

(43) International Publication Date
11 September 2009 (11.09.2009)(10) International Publication Number
WO 2009/109991 A2

(51) International Patent Classification:

C07D 401/04 (2006.01) C07D 403/00 (2006.01)
C07D 401/14 (2006.01)

(21) International Application Number:

PCT/IN2009/000057

(22) International Filing Date:

22 January 2009 (22.01.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

160/MUM/2008 23 January 2008 (23.01.2008) IN

(71) Applicant (for all designated States except US): SUN PHARMA ADVANCED RESEARCH COMPANY LTD., [IN/IN]; 17/b, Mahal Industrial Estate, Off Mahakali Caves Road, Andheri - East, Mumbai 400 093 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SENGUPTA, Prabal [IN/IN]; Sun Pharma Advanced Research Company Ltd., Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN). PURI, Chetan Surjitsingh [IN/IN]; Sun Pharma Advanced Research Company Ltd., Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN). CHOKSHI, Hemantkumar [IN/IN]; Sun Pharma Advanced Research Company Ltd., Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN). CHITTURI, Trinadha Rao [IN/IN]; Sun Pharma Advanced Research Company Ltd., Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN). THENNATI, Rajamannar [IN/IN]; Sun Pharma Advanced Research Company Ltd., Nima Compound, Near Pratham Enclave, Tandalja Road, Baroda 390 020 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

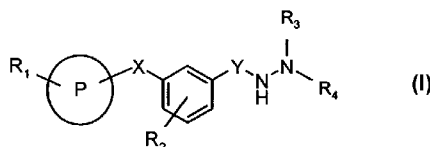
Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: NOVEL HYDRAZIDE CONTAINING TYROSINE KINASE INHIBITORS

(57) Abstract: The present invention relates to compounds of formula (I), and salts thereof, wherein P represents a 5 or 6-membered heteroaryl ring; R₁ is aryl or unsaturated heterocyclyl radical optionally substituted by one or more identical or different radicals R₅.

NOVEL HYDRAZIDE CONTAINING TYROSINE KINASE INHIBITORS

The present invention relates to novel hydrazide containing tyrosine kinase inhibitors, process of preparation thereof, and to the use of the compounds in the preparation of pharmaceutical compositions for the therapeutic treatment of warm-blooded animals.

BACKGROUND OF THE INVENTION

Protein tyrosine kinases are currently recognized as important molecular targets for drug development in the treatment of several disorders, particularly in the treatment of proliferative disorders. Dysregulation of tyrosine kinase activity has emerged as a major mechanism by which cancer cells evade normal physiological constraints on growth, proliferation and survival.

Tyrosine kinases (TKs) are enzymes that catalyze the transfer of phosphate from ATP to tyrosine residues in polypeptides. The human genome contains about 90 TK and 43 TK-like genes, the products of which control of a wide variety of cellular events including cellular proliferation, survival, differentiation, function and motility.

TKs are divided into two main classes viz., receptor TKs and non-receptor TKs. Activities of both types of TKs are under tight control, so that non proliferating cells have very low levels of tyrosyl phosphorylated proteins. Receptor TKs become activated when ligand binds to the extracellular domain, resulting in receptor oligomerization, disruption of the autoinhibitory juxtamembrane interaction, and autophosphorylation of a regulatory tyrosine within the activation loop of the kinase. After activation, autophosphorylation generates binding sites for signaling proteins, recruiting them to the membrane and activating multiple signaling pathways.

The nonreceptor TKs such as c-Abl, are maintained in an inactive state by cellular inhibitor proteins, lipids and through intramolecular autoinhibition. Non-receptor TKs are activated by diverse intracellular signals through dissociation of inhibitors, by recruitment to transmembrane receptors (causing oligomerization and autophosphorylation), and through transphosphorylation by other kinases. TK signaling is terminated in part through the action of tyrosine phosphatases that hydrolyze tyrosyl phosphates and by the induction of inhibitory molecules.

