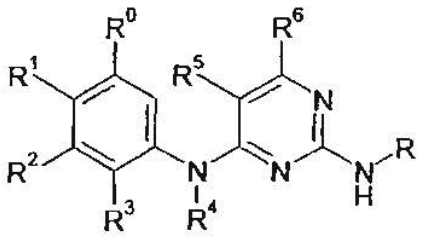
2,4-PYRIMIDINEDIAMINES USEFUL IN THE TREATMENT OF NEOPLASTIC DISEASES, INFLAMMATORY AND IMMUNE SYSTEM DISORDERS.

The present invention relates to the use novel pyrimidine derivatives, the certian novel pyrimidine derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides in a first aspect, the use of a compound of formula I



(I)

wherein

R is selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl and C_{3-10}heterocycloalkyl;

each of R^0, R^1, R^2,and R^3 independently is hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano, nitro, $-S(O)_{0-2}NR_{12}R_{13}$, $-S(O)_{0-2}R_{13}$, $-NR_{12}S(O)_{0-2}R_{13}$, $-C(O)NR_{12}R_{13}$, $-C(O)R_{13}$ and $-C(O)OR_{13}$; wherein R_{12} is selected from hydrogen and C_{1-6}alkyl; and R_{13} is selected from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl;

or R^0 and R^1, R^1 and R^2, and/or R^2 and R^3 form, together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

R^4 is hydrogen or C_1-C_8alkyl;

each of R^5 and R^6 independently is hydrogen, C_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, cyano, or nitro;

R is unsubstituted or substituted by R_7, R_8, R_9, R_{10}, and R'_{10};

R_7, R_8, R_9, R_{10}, or R'_{10} is a substituent independently selected from hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, aminoC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstituted or substituted C_5-C_{10}aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, C_1-C_8alkoxy, hydroxyC_1-C_8alkoxy, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkoxy, unsubstituted or substituted aminoC_1-C_8alkoxy, unsubstituted or substituted C_5-C_{10}arylC_1-C_8alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclylC_1-C_8alkyl, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, unsubstitued or substituted amino, C_1-C_8alkylthio, C_1-C_8alkylsulfinyl, C_1-C_8alkylsulfonyl, C_5-C_{10}arylsulfonyl, heterocyclosulfonyl, halogen, carboxy, C_1-C_8alkylcarbonyl, C_1-C_8alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano, nitro, $-S(O)_{0-2}NR_{12}R_{13}$, $-S(O)_{0-2}R_{12}$, $-C(O)R_{11}$, $-OXR_{11}$, $-NR_{12}XR_{11}$, $-NR_{12}XNR_{12}R_{13}$, $-OXNR_{12}R_{13}$, $-OXOR_{12}$ and $-XR_{11}$;

or two adjacent substituents on R may form together with the carbon atoms to which they are attached, a unsubstitued or substituted 5 or 6 membered carbocyclic or heterocydic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

X is a bond or C_{1-6}alkylene; and

R_{11} is independently selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl and C_{3-10}heterocycloalkyl;

and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_{11} is optionally substituted by 1 to 3 radicals independently selected from C_{1-6}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkyl optionally substituted with C_{1-6}alkyl, $-C(O)R_{12}$, $-C(O)NR_{12}R_{13}$, $-XNR_{12}R_{13}$, $-NR_{12}XNR_{12}R_{13}$ and $-NR_{12}C(O)R_{13}$; wherein X is a bond or C_{1-6}alkylene; R_{12} and R_{13} are independently selected from hydrogen and C_{1-6}alkyl;

and salts thereof in the treatment of of a disease associated to tyrosine kinase activity of anaplastic lymphoma kinase (ALK) or for the manufacture of pharmaceutical compositions for use in the treatment of said diseases, as well as use in the treatment of said diseases, to methods of use of such pyrimidine derivatives in the treatment of said diseases, and to pharmaceutical compositions comprising such pyrimidine derivatives for the treatment of said diseases.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula I.

C_1-C_8alkyl denotes a an alkyl radical having from 1 up to 8, especially up to 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, C_1-C_8alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl; especially methyl, propyl or tert-butyl.

C_2-C_8alkenyl denotes a an alkenyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, C_2-C_8alkenyl is pentenyl, such as 3-methyl-2-buten-2-yl, butenyl, such as 1- or 2-butenyl or 2-buten-2-yl, propenyl, such as 1-propenyl or allyl, or vinyl.

C_2-C_8alkinyl denotes a an alkinyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched; preferably, C_2-C_8alkinyl is propinyl, such as 1-propinyl or propargyl, or acetylenyl.

C_3-C_8cycloalkyl denotes a cycloalkyl radical having from 3 up to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, preferably cyclopropyl, cyclopentyl or cyclohexyl.

C_1-C_8alkoxy is especially methoxy, ethoxy, isopropyloxy, or tert-butoxy.

HydroxyC$_1$-C$_8$alkyl is especially hydroxymethyl, 2-hydroxyethyl or 2-hydroxy-2-propyl.

HydroxyC$_1$-C$_8$alkoxy is especially 2-hydroxyethoxy or 3-hydroxypropoxy.

C$_1$-C$_8$alkoxyC$_1$-C$_8$alkoxy is especially 2-methoxyethoxy.

C$_1$-C$_8$alkoxyC$_1$-C$_8$alkyl is especially methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl.

Halogen is preferably fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

HaloC$_1$-C$_8$alkyl is preferably chloroC$_1$-C$_8$alkyl or fluoroC$_1$-C$_8$alkyl, especially trifluoromethyl or pentafluoroethyl.

HaloC$_1$-C$_8$alkoxy is preferably chloroC$_1$-C$_8$alkoxy or fluoroC$_1$-C$_8$alkoxy, especially trifluoromethoxy.

C$_1$-C$_8$alkoxycarbonyl is especially tert-butoxycarbonyl, iso-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl.

Unsubstitued or substituted carbamoyl is carbamoyl substituted by one or two substituents selected from hydrogen, C$_1$-C$_8$alkyl, C$_2$-C$_8$alkenyl, C$_2$-C$_8$alkinyl, C$_3$-C$_8$cycloalkyl, C$_3$-C$_8$cycloalkylC$_1$-C$_8$alkyl, C$_5$-C$_{10}$arylC$_1$-C$_8$alkyl, hydroxyC$_1$-C$_8$alkyl, C$_1$-C$_8$alkoxyC$_1$-C$_8$alkyl, haloC$_1$-C$_8$alkyl, unsubstitued or substituted C$_5$-C$_{10}$aryl, or aminoC$_1$-C$_8$alkyl, or carbamoyl wherein the substituents and the nitrogen atom of the carbamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably carbamoyl, methylcarbamoyl, dimethylcarbamoyl, propylcarbamoyl, hydroxyethyl-methyl-carbamoyl, di(hydroxyethyl)carbamoyl, dimethylaminoethylcarbamoyl, or pyrrolidinocarbonyl, piperidinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, especially carbamoyl or dimethylcarbamoyl.

Unsubstitued or substituted sulfamoyl is sulfamoyl substituted by one or two substituents selected from hydrogen, C$_1$-C$_8$alkyl, C$_2$-C$_8$alkenyl, C$_2$-C$_8$alkinyl, C$_3$-C$_8$cycloalkyl, C$_3$-C$_8$cycloalkylC$_1$-C$_8$alkyl, C$_5$-C$_{10}$arylC$_1$-C$_8$alkyl, hydroxyC$_1$-C$_8$alkyl, C$_1$-C$_8$alkoxyC$_1$-C$_8$alkyl, haloC$_1$-

C_8alkyl, unsubstitued or substituted C_5-C_{10}aryl, or aminoC_1-C_8alkyl, or sulfamoyl wherein the substituents and the nitrogen atom of the sulfamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably sulfamoyl, methylsulfamoyl, propylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylaminoethylsulfamoyl, dimethylsulfamoyl, hydroxyethyl-methyl-sulfamoyl, di(hydroxyethyl)sulfamoyl, or pyrrolidinosulfonyl, piperidinosulfonyl, N-methylpiperazinosulfonyl or morpholinosulfonyl, especially sulfamoyl or methylsulfamoyl.

Unsubstitued or substituted amino is amino substituted by one or two substituents selected from hydrogen, C_1-C_8alkyl, C_2-C_8alkenyl, C_2-C_8alkinyl, C_3-C_8cycloalkyl, C_3-C_8cycloalkylC_1-C_8alkyl, C_5-C_{10}arylC_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, unsubstitued or substituted C_5-C_{10}aryl, aminoC_1-C_8alkyl, acyl, e.g. formyl, C_1-C_8alkylcarbonyl, C_5-C_{10}arylcarbonyl, C_1-C_8alkylsulfonyl or C_5-C_{10}arylsulfonyl, and is preferably amino, methylamino, dimethylamino, propylamino, benzylamino, hydroxyethyl-methyl-amino, di(hydroxyethyl)amino, dimethylaminoethylamino, acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, especially amino or dimethylamino.

AminoC_1-C_8alkyl is especially aminoethyl, methylaminoethyl, dimethylaminoethyl or dimethylaminopropyl.

Unsubstitued or substituted C_5-C_{10}aryl is, for example, phenyl, indenyl, indanyl, naphthyl, or 1,2,3,4-tetrahydronaphthalenyl, optionally substituted by C_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, haloC_1-C_8alkyl, hydroxy, C_1-C_8alkoxy, methylenedioxy, amino, substituted amino, halogen, carboxy, C_1-C_8alkoxycarbonyl, carbamoyl, sulfamoyl, cyano or nitro; preferably phenyl, tolyl, trifluoromethylphenyl, methoxyphenyl, dimethoxyphenyl, methylenedioxyphenyl, chlorophenyl or bromophenyl, whereby the substituents may be in ortho, meta or para position, preferably meta or para.

C_5-C_{10}aryloxy is especially phenoxy or methoxyphenoxy, e.g. p-methoxyphenoxy.

C_5-C_{10}arylC_1-C_8alkyl is especially benzyl or 2-phenylethyl.

C_5-C_{10}arylC_1-C_8alkoxy is especially benzyloxy or 2-phenylethoxy.

Unsubstitued or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S may be unsaturated, partially unsaturated or saturated, and further condensed to a benzo group or a 5 or 6 membered heterocyclyl group, and may be bound through a hetero or a carbon atom, and is, for example, pyrrolyl, indolyl, pyrrolidinyl, imidazolyl, benzimidazolyl, pyrazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, piperidyl, pyrimidinyl, pyrazinyl, piperazinyl, purinyl, tetrazinyl, oxazolyl, isoxalyl, morpholinyl, thiazolyl, benzothiazolyl, oxadiazolyl, and benzoxadiazolyl. Substituents considered are C_1-C_8alkyl, hydroxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkyl, C_1-C_8alkoxyC_1-C_8alkoxy, haloC_1-C_8alkyl, hydroxy, amino, substituted amino, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkylcarbonyl, C_1-C_8alkoxycarbonyl, carbamoyl, C_1-C_8alkylcarbamoyl, cyano, oxo, or unsubstitued or substituted 5 or 6 membered heterocyclyl as defined in this paragraph. 5 or 6 membered heterocyclyl preferably comprises 1 or 2 hetero atoms selected from N, O and S, and is especially indolyl, pyrrolidinyl, pyrrolidonyl, imidazolyl, N-methylimidazolyl, benzimidazolyl, S,S-dioxoisothiazolidinyl, piperidyl, 4-acetylaminopiperidyl, 4-methylcarbamoylpiperidyl, 4-piperidinopiperidyl, 4-cyanopiperidyl, piperazinyl, N-methylpiperazinyl, N-(2-hydroxyethyl)piperazinyl, morpholinyl, 1-aza-2,2-dioxo-2-thiacyclohexyl, or sulfolanyl.

In unsubstituted or substituted heterocyclyloxy, heterocyclyl has the meaning as defined above, and is especially N-methyl-4-piperidyloxy. In unsubstituted or substituted heterocyclylC_1-C_8alkoxy, heterocyclyl has the meaning as defined above, and is especially 2-pyrrolidinoethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 1-methyl-piperidin-3-ylmethoxy, 3-(N-methylpiperazino)propoxy or 2-(1-imidazolyl)ethoxy.

In a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S, and formed by two adjacent substituents together with the benzene ring, the ring may be further substituted, e.g. by C_1-C_8alkyl, C_1-C_8alkoxy, haloC_1-C_8alkyl, hydroxy, amino, substituted amino, C_1-C_8alkoxy, halogen, carboxy, C_1-C_8alkoxycarbonyl, carbamoyl, cyano, or oxo. The two adjacent substituents forming such a ring are preferably propylene, butylene, 1-aza-2-propylidene, 3-aza-1-propylidene, 1,2-diaza-2-propylidene, 2,3-diaza-1-propylidene, 1-oxapropylene, 1-oxapropylidene, methylenedioxy, difluoromethylene-dioxy, 2-aza-1-oxopropylene, 2-aza-2-methyl-1-oxopropylene, 1-aza-2-oxopropylene, 2-aza-1,1-dioxo-1-thiapropylene or the corresponding butylene derivatives forming a 6 membered ring.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

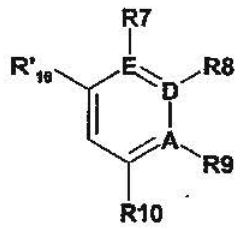
Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compounds of formula I have valuable pharmacological properties, as described hereinbefore and hereinafter.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination. R is C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl or C_{3-10}heterocycloalkyl, preferably R is



wherein R_7, R_8, R_9, R_{10}, or R'_{10} are as defined above;

In each of the following significances A, D or E is C or N but A, D and E may not all be N, preferably A, D or E is C:

(a) each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, $-S(O)_{0-2}NR_{12}R_{13}$, $-S(O)_{0-2}R_{13}$, $-NR_{12}S(O)_{0-2}R_{13}$, $-C(O)NR_{12}R_{13}$, and $-C(O)OR_{13}$ in particular hydrogen;

(b) R^1 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro,

unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;

(c) R^3 is hydrogen, C_1-C_8alkyl, e.g. methyl or ethyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, C_1-C_8alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, propyl-sulfonyl, cyclohexyl-sulfonyl, isopropyl-sulfonyl, C_5-C_{10}arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl, ethyl-amino-carbonyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl dimethyl-sulfamoyl, ethyl-sulfamoyl, 1-ethyl-propyl-sulfamoyl, cyclopentyl-sulfamoyl, cyclobutyl-sulfamoyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;

(d) each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 are $-CH_2-NH-CO-$, $-CH_2-CH_2-NH-CO-$, $-CH_2-CO-NH-$, $-CH_2-CH_2-CO-NH-$, $-CH_2-NH-SO_2-$, $-CH_2-CH_2-NH-SO_2-$, $-CH_2-SO_2-NH-$, $-CH_2-CH_2-SO_2-NH-$, $-CH_2-CH_2-SO_2-$, $-CH_2-CH_2-CH_2-SO_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$, and such pairs wherein hydrogen in NH is replaced by C_1-C_8alkyl; preferably the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 being $-O-CH_2-O-$, and the pair of adjacent substituents R^2 and R^3 being $-CH_2-NH-CO-$ or $-CH_2-NH-SO_2-$.

(e) R^4 is hydrogen or C_1-C_8alkyl, e.g. methyl; preferably hydrogen;

(f) R^5 is hydrogen; C_1-C_8alkyl, e.g. methyl or ethyl, halogen, e.g. chloro or bromo, haloC_1-C_8alkyl, e.g. trifluoromethyl, cyano or nitro; preferably hydrogen, methyl, ethyl, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;

(g) R^6 is hydrogen;

(h) each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, C_1-C_8alkylcarbonyl, e.g methyl carbonyl, aminoalkoxy, e.g diethylaminoethoxy, haloC_1-C_8alkyl, e.g. trifluoromethyl,

unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, heterocyclosulfonyl, e.g piperazinylsulfonyl, heterocyclocarbonyl, e.g. methylpirerazinylcarbonyl, cyano, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

(i) R^6 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, heterocyclylalkyl, e.g. methylpiperazinoethyl, heterocyclylcarbonyl, e.g. piperazinocarbonyl, heterocyclyl C_1-C_8alkylamino, e.g. pyridylethyl(methyl)amino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, C_1-C_8alkylamino-C_1-C_8alkylamino, e.g. dimethylamino-propylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, cyano, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-

piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;

(j) R^{10} is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or butyl, hydroxy, cyano, hydroxyC_1-C_8alkyl, e.g. hydroxyethyl or hydroxybutyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_1-C_8alkoxy, e.g. methoxy or ethoxy, cycloalkylalkoxy, aryloxy, haloC_1-C_8alkoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; carboxy, carbamoyl, or unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and

(k) each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, are –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-O-$, $-CH_2C(CH_3)_2O-$, $-CH=C(CH_3)O-$, $-OCH_2CH_2O-$, -(Morpholinopropyl)N-CH=CH-, -CH=CH-O-, $-O-CH_2-O-$, or $-O-CF_2-O-$; preferably the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 being $-O-CH_2-O-$ or the pair of adjacent substituents R^9 and R^{10} being -NH-CH=CH-, -CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

(l) or R^7, R^8, R^9, R^{10} and R'^{10} are ethoxy, ethyl, propyl, methyl, t-butyl, trifluoromethyl, nitrile, cyclobutyloxy, 2,2,2-trifluoroethoxy, methoxy, isobutyloxy, t-butyloxy, isopropyloxy, methyl-amino-carbonyl, cyclopropyl-methoxy, dimethylamino-propyl-amino, methoxy-ethoxy, $-XR_{11}$, $-C(O)R_{11}$ and $-OXR_{11}$; wherein X is a bond, methylene or ethylene; R_{11} is selected from piperazinyl, piperidinyl, pyrrolidinyl, morpholino, azepanyl and 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl; wherein R_{11} is optionally substituted by 1 to 3 radicals independently selected from methyl, isopropyl, acetyl, acetyl-methyl-amino, 3-dimethylamino-2,2-dimethyl-propylamino, ethyl-methyl-amino-ethoxy, diethyl-amino-ethoxy, amino-carbonyl, ethyl, 2-oxo-pyrrolidin-1-yl, pyrrolidinyl, pyrrolidinyl-methyl, piperidinyl optionally substituted with methyl or ethyl, morpholino, dimethylamino, dimethylamino-propyl-amino, methyl-amino and ethyl-amino.

More preferred are the following meanings, independently, collectively or in any combination or sub-combination:

(a') each of R^0 or R^2 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or

isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, in particular hydrogen;

(b') R^1 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;

(c') R^3 is hydrogen, C_1-C_8alkyl, e.g. methyl or ethyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, C_1-C_8alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, C_1-C_8alkylsulfonyl, e.g. methylsulfonyl, C_5-C_{10}arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;

(d') each pair of adjacent substituents R^0 and R^1, or R^1 and R^2, or R^2 and R^3 are $-CH_2-NH-CO-$, $-CH_2-NH-SO_2-$, $-CH_2-CH_2-SO_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$, and such pairs wherein hydrogen in *NH* is replaced by C_1-C_8alkyl; preferably the pair of adjacent substituents R^0 and R^1, or R^1 and R^2 being $-O-CH_2-O-$, and the pair of adjacent substituents R^2 and R^3 being $-CH_2-NH-CO-$ or $-CH_2-NH-SO_2-$.

(e') R^4 is hydrogen;

(f') R^5 is hydrogen, halogen, e.g. chloro or bromo, haloC_1-C_8alkyl, e.g. trifluoromethyl, or nitro; preferably hydrogen, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;

(g') R^6 is hydrogen;

(h') each of R^7 and R^9 independently is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, unsubstituted or substituted C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

(i') R^8 is hydrogen, C_1-C_8alkyl, e.g. methyl, ethyl or isopropyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_5-C_{10}aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, C_1-C_8alkoxy, e.g. methoxy, ethoxy or isopropoxy, haloC_1-C_8alkoxy, e.g. trifluoromethoxy, C_5-C_{10}aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;

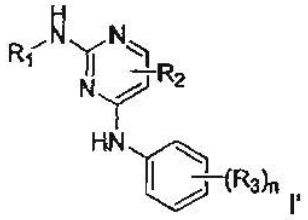
(j') R^{10} is C_1-C_8alkyl, e.g. methyl, ethyl or butyl, haloC_1-C_8alkyl, e.g. trifluoromethyl, C_1-C_8alkoxy, e.g. methoxy or ethoxy, unsubstituted or substituted heterocyclylC_1-C_8alkoxy, e.g. 2-(1-

imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and

(k') each pair of adjacent substituents R^7 and R^8, or R^8 and R^9 or R^9 and R^{10}, are –NH-CH=CH-, -CH=CH-NH-, –NH-N=CH-, –CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$, $-O-CH_2-O-$, or $-O-CF_2-O-$; preferably the pair of adjacent substituents R^7 and R^8 or R^8 and R^9 being $-O-CH_2-O-$ or the pair of adjacent substituents R^9 and R^{10} being -NH-CH=CH-, -CH=N-NH-, $-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-CH_2-$ or $-O-CF_2-O-$.

Most preferred as compounds of the formula I are those wherein the substituents have the meaning given in the Examples.

In another embodiment of the invention the invention provides a compound of formula I' with the proviso that this does not include any of the compounds of examples 1 to 52 inclusive.



I'

in which:

n' is selected from 1, 2 and 3;

R'_1 is selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl and C_{3-10}heterocycloalkyl;

wherein any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R'_1 is optionally substituted by 1 to 3 radicals independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, alkoxy-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, halo-substituted-C_{1-6}alkoxy, $-C(O)NR'_5R'_6$, $-S(O)_{0-2}NR'_5R'_6$, $-S(O)_{0-2}R'_5$, $-C(O)R'_4$, $-OXR'_4$, $-NR'_5XNR'_5R'$, $-OXNR'_5R'_6$, $-OXOR'_5$ and $-XR'_4$;

wherein X' is a bond or C_{1-6}alkylene; R'_5 is selected from hydrogen and C_{1-6}alkyl; R'_6 is selected from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{1-4}alkyl; and R'_4 is independently selected from C_{6-10}aryl, C_{5-10}heteroaryl, C_{3-12}cycloalkyl and C_{3-10}heterocycloalkyl;

and any aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R'_4 is optionally substituted by 1 to 3 radicals independently selected from C_{1-6}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkyl optionally substituted with C_{1-6}alkyl, $-C(O)NR'_5R'_6$, $-XNR'_5R'_6$, $-NR'_5XNR'_5R'_6$ and $-NR'_5C(O)R'_6$; wherein X is a bond or C_{1-6}alkylene; R'_5 and R'_6 are independently selected from hydrogen and C_{1-6}alkyl;

R'_2 is selected from hydrogen and halo, cyano, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl;

R'_3 is selected from halo, $-S(O)_{0-2}NR'_5R'_6$, $-S(O)_{0-2}R'_6$, $-NR'_5S(O)_{0-2}R'_6$, $-C(O)NR'_5R'_6$, $-C(O)R'_6$ and $-C(O)OR'_6$; wherein R'_5 is selected from hydrogen and C_{1-6}alkyl; and R'_6 is selected from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl;

and the pharmaceutically acceptable salts, hydrates, solvates, isomers and prodrugs thereof.

Preferably a compound of fomula I' in which:

n' is selected from 1 and 2;

R'_1 is selected from C_{6-10}aryl and C_{5-10}heteroaryl; wherein any aryl or heteroaryl of R_1 is optionally substituted by 1 to 3 radicals independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, $-C(O)NR'_5R'_6$, $-OX'R'_4$, $-C(O)R'_4$, $-NR'_5X'NR'_5R'_6$, $-OX'NR'_5R'_6$, $-OX'OR'_5$ and $-X'R'_4$; wherein X' is a bond or C_{1-6}alkylene; R'_5 is selected from hydrogen and C_{1-6}alkyl; R'_6 is selected from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl-C_{1-4}alkyl; and R'_4 is C_{3-10}heterocycloalkyl optionally substituted by 1 to 3 radicals independently selected from C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{3-10}heterocycloalkyl-C_{0-4}alkyl optionally substituted with C_{1-6}alkyl, $-C(O)NR'_5R'_6$, $-X'NR'_5R'_6$, $-NR'_5X'NR'_5R'_6$ and $-NR'_5C(O)R'_6$; wherein X' is a bond or C_{1-6}alkylene; R'_5 and R'_6 are independently selected from hydrogen and C_{1-6}alkyl;

R'_2 is selected from hydrogen and halo;

R'_3 is selected from halo, $-S(O)_{0-2}NR'_5R'_6$, $-S(O)_{0-2}R'_6$, $-NR'_5S(O)_{0-2}R'_6$, $-C(O)NR'_5R'_6$ and $-C(O)OR'_6$; wherein R'_5 is selected from hydrogen and C_{1-6}alkyl; and R'_6 is selected from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl.

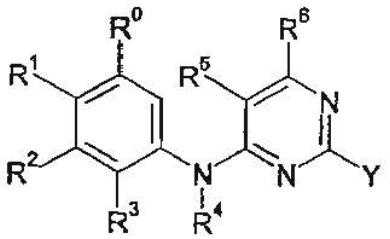
more prefably a compound of formula I' in which R'_1 is selected from phenyl, pyridinyl, pyrazolyl and pyrimidinyl; wherein any aryl or heteroaryl of R'_1 is optionally substituted by 1 to 3 radicals independently selected from ethoxy, ethyl, propyl, methyl, t-butyl, trifluoromethyl, nitrile,

cyclobutyloxy, 2,2,2-trifluoroethoxy, methoxy, isobutyloxy, t-butyloxy, isopropyloxy, methyl-amino-carbonyl, cyclopropyl-methoxy, dimethylamino-propyl-amino, methoxy-ethoxy, -X'R'$_4$, -C(O)R'$_4$ and –OX'R'$_4$; wherein X' is a bond, methylene or ethylene; R'$_4$ is selected from piperazinyl, piperidinyl, pyrrolidinyl, morpholino, azepanyl and 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl; wherein R'$_4$ is optionally substituted by 1 to 3 radicals independently selected from methyl, isopropyl, acetyl, acetyl-methyl-amino, 3-dimethylamino-2,2-dimethyl-propylamino, ethyl-methyl-amino-ethoxy, diethyl-amino-ethoxy, amino-carbonyl, ethyl, 2-oxo-pyrrolidin-1-yl, pyrrolidinyl, pyrrolidinyl-methyl, piperidinyl optionally substituted with methyl or ethyl, morpholino, dimethylamino, dimethylamino-propyl-amino, methyl-amino and ethyl-amino.

Even more preferably a compound of of formula I' in which R'$_2$ is selected from hydrogen and halo; and R'$_3$ is selected from halo, dimethyl-sulfamoyl, isobutyl-sulfamoyl, methyl-sulfamoyl, ethyl-sulfamoyl, propyl-sulfonyl, ethyl-amino-carbonyl, 1-ethyl-propyl-sulfamoyl, cyclopentyl-sulfamoyl, isopropyl-sulfamoyl, cyclohexyl-sulfonyl, cyclopropyl-methyl-sulfamoyl, cyclobutyl-sulfamoyl, isopropyl-sulfonyl,

Most preferably a compound of example 53

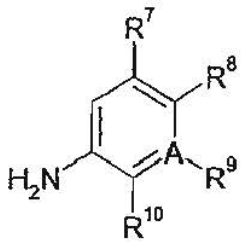
In a yet further embodiment of the invention the present invention also provides a process for the production of a compound of formula I, comprising reacting a compound of formula II



(II)

wherein R^0, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined above, and Y is a leaving group, preferably halogen such as bromide, iodine, or in particular chloride;

with a compound of formula III



(III)

wherein R^7, R^8, R^9 and R^{10} are as defined above;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined above, into another compound of formula I as defined;

and recovering the resulting compound of formula I in free from or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

The reaction can be carried out in a manner known per se, the reaction conditions being dependent especially on the reactivity of the leaving group Y and the reactivity of the amino group in the aniline of formula III, usually in the presence of a suitable solvent or diluent or of a mixture thereof and, if necessary, in the presence of an acid or a base, with cooling or, preferably, with heating, for example in a temperature range from approximately -30°C to approximately +150°C, especially approximately from 0°C to +100°C, preferably from room temperature (approx. +20 °C) to +80 °C, in an open or closed reaction vessel and/or in the atmosphere of an inert gas, for example nitrogen. Alternatively, the reaction can proceed in the presence of a suitable catalyst (for example, palladium di-benzyl-acetone), in the presence of a base (for example, caesium carbonate) and in the presence of a suitable reaction facilitator (for example, xanthphos).

If one or more other functional groups, for example carboxy, hydroxy or amino, are or need to be protected in a compound of formula II or III, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as substitution reaction or

solvolysis. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known per se. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent.

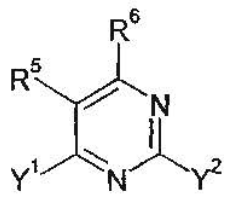
Salts can usually be converted to compounds in free form, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

It should be emphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates.

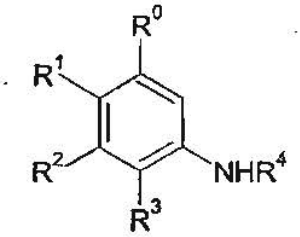
The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

The compound of formula II used as starting materials may be obtained by reacting a compound of formula IV



(IV)

with a compound of formula V



(V)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined above, and Y^1 and Y^2 are identical or different leaving groups as defined above for Y. The reaction conditions are those mentioned above for the reaction of a compound of formula II with a compound of formula III.

The compounds of formula IV and V are known or may be produced in accordance with known procedures.

The compounds of formula I and their pharmaceutically acceptable salts exhibit valuable pharmacological properties when tested in vitro in cell-free kinase assays and in cellular assays, and are therefore useful as pharmaceuticals. In particular, the compounds of the invention are inhibitors of Focal Adhesion Kinase, and are useful as pharmaceuticals to treat conditions caused by a malfunction of signal cascades connected with Focal Adhesion Kinase, in particular tumors as described hereinbelow.

Focal Adhesion Kinase (FAK) is a key enzyme in the integrin-mediated outside-in signal cascade (D. Schlaepfer et al., Prog Biophys Mol Biol 1999, 71, 435-478). Interaction between cells and extracellular matrix (ECM) proteins is transduced as intracellular signals important for growth, survival and migration through cell surface receptors, integrins. FAK plays an essential role in these integrin-mediated outside-in signal cascades. The trigger in the signal transduction cascade is the autophosphorylation of Y397. Phosphorylated Y397 is a SH2 docking site for Src family tyrosine kinases. The bound c-Src kinase phosphorylates other tyrosine residues in FAK. Among them, phsophorylated Y925 becomes a binding site for the SH2 site of Grb2 small adaptor protein. This direct binding of Grb2 to FAK is one of the key steps for the activation of down stream targets such as the Ras-ERK2/MAP kinase cascade.

The inhibition of endogenous FAK signalling results in reduced motility and in some cases induces cell death. On the other hand, enhancing FAK signalling by exogenous expression increases cell motility and transmitting a cell survival signal from ECM. In addition FAK is overexpressed in invasive and metastatic epithelial, mesenchymal, thyroid and prostate cancers. Consequently, an inhibitor of FAK is likely to be a drug for anti-tumor growth and metastasis. The compounds of the invention are thus indicated, for example, to prevent and/or treat a vertebrate and more particularly a mammal, affected by a neoplastic disease, in particular breast tumor, cancer of the bowel (colon and rectum), stomach cancer and cancer of the ovary and prostate, non-small cell lung cancer, small cell lung cancer, cancer of liver, melanoma, bladder tumor and cancer of head and neck.

The relation between FAK inhibition and immuno-system is described e.g. in G.A. van Seventer et al., Eur. J. Immunol. 2001, 31, 1417-1427. Therefore, the compounds of the invention are, for example, useful to prevent and/or treat a vertebrate and more particularly a mammal, affected by immune system disorders, diseases or disorders mediated by T lymphocytes, B lymphocytes, mast cells and/or eosinophils e.g. acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vascular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS disease such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious disease such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. The agent of the invention are also useful in the treatment and/or prevention of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes (type I and II) and the disorders associated with therewith, respiratory diseases such as asthma or inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis), inflammatory eye diseases, e.g. Sjoegren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Compounds of the invention are active in a FAK assay system as described in the Examples, and show an inhibition IC_{50} in the range of 1 nM to 100 nM. Particularly active are the compounds Example No. 3-12 and No. 3-17 described hereinbelow showing IC_{50} vales in the range of 1 to 5 nM.

Some of the compounds of the invention exhibit also ZAP-70 (zeta chain-associated protein of 70 kD) protein tyrosine kinase inhibiting activity. ZAP-70 protein tyrosine kinase interaction of the agents of the invention may be demonstrated by their ability to prevent phosphorylation of e.g. LAT-11 (linker for activation of T cell) by human ZAP-70 protein tyrosine kinase in aqueous solution, as described in the Examples. The compounds of the invention are thus also indicated for the prevention or treatment of disorders or diseases where ZAP-70 inhibition inhibition play a role.
Compounds of the invention are active in a ZAP-70 assay system as described in the Examples, and show an inhibition IC_{50} in the range of 1 μM to 10 μM, e.g. the compounds Example No. 2 and No. 3-2 described hereinbelow.

Compounds of the present invention are also good inhibitors of the IGF-IR (insulin like growth factor receptor 1) and are therefore useful in the treatment of IGF-1R mediated diseases for example such diseases include proliferative diseases, such as tumours, like for example breast, renal, prostate, colorectal, thyroid, ovarian, pancreas, neuronal, lung, uterine and gastro-intestinal tumours as well as osteosarcomas and melanomas. The efficacy of the compounds of the invention as inhibitors of IGF-IR tyrosine kinase activity can be demonstrated using a cellular "Capture ELISA". In this assay the activity of the compounds of the invention against insulin-like growth factor I (IGF-I) induced autophosphorylation of the IGF-IR is determined.

The compounds of formula I and their pharmaceutically acceptable salts exhibit valuable pharmacological properties when tested in vitro in cell-free kinase assays and in cellular assays, and are therefore useful as pharmaceuticals. In particular, the compounds of the invention are inhibitors of Anaplastic Lymphoma Kinase (ALK), and are useful as pharmaceuticals to treat conditions caused by a malfunction of signal cascades connected with Anaplastic Lymphoma Kinase, in particular tumors as described hereinbelow.

ALK-mediated signaling could play a role in the development and/or progression of a number of common solid tumors (Pulford, K., et al., J. Cell. Physiol. 2004 Jun;199(3):330-58). The

compounds of the present invention also exhibit powerful inhibition of the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) and its fusion proteins, particularly the fusion protein of NPM-ALK . This protein tyrosine kinase results from a gene fusion of nucleophosmin (NPM) and the anaplastic lymphoma kinase (ALK), rendering the protein tyrosine kinase activity of ALK ligand-independent. NPM-ALK plays a key role in signal transmission in a number of hematopoetic and other human cells leading to hematological and neoplastic diseases, for example in anaplastic large-cell lymphoma (ALCL) and non-Hodgkin's lymphomas (NHL), specifically in ALK+ NHL or Alkomas, in inflammatory myofibroblastic tumors (IMT) and neuroblastomas. (Duyster J et al. 2001 Oncogene 20, 5623-5637). NPM-ALK has been shown to be a potent oncogene in vitro, being able to transform various cell lines and primary hematopoetic cells. Furthermore, NPM-ALK transduced bone marrow cells are able to induce a lymphoma-like disease after transplantation into irradiated recipient mice. Signaling pathways activated by NPM-ALK include ras, PLC and PI3K pathways and, in addition, STAT5 has been shown to be phosphorylated by NPM-ALK. In addition to NPM-ALK, other gene fusions have been identified in human hematological and neoplastic diseases; mainly TPM3-ALK (a fusion of nonmuscle tropomyosin 3 with ALK). Further, the ALK fusion protein CLTC-ALK, is associated with diseases that include classical T cell or null ALCL, ALK^+ DLBCL and inflammatory myofibroblastic tumors. CLTCL-ALK is also thought to play a role in the pathogenesis of large B-cell lymphomas.

Further, the ALK fusion protein CLTC-ALK is associated with diseases that include classical T cell or null ALCL, ALK^+ DLBCL and inflammatory myofibroblastic tumors. CLTCL-ALK is also thought to play a role in the pathogenesis of large B-cell lymphomas.
Aberrant activity of ALK is involved in the development of brain tumors and overexpression of ALK has been reported in neuroblastomas and several cell lines derived from neural tissue. ALK-mediated signaling could play a role in the development and/or progression of a number of common solid tumors (Pulford, K., et al., J. Cell. Physiol. 2004 Jun;199(3):330-58).

The inhibition of ALK tyrosine kinase activity can be demonstrated using known methods, for example using the recombinant kinase domain of the ALK in analogy to the VEGF-R kinase assay described in J. Wood et al. Cancer Res. 60, 2178-2189 (2000). In vitro enzyme assays using GST-ALK protein tyrosine kinase are performed in 96-well plates as

a filter binding assay in 20 mM Tris-HCl, pH = 7.5, 3 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM DTT, 0.1 µCi/assay (=30 µl) [γ-^{33}P]-ATP, 2 µM ATP, 3 µg/ml poly (Glu, Tyr 4:1) Poly-EY (Sigma P-0275), 1 % DMSO, 25 ng ALK enzyme. Assays are incubated for 10 min at ambient temperature. Reactions are terminated by adding 50 µl of 125 mM EDTA, and the reaction mixture is transferred onto a MAIP Multiscreen plate (Millipore, Bedford, MA, USA), previously wet with methanol, and rehydrated for 5 min with H_2O. Following washing (0.5 % H_3PO_4), plates are counted in a liquid scintillation counter. IC_{50} values are calculated by linear regression analysis of the percentage inhibition. Compared with the control without inhibitor, the compounds of formula I inhibit the enzyme activity by 50 % (IC_{50}), for example in a concentration of from 0.001 to 0.5 µM, especially from 0.01 to 0.1 µM.

The compounds of formula I potently inhibit the growth of human NPM-ALK overexpressing murine BaF3 cells (DSMZ Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany). The expression of NPM-ALK is achieved by transfecting the BaF3 cell line with an expression vector pCIneo™ (Promega Corp., Madison WI, USA) coding for NPM-ALK and subsequent selection of G418 resistant cells. Non-transfected BaF3 cells depend on IL-3 for cell survival. In contrast NPM-ALK expressing BaF3 cells (named BaF3-NPM-ALK hereinafter) can proliferate in the absence of IL-3 because they obtain proliferative signal through NPM-ALK kinase. Putative inhibitors of the NPM-ALK kinase therefore abolish the growth signal and result in antiproliferative activity. The antiproliferative activity of putative inhibitors of the NPM-ALK kinase can however be overcome by addition of IL-3 which provides growth signals through an NPM-ALK independent mechanism. [For an analogous cell system using FLT3 kinase see E Weisberg et al. Cancer Cell; 1, 433-443 (2002)]. The inhibitory activity of the compounds of formula I is determined, briefly, as follows: BaF3-NPM-ALK cells (15,000/microtitre plate well) are transferred to 96-well microtitre plates. The test compounds [dissolved in dimethyl sulfoxide (DMSO)] are added in a series of concentrations (dilution series) in such a manner that the final concentration of DMSO is not greater than 1 % (v/v). After the addition, the plates are incubated for two days during which the control cultures without test compound are able to undergo two cell-division cycles. The growth of the BaF3-NPM-ALK cells is measured by means of Yopro™ staining [T Idziorek et al. J. Immunol. Methods; 185: 249-258 (1995)]: 25 µl of lysis buffer consisting of 20 mM sodium citrate, pH 4.0, 26.8 mM sodium chloride, 0.4 % NP40, 20 mM EDTA and 20 mM is added to each well. Cell lysis is completed within 60 min at room temperature and total amount of Yopro bound to DNA is determined by

measurement using the Cytofluor II 96-well reader (PerSeptive Biosystems) with the following settings: Excitation (nm) 485/20 and Emission (nm) 530/25.
IC_{50} values are determined by a computer-aided system using the formula:

$$IC_{50} = [(ABS_{test} - ABS_{start})/(ABS_{control} - ABS_{start})] \times 100. \text{ (ABS = absorption)}$$

The IC_{50} value in those experiments is given as that concentration of the test compound in question that results in a cell count that is 50 % lower than that obtained using the control without inhibitor. The compounds of formula I exhibit inhibitory activity with an IC_{50} in the range from approximately 0.01 to 1 μM.

The antiproliferative action of the compounds of formula I can also be determined in the human KARPAS-299 lymphoma cell line (DSMZ Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany) [described in WG Dirks et al. Int. J. Cancer 100, 49-56 (2002)] using the same methodology described above for the BaF3-NPM-ALK cell line. The compounds of formula I exhibit inhibitory activity with an IC_{50} in the range from approximately 0.01 to 1 μM.

The action of the compounds of formula I on autophosphorylation of the ALK can be determined in the human KARPAS-299 lymphoma cell line by means of an immunoblot as described in WG Dirks et al. Int. J. Cancer 100, 49-56 (2002). In that test the compounds of formula I exhibit an IC_{50} of approximately from 0.001 to 1 μM.

Among the compounds of formula I, 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide is an especially potent ALK inhibitor, in that this compound inhibits the growth of the BaF3-NPM-ALK cells with an IC_{50} of 97 nM. Further specifically preferred compounds that inhibit the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) are the compounds described hereinafter in the examples 7A and 7B, as well as 7-2, 7-15, 19-5, 21-1, 26-3 and 28-5, respectively, all of which are having an IC_{50} within the range from <0.5 to 200 nM.

For the above uses in the treatment of neoplastic diseases and immune system disorders the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be

obtained systemically at daily dosages of from about 0.1 to about 100 mg/kg body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

The compounds of the invention may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, preferably orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 500 mg of active substance. Topical administration is e.g. to the skin. A further form of topical administration is to the eye.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.

Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredient alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, e.g. Tween 80® (polyoxyethylene(20)sorbitan mono-oleate).

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to

22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of these fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. As fatty acid esters, therefore, the following are mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol), "Labrafil M 1944 CS" (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and consisting of glycerides and polyethylene glycol ester), "Labrasol" (saturated polyglycolized glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; all available from Gattefossé, France), and/or "Miglyol 812" (triglyceride of saturated fatty acids of chain length C_8 to C_{12} from Hüls AG, Germany), but especially vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, by the inclusion of additional excipients, to form tablets or tablet cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

The compounds of the invention may be administered as the sole active ingredient or together with other drugs useful against neoplastic diseases or useful in immunomodulating regimens. For example, the agents of the invention may be used in accordance with the invention in combination with pharmaceutical compositions effective in various diseases as described above, e.g. with cyclophosphamide, 5-fluorouracil, fludarabine, gemcitabine, cisplatinum, carboplatin, vincristine, vinblastine, etoposide, irinotecan, paclitaxel, docetaxel, rituxan, doxorubicine, gefitinib, or imatinib; or also with cyclosporins, rapamycins, ascomycins or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, sirolimus or everolimus, corticosteroids, e.g. prednisone, cyclophosphamide, azathioprene, methotrexate, gold salts, sulfasalazine, antimalarials, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate, mofetil, 15-deoxyspergualine, immuno-suppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, CD40, CD45, CD58, CD80, CD86, CD152, CD137, CD154, ICOS, LFA-1, VLA-4 or their ligands, or other immunomodulatory compounds, e.g. CTLA4Ig.

In accordance with the foregoing, the present invention also provides:

(1) A compound of the invention for use as a pharmaceutical;
(2) a compound of the invention for use as a 5-Chloro-N*2*-{2-methoxy-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-phenyl}-N*4*-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, for example for use in any of the particular indications hereinbefore set forth;
(3) a pharmaceutical composition, e.g. for use in any of the indications herein before set forth, comprising a compound of the invention as active ingredient together with one or more pharmaceutically acceptable diluents or carriers;
(4) a method for the treatment of any particular indication set forth hereinbefore in a subject in need thereof which comprises administering an effective amount of a compound of the invention or a pharmaceutical composition comprising same;
(5) the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which FAK and/or ALK and/or ZAP-70 and/or IGF-I activation plays a role or is implicated, preferably ALK;

(6) the method as defined above under (4) comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;
(7) a combination comprising a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;
(8) use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease which responds to inhibition of the anaplastic lymphoma kinase;
(9) the use according to (8), wherein the disease to be treated is selected from lymphoma, anaplastic large-cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors and neuroblastomas;
(10) the use according to (8) or (9), wherein the compound is 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide or 5-Chloro-N*2*-[2-methoxy-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-phenyl]-N*4*-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine or a pharmaceutically acceptable salt thereof, or any of the the compounds described hereinafter in the examples or a pharmaceutically acceptable salt of any one of these;
(11) a method for the treatment of a disease which responds to inhibition of the anaplastic lymphoma kinase, especially a disease selected from anaplastic large-cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors and neuroblastomas, comprising administering an effective amount of a compound of the invention, especially 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide or 5-Chloro-N*2*-[2-methoxy-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-phenyl]-N*4*-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine or a pharmaceutically acceptable salt thereof.

Additionally preferred a compound according to the present invention that is useful as herein before described is a compound specifically mentioned in the examples.
Additional specifically preferred compounds according to the present invention that are useful either as FAK inhibitor, as ALK inhibitor or for inhibition of both and which may be prepared essentially according to the methods described hereinbefore are the following:
2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide,

N^2-(4-[1,4']Bipiperidinyl-1'-yl-2-methoxy-phenyl)-5-chloro-N^4-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine,
2-{5-Chloro-2-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-N-isopropyl-benzenesulfonamide,
2-[5-Bromo-2-(2-methoxy-5-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide
2-{2-[5-(1-Acetyl-piperidin-4-yloxy)-2-methoxy-phenylamino]-5-bromo-pyrimidin-4-ylamino}-N-methyl-benzenesulfonamide,
N-[5-Bromo-2-(2,5-dimethoxy-phenylamino)-pyrimidin-4-yl]-N-(4-morpholin-4-yl-phenyl)-methanesulfonamide,
5-Bromo-N-4-(4-fluoro-phenyl)-N*2*-(2-methoxy-4-morpholin-4-yl-phenyl)-pyrimidine-2,4-diamine,
2-[5-Chloro-2-(2-methoxy-4-piperazin-1-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide,
2-[5-Bromo-2-(5-fluoro-2-methoxy-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide,
2-[5-Chloro-2-(5-fluoro-2-methoxy-phenylamino)-pyrimidin-4-ylamino]-N-isobutyl-benzenesulfonamide, and
2-{5-Chloro-2-[2-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-N-methyl-benzenesulfonamide,
5-Chloro-N*2*-[2-methoxy-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-phenyl}-N*4*-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine.

The invention also provides a compound of formula 2-{5-Chloro-2-[4-(3-methylamino-pyrrolidin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-N-isopropyl-benzenesulfonamide

The invention also provides a compound of formula 5-Chloro-N*2*-{2-methoxy-4-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-phenyl}-N*4*-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine

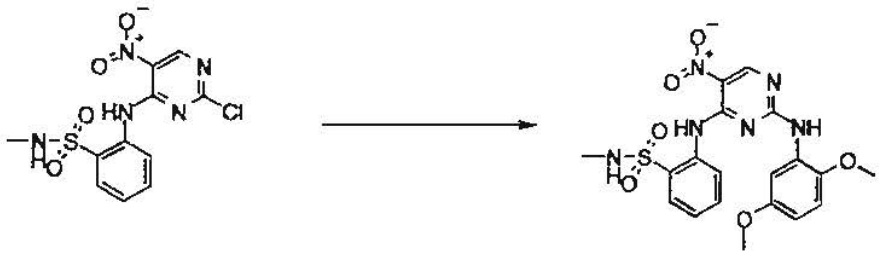
The following Examples serve to illustrate the invention without limiting the invention in its scope.

Examples

Abbreviations

AcOH = acetic acid, ALK = anaplastic lymphoma kinase, ATP = adenosine 5'-triphosphate, brine = saturated sodium chloride solution, BSA = bovine serum albumin, DIAD = diisopropyl azodicarboxylate, DIPCDI = N,N'-diisopropylcarbodiimid, DMAP = 4-dimethylaminopyridine, DMF = N,N-dimethylformamide, DTT = 1,4-dithio-D,L-threitol, EDTA = ethylene diamine tetraacetic acid, Et = ethyl, EtOAc = ethyl acetate, EtOH = ethanol, Eu-PT66 = LANCE™ europium-W1024-labelled anti-phosphotyrosine antibody (Perkin Elmer), FAK = Focal Adhesion Kinase, FRET = fluorescence resonance energy transfer, HEPES = N-2-hydroxyethyl-piperazine-N'-2-ethanesulfonic acid, HOAt = 1-hydroxy-7-azabenzotriazole, Me = methyl, RT-PCR = reverse transcription polymerase chain reaction, SA-(SL)APC = Streptavidin conjugated to SuperLight™ allophycocyanin (Perkin Elmer), subst. = substituted, TBTU = O-(benzotriazol-1-yl)-N,N,N',N'-tetramethylammonium tetrafluoroborate, THF = tetrahydrofuran.

Example 1: 2-[2-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide



To a solution of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (100 mg, 0.29 mmol) in EtOH (3 mL), 2,5-dimethoxyaniline (49 mg, 0.32 mmol) is added at room temperature. The mixture is heated at 78°C for 5 h. The solvent is evaporated, and the mixture is purified by reverse phase HPLC to give the title product in.

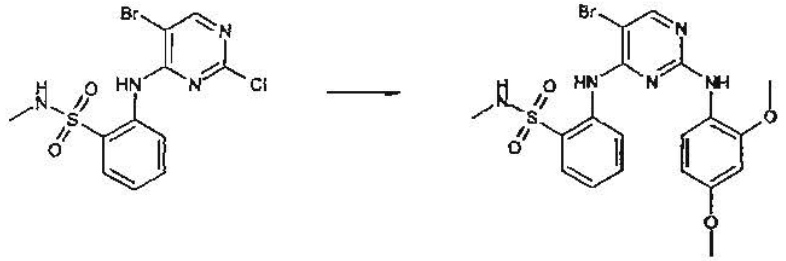
Rf = 0.47 (n-hexane : ethyl acetate = 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.36 (d, 3H), 3.57 (s, 3H), 3.73 (s, 3H), 6.72 (d, 1H), 6.89 (d, 1H), 7.17 (s, 1H), 7.35 (t, 1H), 7.4-7.6 (m, 1H), 7.63 (d, 1H), 7.81 (d, 1H), 8.0-8.2 (m, 1H), 9.13 (s, 1H), 9.41 (br.s, 1H), 11.0 (s, 1H).

Preparation of 2-[2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide:

2,4-Dichloro-5-nitro-pyrimidine (1.94 g, 10 mmol) and 2-amino-N-methyl-benzenesulfonamide (1.86 g, 10 mmol) are dissolved in $CHCl_3$ (30 mL). The reaction mixture is heated at 61°C for 2 h. The solvent is evaporated and the residue is washed with ether to give the title product.

Rf = 0.5 (n-hexane : ethyl acetate = 1:1). ^{1}H-NMR (400MHz, $CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.6-4.7 (m, 2H), 7.41 (dd, 1H), 7.7 (dd, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 9.21 (s, 1H), 11.2 (s, 1H).

Example 2: 2-[5-Bromo-2-(2,4-dimethoxy-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide

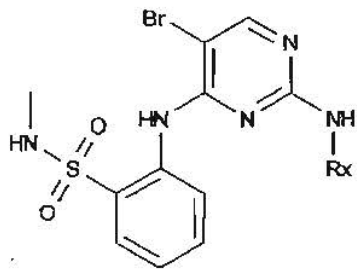


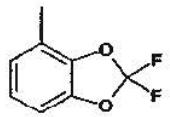
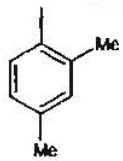
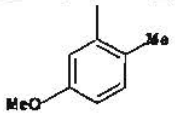
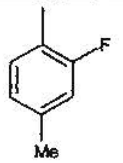
To a solution of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (300 mg, 0.79 mmol), 2,4-dimethoxyaniline (181.5 mg, 1.18 mmol) in ethanol (3 mL), 1 N hydrochloric acid (0.03 mL) is added and stirred under reflux condition for 5 hours. The reaction mixture is cooled to room temperature, poured into water and extracted twice with ethyl acetate. The organic layer is successively washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5:1 to 1:1) to afford the title compound.
^{1}H-NMR ($CDCl_3$), δ (ppm): 8.95 (s, 1H), 8.44 (d, 1H), 8.20 (s, 1H), 7.98 (dd, 1H), 7.58 (ddd, 1H), 7.22-7.32 (m, 1H), 6.51 (d, 1H), 6.40 (d, 1H), 4.56-4.48 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.64 (d, 3H). Rf (n-hexane : ethyl acetate = 1:1): 0.31.

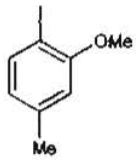
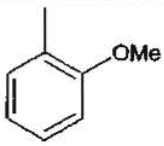
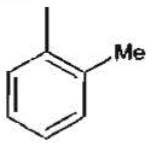
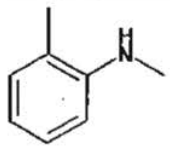
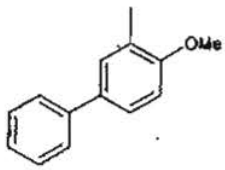
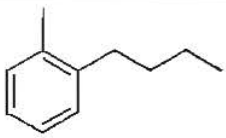
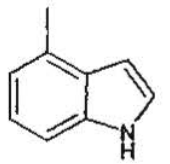
Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide
A solution of 5-bromo-2,4-dichloropyrimidine (684 mg, 3.0 mmol) and 2-amino-N-methyl-benzenesulfonamide (559 mg, 3.0 mmol) in N,N-dimethylformamide (10 mL) containing potassium carbonate (830 mg, 6.0 mmol) is stirred at room temperature for 23 hours. Saturated aqueous ammonium chloride is added and the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane - ethyl acetate gradient) to afford the title compound as a slightly yellow solid.
^{1}H-NMR ($CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.79 (q, 1H), 7.26 (s, 1H), 7.29 (ddd, 1H), 7.66 (ddd, 1H), 7.95 (dd, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 9.52 (s, 1H). Rf (n-hexane : ethyl acetate = 10:3): 0.33.

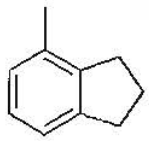
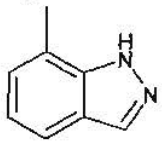
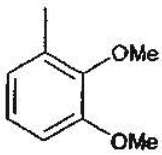
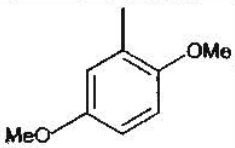
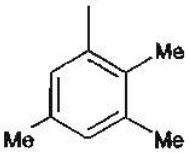
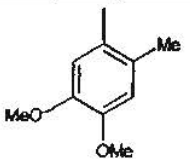
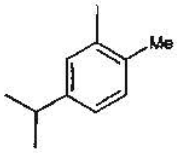
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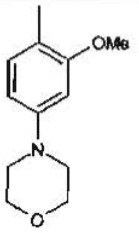
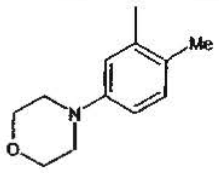
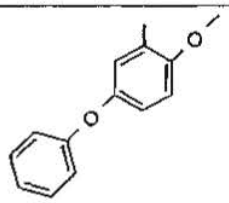
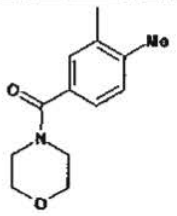
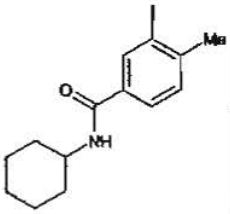
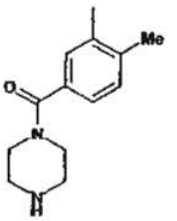
The following 2-[5-bromo-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzene-sulfonamides are prepared from 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 2:

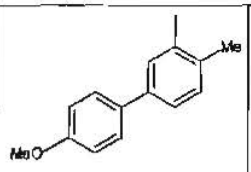
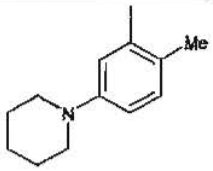
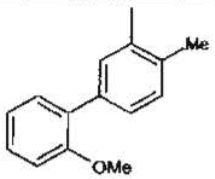
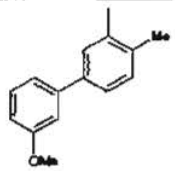
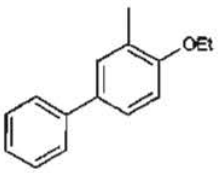
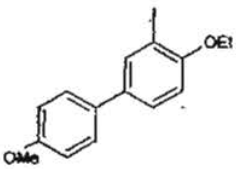
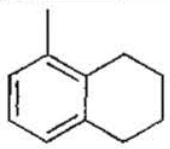


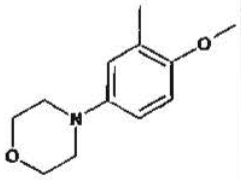
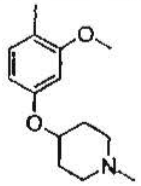
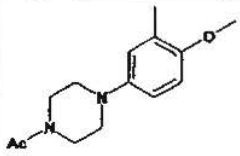
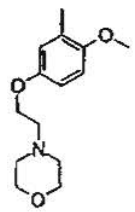
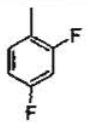
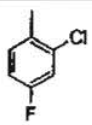
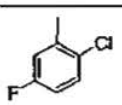
ExplNo.	Rx	Rf (solvent) or MS	^{1}H-NMR (400MHz), δ (ppm)
3-1		0.48 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.64(d, 3H), 4.48-4.40(m, 1H), 6.78(d,1H), 6.87(bs, 1H), 6.99(dd, 1H), 6.82(s, 1H),7.54(ddd, 1H), 7.79(d, 1H), 7.97(dd, 1H), 8.28(s, 1H), 8.32(dd, 1H), 9.07(s, 1H)
3-2		0.58 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.25(s, 3H), 2.33(s, 3H), 2.63(d, 3H), 4.53-4.45(m, 1H), 6.61(bs, 1H), 6.99(dd, 1H), 7.04(s, 1H), 7.18(ddd, 1H), 7.43(ddd, 1H), 7.56(d, 1H), 7.92(dd, 1H), 8.19(s, 1H), 8.41(dd, 1H), 9.08(s, 1H)
3-3		0.36 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.23(s, 3H), 2.62(d, 3H), 3.69(s, 3H), 4.53-4.44(m, 1H), 6.62(dd, 1H), 6.69(bs, 1H), 7.10(d, 1H), 7.19(dd, 1H), 7.48(d, 1H), 7.51(dd, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.44(dd, 1H), 9.09(s1, 1H)
3-4		0.41 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.32(s, 3H), 2.63(d, 3H), 4.45-4.44(m, 1H), 6.85(d, 1H), 6.91(d, 1H), 7.00(bs, 1H), 7.28-7.24(m, 1H), 7.57(dd, 1H), 7.99(dd, 1H), 8.25 (s, 1H), 8.39(d, 1H), 9.00(bs, 1H)

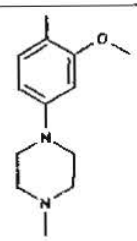
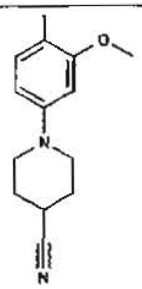
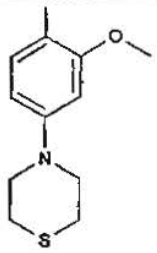
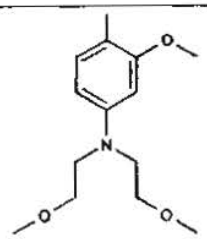
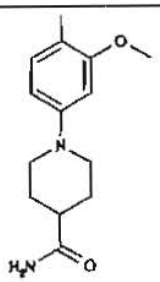
3-5		0.39 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.33(s, 3H), 2.63(d, 3H), 3.87(s, 3H), 4.46-4.44(m, 1H), 6.66(d, 1H), 6.71(s, 1H), 7.48(bs, 1H), 7.63-7.59(m, 1H), 7.97(dd, 1H), 8.05(d, 1H), 8.23 (s, 1H), 8.44(d, 1H), 8.92(bs, 1H)
3-6		0.27 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.63(d, 3H), 3.90(s, 3H), 4.45-4.40(m, 1H), 6.90-6.86(m, 2H), 7.00-6.96(m, 1H), 7.23-7.17 (m, 3H), 7.45(dd, 1H), 7.50-7.60(m, 2H), 7.97(dd, 1H), 8.22(d, 1H), 8.26 (s, 1H), 8.43(d, 1H), 8.94(bs, 1H)
3-7		0.34 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.30(s, 3H), 2.63(d, 3H), 4.44-4.43(m, 1H), 6.68 (bs, 1H), 7.00-6.68(m, 1H), 7.23-7.17(m, 2H), 7.46-7.43(m, 1H), 7.76(d, 1H), 7.93(dd, 1H), 8.22 (s, 1H), 8.40(d, 1H), 9.01(bs, 1H)
3-8		0.12 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.62(d, 3H), 2.81(s, 3H), 4.07-3.98(m, 1H), 4.52-4.45(m, 1H), 6.37(bs, 1H), 6.77-6.73 (m, 2H), 7.12(dd, 1H), 7.24-7.20(m, 1H), 7.30-7.27(m, 1H), 7.35(dd, 1H), 7.88(dd, 1H), 8.18 (s, 1H), 8.41(d, 1H), 9.19(bs, 1H)
3-9		0.28 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.62(d, 3H), 3.94(s, 3H), 4.49-4.43(m, 1H), 6.99-6.90 (m, 3H), 7.18-7.23(m, 1H), 7.31-7.24(m, 3H), 7.63(bs, 1H), 7.93-7.86(m, 1H), 8.28-8.23(m, 1H), 8.28 (s, 1H), 8.45(bs, 1H), 8.89(bs, 1H)
3-10		0.23 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 0.91(t, 3H), 1.37 (dd, 2H), 1.64-1.55 (m, 2H), 2.64-2.60 (m, 2H), 4.45-4.40 (m, 1H), 6.69 (bs, 1H), 7.23-7.10(m, 1H), 7.46-7.38 (m, 1H), 7.73 (d 1H), 7.92 (d, 1H), 8.21 (s, 1H), 8.38-8.46 (m, 1H), 9.09 (bs, 1H)
3-11		0.12 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.63 (d, 3H), 4.15-4.10 (m, 1H), 6.58 (bs, 1H), 7.31-7.10(m, 4H), 7.53-7.49 (m, 1H), 7.71(d 1H), 7.95 (d, 1H), 8.30-8.23 (m, 1H), 8.26 (s, 1H), 8.45 (d, 1H), 9.03 (bs, 1H)

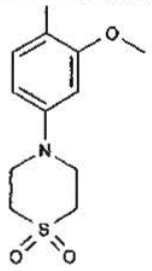
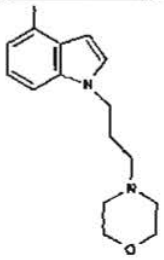
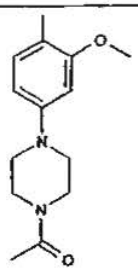
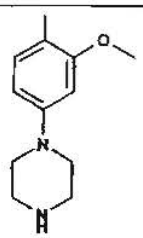
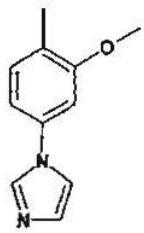
3-12		0.4 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.09 (dd, 2H), 2.63 (d, 3H), 2.85(t, 2H), 2.96 (t, 2H), 4.46-4.43 (m, 2H), 6.73 (bs, 1H), 6.99 (d, 1H), 7.09 (dd, 1H), 7.25-7.20(m, 1H), 7.52 (dd, 1H), 7.74 (d 1H), 7.92 (dd, 1H), 8.22 (s, 1H), 8.42 (d, 1H), 9.02 (bs, 1H)
3-13		0.33 (AcOEt)	$CDCl_3$: 2.63 (d, 3H), 4.63-4.64 (m, 1H), 7.11(d, 2H), 7.18(dd, 1H), 7.42-7.34(m, 1H), 7.58-7.55(m, 1H), 7.96(d, 1H), 8.07(s, 1H), 8.19-8.10(m, 1H), 8.24(s, 1H), 9.15(s, 1H), 11.6-11.4(m, 1H)
3-14		0.28 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.63(d, 3H), 3.88(s, 3H), 3.89(s, 3H), 4.47-4.41(m, 1H), 6.60(d,1H), 6.92 (dd,1H), 7.64 (dd, 1H),7.66-7.61(m,1H), 7.89(d, 1H), 7.98(dd, 1H), 8.26(s, 1H), 8.43(d, 1H), 8.95(s, 1H)
3-15		0.30 (n-hexane: AcOEt=3:1)	$CDCl_3$: 2.63(d, 3H), 3.66(s, 3H), 3.85(s, 3H), 4.45-4.44(m, 1H), 6.48(dd,1H), 6.79(d,1H), 7.64(dd, 1H), 7.97(dd, 2H), 8.26(s, 1H), 8.44(d, 1H), 8.96(s, 1H)
3-16		0.22 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.17(s, 3H), 2.22(s, 3H), 2.64(s, 3H), 2.63(d, 3H), 4.46-4.44(m, 1H), 6.57(bs, 1H), 7.00(s,1H), 7.17(dd,1H), 7.44-7.40(m,1H), 7.44(s, 1H), 7.93(dd, 1H), 8.19(s, 1H), 8.43(d, 1H), 9.06(s, 1H)
3-17		0.46 (AcOEt)	$CDCl_3$: 2.22(s,3H), 2.63(d, 3H), 3.68(s, 3H), 3.89(s, 3H), 4.52-4.47(m, 1H), 6.51(s,1H), 6.74(s,1H), 7.12(s,1H), 7.16-7.12(m,1H), 7.40(dd, 1H), 7.91(dd, 1H), 8.19(s, 1H), 8.42(d, 1H), 9.12(s, 1H)
3-18		0.35 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 1.16(d, 6H), 2.25 (s, 3H), 2.62(d, 3H), 2.77(t, 1H), 4.49-4.48(m, 1H), 7.00(s,1H), 7.15(d,1H), 7.41-7.37(m,1H), 7.49(d,2H), 7.54(dd, 1H), 7.92(dd, 1H), 8.21(s, 1H), 8.32(d, 1H), 9.02(s, 1H)

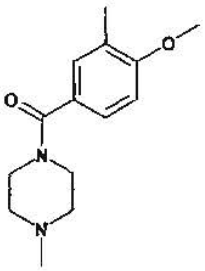
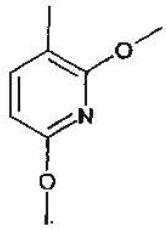
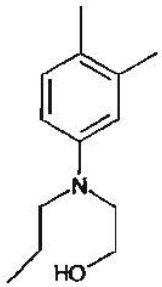
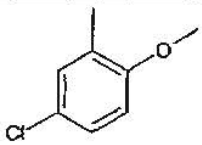
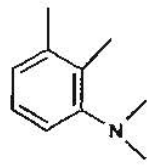
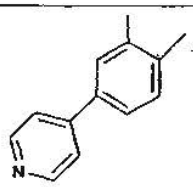
3-19		0.23 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.63(d, 3H), 3.13-3.10 (m, 4H), 3.87(s, 3H), 3.89-3.86(m, 4H), 4.97-4.93(m, 1H), 6.41(dd,1H), 6.52(d,1H), 7.24-7.22(m,1H), 7.32(s,1H), 7.57(dd,1H), 7.96(dd, 1H), 8.01(d, 1H), 8.14(s, 1H), 8.44(d, 1H), 8.98 (s, 1H)
3-20		0.36 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.22(s, 3H), 2.64(d, 3H), 3.00-3.2.97 (m, 4H), 3.76-3.74(m, 4H), 4.54-4.50(m, 1H), 6.64(d,1H), 6.66(dd, 1H), 7.11(d,1H), 7.18(dd,1H), 7.37(d, 1H), 7.46(dd, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.42(d, 1H), 9.09 (s, 1H)
3-21			
3-22		0.27 (AcOEt)	$CDCl_3$: 2.33(s, 3H), 2.65(d, 3H), 3.60-3.45(m, 8H), 4.53-4.49(m, 1H), 6.74(s, 1H), 7.11(d, 1H), 7.22-7.18(m, 1H), 7.58-7.54(m 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.22(s, 1H), 8.37(d, 1H), 9.13(s, 1H)
3-23		0.38 (AcOEt)	$CDCl_3$: 1.24-1.08(m, 2H), 1.46-1.32(m, 2H),1.76-1.67(m, 2H), 1.98-1.90(m, 2H), 2.33(s, 3H), 2.64(d, 3H), 3.95-3.90(m, 1H), 4.49-4.47(m, 1H), 5.89-5.80(m, 1H), 6.66(s, 1H), 7.15(dd, 1H), 7.48-7.31(m, 2H), 7.91(dd, 1H), 8.12(s, 1H), 8.23(s, 1H), 8.41(d, 1H), 9.18(s, 1H)
3-24		0.11 (AcOEt)	$CDCl_3$: 2.35(s, 3H), 2.71(s, 3H), 3.07-2.73(m, 2H), 3.86-3.31(m, 6H), 6.85(s, 1H), 7.10(d, 1H), 7.24-7.19(m, 1H), 7.52-7.48(m, 1H), 7.66-7.59(m, 2H), 7.93(d, 1H), 8.06(s, 1H), 8.27-8.21(m, 1H), 8.23(s, 1H), 9.11(s, 1H)

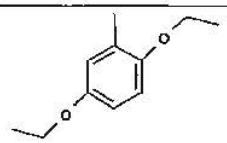
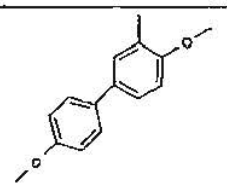
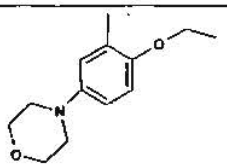
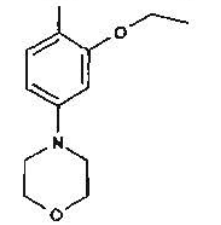
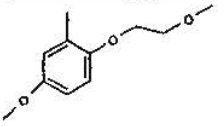
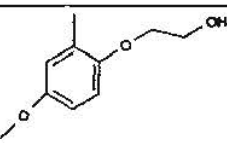
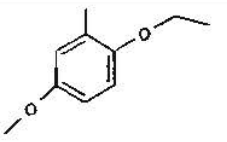
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3-26		0.45 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 1.62-1.34(m, 6H), 2.13(s, 3H), 2.56(d, 3H), 3.01-2.87(m, 4H), 4.54-4.38(m, 1H), 6.59(s, 1H), 6.69-6.59(m, 1H), 7.02(d, 1H), 7.10-7.07(m, 1H), 7.37(dd, 1H), 7.84(dd, 1H), 8.15(s, 1H), 8.34(d, 1H), 9.01(s, 1H)
3-27		0.45 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.32(s, 3H), 2.58(d, 3H), 3.75(s, 3H), 4.37-4.44(m, 1H), 6.77-6.73(m, 1H), 6.89-6.82(m 1H), 6.97-6.91(m, 2H), 6.96(d, 1H), 7.20(dd, 1H), 7.25-7.24(m, 1H), 7.33-7.29(m, 1H)
3-28		0.35 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 2.34(s, 3H), 2.64(d, 3H), 3.81(s, 3H), 4.57-4.50(m, 1H), 6.76(bs, 1H), 6.91-6.84(m, 41H), 7.04(d, 1H), 7.83(dd, 1H), 8.06(d, 1H), 8.19(dd, 1H), 8.23(s, 1H), 9.00(s, 1H)
3-29		0.45 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 1.50(t, 3H), 2.62 (d, 3H), 4.17(dd, 2H), 4.51-4.44(m, 1H), 6.95-6.89 (m, 2H), 6.94(d, 1H), 7.16 (dd, 1H), 7.31-7.23(m, 5H), 7.67(s, 1H), 7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.88(dd, 1H), 8.28-8.23(m, 1H), 8.28(s, 1H), 8.43(s, 1H), 8.89(s, 1H)
3-30		0.45 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 1.49(t, 3H), 2.63(d, 3H), 3.85(s, 3H), 4.16(dd, 2H), 4.55-4.48(m, 1H), 6.81(dd, 1H), 6.95-6.91(m, 3H), 7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.90-7.88(m, 1H), 8.28-8.26(m, 1H), 8.27(s, 1H), 8.39(s, 1H), 8.90(s, 1H)
3-31		0.29 (*n*-hexane: AcOEt=1:1)	^{1}H-NMR : ($CDCl_3$) 1.83-1.72 (4H, m), 2.63 (3H, d), 2.66-2.62 (2H, m), 2.80 (2H, t), 4.41-4.44 (1H, m), 6.64 (1H, br.s), 6.92 (1H, d), 7.09 (1H, dd), 7.18 (1H, dd), 7.45 (1H, dd), 7.59 (1H, dd), 7.92 (1H, d), 8.20 (1H, s), 8.42 (1H, d), 9.08 (1H, br.s).

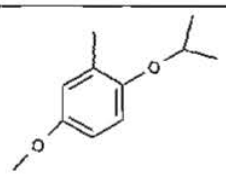
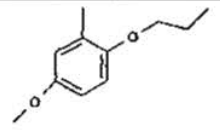
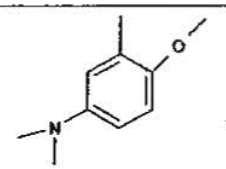
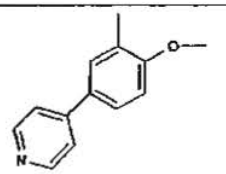
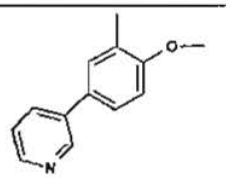
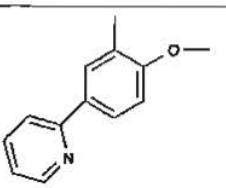
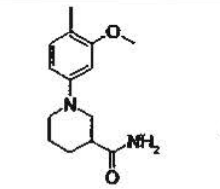
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3-33		0.61 (MeOH: CH2Cl2=1: 1)	DMSO-d_6: 1.59-1.68(m, 2H), 1.88-1.98(m, 2H), 2.13-2.25(m,2H), 2.19(s, 3H), 2.43(s, 3H), 2.60-2.70(m, 2H), 3.75(s, 3H), 4.32-4.40(m, 1H), 6.51(dd, 1H), 6.64(d, 1H), 7.20(dd, 1H), 7.39(d, 1H), 7.75(dd, 1H), 7.70-7.78(s, 1H), 8.22(s, 1H), 8.28(s, 1H), 8.38-8.41(m, 1H), 9.22(s, 1H)
3-34		0.17 (AcOEt)	$CDCl_3$: 2.11(s, 3H), 2.68(d, 3H), 2.76-2.83(m, 2H), 2.89-2.97(m, 2H), 3.47-3.55(m, 2H), 3.58-3.66(m, 2H), 3.86(s, 3H), 4.70-4.78(m, 1H), 6.53(dd, 1H), 6.81(d, 1H), 7.23(dd, 1H), 7.54-7.62(m, 2H), 7.97(dd, 1H), 8.02-8.03(m, 1H), 8.29(s, 1H), 8.40(d, 1H), 8.99(bs, 1H)
3-35		0.22 (AcOEt only)	DMSO-d_6: 2.40-2.48(m, 7H), 2.63(t, 2H), 3.50-3.58(m, 4H), 3.77(s, 3H), 3.91(t, 2H), 6.60(dd, 1H), 6.93(d, 1H), 7.28(dd, 1H), 7.56(d, 1H), 7.60(dd, 1H), 7.75-7.80(m, 1H), 7.80(dd, 1H), 8.10(s, 1H), 8.35(s, 1H), 8.40(d, 1H), 9.21(s, 1H)
3-36		0.4 (n-hexane: AcOEt=1:1)	DMSO-d_6: 2.43(s, 3H), 7.03-7.08(m, 1H), 7.21-7.23(m, 1H), 7.25-7.36(m, 1H), 7.47-7.57(m, 2H), 7.74-7.77(m, 2H), 8.28(s, 1H), 8.35(d, 1H), 9.09(s, 1H), 9.24(s, 1H)
3-37		0.4 (n-hexane: AcOEt=1:1)	$CDCl_3$: 2.64(d, 3H), 4.53-4.54(m, 1H), 6.88-6.93(m, 1H), 7.14-7.28(m, 3H), 7.54-7.58(m, 1H), 7.95-7.98(m, 1H), 8.16-8.21(m, 1H), 8.24(s, 1H), 8.33-8.36(m, 1H), 9.05(s, 1H)
3-38		0.42 (n-hexane: AcOEt=1:1)	$CDCl_3$: 2.64(d, 3H), 4.46-4.47(m, 1H), 6.63-6.68(m, 1H), 7.30-7.32(m, 2H), 7.55(s, 1H), 7.64-7.68(m, 1H), 7.97-7.99(m, 1H), 8.20-8.39(m, 3H), 9.03(s, 1H)

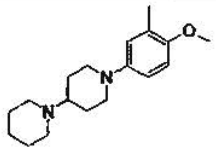
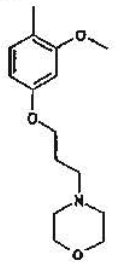
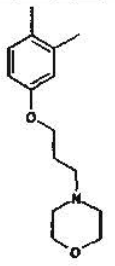
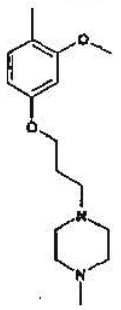
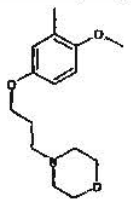
3-39		562, 564 [M+1]+	CDCl3: 2.37(s, 3H), 2.58-2.64(m, 7H), 3.15-3.18(m,4H), 3.87(s, 3H), 4.60-4.65(m,1H), 6.43(dd,1H), 6.44-6.54(m, 1H), 7.22(d, 1H), 7.30(s, 1H), 7.57(dd, 1H), 7.94-7.99(m, 2H), 8.18(s, 1H), 8.45(d, 1H), 8.95(s, 1H)
3-40		572, 574 [M+1]+	DMSO-d6: 1.79-1.88(m,2H), 1.98-2.02(m, 2H), 2.43(s, 3H), 3.02-3.08(m, 3H), 3.28-3.39(m, 2H), 3.76(s, 3H), 6.47(dd, 1H), 6.65(d, 1H), 7.22(dd, 1H), 7.39(d, 1H), 7.45-7.50(m, 1H), 7.74-7.77(m, 2H), 8.18(s, 1H), 8.22(s, 1H), 8.41-8.44(m, 1H), 9.21(bs, 1H)
3-41		565, 567 [M+1]+	DMSO-d6: 2.44(d, 3H), 2.69-2.71(m, 4H), 3.49-3.52(m, 4H), 3.76(s, 3H), 6.45(dd, 1H), 6.62(d, 1H), 7.23(ddd, 1H), 7.38(d, 1H), 7.46-7.50(m, 1H), 7.72-7.77(m, 2H), 8.19(s, 1H), 8.22(s, 1H), 8.42-8.45(m, 1H), 9.22(s, 1H)
3-42		595, 597 [M+1]+	DMSO-d6: 2.44(s, 3H), 3.31(s, 6H), 3.48-3.53(m, 8H), 3.72(s, 3H), 6.24(dd, 1H), 6.37(d, 1H), 7.18-7.21(m, 2H), 7.40-7.55(m, 1H), 7.72-7.76(m, 2H), 8.17-8.19(m, 2H), 8.40-8.50(m, 1H), 9.23(s, 1H)
3-43		590, 592 [M+1]+	DMSO-d6: 1.64-1.71(m, 2H), 1.75-1.82(m, 2H), 2.21-2.28(m,1H), 2.43(d, 3H), 2.62-2.67(m,2H), 3.68-3.74(m, 2H), 3.76(s, 3H), 6.45(dd,1H), 6.63(d, 1H), 6.75-6.81(m, 1H), 7.20(ddd, 1H), 7.25-7.30(m, 1H), 7.35(d, 1H), 7.45-7.52(m, 1H), 7.70-7.77(m, 2H), 8.18(s, 1H), 8.21(s, 1H), 8.40-8.47(m, 1H), 9.22(s, 1H)

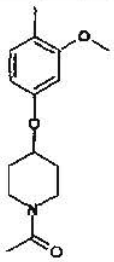
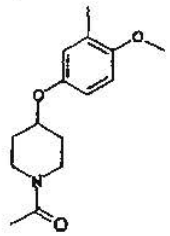
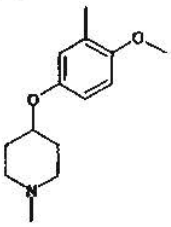
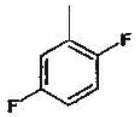
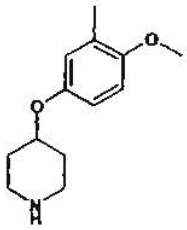
3-44		597, 599 [M+1]+	DMSO-d6: 2.44(s, 3H), 3.12-3.17(m, 4H), 3.68-3.85(m, 4H), 3.79(s, 3H), 6.55(dd, 1H), 6.71(d, 1H), 7.19-7.25(m, 1H), 7.43(d, 1H), 7.46-7.53(m, 1H), 7.73-7.78(m, 2H), 8.19-8.22(m, 1H), 8.22(s, 1H), 8.38-8.45(m, 1H), 9.20(bs, 1H)
3-45		600, 602 [M+1]+	DMSO-d6: 1.85-1.95(m, 2H), 2.19(t, 2H), 2.25-2.35(m, 4H), 2.43(s, 3H), 3.52-3.64(m, 4H), 4.19(t, 2H), 6.65(d, 1H), 7.05(dd, 1H), 7.20(d, 1H), 7.23(ddd, 1H), 7.27(d, 1H), 7.40-7.46(m, 1H), 7.42(d, 1H), 7.70-7.75(m, 1H), 7.76(dd, 1H), 8.32(s, 1H), 8.45(d, 1H), 9.22(s, 1H), 9.23(s, 1H)
3-46		590, 592 [M+1]+	DMSO-d6: 2.05(s, 3H), 2.44(s, 3H), 3.08-3.17(m, 4H), 3.55-3.63(m, 4H), 3.77(s, 3H), 6.48(dd,1H), 6.67(d, 1H), 7.23(dd, 1H), 7.41(d, 1H), 7.45-7.52(m, 1H), 7.76(dd, 1H), 7.72-7.78(m, 1H), 8.19(s, 1H), 8.22(s, 1H), 8.40-8.47(m, 1H), 9.22(bs, 1H)
3-47		548, 550 [M+1]+	DMSO-d6: 2.43(s, 3H), 2.82-2.87(m, 4H), 2.99-3.15(m, 4H), 3.76(s, 3H), 6.43(dd,1H), 6.61(d, 1H), 7.22(dd, 1H), 7.36(d, 1H), 7.43-7.51(m, 1H), 7.75(dd, 1H), 8.17(s, 1H), 8.21(s, 1H), 8.38-8.45(m, 1H), 9.12-9.28(m, 1H)
3-48		MS 530, 532	CDCl3: 2.65 (d, 3H), 3.96 (s, 3H), 4.40-4.48 (m, 1H), 6.85-6.88 (m, 2H), 7.22 (d, 1H), 7.25-7.31 (m, 1H), 7.56-7.65 (m, 3H), 7.79 (s, 1H), 8.00 (dd, 1H), 8.29 (s, 1H), 8.39 (dd, 1H), 9.00 (s, 1H).

