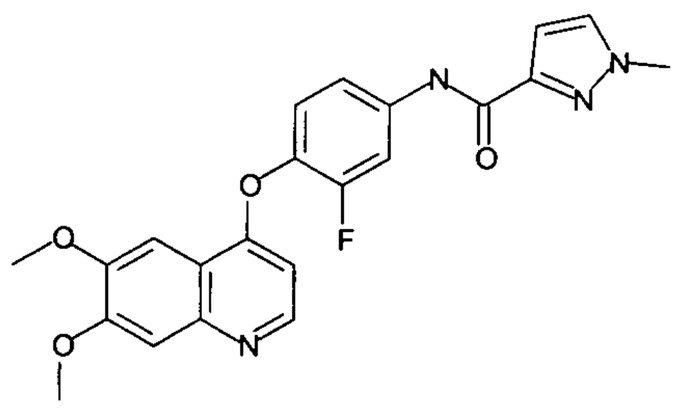
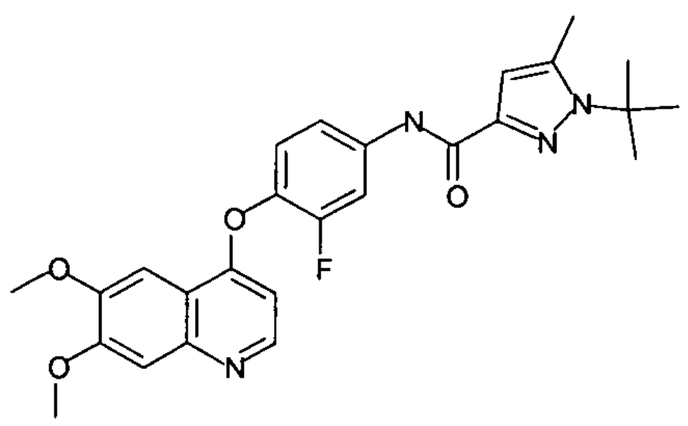
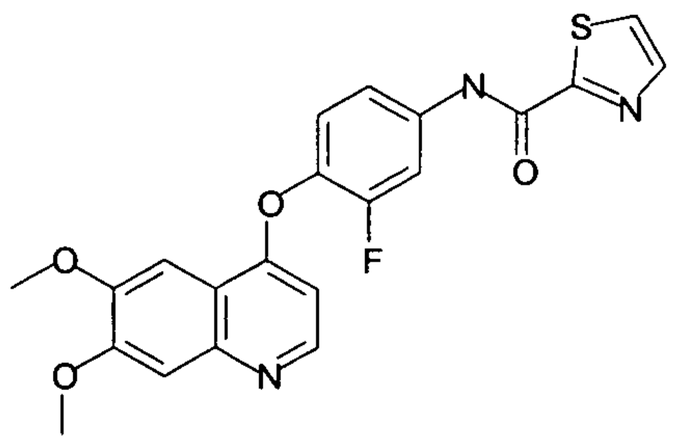
Coloring agents are excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent may vary from about 0.1 to about 5 weight % of the composition, preferably from about 0.1 to about 1 weight %.

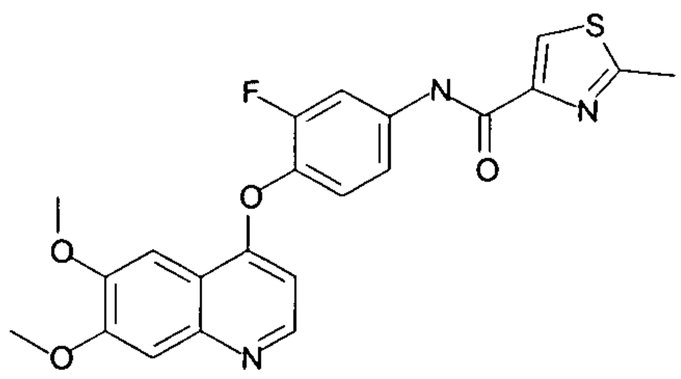
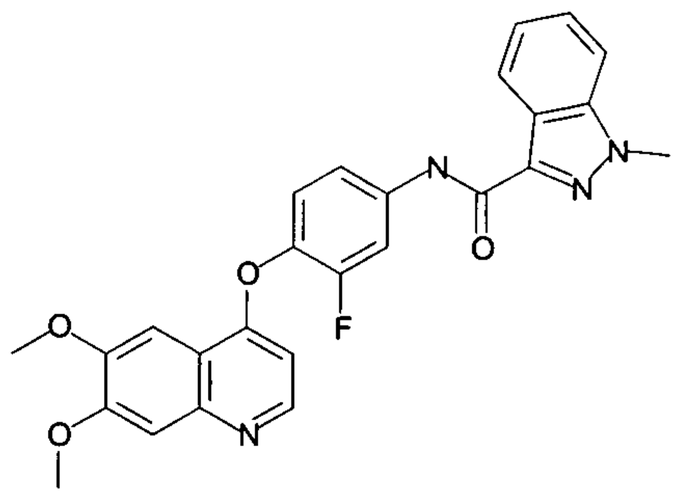
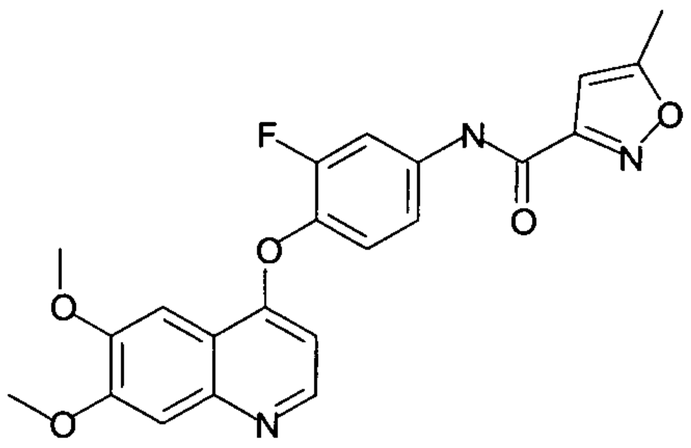
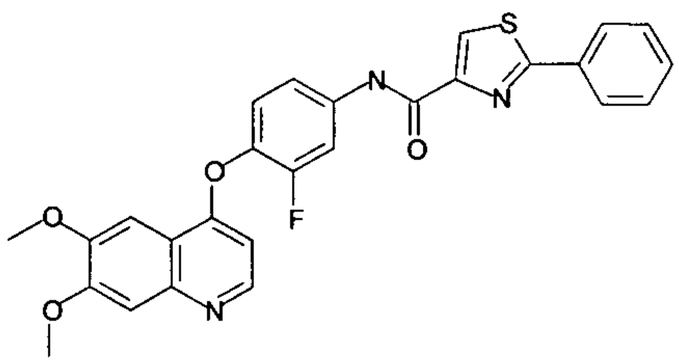
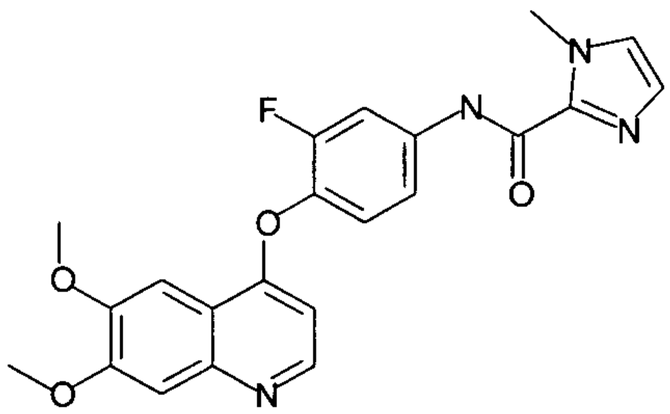
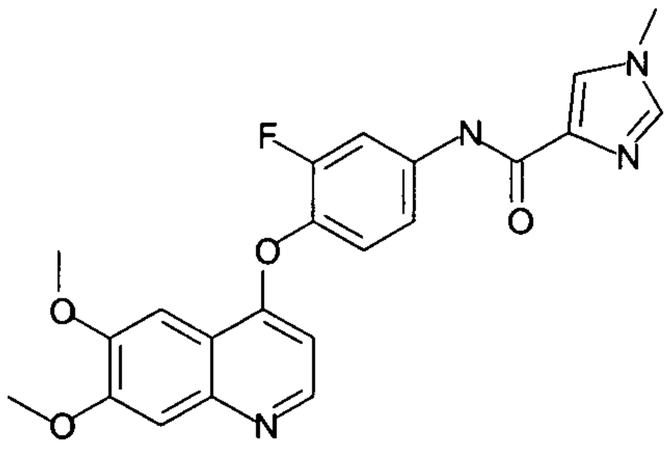
The compounds of the present invention are suitable for use in medicine, particulary in human medicine, but also in veterinary medicine. The dosage of the compounds may be determined by a skilled practitioner according to the type and severity of the disorder to be treated.

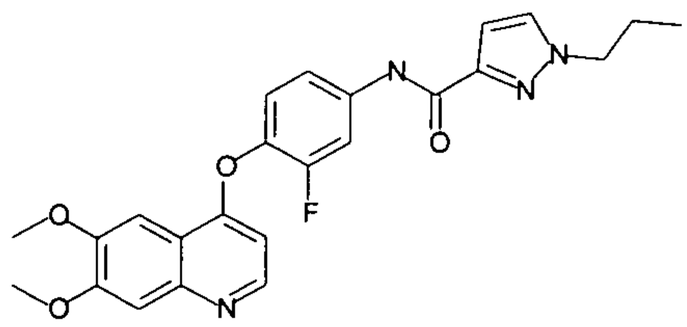
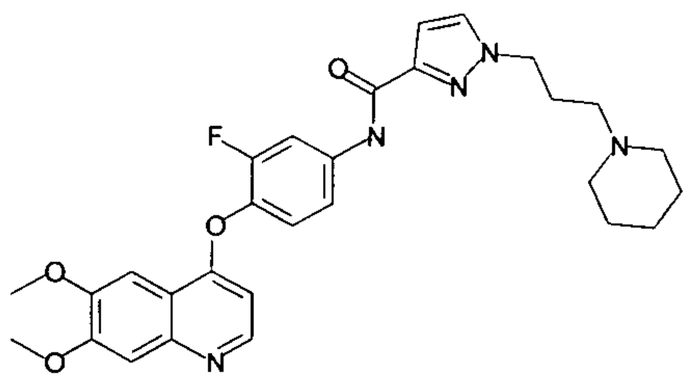
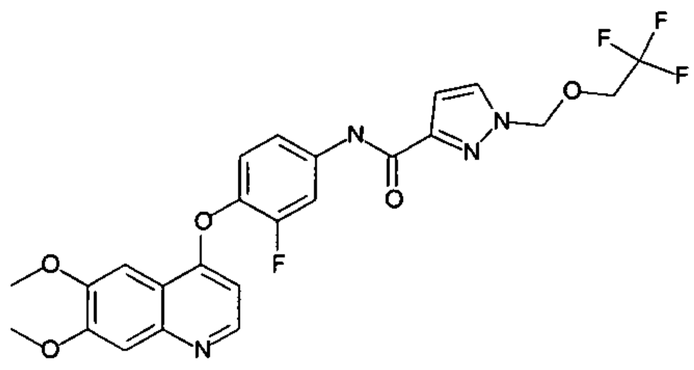
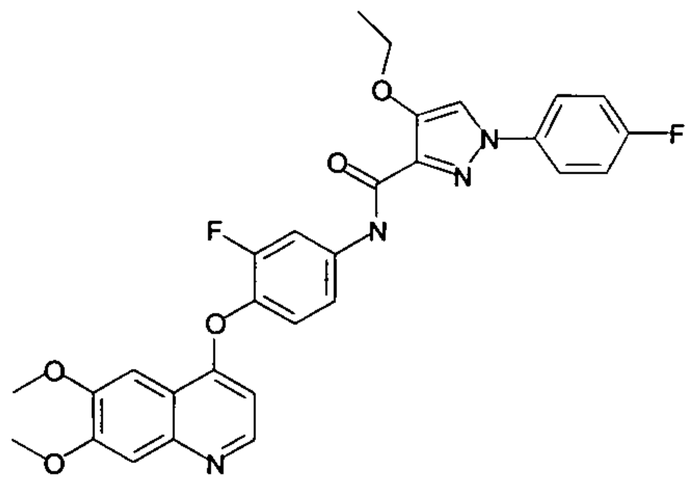
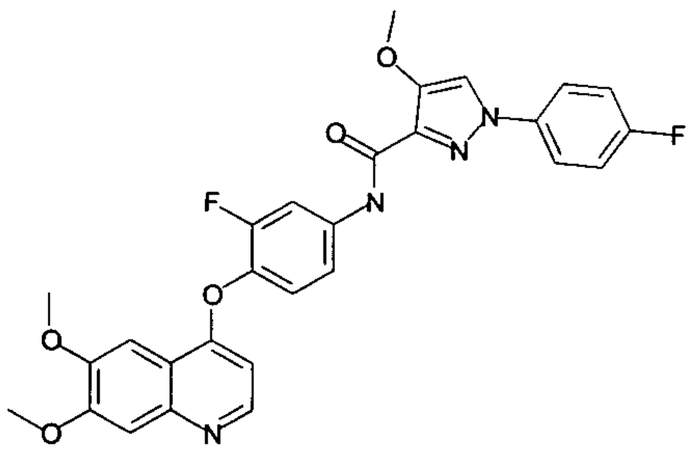
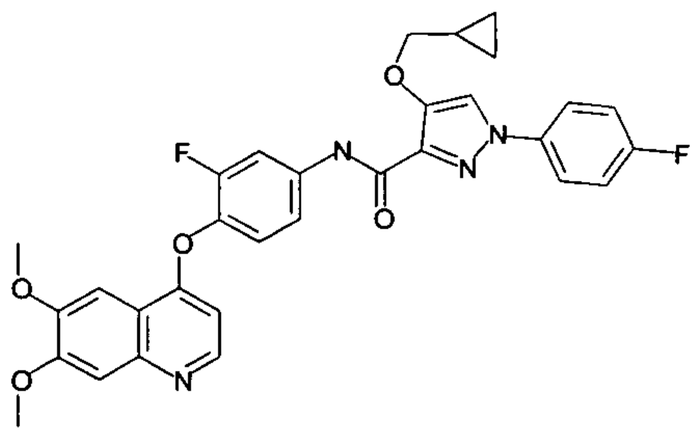
The compounds of the present invention may be admistered as a monotherapy or together with further active agents, particulary chemotherapeutic agents or antitumor antibodies. Furthermore they may be used in combination with surgery and/or irradiation.

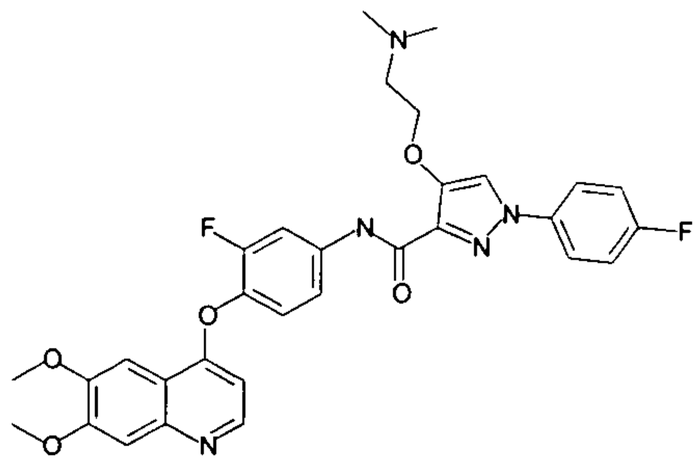
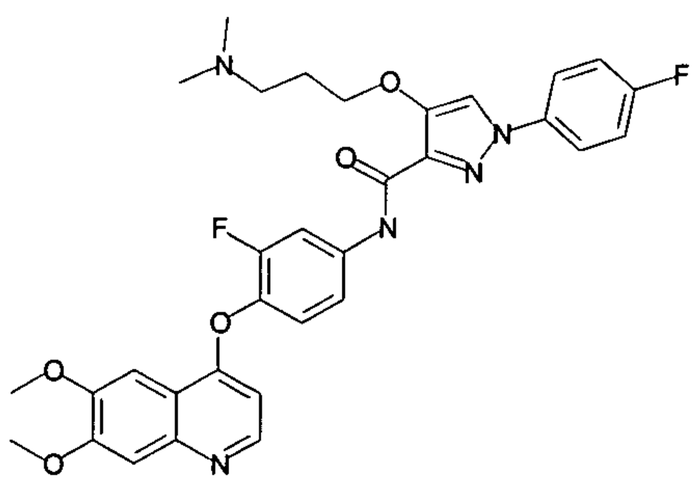
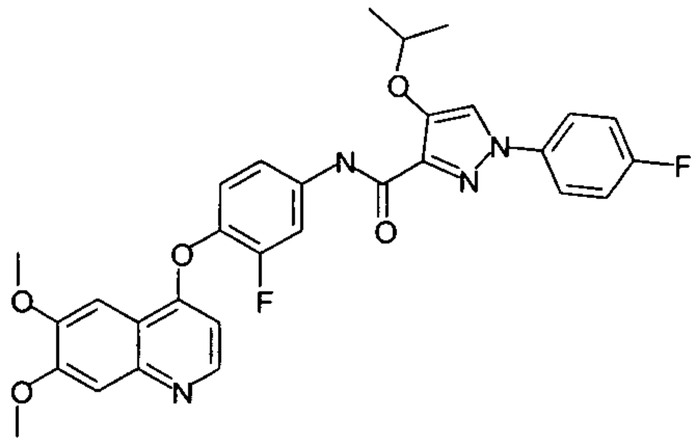
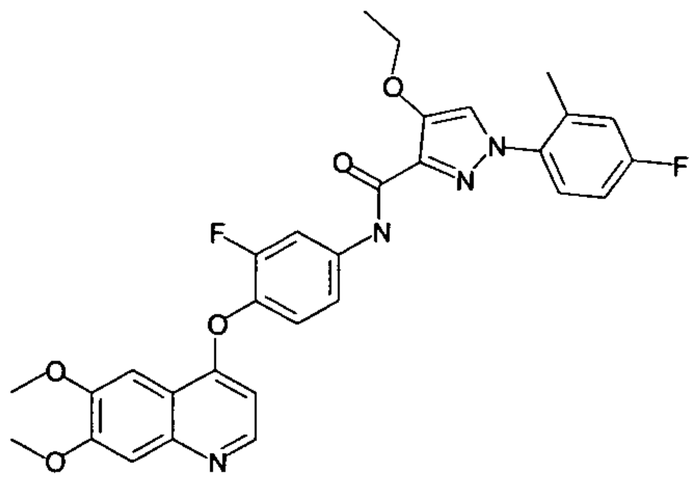
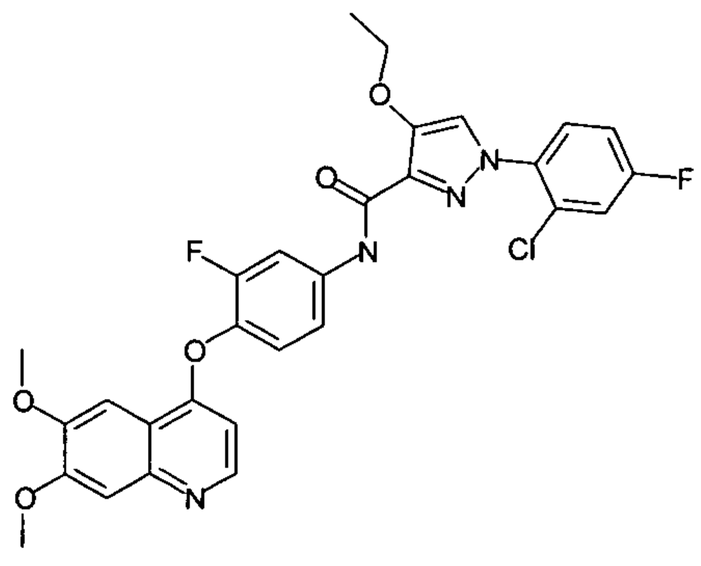
Especially preferred compounds according to the present invention include compounds presented by Table 1.

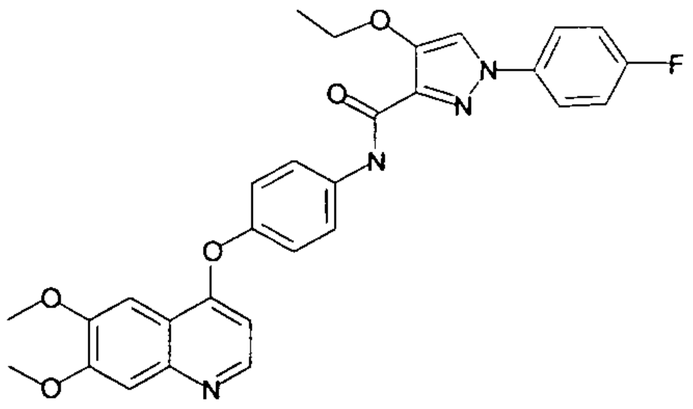
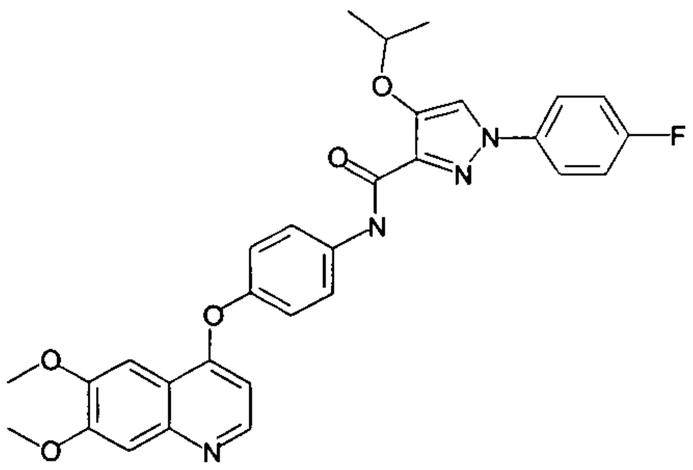
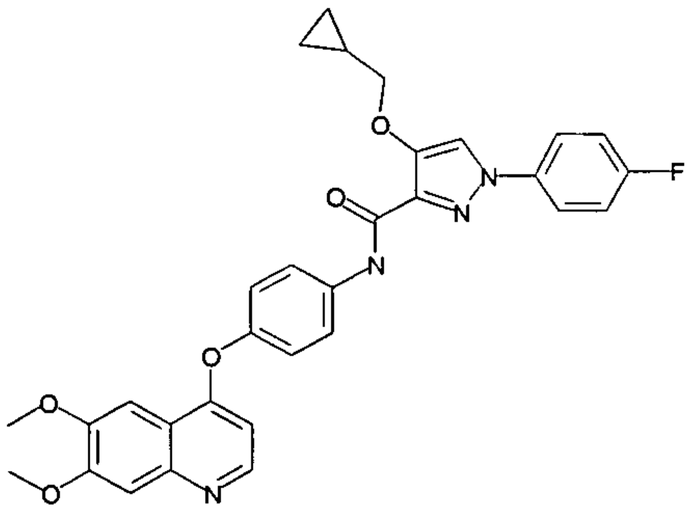
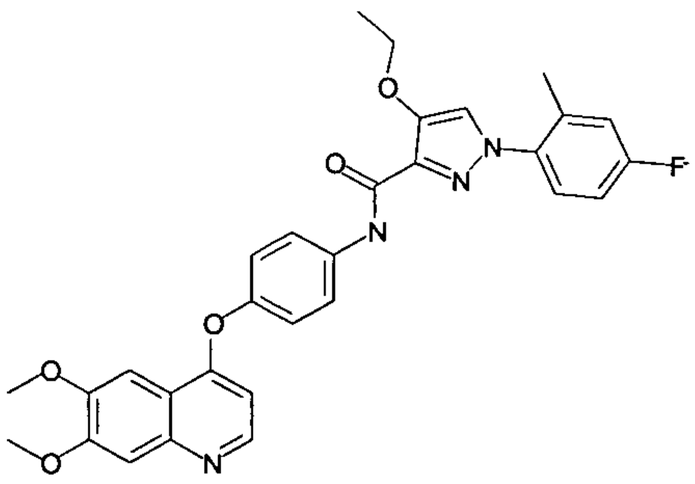
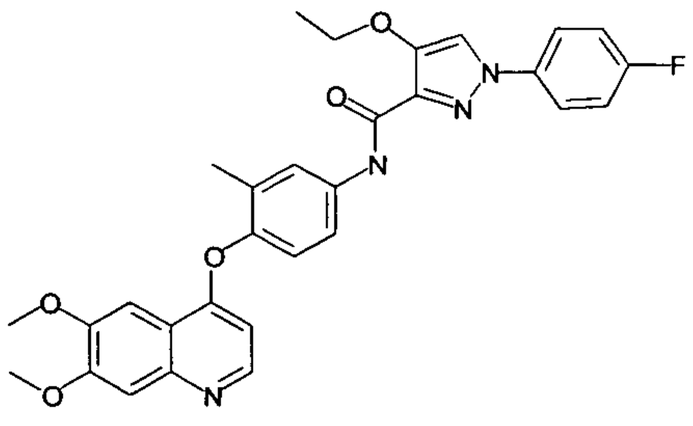
Table 1

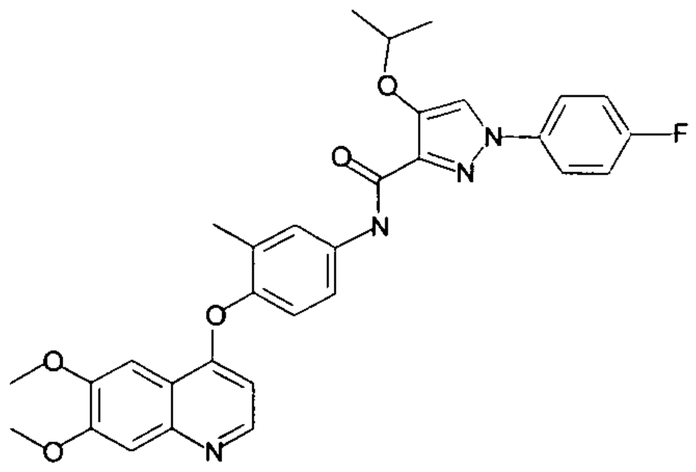
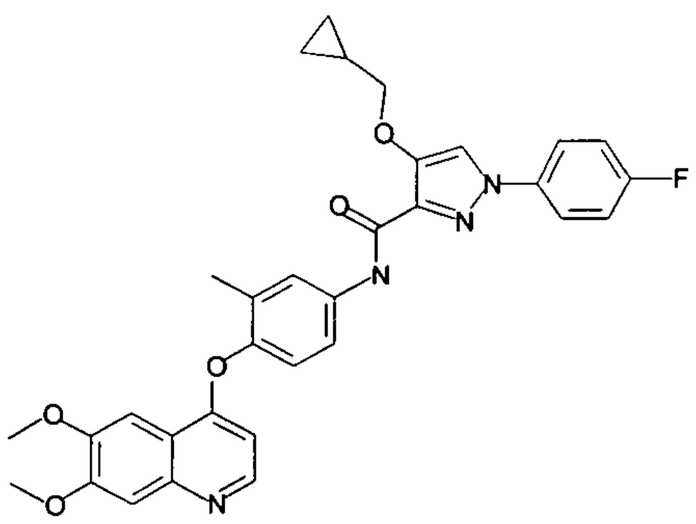
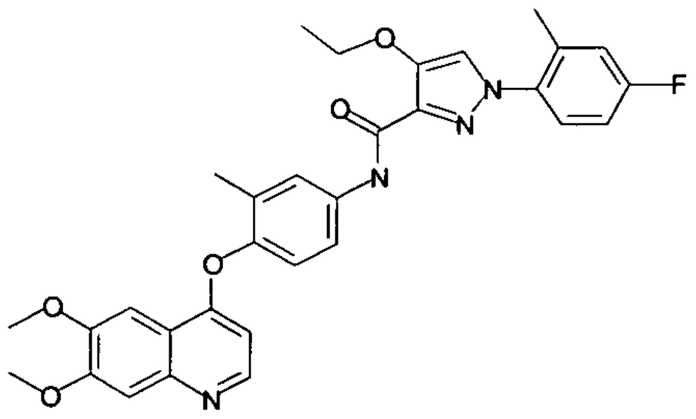
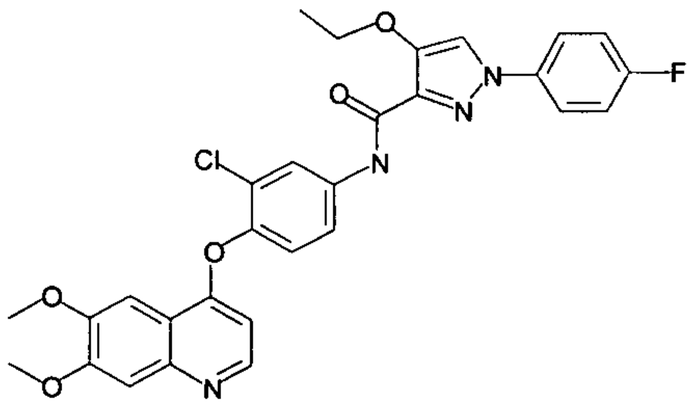
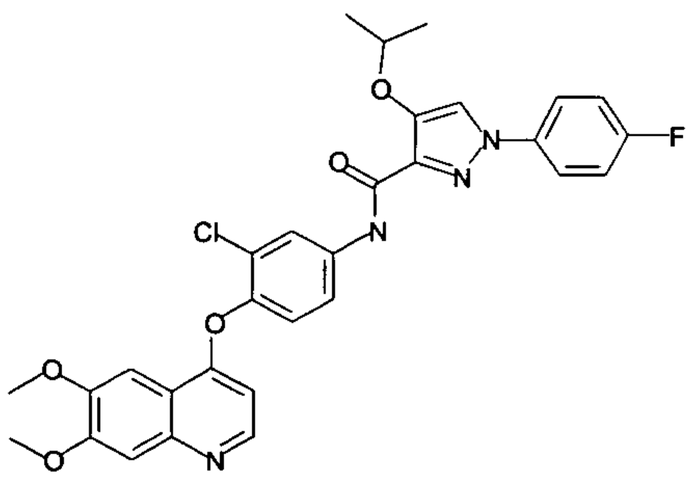
Example	Structure	Nomenclature
1		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1,5-dimethyl-pyrazole-3-carboxamide
2		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-[4-(trifluoromethyl)phenyl]thiazole-4-carboxamide
3		4-bromo-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide
4		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide
5		1-tert-butyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-5-methyl-pyrazole-3-carboxamide
6		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]thiazole-2-carboxamide

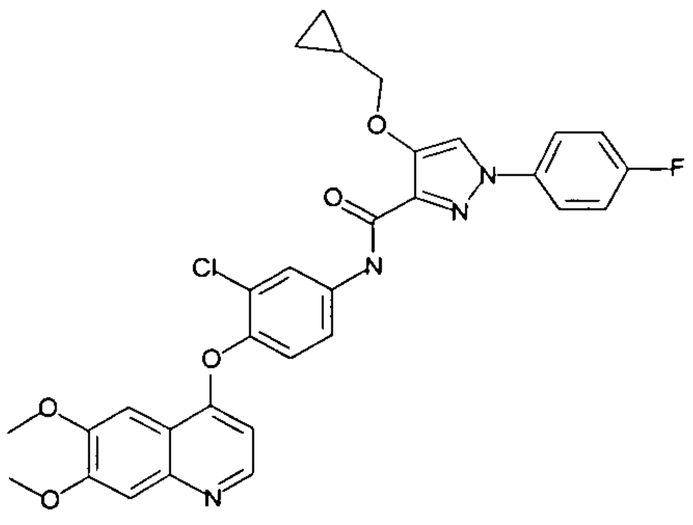
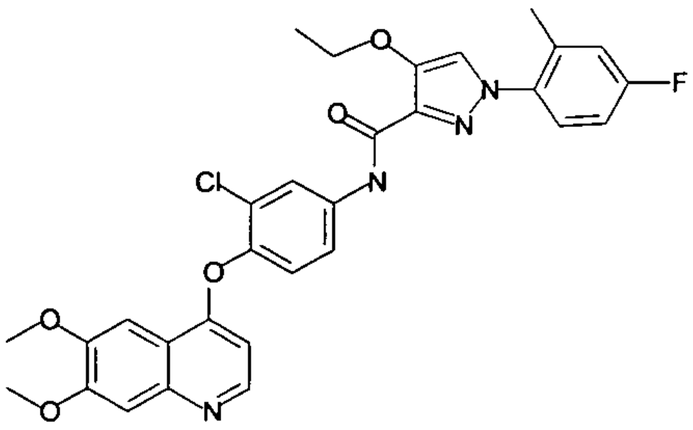
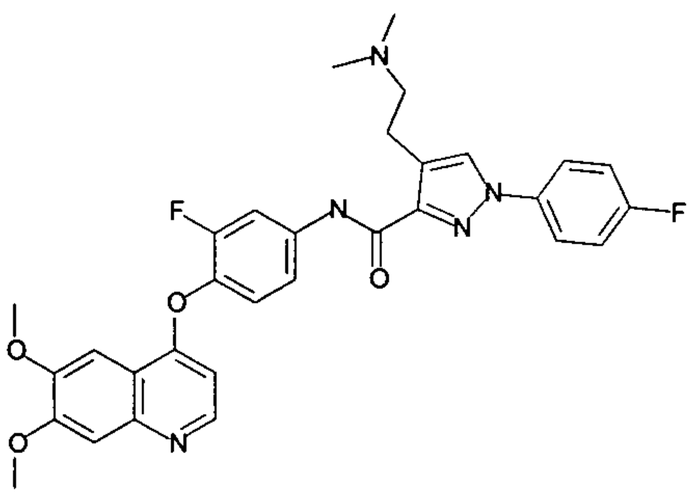
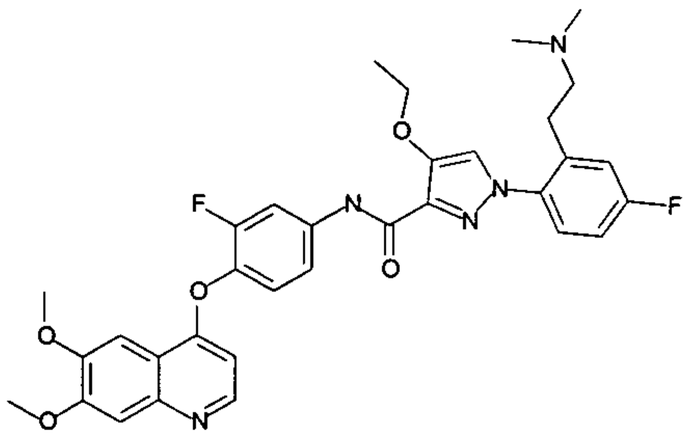
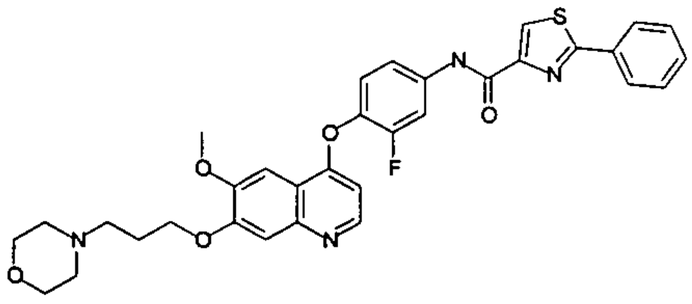
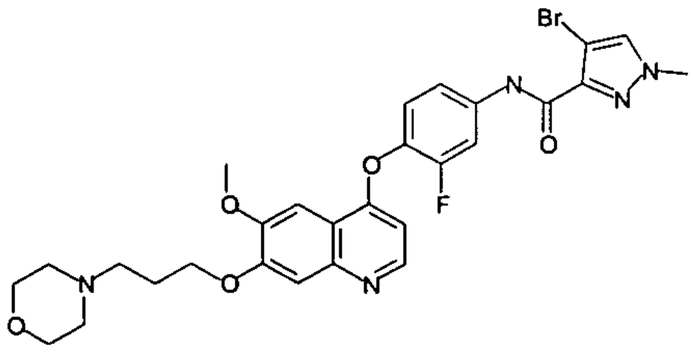
Example	Structure	Nomenclature
7		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-methyl-thiazole-4-carboxamide
8		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-indazole-3-carboxamide
9		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-5-methyl-isoxazole-3-carboxamide
10		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-phenyl-thiazole-4-carboxamide
11		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-imidazole-2-carboxamide
12		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-imidazole-4-carboxamide

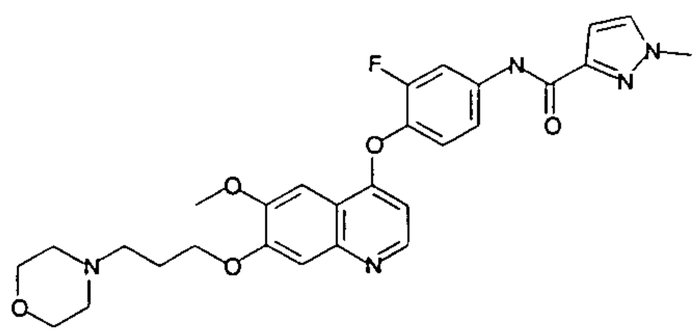
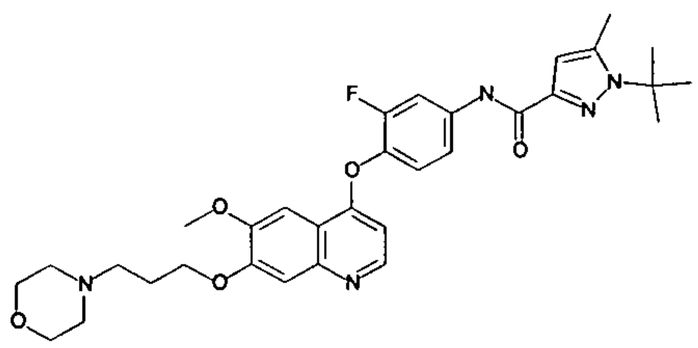
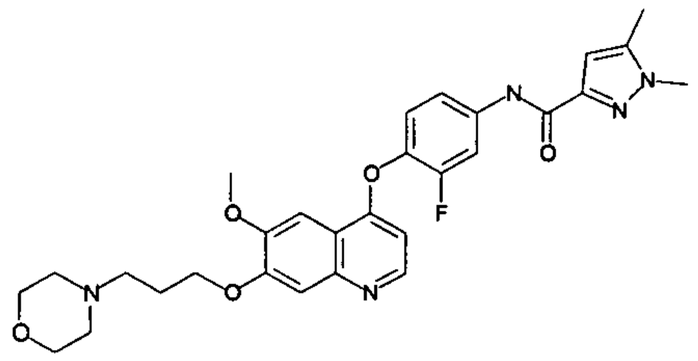
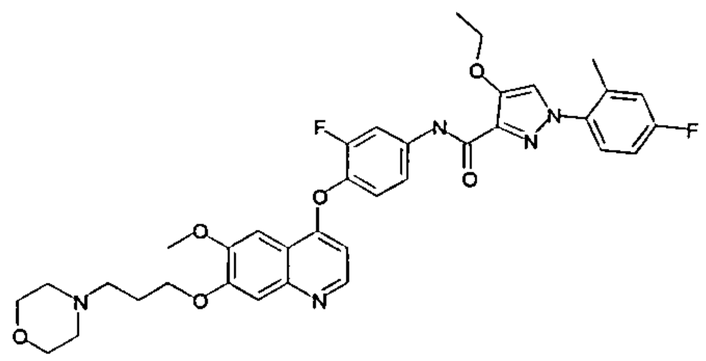
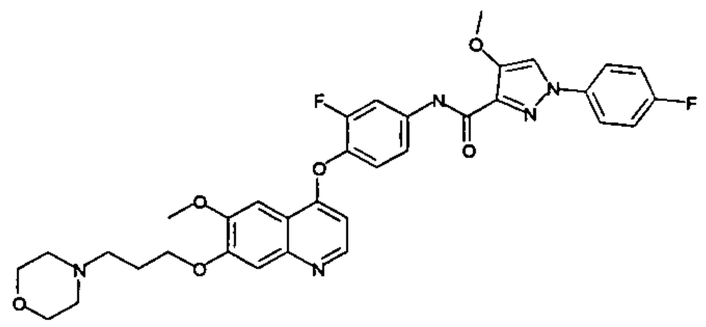
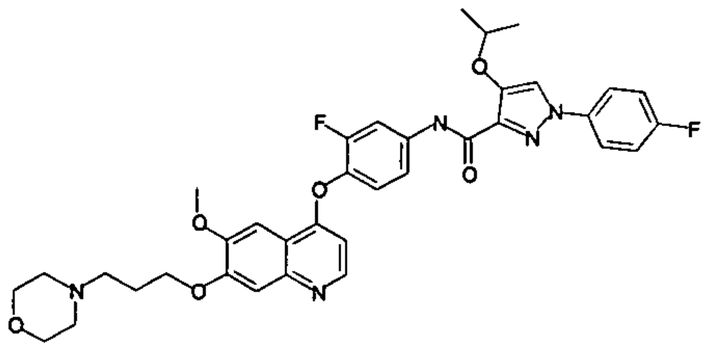
Example	Structure	Nomenclature
13		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-propyl-pyrazole-3-carboxamide
14		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[3-(1-piperidyl)propyl]pyrazole-3-carboxamide
15		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(2,2,2-trifluoroethoxymethyl)pyrazole-3-carboxamide
16		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide
17		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide
18		4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide

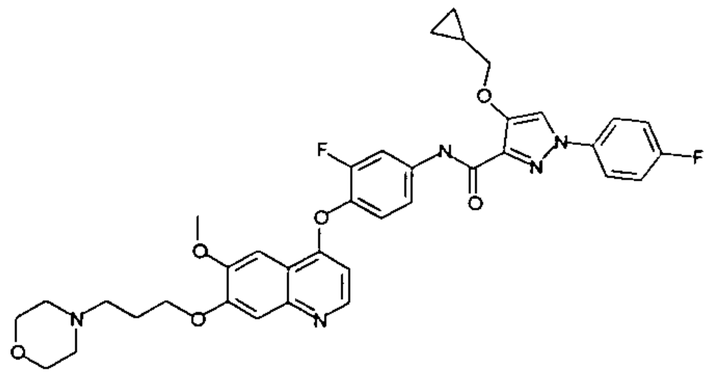
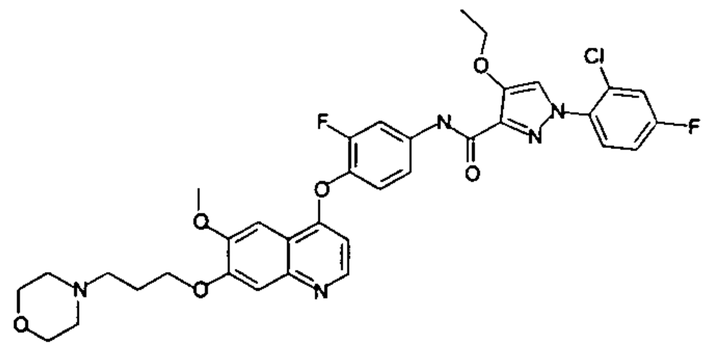
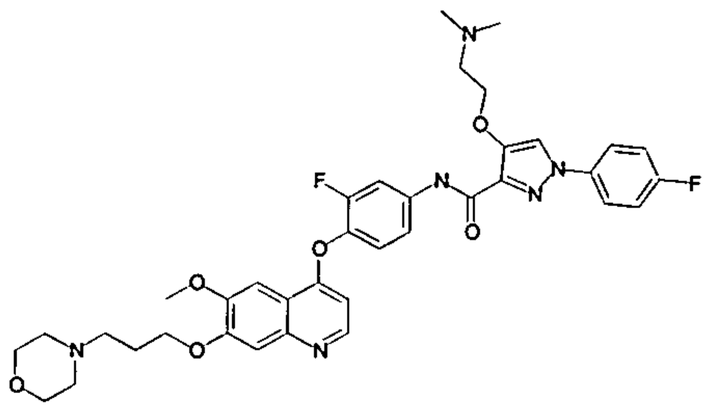
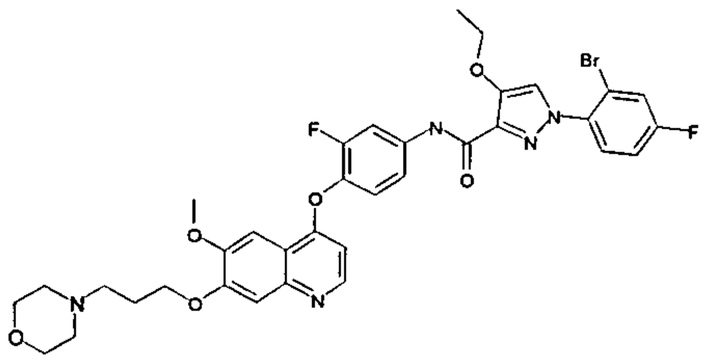
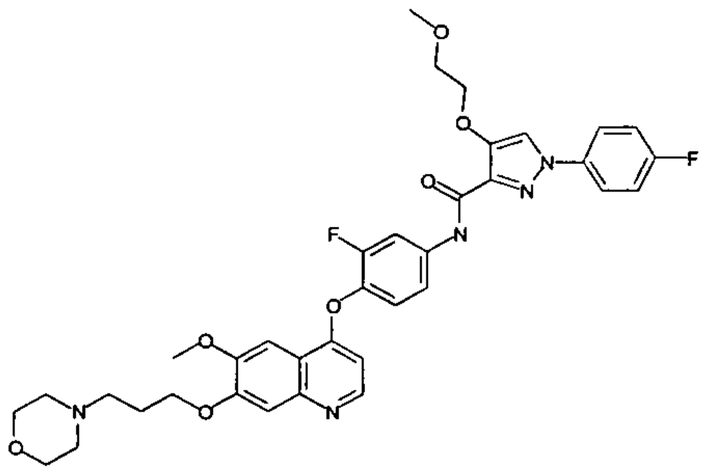
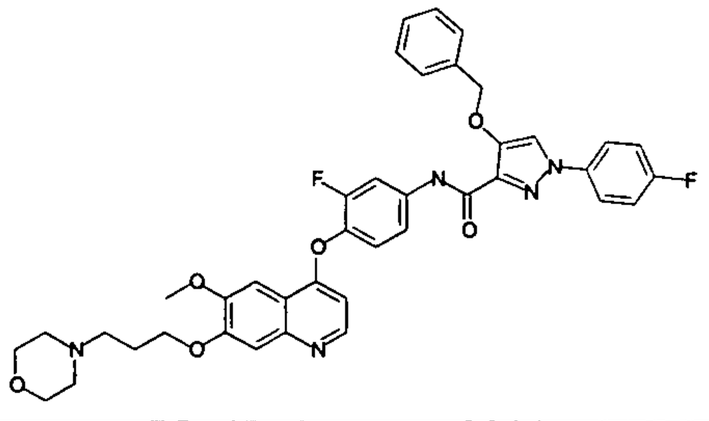
Example	Structure	Nomenclature
19		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide
20		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide
21		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide
22		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
23		1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide

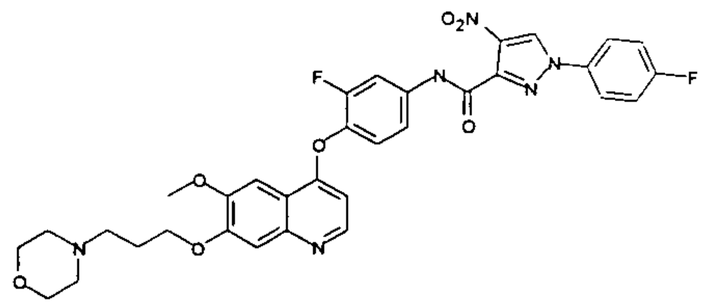
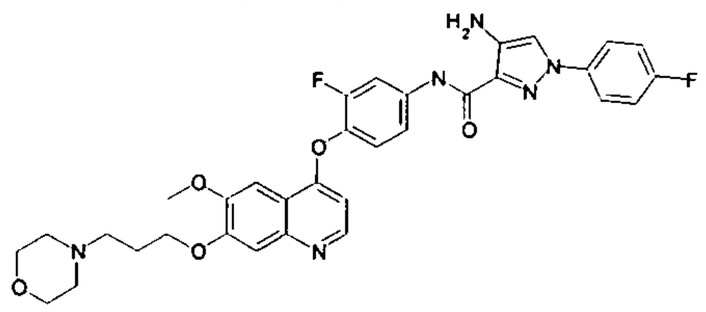
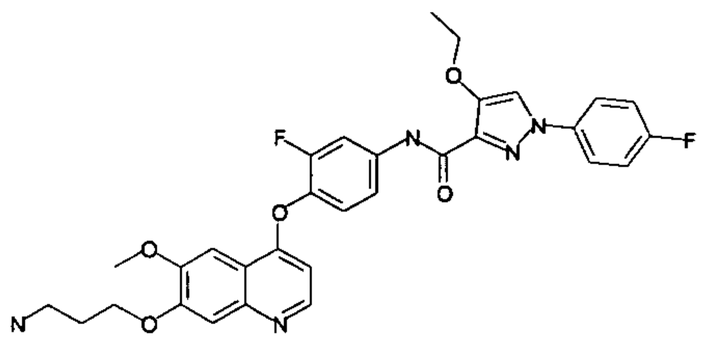
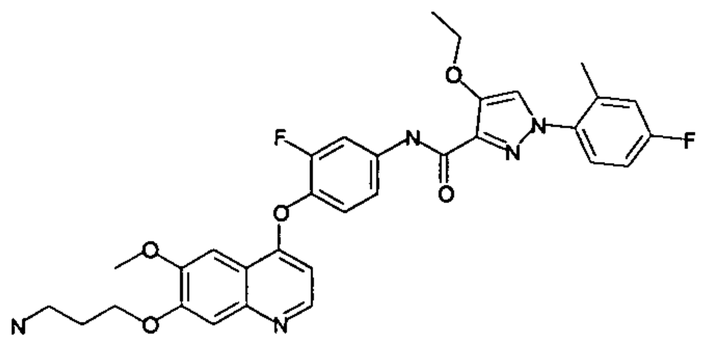
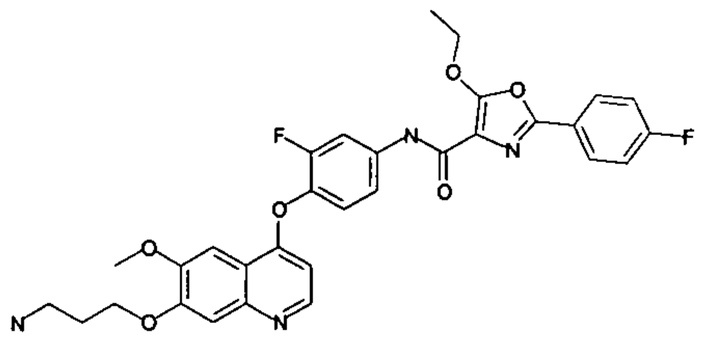
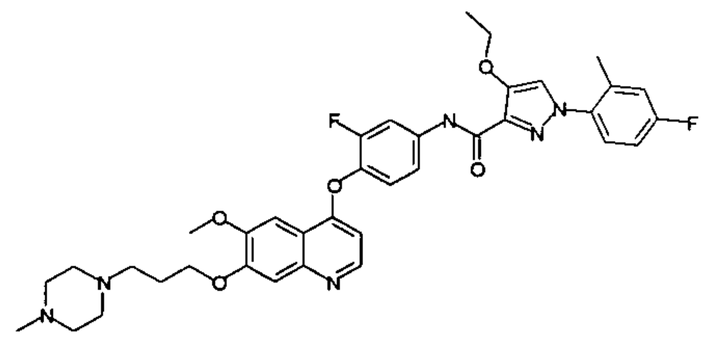
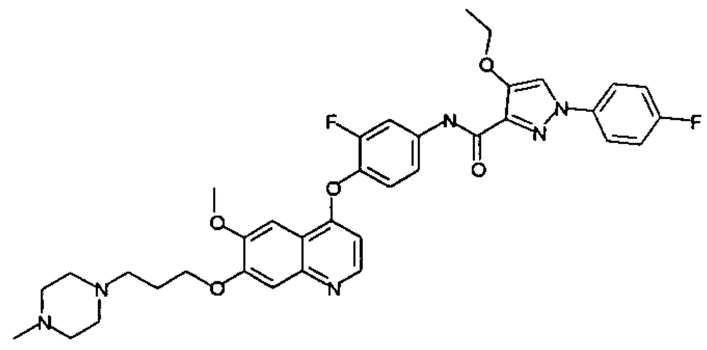
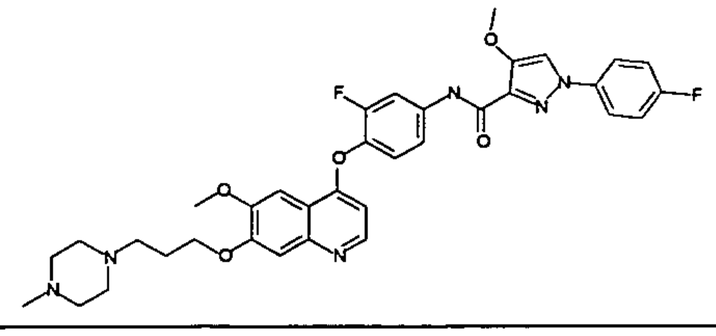
Example	Structure	Nomenclature
24		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide
25		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide
26		4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
27 .		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
28		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide

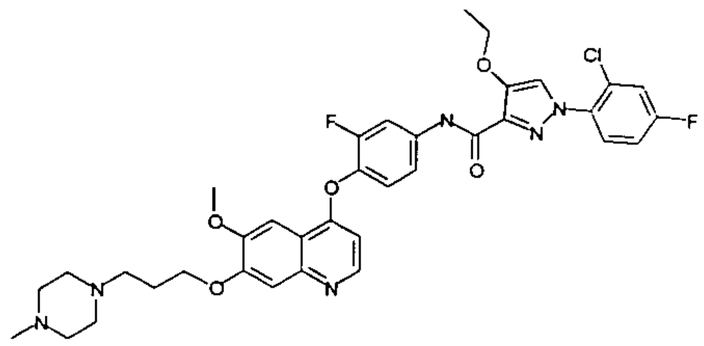
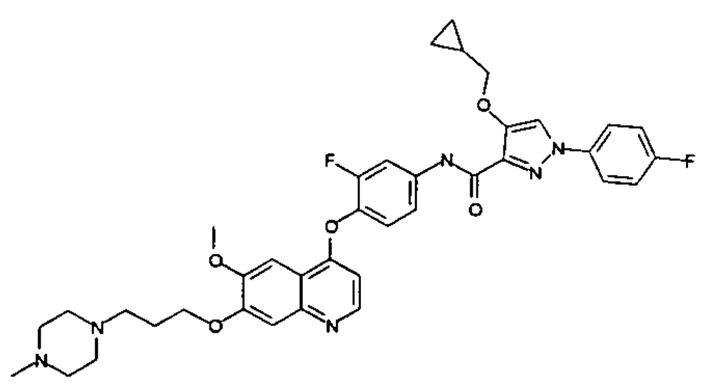
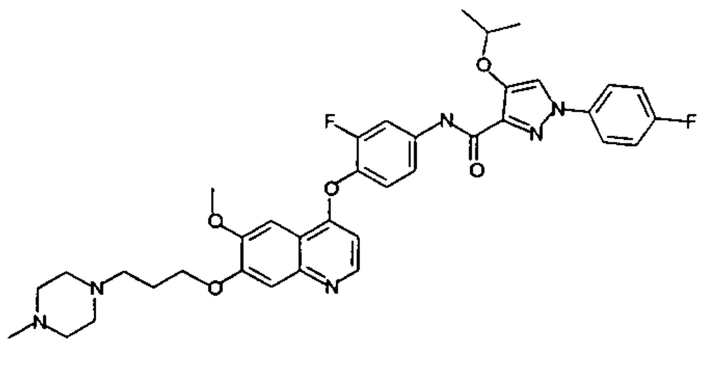
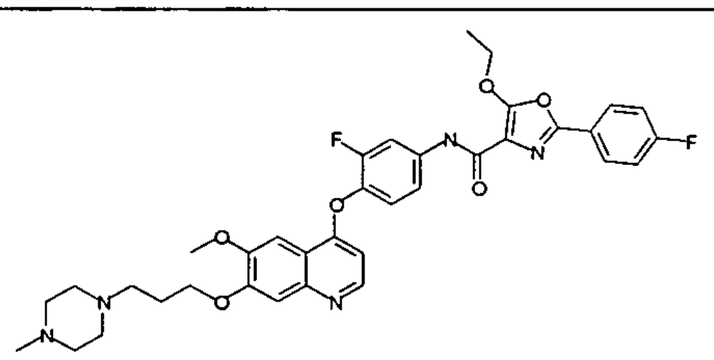
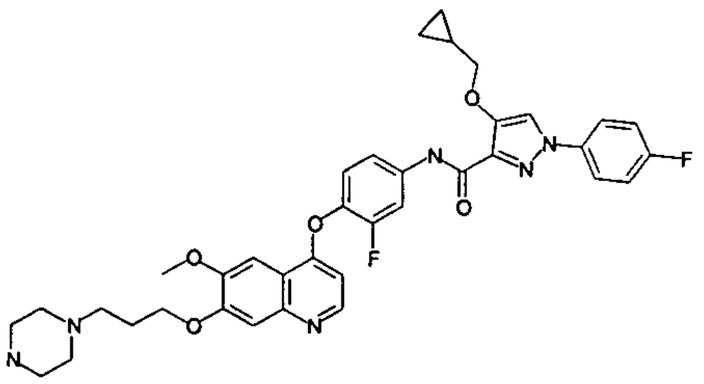
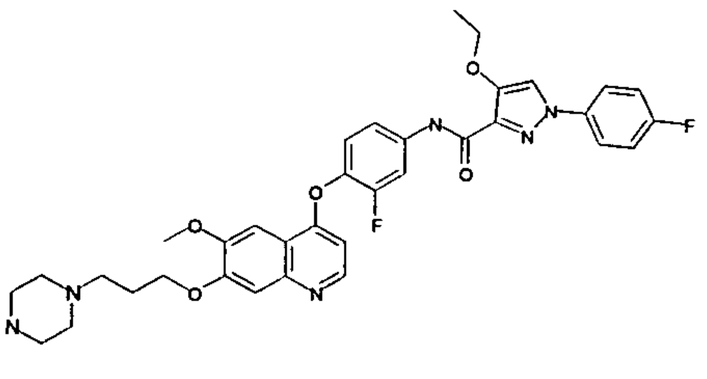
Example	Structure	Nomenclature
29		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide
30		4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
31		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
32		N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide
33		N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide

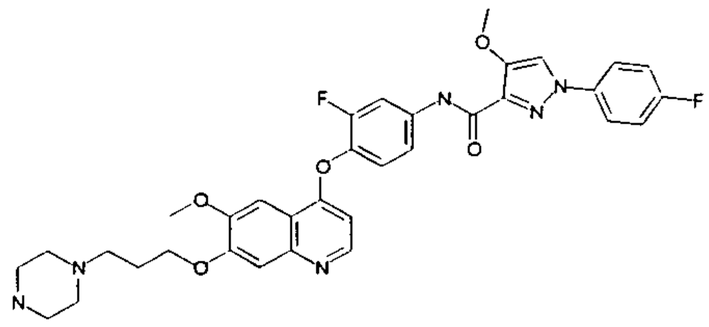
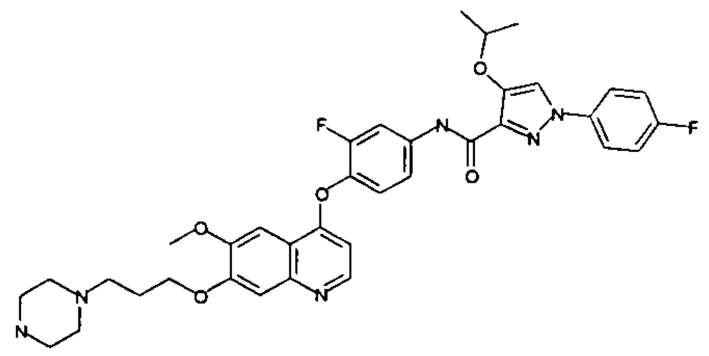
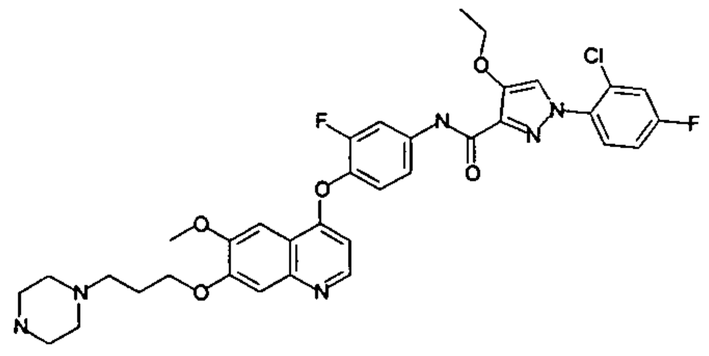
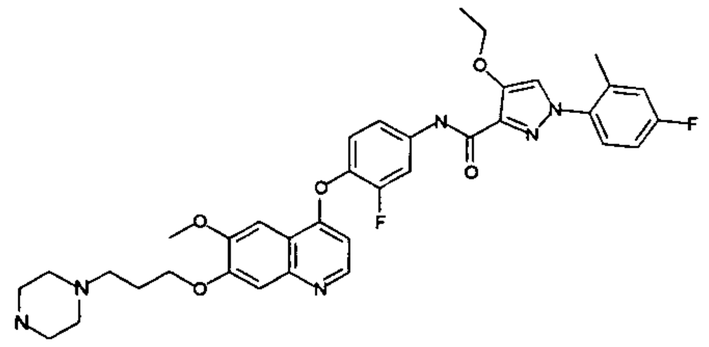
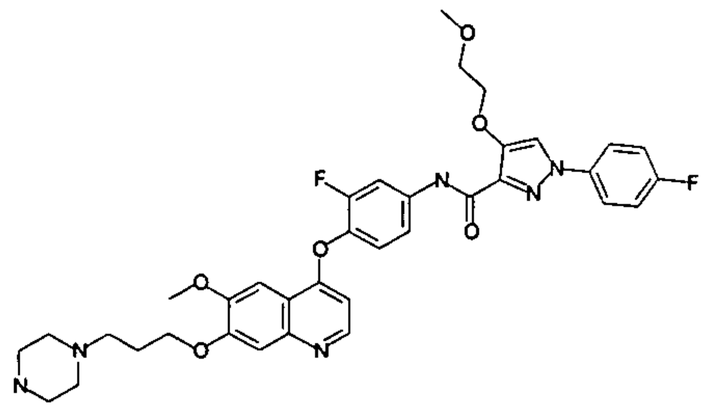
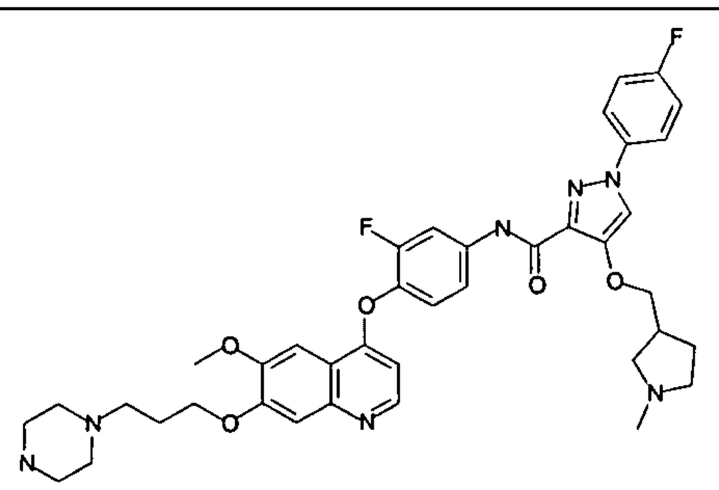
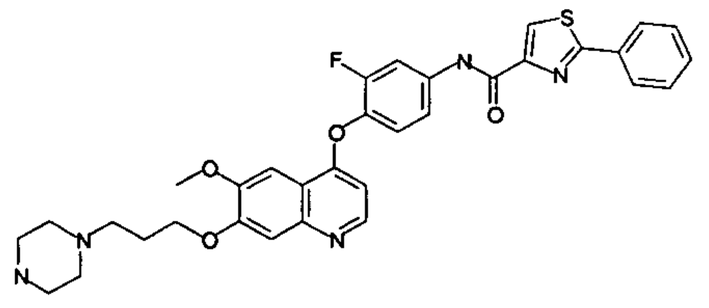
Example	Structure	Nomenclature
34		N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-(cyclopropylmethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide
35		N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
36		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-(2-(dimethylamino)ethyl)-1-(4-fluorophenyl)-1H-pyrazole-3-carboxamide
37		N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[2-(2-dimethylaminoethyl)-4-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide
38		N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide
39		4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide

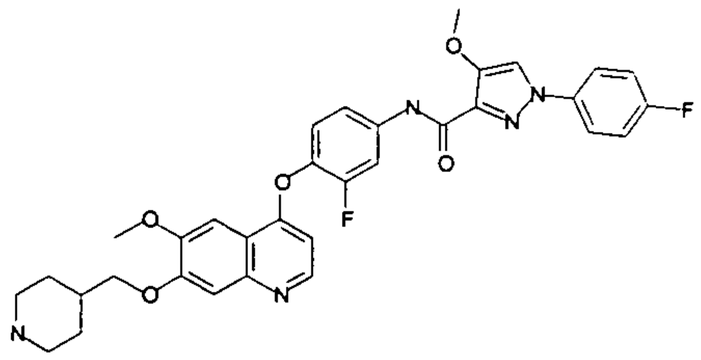
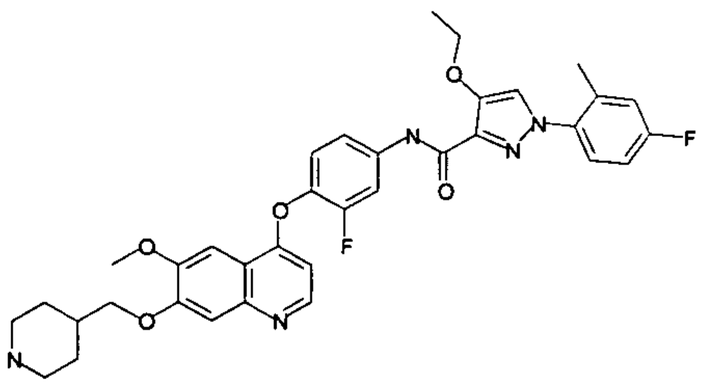
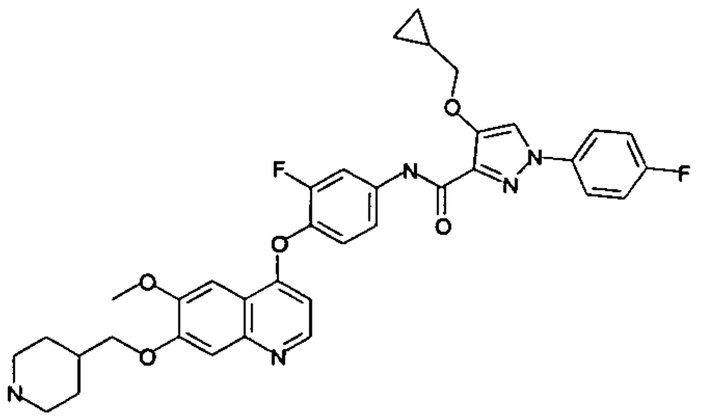
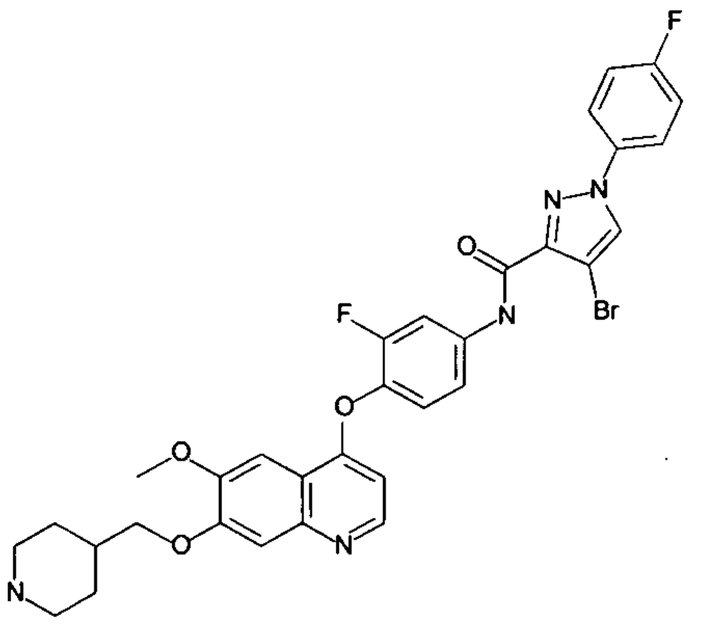
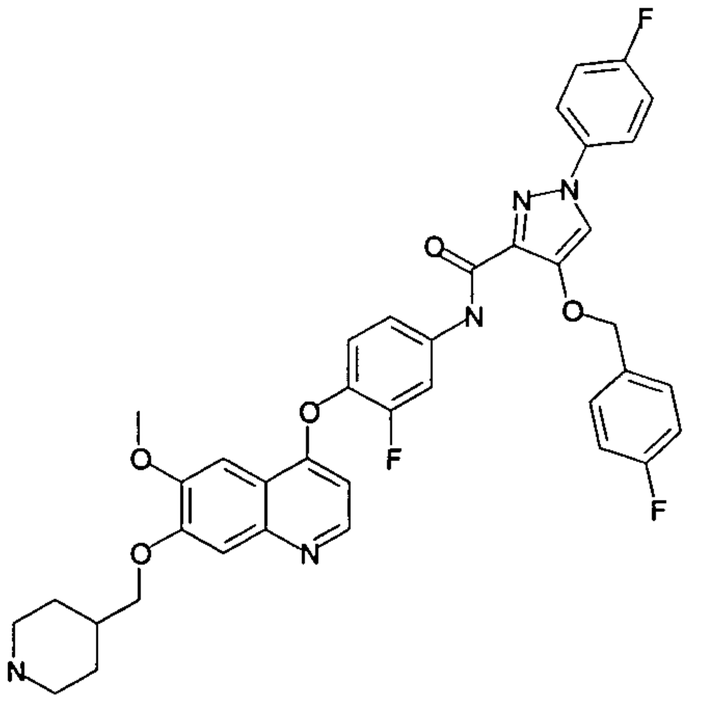
Example	Structure	Nomenclature
40		N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide
41		1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide
42		N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1,5-dimethyl-pyrazole-3-carboxamide
43		4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
44		N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide
45		N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide

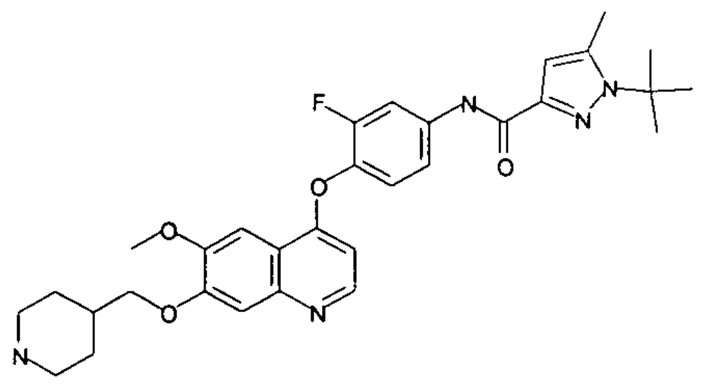
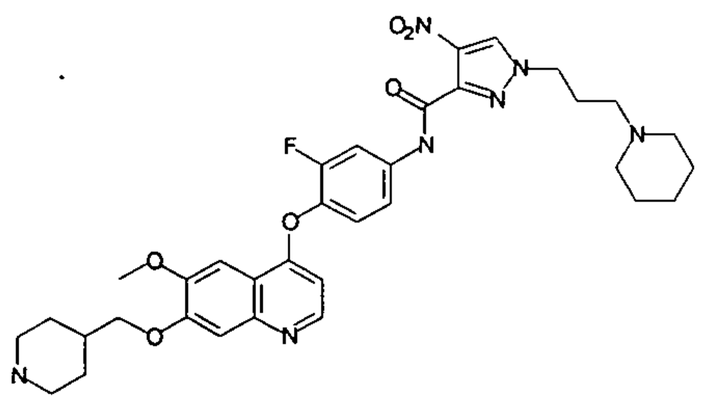
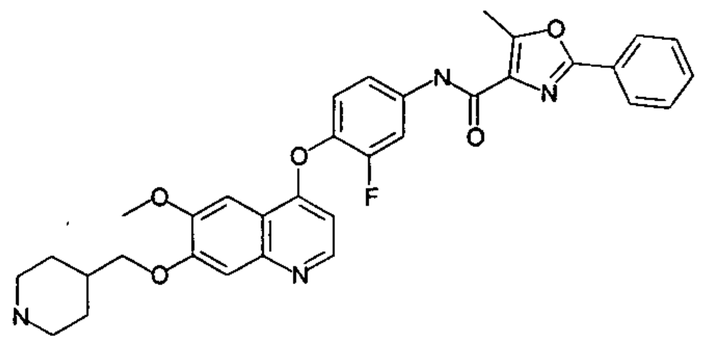
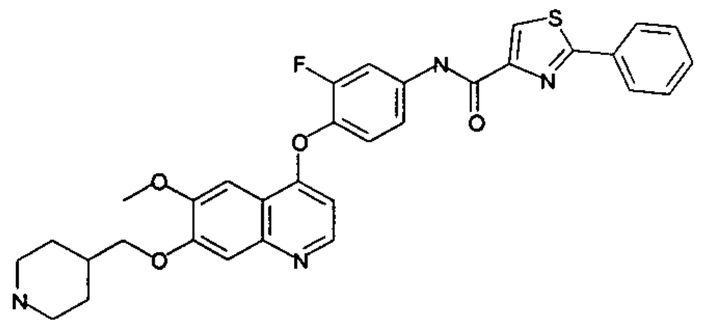
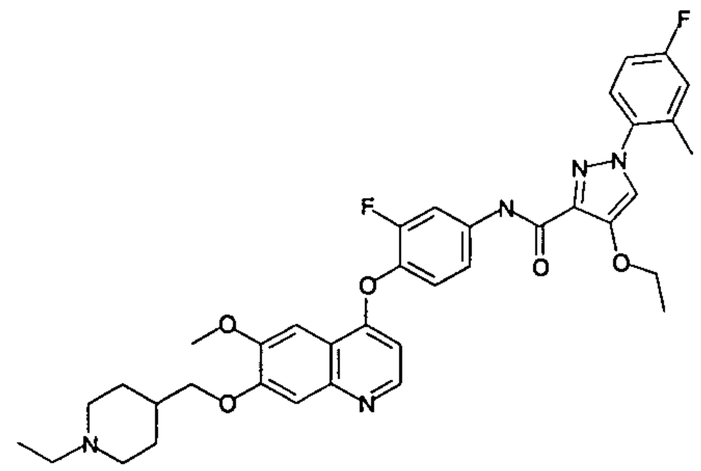
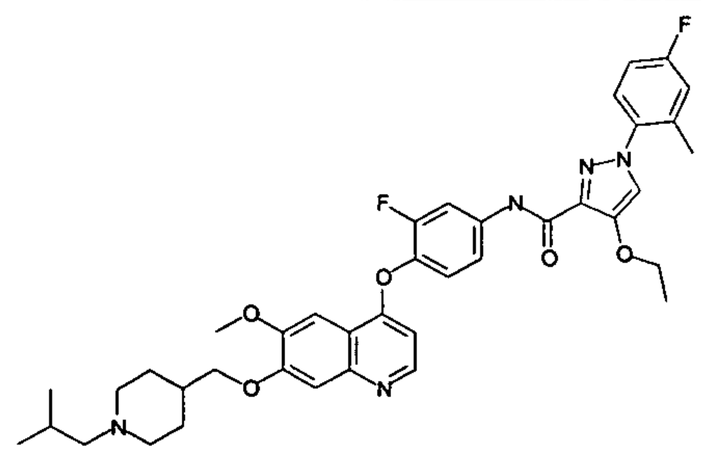
Example	Structure	Nomenclature
46		4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
47		1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide
48		4-(2-dimethylaminoethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
49		1-(2-bromo-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide
50		N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide
51		4-benzyloxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide

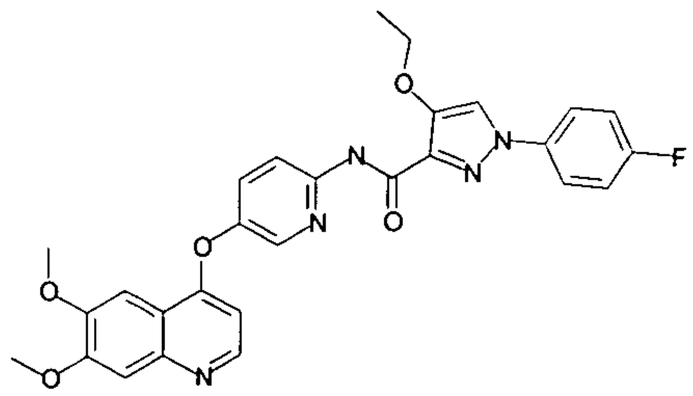
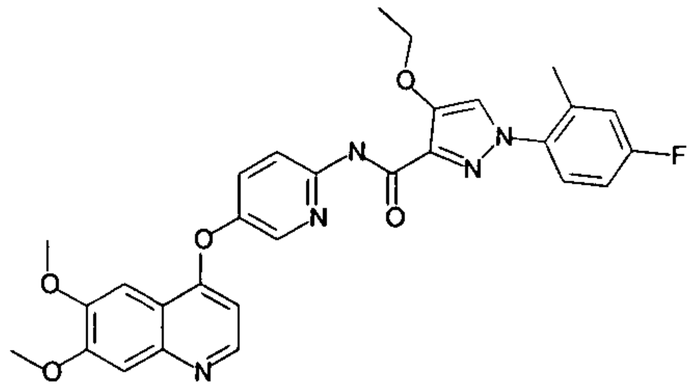
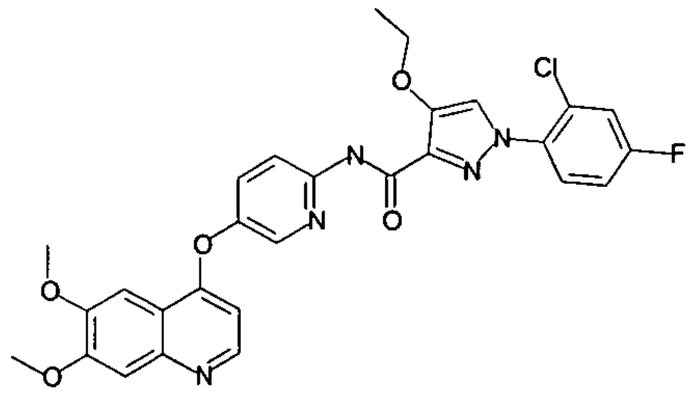
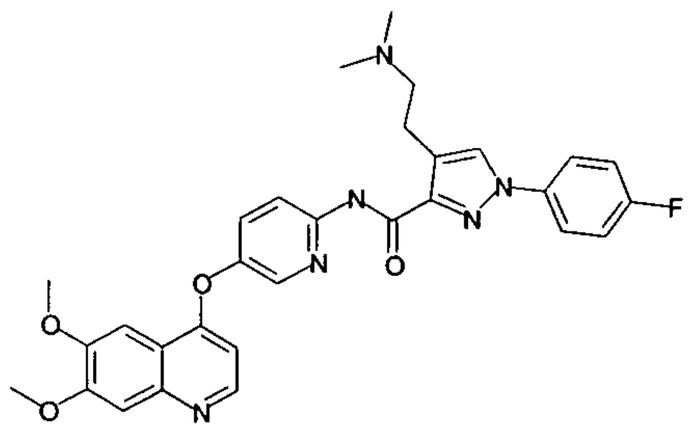
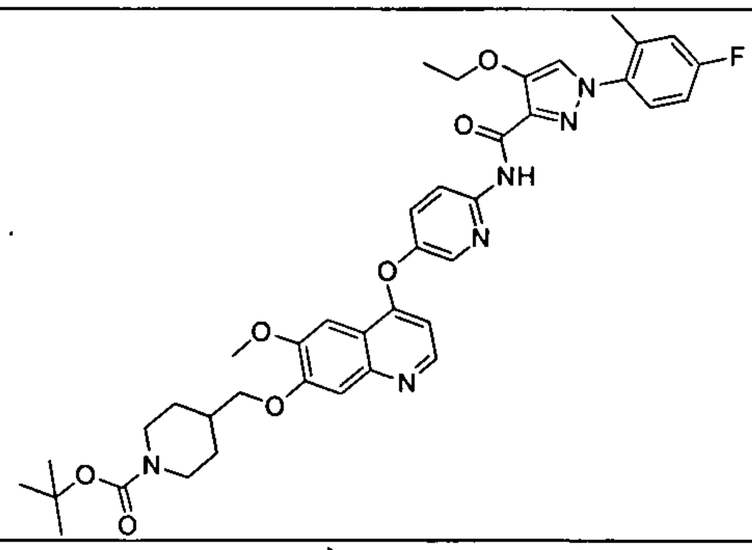
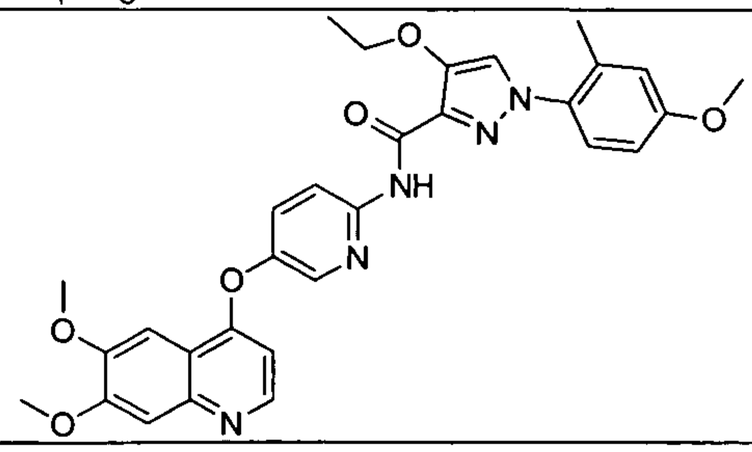
Example	Structure	Nomenclature
52		N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-nitro-pyrazole-3-carboxamide
53		4-amino-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
54		N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide
55		N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
56		N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-5-ethoxy-2-(4-fluorophenyl)oxazole-4-carboxamide
57		4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
58		4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
59		N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide

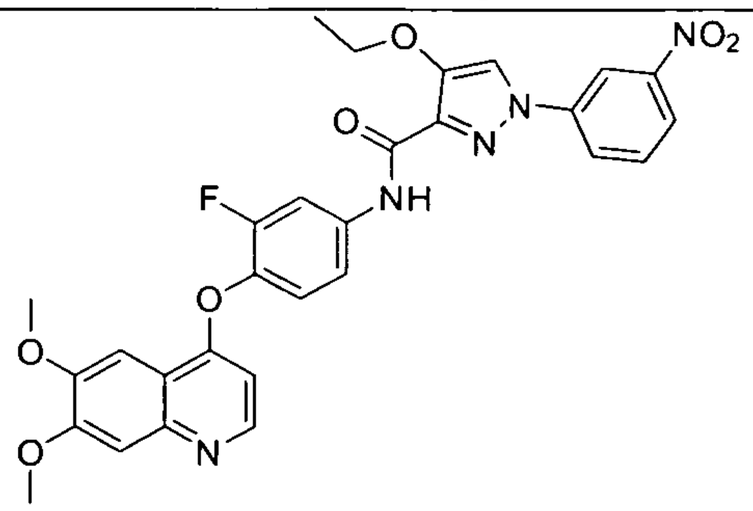
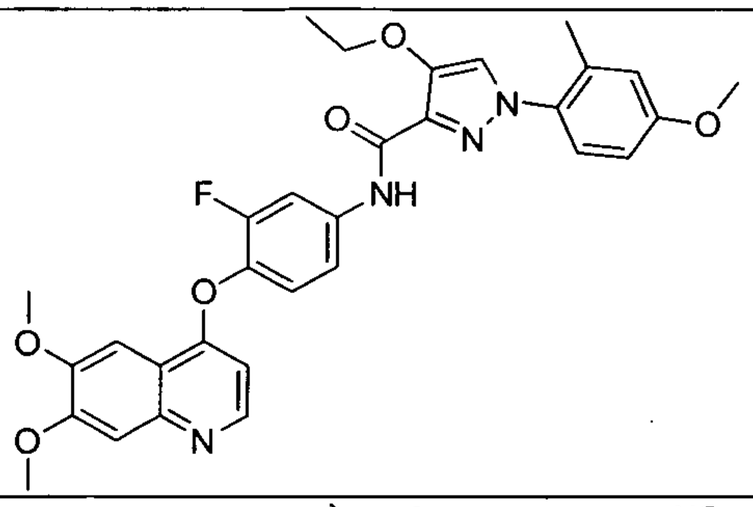
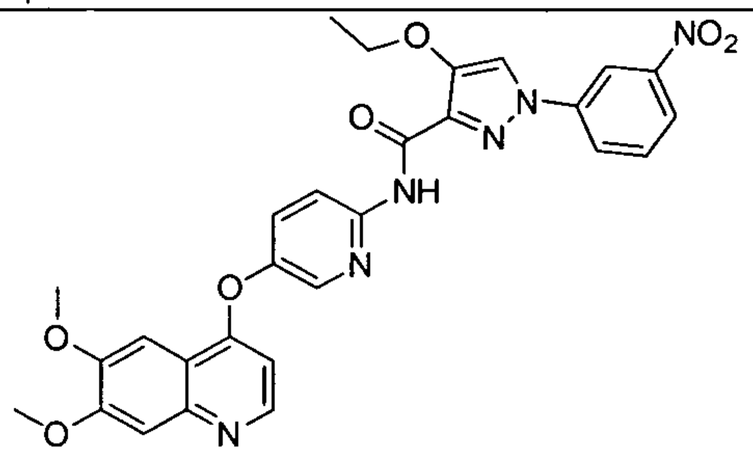
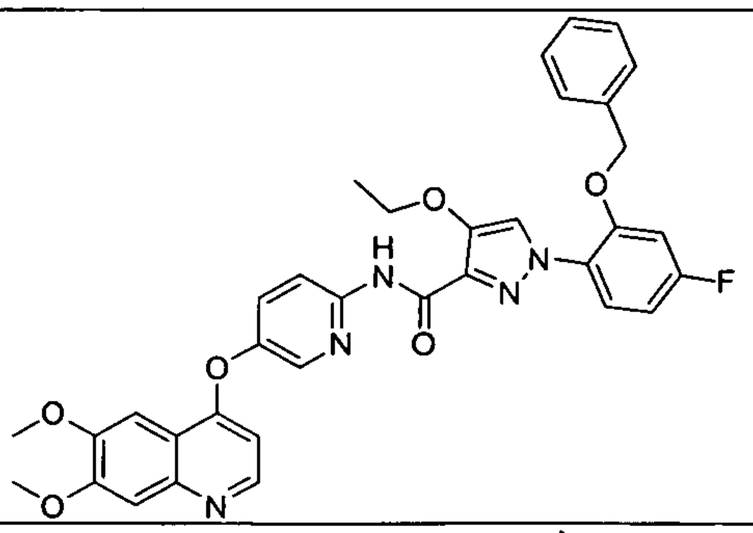
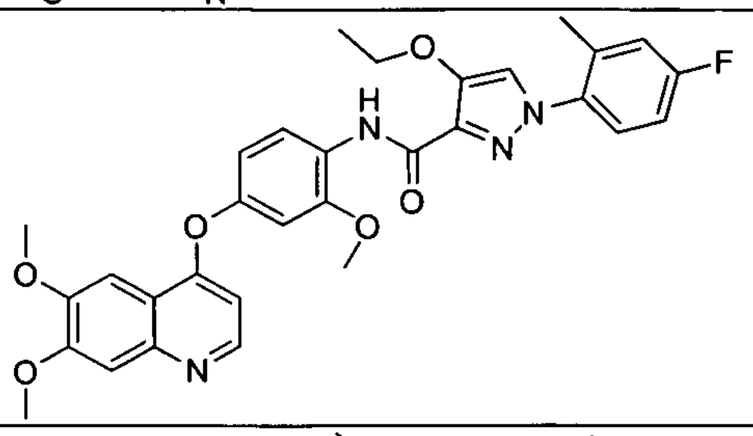
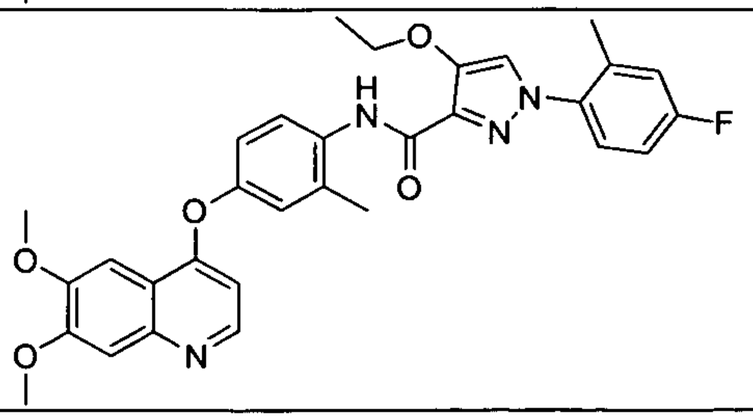
Example	Structure	Nomenclature
60		1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide
61		4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
62		N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide
63		5-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-2-(4-fluorophenyl)oxazole-4-carboxamide
64		4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide trifluoroacetic acid salt
65		4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide

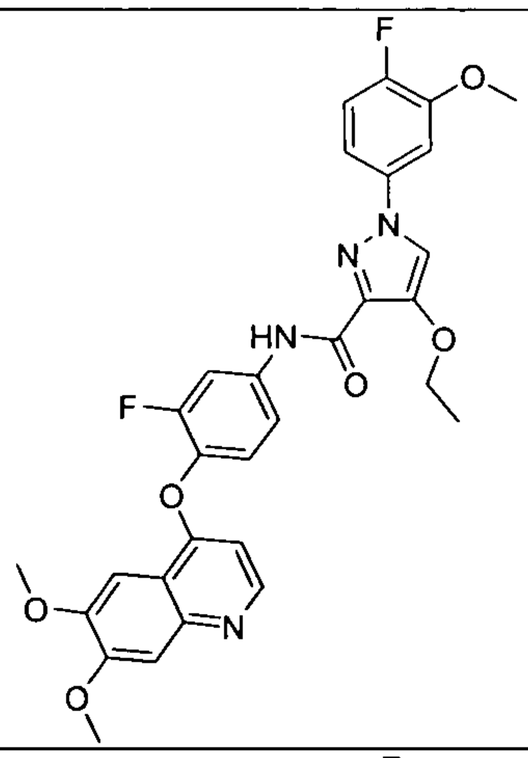
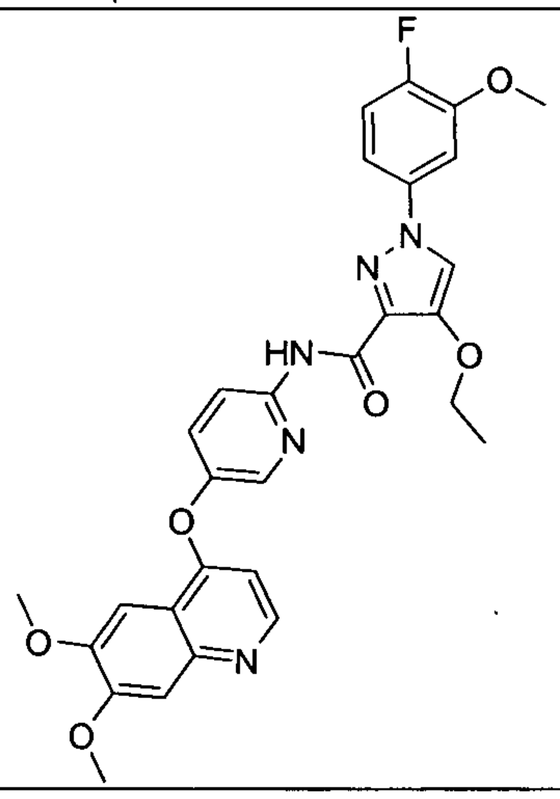
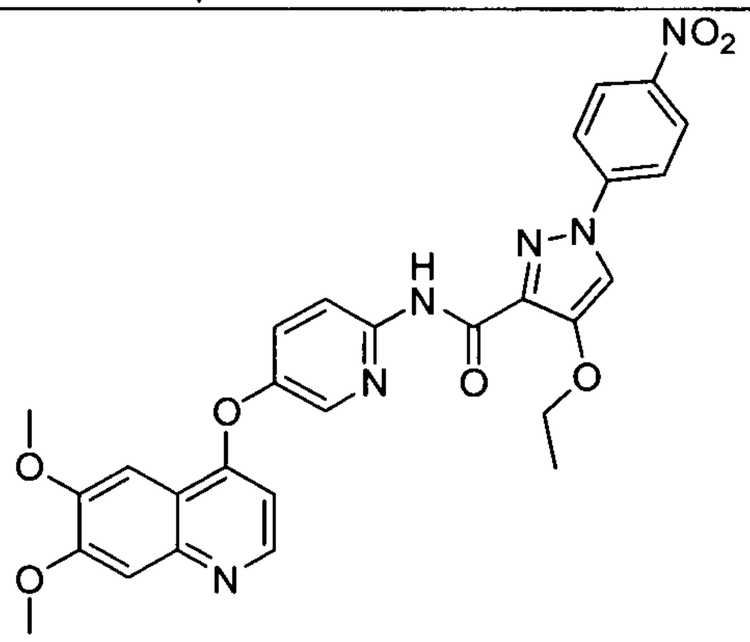
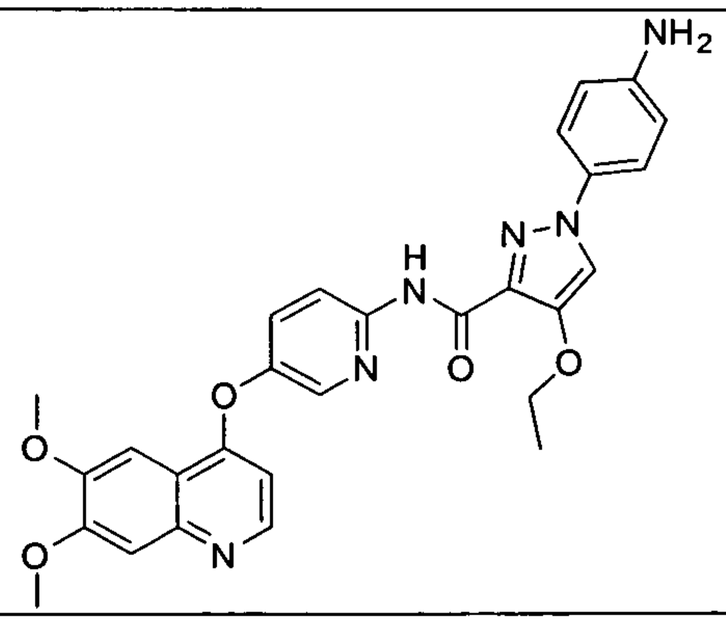
Example	Structure	Nomenclature
66		N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide
67		N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide
68		1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide
69		4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
70		N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide
71		N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(1-methylpyrrolidin-3-yl)methoxy]pyrazole-3-carboxamide
72		N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide

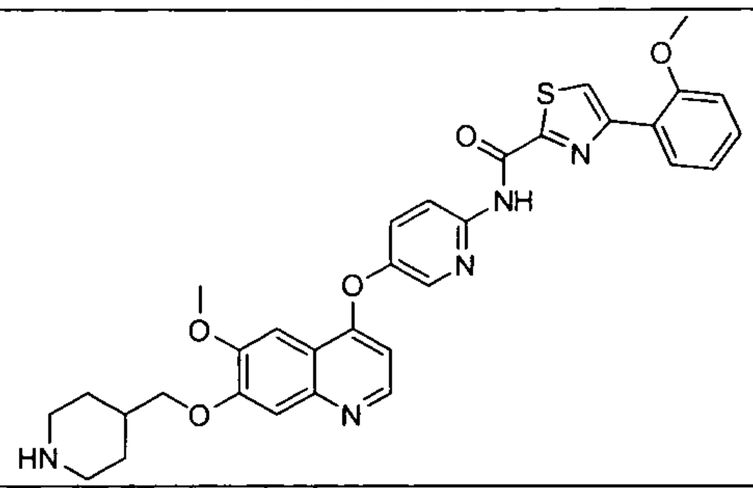
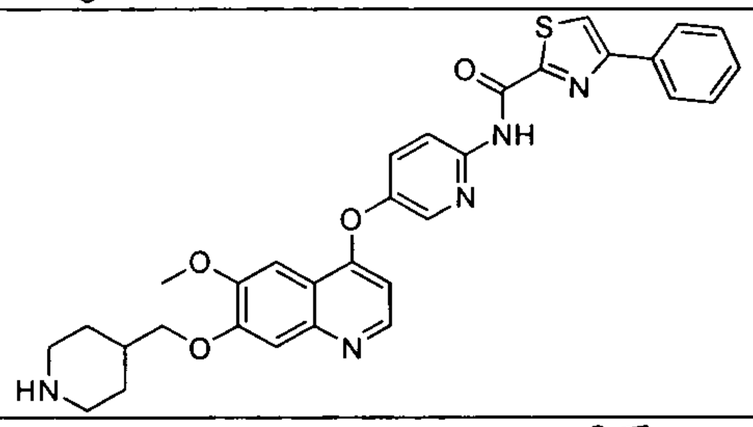
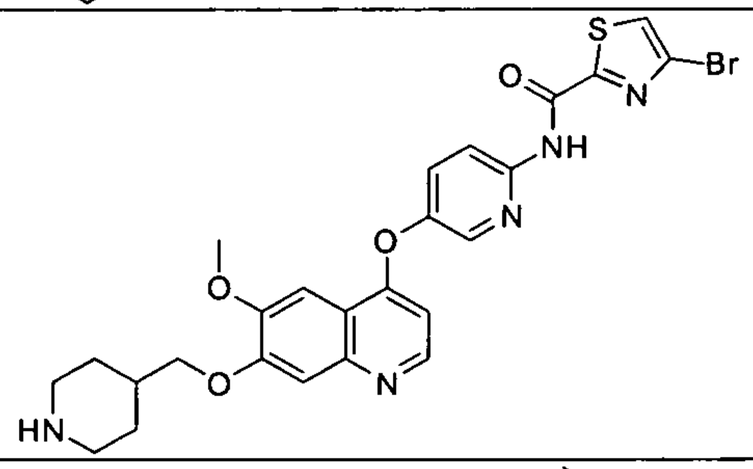
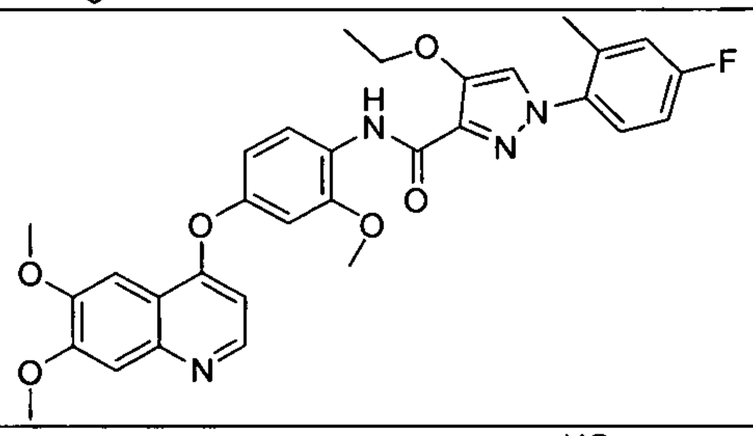
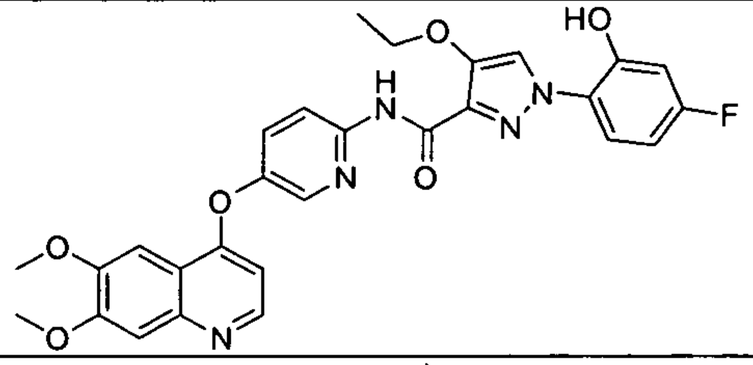
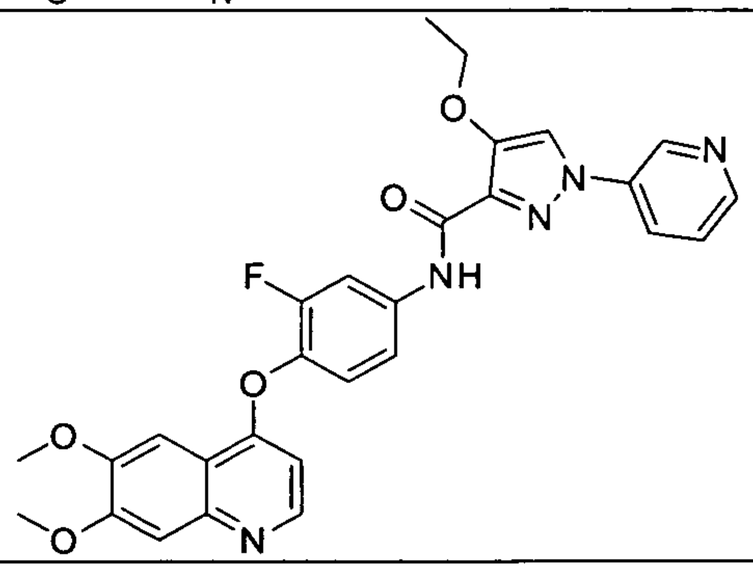
Example	Structure	Nomenclature
73		N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide
74		4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
75		4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
76		4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide
77		N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(4-fluorophenyl)methoxy]pyrazole-3-carboxamide

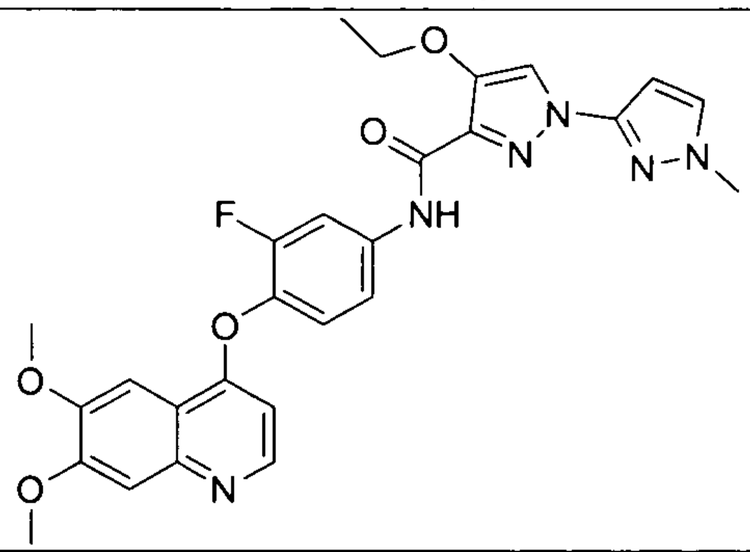
Example	Structure	Nomenclature
78		1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide
79		N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-4-nitro-1-[3-(1-piperidyl)propyl]pyrazole-3-carboxamide
80		N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-2-phenyl-oxazole-4-carboxamide
81		N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide
82		4-ethoxy-N-[4-[[7-[(1-ethyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
83		4-ethoxy-N-[3-fluoro-4-[[7-[(1-isobutyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide

Example	Structure	Nomenclature
84		N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide
85		N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide
86		1-(2-chloro-4-fluoro-phenyl)-N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-pyrazole-3-carboxamide
87		N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-(2-dimethylaminoethyl)-1-(4-fluorophenyl)pyrazole-3-carboxamide
88		tert-butyl 4-(((4-((6-(4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamido)pyridin-3-yl)oxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate
89		N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamide

Example	Structure	Nomenclature
90		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide
91		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamide
92		N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide
93		1-(2-(benzyloxy)-4-fluorophenyl)-N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1H-pyrazole-3-carboxamide
94		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide
95		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methylphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide

Example	Structure	Nomenclature
96		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide
97		N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide
98		N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-nitrophenyl)-1H-pyrazole-3-carboxamide
99		1-(4-aminophenyl)-N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1H-pyrazole-3-carboxamide

Example	Structure	Nomenclature
100		N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-(2-methoxyphenyl)thiazole-2-carboxamide
101		N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-phenylthiazole-2-carboxamide
102		4-bromo-N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)thiazole-2-carboxamide
103		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide
104		N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-2-hydroxyphenyl)-1H-pyrazole-3-carboxamide
105		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide

Example	Structure	Nomenclature
106		N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1'-methyl-1'H-[1,3'-bipyrazole]-3-carboxamide

Examples

Preparation of compounds:

Abbreviations used in the description of the chemistry and in the Examples that follow are:

ACN (acetonitrile); br (broad); $CDCl_3$ (deuterated chloroform); cHex (cyclohexane); DCM (dichloromethane); DIPEA (di-iso-propylethylamine); DMF (dimethylformamide); DMSO (dimethyl sulfoxide); eq. (equivalent); ES (electrospray); EtOAc (ethyl acetate); EtOH (ethanol); HATU (*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate); HCl (hydrochloric acid); HOAc (acetic acid); H_2O (water); K_2CO_3 (potassium carbonate); KOH (potassium hydroxide); MeOH (methanol); MS (mass spectrometry); $NaHCO_3$ (sodium hydrogencarbonate); NH_3 (ammonia); NH_4Cl (ammonium chloride); NMR (nuclear magnetic resonance); $Pd(dppf)Cl_2$ ([1,1'-bis(diphenylphosphino)ferrocene]dichloro palladium(II) complex with dichloromethane); iPrOH (iso-propanol); RT (room temperature); sat. aq. (saturated aqueous); SiO_2 (silica gel); TFA (trifluoroacetic acid); THF (tetrahydrofurane).

Preparative Examples

Example 1:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1,5-dimethyl-pyrazole-3-carboxamide trifluoroacetic acid salt (A3)

Step 1: 4-(2-fluoro-4-nitro-phenoxy)-6,7-dimethoxy-quinoline (A1)

A mixture of 6,7-dimethoxyquinolin-4-ol (1.4g, 6.8mmol, 1.0 eq.), 3,4-difluoro-nitrobenzene (1.44g, 8.84mmol, 1.3eq.) and cesium carbonate (3.6g, 10.9mmol, 1.6eq.) in dry DMF (10mL) was heated for 1 h at 50^0C in a microwave oven. After cooling to RT the mixture was diluted with water and extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/MeOH = 100:0 to 5:1) to yield the desired product **A1** (909mg, 2.64mmol, 38.8%) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 4.04 (s, 3H), 4.06 (s, 3H), 6.55 (d, J = 5.2 Hz, 1H), 7.34 (dd, J = 7.8 Hz, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.46 (s, 1H), 8.13 (m, 1H), 8.19 (dd, J = 9.8 Hz, J = 2.5 Hz, 1H), 8.58 (d, J = 5.2 Hz, 1H). MS (ES) $C_{17}H_{13}FN_2O_5$ requires: 344,

found: 345 $(M+H)^+$. Furthermore an isomer (941mg, 2.74mmol, 40.2%) was isolated as a yellow solid. MS (ES) $C_{17}H_{13}FN_2O_5$ requires: 344, found: 345 $(M+H)^+$.

Step 2: 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-aniline (A2)

To a suspension of **A1** (230mg, 0.67mmol, 1.0 eq.) in MeOH (50mL) Pd/C (10%w/w, 23mg) and aq. HCl-solution (1N, 1.34mL, 2.0 eq.) were added. The reaction mixture was stirred under hydrogen atmosphere (1atm) at RT for 48h. The suspension was filtered through a pad of Celite®. The solvent was removed in vacuo and the crude product was purified using an Isolute ® SPE column SCX, loading the reaction mixture as a MeOH solution and then eluting the desired compound with 2N NH_3 in MeOH. The title compound **A2** was isolated after evaporation of the solvent under reduced pressure as a white solid (200mg, 0.64mmol, 95%). ^1H NMR (400MHz, d_6-DMSO, 300K) δ 3.92 (s, 6H), 4.97 (br s, 2H), 6.38 (d, J = 5.3 Hz, 1H), 6.45 (dd, J = 2.4 Hz, J = 8.5 Hz, 1H), 6.53 (dd, J = 2.4 Hz, J = 13.2 Hz, 1H), 7.05 (t, J = 9.0 Hz, 1H), 7.36 (s, 1H), 7.49 (s, 1H), 8.44 (d, J = 5.3 Hz, 1H). MS (ES) $C_{17}H_{15}FN_2O_3$ requires: 314, found: 315 $(M+H)^+$.

Step3: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1,5-dimethyl-pyrazole-3-carboxamide trifluoroacetate salt (A3)

To a solution of **A2** (100mg, 0.31mmol, 1.0 eq.) in dry DCM (2.5mL) and dry pyridine (2.5mL) was added 1,5-dimethyl-1H-pyrazole-3-carbonyl chloride (56mg, 0.38mmol, 1.2 eq.) and the reaction mixture was stirred at RT overnight. The solvent was removed in vacuo. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O (0.1%TFA) and MeOH (0.1%TFA) as eluents. The desired fractions were lyophilized to yield the title compound **A3** (61.8mg, 36%) as a white powder. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 2.30 (s, 3H), 3.83 (s, 3H), 4.00 (s, 6H), 6.57 (s, 1H), 6.87 (d, J = 6.9 Hz, 1H), 7.51 (m, 2H), 7.69 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.11 (dd, J = 2.3 Hz, J = 13.5 Hz, 1H), 8.74 (d, J = 6.3 Hz, 1H), 10.43 (s, 1H). MS (ES) $C_{23}H_{21}FN_4O_4$ requires: 436, found: 437 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 1.

Example	Name	Mwt	$[M+H]^+$

2	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-[4-(trifluoromethyl)phenyl]thiazole-4-carboxamide trifluoroacetic acid salt	569	570
3	4-bromo-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide trifluoroacetic acid salt	501	501/503
4	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide trifluoroacetic acid salt	422	423
5	1-tert-butyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-5-methyl-pyrazole-3-carboxamide trifluoroacetic acid salt	478	479
6	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]thiazole-2-carboxamide trifluoroacetic acid salt	425	426
7	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-methyl-thiazole-4-carboxamide trifluoroacetic acid salt	439	440
8	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-indazole-3-carboxamide trifluoroacetic acid salt	472	473
9	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-5-methyl-isoxazole-3-carboxamide trifluoroacetic acid salt	423	424
10	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-phenyl-thiazole-4-carboxamide trifluoroacetic acid salt	501	502

Example 11:

N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-imidazole-2-carboxamide trifluoroacetic acid salt (B1)

1-Methyl-1H-imidazol-2-carboxylic acid (126mg, 1mmol, 1.0 eq.) in $SOCl_2$ (10mL) was heated for 6h under reflux. Solvent was removed in vacuo and the crude product was resolved in dry toluene and evaporated under reduced pressure again. The solid was solved in dry DCM (2mL) and dry pyridine (2mL) and 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-aniline (**A2**) (376mg, 1.2mmol, 1.2 eq.) was added. The reaction mixture was stirred at RT overnight. The solvent was removed in vacuo. The residue was purified by

reverse phase RP-HPLC (column: C18), using H_2O (0.1%TFA) and MeOH (0.1%TFA) as eluents. The desired fractions were lyophilized to yield the title compound **B1** (33mg, 0.06mmol, 6%) as a white powder. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 3.99 (s, 3H), 4.02 (s, 3H), 4.03 (s, 3H), 6.94 (d, J = 6.5 Hz, 1H), 7.12 (d, J = 1.0 Hz, 1H), 7.48 (d, J = 1.0 Hz, 1H), 7.55 (t, J = 9.0 Hz, 1H), 7.56 (s, 1H), 7.73 (s, 1H), 7.87 (d, J = 9.0 Hz, 1H), 8.13 (dd, J = 2.4 Hz, J = 13.3 Hz, 1H), 8.79 (d, J = 6.5 Hz, 1H), 10.81(s, 1H). MS (ES) $C_{22}H_{19}FN_4O_4$ requires: 422, found: 423 $(M+H)^+$.

The Example in the following table was prepared according to the procedure described in the previous Example 11.

Example	Name	Mwt	$[M+H]^+$
12	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-imidazole-4-carboxamide	422	423

Example 13:

N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-propyl-pyrazole-3-carboxamide (C1)

C1 was prepared from **A2** and 1-propylpyrazole-3-carboxylic acid following the general procedure reported in Preparative Example 11. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and ACN as eluents. The desired fractions were lyophilized to yield the title compound **C1** (46mg, 0.10mmol, 17%) as a white powder. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 0.85 (t, J = 7.3 Hz, 3H), 1.86 (sext., J = 7.3 Hz, 2H), 3.94 (s, 6H), 4.18 (t, J = 7.3 Hz, 2H), 6.45 (d, J = 5.1 Hz, 1H), 6.79 (d, J = 2.3 Hz, 1H), 7.39 (s, 1H), 7.42 (t, J = 9.0 Hz, 1H), 7.52 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 8.05 (dd, J = 13.4 Hz, J = 2.3 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 10.34 (s, 1H). MS (ES) $C_{24}H_{23}FN_4O_4$ requires: 450, found: 451 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 13.

Example	Name	Mwt	$[M+H]^+$
14	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[3-(1-piperidyl)propyl]pyrazole-3-carboxamide	533	534
15	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(2,2,2-trifluoroethoxymethyl)pyrazole-3-carboxamide	520	521

Example16:

N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (D5)

Step 1: Ethyl 1-(4-fluorophenyl)-4-hydroxy-pyrazole-3-carboxylate (D1)

To a solution of 4-fluoroaniline (10g, 90.0mmol, 1.0 eq.) in DCM/HOAc (1/1, 180mL, 0.5M) at $0^{O}C$ was added dropwise a precooled solution of sodium nitrite (9.02g, 108mmol, 1.2 eq.) in conc. sulfuric acid (40mL). After stirring for 30min at $0^{O}C$ a mixture of ethyl 4-chloroacetoacetate (14.6mL, 17.8g, 108mmol, 1.2eq.) in HOAc (60mL) and H_2O (120mL) was added within 5min. After further 15 min at $0^{O}C$ a solution of sodium acetate (100g, 1.219mol, 13.5eq.) in H_2O (210mL) was added slowly. The mixture was stirred for 30min at $0^{O}C$ and 1h at RT. DCM (200mL) was added and the organic phase was separated. The aq. phase was extracted with DCM (3x 100mL). The combined organic phase was washed with water, phosphate buffer and subsequent with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product ethyl 4-chloro-2-(4-fluorophenyl)azo-3-oxo-butanoate as a orange solid. MS (ES) $C_{12}H_{12}ClFN_2O_3$ requires: 286, found: 287 $(M+H)^+$ and 309 $(M+Na)^+$.

Without further purification the crude material was dissolved in dry ethanol (180mL) and after adding potassium acetate (12.4g, 126mmol, 1.4eq.) the mixture was refluxed for 1h. The reaction mixture was diluted with EtOAc and washed three times with water. The combined aq. phase was extracted with EtOAc. The combined organic phase was then washed with phosphate buffer and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was crystallized from ethanol to give the desired product **D1** as a brown solid (18.21g, 81%). ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.29 (t, J = 7.0 Hz, 3H), 4.28 (q, J = 7.0 Hz, 2H), 7.33 (t, J = 8.8 Hz, 2H), 7.83 (m, 2H), 8.03 (s, 1H), 9.15 (s, 1H). MS (ES) $C_{12}H_{11}FN_2O_3$ requires: 250, found: 251 $(M+H)^+$ and 273 $(M+Na)^+$.

Step 2: ethyl 4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxylate (D2)

To a mixture of **D1** (9.6g, 38mmol, 1.0 eq.) and K_2CO_3 (6.8g, 50mmol, 1.3eq.) in dry DMF (100mL) was added at RT iodoethane (4.0mL, 7.8g, 50mmol, 1.3eq.). After stirring for 72h at RT the mixture was cooled to 0°C. MeOH (5mL) was added, the mixture was diluted with DCM (200mL) and washed with water and phosphate buffer. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product **D2** as a brown solid which was used without further purification in the subsequent step. MS (ES) $C_{14}H_{15}FN_2O_3$ requires: 278, found: 279 $(M+H)^+$.

Step 3: 4-Ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxylic acid (D3)

D2 (38mmol, 1.0eq.) and aq. KOH-solution (3M, 190mmol, 5.0eq.) in EtOH (152mL) were heated for 45min at 50°C. The mixture was cooled to RT and diluted with DCM and water. The aq. phase was washed a second time with DCM. The aq. phase was acidified with aq. HCl-solution (1N) to pH=1 and extracted with EtOAc. The combined organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent yielded the product **D3** as a brown solid (8.88g, 93% over 2 steps). ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.34 (t, J = 7.0 Hz, 3H), 4.02 (q, J = 7.0 Hz, 2H), 7.37 (dd, J = J = 9.0 Hz, 2H), 7.87 (dd, J = 9.0 Hz, J = 4.6 Hz, 2H), 8.38 (s, 1H), 12.68 (br s, 1H). MS (ES) $C_{12}H_{11}FN_2O_3$ requires: 250, found: 251 $(M+H)^+$ and 273 $(M+Na)^+$.

Step 4: 4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carbonyl chloride (D4)

D3 (43mg, 0.17mmol, 1.0 eq.) was heated in thionyl chloride (1mL) for 4h at 67°C. Solvent was removed in vacuo and the crude material was resolved in dry toluene and evaporated under reduced pressure again to yield **D4**. The crude material was used in the next step without further purification.

Step 5: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (D5)

Acid chloride **D4** (0.17mmol, 1.0 eq.) was dissolved in dry pyridine (1.5mL) at 0°C and **A2** (34mg, 0.11mmol, 0.65eq.) was added. The reaction was allowed to reach RT overnight. The mixture was diluted with EtOAc and washed twice with aq. KOH-solution (0.5N), twice with aq. sat. NH_4Cl-solution, and finally once with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM/MeOH = 100:0 to 10:1) to yield the desired product **D5** (31mg, 52% over 2 steps) as a white solid. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.38 (t, J = 7.0 Hz, 3H), 3.94 (s, 6H), 4.09 (q, J = 7.0 Hz,

2H), 6.48 (d, J = 5.3 Hz, 1H), 7.43 (m, 4H), 7.53 (s, 1H), 7.70 (d, J = 9.4 Hz, 1H), 8.01 (m, 3H), 8.47 (m, 2H), 10.17 (s, 1H). MS (ES) $C_{29}H_{24}F_2N_4O_5$ requires: 546, found: 547 $(M+H)^+$.

Example 17:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide trifluoroacetic acid salt (E4)

Step1: ethyl 1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxylate (E1)

E1 was prepared from **D1** following the general procedure reported in Preparative Example 16 Step 2 using methyl iodide for the alkylation. MS (ES) $C_{13}H_{13}FN_2O_3$ requires: 264, found: 265 $(M+H)^+$ and 287 $(M+Na)^+$.

Step 2: 1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxylic acid (E2)

E1 (2mmol, 1.0eq.) and KOH (6mmol, 3.0eq.) in THF/H_20 (1/1, 30mL) were heated for 2h at 60^0C. The mixture was cooled to RT and then acidified with aq. HCl-solution (1N) to pH=1. The aq. phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4. Removal of the solvent yielded the product **E2** as a yellow solid (450mg, 95%). ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 3.80 (s, 3H), 7.37 (dd, J = J = 9.0 Hz, 2H), 7.87 (dd, J = 9.0 Hz, J = 4.7 Hz, 2H), 8.40 (s, 1H), 12.72 (br s, 1H). MS (ES) $C_{11}H_9FN_2O_3$ requires: 236, found: 237 $(M+H)^+$.

Step 3: 1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carbonyl chloride (E3)

E2 (100mg, 0.42mmol, 1.0 eq.) was heated in thionyl chloride (1mL) for 4h under reflux. Solvent was removed in vacuo and the crude material was resolved in dry toluene and evaporated under reduced pressure again to yield **E3**. The crude material was used in the next step without further purification.

Step 4: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide trifluoroacetic acid salt (E4)

Acid chloride **E3** (0.42mmol, 1.0 eq.) was dissolved in dry pyridine (2mL) at RT and **A2** (133mg, 0.42mmol, 1.0eq.) was added. The reaction was stirred at RT overnight. After adding methanol (0.1mL) the reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O (0.1%TFA) and MeOH (0.1%TFA) as eluents. The desired fractions were lyophilized to yield the title compound **E4** (36mg, 0.13mmol, 13%) as a white powder.

^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 3.88 (s, 3H), 4.04 (s, 3H), 4.05 (s, 3H), 6.85 (s, 1H), 6.96 (d, J = 6.4 Hz, 1H), 7.43 (dd, J = J = 9.0 Hz, 2H), 7.57 (s, 1H), 7.59 (t, J = 9.1 Hz, 1H), 7.75 (s, 1H), 7.81 (d, J = 9.1 Hz, 1H), 8.02 (dd, J = 9.0 Hz, J = 4.8 Hz, 2H), 8.12 (dd, J = 13.3 Hz, J = 2.4 Hz, 1H), 8.52 (s, 1H), 8.81 (d, J = 6.5 Hz, 1H), 10.30 (s, 1H). MS (ES) $C_{29}H_{22}F_2N_4O_5$ requires: 532, found: 533 $(M+H)^+$.

Example 18:

4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide (F4)

Step1: ethyl 4-(cyclopropylmethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxylate (F1)

F1 was prepared from **D1** following the general procedure reported in Preparative Example 16 Step 2 using (bromomethyl)cyclopropane for the alkylation. MS (ES) $C_{16}H_{17}FN_2O_3$ requires: 304, found: 305 $(M+H)^+$ and 327 $(M+Na)^+$.

Step 2: 4-(cyclopropylmethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxylic acid (F2)

F2 was prepared from **F1** following the general procedure reported in Preparative Example 16 Step 3. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 0.32 (dt, J = 5.0 Hz, J = 5.0 Hz, 2H), 0.57 (dt, J = 8.0 Hz, J = 5.0 Hz, 2H), 1.27 (m, 1H), 3.81 (d, J = 7.0 Hz, 2H), 7.36 (t, J = 8.9 Hz, 2H), 7.86 (dd, J = 8.9 Hz, J = 4.7 Hz, 2H), 8.37 (s, 1H), 12.69 (br s, 1H). MS (ES) $C_{14}H_{13}FN_2O_3$ requires: 276, found: 277 $(M+H)^+$ and 299 $(M+Na)^+$.

Step 3: 4-(cyclopropylmethoxy)-1-(4-fluorophenyl)pyrazole-3-carbonyl chloride (F3)

F3 was prepared from **F2** following the general procedure reported in Preparative Example 16 Step 4.

Step 4: 4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide (F4)

F4 was prepared from **F3** following the general procedure reported in Preparative Example 16 Step 5. ^{1}H NMR (400MHz, CD_3OD, 300K) δ 0.46 (m, 2H), 0.70 (m, 2H), 1.43 (m, 1H), 4.00 (d, J = 7.2 Hz, 1H), 4.05 (s, 3H), 4.06 (s, 3H), 6.75 (d, J = 5.5 Hz, 1H), 7.25 (t, J = 8.8 Hz, 2H), 7.40 (s, 1H), 7.44 (t, J = 8.8 Hz, 2H), 7.59 (m, 1H), 7.73 (s,

1H), 7.89 (m, 3H), 8.04 (dd, J = 12.6 Hz, J = 2.3 Hz, 1H), 8.18 (s, 1H), 8.55 (m, 1H). MS (ES) $C_{31}H_{26}F_2N_4O_5$ requires: 572, found: 573 $(M+H)^+$.

Example 19:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide (G2)

Step 1: 4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carbonyl chloride (G1)

G1 was prepared from **D1** following the general procedure reported in Preparative Example 16 Step 2-4.

Step 2: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide (G2)

G2 was prepared from **G1** following the general procedure reported in Preparative Example 16 Step 5. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 2.45 (s, 6H), 2.95 (t, J = 5.2 Hz, 2H), 3.96 (s, 6H), 4.25 (t, J = 5.2 Hz, 2H), 6.49 (d, J = 5.3 Hz, 1H), 7.43 (m, 3H), 7.48 (t, J = 9.2 Hz, 1H), 7.54 (s, 1H), 7.71 (d, J = 9.2 Hz, 1H), 8.00 (m, 3H), 8.49 (d, J = 5.1 Hz, 1H), 8.59 (s, 1H), 10.27 (s, 1H). MS (ES) $C_{31}H_{29}F_2N_5O_5$ requires: 589, found: 590 $(M+H)^+$.

Example 20:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(3-dimethylaminopropoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide (H2)

Step 1: 4-(3-dimethylaminopropoxy)-1-(4-fluorophenyl)pyrazole-3-carbonyl chloride (H1)

H1 was prepared from **D1** following the general procedure reported in Preparative Example 16 Step 2-4.

Step 2: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(3-dimethylaminopropoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide (H2)

H2 was prepared from **H1** following the general procedure reported in Preparative Example 16 Step 5. MS (ES) $C_{32}H_{31}F_2N_5O_5$ requires: 603, found: 604 $(M+H)^+$.

Example 21:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide (I3)

Step 1: 1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxylic acid (I1)

I1 was prepared from **D1** following the general procedure reported in Preparative Example 16 Step 2 and 3. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.29 (d, J = 6.0 Hz, 6H), 4.34 (sept, J = 6.0 Hz, 1H), 7.37 (t, J = 8.8 Hz, 2H), 7.88 (dd, J = 8.8 Hz, J = 4.7 Hz, 2H), 8.39 (s, 1H), 12.63 (br s, 1H). MS (ES) $C_{13}H_{13}FN_2O_3$ requires: 264, found: 265 $(M+H)^+$.

Step 2: 1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carbonyl chloride (I2)

I2 was prepared from **I1** following the general procedure reported in Preparative Example 16 Step 4.

Step 3: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide (I3)

I3 was prepared from **I2** following the general procedure reported in Preparative Example 16 Step 5. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.34 (d, J = 6.1 Hz, 6H), 3.94 (s, 6H), 4.43 (sept., J = 6.1 Hz, 1H), 6.47 (d, J = 5.2 Hz, 1H), 7.42 (m, 4H), 7.53 (s, 1H), 7.68 (d, J = 9.1 Hz, 1H), 8.02 (m, 3H), 8.48 (m, 2H), 10.15 (s, 1H). MS (ES) $C_{30}H_{26}F_2N_4O_5$ requires: 560, found: 561 $(M+H)^+$.

Example 22:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide (J5)

Step1: ethyl 1-(4-fluoro-2-methyl-phenyl)-4-hydroxy-pyrazole-3-carboxylate (J1)

J1 was prepared following the general procedure reported in Preparative Example 16 Step 1. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.26 (t, J = 7.1 Hz, 3H), 2.16 (s, 3H), 4.25 (q, J = 7.1 Hz, 2H), 7.15 (ddd, J = 8.5 Hz, J = J = 3.0 Hz, 1H), 7.26 (dd, J = 9.6 Hz, J = 3.0 Hz, 1H), 7.39 (dd, J = 8.5 Hz, J = 5.5 Hz, 1H), 7.60 (s, 1H). MS (ES) $C_{13}H_{13}FN_2O_3$ requires: 264, found: 265 $(M+H)^+$ and 287 $(M+Na)^+$.

Step2: ethyl 4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxylate (J2)

J2 was prepared from **J1** following the general procedure reported in Preparative Example 16 Step 2 using iodoethane for the alkylation. MS (ES) $C_{15}H_{17}FN_2O_3$ requires: 292, found: 293 $(M+H)^+$ and 315 $(M+Na)^+$.

Step 3: 4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxylic acid (J3)

J3 was prepared from **J2** following the general procedure reported in Preparative Example 16 Step 3. MS (ES) $C_{13}H_{13}FN_2O_3$ requires: 264, found: 265 $(M+H)^+$.

Step 4: 4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carbonyl chloride (J4)

J4 was prepared from **J3** following the general procedure reported in Preparative Example 16 Step 4.

Step 5: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide (J5)

J5 was prepared following the general procedure reported in Preparative Example 16 Step 5. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.38 (t, J = 7.0 Hz, 3H), 2.26 (s, 3H), 4.02 (s, 3H), 4.03 (s, 3H), 4.07 (q, J = 7.0 Hz, 2H), 6.89 (d, J = 6.4 Hz, 1H), 7.23 (dt, J = 8.5 Hz, J = 3.0 Hz, 1H), 7.33 (dd, J = 9.9 Hz, J = 3.0 Hz, 1H), 7.53 (m, 3H), 7.72 (s, 1H), 7.78 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 8.11 (dd, J = 13.3 Hz, J = 2.6 Hz, 1H), 8.77 (d, J = 6.4 Hz, 1H), 10.24 (s, 1H). MS (ES) $C_{30}H_{26}F_2N_4O_5$ requires: 560, found: 561 $(M+H)^+$.

Example 23:
1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide (K3)

Step1: 1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-pyrazole-3-carboxylic acid (K1)

K1 was prepared following the general procedure reported in Preparative Example 16 Step 1-3. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.31 (t, J = 7.0 Hz, 3H), 3.96 (q, J =

7.0 Hz, 2H), 7.40 (m, 1H), 7.66 (dd, J = 8.9 Hz, J = 5.6 Hz, 1H), 7.72 (dd, J = 8.5 Hz, J = 2.8 Hz, 1H), 7.98 (s, 1H), 12.64 (br s, 1H). MS (ES) $C_{12}H_{10}ClFN_2O_3$ requires: 284, found: 285 $(M+H)^+$ and 307 $(M+Na)^+$.

Step 2: **1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-pyrazole-3-carbonyl chloride (K2)**

K2 was prepared from **K1** following the general procedure reported in Preparative Example 16 Step 4.

Step 3: 1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide (K3)

K3 was prepared following the general procedure reported in Preparative Example 16 Step 5. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 1.56 (t, J = 6.9 Hz, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 4.18 (q, J = 6.9 Hz, 2H), 6.45 (d, J = 5.3 Hz, 1H), 7.14 (ddd, J = 10.0 Hz, J = 7.4 Hz, J = 2.7 Hz, 1H), 7.23 (t, J = 8.8 Hz, 1H), 7.29 (dd, J = 8.0 Hz, J = 2.7 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.45 (s,1H), 7.55 (s, 1H), 7.59 (s, 1H), 7.62 (dd, J = 8.8 Hz, J = 5.3 Hz, 1H), 7.91 (dd, J = 12.1 Hz, J = 2.7 Hz, 1H), 8.50 (d, J = 5.3 Hz, 1H), 8.90 (s, 1H). MS (ES) $C_{29}H_{23}ClF_2N_4O_5$ requires: 580, found: 581$(M+H)^+$.

Example 24:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (L2)

Step 1: **4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (L1)**

L1 was prepared from 6,7-dimethoxyquinolin-4-ol and 4-fluoro-nitrobenzene following the general procedure reported in Preparative Example 1 Step 1-2. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 3.91 (s, 3H), 3.92 (s, 3H), 5.16 (br s, 2H), 6.36 (d, J = 5.3 Hz, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.34 (s, 1H), 7.49 (s, 1H), 8.41 (d, J = 5.3 Hz, 1H). MS (ES) $C_{17}H_{16}N_2O_3$ requires: 296, found: 297 $(M+H)^+$.

Step 2: **N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (L2)**

L2 was prepared from **L1** and **D4** following the general procedure reported in Preparative Example 16 Step 5. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.38 (t, J = 7.0

Hz, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 6.51 (d, J = 5.4 Hz, 1H), 7.28 (d, J = 9.1 Hz, 2H), 7.39 (m, 3H), 7.53 (s, 1H), 7.91 (d, J = 9.1 Hz, 2H), 7.98 (m, 2H), 8.47 (s, 1H), 8.49 (d, J = 5.4 Hz, 1H), 9.98 (s, 1H). MS (ES) $C_{29}H_{25}FN_4O_5$ requires: 528, found: 529 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 24.

Example	Name	Mwt	$[M+H]^+$
25	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	542	543
26	4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	554	555
27	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	542	543

Example 28:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (M2)

Step 1: 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-aniline (M1)

M1 was prepared from 6,7-dimethoxyquinolin-4-ol and 1-fluoro-2-methyl-4-nitrobenzene following the general procedure reported in Preparative Example 1 Step 1-2. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.93 (s, 3H), 3.92 (s, 6H), 5.06 (br s, 2H), 6.24 (d, J = 5.2 Hz, 1H), 6.48 (dd, J = 8.4 Hz, J = 2.5 Hz, 1H), 6.53 (d, J = 2.5 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 7.53 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H). MS (ES) $C_{19}H_{19}N_2O_3$ requires: 310, found: 311 $(M+H)^+$.

Step 2: N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (M2)

M2 was prepared from **M1** and **D4** following the general procedure reported in Preparative Example 16 Step 5. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.38 (t, J = 7.0 Hz, 3H), 2.11 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 6.30 (d, J = 5.2 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 7.39 (m, 3H), 7.57 (s, 1H), 7.74 (dd, J = 8.7 Hz, J

= 2.4 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 7.99 (m, 2H), 8.44 (d, J = 5.2 Hz, 1H), 8.47 (s, 1H), 9.90 (s, 1H). MS (ES) $C_{30}H_{27}FN_4O_5$ requires: 542, found: 543 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 28.

Example	Name	Mwt	$[M+H]^+$
29	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	556	557
30	4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	568	569
31	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	556	557

Example 32:
N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (N2)

Step 1: 3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]aniline (N1)

N1 was prepared from 6,7-dimethoxyquinolin-4-ol and 2-chloro-1-fluoro-4-nitrobenzene following the general procedure reported in Preparative Example 1 Step 1-2. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 3.92 (s, 6H), 5.45 (br s, 2H), 6.28 (d, J = 5.3 Hz, 1H), 6.61 (dd, J = 8.7 Hz, J = 2.6 Hz, 1H), 6.78 (d, J = 2.6 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 7.36 (s, 1H), 7.50 (s, 1H), 8.42 (d, J = 5.3 Hz, 1H). MS (ES) $C_{17}H_{15}ClN_2O_3$ requires: 330, found: 331$(M+H)^+$.

Step 2: N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (N2)

N2 was prepared from **N1** and **D4** following the general procedure reported in Preparative Example 16 Step 5. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.37 (t, J = 7.0 Hz, 3H), 3.94 (s, 6H), 4.09 (q, J = 7.0 Hz, 2H), 6.37 (d, J = 5.2 Hz, 1H), 7.42 (m, 4H), 7.53 (s, 1H), 7.87 (dd, J = 8.7 Hz, J = 2.5 Hz, 1H), 8.00 (m, 2H), 8.21 (d, J = 2.5 Hz, 1H), 8.46 (m, 2H), 10.16 (s, 1H). MS (ES) $C_{29}H_{24}ClFN_4O_5$ requires: 562, found: 563 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 32.

Example	Name	Mwt	$[M+H]^+$
33	N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	576	577
34	N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-(cyclopropylmethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide	588	589
35	N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	576	577

Example 36:

N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-(2-(dimethylamino)ethyl)-1-(4-fluorophenyl)-1H-pyrazole-3-carboxamide (O3)

Step 1: Ethyl 4-[2-ethoxyvinyl]-1-(4-fluorophenyl)pyrazole-3-carboxylate (O1)

To a solution of **D1** (500mg, 2.0mmol, 1.0eq.) and 2,6-lutidine (0.3mL, 2.8mmol, 1.4eq.) in dry DCM (10mL) at $0^{O}C$ was added trifluoromethanesulfonic anhydride (1M in DCM, 2.4mL, 2.4mmol, 1.2eq.). After 45 min the mixture was diluted with DCM and washed twice with aq. $NaHCO_3$-solution. After drying over $MgSO_4$ the solvent was removed in vacuo.

The crude material was resolved in dry DMF (15mL) under N_2-atmosphere. Than *cis*-tributyl[2-ethoxyethenyl]stannane (1083mg, 3mmol, 1.5eq.) and tetrakis(triphenylphosphine)-palladium (123mg, 0.2mmol, 0.1eq.) were added and the mixture was heated for 5 h at $90^{O}C$. EtOAC was added and the organic phase was washed three times with aq. $NaHCO_3$-solution. The organic phase was dried over $MgSO_4$ and solvents were removed in vacuo. The crude material was used without further purification. MS (ES) $C_{16}H_{17}IFN_2O_3$ requires: 304, found: 305 $(M+H)^+$ and 327 $(M+Na)^+$.

Step 2: 4-(2-dimethylaminoethyl)-1-(4-fluorophenyl)pyrazole-3-carboxylic acid (O2)

A solution of **O1** (2mmol) in TFA/DCM (1/1 mixture, 15mL) was stirred for 2h at RT. The solvents were removed in vacuo. The crude material was resolved in dry EtOH (5mL) and dimethylamine in EtOH (5.6N, 1.07mL, 6mmol, 3.0eq.) was added. After stirring for 2 h, sodium cyanoborohydride (376mg, 6mmol, 3.0eq.) was added and the mixture was stirred further for 12h. After adding water the solvents were removed in vacuo. The crude material was solved in EtOAc and washed twice with aq. $NaHCO_3$-solution, dried over $MgSO_4$ and evaporated in vacuo. The crude material was purified using an Isolute ® SPE column SCX, loading the reaction mixture as a MeOH-solution and than eluting the desired compound with 2N NH_3 in MeOH yielding ethyl 4-(2-(dimethylamino)ethyl)-1-(4-fluorophenyl)-1H-pyrazole-3-carboxylate. MS (ES) $C_{16}H_{20}FN_3O_2$ requires: 305, found: 306 $(M+H)^+$.