Dysregulation of TK activity arising out of mutation, over-expression or dysfunctional autoregulatory mechanisms has been implicated in many diseases, including cancer. Given the multiple levels of regulation of TKs, it is not surprising that TKs are dysregulated in cancer cells in several ways. A common mechanism of TK activation in hematological cancers is the fusion of a receptor or nonreceptor TK with a partner protein, usually as a consequence of a balanced chromosomal translocation. A primary example of this mechanism is Bcr-Abl, the nonreceptor fusion TK in CML, in which a tetramerization domain in Bcr overcomes autoinhibition of Abl catalytic activity through oligomerization and autophosphorylation. With some receptor TKs, absence of the juxtamembrane inhibitory domain in the fusion protein contributes to activation. A second important mechanism of TK dysregulation is a mutation that disrupts autoregulation of the kinase. Mutations in the Fms-like tyrosine kinase 3 (FLT3) receptor in acute myeloid leukemia (AML) render this TK active in the absence of ligand; in another example, small deletions and point mutations in the kinase domain of epidermal growth factor receptor (EGFR) in a subset of non-small-cell lung cancers increase the sensitivity of the receptor to its ligand and alter receptor signaling. A third mechanism of TK dysregulation is increased or aberrant expression of a receptor TK, its ligand, or both. Examples include overexpression of the receptor TK ErbB2 (HER-2/neu) in breast cancer and overexpression of a mutant form of platelet-derived growth factor (PDGF), a receptor TK ligand, in dermatofibrosarcoma protuberans with t(11;17). Lastly, increased TK activity can result from a decrease in factors that limit TK activity, such as impaired tyrosine phosphatase activity or decreased expression of TK inhibitor proteins. Aberrant TK activation can increase the survival, proliferation, and cytotoxic drug resistance of malignant cells and in tumors it can increase angiogenesis, invasiveness and metastatic potential.

The TK family of enzymes has emerged as an important class of targets for therapeutic intervention. TKs can be inhibited pharmacologically through multiple mechanisms. One of the key focus areas in anti-TK drug discovery is the design and development of small molecules that can directly inhibit the catalytic activity of the kinase by interfering with the binding of ATP or substrates. An important advantage of TK-directed therapy is the possibility to perform pharmacodynamic studies that correlate inhibition of the targeted TK in cancer cells with clinical responses to the drug.

The dysregulated TK in the hematological cancers is Bcr-Abl which has been implicated as the direct cause of CML. Imatinib mesylate (Gleevec®), a 2-phenylaminopyrimidine compound by virtue of its inhibition of several TKs — namely, Abl, Abl-related gene product (ARG), c-Kit, and PDGF receptor (PDGFR) has demonstrated remarkable clinical efficacy in CML. It induces complete hematological and cytogenetic remissions in most patients with chronic-phase, however is much less effective in the accelerated and blast-crisis phases of the disease. It is the first TK inhibitor to be approved as first line monotherapy and has

revolutionized the treatment for CML. Recently it has been shown that imatinib mesylate prevents β -cell apoptosis under conditions of β -cell stress (PNAS, 2008, vol. 105, 18895-18900). This together with the observation that improvements in type II diabetes has been noted in patients on imatinib therapy leads to the hypothesis that kinase inhibitors may prove to be beneficial in the treatment of diabetes. The tyrosine kinase EGFR has been targeted with small molecule inhibitors such as Tarceva[®] and Iressa[®] for the treatment of patients with non-small cell lung carcinoma (NSCLC). Sutent[®] is approved for the treatment of certain tumors through its multi-modal action on the tyrosine kinases including the vascular endothelial growth factor receptor (VEGFR), Kit and PDGFR. Inhibition of other kinases with small molecule inhibitors include the tyrosine kinase FLT3 that is expressed on blasts in most cases of acute myeloid leukemia (AML), the tyrosine kinases FGFR1, FGFR3, c-FMS, JAK and SYK in a range of malignant hematological disorders and ALK, c-Met and RET in a host of solid tumors.