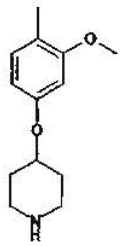
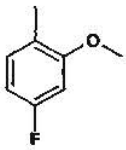
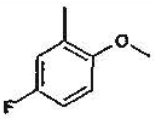
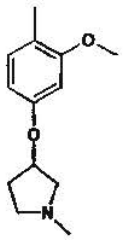
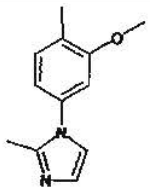
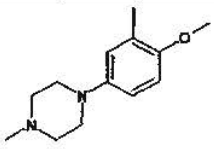
3-49		Rf (AcOEt: MeOH=9:1) 0.20	$CDCl_3$: 2.18-2.50 (m, 4H), 2.28 (s, 3H), 2.65 (d, 3H), 3.10-3.75 (m, 4H), 3.93 (s, 3H), 4.50-4.61 (m, 1H), 6.89 (d, 1H), 7.06 (dd, 1H), 7.59-7.67 (m, 2H), 7.93-7.97 (m, 1H), 8.26 (s, 1H), 8.37-8.43 (m, 2H), 9.02 (s, 1H).
3-50		Rf 0.4 (Hexane/AcOEt=1/1)	CDCl3: 2.63 (d, 3H), 3.90 (s, 3H), 4.00 (s, 3H), 4.39-4.47 (m, 1H), 6.23 (d, 1H), 7.00 (s, 1H), 7.22-7.25 (m, 1H), 7.57 (dd, 1H), 7.96 (dd, 1H), 8.22 (s, 1H), 8.25 (d, 1H), 8.37 (d, 1H), 8.96 (s, 1H)
3-51		MS 535, 537	CDCl3: 1.17 (t, 3H), 1.71-1.79 (m, 1H), 2.28 (s, 3H), 2.62 (d, 3H), 3.41 (q, 2H), 3.46 (t, 2H), 3.79 (q, 2H), 4.41-4.48 (m, 1H), 6.43 (s, 1H), 6.10-6.18 (m, 2H), 7.15 (dd, 1H), 7.33 (d, 1H), 7.35-7.42 (m, 1H), 7.90 (dd, 1H), 8.16 (s, 1H), 8.45 (d, 1H), 9.07 (s, 1H).
3-52		Rf	CDCl3: 2.66 (d, 3H), 3.91 (s, 3H), 4.41-4.47 (m, 1H), 6.80 (d, 1H), 6.92 (dd, 1H), 7.26-7.35 (m, 1H), 7.54 (s, 1H), 7.76 (dd, 1H), 8.00 (dd, 1H), 8.27-8.32 (m, 2H), 8.38 (dd, 1H), 8.97 (s, 1H).
3-53		MS 491, 493	$CDCl_3$: 2.26 (s, 3H), 2.62 (d, 3H), 2.68 (s, 6H), 4.72 (q, 1H), 6.78 (s, 1H), 6.89 (d, 1H), 7.12 (d, 1H), 7.15 (d, 1H), 7.40-7.47 (m, 2H), 7.91 (dd, 1H), 8.40 (s, 1H), 8.41 (dd, 1H), 9.11 (s, 1H).
3-54		MS 525, 527	$CDCl_3$: 2.04 (s, 3H), 2.65 (d, 3H), 4.42-4.48 (m, 1H), 6.79 (s, 1H), 6.96-7.00 (m, 2H), 7.28-7.34 (m, 4H), 7.87-7.91 (m, 1H), 8.18 (s, 1H), 8.23-8.26 (m, 2H), 8.53 (d, 2H), 9.07 (s, 1H).

3-55		Rf (Hexane: AcOEt=3:1) 0.19	$CDCl_3$: 1.34 (t, 3H), 1.44 (t, 3H), 2.63 (d, 3H), 3.81 (q, 2H), 4.06 (q, 2H), 4.46 (q, 1H), 6.43 (dd, 1H), 6.76 (d, 1H), 7.63-7.69 (m, 2H), 7.94 (d, 1H), 7.98 (dd, 1H), 8.42 (d, 1H), 8.93 (s, 1H).
3-56		MS 570, 572	$CDCl_3$: 2.63 (d, 3H), 3.85 (s, 3H), 3.93 (s, 3H), 4.52 (q, 1H), 6.78-6.83 (m, 2H), 6.93 (d, 2H), 6390-7.02 (m, 1H), 7.11-7.15 (m, 1H), 7.21-7.27 (m, 1H), 7.61 (s, 1H), 7.87-7.92 (m, 1H), 8.26 (s, 1H), 8.20-8.30 (m, 1H), 8.38-8.41 (m, 1H), 8.92 (s, 1H).
3-57		Rf (Hexane:AcOEt=3:1) 0.16	$CDCl_3$: 1.44 (t, 3H), 2.65 (d, 3H),2.79-2.89 (m, 4H), 3.65-3.74 (m, 4H), 4.07 (q, 2H), 4.52 (q, 4H), 6.48 (dd, 1H), 6.80 (d, 1H), 7.20-7.25 (m, 1H), 7.55-7.67 (m, 2H), 7.92-7.98 (m, 2H), 8.29 (s, 1H), 8.43 (d, 1H), 8.95 (s, 1H).
3-58		Rf 0.17 (Hexane/AcOEt=1/1)	$CDCl_3$: 1.46 (t, 3H), 2.63 (d, 3H), 3.08-3.13 (m, 4H), 3.83-3.90 (m, 4H), 4.09 (q, 2H), 4.46 (q, 1H), 6.39 (dd, 1H), 6.51 (d, 1H), 7.21-7.28 (m, 1H), 7.37 (s, 1H), 7.58 (dd, 1H), 7.97 (dd, 1H), 8.03 (d, 1H), 8.21 (s, 1H), 8.46 (d, 1H), 8.94 (s, 1H).
3-59		MS 538, 540	$CDCl_3$: 2.63 (d, 3H), 3.44 (s, 3H), 3.65 (s, 3H), 3.69-3.73 (m, 2H), 4.10-4.15 (m, 2H), 4.40 (q, 1H), 6.45 (dd, 1H), 6.85 (d, 1H), 7.19-7.25 (m, 1H), 7.61 (dd, 1H), 7.88 (s, 1H), 7.93-7.97 (m, 2H), 8.27 (s, 1H), 8.46 (d, 1H), 8.95 (s, 1H).
3-60		Rf (AcOEt) 0.54	$CDCl_3$: 2.63 (d, 3H), 3.67 (s, 3H), 4.18 (t, 2H), 4.38-4.49 (m, 3H), 6.46 (dd, 1H), 6.81 (d, 1H), 7.60-7.69 (m, 2H), 7.92-7.99 (m, 2H), 8.27 (s, 1H), 8.49 (d, 1H), 9.00 (s, 1H).
3-61		Rf (Hexane: AcOEt=2:1) 0.46	$CDCl_3$: 1.44 (t, 3H), 2.63 (d, 3H), 3.64 (s, 3H), 4.07 (q, 2H), 4.47 (q, 1H), 6.45 (dd, 1H), 6.78 (d, 1H), 7.21-7.28 (m, 1H), 7.40-7.48 (m, 2H), 7.93-7.99 (m, 2H), 8.26 (s, 1H), 8.44 (d, 1H), 8.96 (s, 1H).

3-62		Rf (Hexane:AcOEt=3:1) 0.31	$CDCl_3$: 1.36 (d, 6H), 2.63 (d, 3H), 3.63 (s, 3H), 4.41-4.52 (m, 2H), 6.45 (dd, 1H), 6.81 (d, 1H), 7.21-7.26 (m, 1H), 7.59-7.68 (m, 2H), 7.91-7.98 (m, 2H), 8.26 (s, 1H), 8.45 (d, 1H), 8.96 (s, 1H).
3-63		Rf (Hexane: AcOEt=3:1) 0.40	$CDCl_3$: 1.07 (t, 3H), 1.84 (m, 2H), 6.63 (d, 3H), 3.64 (s, 3H), 3.96 (t, 2H), 4.40-4.49 (m, 1H), 6.46 (dd, 1H), 6.79 (d, 1H), 7.20-7.27 (m, 1H), 7.58-7.66 (m, 2H), 7.94-7.97 (m, 2H), 8.26 (s, 1H), 8.45 (d, 1H), 8.97 (s, 1H).
3-64		Rf (Hexane:AcOEt=3:1) 0.19	$CDCl_3$: 2.62 (d, 3H), 6.68 (s, 6H), 3.84 (s, 3H), 4.41-4.48 (m, 1H), 6.36 (dd, 1H), 6.80 (d, 1H), 7.17-7.24 (m, 1H), 7.51-7.62 (m, 2H), 7.83 (s, 1H), 7.95 (dd, 1H), 8.27 (s, 1H), 8.3*9-8.45 (m, 1H), 8.91 (s, 1H).
3-65		Rf (Hexane:AcOEt=1:1) 0.12	$CDCl_3$: 2.66 (d, 3H), 3.97 (s, 3H), 4.47-4.55 (m, 1H), 6.98-7.10 (m, 3H), 7.21-7.24 (m, 1H), 7.66 (s, 1H), 7.93 (dd, 1H), 8.25 (d, 1H), 8.31 (s, 1H), 8.47 (d, 2H), 8.59 (s, 1H), 8.96 (s, 1H).
3-66		MS 541, 543	$CDCl_3$: 2.65 (d, 3H), 3.96 (s, 3H), 4.61-4.71 (m, 1H), 6.89-7.05 (m, 3H), 7.16 (dd, 1H), 7.15-7.23 (m, 1H), 7.60 (d, 1H), 7.65 (s, 1H), 7.89 (d, 1H), 8.21 (d, 1H), 8.28 (d, 1H), 8.51 (br. s, 2H), 8.57 (s, 1H), 8.93 (s, 1H).
3-67		MS 541, 543	$CDCl_3$: 2.65 (d, 3H), 3.96 (s, 3H), 4.51 (q, 1H), 6.90-7.06 (m, 3H), 7.11-7.16 (m, 1H), 7.38 (d, 1H), 7.50-7.61 (m, 2H), 7.62-7.67 (m, 1H), 7.89 (dd, 1H), 8.29 (s, 1H), 8.34 (d, 1H), 8.53 (d, 1H), 8.79 (br.s, 1H), 8.94 (s, 1H).
3-68		LC-MS 590	$CDCl_3$: 1.45-1.59 (m, 2H), 1.70-1.78 (m, 1H), 1.82-1.90 (m, 1H), 2.38-2.50 (m, 1H), 2.43 (s, 3H), 2.62-2.77 (m, 2H), 3.56-3.70 (m, 2H), 3.76 (s, 3H), 6.46 (dd, 1H), 6.63 (d, 1H), 6.82-6.88 (br, 1H), 7.22 (dd, 1H), 7.31-7.40 (m, 2H), 7.43-7.51 (m, 1H), 7.50-7.80 (m, 2H), 8.14-8.20 (br, 1H), 8.21 (s, 1H), 8.39-8.48

			(m, 1H), 9.16-9.26 (br, 1H)
3-69		0.34 (CH2Cl2:MeOH=9:1)	$CDCl_3$: 1.58-1.82 (br, 7H), 1.88-2.03 (br, 3H), 2.44-2.45 (m,5H), 3.42-3.52 (m, 3H), 3.75 (s, 3H), 6.66 (dd, 1H), 6.92 (d, 1H), 7.28 (dd, 1H), 7.44 (br, 1H), 7.51 (dd, 1H), 7.79-7.81 (m, 2H), 8.18 (s, 1H), 8.32 (s, 1H), 8.35-8.37 (m, 1H), 9.17 (s, 1H)
3-70		Ms:607, 609	DMSO-d6: 1.84-1.92(m, 2H), 2.34-2.41(m, 4H), 2.41-2.45(m, 3H), 2.44(t, 2H), 3.58(t, 4H), 3.75(s, 3H), 4.02(t, 2H), 6.48(dd, 1H), 6.63(d, 1H), 7.21(dd, 1H), 7.41(d, 1H), 7.46(dd, 1H), 7.72-7.78(m, 1H), 7.76(dd, 1H), 8.22(s, 1H), 8.25(s, 1H), 8.40(d, 1H), 9.22(s, 1H)
3-71		Ms:591, 593	DMSO-d6: 1.84-1.92(m, 2H), 2.14(s, 3H), 2.35-2.4 (m, 4H), 2.43(t, 2H), 2.44(d, 3H), 3.58(t, 4H), 4.01(t, 2H), 6.77(dd, 1H), 6.82(d, 1H), 7.17(dd, 1H), 7.20(d, 1H), 7.3-7.39(m, 1H, 7.71-7.77(m, 2H), 8.2(s, 1H), 8.35-8.44(m, 1H), 8.71(s, 1H), 9.27(s, 1H)
3-72		Ms:620, 622	DMSO-d6: 1.82—1.9 (m, 2H), 2.13-2.17 (m, 3H), 2.25-2.47(m, 13H), 3.75 (s, 3H), 4.01 (t, 2H), 6.47 (dd, 1H), 6.63(d, 1H), 7.19-7.24 (m, 1H), 7.41 (d, 1H), 7.43-7.5(m, 1H), 7.70-7.79(m, 2H), 8.22(s, 1H), 8.25(brs, 1H), 8.37-8.44(m, 1H), 9.22(s, 1H)
3-73		Ms:607, 609	DMSO-d6: 1.78 (t, 2H), 2.32-2.36 (m, 4H9, 2.35-2.38 (m, 3H), 3.54-3.59 (m, 4H), 3.74 (t, 3H), 3.78 (s, 3H), 6.38-6.42 (m, 1H), 6.85 (d, 1H), 6.86-6.95 (m, 1H), 7.33-7.43(m, 2H), 7.63-7.68 (m, 1H), 7.85-8.15 (m, 3H), 8.64-8.8 (m, 1H).

3-74		Ms:605, 607	DMSO-d6: 1.47-1.67(m, 2H), 1.84-2.01(m, 2H), 2.03 (s, 3H), 2.41-2.46 (m, 3H), 3.23-3.39 (m, 2H), 3.65-3.73 (m, 1H), 3.81(s, 3H), 3.8-3.88 (m, 1H), 4.58-4.65 (m, 1H), 6.55 (dd, 1H), 6.68 (d, 1H), 7.2-7.26(m, 1H), 7.43(d, 1H), 7.42-7.51 (m, 1H), 7.7-7.8(m, 2H), 8.23 (s, 1H), 8.26 (brs, 1H), 8.37-8.44(m, 1H), 9.22(brs, 1H)
3-75		Ms:605, 607	DMSO-d6: 1.38-1.6(m, 2H), 1.74-1.9(m, 2H), 2.0 (s, 3H), 2.42-2.47 (m, 3H), 3.12-3.3 (m, 2H), 3.55-3.65 (m, 1H), 3.7-3.8 (m, 1H), 3.78 (s, 3H), 4.27-4.34 (m, 1H), 6.65 (dd, 1H), 6.94 (d, 1H), 7.24-7.3 (m, 1H), 7.53-7.63(m, 2H), 7.74-7.83 (m, 2H), 8.09 (brs, 1H), 8.35 (s, 1H), 8.38(d, 1H), 9.19(brs, 1H)
3-76		Ms:577, 579	DMSO-d6: 1.51-1.61 (m, 2H), 1.79-1.87 (m, 2H), 2.03-2.11 (m, 2H), 2.14 (s, 3H), 2.42-2.47 (m, 3H), 2.52-2.6 (m, 2H), 3.77 (s, 3H), 4.02-4.09 (m, 1H), 6.6 (dd, 1H), 6.92 (d, 1H), 7.24-7.3 (m, 1H), 7.52-7.6(m, 2H), 7.74-7.82 (m, 2H), 8.08 (brs, 1H), 8.34 (s, 1H), 8.4 (d, 1H), 9.2 (brs, 1H)
3-77		Rf : 0.4 (n-hexane: AcOEt=7:3)	DMSO-d6: 2.41-2.45 (m, 3H), 6.89-6.96 (m, 1H), 6.69(bs, 1H), 7.24-7.33 (m, 2H), 7.51-7.57 (m, 1H), 7.63-7.7 (m, 1H), 7.73-7.78 (m, 1H), 7.79 (dd, 1H), 8.37(s, 1H), 8.41(d, 1H), 9.21 (brs, 1H), 9.24 (brs, 1H)
3-78		Ms:563, 565	DMSO-d6: 1.33-1.43 (m, 2H), 1.79-1.86 (m, 2H), 2.43-2.46 (m, 3H), 2.46-2.53 (m, 2H), 2.87-2.94 (m, 2H), 3.77 (s, 3H), 4.07-4.14 (m, 1H), 6.59 (dd, 1H), 6.91 (d, 1H), 7.23-7.28 (m, 1H), 7.53-7.59 (m, 2H), 7.79 (dd, 1H), 8.03 (brs, 1H), 8.32 (s, 1H), 8.38 (d, 1H), 8.7-9.5 (brs, 1H)

3-79		Ms:563, 565	DMSO-d6: 1.41-1.51 (m, 2H), 1.88-1.95 (m, 2H), 2.41-2.45 (m, 3H), 2.54-2.63 (m, 2H), 2.92-3.0 (m, 2H), 3.75 (s, 3H), 4.35-4.43 (m, 1H), 6.50 (dd, 1H), 6.63 (d, 1H), 7.18-7.23 (m, 1H), 7.40 (d, 1H), 7.42-7.48 (m, 1H), 7.75 (dd, 1H), 8.21 (s, 1H), 8.22-8.25 (m, 1H), 8.37-8.42 (m, 1H), 8.9-9.5 (brs, 1H)
3-80		Ms:482, 484	DMSO-d6: 2.4-2.46 (m, 3H), 3.79 (s, 3H), 6.72 (ddd, 1H), 6.99 (dd, 1H), 7.21-7.26 (m, 1H), 7.47-7.53 (m, 1H), 7.59-7.64 (m, 1H), 7.76 (dd, 1H), 8.25 (s, 1H), 8.29-8.37 (m, 2H), 8.8-9.6 (m, 1H)
3-81		Ms:482, 484	DMSO-d6: 2.41-2.49 (m, 3H), 3.82 (s, 3H), 6.80 (ddd, 1H), 7.01 (dd, 1H), 7.3-7.35 (m, 1H), 7.56-7.63 (m, 1H), 7.7-7.8 (m, 1H), 7.82 (dd, 1H), 7.85 (dd, 1H), 8.16 (s, 1H), 8.35 (dd, 1H), 9.18 (brs, 1H)
3-82		Ms:563, 565	DMSO-d6: 1.73-1.82 (m, 1H), 2.23-2.34 (m, 4H), 2.34-2.42(m, 3H), 2.42-2.46 (m, 3H), 2.59 (dd, 1H), 2.62-2.68 (m, 1H), 2.80 (dd, 1H), 3.75 (s, 1H), 4.85-4.91(m, 1H), 6.42 (dd, 1H), 6.57(d, 1H), 7.19-7.24(m, 1H), 7.41 (d, 1H), 7.43-7.51(m, 1H), 7.68-7.79 (m, 2H), 8.22(s, 1H), 8.23(s, 1H), 8.37-8.43 (m, 1H), 9.21 (brs, 1H).
3-83		MS 544, 546	2.36 (s, 3H), 2.65 (d, 3H), 3.93 (s, 3H), 4.46-4.51 (m, 1H), 6.75-6.80 (m, 2H), 6.97-7.04 (m, 2h), 7.25-7.30 (m, 1H), 7.56-7.66 (m, 2H), 7.98 (dd, 1H), 8.29 (s, 1H), 8.36-8.44 (m, 2H), 9.01 (s, 1H).
3-84		MS 562, 564	CDCl3: 2.32 (s, 3H), 2.39-2.47 (m, 4H), 2.64 (d, 3H), 2.89-2.97 (m, 4H), 3.85 (s, 3H), 4.54-4.52 (m, 1H), 6.52 (dd, 1H), 6.79 (d, 1H), 7.22 (m, 1H), 7.52-7.64 (m, 2H), 7.94-7.99 (m, 2H), 8.28 (s, 1H), 8.42 (d, 1H), 8.93 (s, 1H).

Example 4: 2-[5-Bromo-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-propyl-benzene-sulfonamides

These compounds are prepared in analogy to Example 2 using 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide and the corresponding aniline to give compounds No. 4-1 to 4-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide

To a solution of 5-bromo-2,4-dichloropyrimidine (90 µL, 0.70 mmol) and 2-amino-N-propyl-benzenesulfonamide (100 mg, 0.47 mmol), sodium hydride (54.2 mg, 0.56 mmol) in DMSO (1.0 mL) is added and the resulting solution is stirred at 80°C for 3.0 h. The mixture is poured into water and extracted with ethyl acetate three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford the title compound as a slightly yellow solid.

^{1}H-NMR (δ, ppm) : 0.89 (t, 3H), 1.41 (q, 2H), 3.56 (t, 2H), 4.92 (br.s, 2H), 6.71 (dd, 1H), 6.77 (dd, 1H), 7.33 (dd, 1H), 7.54 (dd, 1H), 8.79 (s, 1H)

Rf (hexane : ethyl acetate = 1:1): 0.64.

Example 5: 2-[5-Trifluoromethyl-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamides

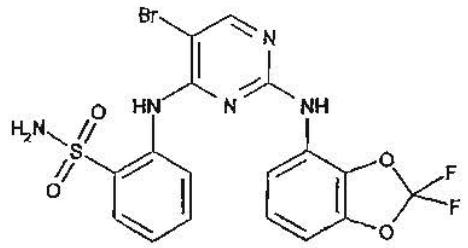
These compounds are prepared in analogy to Example 2 using 2-(2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline to give compounds No. 5-1 to 5-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

Preparation of 2-[2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide

To a solution of 2,4-dichloro-5-trifluoromethyl-pyrimidine (386 mg, 1.79 mmol) in acetonitrile (10 mL), 2-amino-N-methyl-benzenesulfonamide (333 mg, 1.79 mmol) and 1,8-diaza[5.4.0]-bicyclo-7-undecene (280 µL, 1.88 mmol) are added successively at ambient temperature. After stirring for 15 h at room temperature, dichloromethane (30 mL) is added to the mixture, and the solution is washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. The resulting solid is purified by flash chromatography.

^{1}H NMR ($CDCl_3$) δ: 3.73(s, 3H), 6.67-6.69(m, 1H), 6.72-6.73(m, 1H), 7.27-7.31(m, 1H), 7.78 (dd, 1H), 8.60(s, 1H). Rf (hexane : ethyl acetate = 1:1): 0.28.

Example 6: 2-[5-Bromo-2-(2,3-[difluoromethylenedioxy]phenylamino)-pyrimidin-4-ylamino]-benzenesulfonamide



This compound is obtained as a side product formed by N-demethylation on reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)-N-methyl-benzenesulfonamide with 2,3-(difluoromethylenedioxy)aniline following the procedure of Example 2. It may also be prepared by reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)benzenesulfonamide with 2,3-(difluoromethylenedioxy)-aniline.

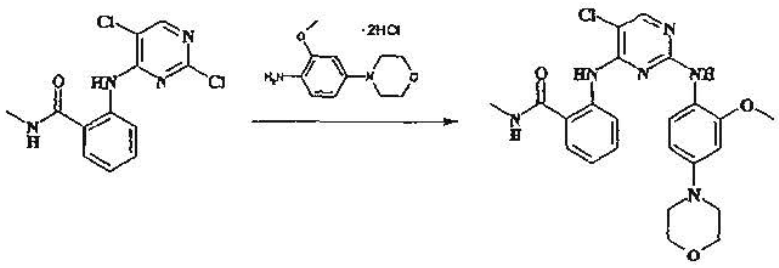
Rf (*n*-hexane: ethyl acetate = 1:1): 0.46.

^{1}H-NMR : ($CDCl_3$) 4.83 (bs, 2H), 6.77 (dd, 1H), 6.86 (s, 1H), 6.97 (dd, 1H), 7.31-7.24 (m, 1H), 7.57 (dd, 1H), 7.81 (d, 1H), 8.02 (dd, 1H), 8.28 (d, 1H), 8.29 (s, 1H), 8.88 (s, 1H).

Preparation of 2-(5-bromo-2-chloropyrimidin-4-ylamino)benzenesulfonamide: To a solution of 5-bromo-2,4-dichloropyrimidine (300 mg, 1.32mmol) and 2-amino-benzenesulfonamide (340 mg, 1.97 mmol) in 2-propanol (3 mL), concentrated hydrochloric acid (0.06 mL) is added and the mixture is stirred at 90°C for 4.5 hours. The mixture is poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate three times. The organic layer is washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by column chromatography (hexane : ethyl acetate = 2:1) to afford the title compound.

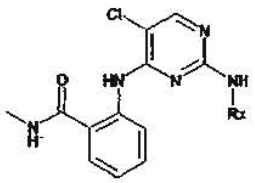
Rf (hexane : ethyl acetate = 1:1): 0.55. ^{1}H-NMR (400MHz, CDCl3) δ : 4.78 (br.s, 2H), 7.22 (dd, 1H), 7.61 (ddd, 1H), 7.95 (dd, 1H), 8.35 (s, 1H), 8.35 (d, 1H), 9.18 (s, 1H).

Example 7A: 2-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide

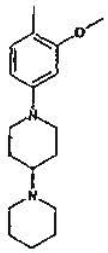
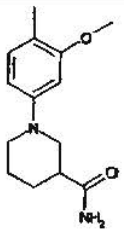
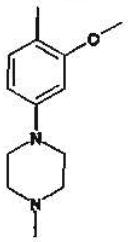
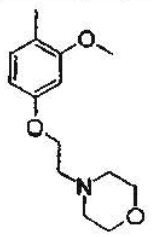
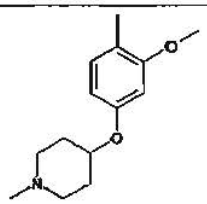


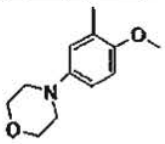
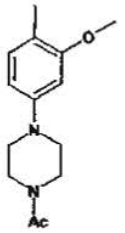
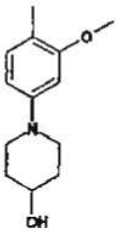
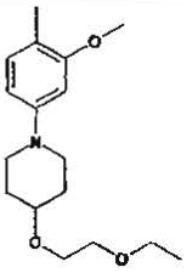
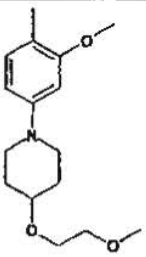
To a suspension of 2-(2,5-dichloro-pyrimidin-4-yl-amino)-*N*-methyl-benzamide (5.05 g, 17.0 mmol) in 90 mL of 2-methoxyethanol are added 2-methoxy-4-morpholinoaniline dihydrochloride (4.56 g, 16.2 mmol) and 17.0 mL of 1N ethanolic solution of hydrogen chloride (17.0 mmol). After the reaction mixture is stirred at 110°C for 4 hours and cooled to room temperature, the mixture is neutralized with 1N aqueous NaOH solution and extracted with EtOAc (100 mL×3). The organic layer is washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting black solid is washed with EtOH (90 mL), then purified with silica gel column chromatography (CH_2Cl_2 to CH_2Cl_2: AcOEt=1:2) to give 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide as a pale yellow solid. ^{1}H-NMR (400MHz, DMSO-d6, δ): 2.80 (d, 3H, J = 4.52 Hz), 3.10-3.20 (m, 4H), 3.78 (s, 3H), 3.70-3.80 (m, 4H), 6.49 (dd, 1H, J = 8.56, 2.52 Hz), 6.66 (d, 1H, J = 2.52 Hz), 7.08 (dd, 1H, J = 8.04, 8.04 Hz), 7.44 (d, 1H, J = 8.56 Hz), 7.71 (dd, 1H, J = 8.04, 1.48 Hz), 8.10 (s, 1H), 8.13 (s, 1H), 8.59 (d, 1H, J = 8.04 Hz) 8.68-8.75 (m, 1H), 11.59 (S, 1H). MS *m/z* 469, 471 $(M+1)^+$.

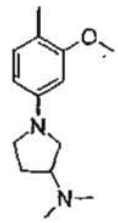
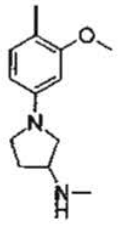
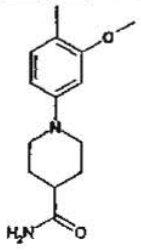
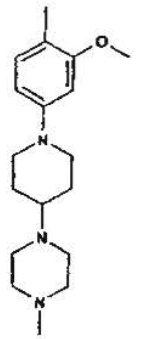
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-methyl-benzamide and the corresponding aniline following the procedure of Example 7A.

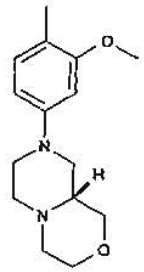
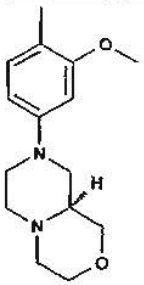
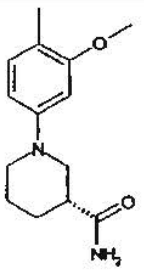
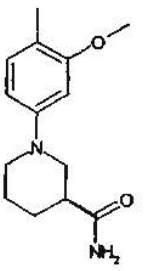


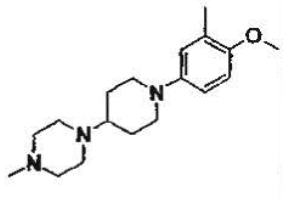
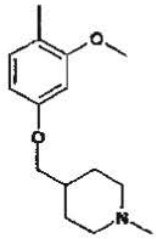
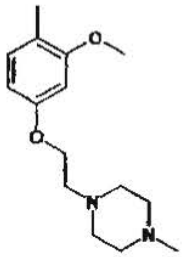
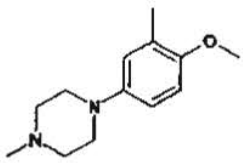
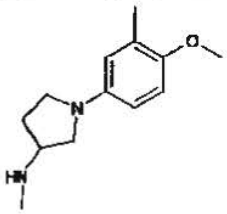
Expl No.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)

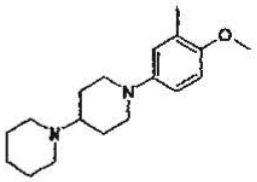
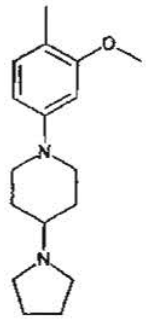
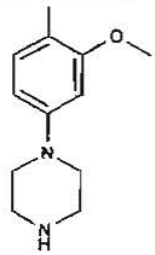
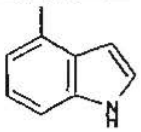
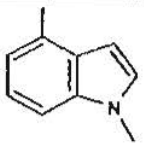
7-1		MS: m/z 550, 552 (M+1)	DMSO-d6: 1.44-1.33 (m, 2H), 1.64-1.45 (m, 6H), 1.73-1.89 (m, 2H), 2.34-2.44 (m, 1H), 2.43-2.55 (m, 4H), 2.65 (t, 2H), 2.80 (d, 3H), 3.75 (s, 3H), 3.72-3.75 (m, 2H), 6.48 (dd, 1H), 6.62 (d, 1H), 7.06 (dd, 1H), 7.32 (dd, 1H), 7.39 (d, 1H), 7.71 (dd, 1H), 8.09(s, 1H), 8.60 (d, 1H), 8.70 (d, 1H), 11.58 (s, 1H)
7-2		0.3 (MeOH: AcOEt =5:95)	$CDCl_3$: 1.70-1.97(m, 4H) ,2.62-2.79(m, 1H), 3.04(d, 3H), 3.02-3.18(m, 2H), 3.23-3.33(m, 2H), 3.88 (s, 3H), 5.39-5.47(m, 1H), 6.15-6.24(m, 1H), 6.55-6.62(m, 2H), 6.74-6.82(m, 1H), 7.09 (dd, 1H),7.23-7.32 (m, 1H), 7.46-7.52(m, 2H), 8.09(s, 1H), 8.15(d, 1H), 8.68(d, 1H) 11.0(bs, 1H)
7-3		MS (ESI) *m/z* 482, 484 $(M+1)^+$	DMSO-d6: 2.24 (s, 3H), 2.45-2.55 (m, 4H), 2.80 (d, 3H, J = 4.52 Hz), 3.12-3.17 (m, 4H), 3.76 (s, 3H), 6.48 (dd, 1H, J = 8.56, 2.52 Hz), 6.63 (d, 1H, J = 2.52 Hz), 7.05-7.10 (m, 1H), 7.27-7.35 (m, 1H), 7.40 (d, 1H, J = 8.56 Hz), 7.69-7.72 (m, 1H), 8.09 (s, 1H), 8.12 (s, 1H), 8.55-8.65 (m, 1H), 8.67-8.75 (m, 1H), 11.59 (s, 1H)
7-4		0.46 (MeOH: CH_2Cl_2=1:4)	DMSO-d6: 2.48-2.55(m, 4H), 2.71(t, 2H), 2.80(d, 3H), 3.58-3.61(m, 4H), 3.76(s, 3H), 4.11(t, 2H), 6.52(dd, 1H), 6.66(d, 1H), 7.06(dd, 1H), 7.32(dd, 1H), 7.46(d, 1H), 7.71(dd, 1H), 8.11(s, 1H), 8.19 (s, 1H), 8.54-8.60(m, 1H), 8.60-8.75(m, 1H), 11.6(s, 1H)
7-5		*m/z* 497, 499 $(M+1)^+$	DMSO-d6: 1.60-1.70 (m, 2H), 1.90-1.98 (m, 2H), 2.13-2.25 (m, 2H), 2.19 (s, 3H), 2.60-2.67 (m, 2H), 2.80 (d, 3H, J = 4.52 Hz), 3.75 (s, 3H), 4.30-4.40 (m, 1H), 6.54 (dd, 1H, J = 8.56, 2.0 Hz), 6.65 (d, 1H, J = 2.0 Hz), 7.04-7.09 (m, 1H), 7.25-7.35 (m, 1H), 7.43 (d, 1H, J = 8.56 Hz), 7.68-7.73 (m, 1H), 8.10 (s, 1H), 8.18 (s, 1H) 8.52-8.59 (m, 1H), 8.68-8.75 (m, 1H), 11.57 (s, 1H)

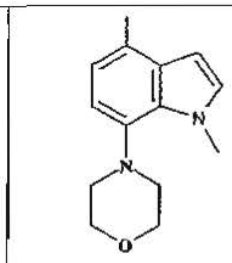
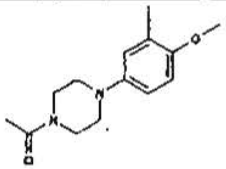
7-6		0.25 (*n*-hexane: AcOEt=1:2)	$CDCl_3$: 2.95 (m, 4H), 3.03 (d, 3H), 3.75 (m, 4H), 3.86 (s, 3H), 6.21-6.19 (br, 1H), 6.49 (dd, 1H), 6.80 (d, 1H), 7.09-7.05 (m, 1H), 7.50 (dd, 1H), 8.08 (d, 1H), 8.13 (s, 1H), 8.68 (d, 1H), 11.07 (s, 1H)
7-7		MS m/z 510, 512 (M+1)	DMSO-d6: 2.06 (s, 3H), 2.80 (d, 3H), 3.11 (t, 2H), 3.16 (t, 2H), 3.60 (dd, 4H), 3.77 (s, 3H), 6.51 (dd, 1H), 6.68 (d, 1H), 7.08 (dd, 1H), 7.33 (dd, 1H), 7.46 (d, 1H), 7.71 (d, 1H), 8.10(s, 1H), 8.12(s, 1H), 8.59-8.61 (m, 1H), 8.70-8.71(m, 1H), 11.59 (s, 1H)
7-8		0.48 (MeOH: AcOEt =5:95)	$CDCl_3$: 1.46(d, 1H), 1.68-1.82(m, 2H), 2.02-2.09(m, 2H), 2.83-2.96 (m, 2H), 3.03(d, 3H),3.44-3.53(m, 2H), 3.82-3.92(m, 1H),3.87(s, 3H), 6.15-6.23(m, 1H), 6.51 (d, 1H), 6.56(bs, 1H), 7.07(dd, 1H), 7.48(d, 2H), 8.08(s, 1H), 8.08-8.10(m, 1H), 8.69(d, 1H), 11.0(bs, 1H)
7-9		0.4 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 1.22 (t, 3H), 1.73-1.85 (m, 2H), 2.00-2.09 (m, 2H), 2.81-2.90 (m, 2H), 3.03 (d, 3H), 3.41-3.56 (m, 3H), 3.56 (dd, 2H), 3.58-3.62 (m, 2H), 3.64-3.68 (m, 2H), 3.86 (s, 3H), 6.15-6.24 (m, 1H), 6.50 (dd, 1H), 6.56 (d, 1H), 7.07(dd, 1H), 7.24-7.30 (m, 1H), 7.45-7.52(m, 2H), 8.08(s, 1H), 8.06-8.08 (m, 1H), 8.69 (d, 1H), 11.0 (bs, 1H)
7-10		0.4 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 1.73-1.85(m, 2H), 2.01-2.10(m, 2H), 2.82-2.90(m, 2H), 3.03(d, 3H), 3.41(s, 3H), 3.45-3.51(m, 2H), 3.56-3.58(m, 2H), 3.65-3.68(m, 2H), 3.86(s, 3H), 6.14-6.22(m, 1H), 6.50 (dd, 1H), 6.56 (d, 1H), 7.07(dd, 1H), 7.23-7.30(m, 1H), 7.44-7.52(m, 2H), 8.08(s, 1H), 8.06-8.08(m, 1H), 8.69(d, 1H), 11.0(bs, 1H)

7-11		0.54 (MeOH: CH_2Cl_2=1:4)	DMSO-d6: 1.78-1.89(m, 1H), 2.13-2.22(m, 1H), 2.22(s, 6H), 2.77-2.87(m, 1H), 2.79(d, 3H), 3.04-3.10(m, 1H), 3.23-3.50(m, 3H), 3.75(s, 3H), 6.11(dd, 1H), 6.22(d, 1H), 7.05(dd1H), 7.21-7.32(m, 1H), 7.26(d, 1H), 7.70(d, 1H), 8.06(s, 1H), 8.08(s, 1H), 8.57-8.66(m, 1H), 8.66-8.73 (m, 1H), 11.6(s, 1H)
7-12		0.27 (MeOH: CH_2Cl_2=1:1)	DMSO-d6: 1.77-1.87(m, 1H), 2.09-2.18(m, 1H), 2.35(s, 3H), 2.79(d, 1H), 3.02-3.07(m, 1H), 3.23-3.50(m, 4H), 3.74(s, 3H), 6.09(dd, 1H), 6.20(d, 1H), 7.04(dd, H), 7.22-7.32(m, 1H), 7.26(d, 1H), 7.70(d, 1H), 8.05(s, 1H), 8.08(s, 1H), 8.57-8.67(m, 1H), 8.67-8.73 (m, 1H), 11.6(s, 1H)
7-13		0.23 (MeOH: AcOEt =5:95)	$CDCl_3$: 1.62-1.74(m, 3H), 1.76-1.85(m, 2H), 2.00-2.09(m, 2H), 2.20-2.31(m, 1H), 2.64-2.69 (m, 2H), 2.79 (d, 3H), 3.56-4.04(m, 2H), 4.04(s, 3H), 6.49(dd, 1H), 6.63(d, 1H), 6.78(bs, 1H), 7.07 (dd, 1H), 7.28-7.38 (m, 1H), 7.39(d, 1H), 7.71(d, 1H), 8.09-8.11(m, 2H), 8.09(s, 1H), 8.60(d, 1H), 8.71(d, 1H),11.6(bs, 1H)
7-14		0.30 (MeOH: CH_2Cl_2=4:1)	DMSO-d6: 1.61-1.46(m, 2H), 1.92-1.82 (m, 2H), 2.14 (s, 3H), 2.41-2.23 (m, 5H, 2.60-2.45 (m, 4H), 2.67 (t, 2H), 2.79 (d, 3H), 3.75 (s, 3H), 3.71-3.75 (m, 2H), 6.48 (dd, 1H), 6.63 (d, 1H), 7.10-7.03 (m, 1H), 7.34-7.27 (m, 1H), 7.43-7.35 (m, 1H), 7.71(dd, 1H), 8.09 (s, 1H), 8.11 (bs, 1H), 8.65-8.56 (m, 1H), 8.75-8.67 (m, 1H), 11.6 (s, 1H)

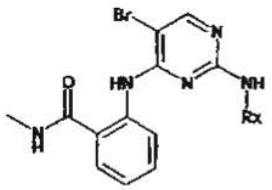
7-15		MS (ESI) *m/z* 524, 526 $(M+1)^+$	DMSO-d6: 2.19-2.37 (m, 4H), 2.65-2.85 (m, 3H), 2.80 (d, 3H, J = 4.5 Hz), 3.15-3.21 (m, 1H), 3.48-3.59 (m, 2H), 3.61-3.67 (m, 1H), 3.72-3.81 (m, 1H), 3.76 (s, 3H), 6.47 (dd, 1H, J = 8.6, 2.5 Hz), 6.65 (d, 1H, J = 2.5 Hz), 7.04-7.10 (m, 1H), 7.28-7.35 (m, 1H), 7.42 (d, 1H, J = 8.6 Hz), 7.69-7.74 (m, 1H), 8.09 (s, 1H), 8.12 (s, 1H), 8.55-8.63 (m, 1H), 8.68-8.73 (m, 1H), 11.60 (s, 1H)
7-16		MS (ESI) *m/z* 524, 526 $(M+1)^+$	DMSO-d6: 2.19-2.37 (m, 4H), 2.65-2.85 (m, 3H), 2.80 (d, 3H, J = 4.5 Hz), 3.15-3.21 (m, 1H), 3.48-3.59 (m, 2H), 3.61-3.67 (m, 1H), 3.72-3.81 (m, 1H), 3.76 (s, 3H), 6.47 (dd, 1H, J = 8.6, 2.5 Hz), 6.65 (d, 1H, J = 2.5 Hz), 7.04-7.10 (m, 1H), 7.28-7.35 (m, 1H), 7.42 (d, 1H, J = 8.6 Hz), 7.69-7.74 (m, 1H), 8.09 (s, 1H), 8.12 (s, 1H), 8.55-8.63 (m, 1H), 8.68-8.73 (m, 1H), 11.60 (s, 1H)
7-17		MS 510	DMSO-d6: 0.98 (t, 3H), 1.81-1.71 (m, 3H), 1.95-1.84 (m, 3H), 2.68-2.63(m, 1H), 2.80 (d, 3H), 3.12-3.08 (m, 4H), 3.28(d, 2H), 3.76(s,3H), 6.50 (dd, 1H), 6.64 (d, 1H), 6.86(bs, 1H), 7.07(dd, 1H), 7.46-7.19 (m, 3H), 7.71 (d, 1H), 8.09(s, 1H), 8.15-8.10 (m, 1H), 8.66-8.58(m, 1H), 8.77-8.70(m, 1H), 11.6(s, 1H)
7-18		MS 510	DMSO-d6: 0.98 (t, 3H), 1.81-1.71 (m, 3H), 1.95-1.84 (m, 3H), 2.68-2.63(m, 1H), 2.80 (d, 3H), 3.12-3.08 (m, 4H), 3.28(d, 2H), 3.76(s,3H), 6.50 (dd, 1H), 6.64 (d, 1H), 6.86(bs, 1H), 7.07(dd, 1H), 7.46-7.19 (m, 3H), 7.71 (d, 1H), 8.09(s, 1H), 8.15-8.10 (m, 1H), 8.66-8.58(m, 1H), 8.77-8.70(m, 1H), 11.6(s, 1H)

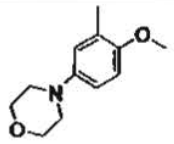
7-19		0.16 (CH2Cl2:MeOH=9:1)	1.40-1.53 (m, 2H), 1.72-1.80 (m, 2H), 2.18 (s, 3H), 2.19-2.44 (m, 5H), 2.80 (d, 3H), 3.46 (m, 2H), 3.74 (s, 3H), 6.65 (dd, 1H), 6.91 (d, 1H), 7.07-7.10 (m, 1H), 7.36-7.40 (m, 1H), 7.45-7.49 (m, 1H), 7.73 (dd, 1H), 8.12 (s, 1H), 8.18 (s, 1H), 8.61 (d, 1H), 8.72-8.77 (m, 1H), 11.68 (s, 1H)
7-20		Ms : 511	1.25-1.37 (m, 2H), 1.62-1.79 (m, 3H), 1.81-1.9 (m, 2H), 2.16 (s, 3H), 2.75-2.85 (m, 5H), 3.76 (s, 3H), 3.8-3.88 (m, 2H), 6.45-6.55 (m, 1H), 6.6-6.67 (m, 1H), 7.02-7.12 (m, 1H), 7.25-7.35 (m, 1H), 7.4-7.5 (m, 1H), 7.67-7.78 (m, 1H), 8.1 (s, 1H), 8.19 (brs, 1H) 8.5-8.62 (m, 1H), 8.66-8.8 (m, 1H), 11.6 (s, 1H)
7-21		Ms : 526	2.17 (s, 3H), 2.29-2.39 (m, 3H), 2.45-2.56 (m, 4H), 2.7 (t, 2H), 3.76 (s, 3H), 4.09 (t, 2H), 6.52 (dd, 1H), 6.66 (d, 1H), 7.06 (dd, 1H), 7.31 (dd, 1H), 7.45 (d, 1H), 7.71 (dd, 1H), 8.1 (s, 1H), 8.19 (s, 1H), 8.5-8.6 (m, 1H), 8.67-8.75 (m, 1H), 11.6 (s, 1H)
7-22		Ms : 482	2.24 (s, 3H), 2.42-2.5 (m, 4H), 2.8 (d, 3H), 2.94-3.0 (m, 4H), 3.74 (s, 3H), 6.65 (dd, 1H), 6.93 (d, 1H), 7.07-7.14 (m, 1H), 7.34-7.4 (m, 1H), 7.45 (d, 1H), 7.73 (dd, 1H), 8.14 (s, 1H), 8.18 (s, 1H), 8.61 (dd, 1H), 8.7-8.77 (m, 1H), 11.7 (s, 1H)
7-23		Ms : 482	1.67-1.76 (m, 1H), 2.0-2.1 (m, 1H), 2.25-2.31 (m, 3H), 2.8 (d, 3H), 2.85-2.91 (m, 1H), 3.04-3.12 (m, 1H), 3.14-3.3 (m, 3H), 3.7 (s, 3H), 6.26 (dd, 1H), 6.91 (d, 1H), 7.01-7.04 (m, 1H), 7.07 (dd, 1H), 7.32 (dd, 1H), 7.72 (d, 1H), 8.14 (s, 1H), 8.17 (s, 1H), 8.63 (d, 1H), 8.7-8.78 (m, 1H), 11.6 (s, 1H)

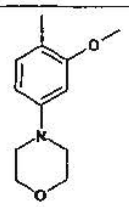
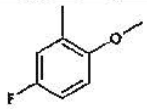
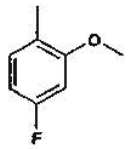
7-24		Ms : 550	1.35-1.57 (m, 8H), 1.7-1.78 (m, 2H), 2.81 (d, 3H), 3.46-3.52 (m, 2H), 3.74 (s, 3H), 6.65 (dd, 1H), 6.91 (d, 1H), 7.05-7.12 (m, 1H), 7.34-7.42 (m, 1H), 7.46 (d, 1H), 7.73 (dd, 1H), 8.11 (s, 1H), 8.18 (s, 1H), 8.62 (dd, 1H),8.71-8.78 (m, 1H), 11.7 (s, 1H)
7-25		536 [M+1]+	DMSO-d6: 1.48-1.58(m, 2H), 1.65-1.72(m, 4H), 1.90-1.97(m, 2H), 2.07-2.14(m, 1H), 2.49-2.55(m, 4H), 2.70-2.77(m, 2H), 2.79(d, 3H), 3.60-3.65(m, 2H), 3.75(s, 3H), 6.48(dd, 1H), 6.63(d, 1H), 7.03-7.09(m, 1H), 7.28-7.34(m, 1H), 7.39(d, 1H), 7.71(dd, 1H), 8.09(s, 1H), 8.11(s, 1H), 8.55-8.65(m, 1H), 8.69-8.73(m, 1H), 11.59(s, 1H)
7-26		468 [M+1]+	DMSO-d6: 2.80(d, 3H), 2.84-2.89(m, 4H), 3.04-3.08(m, 4H), 3.76(s, 3H), 6.47(dd,1H), 6.62(dd, 1H), 7.04-7.10(m, 1H), 7.28-7.35(m, 1H), 7.40(d, 1H), 7.69-7.73(m, 1H), 8.09(s, 1H), 8.12(s, 1H), 8.55-8.63(m, 1H), 8.68-8.73(m, 1H), 11.59(s, 1H) (an aliphatic NH is hidden)
7-27		393 [M+1]+	DMSO-d6: 2.80(d, 3H), 6.64-6.67(m, 1H), 7.01-7.08(m, 2H), 7.15(d, 1H), 7.24-7.29(m, 2H), 7.44(d, 1H), 7.69-7.73(m, 1H), 8.20(s, 1H), 8.65-8.73(m, 2H), 9.15(s, 1H), 11.06(s, 1H), 11.63(s, 1H)
7-28		407 [M+1]+	DMSO-d6: 2.81(d, 3H), 3.79(s, 3H), 6.67(d, 1H), 7.05-7.10(m, 1H), 7.12(d, 1H), 7.17(d, 1H), 7.23(d, 1H), 7.25-7.30(m, 1H), 7.50(d, 1H), 7.70-7.73(m, 1H), 8.20(s, 1H), 8.67(d, 1H), 8.70-8.75(m, 1H), 9.17(s, 1H), 11.64(s, 1H)

7-29		492 [M+1]+	DMSO-d6: 2.80(d, 3H), 2.91-2.99(m, 4H), 3.65-3.81(m, 2H), 3.82-3.95(m, 2H), 4.12(s, 3H), 6.58(d, 1H), 6.90(d, 1H), 7.05-7.09(m, 1H), 7.14(d, 1H), 7.22-7.28(m, 1H), 7.30(d, 1H), 7.70(dd, 1H), 8.16(s, 1H), 8.63-8.67(m, 1H), 8.68-8.72(m, 1H), 9.06(s, 1H), 11.64(s, 1H)
7-30		MS m/z 510	DMSO-d_6: 2.02 (s, 3H), 2.80 (d, 3H), 2.82-2.92 (m, 2H), 2.92-3.01 (m, 2H), 3.44-3.53 (m, 4H), 3.76 (s, 3H), 6.68 (dd, 1H), 6.95 (d, 1H), 7.09 (dd, 1H), 7.35-7.40 (m, 1H), 7.50 (brs, 1H), 7.73 (d, 1H), 8.15 (s, 1H), 8.19 (s, 1H), 8.59 (d, 1H), 8.69-8.76 (m, 1H), 11.66 (s, 1H).

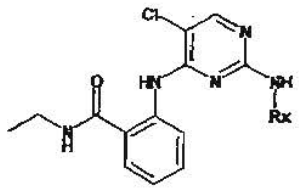
The following 2-[5-Bromo-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-ethyl-benzamide are prepared from 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-ethyl-benzamide and the corresponding aniline following the procedure of Example 7A

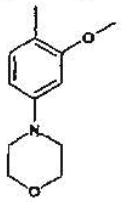


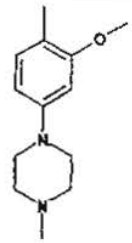
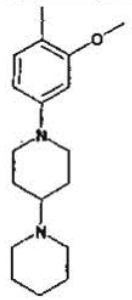
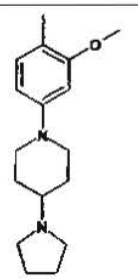
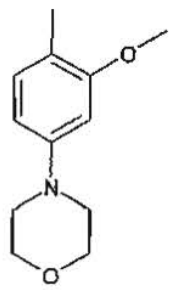
Expl No.	Rx	Rf (solvent) or MS	NMR
8-1		0.27 (*n*-hexane: AcOEt=1:2)	DMSO-d6: 2.80(d, 3H), 2.88(t, 4H), 3.65 (m, 4H), 3.75 (s, 3H), 6.64 (dd, 1H), 6.94 (d, 1H), 7.11-7.08 (m, 1H), 7.38-7.34 (m, 1H), 7.47-7.45 (m, 1H), 7.70 (dd, 1H), 8.11 (s, 1H), 8.26 (s, 1H), 8.51-8.49 (m, 1H), 8.72-8.71 (m, 1H), 11.41 (s, 1H)

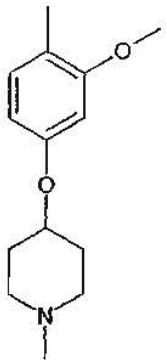
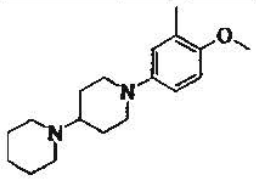
8-2		m/z 513, 515 (M+1)	DMSO-d6: 2.79 (d, 3H, J = 4.04 Hz), 3.10-3.20 (m, 4H), 3.77 (s, 3H), 3.70-3.80 (m, 4H), 6.45-6.55 (m, 1H), 6.63-6.69 (m, 1H), 7.05-7.10 (m, 1H), 7.28-7.34 (m, 1H), 7.40-7.45 (m, 1H), 7.65-7.70 (m, 1H), 8.13 (s, 1H), 8.16 (s, 1H), 8.50-8.56 (m, 1H) 8.65-8.72 (m, 1H), 11.40 (s, 1H)
8-3		0.48 (n-Hexane: AcOEt=4:1)	DMSO-d6: 2.80(d, 3H), 3.83(s, 3H), 4.11(t, 2H), 6.82(ddd, 1H), 7.03(dd, 1H), 7.15(dd, 1H), 7.44(dd, 1H), 7.73(d, 1H), 7.93(dd, 1H), 8.13(s, 1H), 8.33 (s, 1H), 8.50(d, 1H), 8.70-8.77(m, 1H), 11.3(s, 1H).
8-4		MS 446, 448	2.79 (d, 3H), 3.79 (s, 3H), 6.75 (ddd, 1H), 7.0 (dd, 1H), 7.05-7.12 (m, 1H), 7.3-7.36 (m, 1H), 7.62 (dd, 1H), 7.69 (dd, 1H), 8.2 (s, 1H), 8.29 (s, 1H), 8.45 (d, 1H), 8.66-8.73 (m, 1H), 11.4 (brs, 1H).

The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-ethyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-ethyl-benzamide and the corresponding aniline following the procedure of Example 7A

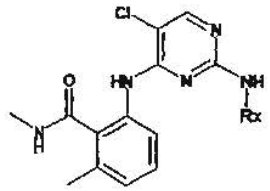


Expl No.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
9-1		0.35 (n-hexane: AcOEt=1:2)	$CDCl_3$: 1.27 (t, 3H), 3.10-3.15 (m, 4H), 3.47-3.58 (m, 2H), 3.85-3.93 (m, 4H), 3.89 (s, 3H), 6.08-6.17 (m, 1H), 6.48 (dd, 1H), 6.53 (d, 1H), 7.05-7.11 (m, 1H), 7.42-7.53 (m, 2H), 8.08 (s, 1H), 8.12 (d, 1H), 8.67 (d, 1H), 10.94 (brs, 1H).

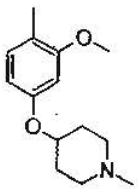
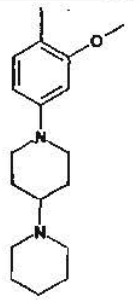
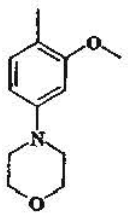
9-2		MS (ESI) *m/z* 497, 499 $(M+1)^+$	$CDCl_3$: 1.26 (t, 3H, J = 7.56Hz), 2.37 (s, 3H), 2.57-2.62 (m, 4H), 3.15-3.20 (m, 4H), 3.49 (dq, 2H, J = 7.56, 1.52 Hz), 3.87 (s, 3H), 6.11-6.16 (m, 1H), 6.49 (dd, 1H, J = 8.56, 2.52 Hz), 6.55 (d, 1H, J = 2.52 Hz), 7.05-7.10 (m, 1H), 7.23 (s, 1H), 7.41-7.50 (m, 2H), 8.07 (s, 1H), 8.08 (d, 1H, J = 8.56Hz), 8.65-8.69 (m, 1H), 10.93 (s, 1H)
9-3		*m/z* 564, 566 $(M+1)^+$	DMSO-d6: 1.26 (t, 3H, J = 7.56Hz), 1.40-1.50 (m, 2H), 1.56-1.64 (m, 4H), 1.67-1.82 (m, 2H), 1.88-1.97 (m, 2H), 2.33-2.44 (m, 1H), 2.52-2.57 (m, 4H), 2.63-2.73 (m, 2H), 3.51 (dq, 2H, J = 7.56, 1.52 Hz), 3.62-3.69 (m, 2H), 3.86 (s, 3H), 6.10-6.15 (m, 1H), 6.49 (dd, 1H, J = 8.56, 2.52 Hz), 6.55 (d, 1H, J = 2.52 Hz), 7.05-7.10 (m, 1H), 7.23 (s, 1H), 7.43-7.50 (m, 2H) 8.05-8.11 (m, 1H), 8.07 (s, 1H), 8.65-8.69 (m, 1H), 10.91 (s, 1H)
9-4		0.39 (MeOH: CH_2Cl_2=1:4)	DMSO-d6: 1.19 (t, 3H), 1.52-1.68 (m, 2H), 1.71-1.79 (m, 4H), 1.92-2.05 (m, 2H), 2.12-2.23 (m, 1H), 2.76-2.85 (m, 2H), 3.65-3.73 (m, 2H), 3.82 (s, 3H), 6.54 (dd, 1H), 6.69 (d, 1H), 7.13 (m, 1H), 7.45 (d, 1H), 7.79 (dd, 1H), 8.15 (s, 1H), 8.15-8.18 (m, 1H), 8.60-8.68 (m, 1H), 8.74-8.83 (m, 1H).
9-5		Rf (Hexane: AcOEt = 1:2): 0.30	CDCl3: 1.27 (t, 3H), 3.08-3.14 (m, 4H), 3.52 (q,2H), 3.71-3.90 (m, 7H), 6.05-6.18 (m, 1H), 6.47 (dd, 1H), 6.53 (dd, 1H), 7.08 (dd, 1H), 7.41-7.53 (m, 2H), 8.08 (s, 1H), 8.12 (d, 1H), 8.67 (d, 1H), 10.94 (s, 1H).

9-6		Rf (AcOEt:MeOH= 4:1) 0.050	DMSO: 1.11 (t, 3H), 1.60-1.69 (m, 1H), 1.88-1.96 (m, 2H), 2.19 (s, 3H), 2.55-2.68 (m, 2H), 3.30-3.45 (m, 2H), 3.75 (s, 3H), 4.33-4.43 (m, 1H), 6.54 (dd, 1H), 6.65 (d, 1H), 7.07 (dd, 1H), 7.30 (dd, 1H), 7.43 (d, 1H), 7.71 (dd, 1H), 8.11 (s, 1H), 8.20 (s, 1H), 8.54 (br.d, 1H), 8.75 (dd, 1H), 11.49 (s, 1H).
9-7		0.44 (CH2Cl2:MeOH=8:2)	CDCl3: 1.34 (t, 3H), 1.62-1.68 (m, 2H), 1.93-2.18 (m, 8H), 2.37-2.40 (br, 2H), 2.74-2.86 (br, 3H), 3.20-3.23 (m, 2H), 3.34 (br, 2H), 3.53 (q, 2H), 3.85 (s, 3H), 6.47 (dd, 1H), 6.76 (d, 1H), 7.04-7.08 (m, 1H), 7.30 (dd, 1H), 7.53 (s, 1H), 8.00 (d, 1H), 8.13-8.17 (m, 1H), 8.22 (d, 1H), 8.42-8.53 (br, 1H), 10.91 (s, 1H), 11.59-11.75 (br, 1H)

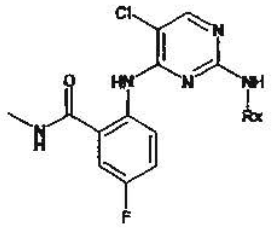
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-6,N-dimethyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-6,N-dimethyl-benzamide and the corresponding aniline following the procedure of Example 7A



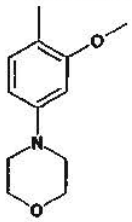
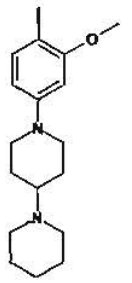
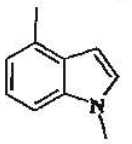
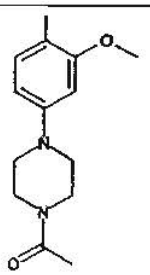
Expl No.	Rx	Identification

10-1		NMR (400MHz, DMSO-d6, δ): 1.58-1.68(m, 2H), 1.87-1.96(m, 2H), 2.13-2.22(m, 2H), 2.18(s, 3H), 2.18(s, 3H), 2.29(s, 3H), 2.57-2.65(m, 2H), 2.76(d, 3H), 3.75(s, 3H), 4.29-4.37(m, 1H), 6.45(dd, 1H), 6.61(d, 1H), 6.98(d, 1H), 7.18(dd, 1H), 7.47(d, 1H), 7.89(d, 1H), 8.02(s, 1H), 8.07 (s, 1H), 8.37-8.43(m, 1H), 8.49(s, 1H). Rf: 0.39 (MeOH: CH_2Cl_2=1:4).
10-2		NMR (400MHz, DMSO-d6, δ): 1.35-1.42 (m, 2H), 1.45-1.60 (m, 6H), 1.75-1.85 (m, 2H), 2.29 (s, 3H), 2.30-2.35 (m, 1H), 2.43-2.50 (m, 4H), 2.57-2.66 (m, 2H), 2.76 (d, 3H, J = 5.0Hz), 3.65-3.74 (m, 2H), 3.76 (s, 3H), 6.40 (dd, 1H, J = 9.0, 2.0 Hz), 6.59 (d, 1H, J = 2.0 Hz), 6.98 (d, 1H, J = 7.6 Hz), 7.20 (dd, 1H, J = 7.6, 7.6 Hz), 7.43 (d, 1H, J = 9.0 Hz), 7.91-7.94 (m, 1H), 7.93 (s, 1H), 8.06 (s, 1H), 8.36-8.42 (m, 1H) 8.47 (s, 1H). MS (ESI) *m/z* 564, 566 $(M+1)^+$
10-3		DMSO-d6: 2.29(s, 3H), 2.77(d, 3H), 3.07-3.11(m, 4H), 3.73-3.76(m, 4H), 3.77(s, 3H), 6.41(dd, 1H), 6.63(d, 1H), 7.00 (d, 1H), 7.21(dd, 1H), 7.49(d, 1H), 7.93(d, 1H), 7.96(s, 1H), 8.07(s, 1H), 8.37-8.42(m, 1H), 8.49(s, 1H). MS m/z 483 $[M+1]^+$

The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-5-fluoro-N-methyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-5-fluoro-N-methyl-benzamide and the corresponding aniline following the procedure of Example 7A



Expl No.	Rx	Identification

11-1		NMR (400MHz, DMSO-d6, δ): 2.79(d, 3H), 3.10-3.15(m, 4H), 3.74-3.78(m, 7H), 6.50(dd, 1H), 6.66(d, 1H), 7.13-7.20 (m, 1H), 7.41(d, 1H), 7.57(dd, 1H), 8.09(s, 1H), 8.14(s, 1H), 8.55-8.65(m, 1H), 8.75-8.82(m, 1H), 11.39(s, 1H). MS (ESI): m/z 487, 489 (M+1).
11-2		NMR (400MHz, DMSO-d6, δ): 1.68-1.33 (m, 8H), 1.93-1.73 (m, 2H), 2.35-2.60 (m, 1H), 2.62-2.74 (m, 2H), 2.67 (t, 2H), 2.74 (d, 3H), 3.25-3.38 (m, 4H), 3.76 (s, 3H), 3.83-3.71 (m, 2H), 6.48 (dd, 1H), 6.49 (dd, 1H), 6.63 (d, 1H), 7.15 (dd, 1H), 7.36 (d, 1H), 7.57 (dd, 1H), 8.09(s, 1H), 8.12(s, 1H), 8.65-8.55 (m, 1H), 8.78(d, 1H), 11.39 (s, 1H) MS (ESI): m/z 568, 570 (M+1)
11-3		DMSO-d6: 2.80(d, 3H), 3.79(s, 3H), 6.64(d,1H), 7.05-7.20(m, 3H), 7.23(d, 1H), 7.42-7.49(d, 1H), 7.57(dd, 1H), 8.20(s, 1H), 8.62-8.69(m, 1H), 8.75-8.82(m, 1H), 9.17(s, 1H), 11.43(s, 1H). MS m/z 425 $[M+1]^+$
11-4		DMSO-d6: 2.06(s, 3H), 2.79(d, 3H), 3.10-3.14(m, 2H), 3.15-3.19(m, 2H), 3.55-3.62(m, 4H), 3.77(s, 3H), 6.52(dd, 1H), 6.69(d, 1H), 7.15-7.23(m, 1H), 7.43(d, 1H), 7.58(dd, 1H), 8.10(s, 1H), 8.14(s, 1H), 8.56-8.65(m, 1H), 8.75-8.81(m, 1H), 11.39(s, 1H). MS m/z 528 $[M+1]^+$

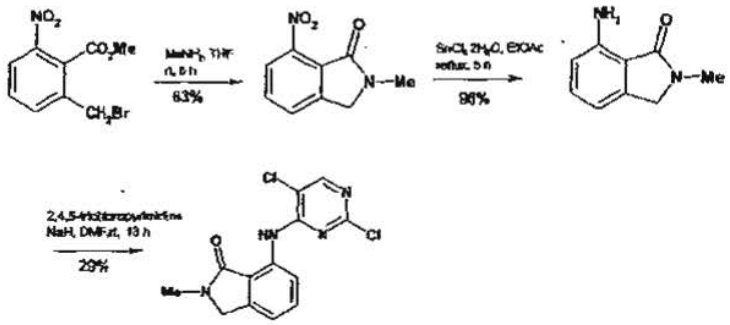
12-1 Preparation of 7-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one

Synthetic procedure for 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-one

N-Methyl-7-nirto-2,3-dihydroisoindole-1-one. At room temperature, a solution of methyl 2-bromomethyl-6-nitrobenzoate (1.26 g, 4.63 mmol) in THF (13 mL) is treated with 2M soln. of methylamine in THF (14 mL), stirred for 5 h, diluted with EtOAc (100 mL), washed with sat. aqueous solution of $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated. A flash chromatography (30 g of silica gel; CH_2Cl_2/EtOAc 1:1) gives N-Methyl-7-nirto-2,3-dihydroisoindole-1-one (0.561 g, 2.92 mmol) in 63%. Yellow solid. R_f (CH_2Cl_2/EtOAc 1:1) 0.46. ^{1}H-NMR (400 MHz, $CDCl_3$) 3.21 (*s*), 4.44 (*s*), 7.63 – 7.69 (*m*, 2 H), 7.70 – 7.75 (*m*, 1 H).

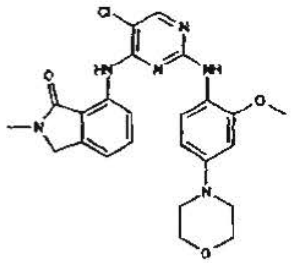
7-Amino-N-methyl-2,3-dihydroisoindole-1-one. At room temperature, a solution of N-Methyl-7-nirto-2,3-dihydroisoindole-1-one (561.0 mg, 2.92 mmol) in EtOAc (8.4 mL) is treated with $SnCl_2 \cdot 2H_2O$ (2.68 g), stirred at 80°C under reflux for 5 h, and treated with 30 mL of 5N NaOH at 0°C. After the both layers are separated, the aqueous layer is extracted with EtOAc (2 x 8 mL), the combined extracts are washed with brine (5 mL), dried ($MgSO_4$), and evaporated to give 7-Amino-N-methyl-2,3-dihydroisoindole-1-one (455.9 g, 2.81 mmol) in 96%. Yellow solid. R_f (CH_2Cl_2/EtOAc 1:1) 0.53. ^{1}H-NMR (400 MHz, $CDCl_3$) 3.12 (*s*), 4.28 (*s*), 5.20 (br. *s*), 6.56 (*d*, *J* = 8.0), 6.68 (*d*, *J* = 8.0), 7.21 (dd, *J* = 8.0, 8.0).

7-(4-Amino-2,5-dichloropyrimidin-4-yl)amino-N-methyl-2,3-dihydroisoindole-1-one. At 0°C, a solution of 7-Amino-N-methyl-2,3-dihydroisoindole-1-one (232.6 mg, 1.43 mmol) in DMF (2.0 mL) is treated with 60% NaH (89.8 mg), stirred at the same temperature for 1.5 h, treated with a solution of 2,4,5-trichloropyrimidine (0.557 g) in DMF (3.5 mL), stirred for 1 h, and warmed to room temperature. After furthermore stirring for 13 h, the mixture is treated with sat. aqueous NH_4Cl (6 mL), and the resulting brown precipitates are collected by a filtration, followed by washing with H_2O, hexane, and CH_3CN to give 7-(4-Amino-2,5-dichloropyrimidin-4-yl)amino-N-methyl-2,3-dihydroisoindole-1-one (130.2 g, 0.416 mmol) in 26%. Brown solid. R_f (CH_2Cl_2/EtOAc 1:1) 0.50. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.22 (*s*), 4.43 (*s*), 7.15 (*d*, *J* = 8.0), 7.59 (*dd*, *J* = 8.0, 8.0), 8.24 (*s*), 8.71 (*d*, *J* = 8.0), 11.05 (br. *s*).



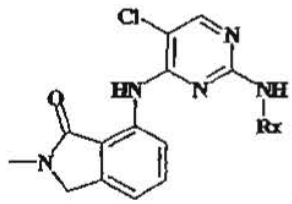
The following 7-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one are prepared from 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-one and the corresponding aniline following the procedure of Example 7A.

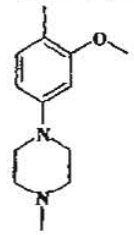
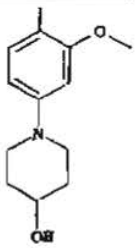
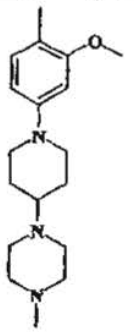
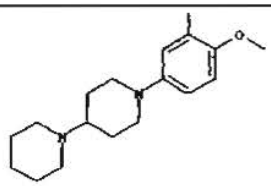
7-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one

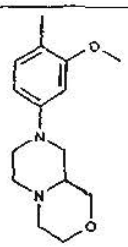


^{1}H-NMR (400MHz, DMSO-d6, δ): 3.07 (s, 3H), 3.13-3.17 (m, 4H), 3.75 (s, 3H), 3.34-3.78 (m, 4H), 4.46 (s, 2H), 6.54 (dd, 1H, J = 8.6, 2.5 Hz), 6.67 (d, 1H, J = 2.5 Hz), 7.15 (d, 1H, J = 7.6 Hz), 7.25-7.34 (m, 1H) 7.36 (d, 1H, J = 8.6 Hz), 8.13 (s, 1H), 8.36 (s, 1H), 8.37-8.50 (m, 1H) 10.57 (s, 1H). MS (ESI) *m/z* 481. 483 $(M+1)^+$

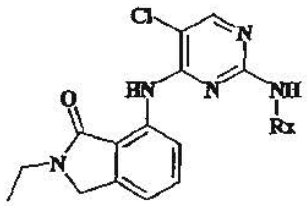
The following7-(5-Chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino)-2-methyl-2,3- dihydro-isoindol-1-ones are prepared from 7-(2,5-Dichloro-pyrimidin-4-ylamino)- 2-methyl-2,3-dihydro-isoindol-1-one and the corresponding aniline following the procedure of Example 2:

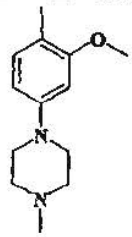


Expl No.	Rx	Mass(m/z)	NMR (400MHz) δ (ppm)
12-2		494 $[M+1]^+$	DMSO-d6: 2.24(s, 3H), 2.45-2.50(m,4H), 3.07(s, 3H), 3.15-3.19(m, 4H), 3.74(s, 3H), 4.46(s, 2H), 6.52(dd, 1H), 6.66(d, 1H), 7.15 (d, 1H), 7.25-7.36(m, 2H), 8.12(s, 1H), 8.35(s, 1H), 8.35-8.45(m, 1H), 10.57(s, 1H)
12-3		495 $[M+1]^+$	DMSO-d6: 1.48-1.57(m, 2H), 1.83-1.88(m, 2H), 2.83-2.90(m, 2H), 3.07(s, 3H), 3.51-3.60(m, 2H), 3.61-3.70(m, 2H), 3.73(s, 3H), 4.46(s, 2H), 4.69(d, 1H), 6.52(dd, 1H), 6.64(d, 1H), 7.14 (d, 1H), 7.25-7.35(m, 2H), 8.12(s, 1H), 8.33(s, 1H), 8.35-8.45(m, 1H), 10.57(s, 1H)
12-4		577 $[M+1]^+$	DMSO-d6: 1.48-1.59(m, 2H), 1.83-1.88(m, 2H), 2.14(s, 3H), 2.25-2.39(m, 4H), 2.42-2.60(m, 5H), 2.66-2.73(m, 2H),3.07(s, 3H), 3.73-3.77(m, 2H), 3.74(s, 3H), 4.46(s, 2H), 6.52(dd, 1H), 6.64(d, 1H), 7.14 (d, 1H), 7.25-7.34(m, 2H), 8.12(s, 1H), 8.34(s, 1H), 8.35-8.45(m, 1H), 10.57(s, 1H)
12-5		562 $[M+1]^+$	DMSO-d6: 1.35-1.65(m, 8H), 1.73-1.85(m, 2H), 2.40-2.59(m, 7H), 3.08(s, 3H), 3.52-3.61(m,2H), 3.73(s, 3H), 4.47(s, 2H), 6.72(dd, 1H), 6.94(d, 1H), 7.17(d, 1H), 7.34-7.39(m, 2H), 8.21(s, 1H), 8.37(s, 1H), 8.45-8.53(m, 1H), 10.64(s, 1H)

12-6		MS m/z 536	DMSO-d_6: 2.19-2.42 (m, 4H), 2.65-2.89 (m, 3H), 3.07 (s, 3H), 3.11-3.30 (m, 1H), 3.48-3.61 (m, 2H), 3.62-3.71 (m, 1H), 3.75 (s, 3H), 3.75-3.83 (m, 2H), 4.47 (s, 2H), 6.48-6.52 (m, 1H), 6.66 (d, 1H), 7.15 (d, 1H), 7.26-7.37 (m, 2H), 8.13 (s, 1H), 8.35 (s, 1H), 8.42 (brs, 1H), 10.57 (s, 1H).