The crude material and sodium hydoxide (160mg, 4.0mmol, 2.0 eq.) was stirred in dioxane/water (1/1, 8mL) for 12h at RT. The solvents were removed in vacuo and the residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and ACN as eluents. The desired fractions were lyophilized to yield the title compound **O2** (198mg, 0.71mmol, 36%) as a white powder. MS (ES) $C_{14}H_{16}FN_3O_2$ requires: 277, found: 278 $(M+H)^+$.

Step3: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-(2-(dimethylamino)ethyl)-1-(4-fluorophenyl)-1H-pyrazole-3-carboxamide (O3)

To a solution of **A2** (50mg, 0.16mmol, 1.0eq), **O2** (44mg, 0.16mmol, 1.0eq.) and DIPEA (62mg, 0.48mmol, 3.0eq.) in dry DMF (4mL) was added HATU (121mg, 0.32mmol, 2.0eq.). The mixture was stirred for 12h at 60°C. Then the mixture was diluted with EtOAc and washed three times with aq. $NaHCO_3$-solution. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and ACN as eluents. The desired fractions were lyophilized to yield the desired compound **O3** with impurities. A subsequent purification by chromatography on silica gel (DCM/MeOH = 20:1) yielded the product **O3** (15mg, 0.026mmol, 16%) as a white solid. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 2.34 (s, 6H), 2.72 (m, 2H), 2.98 (t, J = 7.4 Hz, 2H), 3.94 (s, 6H), 6.47 (d, J = 5.3 Hz, 1H), 7.40 (s, 1H), 7.44 (m, 3H), 7.53 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 8.03 (m, 3H), 8.48 (d, J = 5.3 Hz, 1H), 8.51 (s, 1H), 10.44 (s, 1H). MS (ES) $C_{31}H_{29}F_2N_5O_4$ requires: 573, found: 574 $(M+H)^+$.

Example 37:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[2-(2-dimethylaminoethyl)-4-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide (P7)

Step 1: ethyl 1-(2-bromo-4-fluoro-phenyl)-4-hydroxy-pyrazole-3-carboxylate (P1)

To a solution of 2-bromo-4-fluoroaniline (10g, 52.6mmol, 1.0 eq.) in DCM/HOAc (1/1, 160mL, 0.3M) at 0°C was added dropwise a precooled solution of sodium nitrite (4.1g, 57.9mmol, 1.1 eq.) in conc. sulfuric acid (20mL). After stirring for 30min at 0°C a mixture of ethyl 4-chloroacetoacetate (14.6mL, 17.8g, 108mmol, 1.2eq.) in HOAc (40mL) and H_2O (80mL) was added within 5min. After further 15min at 0°C a solution of sodium acetate (72g, 0.878mol, 16.7eq.) in H_2O (140mL) was added slowly. The mixture stirred for 30min at 0°C and than 12h at RT. DCM (200mL) was added and the organic phase was separated. The aq. phase was extracted with DCM (3x 100mL). The combined organic phase was washed with water, phosphate buffer and subsequent with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product ethyl 2-(2-bromo-4-fluoro-phenyl)azo-4-chloro-3-oxo-butanoate as a red solid. MS (ES) $C_{12}H_{11}BrClFN_2O_3$ requires: 365, found: 365/367 $(M+H)^+$.

Without further purification the crude material was dissolved in dry ethanol (130mL) and after adding potassium acetate (7.1g, 71mmol, 1.4eq.) the mixture was refluxed for 20min. The reaction mixture was diluted with EtOAc and washed three times with water. The combined aq. phase was extracted with EtOAc. The combined organic phase was then washed with phosphate buffer and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The desired product **P1** was obtained as a yellow solid (18.19g, 81%) and was used without further purification in the subsequent step. ^1H NMR (400MHz, $CDCl_3$, 300K) δ 1.44 (t, J = 7.1 Hz, 3H), 4.47 (q, J = 7.1 Hz, 2H), 7.13 (ddd, J = 9.0 Hz, J = 7.5 Hz, J = 2.8 Hz, 1H), 7.41 (s, 1H), 7.42 (dd, J = 7.5 Hz, J = 2.8 Hz, 1H), 7.48 (dd, J = 9.0 Hz, J = 5.5 Hz, 1H). MS (ES) $C_{12}H_{10}BrFN_2O_3$ requires: 329, found: 329/331 $(M+H)^+$ and 351/353 $(M+Na)^+$.

Step 2: ethyl 1-(2-bromo-4-fluoro-phenyl)-4-ethoxy-pyrazole-3-carboxylate (P2)

To a mixture of **P1** (4.3g, 13.1mmol, 1.0 eq.) and K_2CO_3 (2.4g, 17.3mmol, 1.3eq.) in dry DMF (55mL) was added at RT iodoethane (1.38mL, 2.7g, 17.3mmol, 1.3eq.). After stirring for 12h at RT the mixture was cooled to 0°C. MeOH (5mL) was added, the mixture was diluted with DCM (200mL) and washed with water and phosphate buffer.

The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM/MeOH = 100:0 to 5:1) to yield the desired product **P2** (4.1g, 86%) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 1.40 (t, J = 7.1 Hz, 3H), 1.47 (t, J = 7.0 Hz, 3H), 4.06 (q, J = 7.0 Hz, 2H), 4.43 (q, J = 7.1 Hz, 2H), 7.13 (ddd, J = 8.8 Hz, J = 7.5 Hz, J = 2.8 Hz, 1H), 7.41 (s, 1H), 7.42 (dd, J = 8.8 Hz, J = 2.8 Hz, 1H), 7.52 (dd, J = 8.8 Hz, J = 5.3 Hz, 1H). MS (ES) $C_{14}H_{14}BrFN_2O_3$ requires: 357, found: 357/359 $(M+H)^+$.

<u>Step 3:</u> ethyl 4-ethoxy-1-[2-[(Z)-2-ethoxyvinyl]-4-fluoro-phenyl]pyrazole-3-carboxylate (P3)

A mixture of **P2** (1g, 2.8mmol, 1.0 eq.), *cis*-tributyl[2-ethoxyethenyl]stannane (1.3g, 3.1mmol, 1.1eq.) in DMF (9mL) was degassed with a stream of N_2 for 15min. Then $Pd(PPh_3)_4$ (170mg, 0.15mmol, 0.05 eq.) was added and the reaction mixture was heated to 100^{0}C for 45min in the microwave oven. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (cHex/EtOAc = 50:1 to 3:1) to yield the desired product **P3** (820mg, 84%) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 1.35 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.44 (t, J = 7.0 Hz, 3H), 4.00 (m, 4H), 4.40 (q, J = 7.1 Hz, 2H), 4.81 (d, J = 7.3 Hz, 1H), 6.23 (d, J = 7.3 Hz, 1H), 6.88 (m, 1H), 7.26 (m, 2H), 7.88 (dd, J = 10.6 Hz, J = 2.8 Hz, 1H). MS (ES) $C_{19}H_{21}FN_2O_4$ requires: 348, found: 349 $(M+H)^+$.

<u>Step 4:</u> ethyl 4-ethoxy-1-[4-fluoro-2-(2-oxoethyl)phenyl]pyrazole-3-carboxylate (P4)

P3 (820mg, 2.3mmol, 1.0 eq.) was stirred in TFA/DCM (1/2, 7.5mL) at RT for 40h. The mixture was concentrated under reduced pressure to yield the desired product **P4** as an yellow oil. The crude material was used without further purification. MS (ES) $C_{16}H_{17}FN_2O_4$ requires: 320, found: 321 $(M+H)^+$.

<u>Step 5:</u> ethyl 1-[2-(2-dimethylaminoethyl)-4-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxylate (P5)

A mixture of the crude product **P4** (2.3mmol, 1.0 eq.) and a solution of dimethylamine in MeOH (5.6M, 3ml, 7eq.) was stirred at RT for 2h. After addition of sodium

cyanoborohydride (215mg, 3.4mmol, 1.5eq.) the mixture was stirred for 15h at RT. Water was added and the aq. phase was extracted with EtOAc. The combined org. phase was washed with aq. sat. $NaHCO_3$-solution and dried over Na_2SO_4. The solvent was removed in vacuo and the crude was purified using an Isolute ® SPE column SCX, loading the reaction mixture as a MeOH solution and than eluting the desired compound with 2N NH_3 in MeOH. The title compound **P5** was isolated after evaporation of the solvent under reduced pressure as a yellow oil (138mg, 0.4mmol, 17%). MS (ES) $C_{19}H_{24}FN_3O_3$ requires: 349, found: 350 $(M+H)^+$.

<u>Step 6:</u> 1-[2-(2-dimethylaminoethyl)-4-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxylic acid (P6)

P6 was prepared from **P5** following the general procedure reported in Preparative Example 16 Step 3. The residue was purified by reversed-phase flash chromatography (H_20/MeOH = 100:0 to 1:10) to yield the desired product **P6** (112mg, 88%) as a white solid. MS (ES) $C_{16}H_{20}FN_3O_3$ requires: 321, found: 322 $(M+H)^+$.

<u>Step 7:</u> N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-(2-(2-(dimethylamino)ethyl)-4-fluorophenyl)-4-ethoxy-1H-pyrazole-3-carboxamide hydrochloride (P7)

Carboxylic acid **P6** (117mg, 0.36mmol, 1.0eq.) was heated in thionyl chloride (3mL) for 4h under reflux. Solvent was removed in vacuo and the crude material was resolved in dry toluene and evaporated under reduced pressure again.
The crude material was solved in dry pyridine (3mL) and **A2** (115mg, 0.36mmol, 1.0eq.) was added. The mixture was stirred at RT for 12h. Water was added and the mixture was evaporated in vacuo. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and ACN as eluents. The desired fractions were lyophilized. The white solid (70mg) was solved in water and ACN and than 1N HCl (0.13mL) was added. The mixture was lyophilized to yield the title compound **P7** (74mg, 0.113mmol, 32%) as a white powder. ^1H NMR (400MHz, MeOD, 300K) δ 1.57 (t, J = 7.0 Hz, 3H), 2.97 (s, 6H), 3.08 (t, J = 7.6 Hz, 2H), 3.55 (t, J = 7.6 Hz, 2H), 4.04 (s, 3H), 4.05 (s, 3H), 4.28 (q, J = 7.0 Hz, 2H), 6.66 (d, J = 5.8 Hz, 1H), 7.25 (dt, J = 8.6 Hz, J = 2.8 Hz, 1H), 7.35 (dd, J = 9.2 Hz, J = 2.8 Hz, 1H), 7.41 (s, 1H), 7.45 (t, J = 8.6 Hz, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.60 (dd, J = 8.9 Hz, J = 5.0 Hz, 1H), 7.71 (s, 1H), 8.04 (m, 1H), 8.06 (s, 1H), 8.51 (d, J = 5.8 Hz, 1H). MS (ES) $C_{33}H_{33}F_2N_5O_5$ requires: 617, found: 618 $(M+H)^+$.

Example 38:
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide (Q1)

Q1 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and 2-phenyl-1,3-thiazole-4-carbonyl chloride following the general procedure reported in Preparative Example 1 Step 3. ^{1}H NMR (400MHz, d_4-MeOD, 300K) δ 2.17 (m, 2H), 2.73 (m, 4H), 2.81 (t, J = 7.4 Hz, 2H), 3.77 (t, J = 4.7 Hz, 4H), 3.98 (s, 3H), 4.24 (t, J = 6.0 Hz, 2H), 6.50 (d, J = 5.4 Hz, 1H), 7.33 (s, 1H), 7.35 (t, J = 8.8 Hz, 1H), 7.50 (m, 4H), 7.62 (s, 1H), 7.66 (d, J = 8.8 Hz, 1H), 8.01 (dd, J = 12.6 Hz, J = 2.5 Hz, 1H), 8.07 (m, 2H), 8.32 (s, 1H), 8.39 (d, J = 5.4 Hz, 1H). MS (ES) $C_{33}H_{31}FN_4O_5S$ requires: 614, found: 615 $(M+H)^+$.

Example 39:
4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide (Q2)

Q2 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and 4-bromo-1-methyl-1H-pyrazole-3-carbonyl chloride following the general procedure reported in Preparative Example 1 Step 3. ^{1}H NMR (400MHz, d_4-MeOD, 300K) δ 2.20 (m, 2H), 2.73 (m, 4H), 2.81 (t, J = 7.4 Hz, 2H), 3.80 (t, J = 4.7 Hz, 4H), 4.02 (s, 3H), 4.05 (s, 3H), 4.29 (t, J = 6.1 Hz, 2H), 6.54 (dd, J = 5.4 Hz, J = 1.0 Hz, 1H), 7.37 (t, J = 9.0 Hz, 1H), 7.38 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 7.86 (s, 1H), 7.95 (dd, J = 12.9 Hz, J = 2.4 Hz, 1H), 8.45 (d, J = 5.4 Hz, 1H). MS (ES) $C_{28}H_{29}BrFN_5O_5$ requires: 614, found: 614/616 $(M+H)^+$.

Example 40:
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide (Q3)

Q3 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and 1-methyl-1H-pyrazole-3-carbonyl chloride following the general procedure reported in Preparative Example 1 Step 3. ^{1}H NMR (400MHz, d_4-MeOD, 300K) δ 2.10 (m, 2H), 2.52 (m, 4H), 2.62 (t, J = 7.5 Hz, 2H), 3.70 (t, J = 4.7 Hz, 4H), 3.99 (s, 3H), 4.00 (s, 3H), 4.22 (t, J = 6.2 Hz, 2H), 6.49 (d, J = 5.4 Hz, 1H), 6.83 (d, J = 2.3 Hz, 1H), 7.33 (m, 2H), 7.58 (d, J = 8.8 Hz, 1H), 7.62 (s, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.94 (dd, J = 12.7 Hz, J = 2.4 Hz, 1H), 8.40 (d, J = 5.4 Hz, 1H). MS (ES) $C_{28}H_{30}FN_5O_5$ requires: 535, found: 536 $(M+H)^+$.

Example 41:
1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide (Q4)

Q4 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and 1-methyl-5-phenyl-1H-pyrazole-3-carbonyl chloride following the general procedure reported in Preparative Example 1 Step 3. MS (ES) $C_{32}H_{38}FN_5O_5$ requires: 591, found: 592 $(M+H)^+$.

Example 42:
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1,5-dimethyl-pyrazole-3-carboxamide (Q5)

Q5 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and 1,5-dimethyl-1H-pyrazole-3-carbonyl chloride following the general procedure reported in Preparative Example 1 Step 3. MS (ES) $C_{29}H_{32}FN_5O_5$ requires: 549, found: 550 $(M+H)^+$.

Example 43:
4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide (Q6)

Q6 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and **J4** following the general procedure reported in Preparative Example 1 Step 3. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.36 (t J = 7.0 Hz, 3H), 1.96 (m, 2H), 2.25 (s, 3H), 2.38 (m, 4H), 2.46 (t, J = 7.0 Hz, 2H), 3.57 (t, J = 4.5 Hz, 4H), 3.94 (s, 3H), 4.04 (q, J = 7.0 Hz, 2H), 4.19 (t, J = 6.4 Hz, 2H), 6.44 (d, J = 5.1 Hz, 1H), 7.21 (dt, J = 8.6 Hz, J = 2.9 Hz, 1H), 7.31 (dt, J = 9.7 Hz, J = 2.9 Hz, 1H), 7.39 (s, 1H), 7.41 (t, J = 9.0 Hz, 1H), 7.51 (m, 2H), 7.69 (d, J = 8.6 Hz, 1H), 8.02 (s, 1H), 8.02 (dd, J = 13.3 Hz, J = 2.3 Hz, 1H), 8.45 (d, J = 5.2 Hz, 1H), 10.14 (s, 1H). MS (ES) $C_{36}H_{37}F_2N_5O_6$ requires: 673, found: 674 $(M+H)^+$.

Example 44:
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide (Q7)

Q7 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and **E3** following the general procedure reported in Preparative Example 1 Step 3. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 2.01 (m, 2H), 2.51 (m, 6H), 3.61 (m, 4H), 3.86 (s, 3H), 3.94 (s, 3H), 4.20 (t, J = 6.2 Hz, 2H), 6.46 (d, J = 5.3 Hz, 1H),

7.43 (m, 4H), 7.53 (s, 1H), 7.72 (t, J = 9.1 Hz, 1H), 8.01 (m, 3H), 8.47 (d, J = 5.3 Hz, 1H), 8.49 (s, 1H), 10.19 (s, 1H). MS (ES) $C_{34}H_{33}F_2N_5O_6$ requires: 645, found: 646 $(M+H)^+$.

Example 45:
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide (Q8)

Q8 was prepared from 3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]aniline and **I2** following the general procedure reported in Preparative Example 1 Step 3. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.34 (d, J = 6.0 Hz, 6H), 1.97 (m, 2H), 2.38 (m, 4H), 2.47 (m, 2H), 3.57 (t, J = 4.6 Hz, 4H), 3.94 (s, 3H), 4.19 (t, J = 6.3 Hz, 2H), 4.43 (sept, J = 6.0 Hz, 1H), 6.46 (d, J = 5.2 Hz, 1H), 7.42 (m, 4H), 7.59 (s, 1H), 7.68 (t, J = 9.1 Hz, 1H), 8.01 (m, 3H), 8.46 (d, J = 5.2 Hz, 1H), 8.49 (s, 1H), 10.15 (s, 1H). MS (ES) $C_{36}H_{37}F_2N_5O_6$ requires: 673, found: 674 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 45.

Example	Name	Mwt	$[M+H]^+$
46	4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	685	686
47	1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide	694	695
48	4-(2-dimethylaminoethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	702	703
49	1-(2-bromo-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide	738	738/740
50	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide	689	690
51	4-benzyloxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	721	722

52	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-nitro-pyrazole-3-carboxamide	660	661
53	4-amino-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	630	631

Example 54:

N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (R3)

Step 1: tert-butyl N-[3-[[4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-quinolyl]oxy]propyl]carbamate (R1)

To a solution of 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol (511mg, 1.55mmol, 1.0eq.) and potassium carbonate (428mg, 3.1mmol, 2.0eq.) in dry DMF (10mL) was added tert-butyl (3-bromopropyl)carbamate (480mg, 2.01mmol, 1.3eq.). The mixture was stirred for 3 h at 90°C and then cooled to RT. EtOAc was added and the organic phase was washed three times with water. The organic phase was dried over $MgSO_4$ and solvents were removed in vacuo. The desired product **R1** was obtained as brown oil and was used without further purification in the next step. MS (ES) $C_{24}H_{26}FN_3O_7$ requires: 487, found: 488$(M+H)^+$.

Step 2: tert-butyl N-[3-[[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-7-quinolyl]oxy]propyl]carbamate (R2)

A suspension of **R1** (1.55mmol, 1.0 eq.) and Pd/C (10%w/w, 75mg) in MeOH (30mL) was stirred under hydrogen atmosphere (1atm) at RT for 5h. The suspension was filtered through a pad of Celite®. The solvent was removed in vacuo. The product **R2** was obtained as yellow solid (708mg, 1.55mmol, 100%). The crude material was used without further purification. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.37 (s, 9H), 1.92 (quint., J = 6.4 Hz, 2H), 3.13 (quart., J = 6.4 Hz, 2H), 3.93 (s, 3H), 4.14 (t, J = 6.4 Hz, 2H), 5.46 (br s, 2H), 6.36 (d, J = 5.3 Hz, 1H), 6.45 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H), 6.53 (dd, J = 13.1 Hz, J = 2.4 Hz, 1H), 6.88 (m, 1H), 7.05 (t, J = 8.9 Hz, 1H), 7.34 (s, 1H), 7.49 (s, 1H), 8.43 (d, J = 5.3 Hz, 1H). MS (ES) $C_{24}H_{28}FN_3O_5$requires: 457, found: 458 $(M+H)^+$.

Step3: N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide (R3)

Tert-butyl N-[3-[[4-[4-[[4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carbonyl]amino]-2-fluoro-phenoxy]-6-methoxy-7-quinolyl]oxy]propyl]carbamate was prepared from **R2** and **D4** following the general procedure reported in Preparative Example 1 Step 3.
Then the crude material was stirred in TFA/DCM (1/1) for 3h at RT. The reaction mixture was concentrated under reduced pressure and the residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and MeOH as eluents. The desired fractions were lyophilized to yield the title compound **R3** as a white powder. ^1H NMR (400MHz, d_4-MeOD, 300K) δ 1.59 (t, J = 7.0 Hz, 3H), 2.29 (m, 2H), 3.27 (t, J = 6.8 Hz, 2H), 4.03 (s, 3H), 4.19 (q, J = 7.0 Hz, 2H), 4.35 (t, J = 5.6 Hz, 2H), 6.55 (d, J = 5.3 Hz, 1H), 7.24 (t, J = 8.7 Hz, 2H), 7.36 (t, J = 9.0 Hz, 1H), 7.38 (s, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.68 (s, 1H), 7.88 (m, 2H), 7.99 (dd, J = 12.6 Hz, J = 2.4 Hz, 1H), 8.16 (s, 1H), 8.44 (d, J = 5.3 Hz, 1H). MS (ES) $C_{31}H_{29}F_2N_5O_5$ requires: 589, found: 590 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 54.

Example	Name	Mwt	$[M+H]^+$
55	N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	603	604
56	N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-5-ethoxy-2-(4-fluorophenyl)oxazole-4-carboxamide	590	591

Example 57:

4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide (S2)

Step 1: 3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]aniline (S1)

S1 was prepared from 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol and 1-(3-chloropropyl)-4-methylpiperazine following the general procedure reported in Preparative Example 54 Step 1-2. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.95 (quint., J = 6.8 Hz, 2H), 2.14 (s, 3H), 2.22 - 2.47 (m, 10H), 3.94 (s, 3H), 4.17 (t, J = 6.5 Hz, 2H), 5.48 (br.s, 2H), 6.38 (d, J = 5.2 Hz, 1H), 6.46 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H), 6.55 (dd, J = 13.2 Hz, J = 2.4 Hz, 1H), 7.07 (t, J = 9.0 Hz, 1H), 7.36 (s, 1H), 7.50 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H). MS (ES) $C_{24}H_{29}FN_4O_3$ requires: 440, found: 441 $(M+H)^+$.

Step 2: 4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide (S2)

S2 was prepared from **S1** and **J4** following the general procedure reported in Preparative Example 1 Step 3. The crude product was purified by flash chromatography on silica gel (DCM/MeOH = 100:0 to 5:1) to yield the desired product **S2** (60mg, 0.087mmol, 77%) as a white solid. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.36 (t, J = 7.0 Hz, 3H), 1.95 (t, J = 7.3 Hz, 2H), 2.17 (m, 4H), 2.25 (m, 4H), 2.30 - 2.50 (m, 8H), 3.94 (s, 3H), 4.05 (q, J = 7.0 Hz, 2H), 4.17 (t, J = 6.4 Hz, 2H), 6.44 (d, J = 5.2 Hz, 1H), 7.21 (dt, J = 8.6 Hz, J = 2.5 Hz, 1H), 7.31 (dd, J = 9.8 Hz, J = 2.5 Hz, 1H), 7.37 (s, 1H), 7.41 (t, J = 9.0 Hz, 1H), 7.50 (m, 2H), 7.69 (d, J = 9.0 Hz, 1H), 8.01 (dd, J = 13.1 Hz, J = 2.5 Hz, 1H), 8.02 (s, 1H), 8.46 (d, J = 5.2 Hz, 1H), 10.14 (s, 1H). MS (ES) $C_{37}H_{40}F_2N_6O_5$ requires: 686, found: 687 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 57.

Example	Name	Mwt	$[M+H]^+$
58	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	672	673
59	N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide	658	659
60	1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide	706	707
61	4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	698	699
62	N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	686	687
63	5-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-2-(4-fluorophenyl)oxazole-4-carboxamide	673	674

Example 64:
4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide trifluoroacetic acid salt (T2)

Step 1: tert-butyl 4-[3-[[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-7-quinolyl]oxy]propyl]piperazine-1-carboxylate (T1)

T1 was prepared from 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol and tert-butyl 4-(3-chloropropyl)piperazine-1-carboxylate following the general procedure reported in Preparative Example 54 Step 1-2. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.38 (s, 9H), 1.96 (m, 2H), 2.23 (m, 4H), 2.47 (m, 2H), 3.30 (m, 4H), 3.92 (s, 3H), 4.17 (t, J = 6.3 Hz, 2H), 5.46 (br s, 2H), 6.37 (d, J = 5.2 Hz, 1H), 6.45 (dd, J = 8.9 Hz, J = 1.8 Hz, 1H), 6.54 (dd, J = 13.1Hz, J = 2.4 Hz, 1H), 7.05 (t, J = 8.9 Hz, 1H), 7.35 (s, 1H), 7.49 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H). MS (ES) $C_{29}H_{35}FN_4O_5$ requires: 526, found: 527 $(M+H)^+$.

Step 2: 4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide trifluoroacetic acid salt (T2)

Tert-butyl 4-[3-[[4-[4-[[4-(cyclopropylmethoxy)-1-(4-fluorophenyl)pyrazole-3-carbonyl]-amino]-2-fluoro-phenoxy]-6-methoxy-7-quinolyl]oxy]propyl]piperazine-1-carboxylate was prepared from **T1** and **F3** following the general procedure reported in Preparative Example 1 Step 3. The crude material was stirred in TFA/DCM (1/1) for 3h at RT. The reaction mixture was concentrated under reduced pressure and the residue was purified by reverse phase RP-HPLC (column: C18), using H_2O (0.1%TFA) and MeOH (0.1%TFA) as eluents. The desired fractions were lyophilized to yield the title compound **T2** as a white powder. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 0.35 (m, 2H), 0.58 (m, 2H), 1.30 (m, 1H), 1.94 (m, 2H), 2.32 (m, 2H), 2.41 (t, J = 7.2 Hz, 2H), 2.71 (m, 4H), 3.87 (d, J = 7.1Hz, 2H), 3.93 (s, 3H), 4.17 (t, J = 6.4 Hz, 2H), 6.45 (d, J = 5.3 Hz, 1H), 7.39 (m, 4H), 7.45 (t, J = 9.1 Hz, 1H), 7.52 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 8.00 (m, 4H), 8.45 (d, J = 5.3 Hz, 1H), 8.46 (s, 1H), 10.18 (s, 1H). MS (ES) $C_{37}H_{38}F_2N_6O_5$ requires: 684, found: 685 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 64.

Example	Name	Mwt	$[M+H]^+$
65	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	658	659

66	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide	644	645
67	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	672	673
68	1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide	692	693
69	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	672	673
70	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide	688	689
71	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(1-methylpyrrolidin-3-yl)methoxy]pyrazole-3-carboxamide	727	728
72	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide trifluoroacetic acid salt	613	614

Example 73:

N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide (U2)

Step 1: tert-butyl 4-[[4-(4-amino-2-fluoro-phenoxy)-6-methoxy-7-quinolyl]oxymethyl]piperidine-1-carboxylate (U1)

U1 was prepared from 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol and tert-butyl 4-(bromomethyl)piperidine-1-carboxylate following the general procedure reported in Preparative Example 54 Step 1-2. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 1.22 (m, 2H), 1.40 (s, 9H), 1.82 (d, J = 12.7 Hz, 2H), 2.10 (m, 1H), 2.69 (t, J = 12.3 Hz, 2H), 3.77 (m, 2H), 3.96 (s, 3H), 3.97 (m, 2H), 4.10 (m, 2H), 6.31 (d, J = 5.2 Hz, 1H), 6.46 (m, 2H), 6.96 (t, J = 8.7 Hz, 1H), 7.31 (s, 1H), 7.51 (s, 1H), 8.40 (d, J = 5.2 Hz, 1H). MS (ES) $C_{27}H_{32}FN_3O_5$ requires: 497, found: 498 $(M+H)^+$.

Step 2: N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide (U2)

Tert-butyl 4-[[4-[2-fluoro-4-[[1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carbonyl]amino]-phenoxy]-6-methoxy-7-quinolyl]oxymethyl]piperidine-1-carboxylate was prepared from **U1** and **E3** following the general procedure reported in Preparative Example 1 Step 3. The crude material was stirred in TFA/DCM (1/1) for 3h at RT. The reaction mixture was concentrated under reduced pressure and the residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and MeOH as eluents. The desired fractions were lyophilized to yield the title compound **U2** as a white powder. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.50 (q, J = 12.3 Hz, 2H),1.97 (d, J = 13.0 Hz, 2H), 2.18 (m, 1H), 2.95 (m, 2H), 3.33 (m, 2H), 3.85 (s, 3H), 3.95 (s, 3H), 4.07 (d, J = 6.2 Hz, 2H), 6.48 (d, J = 5.2 Hz, 1H), 7.41 (m, 4H), 7.54 (s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 8.00 (m, 3H), 8.47 (d, J = 5.2 Hz, 1H), 8.50 (s, 1H), 10.26 (s, 1H). MS (ES) $C_{33}H_{31}F_2N_5O_5$ requires: 615, found: 616 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 73.

Example	Name	Mwt	$[M+H]^+$
74	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	643	644
75	4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	655	656
76	4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	664	664/666
77	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(4-fluorophenyl)methoxy]pyrazole-3-carboxamide	709	710
78	1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide	561	562

79	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-4-nitro-1-[3-(1-piperidyl)propyl]pyrazole-3-carboxamide	661	662
80	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-2-phenyl-oxazole-4-carboxamide	582	583
81	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide trifluoroacetic acid salt	584	585

Example 82:

4-ethoxy-N-[4-[[7-[(1-ethyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide (V1)

Example 74 (39mg, 0.06mmol, 1.0eq.) and acetaldehyde (5mg, 0.12mmol, 2.0eq.) in dry MeOH (5mL) was stirred for 2 h at RT. After adding sodium cyanoborohydride (6mg, 0.09mmol, 1.5eq.) the mixture was stirred for 12 h. The mixture was diluted with EtOAc and the organic phase was washed twice with aq.$NaHO_3$-solution. The organic phase was dried and solvents were removed in vacuo. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and MeOH as eluents. The desired fractions were lyophilized to yield the title compound **V1** as a white powder. MS (ES) $C_{37}H_{39}F_2N_5O_5$ requires: 671, found: 672 $(M+H)^+$.

The Example in the following table was prepared according to the procedure described in the previous Example 82.

Example	Name	Mwt	$[M+H]^+$
83	4-ethoxy-N-[3-fluoro-4-[[7-[(1-isobutyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	699	700

Example 84:

N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide trifluoroacetic acid salt (W3)

Step 1: 6,7-dimethoxy-4-[(6-nitro-3-pyridyl)oxy]quinoline (W1)

A mixture of 6,7-dimethoxyquinolin-4-ol (2.02g, 9.8mmol, 1.0eq.), 5-fluoro-2-nitro-pyridine (1.96g, 13.78mmol, 1.4eq.) and cesium carbonate (4.8g, 14.7mmol, 1.5eq.) in dry DMF (10mL) was heated for 1h at 80°C in a microwave oven. After cooling to RT the mixture was diluted with water and extracted with DCM. The combined organic phase was dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM/MeOH = 100:0 to 10:1) to yield the desired product **W1** (1.28g, 40%) as a yellow solid. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 3.88 (s, 3H), 3.94 (s, 3H), 6.92 (d, J = 5.2 Hz, 1H), 7.41 (s, 1H), 7.45 (s, 1H), 7.98 (dd, J = 2.7 Hz, J = 9.0 Hz, 1H), 8.40 (d, J = 9.0 Hz, 1H), 8.60 (d, J = 5.2 Hz, 1H), 8.66 (d, J = 2.7 Hz, 1H). MS (ES) $C_{16}H_{13}N_3O_5$ requires: 327, found: 328 $(M+H)^+$.

Step 2: 5-[(6,7-dimethoxy-4-quinolyl)oxy]pyridin-2-amine (W2)

W1 (1.28g, 3.91mmol) in EtOH (40mL) was reduced in an H-Cube® hydrogenation reactor (Pd/C cartridge, H_2=100bar, T = 60°C, flow = 0.7mL/min). After evaporation of the solvent the crude material was purified by flash chromatography on silica gel (DCM/MeOH = 100:0 to 5:1) to yield the desired product **W2** (0.48g, 41%) as a white solid. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 3.92 (s, 6H), 6.03 (br s, 2H), 6.40 (d, J = 5.2 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 7.35 (m, 2H), 7.49 (s, 1H), 7.88 (d, J = 2.9 Hz, 1H), 8.43 (d, J = 5.2 Hz, 1H). MS (ES) $C_{16}H_{15}N_3O_3$ requires: 297, found: 298 $(M+H)^+$.

Step 3: N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide trifluoroacetic acid salt (W3)

W3 was prepared from **W2** and **D4** following the general procedure reported in Preparative Example 1 Step 3. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.42 (t, J = 7.0 Hz, 3H), 4.02 (s, 3H), 4.03 (s, 3H), 4.18 (q, J = 7.0 Hz, 2H), 7.03 (d, J = 6.5 Hz, 1H), 7.40 (t, J = 8.9 Hz, 1H), 7.58 (s, 1H), 7.76 (s, 1H), 7.98 (m, 3H), 8.43 (d, J = 8.9 Hz, 1H), 8.52 (d, J = 3.0 Hz, 1H), 8.56 (s, 1H), 8.82 (d, J = 6.6 Hz, 1H), 9.97 (s, 1H). MS (ES) $C_{28}H_{24}FN_5O_5$ requires: 529, found: 530 $(M+H)^+$.

The Examples in the following table were prepared according to the procedure described in the previous Example 84.

Example	Name	Mwt	$[M+H]^+$
85	N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	543	544
86	1-(2-chloro-4-fluoro-phenyl)-N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-pyrazole-3-carboxamide	563	564
87	N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-(2-dimethylaminoethyl)-1-(4-fluorophenyl)pyrazole-3-carboxamide	556	557

Example 88: Tert-butyl 4-(((4-((6-(4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamido)pyridin-3-yl)oxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate (X1)

X1 was prepared from tert-butyl 4-(((4-((6-aminopyridin-3-yl)oxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate and **J4** following the general procedure reported in Preparative Example 16 Step 5. ^{1}H NMR (400MHz, d_4-MeOH, 300K) δ 1.32 (m, 2H), 1.46 (s, 9H), 1.53 (t, J = 7.0 Hz, 3H), 1.90 (m, 2H), 2.12 (m, 1H), 2.27 (s, 3H), 2.84 (m, 2H), 4.00 (s, 3H), 4.03 (m, 2H), 4.14 (m, 2H), 4.22 (q, J = 7.00 Hz, 3H), 6.59 (d, J = 5.4 Hz, 1H), 7.08 (dt, J = 2.5 Hz, J = 8.2 Hz, 1H), 7.15 (dd, J = 2.5 Hz, J = 9.3 Hz, 1H), 7.32 (s, 1H), 7.42 (m, 1H), 7.63 (s, 1H), 7.76 (m, 1H), 7.84 (s, 1H), 8.31 (m, 1H), 8.45 (m, 2H). MS (ES) $C_{39}H_{43}FN_6O_7$ requires: 726, found: 727 $(M+H)^+$.

Example 89: N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamide (X2)

Following the general procedure reported in Preparative Example 16 Step 5 **X2** was prepared from **W2** and 4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.41(t, J = 7.0 Hz, 3H), 2.21 (s, 3H), 3.81 (s, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 6.54 (d, J = 5.2 Hz, 1H), 6.91 (dd, J = 8.7 Hz, J = 2.8 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 7.41 (s, 1H), 7.53 (s, 1H), 7.85 (dd, J = 2.9 Hz, J = 9.0 Hz, 1H), 8.04 (s, 1H), 8.35 (d, J = 9.0 Hz, 1H), 8.39 (d, J = 2.9 Hz, 1H), 8.49 (d, J = 5.2 Hz, 1H), 9.68 (s, 1H). MS (ES) $C_{30}H_{29}N_5O_6$ requires: 555, found: 556 $(M+H)^+$.

Example 90: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide (X3)

Following the general procedure reported in Preparative Example 16 Step 5 **X3** was prepared from **A2** and 4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. MS (ES) $C_{29}H_{24}N_5O_7$ requires: 573, found: 574 $(M+H)^+$.

Example 91: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamid (X4)

Following the general procedure reported in Preparative Example 16 Step 5 **X4** was prepared from **A2** and 4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.36 (t, J = 7.0 Hz, 3H), 2.20 (s, 3H), 3.80 (s, 3H), 3.94 (s, 6H), 4.05 (q, J = 7.0 Hz, 2H), 6.46 (d, J = 5.2 Hz, 1H), 6.90 (dd, J = 2.9 Hz, J = 8.8 Hz, 1H), 6.98 (d, J = 2.7 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.40 (s, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.53 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.95 (s, 1H), 8.03 (dd, J = 2.4 Hz, J = 13.3 Hz, 1H), 8.47 (d, J = 5.2 Hz, 1H), 10.10 (s, 1H). MS (ES) $C_{31}H_{29}FN_4O_6$ requires: 572, found: 573 $(M+H)^+$.

Example 92: N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide (X5)

Following the general procedure reported in Preparative Example 16 Step 5 **X5** was prepared from **W2** and 4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. MS (ES) $C_{28}H_{24}N_6O_7$ requires: 556, found: 557 $(M+H)^+$.

Example 93: 1-(2-(benzyloxy)-4-fluorophenyl)-N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1H-pyrazole-3-carboxamide (X6)

Following the general procedure reported in Preparative Example 16 Step 5 **X6** was prepared from **W2** and 1-(2-(benzyloxy)-4-fluorophenyl)-4-ethoxy-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 1.45 (t, J = 7.0 Hz, 3H), 4.01 (s, 3H), 4.07 (s, 3H), 5.14 (s, 2H), 6.48 (d, J = 5.3 Hz, 1H), 6.83 (m, 1H), 7.26 (m, 1H), 7.40 (m, 5H), 7.46 (s, 1H), 7.56 (s, 1H), 7.60 (dd, J = 2.9 Hz, J = 9.0 Hz, 1H), 7.76 (s, 1H), 7.85 (m, 1H), 8.26 (d, J = 2.9 Hz, 1H), 8.52 (d, J = 5.3 Hz, 1H), 8.59 (d, J = 9.0 Hz, 1H), 9.53 (s, 1H). MS (ES) $C_{35}H_{30}FN_5O_6$ requires: 635, found: 636 $(M+H)^+$.

Example 94: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide (X7)

Following the general procedure reported in Preparative Example 16 Step 5 **X7** was prepared from **J4** and 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyaniline, which was prepared similar to Preparative Example 1 step 1-2. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 1.58 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 3.91 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 6.52 (d, J = 5.3 Hz, 1H), 6.77 (d, J = 2.5 Hz, 1H), 6.85 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 7.00 (m, 2H), 7.32 (s, 1H), 7.34 (dd, J = 5.3 Hz, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.58 (s, 1H), 8.50 (d, J = 5.3 Hz, 1H), 8.76 (d, J = 8.8 Hz, 1H), 9.50 (s, 1H). MS (ES) $C_{31}H_{29}FN_4O_6$ requires: 572, found: 573 $(M+H)^+$.

Example 95: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methylphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide (X8)

Following the general procedure reported in Preparative Example 16 Step 5 **X8** was prepared from **J4** and 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methylaniline, which was prepared similar to Preparative Example 1 step 1-2. ^{1}H NMR (400MHz, $CDCl_3$, 300K) δ 1.56 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 2.39 (s, 3H), 4.05 (s, 6H), 4.18 (q, J = 7.0 Hz, 2H), 6.51 (d, J = 5.3 Hz, 1H), 7.02 (m, 3H), 7.09 (dd, J = 2.7 Hz, J = 8.8 Hz, 1H), 7.35 (m, 2H), 7.44 (s, 1H), 7.57 (s, 1H), 8.41 (d, J = 8.8 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.78 (s, 1H). MS (ES) $C_{31}H_{29}FN_4O_5$ requires: 556, found: 557 $(M+H)^+$.

Example 96: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide (X9)

Following the general procedure reported in Preparative Example 16 Step 5 **X9** was prepared from **A2** and 4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.39 (t, J = 7.0 Hz, 3H), 3.94 (s, 6H), 3.96 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 6.48 (d, J = 5.2 Hz, 1H), 7.40 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.52 (m, 2H), 7.70 (m, 2H), 8.03 (dd, J = 2.4 Hz, J = 13.2 Hz, 1H), 8.48 (d, J = 5.2 Hz, 1H), 8.52 (s, 1H), 10.19 (s, 1H). MS (ES) $C_{30}H_{26}F_2N_4O_6$ requires: 576, found: 577 $(M+H)^+$.

Example 97: N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide (X10)

Following the general procedure reported in Preparative Example 16 Step 5 **X10** was prepared from **W2** and 4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carbonyl

chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.43 (t, J = 7.0 Hz, 3H), 3.97 (s, 3H), 4.02 (s, 6H), 4.19 (q, J = 7.0 Hz, 2H), 6.99 (d, J = 6.5 Hz, 1H), 7.39 (dd, J = 8.9 Hz, J = 10.9 Hz, 1H), 7.49 (m, 1H), 7.68 (dd, J = 2.5 Hz, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.75 (s, 1H), 8.01 (dd, J = 2.9 Hz, J = 9.0 Hz, 1H), 8.42 (d, J = 9.0 Hz, 1H), 8.52 (d, J = 2.9 Hz, 1H), 8.60 (s, 1H), 8.80 (d, J = 6.5 Hz, 1H), 9.97 (s, 1H). MS (ES) $C_{29}H_{26}FN_5O_6$ requires: 559, found: 560 $(M+H)^+$.

<u>Example 98:</u> N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-nitrophenyl)-1H-pyrazole-3-carboxamide (X11)

Following the general procedure reported in Preparative Example 16 Step 5 **X11** was prepared from **W2** and 4-ethoxy-1-(4-nitrophenyl)-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.43 (t, J = 7.0 Hz, 3H), 3.93 (s, 3H), 3.94 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 6.56 (d, J = 5.2 Hz, 1H), 7.40 (s, 1H), 7.53 (s, 1H), 7.87 (dd, J = 2.9 Hz, J = 9.1 Hz, 1H), 8.22 (d, J = 9.1 Hz, 2H), 8.34 (d, J = 9.1 Hz, 1H), 8.41 (m, 3H), 8.48 (d, J = 5.3 Hz, 1H), 8.75 (s, 1H), 10.04 (s, 1H). MS (ES) $C_{28}H_{24}N_6O_7$ requires: 556, found: 557 $(M+H)^+$.

<u>Example 99:</u> 1-(4-aminophenyl)-N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1H-pyrazole-3-carboxamide (X12)

A suspension of **X11** (357mg, 0.64mmol) and Pd/C (10%w/w, 35mg) in a mixture of aq. HCl-solution (6N, 1.5mL) ,DCM (20mL) and MeOH (40mL) was stirred under hydrogen atmosphere (1atm) at RT for 2 h. The mixture was diluted with DCM (100mL) and aq. $NaHCO_3$-solution (50mL). The org. phase was separated and the aq. phase was extracted twice with DCM (50mL). The combined org. phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was solved in MeCN (20mL) and H_2O (5mL) and lyophilized yielding **X12** (322mg, 95%) as a beige solid. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.42 (t, J = 7.0 Hz, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.17 (q, J = 7.0 Hz, 2H), 5.35 (s, 2H), 6.55 (d, J = 5.2 Hz, 1H), 6.66 (d, J = 8.8 Hz, 2H), 7.41 (s, 1H), 7.54 (m, 3H), 7.86 (dd, J = 2.9 Hz, J = 8.9 Hz, 1H), 8.30 (s, 1H), 8.37 (m, 2H), 8.49 (d, J = 5.3 Hz, 1H), 9.71 (s, 1H). MS (ES) $C_{28}H_{26}N_6O_5$ requires: 526, found: 527 $(M+H)^+$.

<u>Example 100:</u> N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-(2-methoxyphenyl)thiazole-2-carboxamide (X13)

Following the general procedure reported in Preparative Example 16 Step 5 **X13** was prepared from tert-butyl 4-(((4-((6-aminopyridin-3-yl)oxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate and 4-(2-methoxyphenyl)thiazole-2-carbonyl chloride, which was prepared similar to Preparative Example 16 step 4 from commercially available 4-(2-methoxyphenyl)thiazole-2-carboxylic acid. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.40 (m, 2H), 1.87 (d, J = 12.6 Hz, 2H), 2.07 (m, 1H), 2.76 (t, J = 11.8 Hz, 2H), 3.18 (d, J = 12.6 Hz, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 4.02 (d, J = 6.4 Hz, 2H), 6.57 (d, J = 5.2 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.39 (m, 2H), 7.53 (s, 1H), 7.90 (dd, J = 2.8 Hz, J = 9.0 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.49 (m, 4H). MS (ES) $C_{32}H_{31}N_5O_5S$ requires: 597, found: 598 $(M+H)^+$.

Example 101: N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-phenylthiazole-2-carboxamide (X14)

A mixture of tert-butyl 4-(((4-((6-aminopyridin-3-yl)oxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate (70mg, 0.14mmol), 4-phenylthiazole-2-carboxylic acid (46mg, 0.21mmol), DIPEA (56mg, 0.43mmol) and HATU (110mg, 0.29mmol) in dry DMF (5mL) was stirred for 72h at 55^{0}C. The solution was diluted with EtOAc (150mL) and washed twice with aq.$NaHCO_3$-solution and once with brine. The residue was dissolved in 50%TFA in DCM (5mL) and stirred for 2h at RT. The mixture was concentrated under reduced pressure. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and ACN as eluents. The desired fractions were lyophilized to yield the title compound **X14** (25mg, 30%) as a white powder. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.25 (m, 2H), 1.76 (d, J = 12.0 Hz, 2H), 1.95 (m, 1H), 2.55 (t, J = 11.0 Hz, 2H), 3.00 (d, J = 12.0 Hz, 2H), 3.94 (s, 3H), 3.99 (d, J = 6.3 Hz, 2H), 6.58 (d, J = 5.2 Hz, 1H), 7.41 (m, 2H), 7.51 (m, 3H), 7.90 (dd, J = 2.9 Hz, J = 9.0 Hz, 1H), 8.17 (d, J = 7.4 Hz, 2H), 8.29 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 2.9 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 8.55 (s, 1H). MS (ES) $C_3H_{29}N_5O_4S$ requires: 567, found: 568 $(M+H)^+$.

Example 102: 4-bromo-N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)thiazole-2-carboxamide (X15)

Following the general procedure reported in Preparative Example 16 Step 5 **X15** was prepared from tert-butyl 4-(((4-((6-aminopyridin-3-yl)oxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate and 4-bromothiazole-2-carbonyl chloride, which was prepared similar to Preparative Example 16 step 4 from commercially available 4-bromothiazole-2-carboxylic acid. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.53 (m, 2H),

1.98 (d, J = 12.5 Hz, 2H), 2.18 (m, 1H), 2.95 (m, 2H), 3.33 (m, 2H), 3.94 (s, 3H), 4.08 (d, J = 6.3 Hz, 2H), 6.58 (d, J = 5.2 Hz, 1H), 7.45 (s, 1H), 7.54 (m, 1H), 7.87 (dd, J = 2.9 Hz, J = 9.0 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.31 (s, 1H), 8.45 (d, J = 2.9 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H), 10.61 (br s, 1H). MS (ES) $C_{25}H_{24}BrN_5O_4S$ requires: 570, found: 570/572 $(M+H)^+$.

Example 103: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide (X16)

Following the general procedure reported in Preparative Example 16 Step 5 **X16** was prepared from **J4** and 4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyaniline, which was prepared similar to Preparative Example 1 step 1-2.. ^1H NMR (400MHz, d_6-DMSO, 300K) δ 1.58 (t, J = 7.0 Hz, 3H), 2.27 (s, 3H), 3.91 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 6.53 (d, J = 5.3 Hz, 1H), 6.77 (d, J = 2.5 Hz, 1H), 6.85 (dd, J = 2.5 Hz, J = 8.8 Hz, 1H), 7.00 (m, 2H), 7.32 (s, 1H), 7.35 (dd, J = 8.6 Hz, J = 5.3 Hz, 1H), 7.44 (s, 1H), 7.58 (s, 1H), 8.50 (d, J = 5.3 Hz, 1H), 8.76 (d, J = 8.8 Hz, 1H), 9.50 (s, 1H). MS (ES) $C_{31}H_{29}FN_4O_6$ requires: 572, found: 573 $(M+H)^+$.

Example 104: N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-2-hydroxyphenyl)-1H-pyrazole-3-carboxamide (X18)

A suspension of **X6** (60mg, 0.09mmol) and Pd/C (10%w/w, 6mg) in EtOH (50mL) was stirred under hydrogen atmosphere (1atm) at RT for 15 h. The suspension was filtered through a pad of Celite®. The solvent was removed in vacuo. The residue was purified by reverse phase RP-HPLC (column: C18), using H_2O and ACN as eluents. The desired fractions were lyophilized to yield the title compound **X18** (1.2mg, 2%) as a white solid. ^1H NMR (400MHz, $CDCl_3$, 300K) δ 1.61 (t, J = 7.0 Hz, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 4.26 (q, J = 7.0 Hz, 2H), 6.48 (d, J = 5.2 Hz, 1H), 6.68 (dt, J = 2.6 Hz, J = 8.4 Hz, 1H), 6.87 (dd, J = 2.3 Hz, J = 9.8 Hz, 1H), 7.31 (dd, J = 5.7 Hz, J = 9.0 Hz, 1H), 7.44 (s, 1H), 7.56 (s, 1H), 7.61 (dd, J = 2.8 Hz, J = 9.0 Hz, 1H), 7.68 (s, 1H), 8.28 (d, J = 2.8 Hz, 1H), 8.53 (m, 2H), 9.49 (s, 1H). MS (ES) $C_{28}H_{24}FN_5O_5$ requires: 545, found: 546 $(M+H)^+$.

Example 105: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide (X19)

Following the general procedure reported in Preparative Example 16 Step 5 **X19** was prepared from **A2** and 4-ethoxy-1-(pyridin-3-yl)-1H-pyrazole-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.39 (t, J = 7.0 Hz, 3H), 3.96 (s, 6H), 4.10 (q, J = 7.0 Hz, 2H), 6.56 (d, J = 5.5 Hz, 1H), 7.43 (s, 1H), 7.49 (t, J = 9.0 Hz, 1H), 7.57 (s, 1H), 7.60 (dd, J = 4.7 Hz, J = 8.4 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 8.04 (dd, J = 2.4 Hz, J = 13.2 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.54 (d, J = 5.5 Hz, 1H), 8.57 (dd, J = 1.4 Hz, J = 4.7 Hz, 1H), 8.59 (s, 1H), 9.24 (s, 1H), 10.25 (s, 1H). MS (ES) $C_{28}H_{24}FN_5O_5$ requires: 529, found: 530 $(M+H)^+$.

Example 106: N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1'-methyl-1'H-[1,3'-bipyrazole]-3-carboxamide (X20)

Following the general procedure reported in Preparative Example 16 Step 5 **X20** was prepared from **A2** and 4-ethoxy-1'-methyl-1'H-[1,3'-bipyrazole]-3-carbonyl chloride, which was prepared similar to Preparative Example 16 step 1-4. ^{1}H NMR (400MHz, d_6-DMSO, 300K) δ 1.36 (t, J = 7.0 Hz, 3H), 3.85 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 4.06 (q, J = 7.0 Hz, 2H), 6.57 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 6.2 Hz, 1H), 7.52 (s, 1H), 7.56 (m, 2H), 7.71 (s, 1H), 7.76 (d, J = 8.9 Hz, 1H), 8.08 (dd, J = 2.1 Hz, J = 13.1 Hz, 1H), 8.17 (s, 1H), 8.75 (d, J = 6.2 Hz, 1H), 10.34 (s, 1H). MS (ES) $C_{27}H_{25}FN_6O_5$ requires: 532, found: 533 $(M+H)^+$.

Biological Assays

The exemplified compounds described herein were tested for activity and were found to have an IC_{50} value less than 10uM, particularly less than 500nM, in one of the following assays:

1. Enzymatic Axl assay:

The IMAP FP Sreening Express Kit (Molecular Devices) was employed for the detection of Axl activity *in vitro*. In brief, a mix of FITC-labeled substrate peptide (400nM final concentration; 5FITC-KKKKEEIYFFFG-NH_2, Seq ID No. 01) and recombinant Axl kinase (30nM final concentration; Proqinase) was preincubated with a compound according to formula (I) at the suitable concentrations. Reaction was started

by addition of ATP (Adenosine-5'-triphosphate, Sigma Aldrich) to a final concentration of 22µM. Except proteins and substrates the reaction buffer conditions were 20 mM HEPES (2-(4-(2-Hydroxyethyl)-1-piperazine)-ethanesulfonic acid) pH 8.0, 1 mM DTT (Dithiothreitol), 10 mM $MgCl_2$ and 0.01 % Brij35 (all Sigma Aldrich). After incubation of 1 hour the reaction was stopped by addition of IMAP binding buffer, containing the large M(III)-based nanoparticles, who bind to the phosphorylated fluorescent substrat. This reduces the rotational speed of the bound substrate increasing its polarization signal. Finally, the fluorescence polarization was determined using an EnVision Multilabelreader 2104 (Perkin Elmer).

2. Axl binding assay:

The principle behind this assay is based upon the binding and displacement of an Alexa Fluor 647-labeled tracer to the kinase of interest. Binding of the tracer to the kinase is detected using an EU-labeled anti-tag antibody. Simultaneous binding of both the tracer and antibody to the kinase gives rise to a FRET-signal. Binding of an inhibitor to the kinase competes for binding with the tracer, resulting in a loss of FRET-signal. At first a compound according to formula (I) was diluted in 20 mM Hepes pH 8.0, 1 mM DTT, 10 mM $MgCl_2$ and 0.01 % Brij35. Next Axl kinase (5nM final concentration; Proqinase), kinase tracer (15nM final concentration; Invitrogen) and LanthaScreen Eu-Anti-GST antibody (2nM final concentration; Invitrogen) was mixed with suitable compound dilutions and incubated for 1 hour. FRET-signal was quantified employing an EnVision Multilabelreader 2104 (Perkin Elmer).

3. Cellular Axl phosphorylation assay:

HEK293 embryonal kidney fibroblasts were transfected in 96wells with a plasmid containing Axl cDNA. As transfection reagent Superfect (Qiagen) was used. Transfection of the sole vector backbone served as negative control of Axl expression. After overnight incubation the cellular supernatant was replaced with fresh medium. On the following day the Axl-expressing cells were incubated for 1 hour with a compound according to formula (I) at the suitable concentrations. Cells were lysed with buffer and lysates were investigated for Axl expression and phosphorylation employing antibodies H-124 (Santa Cruz) and AF2228 (R&D), respectively. The mesoscale technology was used for quantification.

Table 2 shows activity data in the Axl binding assay and cellular Axl phosphorylation assay for selected compounds of the invention. Inhibition is indicated as IC_{50} with the following key: A = IC_{50} less than 0.5uM; B = IC_{50} greater than 0.5uM, but less than 5.0uM; C = IC_{50} greater than 5.0uM; – = not measured

Table 2

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
1	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1,5-dimethyl-pyrazole-3-carboxamide	B	B
2	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-[4-(trifluoromethyl)phenyl]thiazole-4-carboxamide	B	-
3	4-bromo-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide	B	B
4	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide	B	B
5	1-tert-butyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-5-methyl-pyrazole-3-carboxamide	A	A
6	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]thiazole-2-carboxamide	B	-
8	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-indazole-3-carboxamide	B	-
9	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-5-methyl-isoxazole-3-carboxamide	B	-
10	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-phenyl-thiazole-4-carboxamide	B	B
13	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-propyl-pyrazole-3-carboxamide	B	A
15	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(2,2,2-trifluoroethoxymethyl)pyrazole-3-carboxamide	B	A
16	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
17	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide	A	A
18	4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
19	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-	A	A

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
	fluorophenyl)pyrazole-3-carboxamide		
20	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide	B	B
21	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	A	A
22	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
23	1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide	A	A
24	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
25	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	A	A
26	4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
27	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
28	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
29	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	A	A
30	4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
31	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
32	N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
33	N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	A	A
34	N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-(cyclopropylmethoxy)-1-	A	A

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
	(4-fluorophenyl)pyrazole-3-carboxamide		
35	N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
36	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-(2-(dimethylamino)ethyl)-1-(4-fluorophenyl)-1H-pyrazole-3-carboxamide	A	A
37	N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[2-(2-dimethylaminoethyl)-4-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide	A	A
38	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide	A	A
39	4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide	B	A
40	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide	B	A
41	1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide	A	A
42	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1,5-dimethyl-pyrazole-3-carboxamide	A	A
43	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
44	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide	A	A
45	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	A	A
46	4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
47	1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide	A	A

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
48	4-(2-dimethylaminoethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
49	1-(2-bromo-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide	A	A
50	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide	A	A
51	4-benzyloxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
52	N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-nitro-pyrazole-3-carboxamide	A	A
53	4-amino-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
54	N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
55	N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
56	N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-5-ethoxy-2-(4-fluorophenyl)oxazole-4-carboxamide	A	A
57	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
58	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
59	N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide	A	A
60	1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-	A	A

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
	yl)propoxy]-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide		
61	4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
62	N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	A	A
63	5-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-2-(4-fluorophenyl)oxazole-4-carboxamide	A	A
64	4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide trifluoroacetic acid salt	A	A
65	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
66	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide	A	A
67	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide	A	A
68	1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide	A	A
69	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
70	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide	A	A
71	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(1-methylpyrrolidin-3-	A	B

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
	yl)methoxy]pyrazole-3-carboxamide		
72	N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide	A	A
73	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide	A	A
74	4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
75	4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
76	4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
77	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(4-fluorophenyl)methoxy]pyrazole-3-carboxamide	A	A
78	1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide	A	A
80	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-2-phenyl-oxazole-4-carboxamide	A	A
81	N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide	A	B
82	4-ethoxy-N-[4-[[7-[(1-ethyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
83	4-ethoxy-N-[3-fluoro-4-[[7-[(1-isobutyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide	A	A
84	N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide	A	A
85	N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-	A	A

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
	3-carboxamide		
86	1-(2-chloro-4-fluoro-phenyl)-N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-pyrazole-3-carboxamide	A	A
87	N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-(2-dimethylaminoethyl)-1-(4-fluorophenyl)pyrazole-3-carboxamide	B	A
89	N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamide	A	A
90	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide	A	A
91	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamide	A	A
92	N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide	A	A
94	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide	A	A
95	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methylphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide	A	B
96	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide	A	A
97	N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide	A	A
98	N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-nitrophenyl)-1H-pyrazole-3-carboxamide	B	A
99	1-(4-aminophenyl)-N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1H-pyrazole-3-carboxamide	A	A
100	N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-(2-methoxyphenyl)thiazole-2-carboxamide	B	-
101	N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-phenylthiazole-2-carboxamide	A	A
102	4-bromo-N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-	A	A

Example	Nomenclature	Axl binding assay	Cellular Axl phosphorylation assay
	yl)thiazole-2-carboxamide		
103	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide	A	A
104	N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-2-hydroxyphenyl)-1H-pyrazole-3-carboxamide	A	A
105	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide	A	A
106	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1'-methyl-1'H-[1,3'-bipyrazole]-3-carboxamide	A	-
Ref1	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-1-phenyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide	>10µM	-
Ref2	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-5-phenylisoxazole-3-carboxamide	>10µM	-
Ref3	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)furan-2-carboxamide	>10µM	-
Ref4	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)thiophene-3-carboxamide	7042nM	-
Ref5	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)isonicotinamide	>10µM	-
Ref6	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)thiophene-2-carboxamide	8293nM	-
Ref7	N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)picolinamide	9302nM	-

Source for Reference Examples Ref1 to Ref7:

Ref1: Example 20 on page 106/107 of WO2008035209A2 (D01 in the ESR)

Ref2: Example 21 on page 106/107 of WO2008035209A2

Ref3: Compound 64, Example 53 on page 47 of EP0860433A1 (D02 in the ESR)

Ref4: Compound 65, Example 54 on page 47 of EP0860433A1

Ref5: Compound 71, Example 60 on page 49 of EP0860433A1

Ref6: Compound 72, Example 61 on page 49 of EP0860433A1

Ref7: Compound 77, Example 61 on page 50 of EP0860433A1

It is obvious from Table 2 that all Reference Examples (Ref1 – Ref7) exhibit worse Axl binding assay data which are in the range of 10 µM and higher. In contrast to the seven Reference Examples the compounds of the present invention are in average ten to hundred times more effective in the Axl binding assay.

It seems that the substitution pattern and the position of the hetero atoms and especially the position of the nitrogen atom in the substituent D is important for the better activity of the inventive compounds. Comparing compound 21 of WO2008035209A2 with example 9 of the present invention, both compounds are markedly similar. However compound 21 of WO2008035209A2 shows in the Axl binding assay a worse value of larger than 10 µM while example 9 shows 3.389 µM.

It can be concluded that the position of the heteroatoms and the phenyl substitution in the isoxazole ring (ring D) is not suitable in comparison to example 9 of the present invention. Thus it seems to be important that a nitrogen atom is present in substituent D in direct vicinity to the carbon atom which is attached to the amide group. Thus the isoxazole residue as substituent D should be linked through the 3-yl-carbon atom to the amide group and not through the 4-yl-carbon atom or the 5-yl-carbon atom as done in compound 21 of WO2008035209A2. From Example 80 (Axl binding assay 0.184uM) of the present invention it can be followed that the oxazole group as substituent D should be linked to the amide group through 2-yl-carbon atom or the 4-yl-carbon atom but not through the 5-yl-carbon atom.

The same conclusion can be drawn from the comparison of compound 20 of WO2008035209A2 with example 17 of the present invention which are again very similar and differ only in the substitution pattern of substituent D. Example 17 wherein the pyrazole residue is linked to the amide group through the 3-yl-carbon atom shows in the Axl binding assay a value of 0.172 µM, while compound 20 of WO2008035209A2, wherein the pyrazole residue is linked to the amide group through the 4-yl-carbon atom shows with >10µM a much more worse binding / inhibition in the Axl binding assay.

Thus it can be concluded that the compounds disclosed in WO2008035209A2 which are very similar to the compounds of the present invention exhibit the wrong substitution pattern especially in regard to substituent D and thus have lower activity and potency as anti-cancer drug for Axl receptor tyrosine kinase induced disorders as proved by the Axl binding assay.

In regard to the compounds 64, 65, 71, 72 and 77 as disclosed in EP0860433A1 which was cited as D02 in the European Search Report it can be stated that all these compounds are not potent in the Axl binding assay, since they exhibit values of about 10 µM and higher which is in average 10 to 100 times less potent than the compounds of the present invention. Since these compounds 64, 65, 71, 72 and 77 as disclosed in EP0860433A1 differ in comparision to the inventive compounds mainly in the substituent D it can be concluded that furane, thiophene and pyridine substituents as ring D are not suitable substituents in order to obtain highly potent inhibitors of the Axl receptor tyrosine kinase. Thus it seems important that substituent D is a five-membered heterocyclic ring and not a six-membered heterocyclic ring and that it is moreover important that the substituent D contains at least one nitrogen and still more preferably two nitrogen atoms.

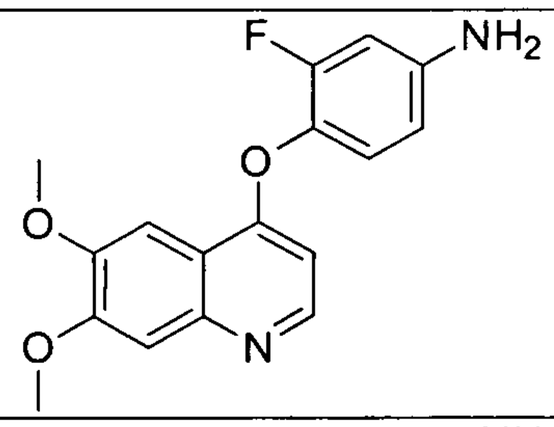
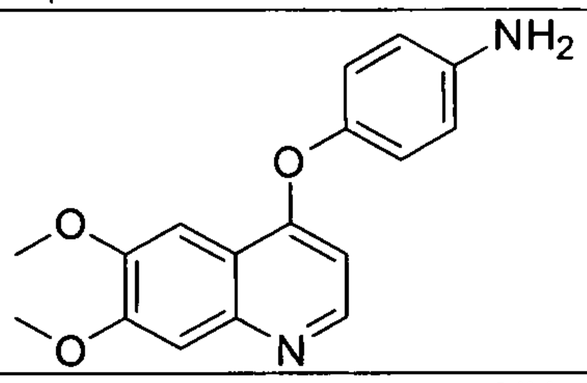
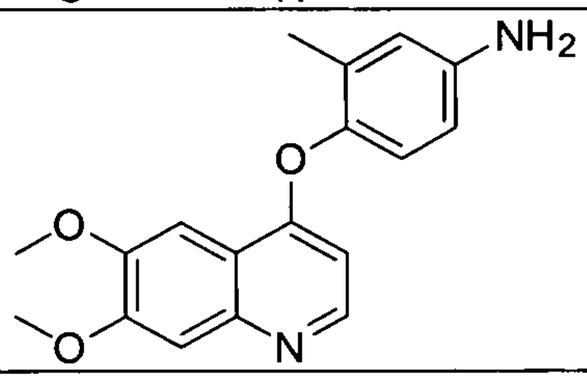
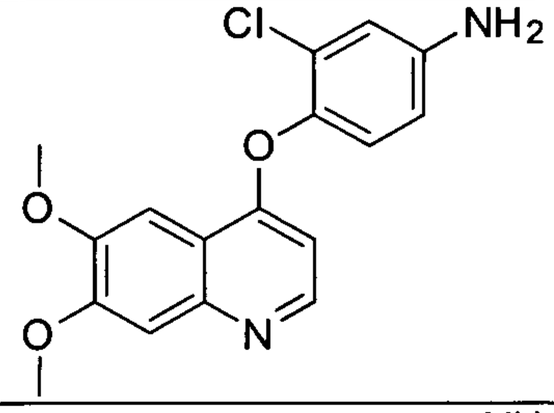
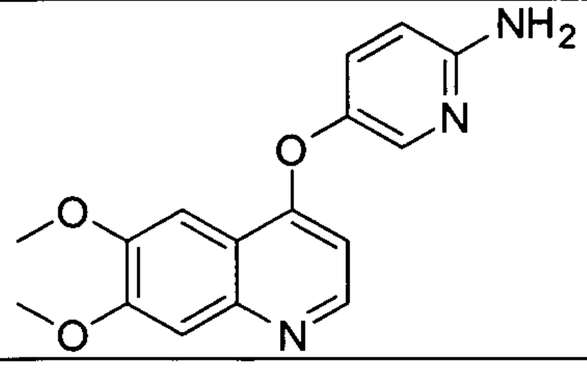
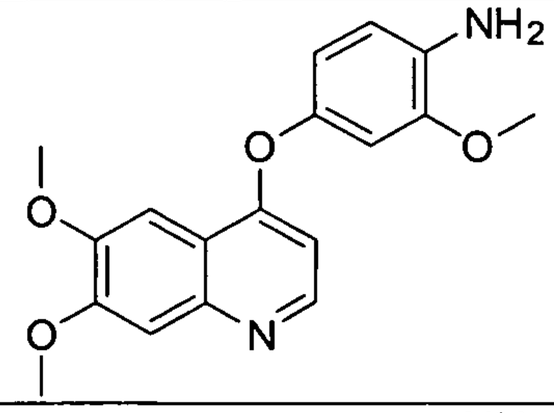
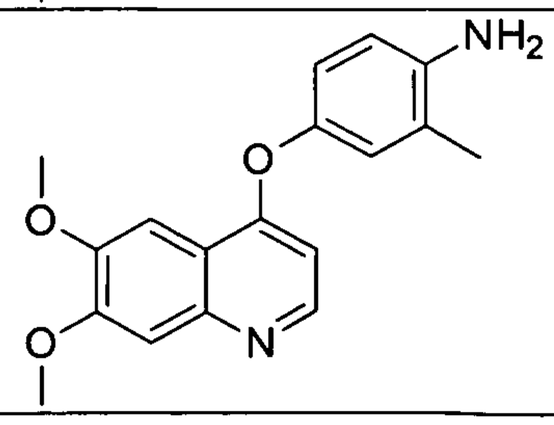
However, in regard to the most similar compounds 64, 65, 71, 72 and 77 disclosed in EP0860433A1 it can be stated that they do not have the right substitution pattern especially at substituent D and that the compounds of the present invention are much more potent as demonstrated by the data of the Axl binding assay.