Inhibiting TKs with ATP-competitive kinase inhibitors blocks enzymatic activity of the kinases. Often treatment therapies result in drug resistance over a period. Quite often, drug resistance is largely on account of mutations that occur to prevent the pressures exerted by drug binding. Thus, despite success with Gleevec[®] to treat CML through inhibition of the oncogene *Bcr-abl*, clinical resistance to the drug has been observed. Of the multiple mechanisms of drug resistance, mutations of the Bcr-Abl kinase have been particularly problematic with 50-90% of the resistance to Gleevec[®] arising from mutations in the kinase domain. Over 22 mutations have been reported to date, some of the most common being G250E, Q252H, Y253F/H, E255K/V, T315A/I, F317L/V, M351T, F359V and H396R.

The second generation agents such as nilotinib (Tasigna[®]) and dasatinib (Sprycel[®]), are able to inhibit a large number of clinically relevant mutations. However, neither of these inhibit the T315I mutation (also known as the gatekeeper mutation), although this mutation is the largest singly occurring mutation to the current standard of care for CML viz. Gleevec[®]. Mutation of the gatekeeper residue enables the protein to bind ATP and continue to function. At the same time Gleevec[®] is selectively rejected since it makes use of a hydrophobic pocket close to the ATP binding site, which ATP does not utilize. In fact, almost all small molecule inhibitors that are ATP-competitive utilize this hydrophobic pocket to attain much higher potency over ATP, Gleevec[®] is no exception. It is therefore, not surprising that the gatekeeper and its mutation across numerous kinases is well known since most small molecule inhibitors of kinases are ATP competitive.

c-Kit is a receptor tyrosine kinase expressed on the surface of mast cells, to which stem cell factor (SCF) is a ligand. Aberrant c-Kit signaling is believed to be a mediator of certain autoimmune diseases. Binding of

SCF to the c-Kit receptor mediates various functions of the mast cell. As an important mediator of mast cell function, c-Kit is also thought to play a role in pathologies associated with mast cells.

PDGF (Platelet-derived Growth Factor) is a very commonly occurring growth factor which plays an important role both in normal growth and also in pathological cell proliferation, such as is seen in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. Compounds that can inhibit PDGF receptor (PDGFR) activity are suitable for the treatment of tumor diseases such as gliomas, sarcomas, prostate tumors, tumors of the colon, breast and ovary.

The Src family which consists of at least eight members (Src, Fyn, Lyn, Yes, Lck, Fgr, Hck and Blk) that participate in a variety of signaling pathways represents the major family of cytoplasmic protein tyrosine kinases. The prototypical member of this tyrosine kinase family is Src, which is involved in proliferation and migration responses in many cell types. Src activity has been shown to be elevated in different cancers, e.g. breast, colon, pancreatic and liver tumors. Highly increased Src activity is also associated with metastasis and poor prognosis. Antisense Src message impedes growth of colon tumor cells in nude mice, suggesting that Src inhibitors could slow tumor growth. Furthermore, in addition to its role in cell proliferation, Src also acts in stress response pathways, including the hypoxia response.

Classical tyrosine kinase inhibitors that are currently in clinical use are described in the following patent literature

- **United States patent No. 5521184** (the '184 patent; Indian reference not available): Exemplifies 4-[(Methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate (Imatinib mesylate, Gleevec®)
- **United states patent No. 0167015** (the '015 patent; Indian reference not available): Exemplifies 4-Methyl-*N*-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide (Nilotinib, Tassigna®)
- **United states patent No 6596746** (the '746 patent; Indian reference not available): Exemplifies *N*-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (Dasatinib, Sprycel®)

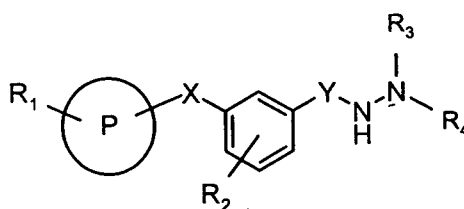
While the second generation TK inhibitors in clinic viz. Tassigna® and Sprycel® have provided additional treatment option to patients who have developed resistance to imatinib, there are certain shortcomings with regard to side effects. These include QT prolongation, myelosuppression, hepatotoxicity, bleeding,

electrolyte abnormalities, fluid retention etc. Hence there is need for newer selective TK inhibitors which are safer and efficacious.