The following 7-(5-Chloro-2-(subst.phenylamino) -pyrimidin-4-ylamino)-2-ethyl-2,3-dihydroisoindol-1-ones are prepared from 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2- ethyl-2,3-dihydro-isoindol-1-one and the corresponding aniline following the procedure of Example 2:



Expl No.	Rx	Mass(m/z)	NMR (400MHz) δ (ppm)
13-1		508 $[M+1]^+$	DMSO-d6: 1.19(t, 3H), 2.24(s, 3H), 2.47-2.51(m, 4H), 3.15-3.21(m, 4H), 3.54(q, 2H), 3.74(s, 3H), 4.48(s, 2H), 6.54(dd, 1H), 6.65(d, 1H), 7.16 (d, 1H), 7.26-7.36(m, 2H), 8.12(s, 1H), 8.34(s, 1H), 8.37-8.48(m, 1H), 10.58(s, 1H)

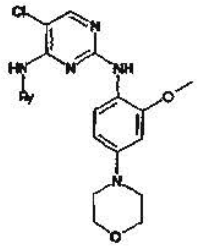
Example 7B: 2-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide (alternative synthesis to Example 7A)

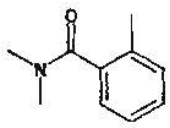
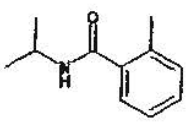
To a suspension of 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzoic acid (5.5 g, 12.1 mmol) in 100 mL of THF are added Et_3N (2.06 mL, 14.8 mmol) and isobutyl chloroformate (1.7 mL, 12.8 mmol) at -5°C. After stirring at the same temperature for 30 min, the reaction mixture is further stirred at room temperature for 1 hour and then H_2O is added to the reaction mixture. The resulting precipitate is collected by filtration,

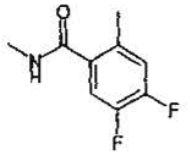
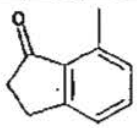
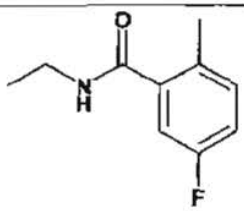
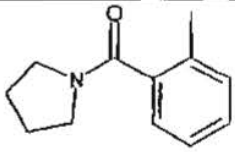
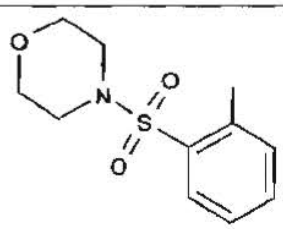
washed with H_2O, and dried under reduced pressure to give an intermediate (4.80 g) (10.96 mmol, 91%) as yellow solid.
NMR (400MHz, DMSO-d6, δ): 3.10-3.20 (m, 4H), 3.70-3.80 (m, 4H), 3.93 (s, 3H), 6.53 (dd, 1H, J = 9.08, 2.0 Hz), 6.70 (d, 1H, J = 2.0 Hz), 7.49-7.54 (m, 1H), 7.67 (d, 1H, J = 8.56 Hz), 7.89 (s, 1H), 7.85-7.95 (m, 1H), 8.23 (d, 1H, J = 9.08 Hz), 8.26 (d, 1H, J = 8.56Hz), 12.60 (s, 1H).

To a 1M solution of methylamine in THF (560 µl, 0.56 mmol) is added 82 mg of the obtained intermediate (0.187 mmol) followed by 1M solution of NaHMDS in THF (560 µl, 0.56 mmol) dropwise. After the reaction mixture is stirred for 10 minutes, 5 mL of H_2O is added and extraction is performed with AcOEt. The organic layer is washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (Hexane: AcOEt=1:1 to AcOEt) to give the title compound as a pale yellow solid. Data are given in Example 7A.

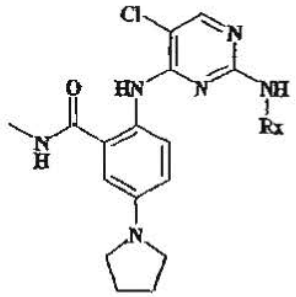
By repeating the procedures described above using appropriate starting materials and conditions the following compounds are obtained as identified below.

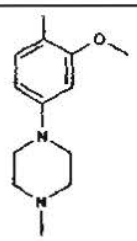
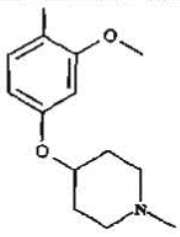


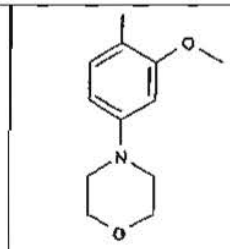
Expl No.	Ry	Rf (solvent) or MS	NMR (400MHz), δ (ppm)
14-1		0.10 (n-hexane: AcOEt=1:1)	$CDCl_3$: 3.02-3.19 (m, 10H), 3.83-3.91 (m, 4H), 3.87 (s, 3H), 6.45 (dd, 1H), 6.52 (d, 1H), 7.09-7.14 (m, 1H), 7.29 (m, 1H), 7.31 (dd, 1H), 7.38-7.45 (m, 1H), 8.06 (s, 1H), 8.14 (d, 1H), 8.39 (d, 1H), 8.97 (s, 1H).
14-2		0.36 (n-hexane: AcOEt=1:2)	$CDCl_3$: 1.27 (d, 6H), 3.09-3.16 (m, 4H), 3.81-3.92 (m, 4H), 3.89 (s, 3H), 4.26-4.37 (m, 1H), 5.93-5.98 (m, 1H), 6.48 (dd, 1H), 6.53 (d, 1H), 7.05-7.11 (m, 1H), 7.42-7.49 (m, 2H), 8.08 (s, 1H), 8.12 (d, 1H), 8.65 (d,

			1H), 10.88 (br.s, 1H).
14-3		505 [M+1]+	DMSO-d6: 2.79(d, 3H), 3.09-3.14(m, 4H), 3.74-3.77(m, 4H), 3.75(s, 3H), 6.49(dd, 1H), 6.65(d, 1H), 7.30 (d, 1H), 7.84(dd, 1H), 8.12(s, 1H), 8.40(s, 1H), 8.65-8.79(m, 2H), 11.39(s, 1H)
14-4		466 [M+1]+	DMSO-d6: 2.70-2.75(m, 2H), 3.04-3.09(m, 2H), 3.12-3.18(m, 4H), 3.74-3.80(m, 4H), 3.75(s, 3H), 6.54(dd, 1H), 6.67(d, 1H), 7.14 (d, 1H), 7.34(d, 1H), 7.37-7.44(m, 1H), 8.17(s, 1H), 8.35-8.50(m, 1H), 8.44(s, 1H), 10.59(s, 1H)
14-5		Rf (Hexane : AcOEt=1:2) : 0.31	DMSO: 1.18 (t, 3H), 3.11-3.21 (4, 4H), 3.30-3.60 (m, 2H), 3.71-3.85 (m, 7H), 6.50-6.58 (m, 1H), 6.71 (d, 1H), 7.17-7.26 (m, 1H), 7.46 (d, 1H), 7.64 (dd, 1H), 8.14 (s, 1H), 8.19 (s, 1H), 8.57-8.68 (m, 1H), 8.80-8.87 (m, 1H), 11.36 (s, 1H).
14-6		Rf (Hexane : AcOEt=1:1) : 0.051	DMSO: 1.71-1.92 (m, 2H), 1.92-2.06 (m, 2H), 3.08-3.14 (m, 4H), 3.48-3.57 (m, 2H), 3.63-3.75 (m, 2H), 3.84-3.90 (m, 7H), 6.47 (dd, 1H), 6.53 (d, 1H), 7.09 (ddd, 1H), 7.25-7.29 (m, 1H), 7.38-7.44 (m, 1H), 8.06 (s, 1H), 8.15 (d, 1H), 8.45 (dd, 1H), 9.60 (s, 1H).
14-7			^{1}H-NMR (400MHz, δ ppm, $CDCl_3$): 3.04-3.10 (m, 4H), 3.10-3.16 (m, 4H), 3.63-3.68 (m, 4H), 3.85-3.90 (m, 7H), 6.46 (dd, 1H), 6.53 (d, 1H), 7.20-7.25 (m, 1H), 7.33 (brs, 1H), 7.56-7.62 (m, 1H), 7.85 (dd, 1H), 8.03 (d, 1H), 8.12 (s, 1H), 8.57-8.61 (m, 1H), 9.30 (s, 1H).

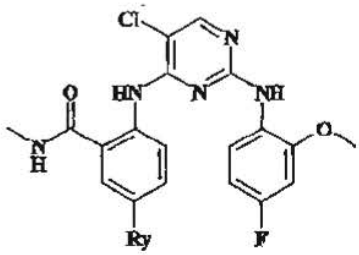
The following 2-(5-Chloro-2-(subst. phenylamino)-pyrimidin-4-ylamino)-N-methyl-5- pyrrolidin-1-yl-benzamides are prepared from 2-(5-Chloro-2-methyl-pyrimidin-4- ylamino)-N-methyl-5-pyrrolidin-1-yl-benzamide and the corresponding aniline following the procedure of Example 2:

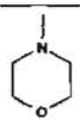


Expl No.	Rx	Mass(m/z)	NMR (400MHz) δ (ppm)
15-1		551 $[M+1]^+$	DMSO-d6: 1.94-1.99(m, 4H), 2.23(s, 3H), 2.43-2.48(m, 4H), 2.78(d, 3H), 3.11-3.17(m, 4H), 3.22-3.29(m, 4H), 3.76(s, 3H), 6.46(dd, 1H), 6.48-6.53(m, 1H), 6.63(d, 1H), 6.79(d, 1H), 7.44(d, 1H), 7.89(s, 1H), 7.99(s, 1H), 8.24(d, 1H), 8.60(d, 1H), 10.88(s, 1H)
15-2		566 $[M+1]^+$	DMSO-d6: 1.60-1.70(m, 2H), 1.90-2.00(m, 6H), 2.12-2.20(m, 2H), 2.18(s, 3H), 2.60-2.65(m, 2H), 2.78(d, 3H), 3.22-3.28(m, 4H), 3.75(s, 3H), 4.25-4.37(m, 1H), 6.49-6.55(m, 2H), 6.62(d, 1H), 6.80(d, 1H), 7.53(d, 1H), 7.90(s, 1H), 8.00(s, 1H), 8.24(d, 1H), 8.58-8.63(m, 1H), 10.88(s, 1H)

15-3		538 $[M+1]^+$	DMSO-d6: 1.94-1.99(m, 4H), 2.78(d, 3H), 3.09-3.15(m, 4H), 3.22-3.27(m, 4H), 3.73-3.77(m, 4H), 3.76(s, 3H), 6.47(dd, 1H), 6.47-6.53(m, 1H), 6.65(d, 1H), 6.79(d, 1H), 7.47(d, 1H), 7.90(s, 1H), 7.99(s, 1H), 8.24(d, 1H), 8.60(d, 1H), 10.88(s, 1H)

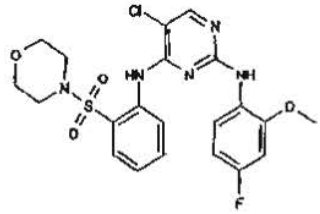
The following 2-[5-Chloro-2-(4-fluoro-2-methoxy-phenylamino)-pyrimidin-4- ylamino]-5-subst.-N-methyl-benzamide are prepared from the corresponding aniline following the procedure of Example 2:



Expl No.	Ry	Mass(m/z)	NMR (400MHz) δ (ppm)
16-1		487 $[M+1]^+$	DMSO-d6: 2.79(d, 3H), 3.11-3.15(m, 4H), 3.74-3.81(m, 4H), 3.81(s, 3H), 6.76(ddd, 1H), 6.95-7.05(m, 2H), 7.21(d, 1H), 7.72(dd, 1H), 8.08(s, 1H), 8.09(s, 1H), 8.33(d, 1H), 8.63-8.73(m, 1H), 11.17(s, 1H)
16-2		500 $[M+1]^+$	DMSO-d6: 2.24(s, 3H), 2.45-2.52(m, 4H),2.79(d, 3H), 3.13-3.18(m, 4H), 3.81(s, 3H), 6.75(ddd, 1H), 6.94-7.02(m, 2H), 7.20(d, 1H), 7.73(dd, 1H), 8.03-8.11(m, 2H), 8.30(d, 1H), 8.60-8.70(m, 1H), 11.14(s, 1H)
16-3		432 $[M+1]^+$	DMSO-d6: 2.79(d, 3H), 3.80-3.81(m, 6H), 6.75(ddd, 1H), 6.90-7.02(m, 2H), 7.27(d, 1H), 7.67(dd, 1H), 8.10(s, 1H), 8.16(s, 1H), 8.39(d, 1H), 8.70-8.76(m, 1H), 11.20(s, 1H)

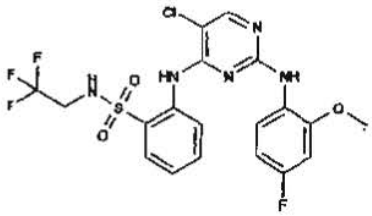
16-4		568 $[M+1]^+$	DMSO-d6: 1.35-1.62(m, 8H), 1.78-1.85(m, 2H), 2.30-2.40(m, 1H), 2.41-2.52(m, 4H), 2.60-2.70(m, 2H), 2.78(d, 3H), 3.70-3.80(m, 2H), 3.81(s, 3H), 6.75(ddd, 1H), 6.95-7.02(m, 2H), 7.20(d, 1H), 7.72(dd, 1H), 8.05-8.08(m, 2H), 8.28(d, 1H), 8.63-8.69(m, 1H), 11.12(s, 1H)

Example 16B



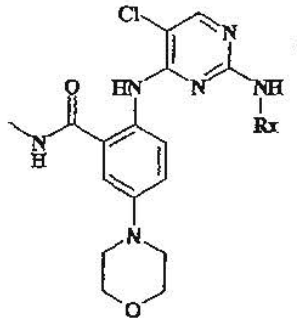
$CDCl_3$: 3.01-3.10 (m, 4H), 3.63-3.68 (m, 4H), 3.89 (s, 3H), 6.59 (ddd, 1H), 6.66 (dd, 1H), 7.20-7.26 (m, 1H), 7.36 (s, 1H), 7.57-7.63 (m, 1H), 7.84 (dd, 1H), 8.09-8.14 (m, 1H), 8.14 (s, 1H), 8.53 (d, 1H), 9.30 (s, 1H).

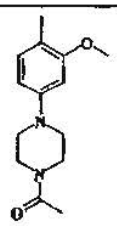
Example 16C



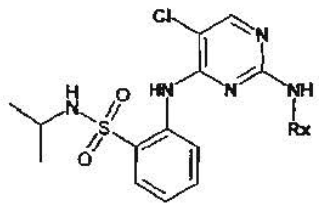
$CDCl_3$: 3.56-3.65 (m, 2H), 3.88 (s, 3H), 5.11-5.19 (m, 1H), 6.50-6.56 (m, 1H), 6.61-6.66 (m, 1H), 7.25-7.29 (m, 1H), 7.38 (brs, 1H), 7.58-7.62 (m, 1H), 7.97 (dd, 1H), 8.02-8.10 (m, 1H), 8.15 (s, 1H), 8.41 (dd, 1H), 8.81 (s, 1H).

The following 2-(5-Chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino)-5-fluoro-N-methyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-5-fluoro-N-methyl-benzamideand the corresponding aniline following the procedure of Example 2:

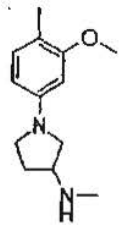
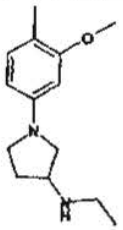
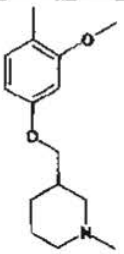
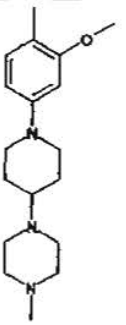
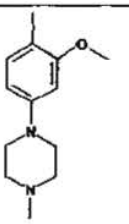


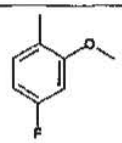
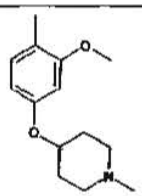
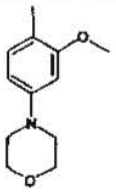
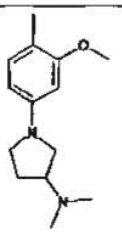
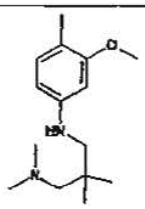
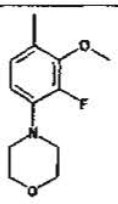
Expl No.	Rx	Mass(m/z)	NMR (400MHz) δ (ppm)
18-1		595 $[M+1]^+$	DMSO-d6: 2.06 (s, 3H), 2.78 (d, 3H), 3.05-3.18 (m, 8H), 3.53-3.64 (m, 4H), 3.68-3.77 (m, 4H), 3.77 (s, 3H), 6.51 (dd, 1H), 6.69 (d, 1H), 6.88 (br.d, 1H), 7.20 (d, 1H), 7.43 (d, 1H), 7.99-8.03 (m, 2H), 8.34 (br.d, 1H), 8.63-8.71 (m, 1H), 11.15 (s, 1H).

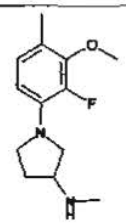
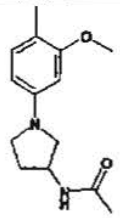
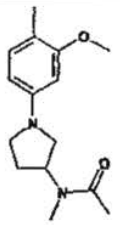
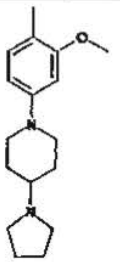
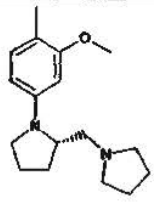
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-isopropyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-isopropyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A

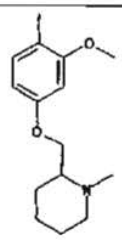
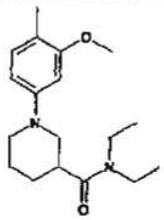
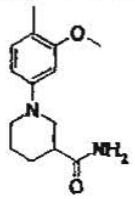
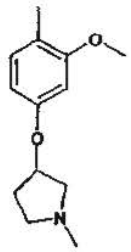
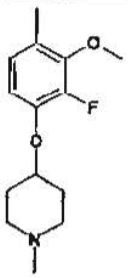


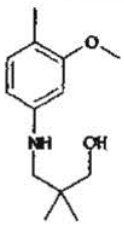
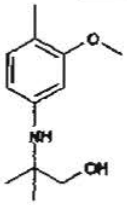
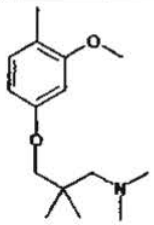
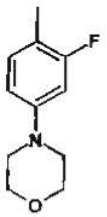
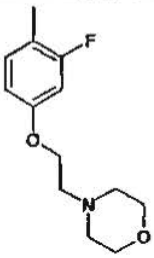
ExplNo.	Rx	Rf (solvent) Or MS	NMR (400MHz), δ (ppm)

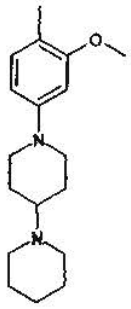
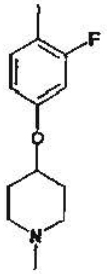
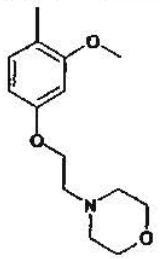
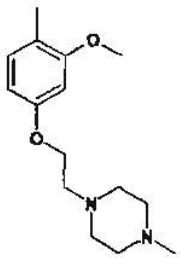
19-1		0.39 (MeOH: CH_2Cl_2=1:4)	DMSO-d6: 0.94(d, 6H), 1.75-1.84(m, 1H), 2.07-2.16(m, 1H), 2.33(s, 3H), 2.98-3.04(m, 1H), 3.22-3.36(m, 5H), 3.42-3.47(m, 1H), 3.74(s, 3H), 6.05(dd, 1H), 6.18(d, 1H), 7.18(dd, 1H), 7.25(d, 1H), 7.35-7.45(m, 1H), 7.77-7.82(m, 1H), 7.70-8.10(m, 1H), 8.09-8.17 (m, 2H), 8.45-8.63(m, 1H), 9.34(s, 1H)
19-2		0.40 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 1.00(d, 6H), 1.13(t, 3H), 1.83-1.92(m, 1H), 2.23-2.30(m,1H), 2.70-2.78(m, 2H), 3.08-3.13(m, 1H), 3.27-3.54 (m, 5H), 3.85(s, 3H), 4.33(d, 1H), 6.05(d, 1H), 6.13(s, 1H), 7.13(bs, 1H), 7.18-7.22(m, 1H), 7.52-7.56(m, 1H), 7.83-7.86(m, 1H), 7.95-7.98(m, 1H), 8.09(s, 1H), 8.47-8.49(m, 1H), 8.89(s, 1H)
19-3		0.30 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 0.93 (d, 6H), 1.05-1.09(m, 1H), 1.48-1.99(m, 6H), 2.16(s,3H), 2.61-2.67(m, 1H), 2.80-2.83(m, 1H), 3.75(s, 3H), 3.80-3.89(m, 2H), 6.44-6.47(m, 1H), 6.62-6.63(m, 1H), 7.18-7.22(m, 1H), 7.42-7.46(m, 1H), 7.80-7.89(m, 2H), 8.17(s, 1H), 8.23(s, 1H), 8.42-8.44(m, 1H), 8.89(s, 1H)
19-4		0.69 (MeOH: CH_2Cl_2=1:3)	DMSO-d6 : 0.94(d, 6H), 1.45-1.57(m, 2H), 1.80-1.88(m, 2H), 2.14(s, 3H), 2.25-2.35(m, 4H), 2.45-2.55(m, 4H), 2.62-2.70(m, 2H), 3.28-3.37(m, 1H), 3.68-3.74(m, 2H), 3.75(s, 3H), 6.44(dd, 1H, J=8.82, 2.0Hz), 6.61(d, 1H, J=2.0Hz), 7.21(dd, 1H), 7.37(d, 1H), 7.45(dd, 1H), 7.81(dd, 1H, J=1.82, 1.52Hz), 7.84-7.92(m, 1H), 8.12-8.20(m, 1H), 8.16(s, 1H), 8.43 - 8.51(m, 1H), 9.31(s, 1H)
19-5		0.35 (n-hexane: AcOEt=1:1)	$CDCl_3$: 0.93(d, 6H), 2.23(s, 3H), 2.45-2.48(m, 4H), 3.12-3.15(m,4H), 3.75(s, 3H), 6.42-6.45(m, 1H), 6.63 (s, 1H), 7.19-7.23(m, 1H), 7.38-7.47(m, 2H), 7.80-7.89(m, 2H), 8.16(s, 1H), 8.46-8.48(m, 1H), 9.34(s, 1H)

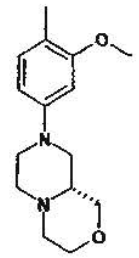
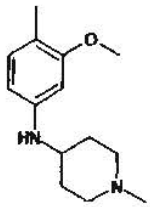
19-6		0.45 (n-hexane: AcOEt=1:1)	$CDCl_3$: 0.99(d, 6H), 3.40-3.49(m, 1H), 3.88(s, 3H), 4.29-4.31(d, 1H), 6.51-6.56(m, 1H), 6.62-6.65 (m, 1H), 7.24-7.28(m, 1H), 7.37(s, 1H), 7.56-7.60(m, 1H), 7.98-8.15(m, 3H), 8.34-8.37(m, 1H), 8.89(s, 1H)
19-7		0.28 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.93(d, 6H), 1.59-1.67(m, 2H), 1.90-1.93(m, 2H), 2.10-2.24(m, 5H), 2.60-2.67(m, 2H), 3.74(s, 3H), 4.33-4.37(m, 1H), 6.47-6.50(m, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.41-7.45(m, 2H), 7.79-7.87(m, 2H), 8.16(s, 1H), 8.21(s, 1H), 8.41 - 8.43(m, 1H), 9.29(s, 1H)
19-8		0.25 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.93(d, 6H), 3.09-3.12(m, 4H), 3.74-3.76(m, 7H), 6.43-6.46(m, 1H), 6.64(s, 1H), 7.19-7.23(m, 1H), 7.41-7.48(m, 2H), 7.80(d, 1H), 7.82(d, 1H), 8.17(s, 1H), 8.46-8.48(m, 1H), 9.31(s, 1H)
19-9		0.56 (MeOH: CH_2Cl_2=1:4)	DMSO-d6 : 0.93(d, 6H), 1.89-1.90(m, 1H), 2.30(bs, 6H), 3.13-3.50(m, 6H), 3.74(s, 3H), 6.10(d, 1H), 6.22(s, 1H), 7.16-7.20(m, 1H), 7.25-7.27(m, 1H), 7.40(bs, 1H), 7.79-7.81(m, 1H), 7.86-7.88(m, 1H), 8.12(s, 1H), 8.15(s, 1H), 8.51(s, 1H), 9.34(s, 1H)
19-10		0.45 (MeOH: CH_2Cl_2=1:4)	$CDCl_3$: 0.99(d, 12H), 2.27(s, 2H), 2.31(s, 6H), 2.96(s, 2H), 3.39-3.48(m, 1H), 3.83(s, 3H), 4.30(d, 1H), 6.09-6.12(m, 1H), 6.19(d, 1H), 7.11(s, 1H), 7.19-7.23(m, 1H), 7.51-7.57(m, 1H), 7.76-7.79(m, 1H), 7.95(d, 1H), 8.09(s, 1H), 8.46-8.49(m, 1H), 8.88(s, 1H)
19-11		0.30 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.93(d, 6H), 2.96-2.99(m, 4H), 3.74-3.76(m, 7H), 6.67-6.72(m, 1H), 7.21-7.25(m, 1H), 7.31-7.34(m, 1H), 7.44-7.48(m, 1H), 7.80-7.83(m, 1H), 7.88(d, 1H), 8.21(s, 1H), 8.42(d, 1H), 8.58(s, 1H), 9.30 (s, 1H)

19-12		0.42 (MeOH: CH_2Cl_2=1:4)	DMSO-d6: 0.94(d, 6H), 1.68-1.76(m, 1H), 1.99-2.07(m, 1H), 2.29(s, 3H), 3.05-3.49(m, 6H), 3.75(s, 3H), 6.36-6.40(m, 1H), 7.10-7.37(m, 3H), 7.70-7.80(m, 1H), 8.08-8.39(m, 3H), 9.24(s, 1H)
19-13		0.50 (MeOH: CH_2Cl_2=1:4)	$CDCl_3$: 1.01(d, 6H), 1.94-1.96(m, 1H), 2.01(s, 3H), 2.29-2.37(m, 1H), 3.19-3.58(m, 5H), 3.86(s, 3H), 4.42(d, 1H), 4.59-4.63(m, 1H), 5.70(d, 1H), 6.05-6.08(m, 1H), 6.15-6.16(m, 1H), 7.17-7.24(m, 2H), 7.53-7.57(m, 1H), 7.90(d, 1H), 7.91-7.98(m, 1H), 8.09(s, 1H), 8.47(d, 1H), 8.91(s, 1H)
19-14		0.53 (MeOH: CH_2Cl_2=1:4)	$CDCl_3$: 1.00(d, 6H), 2.04(s, 3H), 2.05-2.29(m, 2H), 2.96(s, 3H), 3.19-3.54(m, 5H), 3.86(s, 3H), 4.57-4.63(m, 1H), 5.39-5.46(m, 1H), 6.07-6.09(m, 1H), 6.16(d, 1H), 7.18-7.26(m, 2H), 7.53-7.57(m, 1H), 7.89-7.98(m, 2H), 8.08(s, 1H), 8.47(d, 1H), 8.94(d, 1H)
19-15		0.56 (MeOH: CH_2Cl_2=1:4)	DMSO-d6 : 0.93(d, 6H), 1.48-1.56(m, 2H), 1.65-1.75(m, 4H), 1.90-1.93(m, 2H), 2.05-2.15(m, 1H), 2.45-2.55(m, 5H), 2.69-2.75(m, 2H), 3.61(d, 2H), 3.74(s, 1H), 6.42-6.51(m, 1H), 6.61(d, 1H), 7.18-7.22(m, 1H), 7.37(d, 1H), 7.43-7.47(m, 1H), 7.80(d, 1H), 7.81-7.89(m, 1H), 8.16(d, 1H), 8.46-8.48(m, 1H), 9.31(s, 1H)
19-16		0.56 (MeOH: CH_2Cl_2=1:4)	DMSO-d6 : 0.92(d, 6H), 1.65-1.75(m, 4H), 1.88-2.00(m, 4H), 2.39-2.43(m, 2H), 2.60-2.65(m, 2H), 3.03-3.07(m, 1H), 3.03-3.40(m, 2H), 3.70(s, 3H), 3.77-3.78(m, 1H), 6.09(d, 1H), 6.23(s, 1H), 7.13-7.17(m, 1H), 7.23-7.25(m, 1H), 7.30-7.42(m, 1H), 7.78(d, 1H), 7.86(d, 1H), 8.10(s, 1H), 8.13(s, 1H), 8.40-8.50(m, 1H), 9.31(s, 1H)

19-17		0.23 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.93(d, 6H), 1.24-1.57(m, 4H), 1.69-1.78(m, 2H), 1.98-2.04(m, 1H), 2.15-2.33(m, 5H), 2.70-2.80(m, 1H), 3.74(s, 3H), 3.91-3.94(m, 1H), 4.05-4.09(m, 1H), 6.46-6.49(m, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.42-7.46(m, 2H), 7.80(d, 1H), 7.89(d, 1H), 8.17(s, 1H), 8.25(s, 1H), 8.42 -8.44(m, 1H), 9.31(s, 1H)
19-18		0.48 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.93(d, 6H), 1.03(t, 3H), 1.13(t, 3H), 1.42-1.81(m, 4H), 2.57-2.83(m, 4H), 3.17-3.41(m, 4H), 3.65-3.75(m, 1H), 3.80(s, 3H), 4.21(bs, 1H), 6.42-6.47(m, 2H), 6.51(d, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.38-7.47(m, 2H), 7.80-7.82(m, 1H), 7.89(d, 1H), 8.16(s, 1H), 8.47 -8.49(m, 1H), 9.31(s, 1H)
19-19		0.44 (CH2Cl2:MeOH=9:1)	CDCl3: 1.45-1.62 (m, 2H), 1.72-1.78 (m, 1H), 1.82-1.90 (m, 1H), 2.40-2.46 (m, 1H), 2.61-2.75 (m, 2H), 3.75-3.70 (m, 2H), 3.76 (s, 3H), 6.45 (dd, 1H), 6.62 (d, 1H), 6.85 (s, 1H), 7.19-7.23 (m, 1H), 7.36-7.48 (m, 3H), 7.80-7.82 (m, 1H), 7.85-7.93 (br, 1H), 8.16 (s, 2H), 8.43-8.52 (m, 1H), 9.31 (s, 1H)
19-20		Ms : 547	DMSO-d6 : 0.94 (d, 6H), 1.73-1.82 (m, 1H), 2.23-2.33 (m, 4H), 2.34-2.41 (m, 1H), 2.54-2.62 (m, 1H), 2.62-2.69 (m, 1H), 2.77-2.82 (m, 1H), 3.25-3.35 (m, 1H), 3.74 (s, 3H), 4.85-4.92 (m, 1H), 6.4 (dd, 1H), 6.57 (d, 1H), 7.16-7.24 (m, 1H), 7.38-7.51 (m, 1H), 7.81 (d, 1H), 7.82-7.94 (m, 1H), 8.16 (s, 1H), 8.22 (brs, 1H), 8.38-8.48 (m, 1H), 9.3 (brs, 1H)
19-21		Ms : 579	DMSO-d6 : 0.92 (d, 6H), 1.61-1.71 (m, 2H), 1.86-1.96 (m, 2H), 2.12-2.22 (m, 5H), 2.57-2.64 (m, 2H), 3.2-3.4 (m, 1H), 3.77 (s, 3H), 4.27-4.35(m, 1H), 6.86 (dd, 1H), 7.19-7.27 (m, 1H), 7.39-7.46 (m, 1H), 7.81 (dd, 1H), 7.84-7.92 (m, 1H), 8.21 (s, 1H), 8.36-8.42 (m, 1H), 8.62 (s, 1H), 9.28 (s, 1H)

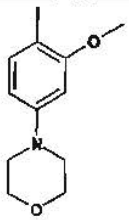
19-22		Ms : 549	DMSO-d6 : 0.90 (s, 6H), 0.94 (d, 6H), 2.9 (d, 2H), 3.24 (d, 2H), 3.25-3.35(m, 1H), 3.27-3.36 (m, 1H), 3.68 (s, 3H), 4.58 (t, 1H), 5.3 (t, 1H), 6.16 (dd, 1H), 6.39 (d, 1H), 7.13 (d, 1H), 7.15-7.21 (m, 1H), 7.35-7.45 (m, 1H), 7.8 (dd, 1H), 7.83-7.92 (m, 1H), 8.09 (s, 1H), 8.11 (s, 1H), 8.45-8.57 (m, 1H), 9.33 (s, 1H)
19-23		Rf : 0.51 (n-hexane : AcOEt=1:1)	DMSO-d6 : 0.94 (d, 6H), 1.22 (s, 6H), 3.25-3.35 (m, 1H), 3.36 (d, 2H), 3.68 (s, 3H), 4.73-4.79 (brs, 1H), 4.81 (t, 1H), 6.29 (dd, 1H), 6.44 (d, 1H), 7.14-7.22 (m, 2H), 7.38-7.46 (m, 1H), 7.8 (dd, 1H), 7.85-7.9 (m, 1H), 8.1 (s, 1H), 8.13 (s, 1H), 8.45-8.55 (m, 1H), 9.32 (s, 1H)
19-24		Ms : 577	DMSO-d6 : 0.93 (d, 6H), 0.96 (s, 6H), 2.22 (s, 6H), 3.25-3.35 (m, 1H), 3.7 (s, 3H), 3.75 (s, 3H), 6.46 (dd, 1H), 6.62 (d, 1H), 7.16-7.23 (m, 1H), 7.38-7.47 (m, 1H), 7.81 (dd, 1H), 7.85-7.9 (m, 1H), 8.17 (s, 1H), 8.23 (s, 1H), 8.38-8.48 (m, 1H), 9.31 (s, 1H)
19-25		Ms : 521	DMSO-d6 : 0.94 (d, 6H), 3.12 (t, 4H), 3.25-3.35 (m, 1H), 3.75 (t, 4H), 6.73 (dd, 1H), 6.85 (dd, 1H), 7.16-7.24 (m, 1H), 7.25-7.32 (m, 1H), 7.38-7.47 (m, 1H), 7.8 (dd, 1H), 7.88 (d, 1H), 8.18 (s, 1H), 8.42-8.52 (m, 1H), 8.86 (s, 1H), 9.36 (s, 1H)
19-26		Ms : 565	DMSO-d6 : 0.93 (d, 6H), 2.4-2.56 (m, 4H), 2.69 (t, 2H), 3.25-3.38 (m, 1H), 3.59 (t, 4H), 4.11 (t, 1H), 6.75 (dd, 1H), 6.93 (dd, 1H), 7.16-7.23 (m, 1H), 7.3-7.4 (m, 1H), 7.4-7.38 (m, 1H), 7.8 (dd, 1H), 7.88 (d, 1H), 8.19 (s, 1H), 8.36-8.5 (m, 1H), 8.92 (s, 1H), 9.34 (s, 1H)

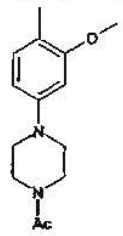
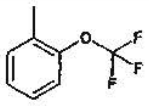
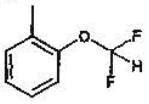
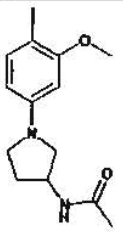
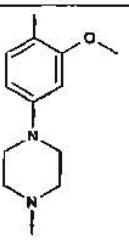
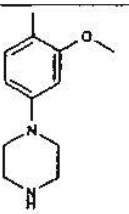
19-27		Ms : 614	DMSO-d6 : 0.93 (d, 6H), 1.3-1.62 (m, 8H), 1.75-1.85 (m, sH), 2.26-2.4 (m, 1H), 2.4-2.58 (m, 4H), 3.28-3.38 (m, 1H), 3.68-3.78 (m, 5H), 6.42 (dd, 1H), 6.64 (d, 1H), 7.18-7.24 (m, 1H), 7.42-7.5 (m, 2H), 7.77 (d, 1H), 7.82 (dd, 1H), 8.13 (s, 1H), 8.17 (s, 1H), 8.4-8.5 (m, 1H), 9.36 (s, 1H)
19-28		Rf : 0.5 (MeOH: CH2Cl2=3: 7)	DMSO-d6 : 0.93 (d, 6H), 1.6-1.7 (m, 2H), 1.88-1.98 (m, 2H), 2.17-2.35 (m, 5H), 2.6-2.73 (m, 2H), 3.25-3.4 (m, 1H), 4.34-4.44 (m, 1H), 6.75 (dd, 1H), 6.93 (dd, 1H), 7.16-7.23 (m, 1H), 7.29-7.36 (m, 1H), 7.37-7.47 (m, 1H), 7.8 (dd, 1H), 7.89 (d, 1H), 8.19 (s, 1H), 8.36-8.46 (m, 1H), 8.92 (s, 1H), 9.31 (s, 1H)
19-29		Ms : 577	DMSO-d6 : 0.93 (d, 6H), 2.45-2.55 (m, 4H), 2.7 (t, 2H), 3.25-3.35 (m, 1H), 3.59 (t, 3H), 3.76 (s, 3H), 4.1 (t, 1H), 6.48 (dd, 1H), 6.65 (d, 1H), 7.18-7.24 (m, 1H), 7.4-7.5 (m, 2H), 7.82 (dd, 1H), 7.88 (d, 1H), 8.17 (s, 1H), 8.24 (s, 1H), 8.4-8.48 (m, 1H), 9.31 (s, 1H)
19-30		Ms : 590	DMSO-d6 : 0.93 (d, 6H), 2.15 (s, 3H), 2.2-2.4 (m, 4H), 2.4-2.6 (m, 4H), 2.69 (t, 2H), 3.25-3.35 (m, 1H), 3.75 (s, 3H), 4.08 (t, 2H), 6.47 (dd, 1H), 6.64 (d, 1H), 7.18-7.24 (m, 1H), 7.41-7.49 (m, 2H), 7.81 (dd, 1H), 7.86-7.91 (m, 1H), 8.17 (s, 1H), 8.24 (s, 1H), 8.39-8.46 (m, 1H), 9.31 (s, 1H)

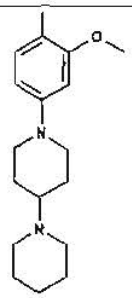
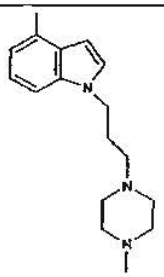
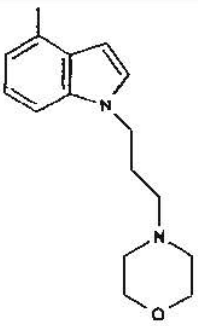
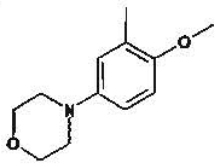
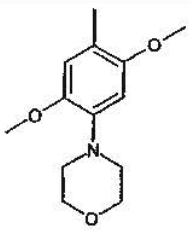
19-31		Ms : 588	DMSO-d6 : 0.94 (d, 6H), 2.19-2.36 (m, 4H), 2.66-2.85 (m, 3H), 3.15-3.21 (m, 1H), 3.73-3.8 (m, 5H), 6.43 (dd, 1H), 6.63 (d, 1H), 7.18-7.25 (m, 1H), 7.4 (d, 1H), 7.43-7.5 (m, 1H), 7.81 (dd, 1H), 7.89 (d, 1H), 8.16 (s, 1H), 8.17 (s, 1H), 8.42-8.52 (m, 1H), 9.32 (s, 1H)
19-32		Ms : 560	CDCl3 : 1.01(s, 6H), 1.45-1.56 (m, 2H), 2.03-2.11 (m, 2H), 2.11-2.2 (m, 2H), 2.31 (s, 3H), 2.78-2.87 (m, 2H), 3.22-3.31 (m, 1H), 3.39-3.5 (m, 1H), 3.82 (s, 3H), 4.5-4.6 (m, 1H), 6.13 (dd, 1H), 6.21 (d, 1H), 7.16 (s, 1H), 7.18-7.24 (m, 1H), 7.5-7.57 (m, 1H), 7.82 (d, 1H), 7.97 (dd, 1H), 8.16 (s, 1H), 8.08 (s, 1H), 8.46 (d, 1H), 8.92 (s, 1H)

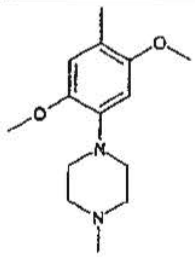
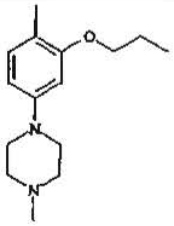
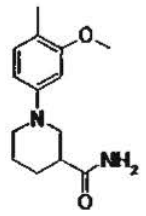
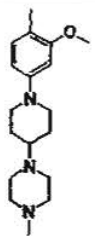
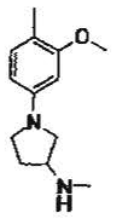
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline following the procedure of Example A

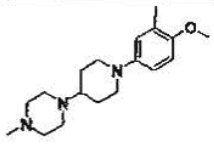
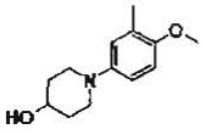
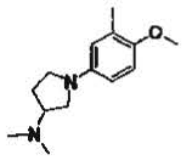
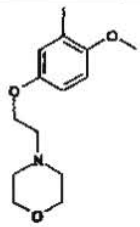
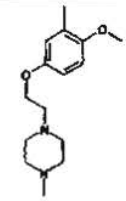


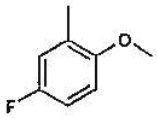
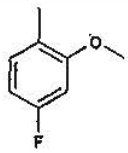
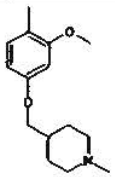
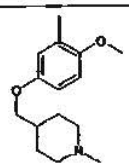
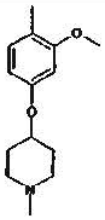
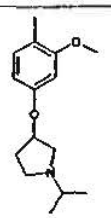
ExplNo.	Rx	Rf (solvent) or MS	NMR (400MHz), δ (ppm)
20-1		0.50 (AcOEt)	$CDCl_3$: 2.63(d, 3H), 3.14(t, 4H), 3.87-3.90(m,7H), 4.64(m,1H), 6.45(dd, 1H), 6.55(d, 1H), 7.23-7.26(m, 1H), 7.51-7.55(m, 1H), 7.91(d, 1H), 7.95(dd, 1H), 8.06(s, 1H), 8.47(d, 1H), 9.26(s, 1H)

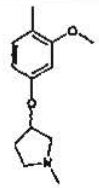
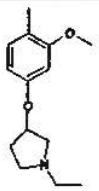
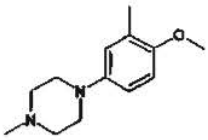
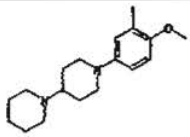
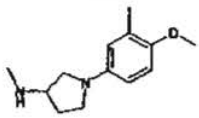
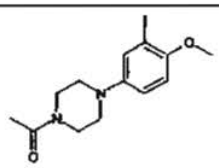
20-2		m/z 546, 548 (M+1)	DMSO-d6: 2.06 (s, 3H), 2.43 (s, 3H), 3.10 (m, 2H), 3.16 (m, 2H), 3.59-3.62 (m, 4H), 3.77 (s, 3H), 6.49 (dd, 1H), 6.68 (d, 1H), 7.21-7.25 (m, 1H), 7.42 (d, 1H), 7.49 (dd, 1H), 7.75-7.77 (m, 1H), 7.78(s, 1H), 8.16(s, 1H), 8.21 (s, 1H), 8.50(d, 1H), 9.35 (s, 1H)
20-3		0.27 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.65(d, 3H), 4.45-4.49(m, 1H), 6.99-7.04(m, 1H), 7.17-7.28(m, 4H), 7.56-7.60(m, 1H), 7.96-7.98(m, 1H), 8.18(s, 1H), 8.31-8.34(m, 1H), 8.41-8.44(m, 1H), 9.14(s, 1H)
20-4		0.27 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 2.65(d, 3H), 4.54-4.58(m, 1H), 6.53(dd, 1H), 6.98-7.02(m, 1H), 7.11-7.15(m, 2H), 7.24-7.28(m, 1H), 7.35(bs, 1H), 7.57-7.61(m, 1H), 7.95-7.98(m, 1H), 8.16(s, 1H), 8.29-8.32(m, 1H), 8.42-8.46(m, 1H), 9.14(s, 1H)
20-5		0.46 (MeOH: CH_2Cl_2=1:4)	$CDCl_3$: 1.95-2.00(m, 5H), 2.29-2.37(m, 1H), 2.62(d, 3H), 3.20-3.78(m, 4H), 3.86(s, 3H), 4.60-4.64(m, 2H), 5.68-5.69(m, 1H), 6.09-6.16(m, 2H), 7.15(bs, 1H), 7.19-7.23(m, 1H), 7.54-7.58(m, 1H), 7.88-7.95(m, 2H), 8.06(s, 1H), 8.55-8.57(m, 1H), 9.08(s, 1H)
20-6		518 [M+1]+	DMSO-d6: 2.23(s, 3H), 2.43(s, 3H), 2.45-2.50(m, 4H), 3.12-3.17(m, 4H), 3.76(s, 3H), 6.45(dd,1H), 6.63(d, 1H), 7.22(dd, 1H), 7.37(d, 1H), 7.45-7.50(m, 1H), 7.74-7.78(m, 1H), 7.76(d, 1H), 8.15(s, 1H), 8.19(s, 1H), 8.46-8.53(m, 1H), 9.35(bs, 1H)
20-7		504 [M+1]+	DMSO-d6: 2.43(s, 3H), 2.80-2.89(m, 4H), 2.99-3.07(m, 4H), 3.76(s, 3H), 6.44(dd,1H), 6.61(d, 1H), 7.18-7.24(m, 1H), 7.37(d, 1H), 7.44-7.50(m, 1H), 7.76(dd, 1H), 8.15(s, 1H), 8.18(s, 1H), 8.45-8.55(m, 1H), 9.20-9.45(m, 1H)

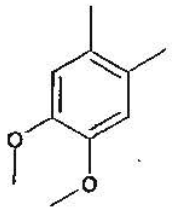
20-8		586 [M+1]+	DMSO-d6: 1.35-1.43(m, 2H), 1.45-1.61(m, 6H), 1.75-1.85(m,2H), 2.30-2.40(m, 1H), 2.43(d, 3H), 2.42-2.55(m, 4H), 2.60-2.70(m, 2H), 3.68-3.77(m, 2H), 3.75(s, 3H), 6.45(dd, 1H), 6.62(d, 1H), 7.21(dd, 1H), 7.36(d, 1H), 7.43-7.51(m, 1H), 7.73-7.81(m, 1H), 7.75(dd, 1H), 8.15(s, 1H), 8.17(s, 1H), 8.45-8.52(m, 1H), 9.34(bs, 1H)
20-9		569 [M+1]+	DMSO-d6: 1.85-1.95(m, 2H), 2.15(s, 3H), 2.18(t, 2H), 2.22-2.40(m, 8H), 2.43(s, 3H), 4.17(t, 2H), 6.65(d, 1H), 7.06(dd, 1H), 7.20(d, 1H), 7.22(ddd, 1H), 7.25(d, 1H), 7.39-7.47(m, 2H), 7.72-7.82(m, 1H), 7.77(dd, 1H), 8.26(s, 1H), 8.52(d, 1H), 9.22(s, 1H), 9.36(s, 1H)
20-10		556 [M+1]+	DMSO-d6: 1.85-1.95(m, 2H), 2.19(t, 2H), 2.25-2.35(m, 4H), 2.43(s, 3H), 3.55-3.60(m, 4H), 4.19(t, 2H), 6.66(d, 1H), 7.06(dd, 1H), 7.17-7.24(m, 1H), 7.21(d, 1H), 7.27(d, 1H), 7.39-7.45(m, 1H), 7.44(d, 1H), 7.70-7.80(m, 1H), 7.76(dd, 1H), 8.26(s, 1H), 8.52(d, 1H), 9.21(s, 1H), 9.36(s, 1H)
20-11		Rf (Hexane : AcOEt=1:1) 0.29	DMSO-d6: 2.64 (d, 3H), 2.87-2.96 (m, 4H), 3.65-3.74 (m, 4H), 3.86 (s, 3H), 4.41-4.51 (m, 1H), 6.50 (dd, 1H), 6.81 (d, 1H), 7.55-7.64 (m, 2H), 7.96 (d, 1H), 8.01 (s, 1H), 8.19 (s, 1H), 8.49 (d, 1H), 9.07 (s, 1H).
20-12		MS 535	DMSO-d6: 2.64 (d, 3H), 3.05 (bs, 4H), 3.59 (bs, 3H), 3.87(bs, 3H), 3.89 (bs, 4H), 4.52-4.48 (m, 1H), 6.57(bs, 1H), 7.25-7.20(m, 1H), 7.44-7.32 (m, 1H), 7.63-7.52 (m, 1H), 7.94(bs, 1H), 8.06 (d, 1H), 8.25(s, 1H), 8.48(d, 1H), 9.06(bs, 1H)

20-13		MS 548	DMSO-d6: 2.17 (bs, 3H), 2.63 (d, 3H), 2.68 (bs, 4H), 3.10(bs, 4H), 3.57 (s, 3H), 4.54-4.46 (m, 1H), 6.59(bs, 1H), 7.27-7.18(m, 1H), 7.37 (bs, 1H), 7.62-7.55 (m, 1H), 7.94(bs, 1H), 7.95 (d, 1H), 8.16(s, 1H), 8.48(d, 1H), 9.04(bs, 1H)
20-14		MS 546	DMSO-d6: 1.06 (t, 3H), 1.86 (dd, 2H), 2.37 (s, 3H), 2.62-2.59 (m, 4H), 2.64(d, 3H), 4.00-3.97 (m, 4H), 4.62-4.54 (m, 1H), 6.44 (dd, 1H), 6.54(d, 1H), 7.27-7.22(m, 1H), 7.34(bs, 1H), 7.58-7.54(m, 1H), 7.95(dd, 1H), 8.02(d, 1H), 8.11(s, 1H), 8.53(d, 1H), 9.07(bs, 1H)
20-15		LC-MS 545	DMSO-d6: 1.46-1.62 (m, 2H), 1.72-1.79 (m, 1H), 1.82-1.90 (m, 1H), 2.38-2.46 (m, 1H), 2.43 (s, 3H), 2.62-2.76 (m, 2H), 3.59-3.69 (m, 2H), 3.43 (s, 3H), 6.47 (dd, 1H), 6.63 (d, 1H), 6.82-6.89 (br, 1H), 7.21 (dd, 1H), 7.32-7.41 (m, 2H), 7.44-7.62 (m, 1H), 7.71-7.82 (m, 2H), 8.15 (s, 1H), 8.15-8.20 (br, 1H), 8.44-8.53 (m, 1H), 9.28-9.38 (m, 1H)
20-16		0.24 (CH2Cl2:MeOH=8:2)	DMSO-d6: 1.47-1.55 (m, 2H), 1.80-1.91 (m, 2H), 2.16 (s, 3H), 2.25-2.41 (m, 5H), 2.42-2.48 (m, 3H), 2.61-2.73 (m, 2H), 3.68-3.79 (m, 5H), 6.45 (dd, 1H), 6.62 (d, 1H), 7.21 (dd, 1H), 7.34 (d, 1H), 7.45-7.49 (m, 1H), 7.73-7.80 (m, 2H), 8.15 (s, 1H), 8.20 (s, 1H), 8.45-8.54 (m, 1H), 9.34 (s, 1H)
20-17		LC-MS 518	DMSO-d6: 1.76-1.84 (m, 1H), 2.08-2.16 (m, 1H), 2.33 (s, 3H), 2.42 (s, 3H), 3.00-3.03 (m, 1H), 3.23-3.27 (m, 3H), 3.42-3.46 (m, 1H), 3.74 (s, 3H), 6.06 (dd, 1H), 6.18- 6.20 (m, 1H), 7.17-7.23 (m, 1H), 7.38-7.48 (br, 1H), 7.72-7.77 (m, 1H), 8.12 (s, 1H), 8.17-8.21 (br, 1H), 8.46-8.58 (br, 1H), 9.30-9.40 (br, 1H)

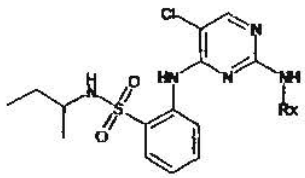
20-18		LC-MS 601	DMSO-d6: 1.36-1.49 (m, 2H), 1.69-1.76 (m, 2H), 2.13 (s, 3H), 2.15-2.23 (m, 1H), 2.24-2.36 (br, 4H), 2.39-2.48 (m, 5H), 2.43 (s, 3H), 3.27-3.40 (m, 2H), 3.74 (s, 3H), 6.62 (dd, 1H), 6.90 (d, 1H), 7.22-7.26 (m, 1H), 7.41-7.46 (m, 1H), 7.49-7.53 (m, 1H), 7.55-7.86 (br, 1H), 7.77 (dd, 1H), 8.16 (s, 1H), 8.25 (s, 1H), 8.42 (d, 1H), 9.28 (s, 1H)
20-19		LC-MS 519	DMSO-d6: 1.37-1.46 (m, 2H), 1.69-1.75 (m, 2H), 2.43 (s, 3H), 2.53-2.61 (m, 2H), 3.18-3.26 (m, 2H), 3.40-3.74 (m, 2H), 4.62 (d, 1H), 6.62 (dd, 1H), 6.90 (d, 1H), 7.22-7.26 (m, 1H), 7.42-7.46 (br, 1H), 7.48-7.55 (m, 1H), 7.77-7.80 (m, 2H), 8.13-8.18 (br, 1H), 8.25 (s, 1H), 8.40-8.45 (m, 1H), 9.25-9.30 (m, 1H)
20-20		LC-MS 532	DMSO-d6: 1.66-1.76 (m, 1H), 2.00-2.07 (m, 1H), 2.14 (s, 6H), 2.43 (s, 3H), 2.68-2.76 (m, 1H), 2.87-2.91 (m, 1H), 2.99-3.10 (m, 2H), 3.24-3.28 (m, 1H), 3.71 (s, 3H), 6.25 (dd, 1H), 6.90 (d, 1H), 7.00-7.03 (m, 1H), 7.21-7.24 (m, 1H), 7.40-7.45 (m, 1H), 7.78-7.83 (m, 2H), 8.19 (s, 1H), 8.24 (s, 1H), 8.46 (d, 1H), 9.27-9.36 (br, 1H)
20-21		Ms : 549	DMSO-d6: 2.37-2.47 (m, 4H), 2.48-2.53 (m, 3H), 2.64 (t, 2H), 3.57 (t, 3H), 3.77 (s, 3H), 3.92 (t, 2H), 6.61(dd, 1H), 6.93 (d, 1H), 7.28 (dd, 1H), 7.56-7.63 (m, 2H), 7.75-7.85 (m, 2H), 7.74-7.84 (m, 2H), 8.14 (s, 1H), 8.29 (s, 1H) 8.46 (d, 1H), 9.33(s, 1H)
20-22		Ms:562	DMSO-d6: 2.20 (s, 3H), 2.3-2.5 (m, 11H), 2.64 (t, 2H), 3.77 (s, 3H), 3.91 (t, 2H), 6.61(dd, 1H), 6.94 (d, 1H), 7.25-7.31(m, 1H), 7.57 (d, 1H), 7.58-7.64 (m, 1H), 7.74-7.84 (m, 2H), 8.12 (brs, 1H), 8.28 (s, 1H) 8.46 (d, 1H), 9.33(brs, 1H)

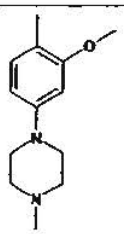
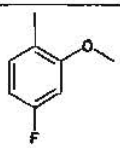
20-23		Ms:438	DMSO-d6: 2.42-2.45 (m, 3H), 3.83 (s, 2H), 6.8 (ddd, 1H), 7.02 (dd, 1H), 7.3-7.36 (m, 1H), 7.58-7.64 (m, 1H), 7.74-7.8 (m, 1H), 7.82 (dd, 1H), 7.85 (dd, 1H), 8.18 (brs, 1H), 8.31 (s, 1H), 8.41 (d, 1H), 9.3 (brs, 1H)
20-24		Ms:438	DMSO-d6: 2.41-2.45 (m, 3H), 3.79 (s, 2H), 6.74 (ddd, 1H), 7.0 (dd, 1H), 7.22-7.28 (m, 1H), 7.49-7.55 (m, 1H), 7.6 (dd, 1H), 7.75-7.8 (m, 2H), 8.21 (s, 1H), 8.37 (brs, 1H), 8.39-8.45 (m, 1H), 9.34 (brs, 1H)
20-25		Ms:547	DMSO-d6: 1.24-1.38 (m, 2H), 1.64-1.8 (m, 3H), 1.83-1.92 (m, 2H), 2.16 (s, 3H), 2.41-2.45(m, 3H), 2.76-2.83 (m, 2H), 3.75 (s, 3H), 3.84 (d, 2H), 6.48 (dd, 1H), 6.64 (d, 1H), 7.2-7.25 (m, 1H), 7.41 (d, 1H), 7.43-7.5 (m, 1H), 7.74-7.8 (m, 2H), 8.16 (s, 1H), 8.26 (brs, 1H) 8.44-8.5 (m, 1H), 9.34 (brs, 1H)
20-26		Ms:547	DMSO-d6: 1.18-1.3 (m, 2H), 1.56-1.7 (m, 3H), 1.8-1.88 (m, 2H), 2.15 (s, 3H), 2.41-2.45(m, 3H), 2.73-2.8 (m, 2H), 3.75 (s, 3H), 3.65 (d, 2H), 3.77 (s, 3H), 6.57 (dd, 1H), 6.93 (d, 1H), 7.25 (dd, 1H), 7.51-7.6 (m, 2H), 7.7-7.9 (m, 2H), 8.09 (brs, 1H), 8.28 (s, 1H), 8.45 (d, 1H), 9.31 (brs, 1H)
20-27		Ms:533	DMSO-d6: 1.62-1.72 (m, 2H), 1.9-1.99 (m, 2H), 2.3-2.35 (m, 5H), 2.41-2.45(m, 3H), 2.64-2.74 (m, 2H), 3.75 (s, 3H), 4.35-4.43 (m, 1H), 6.52 (dd, 1H), 6.65 (d, 1H), 7.19-7.25 (m, 1H), 7.41 (d, 1H), 7.43-7.49 (m, 1H), 7.74-7.8 (m, 2H), 8.16 (s, 1H), 8.27 (brs, 1H), 8.42-8.5 (m, 1H), 9.34 (brs, 1H)
20-28		Ms:547	DMSO-d6: 0.96-1.2 (m, 2H), 1.75-1.9 (m, 1H), 2.2-2.3 (m, 1H), 2.35-2.45 (m, 1H), 2.41-2.45(m, 2H), 2.43(d, 3H), 2.6-3.0 (m, 3H), 3.76 (s, 3H), 4.85-5.0 (m, 1H), 6.43-6.49 (m, 1H), 6.57-6.64 (m, 1H), 7.18-7.25 (m, 1H), 7.39-7.52 (m, 2H), 7.73-7.83 (m, 2H), 8.17 (s, 1H), 8.27 (brs, 1H), 8.44-8.51 (m, 1H), 9.35 (brs, 1H)

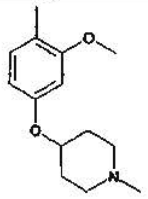
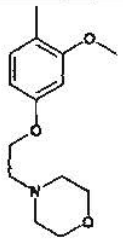
20-29		Ms:519	DMSO-d6: 1.74-1.83 (m, 1H), 2.23-2.31 (m, 1H), 2.28 (s, 3H), 2.35-2.4 (m, 1H), 2.41-2.45(m, 3H), 2.58-2.63 (m, 1H), 2.63-2.7 (m, 1H), 2.78-2.83 (m, 1H), 3.75 (s, 3H), 4.86-4.92 (m, 1H), 6.43 (dd, 1H), 6.58 (d, 1H), 7.19-7.25 (m, 1H), 7.41 (d, 1H), 7.44-7.51 (m, 1H), 7.73-7.83 (m, 2H), 8.16 (s, 1H), 8.26 (brs, 1H), 8.43-8.52 (m, 1H), 9.34 (brs, 1H)
20-30		Ms : 533	DMSO-d6: 1.04 (t, 3H), 1.74-1.82 (m, 1H), 2.23-2.33 (m, 1H), 2.47-2.5(m, 6H), 2.62-2.72 (m, 2H), 2.8-2.87 (m, 1H), 3.75 (s, 3H), 4.86-4.92 (m, 1H), 6.44 (dd, 1H), 6.59 (d, 1H), 7.19-7.25 (m, 1H), 7.41 (d, 1H), 7.44-7.51 (m, 1H), 7.73-7.8 (m, 2H), 8.16 (s, 1H), 8.26 (brs, 1H), 8.44-8.51 (m, 1H), 9.34 (brs, 1H)
20-31		Ms : 518	DMSO-d6: 2.23(s, 3H), 2.38-2.47 (m, 7H), 2.87-2.93 (m, 4H), 3.75 (s, 3H), 6.63 (dd, 1H), 6.93 (d, 1H), 7.22-7.28 (m, 1H), 7.42 (d, 1H), 7.48-7.54 (m, 1H), 7.76-7.84 (m, 1H), 8.2 (s, 1H), 8.25(s, 1H), 8.43 (dd, 1H) 9.29 (s, 1H)
20-32		Ms : 586	DMSO-d6: 1.35-1.55 (m, 8H), 1.66-1.75 (m, 2H), 2.23(s, 3H), 2.41-2.45 (m, 3H), 3.74 (s, 3H), 6.63 (dd, 1H), 6.91 (d, 1H), 7.21-7.28 (m, 1H), 7.44 (d, 1H), 7.48-7.54 (m, 1H), 7.76-7.87 (m, 1H), 8.16 (s, 1H), 8.25 (s, 1H), 8.43 (dd, 1H) 9.29 (s, 1H)
20-33		Ms : 518	DMSO-d6: 1.62-1.71 (m, 1H), 1.95-2.04 (m, 1H), 2.23-2.27 (m, 3H), 2.39-2.43 (m, 3H), 2.93-3.1 (m, 2H), 3.13-3.26 (m, 2H), 3.71 (s, 3H), 6.19 (dd, 1H), 6.88 (d, 1H), 7.07-7.13 (m, 1H), 7.13-7.2 (m, 1H), 7.4-7.48 (m, 1H), 7.75 (dd, 1H), 8.06 (brs, 1H), 8.18 (s, 1H), 8.4 (d, 1H)
20-34		Ms : 546	DMSO-d6: 2.02 (m, 1H), 2.42-2.46 (m, 3H), 2.71-2.91 (m, 4H), 3.44-3.51 (m, 4H), 3.76 (s, 3H), 6.66 (dd, 1H), 6.94 (d, 1H), 7.21-7.27 (m, 1H), 7.75-7.85 (m, 2H), 8.19 (s, 1H), 8.26 (s, 1H), 8.41 (d, 1H), 9.28 (brs, 1H).

20-35		MS (ESI) 464 (M+H)	HPLC Retention time (min) 2.68

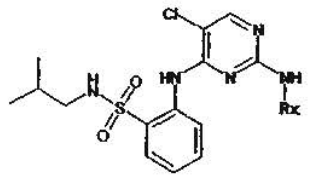
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-sec-butyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-sec-butyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A

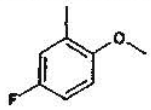


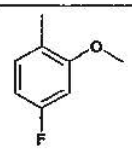
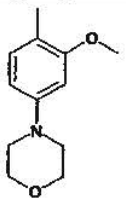
ExplNo.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
21-1		0.35 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 0.62(t, 3H), 0.88(d, 3H), 1.22-1.29(m, 2H), 2.23(s,3H), 2.45-2.47(m, 4H), 3.05-3.14(m, 5H), 3.75 (s, 3H), 6.40-6.43(m, 1H), 6.62(s, 1H), 7.18-7.22(m, 1H), 7.39-7.47(m, 2H), 7.80-7.82(m, 1H), 8.15-8.16(m, 2H), 8.44-8.46(m, 1H), 9.32(s, 1H)
21-2		0.30 (*n*-hexane: AcOEt=3:1)	DMSO-d6 : 0.62(t, 3H), 0.87(d, 3H), 1.17-1.26(m, 2H), 3.03-3.10(m, 1H), 3.79(s, 3H), 6.66-6.71(m, 1H), 6.96-7.00(m, 1H), 7.21-7.25(m, 1H), 7.47-7.51(m, 1H), 7.60-7.64(m, 1H), 7.79-7.83(m, 2H), 8.21(s, 1H), 8.31(s, 1H), 8.35-8.37(m, 1H), 9.29(s, 1H)

21-3		0.30 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.61(t, 3H), 0.87(d, 3H), 1.21-1.29(m, 2H), 1.58-1.67(m, 2H), 1.86-1.93(m, 2H), 2.14-2.20(m, 5H), 2.59-2.67(m, 2H), 3.06-3.08(m, 1H), 3.74(s, 3H), 4.32-4.36(m, 1H), 6.46-6.48(m, 1H), 6.63(d, 1H), 7.17-7.21(m, 1H), 7.40-7.50(m, 2H), 7.79-7.81(m, 2H), 8.16(s, 1H), 8.21(bs, 1H), 8.35-8.42(m, 1H), 9.29(s, 1H)
21-4		0.30 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.61(t, 3H), 0.87(d, 3H), 1.22-1.29(m, 2H), 2.43-2.47(m, 2H), 2.61-2.63(m, 1H), 2.68-2.70(m, 2H), 3.04-3.11(m, 1H), 3.56-3.60(m, 5H), 3.75(s, 3H), 3.93-3.96(m, 1H), 4.08-4.11(m, 2H), 6.45-6.47(m, 1H), 6.64(d, 1H), 7.18-7.22(m, 1H), 7.43-7.46(m, 2H), 7.80-7.82(m, 2H), 8.17(s, 1H), 8.21(s, 1H), 8.42-8.44(m, 1H), 9.31(s, 1H)

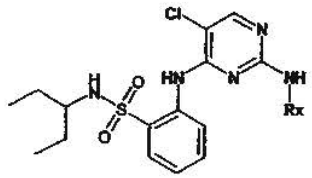
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-*isc*-butyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-*sec*-butyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A

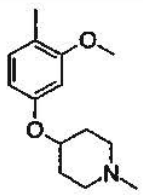


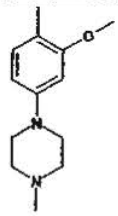
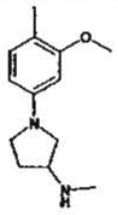
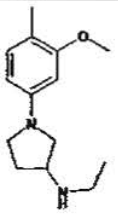
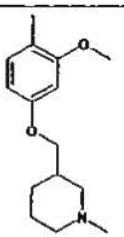
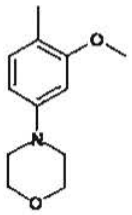
ExplNo.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
22-1		0.30 (*n*-hexane: AcOEt=3:1)	DMSO-d6 : 0.69(d, 6H), 1.52-1.59(m, 1H), 2.57-2.58(m, 2H), 3.82(s, 3H), 6.75-6.80(m, 1H), 6.99-7.02(m, 1H), 7.29-7.33(m, 1H), 7.56-7.60(m, 1H), 7.82-7.93(m, 3H), 8.14(bs, 1H), 8.31(s, 1H), 8.33(s, 1H), 9.23(s, 1H)

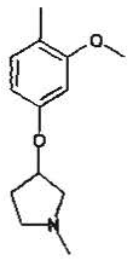
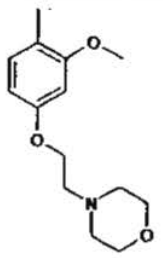
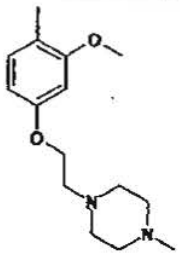
22-2		0.30 (*n*-hexane: AcOEt=3:1)	$CDCl_3$: 0.74(d, 6H), 1.57-1.64(m, 1H), 2.72-2.76(m,2H), 3.88(s, 3H), 4.55-4.56(m, 1H), 6.52-6.57 (m, 1H), 6.62-6.65(m, 1H), 7.24-7.28(m, 2H), 7.36(bs, 1H), 7.56-7.60(m, 1H), 7.95-8.08(m, 1H), 8.10-8.14(m, 2H), 8.36-8.39(m, 1H), 8.98(bs, 1H)
22-3		0.54 (AcOEt)	DMSO-d6 : 0.73(d, 6H), 1.55-1.62(m, 1H), 2.56-2.59(m, 2H), 3.10-3.12(m, 4H), 3.74-3.76(m, 7H), 6.43-6.46(m, 1H), 6.65(d, 1H), 7.20-7.24(m, 1H), 7.40-7.48(m, 2H), 7.76-7.78(m, 1H), 7.90-7.95(m, 1H), 8.16(s, 1H), 8.17(s, 1H), 8.43-8.45(m, 1H), 9.32(s, 1H)

The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-(1-ethyl-propyl)-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-(1-ethyl-propyl)-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A

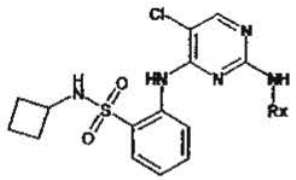


ExplNo.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
23-1		0.46 (MeOH: CH_2Cl_2=3:7)	DMSO-d6: 0.58(t, 6H), 1.14-1.34(m, 4H), 1.58-1.68(m, 2H), 1.87-1.96(m, 2H), 2.12-2.22(m, 2H), 2.18(s, 3H), 2.57-2.65(m, 2H), 2.86-2.96(m, 1H), 3.75(s, 3H), 4.30-4.39(m, 1H), 6.46(dd, 1H), 6.63(d, 1H), 7.19(dd, 1H), 7.39-7.48(m, 2H), 7.75-7.84(m, 2H), 8.18(s, 1H), 8.20 (s, 1H), 8.39(m, 1H), 9.33(bs, 1H)

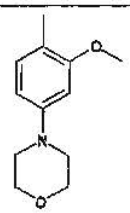
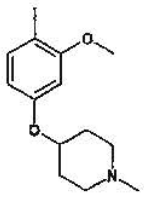
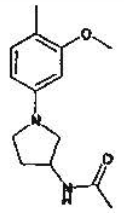
23-2		0.35 (*n*-hexane: AcOEt=1:1)	$CDCl_3$: 0.59(t, 6H), 1.14-1.34(m, 4H), 2.23(s,3H), 2.45-2.47(m, 4H), 2.90-2.95(m, 1H), 3.11-3.14(m, 4H), 3.76 (s, 3H), 6.39-6.42(m, 1H), 6.62(s, 1H), 7.18-7.22(m, 1H), 7.41-7.46(m, 2H), 7.76-7.82(m, 2H), 8.12(s, 1H), 8.16(s, 1H), 8.43-8.44(m, 1H), 9.35(s, 1H)
23-3		0.41 (MeOH: CH_2Cl_2=1:4)	DMSO-d6: 0.59(t, 6H), 1.16-1.35(m, 4H), 1.75-1.89(m, 1H), 2.08-2.15(m, 1H), 2.32(s, 3H), 2.90-3.02(m, 2H), 3.21-3.45(m, 4H), 3.73(s, 3H), 6.02(dd, 1H), 6.18(d, 1H), 7.16(dd, 1H), 7.27(d, 1H), 7.35-7.45(m, 1H), 7.77-7.82(m, 2H), 8.10 (s, 1H) 8.12 (s, 1H), 8.45-8.55(m, 1H), 9.38(s, 1H)
23-4		0.41 (MeOH: CH_2Cl_2=1:4)	DMSO-d6: 0.60(t, 6H), 1.04(t, 3H), 1.17-1.35(m, 4H), 1.76-1.83(m, 1H), 2.10-2.15(m, 1H), 2.56-2.64(m, 2H), 2.91-3.01(m, 2H), 3.21-3.47(m, 4H), 3.74(s, 3H), 6.02(dd, 1H), 6.18(d, 1H), 7.14-7.17(m, 1H), 7.28(d, 1H), 7.35-7.45(m, 1H), 7.77-7.82(m, 2H), 8.11 (s, 1H) 8.12 (s, 1H), 8.45-8.55(m, 1H), 9.38(s, 1H)
23-5		0.25 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 0.58(t, 6H), 1.06-2.16(m, 11H), 2.16(s, 3H), 2.62-2.67(m, 1H), 2.81-2.94(m, 2H), 3.75(s, 3H), 3.80-3.89(m, 2H), 6.41-6.44(m, 1H), 6.62(d, 1H), 7.17-7.21(m, 1H), 7.42-7.47(m, 2H), 7.77-7.82(m, 2H), 8.18(s, 1H), 8.19(s, 1H), 8.35 -8.42(m, 1H), 9.35(s, 1H)
23-6		Ms : 561	DMSO-d6 : 0.59 (t, 6H), 1.14-1.38 (m, 4H), 2.87-2.98 (m, 1H), 3.1 (t, 4H), 3.72-3.79 (m, 7H), 6.42 (dd, 1H), 6.64 (d, 1H), 7.18-7.24 (m, 1H), 7.42-7.5 (m, 2H), 7.77 (d, 1H), 7.81 (dd, 1H), 8.13 (s, 1H), 8.17 (s, 1H), 8.4-8.5 (m, 1H), 9.36 (s, 1H)

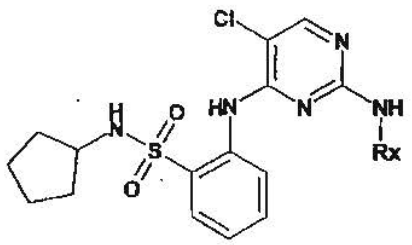
23-7		Ms : 575	DMSO-d6 : 0.58 (t, 6H), 1.13-1.37 (m, 4H), 1.72-1.82 (m, 1H), 2.21-2.31 (m, 4H), 2.32-2.4 (m, 1H), 2.54-2.61 (m, 1H), 2.62-2.68 (m, 1H), 2.75-2.82 (m, 1H), 2.87-2.97 (m, 1H), 3.75 (s, 3H), 4.84-4.91 (m, 1H), 6.37 (dd, 1H), 6.56 (d, 1H), 7.14-7.24 (m, 1H), 7.38-7.52 (m, 2H), 7.72-7.86 (m, 1H), 8.12-8.25 (m, 2H), 8.34-8.45 (m, 1H), 9.33 (brs, 1H)
23-8		Ms : 605	DMSO-d6 : 0.58 (t, 6H), 1.14-1.36 (m, 4H), 2.43-2.53 (m, 4H), 2.69 (t, 2H), 2.89-2.95 (m, 1H), 3.59 (t, 4H), 3.76 (s, 3H), 4.09 (t, 1H), 6.45 (dd, 1H), 6.64 (d, 1H), 7.17-7.23 (m, 1H), 7.41-7.52 (m, 2H), 7.78 (d, 1H), 7.81 (dd, 1H), 8.18 (s, 1H), 8.19 (s, 1H), 8.36-8.46 (m, 1H), 9.35 (s, 1H)
23-9		Ms : 618	DMSO-d6 : 0.58 (t, 6H), 1.14-1.37 (m, 4H), 2.15 (s, 1H), 2.25-2.4 (m, 4H), 2.45-2.55 (m, 4H), 2.68 (t, 2H), 2.88-2.97 (m, 1H), 3.76 (s, 3H), 4.07 (t, 1H), 6.44 (dd, 1H), 6.64 (d, 1H), 7.15-7.23 (m, 1H), 7.41-7.51 (m, 2H), 7.7-7.84 (m, 2H), 8.12-8.22 (m, 1H), 8.34-8.44 (m, 1H), 9.34 (s, 1H)

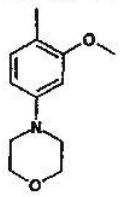
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-*iso*-butyl-benzene-sulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-cyclobutyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A

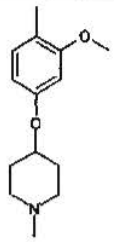


ExpiNo.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)

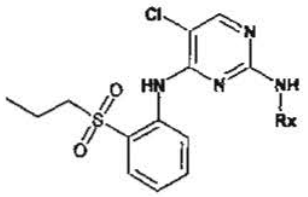
24-1		0.35 (*n*-hexane: AcOEt=1:1)	DMSO-d6 : 1.37-1.48(m, 2H), 1.69-1.91(m, 4H), 3.09-3.12(m, 4H), 3.63-3.74(m, 1H), 3.76(s, 3H), 6.43-6.45(m, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.41-7.47(m, 2H), 7.76-7.78(m, 1H), 8.17-8.24(m, 3H), 8.46(d, 1H), 9.33(s, 1H)
24-2		0.46 (MeOH: CH_2Cl_2=3:7)	DMSO-d6: 1.37-1.93(m, 10H), 2.18(s, 3H), 2.59-2.62(m, 1H), 3.60-3.74(m, 1H), 3.77(s, 3H), 4.32-4.36(m, 1H), 6.46-6.49(m, 1H), 6.62(d, 1H), 7.16-7.20(m, 1H), 7.41-7.44(m, 2H), 7.75-7.77(m, 1H), 8.16(s, 1H), 8.22 (bs, 1H), 8.40-8.42(m, 1H), 9.30(bs, 1H)
24-3		0.46 (MeOH: CH_2Cl_2=1:4)	$CDCl_3$: 1.45-1.75(m, 5H), 1.94-2.06(m, 6H), 2.29-2.37(m, 1H), 3.21-3.56(m, 4H), 3.72-3.81(m, 1H), 3.86(s, 3H), 4.55-4.65(m, 1H), 4.90(d, 1H), 5.72(d, 1H), 6.07(bs, 1H), 6.15(bs, 1H), 7.18-7.22(m, 2H), 7.52-7.56(m, 1H), 7.89-7.94(m, 2H), 8.08(s, 1H), 8.50(d, 1H), 9.00(s, 1H)