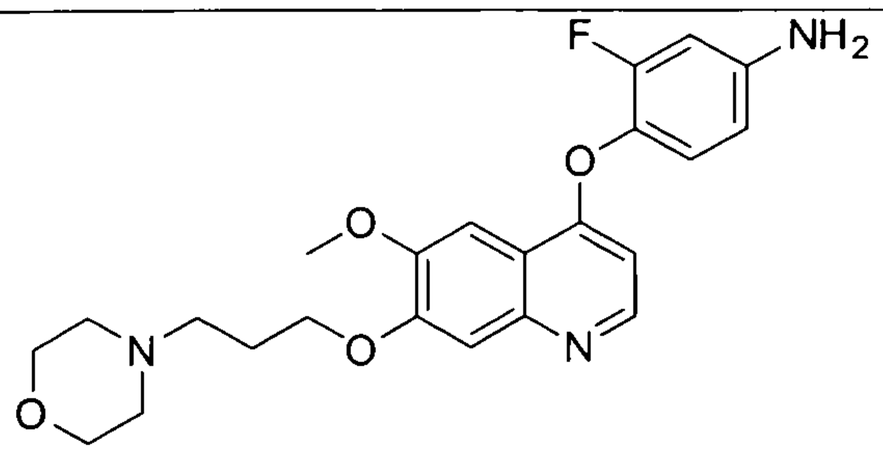
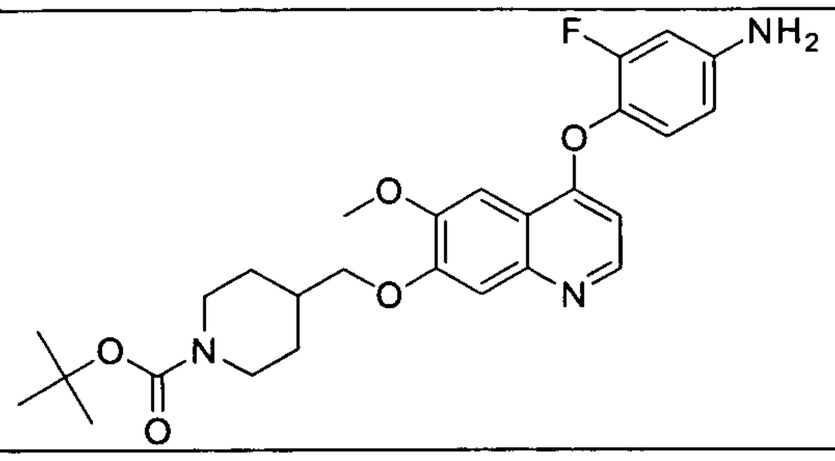
Thus the compounds of the present invention are superior in regard to the compounds of EP0860433A1 as well as of WO2008035209A2.

WO2007146824A2 was cited as D03 in the European Search Report (ESR). D03 does not cite any novelty destroying compounds for the present invention and does even not cite any similar compound. In WO2007146824A2 not a single compound is disclosed which has a 5-membered nitrogen heterocycle as substituent D so that the compounds of WO2007146824A2 are regarded as less relevant. Even compounds such as compounds 134, 172, 175, 176, 177, 178, 195 or 196 are only insignificantly similar to the compounds of the present invention.

Furthermore we have observed that the quinolines without such carboxy-substituted residue D of the present invention shows very weak to no activity in the Axl binding assay (Table 3). Through the introduction of a carboxy-substituted residue D described in this invention very potent inhibitors of the Axl kinase were invented. This further stresses the importance of the carboxy-substituted residue D of the present invention for obtaining potent inhibitors of the Axl kinase.

Table 3

Nomenclature	Structure	Axl binding assay
4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline		> 10000nM
4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline		> 10000nM
4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-methylaniline		> 10000nM
3-chloro-4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline		> 10000nM
5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-amine		> 10000nM
4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyaniline		> 10000nM
4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methylaniline		> 10000nM

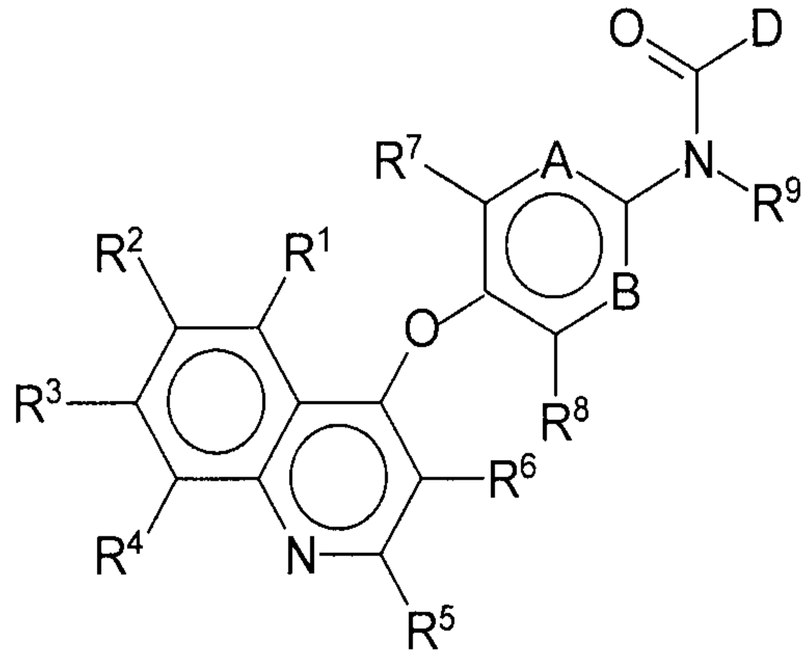
Nomenclature	Structure	Axl binding assay
3-fluoro-4-((6-methoxy-7-(3-morpholinopropoxy)quinolin-4-yl)oxy)aniline		8503nM
tert-butyl 4-(((4-(4-amino-2-fluorophenoxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate		> 10000nM

Example 22 of the present invention was tested in an oncology in vivo model (orthotopic breast cancer model for metastasis):

Female BALB/c mice which developed tumours from 4T1 mouse breast tumour cells, (orthotopically inoculated into the third mammary fat pad) were selected for the study. The mice were randomised, based on tumour volume into four groups on Day 0 of the study. The mice in each group received treatment with either Vehicle Control (PEG400:H_20 (70:30, v/v)), Example 22 (32 or 106.5 mg/kg) or Cisplatin (4 mg/kg). The Vehicle Control and Example 22 were administered orally, twice daily (12 hours apart) for 15 days (Day 0-14) in a dosing volume of 5 mL/kg. Cisplatin was administered intravenously on Day 0, 7 and 14 in a dosing volume of 10 mL/kg. Remaining liver tissue from untreated and treated mice, and the liver from mice treated with Cisplatin was preserved in 10% neutral buffered formalin and embedded in paraffin. Liver sections were stained with haematoxylin and eosin, and micro-metastases were quantified. The number of liver metastasis was reduced significantly to roughly 50% by Example 22 (dosing 106.5mg/kg) without any side effects.

CLAIMS

1. A compound having the general formula (I)



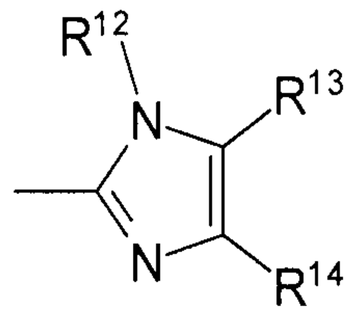
formula (I)

wherein:

A represents C–R^{10} or N;

B represents C–R^{11} or N;

D represents a heterocycle which is: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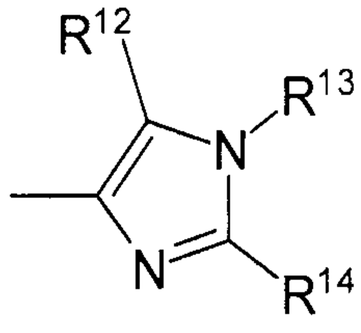
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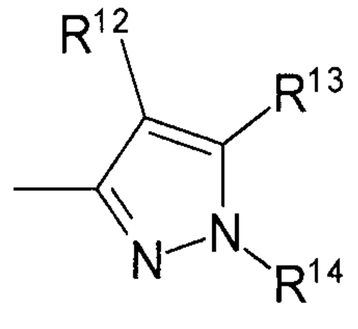
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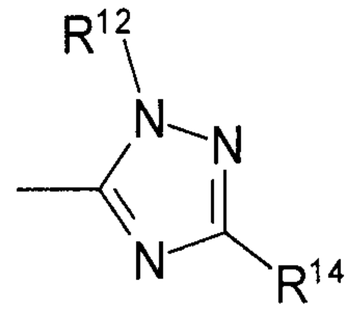
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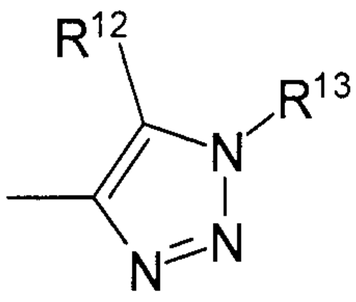
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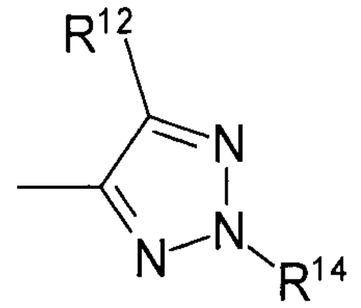
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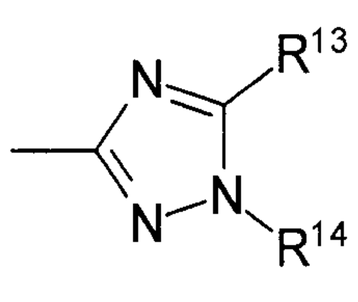
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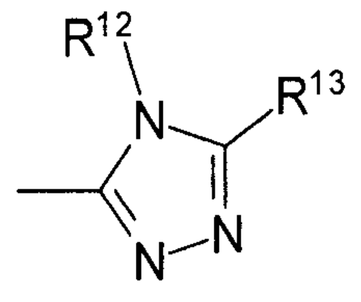
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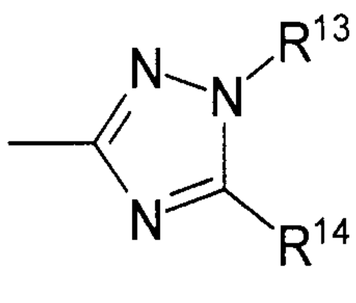
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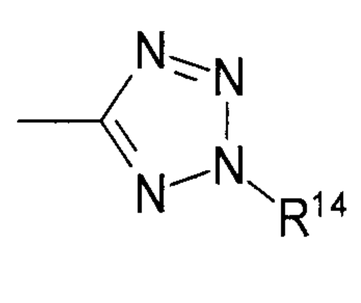
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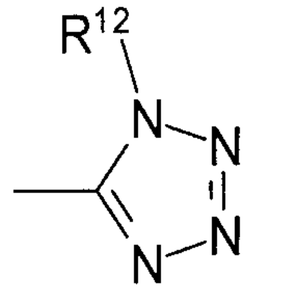
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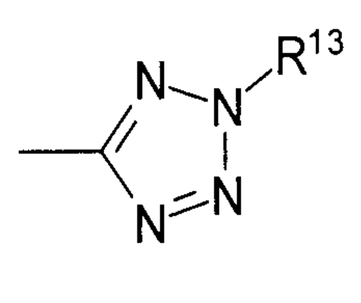
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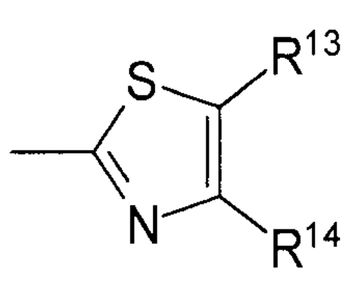
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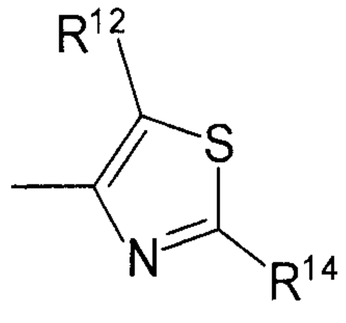
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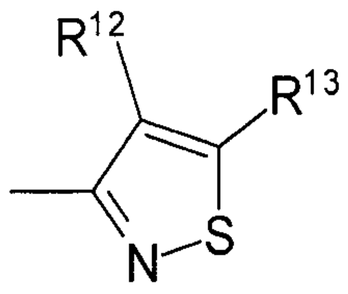
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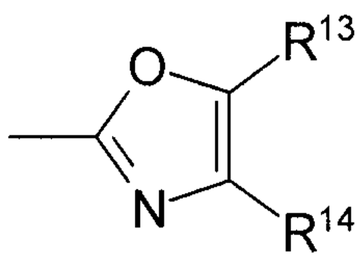
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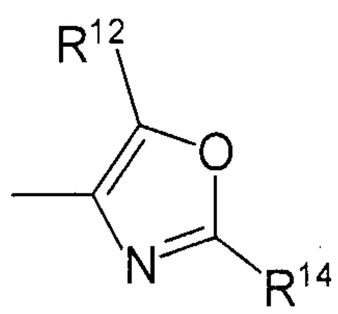
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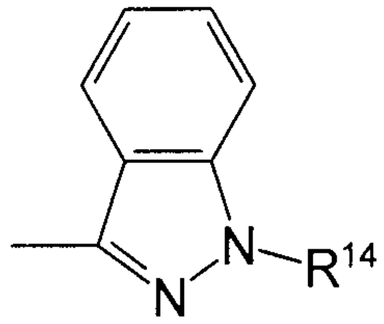
;

R^1, R^4, R^{88}, R^{92}, R^{100} are each independently: –H, –F, –Cl, –Br, –I, –OH, $–NH_2$, $–NHR^{19}$, $–NR^{19}R^{20}$, $–OCH_3$, $–OC_2H_5$, $–OC_3H_7$, $–OCH(CH_3)_2$, $–OC(CH_3)_3$, $–OC_4H_9$, $–NO_2$, –CHO, $–COCH_3$, $–COC_2H_5$, –O-cyclo-C_3H_5, $–OCH_2$-cyclo-C_3H_5, –O–C_2H_4-cyclo-C_3H_5, –OPh, $–COC_3H_7$, $–COCH(CH_3)_2$, $–COC(CH_3)_3$, –COOH, $–COOCH_3$, $–COOC_2H_5$, $–COOC_3H_7$, $–COOCH(CH_3)_2$, $–COOC(CH_3)_3$, $–OOC–CH_3$, $–OOC–C_2H_5$, $–OOC–C_3H_7$, $–OOC–CH(CH_3)_2$, $–OOC–C(CH_3)_3$, $–NHCH_3$, $–NHC_2H_5$, $–NHC_3H_7$, $–NHCH(CH_3)_2$, $–NHC(CH_3)_3$, $–N(CH_3)_2$, $–N(C_2H_5)_2$, $–N(C_3H_7)_2$, $–N[CH(CH_3)_2]_2$, $–N[C(CH_3)_3]_2$, $–OCF_3$, $–OC_2F_5$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2Cl$, $–CH_2Br$, $–CH_2I$, $–CH_2–CH_2F$, $–CH_2–CHF_2$, $–CH_2–CF_3$, $–CH_2–CH_2Cl$, $–CH_2–CH_2Br$, $–CH_2–CH_2I$, cyclo-C_3H_5, $–CH_2–$cyclo–C_3H_5, $–CH_3$, $–C_2H_5$, $–C_3H_7$, $–CH(CH_3)_2$, $–C_4H_9$, $–CH_2–CH(CH_3)_2$, $–CH(CH_3)–C_2H_5$, $–C(CH_3)_3$, $–C_5H_{11}$, $–CH(CH_3)–C_3H_7$, $–CH_2–CH(CH_3)–C_2H_5$, $–CH(CH_3)–CH(CH_3)_2$, $–C(CH_3)_2–C_2H_5$, $–CH_2–C(CH_3)_3$, $–CH(C_2H_5)_2$, $–C_2H_4–CH(CH_3)_2$, $–C_6H_{13}$, $–C_3H_6–CH(CH_3)_2$, $–C_2H_4–CH(CH_3)–C_2H_5$, $–CH(CH_3)–C_4H_9$, $–CH_2–CH(CH_3)–C_3H_7$, $–CH(CH_3)–CH_2–CH(CH_3)_2$, $–CH(CH_3)–CH(CH_3)–C_2H_5$, $–CH_2–CH(CH_3)–CH(CH_3)_2$, $–CH_2–C(CH_3)_2–C_2H_5$, $–C(CH_3)_2–C_3H_7$, $–C(CH_3)_2–CH(CH_3)_2$, $–C_2H_4–C(CH_3)_3$, $–CH(CH_3)–C(CH_3)_3$, $–CH=CH_2$, $–CH_2–CH=CH_2$, $–C(CH_3)=CH_2$, –CH=CH–CH_3, $–C_2H_4–CH=CH_2$, $–CH_2–CH=CH–CH_3$, $–CH=CH–C_2H_5$, $–CH_2–C(CH_3)=CH_2$, $–CH(CH_3)–CH=CH$, $–CH=C(CH_3)_2$, $–C(CH_3)=CH–CH_3$, –CH=CH–$CH=CH_2$, $–C_3H_6–CH=CH_2$, $–C_2H_4–CH=CH–CH_3$, $–CH_2–CH=CH–C_2H_5$, –CH=CH–C_3H_7, $–CH_2–CH=CH–CH=CH_2$, –CH=CH–CH=CH–CH_3, –CH=CH–$CH_2–CH=CH_2$, $–C(CH_3)=CH–CH=CH_2$, $–CH=C(CH_3)–CH=CH_2$, –CH=CH–$C(CH_3)=CH_2$, $–C_2H_4–C(CH_3)=CH_2$, $–CH_2–CH(CH_3)–CH=CH_2$, $–CH(CH_3)–CH_2–CH=CH_2$, $–CH_2–CH=C(CH_3)_2$, $–CH_2–C(CH_3)=CH–CH_3$, $–CH(CH_3)–CH=CH–CH_3$, –CH=$CH–CH(CH_3)_2$, $–CH=C(CH_3)–C_2H_5$, $–C(CH_3)=CH–C_2H_5$, $–C(CH_3)=C(CH_3)_2$, $–C(CH_3)_2–CH=CH_2$,

–$CH(CH_3)$–$C(CH_3)=CH_2$, –$C(CH_3)=CH$–$CH=CH_2$, –$CH=C(CH_3)$–$CH=CH_2$,
–$CH=CH$–$C(CH_3)=CH_2$, –C_4H_8–$CH=CH_2$, –$CH=CH$–C_4H_9,
–C_2H_4–$CH=CH$–C_2H_5, –CH_2–$CH=CH$–C_3H_7, –C_2H_4–$CH(CH_3)$–$CH=CH_2$,
–C_3H_6–$C(CH_3)=CH_2$, –$CH(CH_3)$–C_2H_4–$CH=CH_2$,
–CH_2–$CH(CH_3)$–CH_2–$CH=CH_2$, –CH_2–$CH(CH_3)$–$CH=CH$–CH_3,
–C_2H_4–$CH=C(CH_3)_2$, –C_2H_4–$C(CH_3)=CH$–CH_3, –CH_2–$CH=CH$–$CH(CH_3)_2$,
–$CH(CH_3)$–CH_2–$CH=CH$–CH_3, –CH_2–$C(CH_3)=CH$–C_2H_5,
–CH_2–$CH=C(CH_3)$–C_2H_5, –$CH=CH$–CH_2–$CH(CH_3)_2$,
–$CH(CH_3)$–$CH=CH$–C_2H_5, –$CH=C(CH_3)$–C_3H_7, –$C(CH_3)=CH$–C_3H_7,
–$CH=CH$–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–CH_2–$C(CH_3)=CH_2$,
–CH_2–$CH(CH_3)$–$C(CH_3)=CH_2$, –CH_2–$C(CH_3)_2$–$CH=CH_2$,
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–$C(CH_3)_2$–$CH=CH$–CH_3, –$C(CH_3)=CH$–$CH(CH_3)_2$, –$C(CH_3)=C(CH_3)$–C_2H_5,
–$CH=C(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–$C(CH_3)=CH_2$, –$CH(C_2H_5)$–$C(CH_3)=CH_2$,
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–$C(CH_3)(C_2H_5)$–$CH=CH_2$, –$CH(C_2H_5)$–$CH=CH$–CH_3, –$C(C_4H_9)=CH_2$,
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–$C(C_3H_7)=CH$–CH_3, –$C[CH(CH_3)(C_2H_5)]=CH_2$, –$C[CH_2$–$CH(CH_3)_2]=CH_2$,
–$C[C(CH_3)_3]=CH_2$, –CH_2–$CH=CH$–CH_2–$CH=CH_2$,
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–$CH=CH$–C_2H_4–$CH=CH_2$, –$CH=CH$–$CH=CH$–C_2H_5,
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–$CH=C(CH_3)$–CH_2–$CH=CH_2$, –$CH=CH$–$C(CH_3)=CH$–CH_3,
–$CH=CH$–$CH=C(CH_3)_2$, –$C(CH_3)=CH$–$CH=CH$–CH_3,
–$CH=C(CH_3)$–$CH=CH$–CH_3, –$C(CH_3)=CH$–$C(CH_3)=CH_2$,
–$CH=C(CH_3)$–$C(CH_3)=CH_2$, –$C(CH_3)=C(CH_3)$–$CH=CH_2$, –$CH=CH$–$CH=CH$–$CH=CH_2$, –$C\equiv CH$,
–$C\equiv C$–CH_3, –CH_2-$C\equiv CH$, –C_2H_4–$C\equiv CH$, –CH_2–$C\equiv C$–CH_3, –$C\equiv C$–C_2H_5,
–C_3H_6–$C\equiv CH$, –C_2H_4–$C\equiv C$–CH_3, –CH_2–$C\equiv C$–C_2H_5, –$C\equiv C$–C_3H_7,
–$CH(CH_3)$–$C\equiv CH$, –CH_2–$CH(CH_3)$–$C\equiv CH$, –$CH(CH_3)$–CH_2–$C\equiv CH$,
–$CH(CH_3)$–$C\equiv C$–CH_3, –C_4H_8–$C\equiv CH$, –C_3H_6–$C\equiv C$–CH_3, –C_2H_4–$C\equiv C$–C_2H_5,
–CH_2–$C\equiv C$–C_3H_7, –$C\equiv C$–C_4H_9, –C_2H_4–$CH(CH_3)$–$C\equiv CH$,
–CH_2–$CH(CH_3)$–CH_2–$C\equiv CH$, –$CH(CH_3)$–C_2H_4–$C\equiv CH$,
–CH_2–$CH(CH_3)$–$C\equiv C$–CH_3, –$CH(CH_3)$–CH_2–$C\equiv C$–CH_3,

$-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$, $-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$, $-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$, $-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$, $-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$, $-CH_2-CH(C\equiv CH)_2$, $-CH(C\equiv CH)-C\equiv C-CH_3$, R^{21}, R^{35}, or R^{36} ;

R^2 and R^3 are each independently: $-R^{88}$, $-R^{37}$, $-R^{38}$, $-R^{54}$, $-O-R^{54}$, $-R^{55}$, $-O-R^{55}$, $-R^{56}$, $-O-R^{56}$, $-R^{57}$, or $-O-R^{57}$, wherein the $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl and $C_{1\text{-}6}$alkoxy groups represented by R^{88} are optionally mono- or polysubstituted by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-O-R^{71}$, R^{72}, $-R^{138}$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-(C=O)-NR^{16}R^{17}$, $-SO_2-NR^{16}R^{17}$, $-SO_m-R^{16}R^{17}$, $-CR^{16}R^{17}H$, or $-NR^{16}R^{17}$;

or R^2 and/or R^3 are each independently: $-O-R^{18}$, $-O-CR^{73}R^{74}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-CR^{79}R^{80}-R^{18}$, $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-CR^{79}R^{80}-CR^{81}R^{82}-R^{18}$, or $-O-CR^{73}R^{74}-CR^{75}R^{76}-CR^{77}R^{78}-CR^{79}R^{80}-CR^{81}R^{82}-CR^{83}R^{84}-R^{18}$,

R^{73} – R^{84} each independently represents: $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, or $-R^{85}$;

R^{18} represents: $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-O-R^{86}$, $-R^{87}$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-(C=O)-NR^{16}R^{17}$, $-SO_2-NR^{16}R^{17}$, $-SO_m-R^{16}R^{17}$, $-CR^{16}R^{17}H$, or $-NR^{16}R^{17}$;

m = 0, 1, 2;

R^5 and R^6, may be the same or different, each represents: $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, cyclo-C_3H_5, $-CH_2$–cyclo–C_3H_5, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$,

$-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$,
$-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$,
$-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$,
$-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$,
$-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$,
$-CH=CH-C_3H_7$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$,
$-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$,
$-CH=CH-C(CH_3)=CH_2$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$,
$-CH(CH_3)-CH_2-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C(CH_3)=CH-CH_3$,
$-CH(CH_3)-CH=CH-CH_3$, $-CH=CH-CH(CH_3)_2$, $-CH=C(CH_3)-C_2H_5$,
$-C(CH_3)=CH-C_2H_5$, $-C(CH_3)=C(CH_3)_2$, $-C(CH_3)_2-CH=CH_2$,
$-CH(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$,
$-CH=CH-C(CH_3)=CH_2$, $-C_4H_8-CH=CH_2$, $-C_3H_6-CH=CH-CH_3$,
$-C_2H_4-CH=CH-C_2H_5$, $-CH_2-CH=CH-C_3H_7$, $-CH=CH-C_4H_9$,
$-C_3H_6-C(CH_3)=CH_2$, $-C_2H_4-CH(CH_3)-CH=CH_2$,
$-CH_2-CH(CH_3)-CH_2-CH=CH_2$, $-CH(CH_3)-C_2H_4-CH=CH_2$,
$-C_2H_4-CH=C(CH_3)_2$, $-C_2H_4-C(CH_3)=CH-CH_3$, $-CH_2-CH(CH_3)-CH=CH-CH_3$,
$-CH(CH_3)-CH_2-CH=CH-CH_3$, $-CH_2-CH=CH-CH(CH_3)_2$,
$-CH_2-CH=C(CH_3)-C_2H_5$, $-CH_2-C(CH_3)=CH-C_2H_5$,
$-CH=CH-CH_2-CH(CH_3)_2$,
$-CH(CH_3)-CH=CH-C_2H_5$, $-CH=C(CH_3)-C_3H_7$, $-C(CH_3)=CH-C_3H_7$,
$-CH=CH-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH_2-C(CH_3)=CH_2$,
$-CH_2-CH(CH_3)-C(CH_3)=CH_2$, $-CH_2-C(CH_3)_2-CH=CH_2$,
$-CH(CH_3)-CH(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)=C(CH_3)_2$, $-CH(CH_3)-CH=C(CH_3)_2$,
$-C(CH_3)_2-CH_2-CH=CH_2$, $-CH(CH_3)-C(CH_3)=CH-CH_3$,
$-C(CH_3)_2-CH=CH-CH_3$, $-C(CH_3)=CH-CH(CH_3)_2$, $-C(CH_3)=C(CH_3)-C_2H_5$,
$-CH=C(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C(CH_3)=CH_2$, $-CH(C_2H_5)-C(CH_3)=CH_2$,
$-CH=CH-C(CH_3)_3$, $-CH(CH_3)-C(C_2H_5)=CH_2$, $-CH_2-C(C_3H_7)=CH_2$,
$-C(CH_3)(C_2H_5)-CH=CH_2$, $-CH(C_2H_5)-CH=CH-CH_3$, $-C(C_4H_9)=CH_2$,
$-CH_2-C(C_2H_5)=CH-CH_3$, $-C(C_2H_5)=CH-C_2H_5$, $-C(C_2H_5)=C(CH_3)_2$,
$-C(C_3H_7)=CH-CH_3$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$,
$-C[C(CH_3)_3]=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$,
$-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$,
$-CH=CH-C_2H_4-CH=CH_2$, $-CH=CH-CH=CH-C_2H_5$,
$-CH=CH-CH_2-CH=CH-CH_3$, $-CH_2-CH=C(CH_3)-CH=CH_2$,
$-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$,
$-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$,
$-CH=CH-CH_2-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH_2-CH=CH_2$,
$-CH=C(CH_3)-CH_2-CH=CH_2$,

$-CH=CH-CH=C(CH_3)_2$, $-CH=CH-C(CH_3)=CH-CH_3$,
$-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$,
$-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$,
$-C(CH_3)=C(CH_3)-CH=CH_2$, $-CH=CH-CH=CH-CH=CH_2$, $-C\equiv CH$,
$-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$,
$-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$,
$-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-CH_2-C\equiv CH$,
$-CH(CH_3)-C\equiv C-CH_3$, $-C_4H_8-C\equiv CH$, $-C_3H_6-C\equiv C-CH_3$, $-C_2H_4-C\equiv C-C_2H_5$,
$-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$,
$-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$,
$-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$,
$-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$,
$-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$,
$-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$,
$-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$,
$-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$,
$-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$,
$-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$,
$-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$,
$-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$,
$-CH_2-CH(C\equiv CH)_2$, $-CH(C\equiv CH)-C\equiv C-CH_3$, or $-O-R^{89}$;

R^7, R^8, R^{10} and R^{11}, may be the same or different, each represents: $-H$, $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, cyclo-C_3H_5, $-CH_2-$cyclo$-C_3H_5$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$, $-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$, $-CH=CH-C_3H_7$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$, $-CH=CH-C(CH_3)=CH_2$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$,

–$CH(CH_3)$–CH_2–$CH=CH_2$, –CH_2–$CH=C(CH_3)_2$, –CH_2–$C(CH_3)=CH$–CH_3,
–$CH(CH_3)$–$CH=CH$–CH_3, –$CH=CH$–$CH(CH_3)_2$, –$CH=C(CH_3)$–C_2H_5,
–$C(CH_3)=CH$–C_2H_5, –$C(CH_3)=C(CH_3)_2$, –$C(CH_3)_2$–$CH=CH_2$,
–$CH(CH_3)$–$C(CH_3)=CH_2$, –$C(CH_3)=CH$–$CH=CH_2$, –$CH=C(CH_3)$–$CH=CH_2$,
–$CH=CH$–$C(CH_3)=CH_2$, –C_4H_8–$CH=CH_2$, –C_3H_6–$CH=CH$–CH_3,
–C_2H_4–$CH=CH$–C_2H_5, –CH_2–$CH=CH$–C_3H_7, –$CH=CH$–C_4H_9,
–C_3H_6–$C(CH_3)=CH_2$, –C_2H_4–$CH(CH_3)$–$CH=CH_2$,
–CH_2–$CH(CH_3)$–CH_2–$CH=CH_2$, –$CH(CH_3)$–C_2H_4–$CH=CH_2$,
–C_2H_4–$CH=C(CH_3)_2$, –C_2H_4–$C(CH_3)=CH$–CH_3, –CH_2–$CH(CH_3)$–$CH=CH$–CH_3,
–$CH(CH_3)$–CH_2–$CH=CH$–CH_3, –CH_2–$CH=CH$–$CH(CH_3)_2$,
–CH_2–$CH=C(CH_3)$–C_2H_5, –CH_2–$C(CH_3)=CH$–C_2H_5,
–$CH(CH_3)$–$CH=CH$–C_2H_5, –$CH=CH$–CH_2–$CH(CH_3)_2$,
–$CH=CH$–$CH(CH_3)$–C_2H_5, –$CH=C(CH_3)$–C_3H_7, –$C(CH_3)=CH$–C_3H_7,
–CH_2–$CH(CH_3)$–$C(CH_3)=CH_2$, –$CH(CH_3)$–CH_2–$C(CH_3)=CH_2$,
–$CH(CH_3)$–$CH(CH_3)$–$CH=CH_2$, –CH_2–$C(CH_3)_2$–$CH=CH_2$,
–$C(CH_3)_2$–CH_2–$CH=CH_2$, –CH_2–$C(CH_3)=C(CH_3)_2$, –$CH(CH_3)$–$CH=C(CH_3)_2$,
–$C(CH_3)_2$–$CH=CH$–CH_3, –$CH(CH_3)$–$C(CH_3)=CH$–CH_3,
–$CH=C(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)=CH$–$CH(CH_3)_2$, –$C(CH_3)=C(CH_3)$–C_2H_5,
–$CH=CH$–$C(CH_3)_3$, –$C(CH_3)_2$–$C(CH_3)=CH_2$, –$CH(C_2H_5)$–$C(CH_3)=CH_2$,
–$C(CH_3)(C_2H_5)$–$CH=CH_2$, –$CH(CH_3)$–$C(C_2H_5)=CH_2$, –CH_2–$C(C_3H_7)=CH_2$,
–CH_2–$C(C_2H_5)=CH$–CH_3, –$CH(C_2H_5)$–$CH=CH$–CH_3, –$C(C_4H_9)=CH_2$,
–$C(C_3H_7)=CH$–CH_3, –$C(C_2H_5)=CH$–C_2H_5, –$C(C_2H_5)=C(CH_3)_2$,
–$C[C(CH_3)_3]=CH_2$, –$C[CH(CH_3)(C_2H_5)]=CH_2$, –$C[CH_2$–$CH(CH_3)_2]=CH_2$,
–C_2H_4–$CH=CH$–$CH=CH_2$, –CH_2–$CH=CH$–CH_2–$CH=CH_2$,
–$CH=CH$–C_2H_4–$CH=CH_2$, –CH_2–$CH=CH$–$CH=CH$–CH_3,
–$CH=CH$–CH_2–$CH=CH$–CH_3, –$CH=CH$–$CH=CH$–C_2H_5,
–CH_2–$CH=CH$–$C(CH_3)=CH_2$, –CH_2–$CH=C(CH_3)$–$CH=CH_2$,
–CH_2–$C(CH_3)=CH$–$CH=CH_2$, –$CH(CH_3)$–$CH=CH$–$CH=CH_2$,
–$CH=CH$–CH_2–$C(CH_3)=CH_2$, –$CH=CH$–$CH(CH_3)$–$CH=CH_2$,
–$CH=C(CH_3)$–CH_2–$CH=CH_2$, –$C(CH_3)=CH$–CH_2–$CH=CH_2$,
–$CH=CH$–$CH=C(CH_3)_2$, –$CH=CH$–$C(CH_3)=CH$–CH_3,
–$CH=C(CH_3)$–$CH=CH$–CH_3, –$C(CH_3)=CH$–$CH=CH$–CH_3,
–$CH=C(CH_3)$–$C(CH_3)=CH_2$, –$C(CH_3)=CH$–$C(CH_3)=CH_2$,
–$C(CH_3)=C(CH_3)$–$CH=CH_2$, –$CH=CH$–$CH=CH$–$CH=CH_2$, –$C\equiv CH$,
–$C\equiv C$–CH_3, –CH_2-$C\equiv CH$, –C_2H_4–$C\equiv CH$, –CH_2–$C\equiv C$–CH_3, –$C\equiv C$–C_2H_5,
–C_3H_6–$C\equiv CH$, –C_2H_4–$C\equiv C$–CH_3, –CH_2–$C\equiv C$–C_2H_5, –$C\equiv C$–C_3H_7,
–$CH(CH_3)$–$C\equiv CH$, –CH_2–$CH(CH_3)$–$C\equiv CH$, –$CH(CH_3)$–CH_2–$C\equiv CH$,
–$CH(CH_3)$–$C\equiv C$–CH_3, –C_4H_8–$C\equiv CH$, –C_3H_6–$C\equiv C$–CH_3, –C_2H_4–$C\equiv C$–C_2H_5,

$-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$,
$-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$,
$-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$,
$-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$,
$-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$,
$-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$,
$-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$,
$-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$,
$-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$,
$-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$,
$-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$,
$-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$,
$-CH_2-CH(C\equiv CH)_2$, $-CH(C\equiv CH)-C\equiv C-CH_3$, $-O-R^{90}$, $-O-R^{110}$, or $-O-R^{111}$,
wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}alkoxy groups are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, or –I ;

R^9represents –H, or $-R^{91}$;

R^{12} represents: $-R^{92}$, –CN, $-R^{93}$, $-R^{94}$, $-OR^{94}$, phenyl, or naphtalinyl, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}alkoxy groups represented by R^{92} are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, –I, $-O-R^{95}$, R^{96}, –COOH, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-(C=O)-NR^{16}R^{17}$, $-SO_2-NR^{16}R^{17}$, $-SO_m-R^{16}R^{17}$, $-CR^{16}R^{17}H$, or $-NR^{16}R^{17}$; and wherein the saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring systems represented by R^{137} are optionally mono- or polysubstituted by –OH, –F, –Cl, –Br, –I, or $-R^{96}$;

R^{13} is: –H, –OH, –F, –Cl, –Br, –I, $-NO_2$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-C_5H_{11}$, $-CH(CH_3)-C_3H_7$, $-CH_2-CH(CH_3)-C_2H_5$, $-CH(CH_3)-CH(CH_3)_2$, $-C(CH_3)_2-C_2H_5$, $-CH_2-C(CH_3)_3$, $-CH(C_2H_5)_2$, $-C_2H_4-CH(CH_3)_2$, $-C_6H_{13}$, $-C_3H_6-CH(CH_3)_2$, $-C_2H_4-CH(CH_3)-C_2H_5$, $-CH(CH_3)-C_4H_9$, $-CH_2-CH(CH_3)-C_3H_7$, $-CH(CH_3)-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, $-CH(CH_3)-C(CH_3)_3$, $-CH=CH_2$, $-CH_2-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CH-CH_3$, $-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH_3$, $-CH=CH-C_2H_5$, $-CH_2-C(CH_3)=CH_2$, $-CH(CH_3)-CH=CH$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH_3$, $-CH=CH-CH=CH_2$,

$-C_3H_6-CH=CH_2$, $-C_2H_4-CH=CH-CH_3$, $-CH_2-CH=CH-C_2H_5$,
$-CH=CH-C_3H_7$, $-CH_2-CH=CH-CH=CH_2$, $-CH=CH-CH=CH-CH_3$,
$-CH=CH-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$,
$-CH=CH-C(CH_3)=CH_2$, $-C_2H_4-C(CH_3)=CH_2$, $-CH_2-CH(CH_3)-CH=CH_2$,
$-CH(CH_3)-CH_2-CH=CH_2$, $-CH_2-CH=C(CH_3)_2$, $-CH_2-C(CH_3)=CH-CH_3$,
$-CH(CH_3)-CH=CH-CH_3$, $-CH=CH-CH(CH_3)_2$, $-CH=C(CH_3)-C_2H_5$,
$-C(CH_3)=CH-C_2H_5$, $-C(CH_3)=C(CH_3)_2$, $-C(CH_3)_2-CH=CH_2$,
$-CH(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-CH=CH_2$, $-CH=C(CH_3)-CH=CH_2$,
$-CH=CH-C(CH_3)=CH_2$, $-C_4H_8-CH=CH_2$, $-C_3H_6-CH=CH-CH_3$,
$-C_2H_4-CH=CH-C_2H_5$, $-CH_2-CH=CH-C_3H_7$, $-CH=CH-C_4H_9$,
$-C_3H_6-C(CH_3)=CH_2$, $-C_2H_4-CH(CH_3)-CH=CH_2$,
$-CH_2-CH(CH_3)-CH_2-CH=CH_2$, $-CH(CH_3)-C_2H_4-CH=CH_2$,
$-C_2H_4-CH=C(CH_3)_2$, $-C_2H_4-C(CH_3)=CH-CH_3$, $-CH_2-CH(CH_3)-CH=CH-CH_3$,
$-CH(CH_3)-CH_2-CH=CH-CH_3$, $-CH_2-CH=CH-CH(CH_3)_2$,
$-CH_2-CH=C(CH_3)-C_2H_5$, $-CH_2-C(CH_3)=CH-C_2H_5$,
$-CH(CH_3)-CH=CH-C_2H_5$, $-CH=CH-CH_2-CH(CH_3)_2$,
$-CH=CH-CH(CH_3)-C_2H_5$, $-CH=C(CH_3)-C_3H_7$, $-C(CH_3)=CH-C_3H_7$,
$-CH_2-CH(CH_3)-C(CH_3)=CH_2$, $-CH(CH_3)-CH_2-C(CH_3)=CH_2$,
$-CH(CH_3)-CH(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)_2-CH=CH_2$,
$-C(CH_3)_2-CH_2-CH=CH_2$, $-CH_2-C(CH_3)=C(CH_3)_2$, $-CH(CH_3)-CH=C(CH_3)_2$,
$-C(CH_3)_2-CH=CH-CH_3$, $-CH(CH_3)-C(CH_3)=CH-CH_3$,
$-CH=C(CH_3)-CH(CH_3)_2$, $-C(CH_3)=CH-CH(CH_3)_2$, $-C(CH_3)=C(CH_3)-C_2H_5$,
$-CH=CH-C(CH_3)_3$, $-C(CH_3)_2-C(CH_3)=CH_2$, $-CH(C_2H_5)-C(CH_3)=CH_2$,
$-C(CH_3)(C_2H_5)-CH=CH_2$, $-CH(CH_3)-C(C_2H_5)=CH_2$, $-CH_2-C(C_3H_7)=CH_2$,
$-CH_2-C(C_2H_5)=CH-CH_3$, $-CH(C_2H_5)-CH=CH-CH_3$, $-C(C_4H_9)=CH_2$,
$-C(C_3H_7)=CH-CH_3$, $-C(C_2H_5)=CH-C_2H_5$, $-C(C_2H_5)=C(CH_3)_2$,
$-C[C(CH_3)_3]=CH_2$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$,
$-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$,
$-CH=CH-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$,
$-CH=CH-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH-C_2H_5$,
$-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)-CH=CH_2$,
$-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$,
$-CH=CH-CH_2-C(CH_3)=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$,
$-CH=C(CH_3)-CH=CH_2$, $-C(CH_3)=CH-CH=CH_2$,
$-CH=CH-CH=C(CH_3)_2$, $-C(CH_3)=CH-CH=CH-CH_3$,
$-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$,
$-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$,
$-C(CH_3)=C(CH_3)-CH=CH_2$, $-CH=CH-CH=CH-CH=CH_2$, $-C\equiv CH$,

$-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$, $-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C\equiv C-CH_3$, $-C_4H_8-C\equiv CH$, $-C_3H_6-C\equiv C-CH_3$, $-C_2H_4-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$, $-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$, $-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$, $-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$, $-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$, $-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$, $-CH_2-CH(C\equiv CH)_2$, $-CH(C\equiv CH)-C\equiv C-CH_3$, cyclo-$C_3H_5$, $-O-R^{97}$, $-R^{98}$, or $-R^{99}$;

when R^{12} and R^{13} represent alkenylene groups, R^{12} and R^{13} may combine to form a condensed aromatic ring together with the atoms of residue D to which R^{12} and R^{13} are attached in order to form a bicyclic group with residue D;

R^{14} represents:

(i) $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NO_2$, $-CN$, or $-NH_2$;

(ii) $-R^{100}$, $-R^{101}$, $-R^{102}$, $-O-R^{102}$, $-R^{103}$, $-O-R^{103}$, or $-R^{136}$, wherein the C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{1-6}alkoxy groups represented by R^{100} and the ether groups represented by $-R^{136}$ are optionally mono- or polysubstituted by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-O-R^{104}$, $-R^{105}$, $-COOH$, $-COOCH_3$, $-COOC_2H_5$, $-COOC_3H_7$, $-COOCH(CH_3)_2$, $-COOC(CH_3)_3$, $-(C=O)-NR^{16}R^{17}$, $-SO_2-NR^{16}R^{17}$, $-SO_m-R^{16}R^{17}$, $-CR^{16}R^{17}H$, or $-NR^{16}R^{17}$; or

(iii) $-R^{113}$, wherein the saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system represented by $-R^{113}$ is optionally mono- or polysubstituted by $-F$, $-Cl$, $-Br$, $-I$, $-OH$, $-NO_2$, $-NH_2$, $-C_2H_4-N(CH_3)_2$, $-CN$, $-CF_3$, $=O$, $-R^{16}$, $-R^{17}$, $-R^{106}$, $-O-R^{107}$, $-R^{108}$, $-R^{109}$, or a saturated or unsaturated three- to eight-membered carbocyclic or heterocyclic group, wherein the C_{1-6}alkyl groups represented by R^{106}, the C_{1-6}alkenyl groups represented by R^{108}, the C_{2-6}alkynyl groups represented by R^{109}, the C_{1-6}alkoxy groups represented by $-O-R^{107}$ are optionally mono- or polysubstituted by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-O-R^{104}$, $-R^{105}$,

–COOH, –$COOCH_3$, –$COOC_2H_5$, –$COOC_3H_7$, –$COOCH(CH_3)_2$, –$COOC(CH_3)_3$, –(C=O)–$NR^{16}R^{17}$, –SO_2–$NR^{16}R^{17}$, –SO_m–$R^{16}R^{17}$, –$CR^{16}R^{17}H$, or –$NR^{16}R^{17}$;

R^{16} and R^{17}, may be the same or different, each represents: –H, –R^{112}, optionally substituted by –OH, –F, –Cl, –Br, –I, –NH_2, or –CN;

or alternatively R^{16} and R^{17} may combine with the nitrogen atom attached thereto to form a saturated or unsaturated five to eight-membered heterocyclic group which is –R^{114}; which is optionally mono- or poysubstituted by –OH, =O, –R^{116}, –R^{117}, –R^{118}, –O–R^{119}, –R^{120}, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system which is –R^{115}; wherein the C_{1-6}alkyl group represented by R^{116}, C_{2-6}alkenyl group represented by R^{117}, C_{2-6}alkynyl group represented by R^{118} are optionally substituted by –OH, –R^{122}, or a saturated or unsaturated three- to twelve-membered carbocylic or heterocyclicring system which is –R^{121};

amino group in which one or two hydrogen atoms on the amino group are optionally substituted by –R^{123}, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system which is –R^{124}, and the C_{1-6}alkyl group represented by R^{123} is optionally substituted by –OH, –R^{125}, or a saturated or unsaturated three- to twelve-membered carbocylic or heterocyclic ring system which is –R^{126};

or a saturated or unsaturated three- to twelve-membered carbocyclic ring system which is –R^{127}; optionally substituted by –OH, =O, –R^{128}, –R^{129}, –R^{130}, –O–R^{131}, –R^{132}, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system which is –R^{133}, wherein the C_{1-6}alkyl group represented by R^{128}, C_{2-6}alkenyl group represented by R^{129} and C_{2-6}alkynyl group represented by R^{130} are optionally substituted by –OH, –R^{134}, or a saturated or unsaturated three- to twelve-membered carbocyclic or heterocyclic ring system which is –R^{135};

when the carbocyclic or heterocyclic group is substituted by C_{1-6}alkyl groups, two alkyl groups may combine together to form an alkylene chain; and the carbocyclic or heterocyclic group may be condensed with another saturated or unsaturated five to seven-membered carbocyclic or heterocyclic group to form a bicyclic group;

R^{19}, R^{20}, R^{71}, R^{85}, R^{86}, R^{89}, R^{90}, R^{91}, R^{95}, R^{97}, R^{104}, R^{106}, R^{107}, R^{110}, R^{111}, R^{112}, R^{116}, R^{119}, R^{122}, R^{123}, R^{125}, R^{128}, R^{131} and R^{134} each independently represents: –CH_3, –H, –CF_3, –Ph, –CH_2–Ph, –C_2H_5, –C_3H_7, –$CH(CH_3)_2$, –C_4H_9, –CH_2–$CH(CH_3)_2$, –$CH(CH_3)$–C_2H_5, –$C(CH_3)_3$, –C_5H_{11}, –$CH(CH_3)$–C_3H_7, –CH_2–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–$CH(CH_3)_2$, –$C(CH_3)_2$–C_2H_5, –CH_2–$C(CH_3)_3$, –$CH(C_2H_5)_2$, –C_2H_4–$CH(CH_3)_2$, –C_6H_{13}, –C_3H_6–$CH(CH_3)_2$, –C_2H_4–$CH(CH_3)$–C_2H_5, –$CH(CH_3)$–C_4H_9, –CH_2–$CH(CH_3)$–C_3H_7, –$CH(CH_3)$–CH_2–$CH(CH_3)_2$,

$-CH(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-CH(CH_3)-CH(CH_3)_2$, $-CH_2-C(CH_3)_2-C_2H_5$, $-C(CH_3)_2-C_3H_7$, $-C(CH_3)_2-CH(CH_3)_2$, $-C_2H_4-C(CH_3)_3$, or $-CH(CH_3)-C(CH_3)_3$;

R^{21} and R^{98} each independently represents: $-CR^{22}R^{23}R^{24}$, $-CR^{23}R^{24}-CR^{25}R^{26}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, or $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$;

R^{22} – R^{34} each independently represents: –H, –F, –Cl, –Br, –I, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-C_2H_5$, or $-C_3H_7$;

R^{35} and R^{99} each independently represents: $-O-CR^{22}R^{23}R^{24}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}R^{22}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, or $-O-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$;

R^{36}, R^{72}, R^{87}, R^{96}, R^{105}, R^{120}, R^{132} and R^{136} each independently represents: $-CR^{23}R^{24}-XH$, $-X-CR^{22}R^{23}R^{24}$, $-X-CR^{23}R^{24}-CR^{25}R^{26}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}$ $-X-CR^{27}R^{28}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-X-CR^{27}R^{28}-CR^{29}R^{30}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-X-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-X-CR^{29}R^{30}-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-X-CR^{31}R^{32}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-XH$, $-X-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-X-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-X-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-X-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-X-CR^{31}R^{32}-CR^{33}R^{34}R^{22}$, $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-X-CR^{33}R^{34}R^{22}$, or $-CR^{23}R^{24}-CR^{25}R^{26}-CR^{27}R^{28}-CR^{29}R^{30}-CR^{31}R^{32}-CR^{33}R^{34}-XH$;

X represents: –O–, –CO–, or –O–CO–;

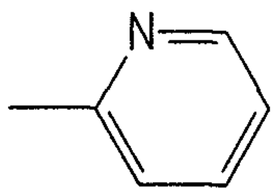
R^{37}, R^{38}, R^{93} and R^{101} each independently represents: $-CR^{40}R^{41}-YH$, $-Y-CR^{39}R^{40}R^{41}$, $-Y-CR^{40}R^{41}-CR^{42}R^{43}R^{39}$, $-CR^{40}R^{41}-Y-CR^{42}R^{43}R^{39}$, $-CR^{40}R^{41}-$

$CR^{42}R^{43}$–YH, –Y–$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}R^{39}$, –$CR^{40}R^{41}$–Y–$CR^{42}R^{43}$–$CR^{44}R^{45}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–Y–$CR^{44}R^{45}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–YH, –Y–$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}R^{39}$, –$CR^{40}R^{41}$–Y–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–Y–$CR^{44}R^{45}$–$CR^{46}R^{47}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–Y–$CR^{46}R^{46}R^{39}$, –$CR^{40}R^{42}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–YH, –Y–$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}R^{39}$, –$CR^{40}R^{41}$–Y–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–Y–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–Y–$CR^{46}R^{47}$–$CR^{48}R^{49}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–YH, –Y–$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}$–$CR^{50}R^{51}R^{39}$, –$CR^{40}R^{41}$–Y–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}$–$CR^{50}R^{51}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–Y–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}$–$CR^{50}R^{51}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–Y–$CR^{48}R^{49}$–$CR^{50}R^{51}R^{39}$, –$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}$–Y–$CR^{50}R^{51}R^{39}$, or –$CR^{40}R^{41}$–$CR^{42}R^{43}$–$CR^{44}R^{45}$–$CR^{46}R^{47}$–$CR^{48}R^{49}$–$CR^{50}R^{51}$–YH;

R^{39} – R^{53} each independently represents: –H, $–CH_3$, $–C_2H_5$, or $–C_3H_7$;

Y represents: –NR^{52}–CO–, or –CO–NR^{53}–;