The current invention describes novel hydrazide derivatives of aryl carboxylic or sulfonic acids of formula I which are potent and selective inhibitors of protein tyrosine kinases. The compounds of formula I, described below in more detail, show inhibition of one or more tyrosine kinases, Bcr-Abl and Abl kinase, ARG, kinases from the Src family, especially c-Src kinase, c-Yes, Lck, and Fyn; also kinases of the EGF family, e.g. ErbB2 kinase (HER-2), ErbB3 kinase, ErbB4 kinase; insulin-like growth factor receptor kinase (IGF-1 kinase), especially members of the PDGF-receptor tyrosine kinase family, such as PDGF- α & PDGF- β receptor kinase, JAK-2, CSF-1-receptor kinase, Kit-receptor kinase, Flt-3, Flt-4, FGFR-1, FGFR-3, FGFR-4, c-Met, RON, c-Ret, ALK and VEGF-receptor kinase. In view of their potent and selective TK inhibitory activities, the compounds could be used for the treatment of diseases especially related to aberrant or excessive activity of such types of kinases.

SUMMARY OF THE INVENTION

The present invention relates to compounds of formula I, and salts thereof,



Formula I

wherein

P represents a 5 or 6-membered heteroaryl ring;

R₁ is aryl or unsaturated heterocyclyl radical optionally substituted by one or more identical or different radicals R₅;

R₂ is selected from the group consisting of hydrogen, halogen, lower alkyl, haloalkyl, -O-lower alkyl, -S-lower alkyl, -S(O)-lower alkyl, -SO₂-lower alkyl, -SO₂NH₂, -SO₂NH-(lower alkyl), -SO₂N(lower alkyl)₂, -NH₂, -NH(lower alkyl), -N(lower alkyl)₂, -CN and -NO₂;

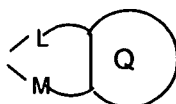
R₃ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, arylalkyl and a heterocyclyl radical;

R₄ represents the radical R₃ or a radical -Z-R₆, wherein Z is selected from the group consisting of C=O, C=S, SO₂, C(O)NR₃, and C=N(OR₇) and R₆ is selected from the group consisting of C₁-C₁₀-alkyl, aryl and

heterocyclyl or optionally in each case can have one or more hydrogen atoms replaced with one or more identical or different radicals R_5 ;

R_7 represents H or the radical R_6 ;

or R_3 & R_4 together with the nitrogen atom to which they are attached can form a cyclic system as represented by formula IA



Formula IA

wherein L & M independently or together represent C=O, C=S, SO₂, CH₂, CH(lower alkyl), C(lower alkyl)₂, and Q is an aryl or heterocyclyl system, optionally substituted with one or more identical or different radicals R_5 .