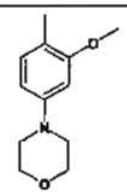
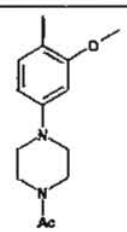


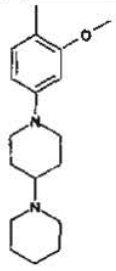
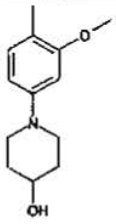
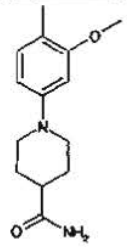
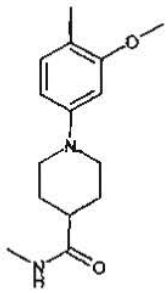
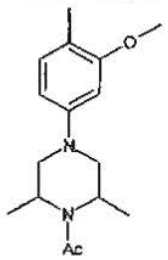
Expl No.	Rx	Ms	NMR (400MHz), δ (ppm)
25-1		Ms : 559	DMSO-d6 : 1.2-1.38 (m, 4H), 1.4-1.65 (m, 4H), 3.11 (t, 4H), 3.42-3.5 (m, 1H), 3.7-3.8 (m, 7H), 6.44 (dd, 1H), 6.64 (d, 1H), 7.18-7.26 (m, 1H), 7.38-7.5 (m, 2H), 7.81 (d, 1H), 7.88-7.96 (m, 1H), 8.16 (s, 1H), 8.17 (s, 1H), 8.4-8.5 (m, 1H), 9.34 (s, 1H)

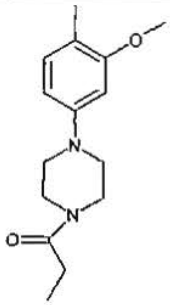
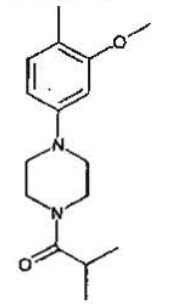
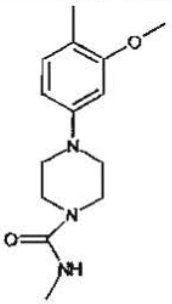
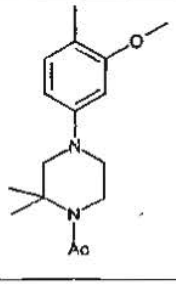
25-2		Ms : 587	DMSO-d6 : 1.2-1.38 (m, 4H), 1.42-1.6 (m, 6H), 1.88-1.98 (m, 2H), 2.1-2.25 (m, 5H), 2.55-2.65 (m, 2H), 3.4-3.5 (m, 1H), 3.74 (s, 3H), 4.3-4.4 (m, 1H), 6.48 (dd, 1H), 6.63 (d, 1H), 7.18-7.24 (m, 1H), 7.38-7.47 (m, 1H), 7.77-7.82 (m, 1H), 7.88-7.96 (m, 1H), 8.17 (s, 1H), 8.22 (s, 1H), 8.36-8.46 (m, 1H), 9.31 (s, 1H)

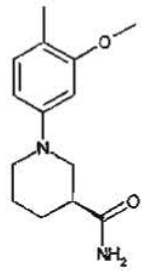
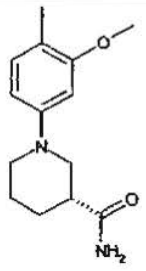
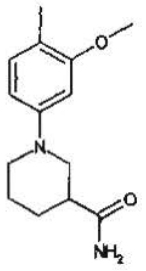
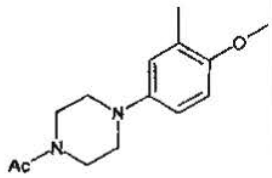
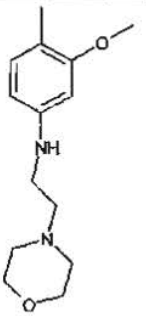
The following 5-Chloro-N^2-(substituted phenyl)-N^4-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-1-sulfonyl)-phenyl]-amine and the corresponding aniline following the procedure of Example 7A

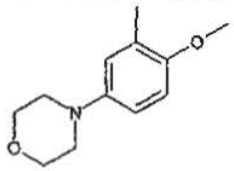
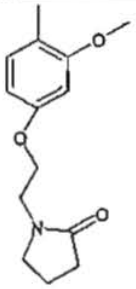
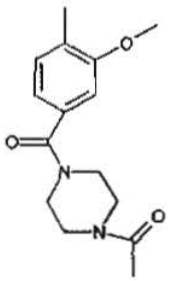
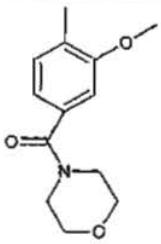
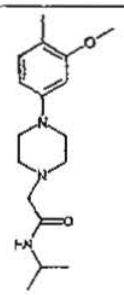


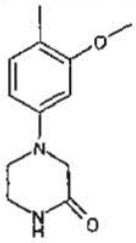
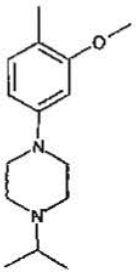
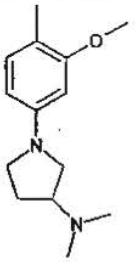
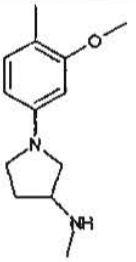
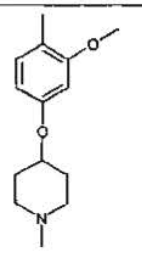
ExpIN o.	Rx	Rf (solvent) , MS or Mp	NMR (400MHz) , δ (ppm)
26-1		0.58 (AcOEt)	$CDCl_3$: 0.97(t,3H), 1.72-1.82(m, 2H), 3.08-3.14(m, 6H), 3.87-3.89(m, 7H), 6.46(dd, 1H), 6.53(d,1H), 7.24-7.28(m,1H), 7.30(s, 1H), 7.60-7.64(m, 1H), 7.94(dd, 1H), 8.05(d, 1H), 8.15(s, 1H), 8.59(d, 1H), 9.40(s, 1H)
26-2		0.57 (MeOH: AcOEt=1:4)	$CDCl_3$: 0.98(t, 3H), 1.85-1.68(m, 2H), 2.15(s, 3H), 3.16-3.07(m, 6H), 3.67-3.62(m, 2H), 3.81-3.78(m, 2H), 3.89(s, 3H), 6.47(d, 1H), 6.55(d, 1H), 7.36-7.33(m, 1H), 7.62 (dd, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H),8.58(d, 1H), 9.41(s, 1H)

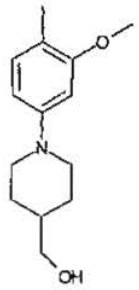
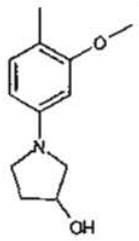
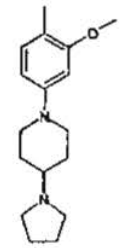
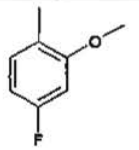
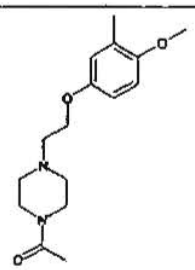
26-3		0.13 (MeOH: AcOEt=1:4)	$CDCl_3$: 0.97(t, 3H), 1.43-1.52(m, 2H), 1.52-1.67 (m, 4H), 1.69-1.72(m, 4H), 1.90-1.98(m, 2H), 2.34-2.46(m, 1H), 2.51-2.59(m, 4H), 2.64-2.74(m, 2H), 3.11(dd, 2H), 3.64-3.73(m, 2H), 3.87(s, 3H), 6.47(dd, 1H), 6.56 (d, 1H), 7.24-7.33(m, 1H), 7.62(dd, 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.39(bs, 1H).
26-4		0.22 (AcOEt)	$CDCl_3$: 0.97(t, 3H), 1.45(d, 1H), 1.68-1.82(m, 4H), 2.0-2.1(m, 2H), 2.91(ddd, 2H),3.10(ddd, 2H), 3.46-3.51 (m, 2H), 3.84-3.92(m, 1H), 3.88 (s, 1H), 6.48(dd, 1H), 6.57(d, 1H), 7.23-7.32 (m, 1H), 7.62(dd, 1H), 7.94(dd,1H), 8.02 (dd, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.39(bs, 1H)
26-5		0.1 (AcOEt)	$CDCl_3$: 0.97(t, 3H) ,1.71-1.82(m, 2H), 1.86-1.98(m, 2H), 2.01-2.08(m, 2H), 2.25-2.37(m, 1H), 2.75 (ddd, 2H), 3.10(ddd, 2H), 3.63-3.66(m, 2H), 3.88(s, 3H), 5.25-5.40(m, 1H), 5.40-5.58 (m, 1H), 6.48(dd, 1H), 6.57(d, 1H), 7.22-7.34 (m, 1H), 7.62(ddd, 1H), 7.93 (d, 1H), 7.94 (dd, 1H), 8.02 (d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.40(m, 1H)
26-6		MS 587	$CDCl_3$: 0.97 (t, 3H), 1.77 (ddd, 2H), 2.00-1.85 (m, 4H), 2.27-2.18(m, 1H), 2.72(ddd, 2H) 3.12-3.08 (m, 2H), 3.69-3.61(m, 2H), 3.58-3.46(m, 1H), 3.64 (t, 2H), 3.80(t, 2H), 3.88(s,3H), 5.56-5.46 (m, 1H), 6.47(dd, 1H), 6.55(d, 1H), 7.32-7.23 (m, 1H), 7.30(bs, 1H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 8.02(d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.40(s, 1H)
26-7		MS 587	$CDCl_3$: 0.98 (t, 3H), 1.46(bs, 6H) 1.82-1.73 (m, 2H), 2.17(s, 3H), 3.58-3.46(m, 1H), 2.95-2.84 (m, 2H), 3.12-3.08 (m, 2H), 3.90(s,3H), 6.48(dd, 1H), 6.52(d, 1H), 7.30-7.22 (m, 1H), 7.31(bs, 1H), 7.66-7.60(m, 1H), 7.95(dd, 1H), 8.06(d, 1H), 8.15(s, 1H), 8.59(d, 1H), 9.43(s, 1H)

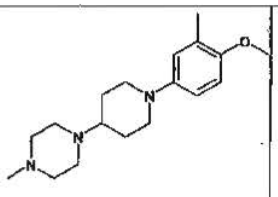
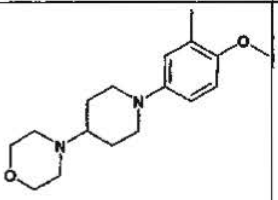
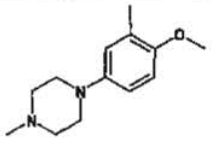
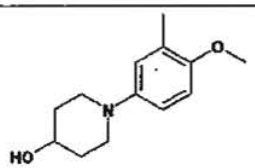
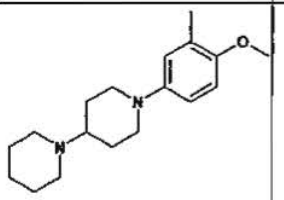
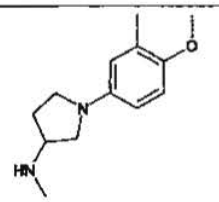
26-8		MS 573	$CDCl_3$: 0.97 (t, 3H), 1.19(t, 3H), 1.77 (ddd, 2H), 2.41(m, 2H), 3.18-3.09(m, 6H), 3.68-3.64 (m, 2H), 3.85-3.78 (m, 2H), 3.89(s,3H), 6.47(dd, 1H), 6.55(d, 1H), 7.29-7.25 (m, 1H), 7.34(bs, 1H), 7.64-7.60(m, 1H), 7.95(dd, 1H), 8.07(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H)
26-9		MS 587	$CDCl_3$: 0.97 (t, 3H), 1.17(d, 3H) 1.76 (ddd, 2H), 2.88-2.81(m, 2H), 3.18-3.05(m, 6H), 3.74-3.67 (m, 2H), 3.86-3.78 (m, 2H), 3.89(s,3H), 6.47(dd, 1H), 6.55(d, 1H), 7.29-7.20(m, 1H), 7.34(bs, 1H), 7.64-7.60(m, 1H), 7.95(dd, 1H), 8.07(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H)
26-10		MS 517	$CDCl_3$: 0.97 (t, 3H), 1.76 (ddd, 2H), 2.86(d, 3H), 3.14-3.08(m, 2H), 3.13(t, 4H), 3.55 (t, 4H), 3.89(s,3H), 4.48-4.39 (m, 1H), 6.46(dd, 1H), 6.55(d, 1H), 7.29-7.21(m, 1H), 7.34(bs, 1H), 7.64-7.60(m, 1H), 7.95(dd, 1H), 8.06(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H)
26-11		MS 587	$CDCl_3$: 0.98 (t, 3H), 1.51 (s, 6H), 1.82-1.72 (m, 1H), 2.13 (s, 3H), 3.12-3.08 (m, 2H), 3.26(s, 2H), 3.44 (t, 2H), 3.74(t, 2H), 3.88(s,3H), 5.56-5.46 (m, 1H), 6.45(dd, 1H), 6.51(d, 1H), 7.00(bs, 1H), 7.62-7.58 (m, 1H), 7.64-7.60(m, 1H), 7.93(d, 1H), 7.96(dd, 1H), 8.13(s, 1H), 8.62(d, 1H), 9.42(s, 1H)

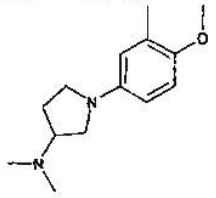
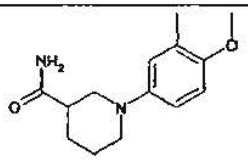
26-12		MS 559	$CDCl_3$: 0.98 (t, 3H), 1.81-1.71 (m, 3H), 1.95-1.84 (m, 3H), 2.68-2.63(m, 1H), 3.12-3.08 (m, 4H), 3.28(d, 2H), 3.89(s,3H), 5.45-5.38 (m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.71-6.62 (m, 1H), 7.28-7.21 (m, 1H), 7.35(bs, 1H), 7.65-7.61(m, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H)
26-13		MS 559	$CDCl_3$: 0.98 (t, 3H), 1.81-1.71 (m, 3H), 1.95-1.84 (m, 3H), 2.68-2.63(m, 1H), 3.12-3.08 (m, 4H), 3.28(d, 2H), 3.89(s,3H), 5.45-5.38 (m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.71-6.62 (m, 1H), 7.28-7.21 (m, 1H), 7.35(bs, 1H), 7.65-7.61(m, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H)
26-14		MS 559	$CDCl_3$: 0.98 (t, 3H), 1.85-1.74 (m, 3H), 2.00-1.86 (m, 3H), 2.70-2.51(m, 1H), 3.13-3.08 (m, 4H), 3.29-3.27 (m, 2H), 3.89(s,3H), 5.46-5.37 (m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.69-6.56 (m, 1H), 7.29-7.19 (m, 1H), 7.34(bs, 1H), 7.65-7.61(m, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H)
26-15		MS 559	$CDCl_3$: 0.99(t, 3H), 1.79-1.72 (m, 2H), 2.92 (t, 2H), 2.98(t, 2H), 3.16-3.12 (m, 2H), 3.53(t, 2H), 3.67(t, 2H), 3.87(s,3H), 6.54(dd, 1H), 6.82 (d, 1H), 7.29-7.19 (m, 1H), 7.56(bs, 1H), 7.67-7.62(m, 1H), 7.96(dd, 1H), 8.07(d, 1H), 8.21(s, 1H), 8.59(dd, 1H), 9.46(s, 1H)
26-16		MS 561	$CDCl_3$: 0.98 (t, 3H), 1.81-1.72 (m, 2H), 2.49 (t, 4H), 2.66 (t, 2H), 3.12-3.08(m, 2H), 3.18 (t, 2H), 3.74(t, 4H), 3.86(s,3H), 6.53(dd, 1H), 6.20(dd, 1H), 6.26 (d, 1H), 7.13(bs, 1H), 7.25-7.21 (m, 1H), 7.62-7.57(m, 1H), 7.87(dd, 1H), 7.93(dd, 1H), 8.12(s, 1H), 8.62(d, 1H), 9.40(s, 1H)

26-17		MS 518	$CDCl_3$: 0.98 (t, 3H), 1.78-1.73 (m, 2H), 2.49 (t, 4H), 2.66 (t, 2H), 2.94-2.92 (m, 4H), 3.15-3.11(m, 2H), 3.76-3.73(m, 4H), 3.88(s,3H), 6.52(dd, 1H), 6.82(d, 1H), 7.28-7.24 (m, 1H), 7.57(bs, 1H), 7.25-7.21 (m, 1H), 7.68-7.63(m, 1H), 7.95(dd, 1H), 8.02(d, 1H), 8.20(s, 1H), 8.56(d, 1H), 9.41(s, 1H)
26-18		MS 559	$CDCl_3$: 0.97 (t, 3H), 1.81-1.72 (m, 2H), 2.08-2.00 (m, 2H), 2.49 (t, 4H), 2.66 (t, 2H), 2.40 (t, 2H), 3.59 (t, 2H), 3.69(t, 2H), 3.87(s,3H), 6.41 (dd, 1H), 6.51(d, 1H), 7.29-7.25 (m, 2H), 7.65-7.60(m, 1H), 7.95(dd, 1H), 8.05(d, 1H), 8.15(s, 1H), 8.56(d, 1H), 9.41(s, 1H)
26-19		MS 587	$CDCl_3$: 0.98 (t, 3H), 1.82-1.73 (m, 2H), 2.14 (s, 3H), 3.12-3.08 (m, 2H), 3.55-3.45(m, 2H), 3.66-3.56 (m, 4H), 3.79-3.68 (m, 2H), 3.95(s,3H), 6.95(dd, 1H), 7.03 (d, 1H), 7.32-7.28(m, 1H), 7.69-7.64 (m, 1H), 7.71(s, 1H), 7.97(dd, 1H), 8.22 (s, 1H), 8.39(d, 1H), 8.52(d, 1H), 9.46(s, 1H)
26-20		MS 546	$CDCl_3$: 0.97 (t, 3H), 1.82-1.73 (m, 2H), 3.12-3.08 (m, 2H), 3.80-3.58(m, 8H), 3.94(s,3H), 6.94(dd, 1H), 7.02 (d, 1H), 7.32-7.28(m, 1H), 7.69-7.64 (m, 1H), 7.32-7.28(m, 1H), 7.97(dd, 1H), 8.21 (s, 1H), 8.34(d, 1H), 8.52(d, 1H), 9.45(s, 1H)
26-21		MS 615	$CDCl_3$: 0.97 (t, 3H), 1.82-1.72 (m, 2H), 2.71 (t, 3H), 3.05 (s, 2H), 3.10 (m, 2H), 3.18 (t, 4H), 3.88(s,3H), 4.17-4.08 (m, 1H), 6.47 (dd, 1H), 6.54 (d, 1H), 6.99-6.89(m, 1H), 7.28-7.24 (m, 1H), 7.31(bs, 1H), 7.65-7.60 (m, 1H), 7.32-7.28(m, 1H), 7.95(dd, 1H), 8.05 (d, 1H), 8.15(s, 1H), 8.59(d, 1H), 9.41(s, 1H)

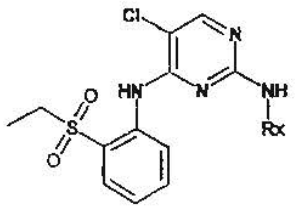
26-22		MS 530	$CDCl_3$: 0.98 (t, 3H), 1.80-1.74 (m, 2H), 3.12-3.08 (m, 2H), 3.45-3.42 (m, 2H), 3.55-3.53 (m, 2H), 3.87 (s, 2H), 3.89(s,3H), 5.98-5.89 (m, 1H), 6.44 (dd, 1H), 6.50(d, 1H), 7.35-7.19 (m, 2H), 7.62-7.58(m, 1H), 7.95(dd, 1H), 8.09 (d, 1H), 8.15(s, 1H), 8.57(d, 1H), 9.43(s, 1H)
26-23		MS 558	$CDCl_3$: 0.97 (t, 3H), 1.10 (s, 3H), 1.12 (s, 3H), 1.80-1.74(m, 2H), 2.80-2.63 (m, 5H), 3.12-3.08 (m, 2H), 3.19-3.17 (m, 4H), 3.87(s,3H), 6.48 (dd, 1H), 6.56(d, 1H), 7.30-7.23 (m, 2H), 7.62-7.58(m, 1H), 7.94(dd, 1H), 8.00 (d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.40(s, 1H)
26-24		MS 544	$CDCl_3$: 0.98 (t, 3H), 1.81-1.72 (m, 2H), 2.03-1.91 (m, 1H), 2.28-2.19 (m, 1H), 2.33 (s, 6H), 2.92-2.84 (m, 1H), 3.12-3.08 (m, 2H), 3.17(t, 1H), 3.35(ddd, 1H), 3.51-3.42 (m, 2H), 3.87 (s, 3H), 6.11 (dd, 1H), 6.14 (d,1H), 7.09 (s, 1H), 7.26-7.20(m, 1H), 7.60-7.56 (m, 1H), 7.85(d, 1H), 7.92(dd, 1H), 8.11(s, 1H), 8.38(d, 1H), 9.41(s, 1H)
26-25		MS 530	$CDCl_3$: 0.98 (t, 3H), 1.82-1.71 (m, 2H), 1.96-1.86 (m, 1H), 2.33-2.20 (m, 1H), 2.51 (s, 1H), 3.17-3.08 (m, 3H), 3.35-3.30 (m, 1H), 3.54-3.30 (m, 3H), 3.87 (s, 3H), 6.12 (dd, 1H), 6.16 (d,1H), 7.09 (s, 1H), 7.32-7.21(m, 1H), 7.58 (dd, 1H), 7.85(d, 1H), 7.92(dd, 1H), 8.11(s, 1H), 8.64(d, 1H), 9.40(s, 1H)
26-26		MS 546	$CDCl_3$: 0.98 (t, 3H), 1.83-1.71 (m, 2H), 1.98-1.81 (m, 2H), 2.16-2.02(m, 2H), 2.53-2.28 (m, 5H), 2.87-2.72 (m, 2H), 3.12-3.08 (m, 2H), 3.88 (s, 3H), 4.32 (bs, 3H), 6.44 (dd, 1H), 6.53(d, 1H), 7.32-7.25 (m, 2H), 7.63-7.59 (m, 2H), 7.94(dd, 1H), 8.04 (d, 1H), 8.15(s, 1H), 8.57(d, 1H), 9.42(s, 1H)

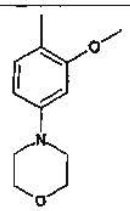
26-27		MS 545	$CDCl_3$: 0.97 (t, 3H), 1.38-1.30 (m, 1H), 1.49-1.40 (m, 2H), 1.70-1.62 (m, 1H), 1.83-1.72 (m, 2H), 1.89 (d, 2H), 2.74-2.10 (m, 2H), 3.12-3.08 (m, 2H), 3.57 (d, 2H), 3.63 (d, 2H), 3.90 (s,3H), 6.50 (d, 1H), 6.58 (s, 1H), 7.34-7.24 (m, 2H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 8.02 (d, 1H), 8.14(s, 1H), 8.60(dd, 1H), 9.40(s, 1H)
26-28		MS 517	$CDCl_3$: 0.97 (t, 3H), 1.88-1.65 (m, 3H), 2.05-1.97 (m, 2H), 2.21-2.08 (m, 1H), 2.67-2.55 (m, 4H), 2.78-2.71(m, 2H), 3.12-3.08 (m, 2H), 3.61 (d, 2H), 3.87 (s,3H), 6.47 (dd, 1H), 6.56 (d, 1H), 7.28-7.23 (m, 2H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 7.99 (d, 1H), 8.13(s, 1H), 8.60(dd, 1H), 9.39(s, 1H)
26-29		MS 585	$CDCl_3$: 0.97 (t, 3H), 1.89-1.65 (m, 8H), 2.03 (d, 2H), 2.20-2.10 (m, 1H), 2.68-2.58 (m, 4H), 2.78-2.72 (m, 2H), 3.12-3.08 (m, 2H), 3.61(d, 2H), 3.87(s,3H), 6.47 (dd, 1H), 6.56(d, 1H), 7.30-7.23 (m, 2H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 7.99 (dd, 1H), 8.13(s, 1H), 8.60(dd, 1H), 9.39 (s, 1H)
26-30		MS 451, 453	0.97 (t, 3H), 1.71-1.82 (m, 2H), 3.06-3.14 (m, 2H), 3.89 (s, 1H), 6.60 (ddd, 1H), 6.66 (dd, 1H), 7.25-7.30 (m, 1H), 7.35 (br.s, 1H), 7.63 (dd, 1H), 7.95 (dd, 1H), 8.09-8.18 (m, 1H), 8.17 (s, 1H), 8.52 (dd, 1H), 9.42 (s, 1H).
26-31		MS 647, 649	0.98 (t, 3H), 1.71-1.83 (m, 2H), 2.18 (s, 3H), 2.47-2.64 (m, 4H), 2.72-2.84 (m, 2H), 3.08-3.15 (m, 2H), 3.42-3.54 (m, 2H), 3.58-3.69 (m, 2H), 3.84 (s, 3H), 3.94-4.03 (m, 2H), 6.45-6.51 (m, 1H), 6.78 (d, 1H), 7.22-7.27 (m, 1H), 7.60 (s, 1H), 7.67-7.74 (m, 1H), 7.93-7.97 (m, 1H), 7.73 (d, 1H), 8.02 (s, 1H), 8.54 (d, 1H), 9.33 (s, 1H).

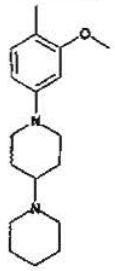
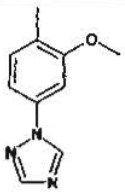
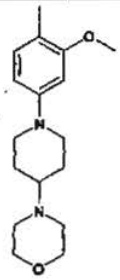
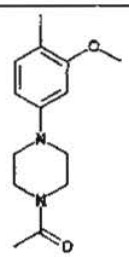
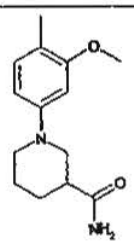
26-32		m.p. 139,4	400MHz, CDCl3, δ (ppm): 0.98 (t; 3H), 1.55-1.90 (m; 6H), 2.38 (s; 3H), 2.45-2.80 (m; 6H), 3.13 (m; 2H), 3.47 (m; 2H), 3.84 (s; 3H), 6.54 (dd; 1H), 6.79 (d; 1H), 7.23 (dd; 1H); 7.51 (s; 1H), 7.64 (dd: 1H), 7.92 (d; 1H), 8.00 (s; 1H), 8.19 (s; 1H), 8.57 (d; 1H), 9.41 (s; 1H).
26-33		m.p. 163,4	400MHz, CDCl3, δ (ppm): 0.98 (t; 3H), 1.50-1.90 (m; 6H), 2.24 (bs; 1H), 2.45-2.65 (m; 6H), 3.12 (m; 2H), 3.45 (m; 2H), 3.77 (m; 4H9, 3.85 (s; 3H), 6.55 (dd; 1H); 6.79 (d; 1H), 7.24 (dd; 1H). 7.52 (s; 1H), 7.64 (dd; 1H), 7.93 (d; 1H), 8.01 (s; 1H), 8.20 (s; 1H9, 9.42 (s; 1H).
26-34		m.p. 232,9	400MHz, CDCl3, δ (ppm): 1.00 (s; 3H), 1.78 (m; 2H), 2.83 (s; 3H), 3.03 (m; 2H), 3.12 (m; 2H), 3.38-3.60 (m; 8H), 3.88 (s; 3H), 6.56 (m; 1H), 6.82 (d; 1H), 7.29 (m; 1H), 7.60 (s; 1H), 7.64 (m; 1H), 7.95 (d; 1H), 8.12 (s; 1H), 8.20 (s; 1H), 8.59 (d; 1H), 9.50 (s; 1H).
26-35		m.p. 197,3	400MHz, CDCl3, δ (ppm): 0.99 (t; 3H), 1.43 (m; 1H), 1.63 (m; 2H), 1.77 (m; 2H), 1.90 (m; 2H), 2.70 (m; 2H), 3.13 (m; 2H), 3.28 (m; 2H), 3.75 (s; 1H), 3.84 (s; 3H), 6.55 (m; 1H), 6.80 (d; 1H), 7.24 (m; 1H), 7.53 (s; 1H), 7.64 (s; 1H), 7.93 (d; 1H), 8.02 (s; 1H), 8.20 (s; 1H), 8.58 (d; 1H), 9.41 (s; 1H).
26-36		m.p. 147,6	400MHz, CDCl3, δ (ppm): 1.00 (t; 3H), 1.78 (m; 2H), 3.12 (m; 2H), 3.56 (m; 1H), 3.87 (s; 3H), 6.53 (dd; 1H), 6.80 (d; 1H), 7.30 (dd; 1H), 7.52 (s; 1H), 7.64 (m; 1H), 7.95 (dd; 1H), 8.08 (s; 1H), 8.20 (s; 1H), 8.60 (d; 1H), 9.48 (s; 1H).
26-37		m.p. 143.2	500MHz, CDCl3, δ (ppm): 0.96 (t; 3H), 1.70 (m; 2H), 2.11 (m; 1H), 2.39 (m; 1H), 2.75 (s; 3H), 3.02 (m; 1H), 3.22 (m; 2H), 3.43 (d; 2H), 3.82 (s; 3H), 3.86 (m; 1H), 6.40 (dd; 1H), 6.94 (d; 1H), 7.34 (ddd; 1H), 7.47 (s; 1H), 7.63 (ddd; 1H), 7.93 (dd; 1H), 8.18 (s; 1H), 8.51

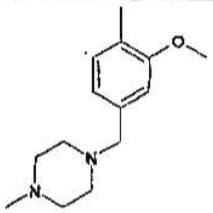
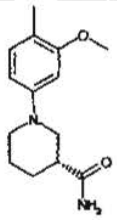
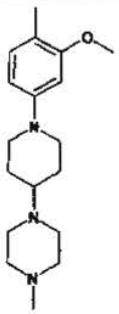
			(d; 1H).
26-38		m.p. 133.5	400MHz, CDCl3, δ (ppm): 1.00 (t; 3H), 1.70-1.95 (m; 6H), 2.63 (s; 1H), 2,92 (s; 1H), 3.00-3.25 (m; 5H), 3.89 (s; 3H), 5.42 (s; 1H), 6.70 (s; 1H), 6.83 (m; 2H), 7.25 (m; 1H), 7.55 (s; 1H), 7.63 (m; 1H9, 8.95 (m; 1H), 8.15 (s; 1H), 8.23 (s; 1H), 8.54 (d; 1H), 9.45 (s; 1H).
26-39		m.p. 188.8	400MHz, CDCl3, δ (ppm): 0.99 (t; 3H), 1.70-1.90 (m; 3H), 2.08 (m; 1H), 2.28 (s; 6H9, 2.83 (s; 1H), 3.00-3.23 (m; 4H9, 3.37 (m; 1H), 3.83 (s; 3H), 6.19 (dd; 1H), 6.83 (d; 1H), 7.23 (dd; 1H), 7.50 (s; 1H), 7.59 (m; 2H), 7.93 (d; 1H), 8.19 (s; 1H), 8.60 (d; 1H), 9.42 (s; 1H).

The following 5-Chloro-N^2-(substituted phenyl)-N^4-[2-ethanesulfonyl-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-ethanesulfonyl-phenyl]-amine and the corresponding aniline following the procedure of Example 7A



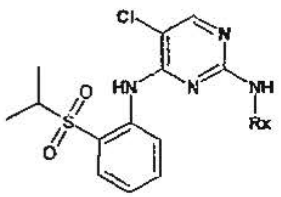
Expl No.	Rx	Rf (solvent) or MS	NMR (400MHz), δ (ppm) or Retention time min. (HPLC)
27-1		0.53 (AcOEt)	$CDCl_3$: 1.28(t,3H), 3.12-3.19(m, 6H), 3.87-3.89(m, 7H), 6.45(dd, 1H), 6.53(d,1H), 7.24-7.28(m,1H), 7.31(s, 1H), 7.60-7.64(m, 1H), 7.95(dd, 1H), 8.04(d, 1H), 8.14(s, 1H), 8.58(d, 1H), 9.39(s, 1H)

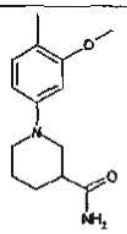
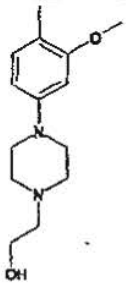
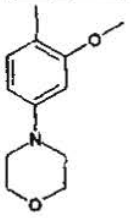
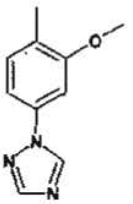
27-2		585 (M+H)	2.38
27-3		486 (M+H)	3.07
27-4		587 (M+H)	2.29
27-5		545 (M+H)	2.59
27-6		545 (M+H)	2.45

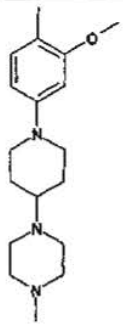
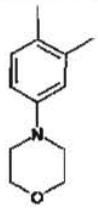
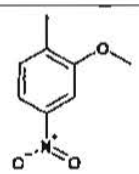
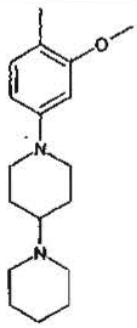
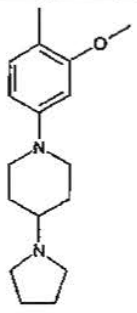
27-7		531 (M+H)	2.25
27-8		545 (M+H)	2.45
27-9		600 (M+H)	2.17

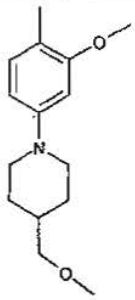
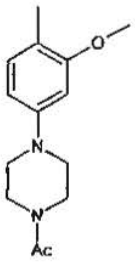
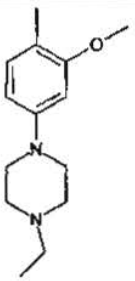
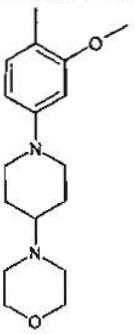
HPLC condition
Column: YMC CombiScreen ODS-A (5um, 12nm), 50 x 4.6 mm I.D.
Flow rate: 2.0 ml/min
Eluent: A) TFA/water (0.1/100), B) TFA/acetonitrile (0.1/100)
Gradient: 5-100%B (0-5min)
Detection: UV at 215nm

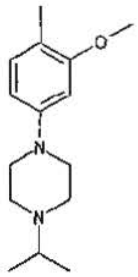
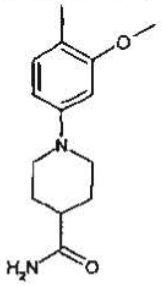
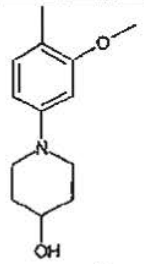
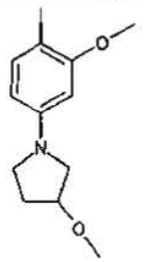
The following 5-Chloro-N^2-(substituted phenyl)-N^4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-2-sulfonyl)-phenyl]-amine and the corresponding aniline following the procedure of Example 7A

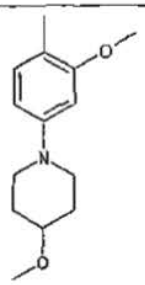
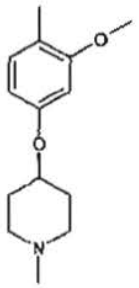
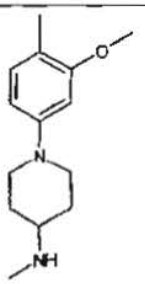
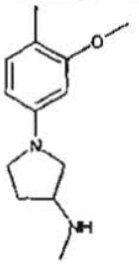


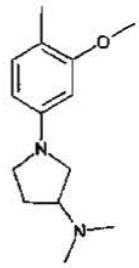
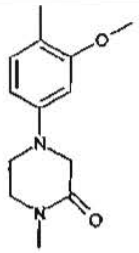
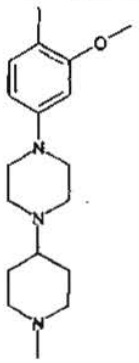
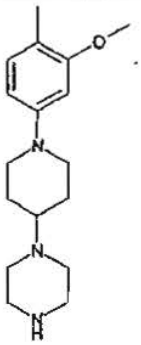
ExpIN o.	Rx	Rf (solvent) or MS	NMR (400MHz) , δ (ppm) or Retention time min. (HPLC)
28-1		0.2 (AcOEt)	$CDCl_3$: 1.31 (d, 6H), 1.85-1.73 (m, 1H), 1.86-1.98 (m, 3H), 2.62-2.70 (m, 1H), 3.11-3.13 (m, 2H), 3.21-8.28 (m, 1H), 3.28 (m, 2H), 3.88 8s, 3H), 5.41 (brs, 1H), 6.53 (d, 1H), 6.59 (d, 1H), 6.64 (brs, 1H), 7.28-7.34 (m, 1H), 7.34 (s, 1H), 7.60-7.67 (m, 1H), 7.91 (dd, 1H), 8.08 (d, 1H), 8.13 (s, 1H), 8.60 (d, 1H), 9.55 (s, 1H).
28-2		MS m/z 561, 563 (M+1).	$CDCl_3$: 1.31(d, 6H), 2.64 (t, 2H), 2.68-2.77 (m, 4H), 3.19(t, 4H), 3.17-3.28(m, 1H), 3.68(t, 2H), 3.88(s, 3H), 6.48(dd, 1H), 6.55 (d, 1H), 7.23-7.32(m, 1H), 7.62(ddd, 1H), 7.91(dd, 1H), 8.04(dd, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.54(bs, 1H)
28-3		0.55 (AcOEt)	$CDCl_3$: 1.31(d, 6H), 3.12-3.14(m, 4H), 3.21-3.27(m, 1H), 3.87-3.89(m, 7H), 6.46(dd, 1H), 6.53(d,1H), 7.23-7.27(m, 1H), 7.30(s, 1H), 7.59-7.64(m, 1H), 7.91(dd, 1H), 8.05(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.55(s, 1H)
28-4		0.37 (AcOEt)	$CDCl_3$: 1.32(d, 6H), 3.21-3.27(m, 1H), 4.00(s, 1H), 7.11(dd, 1H), 7.26-7.27(m, 1H), 7.29-7.33(m, 1H), 7.64(s, 1H), 7.66-7.71(m, 1H), 7.95(dd, 1H), 8.10(s, 1H), 8.21(s, 1H), 8.46(d, 1H), 8.50(s, 1H), 8.54(d, 1H), 9.59(s, 1H)

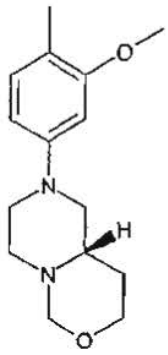
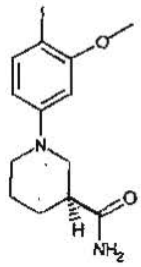
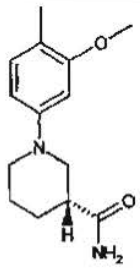
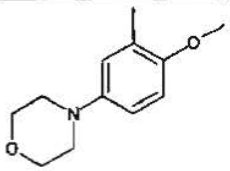
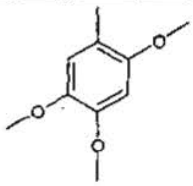
28-5		0.03 (AcOEt)	$CDCl_3$: 1.31(d, 6H), 1.67-1.77(m, 2H), 1.95-2.05 (m, 2H), 2.39-2.48 (m, 1H), 2.48-2.61(m, 2H), 2.63-2.78(m, 8H), 3.24 (sept, 1H), 3.71-3.83 (m, 2H), 3.87(s, 3H), 6.47(dd, 1H), 6.55 (d, 1H), 7.21-7.28(m, 1H), 7.61(ddd, 1H), 7.91(dd, 1H), 8.00(dd, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.53(bs, 1H)
28-6		502 (M+H)	2.84
28-7		478 (M+H)	4.53
28-8		MS 599	$CDCl_3$: 1.31(d, 6H),1.51-1.42(m, 2H), 1.67-1.53(m, 4H), 1.81-1.68(m, 2H), 1.96-1.89(m, 2H), 2.47-2.36(m, 1H), 2.57-2.54(m, 4H), 2.69(dd, 2H)3.24(sept, 1H), 3.67(d,1H), 3.87(s , 1H), 6.48 (dd, 1H), 6.56 (d, 1H), 7.31-7.21(m, 1H), 7.63-7.59 (m, 1H), 8.00(d, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.55(s, 1H)
28-9		MS 585	$CDCl_3$: 1.26 (t, 3H), 1.31(d, 6H),1.74-1.68(m, 2H), 1.85-1.76(m, 4H), 2.08-1.98(m, 2H), 2.19-2.10(m, 2H), 2.67-2.58(m, 4H), 2.79-2.72(m, 2H), 3.24(sept, 1H) 3.61(d, 2H), 3.87(s,3H), 6.48(dd, 1H), 6.56 (d, 1H), 7.29-7.22 (m, 1H), 7.62(dd, 1H), 7.90(dd, 1H), 7.99(d, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.53(s, 1H)

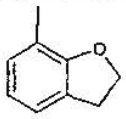
28-10		MS 559	$CDCl_3$: 1.31(d, 6H),1.59-1.37(m, 2H), 1.81-1.69(m, 1H), 1.87(d, 2H), 2.73-2.67(m, 2H), 3.28-3.21(m, 1H), 3.37(s, 3H),3.61(d, 1H),3.87(s, 3H),6.49(dd, 1H),6.57(s, 1H), 7.31-7.21(m, 1H),7.64-7.60 (m, 1H), 7.91(dd, 1H), 8.00(d, 1H), 8.60(d, 1H) 9.53(s, 1H)
28-11		MS 558	$CDCl_3$: 1.31(d, 6H), 2.15(s, 3H), 3.12(ddd, 4H), 3.24(sept, 1H), 3.64 (t, 2H), 3.80(t, 2H), 3.89(s, 3H),6.47(dd, 1H),6.55(d, 1H),7.29-7.24(m, 1H),7.33(bs, 1H), 7.62(m, 1H),7.92(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H) 9.55(s, 1H)
28-12		MS 544	$CDCl_3$: 1.16, (t, 3H), 1.31(d, 6H), 2.56-2.44(b, 2H), 2.71-2.60 (m, 4H), 3.28-3.17(m, 5H), 3.88(s, 3H), 6.48(dd, 1H),6.58(d, 1H),7.30-7.22(m, 1H), 7.63-7.58(m, 1H),7.90(dd, 1H), 8.01(d, 1H), 8.12(s, 1H), 8.60(d, 1H) 9.54(s, 1H)
28-13		MS 601	$CDCl_3$: 1.31(d, 6H, J=6.55),1.75-1.63(m, 2H),2.00-1.91(m, 2H),2.37-2.27(m, 1H),2.60 (t, 4H, J=4.79), 2.74-2.59(m, 2H), 3.24(sept, 1H), 3.66 (d, 2H, J=12.1), 3.75(t, 4H, J=4.53), 3.88(s, 3H), 6.48(dd, 1H, J=2.52, 8.56),6.56(d, 1H, J=2.52),7.33-7.22(m, 1H), 7.64-7.59 (m, 1H),7.91(dd, 1H, J=8.05, 1.51), 8.01(d, 1H, J=8.56), 8.12(s, 1H), 8.61(d, 1H, J=7.55) 9.54(s, 1H)

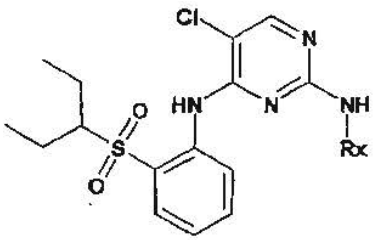
28-14		MS 559	$CDCl_3$: 1.11 (d, 6H, J=6.55), 1.31(d, 6H, J=7.05), 2.82-2.68(m, 5H), 3.20-3.17(m, 4H), 3.28-3.17(m, 1H), 3.87(s, 3H), 6.48(dd, 1H, J=2.52, 8.56),6.56(d, 1H, J=2.52),7.33-7.24(m, 1H), 7.62-7.58(m, 1H),7.90(dd, 1H, J=), 8.01(d, 1H, J=8.56), 8.12(s, 1H), 8.60(d, 1H, J=8.56) 9.54(s, 1H)
28-15		MS 559	$CDCl_3$: 1.31 (d, 6H, J=7.05), 1.97-1.85(m, 2H), 2.17-1.98(m, 2H), 2.35-2.25(m, 1H), 2.75(m, 2H), 3.24(sept, 1H), 3.65(d, 2H), 3.88(s, 3H), 5.30 (bs, 1H), 5.48(bs, 1H), 6.48(dd, 1H, J=2.51, 8.56), 6.56(d, 1H, J=2.52), 7.33-7.21(m, 1H), 7.62 (m, 1H), 7.91(dd, 1H, J=1.51, 8.06), 8.03(dd, 1H, J=3.02, 8.56), 8.13(s, 1H), 8.60(d, 1H, J=8.57), 9.54(s, 1H)
28-16		MS 532	$CDCl_3$: 1.31 (d, 6H, J=7.06), 1.46-1.43(m, 1H), 1.79-1.68(m, 2H), 2.08-1.99(m, 2H),2.99-2.88(m, 2H), 3.24(sept, 1H), 3.51-3.45(m, 2H), 3.91-3.80(m, 1H), 3.88(s, 3H), 6.49(dd, 1H, J=2.52, 8.56),6.57(d, 1H, J=2.52),7.34-7.23(m, 1H), 7.64-7.60(m, 1H),7.91(dd, 1H, J=1.51, 8.06), 8.02(dd, 1H, J=3.02, 9.06), 8.13(s, 1H), 8.60(d, 1H, J=8.06) 9.53 (s, 1H)
28-17		MS 532	$CDCl_3$: 1.31 (d, 6H, J=6.96), 2.18-2.12(m, 2H), 3.24(sept, 1H),3.37-3.32(m, 2H), 3.39(s, 3H), 3.43(d, 1H, J=8.56), 3.51(dd, 1H, J=5.04, 10.6), 3.87(s, 3H), 4.17—4.09 (m,1H) 6.13 (dd, 1H, J=2.51, 8.56),6.16(d, 1H, J=2.52),7.09(bs, 1H),7.31-7.21(m, 1H), 7.60-7.56 (m, 1H),7.85(d, 1H, J=8.56), 7.89(dd, 1H, J=1.51, 8.06), 8.10(s, 1H), 8.65(d, 1H, J=9.06) 9.54 (s, 1H)

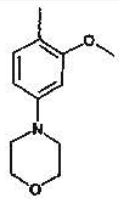
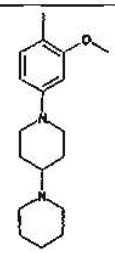
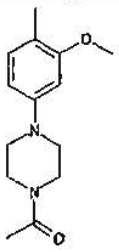
28-18		MS 546	$CDCl_3$: 1.31 (d, 6H, J=7.05), 1.82-1.70(m, 2H), 2.08-1.99(m, 2H),2.96-2.87(m, 2H), 3.24(sept, 1H), 3.41-3.33(m, 1H), 3.40(s, 3H),3.51-3.42(m, 2H), 3.87(s, 3H), 6.49(dd, 1H, J=2.52, 9.07),6.57(d, 1H, J=2.52),7.32-7.22(m, 1H), 7.64-7.60 (m, 1H),7.91(dd, 1H,), 8.00(dd, 1H, J=3.02, 9.06), 8.12(s, 1H), 8.60(d, 1H, J=8.56) 9.53 (s, 1H)
28-19		0.33 (AcOEt)	$CDCl_3$: 1.31 (d, 6H, J=7.05), 1.82-1.70(m, 2H), 2.08-1.99(m, 2H),2.96-2.87(m, 2H), 3.24(sept, 1H), 3.41-3.33(m, 1H), 3.40(s, 3H),3.51-3.42(m, 2H), 3.87(s, 3H), 6.49(dd, 1H, J=2.52, 9.07),6.57(d, 1H, J=2.52),7.32-7.22(m, 1H), 7.62(m, 1H),7.91(dd, 1H,), 8.00(dd, 1H, J=3.02, 9.06), 8.12(s, 1H), 8.60(d, 1H, J=8.56) 9.53 (s, 1H)
28-20		MS 544	$CDCl_3$: 1.31 (d, 6H), 1.66-1.53(m, 2H), 2.10-2.01(m, 2H),2.51 (s, 3H), 2.70-2.13(m, 1H),2.83-2.74(m, 2H), 3.24(Sept, 1H), 3.63-3.55(m, 2H), 3.87(s, 3H), 4.34-4.25(m, 1H), 6.48(dd, 1H),6.56(d, 1H),7.34-7.24(m, 1H), 7.64-7.60(m, 1H),7.90(dd, 1H), 8.00(d, 1H), 8.12(s, 1H), 8.60(dd, 1H), 9.53(s, 1H)
28-21		MS 531	$CDCl_3$: 1.30 (s, 3H),1.32 (s, 3H), 2.33-2.22(m, 1H), 2.54(s, 3H), 3.37-3.20(m, 3H),3.57-3.44(m, 3H), 3.86(s, 3H), 6.12(dd, 1H),6.16(d, 1H),7.14-7.08(m, 1H), 7.30-7.20(m, 1H),7.65-7.58(m, 1H), 7.93-7.87(m, 1H,), 8.10(s, 1H), 8.64(d, 1H) 9.54 (s, 1H)

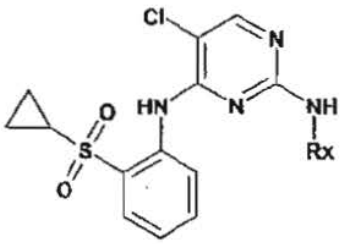
28-22		MS 545	$CDCl_3$: 1.30 (s, 3H), 1.32 (s, 3H), 2.03-1.89(m, 1H),2.30-2.18(m, 1H), 2.34(s, 6H),2.96-2.83(m, 1H), 3.29-3.16(m, 2H), 3.40-3.34(m, 1H),3.53-3.43(m, 2H), 3.87(s, 3H), 6.11(dd, 1H,) 6.13(dd, 1H),7.08(bs, 1H),7.31-7.21(m, 1H), 7.60-7.56(m, 1H),7.85(d, 1H), 7.89(dd, 1H), 8.10(s, 1H), 8.66(d, 1H) 9.54(s, 1H)
28-23		MS 545	$CDCl_3$: 1.31 (s, 3H), 1.32 (s, 3H),3.05(s, 3H), 3.24(sept, 1H), 3.50-3.43(m, 4H),3.85(s, 2H), 3.89(s, 3H), 6.11(dd, 1H,) 6.43(dd, 1H),6.50(d, 1H),7.31-7.28(m, 1H), 7.64-7.60(m, 1H),7.92(dd, 1H), 8.09(d, 1H), 8.13(s, 1H), 8.58(d, 1H) 9.55(s, 1H)
28-24		0.05 (AcOEt/MeOH=4/1)	$CDCl_3$: 1.30 (s, 3H), 1.32 (s, 3H), 1.92-1.83(m, 1H),2.17-1.95(m, 1H), 2.43-2.27(m, 2H),2.79-2.71(m, 4H), 3.15-2.97(m, 4H), 3.23-3.16(m, 4H),3.24(sept, 1H), 3.87(s, 3H), 6.11(dd, 1H,) 6.47(dd, 1H),6.55(d, 1H),7.33-7.23(m, 1H), 7.63-7.59(m, 1H),7.95(dd, 1H), 8.01(dd, 1H), 8.12(s, 1H), 8.60(d, 1H) 9.54(s, 1H)
28-25		MS 600	$CDCl_3$: 1.30 (s, 3H), 1.32 (s, 3H), 1.80-1.70(m, 2H),2.01-1.93(m, 2H), 2.49-2.28(m, 12H),2.76-2.62(m, 4H), 3.04-2.96(m, 4H), 3.16-3.05(m, 2H),3.24(sept, 1H), 3.72-3.63(m, 2H), 3.87(s, 3H),6.48(dd, 1H),6.55(d, 1H),7.31-7.23(m, 1H), 7.66-7.589(m, 1H),7.91(dd, 1H), 8.01(d, 1H), 8.12(s, 1H), 8.60(d, 1H) 9.53(s, 1H)

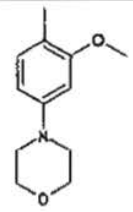
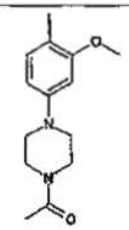
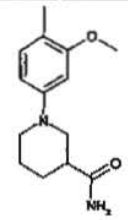
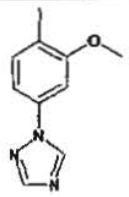
28-26		MS 573	$CDCl_3$: 1.30 (s, 3H), 1.32 (s, 3H), 2.59-2.43 (m, 4H),2.78-2.73(m, 1H), 3.00-2.86(m, 2H),3.38-3.20(m, 3H), 3.54-2.45(m, 1H), 3.73(dd, 1H),3.84-3.77(m, 1H), 3.94-3.87(m, 1H), 3.88(s, 3H),6.46(dd, 1H),6.53(d, 1H),7.32-7.23(m, 1H), 7.31 (bs, 1H), 7.63-7.52(m, 1H),7.91(dd, 1H), 8.04(d, 1H), 8.13(s, 1H), 8.60(d, 1H) 9.54(s, 1H)
28-27		MS 559	$CDCl_3$: 1.30(s, 3H), 1.32 (s, 3H), 1.82-1.73 (m, 1H), 1.97-1.84(m, 3H), 2.73-2.51 (m, 1H), 3.12(t, 2H), 3.31-3.20 (m, 3H), 3.90(s,3H), 5.46-5.37(m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.68-6.62 (m, 1H), 7.28-7.21 (m, 1H), 7.33(bs, 1H), 7.65-7.61(m, 1H), 7.92(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.55(s, 1H)
28-28		MS 559	$CDCl_3$: 1.30(s, 3H), 1.32 (s, 3H), 1.82-1.73 (m, 1H), 1.97-1.84(m, 3H), 2.73-2.51 (m, 1H), 3.12(t, 2H), 3.31-3.20 (m, 3H), 3.90(s,3H), 5.46-5.37(m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.68-6.62 (m, 1H), 7.28-7.21 (m, 1H), 7.33(bs, 1H), 7.65-7.61(m, 1H), 7.92(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.55(s, 1H)
28-29		MS 413	$CDCl_3$: 1.31 (s, 3H), 1.33(s, 3H),2.92(t, 4H), 3.28(sept, 1H) 3.73(t, 4H), 3.87(s,3H), 6.51(dd, 1H), 6.82(d, 1H), 7.32-7.23 (m, 1H), 7.57(bs, 1H), 7.70-7.64(m, 1H), 7.92(dd, 1H), 8.01(bs, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.53(s, 1H)
28-30		MS 493	$CDCl_3$: 1.30 (s, 3H), 1.33(s, 3H), 3.25(sept, 1H) 3.60 (bs,3H), 3.89(s, 3H), 6.59(s, 1H), 7.27-7.18 (m, 1H),7.61(dd, 1H), 7.83(bs, 1H), 7.90(dd, 1H), 8.15 (s , 1H), 8.55(d, 1H), 9.55(s, 1H)

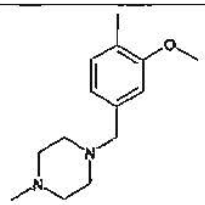
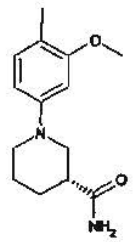
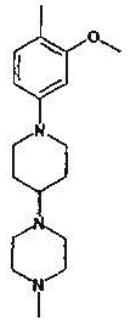
28-31		MS 445	$CDCl_3$: 1.31(d, 6H),1.59-1.37(m, 2H), 1.81-1.69(m, 1H), 1.87(d, 2H), 2.73-2.67(m, 2H), 3.28-3.21(m, 1H), 3.37(s, 3H),3.61(d, 1H),3.87(s, 3H),6.49(dd, 1H),7.025(bs, 1H), 7.28-7.23(m, 1H),7.64-7.59(m, 1H), 7.93-7.89(m, 2H), 8.15(s, 1H), 8.57(dd, 1H) 9.56(s, 1H)

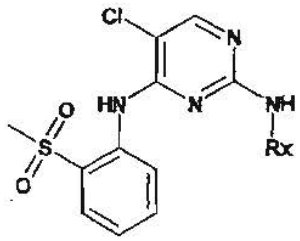


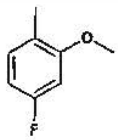
Expl No.	Rx	HPLC Retention time (min)	Mass (ESI) m/z
29-1		3.30	546 (M+H)
29-2		2.82	627 (M+H)
29-3		3.07	587 (M+H)

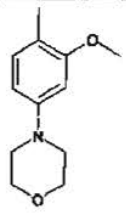


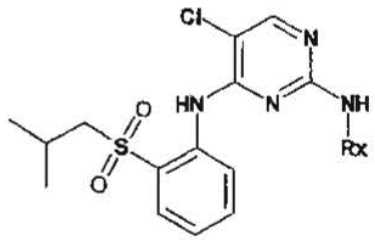
Expl No.	Rx	HPLC Retention time (min)	Mass (ESI) m/z
30-1		2.82	516 (M+H)
30-2		2.65	557 (M+H)
30-3		2.50	557 (M+H)
30-4		3.10	498 (M+H)

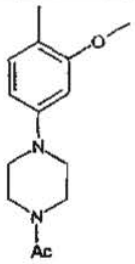
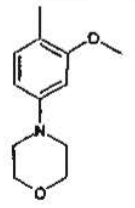
30-5		2.30	543 (M+H)
30-6		2.52	557 (M+H)
30-7		2.23	612 (M+H)

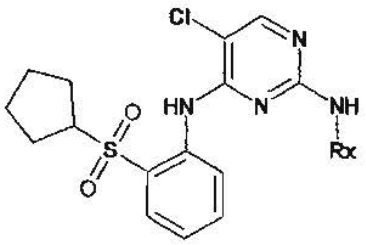


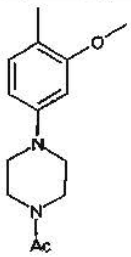
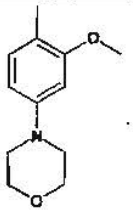
Expl No.	Rx	HPLC Retention time (min)	Mass (ESI) m/z
31-1		3.15	423 (M+H)

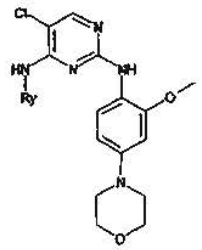
31-2		2.62	490 (M+H)

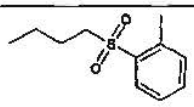


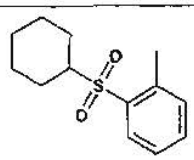
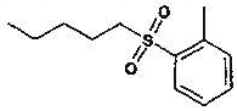
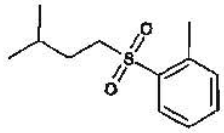
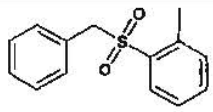
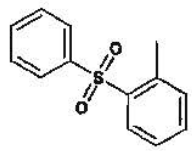
Expl No.	Rx	MS	NMR (400MHz) in $CDCl_3$, δ (ppm)
32-1		585.3	1.03 (s, 3H), 1.04(s, 3H),2.15(s, 3H), 2.32(sept, 1H) 3.00(d, 2H) 3.10(t, 2H), 3.13(t, 2H), 3.64(t, 2H),3.79(t, 2H), 3.89(s,3H), 6.45(dd, 1H), 6.55(d, 1H), 7.34-7.26 (m, 1H), 7.52(bs, 1H), 7.64-7.60(m, 1H), 7.97(dd, 1H), 8.07(d, 1H), 8.15(s, 1H), 8.54(d, 1H), 9.32(s, 1H)
32-2		532 (M+H)	3.17

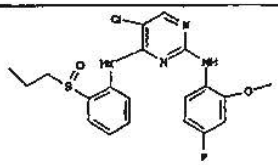
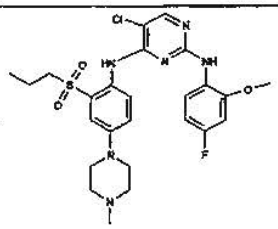


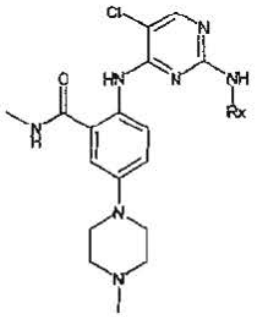
Expl No.	Rx	MS	NMR (400MHz) in $CDCl_3$, δ (ppm)
33-1		585.3	1.66-1.52 (m, 2H), 1.92-1.73 (m, 4H), 2.12-2.03 (m, 2H), 2.15(s, 3H), 3.00(d, 2H) 3.11(t, 2H), 3.14(t, 2H), 3.58-3.46(m, 1H), 3.64 (t, 2H),3.80(t, 2H), 3.89(s,3H), 6.48(dd, 1H), 6.55(d, 1H), 7.30-7.24 (m, 1H), 7.52(bs, 1H), 7.63-7.58(m, 1H), 7.94(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.54(s, 1H)
33-2		544 (M+H)	3.15

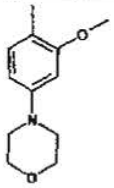
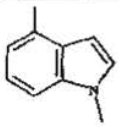


Expl No.	Rx	HPLC Retention time (min)	Mass (ESI) m/z
34-1		3.15	532 (M+H)

34-2		3.34	558 (M+H)
34-3		3.35	546 (M+H)
34-4		3.32	546 (M+H)
34-5		3.09	566 (M+H)
34-6		2.87	552 (M+H)

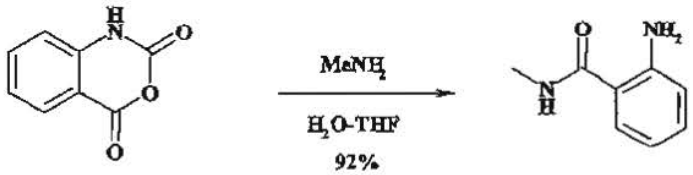
Ex No		MS	NMR (400MHz), $CDCl_3$, δ ppm
34-7		MS 435, 436	1.05 (t, 3H), 1.69-1.78 (m, 2H), 2.86-2.95 (m, 1H), 3.16-3.25 (m, 1H), 6.57-6.68 (m, 2H), 7.17 (dd, 1H), 7.35-7.39 (m, 1H), 7.50 (dd, 1H), 8.13 (s, 1H), 8.16-8.21 (m, 1H), 8.48 (d, 1H), 10.14 (s, 1H)
34-8		MS 549, 551	0.94 (t, 3H), 1.69-1.80 (m, 2H), 2.38 (s, 3H), 2.55-2.64 (m, 4H), 3.02-3.08 (m, 2H), 3.22-3.29 (m, 4H), 3.88 (s, 3H), 6.55 (ddd, 1H), 6.60-6.66 (m, 1H), 7.13-7.18 (m, 1H), 7.34 (br.s, 1H), 7.44 (d, 1H), 8.10 (s, 1H), 8.10-8.23 (m, 2H), 8.88 (s, 1H).



35-1		567 [M+1]+	DMSO-d6: 2.24 (s, 3H), 2.45-2.50 (m, 4H), 2.78 (d, 3H), 3.10-3.17 (m, 8H), 3.74-3.79 (m, 7H), 6.49 (dd, 1H), 6.66 (d, 1H), 6.85-6.89 (m, 1H), 7.18 (d, 1H), 7.40 (d, 1H), 7.98-8.02 (m, 2H), 8.29 (br.d, 1H), 8.60-8.66 (m, 1H), 11.17 (s, 1H).
35-2		505 [M+1]$^+$	DMSO-d6: 2.24(s, 3H), 2.46-2.50(m, 4H), 2.79(d, 3H), 3.13-3.17(m, 4H), 3.78(s, 3H), 6.69(d, 1H), 6.87(dd, 1H), 7.07-7.17(m, 2H), 7.19-7.23(m, 2H), 7.54(d, 1H), 8.13(s, 1H), 8.45(s, 1H), 8.65-8.75(m, 1H), 9.04(s, 1H), 11.19(s, 1H)

Example 36 (Intermediates for Left anilines)

36-1 Preparation of 2-amino-*N*-methyl-benzamide



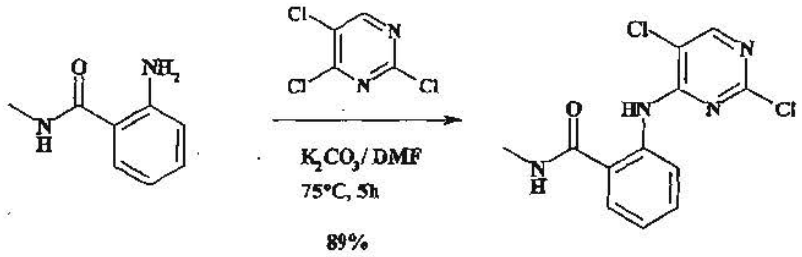
To a suspension of 16.3 g (100 mmol) of isatoic anhydride in 100mL of H_2O is added portionwise 100mL of 2N methylamine - tetrahydrofuran solution (200 mmol) at room temperature. The reaction mixture is stirred for 1 hour and then extracted with AcOEt. The organic layer is washed with H_2O and brine, dried over Na_2SO_4, and concentrated under

reduced pressure to give 13.79 g of desired product, 2-amino-*N*-methyl-benzamide (92 mmol, 92%) as colorless solid.

NMR (400MHz, CDCl3, δ): 2.97 (d, 3H, J = 4.52 Hz), 5.49 (bs, 1H), 6.07 (bs, 1H), 6.64 (ddd, 1H, J = 8.04, 7.56, 1.0 Hz), 6.68 (dd, 1H, J = 8.32, 1.0 Hz), 7.20 (ddd, 1H, J = 8.32, 7.56, 1.52 Hz), 7.29 (dd, 1H, J = 8.04, 1.52 Hz).

36-2

2-(2,5-Dichloro-pyrimidin-4-ylamino)-*N*-methyl-benzamide



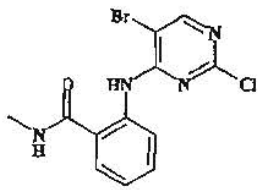
To a solution of 15.0 g (99.8 mmol) of 2-amino-*N*-methyl-benzamide in DMF (300mL) are added 2, 4, 5-trichloropyrimidine (23.8 g, 130 mmol) and potassium carbonate (17.9 g, 130 mmol). The reaction mixture is stirred at 75°C for 5 hours, cooled to room temperature, and then poured into H_2O (600mL). The resulting precipitate is collected by a filtration followed by washing with 50% aqueous CH_3CN (200mL) and dried under reduced pressure (40°C, 10 hours) to give desired 2-(2,5-dichloro-pyrimidin-4-yl-amino)-*N*-methyl-benzamide as ivory solid (26.4 g, 88.9 mmol, 89%).

NMR (400MHz, DMSO-d6, δ): 2.81 (d, 3H, J = 4.52 Hz), 7.22 (dd, 1H, J = 8.56, 8.04 Hz), 7.60 (ddd, 1H, J = 8.56, 8.56, 1.0 Hz), 7.81 (dd, 1H, J = 8.04, 1.0 Hz), 8.48 (s, 1H), 8.52 (d, 1H, J = 8.56 Hz) 8.80-8.90 (m, 1H), 12.18 (s, 1H).

According the manner described above, the following compounds are prepared.

36-3

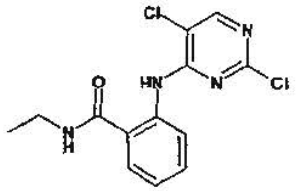
2-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzamide



NMR (400MHz, DMSO-d_6, δ): 2.81(d, 3H), 7.23(ddd, 1H, J=7.54, 7.54, 1.0Hz), 7.59(ddd, 1H, J=7.93, 8.06, 1.52Hz),7.79(dd, 1H, J=7.8, 1.52Hz), 8.47(dd, 1H J=8.06, 1.0Hz), 8.55(s, 1H), 8.81-8.87(m, 1H), 12.0(brs, 1H). Rf: 0.46 (n-Hexane: AcOEt=7:3).

36-4

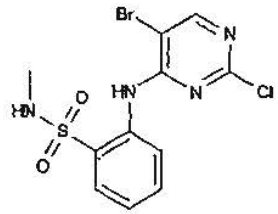
2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-ethyl-benzamide



NMR (400MHz, $CDCl_3$, δ): 1.28 (t, d=7.04, 3H), 3.48-3.57 (m, 2H), 6.22 (br. s, 1H), 7.11-7.17 (m, 1H), 7.51 (dd, J=1.0, 8.04, 1H), 7.53-7.61 (m, 1H), 8.22 (s, 1H), 8.69-8.74 (m, 1H), 11.66 (br. s, 1H). Rf : 0.60 (Hexane :AcOEt=1 :1).

36-5

Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide



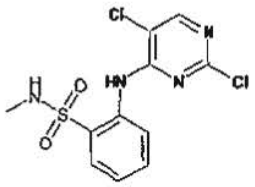
A suspension of 5-bromo-2,4-dichloropyrimidine (684 mg, 3.0 mmol) and 2-amino-N-methyl-benzenesulfonamide (559 mg, 3.0 mmol) in N,N-dimethylformamide (10 mL) containing potassium carbonate (830 mg, 6.0 mmol) is stirred at room temperature for 23 hours. Saturated aqueous ammonium chloride is added and the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane - ethyl acetate gradient) to afford the title compound as a slightly yellow solid.

^{1}H-NMR ($CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.79 (q, 1H), 7.26 (s, 1H), 7.29 (ddd, 1H), 7.66 (ddd, 1H), 7.95 (dd, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 9.52 (s, 1H). Rf (n-hexane : ethyl acetate = 10:3): 0.33.

According to the manner described above, the following compound is prepared.

36-6

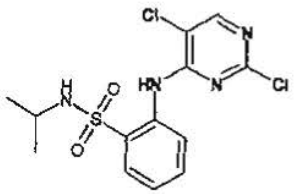
2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide



^{1}H-NMR (400MHz, $CDCl_3$, δ);2.67(d, 3H),4.97-5.04(m, 1H), 7.29(ddd, 1H, *J*=7.54, 7.54, 1.0Hz), 7.66(ddd, 1H, *J*=7.93, 8.08, 1.48Hz),7.94(dd, 1H, *J*=8.04, 1.52Hz), 8.24(s, 1H), 8.51(dd, 1H *J*=8.06, 1.0Hz), 9.64(brs, 1H). Rf: 0.45 (n-Hexane: AcOEt=4:1).

36-7

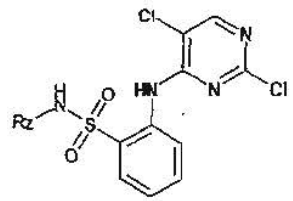
2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-isopropyl-benzenesulfonamide

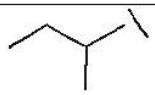
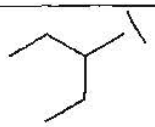


To a solution of 2-amino-N-isopropyl-benzenesulfonamide (16.1g, 75.1mmol) in DMI (150mL) is added sodium hydride (6.6g, 165.3mmol) portionwise at 0°C. After the mixture is stirred at room temperature for one hour, 2, 4, 5-trichloropyrimidine (20.7g, 112.7mmol) is added at 0°C. After further stirring at room temperature for 5 hrs, water is added and the mixture is extracted with AcOEt three times. Organic layer is washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue is purified by silica gel column chromatography (Hexane to Hexane:AcOEt=4:1) to afford the title compound as pale brown solid (10.2g, 38%).

^{1}H-NMR (400MHz, $CDCl_3$, δ);1.06(d, 6H), 3.43-3.53(m, 1H), 4.38(d,1H), 7.29(dd, 1H), 7.66(dd, 1H), 7.98(d, 1H), 8.29(s, 1H), 8.51(d, 1H), 9.51(brs, 1H). Rf: 0.45 (n-Hexane:AcOEt=4:1)

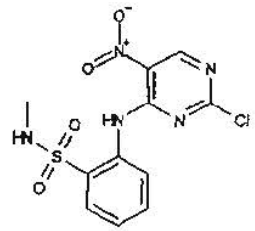
The following compounds are prepared in the same manner described above.



Expl No.	Rz	Rf (solvent) or MS	NMR (400MHz) , δ (ppm)
36-8		0.45 (n-Hexane: AcOEt=4:1)	DMSO-d_6; 0.63(t, 6H), 0.86(d, 3H), 1.21-1.31(m, 2H), 3.02-3.12(m, 1H), 7.37(dd,1H), 7.71(dd, 1H), 7.85(d, 1H), 7.89(d, 1H), 8.20(d, 1H), 8.56(s, 1H), 9.51(brs, 1H)
36-9		0.46 (n-Hexane: AcOEt=7:3)	$CDCl_3$; 0.70(t, 6H),1.23-1.45(m, 4H), 3.03-3.13(m, 1H), 4.27(d,1H), 7.27(dd, 1H), 7.65(dd, 1H), 7.98(d, 1H), 8.29(s, 1H), 8.52(d, 1H), 9.59(brs, 1H)

36-10

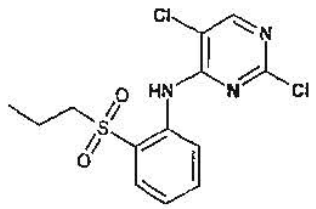
Preparation of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide:



2,4-Dichloro-5-nitro-pyrimidine (1.94 g, 10 mmol) and 2-amino-N-methyl-benzenesulfonamide (1.86 g, 10 mmol) are dissolved in $CHCl_3$ (30 mL). The reaction mixture is heated at 61°C for 2 h. The solvent is evaporated and the residue is washed with ether to give the title product.
Rf = 0.5 (n-hexane : ethyl acetate = 1:1). ^{1}H-NMR (400MHz, $CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.6-4.7 (m, 2H), 7.41 (t, 1H), 7.7 (t, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 9.21 (s, 1H), 11.2 (s, 1H).

36-11

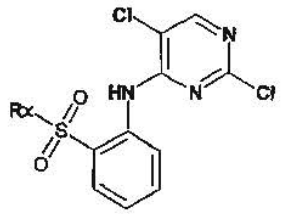
Preparation of (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-1-sulfonyl)-phenyl]-amine



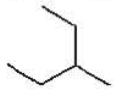
To a solution of 2-(Propane-1-sulfonyl)-phenylamine (3.69g, 18.5 mmol) of N,N-dimethylformamide (40mL), sodium hydride (1.48g, 37 mmol) is added portionwise at 0°C. After stirring, 2,4,5-trichloropyrimidine (2.1mL, 18.5 mmol) is added. The mixture is stirred at 0°C for 30 minutes and is further stirred at room temperature for 7hrs. After adding saturated aqueous ammonium chloride, the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane - ethyl acetate gradient) to afford the title compound as colorless solids.

^{1}H-NMR ($CDCl_3$), δ (ppm): 0.99 (t, 3H), 1.77 (d, 2H), 3.07-3.11 (m, 2H), 7.26 (s, 1H), 7.32 (ddd, 1H), 7.73 (ddd, 1H), 7.95 (dd, 1H), 8.31 (s, 1H), 8.61 (dd, 1H), 9.94 (bs, 1H). Rf (n-hexane : ethyl acetate = 3:1): 0.63

According to the manner described above, the following compounds are prepared.



ExpIN o.	Rx	Identification
36-12		^{1}H-NMR ($CDCl_3$), δ (ppm): 1.35(d, 6H), 3.18-3.24(m, 1H), 7.30-7.34(m, 1H), 7.70-7.75(m, 1H), 7.92(dd, 1H), 8.30(s, 1H), 8.63(d, 1H), 10.06(s, 1H). Rf 0.70: (AcOEt)
36-13		NMR (400MHz) in $CDCl_3$, δ (ppm): 1.29(t, 3H), 3.15(q, 1H), 7.31-7.35(m, 1H), 7.71-7.75(m, 1H), 7.96(dd,

		1H), 8.31(s, 1H), 8.60(d, 1H), 9.92(s, 1H). Rf: 0.67 (AcOEt).
36-14		1.01-1.06(m, 2H), 1.32-1.37(m, 2H), 2.49-2.55(m,1H), 7.29-7.33(m, 1H), 7.69-7.73(m, 1H), 7.91(dd, 1H), 8.31(s, 1H), 8.58(d, 1H), 9.90(s, 1H). Rf 0.69 (AcOEt)
36-15		0.99(t, 6H), 1.72-1.90(m, 4H), 2.76-2.82(m, 1H), 7.26-7.34(m, 1H), 7.69-7.74(m, 1H), 7.92(dd, 1H), 8.30(s, 1H), 8.62(d, 1H), 10.02(s, 1H). Rf: 0.73 (AcOEt)

Example 36-16

Synthesis of substituted amines which are commercially not available:

Preparation of 3-amino-4'-methoxy-4-methylbiphenyl

To a solution of 4-methoxyphenyl-boronic acid (500 mg, 3.29 mmol) in toluene (5.2 mL) and ethanol (1.3 mL), potassium carbonate (910 mg, 6.58 mmol), tetrakis(triphenylphosphine)-palladium (228.1 mg, 0.099 mmol) and 4-bromo-1-methyl-2-nitrobenzene (711 mg, 3.29 mmol) are added and stirred at 100°C for 7 hours. The mixture is poured into water and extracted with ethyl acetate two times. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford the 4'-methoxy-4-methyl-3-nitro-biphenyl as a yellow solid.