R^{54}, R^{55} and R^{102} each independently represents: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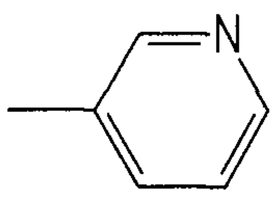
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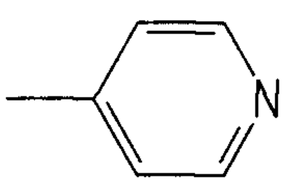
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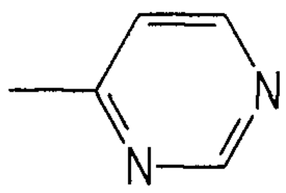
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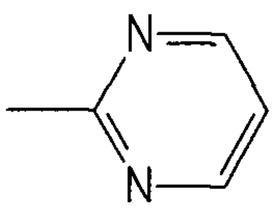
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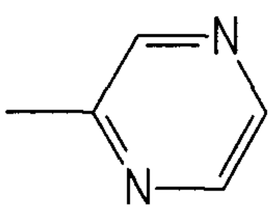
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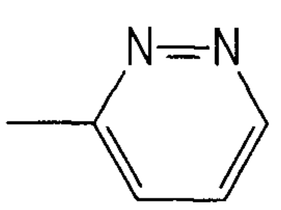
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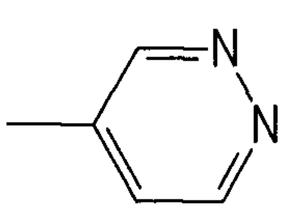
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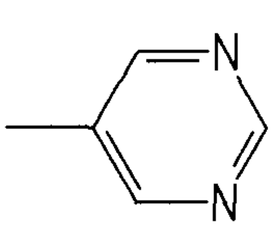
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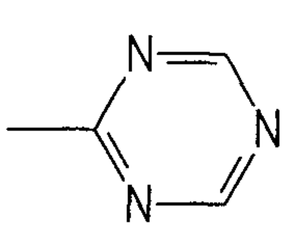
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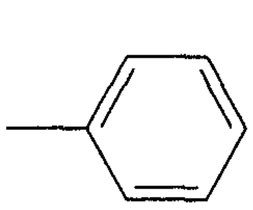
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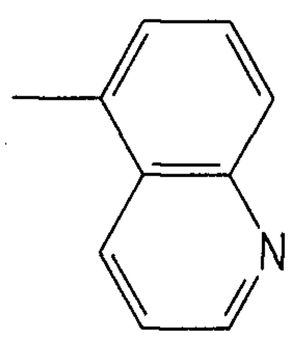
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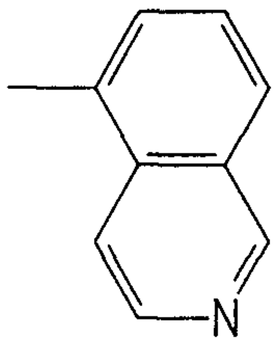
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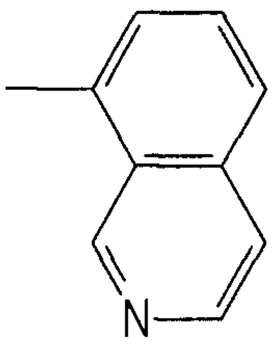
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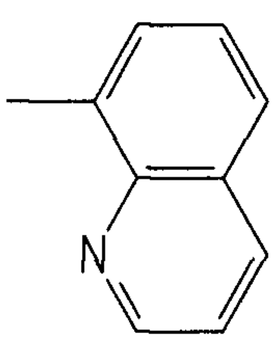
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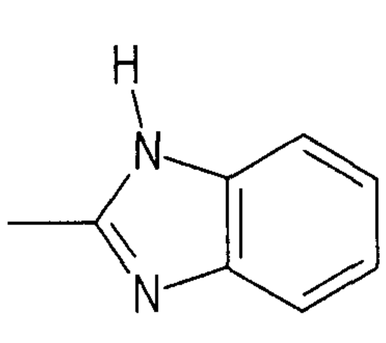
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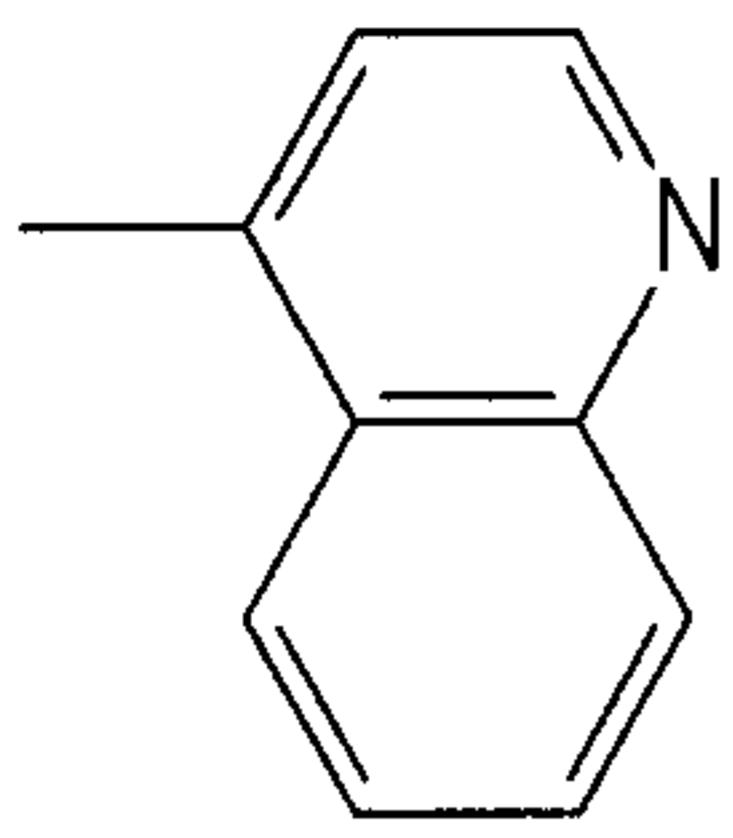
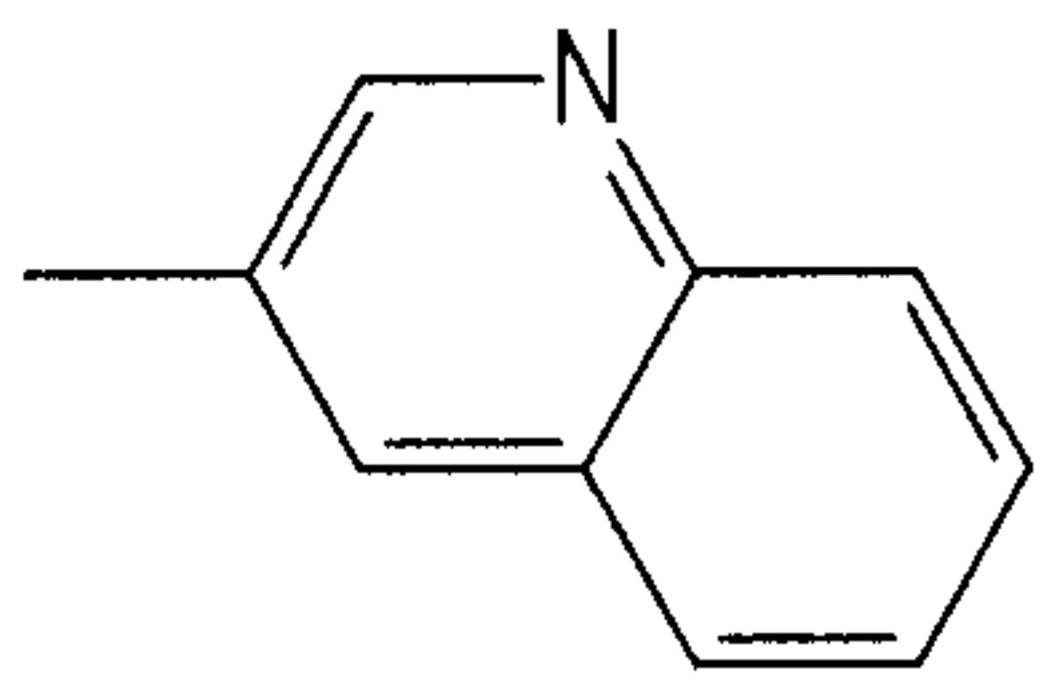
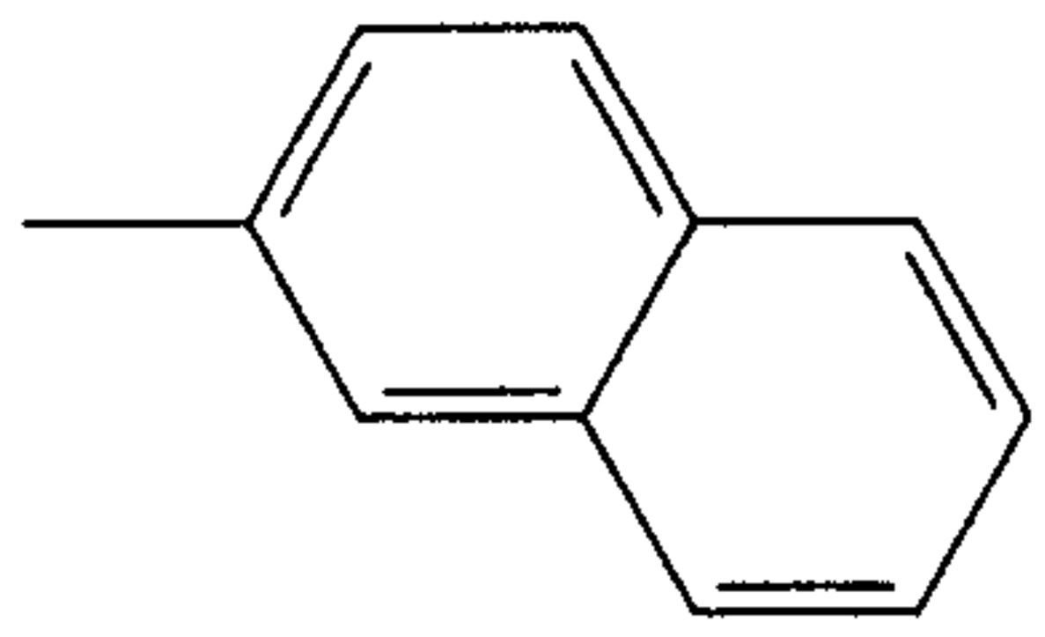
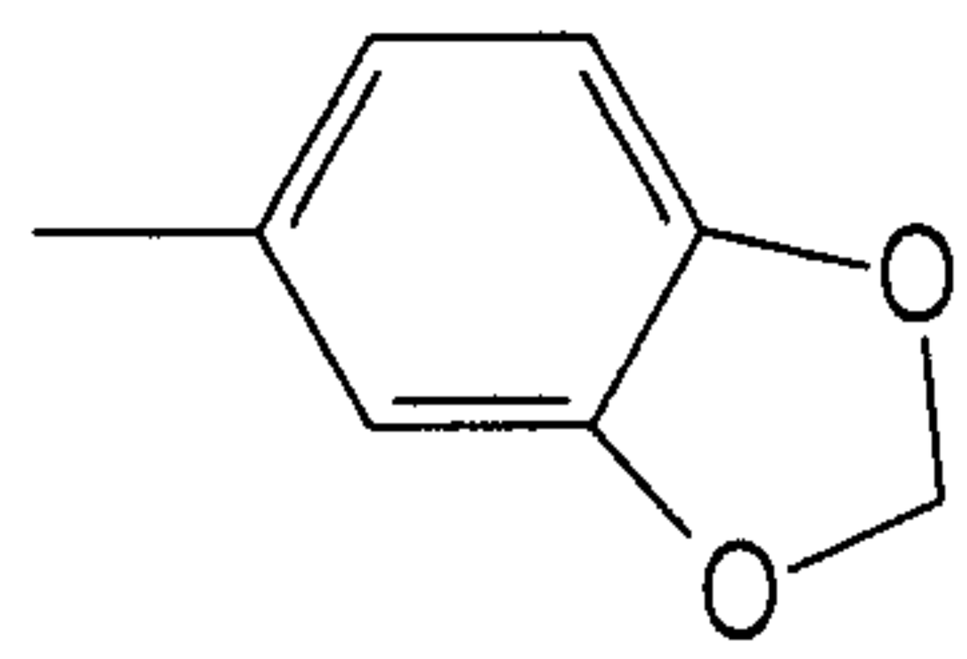
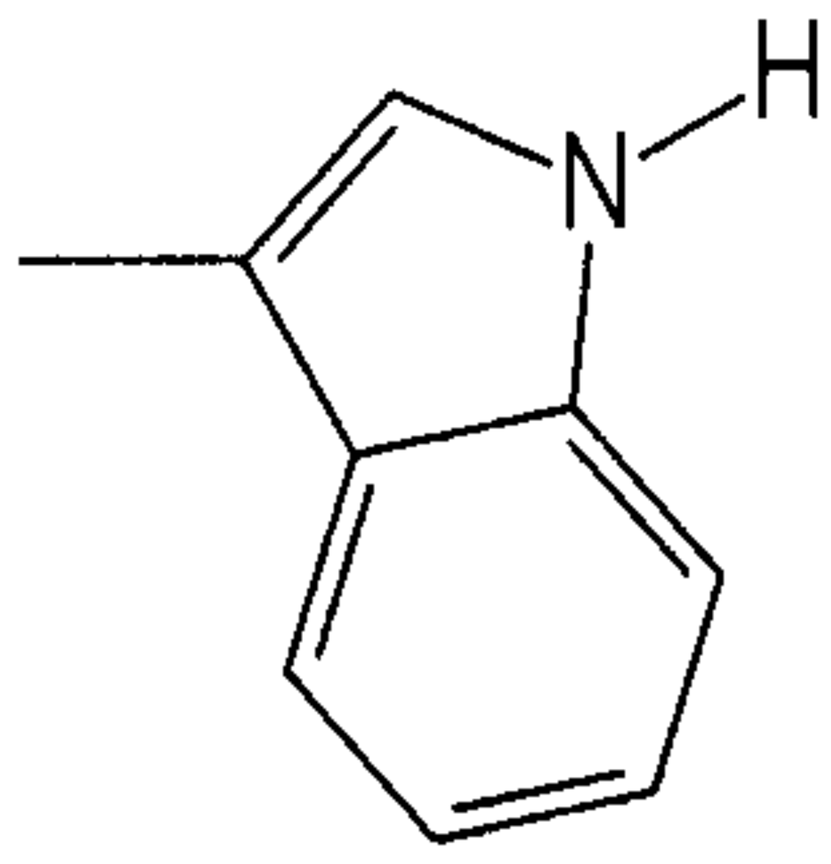
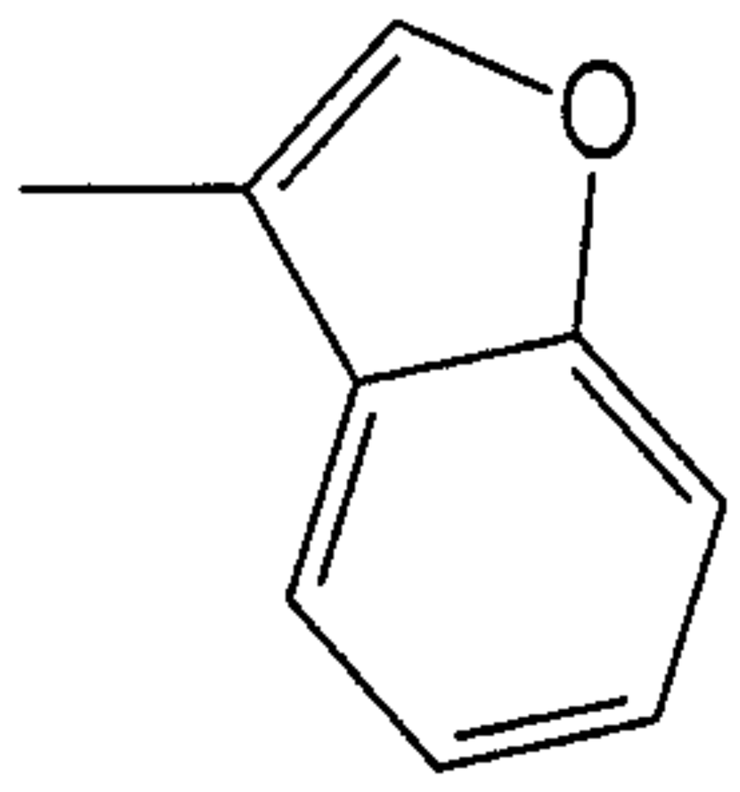
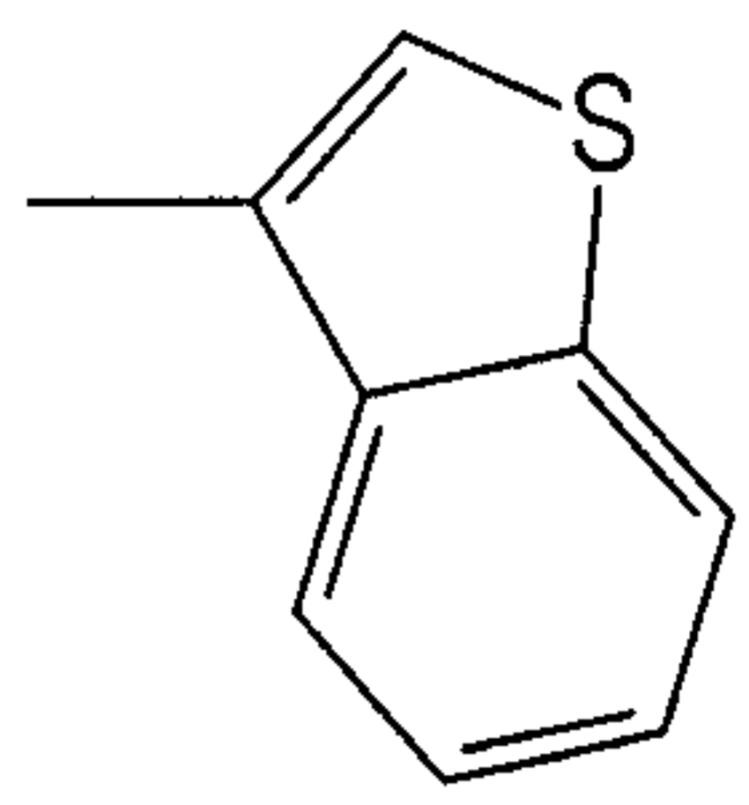
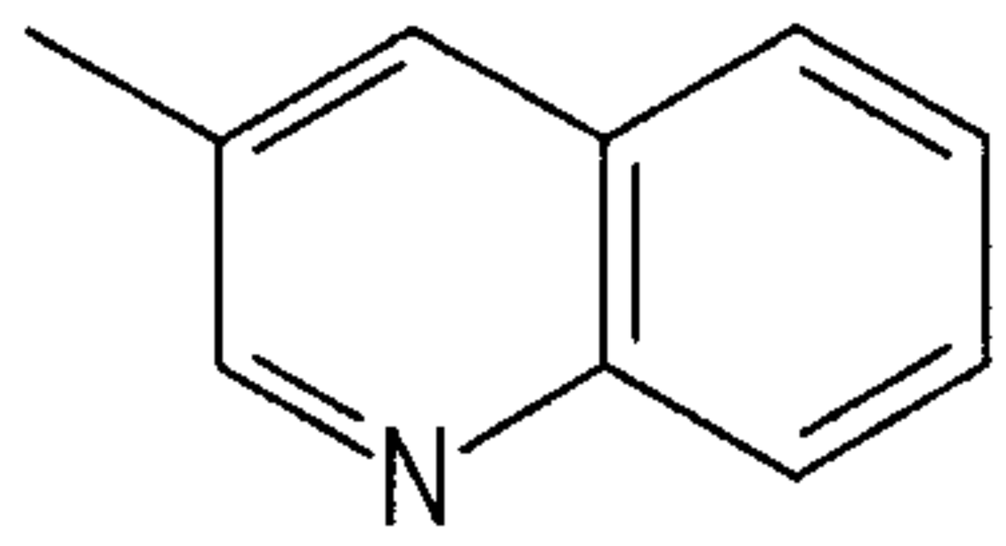
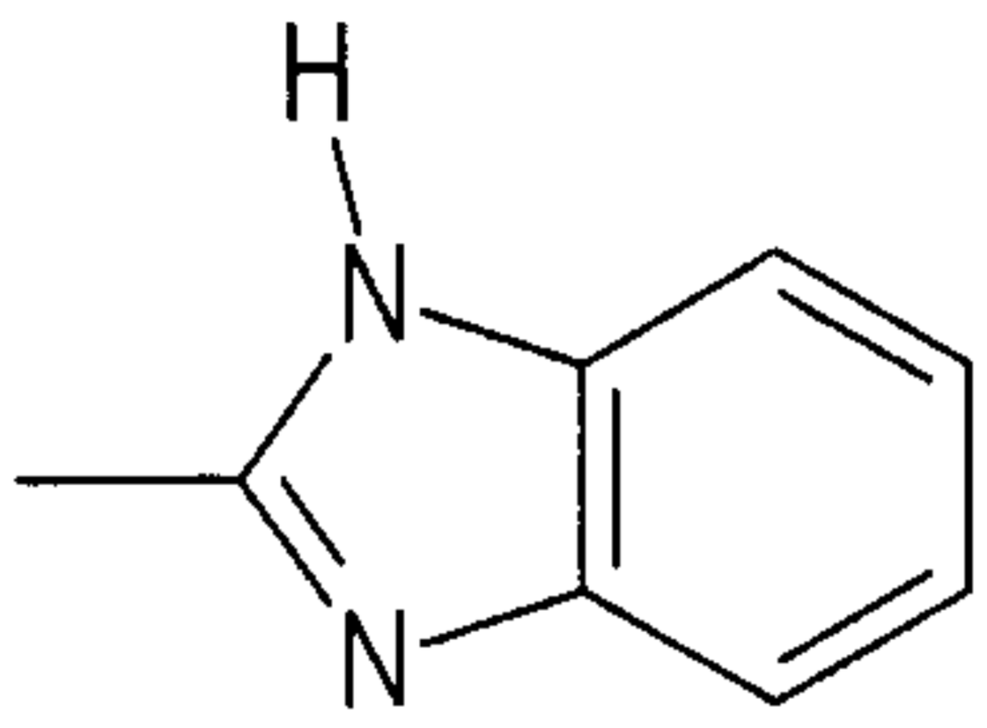
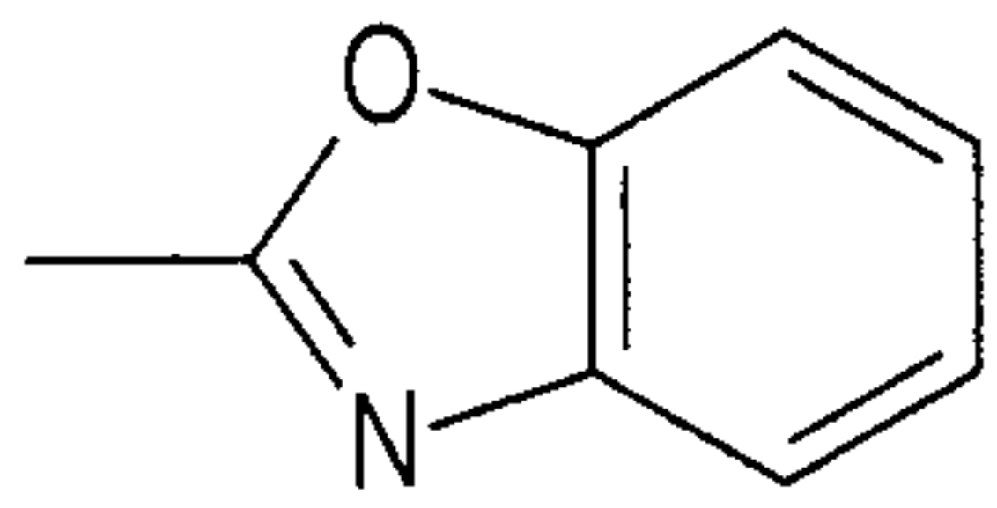
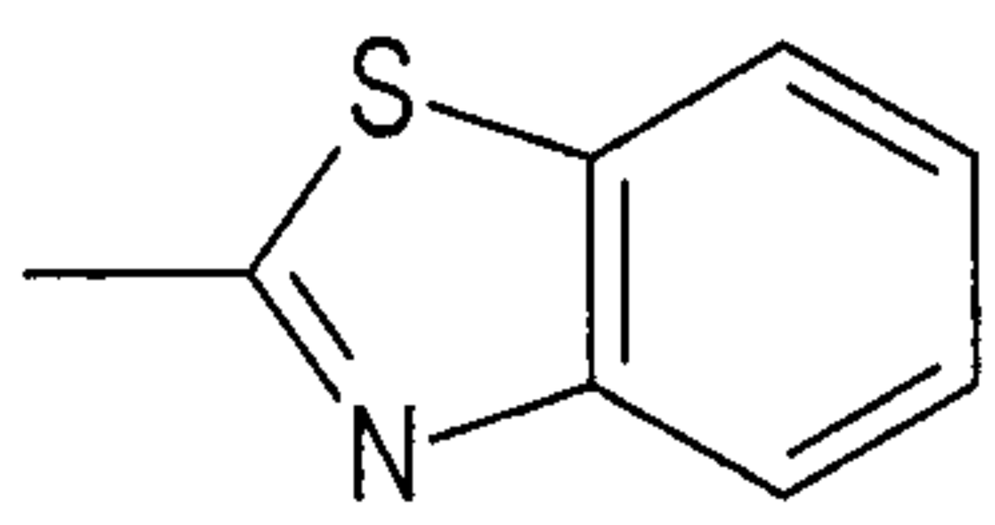
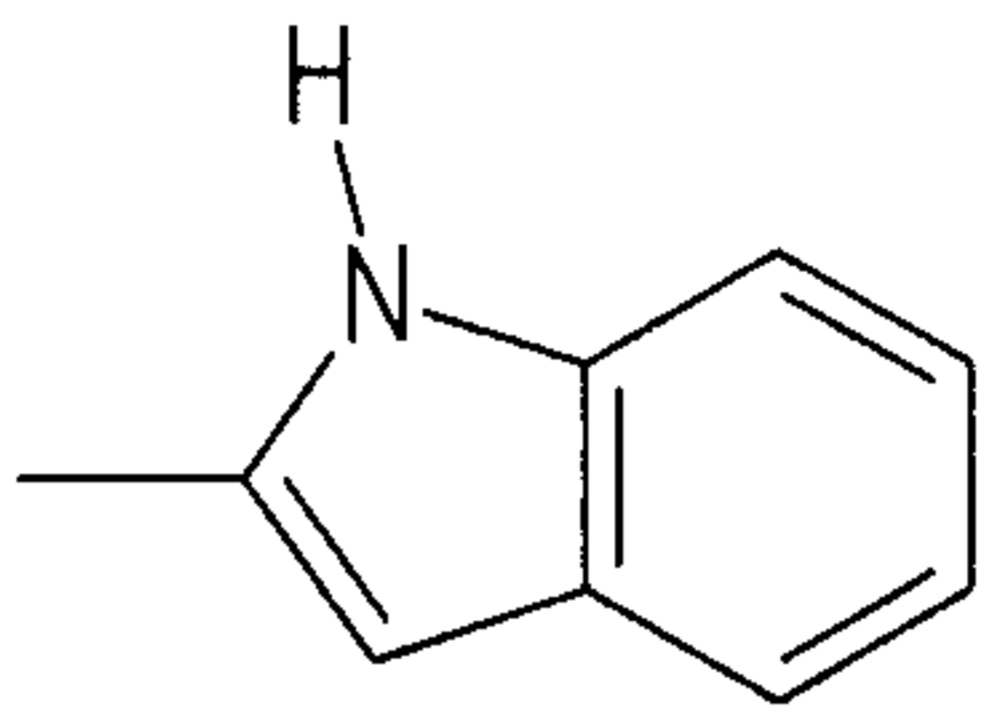
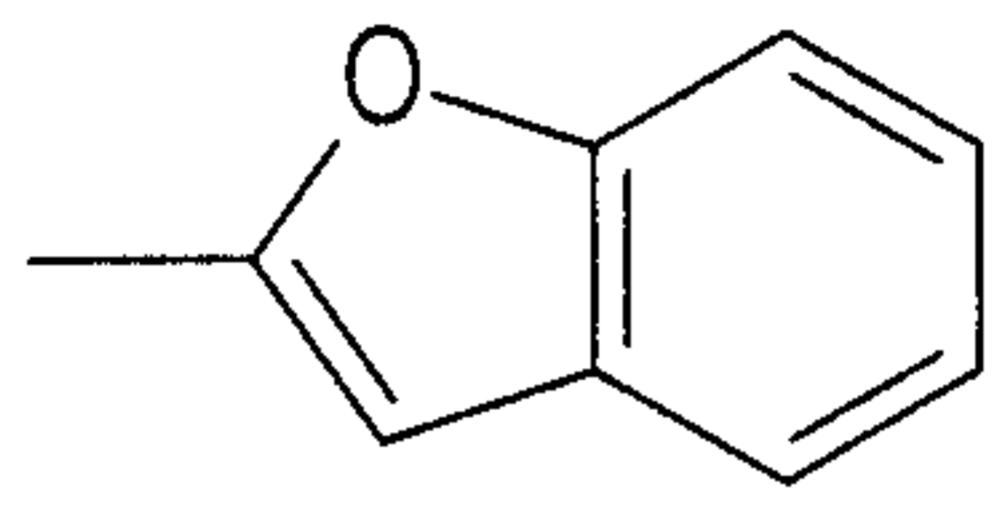
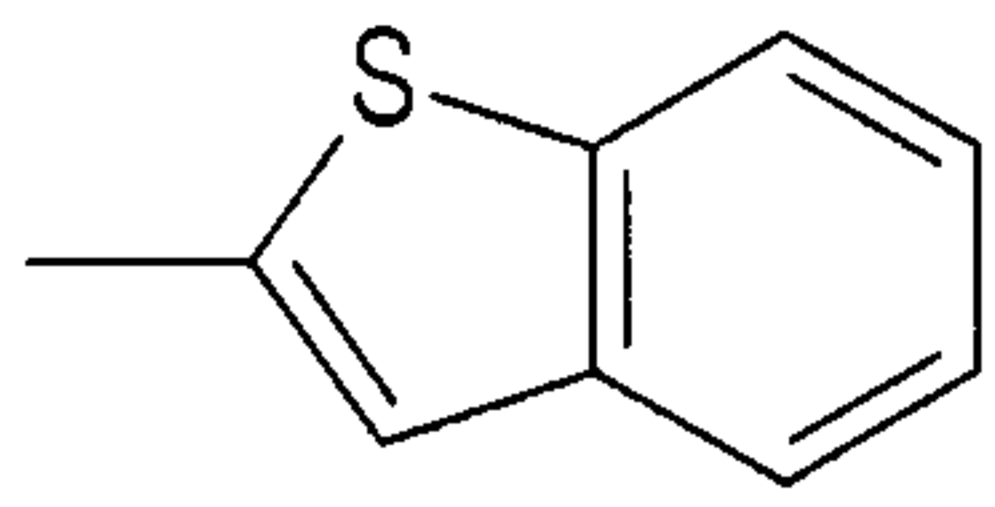
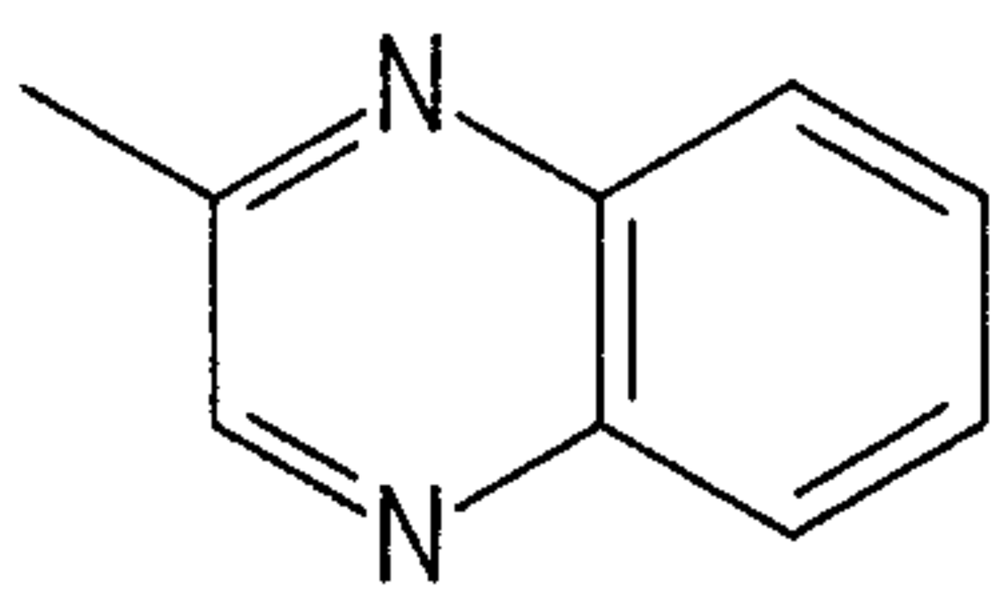
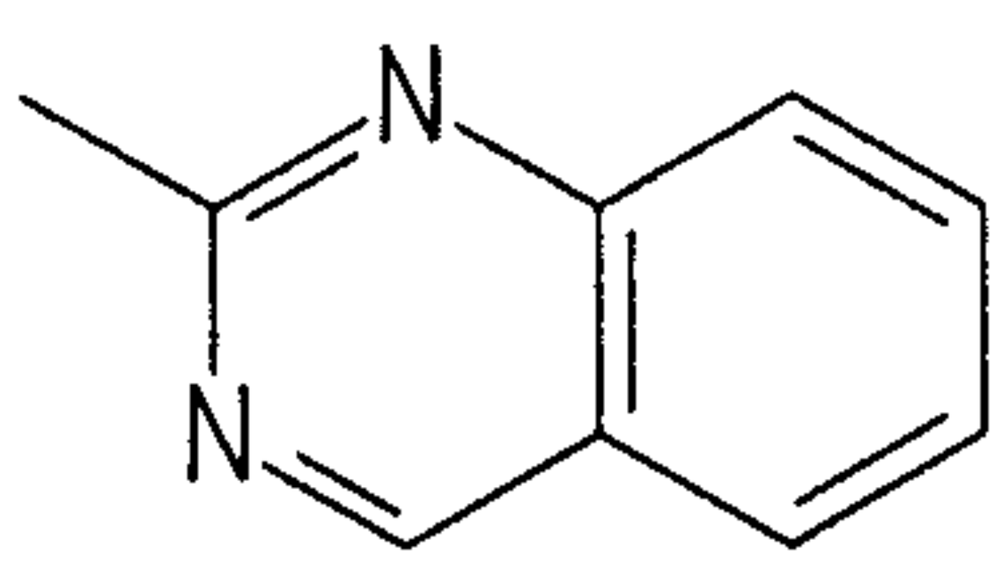
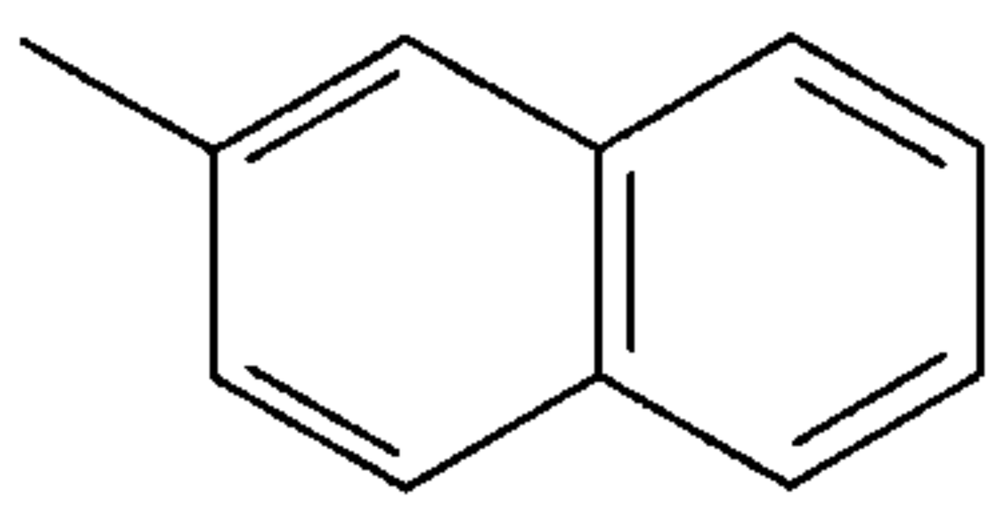
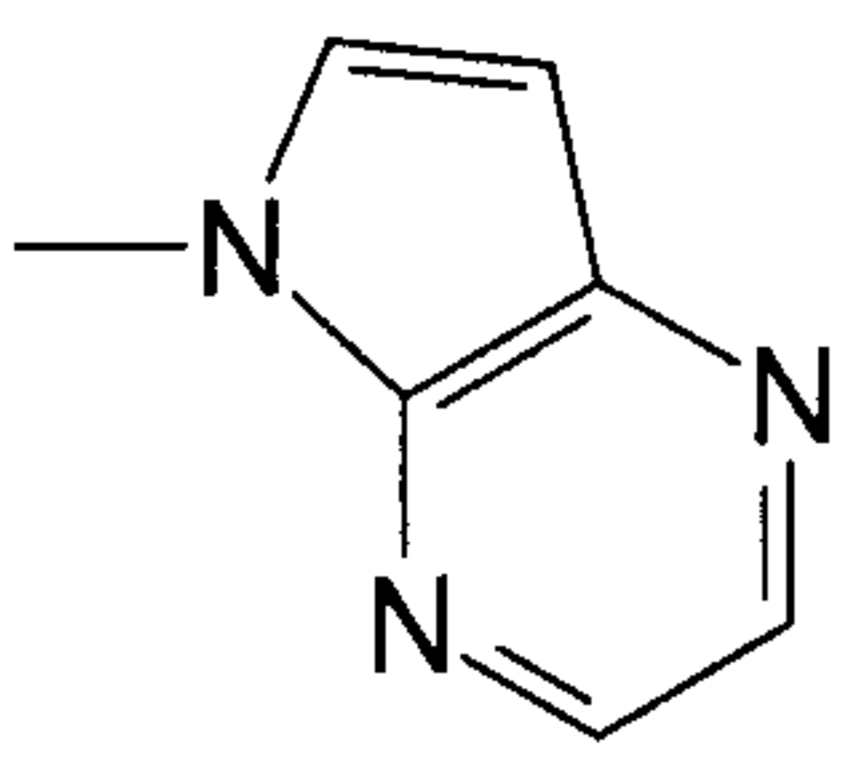
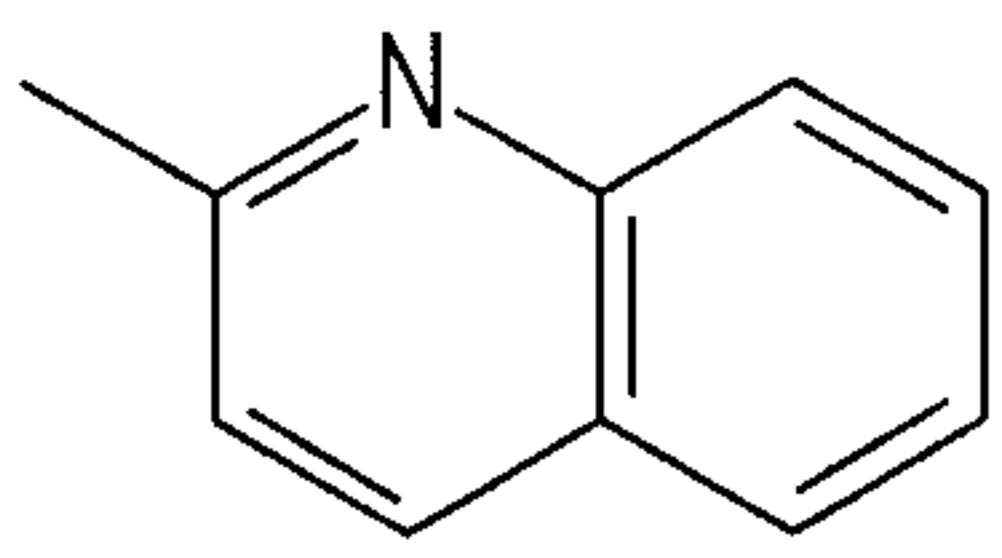
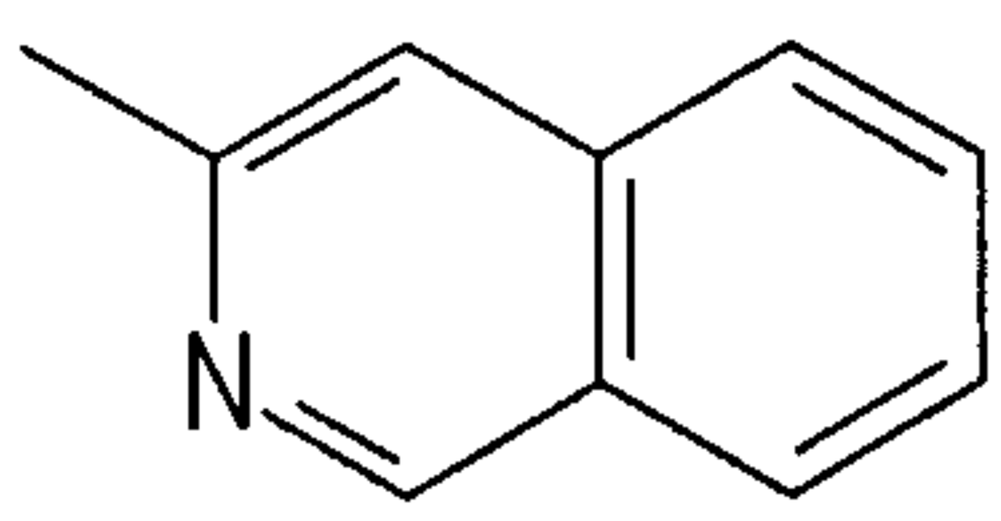
 ,  ,  ,  ,

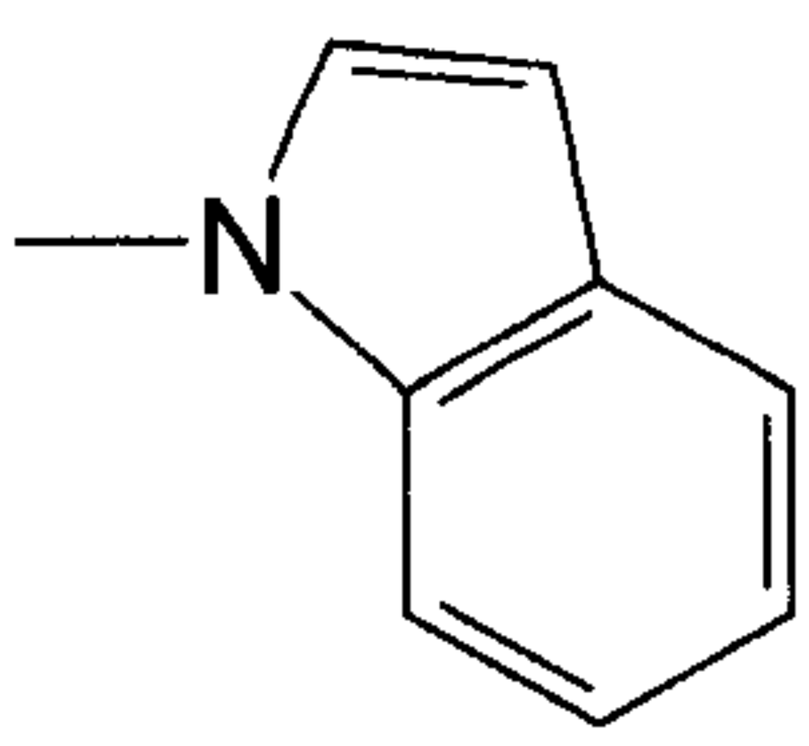
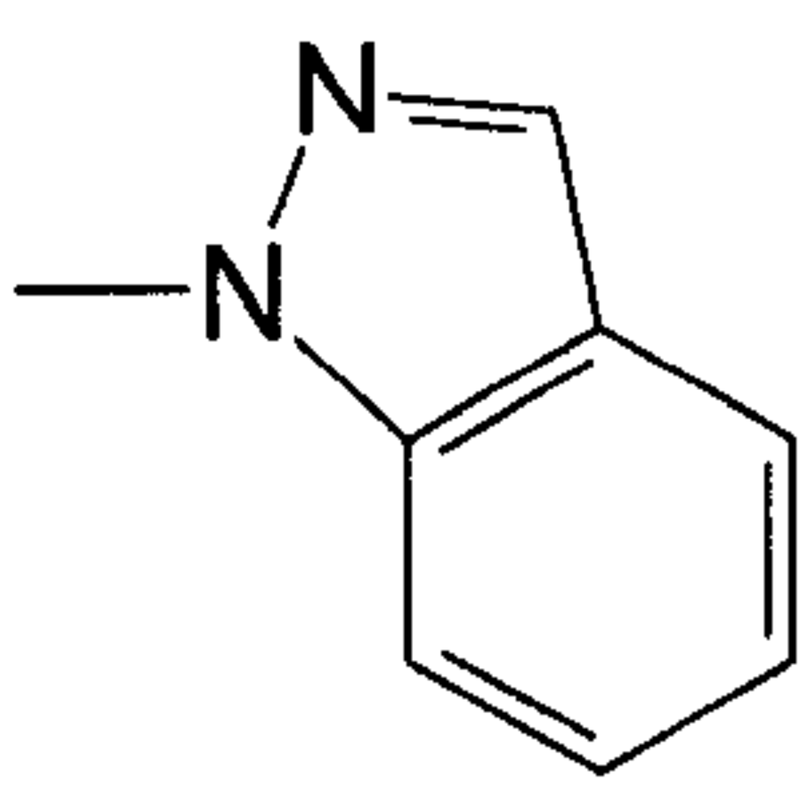
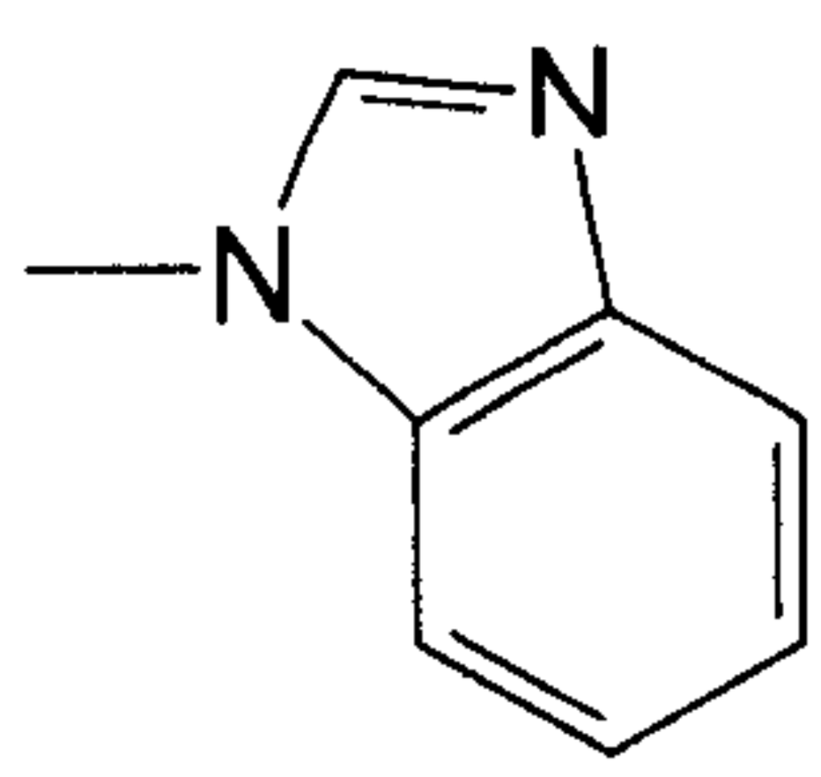
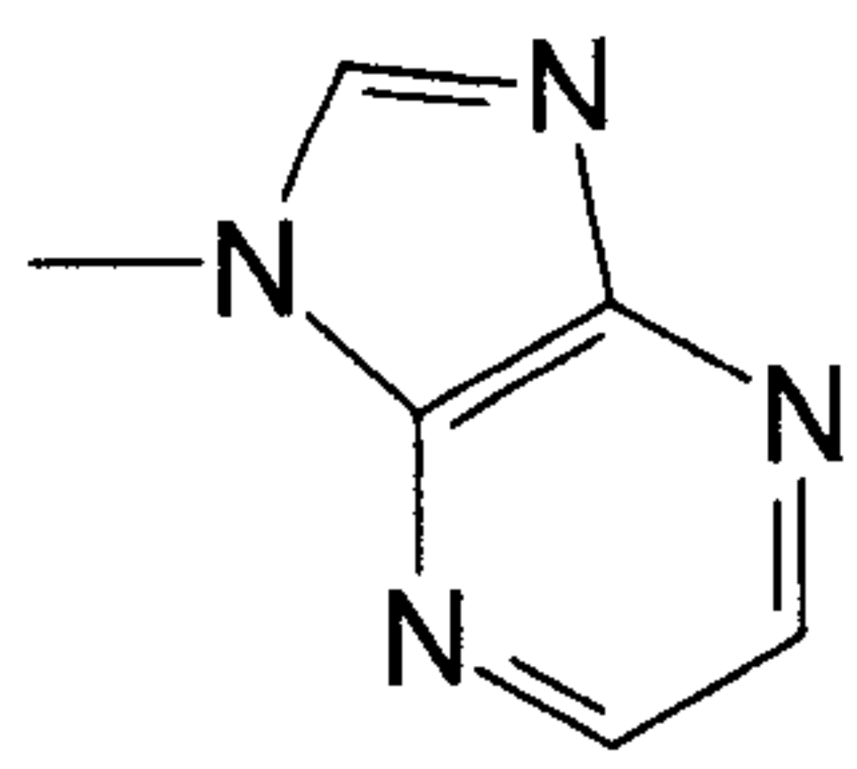
 ,  ,  ,  ,

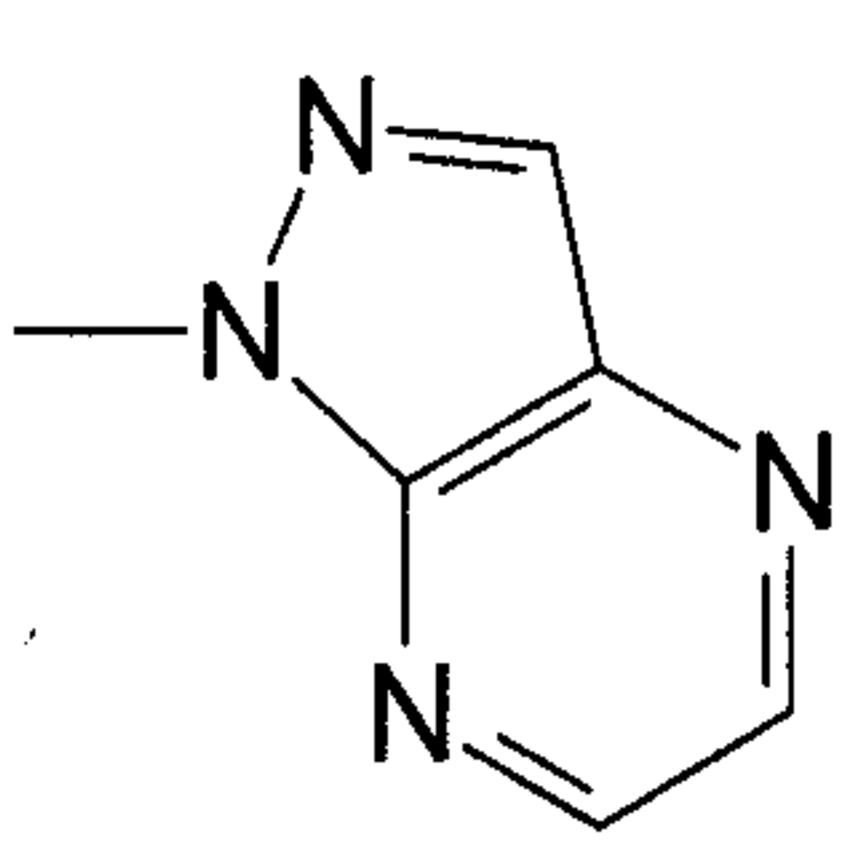
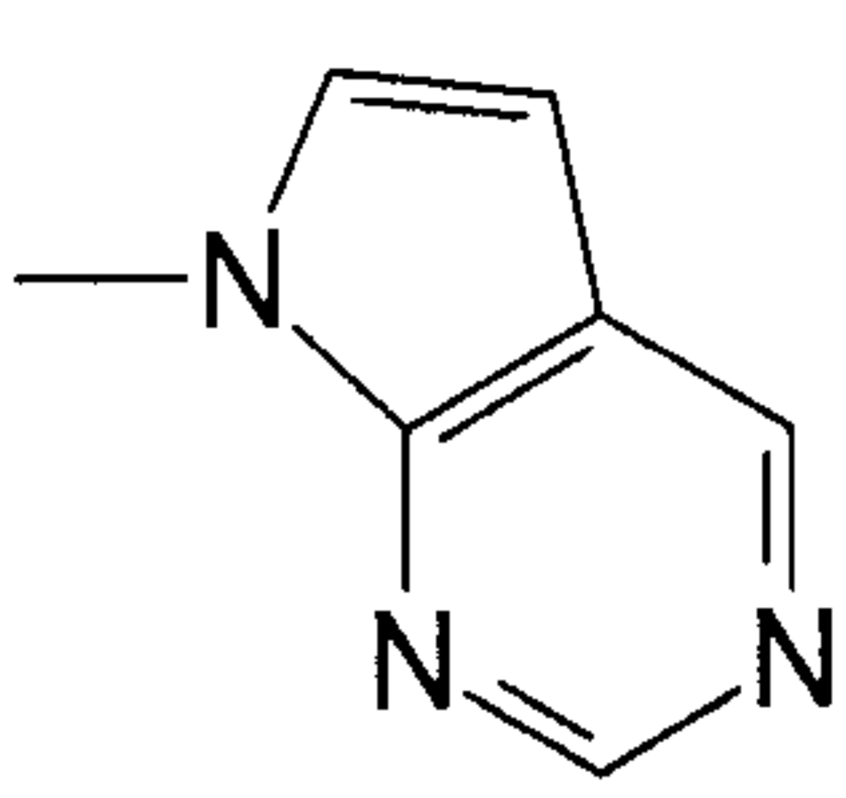
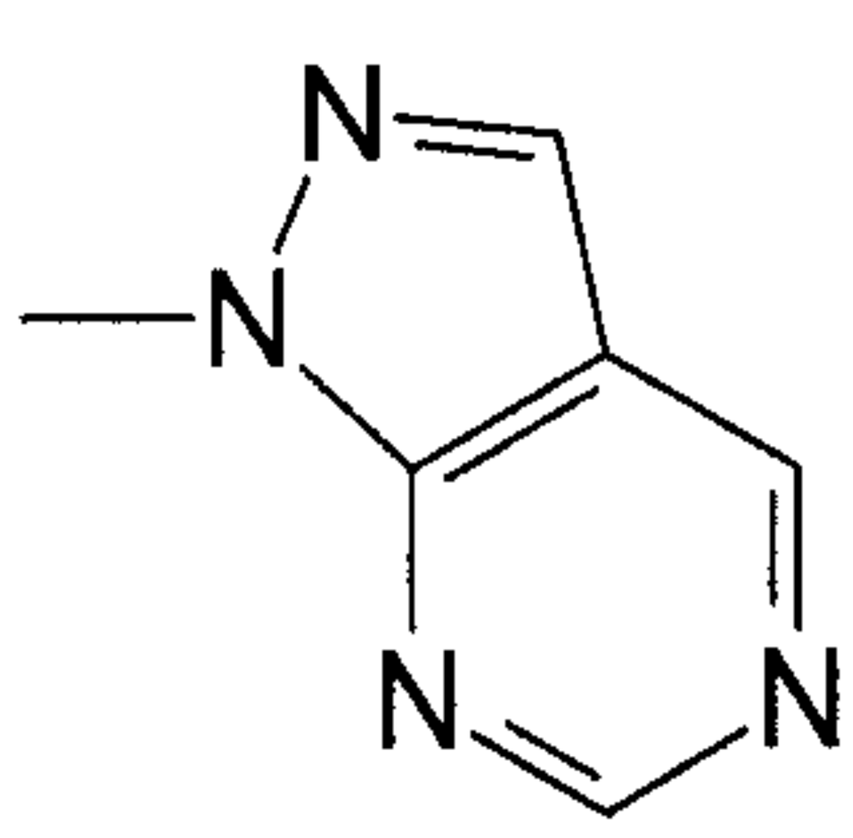
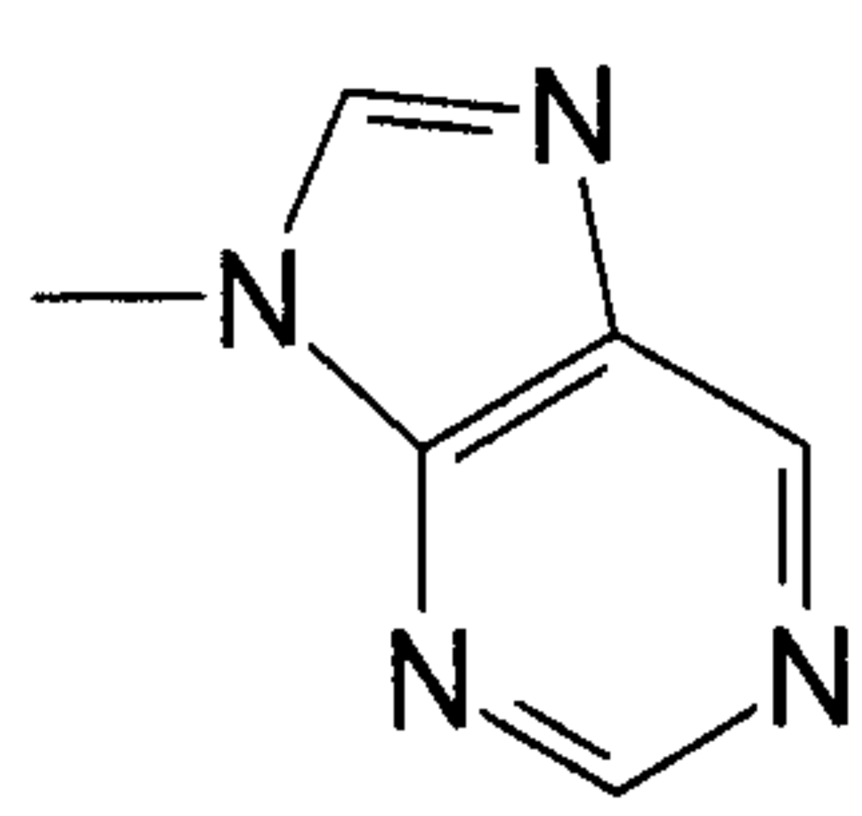
 ,  ,  ,

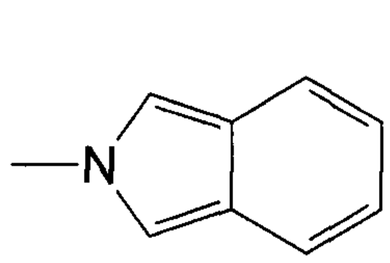
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,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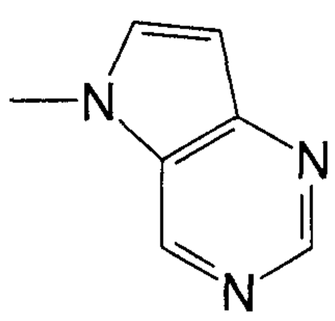
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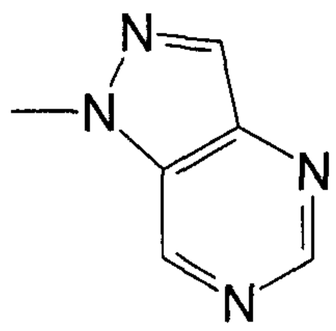
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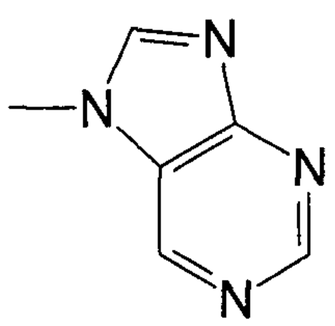
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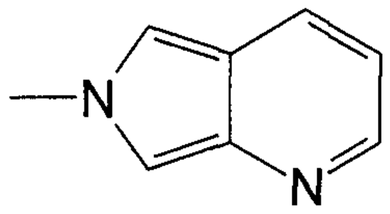
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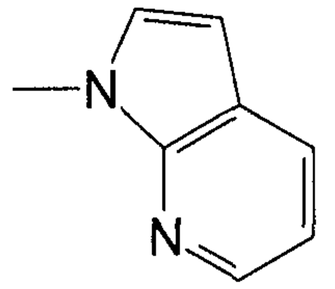
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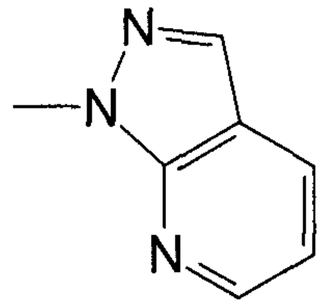
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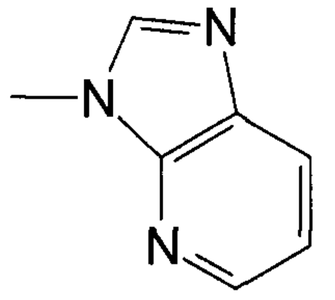
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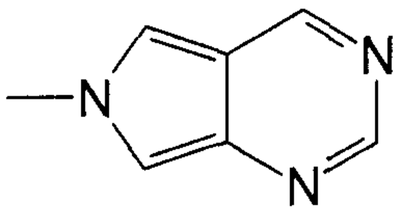
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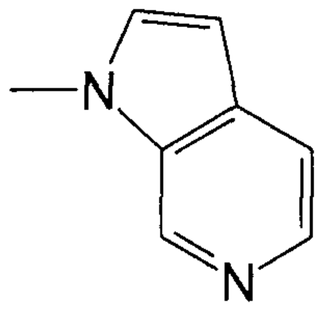
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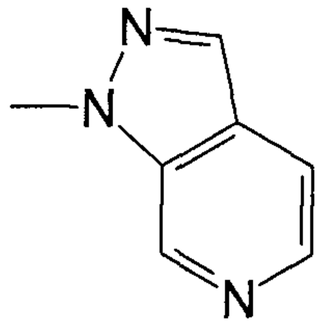
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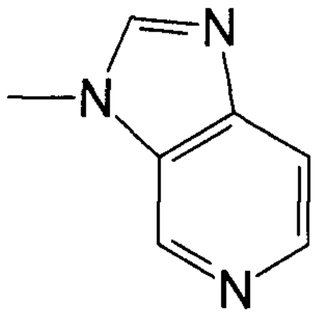
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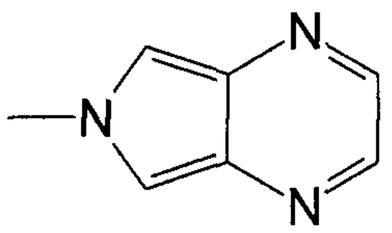
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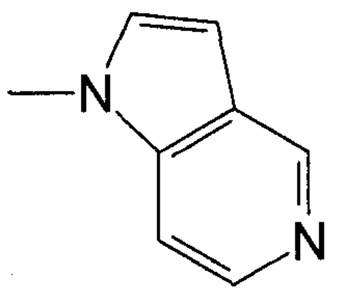
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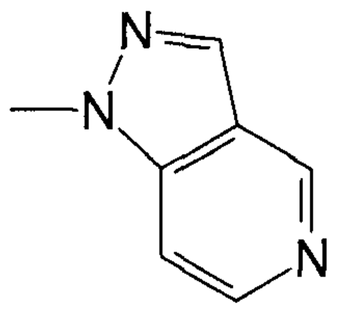
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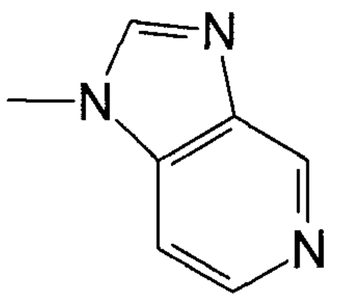
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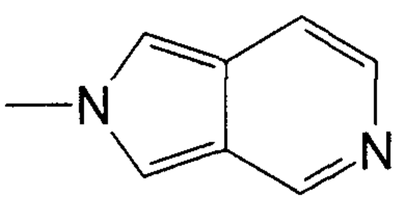
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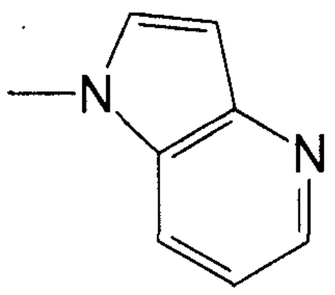
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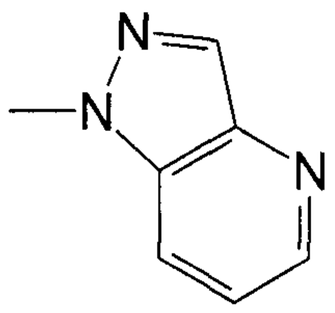
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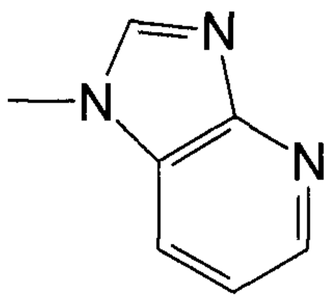
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R^{56}, R^{57}, R^{94} and R^{103} each independently represents: $-CR^{58}R^{16}R^{17}$, $-CR^{58}R^{59}R^{60}$, $-CR^{16}R^{17}-CR^{61}R^{62}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}R^{58}$, $-CR^{16}R^{17}-CR^{61}R^{62}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}-CR^{63}R^{64}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}R^{58}$, $-CR^{16}R^{17}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}-CR^{63}R^{64}-CR^{66}R^{67}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}-CR^{65}R^{66}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{16}R^{17}R^{58}$, $-CR^{16}R^{17}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}-CR^{65}R^{66}-CR^{67}R^{68}R^{69}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{16}R^{17}-CR^{67}R^{68}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{16}R^{17}R^{58}$, $-CR^{16}R^{17}-CR^{61}R^{62}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}-CR^{69}R^{70}R^{58}$, $-CR^{59}R^{60}-CR^{16}R^{17}-CR^{63}R^{64}-CR^{65}R^{66}-CR^{67}R^{68}-CR^{69}R^{70}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-CR^{16}R^{17}-CR^{65}R^{66}-CR^{67}R^{68}-CR^{69}R^{70}R^{58}$, $-CR^{59}R^{60}-CR^{61}R^{62}-$

$CR^{63}R^{64}–CR^{16}R^{17}–CR^{67}R^{68}–CR^{69}R^{70}R^{58}$, $–CR^{59}R^{60}–CR^{61}R^{62}–CR^{63}R^{64}–CR^{65}R^{66}–CR^{16}R^{17}–CR^{69}R^{70}R^{58}$, or $–CR^{59}R^{60}–CR^{61}R^{62}–CR^{63}R^{64}–CR^{65}R^{66}–CR^{67}R^{68}–CR^{16}R^{17}R^{58}$;

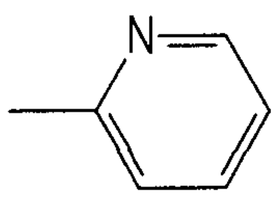
$R^{58} – R^{70}$ each independently represents: –H, $–NH_2$, –OH, –F, –Cl, –Br, –I, $–R^{71}$, $–O–R^{71}$, $–R^{72}$, $–O–R^{95}$, $–R^{96}$, $–O–R^{104}$, $–R^{105}$, –COOH, $–COOCH_3$, $–COOC_2H_5$, $–COOC_3H_7$, $–COOCH(CH_3)_2$, $–COOC(CH_3)_3$, $–(C=O)–NR^{16}R^{17}$, $–SO_2–NR^{16}R^{17}$, $–SO_m–R^{16}R^{17}$, $–CR^{16}R^{17}H$, or $–NR^{16}R^{17}$;

R^{108}, R^{117} and R^{129} each independently represents: $–CH=CH_2$, $–CH_2–CH=CH_2$, –H, $–C(CH_3)=CH_2$, $–CH=CH–CH_3$, $–C_2H_4–CH=CH_2$, $–CH_2–CH=CH–CH_3$, $–CH=CH–C_2H_5$, $–CH_2–C(CH_3)=CH_2$, $–CH(CH_3)–CH=CH$, $–CH=C(CH_3)_2$, $–C(CH_3)=CH–CH_3$, $–CH=CH–CH=CH_2$, $–C_3H_6–CH=CH_2$, $–C_2H_4–CH=CH–CH_3$, $–CH_2–CH=CH–C_2H_5$, $–CH=CH–C_3H_7$, $–CH_2–CH=CH–CH=CH_2$, $–CH=CH–CH=CH–CH_3$, $–CH=CH–CH_2–CH=CH_2$, $–C(CH_3)=CH–CH=CH_2$, $–CH=C(CH_3)–CH=CH_2$, $–CH=CH–C(CH_3)=CH_2$, $–C_2H_4–C(CH_3)=CH_2$, $–CH_2–CH(CH_3)–CH=CH_2$, $–CH(CH_3)–CH_2–CH=CH_2$, $–CH_2–CH=C(CH_3)_2$, $–CH_2–C(CH_3)=CH–CH_3$, $–CH(CH_3)–CH=CH–CH_3$, $–CH=CH–CH(CH_3)_2$, $–CH=C(CH_3)–C_2H_5$, $–C(CH_3)=CH–C_2H_5$, $–C(CH_3)=C(CH_3)_2$, $–C(CH_3)_2–CH=CH_2$, $–CH(CH_3)–C(CH_3)=CH_2$, $–C(CH_3)=CH–CH=CH_2$, $–CH=C(CH_3)–CH=CH_2$, $–CH=CH–C(CH_3)=CH_2$, $–C_4H_8–CH=CH_2$, $–C_3H_6–CH=CH–CH_3$, $–C_2H_4–CH=CH–C_2H_5$, $–CH_2–CH=CH–C_3H_7$, $–CH=CH–C_4H_9$, $–C_3H_6–C(CH_3)=CH_2$, $–C_2H_4–CH(CH_3)–CH=CH_2$, $–CH_2–CH(CH_3)–CH_2–CH=CH_2$, $–CH(CH_3)–C_2H_4–CH=CH_2$, $–C_2H_4–CH=C(CH_3)_2$, $–C_2H_4–C(CH_3)=CH–CH_3$, $–CH_2–CH(CH_3)–CH=CH–CH_3$, $–CH(CH_3)–CH_2–CH=CH–CH_3$, $–CH_2–CH=CH–CH(CH_3)_2$, $–CH_2–CH=C(CH_3)–C_2H_5$, $–CH(CH_3)–CH=CH–C_2H_5$, $–CH=CH–CH_2–CH(CH_3)_2$, $–CH=CH–CH(CH_3)–C_2H_5$, $–CH=C(CH_3)–C_3H_7$, $–C(CH_3)=CH–C_3H_7$, $–CH_2–CH(CH_3)–C(CH_3)=CH_2$, $–CH(CH_3)–CH_2–C(CH_3)=CH_2$, $–CH(CH_3)–CH(CH_3)–CH=CH_2$, $–CH_2–C(CH_3)_2–CH=CH_2$, $–C(CH_3)_2–CH_2–CH=CH_2$, $–CH_2–C(CH_3)=C(CH_3)_2$, $–CH(CH_3)–CH=C(CH_3)_2$, $–C(CH_3)_2–CH=CH–CH_3$, $–CH(CH_3)–C(CH_3)=CH–CH_3$, $–CH=C(CH_3)–CH(CH_3)_2$, $–C(CH_3)=CH–CH(CH_3)_2$, $–C(CH_3)=C(CH_3)–C_2H_5$, $–CH=CH–C(CH_3)_3$, $–C(CH_3)_2–C(CH_3)=CH_2$, $–CH(C_2H_5)–C(CH_3)=CH_2$, $–C(CH_3)(C_2H_5)–CH=CH_2$, $–CH(CH_3)–C(C_2H_5)=CH_2$, $–CH_2–C(C_3H_7)=CH_2$, $–CH_2–C(C_2H_5)=CH–CH_3$, $–CH(C_2H_5)–CH=CH–CH_3$, $–C(C_4H_9)=CH_2$, $–C(C_3H_7)=CH–CH_3$, $–C(C_2H_5)=CH–C_2H_5$, $–C(C_2H_5)=C(CH_3)_2$,

$-C[C(CH_3)_3]=CH_2$, $-C[CH(CH_3)(C_2H_5)]=CH_2$, $-C[CH_2-CH(CH_3)_2]=CH_2$, $-C_2H_4-CH=CH-CH=CH_2$, $-CH_2-CH=CH-CH_2-CH=CH_2$, $-CH=CH-C_2H_4-CH=CH_2$, $-CH_2-CH=CH-CH=CH-CH_3$, $-CH=CH-CH_2-CH=CH-CH_3$, $-CH=CH-CH=CH-C_2H_5$, $-CH_2-CH=CH-C(CH_3)=CH_2$, $-CH_2-CH=C(CH_3)-CH=CH_2$, $-CH_2-C(CH_3)=CH-CH=CH_2$, $-CH(CH_3)-CH=CH-CH=CH_2$, $-CH=CH-CH_2-C(CH_3)=CH_2$, $-CH=CH-CH(CH_3)-CH=CH_2$, $-CH=C(CH_3)-CH_2-CH=CH_2$, $-C(CH_3)=CH-CH_2-CH=CH_2$, $-CH=CH-CH=C(CH_3)_2$, $-CH=CH-C(CH_3)=CH-CH_3$, $-CH=C(CH_3)-CH=CH-CH_3$, $-C(CH_3)=CH-CH=CH-CH_3$, $-CH=C(CH_3)-C(CH_3)=CH_2$, $-C(CH_3)=CH-C(CH_3)=CH_2$, $-C(CH_3)=C(CH_3)-CH=CH_2$, or $-CH=CH-CH=CH-CH=CH_2$;

R^{109}, R^{118} and R^{130} each independently represents: $-H$, $-C\equiv CH$, $-C\equiv C-CH_3$, $-CH_2-C\equiv CH$, $-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-CH_3$, $-C\equiv C-C_2H_5$, $-C_3H_6-C\equiv CH$, $-C_2H_4-C\equiv C-CH_3$, $-CH_2-C\equiv C-C_2H_5$, $-C\equiv C-C_3H_7$, $-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C\equiv C-CH_3$, $-C_4H_8-C\equiv CH$, $-C_3H_6-C\equiv C-CH_3$, $-C_2H_4-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-C_3H_7$, $-C\equiv C-C_4H_9$, $-C_2H_4-CH(CH_3)-C\equiv CH$, $-CH_2-CH(CH_3)-CH_2-C\equiv CH$, $-CH(CH_3)-C_2H_4-C\equiv CH$, $-CH_2-CH(CH_3)-C\equiv C-CH_3$, $-CH(CH_3)-CH_2-C\equiv C-CH_3$, $-CH(CH_3)-C\equiv C-C_2H_5$, $-CH_2-C\equiv C-CH(CH_3)_2$, $-C\equiv C-CH(CH_3)-C_2H_5$, $-C\equiv C-CH_2-CH(CH_3)_2$, $-C\equiv C-C(CH_3)_3$, $-CH(C_2H_5)-C\equiv C-CH_3$, $-C(CH_3)_2-C\equiv C-CH_3$, $-CH(C_2H_5)-CH_2-C\equiv CH$, $-CH_2-CH(C_2H_5)-C\equiv CH$, $-C(CH_3)_2-CH_2-C\equiv CH$, $-CH_2-C(CH_3)_2-C\equiv CH$, $-CH(CH_3)-CH(CH_3)-C\equiv CH$, $-CH(C_3H_7)-C\equiv CH$, $-C(CH_3)(C_2H_5)-C\equiv CH$, $-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-C\equiv CH$, $-C\equiv C-C\equiv C-CH_3$, $-CH(C\equiv CH)_2$, $-C_2H_4-C\equiv C-C\equiv CH$, $-CH_2-C\equiv C-CH_2-C\equiv CH$, $-C\equiv C-C_2H_4-C\equiv CH$, $-CH_2-C\equiv C-C\equiv C-CH_3$, $-C\equiv C-CH_2-C\equiv C-CH_3$, $-C\equiv C-C\equiv C-C_2H_5$, $-C\equiv C-CH(CH_3)-C\equiv CH$, $-CH(CH_3)-C\equiv C-C\equiv CH$, $-CH(C\equiv CH)-CH_2-C\equiv CH$, $-C(C\equiv CH)_2-CH_3$, $-CH_2-CH(C\equiv CH)_2$, or $-CH(C\equiv CH)-C\equiv C-CH_3$;

R^{113}, R^{115}, R^{121}, R^{124}, R^{126}, R^{127}, R^{133}, R^{135}, R^{137} and R^{138} each independently represents: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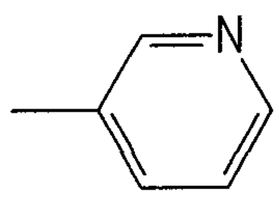
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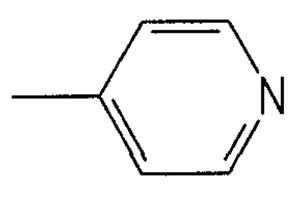
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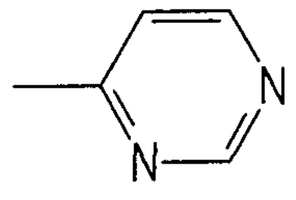
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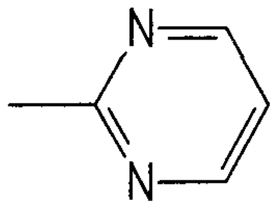
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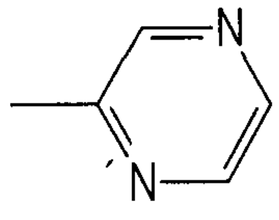
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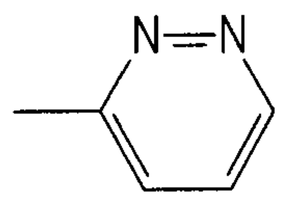
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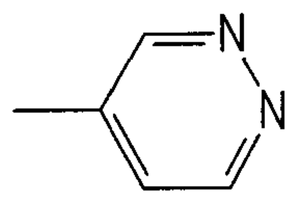
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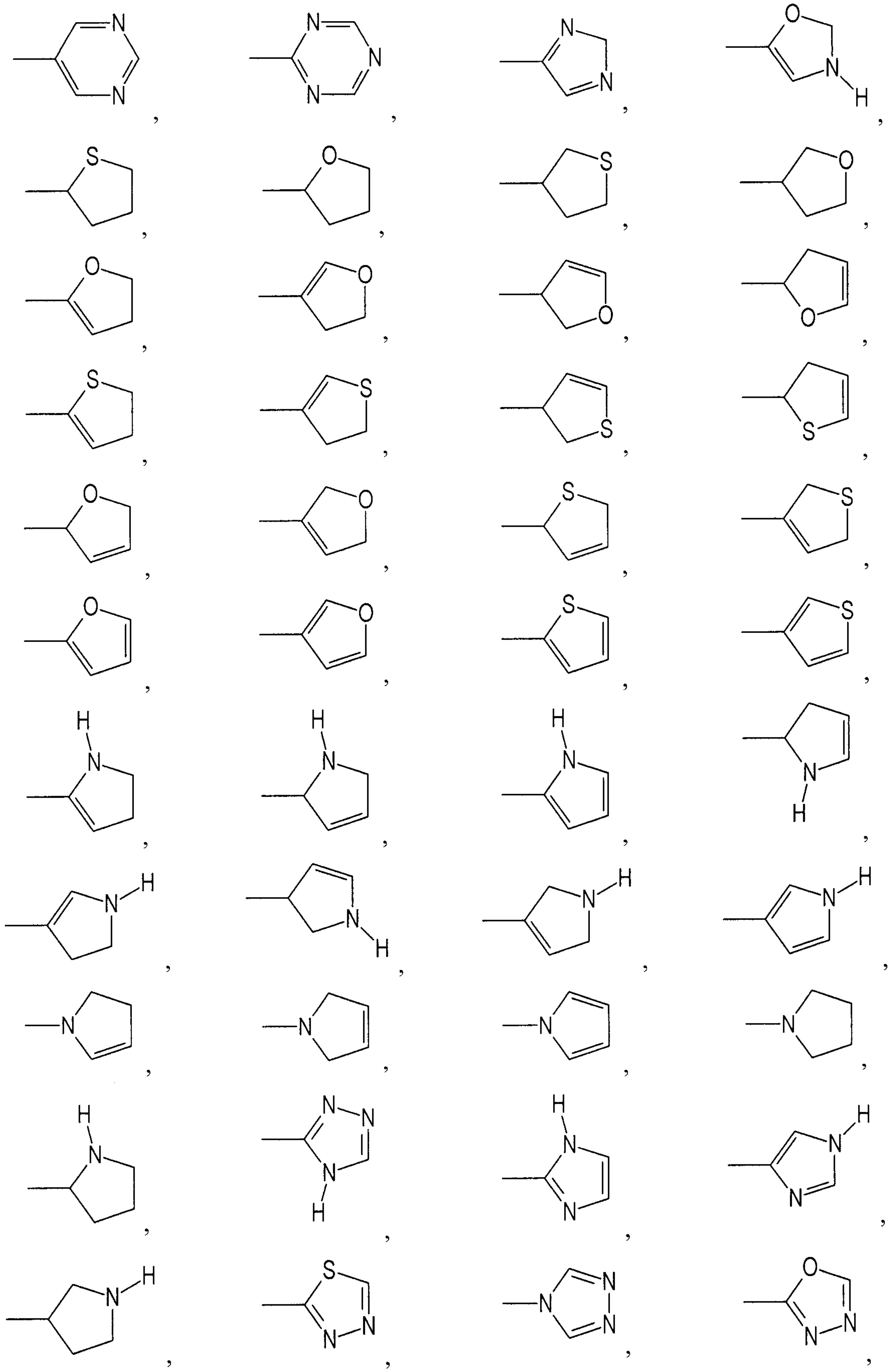