R_5 is selected from the group consisting of halogen, -OH, -CN, -NO₂, -lower-alkyl, -cycloalkyl, -O-lower alkyl, -O-cycloalkyl, -O-aryl, -O-heterocyclyl, -lower alkyl-O-lower alkyl, -O-lower alkyl-O-lower alkyl, -O-lower alkyl-NH(lower alkyl), -O-lower alkyl-N(lower alkyl)₂, -O-lower alkyl-(heterocyclyl), -C(O)-lower alkyl, -COOH, -C(O)NH₂, -C(O)NH-lower alkyl, -C(O)N(lower alkyl)₂, -C(O)O-lower alkyl, -lower halo-alkyl, -lower alkenyl, -lower alkynyl, -OC(O)-NH₂, -OC(O)-NH(lower alkyl), -OC(O)-N(lower alkyl)₂, -NH₂, -NH(lower alkyl), -N(lower alkyl)₂, -NH-SO₂-lower alkyl, -N(lower alkyl)-SO₂-lower alkyl, -NH-C(O)-(lower alkyl), -N(lower alkyl)-C(O)-(lower alkyl), -NH-C(O)O-lower alkyl, -N(lower alkyl)-C(O)O-lower alkyl, -NH-C(O)-NH₂, -NH-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-N(lower alkyl)₂, -NH-C(O)-NH-SO₂-lower alkyl, -N(lower alkyl)-C(O)-NHSO₂-lower alkyl, -N(lower alkyl)-C(O)-N(lower alkyl)-SO₂-lower alkyl, -S-lower alkyl, -S(O)-lower alkyl, -SO₂-lower alkyl, -S-aryl, -S(O)-aryl, SO₂-aryl, -S-heterocyclyl, -SO-heterocyclyl, -SO₂-heterocyclyl, -SO₂NH₂, -SO₂NH-(lower alkyl), -SO₂N(lower alkyl)₂, heterocyclyl and an aryl group in each case are unsubstituted or mono- or polysubstituted;

X is O, S or NH;

Y is C=O, C=S, SO₂;

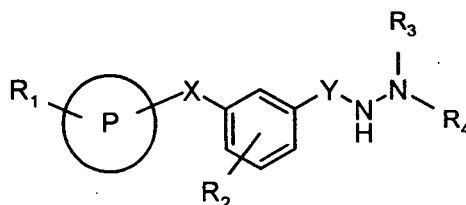
with the proviso that when P is a 5 membered heteroaryl ring then it does not contain more than 2 nitrogen atoms.

The invention also provides a pharmaceutical composition comprising a compound of formula I, as defined above, and a pharmaceutically acceptable carrier.

Additionally provided is a method of treating a condition associated with at least one tyrosine kinase enzyme comprising administering to a mammalian species in need of such treatment an effective amount of a compound of formula I, as defined above.

DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula I, and salts thereof,



Formula I

wherein

P represents a 5 or 6-membered heteroaryl ring;

R₁ is aryl or unsaturated heterocyclyl radical optionally substituted by one or more identical or different radicals R₅;

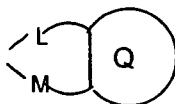
R₂ is selected from the group consisting of hydrogen, halogen, lower alkyl, haloalkyl, -O-lower alkyl, -S-lower alkyl, -S(O)-lower alkyl, -SO₂-lower alkyl, -SO₂NH₂, -SO₂NH-(lower alkyl), -SO₂N(lower alkyl)₂, -NH₂, -NH(lower alkyl), -N(lower alkyl)₂, -CN and -NO₂;

R₃ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, arylalkyl and a heterocyclyl radical;

R₄ represents the radical R₃ or a radical -Z-R₆, wherein Z is selected from the group consisting of C=O, C=S, SO₂, C(O)NR₃ and C=N(OR₇) and R₆ is selected from the group consisting of C₁-C₁₀-alkyl, aryl and heterocyclyl or optionally in each case can have one or more hydrogen atoms replaced with one or more identical or different radicals R₅;

R₇ represents H or the radical R₆;

or R₃ & R₄ together with the nitrogen atom to which they are attached can form a cyclic system as represented by formula IA

**Formula IA**

wherein L & M independently or together represent C=O, C=S, SO₂, CH₂, CH(lower alkyl), C(lower alkyl)₂, and Q is an aryl or heterocyclyl system, optionally substituted with one or more identical or different radicals R₅.