^{1}H-NMR (δ, ppm) : 2.62 (s, 3H), 3.86 (s, 3H), 7.02-6.98 (m, 2H), 7.37 (d, 1H), 7.54 (dd, 2H), 7.68 (dd, 1H), 8.18 (d, 1H). Rf (hexane : ethyl acetate = 3:1): 0.40.

A suspension of 4'-methoxy-4-methyl-3-nitrobiphenyl (630 mg, 2.95 mmol) and 10% palladium on charcoal (63 mg, 0.059 mmol) in methanol (6 mL) is stirred under hydrogen atmosphere for 12 hours. Palladium catalyst is removed by filtration and the resulting solution is evaporated in vacuo to afford the title compound.

^{1}H-NMR (δ, ppm) : 2.20 (s, 3H), 3.84 (s, 3H), 6.87 (d, 1H), 6.89 (dd, 1H), 6.95 (d, 2H), 7.09 (d, 1H), 7.48 (d, 2H). Rf (n-hexane : ethyl acetate = 1:1): 0.50.

Preparation of 4-(3-amino-4-methylbenzoyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 4-methyl-3-nitro-benzoic acid (300 mg, 2.76 mmol), N-butoxycarbonyl-piperazine (340 mg, 1.83 mmol) in DMF (3.0 mL), triethylamine (300 μL, 3.59 mmol), TBTU (800 mg, 2.49 mmol) and HOAt (270.5 mg,1.99 mmol) are added and stirred at room temperature for 24 hours. The mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3-nitrobenzoyl)-piperazine-1-carboxylic acid tert-butyl ester as a colorless solid.

^{1}H-NMR (δ, ppm) : 1.47 (s, 9H), 2.64 (s, 3H), 3.28-3.88 (m, 8H), 7.42 (d, 1H), 7.56 (dd, 1H), 8.03 (d, 1H). Rf (hexane : ethyl acetate = 10:1): 0.13.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Preparation of 4-(3-amino-4-methylphenyl)-morpholine

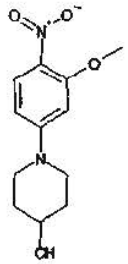
To a solution of 4-bromo-1-methyl-2-nitrobenzene (225 mg, 1.04 mmol), morpholine (125 μL, 1.25 mmol), and cesium carbonate (474.4 mg, 1.46 mmol) in toluene, palladium diacetate (31.2 mg, 0.139 mmol) and 2-(di-t-butylphosphino)biphenyl (125 mg, 0.403 mmol) are added and stirred at 100°C for 5 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3-nitrophenyl)-morpholine as a yellow solid.

^{1}H-NMR (δ, ppm) : 2.50 (s, 3H), 3.17-3.19 (m, 4H), 3.86-3.88(m, 4H), 7.04 (dd, 1H), 7.21 (d, 1H), 7.47 (d, 1H). Rf (hexane : ethyl acetate = 5:1): 0.20.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

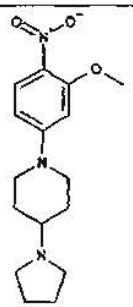
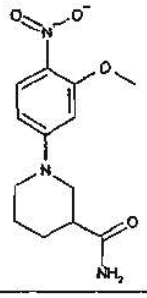
Example 37: Synthesis of substituted amines which are commercially not available:

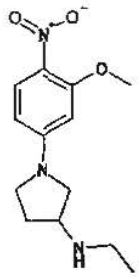
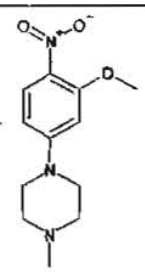
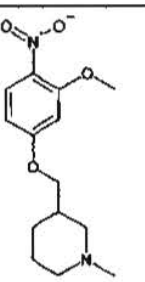
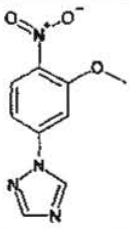
37-1
Preparation of 1-(3-Methoxy-4-nitro-phenyl)-piperdin-4-ol

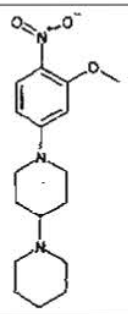
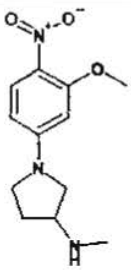
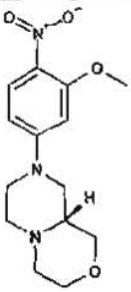
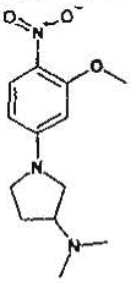


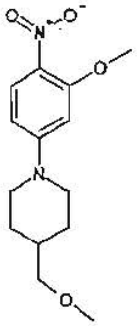
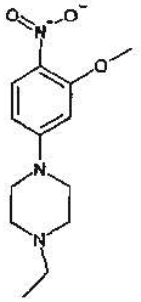
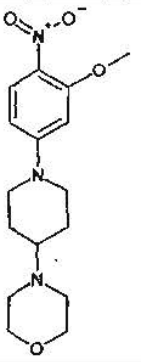
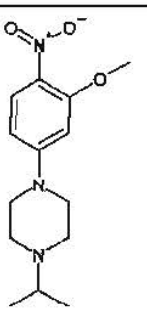
To a suspension of piperidin-4-ol (2.79g, 28 mmol) and potassium carbonate (3.88 g, 28 mmol) in N,N-dimethylformamide (40 mL), 4-Fluoro-2-methoxy-1-nitro-benzene (4.0g, 23 mmol) is added and stirred at room temperature for 24 hours. The mixture is poured into water and the precipitate is collected by a filtration. The resulting solid is dried in vacuo at 50°C to afford 1-(3-methoxy-4-nitro-phenyl)-piperidin-4-ol (5.23g) as yellow solids in 89% yield.
^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) :1.54(d, 1H), 1.62-1.71(m, 2H), 1.98-2.04(m, 2H), 3.22(ddd, 4H), 3.73-3.80(m, 2H), 3.95(s, 3H), 3.98-4.02(m, 1H), 6.33(d, 1H), 6.43(dd, 1H), 8.00(d, 1H).

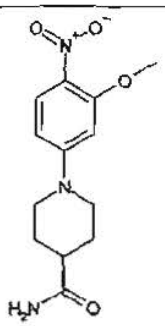
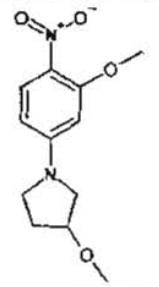
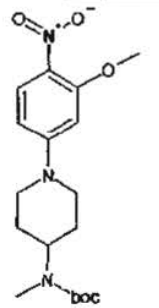
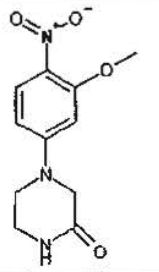
By repeating the procedures described above using appropriate starting materials and conditions the following compounds are obtained.

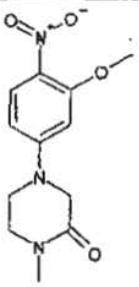
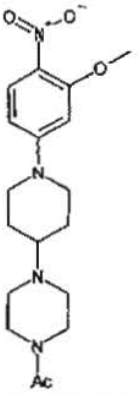
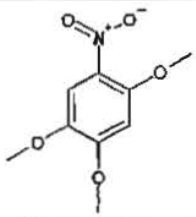
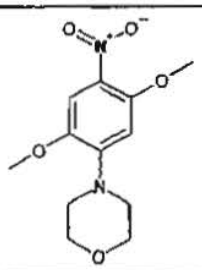
Ex-No	Rx	Identification
37-2		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) :1.53-1.72(m, 2H), 1.80-1.83(m, 4H), 1.99-2.04(m, 2H), 2.24-2.31(m, 1H), 2.54-2.67(m, 4H), 3.03(dt, 2H), 3.84-3.89 (m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.01(d, 1H). Rf 0.54 (AcOEt)
37-3		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.81-1.91(m, 2H), 1.99-2.04(m, 2H), 2.38-2.48(m, 1H), 3.03(ddd, 2H), 3.91-3.96(m, 2H), 3.95(s, 3H), 5.22-5.41(m, 1H), 5.40-5.53(m, 1H), 6.36(d, 1H), 6.43(dd, 1H), 8.00(d, 1H). Rf 0.15 (AcOEt)

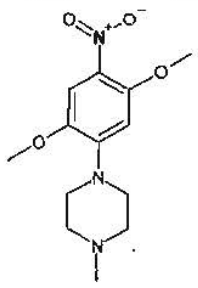
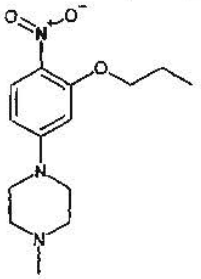
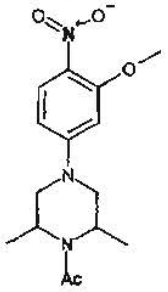
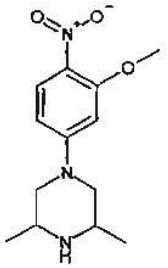
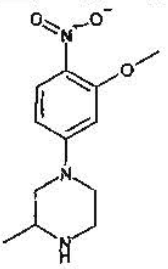
37-4	 Ethyl-[1-(3-methoxy-4-nitro-phenyl)-pyrrolidin-3-yl]-amine	^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.15(t, 3H),1.88-1.96(m, 1H), 2.22-2.30(m,1H), 2.68-2.77(m, 2H),3.15-3.18(m, 1H), 3.38-3.44(m, 1H), 3.52-3.62(m, 2H), 3.93(s, 3H), 5.92(d, 1H), 6.07-6.10(m, 1H), 8.00-8.02(m, 1H). Rf 0.65 (*n*-hexane: AcOEt=1:1).
37-5	 1-(3-Methoxy-4-nitro-phenyl)-4-methyl-piperazine	^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.36(s, 3H), 2.52-2.57(m, 4H), 3.40-3.43(m, 4H), 3.95(s, 3H), 6.32(d, 1H, *J*=2.52Hz), 6.43(dd, 1H, *J*=9.56, 2.52Hz), 7.99(d, 1H, *J*=9.08Hz). Rf 0.60 (MeOH : CH_2Cl_2=4:1).
37-6	 3-(3-Methoxy-4-nitro-phenoxymethyl)-1-methyl-piperidine	^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.10-1.19(m, 1H), 1.59-2.18(m, 6H), 2.28(s,3H), 2.71-2.74(m, 1H), 2.88-2.91(m, 1H), 3.86-3.95 (m, 5H), 6.47-6.52(m, 2H), 7.97-8.00(m, 1H). Rf 0.65 (*n*-hexane: AcOEt=1:1)
37-7		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 4.08(s,3H), 7.30(dd,1H), 7.58(d, 1H), 8.05(d, 1H), 8.15(s, 1H), 8.67(s, 1H). Rf: 0.42 (AcOEt)

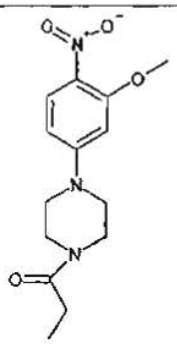
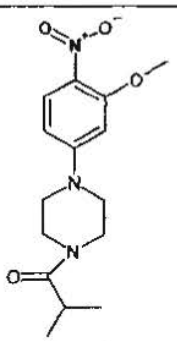
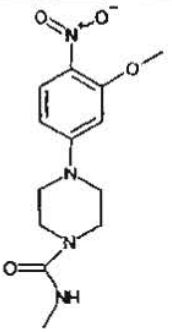
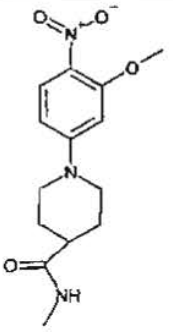
37-8		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm): 1.40 – 1.50 (m, 2H), 1.55 – 1.69 (m, 6H), 1.90 – 1.96 (m, 2H), 2.45 – 2.53 (m, 5H), 2.90 – 2.99 (m, 2H), 3.90 – 4.00 (m, 2H), 3.94 (s, 3H), 6.30 (d, 1H, J =, 2.5 Hz), 6.41 (dd, 1H, J = 9.0, 2.5 Hz), 7.99 (d, 1H, J = 9.0 Hz)
37-9		^{1}H-NMR (400MHz, DMSO-d6, δ, ppm) : 1.95-1.82(m, 2H), 2.15-2.06 (m, 1H), 2.30 (s, 3H), 3.17 (dd, 1H), 3.32-3.23 (m, 1H), 3.56-3.34 (m, 3H), 3.96 (s, 1H), 6.09 (d, 1H), 6.21 (dd, 1H), 7.91 (d, 1H)
37-10		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm): 2.30 - 2.48 (m, 3H), 2.59 - 2.68 (m, 1H), 2.70 - 2.76 (m, 1H), 2.86 - 2.92 (m, 1H), 3.09 - 3.17 (m, 1H), 3.30 - 3.34 (m, 1H), 3.52 - 3.58 (m, 1H), 3.68 - 3.84 (m, 3H), 3.87 - 3.91 (m, 1H), 3.96 (s, 3H), 6.32 (d, 1H, J = 2.5 Hz), 6.42 (dd, 1H, J = 9.6, 2.5 Hz), 8.00 (d, 1H, J = 9.6 Hz)
37-11		^{1}H-NMR (400MHz, DMSO-d6, $CDCl_3$, δ, ppm) : 1.90-1.79(m, 1H), 2.25-2.15 (m, 1H), 2.21 (s, 3H), 2.87-2.77 (m, 1H), 3.16 (dd, 1H), 3.42-3.32 (m, 1H), 3.59-3.52 (m, 1H), 3.67-3.61 (m, 1H), 3.91 (s, 3H), 6.13 (d, 1H), 6.24 (dd, 1H)), 7.91 (dd, 1H)

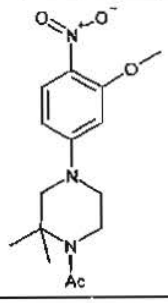
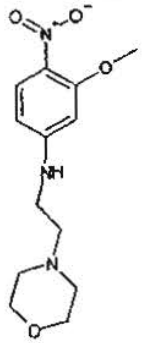
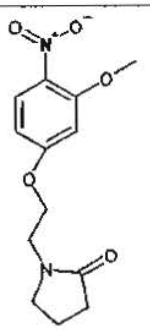
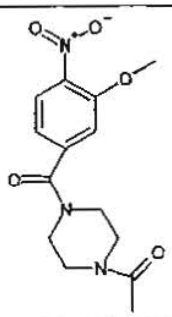
37-12		^{1}H-NMR (400MHz, $CDCl_3$): 1.43-1.00(m, 2H),1.95-1.81 (m, 2H),2.94-2.17(m, 2H),2.96(s, 3H),3.27 (d, 2H), 3.35(s, 3H),3.97-3.90 (m, 2H), 3.95(s, 3H), 6.30(d, 1H), 6.42(dd, 1H) 8.00(d, 1H). Rf: 0.25 (AcOEt)
37-13		^{1}H-NMR (400MHz, $CDCl_3$): 1.14(t, 3H),2.48(dd, 2H), 2.59(t, 4H),3.42 (t, 4H), 3.95(s,3H), 6.32(d, 1H), 6.43(dd, 1H) 8.01(d, 1H). Rf 0.15 (AcOEt)
37-14		^{1}H-NMR (400MHz, $CDCl_3$): 1.02-0.89 (m, 2H), 2.01-1.94 (m, 2H), 2.52-2.38 (m, 1H), 2.65-2.53 (m, 4H),3.04-2.94(m, 2H), 3.79-3.69(m, 4H),3.97-3.88 (m, 2H), 3.95(s,3H), 6.32(d, 1H), 6.42(dd, 1H) 8.00(d, 1H). . Rf 0.10 (AcOEt)
37-15		^{1}H-NMR (400MHz, $CDCl_3$): 1.08 (s, 3H),1.09(s, 3H), 2.66(t, 4H),2.74 (sept, 1H), 3.41 (t, 4H), 3.95(s,3H), 6.32(d, 1H), 6.42(dd, 1H) 8.00(d, 1H). Rf 0.15 (AcOEt)

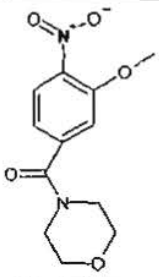
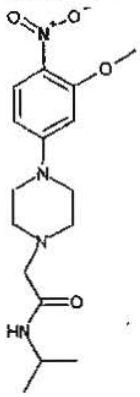
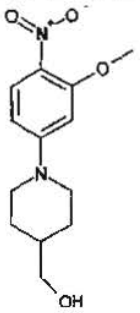
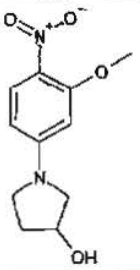
37-16		^{1}H-NMR (400MHz, $CDCl_3$): 1.91-1.81 (m, 2H), 2.06-1.97(m, 2H),2.48-2.40(m, 1H), 3.07-2.98(m, 2H),3.97-3.93(m, 2H), 3.93(s,3H), 5.37-5.30(m, 1H),5.55-5.43 (m, 1H), 6.33(d, 1H), 6.43(dd, 1H) 8.00(d, 1H). Rf 0.10 (AcOEt)
37-17		^{1}H-NMR (400MHz, $CDCl_3$): 2.18-2.07 (m, 1H), 2.30-2.22 (m, 1H), 3.38(s, 3H), 3.56-3.44(m, 4H),3.95 (s, 3H), 4.13 (ddd,1H), 5.96(d, 1H), 6.12(dd, 1H) 8.03(d, 1H). Rf 0.30 (AcOEt)
37-18		^{1}H-NMR (400MHz, $CDCl_3$): 1.46(s, 9H),1.81-1.68(m, 4H), 2.73(bs, 3H),3.07-2.97(m, 2H), 3.95(s,3H), 4.03-3.94 (m, 2H), 6.32(d, 1H), 6.43(dd, 1H) 8.00(d, 1H). Rf 0.55 (Hexane:AcOEt)
37-19		^{1}H-NMR (400MHz, $CDCl_3$): 3.60-3.57(m, 2H),3.68-3.65(m, 2H), 3.97(s, 3H),4.07(s, 2H), 6.17(bs, 1H), 6.26(d, 1H), 6.39(dd, 1H) 8.04(d, 1H). Rf 0.85 (AcOEt)

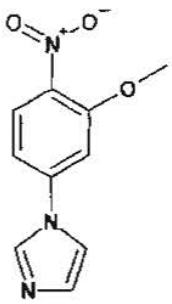
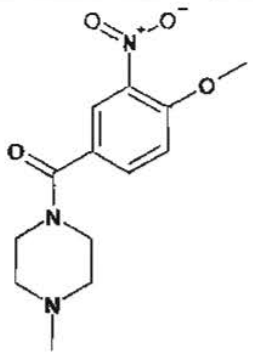
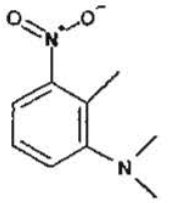
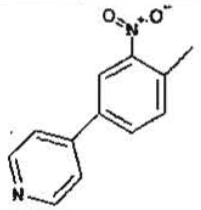
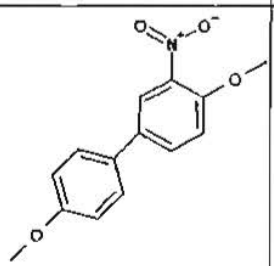
37-20		^{1}H-NMR (400MHz, $CDCl_3$): 3.08(s, 3H), 3.54(dd, 2H),3.67(dd, 2H), 3.96 (s, 3H), 4.05(s, 2H), 6.25(d, 1H), 6.38(dd, 1H) 8.03(d, 1H) . Rf 0.30 (AcOEt)
37-21		^{1}H-NMR (400MHz, $CDCl_3$): 1.73-1.55 (m, 2H), 1.99-1.91 (m, 2H), 2.09(s, 3H),2.61-2.49 (m, 5H), 3.47(t, 2H),3.63(t, 2H), 3.99-3.89 (m, 3H), 3.95 (s, 3H), 6.32(d, 1H), 6.42(dd, 1H) 8.01(d, 1H) . Rf 0.10 (AcOEt:MeOH=4:1)
37-22		^{1}H-NMR (400MHz, $CDCl_3$): 3.90(s, 3H), 3.98(s, 3H), 3.98 (s, 3H), 6.56(s, 1H), 7.59(s, 1H) . Rf 0.605 (AcOEt)
37-23		^{1}H-NMR (400MHz, $CDCl_3$): 3.25-3.22 (m, 4H), 3.90-3.87 (m, 4H), 3.95(s, 3H), 6.48(s, 1H), 7.57(s, 1H) . Rf 0.060 (Hexane:AcOEt=5:1)

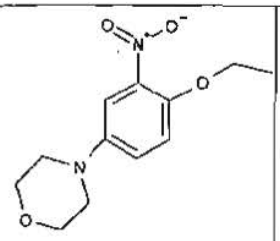
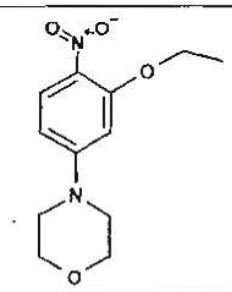
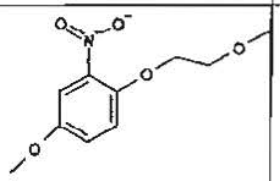
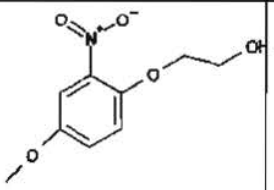
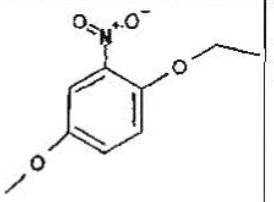
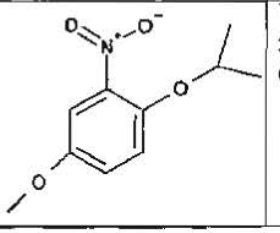
37-24		^{1}H-NMR (400MHz, $CDCl_3$): 2.37 (s, 3H), 2.61 (bs, 4H),3.27 (bs, 4H), 3.88 (s, 3H), 3.95(s, 3H), 6.48(s, 1H), 7.56(s, 1H) . Rf 0.10 (AcOEt:MeOH=5:1)
37-25		^{1}H-NMR (400MHz, $CDCl_3$): 1.09(t, 3H), 1.89(dd, 2H), 2.36(s, 3H), 2.55(t, 4H), 3.39(t, 4H), 4.03(t, 2H), 6.32(d, 1H), 6.42(dd, 1H), 7.98(d, 1H) . Rf 0.12 (AcOEt:MeOH=9:1)
37-26		^{1}H-NMR (400MHz, $CDCl_3$): 1.36(s, 3H), 1.38 (s, 3H), 2.10 (s, 2H), 2.17(s, 3H), 3.27-2.96 (m, 2H), 3.71 (d, 2H), 3.96 (s, 3H), 6.33(d, 1H), 6.43(dd, 1H), 8.02(d, 1H) . Rf 0.10 (AcOEt)
37-27		^{1}H-NMR (400MHz, $CDCl_3$): 1.16(s, 3H), 1.18 (s, 3H), 2.50(dd, 2H), 3.02-2.47 (m, 2H), 3.69 (dd, 2H), 3.96 (s, 3H), 6.31(d, 1H), 6.43(dd, 1H), 8.00(d, 1H) . Rf 0.070(AcOEt)
37-28		^{1}H-NMR (400MHz, $CDCl_3$): 1.16(d, 3H), 2.57(dd, 1H), 3.00-2.89 (m, 4H), 3.18-3.11 (m, 1H), 3.75-3.68 (m, 2H),3.96 (s, 3H), 6.31(d, 1H), 6.43(dd, 1H), 8.01(d, 1H) . Rf 0.070 (AcOEt)

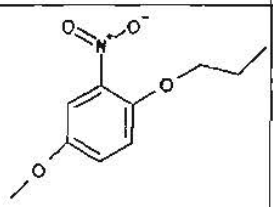
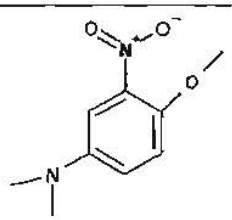
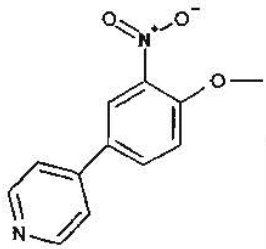
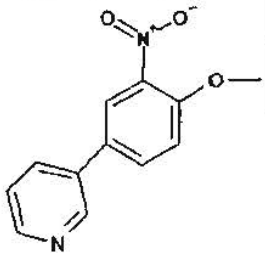
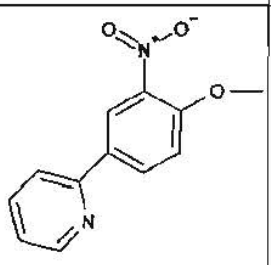
37-29		^{1}H-NMR (400MHz, $CDCl_3$): 1.18(t, 3H), 2.40(dd, 2H), 3.47-3.38(m, 4H), 3.71-3.63(m, 2H), 3.85-3.79(m, 2H), 3.96(s, 3H), 6.32(d, 1H), 6.42(dd, 1H), 8.01(d, 1H) . Rf 0.20 (AcOEt)
37-30		^{1}H-NMR (400MHz, $CDCl_3$): 1.16(s, 3H), 1.18(s, 3H), 2.82(sept, 1H), 3.50-3.37(m, 4H), 3.77-3.65(m, 2H), 3.86-3.78(m, 2H), 3.96(s, 3H), 6.33(d, 1H), 6.43(dd, 1H), 8.01(d, 1H) . Rf 0.48 (AcOEt)
37-31		^{1}H-NMR (400MHz, $CDCl_3$): 2.86(d, 3H), 3.48-3.45(m, 4H), 3.61-3.58(m, 4H), 3.96(s, 3H), 4.48-4.37 (m, 1H), 6.29(d, 1H), 6.40(dd, 1H), 8.01(d, 1H) . Rf 0.20 (AcOEt)
37-32		^{1}H-NMR (400MHz, $CDCl_3$): 1.72-1.60(m, 2H), 2.06-1.97(m, 2H), 3.25-3.17 (d, 3H), 3.78-3.70(m, 2H), 3.95(s, 3H), 4.04-3.99(m, 1H), 6.33(d, 1H), 6.43(dd, 1H), 8.00(d, 1H) . Rf 0.20 (AcOEt)

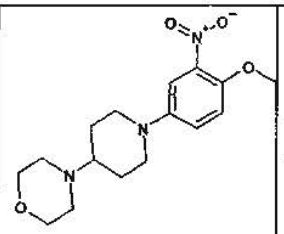
37-33		^{1}H-NMR (400MHz, $CDCl_3$): 1.53 (s, 6H), 2.14(s, 3H), 3.50(s, 2H), 3.61-3.58(m, 2H), 3.97-3.81(m, 2H), 3.97 (s, 3H), 6.10 (d, 1H), 6.26(dd, 1H), 8.05(d, 1H) . Rf 0.030 (AcOEt)
37-34		^{1}H-NMR (400MHz, $CDCl_3$): 2.54-2.23 (m, 4H), 2.67 (t, 2H), 3.29-3.23(m, 2H), 3.74(t, 4H), 3.94(s, 3H), 6.07(d, 1H), 6.16 (dd, 1H), 8.00(d, 1H) . Rf 0.15 (AcOEt)
37-35		^{1}H-NMR (400MHz, $CDCl_3$): 2.10-2.02 (m, 2H), 2.41(t, 2H), 3.56(dd, 2H), 3.71(t, 2H), 3.95(s, 3H), 4.19(t, 2H), 6.49(dd, 1H), 6.55(d, 1H), 7.99(d, 1H) . Rf 0.10 (AcOEt)
37-36		^{1}H-NMR (400MHz, $CDCl_3$): 2.14(s, 3H), 3.87-3.34(m, 8H), 3.99 (s, 3H), 7.01(dd, 1H), 7.16(d, 1H), 7.88(d, 1H) . Rf 0.25 (AcOEt)

37-37		^{1}H-NMR (400MHz, $CDCl_3$): 3.49-3.37(m, 2H), 3.88-3.55(m, 6H), 3.99 (s, 3H), 7.00(dd, 1H), 7.16(d, 1H), 7.87(d, 1H) . Rf 0.50 (AcOEt)
37-38		^{1}H-NMR (400MHz, $CDCl_3$): 1.17 (s, 3H), 1.19(s, 3H), 2.69 (t, 4H), 3.06(s, 2H), 3.42 (t, 4H), 3.96(s, 3H),4.13(sept, 1H), 6.34 (d, 1H), 6.44(dd, 1H), 6.90-6.79(m, 1H), 8.00(d 1H) . Rf 0.20 (AcOEt)
37-39		^{1}H-NMR (400MHz, $CDCl_3$): 1.44-1.34 (m, 2H),1.84-1.77 (m, 1H), 1.94-1.85 (m, 2H), 3.04-2.94 (m, 2H), 3.55 (t, 2H), 3.96-3.57(m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.00(d, 1H) . Rf 0.30 (AcOEt)
37-40		^{1}H-NMR (400MHz, $CDCl_3$): 1.44-1.34 (m, 2H),1.84-1.77 (m, 1H), 1.94-1.85 (m, 2H), 3.04-2.94 (m, 2H), 3.55 (t, 2H), 3.96-3.57(m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.04(d, 1H) . Rf 0.45 (AcOEt)

37-41		^{1}H-NMR (400MHz, $CDCl_3$) : 4.05 (s, 3H), 7.07 (d, 1H), 7.08 (d, 1H), 7.27-7.26 (m, 1H), 7.33 (t, 1H), 7.92 (s, 1H), 8.04 (d, 1H). Rf: 0.20 (AcOEt)
37-42		^{1}H-NMR (400MHz, $CDCl_3$) :2.34 (s, 3H), 2.55-2.37 (m, 4H), 3.86-3.38 (m, 4H), 4.00 (s, 3H), 7.13 (d, 1H). 7.66 (dd, 1H).7.93 (d, 1H). Rf: 0.30 (AcOEt:MeOH=4:1)
37-43		^{1}H-NMR (400MHz, $CDCl_3$) : 2.43 (s, 3H), 2.74 (s, 6H), 7.91 (dd, 1H), 7.23 (d, 1H), 7.24 (d, 1H), 7.46 (dd, 1H). Rf: 0.70 (Hexane:AcOEt=5:1)
37-44		^{1}H-NMR (400MHz, $CDCl_3$) :2.15 (s, 3H), 3.80-3.48 (m, 2H), 6.87 (dd, 1H), 6.92(dd, 1H), 7.09 (d, 1H), 7.40 (dd, 2H), 8.54 (dd, 2H).
37-45		^{1}H-NMR (400MHz, $CDCl_3$) :3.86 (s, 3H), 4.00 (s, 3H), 6.78 (d, 1H), 6.99 (dd, 2H), 7.14(d, 1H), 7.48 (dd, 2H), 7.71 (dd, 1H), 8.03 (d, 1H). Rf: 0.30 (Hexane:AcOEt=3:1)

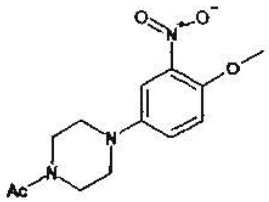
37-46		^{1}H-NMR (400MHz, $CDCl_3$) :1.44 (t, 3H), 3.10 (t, 4H), 3.86 (t, 4H), 4.13 (q, 2H), 7.01(dd, 1H), 7.08 (dd, 1H), 7.35 (d, 1H). Rf: 0.25 (Hexane:AcOEt=3:1)
37-47		^{1}H-NMR (400MHz, $CDCl_3$) :1.26 (t, 3H), 3.32 (t, 4H), 3.85 (t, 4H), 4.15 (q, 2H), 6.34(d, 1H), 6.42 (dd, 1H), 7.98 (d, 1H). Rf: 0.45 (Hexane:AcOEt=5:1)
37-48		^{1}H-NMR (400MHz, $CDCl_3$) :3.45 (s, 3H), 3.77 (dd, 2H), 3.81 (s, 3H), 4.06 (t, 2H), 7.08-7.08(m, 2H), 7.37 (t, 1H). Rf: 0.45 (Hexane:AcOEt=3:1)
37-49		^{1}H-NMR (400MHz, $CDCl_3$) :2.44 (t, 1H), 3.83 (s, 3H), 3.96 (ddd, 2H), 4.20 (t, 2H), 7.06 (d, 1H), 7.12(dd, 1H), 7.40 (d, 1H). Rf: 0.10 (Hexane:AcOEt=3:1)
37-50		^{1}H-NMR (400MHz, $CDCl_3$) :1.45 (t, 3H), 3.81 (s, 3H), 4.13 (q, 2H), 7.01(d, 1H), 7.08 (dd, 1H), 7.36 (d, 1H). Rf: 0.20 (Hexane:AcOEt=3:1)
37-51		^{1}H-NMR (400MHz, $CDCl_3$) :1.35 (s, 3H), 1.36(s, 3H), 3.81(s, 3H), 4.52 (sept, 1H), 7.08-7.01 (m, 2H), 7.31 (d, 1H). Rf: 0.30 (Hexane:AcOEt=3:1)

37-52		^{1}H-NMR (400MHz, $CDCl_3$) :1.05 (t, 3H), 1.83 (ddd, 2H), 3.81(s, 3H), 4.01(t, 2H), 7.01 (d, 1H), 7.08 (dd, 1H), 7.36 (d, 1H). Rf: 0.35 (Hexane:AcOEt=3:1)
37-53		^{1}H-NMR (400MHz, $CDCl_3$) :3.86 (s, 6H), 3.79 (s, 3H), 6.91 (dd, 1H), 7.00 (d, 1H), 7.18 (d, 1H). Rf: 0.5 (Hexane:AcOEt=9:1)
37-54		^{1}H-NMR (400MHz, $CDCl_3$) :4.04(s, 3H), 7.22 (d, 1H), 7.48(dd, 2H), 7.83 (dd, 1H), 8.16 (d, 1H), 8.69 (dd, 2H). Rf: 0.12 (Hexane:AcOEt=1:1)
37-55		^{1}H-NMR (400MHz, $CDCl_3$) :4.02 (s, 3H), 7.22 (d, 1H), 7.39 (ddd, 1H), 7.77(dd, 1H), 7.85(ddd, 1H), 8.08 (d, 1H), 8.63(dd, 1H), 8.83 (d, 1H). Rf: 0.55 (Hexane:AcOEt=2:1)
37-56		^{1}H-NMR (400MHz, $CDCl_3$) :4.03 (s, 3H), 7.19 (d, 1H), 7.28-7.24 (m, 1H), 7.72(dd, 1H), 7.80-7.76(m, 1H), 8.25 (dd, 1H), 8.52 (d, 1H), 8.69 (ddd, 1H). Rf: 0.55 (Hexane:AcOEt=2:1)

37-57		mp 90.7 °C; ^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm): 1.68 (m; 2H), 2.00 (m; 2H), 2.36 (s; 1H), 2.62 (bs; 4H), 2.72 (m; 2H), 3.62 (m; 2H), 3.78 (bs; 4H), 3.90 (s; 3H), 6.99 (d; 1H); 7.13 (dd; 1H), 7.26 (s; 1H); 7.40 (s; 1H).

38

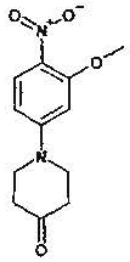
Preparation of 1-[4-(4-Methoxy-3-nitro-phenyl)-piperazin-1-yl]-ethanone



To a solution of 5-bromo-1-methoxy-2-nitrobenzene (300 mg, 1.29 mmol) in dioxane, 1-acetyl piperazine (400mg, 3.12 mmol), cesium carbonate (1.0g, 3.07 mmol), palladium diacetate (29.0 mg, 0.129 mmol) and 2-(di-t-butylphosphino)biphenyl (77 mg, 0.258 mmol) are added and stirred at 100°C for 8 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane : ethyl acetate gradient) to afford 1-[4-(4-Methoxy- 3-nitro-phenyl)-piperazin-1-yl]-ethanone (319mg, 44%) as yellow solids. ^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.14 (s, 3H), 3.63 (ddd, 4H), 3.63 (t, 2H), 3.78 (t, 2H), 3.92 (s, 3H), 7.03 (d, 1H), 7.12 (d, 1H), 7.41 (d, 1H). Rf (ethyl acetate): 0.18

39

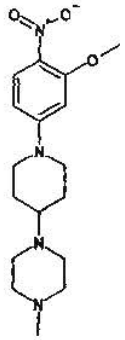
Preparation of 1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-one



To a solution of 4-piperidone hydrochloride monohydrate (10.0 g, 0.065mol) in DMF (80 mL) are added 4-Fluoro-2-methoxy-1-nitro-benzene (10.0 g, 0.058 mol) and potassium carbonate

(20.2 g), and the mixture is stirred at 70°C for 20 h. After a filtration, the filtrate is poured into H_2O (*ca.* 300 mL), and the resulting precipitates are collected by a filtration followed by washing with H_2O for several times to give title compound (8.98 g) in 61% yield. Orange solid. ^{1}H-NMR (400 MHz, $CDCl_3$, δ): 2.65-2.62 (4H, *m*), 3.81-3.78 (4H, *m*), 3.98 (3H, *s*), 6.34 (1H, *d*), 6.45 (1H, *dd*), 8.05 (1H, *d*).

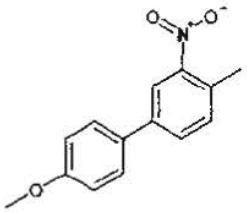
40
Preparation of 1-[1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-yl]-4-methyl-piperazine



To a solution of 1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-one (4.96g, 0.020mol) in dichloroethane (50 ml) is added N-methylpiperazine (2.7ml, 0.024 mol) at 0 °C and the mixture is stirred at room temperature. After 4 h, sodium triacetoxy-borohydride (5.04g, 0.024mol) is added and the mixture is further stirred at room temperature for 24 h. After addition of 1N sodium hydroxide at 0 °C, the mixture is poured into water and extracted three times with dichloromethane. The organic layer is combined and extracted three times with 1N hydrochloride. The water layer is basified with 2N sodium hydroxide and extracted three times with dichloromethane. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo to give the title compound as yellow solids (6.04g) in 91% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ): 1.70-1.57 (2H, *m*), 2.03-1.93 (2H, *m*), 2.29 (3H, *s*), 2.55-2.38 (5H, *m*), 2.70-2.56 (4H, m), 2.97 (2H, *ddd*), 3.97-3.92 (2H, *m*), 3.95 (3H, *s*), 6.31 (1H, *d*,), 6.42 (1H, *dd*), 8.00 (1H, *d*).

41
Preparation of 4'-Methoxy-4-methyl-3-nitro-biphenyl

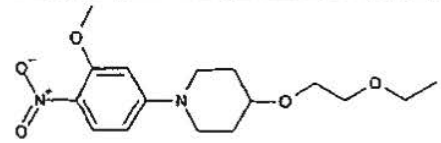


To a solution of 4-methoxyphenyl-boronic acid (500 mg, 3.29 mmol) in toluene (5.2 mL) and ethanol (1.3 mL), potassium carbonate (910 mg, 6.58 mmol), tetrakis(triphenylphosphine)-palladium (228.1 mg, 0.099 mmol) and 4-bromo-1-methyl- 2-nitrobenzene (711 mg, 3.29 mmol) are added and stirred at 100°C for 7 hours. The mixture is poured into water and extracted with ethyl acetate two times. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (*n*-hexane : ethyl acetate = 5 : 1) to afford the 4'-methoxy-4-methyl-3-nitro-biphenyl (630mg, 79%) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.62 (s, 3H), 3.86 (s, 3H), 7.02-6.98 (m,2H), 7.37 (d, 1H), 7.54 (dd, 2H), 7.68 (dd, 1H), 8.18 (d, 1H). Rf (hexane : ethyl acetate = 3:1): 0.40.

42

Preparation of 4-(2-Ethoxy-ethoxy)-1-(3-methoxy-4-nitro-phenyl)-piperidine

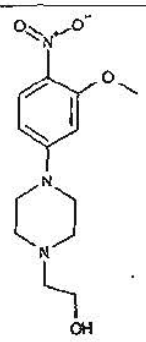
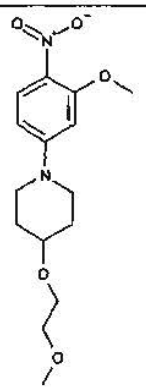


To a solution of 1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-ol (300mg, 1.2 mmol) in N,N-dimethylformamide (3.0 mL), sodium hydride (1.52g, 3.8 mmol) is added. After stirring, 2-bromoethyl methyl ether (150µl, 1.6 mmol) is added and the mixture is further stirred at 70°C for 15 hours. After addition of saturated aqueous ammonium chloride, the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane - ethyl acetate gradient) to afford 4-(2-Methoxy-ethoxy)-1-(3-methoxy-4-nitro-phenyl)-piperidine (111mg, 29%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.52(t, 3H), 1.95-2.00(m, 2H), 1.70-1.79(m, 2H), 3.23(ddd, 2H), 3.58-3.64(m, 2H), 3.65-3.68(m, 2H), 3.64-3.72(m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.00(d, 1H). Rf 0.53 (*n*-hexane: AcOEt=1:1).

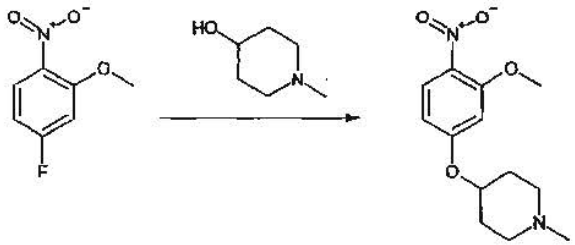
According the procedure described above using appropriate alkyl halides, the following compounds are prepared.

Ex-No.	Rx	Identification

42-1		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.04-2.21(m, 1H), 2.63(t, 2H), 2.68(t, 2H), 3.42(t, 4H), 3.87(t, 4H), 3.96(s, 3H), 6.33(d, 1H), 6.44(dd, 1H), 8.02(d, 1H). Rf 0.09 (AcOEt).
42-2		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.71-1.79(m, 2H), 1.95-2.02(m, 2H), 3.22(ddd, 2H), 3.40(s, 3H), 3.55-3.67(m, 2H), 3.59-3.73(m, 3H), 3.65-3.67(m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.00(d, 1H). Rf 0.35 (*n*-hexane: AcOEt=1:1)

Example : 43

2-Methoxy-4-(1-methyl-piperidin-4-yloxy)-phenylamine 4-(3-Methoxy-4-nitro-phenoxy)-1-methyl-piperidine



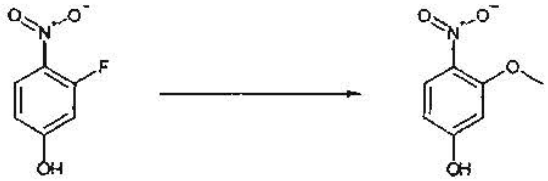
To a solution of 4-Fluoro-2-methoxy-1-nitro-benzene (10.3g, 60 mmol) in toluene (50 mL) and 25% KOH aq.(50mL), 4-hydroxy-1-methylpiperidine (13.8g, 120 mmol) and tetra-n-butyl ammonium bromide (3.87g, 12mmol) are added at room temperature. The mixture is heated at 60°C for 1 day. The reaction mixture is cooled to room temperature, poured into ice water and extracted twice with ethyl acetate. The organic layer is successively washed with dil.HCl and brine, dried over sodium sulfate, and evaporated in vacuo to afford the crude compound in quantitative yield (13.4g).

Rf = 0.22 (methanol : dichloromethane = 1:4). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 1.84-1.92(m, 2H), 2.0-2.1(m, 2H), 2.3-2.4 (m, 2H), 2.33 (s, 3H), 2.65-2.75(m, 2H), 3.94(s, 3H), 4.39-4.46(m, 1H), 6.49 (dd, 1H), 6.99 (d, 1H), 6.54 (d, 1H), 7.99 (d, 1H).

Example : 44

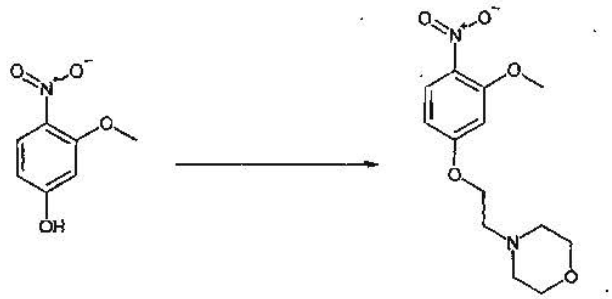
2-Methoxy-4-(2-morpholin-4-yl-ethoxy)-phenylamine

3-Methoxy-4-nitro-phenol



To a solution of 3-Fluoro-4-nitro-phenol (15.7g, 100 mmol) in THF (300 mL) , 30% KOMe in Methanol(49mL, 210mmol) is added at 0°C. The mixture is heated to gentle reflux for 18 hours.

4-[2-(3-Methoxy-4-nitro-phenoxy)-ethyl]-morpholine



To a solution of 3-Methoxy-4-nitro-phenol (1.69g, 10 mmol) in DMF (25 mL) , 4-(2-Chloroethyl)morpholine hydrochloride(2.05g, 11mmol), K2CO3(1.52g, 11mmol), KI(332mg, 2mmol) are added at room temperature. The mixture is heated to gentle reflux for 4 hours. The reaction mixture is cooled to room temperature and quenched with water. The resulting mixture is extracted twice with ethyl acetate and then the organic layer is successively washed with water and brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in 90% yield (2.55g).

Rf = 0.11 (AcOEt only). ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.56-2.61(m, 4H), 2.83(t, The reaction mixture is cooled to room temperature and quenched slowly with 1NHCl aq at 0°C. The resulting mixture is extracted twice with ethyl acetate and then the organic layer is successively washed with brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in 94% yield(15.9g).

Rf = 0.22 (methanol : dichloromethane = 1:4). ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 3.95(s, 3H), 5.49(s, 1H), 6.44 (dd, 1H, J=8.8, 2.52Hz), 6.54 (d, 1H, J=2.52Hz), 7.96 (d, 1H J=8.6Hz).

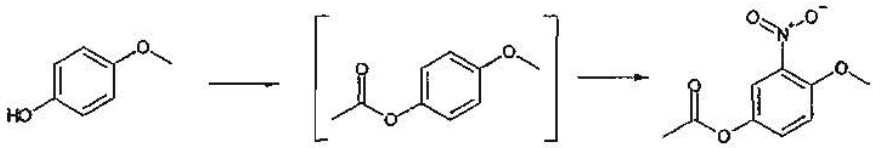
3.72-3.76(m, 4H), 3.94(s, 3H), 4.18(t, 2H), 6.51 (dd, 1H, *J*=9.08, 2.52Hz), 6.56 (d, 1H, *J*=2.48Hz), 8.00 (d, 1H *J*=9.08Hz).

2H),

Example : 45

2-Methoxy-4-(2-morpholin-4-yl-ethoxy)-phenylamine

Acetic acid 4-methoxy-3-nitro-phenyl ester



To a solution of 4-Methoxyphenol (12.4g, 100 mmol) in AcOH (50 mL), Ac_2O (50mL) is added at room temperature. The mixture is heated to gentle reflux for 1.5 hour. The reaction mixture is cooled to room temperature and c.HNO_3 (d=1.38, 10mL) is added slowly at 0 °C. The mixture is heated to 55°C for 1.5h. The reaction mixture is cooled to room temperature and quenched with water at 0oC. The resulting solid is filtered on Buchner funnel to afford the crude compound in 76% yield (16.0g).

Rf = 0.59 (AcOEt : n-Hexane = 3:7). ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.31(s, 3H), 3.96(s, 3H), 7.08 (d, 1H, *J*=9.04Hz), 7.31 (dd, 1H, *J*=9.04, 3.04Hz), 7.96 (d, 1H *J*=3.04 Hz).

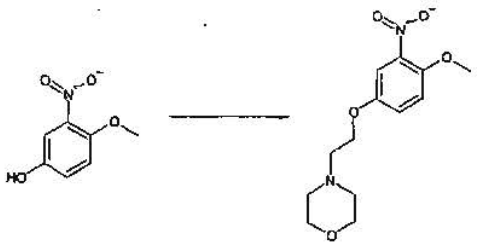
4-Methoxy-3-nitro-phenol



To a solution of Acetic acid 4-methoxy-3-nitro-phenyl ester (1.06g, 5 mmol) in EtOH (20 mL), 1N NaOH aq (5.5mL) is added at 0°C. The mixture is stirred at room temperature for 2 hours. The reaction mixture is quenched with AcOH and extracted twice with ethyl acetate. The organic layer is successively washed with water and brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in quantitative yield (840mg).

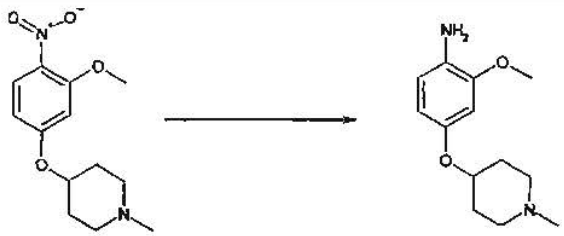
Rf = 0.59 (AcOEt : n-Hexane = 3:7). ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 3.91(s, 3H), 6.99 (d, 1H, *J*=9.04Hz), 7.17 (dd, 1H, *J*=9.04, 3.00Hz), 7.38 (d, 1H *J*=3.04 Hz).

4-[2-(4-Methoxy-3-nitro-phenoxy)-ethyl]-morpholine



To a solution of 4-Methoxy-3-nitro-phenol (1.01g, 6 mmol) in DMF (15 mL) , 4-(2-Chloroethyl)morpholine hydrochloride (1.34g, 7.2mmol), K2CO3 (2.49g, 18mmol), KI(2.99g, 18mmol) are added at room temperature. The mixture is heated to 80°C for 4 hours. The reaction mixture is cooled to room temperature and quenched with saturated NH4Cl solution in water. The resulting mixture is extracted twice with ethyl acetate and then the organic layer is successively washed with water and brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in quantitative yield (1.70g). Rf = 0.14 (AcOEt only). ^{1}H-NMR (400MHz, DMSO, δ, ppm) : 2.36-2.51 (m, 4H), 2.67 (t, J=5.5, 2H), 3.52-3.60 (m, 4H), 3.86 (s, 3H), 4.11 (t, J=6.0, 2H), 7.25-7.29 (m, 2H), 7.46-7.49 (m, 1H).

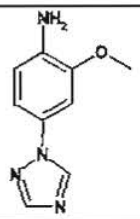
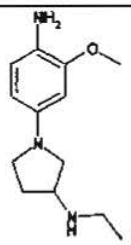
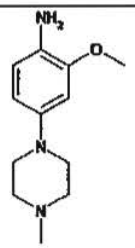
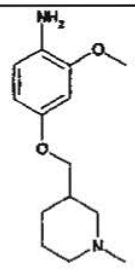
Preparation of 2-Methoxy-4-(1-methyl-piperidin-4-yloxy)-phenylamine:

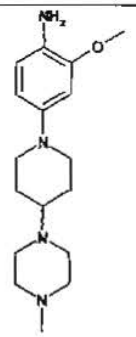
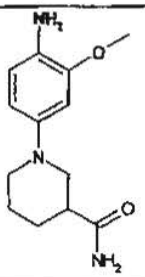
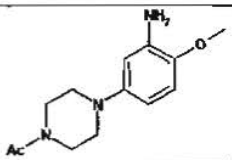
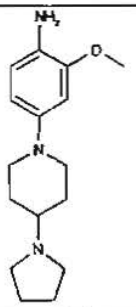
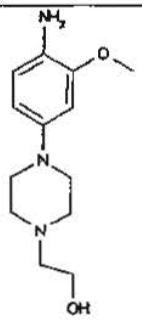


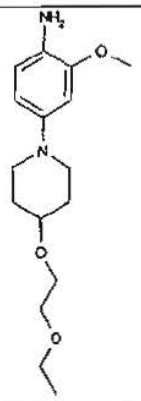
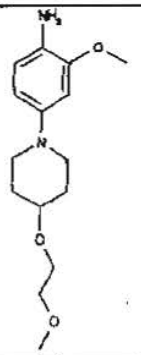
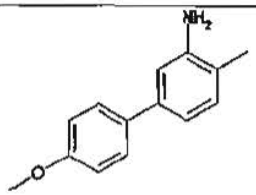
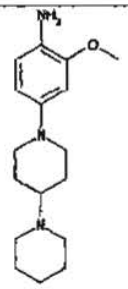
To a solution of 4-(3-Methoxy-4-nitro-phenoxy)-1-methyl-piperidine (3.0g, 11.3 mmol) in ethanol (50 mL), 5% palladium on carbon(300mg) is added under a nitrogen atmosphere. The reaction vessel is fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction is under a hydrogen atmosphere. The reaction is allowed to stir overnight. The reaction mixture is filtered through a pad of Celite and washed with methanol. The filtrate is concentrated in vacuo to afford 2-Methoxy-4-(1-methyl-piperidin-4-yloxy)-phenylamine in quantitative yield (2.7g).

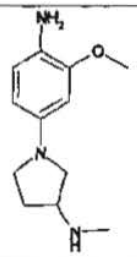
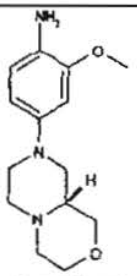
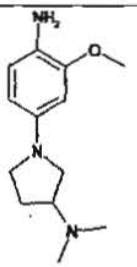
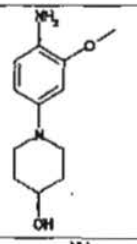
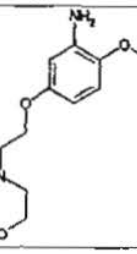
Rf = 0.41 (methanol : dichloromethane = 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.75-1.86(m, 2H), 1.92-2.05(m, 2H), 2.2-2.32 (m, 2H), 2.30 (s, 3H), 3.4-3.7(brs, 2H), 3.82(s, 3H), 4.1-4.2(m, 1H), 6.37(dd, 1H), 6.46 (d, 1H), 6.61 (d, 1H).

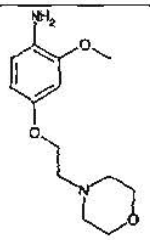
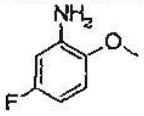
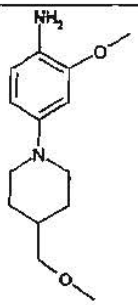
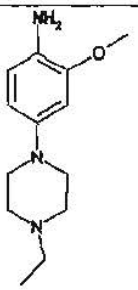
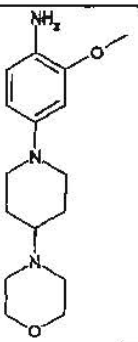
By repeating the procedures described above using appropriate starting materials and conditions the following compounds are obtained.

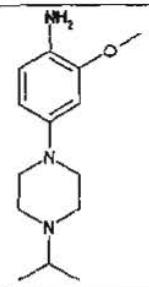
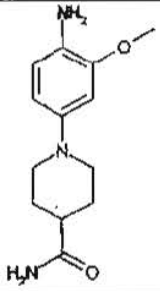
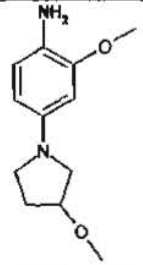
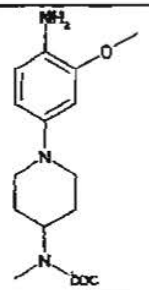
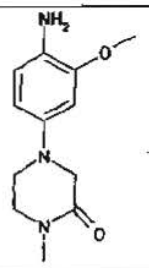
Ex-No.	Rx	Identification
46-1		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 3.92(s,3H), 3.97(br,2H), 6.75(d,1H), 7.00(dd, 1H), 7.12(d, 1H), 8.06(s, 1H), 8.41(s, 1H). Rf 0.32 (AcOEt)
46-2	 [1-(4-Amino-3-methoxy-phenyl)-pyrrolidin-3-yl]-ethyl-amine	^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.13(t, 3H), 1.77-1.86(m, 1H), 2.19-2.27(m,1H), 2.67-2.75(m, 2H), 3.01-3.06(m, 1H), 3.20-3.26(m, 1H), 3.33-3.38(m, 1H), 3.42-3.49(m, 2H), 3.84(s, 3H), 6.04-6.07(m, 1H), 6.14-6.15(m, 1H), 6.64-6.66(m, 1H). Rf 0.2 (AcOEt only)
46-3	 2-Methoxy-4-(4-methyl-piperazin-1-yl)-phenylamine	^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.44(s, 3H), 2.70-2.73(m, 4H), 3.13-3.17(m, 4H), 3.48(brs, 2H), 3.84(s, 3H), 6.41(dd, 1H, J=8.5, 2.52Hz), 6.51(d, 1H, J=2.52Hz), 6.64(d, 1H, J=8.5Hz). Rf 0.2 (AcOEt only).
46-4	 2-Methoxy-4-(1-methyl-piperidin-3-ylmethoxy)-phenylamine	^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.01-1.12(m, 1H), 1.57-2.13(m, 6H), 2.26(s,3H), 2.74-2.77(m, 1H), 2.93-2.96(m, 1H), 3.47 (bs, 2H), 3.70-3.80(m, 2H), 3.82(s, 3H), 6.31-6.34(m, 1H), 6.44-6.45(m, 1H), 6.60-6.62(m, 1H). Rf 0.2 (AcOEt only)

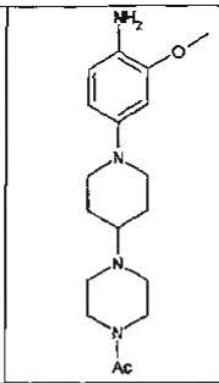
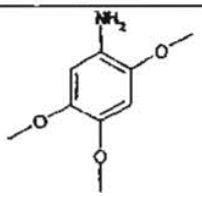
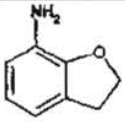
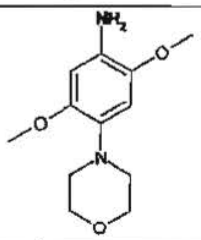
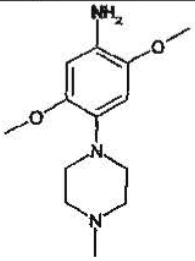
46-5		^{1}H-NMR (400 MHz, $CDCl_3$) 1.80-1.67 (2H, *m*), 1.99-1.90 (2H, *m*), 2.42-2.27 (1H, *m*), 2.56-2.43 (4H, *m*), 2.68-2.58 (2H, *m*), 2.76-2.58 (4H, *m*), 3.57-3.48 (2H, *m*), 3.83 (3H, *s*), 6.41 (1H, *dd*), 6.52 (1H, *d*), 6.63 (1H, *d*). R_f (hexane/acetone 1:1) 0.44.
46-6		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.83-1.95 (m, 2H), 1.97-2.08 (m, 2H), 2.20-2.31 (m, 1H), 2.60-2.72 (m, 2H), 3.46-3.53 (m, 2H), 3.84 (s, 3H), 5.42-5.60 (m, 1H), 6.43 (dd, 1H), 6.53 (d, 1H), 6.64 (d, 1H).
46-7		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.13 (s, 3H), 3.01-3.05 (m, 4H), 3.59 (t, 2H), 3.75 (t, 2H), 3.81 (s, 3H), 6.30 (dd, 1H), 6.39 (bs, 1H), 6.71 (d, 1H).
46-8		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.84-1.97 (m, 2H), 1.98-2.07 (m, 2H), 2.20-2.32 (m, 1H), 2.61-2.72 (m, 2H), 3.47-3.55 (m, 2H), 3.95 (s, 3H), 5.20-5.38 (m, 1H), 5.40-5.56 (m, 2H), 6.43 (d, 1H), 6.53 (bs, 1H), 6.64 (d, 1H).
46-9		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.59-2.67 (m, 2H), 2.77-2.68 (m, 4H), 3.08-3.15 (m, 4H), 3.49-3.56 (m, 1H), 3.67-3.77 (m, 2H), 3.98 (s, 3H), 6.41-6.43 (m, 1H), 6.52 (bs, 1H), 6.65 (d, 1H).

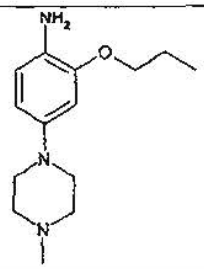
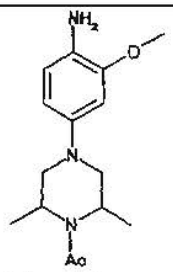
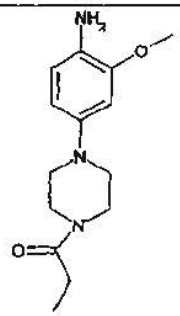
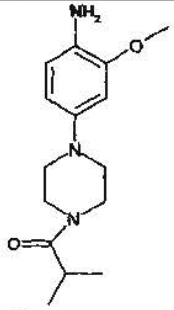
46-10		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.72-1.96 (m, 2H), 1.98-2.10 (m, 2H), 2.63 (s, 3H), 2.73-2.84 (m, 2H), 3.40 (s, 3H), 3.34-3.42 (m, 2H), 3.44-3.49 (m, 1H), 3.55-3.57 (m, 2H), 3.64-3.66 (m, 2H), 3.83 (s, 3H), 6.41-6.43 (m, 1H), 6.53 (bs, 1H), 6.63 (d, 1H).
46-11		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.22(t, 3H), 1.72-1.84 (m, 2H), 2.00-2.10 (m, 2H), 2.72-2.82 (m, 2H), 3.33-3.38 (m, 2H), 3.43-3.49 (m, 1H), 3.55 (q, 2H), 3.58-3.61 (m, 2H), 3.64-3.66 (m, 2H), 3.83 (s, 3H), 6.41-6.43 (m, 1H), 6.53 (bs, 1H), 6.63 (d, 1H).
46-12		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 2.20 (s, 3H), 3.84 (s, 3H), 6.87 (d, 1H), 6.89 (dd, 1H), 6.95 (d, 2H), 7.09 (d, 1H), 7.48 (d, 2H). Rf (n-hexane : ethyl acetate = 1:1): 0.50.
46-13		^{1}H- NMR (400MHz, $CDCl_3$, δ, ppm): 1.49 – 1.59 (m, 3H), 1.70 – 1.95 (m, 6H), 2.00 – 2.20 (m, 2H), 2.60 – 2.90 (m, 7H), 3.50 – 3.60 (m, 3H), 3.83 (s, 3H), 3.85 - 3.91 (m, 1H), 6.41 (dd, 1H, J = 8.0, 2.5 Hz), 6.50 (d, 1H, J = 2.5 Hz), 6.63 (d, 1H, J = 8.0 Hz)

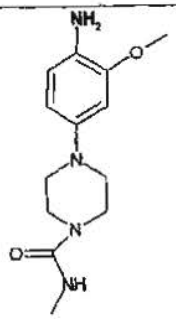
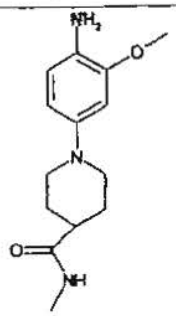
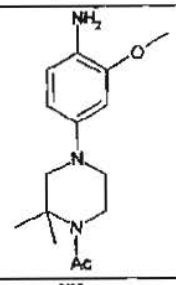
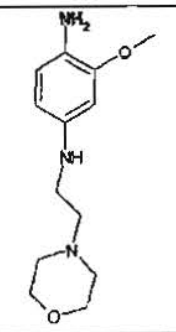
46-14		^{1}H-NMR (400MHz, DMSO-d6, δ, ppm) : 1.87-1.79(m, 1H), 2.22 (ddd, 1H), 2.48 (s, 3H), 3.05 (dd, 1H), 3.28-3.21 (m, 1H), 3.40-3.32 (m, 2H), 3.45 (dd, 1H), 3.84 (s, 3H), 6.06 (dd, 1H), 6.15 (d, 1H)), 6.66 (d, 1H)
46-15		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm): 2.35 - 2.73 (m, 4H), 2.68 - 2.75 (m, 1H), 2.82 - 2.93 (m, 2H), 3.14 – 3.19 (m, 1H), 3.29 - 3.40 (m, 2H), 3.50 - 3.60 (bs, 2H), 3.69 - 3.78 (m, 2H), 3.84 (s, 3H), 3.85 - 3.91 (m, 1H), 6.40 (dd, 1H, J = 8.0, 2.5 Hz), 6.50 (d, 1H, J = 2.5 Hz), 6.64 (d, 1H, J = 8.0 Hz)
46-16		^{1}H-NMR (400MHz, DMSO-d6, δ, ppm) : 1.95-1.85(m, 1H), 2.22-2.14 (m, 1H), 2.31 (s, 3H), 2.89-2.79 (m, 1H), 3.10 (t, 1H), 3.39-3.25 (m, 3H), 3.42 (t, 1H), 3.85 (s, 3H), 6.05 (dd, 1H), 6.14 (d, 1H), 6.67 (d, 1H)
46-17		^{1}H-NMR (400MHz, $CDCl_3$, δ, ppm) : 1.68-1.81 (m, 2H), 1.97-2.09 (m, 2H), 2.74-2.87 (m, 2H), 3.31-3.41 (m, 2H), 3.77-3.88 (m, 1H), 3.84 (s, 3H), 6.40-6.48 (m, 1H), 6.65 (bs, 1H), 6.64 (d, 1H).
46-18		^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.55-2.61(m, 4H), 2.80(t, 2H), 3.72-3.77(m, 4H), 3.81(s, 3H), 4.05(t, 2H), 6.24 (dd, 1H, J=8.56, 2.52Hz), 6.34 (d, 1H, J=2.52Hz), 6.68 (d, 1H J=8.56Hz). Rf = 0.31 (methanol : dichloromethane = 1:9).

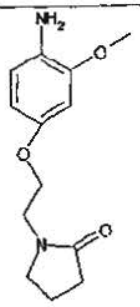
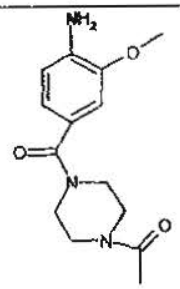
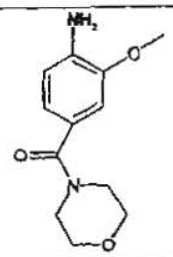
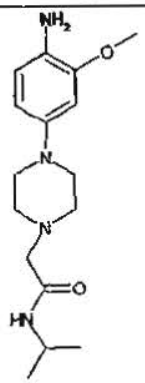
46-19		^{1}H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.55-2.61(m, 4H), 2.78(t, 2H), 3.72-3.77(m, 4H), 3.82(s, 3H), 4.05(t, 2H), 6.35 (dd, 1H, J=8.56, 2.52Hz), 6.47 (d, 1H, J=2.52Hz), 6.63 (d, 1H J=8.56Hz). Rf = 0.61 (methanol : dichloromethane = 1:4).
46-20		^{1}H-NMR (DMSO), δ (ppm): 3.84 (s, 3H), 6.95-7.00 (m, 1H), 7.08-7.12 (m, 2H).
46-21		^{1}H-NMR (400MHz, $CDCl_3$): 1.47-1.34(m, 2H), 1.75-1.63 (m, 1H), 1.86-1.79(m, 2H), 2.64-2.58 (m, 2H), 3.28(d, 2H),3.61(d, 3H),3.87(s, 3H), 3.36(s, 1H),3.49-3.45 (m, 2H), 3.84(s,3H), 6.43(dd, 1H), 6.53(d, 1H) 6.64(d, 1H)
46-22		^{1}H-NMR (400MHz, $CDCl_3$): 1.13(t, 3H),2.49(dd, 2H), 2.68-2.59 (m, 4H),3.10 (t, 4H), 3.84(s,3H), 6.43(dd, 1H), 6.53(d, 1H) 6.65(d, 1H)
46-23		^{1}H-NMR (400MHz, $CDCl_3$): 1.78-1.68 (m, 2H), 1.99-1.89 (m, 2H), 2.36-2.20(m, 1H),2.67-2.50(m, 6H), 3.56-3.48(m, 2H),3.79-3.69(m, 4H), 3.84(s,3H), 6.42(dd, 1H), 6.52(d, 1H) 6.64(d, 1H)

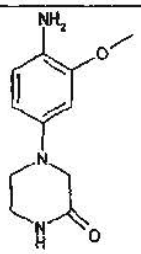
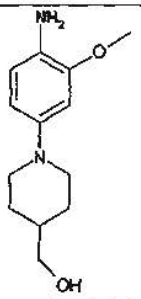
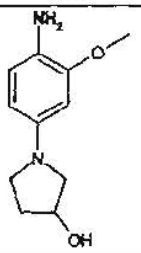
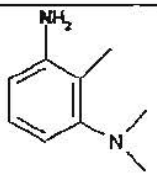
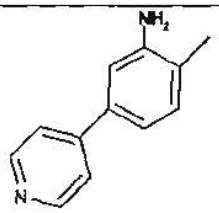
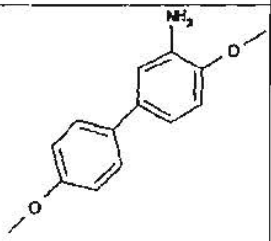
46-24		^{1}H-NMR (400MHz, $CDCl_3$): 1.08 (s, 3H),1.10 (s, 3H), 2.69(t, 4H),2.72-2.68 (m, 1H), 3.08 (t, 4H), 3.83(s,3H), 6.42(dd, 1H), 6.53(d, 1H) 6.64(d, 1H)
46-25		^{1}H-NMR (400MHz, $CDCl_3$): 1.96-1.84 (m, 2H), 2.07-1.99 (m, 2H), 2.32-2.28(m, 1H), 2.70-2.60(m, 2H), 3.54-3.47(m, 2H), 3.84(s, 3H), 5.35-5.24(m,1H), 5.50-5.45 (m, 1H), 6.42(dd, 1H), 6.52(d, 1H) 6.64(d, 1H)
46-26		^{1}H-NMR (400MHz, $CDCl_3$): 2.18-2.03 (m, 2H), 3.28-3.19 (m, 2H), 3.39-3.31(m, 1H), 3.36(s, 3H), 3.49-3.42 (m, 1H), 3.85 (s,3H), 6.07(dd, 1H), 6.16(d, 1H), 6.66(d, 1H)
46-27		^{1}H-NMR (400MHz, $CDCl_3$): 1.48(s, 9H), 1.88-1.71 (m, 2H), 1.97-1.82 (m, 2H), 2.78 (s, 3H), 2.84-2.64(m, 2H), 3.55-3.48(m, 2H), 3.95(s,3H), 3.84 (s, 3H), 6.43(d, 1H), 6.52(bs, 1H), 6.64(d, 1H)
46-28		^{1}H-NMR (400MHz, $CDCl_3$): 3.02(s, 3H), 3.33(dd, 2H), 3.44(t, 2H), 3.74 (s, 2H), 3.83(s, 3H), 6.38(dd, 1H), 6.47(d 1H), 6.66(d, 1H)

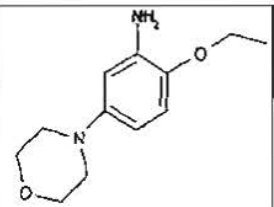
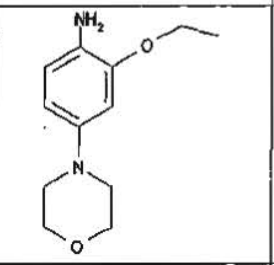
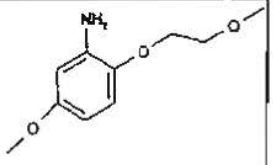
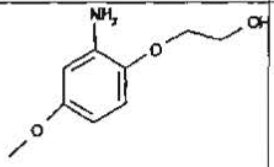
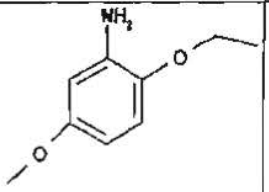
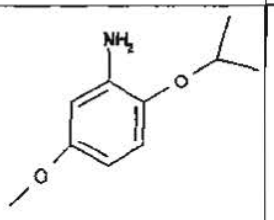
46-29		^{1}H-NMR (400MHz, $CDCl_3$): 1.78-1.38 (m, 2H), 1.96-1.89 (m, 2H), 2.30(s, 3H),2.39-2.31(m, 1H), 2.55-2.42(m, 4H),2.71-2.56(m, 6H), 3.35-3.49 (m,2H), 3.83 (s, 3H), 6.41(dd, 1H), 6.52(d, 1H) 6.63(d, 1H)
46-30		^{1}H-NMR (400MHz, $CDCl_3$): 3.80(s, 3H), 3.82(s, 3H), 3.82 (s, 3H), 6.40(s, 1H), 6.54(s, 1H)
46-31		^{1}H-NMR (400MHz, $CDCl_3$): 3.20(t, 2H), 4.57(t, 2H), 6.55(dd, 1H), 6.70-6.65(m, 1H), 6.68 (d, 1H). Rf 040 (AcOEt)
46-32		^{1}H-NMR (400MHz, $CDCl_3$): 2.98 (t, 4H), 3.62 (bs, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 3.87(t, 4H), 6.36(s, 1H), 6.53(s, 1H)
46-33		^{1}H-NMR (400MHz, $CDCl_3$): 2.37 (s, 3H), 2.61 (t, 4H), 3.27 (t, 4H), 3.88 (s, 3H), 3.95(s, 3H), 6.48(s, 1H), 7.56(s, 1H)

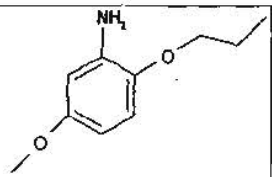
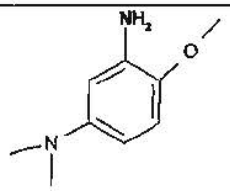
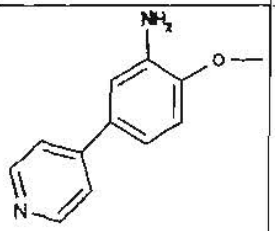
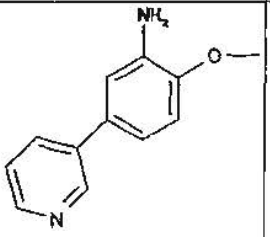
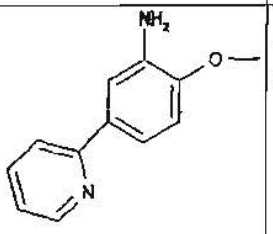
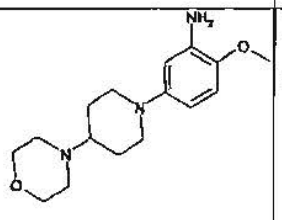
46-34		^{1}H-NMR (400MHz, $CDCl_3$): 1.05(t, 3H), 1.83 (ddd, 2H), 2.35(s, 3H), 2.58(t, 4H), 3.07(t, 4H), 3.94(t, 2H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H)
46-35		^{1}H-NMR (400MHz, $CDCl_3$): 1.28(s, 3H), 1.30 (s, 3H), 2.04 (s, 2H), 2.17(s, 3H), 2.84-2.72 (m, 2H), 3.20 (d, 2H), 3.86 (s, 3H), 6.41(d, 1H), 6.46(dd, 1H), 6.66(d, 1H),
46-36		^{1}H-NMR (400MHz, $CDCl_3$): 1.18(t, 3H), 2.39(dd, 2H), 3.07-2.98(m, 4H), 3.61(t, 2H), 3.78(t, 2H), 3.88(s, 3H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H)
46-37		^{1}H-NMR (400MHz, $CDCl_3$): 1.15(s, 3H), 1.16(s, 3H), 2.83(sept, 1H), 3.07-2.98(m, 4H), 3.73-3.64(m, 2H), 3.83-3.76(m, 2H), 3.84(s, 3H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H)

46-38		^{1}H-NMR (400MHz, $CDCl_3$): 2.84(d, 3H), 3.02(t, 4H), 3.51(t, 4H), 3.84(s, 3H), 4.48-4.38(m, 1H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H)
46-39		^{1}H-NMR (400MHz, $CDCl_3$): 1.99-1.81 (m, 2H), 2.23-2.12(m, 2H), 2.69-2.58(m, 2H), 2.84 (d, 3H), 3.54-3.45(m, 2H), 3.84(s, 3H), 5.55-5.45(m, 1H), 6.42(dd, 1H), 6.52(d, 1H), 6.64(d, 1H)
46-40		^{1}H-NMR (400MHz, $CDCl_3$): 1.53 (s, 6H), 2.11(s, 3H), 3.05(s, 2H), 3.28(t, 2H), 3.64(t, 2H), 3.86 (s, 3H), 6.26 (dd, 1H), 6.33(d, 1H), 6.67(d, 1H)
46-41		^{1}H-NMR (400MHz, $CDCl_3$): 2.55-2.41 (m, 4H), 2.63 (t, 2H), 3.13(t, 2H), 3.77-3.68(m, 4H), 3.83(s, 3H), 6.15(dd, 1H), 6.25 (d, 1H), 6.62(d, 1H)

46-42		^{1}H-NMR (400MHz, $CDCl_3$): 2.05-2.00 (m, 2H), 2.39(t, 2H), 3.57(t, 2H), 3.64 (t, 2H), 3.83(s, 3H), 4.04(t, 2H), 6.32 (dd, 1H), 6.44(d, 1H), 6.63(d, 1H)
46-43		^{1}H-NMR (400MHz, $CDCl_3$): 2.13 (s, 3H), 3.53-3.46 (m, 2H), 3.65-3.55(m, 4H), 3.71-3.66(m, 2H), 3.88 (s, 3H), 6.67(d, 1H), 6.87(dd, 1H), 6.95(d, 1H)
46-44		^{1}H-NMR (400MHz, $CDCl_3$): 3.73-3.61(m,8H), 3.87(s, 3H), 6.85(d, 1H), 6.86(dd, 1H), 6.95(d, 1H)
46-46		^{1}H-NMR (400MHz, $CDCl_3$): 1.17 (s, 3H), 1.19(s, 3H), 2.69(t, 4H), 3.04 (s, 2H), 3.08(t, 4H),4.15-4.07(m, 1H), 6.41 (dd, 1H), 6.51(d, 1H), 6.65(d, 1H), 7.01-6.94(m 1H)

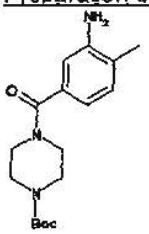
46-47		^{1}H-NMR (400MHz, $CDCl_3$): 3.35-3.28 (m, 2H), 3.53-3.46(m, 2H), , 3.76 (s, 2H), 3.84(s, 3H), 5.92-5.83 (m, 1H), 6.40(dd, 1H), 6.48(d, 1H), 6.67 (d,1H)
46-48		^{1}H-NMR (400MHz, $CDCl_3$): 2.09-2.00 (m, 2H), 2.25-2.15 (m, 2H), 3.29-3.20 (m, 2H), 3.51-3.40(m, 4H), 3.85(s, 3H), 4.62-4.55(m, 1H), 6.08(d, 1H), 6.18(d, 1H), 6.67(d, 1H)
46-49		^{1}H-NMR (400MHz, $CDCl_3$): 1.52-1.40 (m, 2H), 1.90-1.84 (m, 2H), 2.68-2.59 (m, 2H), 3.51-3.45(m, 2H), 3.84(s, 3H), 6.44(dd, 1H), 6.54(d, 1H), 6.64(d, 1H)
46-50		^{1}H-NMR (400MHz, $CDCl_3$) : 2.14 (s, 3H), 2.66 (s, 6H), 6.44 (d, 1H), 6.54 (d, 1H), 6.98 (t, 1H).
46-51		^{1}H-NMR (400MHz, $CDCl_3$) :2.63 (s, 3H), 7.49-7.45 (m, 1H), 7.74-7.62 (m, 2H), 7.76 (dd, 1H), 8.24(d, 1H), 8.77-8.64 (m, 2H).
46-52		^{1}H-NMR (400MHz, $CDCl_3$) :3.84 (s, 3H), 3.88 (s, 3H), 6.78(d, 1H), 6.83 (d, 1H), 7.00-6.89 (m, 3H), 7.45 (d, 1H).