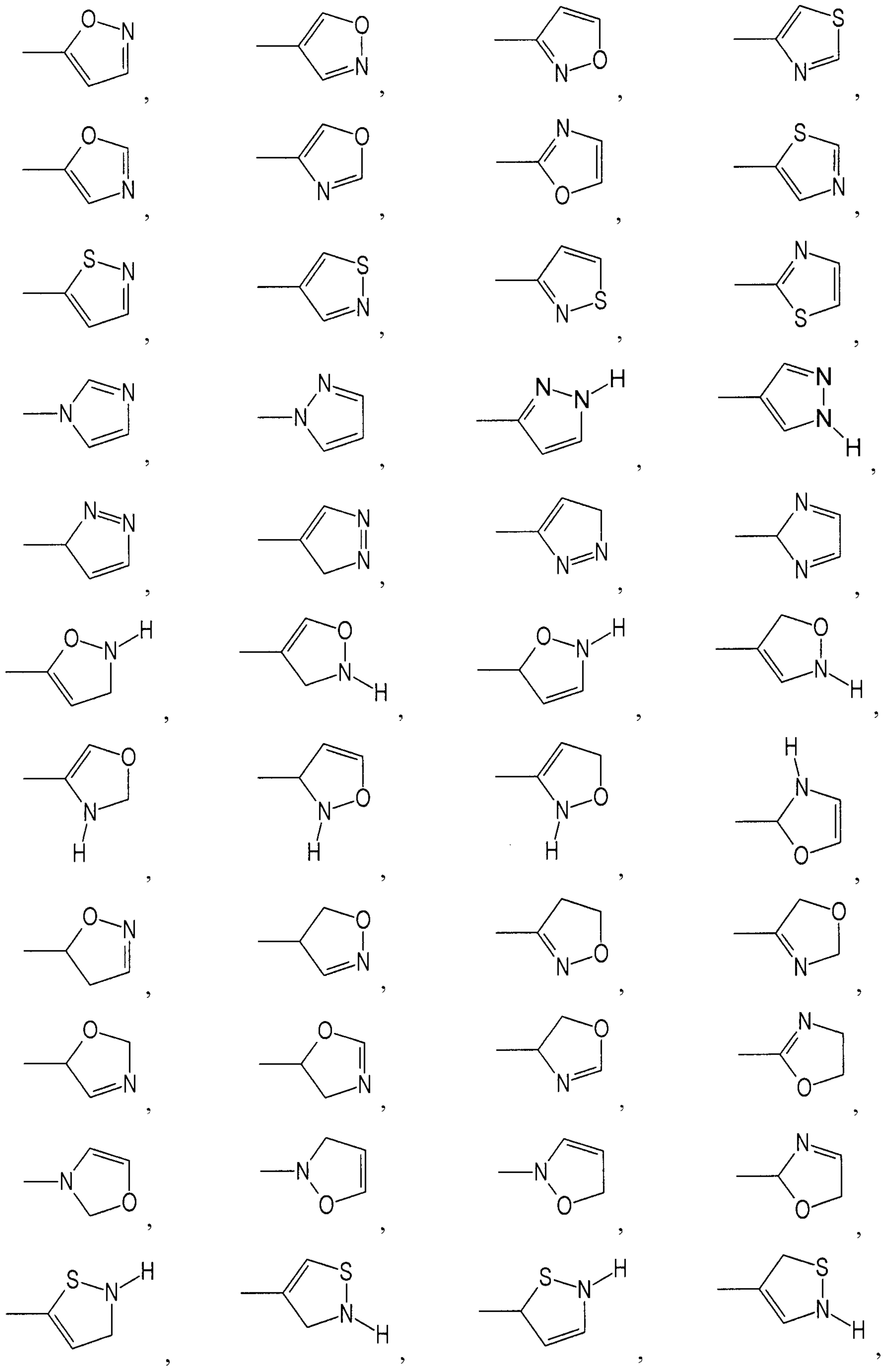
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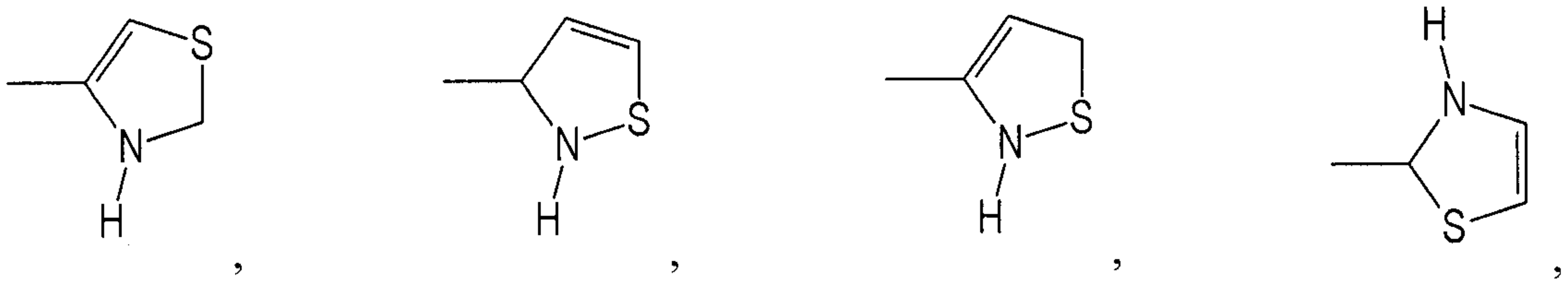
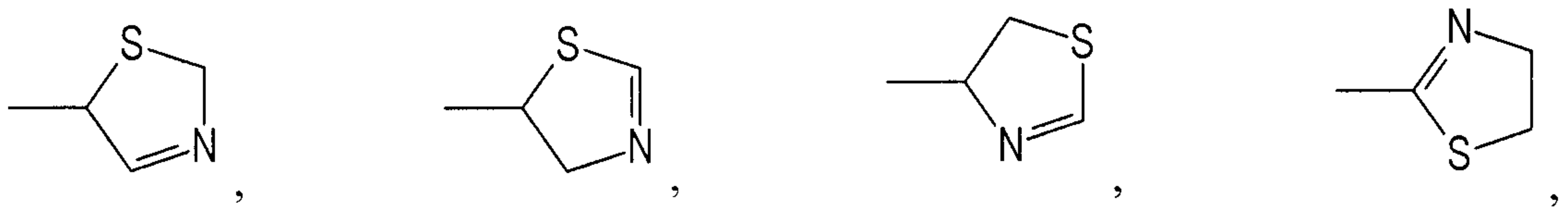
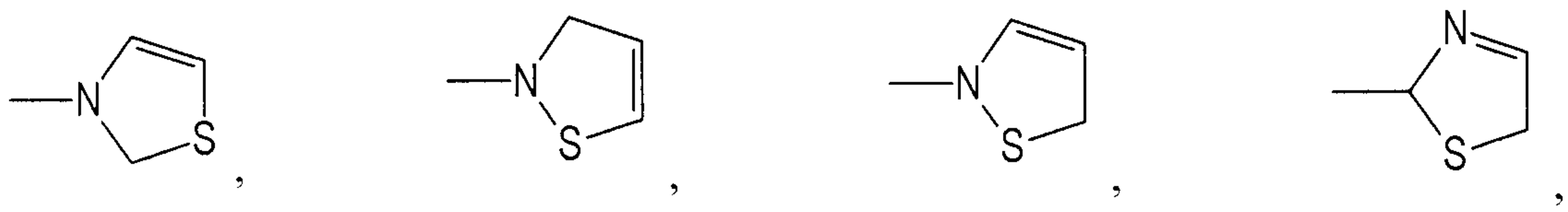
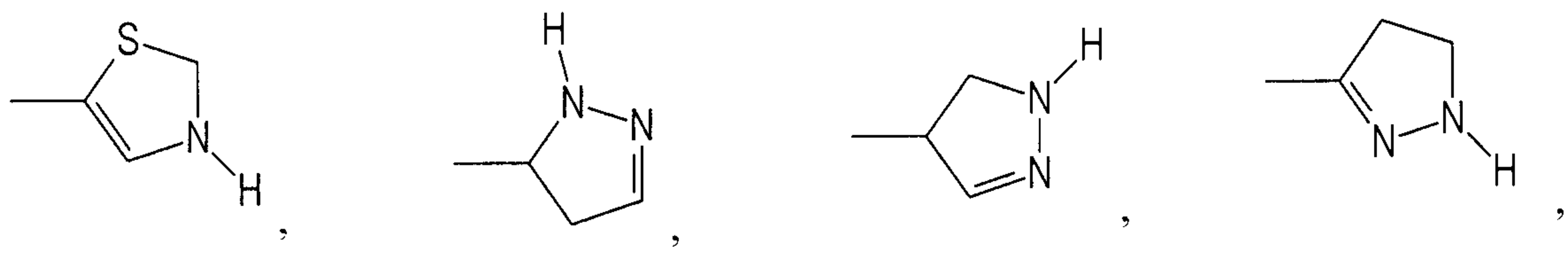
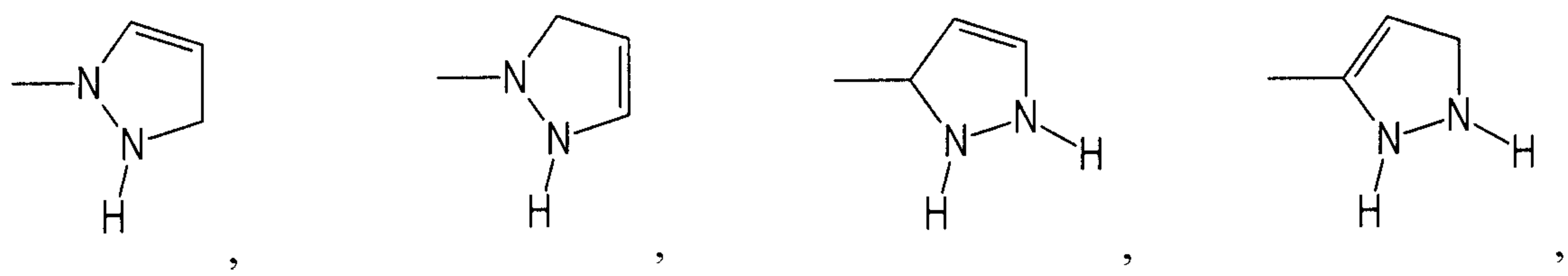
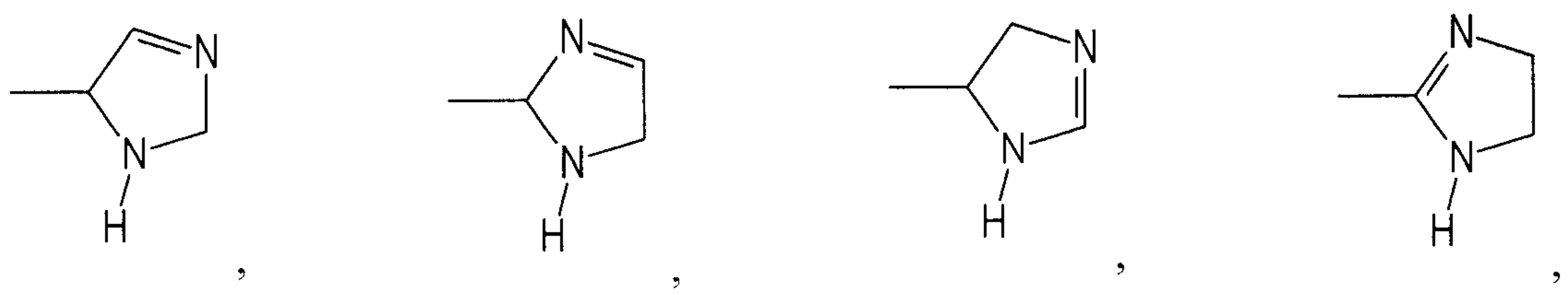


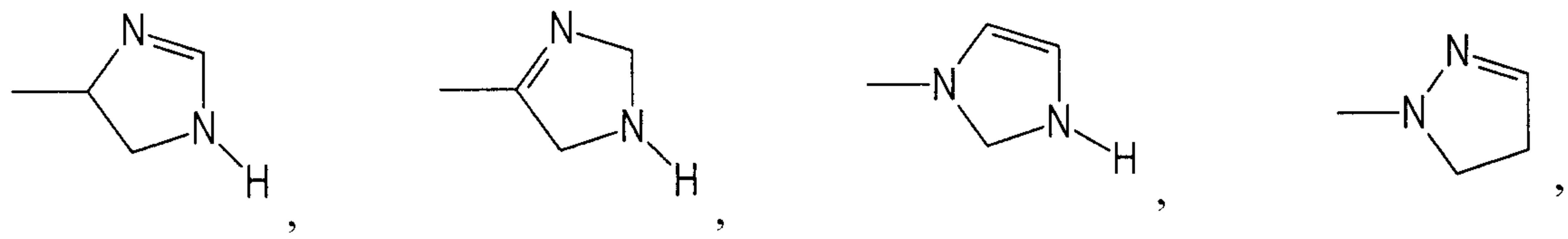


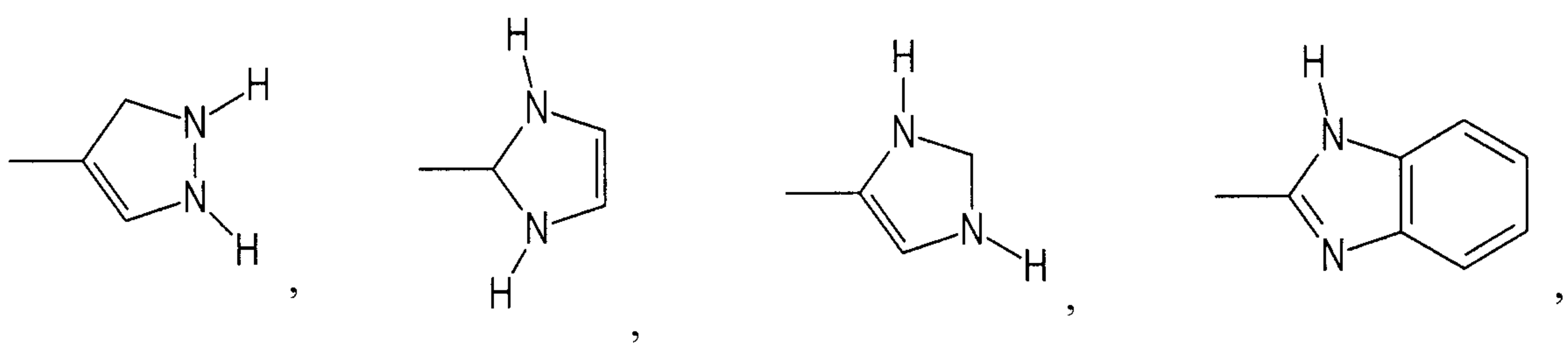


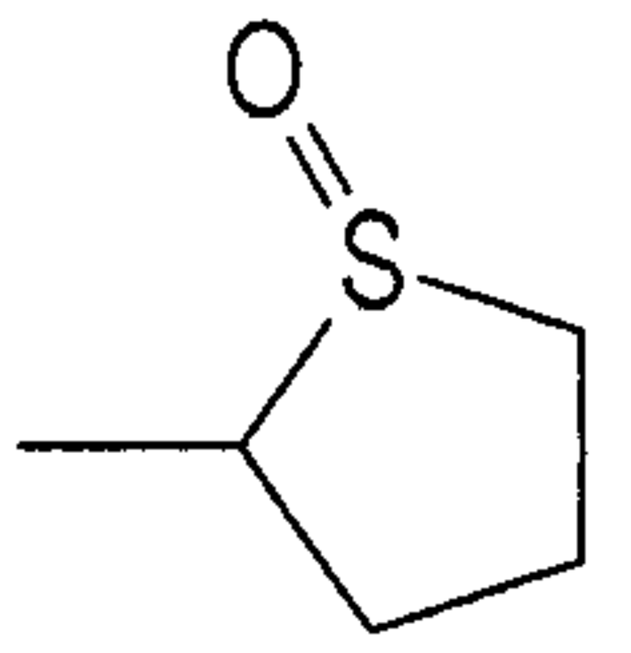
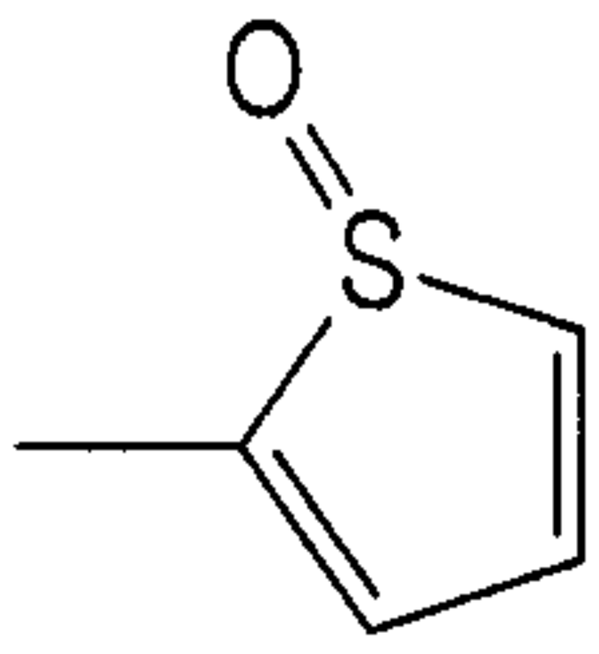
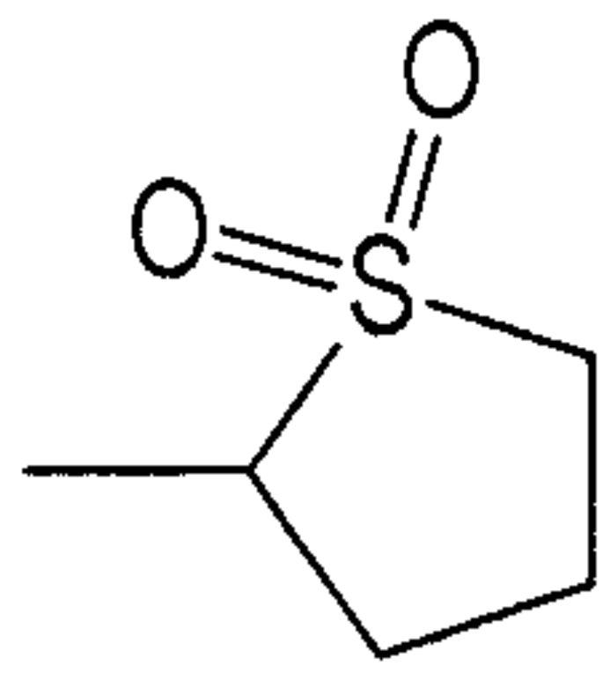
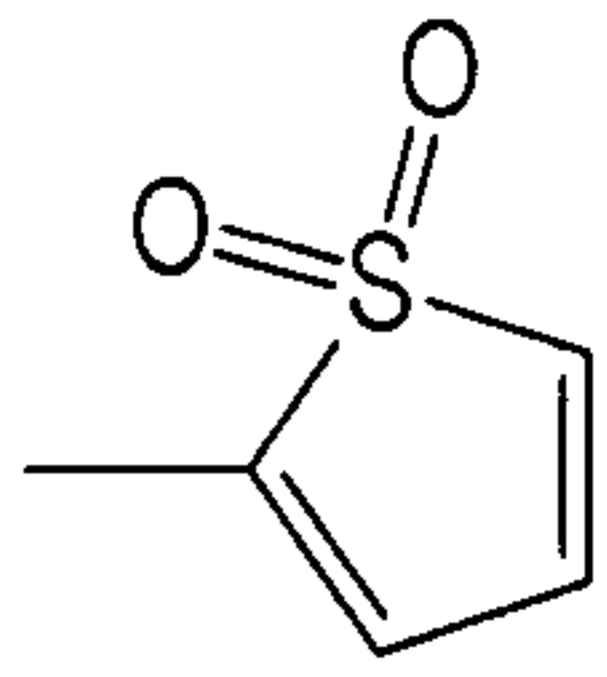


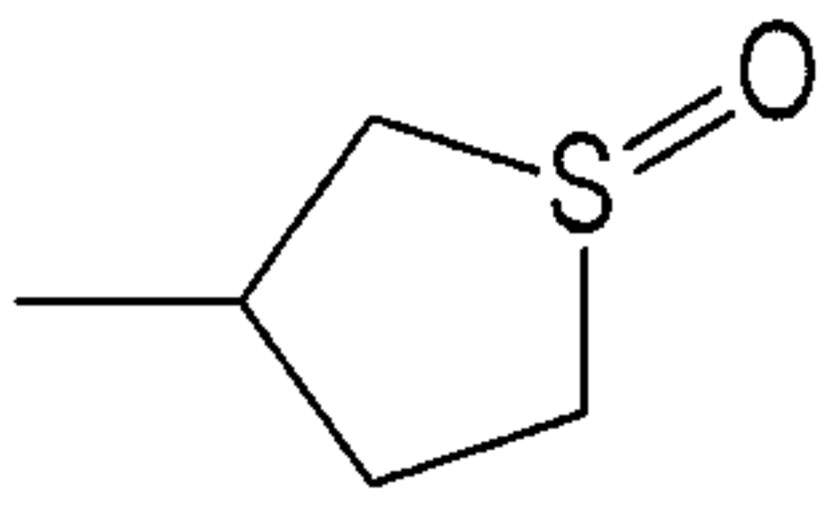
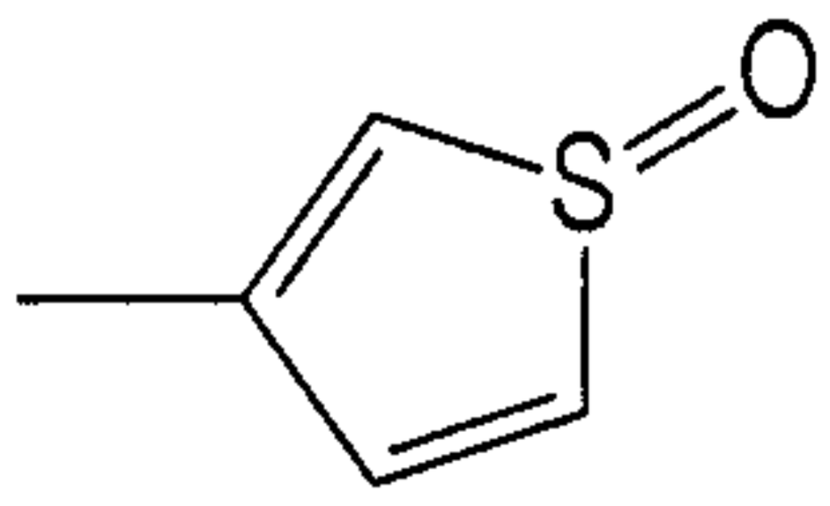
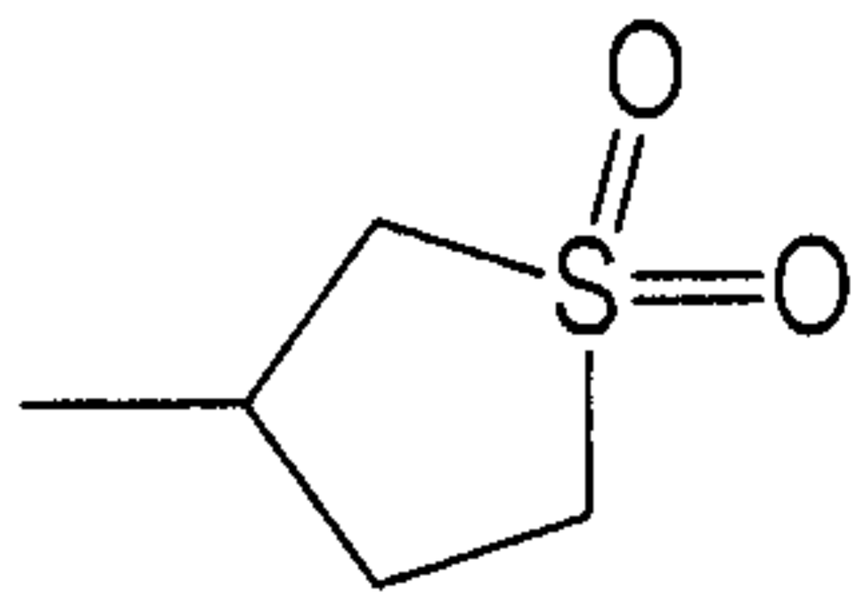
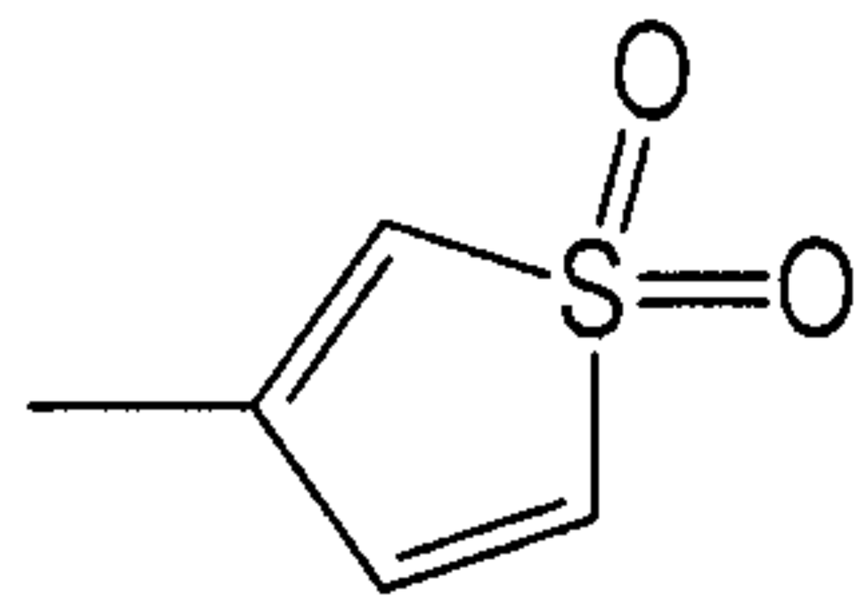


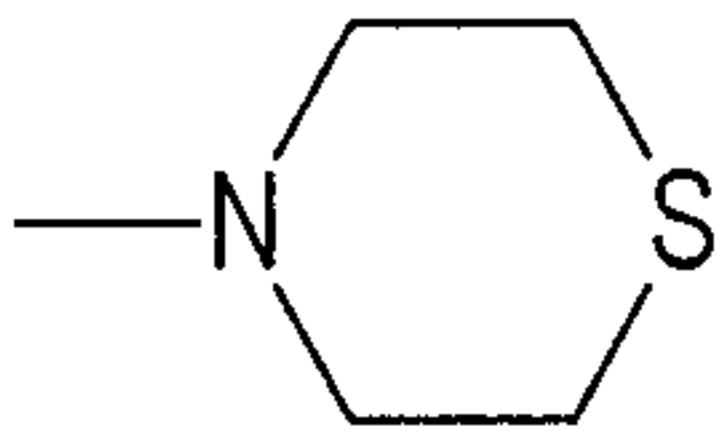
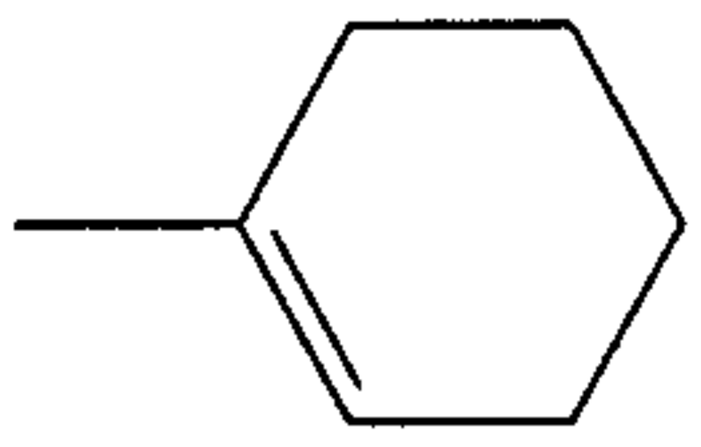
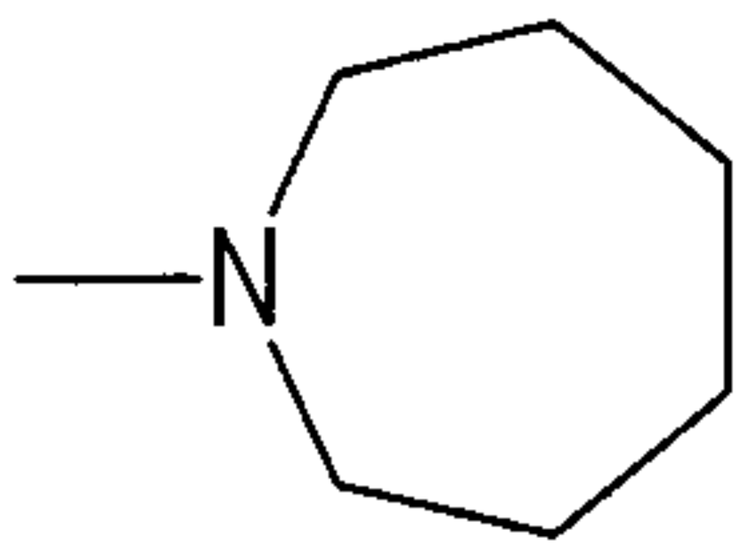
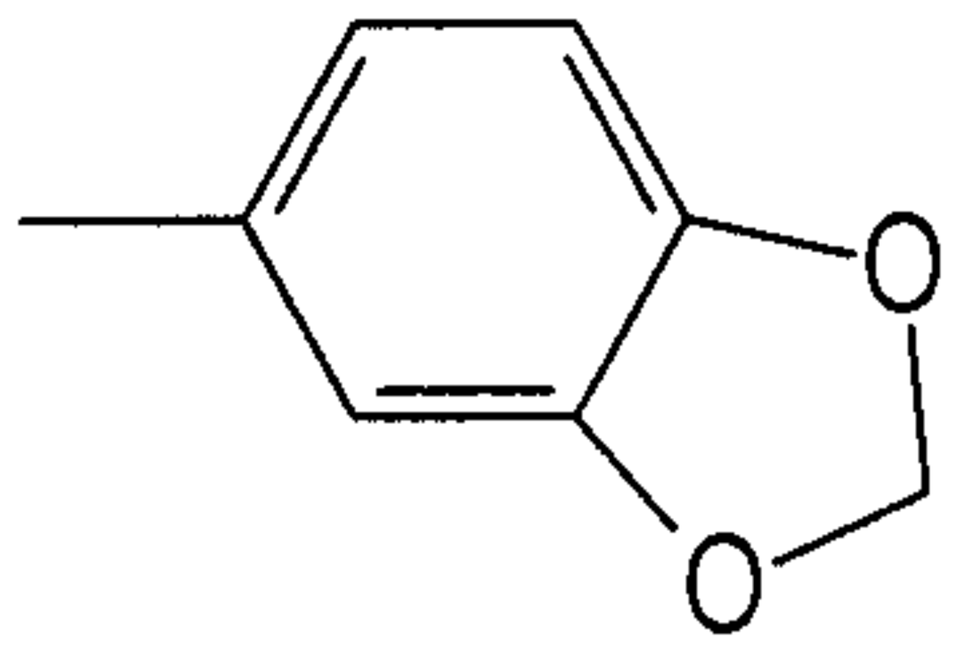


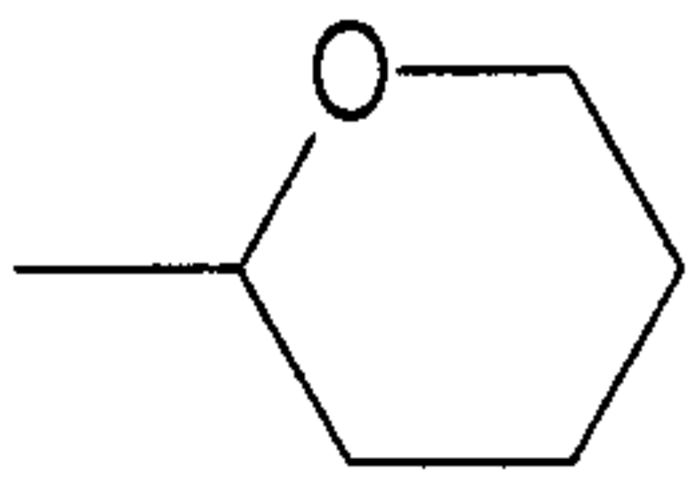
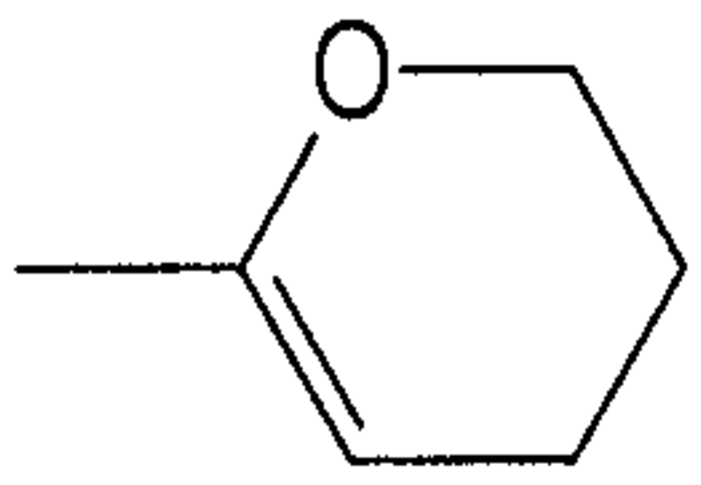
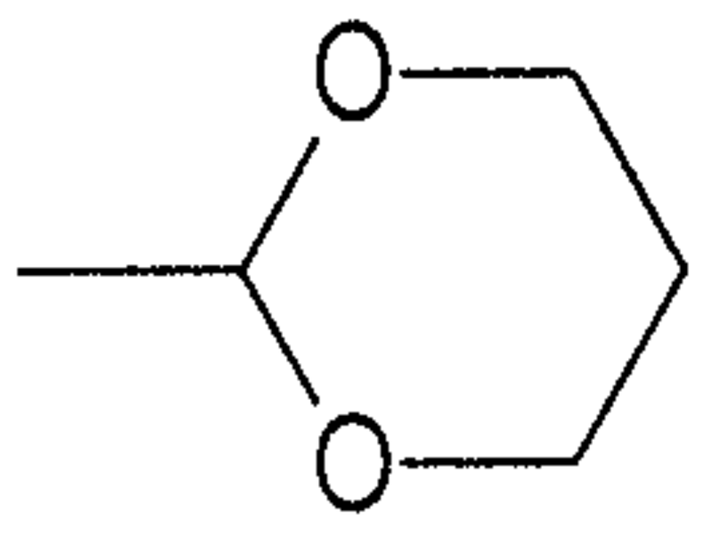
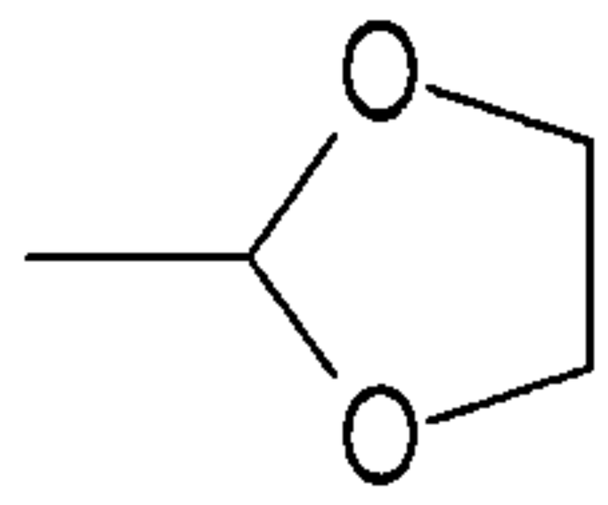


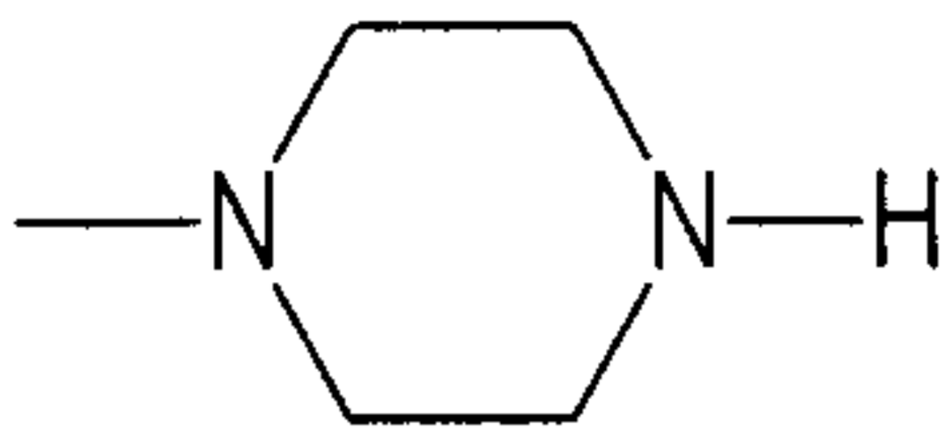
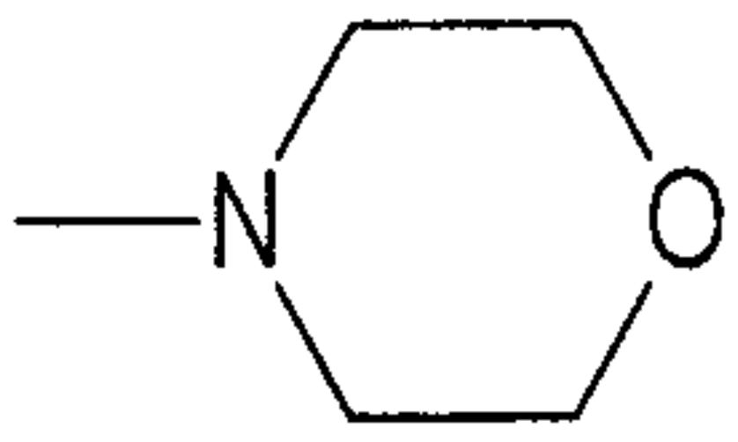
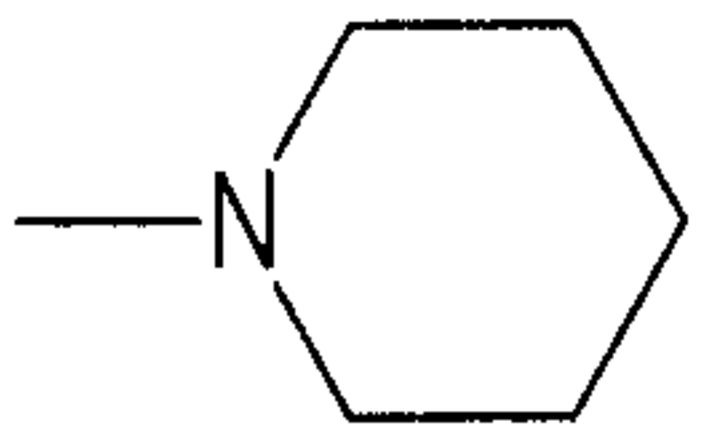
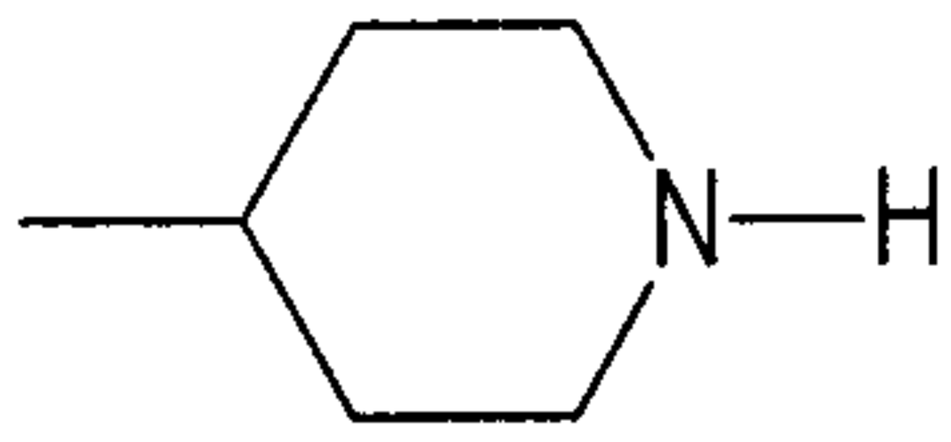


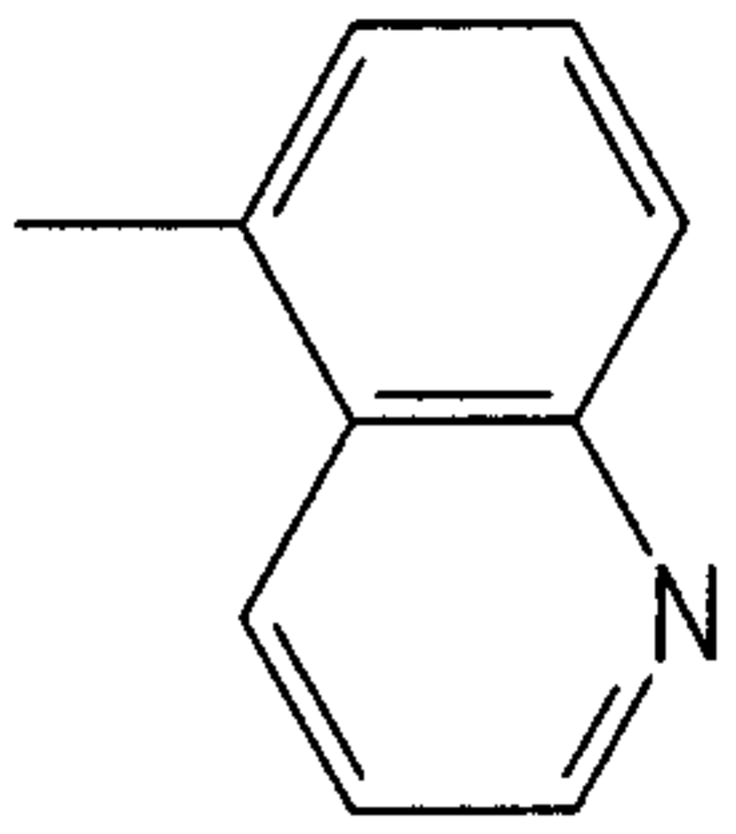
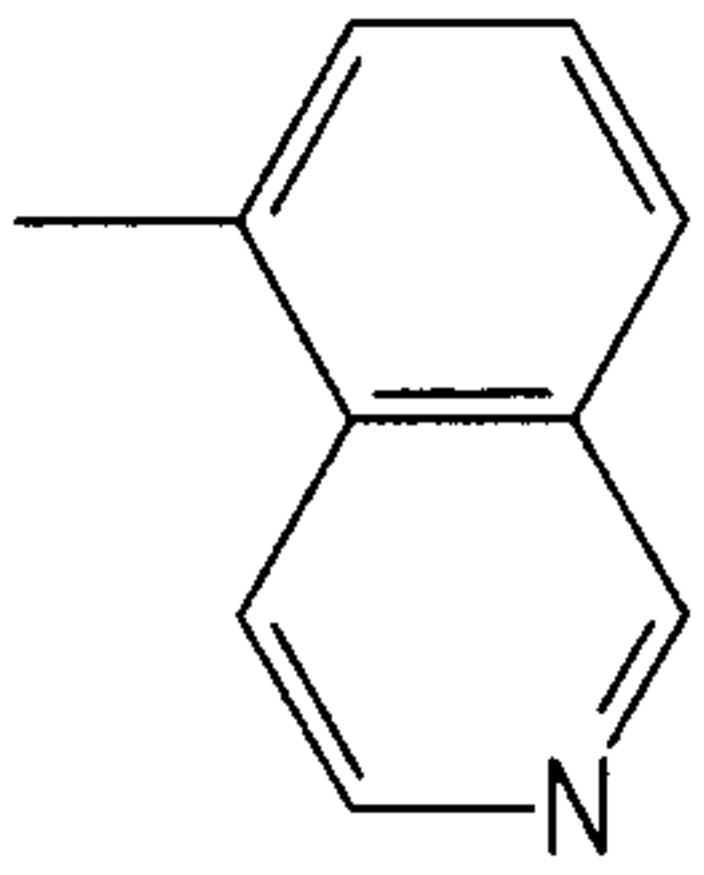
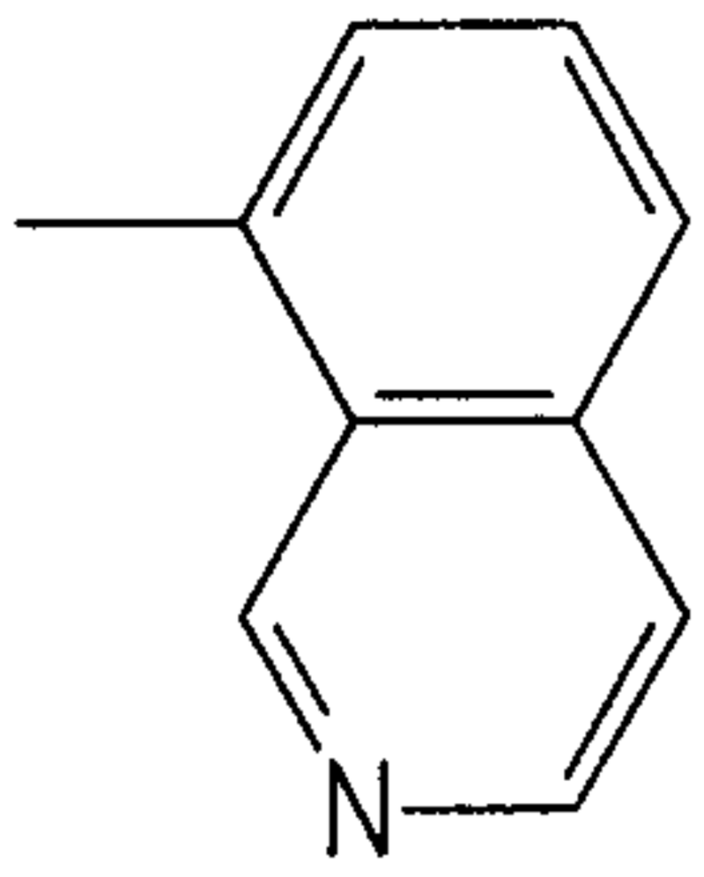
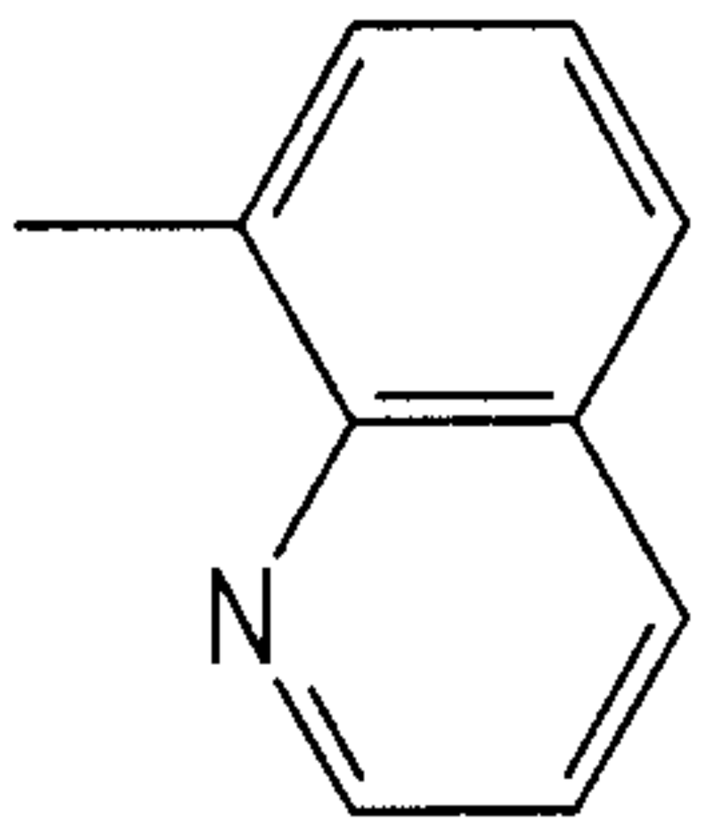
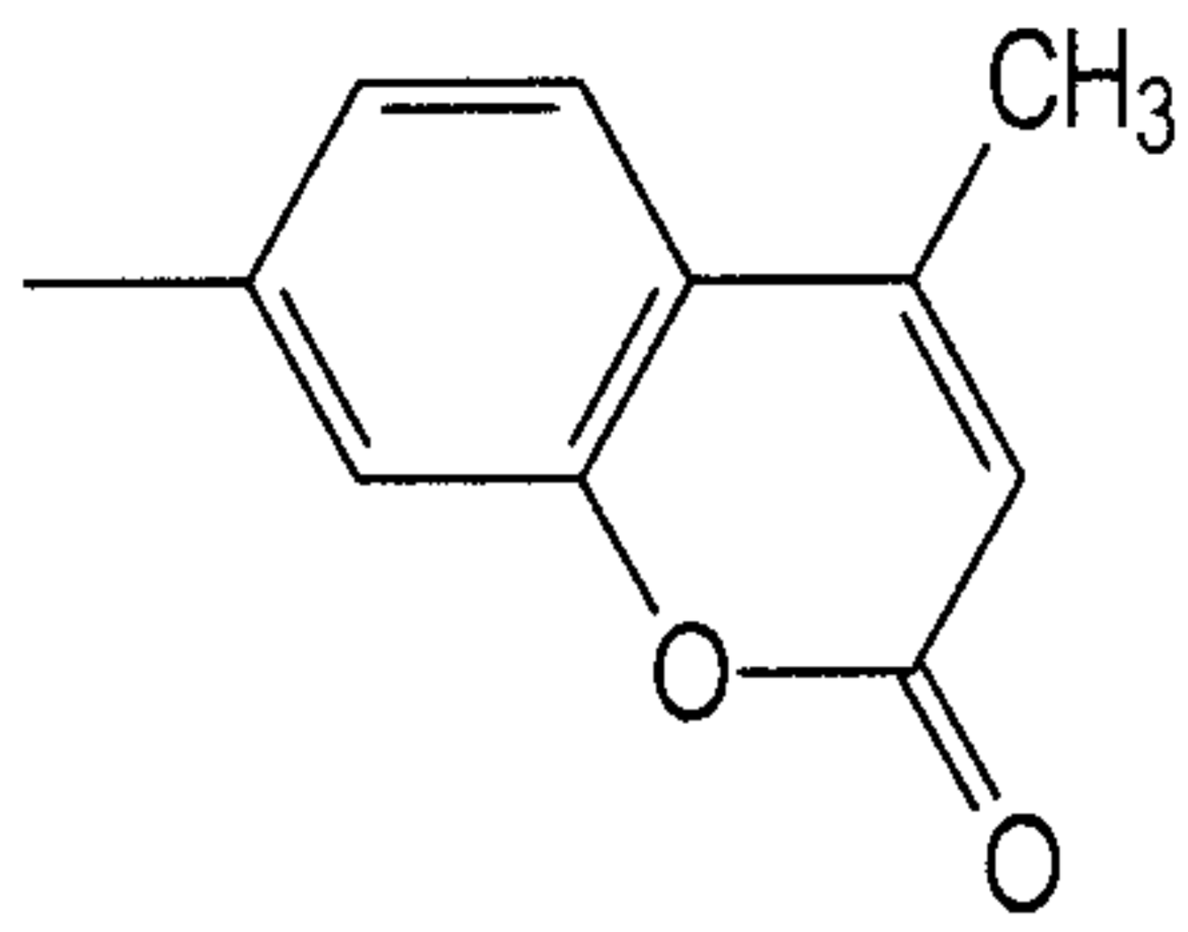
 ,
 ,
 ,
 ,

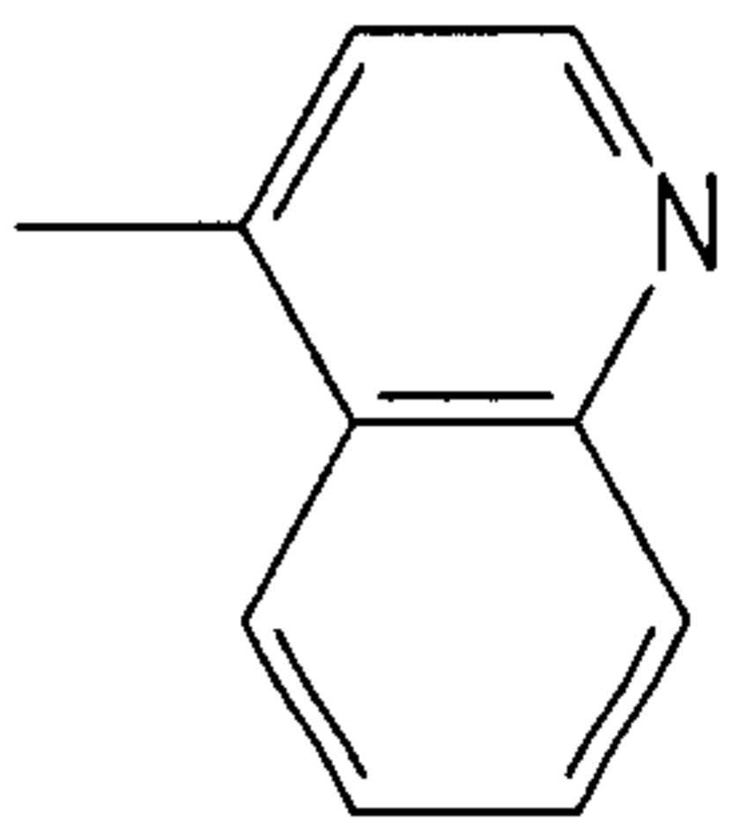
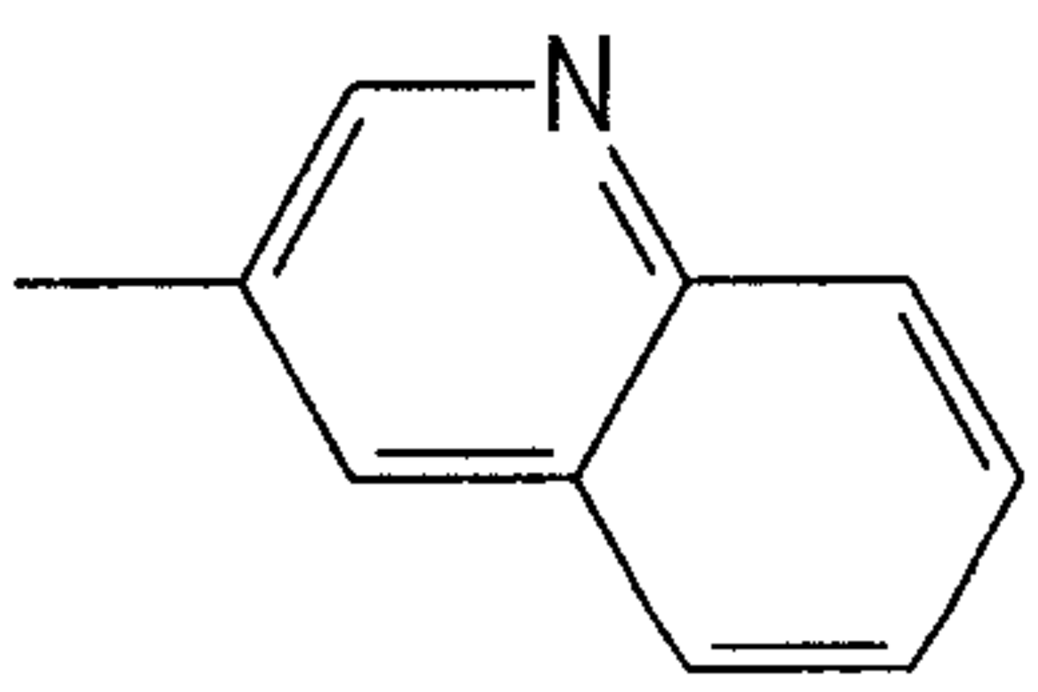
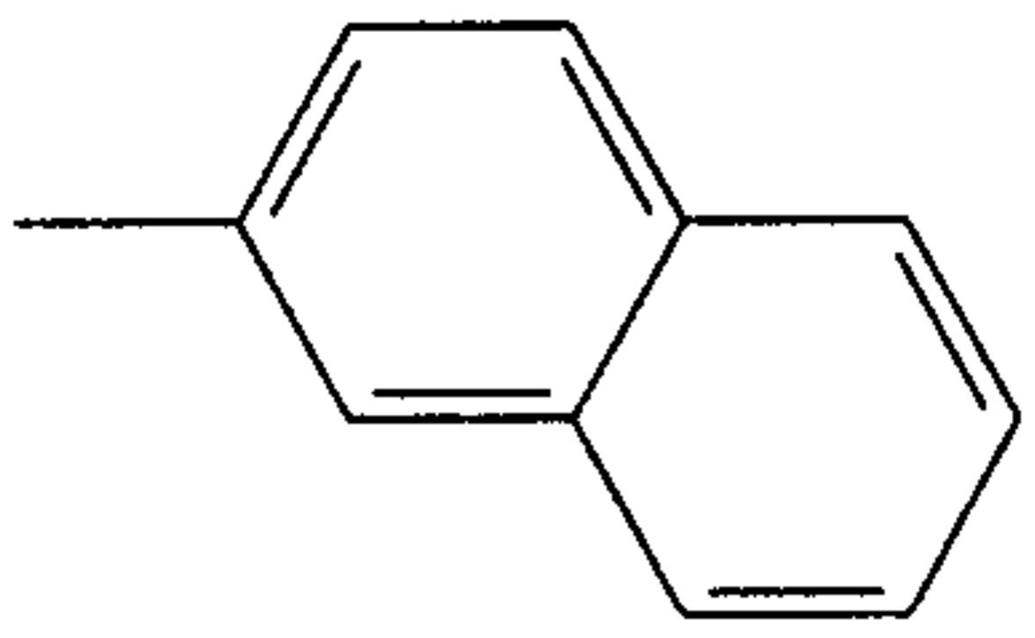
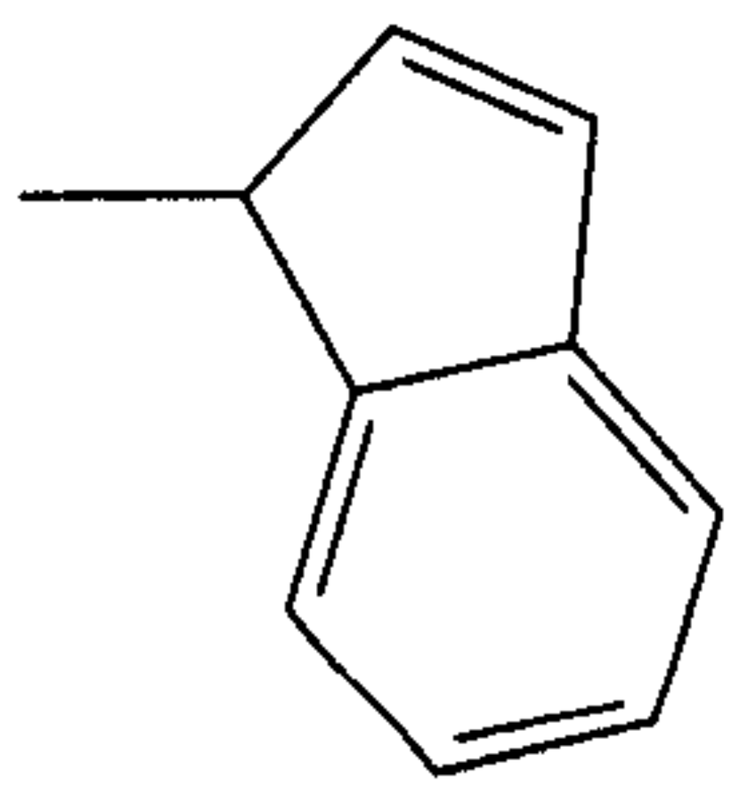
 ,
 ,
 ,


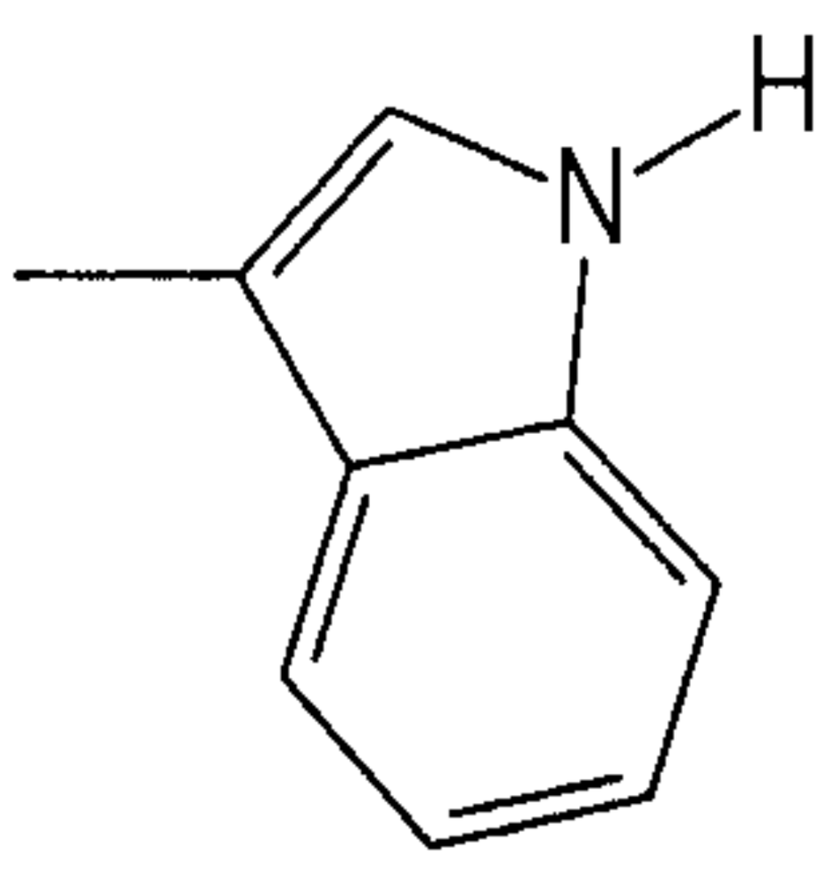
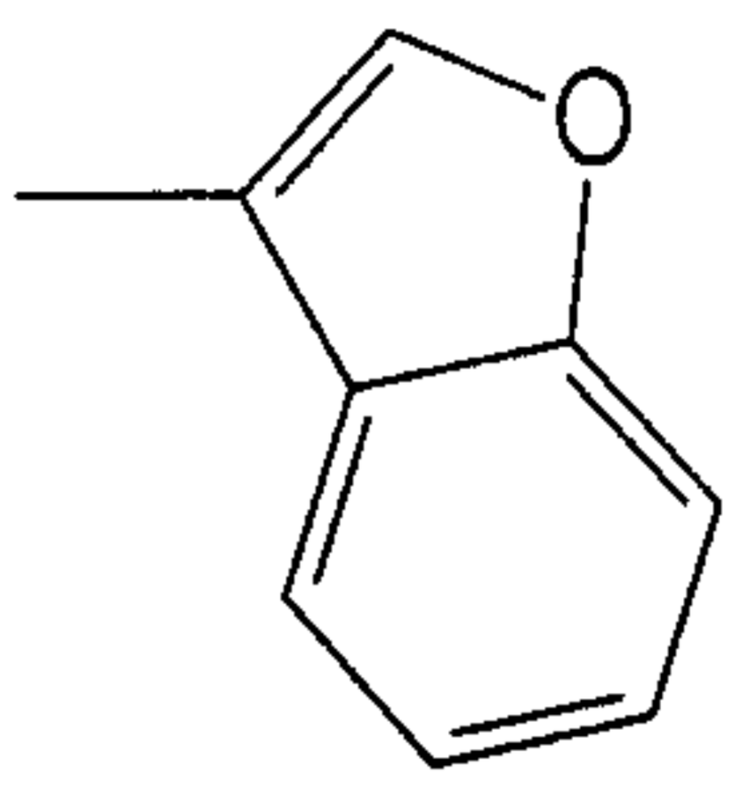
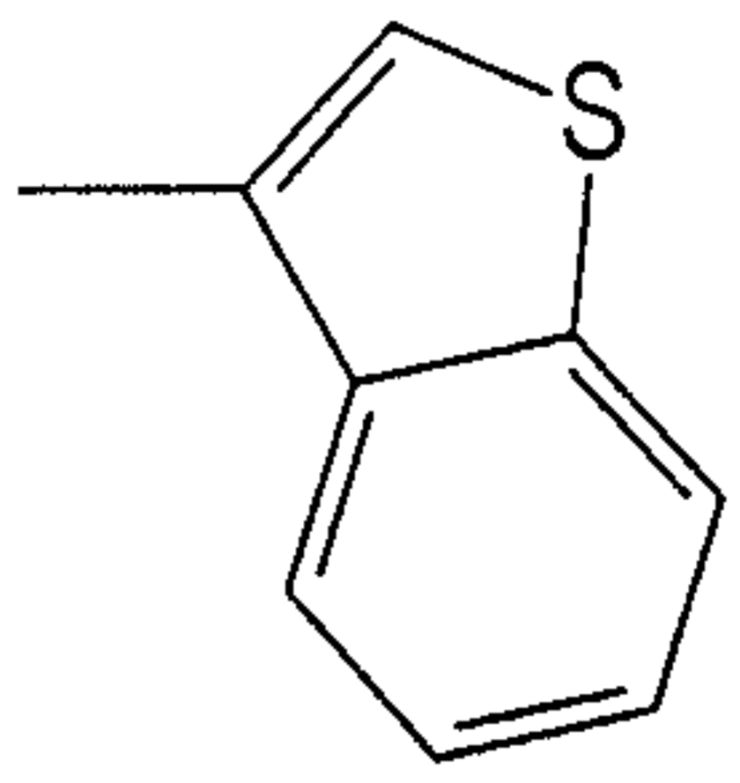
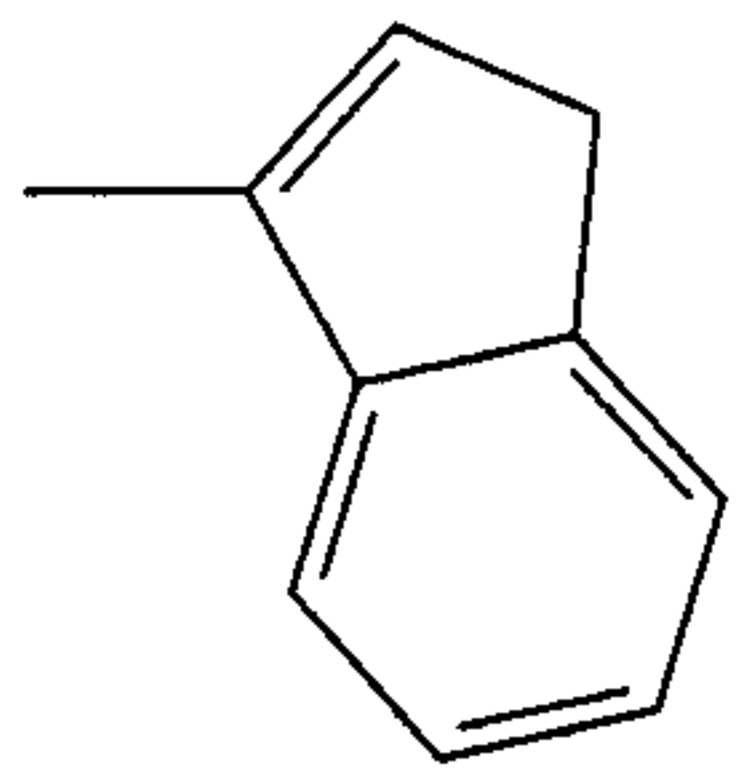
 ,
 ,
 ,
 ,

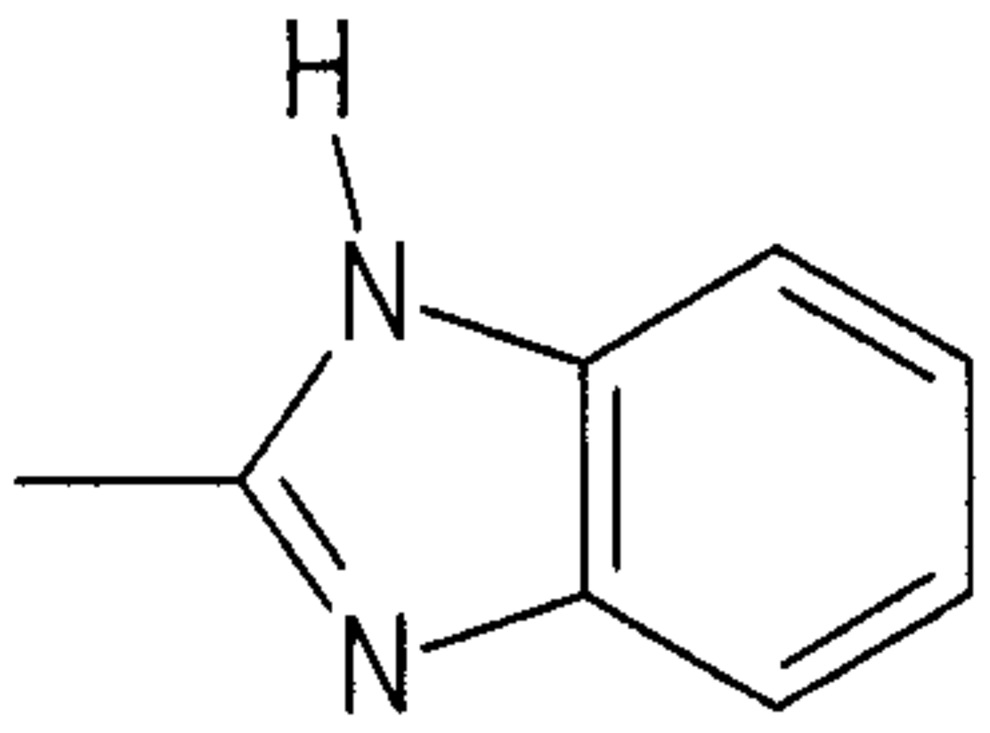
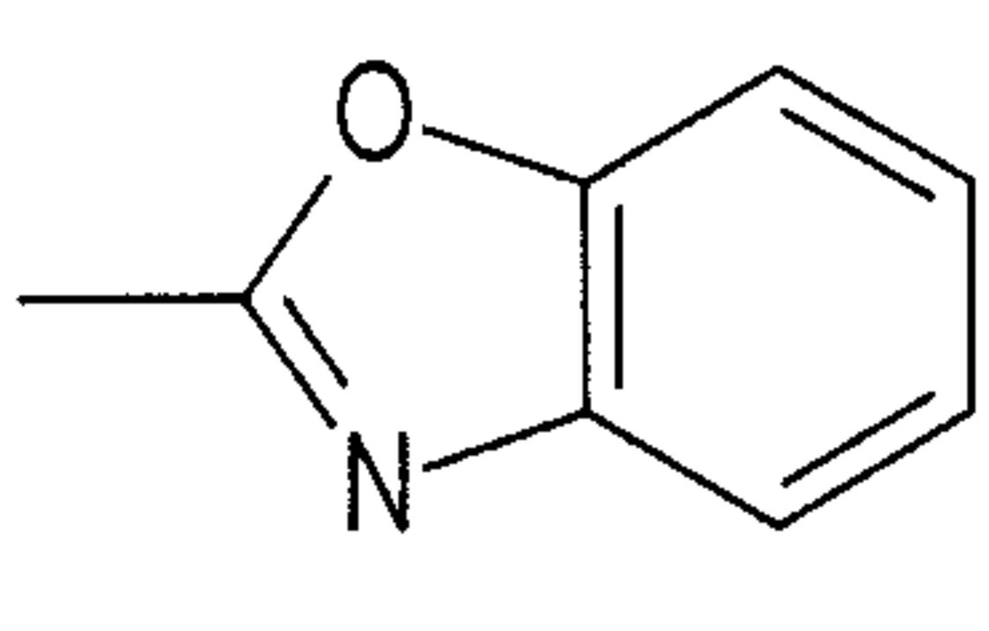
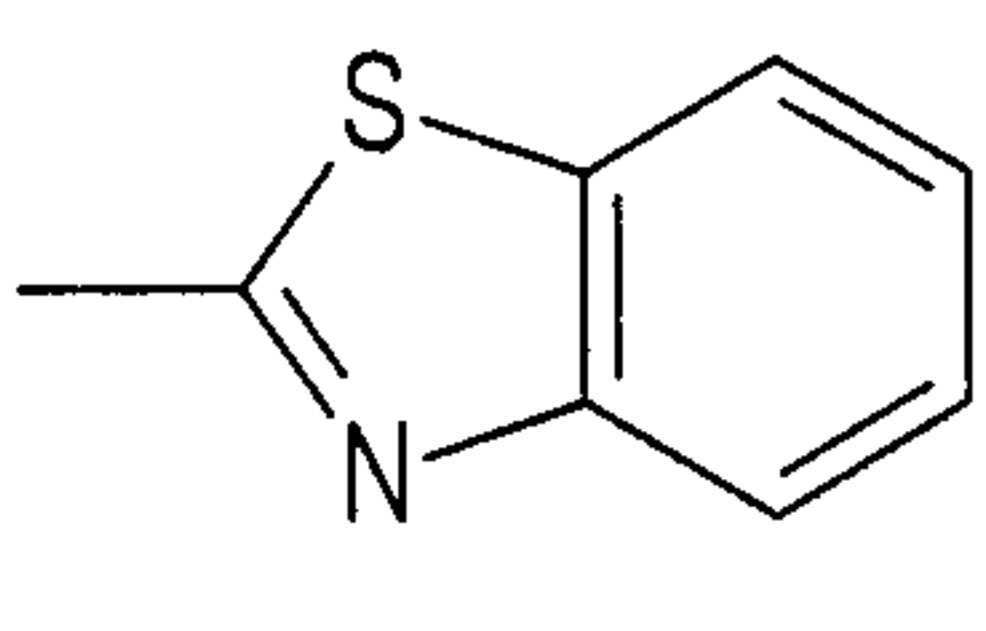
 ,
 ,
 ,
 ,