R₅ is selected from the group consisting of halogen, -OH, -CN, -NO₂, -lower-alkyl, -cycloalkyl, -O-lower alkyl, -O-cycloalkyl, -O-aryl, -O-heterocyclyl, -lower alkyl-O-lower alkyl, -O-lower alkyl-O-lower alkyl, -O-lower alkyl-NH(lower alkyl), -O-lower alkyl-N(lower alkyl)₂, -O-lower alkyl-(heterocyclyl), -C(O)-lower alkyl, -COOH, -C(O)NH₂, -C(O)NH-lower alkyl, -C(O)N(lower alkyl)₂, -C(O)O-lower alkyl, -lower halo-alkyl, -lower alkenyl, -lower alkynyl, -OC(O)-NH₂, -OC(O)-NH(lower alkyl), -OC(O)-N(lower alkyl)₂, -NH₂, -NH(lower alkyl), -N(lower alkyl)₂, -NH-SO₂-lower alkyl, -N(lower alkyl)-SO₂-lower alkyl, -NH-C(O)-(lower alkyl), -N(lower alkyl)-C(O)-(lower alkyl), -NH-C(O)O-lower alkyl, -N(lower alkyl)-C(O)O-lower alkyl, -NH-C(O)-NH₂, -NH-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-N(lower alkyl)₂, -NH-C(O)-NH-SO₂-lower alkyl, -N(lower alkyl)-C(O)-NHSO₂-lower alkyl, -N(lower alkyl)-C(O)-N(lower alkyl)-SO₂-lower alkyl, -S-lower alkyl, -S(O)-lower alkyl, -SO₂-lower alkyl, -S-aryl, -S(O)-aryl, SO₂-aryl, -S-heterocyclyl, -SO-heterocyclyl, -SO₂-heterocyclyl, -SO₂NH₂, -SO₂NH-(lower alkyl), -SO₂N(lower alkyl)₂, heterocyclyl and an aryl group in each case are unsubstituted or mono- or polysubstituted;

X is O, S or NH;

Y is C=O, C=S, SO₂;

with the proviso that when P is a 5 membered heteroaryl ring then it does not contain more than 2 nitrogen atoms.

The invention also provides a pharmaceutical composition comprising a compound of formula I, as defined above, and a pharmaceutically acceptable carrier.

Additionally provided is a method of treating a condition associated with at least one tyrosine kinase enzyme comprising administering to a mammalian species in need of such treatment an effective amount of a compound of formula I, as defined above.

The following are definitions of the terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

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

The prefix "lower" denotes a radical having upto and including a maximum of 7 carbon atoms, the radicals in question being either linear or branched with a single or multiple branching.

As used herein 'alkyl' can be straight-chain or branched hydrocarbon, and can optionally contain one or more unsaturations. Optionally, in each case one or more hydrogen atoms of the alkyl may be replaced by halogen, -OH, -O-lower alkyl, -NH₂, -N(lower alkyl), -N(lower alkyl)₂, -NH(lower alkyl)-OC(O)-lower alkyl, -OC(O)-lower alkyl, -(C₃-C₁₃)-cycloalkyl, -SH, -S-lower alkyl, substituted or unsubstituted aryl or heterocyclyl radical.

As used herein alkyl 'containing one or more unsaturations' is to be understood as meaning 'alkenyl' and/or 'alkynyl'. Examples of alkyl groups include methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 1-pentyl, 3-pentyl, 2-octyl and the like. Examples of alkenyl groups include ethenyl, propenyl, 1-butenyl, (Z)-2-butenyl, (E)-3-methylbut-2-enyl, (E)-2,4-pentadienyl, (Z)-3-heptenyl and the like. Exemplary alkynyl groups include ethynyl, propynyl, 1-butyne, 2-butyne, 4-methyl-2-pentyne, 2,4-hexadienyl and the like.

As used herein 'cycloalkyl' is to be understood as meaning monocyclic, bicyclic, tricyclic and polycyclic ring systems such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl and the like. The term 'cycloalkyl' as used herein can optionally contain one or more unsaturations and having substitutions for e.g. halogen, -OH, -O-lower alkyl, -OC(O)-lower alkyl, substituted or unsubstituted aryl or heterocyclic radical.