46-53		^{1}H-NMR (400MHz, $CDCl_3$) :1.40 (t, 3H), 3.03 (t, 4H), 3.84 (t, 4H), 4.00 (q, 2H), 6.27 (dd, 1H), 6.38 (d, 1H), 6.71 (dd, 1H),
46-54		^{1}H-NMR (400MHz, $CDCl_3$) :1.26 (t, 3H), 3.02 (t, 4H), 3.85 (t, 4H), 4.05 (q, 2H), 6.40(dd, 1H), 6.49 (d, 1H), 6.66 (d, 1H),
46-55		^{1}H-NMR (400MHz, $CDCl_3$) :3.44 (s, 3H), 3.73 (s, 3H), 3.74-3.68 (m, 2H), 3.95-3.85 (m, 2H), 4.10-4.05 (m, 2H), 6.21 (dd, 1H), 6.32(d, 1H), 6.75 (d, 1H).
46-56		^{1}H-NMR (400MHz, $CDCl_3$) :2.35-2.26 (m, 1H), 3.74 (s, 3H), 3.93-3.86 (m, 2H), 4.09-4.07 (m, 2H), 6.25 (dd, 1H), 6.34(d, 1H), 6.76 (d, 1H).
46-57		^{1}H-NMR (400MHz, $CDCl_3$) :1.40 (t, 3H), 3.71 (s, 3H), 4.00 (q, 2H), 6.22(dd, 1H), 6.33 (d, 1H), 6.69 (d, 1H).
46-58		^{1}H-NMR (400MHz, $CDCl_3$) :1.32(d, 6H), 3.73(s, 3H), 3.85-3.71 (m, 2H), 4.37 (sept, 1H), 6.22 (dd, 1H), 6.32 (d, 1H), 6.72 (d, 1H).

46-59		^{1}H-NMR (400MHz, $CDCl_3$) :1.04 (t, 3H), 1.80 (ddd, 2H), 3.72 (s, 3H), 3.85-3.75 (m, 2H), 3.90 (t, 2H), 6.22 (dd, 1H), 6.33 (d, 1H), 6.69 (d, 1H).
46-60		^{1}H-NMR (400MHz, $CDCl_3$) :2.94 (s, 6H), 3.89 (s, 3H), 6.16 (dd, 1H), 6.25 (d, 1H), 6.72 (d, 1H).
46-61		^{1}H-NMR (400MHz, $CDCl_3$) :3.91(s, 3H), 6.87 (d, 1H), 7.02 (dd, 1H), 7.05 (d, 1H), 7.44 (dd, 2H), 8.59 (dd, 2H).
46-62		^{1}H-NMR (400MHz, $CDCl_3$) :3.91 (s, 3H), 6.88 (d, 1H), 6.96-6.93(m, 1H), 7.31(ddd, 1H), 7.83-7.80 (m, 1H), 8.51(dd, 1H), 8.78(dd, 1H).
46-63		^{1}H-NMR (400MHz, $CDCl_3$) :3.91 (s, 3H), 6.87 (dd, 1H), 7.16(ddd, 1H), 7.34(dd, 1H), 7.43 (d, 1H), 7.72-7.64 (m, 2H), 8.63-8.61 (m, 1H).
46-64		mp 146.6°C; ^{1}H-NMR (500MHz, $CDCl_3$) δ (ppm): 1.63 (m; 2H), 1.99 (m; 2H), 2.27 (m; 1H), 2.60 (m; 6H), 3.52 (m; 2H), 3.71 (m; 4H), 3.78 (s; 3H), 6.36 (dd; 1H); 6.52 (d; 1H), 6.73 (d; 1H).

46-65		

47
Preparation of 4-(3-amino-4-methylbenzoyl)-piperazine-1-carboxylic acid tert-butyl ester

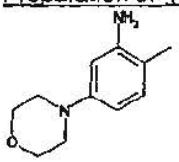


To a solution of 4-methyl-3-nitro-benzoic acid (300 mg, 2.76 mmol), N-butoxycarbonyl-piperazine (340 mg, 1.83 mmol) in DMF (3.0 mL), triethylamine (300 μL, 3.59 mmol), TBTU (800 mg, 2.49 mmol) and HOAt (270.5 mg,1.99 mmol) are added and stirred at room temperature for 24 hours. The mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3- nitrobenzoyl)-piperazine-1-carboxylic acid tert-butyl ester as a colorless solid.

^{1}H-NMR (δ, ppm) : 1.47 (s,9H), 2.64 (s, 3H), 3.88-3.28 (m, 8H), 7.42 (d, 1H), 7.56 (dd, 1H), 8.03 (d, 1H). Rf (hexane : ethyl acetate = 10:1): 0.13.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

48
Preparation of 4-(3-amino-4-methylphenyl)-morpholine



To a suspension of 4-bromo-1-methyl-2-nitrobenzene (225 mg, 1.04 mmol), morpholine (125 μL, 1.25 mmol), and cesium carbonate (474.4 mg, 1.46 mmol) in toluene, palladium diacetate (31.2 mg, 0.139 mmol) and 2-(di-t-butylphosphino)biphenyl (125 mg, 0.403 mmol) are added and stirred at 100°C for 5 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in

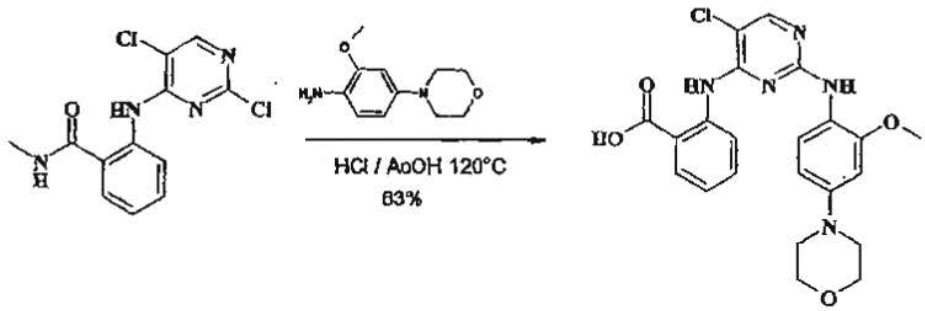
vacuo. The residue is purified with silica gel column chromatography (*n*-hexane : ethyl acetate = 5 : 1) to afford 4-(4-methyl-3-nitrophenyl)-morpholine as a yellow solid.

1H-NMR (δ, ppm) : 2.50 (s, 3H), 3.19-3.17 (m, 4H), 3.88-3.86 (m, 4H), 7.04 (dd, 1H), 7.21 (d, 1H), 7.47 (d, 1H). Rf (hexane : ethyl acetate = 5:1): 0.20.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

49

Preparation of 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzoic acid



To a solution of 1.0 g (3.37 mmol) of 2-(2,5-dichloro-pyrimidin-4-ylamino)-*N*-methyl-benzamide in 15 mL of acetic acid are added 2-methoxy-4-morpholinoaniline dihydrochloride (1.9 g, 6.73 mmol) and 6.0 mL of 1N ethanolic solution of hydrogen chloride (6.0 mmol). After the reaction mixture is stirred at 120°C for 16 hours and cooled to room temperature, aqueous $NaHCO_3$ solution is added to adjust the acidity between pH 5 and pH 6. The resulting precipitate is collected by a filtration and dried under reduced pressure to give 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenyl-amino)-pyrimidin-4-ylamino]-benzoic acid (970 mg, 2.12 mmol, 63%) as ivory solid.

NMR (400MHz, DMSO-d6, δ): 3.10-3.20 (m, 4H), 3.78 (s, 3H), 3.70-3.80 (m, 4H), 6.52 (dd, 1H, J = 8.56, 2.52 Hz), 6.67 (d, 1H, J = 2.52 Hz), 7.08 (dd, 1H, J = 8.04, 8.04 Hz), 7.39 (d, 1H, J = 8.56 Hz), 7.35-7.45 (m, 1H), 7.99 (dd, 1H, J = 8.04, 1.52Hz), 8.14 (s, 1H), 8.28 (s, 1H) 8.70-8.80 (m, 1H).

Example 50: Sulfonamide moieties are prepared as follows:

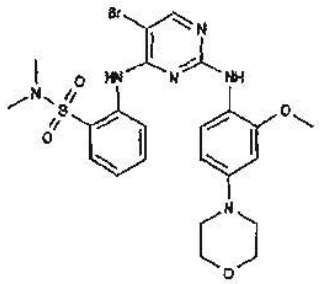
Preparation of 2-amino-4-chloro-5-methyl-benzenesulfonyl chloride

To a solution of 2-amino-5-chloro-4-methyl-benzenesulfonic acid (3.0 g, 1.35 mmol) in dichloroethane (10 mL) is added sulfuryl chloride (4.4 mL, 3.83 mmol) and stirred at 60°C. After one hour, thionyl chloride (1.3 mL) is added and the mixture is further stirred at 100°C for 7.0 hours. The mixture is poured into iced water and extracted with ether three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo. ^{1}H-NMR (δ, ppm) : 2.35 (s, 3H), 6.68 (s, 1H), 7.75 (s, 1H).

This substituted sulfonyl chloride is reacted with a suitable amine. On reaction e.g. with methylamine, 2-amino-5-chloro-4,N-dimethylbenzenesulfonamide is formed.

Example 51

Preparation of 2-[5-bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N, N-dimethyl-benznensulfonamide

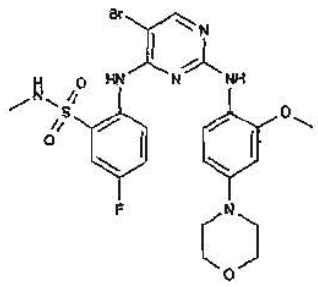


To a solution of 2-[5-Bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide (Ex3-19) (1.0g, 1.82mmol) in DMF (10mL), potassium carbonate (300mg, 2.17mmol) and iodomethane (116μl, 1.86mmol) are added. The resulting suspension is stirred at 50°C for 1h. To the reaction mixture, water is added and extracted with ethyl acetate three times. The organic layer is washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by aluminum oxide column chromatography (AcOEt) to afford the title compound (728mg, 71% yield).

NMR (400MHz, $CDCl_3$, δ): 2.74 ((s, 6H), 3.05-3.18 (m, 4H), 3.84-3.93 (m, 4H), 3.88 (s, 3H), 6.43 (dd, 1H), 6.53 (d, 1H), 7.24 (m, 1H), 7.31 (s, 1H), 7.56 (m, 1H), 7.87 (dd, 1H), 8.05 (d, 1H), 8.21 (s, 1H), 8.49 (d, 1H), 8.49 (d, 1H), 9.27 (s, 1H). Rf: 0.23 (AcOEt:Hexane=1:1).

Example 52

Preparation of 2-[5-Bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-5-fluoro-N-methyl-benzenesulfonamide



Preparation of 7-Fluoro-1,1-dioxo-1,4-dihydro-2H-1 λ^6-benzo[1,2,4]thiadiazin-3-one

To a solution of chlorosulfonylisocyanate (1.2mL, 13.5mmol) in nitroethane (10mL), 4-fluoroaniline (1.0g, 8.97mmol) is added dropwise at 0°C and the reaction mixture is stirred for 30min. To the solution, aluminum chloride (1.3g, 9.87mmol) is added at 0°C and the mixture is stirred at 100°C for 1 hour. After cooling to room temperature, water is added and the mixture is extracted with ethyl acetate twice. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting solids are collected by a filtration and wahed with ether to give slightly gray solids (803.9mg, 41%).

NMR (400MHz, DMSO-d6, δ): 7.22-7.28 (m, 1H), 7.45-7.57 (m, 1H), 7.60 (m, 1H), 11.15-11.30 (m, 1H). Rf: 0.43 (MeOH:AcOEt=1:5).

Preparation of 7-Fluoro-2-methyl-1,1-dioxo-1,4-dihydro-2H-1 λ^6-benzo[1,2,4]thiadiazin-3-one

To a solution of 7-Fluoro-1,1-dioxo-1,4-dihydro-2H-1- λ^6-benzo[1,2,4]thiadiazin-3-one (5.19g, 24.0mmol) in DMF (50mL), sodium hydride (1.04g, 26.0mmol) and iodomethane (1.5mL, 24.0mmol) are added successively and the mixture is stirred for 1 hour at 70°C. After cooling to room temperature, the mixture is poured into water and the precipitate is collected by a filtration and washed with water and hexane, successively, to give slightly gray solids (5.38g, 94%).

NMR (400MHz, DMSO-d6, δ): 3.32 (s, 3H), 7.44 (dd, 1H), 7.75 (ddd, 1H), 7.94 (dd, 1H).

Rf (MeOH:AcOEt = 1:5): 0.21. Rf: 0.39 (Hexane:AcOEt=1:1).

Preparation of 2-Amino-5-fluoro-N-methyl-benzenesulfonamide

6.79g of 7-Fluoro-2-methyl-1,1-dioxo-1,4-dihydro-2H-1 λ^6-benzo[1,2,4]thiadiazin-3-one (29.5mmol) is dissolved in 20% aq. sodium hydroxide and the resulting solution is stirred at 100°C for 13.5 hours. The mixture is cooled to room temperature and poured into water. 78mL of 5M HCl aq. is added and the precipitate is collected by a filtration and washed with water to afford slightly purple solids (3.96g, 65%).

NMR (400MHz, $CDCl_3$, δ): 2.60 (d, 3H), 4.55-4.82 (m, 3H), 6.74 (dd, 1H), 7.05-7.12 (m, 1H), 7.45 (dd, 1H). Rf: 0.41 (Hexane:AcOEt=1:1).

2-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-5-fluoro-N-methyl-benzenesulfonamide

The reaction of pyrimidine with 2-Amino-5-fluoro-N-methyl-benzenesulfonamide is performed in the same manner described in example B.

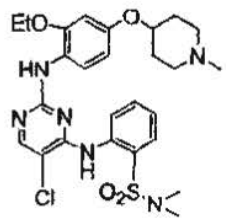
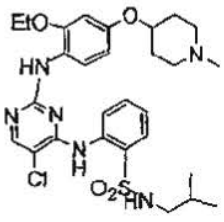
NMR (400MHz, $CDCl_3$, δ): 2.67 (d, 3H), 4.56 (m, 1H), 7.36-7.45 (m, 1H), 7.68 (dd, 1H), 8.39 (s, 1H), 8.42 (dd, 1H), 9.26 (s, 1H). Rf 0.59 (Hexane:AcOEt = 1:1).

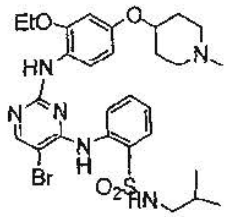
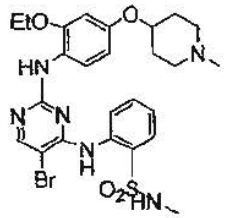
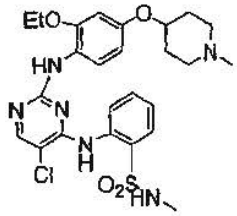
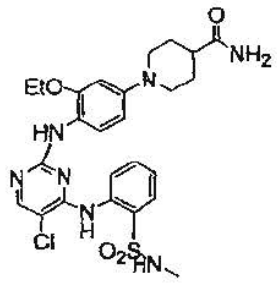
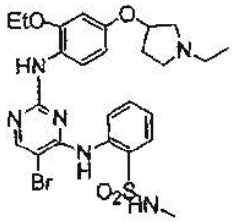
2-[5-Bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-5-fluoro-N-methyl-benzenesulfonamide

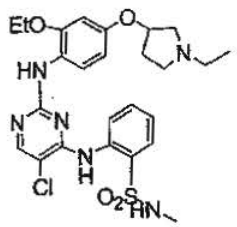
The introduction of substituted aniline is performed according to the manner described in Example A.

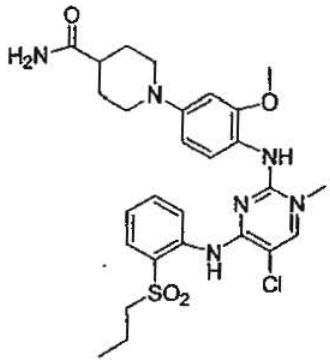
NMR (400MHz, $CDCl_3$, δ): 2.65 (d, 3H), 3.09-3.16 (m, 4H), 3.87 (s, 3H), 4.50 (q, 1H), 6.41 (dd, 1H), 6.52 (d, 1H), 7.25-7.33 (m, 2H), 7.69 (dd, 1H), 7.95 (d, 1H), 8.20 (s, 1H), 8.37 (dd, 1H), 8.70 (s, 1H). Rf 0.30 (Hexane:AcOEt = 1:1)

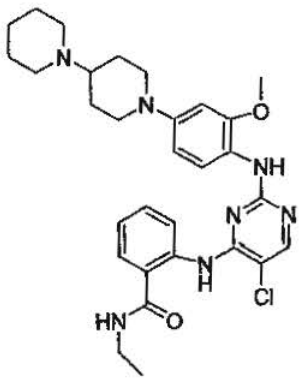
Example 53:

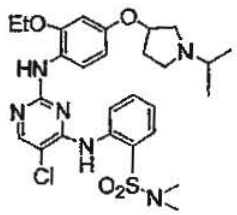
Compound Number	Structure	Physical Data ^{1}H NMR 400 MHz (DMSO-d_6) and/or MS (m/z)
5		^{1}H NMR 400 MHz ($CDCl_3$) δ 12.5 (s, br, 1H), 10.3 (s, 1H), 8.39 (d, 1H, J = 8.38 Hz), 7.97 (s, 1H), 7.87 (dd, 1H, J = 1.63, 7.55 Hz), 7.49 (d, 1H, J = 8.69 Hz), 6.54 (d, 1H, J = 2.49 Hz), 6.43 (dd, 1H, J = 2.51, 8.73 Hz), 4.70 (s, 1H), 4.04 (q, 2H, J = 6.98 Hz), 3.51 (m, 2H), 3.29 (d, 1H, J = 19.2 Hz), 3.18 (m, 2H), 2.89 (d, 3H, J = 3.26 Hz), 2.77 (s, 6H), 2.39 (m, 2H), 2.22 (m, 2H), 1.40 (t, 3H, J = 6.97 Hz). MS *m/z* 561.4 (M + 1)
6		MS *m/z* 589.4 (M + 1)

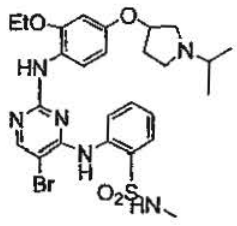
7		MS *m/z* 633.4/635.4 (M + 1).
8		MS *m/z* 591.3/593.3 (M + 1).
9		MS *m/z* 547.4 (M + 1).
10		^{1}H NMR 400 MHz (acetone-d_6) δ 9.45 (br, 1H), 8.88 (br, 1H), 8.23 (m, 1H), 8.07 (s, 1H), 7.83 (m, 1H), 7.72 (dd, 1H, J = 1.25, 7.96 Hz), 7.45 (m, 1H), 7.14 (m, 2H), 6.86 (m, 1H), 6.79 (br, 1H), 6.62 (m, 1H), 6.13 (m, 1H), 3.97 (t, 2H, J = 6.98 Hz), 3.63 (m, 2H), 3.21 (m, 2H), 2.44 (m, 1H), 2.34 (s, 3H), 1.99 (m, 4H), 1.17 (t, 3H, J = 6.98 Hz). MS *m/z* 560.4 (M + 1).
11		MS *m/z* 561.4 (M + 1).
12		MS *m/z* 591.3/593.3 (M + 1).

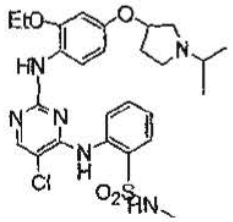
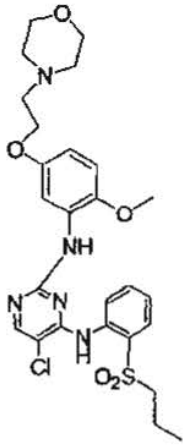
13  MS *m/z* 547.4 (M + 1).

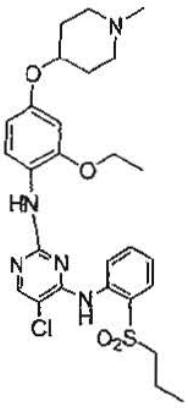
14  MS *m/z* 559.4 (M + 1).

15  MS *m/z* 564.5 (M + 1).

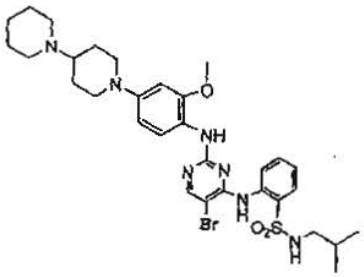
16  MS *m/z* 575.4 (M + 1).

17  MS *m/z* 605.3/607.3 (M + 1).

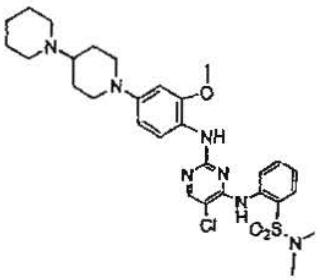
18		MS *m/z* 561.4 (M + 1).
19		MS *m/z* 532.4 (M + 1).
20		^{1}H NMR 400 MHz (acetone-d_6) δ 8.60 (d, 1H, J = 8.27 Hz), 8.40 (s, 1H), 8.00 (dd, J = 1.55, 7.95 Hz), 7.76 (m, 2H), 7.49 (m, 1H), 7.08 (d, J = 8.94 Hz, 1H), 6.84 (dd, J = 3.00, 8.91 Hz, 1H), 4.50 (t, J = 4.99 Hz, 2H), 4.08 (m, 2H), 4.00 (m, 2H), 3.90 (s, 3H), 3.78 (m, 4H), 3.37 (m, 4H), 1.78 (m, 2H), 0.99 (t, J = 7.44 Hz, 3H). MS *m/z* 562.4 (M + 1).

21 

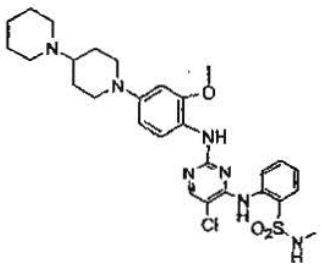
MS *m/z* 560.4 (M + 1).

22 

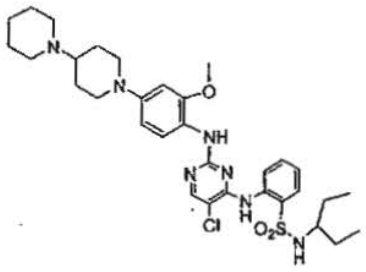
^{1}H NMR 600 MHz (acetone-d_6) δ 11.20 (br, 1H), 9.75 (d, J = 15.25 Hz, 1H), 8.46 (m, 2H), 8.04 (dd, J = 1.12, 7.93 Hz, 1H), 7.71 (m, 1H), 7.69 (m, 1H), 7.47 (t, J = 7.63 Hz, 1H), 7.06 (m, 1H), 7.02 (m, 1H), 4.07 (m, 2H), 3.99 (s, 3H), 3.77 (m, 2H), 3.67 (m, 1H), 3.27 (m, 2H), 3.13 (t, J = 12.2 Hz, 2H), 2.85 (m, 2H), 2.48 (m, 2H), 2.26 (m, 3H), 2.08 (m, 3H), 1.95 (m, 1H), 1.75 (m, 1H), 1.66 (m, 1H), 0.89 (d, J = 6.65 Hz, 6H). MS *m/z* 672.4/674.4 (M + 1).

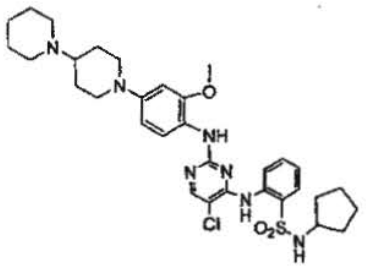
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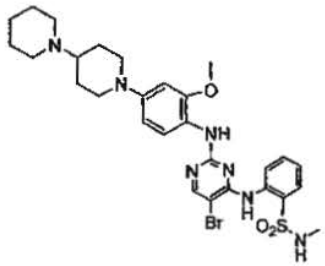
MS *m/z* 600.4 (M + 1).

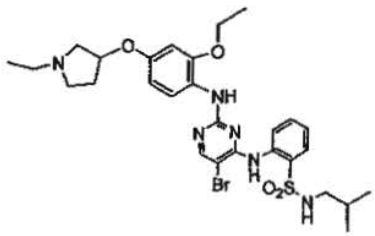
24 

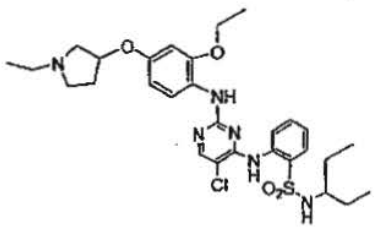
MS *m/z* 586.4 (M + 1).

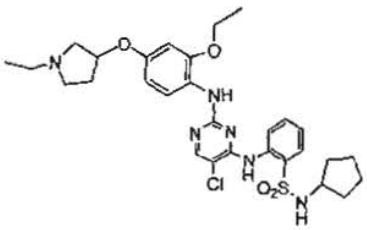
25  MS *m/z* 642.5 (M + 1).

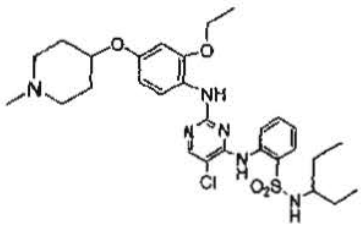
26  MS *m/z* 640.5 (M + 1).

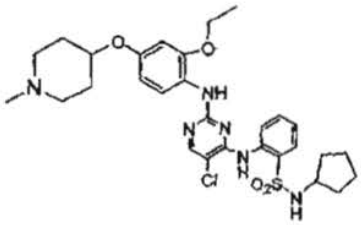
27  MS *m/z* 630.3/632.3 (M + 1).

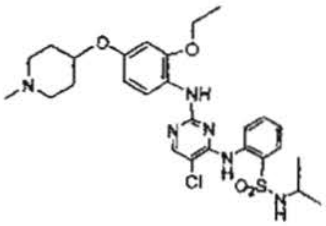
28  MS *m/z* 633.4/635.3 (M + 1).

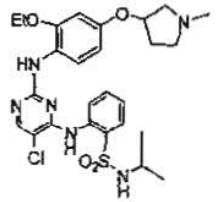
29  MS *m/z* 603.4 (M + 1).

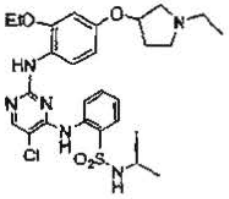
30  MS *m/z* 601.4 (M + 1).

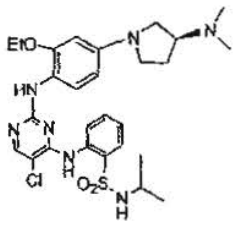
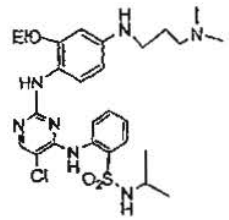
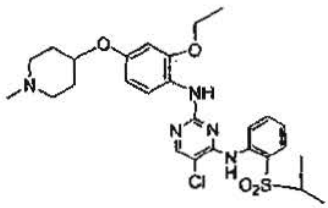
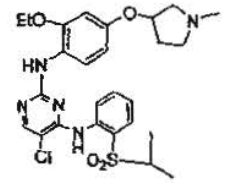
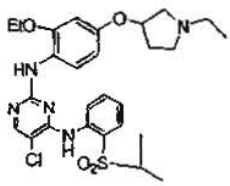
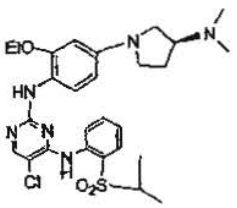
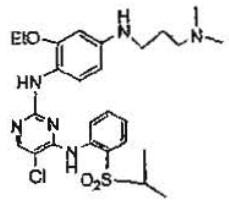
31  MS *m/z* 603.4 (M + 1).

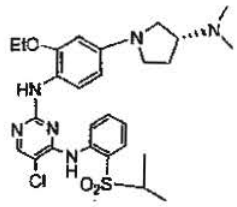
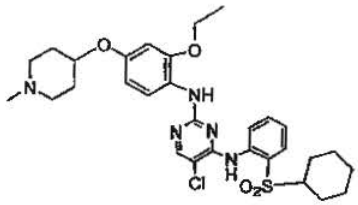
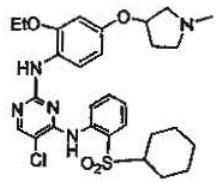
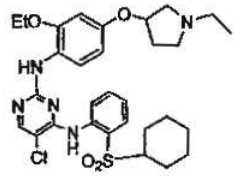
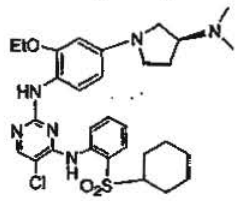
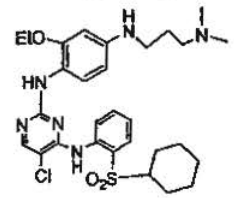
32  MS *m/z* 601.4 (M + 1).

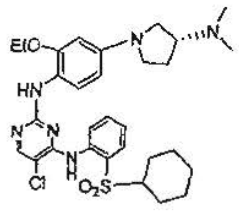
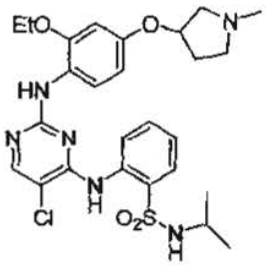
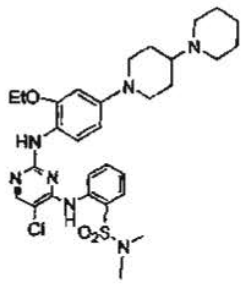
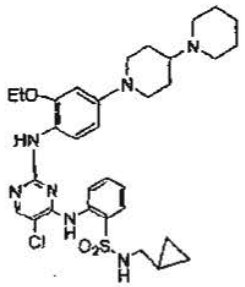
33  MS *m/z* 575.4 (M + 1).

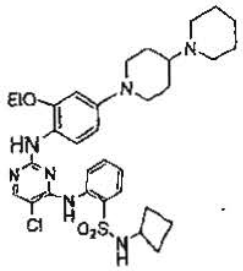
34  MS *m/z* 561.4 (M + 1).

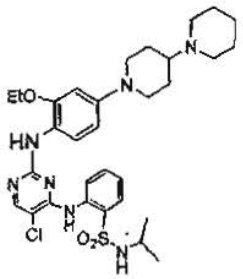
35  ^{1}H NMR 600 MHz (acetone-d_6) δ 8.47(d, J = 7.13, 1H), 8.43 (s, 1H), 8.09 (d, J = 7.85 Hz, 1H), 7.83 (m, 1H), 7.73 (t, J = 7.67 Hz, 1H), 7.50 (m, 1H), 6.87 (m, 1H), 6.71 (m, 1H), 5.46 (d, J = 31.2 Hz, 1H), 4.22 (m, 3H), 3.55 (m, 5H), 2.51 (m, 1H), 2.49 (m, 1H), 2.21 (m, 1H), 1.50 (m, 6H), 1.10 (d, J = 6.56 Hz, 6H) .MS *m/z* 575.4 (M + 1).

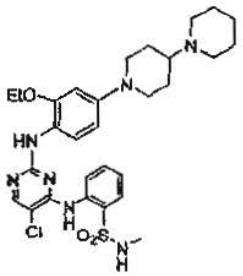
36		MS *m/z* 574.4 (M + 1).
37		MS *m/z* 562.4 (M + 1).
38		MS *m/z* 560.4 (M + 1).
39		MS *m/z* 546.4 (M + 1).
40		MS *m/z* 560.4 (M + 1).
41		MS *m/z* 559.4 (M + 1).
42		MS *m/z* 547.4 (M + 1).

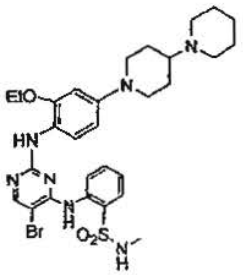
43		MS *m/z* 559.4 (M + 1).
44		MS *m/z* 600.4 (M + 1).
45		MS *m/z* 586.4 (M + 1).
46		MS *m/z* 600.4 (M + 1).
47		MS *m/z* 599.4 (M + 1).
48		MS *m/z* 587.4 (M + 1).

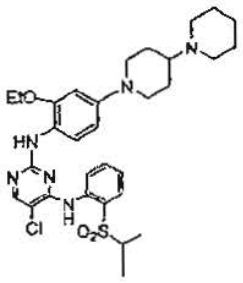
49		^{1}H NMR 600 MHz (acetone-d_6) δ 10.35 (m, 1H), 8.72 (s, br, 1H), 8.42 (s, 1H), 8.00 (d, J = 7.93 Hz, 1H), 7.73 (m, 1H), 7.64 (m, 1H), 7.50 (t, J = 7.77 Hz, 1H), 6.55 (s, 1H), 6.43 (d, J = 8.51 Hz, 1H), 4.31 (m, 1H), 4.22 (q, J = 6.93 Hz, 2H), 3.97 (m, 2H), 3.80 (t, J = 8.45 Hz, 1H), 3.58 (q, J = 8.38 Hz, 1H), 3.36 (m, 1H), 3.17 (s, 1H), 2.78 (m, 1H), 2.66 (m, 1H), 2.15 (m, 2H), 1.73 (d, J = 12.9 Hz, 2H), 1.59 (d, J = 12.9 Hz, 1H), 1.55 (m, 2H), 1.43 (m, 3H), 1.35 (m, 2H), 1.25 (m, 1H). MS *m/z* 599.4 (M + 1).
50		MS *m/z* 562.4 (M + 1).
51		MS *m/z* 614.5 (M + 1).
52		MS *m/z* 640.5 (M + 1).

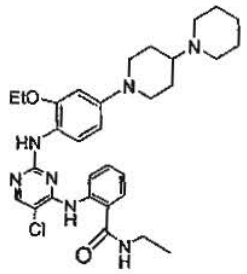
53  MS *m/z* 640.5 (M + 1).

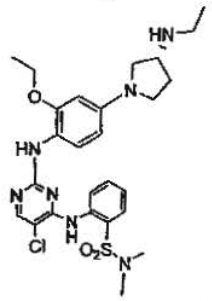
54  MS *m/z* 628.5 (M + 1).

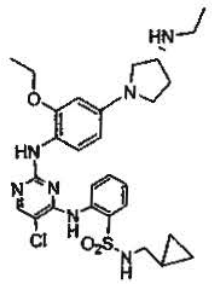
55  MS *m/z* 600.4 (M + 1).

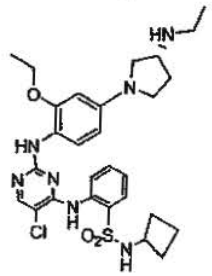
56  MS *m/z* 644.4/646.4 (M + 1).

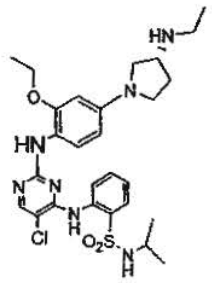
57  MS *m/z* 613.5 (M + 1).

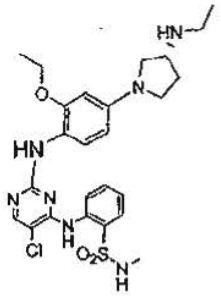
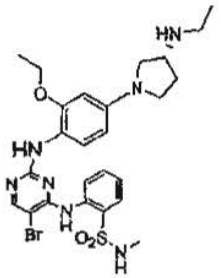
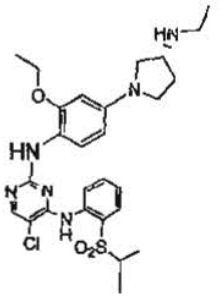
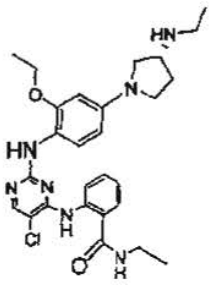
58  MS *m/z* 578.5 (M + 1).

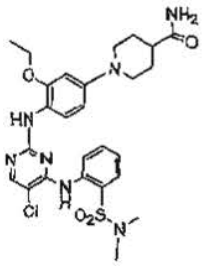
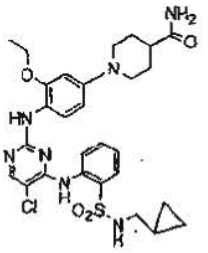
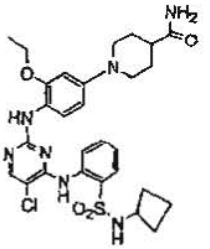
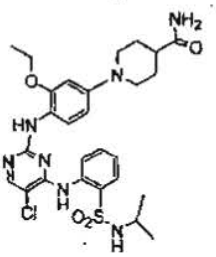
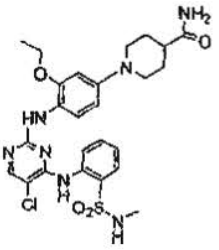
59  MS *m/z* 560.4 (M + 1).

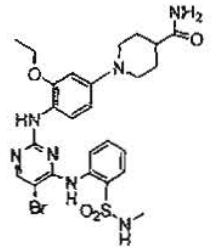
60  MS *m/z* 586.4 (M + 1).

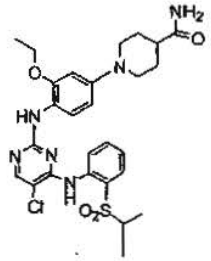
61  MS *m/z* 586.4 (M + 1).

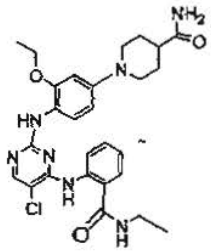
62  MS *m/z* 574.4 (M + 1).

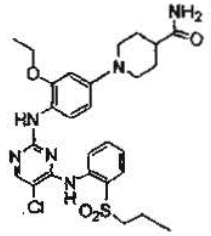
63		MS *m/z* 546.4 (M + 1).
64		MS *m/z* 590.4/592.4 (M + 1).
65		MS *m/z* 559.4 (M + 1).
66		^{1}H NMR 600 MHz (CD_3OD) δ 8.65 (br, 1H), 8.03 (br, 1H), 7.78 (d, J = 7.76 Hz, 1H), 7.49 (br, 1H), 7.30 (s, 1H), 6.38 (m, 1H), 6.33 (dd, J = 1.69, 8.64 Hz, 1H), 4.12 (q, J = 6.96 Hz, 2H), 4.06 (m, 1H), 3.71 (dd, J = 6.68, 10.74 Hz, 1H), 3.66 (m, 1H), 3.56 (dd, J = 4.71, 10.76 Hz, 1H), 3.42 (m, 3H), 3.22 (q, J = 7.28 Hz, 2H), 2.57 (m, 1H), 2.26 (m, 1H), 1.39 (t, J = 7.28 Hz, 3H), 1.34 (t, J = 6.96 Hz, 3H). MS *m/z* 524.4 (M + 1).

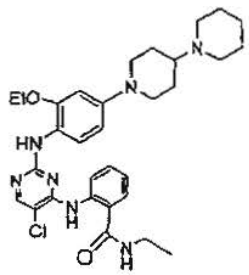
67		MS *m/z* 574.4 (M + 1).
68		^{1}H NMR 600 MHz (CD_3OD) δ 8.23 (s, 1H), 8.18 (d, J = 8.16 Hz, 1H), 7.98 (d, J = 8.44 Hz, 2H), 7.68 (m, 1H), 7.43 (m, 1H), 7.22 (d, J = 2.29 Hz, 1H), 6.97 (dd, J = 2.30, 8.81 Hz, 1H), 4.20 (q, J = 6.99 Hz, 2H), 3.77 (m, 2H), 3.58 (m, 2H), 2.75 (d, J = 7.03 Hz, 2H), 2.72 (m, 1H), 2.18 (m, 4H), 1.47 (t, J = 6.97 Hz, 3H), 0.75 (m, 1H), 0.30 (m, 2H), 0.00 (m, 2H). MS *m/z* 600.4 (M + 1).
69		MS *m/z* 600.4 (M + 1).
70		MS *m/z* 588.4 (M + 1).
71		MS *m/z* 560.4 (M + 1).

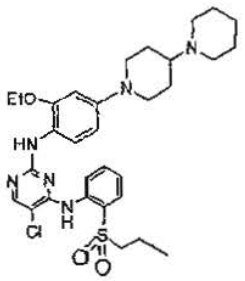
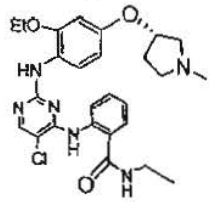
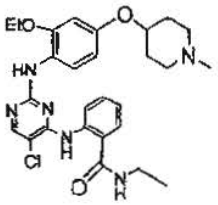
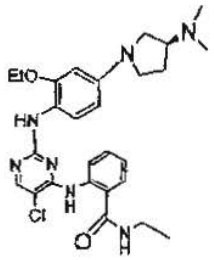
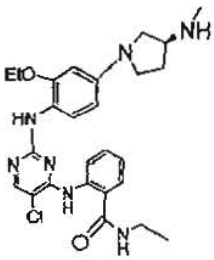
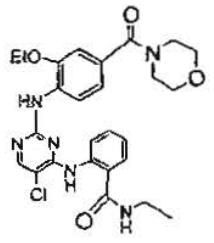
72  MS *m/z* 604.3/606.3 (M + 1).

73  MS *m/z* 573.4 (M + 1).

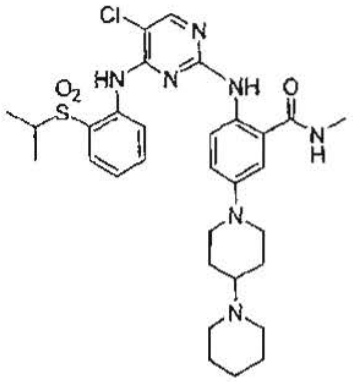
74  MS *m/z* 538.4 (M + 1).

75  MS *m/z* 573.4 (M + 1).

76  MS *m/z* 578.5 (M + 1).

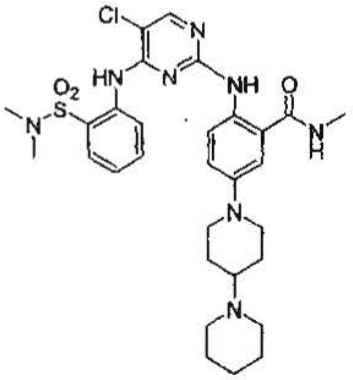
77		MS *m/z* 613.5 (M + 1).
78		MS *m/z* 511.4 (M + 1).
79		MS *m/z* 525.5 (M + 1).
80		MS *m/z* 524.5 (M + 1).
81		MS *m/z* 510.5 (M + 1).
82		MS *m/z* 525.4 (M + 1).

83



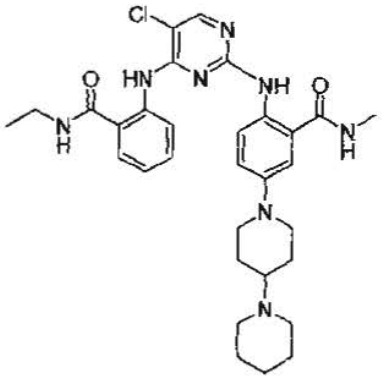
MS *m/z* 627.5 (M + 1).

84



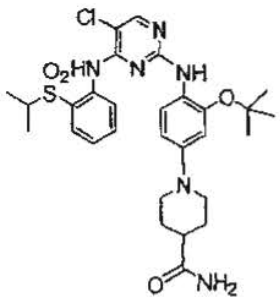
^{1}H NMR 600 MHz (CD_3OD) δ 9.18 (m, 2H), 8.05 (d, J = 7.93 Hz, 1H), 7.93 (t, J = 7.64 Hz, 1H), 7.78 (m, 1H), 7.68 (m, 2H), 7.58 (t, J = 7.54 Hz, 1H), 4.72 (s, 2H), 4.07 (d, J = 12.4 Hz, 2H), 3.34 (br, 4H), 2.96 (t, J = 12.3 Hz, 2H), 2.87 (s, 6H), m, 2H), 2.28 (s, 1H), 2.00 (br, 7H), 1.81 (br, 2H). MS *m/z* 627.5 (M + 1).

85

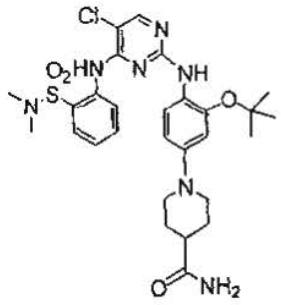
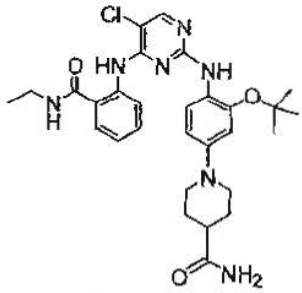
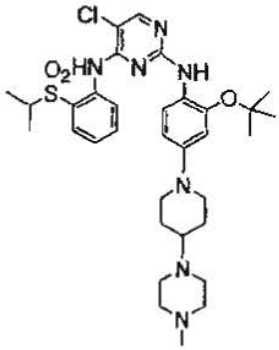
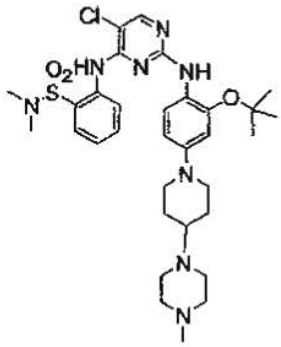


MS *m/z* 591.5 (M + 1).

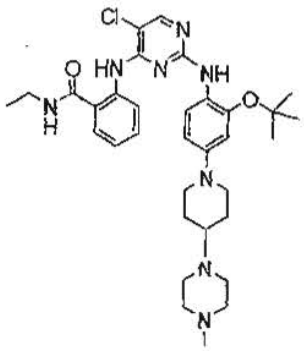
86



MS *m/z* 601.5 (M + 1).

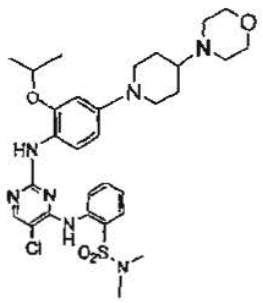
87		MS *m/z* 602.4 (M + 1).
88		MS *m/z* 566.5 (M + 1).
89		MS *m/z* 656.5 (M + 1).
90		^{1}H NMR 600 MHz (CD_3OD) δ 8.16 (d, J = 8.16 Hz, 1H), 8.23 (s, 1H), 7.94 (dd, J = 1.42, 7.98 Hz, 1H), 7.79 (d, J = 9.24 Hz, 1H), 7.72 (m, 1H), 7.48 (m, 1H), 7.15 (d, J = 2.53 Hz, 1H), 7.03 (dd, J = 2.58, 8.91 Hz, 1H), 4.00 (s, 1H), 3.82 (d, J = 12.63 Hz, 2H), 3.50 (s, br, 4H), 3.29 (m, 5H), 3.19 (m, 1H), 2.96 (s, 3H), 2.73 (s, 6H), 2.25 (d, J = 12.40 Hz, 2H), 2.03 (m, 2H), 1.40 (s, 9H). MS *m/z* 657.5 (M + 1).

91



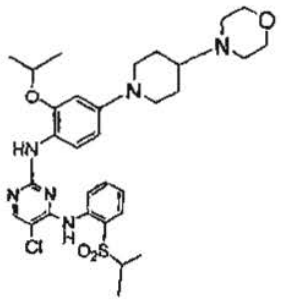
MS *m/z* 621.6 (M + 1).

92



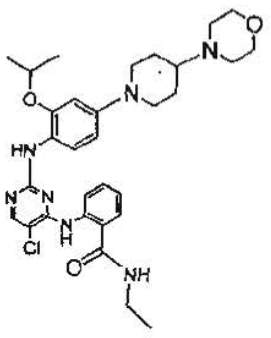
^{1}H NMR 600 MHz (CD_3OD) δ 8.31 (d, J = 7.65 Hz, 1H), 8.19 (s, 1H), 7.94 (dd, J = 1.33, 7.96 Hz, 1H), 7.67 (t, J = 7.70 Hz, 1H), 7.49 (t, J = 7.68 Hz, 1H), 7.44 (d, J = 8.56 Hz, 1H), 6.83 (d, J = 1.37 Hz, 1H), 6.65 (d, J = 8.66 Hz, 1H), 4.69 (m, 1H), 4.11 (br, 2H), 3.91 (d, J = 12.68 Hz, 2H), 3.83 (br, 2H), 3.58 (br, 2H), 3.46 (m, 1H), 3.23 (br, 2H), 3.00 (t, J = 12.19 Hz, 2H), 2.73 (s, 6H), 2.33 (d, J = 12.14 Hz, 2H), 1.97 (m, 2H), 1.30 (d, J = 6.04 Hz, 6H).
MS *m/z* 630.5 (M + 1).

93

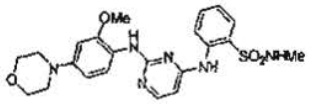
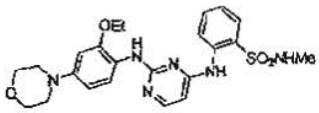
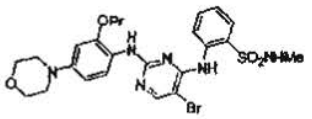
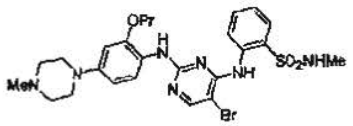
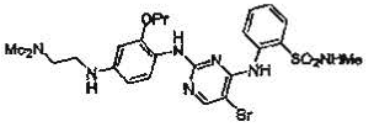
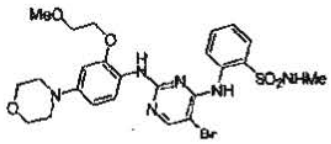


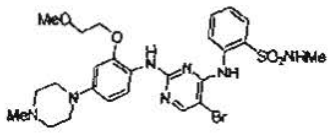
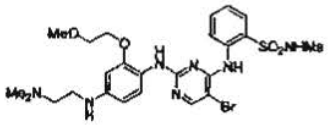
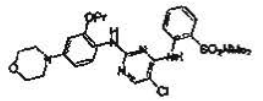
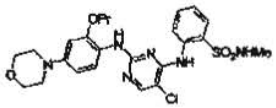
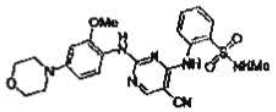
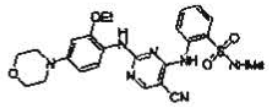
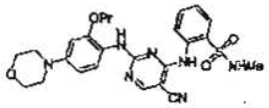
MS *m/z* 629.5 (M + 1).

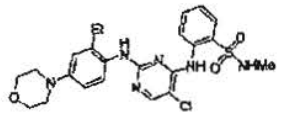
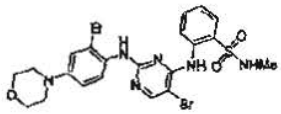
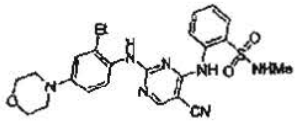
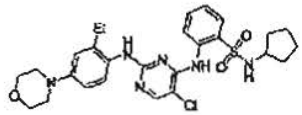
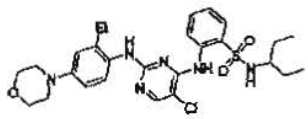
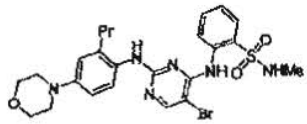
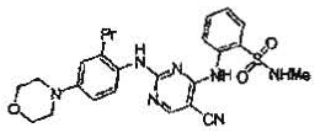
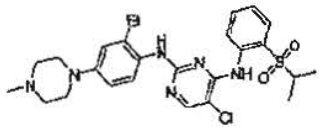
94

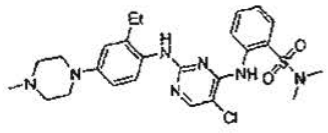
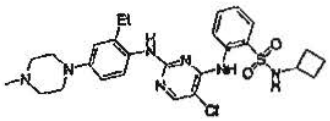
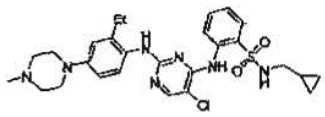
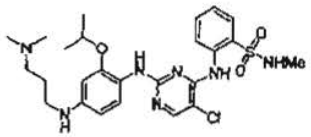
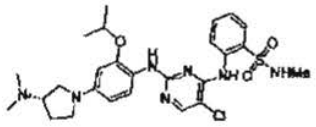
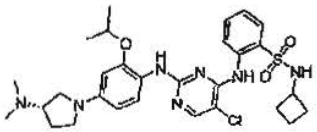
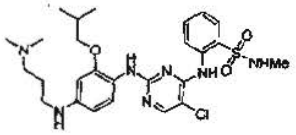


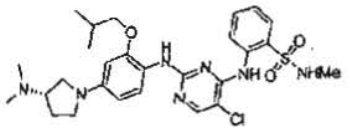
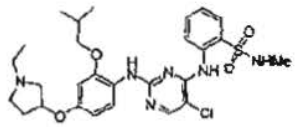
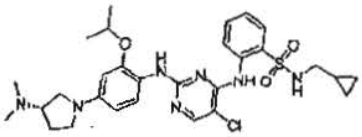
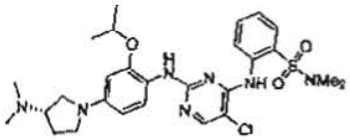
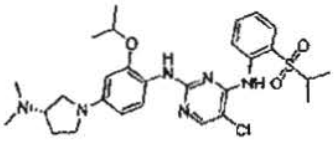
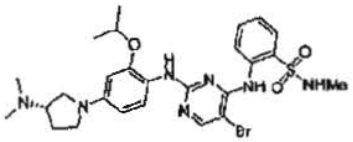
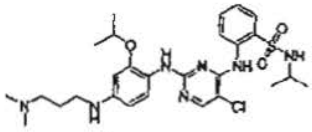
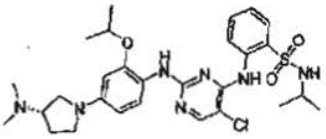
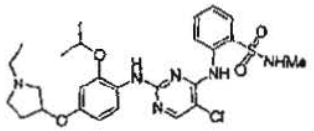
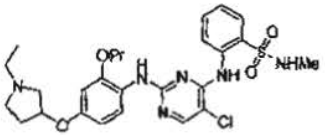
MS *m/z* 594.5 (M + 1).

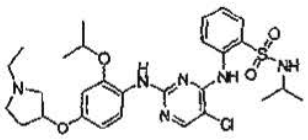
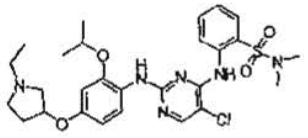
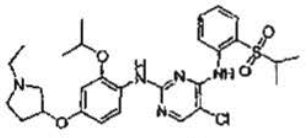
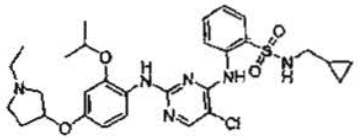
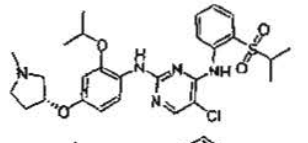
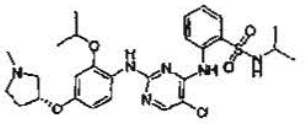
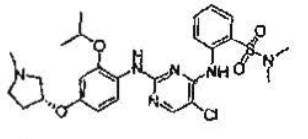
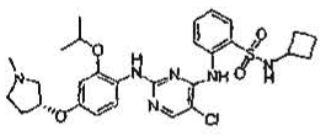
95		MS *m/z* 471.1 (M + 1).
96		^{1}H NMR 600 MHz (DMSO-d_6) δ 11.7 (bs, 1H), 11.14 (bs, 1H), 9.50 (b, 2H), 7.89 (d, 1H, J = 9.1 Hz), 7.72 (m, 2H), 7.65 (m, 2H), 7.18 (m, 1H), 6.62 (s, 1H), 6.48 (m, 1H), 4.05 (q, 2H, J = 6.6 Hz), 3.73 (t, 4H, J = 4 .8 Hz), 3.11 (m, 4H), 2.40 (m, 3H), 1.24 (m, 3H); MS *m/z* 485.1 (M + 1).
97		MS *m/z* 577.1 (M + 1).
98		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.97 (bs, 1H), 9.34 (s, 1H), 8.48 (bs, 1H), 8.34 (bs, 1H), 8.28 (s, 1H), 7.80 (q, 1H, J = 4.8 Hz), 7.77 (d, 1H, J = 7.8 Hz), 7.48 (m, 1H), 7.39 (d, 1H, J = 8.4 Hz,), 7.25 (t, 1H, J = 7.2 Hz), 6.71 (s, 1H), 6.49 (d, 1H, J = 8.4 Hz), 3.93 (t, 2H, J = 6.0 Hz), 3.85 (d, 2H, J = 12 Hz), 3.54 (d, 2H, J = 12 Hz), 3.18 (q, 2H, J = 9.0 Hz), 2.94 (t, 2H, J = 11 Hz), 2.88 (s, 3H), 2.42 (d, 3H, J = 4.8 Hz), 1.64 (m, 2H), 0.85 (t, 3H, J = 7.2 Hz); MS *m/z* 590.1 (M + 1).
99		MS *m/z* 578.1 (M + 1).
100		MS *m/z* 593.1 (M + 1).

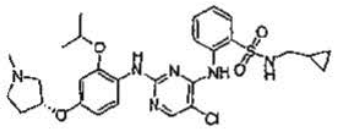
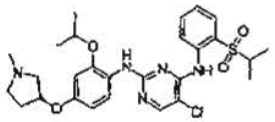
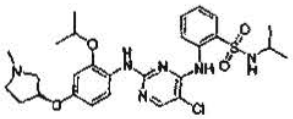
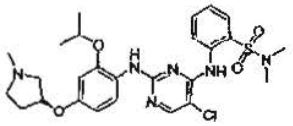
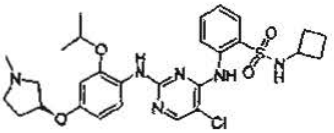
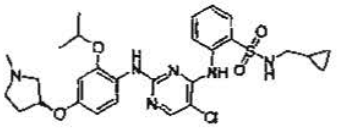
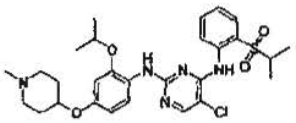
101		^{1}H NMR 500 MHz (DMSO-d_6) δ 10.0 (bs, 1H), 9.34 (s, 1H), 8.47 (bs, 1H), 8.33 (bs, 1H), 8.30 (s, 1H), 7.79 (s, 1H), 7.78 (d, 1H, J = 7.2 Hz), 7.50 (m, 2H), 7.27 (t, 1H, J = 7.8 Hz,), 6.75 (s, 1H), 6.53 (d, 1H, J = 7.8 Hz), 4.12 (t, 2H, J = 4.8 Hz), 3.84 (d, 2H, J = 12 Hz), 3.59 (t, 2H, J = 4.8 Hz), 3.53 (d, 2H, J = 12 Hz), 3.23 (s, 3H), 3.17 (q, 2H, J = 9.0 Hz), 2.94 (t, 2H, J = 11 Hz), 2.88 (s, 3H), 2.43 (d, 3H, J = 4.8 Hz); MS *m/z* 606.1 (M + 1).
102		MS *m/z* 594.1 (M + 1).
103		MS *m/z* 547.1 (M + 1).
104		MS *m/z* 533.1 (M + 1).
105		MS *m/z* 496.4 (M + 1).
106		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.35 (s, 1H), 9.02 (s, 1H), 8.52 (s, 1H), 8.17 (bs, 1H), 7.80 (m, 2H), 7.45 (bs, 1H), 7.29 (m, 2H), 6.66 (s, 1H), 6.47 (d, 1H, J = 8.0 Hz), 4.02 (q, 2H, J = 7.2 Hz), 3.76 (t, 4H, J = 4.8 Hz), 3.14 (t, 4H, J = 4.8 Hz), 2.41 (d, 3H, J = 4.0 Hz), 1.23 (t, 3H, J = 7.2 Hz); MS *m/z* 510.4 (M + 1).
107		MS *m/z* 524.5 (M + 1).

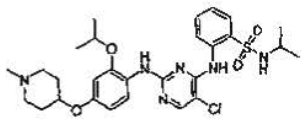
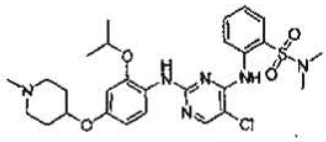
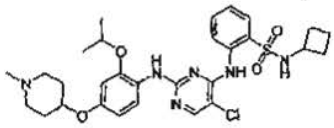
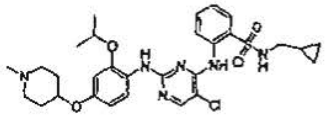
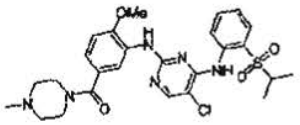
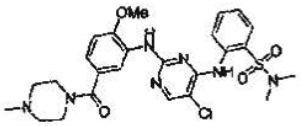
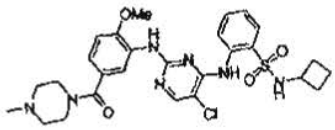
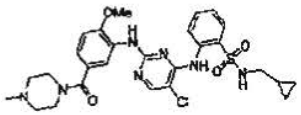
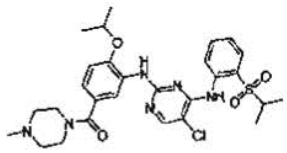
108		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.61 (s, 1H), 9.10 (bs, 1H), 8.35 (bs, 1H), 8.18 (s, 1H), 7.77 (m, 2H), 7.41 (bs, 1H), 7.26 (t, 1H, J = 7.2 Hz), 7.15 (d, 1H, J = 7.8 Hz), 6.89 (s, 1H), 6.85 (d, 1H, J = 9.6 Hz), 3.77 (t, 4H, J = 4.8 Hz), 3.15 (t, 4H, J = 4.8 Hz), 2.52 (q, 2H, J = 7.2 Hz), 2.41 (d, 3H, J = 4.8 Hz), 1.06 (t, 3H, J = 7.2 Hz); MS *m/z* 503.2 (M + 1).
109		MS *m/z* 547.2 (M + 1).
110		MS *m/z* 494.2 (M + 1).
111		MS *m/z* 557.3 (M + 1).
112		MS *m/z* 559.3 (M + 1).
113		MS *m/z* 561.2 (M + 1).
114		MS *m/z* 508.2 (M + 1).
115		MS *m/z* 529.2 (M + 1).

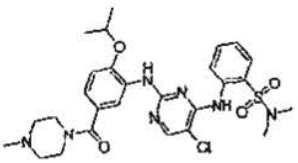
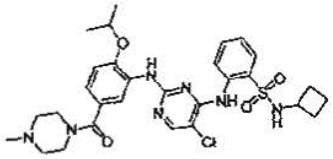
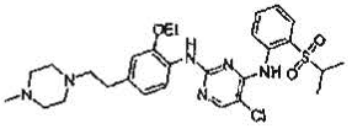
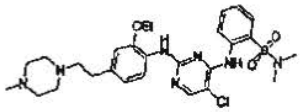
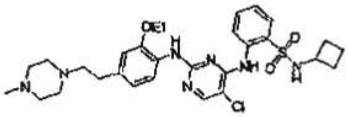
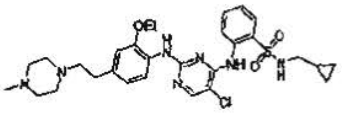
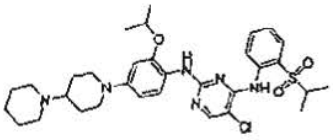
116		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.91 (bs, 1H), 9.50 (s, 1H), 8.94 (s, 1H), 8.49 (bs, 1H), 8.17 (s, 1H), 7.74 (d, 1H, J = 7.6 Hz), 7.41 (bs, 1H), 7.23 (t, 1H, J = 7.2 Hz), 7.18 (d, 1H, J = 8.0 Hz), 6.89 (m, 2H), 3.84 (d, 2H, J = 11.4 Hz), 3.54 (d, 2H, J = 11.4 Hz), 3.18 (q, 2H, J = 8.0 Hz), 2.95 (t, 2H, J = 11.4 Hz), 2.88 (s, 3H), 2.64 (s, 6H), 2.53 (m, 2H), 1.06 (t, 3H, J = 8.0 Hz); MS *m/z* 530.2 (M + 1).
117		MS *m/z* 556.2 (M + 1).
118		MS *m/z* 556.2 (M + 1).
119		MS *m/z* 548.2 (M + 1).
120		^{1}H NMR 400 MHz (DMSO-d_6) δ 10.24 (bs, 1H), 9.54 (s, 1H), 8.50 (bs, 1H), 8.41 (d, 1H, J = 7.2 Hz), 8.21 (s, 1H), 7.80 (m, 2H), 7.50 (t, 1H, J = 7.2 Hz), 7.32 (d, 1H, J = 8.4 Hz), 7.28 (t, 1H, J = 8.0 Hz), 6.32 (d, 1H, J = 2.4 Hz), 6.17 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 4.61 (m, 2H), 4.01 (m, 1H), 3.60 (m, 1H), 3.48 (m, 2H), 3.25 (q, 1H, J = 8.8 Hz), 2.88 (s, 6H), 2.42 (d, 3H, J = 4.8 Hz), 2.19 (m, 1H), 1.20 (d, 6H, J = 4.8 Hz); MS *m/z* 560.2 (M + 1).
121		MS *m/z* 600.2 (M + 1).
122		MS *m/z* 562.2 (M + 1).

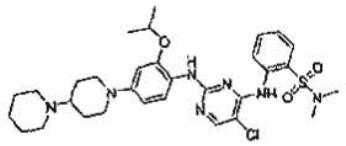
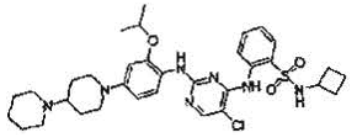
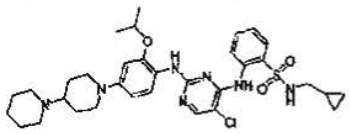
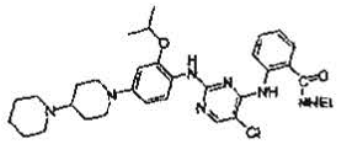
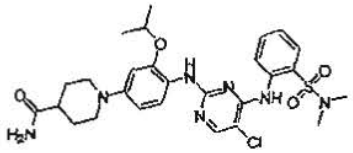
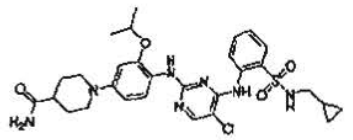
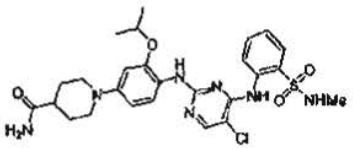
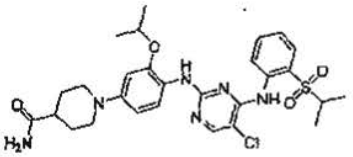
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124		MS *m/z* 575.2 (M + 1).
125		MS *m/z* 600.2 (M + 1).
126		MS *m/z* 574.2 (M + 1).
127		MS *m/z* 573.2 (M + 1).
128		MS *m/z* 604.1 (M + 1).
129		MS *m/z* 576.2 (M + 1).
130		MS *m/z* 588.2 (M + 1).
131		MS *m/z* 561.2 (M + 1).
132		MS *m/z* 561.1 (M + 1).

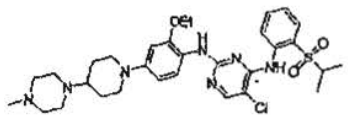
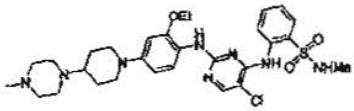
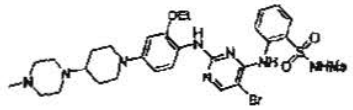
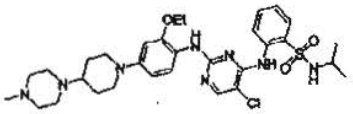
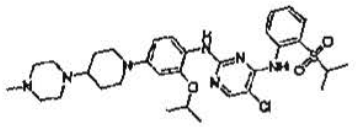
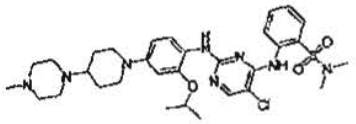
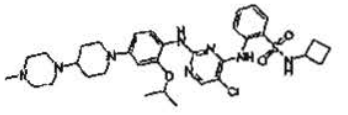
133		MS *m/z* 589.2 (M + 1).
134		MS *m/z* 575.2 (M + 1).
135		MS *m/z* 574.2 (M + 1).
136		MS *m/z* 601.2 (M + 1).
137		MS *m/z* 560.2 (M + 1).
138		MS *m/z* 575.2 (M + 1).
139		^{1}H NMR 600 MHz (DMSO-d_6) δ 10.35 (bs, 1H), 9.45 (s, 1H), 8.47 (d, 1H, J = 7.2 Hz), 8.33 (s, 1H), 8.23 (s, 1H), 7.79 (d, 1H, J = 8.4 Hz), 7.57 (t, 1H, J = 7.2 Hz), 7.52 (d, 1H, J = 9.6 Hz), 7.23 (t, 1H, J = 7.2 Hz), 6.68 (s, 0.4H), 6.64 (s, 0.6H), 6.50 (s, 0.6H), 6.49 (s, 0.4H), 5.19 (s, 0.6H), 5.15 (s, 0.4H), 4.58 (m, 1H), 3.99 (m, 0.4H), 3.73 (m, 1.6H), 3.36 (m, 0.6H), 3.26 (m, 0.8H), 3.15 (m, 0.6H), 2.96 (s, 1.2H), 2.89 (s, 1.8H), 2.64 (s, 6H), 2.60 (m, 1H), 2.24 (m, 0.6H), 2.07 (m, 0.4H), 1.20 (d, 6H, J = 6.0 Hz); MS *m/z* 561.2 (M + 1).
140		MS *m/z* 587.2 (M + 1).

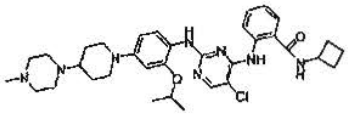
141		MS *m/z* 587.2 (M + 1).
142		MS *m/z* 560.2 (M + 1).
143		MS *m/z* 575.2 (M + 1).
144		MS *m/z* 561.2 (M + 1).
145		MS *m/z* 587.2 (M + 1).
146		MS *m/z* 587.2 (M + 1).
147		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.81 (bs, 0.4H), 9.74 (bs, 0.6H), 9.59 (bs, 1H), 8.48 (bs, 1H), 8.34 (s, 0.4H), 8.33 (s, 0.6H), 8.232 (s, 0.6H), 8.228 (s, 0.4H), 7.82 (d, 1H, J = 7.8 Hz), 7.59 (m, 1H), 7.49 (d, 0.6H, J = 8.4 Hz), 7.47 (d, 0.4H, J = 8.4 Hz), 7.34 (q, 1H, J = 7.2 Hz), 6.75 (s, 1H), 6.68 (s, 1H), 6.57 (dd, 0.6H, J_1 = 2.4 Hz, J_2 8.4 Hz), 6.54 (dd, 0.4H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 4.73 (m, 0.6H), 4.58 (m, 1H), 4.52 (m, 0.4H), 3.52 (m, 1H), 3.43 (m, 1H), 3.35 (m, 0.4H), 3.33 (m, 0.6H), 3.21 (m, 1H), 3.11 (m, 1H), 2.85 (d, 1.8H, J = 4.8 Hz), 2.82 (d, 1.2H, J = 3.0 Hz), 2.25 (m, 1H), 2.07 (m, 0.4H), 2.05 (m, 0.6H), 1.98 (m, 1H), 1.76 (m, 1H), 1.20 (d, 3.6H, J = 6.0 Hz), 1.18 (d, 2.4H, J = 6.0 Hz), 1.15 (d, 6H, J = 7.2 Hz); MS *m/z* 574.2 (M + 1).

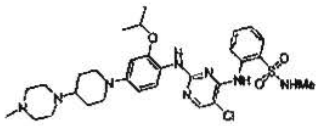
148		MS *m/z* 589.3 (M + 1).
149		MS *m/z* 575.2 (M + 1).
150		MS *m/z* 601.3 (M + 1).
151		MS *m/z* 601.3 (M + 1).
152		MS *m/z* 559.1 (M + 1).
153		^{1}H NMR 400 MHz (DMSO-d_6) δ 10.07 (bs, 1H), 9.44 (s, 1H), 8.54 (s, 1H), 8.52 (bs, 1H), 8.29 (s, 1H), 7.91 (s, 1H), 7.79 (d, 1H, J = 8.0 Hz), 7.61 (t, 1H, J = 7.6 Hz), 7.32 (t, 1H, J = 7.6 Hz), 7.22 (d, 1H, J = 8.8 Hz), 7.14 (d, 1H, J = 8.8 Hz), 4.10 (m, 2H), 3.86 (s, 3H), 3.46 (m, 2H), 3.22 (m, 2H), 3.08 (m, 2H), 2.83 (s, 3H), 2.66 (s, 6H); MS *m/z* 560.1 (M + 1).
154		MS *m/z* 586.1 (M + 1).
155		MS *m/z* 586.1 (M + 1).
156		MS *m/z* 587.2 (M + 1).

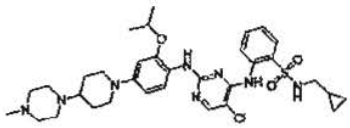
157		^{1}H NMR 400 MHz (DMSO-d_6) δ 10.05 (bs, 1H), 9.42 (s, 1H), 8.43 (d, 1H, J = 7.6 Hz), 8.35 (s, 1H), 8.31 (s, 1H), 7.91 (s, 1H), 7.79 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.58 (t, 1H, J = 8.0 Hz), 7.32 (t, 1H, J = 8.4 Hz), 7.15 (m, 2H), 4.70 (m, 1H), 4.07 (m, 2H), 3.45 (m, 2H), 3.21 (m, 2H), 3.06 (m, 2H), 2.83 (s, 3H), 2.65 (s, 6H), 1.27 (d, 6H, J = 6.0 Hz); MS *m/z* 588.2 (M + 1).
158		MS *m/z* 614.2 (M + 1).
159		MS *m/z* 573.2 (M + 1).
160		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.45 (s, 1H), 8.44 (d, 1H, J = 7.8 Hz), 8.38 (s, 1H), 8.27 (s, 1H), 7.81 (d, 1H, J = 7.8 Hz), 7.66 (d, 1H, J = 8.4 Hz), 7.64 (t, 1H, J = 7.2 Hz), 7.35 (t, 1H, J = 7.2 Hz), 6.97 (s, 1H), 6.76 (d, 1H, J = 8.4 Hz), 4.06 (q, 2H, J = 7.2 Hz), 3.59 (m, 8H), 3.29 (m, 4H), 2.92 (m, 2H), 2.86 (s, 3H), 2.64 (s, 6H), 1.31 (t, 3H, J = 6.6 Hz); MS *m/z* 574.2 (M + 1).
161		MS *m/z* 600.2 (M + 1).
162		MS *m/z* 600.2 (M + 1).
163		MS *m/z* 627.5 (M + 1).

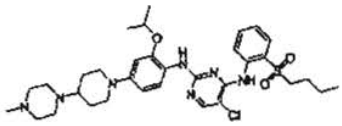
164		MS *m/z* 628.5 (M + 1).
165		MS *m/z* 654.5 (M + 1).
166		MS *m/z* 654.5 (M + 1).
167		MS *m/z* 592.3 (M + 1).
168		MS *m/z* 588.2 (M + 1).
169		MS *m/z* 614.2 (M + 1).
170		MS *m/z* 574.2 (M + 1).
171		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.66 (s, 1H), 8.48 (bs, 1H), 8.40 (d, 1H, J = 8.8 Hz), 8.30 (s, 1H), 7.66 (dd, 1H, J = 1.6 Hz, J_2 = 7.6 Hz), 7.71 (t, 1H, J = 8.4 Hz), 7.48 (s, 1H), 7.41 (t, 1H, J = 8.0 Hz), 7.17 (bs, 1H), 6.96 (s, 1H), 6.93 (bs, 1H), 4.67 (m, 1H), 4.02 (q, 1H, J = 7.2 Hz), 3.65 (m, 2H), 3.46 (m, 1H), 3.34 (m, 1H), 2.54 (m, 1H), 1.94 (m, 4H), 1.26 (d, 6H, J = 6.0 Hz), 1.15 (d, 6H, J = 6.0 Hz); MS *m/z* 587.2 (M + 1).