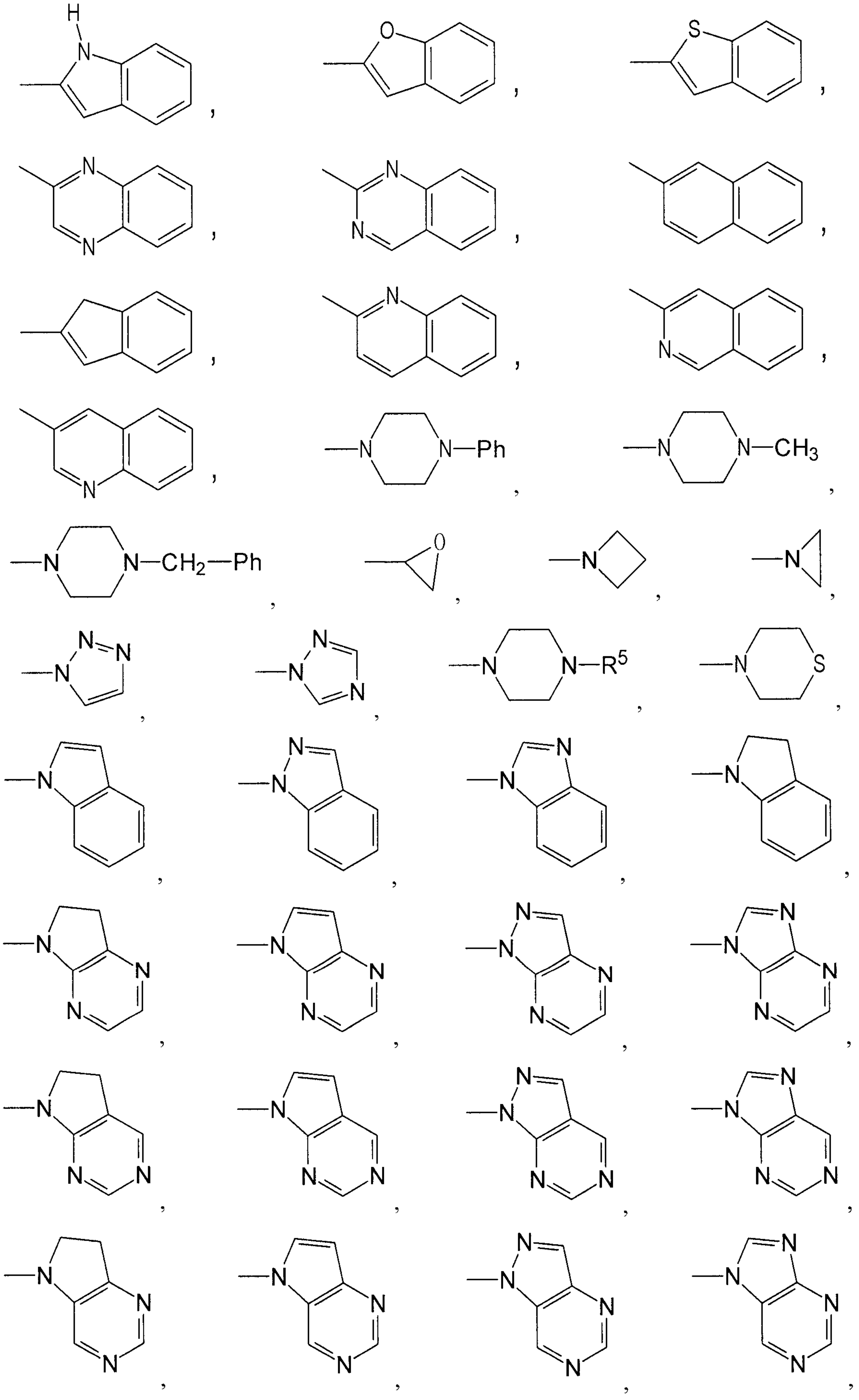
 ,
 ,
 ,
 ,

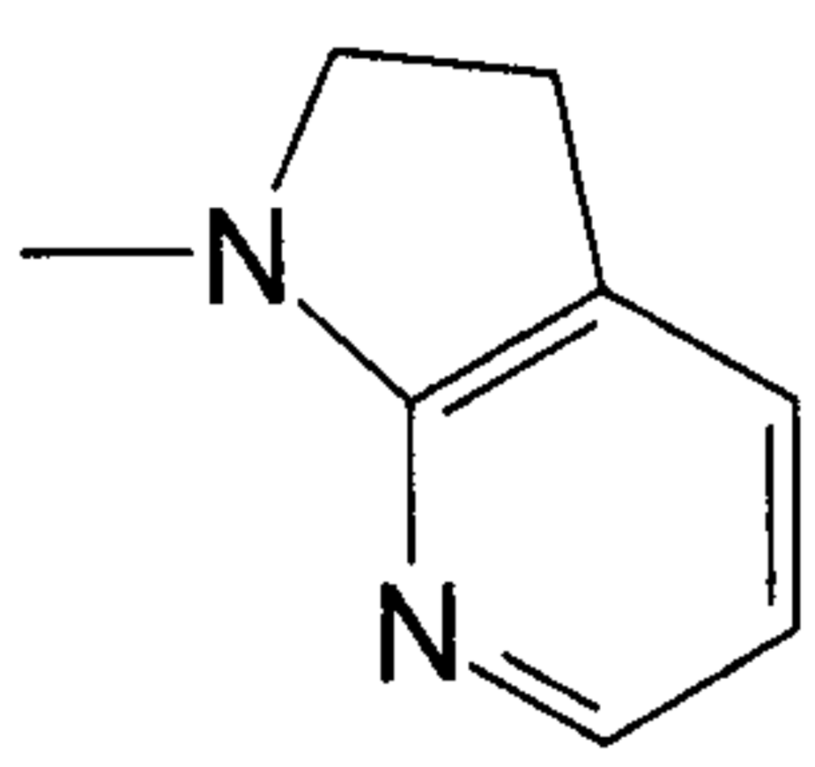
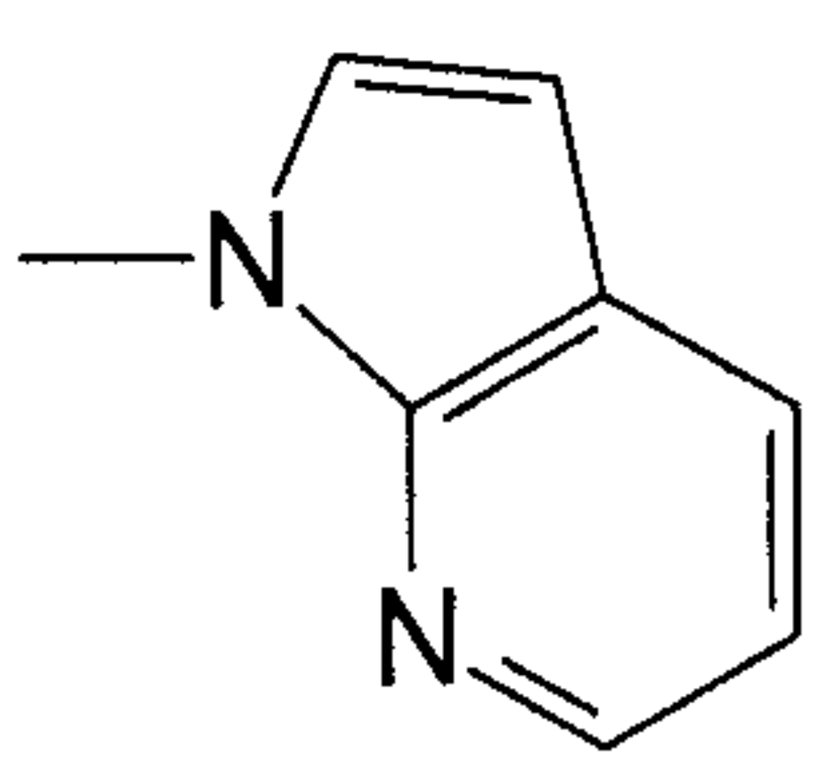
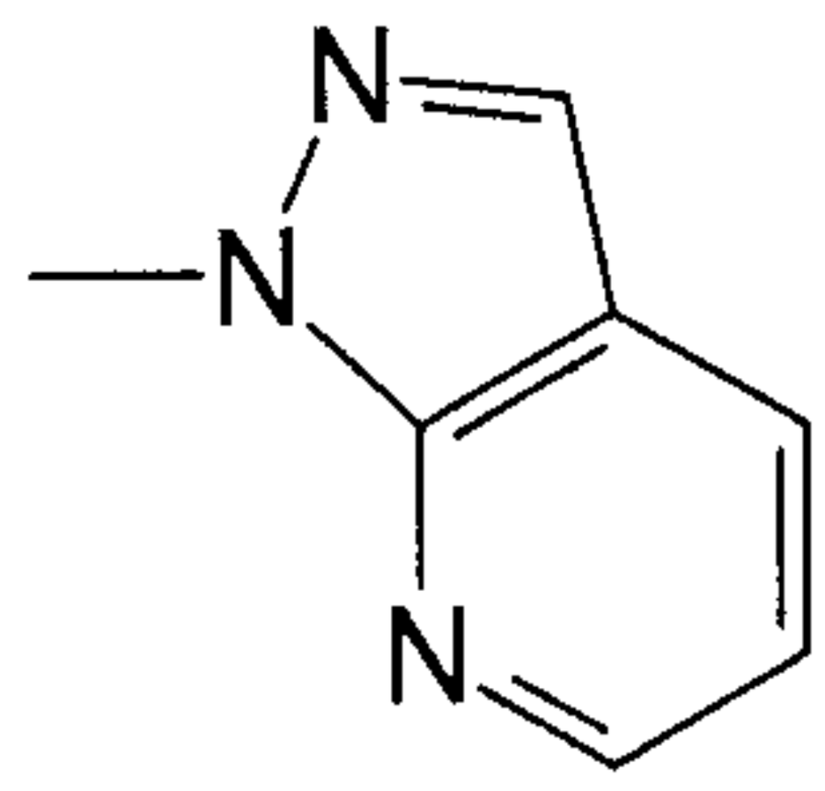
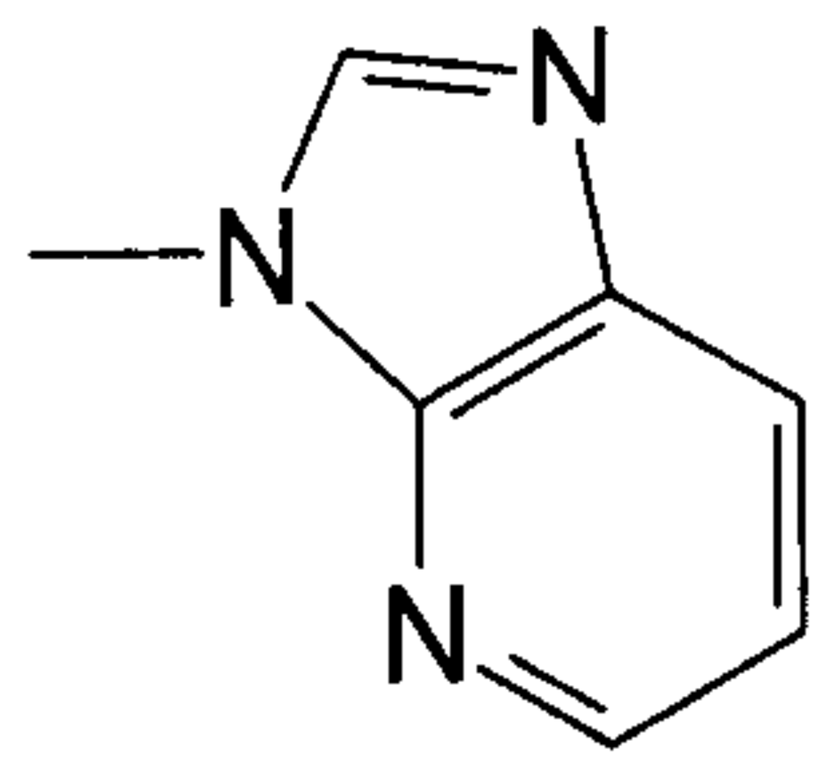
 ,
 ,
 ,
 ,
 ,

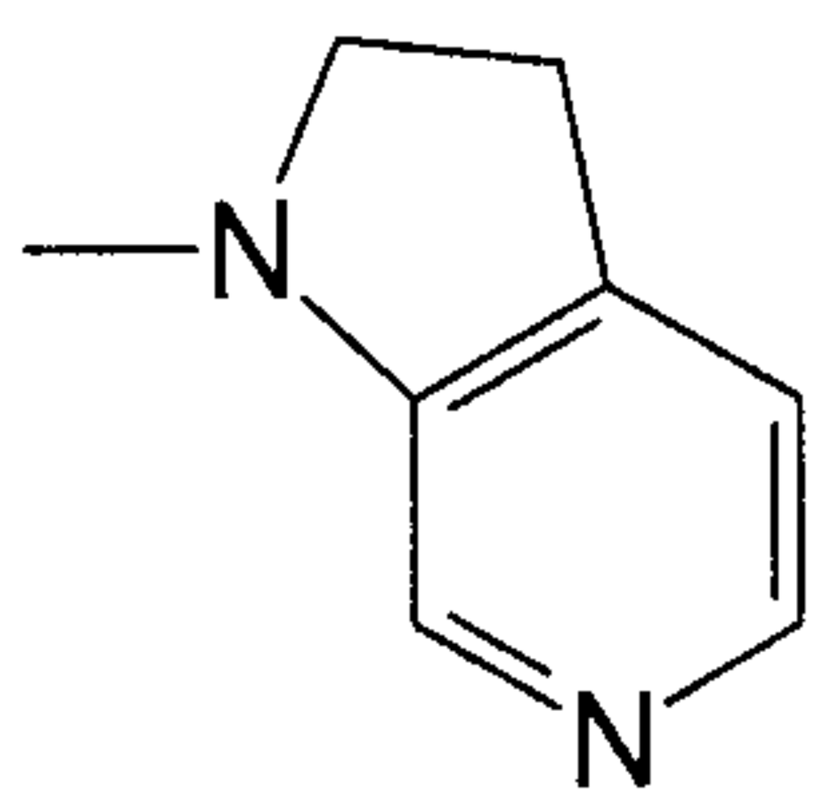
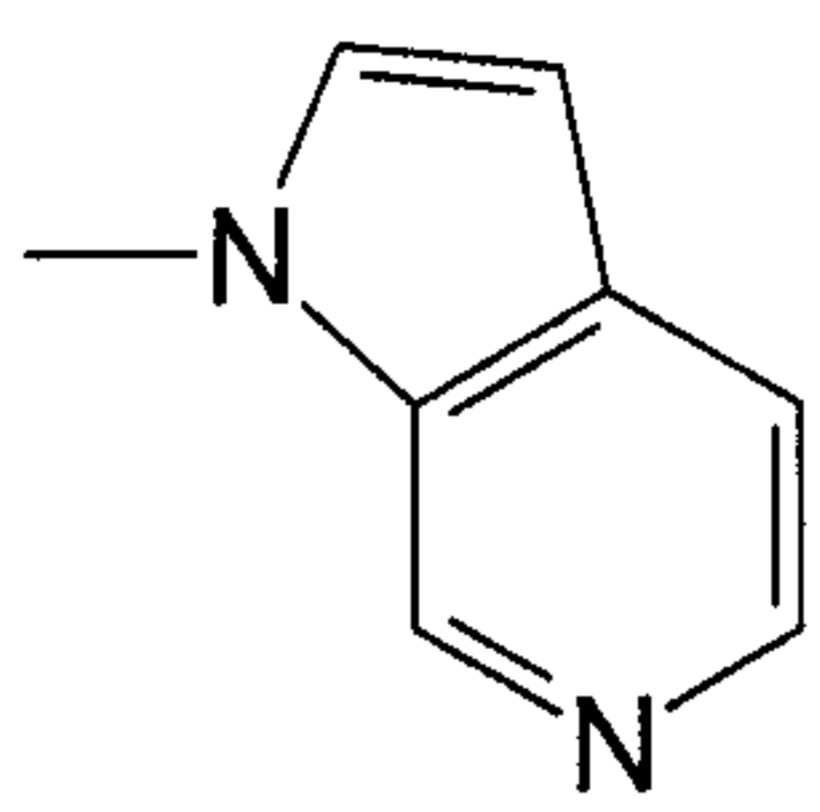
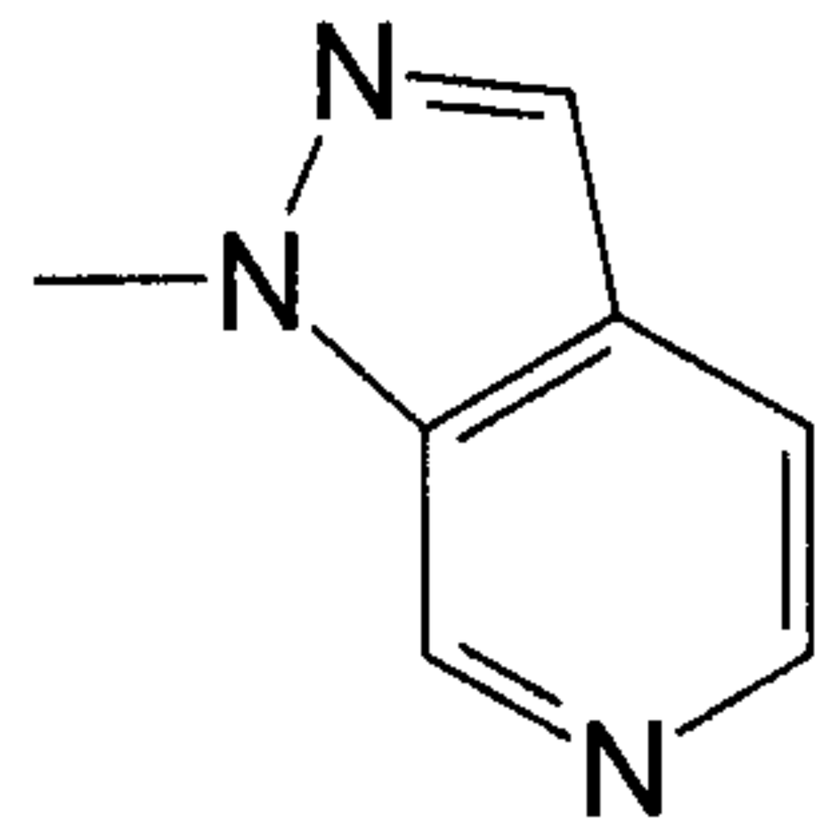
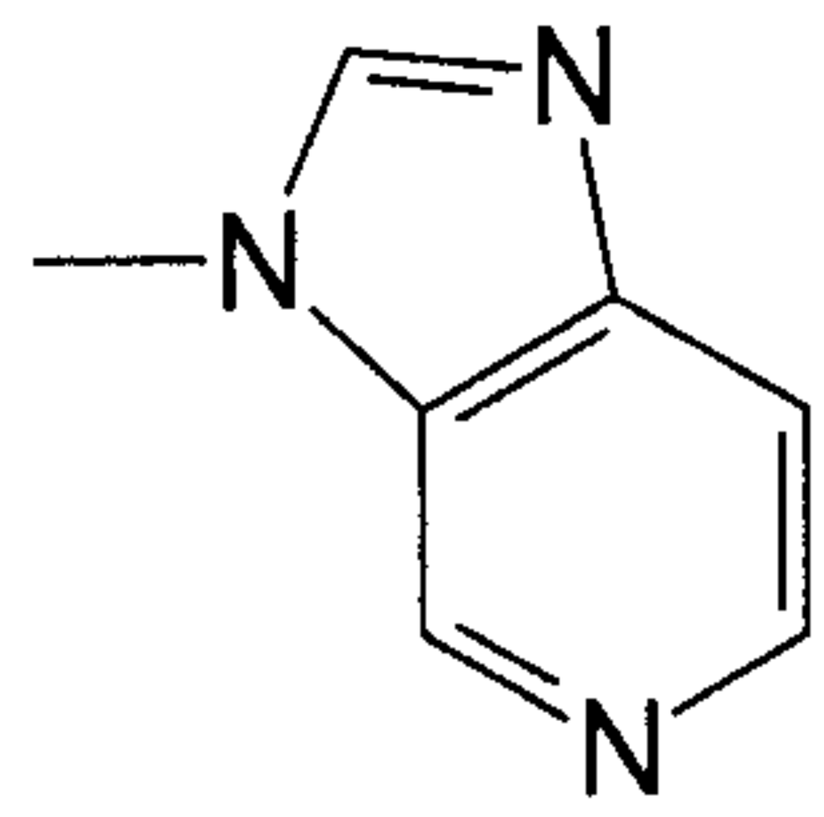
 ,
 ,
 ,
 ,

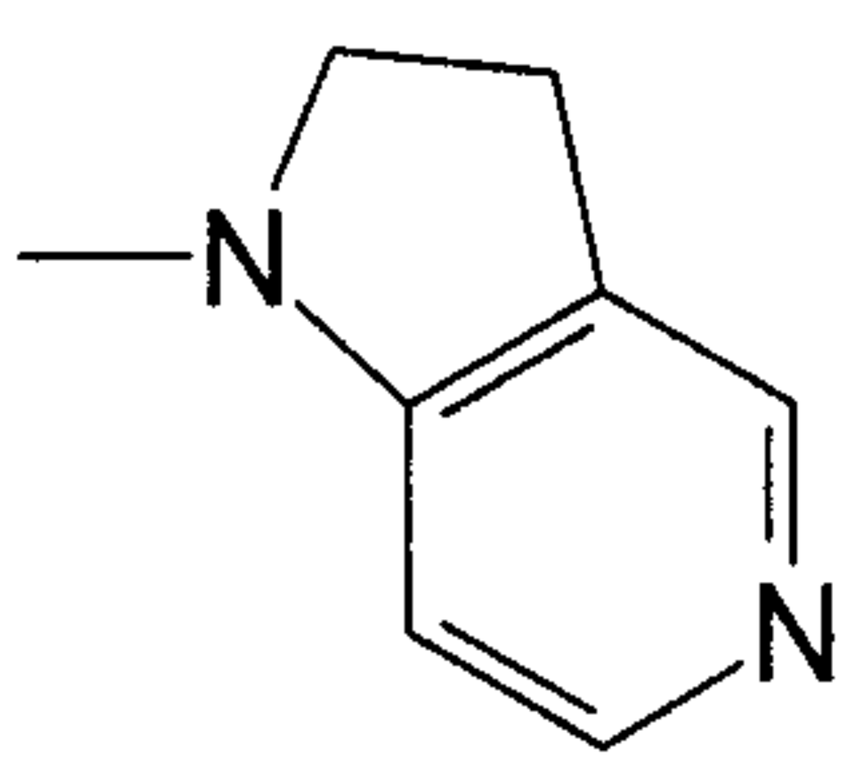
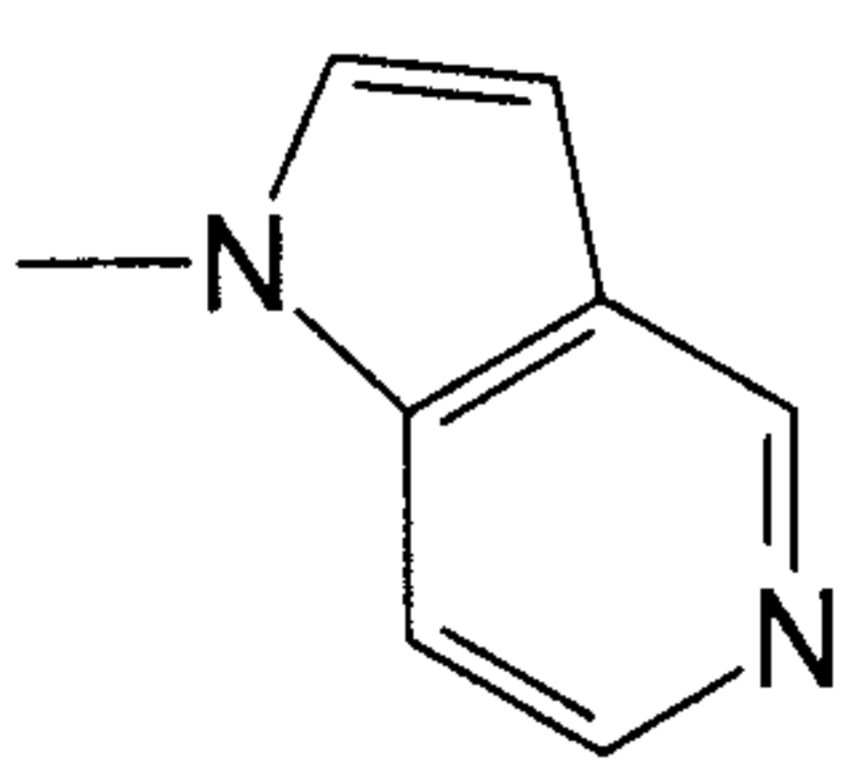
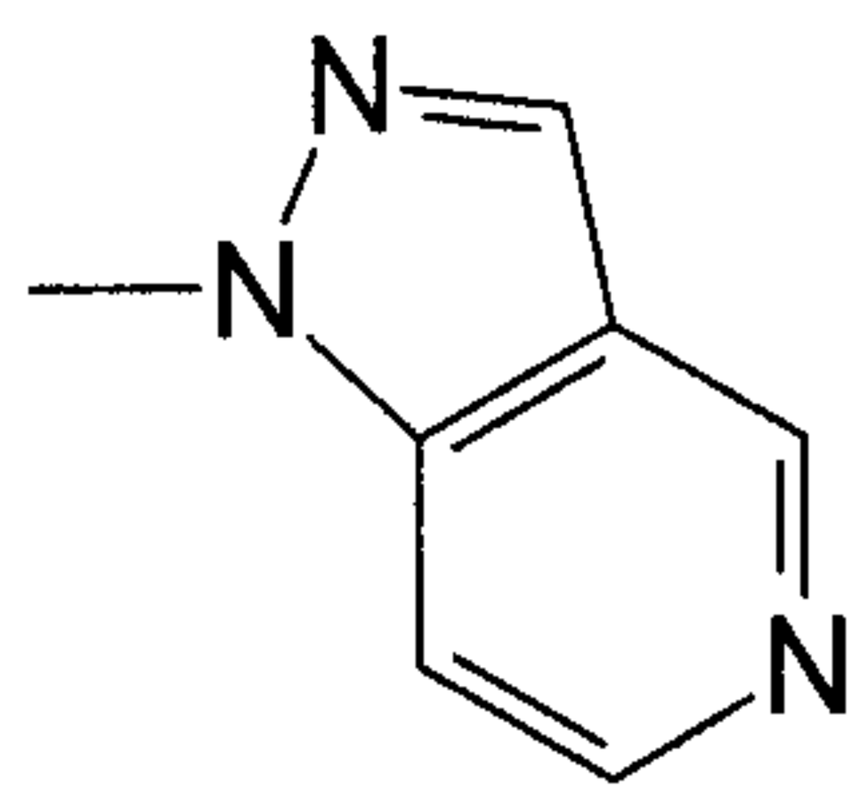
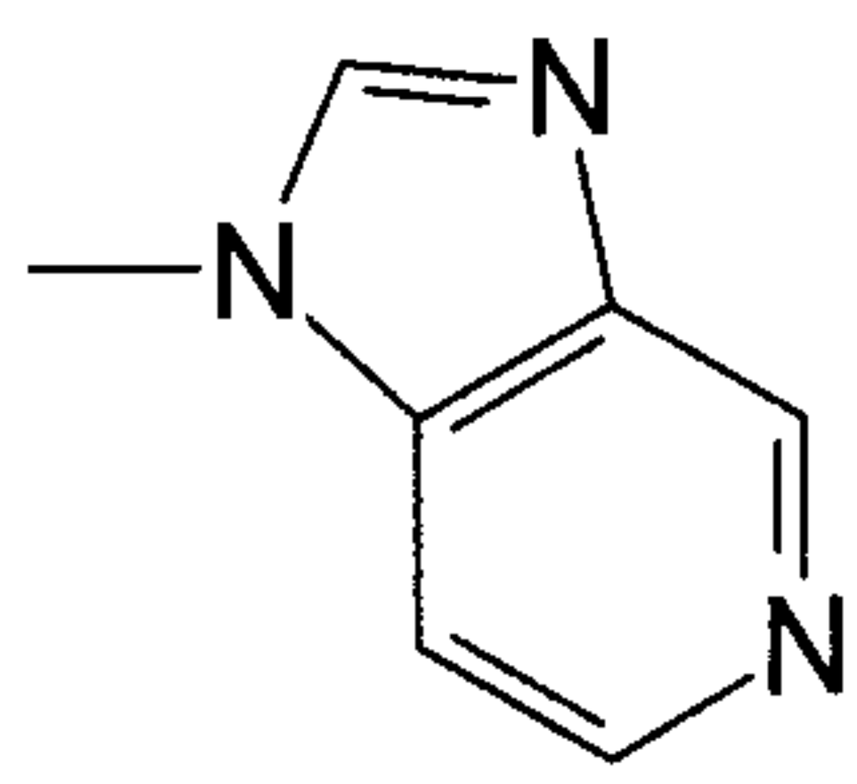
 ,
 ,
 ,
 ,

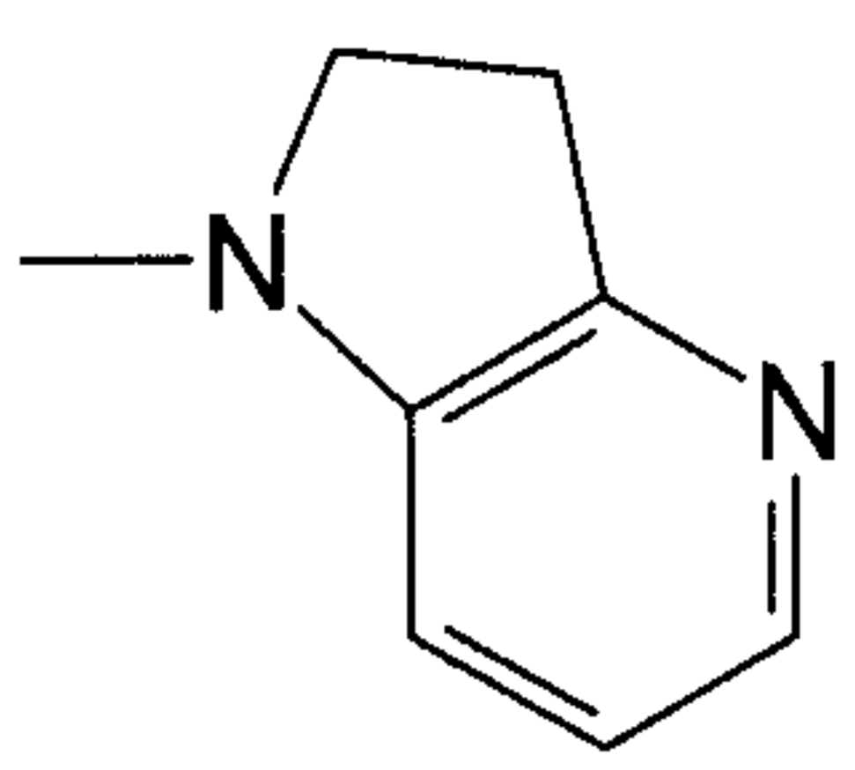
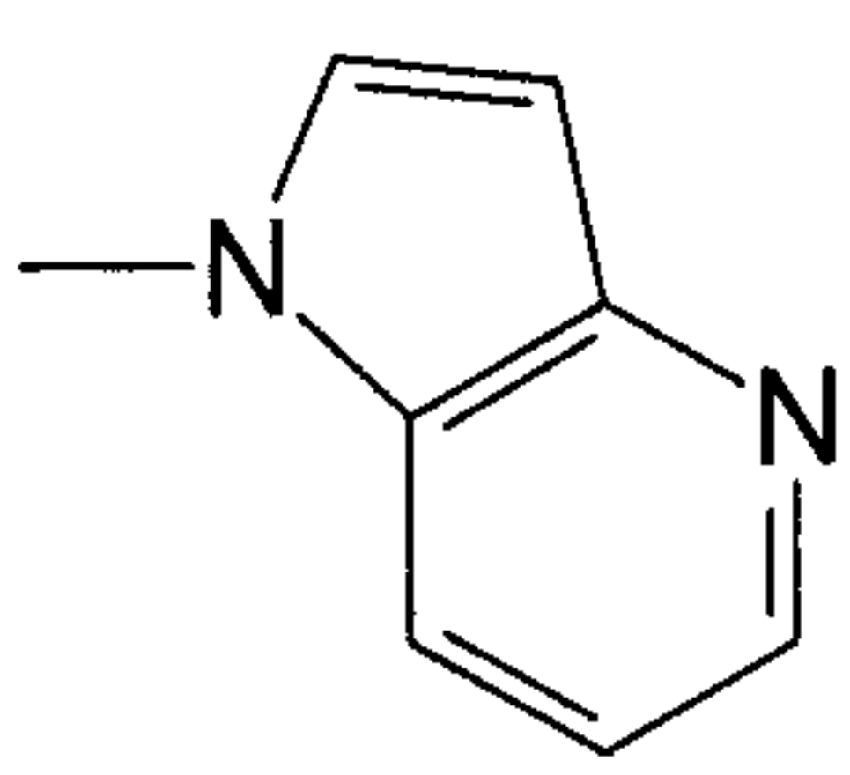
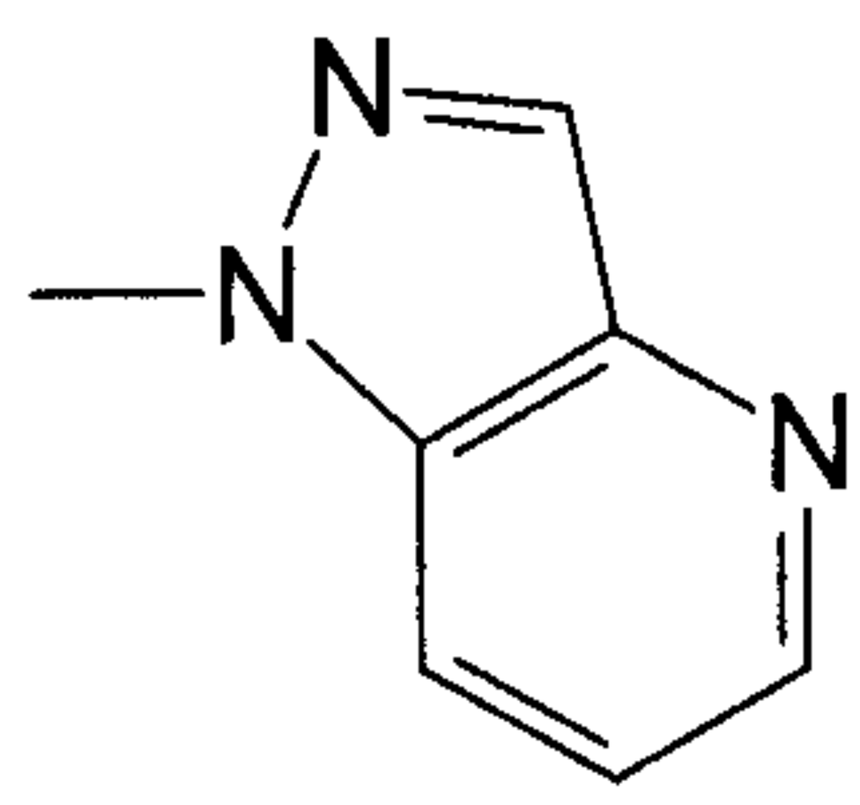
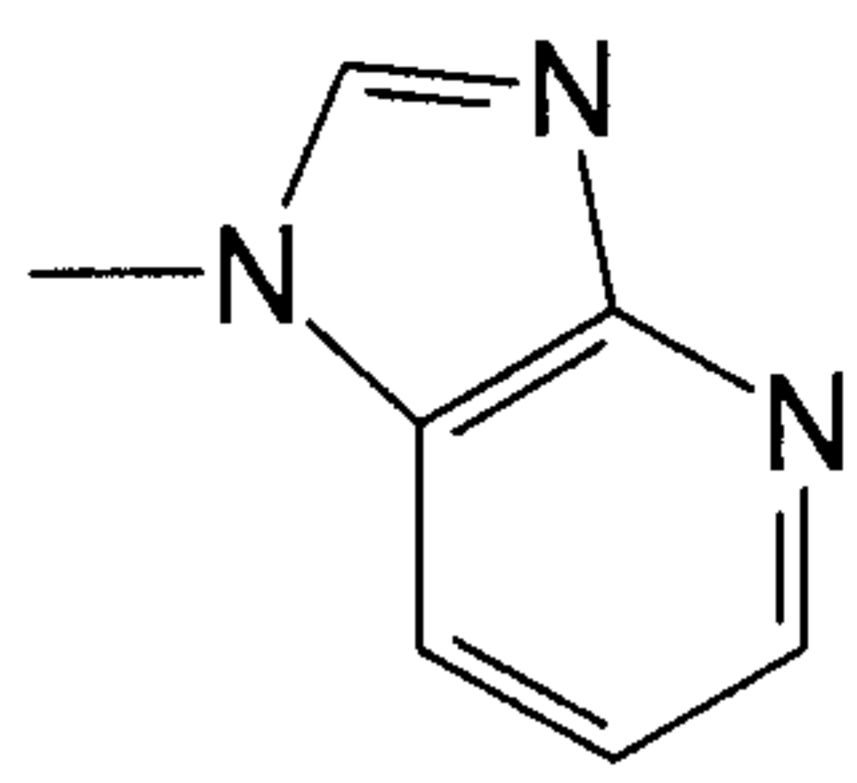
 ,
 ,
 ,

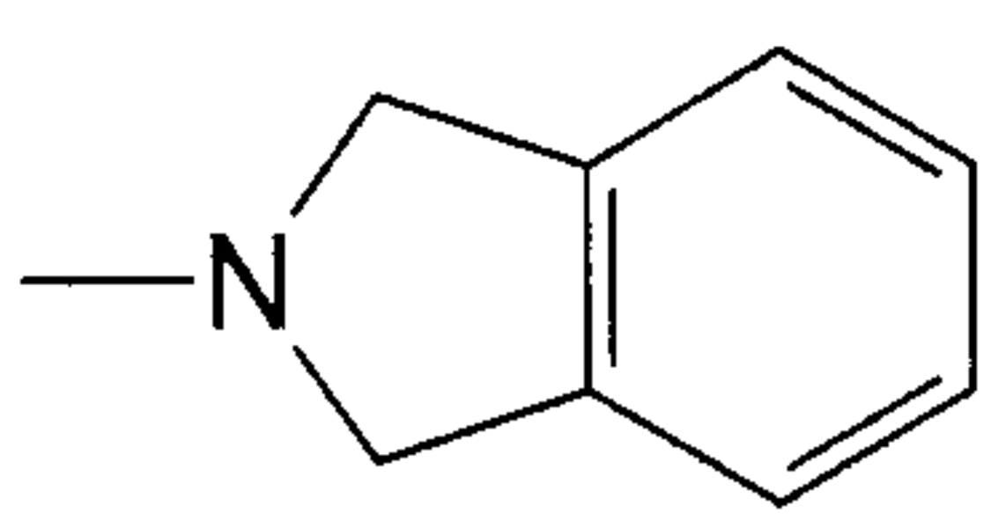
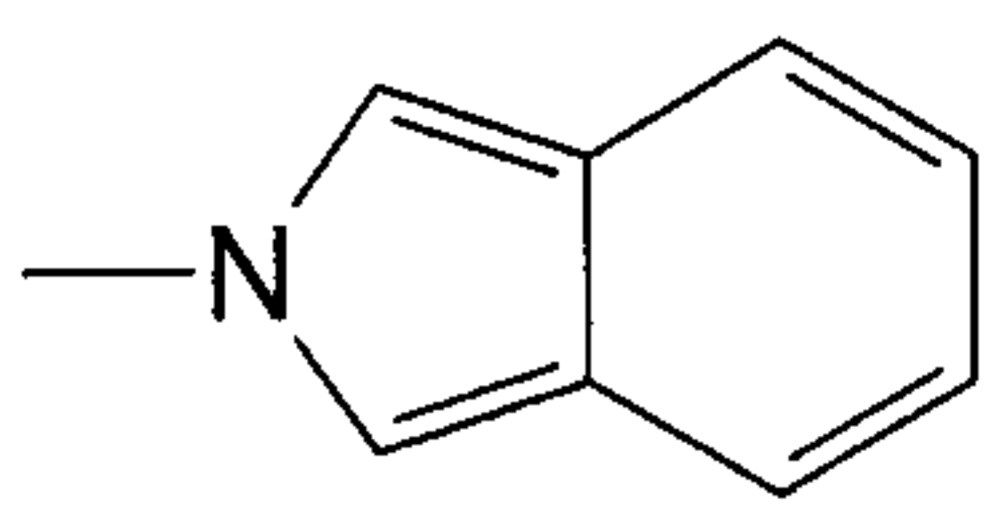
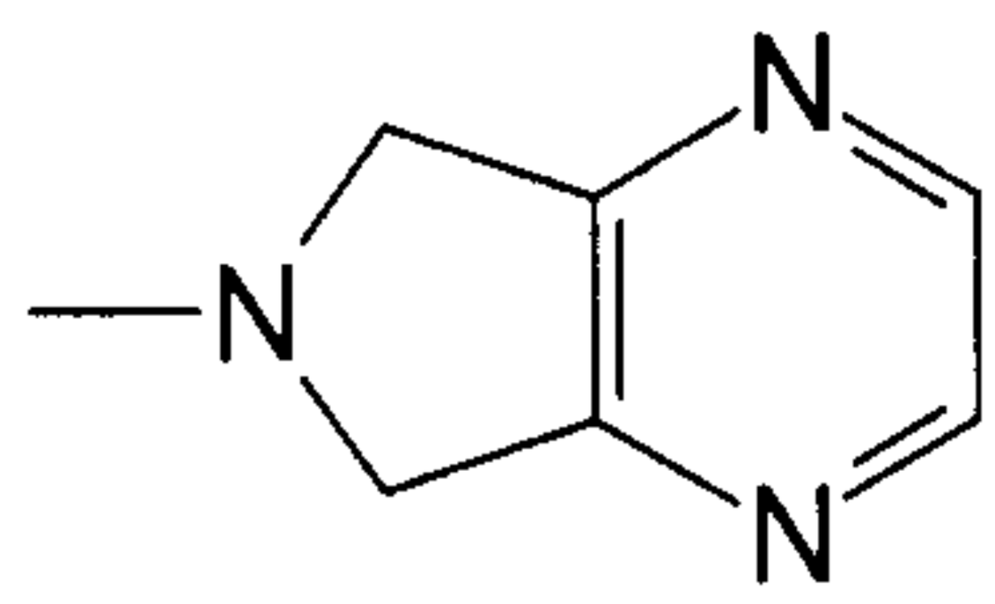


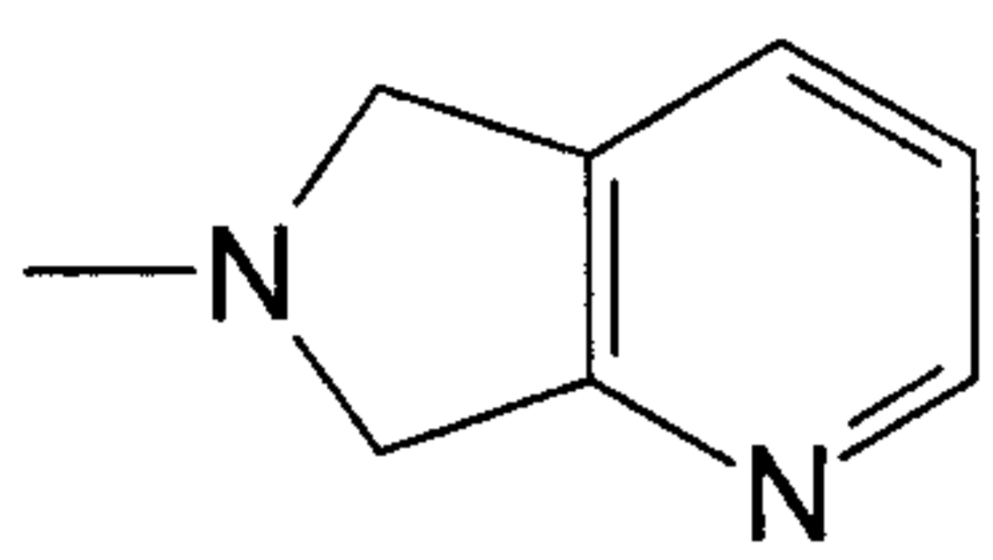
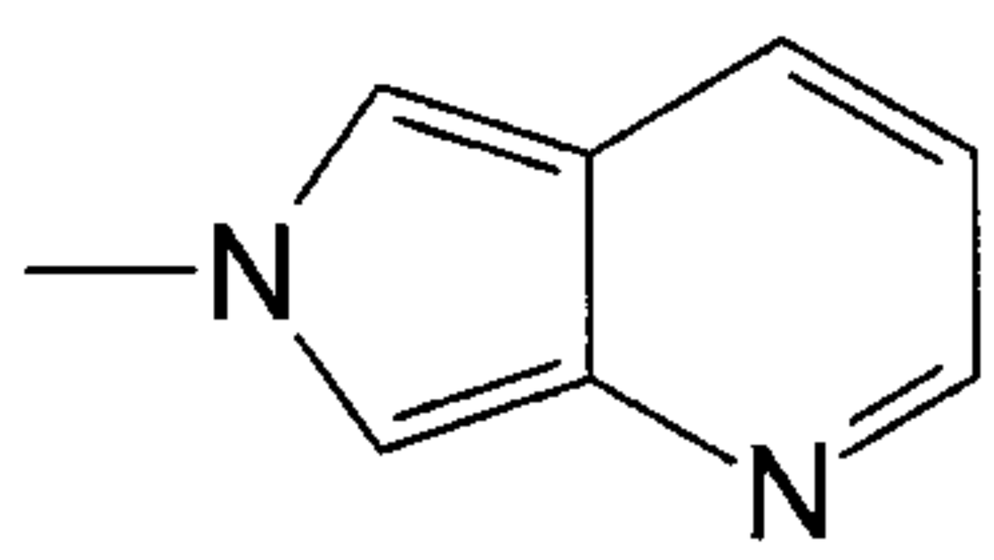
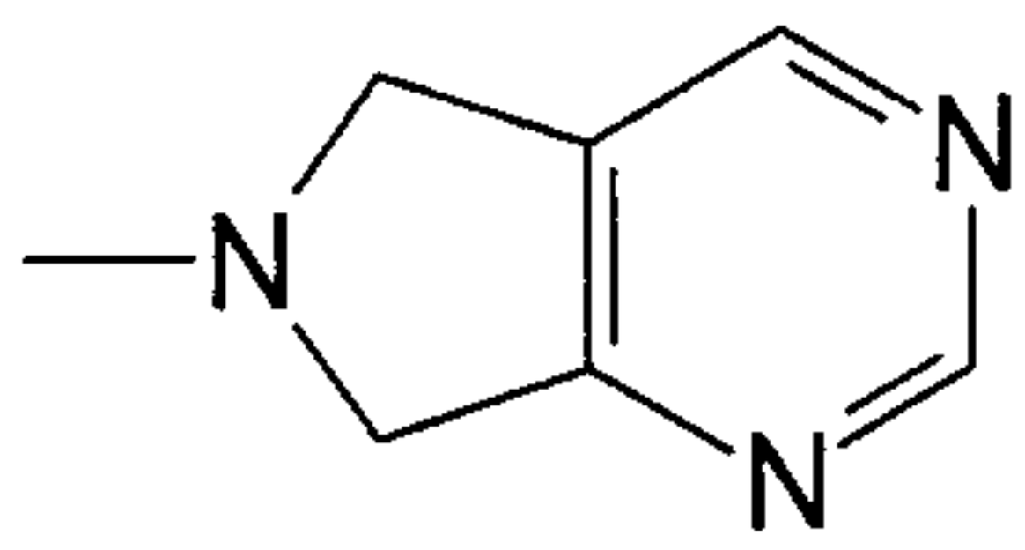
 ,  ,  ,  ,

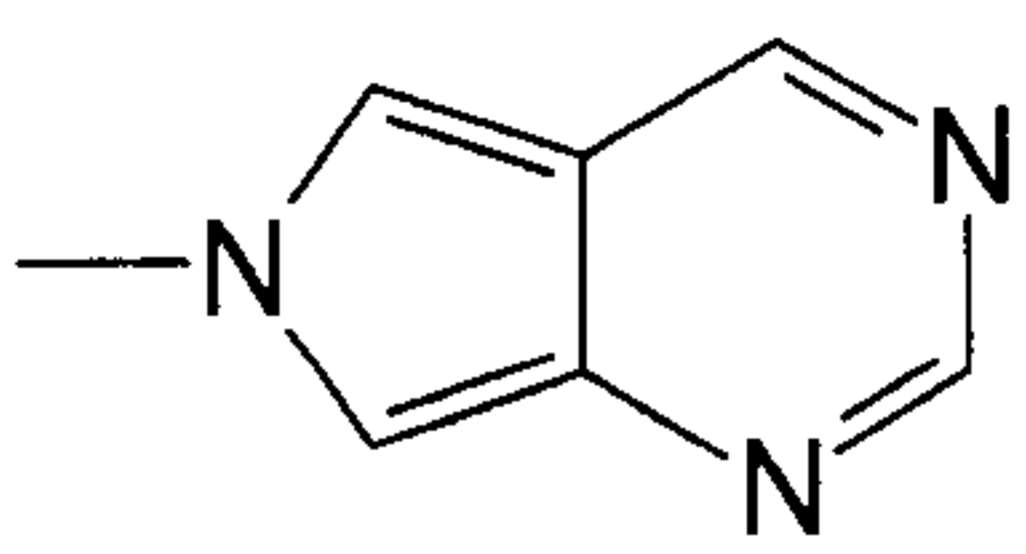
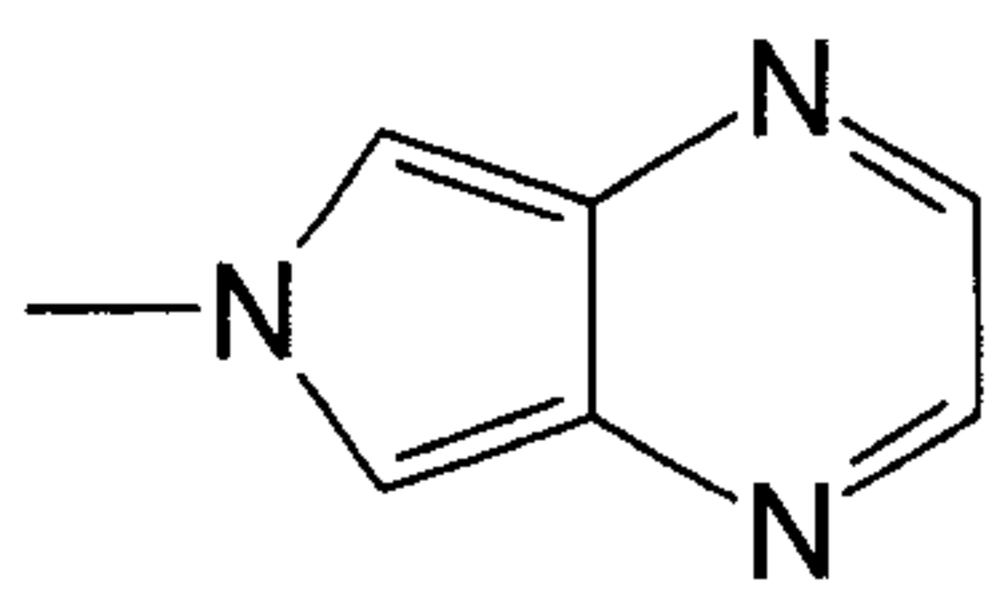
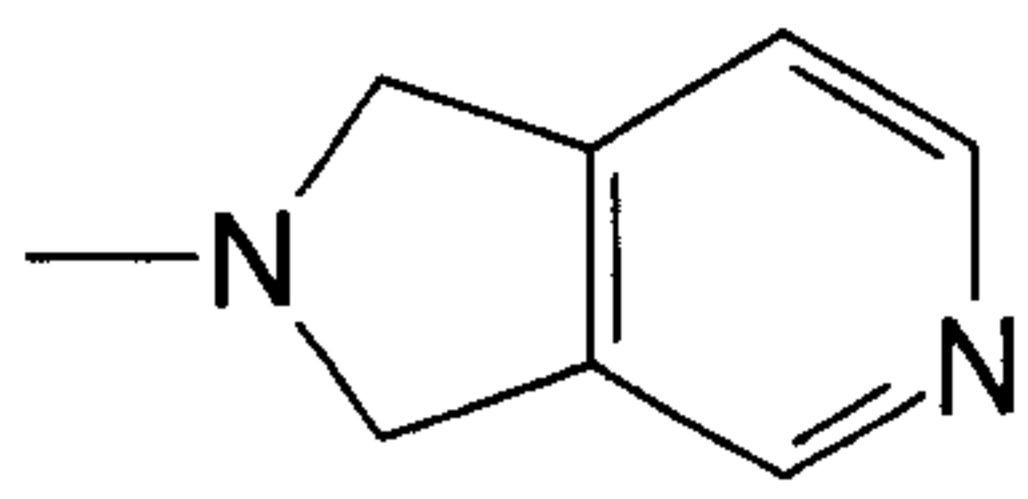
 ,  ,  ,  ,

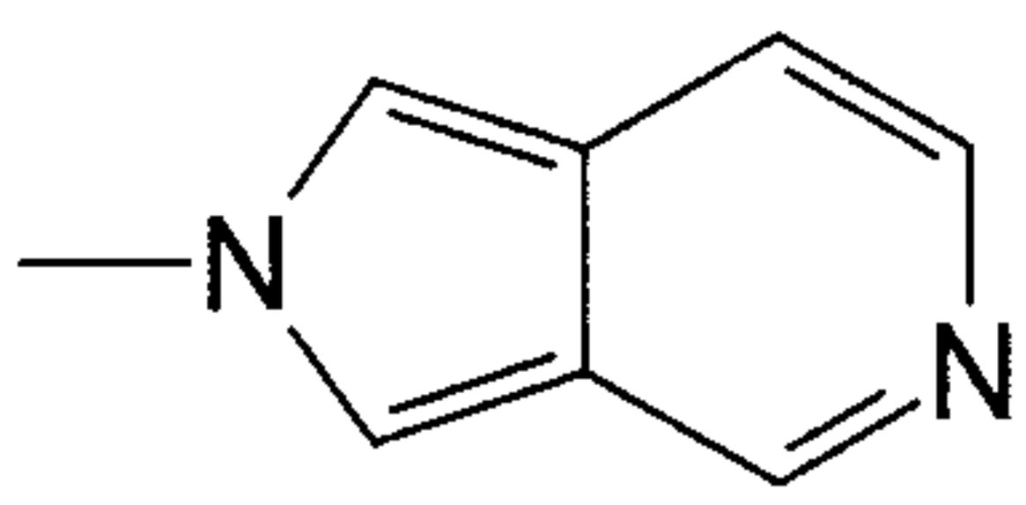
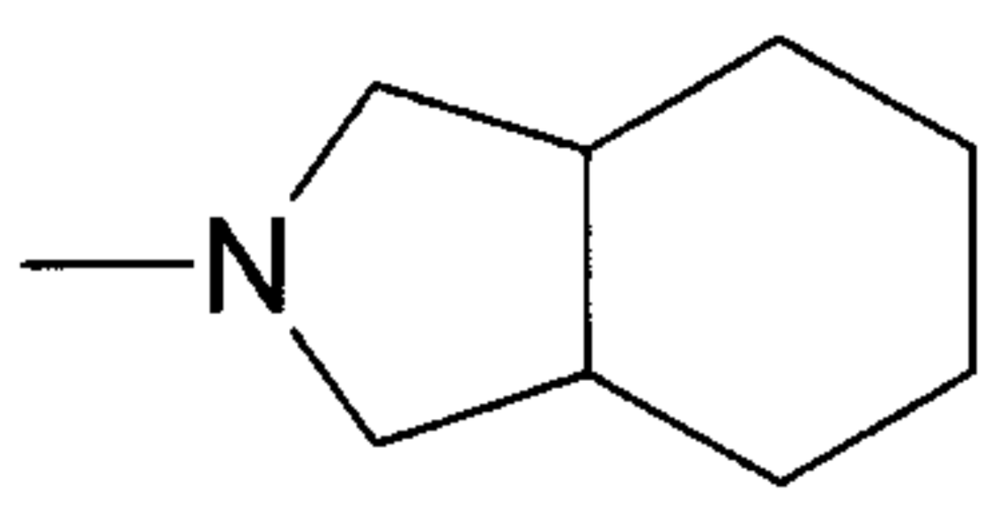
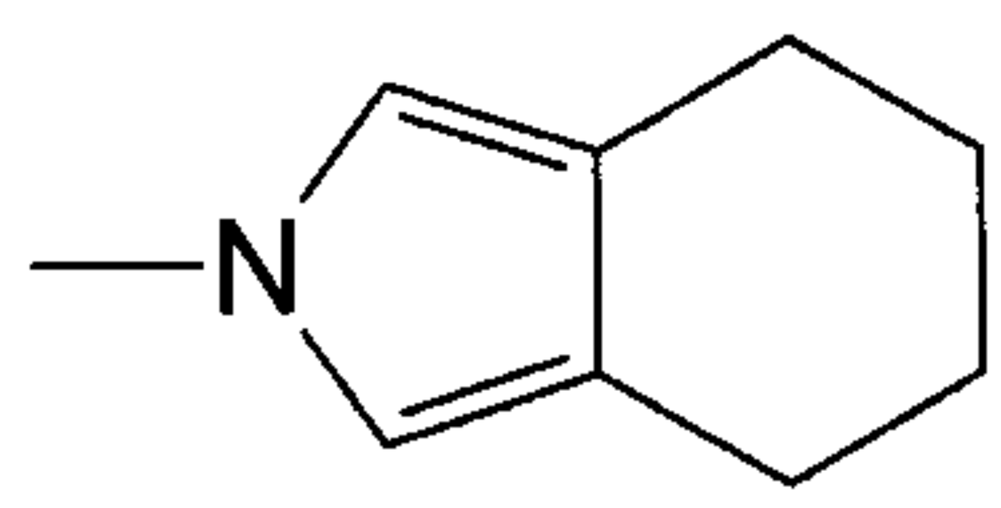
 ,  ,  ,  ,

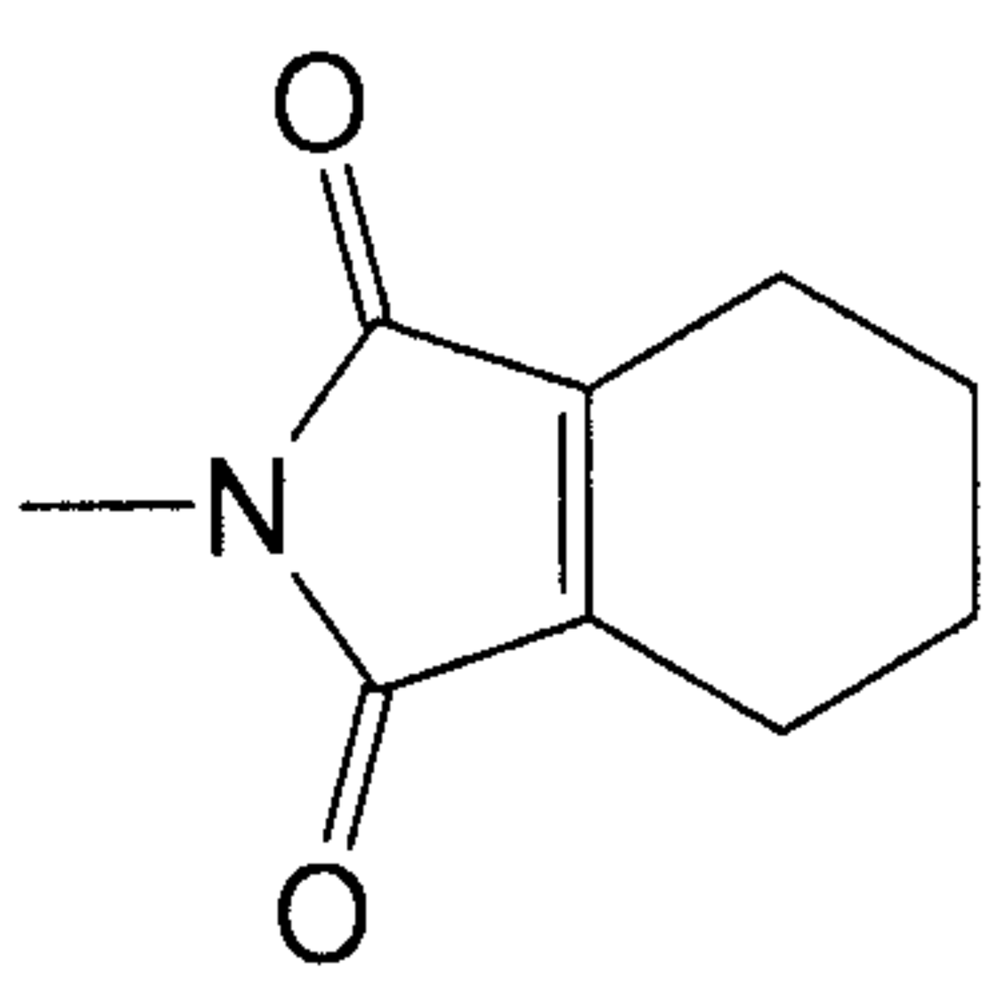
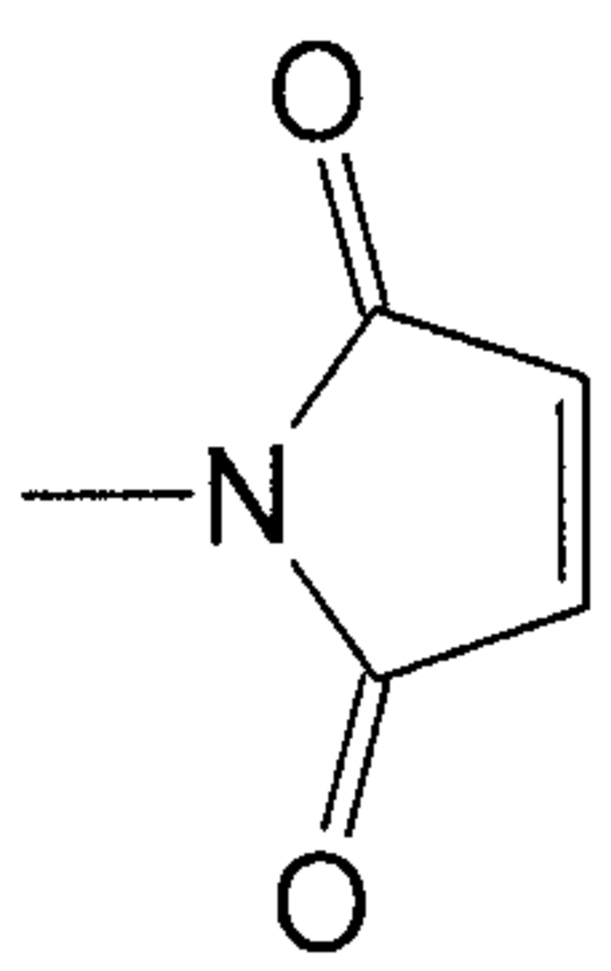
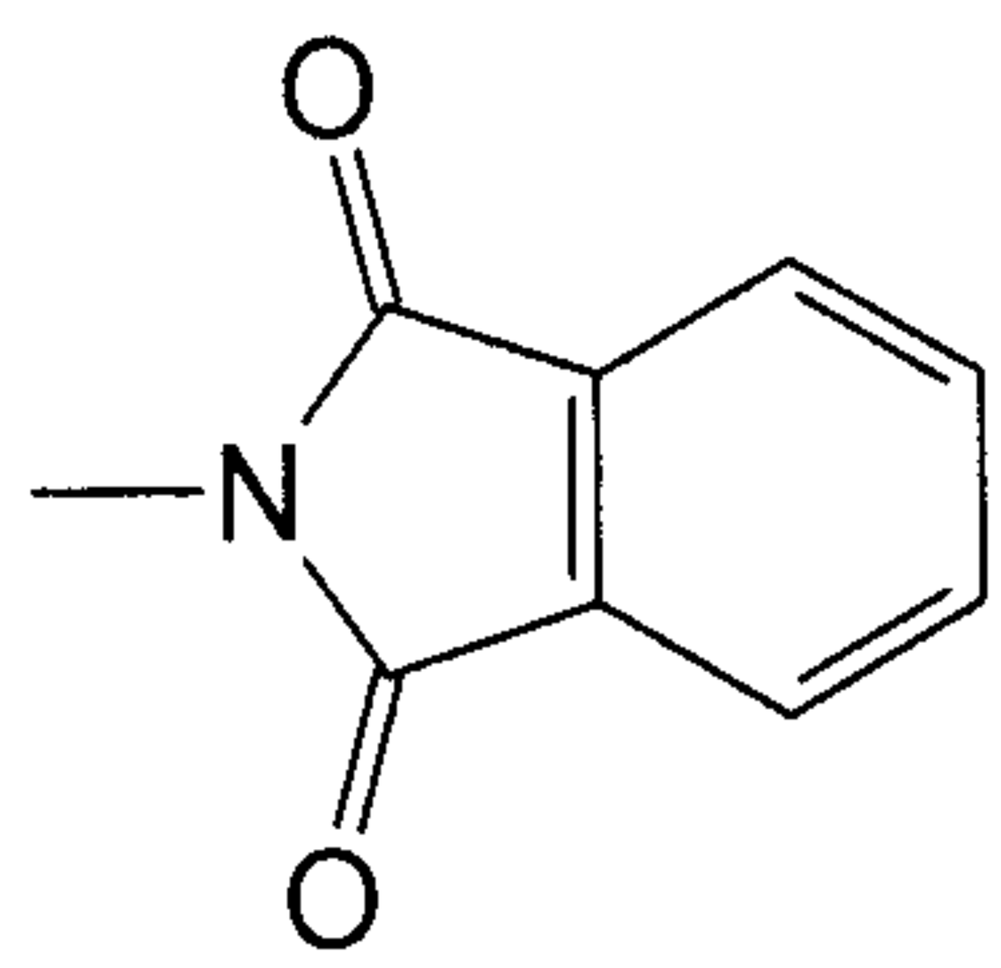
 ,  ,  ,  ,

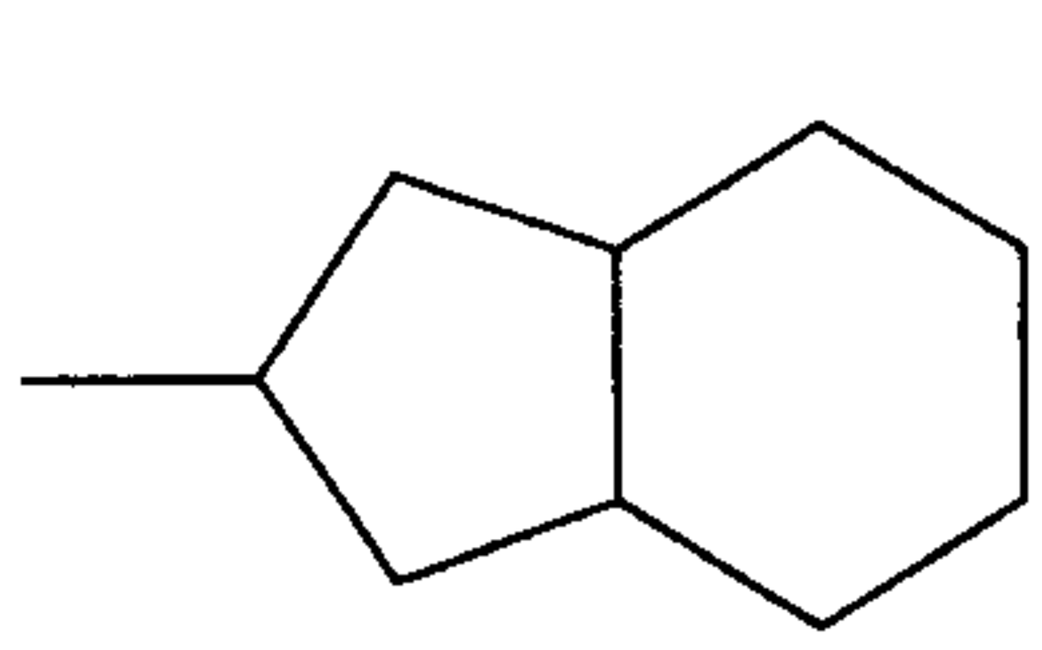
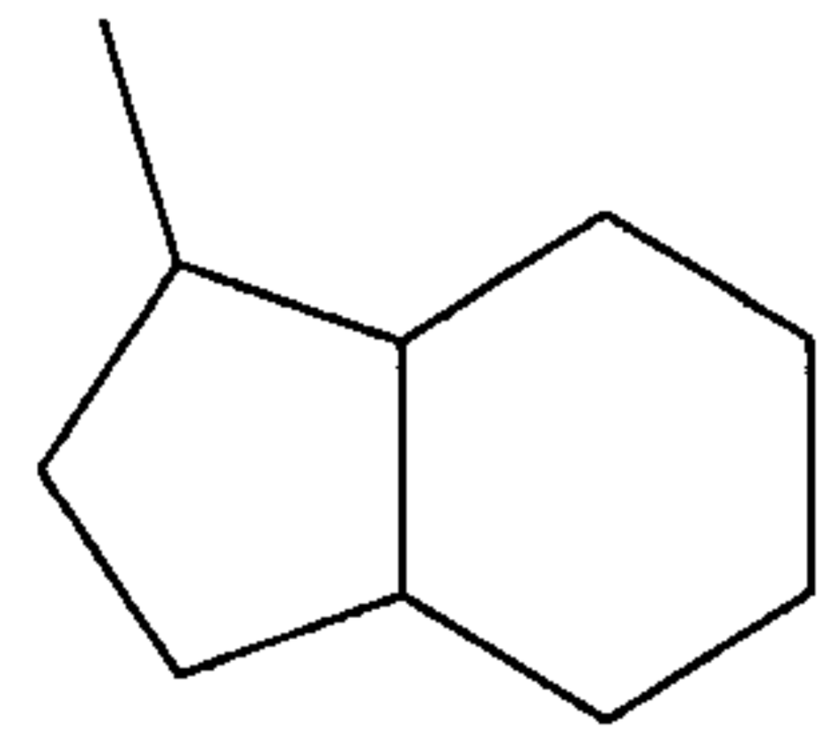
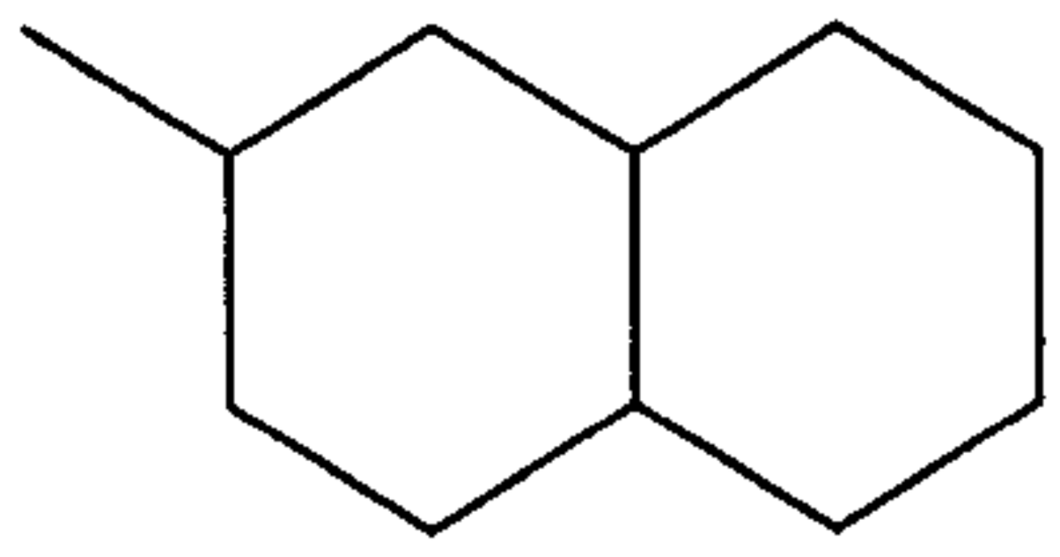
 ,  ,  ,