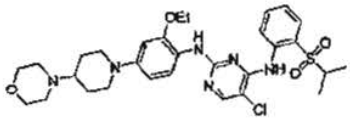
172		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.63 (bs, 1H), 8.50 (bs, 1H), 8.46 (bs, 1H), 8.29 (s, 1H), 7.82 (d, 1H, J = 7.2 Hz), 7.61 (t, 1H, J = 7.2 Hz), 7.43 (d, 1H, J = 8.4 Hz), 7.34 (t, 1H, J = 7.2 Hz), 6.75 (s, 1H), 6.58 (d, 1H, J = 6.6 Hz), 4.04 (q, 2H, J = 7.2 Hz), 3.82 (m, 2H), 3.76 (m, 5H), 3.44 (m, 1H), 3.22 (m, 4H), 2.85 (s, 3H), 2.82 (m, 2H), 2.09 (m, 2H), 1.71 (m, 2H), 1.25 (t, 3H, J = 7.2 Hz), 1.16 (d, 6H, J = 7.2 Hz); MS *m/z* 628.2 (M + 1).
173		MS *m/z* 615.2 (M + 1).
174		MS *m/z* 659.1 (M + 1).
175		^{1}H NMR 600 MHz (DMSO-d_6) δ 9.43 (s, 1H), 8.45 (bs, 1H), 8.38 (bs, 1H), 8.24 (s, 1H), 7.91 (d, 1H, J = 8.4 Hz), 7.84 (d, 1H, J = 8.4 Hz), 7.51 (t, 1H, J = 7.2 Hz), 7.48 (d, 1H, J = 8.4 Hz), 7.26 (t, 1H, J = 7.2 Hz), 6.76 (s, 1H), 6.55 (d, 1H, J = 7.2 Hz), 4.05 (q, 2H, J = 6.6 Hz), 3.82 (m, 2H), 3.59 (m, 5H), 3.30 (m, 1H), 3.25 (m, 4H), 2.85 (s, 3H), 2.82 (m, 2H), 2.09 (m, 2H), 1.71 (m, 2H), 1.26 (t, 3H, J = 6.6 Hz), 0.92 (d, 6H, J = 7.2 Hz); MS *m/z* 643.2 (M + 1).
176		MS *m/z* 642.2 (M + 1).
177		MS *m/z* 643.3 (M + 1).
178		MS *m/z* 669.3 (M + 1).

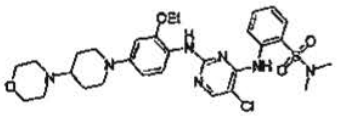
179  MS *m/z* 633.3 (M + 1).

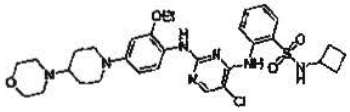
180  MS *m/z* 629.2 (M + 1).

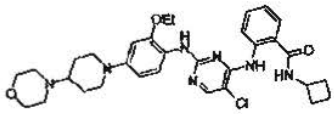
181  MS *m/z* 669.2 (M + 1).

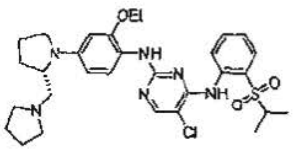
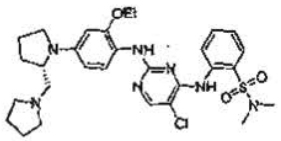
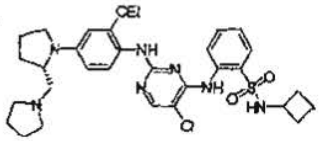
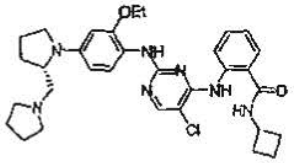
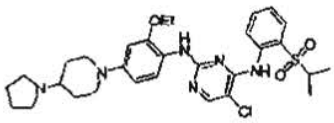
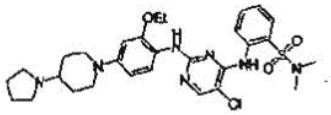
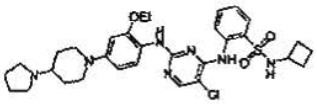
182  MS *m/z* 642.2 (M + 1).

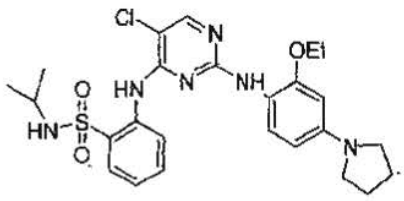
183  MS *m/z* 615.3 (M + 1).

184  ^{1}H NMR 400 MHz (DMSO-d_6) δ 9.94 (bs, 1H), 9.53 (s, 1H), 8.49 (m, 2H), 8.23 (s, 1H), 7.79 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.0 Hz), 7.58 (t, 1H, J = 7.6 Hz), 7.38 (d, 1H, J = 9.2 Hz), 7.32 (t, 1H, J = 8.0 Hz), 6.68 (d, 1H, J = 2.0 Hz), 6.51 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 4.21 (m, 2H), 4.04 (q, 2H, J = 6.8 Hz), 3.86 (d, 2H, J = 12 Hz), 3.68 (t, 2H, J = 12 Hz), 3.51 (d, 2H, J = 11.2 Hz), 3.38 (t, 1H, J = 12 Hz), 3.13 (m, 2H), 2.73 (t, 2H, J = 11.2 Hz); 2.64 (s, 6H), 2.16 (d, 2H, J = 11.2 Hz), 1.73 (m, 2H), 1.24 (t, 3H, J = 7.2 Hz); MS *m/z* 616.3 (M + 1).

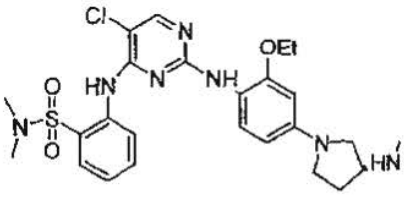
185  MS *m/z* 642.3 (M + 1).

186  MS *m/z* 606.7 (M + 1).

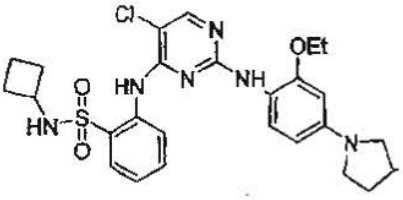
187		MS *m/z* 599.3 (M + 1).
188		MS *m/z* 600.3 (M + 1).
189		MS *m/z* 626.3 (M + 1).
190		MS *m/z* 590.3 (M + 1).
191		MS *m/z* 599.3 (M + 1).
192		^{1}H NMR 400 MHz (DMSO-d_6) δ 9.86 (bs, 1H), 9.56 (s, 1H), 8.59 (bs, 1H), 8.47 (bs, 1H), 8.24 (s, 1H), 7.79 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.58 (t, 1H, J = 8.0 Hz), 7.38 (d, 1H, J = 8.4 Hz), 7.33 (t, 1H, J = 7.2Hz), 6.70 (d, 1H, J = 2.4 Hz), 6.51 (dd, 1H, J_1 = 2.4 Hz, J_2 = 8.4 Hz), 4.03 (q, 2H, J = 6.8 Hz), 3.81 (d, 2H, J = 12.4 Hz), 3.58 (m, 2H), 3.28 (m, 1H), 3.11 (m, 2H), 2.74 (t, 2H, J = 12 Hz), 2.64 (s, 6H), 2.15 (d, 2H, J = 11.6 Hz), 2.03 (m, 2H), 1.86 (m, 2H), 1.73 (m, 2H), 1.24 (t, 3H, J = 6.8 Hz); MS *m/z* 600.2 (M + 1).
193		MS *m/z* 626.2 (M + 1).

194 

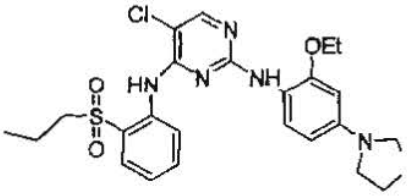
^{1}H NMR 400 MHz (CD_3OD) δ 8.29 (s, br, 1H), 8.07 (s, br, 1H), 7.96 (d, 1H, J=7.8 Hz), 7.60 (m, 1H), 7.39 (t, 1H, J=7.2 Hz), 7.22(s, br, 1H), 6.31 (s, 1H), 6.22 (s, br, 1H), 4.08(q, 1H, J=6.6 Hz), 3.95 (p, 1H, J=6.0 Hz), 3.61 (m, 2H), 3.53 (dd, 1H, J=4.2, 11.4 Hz), 3.36 (m, 2H), 2.78 (s, 3H), 2.52 (m, 1H), 2.22 (m, 1H), 1.31(t, 3H, J=6.6 Hz), 0.98 (d, 6H, J=6.6Hz); MS *m/z* 560.40 (M + 1).

195 

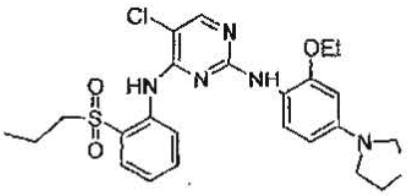
^{1}H NMR 400 MHz (CD_3OD) δ 8.30 (s, br, 1H), 8.05 (s, br, 1H), 7.87 (d, 1H, J=7.8 Hz), 7.60 (m, 1H), 7.42 (m, 1H), 7.17 (s, br, 1H), 6.28 (s, 1H), 6.19 (s, br, 1H), 4.04 (q, 2H, J=6.6 Hz), 3.91 (p, 1H, J=5.4 Hz), 3.60 (m, 2H), 3.50(dd, 1H, J=3.6, 10.8Hz), 3.33 (m, 1H), 2.75 (s, 3H), 2.66 (s, 6H), 2.48 (m, 1H), 2.20 (m, 1H), 1.27 (t, 3H, J=6.6 Hz); MS *m/z* 546.40 (M + 1).

196 

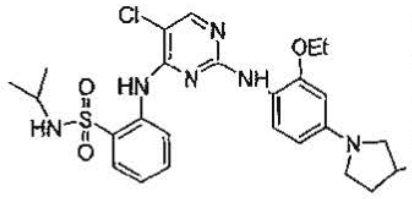
MS *m/z* 572.40 (M + 1).

197 

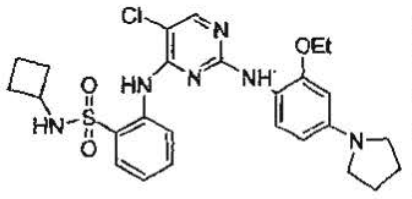
MS *m/z* 545.40 (M + 1).

198 

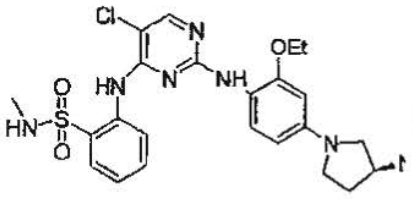
MS *m/z* 545.40 (M + 1).

199 

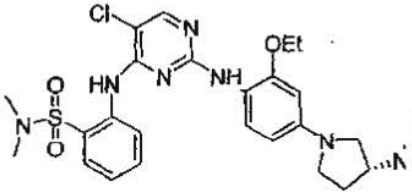
^{1}H NMR 400 MHz (CD_3OD) δ 8.37 (s, br 1H), 8.11(s, br, 1H), 8.00 (d, 1H, J=7.8 Hz,), 7.65 (s, br, 1H), 7.43 (t, 1H, J=7.2 Hz), 7.25 (s, br, 1H), 6.34 (s, 1H), 6.25 (s, 1H), 4.11(q, 2H, J=7.2 Hz), 3.99 (m, 1H), 3.65 (m, 2H), 3.57 (dd, 1H, J=3.6, 10.8 Hz), 3.41 (m, 2H), 2.82 (s, 3H), 2.56 (m, 1H), 2.28 (m, 1H), 1.35 (t, 3H, J=6.6 Hz), 1.01 (d, 6H, J=6.6 Hz); MS *m/z* 560.40 (M + 1).

200 

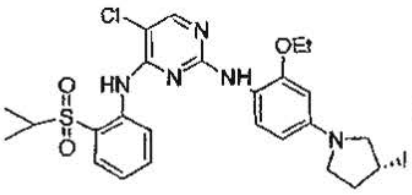
^{1}H NMR 400 MHz (CD_3OD) δ 8.30 (s, br, 1H), 8.10 (s, br, 1H), 7.91 (d, 1H, J=7.8 Hz), 7.57 (s, br, 1H), 7.38 (t, 1H, J=7.2 Hz), 7.21 (s, 1H), 6.30 (s, 1H), 6.21 (s, 1H), 4.08 (q, 2H, J=7.2 Hz), 3.95 (m, 1H), 3.68 (m, 1H), 3.62 (m, 2H), 3.53 (dd, 1H, J=4.2, 10.8 Hz), 3.36 (m, 1H), 2.78 (s, 3H), 2.50 (m, 1H), 2.25 (m, 1H), 1.94 (m, 2H), 1.75 (m, 2H), 1.50 (m, 2H), 1.31 (t, 3H, J=7.2 Hz); MS *m/z* 572.40 (M + 1).

201 

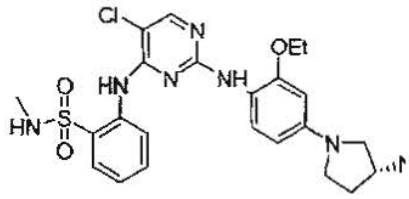
MS *m/z* 532.40 (M + 1).

202 

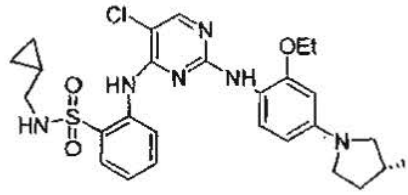
MS *m/z* 546.40 (M + 1).

203 

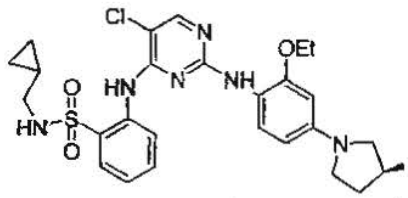
MS *m/z* 545.40 (M + 1).

204 

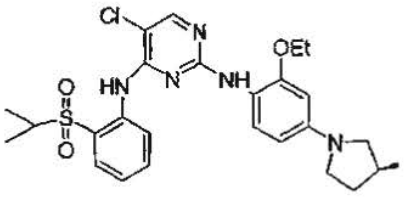
MS *m/z* 532.40 (M + 1).

205 

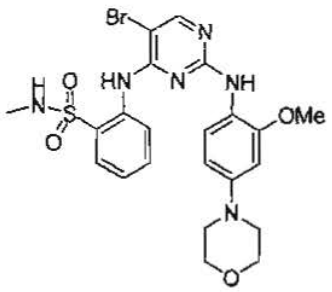
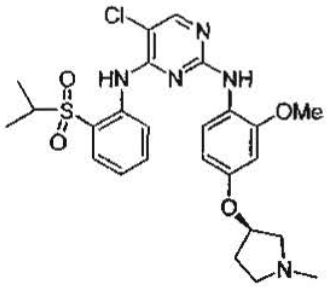
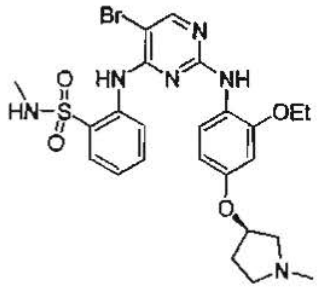
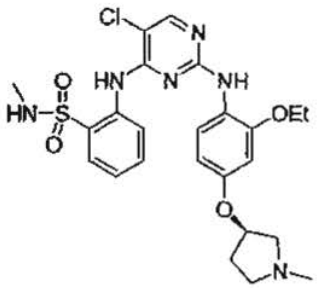
^{1}H NMR 400 MHz (CD_3OD) δ 8.27 (s, br, 1H), 8.07 (m,1H), 7.94 (d, 1H, J=7.8 Hz), 7.61 (s, br, 1H), 7.40(t, 1H, J=7.2Hz), 7.20 (s, 1H), 6.30 (s, 1H), 6.20 (s, 1H), 4.08 (q, 2H, J=7.2 Hz), 3.95 (m, 1H), 3.60 (m, 2H), 3.53 (dd, 1H, J=4.2, 10.8 Hz), 3.35 (m, 1H), 2.78 (s, 3H), 2.73 (d, 1H, J=6.6 Hz), 2.51 (m, 1H), 2.23 (m, 1H), 1.31 (t, 3H, J=7.2 Hz), 0.742 (s, br 1H), 0.32 (s, 2H), 0.00(s,2H); MS *m/z* 572.40 (M + 1).

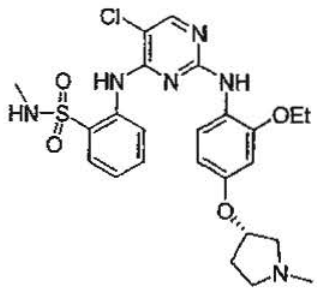
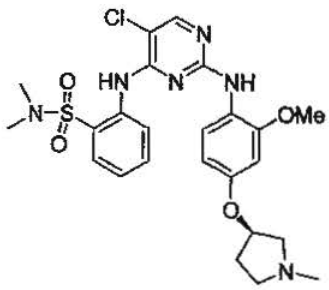
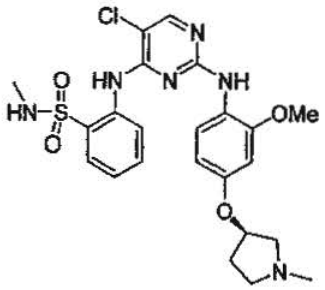
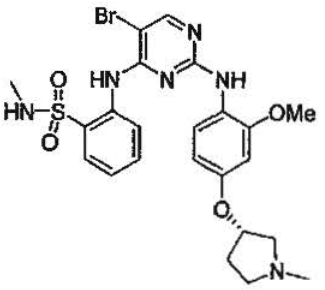
206 

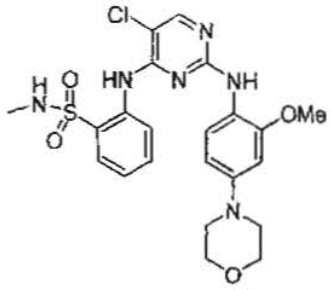
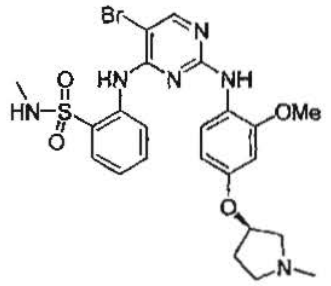
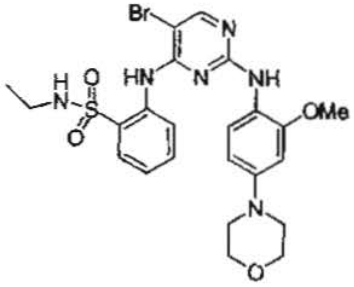
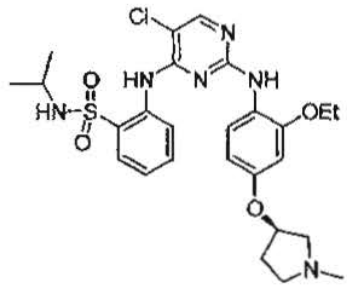
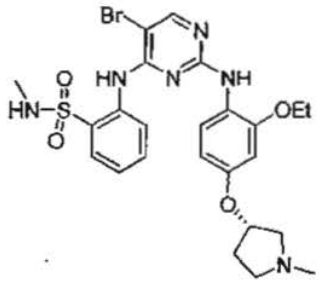
^{1}H NMR 400 MHz (CD_3OD) δ 8.24 (s, br, 1H), 8.07 (s, br, 1H), 7.93 (d, 1H, J=8.4 Hz), 7.57 (s, 1H), 7.38 (t, 1H, J=7.2 Hz), 7.20 (s, 1H), 6.29 (s, 1H), 6.19 (s, br, 1H), 4.06 (q, 2H, J=7.2 Hz), 3.93 (m, 1H), 3.60 (m, 2H), 3.50 (dd, 1H, J=6.0, 10.8 Hz), 3.35 (m, 1H), 2.76 (s, 3H), 2.72 (d, 1H, J=6.6 Hz), 2.50 (m, 1H), 2.22 (m, 1H), 1.30 (t, 3H, J=7.2 Hz), 0.73 (m, 1H), 0.31 (m, 2H), 0.01(m, 2H); MS *m/z* 572.40 (M + 1).

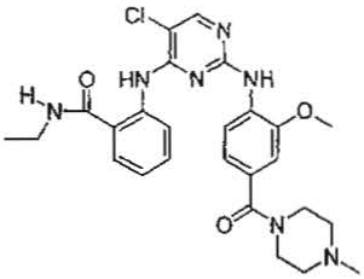
207 

MS *m/z* 545.40 (M + 1).

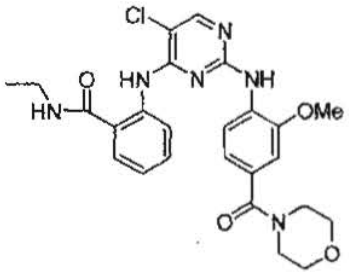
208		MS *m/z* 549.10 (M + 1).
209		MS *m/z* 532.40 (M + 1).
210		^{1}H NMR 400 MHz (CD_3OD) δ 8.22 (d, 1H, J=7.8Hz), 8.20 (s, 1H), 7.92 (dd, 1H, J=1.2, 7.8 Hz), 7.58 (t, 1H, J=6Hz), 7.48(d, 1H, J=9.1Hz), 7.38 (t, 1H, J=7.8Hz), 6.65 (s, 1H), 6.46 (d, 1H, J=7.8Hz), 5.20 (s, 1H), 4.06 (q, 2H, J=7.2Hz), 3.86 (m, 1H), 3.38 (m, 1H),, 3.05 (m, 3H), 2.64 (m, 1H), 2.60 (s, 3H), 2.30 (m, 1H), 1.34 (t, 3H, J=7.2 Hz); MS *m/z* 577.30 (M + 1).
211		MS *m/z* 533.30 (M + 1).

212		^{1}H NMR 400 MHz (CD_3OD) δ 8.30 (d, 1H, J=7.8Hz), 8.11 (s, 1H), 7.91 (d, 1H, J=7.8Hz), 7.58)t, 1H, J=7.8 Hz), 7.55 (d, 1H, J=8.4 Hz), 7.36 (t, 1H, J=7.8 Hz), 6.65 (s, 1H), 6.47 (d, 1H, J=8.4 Hz), 5.20 (s, 1H), 4.07 (q, 2H, J=7.2 Hz), 3.87 (m, 1H), 3.38 (m, 1H), 3.23 (m, 1H), 3.00 (m, 2H), 2.64 (m, 1H), 2.50 (s, 3H), 2.38 (m, 1H), 1.35 (t, 3H, J=7.2Hz); MS *m/z* 533.30 (M + 1).
213		MS *m/z* 533.30 (M + 1).
214		MS *m/z* 519.30 (M + 1).
215		MS *m/z* 563.30 (M + 1).

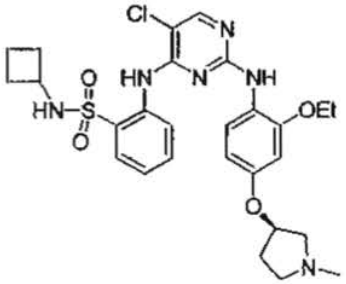
216		MS *m/z* 505.10 (M + 1).
217		MS *m/z* 563.30 (M + 1).
218		MS *m/z* 563.10 (M + 1).
219		MS *m/z* 561.40 (M + 1).
220		MS *m/z* 577.30 (M + 1).

221 

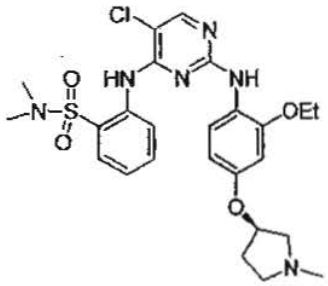
MS *m/z* 524.45 (M + 1).

222 

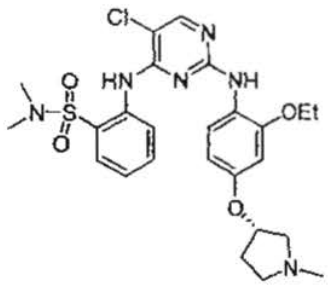
MS *m/z* 511.20 (M + 1).

223 

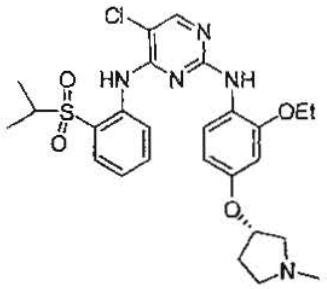
MS *m/z* 573.40 (M + 1).

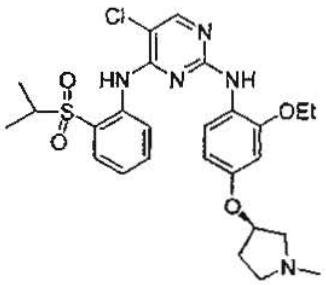
224 

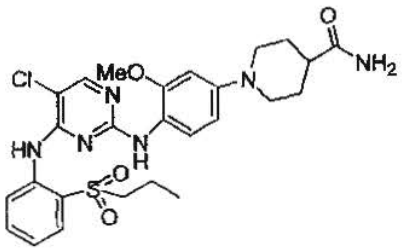
MS *m/z* 547.40 (M + 1).

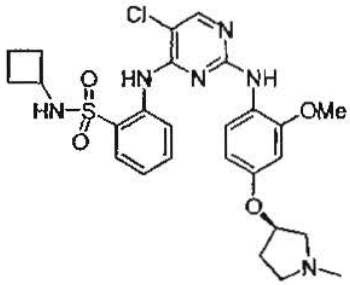
225 

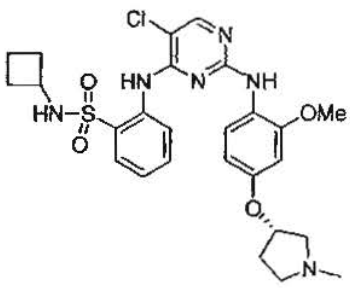
MS *m/z* 547.40 (M + 1).

226  MS *m/z* 546.40 (M + 1).

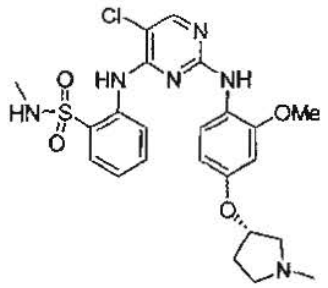
227  MS *m/z* 546.40 (M + 1).

228  MS *m/z* 559.40 (M + 1).

229  MS *m/z* 559.40 (M + 1).

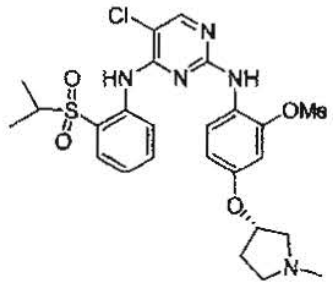
230  MS *m/z* 559.40 (M + 1).

231



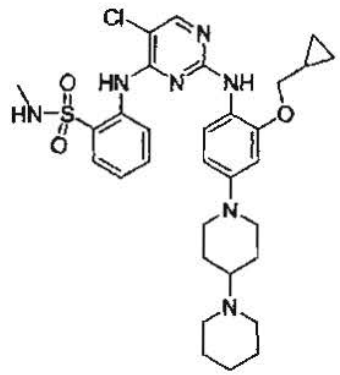
MS *m/z* 519.35 (M + 1).

232



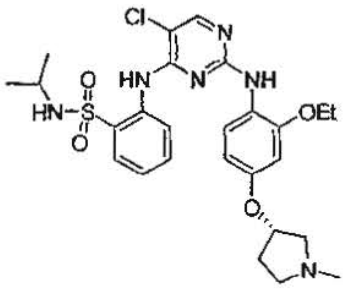
MS *m/z* 532.35 (M + 1).

233



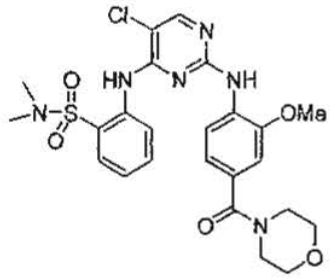
^{1}H NMR 400 MHz (CD_3OD) δ 8.06 (d, 1H, J=8.0 Hz), 7.92 (s, 1H), 7.73 (dd, 1H, J=1.6, 8.0 Hz), 7.40 (t, 1H, J=7.6 Hz), 7.22 (m, 1H), 7.10 (d, 1H, J=8.8 Hz), 6.50 (d, 1H, J=2.4 Hz), 6.38 (dd, 1H, J=2.0, 8.8 Hz), 3.67 (m, 4H), 3.35 (m, 2H), 3.15 (m, 1H), 2.84 (m, 2H), 2.69(m, 2H), 2.30 (s, 3H), 2.01 (m, 2H), 1.69 (m, 7H), 1.27 (m, 1H), 0.95 (m, 1H), 0.33 (m, 2H), 0.05 (m, 2H); MS *m/z* 626.5 (M + 1).

234



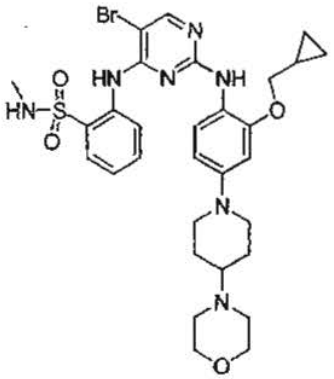
MS *m/z* 561.4 (M + 1).

235



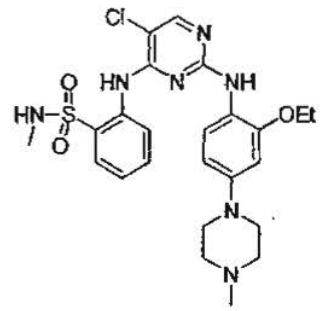
MS *m/z* 547.25 (M + 1).

236



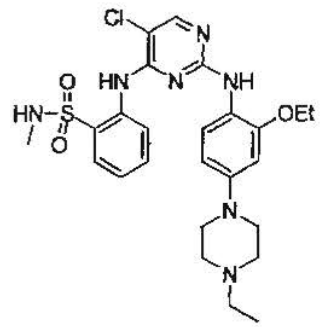
^{1}H NMR 400 MHz (CD_3OD) δ 8.23 (d, 1H, J=7.6Hz), 8.15 (s, 1H), 7.90 (dd, 1H, J=1.6, 8.0Hz), 7.56 (t, 1H, J=7.2 Hz), 7.36 (t, 1H, J=7.6 Hz), 7.31 (d, 1H, J=8.8 Hz), 6.63 (d, 1H, J=2.4 Hz), 6.51 (m, 1H), 4.10 (m, 2H), 3.83 (m, 6H), 3.34 (m, 2H), 2.82 (m, 2H), 2.48 (s, 3H), 2.23 (m, 2H), 1.78 (m, 2H), 1.14 (m, 1H), 0.51 (m, 2H), 0.23 (m, 2H); MS *m/z* 672.4 (M + 1).

237

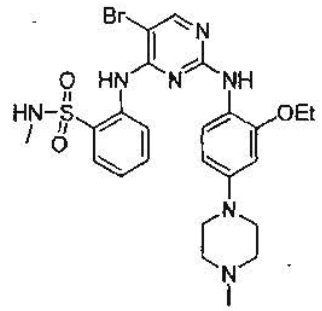


MS *m/z* 532.4 (M + 1).

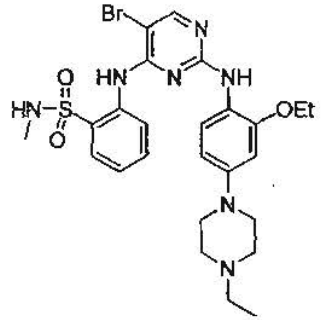
238



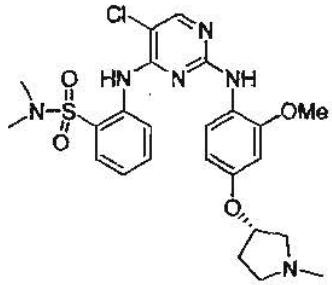
MS *m/z* 546.4 (M + 1).

239 

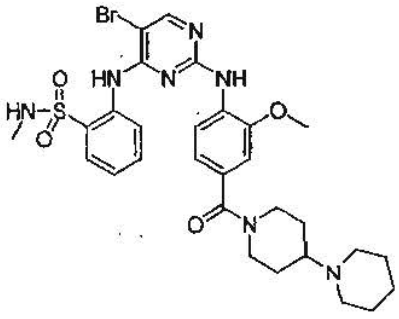
MS *m/z* 576.3 (M + 1).

240 

MS *m/z* 590.4 (M + 1).

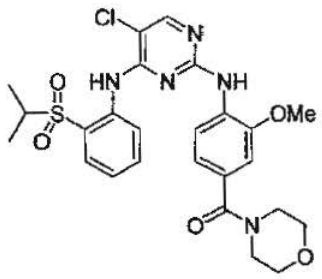
241 

MS *m/z* 533.3 (M + 1).

242 

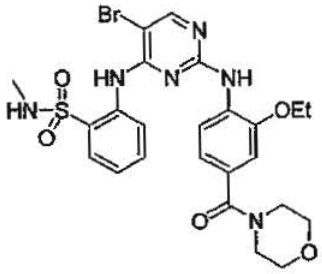
^{1}H NMR 400 MHz (CD_3OD) δ 8.26 (s, 1H), 8.10 (d, 1H, J=8.0 Hz), 7.90 (dd, 1H, J=1.2, 8.0Hz), 7.80 (d, 1H, J=8.4Hz), 7.62 (m, 1H), 7.38 (t, 1H, J=8.0Hz), 7.05 (d, 1H, J=1.6Hz), 6.83 (dd, 1H, J=1.6, 8.4Hz), 3.86 (s, 3H), 3.43 (m, 4H), 3.00(m, 4H), 2.10 (m, 2H), 1.95 (m,2H), 1.72 (m, 6H), 1.45 (m, 2H); MS *m/z* 658.4 (M + 1).

243



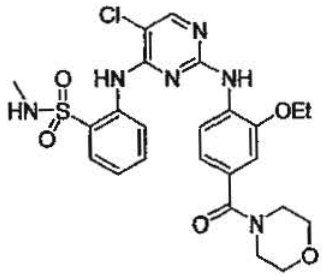
MS *m/z* 546.3 (M + 1).

244



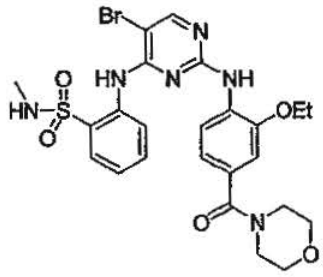
MS *m/z* 591.2 (M + 1).

245



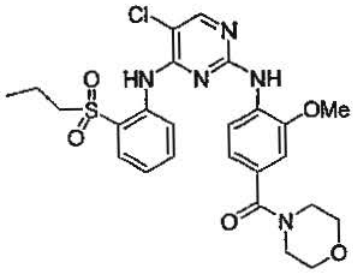
MS *m/z* 547.3 (M + 1).

246



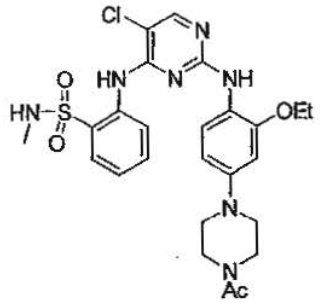
MS *m/z* 591.2 (M + 1).

247



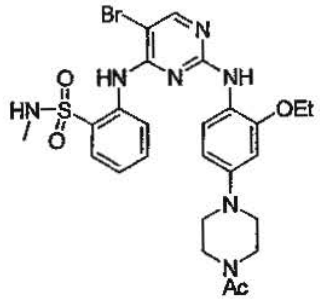
MS *m/z* 546.1 (M + 1).

248



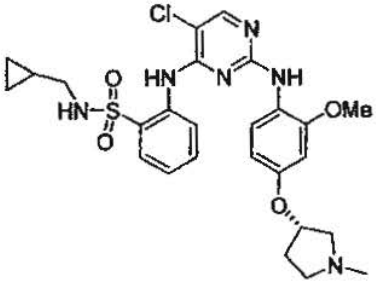
MS *m/z*.560.2 (M + 1).

249



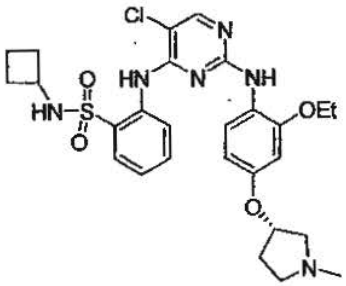
MS *m/z*.604.3 (M + 1).

250

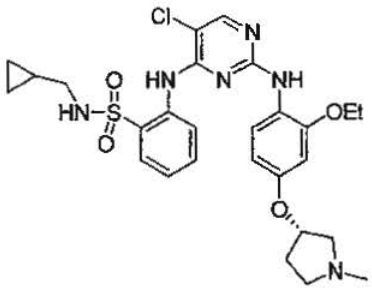


MS *m/z*.559.4 (M + 1).

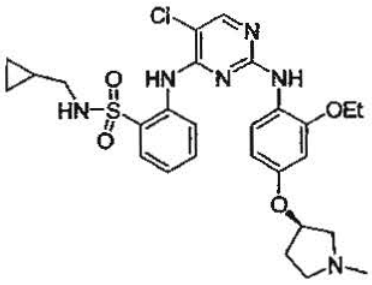
251



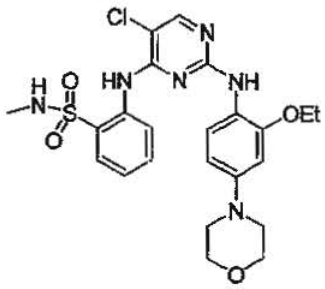
MS *m/z*.573.4 (M + 1).

252 

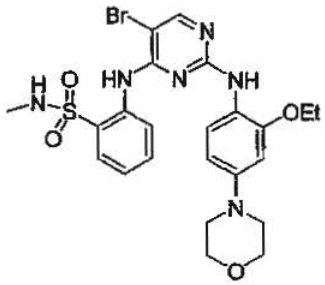
MS *m/z*.573.4 (M + 1).

253 

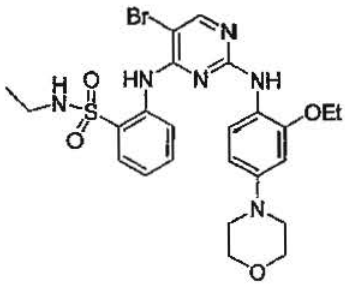
MS *m/z*.573.4 (M + 1).

254 

MS *m/z*.519.1 (M + 1).

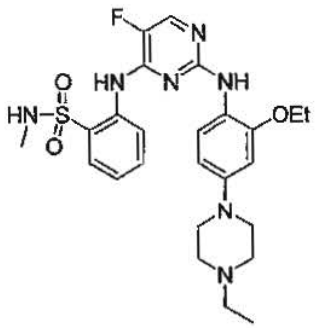
255 

MS *m/z*.563.1 (M + 1).

256 

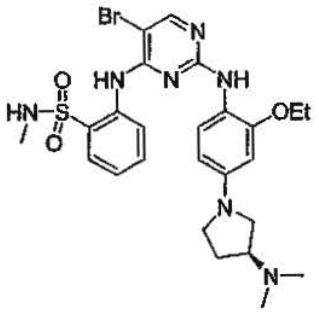
MS *m/z*.577.1 (M + 1).

257



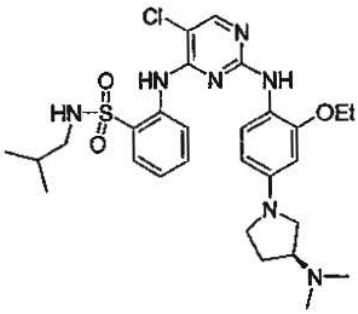
MS *m/z*.530.4 (M + 1).

258



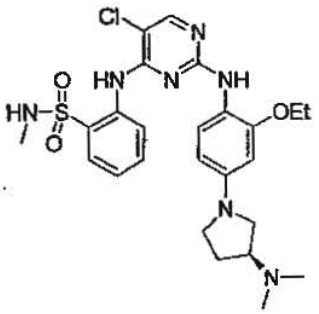
MS *m/z*.590.4 (M + 1).

259

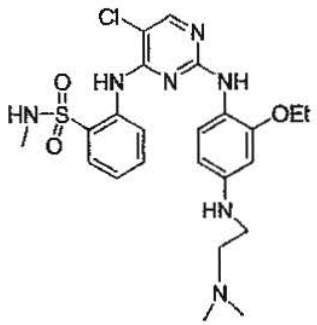


MS *m/z*.588.2 (M + 1).

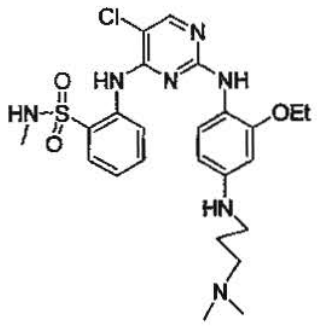
260



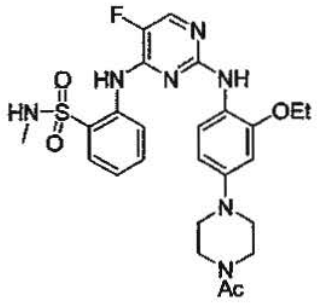
MS *m/z*.546.4 (M + 1).

261 

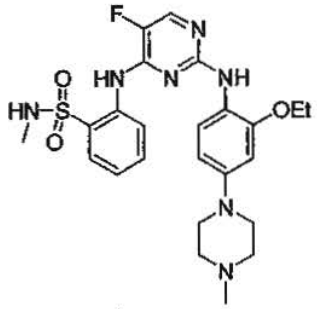
MS *m/z*.520.4 (M + 1).

262 

MS *m/z*.534.4 (M + 1).

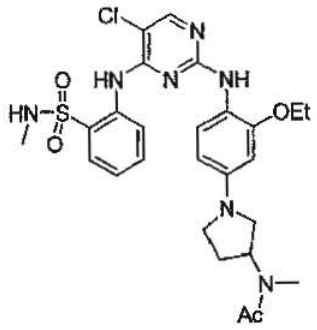
263 

MS *m/z*.544.2 (M + 1).

264 

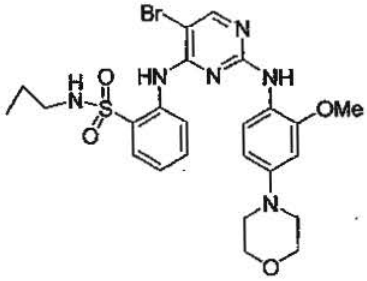
MS *m/z*.516.4 (M + 1).

265



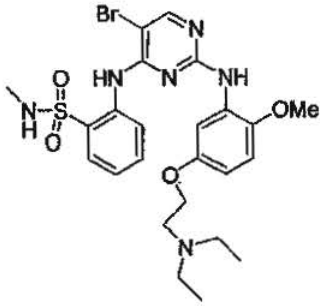
MS *m/z*.574.2 (M + 1).

266



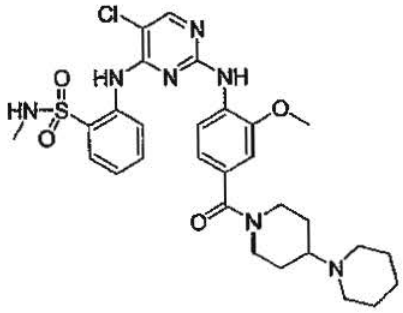
MS *m/z*.577.1 (M + 1).

267



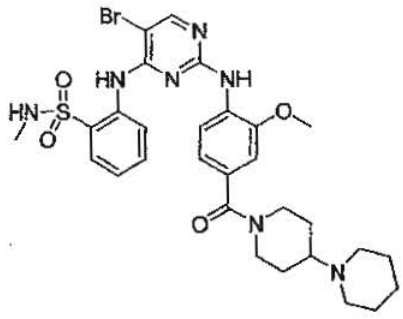
MS *m/z*.579.3 (M + 1)

268



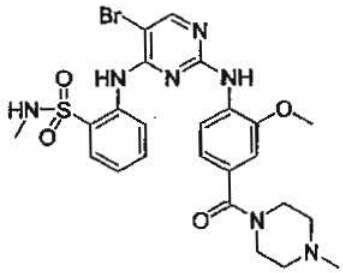
MS *m/z*.614.5 (M + 1)

269



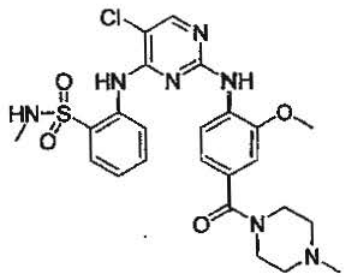
MS *m/z*.658.4 (M + 1)

270



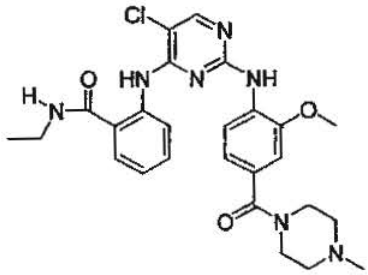
MS *m/z*.590.3 (M + 1)

271



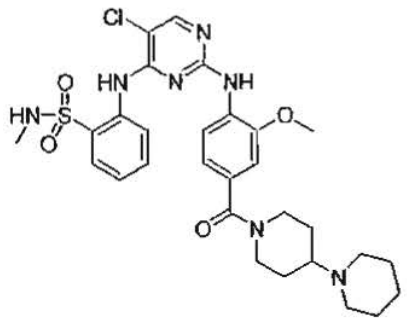
MS *m/z*.546.4 (M + 1)

272



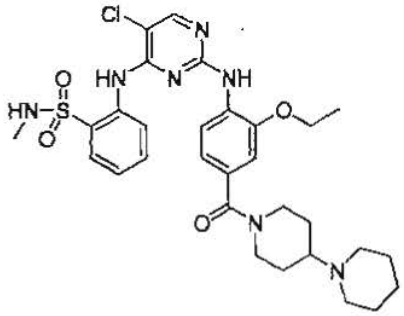
MS *m/z*.524.4 (M + 1)

273



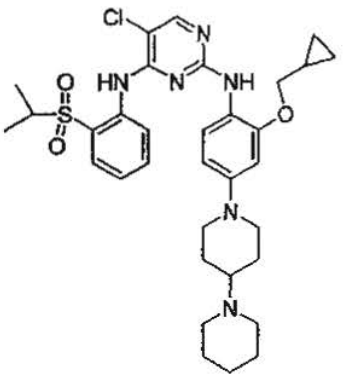
MS *m/z*.614.5 (M + 1)

274



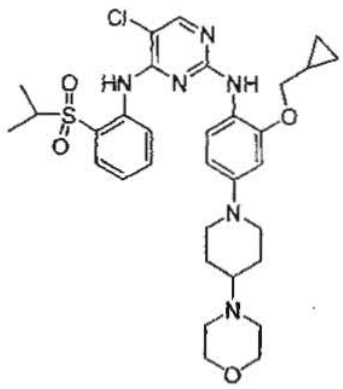
^{1}H NMR 400 MHz (CD_3OD) δ 8.17 9s, 1H0, 8.15 (d, 1H, J=8.0Hz), 7.89 9dd, 1H, J=1.2, 8.0 Hz), 7.86 (d, 1H, J=8.4hz), 7.61 (m, 1H), 7.36 (m, 1H), 7.01 (d, 1H, J=1.6Hz), 6.81(dd, 1H, J=1.6, 8.0Hz), 4.10 (q, 2H, J=7.2Hz), 3.45 (m, 3H), 2.94 9m, 4H), 2.44 (s, 3H), 2.08 (m, 2H), 1.94 (m, 2H), 1.75 (m, 6H), 1.49 (m, 1H), 1.37 (t, 3H, J=6.8Hz); MS *m/z*.628.5 (M + 1)

275



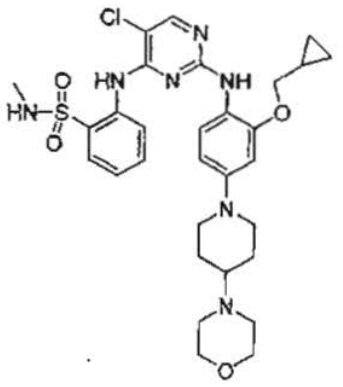
^{1}H NMR 400 MHz (CD_3OD) δ 8.17 (d, 1H, J=8.0 Hz), 7.93 (s, 1H), 7.74 (dd, 1H, J=1.6, 8.0Hz), 7.47 (t, 1H, J=8.0 Hz), 7.25 (m, 1H), 7.13 (d, 1H, 8.8Hz), 6.48 (d, 1H, J=2.4 Hz), 6.37 (dd, 1H, J=2.4, 8.8Hz), 3.66 (m, 4H), 3.34 (m, 2H), 3.14 (m, 4H), 2.81 (m, 2H), 2.65 (m, 2H), 2.98 (d, 2H, J=12Hz), 1.68 (m, 7H), 1.30 (m, 1H), 1.02 (d, 6H, J=6.8 Hz), 0.99 (m, 1H), 0.32 (m, 2H), 0.04 (m,2H); MS *m/z*.639.5 (M + 1)

276



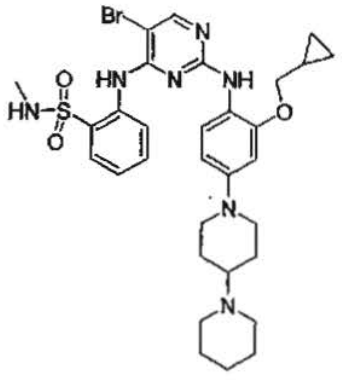
^{1}H NMR 400 MHz (CD_3OD) δ 8.32 (d, 1H, J=8.0 Hz), 8.11 (s, 1H), 7.92 (dd, 1H, J=1.6, 8.0Hz), 7.65 (t, 1H, J=7.6Hz), 7.43 (t, 1H, J=7.6Hz), 7.28 (d, 1H, J=8.4Hz), 6.67 (d, 1H, J=2.4Hz), 6.56 (dd, 1H, J=2.4, 8.8Hz), 4.03 (m,2H), 3.86 (m,4H), 3.73 (m, 2H), 3.36 (m, 2H), 3.35 (m, 2H), 3.23 (m, 2H), 2.85 (m, 2H), 2.23 (m, 2H), 1.83 (m, 2H), 1.19 (d, 6H), 1.13 (m, 1H), 0.48 (m, 2H), 0.21 (m, 2H); MS *m/z* 641.5 (M + 1)

277

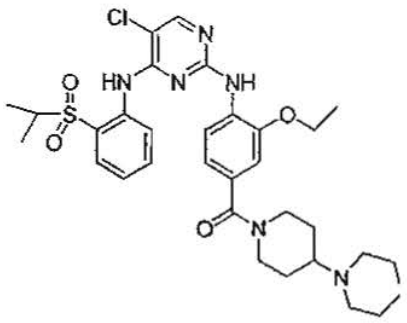


^{1}H NMR 400 MHz (CD_3OD) δ 8.06 (d, 1H, J=7.6Hz), 7.91 (S, 1H), 7.72 (dd, 1H), J=1.6, 8.0Hz), 7.39 (t, 1H, J=7.6 Hz), 7.20 (m, 1H), 7.10 (d, 1H, J=4.8 Hz), 6.48 (d, 1H, 2.4Hz), 6.36 (dd, 1H, J=2.4, 8.8Hz), 3.85 (m, 2H), 3.66 (m,4H), 3.56 (m,2H), 3.18 (m, 2H), 3.16 (m, 1H), 2.98 (m, 2H), 2.65 (t, 2H, J=12Hz), 2.29 (s, 3H), 2.05 (m,2H), 1.64 (m, 2H), 0.95 (m, 1H), 0.32 (m, 2H), 0.03 (m, 2H); MS *m/z* 628.5 (M + 1)

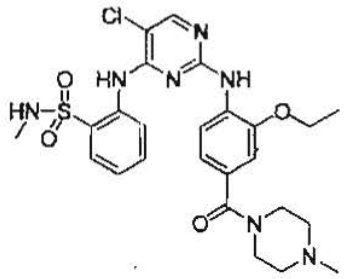
278



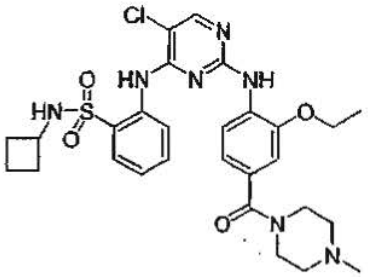
^{1}H NMR 400 MHz (CD_3OD) δ 8.18 (d, 1H, J=8.0Hz), 8.15 (s, 1H), 7.89 (dd, 1H, J=1.6, 8.0Hz), 7.56 (t, 1H, J=7.2Hz), 7.38 (m, 1H), 7.25 (d, 1H, J=8.8 Hz), 6.65 (d, 1H, J=2.4 Hz), 6.53 (dd, 1H, J=2.4, 8.8 Hz), 3.82 (m, 4H), 3.49(m, 2H), 3.31 (m, 1H), 2.95 (m, 2H), 2.83 (m, 2H), 2.47 (s, 3H), 2.17 (m, 2H), 1.86(m, 7H), 1.52 (m, 1H), 1.15 (m, 1H), 0.49 (m, 2H), 0.21 (m, 2H); MS *m/z* 670.4 (m + 1)

279 

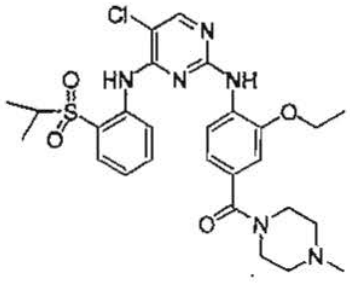
MS *m/z* 641.5 (M + 1)

280 

^{1}H NMR 400 MHz (CD_3OD) δ 8.13 (s, 1H), 8.10 (d, 1H, J=8.0Hz), 7.85 (t, 1H, J=1.6Hz), 7.83 (t, 1H, J=1.6Hz), 7.57 (m, 1H), 7.32 (m,1H), 7.02 (d, 1H, J=1.2Hz), 6.81 (dd, 1H, J=1.6, 8.4Hz), 4.05 (q, 2H, J=6.8Hz), 3.36 (m, 4H), 3.08 (m, 2H), 2.84 (s, 3H), 2.40 (s, 3H), 1.33 (t, 3H, J=6.8Hz); MS *m/z* 560.4 (M + 1)

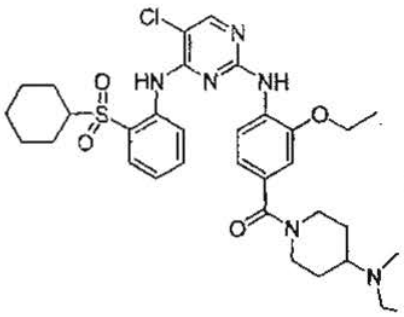
281 

AMS *m/z* 600.5 (M + 1)

282 

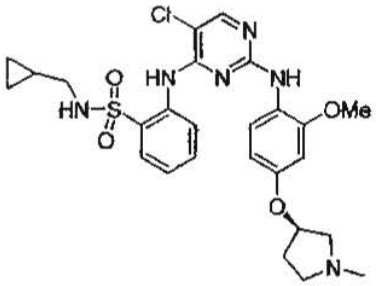
NMR 400 MHz (CD_3OD) δ 8.30 (d, 1H, J=8.0Hz), 8.21 (s, 1H), 8.00 (d, 1H, J=8.4 Hz), 7.91(dd, 1H, J=1.63, 8.0 Hz), 7.71 (m, 1H), 7.42 (m, 1H), 7.08 (d, 1H, J=2.0 Hz), 6.91 (dd, 1H, J=1.6, 8.4 Hz), 4.30 (m, 2H), 4.13(q, 2H, J=7.2 Hz), 3.60 (m, 4H), 3.16 (m, 2H),1.41 (t, 3H, J=7.2 Hz), 1.90 9d, 6H, J=6.8 Hz); MS *m/z* 573.40 (M + 1)

283



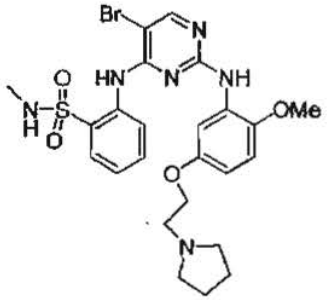
MS *m/z*.681.5 (M + 1)

284



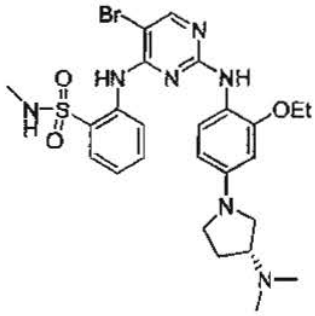
MS *m/z*.559.4 (M + 1)

285

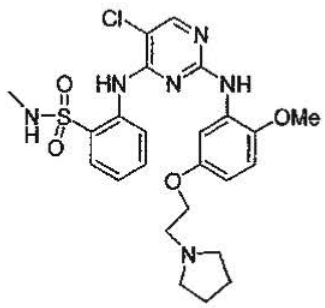
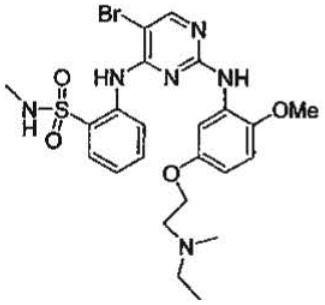
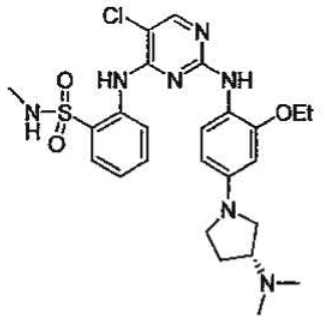
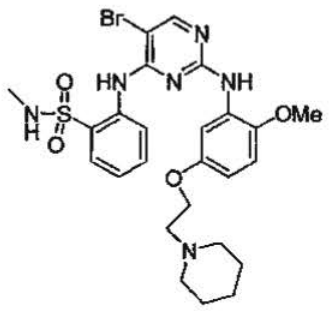


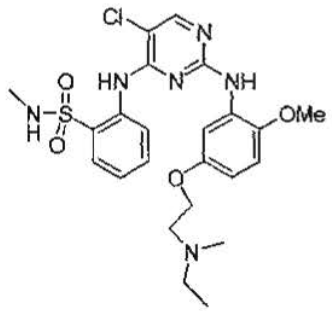
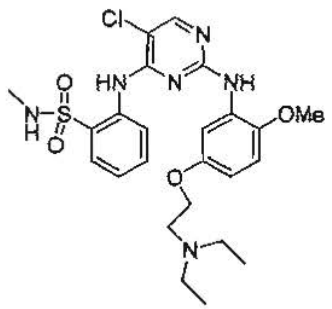
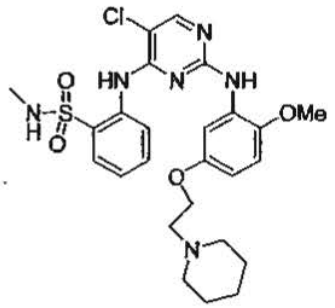
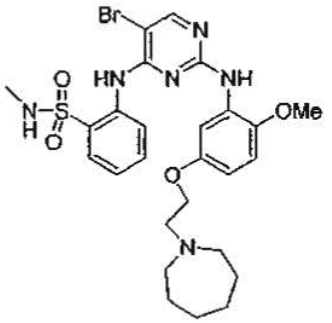
MS *m/z*.577.3 (M + 1)

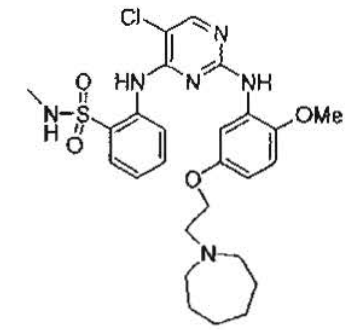
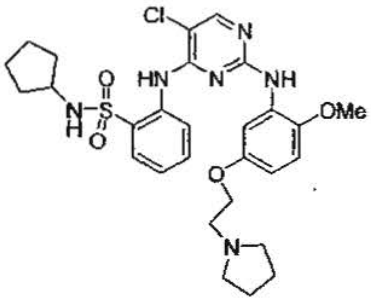
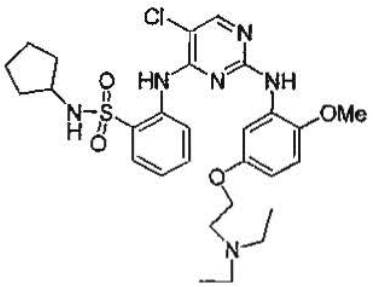
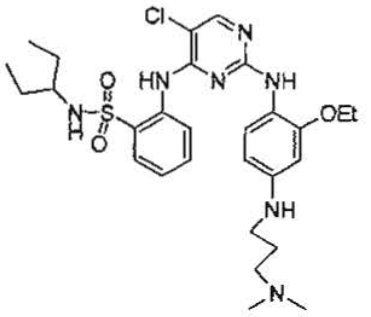
286



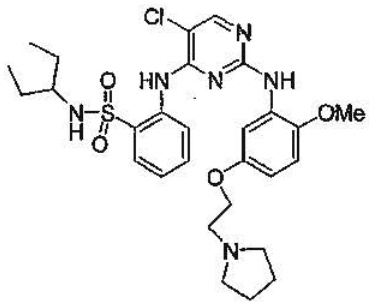
NMR 400 MHz (CD_3OD) δ 8.28 (s, br, 1H), 8..11 (s, br, 1H), 7.89 (d, 1H, J=8.4 Hz), 7.53 (s, br, 1H), 7.35 (t, 1H, J=6.0 Hz), 7.29 (m, 1H), 6.30 (s, 1H), 6.20 (d, 1H, J=7.8 Hz), 4.07 (q, 2H, J=7.2 Hz), 4.02 (m, 1H), 3.68 (m, 1H), 3.60 (m, 1H), 3.54 (m, 1H), 3.34 (m, 1H), 2.95 (s, 6H), 2.57 (m, 1H), 2.51 (s, 3H), 2.25 (m, 1H), 1.30 (t, 3H, J=7.2 Hz); MS *m/z*.590.3 (M + 1)

287		MS *m/z*.533.3 (M + 1)
288		MS *m/z*.565.3 (M + 1)
289		MS *m/z*.546.4 (M + 1)
290		NMR 400 MHz (CD_3OD) δ 8.29 (d, 1H, J=8.4 Hz), 8.24 (s, 1H), 7.91 (dd, 1H, J=1.2, 7.8 Hz), 7.57 (m, 2H), 7.35 (t, 1H, J=7.2 Hz), 6.98 (d, 1H, J=9.0 Hz), 6.77 (dd, 1H, J=3.0, 9.0 Hz), 4.18 (t, 2H, J=4.8 Hz), 3.82 (s, 3H), 3.56 (m, 2H), 3.17 (t, 2H, J=4.8 Hz), 3.3 (s, 1H), 3.01 (m, 2H), 2.53 (s, 3H), 1.92 (m, 2H), 1.79 (m, 3H), 1.53 (m, 1H); MS *m/z*.591.3 (M + 1)

291		MS *m/z*.521.4 (M + 1)
292		NMR 400 MHz (CD_3OD) δ 8.28 (d, 1H, J=8.4 Hz), 8.15 (s, 1H), 7.89 (dd, 1H, J=2.4, 7.8 Hz), 7.55 (t, 1H, J=7.2 Hz), 7.44 (d, 1H, J=3.0 Hz), 7.33 (t, 1H, J=7.2 Hz), 6.99 (dd, 1H, J=3.6, 9.0 Hz), 6.80 (dd, 1H, J=3.0, 9.0 Hz), 4.18 (t, 2H, J=4.8 Hz), 3.80 (s, 3H), 3.51 (t, 2H, J=4.8 Hz), 3.29 (m, 4H), 2.50 (s, 3H), 1.30 (m, 6H); MS *m/z*.535.4 (M + 1)
293		NMR 400 MHz (CD_3OD) δ 8.31 (d, 1H, J=8.4 Hz), 8.14 (s, 1H), 7.90 (dd, 1H, J=1.2, 7.6 Hz), 7.59 (m, 1H), 7.53 (d, 1H, J=3.0 Hz), 7.33 (t, 1H, J=7.8 Hz), 6.96 (d, 1H, J=9.0 Hz), 6.76 (dd, 1H, J=3.0, 8.4 Hz), 4.18 (t, 2H, J=4.2 Hz), 3.80 (s, 3H), 3.55 (m, 2H), 3.46 (t, 2H, J=4.8 Hz), 3.00 (t, 2H, J=12.0 Hz), 2.50 (s, 3H), 1.89 (m, 2H), 1.77 (m, 3H), 1.52 (m, 1H); MS *m/z*.547.4 (M + 1)
294		MS *m/z*.605.3 (M + 1)

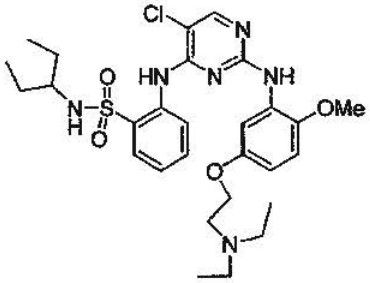
295		NMR 400 MHz (CD_3OD) δ .8.33 (d, 1H, J=8.4 Hz), 8.14)s, 1H), 7.90 (dd, 1H, J=1.2, 7.8 Hz), 7.57 (m, 1H), 7.53 (d, 1H, J=3.0 Hz), 7.33 (t, 1H, J=7.2 Hz), 6.95 (d, 1H, J=9.0 Hz), 6.74 (dd, 1H, J=3.0, 9.0 Hz), 4.17 (t, 1H, J=4.8 Hz), 3.80 (s, 3H), 3.51 (m, 4H), 3.27 (m, 2H), 2.50 (s, 3H), 1.85 (m, 4H0, 1.70 (m, 4H); *m/z*.561.4 (M + 1)
296		MS *m/z*.587.4 (M + 1)
297		MS *m/z*.589.4 (M + 1)
298		MS *m/z*.590.4 (M + 1)

299



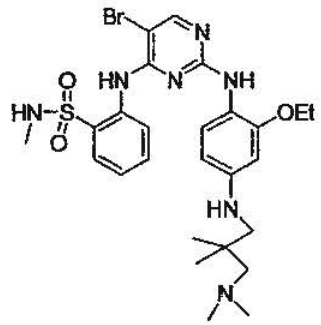
MS *m/z*.589.4 (M + 1)

300



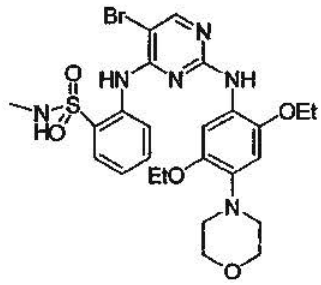
MS *m/z*.591.4 (M + 1)

301

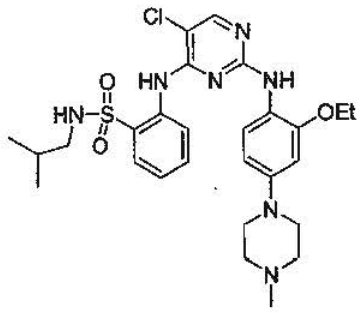


MS *m/z*.606.4 (M + 1)

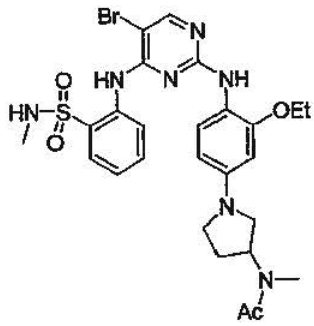
302



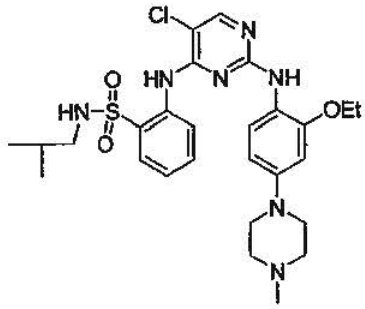
MS *m/z*.607.1 (M + 1)

303 

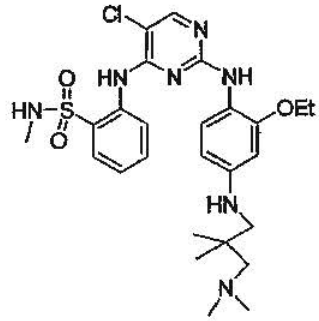
MS *m/z*.574.4 (M + 1)

304 

MS *m/z*.618.2 (M + 1)

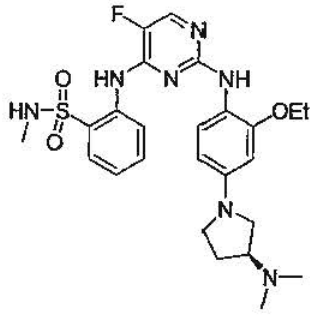
305 

MS *m/z*.588.2 (M + 1)

306 

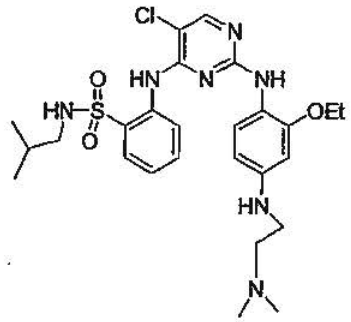
MS *m/z*.562.4 (M + 1)

307



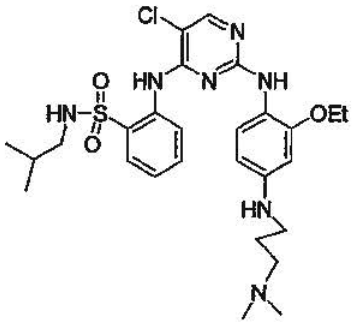
MS *m/z*.530.4 (M + 1)

308



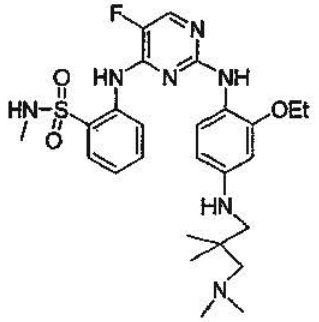
MS *m/z*.562.4 (M + 1)

309

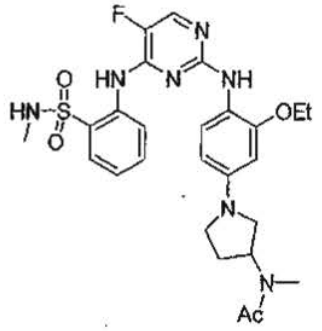


MS *m/z*.576.2 (M + 1)

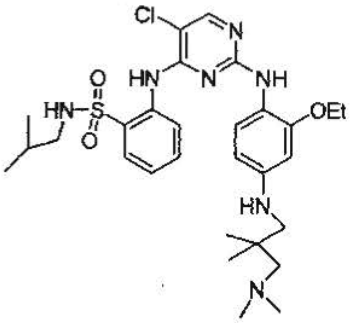
310



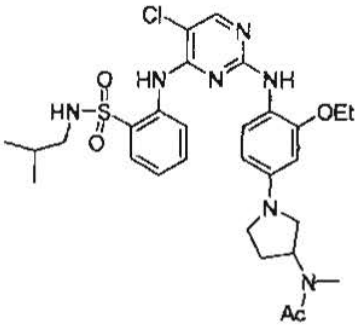
MS *m/z*.546.5 (M + 1)

311 

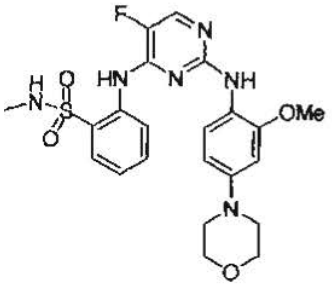
MS *m/z*.558.2 (M + 1)

312 

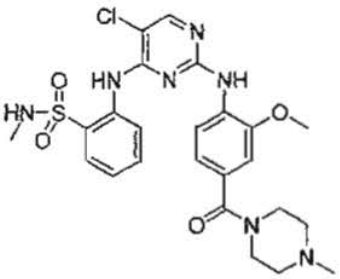
MS *m/z*.604.5 (M + 1)

313 

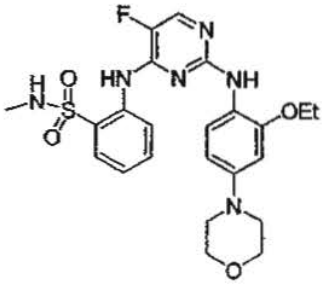
MS *m/z*.616.5 (M + 1)

314 

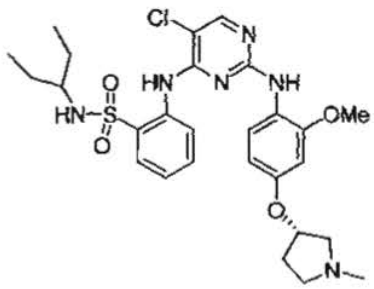
NMR 400 MHz (CD_3OD) δ 8.17 (d, 1H, J=8.0 Hz), 7.88 (m, 2H), 7.56 (t, 1H, J=8.0 Hz), 7.37 (m, 1H), 7.17 (d, 1H, J=8.8 Hz), 6.61 (d, 1H, J=2.4 Hz), 6.47 9dd, 1H, J=2.4, 8.4 Hz), 3.75(m, 7H), 3.12 (m, 4H), 2.42 (s, 3H); MS *m/z*.489.1 (M + 1)

315 

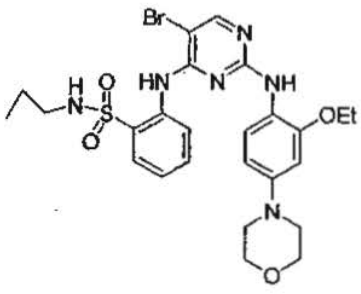
MS *m/z*.546.4 (M + 1)

316 

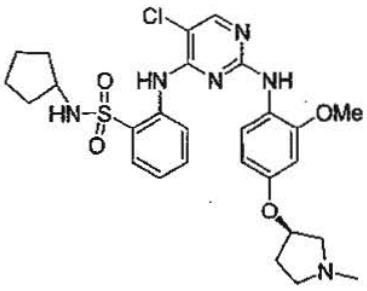
NMR 400 MHz (CD_3OD) δ 8.22 (d, 1H, J=8.4 Hz), 7.90 (d, 1H, J=4.4 Hz), 7.86 (dd, 1H, J=1.6, 8.0Hz), 7.55 (m, 1H), 7.34 (m, 1H), 7.27(d, 1H, J=8.8Hz), 6.59 (d, 1H, J=2.4 Hz), 6.45 (dd, 1H, J=1.6, 8.8 H), 4.00 (q, 2H, J=6.8 Hz), 3.75 (t, 4H, J=4.8 Hz), 3.10 (m, 4H), 2.42 (s, 3H), 1.94 (m, 6H), 1.25 (t, 3H, J=6.8Hz); MS *m/z*.503.2 (M + 1)

317 

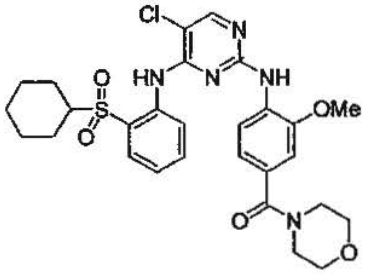
MS *m/z*.575.4 (M + 1)

318 

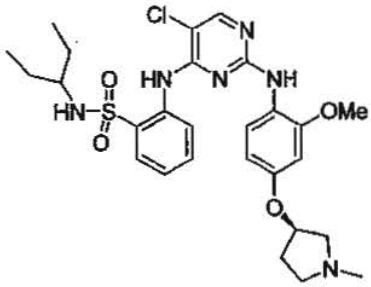
NMR 400 MHz (CD_3OD) δ 8.24 9d, 1H, J=7.6 Hz), 8.17 9s, 1H), 7.94 9dd, 1H, J=1.6, 8.0 Hz), 7.60 (t, 1H, J=7.6 Hz), 7.44 (m, 1H), 7.39(t, 1H, J=7.23 Hz), 6.68 (s, 1H), 6.50 (m, 1H), 4.10 (q, 2H, J=7.2 Hz), 3.84 (m, 4H), 3.16 (m, 4H), 2.83 (t, 2H, J=7.2 Hz), 1.37 (m, 6H), 0.75(t, 3H, J=7.6 hz); MS *m/z*.591.1 (M + 1)

319 

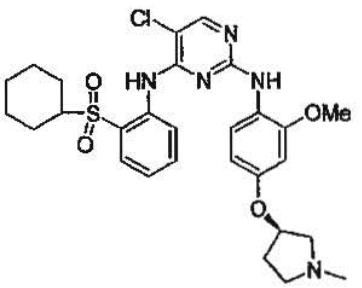
MS *m/z*.573.4 (M + 1)

320 

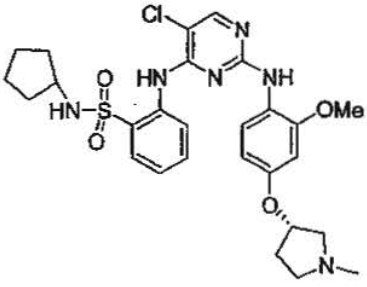
MS *m/z*.586.1 (M + 1)

321 

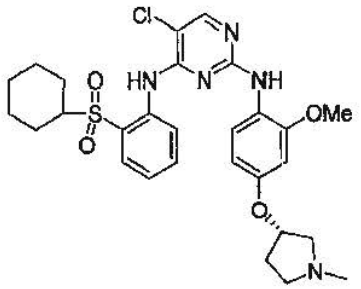
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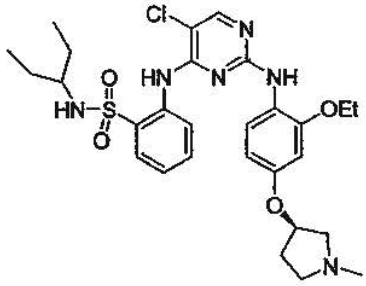
322 

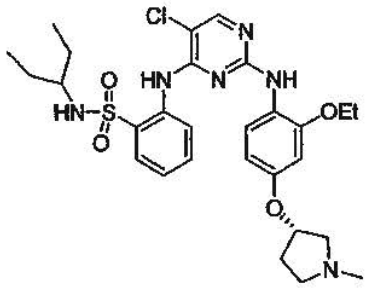
MS *m/z*.572.4 (M + 1)

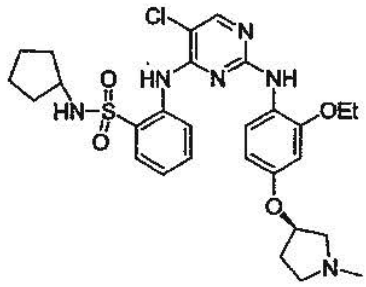
323 

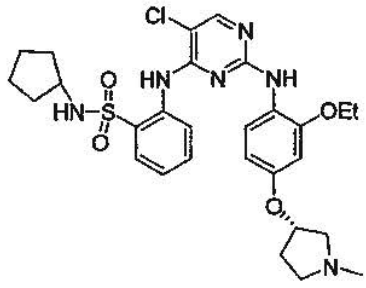
MS *m/z*.573.4 (M + 1)