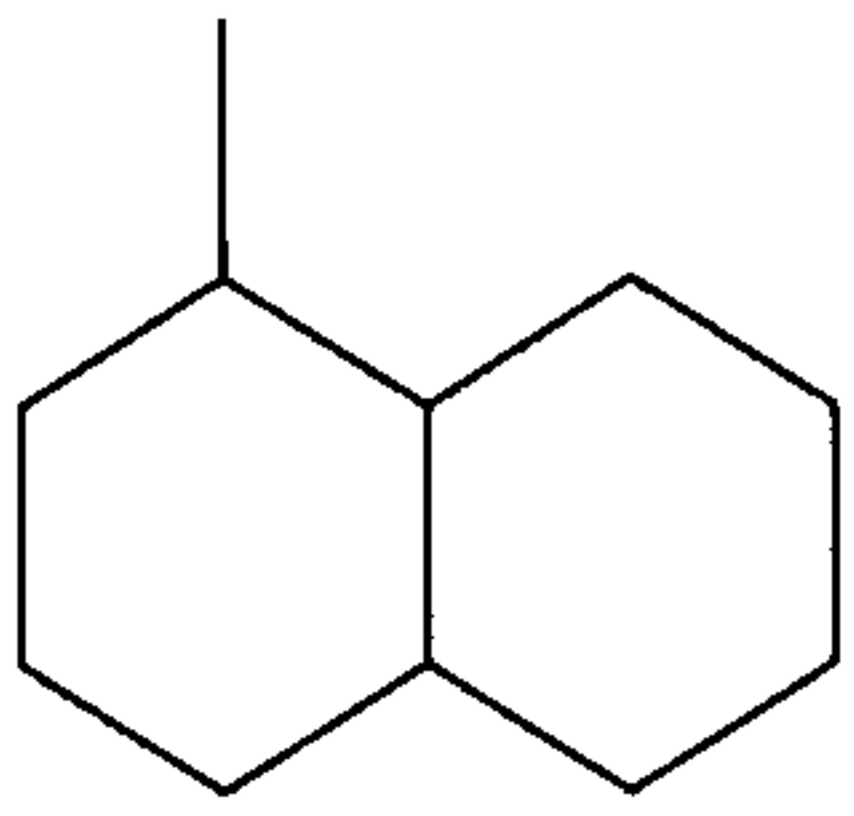
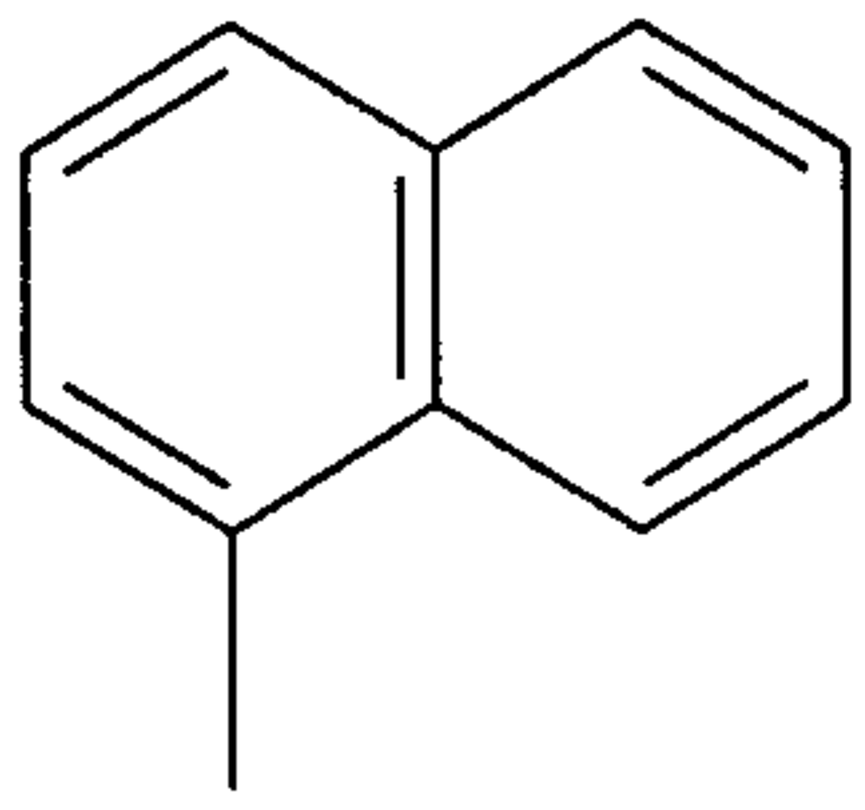
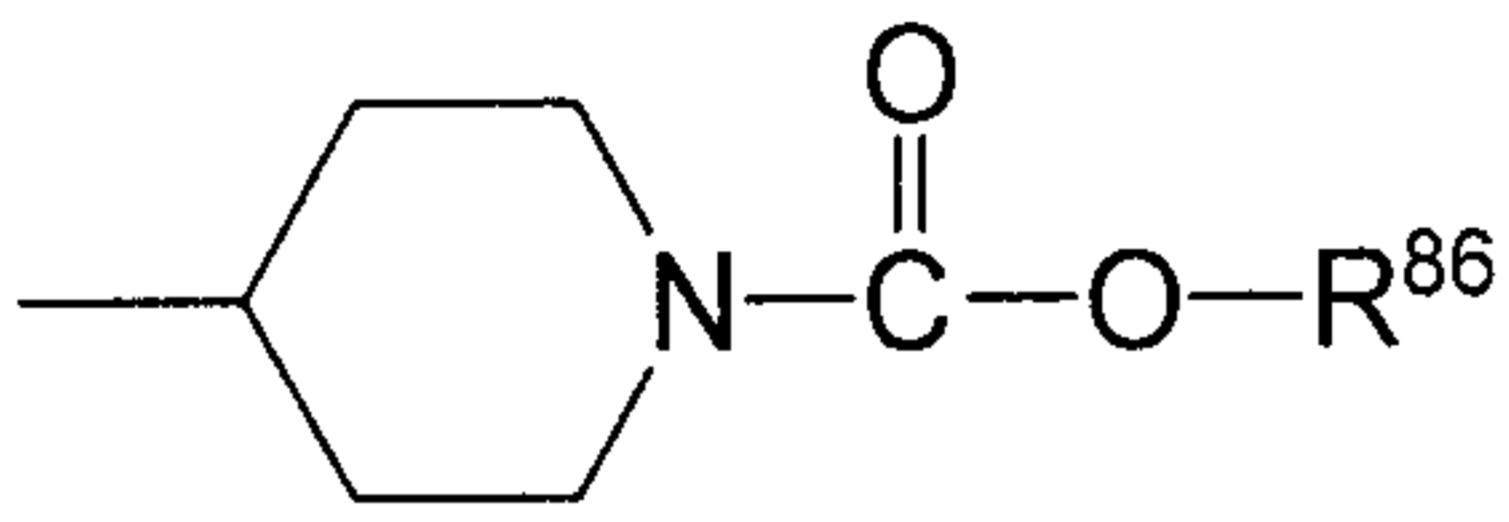
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  , 

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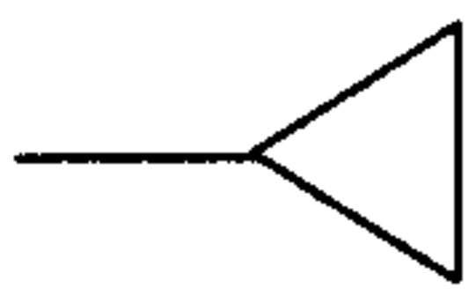
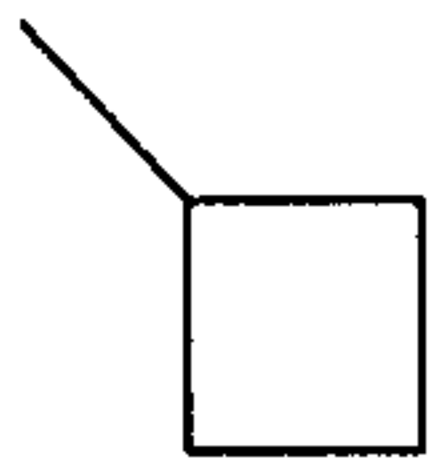
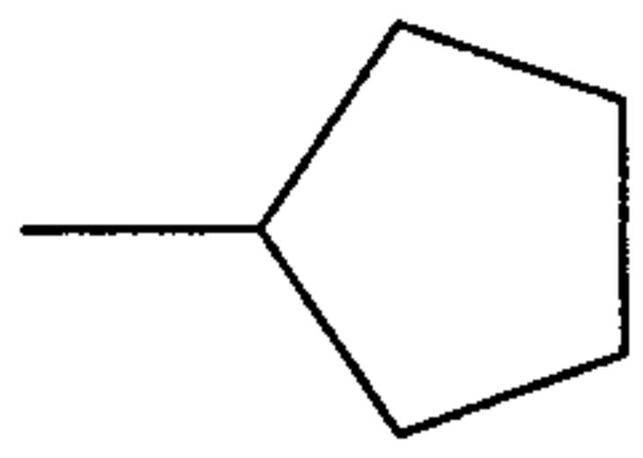
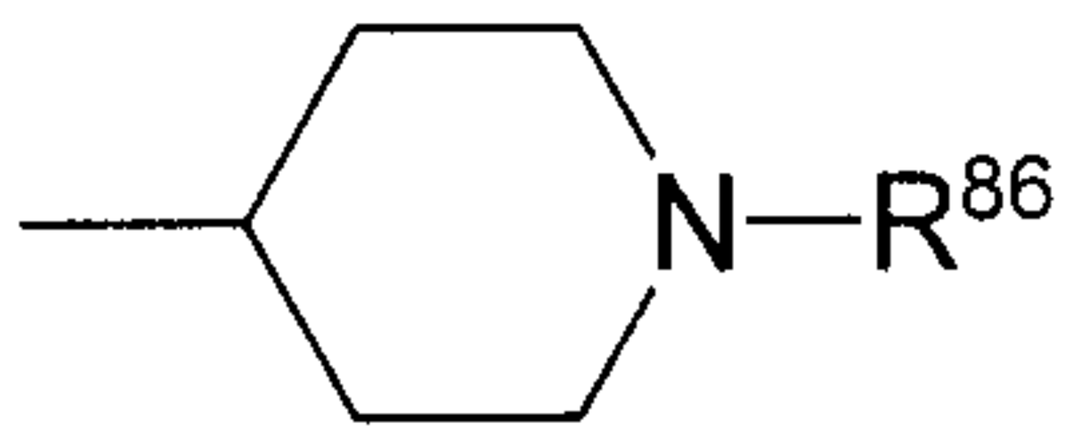
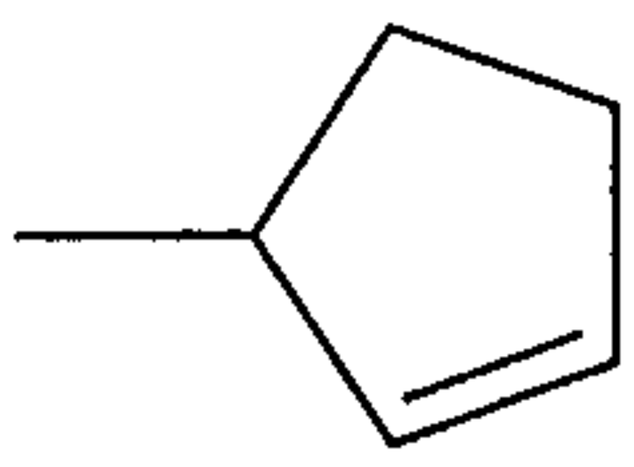
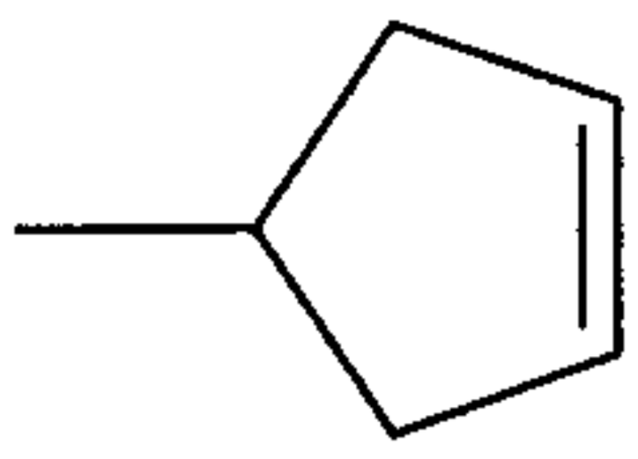
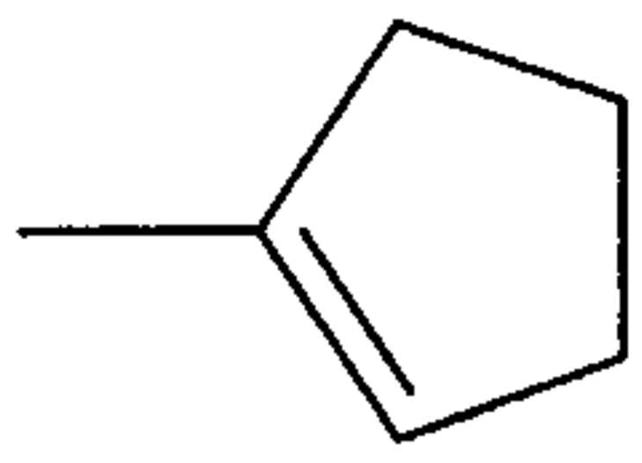
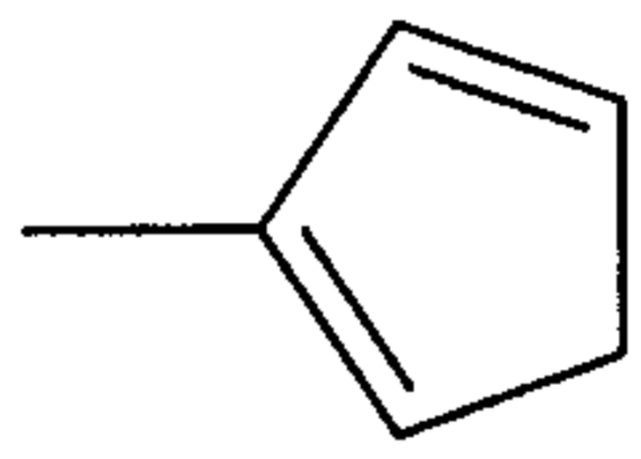
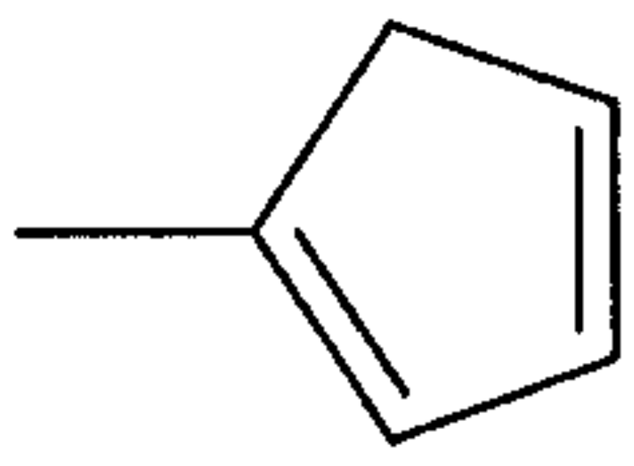
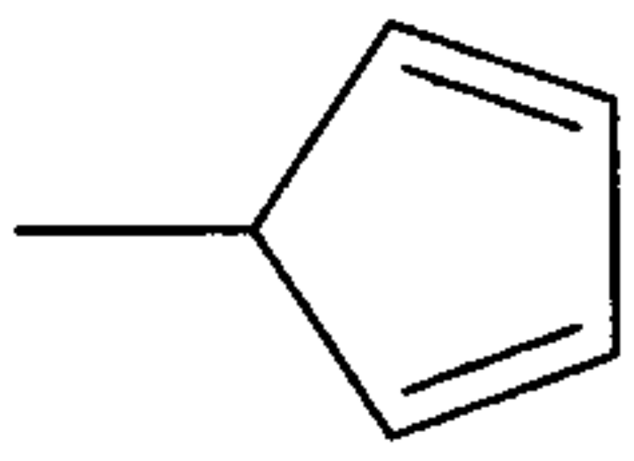
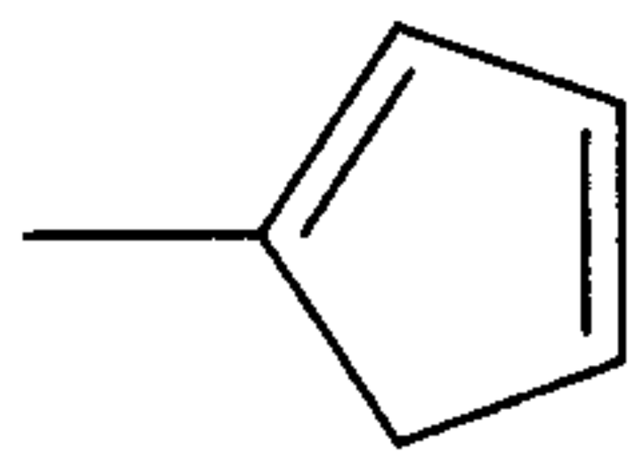
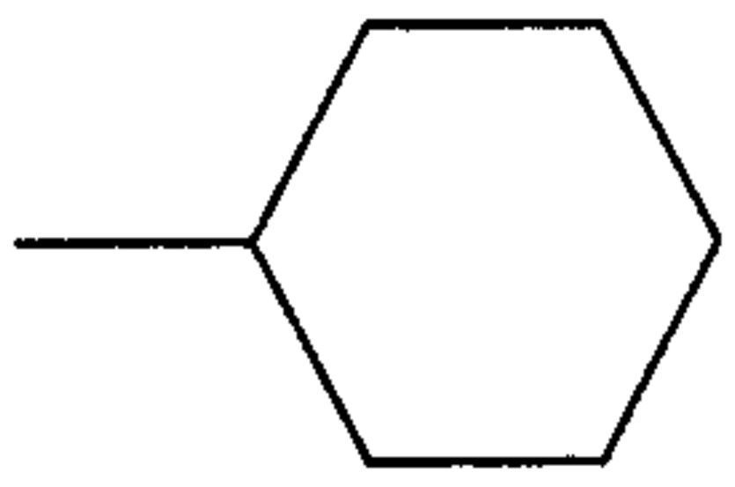
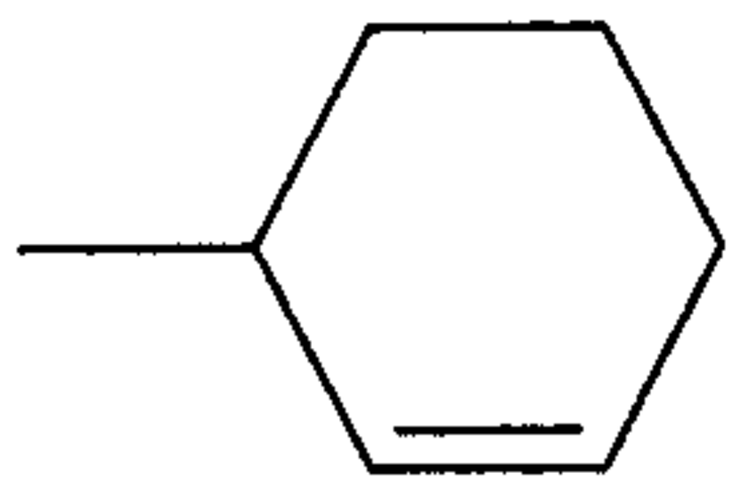
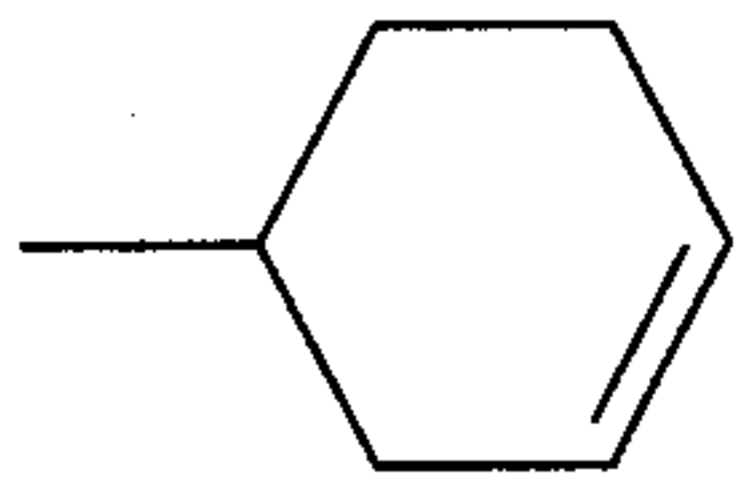
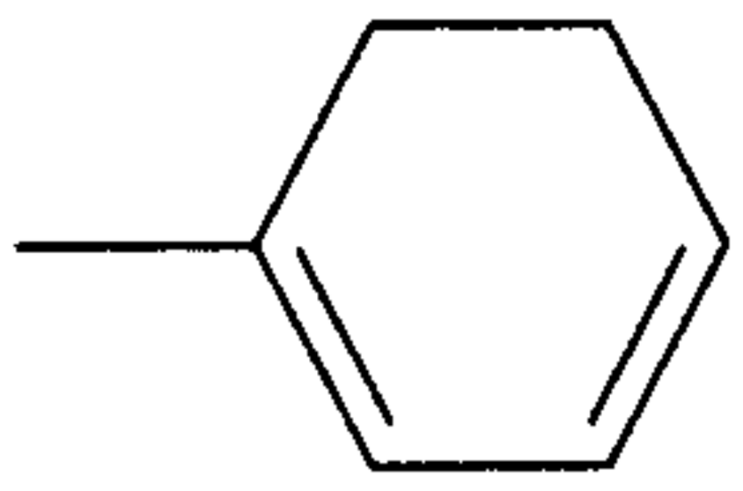
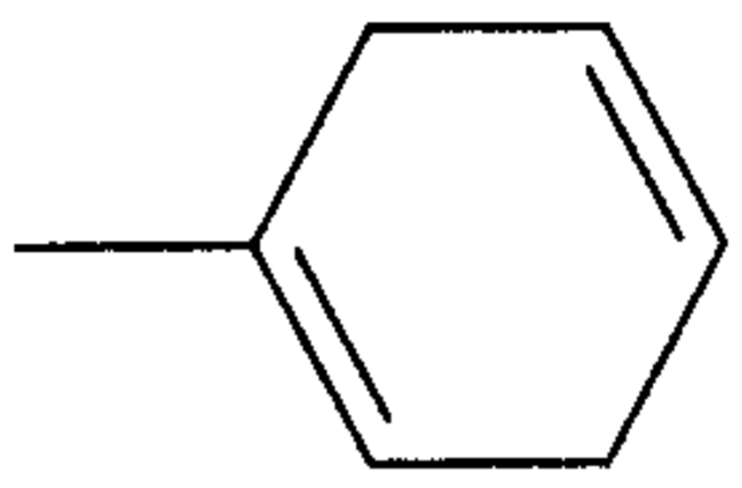
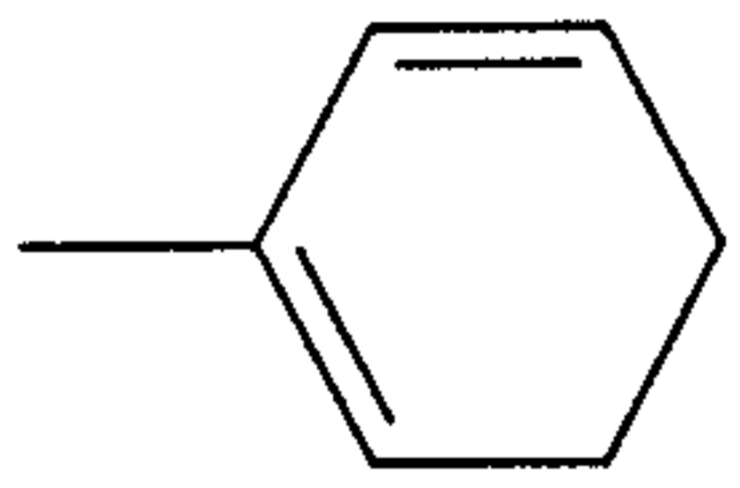
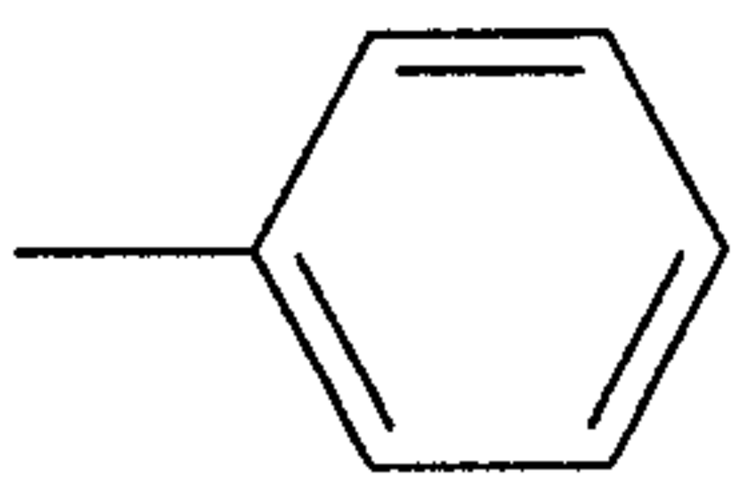
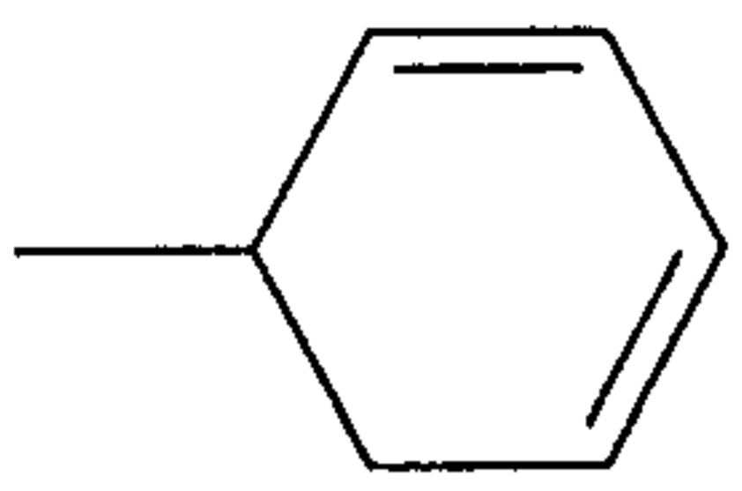
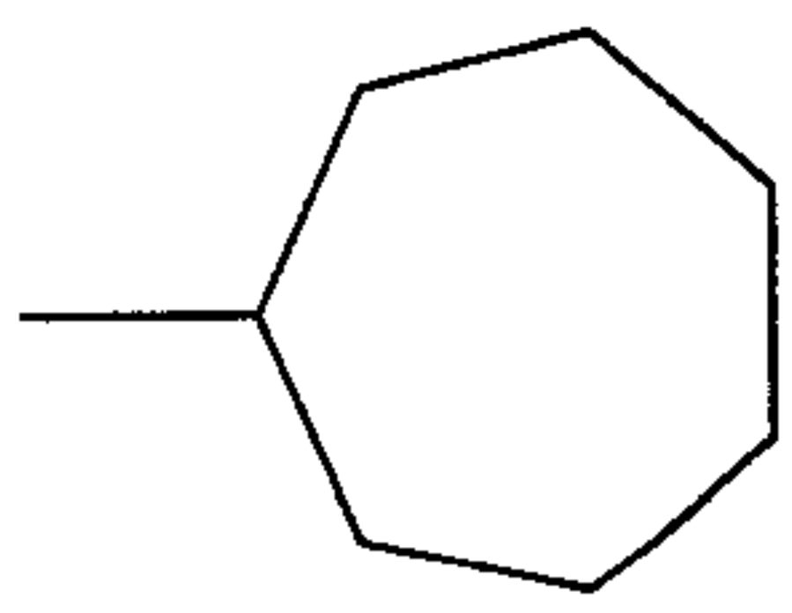
 ,  ,  , 

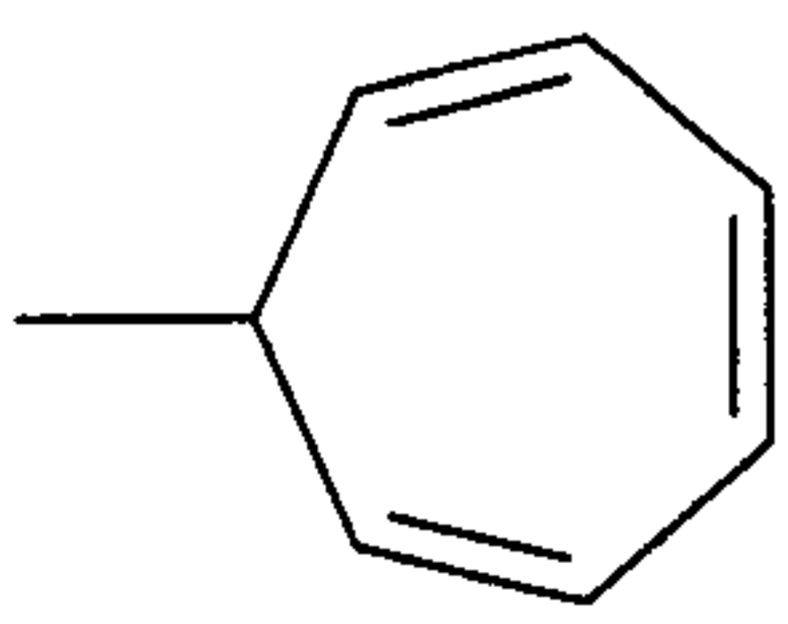
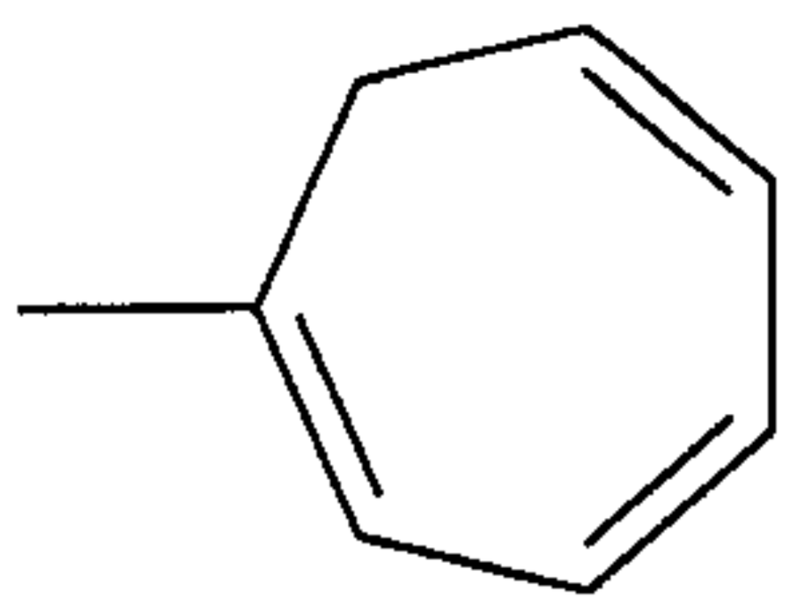
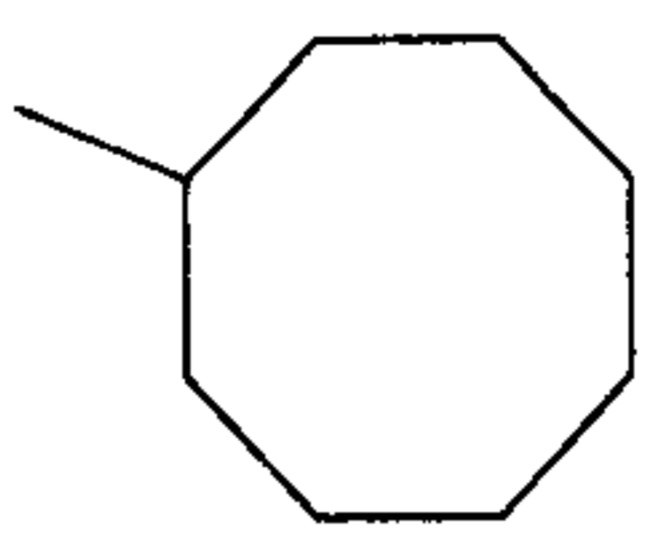
 ,  ,  ,  ,

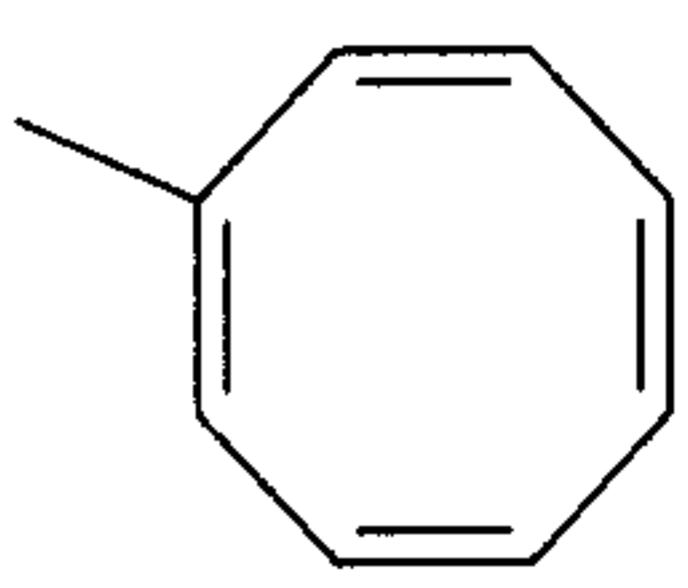
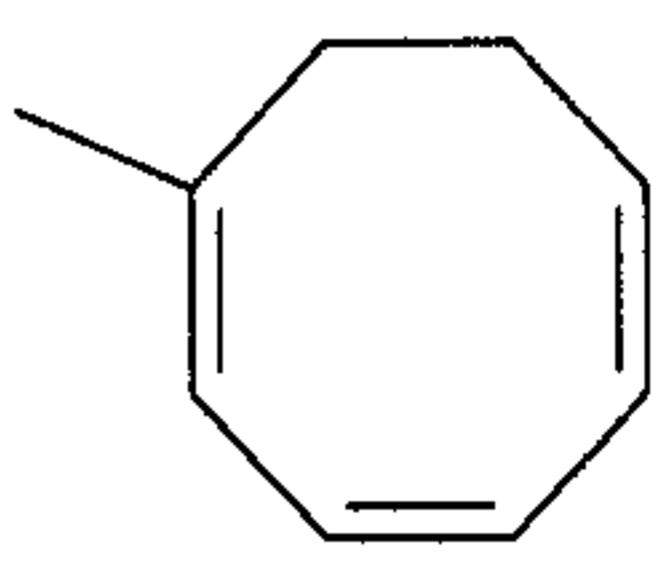
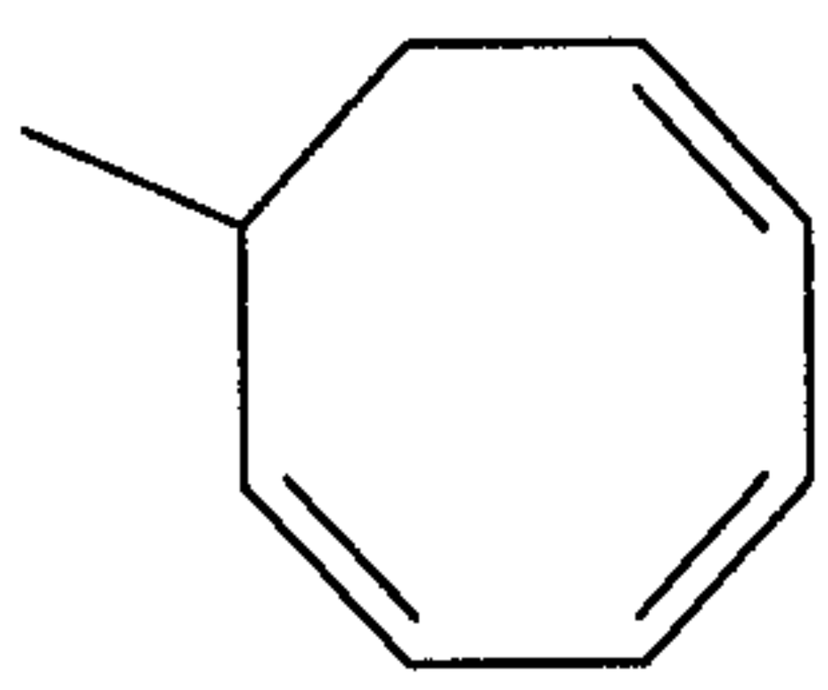
 ,  ,  ,

 ,  ,  ,

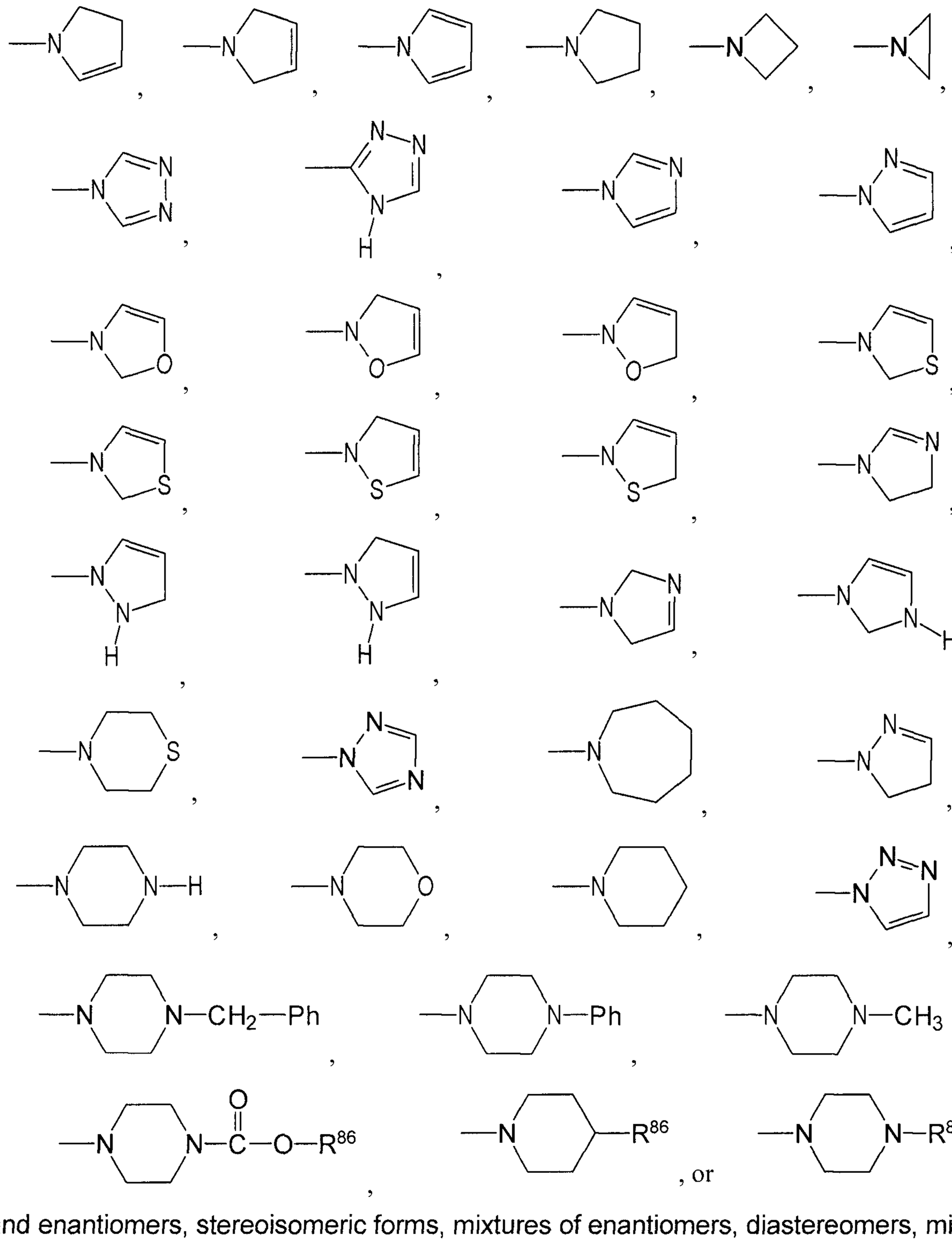
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

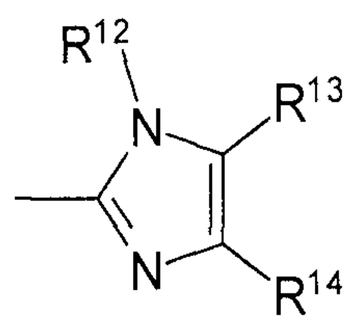
 ,  or  ,

R^{114} represents:



and enantiomers, stereoisomeric forms, mixtures of enantiomers, diastereomers, mixtures of diastereomers, prodrugs, hydrates, solvates, acid salt forms, tautomers, and racemates of the above mentioned compounds and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein the residue D represents a heterocycle which is: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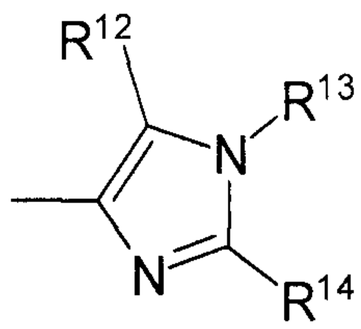
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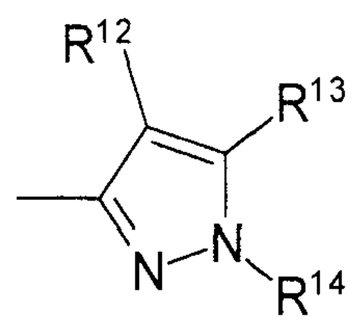
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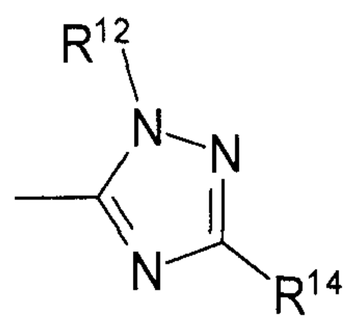
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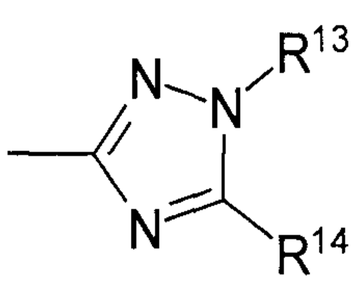
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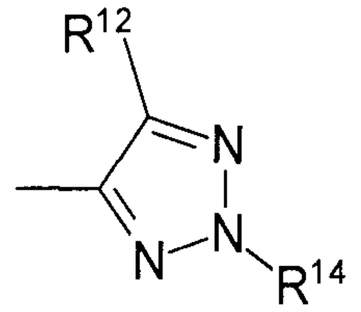
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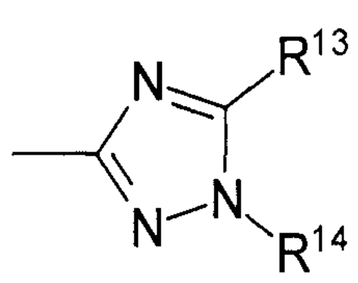
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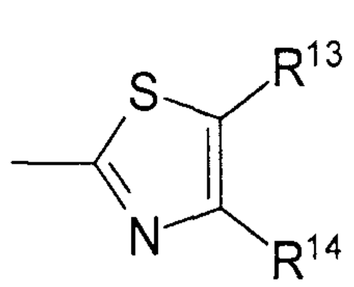
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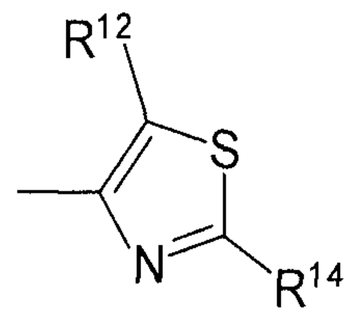
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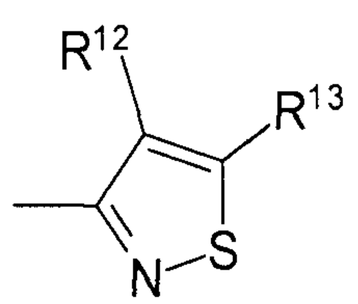
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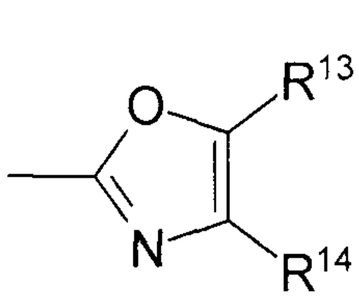
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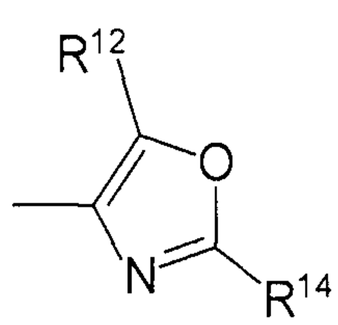
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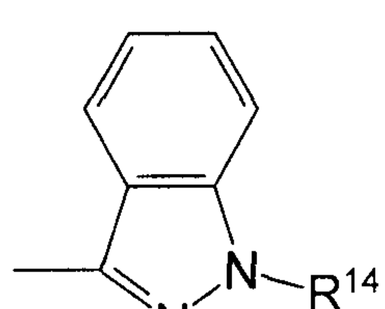
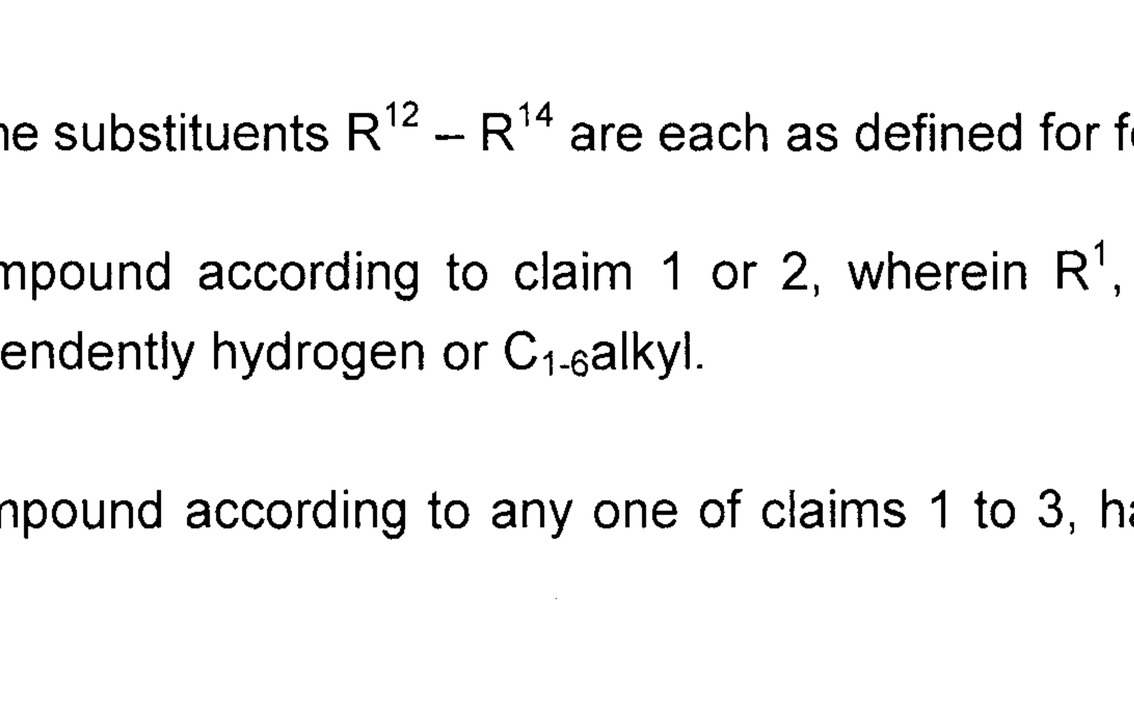

;

and the substituents R^{12} – R^{14} are each as defined for formula (I).

3. A compound according to claim 1 or 2, wherein R^1, R^4, R^5 and R^6 are each independently hydrogen or C_{1-6}alkyl.

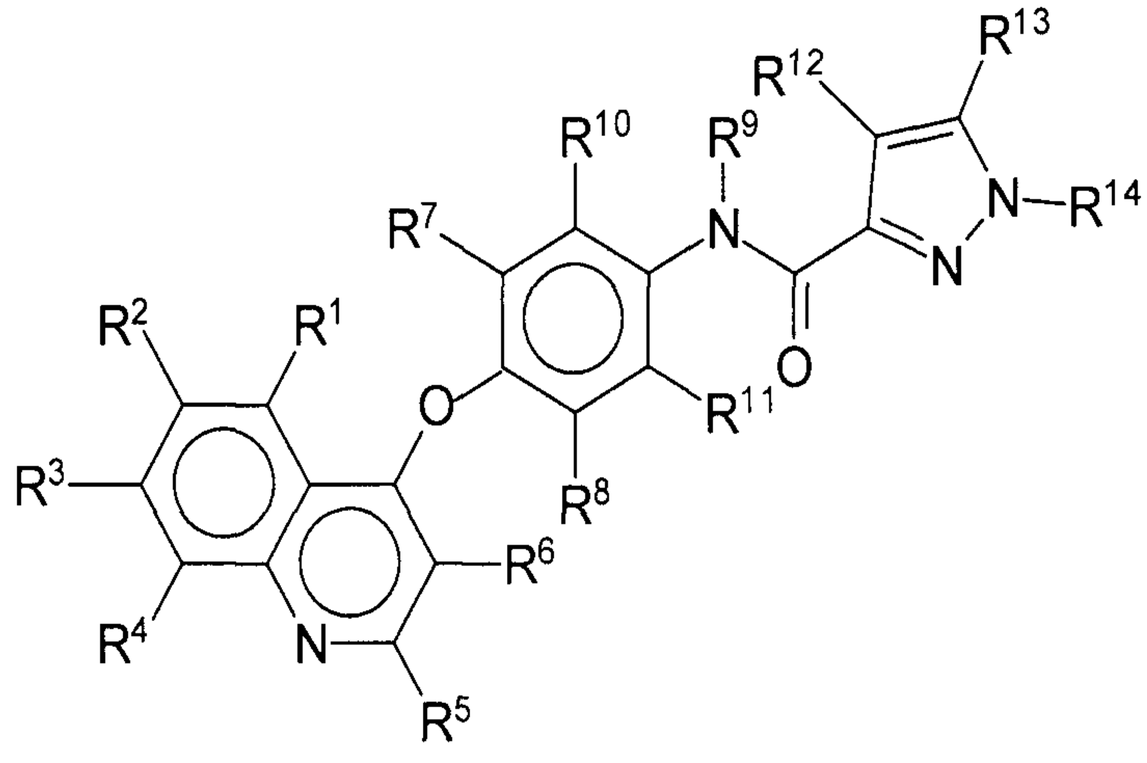
4. A compound according to any one of claims 1 to 3, having the general formula (Ia)



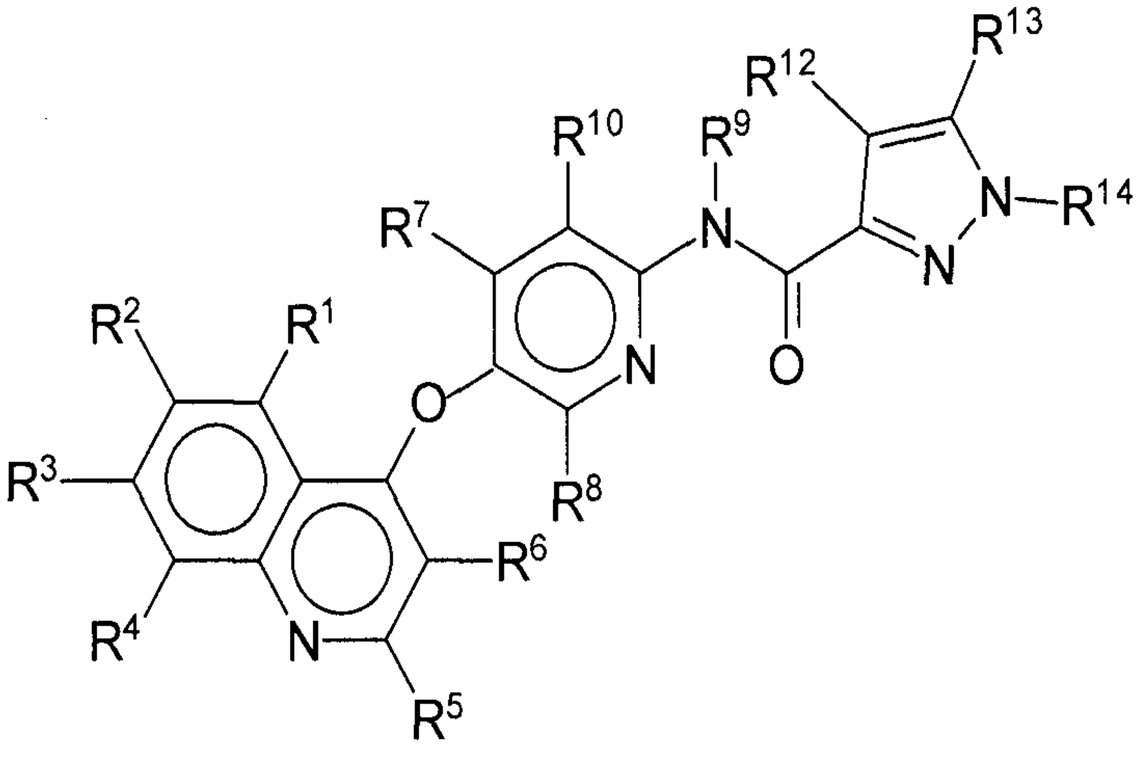
Formula (Ia),

wherin A, B, R^1-R^9 and R^{12}-R^{14} are each as defined for formula (I).

5. A compound according to any one of claims 1 to 4, having the general formula (Ib) or the general formula (Ic)



Formula (Ib)



Formula (Ic),

wherein R^1-R^{14} are each as defined for formula (I).

6. A compound according to any one of claims 1 to 5, wherein R^9 is a hydrogen atom.

7. A compound according to any one of claims 1 to 6, which is:
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1,5-dimethyl-pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-[4-(trifluoromethyl)phenyl]thiazole-4-carboxamide,

4-bromo-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-pyrazole-3-carboxamide,
1-tert-butyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-5-methyl-pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]thiazole-2-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-methyl-thiazole-4-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-indazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-phenyl-thiazole-4-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-imidazole-2-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-methyl-imidazole-4-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-propyl-pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[3-(1-piperidyl)propyl]pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(2,2,2-trifluoroethoxymethyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide,
4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-(2-dimethylaminoethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,

1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide,
4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide,
4-(cyclopropylmethoxy)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-methyl-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide,
N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-(cyclopropylmethoxy)-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[3-chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-(2-(dimethylamino)ethyl)-1-(4-fluorophenyl)-1H-pyrazole-3-carboxamide,
N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[2-(2-dimethylaminoethyl)-4-fluoro-phenyl]-4-ethoxy-pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide,
4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-methyl-pyrazole-3-carboxamide,
1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide,

N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1,5-dimethyl-pyrazole-3-carboxamide,
4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide,
4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide,
4-(2-dimethylaminoethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
1-(2-bromo-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide,
4-benzyloxy-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-nitro-pyrazole-3-carboxamide,
4-amino-N-[3-fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
N-[4-[[7-(3-aminopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-5-ethoxy-2-(4-fluorophenyl)oxazole-4-carboxamide,
4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide,
1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide,

4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide,
5-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]-4-quinolyl]oxy]phenyl]-2-(4-fluorophenyl)oxazole-4-carboxamide,
4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide trifluoroacetic acid salt,
4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-isopropoxy-pyrazole-3-carboxamide,
1-(2-chloro-4-fluoro-phenyl)-4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]pyrazole-3-carboxamide,
4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-(2-methoxyethoxy)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(1-methylpyrrolidin-3-yl)methoxy]pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(3-piperazin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-methoxy-pyrazole-3-carboxamide,
4-ethoxy-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
4-(cyclopropylmethoxy)-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
4-bromo-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-4-[(4-fluorophenyl)methoxy]pyrazole-3-carboxamide,
1-tert-butyl-N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-pyrazole-3-carboxamide,

N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-4-nitro-1-[3-(1-piperidyl)propyl]pyrazole-3-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-5-methyl-2-phenyl-oxazole-4-carboxamide,
N-[3-fluoro-4-[[6-methoxy-7-(4-piperidylmethoxy)-4-quinolyl]oxy]phenyl]-2-phenyl-thiazole-4-carboxamide,
4-ethoxy-N-[4-[[7-[(1-ethyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
4-ethoxy-N-[3-fluoro-4-[[7-[(1-isobutyl-4-piperidyl)methoxy]-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluorophenyl)pyrazole-3-carboxamide,
N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-1-(4-fluoro-2-methyl-phenyl)pyrazole-3-carboxamide,
1-(2-chloro-4-fluoro-phenyl)-N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-ethoxy-pyrazole-3-carboxamide,
N-[5-[(6,7-dimethoxy-4-quinolyl)oxy]-2-pyridyl]-4-(2-dimethylaminoethyl)-1-(4-fluorophenyl)pyrazole-3-carboxamide,
tert-butyl 4-(((4-((6-(4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamido)pyridin-3-yl)oxy)-6-methoxyquinolin-7-yl)oxy)methyl)piperidine-1-carboxylate,
N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-methoxy-2-methylphenyl)-1H-pyrazole-3-carboxamide,
N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(3-nitrophenyl)-1H-pyrazole-3-carboxamide,
1-(2-(benzyloxy)-4-fluorophenyl)-N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1H-pyrazole-3-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methylphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide,

N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-3-methoxyphenyl)-1H-pyrazole-3-carboxamide,
N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-nitrophenyl)-1H-pyrazole-3-carboxamide,
1-(4-aminophenyl)-N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1H-pyrazole-3-carboxamide,
N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-(2-methoxyphenyl)thiazole-2-carboxamide,
N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)-4-phenylthiazole-2-carboxamide,
4-bromo-N-(5-((6-methoxy-7-(piperidin-4-ylmethoxy)quinolin-4-yl)oxy)pyridin-2-yl)thiazole-2-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2-methoxyphenyl)-4-ethoxy-1-(4-fluoro-2-methylphenyl)-1H-pyrazole-3-carboxamide,
N-(5-((6,7-dimethoxyquinolin-4-yl)oxy)pyridin-2-yl)-4-ethoxy-1-(4-fluoro-2-hydroxyphenyl)-1H-pyrazole-3-carboxamide,
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1-(pyridin-3-yl)-1H-pyrazole-3-carboxamide, or
N-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluorophenyl)-4-ethoxy-1'-methyl-1'H-[1,3'-bipyrazole]-3-carboxamide.

8. A compound according to any one of claims 1 to 7, for use as pharmaceutically active agent.

9. A compound according to any one of claims 1 to 7, for use as inhibitor of TAM family RTKs.

10. A compound according to any one of claims 1 to 7, for use as suitable pharmaceutically active agent in the treatment or prevention of disorders associated with, accompanied by or caused by TAM family RTKs hyperfunction.

11. A compound according to any one of claims 1 to 7, for use in the treatment or prevention of Axl receptor tyrosine kinase induced disorders.

12. A compound according to claim 11, wherein the Axl receptor tyrosine kinase induced disorders are hyperproliferative disorders.

13. A compound according to claim 11, wherein the Axl receptor tyrosine kinase induced disorders are cancer or primary tumor metastases.

14. A compound according to claim 11, wherein the Axl receptor tyrosine kinase induced disorders are: adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome, colorectal cancer, small intestine cancer, small intestinal tumors, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumors, gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, glioblastomas, gynecologic tumors, ear tumors, nose tumors and throat tumors, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumors, brain metastases, testicle cancer, hypophysis tumor, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head and neck tumors, colon carcinoma, craniopharyngiomas, oral cancer, cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer, lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumors of the gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma, thymoma, tube carcinoma, eye tumors, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma or tongue cancer.

15. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 7 as active ingredient, and a pharmaceutically acceptable carrier, excipient or diluent.

16. Use of a compound as defined in any one of claims 1 to 7 or a pharmaceutical composition as defined in claim 15, in the treatment or prevention of disorders associated with, accompanied by or caused by TAM family RTKs hyperfunction.

17. Use of a compound as defined in any one of claims 1 to 7 or a pharmaceutical composition as defined in claim 15, in the treatment or prevention of Axl receptor tyrosine kinase induced disorders.

18. Use according to claim 17, wherein the Axl receptor tyrosine kinase induced disorders are hyperproliferative disorders.

19. Use according to claim 17, wherein the Axl receptor tyrosine kinase induced disorders are cancer or primary tumor metastases.

20. Use according to claim 17, wherein the Axl receptor tyrosine kinase induced disorders are: adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome, colorectal cancer, small intestine cancer, small intestinal tumors, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumors, gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, glioblastomas, gynecologic tumors, ear tumors, nose tumors and throat tumors, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumors, brain metastases, testicle cancer, hypophysis tumor, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head and neck tumors, colon carcinoma, craniopharyngiomas, oral cancer, cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer, lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumors of the gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma,

Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma, thymoma, tube carcinoma, eye tumors, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma or tongue cancer.

21. Use of a compound as defined in any one of claims 1 to 7, in the manufacture of a medicament for treating or preventing disorders associated with, accompanied by or caused by TAM family RTKs hyperfunction.

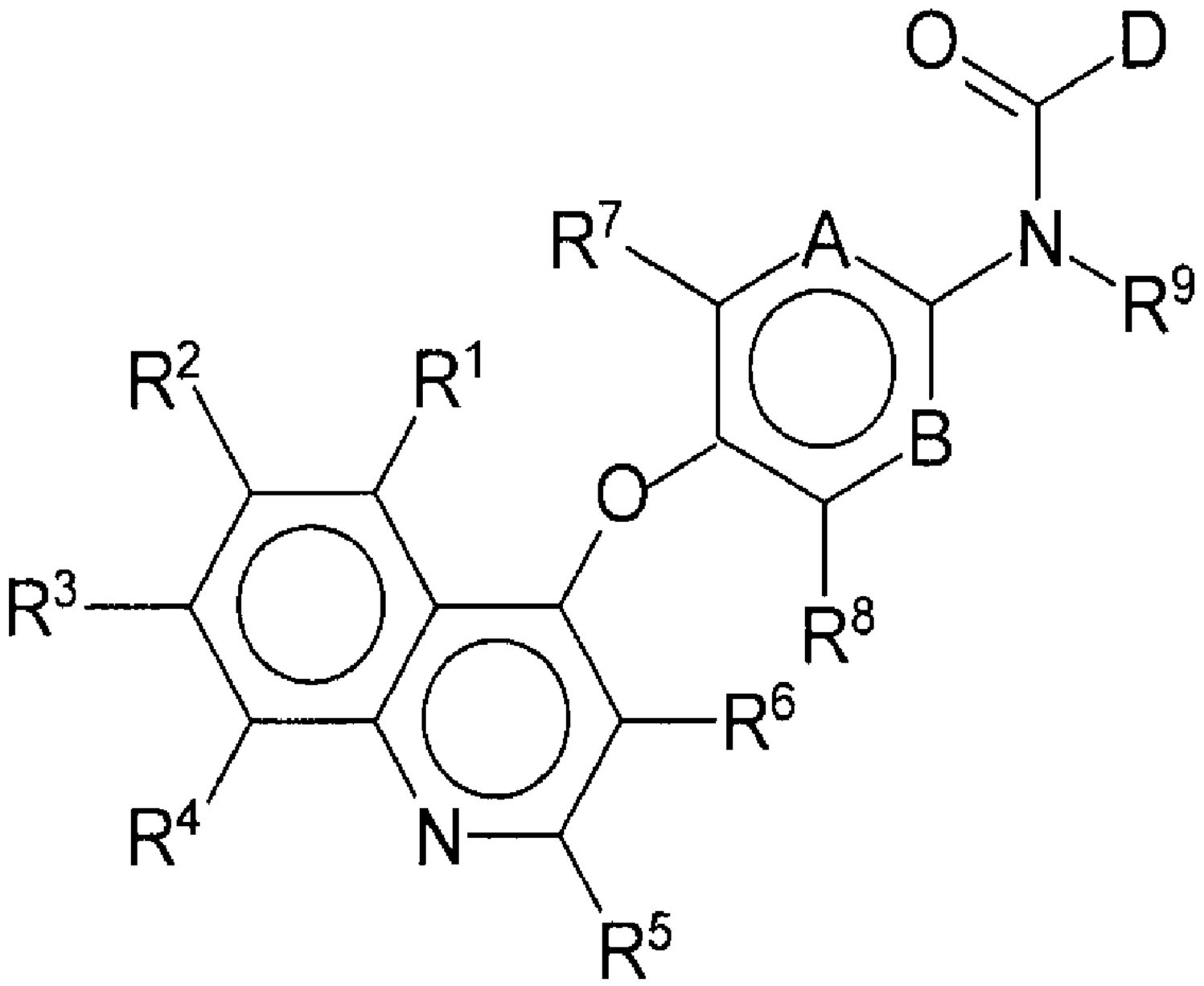
22 Use of a compound as defined in any one of claims 1 to 7, in the manufacture of a medicament for treating or preventing Axl receptor tyrosine kinase induced disorders.

23. Use according to claim 22, wherein the Axl receptor tyrosine kinase induced disorders are hyperproliferative disorders.

24. Use according to claim 23, wherein the Axl receptor tyrosine kinase induced disorders are cancer or primary tumor metastases.

25. Use according to claim 23, wherein the Axl receptor tyrosine kinase induced disorders are: adenocarcinoma, choroidal melanoma, acute leukemia, acoustic neurinoma, ampullary carcinoma, anal carcinoma, astrocytoma, basal cell carcinoma, pancreatic cancer, desmoid tumor, bladder cancer, bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus cancer, CUP-syndrome, colorectal cancer, small intestine cancer, small intestinal tumors, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumors, gastrointestinal tumors, gastric cancer, gallbladder cancer, gall bladder carcinomas, uterine cancer, cervical cancer, glioblastomas, gynecologic tumors, ear tumors, nose tumors and throat tumors, hematologic neoplasias, hairy cell leukemia, urethral cancer, skin cancer, skin testis cancer, brain tumors, brain metastases, testicle cancer, hypophysis tumor, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumor, bone cancer, colorectal carcinoma, head and neck tumors, colon carcinoma, craniopharyngiomas, oral cancer, cancer of the central nervous system, liver cancer, liver metastases, leukemia, eyelid tumor, lung cancer, lymph node cancer, lymphomas, stomach cancer, malignant melanoma, malignant neoplasia, malignant tumors of the gastrointestinal tract, breast carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Hodgkin's disease, mycosis fungoides, nasal cancer, neurinoma,

neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, esophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcomas, ovarial carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, prostate cancer, pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberger disease, esophageal cancer, spinalioms, T-cell lymphoma, thymoma, tube carcinoma, eye tumors, urologic tumors, urothelial carcinoma, vulva cancer, wart appearance, soft tissue tumors, soft tissue sarcoma, Wilm's tumor, cervical carcinoma or tongue cancer.



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