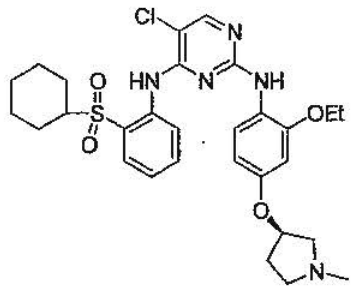
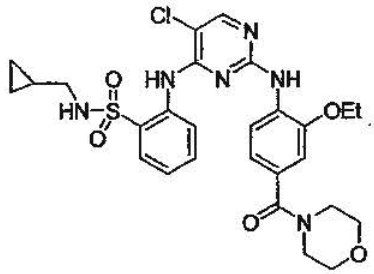
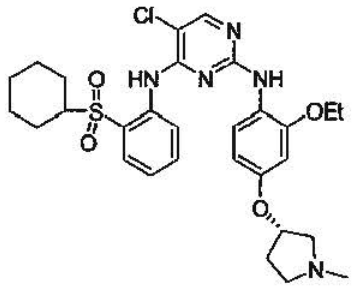
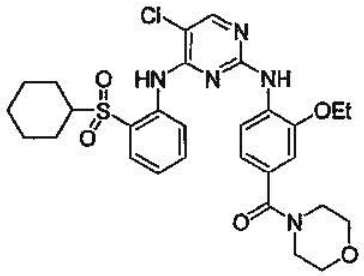
324  MS *m/z*.572.4 (M + 1)

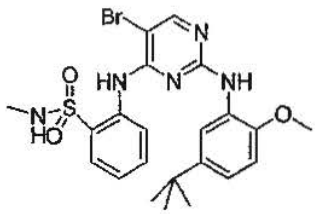
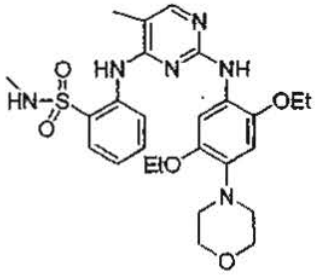
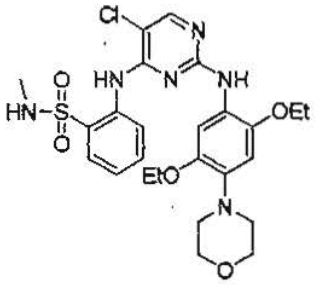
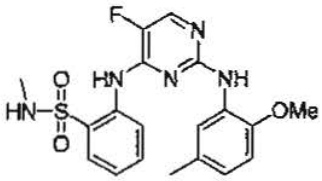
325  MS *m/z*.589.4 (M + 1)

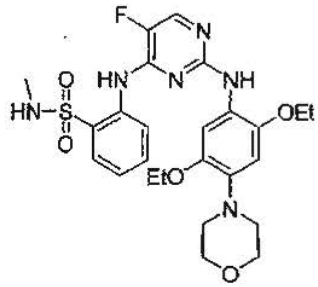
326  MS *m/z*.589.4 (M + 1)

327  MS *m/z*.587.4 (M + 1)

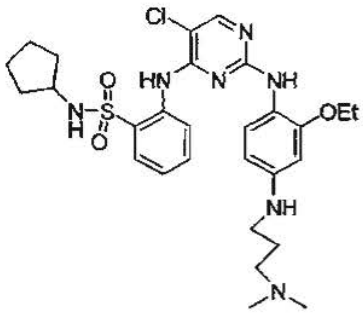
328  MS *m/z*.587.4 (M + 1)

329		MS *m/z*.586.4 (M + 1)
330		MS *m/z*.587.1 (M + 1)
331		MS *m/z*.586.4 (M + 1)
332		MS *m/z*.600.2 (M + 1)
333		MS *m/z*.434.2 (M + 1)

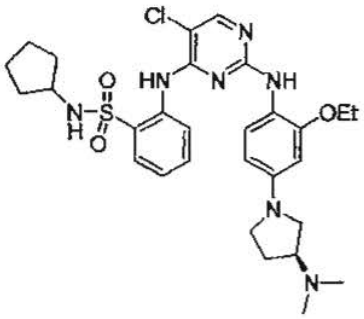
334		MS *m/z*.520.0 (M + 1)
335		MS *m/z*.478.0 (M + 1)
336		MS *m/z*.543.2 (M + 1)
337		MS *m/z*.563.2 (M + 1)
338		NMR 400 MHz (CD_3OD) δ 8.18 (d, 1H, J=7.6 Hz), 7.98 (d, 1H, J=4.4 Hz), 7.86 (dd, 1H, J=1.6, 8.0 Hz), 7.56 (m, 1H), 7.46 (s, 1H), 7.30 (m, 1H), 6.83 (m, 2H), 3.75 (s, 3H), 2.40 (s, 3H), 2.08 (s, 3H); MS *m/z*.418.1 (M + 1)

339 

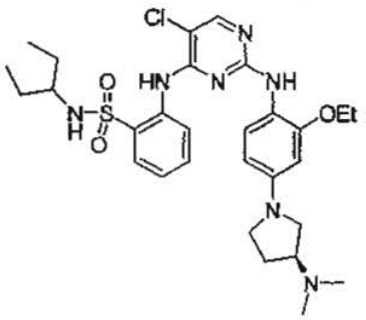
NMR 400 MHz (CD_3OD) δ 8.17 (d, 1H, J=8.0 Hz), 8.00 (d, 1H, J=4.4 Hz), 7.86 (dd, 1H, J=1.6, 8.0Hz), 7.53 (m, 1H), 7.43 (s, 1H), 7.32 (m, 1H), 6.79 (s, 1H), 4.00 (q, 2H, J=6.8Hz), 3.83 9m, 4H), 3.76 (m, 2H), 2.44 (s, 3H), 1.29 (t, 3H, J=7.2 Hz), 1.24 (t, 3H, J=7.2 Hz); MS *m/z* 547.2 (M + 1)

340 

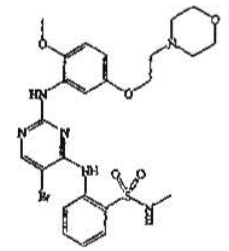
MS *m/z* 588.4 (M + 1)

341 

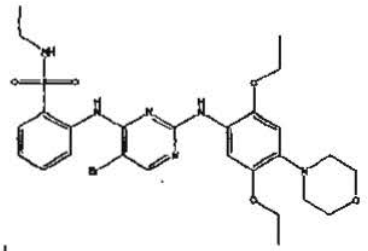
MS *m/z* 600.4 (M + 1)

342 

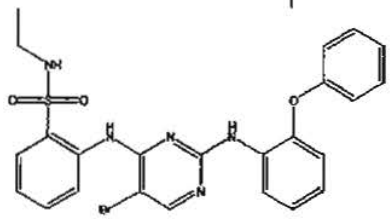
MS *m/z* 602.4 (M + 1)

343 

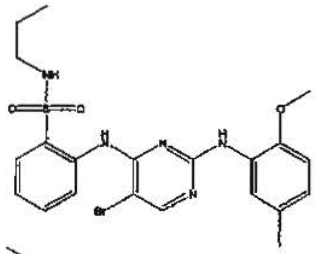
MS m/z 593.00/ 595.00 (M + 1)

344 

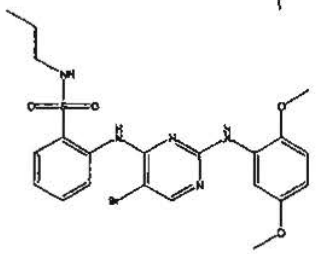
MS m/z 621.20 / 823.20 (M + 1)

345 

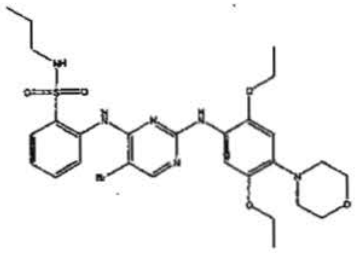
^{1}H NMR 400 MHz (DMSO-d_6) δ 8.95 (s, br, 1H), 8.49 (s, br, 2H), 7.80 (dd, J = 7.54, 2.13 Hz, 1H), 7.34 (t, J = 8.36, 2H), 7.14 (m, 3 H), 6.93 (m, 3 H); MS m/z 540.10 / 542.10 (M + 1)

346 

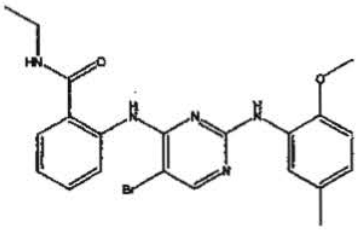
MS m/z 506.10 / 508.10 (M + 1)

347 

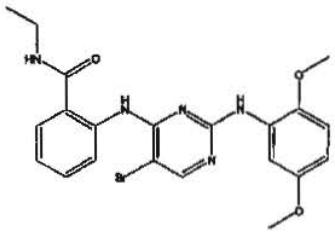
MS m/z 522.10 / 524.10 (M + 1)

348 

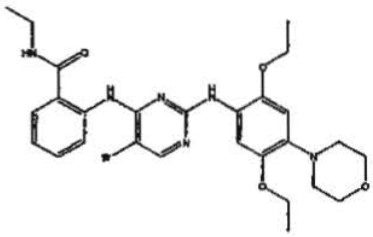
MS m/z 635.20 / 637.20 (M + 1)

349 

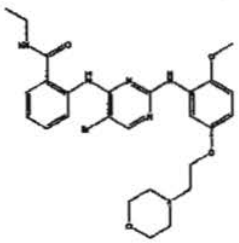
MS m/z 456.10 /458.10 (M + 1)

350 

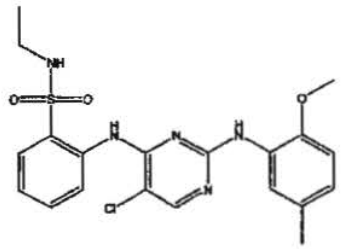
MS m/z 472.10 / 474.10 (M + 1)

351 

MS m/z 585.20 / 587.20 (M + 1)

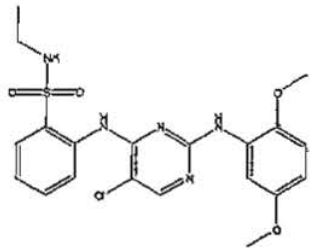
352 

MS m/z 571.20 / 573.10 (M + 1)

353 

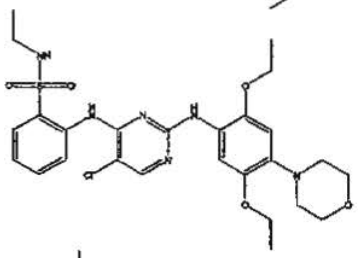
MS m/z 448.10 / 450.10 (M + 1)

354



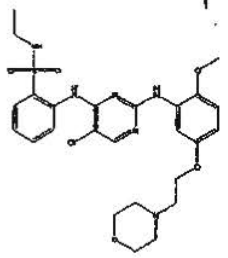
MS m/z 464.10 / 466.10 (M + 1)

355

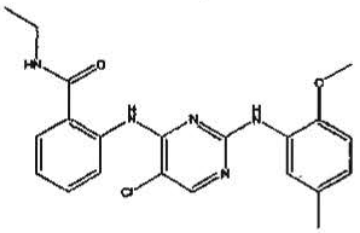


^{1}H NMR 400 MHz (DMSO-d_6) δ 9.54 (s, br, 1H), 8.76 (s, br, 1H), 8.31 (s, 1), 8.28 (d, J = 8.14Hz, 1H), 7.95 (t, J = 5.64 Hz, 7.85 (dd, J = 7.95, 1.48 Hz, 1H), 7.51 (t, J = 7.53 Hz, 1H), 7.33 (m, 2H), 6.73 (s, 1H), 4.05 (q, J = 6.92, 2H), 3.98 (m, 4H), 3.71 (m, 2H), 3.12 (m, 4H), 2.82 (p, J = 5.77
MS m/z 563.20 / 565.20 (M + 1)

356

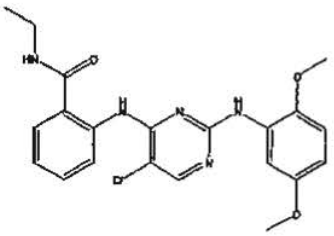


357



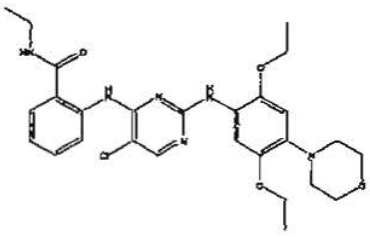
MS m/z 412.10 / 414.10 (M + 1)

358

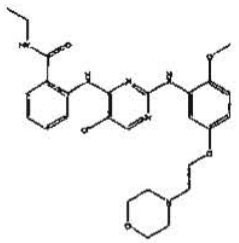


MS m/z 428.10 / 430.10 (M + 1)

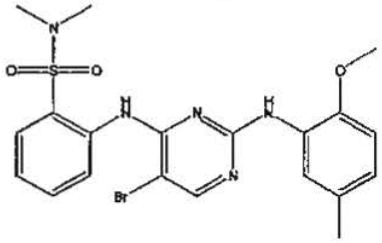
359



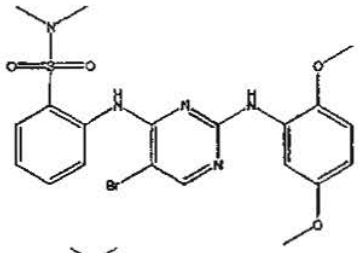
MS m/z 541.20 / 543.20 (M + 1)

360 

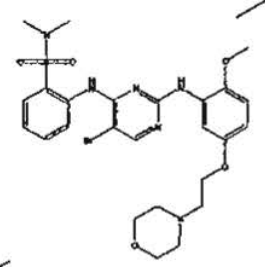
MS m/z 527.20 / 529.20 (M + 1)

361 

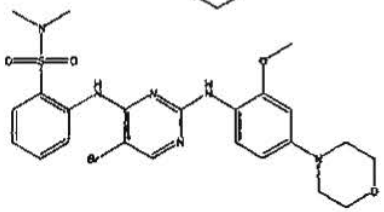
MS m/z 492.10 / 494.10 (M + 1)

362 

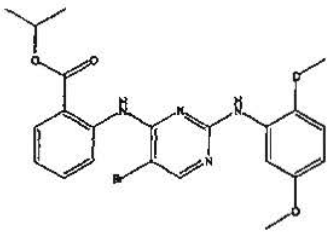
MS m/z 508.00 / 510.05 (M + 1)

363 

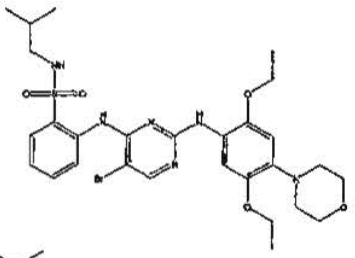
MS m/z 807.10 / 609.10 (M + 1)

364 

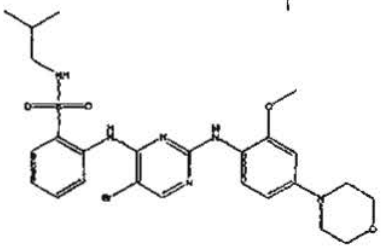
MS m/z 563.10 / 565.10 (M + 1)

365 

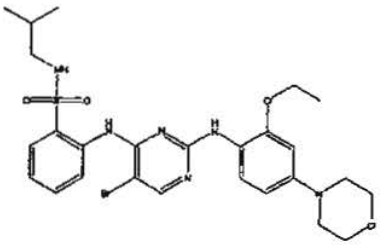
MS m/z 487.10 / 489.10 (M + 1)

366 

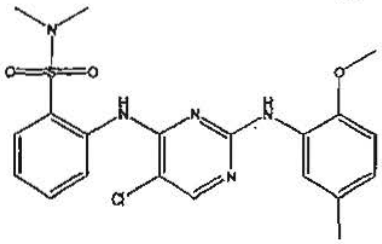
MS m/z 649.20 / 651.20 (M + 1)

367 

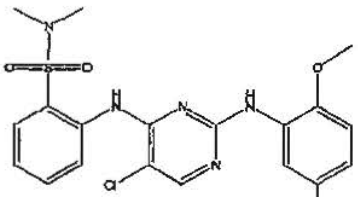
MS m/z 591.20 / 593.20 (M + 1)

368 

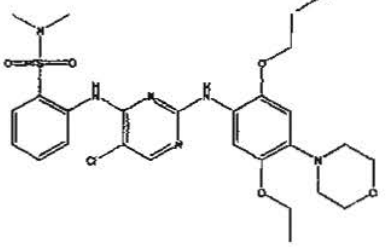
MS m/z 605.20 / 607.20 (M + 1)

369 

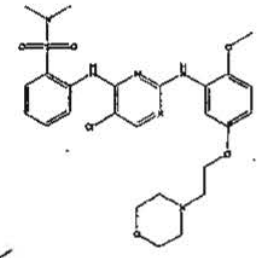
MS m/z 448.10 / 450.10 (M + 1)

370 

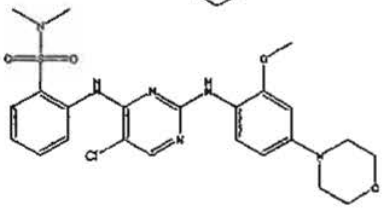
^{1}H NMR 600 MHz (DMSO-d_6) δ 9.46 (s, 1H), 8.46 (s, 1H), 8.37 (d, J = 8.12 Hz, 1H), 8.25 s, (1H), 7.75 (dd, 7.87, 1.40 Hz, 1H), 7.55 (t, J = 7.50 Hz, 1H), 7.37 (s, 1H), 7.30 (dt, J = 8.05, 0.8 Hz, 1H), 6.91 (d, J = 8.92 Hz, 1H), 6.58 (dd, J = 8.88, 3.04 Hz, 1H), 3.70 (s, 3H), 3.55 (s, 3H), 2.58 (s.

371 

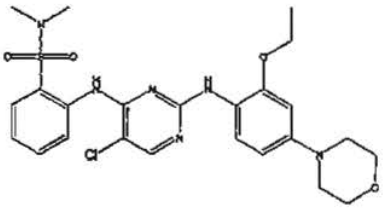
MS m/z 577.20 / 579.20 (M + 1)

372 

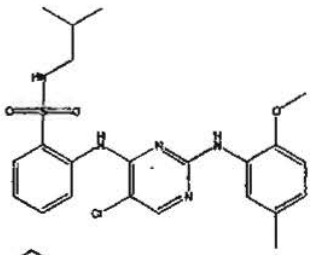
MS m/z 563.20 / 565.20 (M + 1)

373 

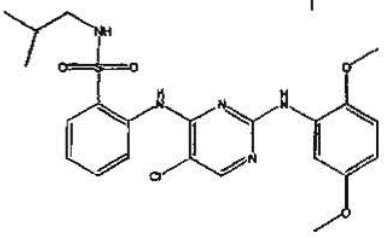
MS m/z 519.20 / 521.20 (M + 1)

374 

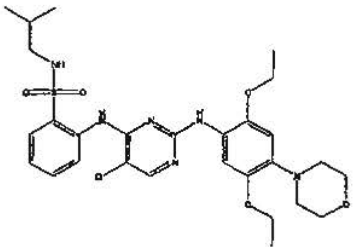
MS m/z 533.20 / 535.20 (M + 1)

375 

MS m/z 476.20 / 478.20 (M + 1)

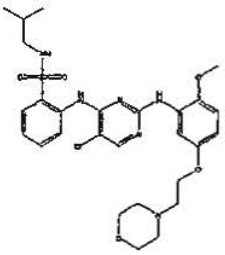
376 

^{1}H NMR 600 MHz (DMSO-d_6) δ 9.39 (s, 1H), 8.37 (s, 1H), 8.27 (s, 1H), 8.25 (s, 1H), 7.88 (t, J = 6.02 Hz, 1H), 7.76 (dd, J = 7.94, 1.35 Hz, 1H), 7.50 (dt, J = 8.24, 1.69 Hz, 1H), 7.40 (s, 1H), 7.25 (t, J = 7.39 Hz, 1H), 6.90 (d, J = 8.92 Hz, 1H) 5.65 (dd, J = 8.87, 3.03 Hz, 1H).. 3.70 (s, 3H). 3.54 (s.

377 

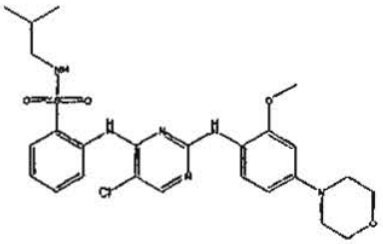
MS m/z 605.30 / 607.20 (M + 1)

378



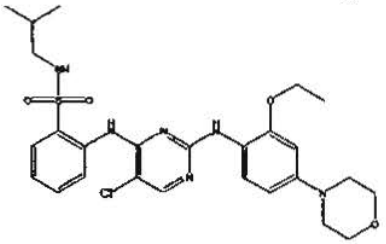
MS m/z 591.20 / 593.20 (M + 1)

379



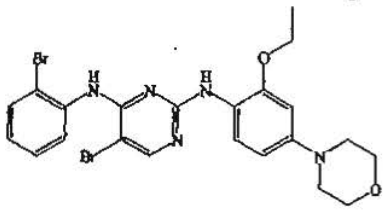
MS m/z 547.20 / 549.20 (M + 1)

380



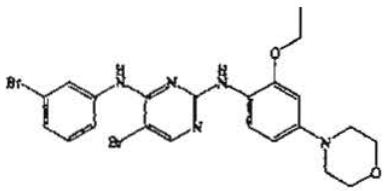
MS m/z 561.20 / 563.20 (M + 1)

381



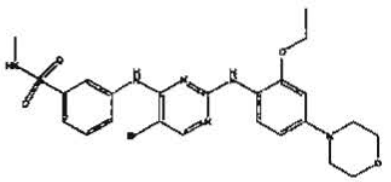
MS m/z 548.20 / 550.20 / 552.20 (M + 1)

382

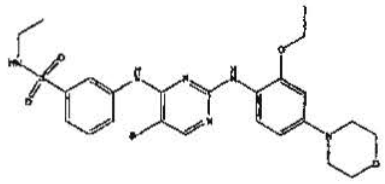
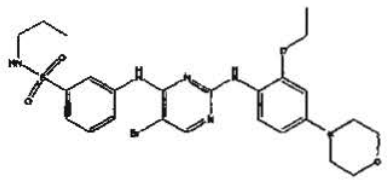
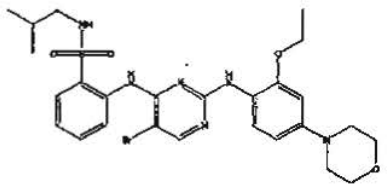
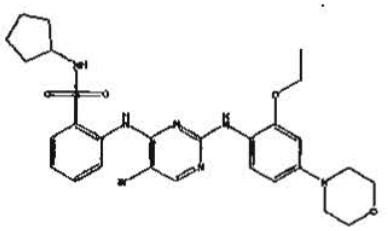
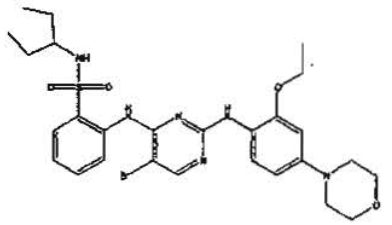
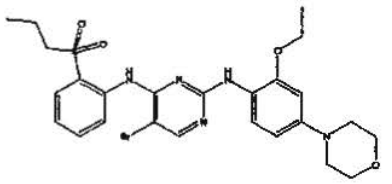


MS m/z 548.20 / 550.20 / 552.20 (M + 1)

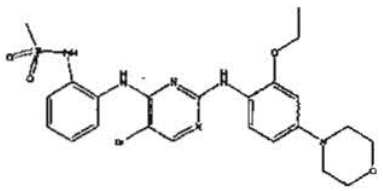
383



MS m/z 563.30 / 565.30 (M + 1)

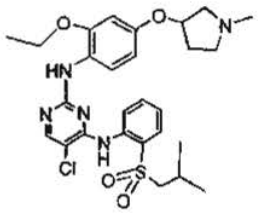
384		MS m/z 577.30 / 579.30 (M + 1)
385		MS m/z 591.40 / 593.30 (M + 1)
386		MS m/z 605.40 / 607.40 (M + 1)
387		MS m/z 617.40 / 619.40 (M + 1)
388		MS m/z 619.40 / 621.40 (M + 1)
389		MS m/z 576.30 / 578.30 (M + 1)

390



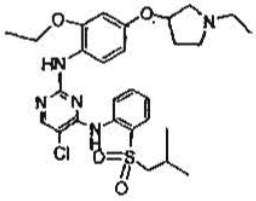
MS m/z 563.30 / 565.30 (M + 1)

391



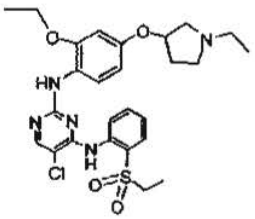
MS m/z 560.40 / 562.40 (M + 1)

392



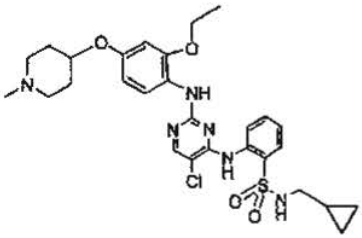
MS m/z 574.40 / 576.50 (M + 1)

393



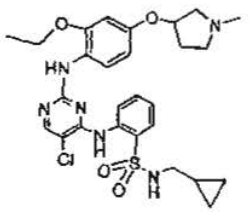
^{1}H NMR 400 MHz (DMSO-d_6) δ 9.47 (s, 1H), 8.45 (d, J = 7.37 Hz, 1H), 8.36 (s, 1H), 8.20 (s, 1H), 7.83 (d, J = 7.93 Hz, 1H), 7.59 (t, J = 8.07 Hz, 1H), 7.47 (d, J = 8.69 Hz, 1H), 7.32 (t, J = 7.54 Hz, 1H), 6.63 (dd, J = 12.67, 2.42 Hz, 1H), 6.49 (m, 1H), 5.16 (m, 1H), 4.01-3.68 (m, 3H), 3.46-

394

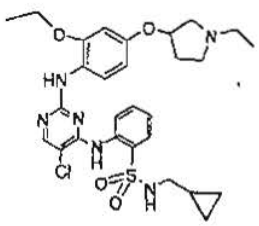
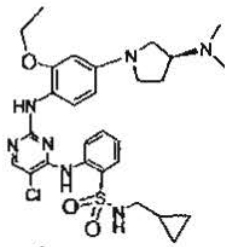
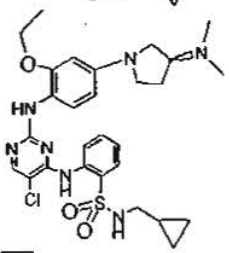
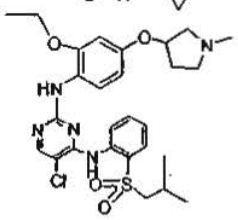
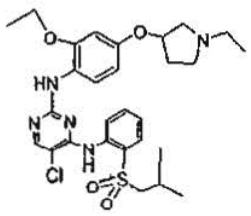
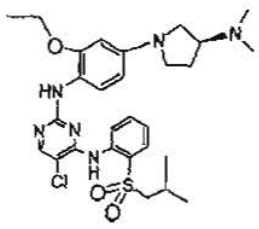


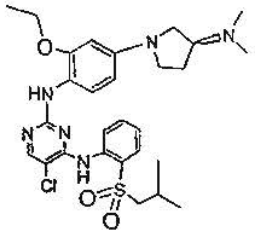
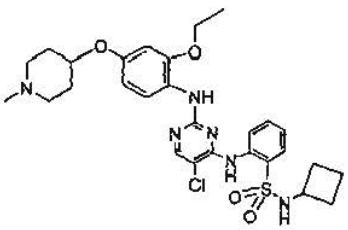
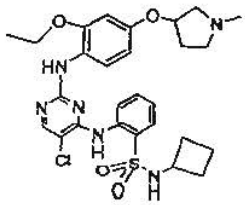
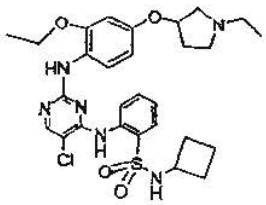
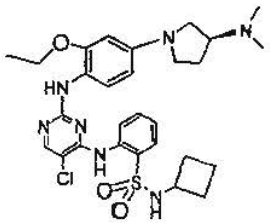
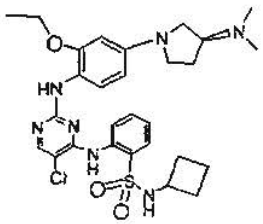
MS m/z 587.40 / 589.40 (M + 1)

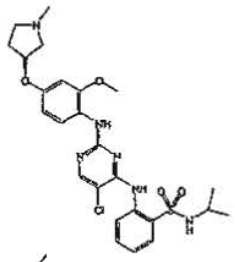
395



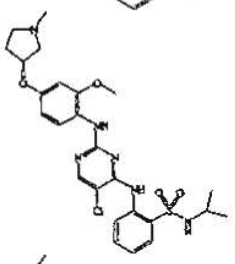
MS m/z 573.40 / 575.40 (M + 1)

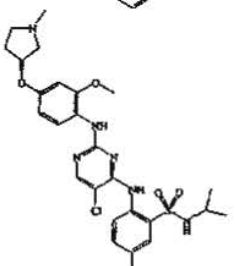
396		MS m/z 587.40 / 589.40 (M + 1)
397		MS m/z 586.40 / 588.40 (M + 1)
398		MS m/z 586.40 / 588.40 (M + 1)
399		MS m/z 560.40 / 562.40 (M + 1)
400		^{1}H NMR 400 MHz (DMSO-d_6) δ 10.30 (s, br, 1H), 9.53 (s, 1H), 8.53 (s, 1H), 8.41 (d, J = 7.90 Hz, 1H), 8.26 (s, 1H), 7.90 (dd, J = 7.91,1.25 Hz, 1H), 7.64 (t, J = 7.93 Hz, 1H), 7.46 (d, J = 8.70 Hz, 1H), 7.38 (t, J = 7.48 Hz, 1H), 6.67 (dd, J = 13.68, 2.49 Hz, 1H), 6.46 (m, 1H), 5.19 (m, 1H), 4.04 (m,
401		MS m/z 573.20 / 575.20 (M + 1)

402		MS m/z 573.20 / 575.20 (M + 1)
403		MS m/z 587.40 / 589.40 (M + 1)
404		MS m/z 573.40 / 575.40 (M + 1)
405		MS m/z 587.40 / 589.40 (M + 1)
406		MS m/z 586.40 / 588.40 (M + 1)
407		MS m/z 586.40 / 588.40 (M + 1)

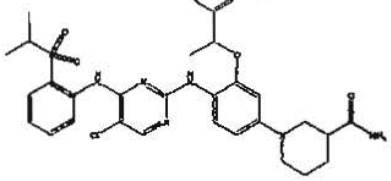
408 

^{1}H NMR 600 MHz (CD_3OD) δ 8.18 (d, J = 7.80 Hz, 1H), 8.03 (s, 1H), 7.87 (dd, J = 7.96, 1.21 Hz, 1H), 7.47 (m, 2H), 7.25 (t, J = 7.82 Hz, 1H), 6.59 (s, 1H), 6.40 (d, J = 8.56 Hz, 1H), 5.13 (s, 1H), 3.78 (m, 4H), 3.30 (m, 2H), 3.28 (s, 3H), 2.92 (m, 2H), 2.56 (m, 1H), 2.30 (m, 2H), 0.89 (d, J = MS m/z 547.40 / 549.40 (M + 1)

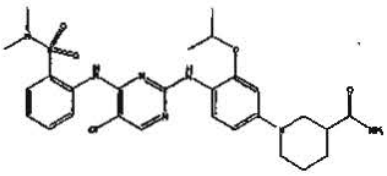
409 

410 

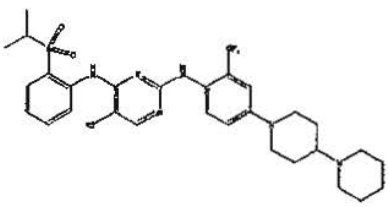
MS m/z 547.40 / 549.40 (M + 1)

411 

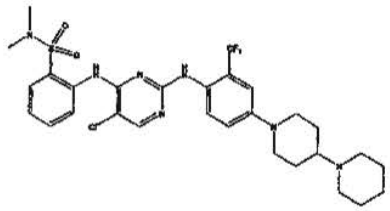
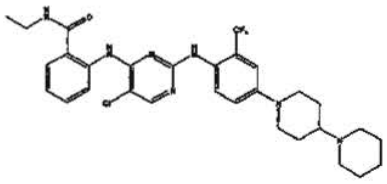
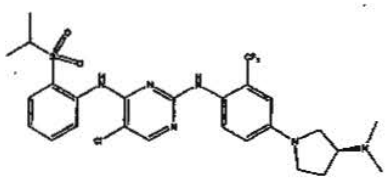
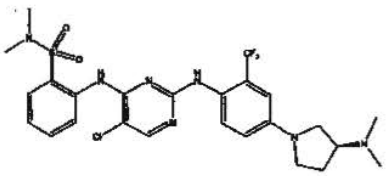
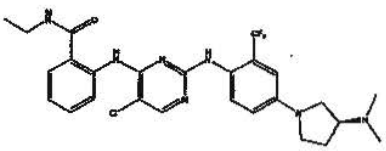
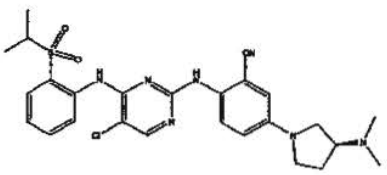
MS m/z 587.50 / 589.40 (M + 1)

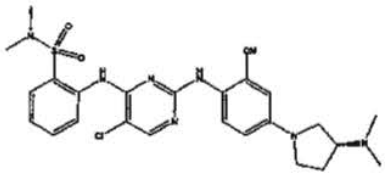
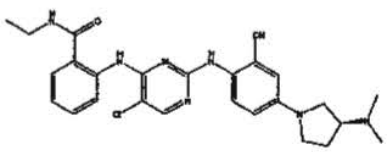
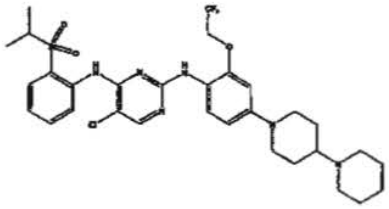
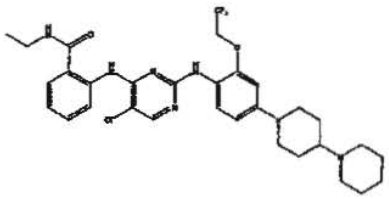
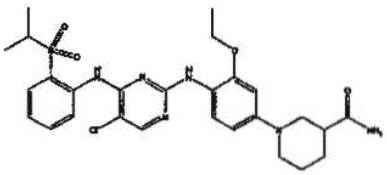
412 

MS m/z 588.50 / 590.40 (M + 1)

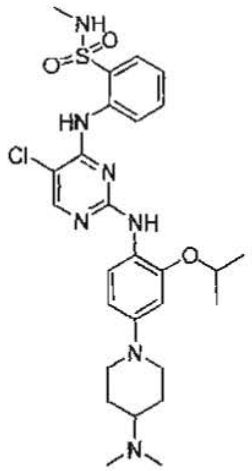
413 

MS m/z 637.50 / 639.50 (M + 1)

414		MS m/z 638.50 / 640.50 (M + 1)
415		MS m/z 602.50 / 604.50 (M + 1)
416		MS m/z 583.40 / 585.40 (M + 1)
417		MS m/z 584.40 / 586.40 (M + 1)
418		MS m/z 548.40 / 550.40 (M + 1)
419		MS m/z 540.40 / 542.40 (M + 1)

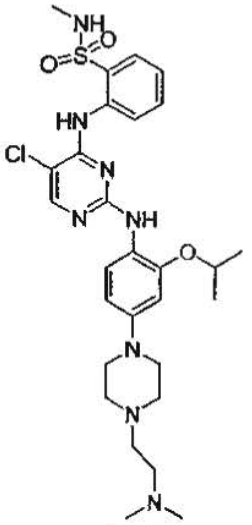
420		MS m/z 541.40 / 543.40 (M + 1)
421		MS m/z 505.40 / 507.40 (M + 1)
422		MS m/z 667.30 / 669.30 (M + 1)
423		MS m/z 632.30 / 634.30 (M + 1)
424		MS m/z 573.40 / 575.40 (M + 1)

425



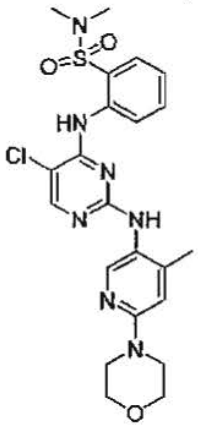
^{1}H NMR 400 MHz (CD_3OD) δ 8.34 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H), 7.96 (dd, J = 1.2, 7.8 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.43 (m, 2H), 6.72 (d, J = 2.4 Hz, 1H), 6.57 (m, 1H), 4.07 (m, 1H), 3.40 (m, 1H), 3.02 (t, J=10.6 Hz, 1H), 2.80 (t, J=11.8, 1H), 2.65 (m, 4H), 2.54, (s, 3H), 2.26 (s, 6H), 1.56 (m, 4H), 1.36 (d, J = 7.2 Hz, 6H). MS *m/z* 574.20 (M + 1).

426



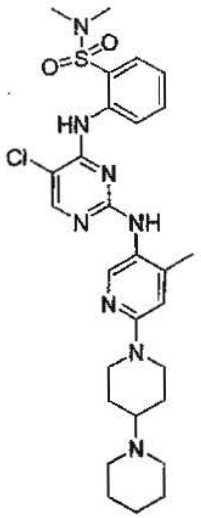
MS *m/z* 603.20 (M + 1).

427



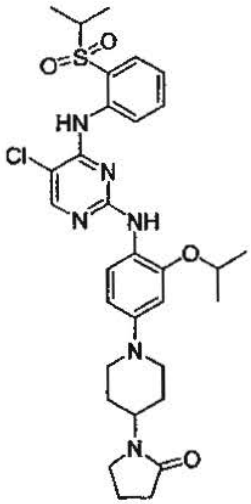
MS *m/z* 504.20 (M + 1).

428



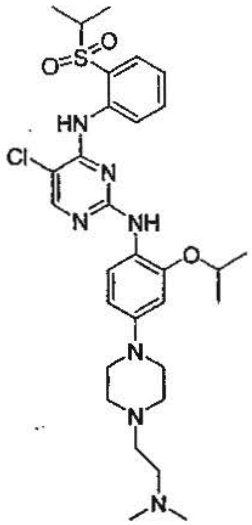
MS *m/z* 585.30 (M + 1).

429



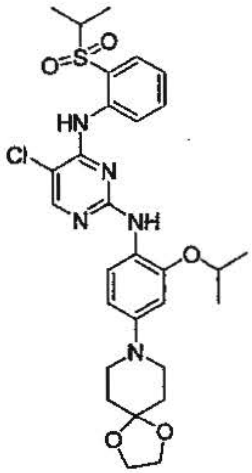
MS *m/z* 627.20 (M + 1).

430



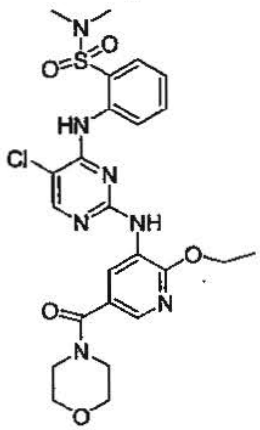
MS *m/z* 616.20 (M + 1).

431



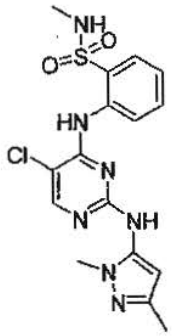
MS *m/z* 602.20 (M + 1).

432



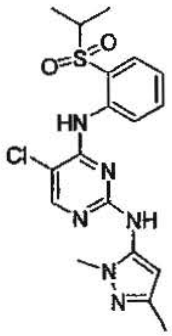
MS *m/z* 562.10 (M + 1).

433



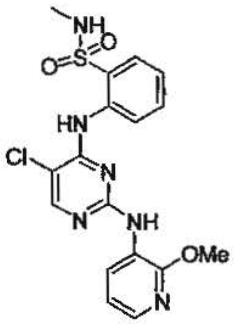
MS *m/z* 408.1 (M + 1).

434



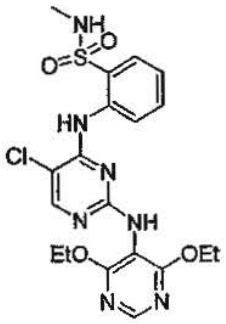
MS *m/z* 421.1 (M + 1).

435

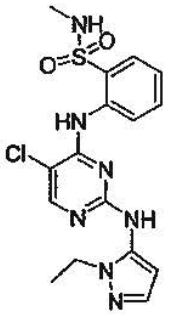
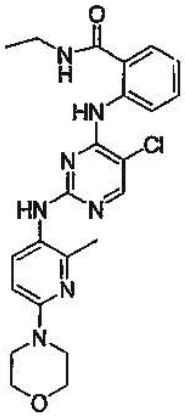


MS *m/z* 421.1 (M + 1).

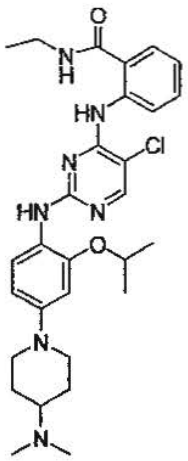
436



MS *m/z* 480.10 (M + 1).

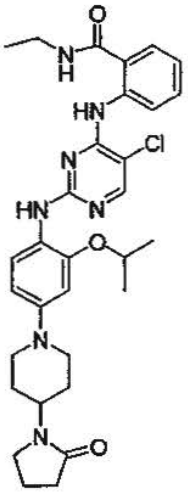
437		MS *m/z* 394.10 (M + 1).
438		MS *m/z* 408.10 (M + 1).
439		^{1}H NMR 400 MHz (CD_3OD) δ 8.34 (d, J = 8.4 Hz, 1H), 8.13 (s, 1H), 7.96 (dd, J = 1.3, 7.9 Hz, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.43 (m, 1H), 7.13 (d, J=2.8 Hz, 1H), 6.24 (d, J = 2.8 Hz, 1H), 4.08(m, 1H), 3.41(m, 1H), 2.58 (s, 6H), 2.54 (s, 3H). MS *m/z* 574.20 (M + 1).
440		MS *m/z* 468.20 (M + 1).

441



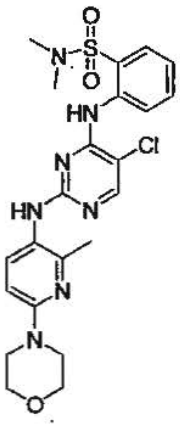
MS *m/z* 552.30 (M + 1).

442



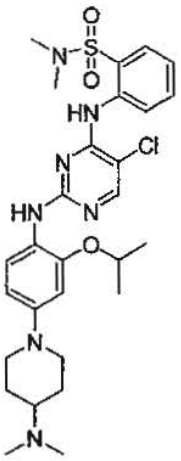
MS *m/z* 592.30 (M + 1)

443



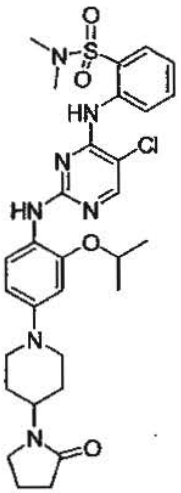
MS *m/z* 504.20 (M + 1)

444



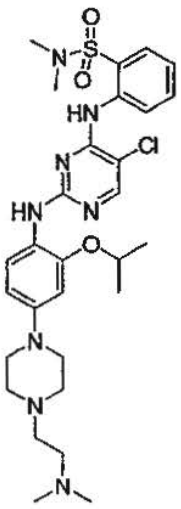
MS *m/z* 588.30 (M + 1)

445

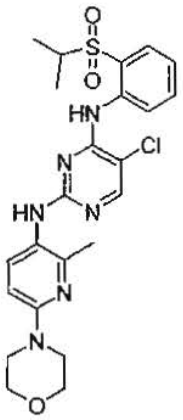


MS *m/z* 628.30 (M + 1)

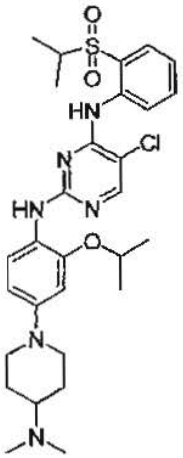
446



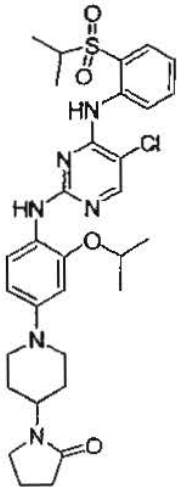
MS *m/z* 617.20 (M + 1)

447 

MS *m/z* 503.20 (M + 1)

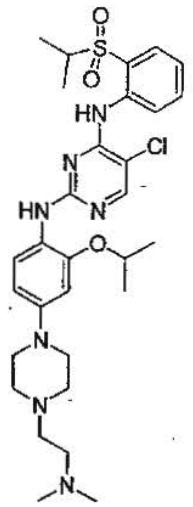
448 

MS *m/z* 587.20 (M + 1)

449 

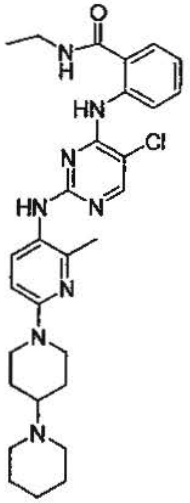
MS *m/z* 627.30 (M + 1)

450



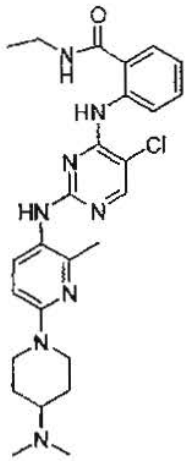
MS *m/z* 616.30 (M + 1)

451



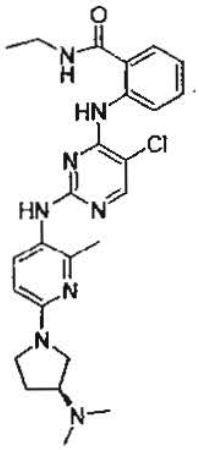
MS *m/z* 549.30 (M + 1)

452



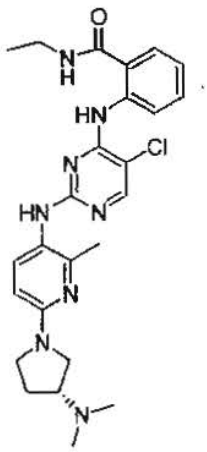
MS *m/z* 509.30 (M + 1)

453

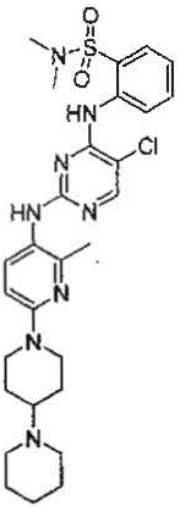


MS *m/z* 495.20 (M + 1)

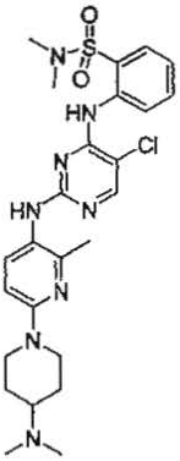
454



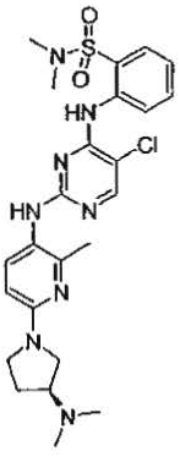
MS *m/z* 495.20 (M + 1)

455 

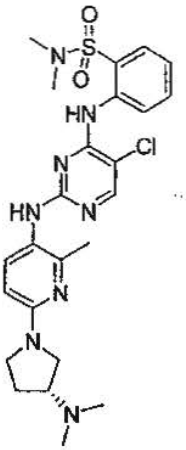
MS *m/z* 585.20 (M + 1)

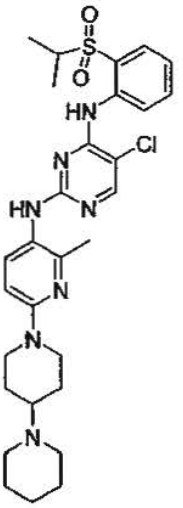
456 

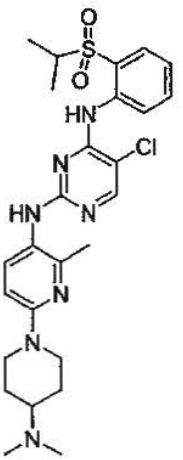
MS *m/z* 545.20 (M + 1)

457 

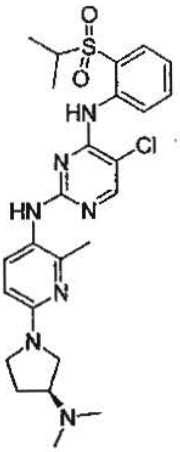
MS *m/z* 531.20 (M + 1)

458  MS *m/z* 531.20 (M + 1)

459  MS *m/z* 584.30 (M + 1)

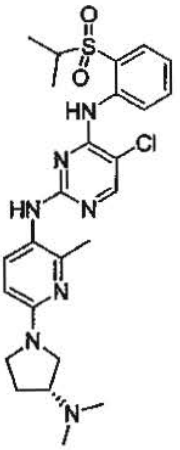
460  MS *m/z* 544.20 (M + 1)

461



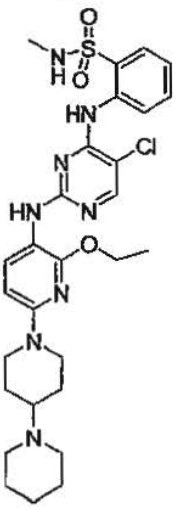
MS *m/z* 530.20 (M + 1)

462

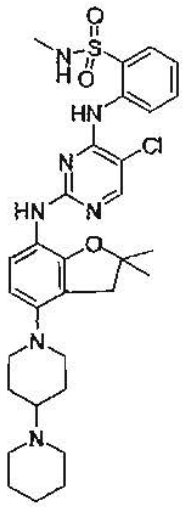


MS *m/z* 530.20 (M + 1)

463



MS *m/z* 601.30 (M + 1)

464  MS *m/z* 626.30 (M + 1)

Example 54: Cell-free ZAP-70 Kinase assay

The ZAP-70 kinase assay is based on time-resolved fluorescence resonance energy transfer (FRET). 80 nM ZAP-70 are incubated with 60 nM Lck (lymphoid T-cell protein tyrosine kinase) and 4 µM ATP in ZAP-70 kinase buffer (20 mM Tris, pH 7.5, 10 µM Na_3VO_4, 1 mM DTT, 1 mM $MnCl_2$, 0.01 % BSA, 0.05 % Tween-20) for 1 hour at room temperature in a siliconized polypropylene tube. Then, the selective Lck inhibitor PP2 (1-tert-butyl-3-(4-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine; Alexis Biochemicals) is added (final concentration 1.2 µM) and incubated for further 10 min. 10 µL of this solution is mixed with the 10 µL biotinylated peptide LAT-11 (1 µM) as substrate and 20 µL of serial dilutions of inhibitors and incubated for 4 hours at room temperature. The kinase reaction is terminated with 10 µL of a 10 mM EDTA solution in detection buffer (20 mM Tris, pH 7.5, 0.01 % BSA, 0.05 % Tween-20). 50 µL europium-labelled anti-phosphotyrosine antibody (Eu-PT66; final concentration 0.125 nM); and 50 µL streptavidin-allophycocyanine (SA-APC; final concentration 40 nM) in detection buffer are added. After 1 hour incubation at room temperature fluorescence is measured on the Victor2 Multilabel Counter (Wallac) at 665 nm. Background values (low control) are obtained in the absence of test samples and ATP and are subtracted from all values. Signals obtained in the absence of test samples are taken as 100% (high control). The inhibition obtained in the presence of test compounds is calculated as percent inhibition of the high control. The concentration of test compounds resulting in 50% inhibition (IC_{50}) is determined from the dose-response curves. In this assay, the agents of the invention have IC_{50} values in the range of 10 nM to 2 µM, preferably from 10 nM to 100 nM.

Recombinant ZAP-70 kinase is obtained as follows: A nucleic acid encoding full-length human ZAP-70 (GenBank #L05148) is amplified from a Jurkat cDNA library by RT-PCR and cloned into the pBluescript KS vector (Stratagene, California, USA). The authenticity of the ZAP-70 cDNA insert is validated by complete sequence analysis. This donor plasmid is then used to construct a recombinant baculovirus transfer vector based on the plasmid pVL1392 (Pharmingen, California, USA) featuring in addition an N-terminal hexahistidine tag. Following co-transfection with AcNPV viral DNA, 10 independent viral isolates are derived via plaque-purification, amplified on small scale and subsequently analyzed for recombinant ZAP-70 expression by Western Blot using a commercially available anti-ZAP-70 antibody (Clone 2F3.1, Upstate Biotechnology, Lake Placid, NY, USA). Upon further amplification of one positive recombinant plaque, titrated virus stocks are prepared and used for infection of Sf9 cells grown in serum-free SF900 II medium (Life Technologies, Basel, Switzerland) under defined, optimized conditions. ZAP-70 protein is isolated from the lysate of infected Sf9 cells by affinity chromatography on a Ni-NTAcolumn (Qiagen, Basel, Switzerland).
Recombinant His-tagged ZAP-70 is also available from PanVera LLC, Madison, Wisconsin, USA.

LAT-11 (linker for activation of T cell): The biotinylated peptide LAT-11 (Biotin-EEGAPDYENLQELN) used as a substrate in the ZAP-70 kinase assay is prepared in analogy to known methods of peptide synthesis. The N-α Fmoc group of Fmoc-Asn(Trt)-oxymethyl-4-phenoxymethyl-co(polystyrene-1%-divinyl-benzene), content of Asn approx. 0.5 mmol/g, is cleaved using piperidine, 20% in DMF. Four equivalents per amino-group of Fmoc-amino acid protected in their side chains [Asp(OtBu), Glu(OtBu), Asn(Trt), Gln(Trt) and Tyr(tBu)] are coupled using DIPCDI and HOBt in DMF. After complete assembly of the peptide chain the terminal Fmoc-protecting group is removed with piperidine in DMF as before. L(+)-biotinyl-aminohexanoic acid is then coupled to the terminal amino group using DIPCDI and HOBt in DMF using four equivalents of the reagents for four days at RT. The peptide is cleaved from the resin support and all side-chain protecting groups are simultaneously removed by using a reagent consisting of 5% dodecylmethylsulfide and 5% water in TFA for two hours at RT. Resin particles are filtered off, washed with TFA and the product is precipitated from the combined filtrates by the addition of 10 to 20 volumes of diethyl ether, washed with ether and dried. The product is purified by chromatography on a C-18 wide-pore silica column using a gradient of acetonitrile in 2% aqueous phosphoric acid. Fractions containing the pure compound are

collected, filtered through an anion-exchange resin (Biorad, AG4-X4 acetate form) and lyophilized to give the title compound. MS: 1958.0 $(M-H)^{-1}$

Example 56: Anchorage-independent tumor cell growth assay

Mouse mammary carcinoma 4T1 cells (5 x 10^3) are plated in 96-well Ultra low Attachment plates (#3474, Corning Inc.) in 100 µL of Dulbecco's modified eagle medium containing 10% FBS. Cells are cultured for 2 h and inhibitors are added at various concentrations in a final concentration of 0.1% DMSO. After 48 h, cell growth is assayed with the cell counting kit-8 (Wako Pure Chemical), which uses a water soluble tetrazolium salt WST8. Twenty µL of the reagent is added into each well and cells are further cultured for 2 h. The optical density is measured at 450 nm. The concentration of compound causing 50 % inhibition of growth is determined.

Example 59 *In vivo* activity in the nude mouse xenograft model:

female or male BALB/c nude mice (5–8 weeks old, Charles River Japan, Inc., Yokohama, Japan) are kept under sterile conditions with water and feed *ad libitum*. Tumours are induced by subcutaneous injection of tumour cells (human epithelial cell line MIA PaCa-2; European Collection of Cell Cultures (ECACC), Salisbury, Wiltshire, UK, Catalogue Number 85062806; cell line from a 65 year old Caucasian male; undifferentiated human pancreatic carcinoma cell line) into left or right flank of mice under Forene® anaesthesia (Abbott Japan Co., Ltd., Tokyo, Japan). Treatment with the test compound is started when the mean tumor volumes reached approximately 100 mm^3. Tumour growth is measured two times per week and 1 day after the last treatment by determining the length of two perpendicular axis. The tumour volumes are calculated in accordance with published methods (see Evans et al., Brit. J. Cancer 45, 466-8, 1982). The anti-tumour efficacy is determined as the mean increase in tumour volume of the treated animals divided by the mean increase in tumour volume of the untreated animals (controls) and, after multiplication by 100, is expressed as delta T/C [%]. Tumour regression is reported as the mean changes of tumor volume of the treated animals divided by the mean tumor volume at start of treatment and, after multiplication by 100, is expressed as regression [%]. The test compound is orally administered daily with or without drug holidays.

As an alternative to cell line MIA PaCa-2, another cell line may also be used in the same manner, for example:
- the 4T1 breast carcinoma cell line (ATCC Number CRL-2539; see also Cancer. 88(12 Supple), 2979-2988, 2000) with female BALB/c mice (injection into mammary fat pad).

On the basis of these studies, a compound of formula I according to the invention shows therapeutic efficacy especially against proliferative diseases responsive to an inhibition of a tyrosine kinase.

Example 60: Tablets

Tablets comprising 50 mg of active ingredient, for example one of the compounds of formula I described in Examples 1 to 131, and having the following composition are prepared in customary manner:

Composition:

active ingredient	50 mg
wheat starch	150 mg
lactose	125 mg
colloidal silicic acid	12.5 mg
talc	22.5 mg
magnesium stearate	2.5 mg
Total:	362.5 mg

Preparation: The active ingredient is mixed with a portion of the wheat starch, with the lactose and the colloidal silicic acid and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste, on a water bath, with five times the amount of water and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained.

The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are again forced through a sieve. Then the remainder of the wheat starch, the talc and the magnesium stearate are mixed in and the mixture is compressed to form tablets weighing 145 mg and having a breaking notch.

Example 61: Soft Capsules

5000 soft gelatin capsules comprising each 50 mg of active ingredient, for example one of the compounds of formula I described in Examples 1 to 131, are prepared in customary manner:

Composition:

active ingredient	250 g
Lauroglykol	2 litres

Preparation: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to a particle size of approx. 1 to 3 µm. 0.419 g portions of the mixture are then dispensed into soft gelatin capsules using a capsule-filling machine.

Biological results:

Example	FAK IC50 (nM)	Phos IC50 (μM)	Growth IC50 (μM)	Cell Migration IC50 (μM)	IGF-1R IC50 (μM)
1.00	140	0.7	>10		
2.00	13	1.2			
3.01	44	0.34	>10		
3.02	36	0.85	4		
3.03	9.1	0.14	0.8		
3.04	32	0.53	2		
3.05	21	0.17	2		>10
3.06	13	0.11	2		
3.07	16	0.45	2		
3.08	74	0.3	6		
3.09	48	0.5	0.7		
3.10	52	0.95	>10		
3.11	9	0.04	0.3		0.2
3.12	5.4	0.01	1		
3.13	58	1.7	0.6		0.74
3.14	54	0.4	5		
3.15	7	0.02	0.8		0.94
3.16	48	1.1	3		
3.17	2.8	0.03	0.2		<0.08
3.18	130	1.5	9		
3.19	6.8	0.35	0.8		0.1
3.20	18	0.22	0.3		
3.22	120	0.9	2		
3.23	38	0.39	0.5		
3.24	64	3.5	5		
3.25	22	0.3	0.3		0.81
3.26	50	0.79	2		
3.28	43	0.71	0.7		
3.29	89	0.6	>10		
3.30	69	0.6	3		
3.31	13	1.1	5		
3.32	14	0.18	0.49	0.28	0.12
3.33	2.9	0.03	0.05	0.09	0.13
3.34	7	0.1	0.24	0.13	<0.08
3.36	13	0.02	0.17	0.8	3.55
3.36	43	1.8	2.8		
3.37	39	1.1	2.6		
3.38	64	1.7	3.8		
3.39	2	0.02	0.03	1	0.09
3.40	9	>10	0.9		
3.41	22	>10	0.43		
3.42	29	0.35	0.3		
3.43	5.6	0.2	0.11		0.27
3.44	11	0.05	0.09		0.09
3.45	0.9	0.02	0.02		
3.46	4	0.1	0.18	0.3	

3.47	1	0.1	0.06			
3.48	7	0.07	0.3			0.21
3.49	39	10	0.39			
3.50	13	0.12	1			1.19
3.51	29	0.2	0.4			0.41
3.52	29	0.42	2			
3.53	6	0.07	0.21			
3.54	0.9	0.01	0.07			<0.0 8
3.55	34	>10	3			
3.56	28	0.53	0.15			
3.57	28	0.61	3			
3.58	21	0.08	0.3			0.14
3.59	95	1.2	>10			
3.60	90	0.93	2			
3.61	12	10	>10			
3.62	63	>10	>10			
3.63	27	>10	>10			
3.64	5	0.13	0.7	1	0.2	
3.65	8	0.08	0.1			0.15
3.66	1	0.08	0.07			0.25
3.67	6	0.38	0.39			
3.68	5.5	0.2	0.63		1	
3.69	4	0.2	0.11	8	0.5	
3.70	3.5	0.02	0.13			
3.71	11	0.05	0.08			
3.72	2.1	0.11	0.06			
3.73	11	0.03	0.29			1.63
3.74	15	0.1	0.15			
3.75	72	0.5	1.3			
3.76	15	0.29	1.3		0.7	
3.77	65	>10	3			
3.78	10	>10	0.22			
3.79	5	1.3	0.12			
3.80	12	0.22	0.45			5
3.81	21	0.52	0.98			>10
3.82	4.8	0.2	0.07			
3.83	20	0.08	0.32			0.68
3.84	10	1	0.08			
6.00	110	0.35	5			
7.00	5.3	0.21	0.47	4	0.0	0.19
7.01	4.7	0.6	0.54			0.19
7.02	7.5	0.1	0.36			0.77
7.03	2.9	0.3	0.39			0.27
7.04	5.2	1	0.29			
7.05	6.2	0.3	0.2			0.25
7.06	17	0.8	1.09	5	0.2	
7.07	4.1	0.9	0.18			
7.08	8.7	0.8	1			
7.09	8.2	1	0.85			
7.10	6.6	1	0.98			
7.11	2.5	0.6	1.2			0.77
7.12	1.9	0.9	1		0.3	0.62

				1	
7.13	5.5	0.8	1.22		
7.14	7.6	0.3	0.36		0.33
7.15	4.5	0.06	0.19		0.26
7.16	6.4	0.2	0.42		
7.17	4.3	0.7	0.69		
7.18	6.2	0.5	0.7		
7.19	13		0.33		
7.20	2.5	>10	0.11		
7.21	3.3	>10	0.46		
7.22	25		0.48		
7.23	1.4		0.25		
7.24	5.1		0.09		
7.25	13	0.2	0.73		
7.25	2	>10	0.57		
7.26	4.1		0.15		
7.27	21	0.5	0.22		
7.28	34	1	0.15		
7.29	57	2	0.48		
7.30	2.1		0.3	1	
8.01	6.6	0.6	0.33		
8.02	2.4	0.5	0.99		
8.03	13	0.22	1		>10
8.04	8	>10	1.1		
9.01	22	0.36	1	0.6	
9.02	15	0.5	0.81		
9.03	18	0.1	0.37		
9.04	13	0.2	0.73		
9.05	22	0.36	1.6		0.6
9.06	23	3	0.4	0.3	
9.07	17	>10	0.26		
10.01	39	1	0.44		
10.02	26	0.9	1.06		
10.03	23	0.9	2.4		
11.01	9	0.7	0.85		
11.02	4.1	0.8	0.69		
11.03	26	0.41	0.1		
11.04	4.3	>10	3.2		
12.01	2.5	0.09	0.4	0.2 2	
12.02	1.6		0.05		
12.03	2.3		0.25		
12.04	1.1		0.14		
12.06	2.6				
13.01	65		0.81		
14.01	19	0.2	1.47	0.2 8	
14.02	190	2	1.1	1	
14.03	30	10	1.01		
14.04	18		0.54		
14.05	37	>10	1		
14.06	63	10	1.11		
14.07	7.5	0.2	1.4		
15.01	15	10	0.47		
15.02	21	>10	0.66		
15.03	44	2	1.67		
16.01	44	>10	4		

16.02	6	>10	0.6			
16.03	21	3	>10			
16.04	9.5	>10	0.92			
16B	11	3	7			
16.C	28	0.9	>10			
18.01	19	>10	1.29			
19.01	<1	0.2	0.3	9	0.2	1.41
19.02	1.6	0.13	0.38			0.91
19.03	<1	0.3	0.09			0.64
19.04	1.6	0.2	0.34			0.14
19.05	1.8	0.2	0.67	7	0.0	0.47
19.06	5	1	0.7			
19.07	2.1	0.3	0.11			
19.08	3.2	0.03	0.4	9	0.2	0.13
19.09	1.3	0.17	0.39		0.3	0.48
19.10	1.3	0.06	0.56			1.02
19.11	38	>10	2			
19.12	9	>10	0.7			0.63
19.13	2.5	0.3	1.1			
19.14	2.6	0.4	1.13			0.44
19.15	3.1	0.5	0.36			
19.16	2.3	0.7	1.1			
19.17	1	>10	0.17			
19.18	7	0.13	0.87			
19.19	5.7		0.4			
19.20	1.6	0.03	0.07			0.23
19.21	84	>10	1.71			
19.22	3.4	0.12	0.51			
19.23	5.4	0.7	0.71			
19.24	1.8	0.05	0.12			
19.25	7.2	1	0.49			0.24
19.26	6.1	0.1	0.3			
19.27	1.5	0.3	0.4			
19.28	4.8	0.1	0.12		0.3	0.46
19.29	1.9					
19.30	<1	0.06	0.1			
19.31	1.8	0.4	0.38			
19.32	1.4	0.2	0.31			
20.01	10	0.3	0.18	5	0.2	0.7
20.02	9	0.12	0.17	5	0.7	0.52
20.03	42	0.4	2.5			2.78
20.04	23	0.58	1.9			
20.05	6.8	0.87	1.46			
20.06	5	0.36	0.14		49	
20.07	3	0.1	0.05			0.38
20.08	6.8	0.17	0.05	9	0.2	
20.09	2	0.3	0.01			
20.10	2	0.1	0.02			
20.11	26	2	0.4			
20.12	9.5					
20.13	6.3		0.04			

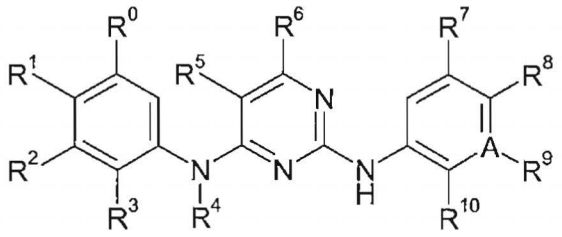
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20.15	14	0.4	0.97	0.3	
20.16	7.5		0.06		
20.17	2		0.14		
20.18	15		0.81		
20.19	28		0.21		
20.20	3.1				0.1
	2				
20.21	26	3	0.68		
20.22	8	>10	0.19		
20.23	30	0.49	3		
20.24	19	0.48	2		
20.25	6.2	0.21	0.06		
20.26	5.3	0.76	0.27		
20.27	12	0.85	0.05		0.29
20.28	9.2	0.17	0.08		0.42
20.29	6.1	0.2	0.05		0.31
20.30	7.6	0.3	0.08		0.67
20.31	39		0.5		
20.32	13		0.11		
20.33	2.5		0.38		
20.34	13	1	0.12		
20.35	8.7	0.09	0.09		0.15
21.01	1	0.07	0.19		0.47
21.02	8.5	0.33	>10		
21.03	1.7	0.3	0.3		
21.04	1.8	0.05	0.3		
22.01	43	>10	>10		
22.02	26	1	3		
22.03	6.6	0.09	0.15		0.26
23.01	3.4	0.6	0.2	0.6 3	0.53
23.02	1.5	0.2	0.4		0.8
23.03	1.7	1	1.12		0.82
23.04	1.2	0.9	1.07		0.6
23.05	1.9	>10	0.59		
23.06	16	1	0.57		
23.07	2.1	3	0.84		
23.08	6.7	0.3	0.49		
23.09	2.1	0.2	0.28		
24.01	3.6	0.11	0.44		0.05
24.02	2.1	0.5	0.11		0.39
24.03	1	0.3	1.08		
25.01	8.5	3	1		
25.02	3	0.4	0.13		0.64
26.01	4.4	0.05	0.35		0.29
26.02	1.9	0.03	0.12	0.0 9	0.39
26.03	1.4	0.1	0.13		0.23
26.04	4.9	0.05	0.43	0.2 9	1.16
26.05	2.1	0.09	0.23		1.5
26.06	4.4	0.1	0.35		
26.07	11	0.5	0.95		
26.08	2.9	0.01	0.18		
26.09	2.3	0.04	0.22		
26.10	2	0.01	0.14		

26.11	4.4	0.4	0.78	0.5	
26.12	3.7	0.2	0.19		
26.13	1.6	0.2	0.44		
26.14	5		0.19		
26.15	6.9	1.2	0.08		0.07
26.16	9	0.32	2		
26.17	17	0.3	0.1	0.2 6	
26.18	1.3	6	1.17		
26.19	9.2	0.43	0.79		
26.20	10	0.14	0.22	0.6	0.49
26.21	1.1	0.1	0.49		
26.22	<1	0.1	0.28		
26.23	1.4	0.3	0.09	0.3	0.18
26.24	1	0.5	0.48	0.9	
26.25	<1	0.6	0.73	0.3	
26.26	1.9	0.2	0.07		0.34
26.27	4.8	0.6	1.49		
26.28	2.1	0.5	1.52		
26.29	<1	0.31	0.26		
26.30	4.4	1	0.76		
26.31	2	0.3	0.16		
26.32	1.6		0.05	0.8	
26.33	4		0.06	0.2 3	
26.34	7		0.1	0.2 5	
26.35	4.5		0.05	0.3	
26.36	1.9		0.07	0.0 9	
26.37	<1				
26.38	<1				
26.39	3.1				
27.01	14	0.06	0.47		
27.02	5.1	0.5	1.1		
27.03	6.3	>10	0.56		
27.04	11	0.1	0.27		
27.05	8.2	0.04	0.3		
27.06	1	0.08	0.31		
27.07	5.5	2	0.57		
27.08	9.3	0.6	0.75		
27.09	4.2	0.5	0.36		
28.01	12	0.3	0.46		0.3
28.02	1.9	0.08	0.44		3.71
28.03	7.4	0.07	0.29		
28.04	7.5	0.3	0.3		
28.05	6.7	0.1	0.12		1.39
28.06	17	0.6	0.56		
28.07	47	3	>10		
28.08	4.6	0.4	0.37		
28.09	3.1	0.5	0.36		
28.10	20	3	1.85		
28.11	4.2	0.5	0.63		
28.12	3.2	0.3	0.43		0.1
28.13	7.8	0.1	0.55	0.2 9	
28.14	3	0.1	1.44		

28.15	10	0.5	0.69		
28.16	11	0.11	1	0.6	
28.17	15	0.16	1.9		
28.18	9.1	>10	2.03		
28.19	3.7	0.5	0.14		
28.20	4.4	2	0.4		
28.21	1.3	0.1	0.23		
28.22	1.3	0.1	0.3		
28.23	5.9	0.5	0.28		
28.24	2.9	0.2	0.09		2.57
28.25	3.9	0.04	0.13		
28.26	6.6	0.2	0.57		
28.27	2.4	0.3	0.42	0.5	
28.28	5.2	0.4	0.52	1	
28.29	11	0.4	0.36		
28.30	2.3	0.9	0.11		
28.31	7.4	0.06	1.06		
29.01	13	0.7	2.2		0.09
29.02	3.3	0.7	1.1		
29.03	5.6	0.1	0.99		
30.01	22	0.2	0.89		
30.02	12	0.2	0.47		
30.03	19	0.5	0.68		
30.04	25	0.3	0.99		
30.05	8.5	2	0.29		
30.06	15	1	1.03		
30.07	8.8	0.6	0.47		
31.01	30	>10	1.6		
31.02	31	0.28	0.29		0.42
32.01	4.1	0.1	0.29		
32.02	5.9	0.05	0.37		0.12
33.01	2.5	0.08	0.25		
33.02	5.2	0.06	0.25		0.1
34.01	8	0.1	0.37		0.28
34.02	11	0.08	1.17		
34.03	33	0.19	2.25		
34.04	13	>10	1.22		
34.05	51	0.36	5.1		
34.06	14	>10	3		
34.07	27	>10	2.7		
34.08	8.7	>10	1.9		
35.01	6.8	>10	1.43		
35.02	6.1	0.7	0.23		
51.00	8.1	0.01 3	0.19		0.2
52.00	13	0.2	0.41		<0.0 8

CLAIMS

1. A compound of formula I



(I)

wherein

each of R^0, R^1, and R^2 independently is hydrogen, $-S(O)_{0-2}NR_{12}R_{13}$, $-S(O)_{0-2}R_{13}$, $-NR_{12}S(O)_{0-2}R_{13}$ or $-C(O)NR_{12}R_{13}$;

R^3 is $-S(O)_{0-2}R_{13}$ or $-C(O)NR_{12}R_{13}$;

wherein R_{12} is selected from hydrogen and C_{1-6}alkyl; and R_{13} is selected from hydrogen, C_{1-6}alkyl and C_{3-12}cycloalkyl;

R^4 is hydrogen;

each of R^5 and R^6 independently is hydrogen or halogen; and

each of R^7, R^8, R^9, and R^{10} independently is ethoxy, ethyl, propyl, t-butyl, trifluoromethyl, nitrile, cyclobutyloxy, 2,2,2-trifluoroethoxy, isobutyloxy, t-butyloxy, isopropyloxy, methyl-amino-carbonyl, cyclopropyl-methoxy, dimethylamino-propyl-amino, methoxy-ethoxy, $-XR_{11}$, $-C(O)R_{11}$ or $-OXR_{11}$; wherein X is a bond, methylene or ethylene; R_{11} is selected from piperazinyl, piperidinyl, pyrrolidinyl, morpholino, azepanyl and 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl; wherein R_{11} is optionally substituted by 1 to 3 radicals independently selected from methyl, isopropyl, acetyl, acetyl-methyl-amino, 3-dimethylamino-2,2-dimethyl-propylamino, ethyl-methyl-amino-ethoxy, diethyl-amino-ethoxy, amino-carbonyl, ethyl, 2-oxo-pyrrolidin-1-yl, pyrrolidinyl, pyrrolidinyl-methyl, piperidinyl optionally substituted with methyl or ethyl, morpholino, dimethylamino, dimethylamino-propyl-amino, methyl-amino and ethyl-amino;

wherein one of R^7, R^8 and R^9 independently of each other can also be hydrogen;

A is C; or salts thereof.

2. A compound of formula I according to claim 1, wherein

each of R^0 or R^2 independently is hydrogen;

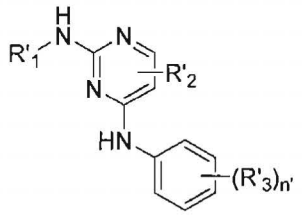
R^1 is hydrogen; and

R^3 is selected from propyl-sulfonyl, ethyl-amino-carbonyl, cyclohexyl-sulfonyl, and isopropyl-sulfonyl.

3. A pharmaceutical composition comprising a compound according to claim 1, as active ingredient together with one or more pharmaceutically acceptable diluents or carriers.

4. A combination comprising a therapeutically effective amount of a compound according to claim 1 and one or more further known drug substances, said further drug substance being useful in the treatment of neoplastic diseases or immune system disorders.

5. A compound of Formula I'



I'

in which:

n' is selected from 1 and 2;

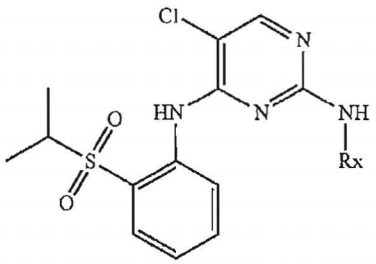
R'_1 is selected from phenyl, pyridinyl, pyrazolyl and pyrimidinyl; wherein the phenyl, pyridinyl, pyrazolyl and pyrimidinyl of R'_1 is substituted by 2 to 3 radicals independently selected from ethoxy, ethyl, propyl, methyl, t-butyl, trifluoromethyl, nitrile, cyclobutyloxy, 2,2,2-trifluoroethoxy, isobutyloxy, t-butyloxy, isopropyloxy, methyl-amino-carbonyl, cyclopropyl-methoxy, dimethylamino-propyl-amino, methoxy-ethoxy, -X'R'$_4$, -C(O)R'$_4$ and –OX'R'$_4$; wherein X' is a bond, methylene or ethylene; R'$_4$ is selected from piperazinyl, piperidinyl, pyrrolidinyl, morpholino, azepanyl and 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl; wherein R'$_4$ is optionally substituted by 1 to 3 radicals independently selected from methyl, isopropyl, acetyl, acetyl-methyl-amino, 3-dimethylamino-2,2-dimethyl-propylamino, ethyl-methyl-amino-ethoxy, diethyl-amino-ethoxy, amino-carbonyl, ethyl, 2-oxo-pyrrolidin-1-yl, pyrrolidinyl, pyrrolidinyl-methyl, piperidinyl optionally substituted with methyl or ethyl, morpholino, dimethylamino, dimethylamino-propyl-amino, methyl-amino and ethyl-amino.

R'_2 is selected from hydrogen and halo;

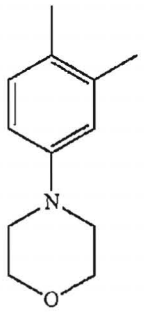
R'_3 is selected from propyl-sulfonyl, ethyl-amino-carbonyl, cyclohexyl-sulfonyl, and isopropyl-sulfonyl;

or the pharmaceutically acceptable salts thereof;

with the proviso that the compound of Formula I' is not



wherein Rx is



6. A pharmaceutical composition comprising a compound according to claim 5, as active ingredient together with one or more pharmaceutically acceptable diluents or carriers.

7. A combination comprising a therapeutically effective amount of a compound according to claim 5 and one or more further known drug substances, said further drug substance being useful in the treatment of neoplastic diseases or immune system disorders.