As used herein 'halogen' or 'halo group' refers to -F, -Cl, -Br, or -I.

As used herein aryl is to be understood as meaning aromatic ring systems such as phenyl, naphthyl, anthracenyl, phenanthryl, preferably aryl is phenyl.

As used herein 'heterocyclyl' or 'heterocyclic ring' is to be understood as meaning unsubstituted or substituted stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic ring system, which in addition to carbon also contain hetero atoms, such as, for example, nitrogen, oxygen or sulfur. These ring systems may be unsaturated, or wholly or partially saturated. This definition also includes "heteroaryl" systems, i.e. unsaturated heterocyclyl ring systems in which the heterocyclyl rings are aromatic.

The term "unsaturated heterocyclyl" represents an unsubstituted or substituted stable 5 to 7-membered monocyclic or 7 to 10-membered bicyclic heterocyclic ring which has one or more double bonds and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur. The term "unsaturated heterocyclyl radical" also encompasses "heteroaryl" radicals.

The heterocyclyl systems containing nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quarternized. Furthermore, the heterocyclyl radical can be fused with an aryl or a heteroaryl ring. In substituted heterocyclic systems, the substituents likely to be present are halogen, -OH, -CN, -NO₂, -lower alkyl -cycloalkyl, -O-lower alkyl, -O-cycloalkyl, -O-aryl, -O-heterocyclyl, -lower alkyl-O-lower alkyl, -O-lower alkyl-O-lower alkyl, -O-lower alkyl-NH(lower alkyl), -O-lower alkyl-N(lower alkyl)₂, -O-lower alkyl-(heterocyclyl), -C(O)-lower alkyl, -COOH, -C(O)NH₂, -C(O)NH-lower alkyl, -C(O)N(lower alkyl)₂, -C(O)O-lower alkyl, -lower halo alkyl, -lower alkenyl, -lower alkynyl, -OC(O)-NH₂, -OC(O)-NH(lower alkyl), -OC(O)-N(lower alkyl)₂, -NH₂, -NH(lower alkyl), -N(lower alkyl)₂, -NH-SO₂-lower alkyl, N(lower alkyl)-SO₂-lower alkyl, -NH-C(O)-(lower alkyl) -N(lower alkyl)-C(O)-(lower alkyl), -NH-C(O)O-lower alkyl, -N(lower alkyl)-C(O)O-lower alkyl, -NH-C(O)-NH₂, -NH-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-N(lower alkyl)₂, -NH-C(O)-NH-SO₂-lower alkyl, -N(lower alkyl)-C(O)-NH-SO₂-lower alkyl, -N(lower alkyl)-C(O)-N(lower alkyl)-SO₂-lower alkyl, -S-lower alkyl, -S(O)-lower alkyl, -SO₂-lower alkyl, -S-aryl, -S(O)-aryl, SO₂-aryl, -S-heterocyclyl, -SO-heterocyclyl, -SO₂-heterocyclyl, -SO₂NH₂, -SO₂NH-(lower alkyl), -SO₂N(lower alkyl)₂, heterocyclyl and an aryl group in each case are unsubstituted or mono- or polysubstituted.

Examples of some heterocyclyl radicals that are wholly saturated are 2-piperazinyl, 2- or 3-pyrrolidinyl, 2-oxo-5-pyrrolidinyl, piperidinyl, N-benzyl-4-piperidinyl, N-lower alkyl-4-piperidinyl, N-lower alkyl-piperazinyl, morpholinyl, e.g. 2- or 3-morpholinyl, 2-oxo-1*H*-azepin-3-yl, 2-tetrahydrofuranyl, or 2-methyl-1,3-dioxolan-2-yl, quinuclidinyl etc.

Examples of heteroaryl rings systems include monocyclic rings such as 2- or 3- pyrrolyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 3- or 4-pyridinyl, 2-, 4- or 5-imidazolyl, 3-, 4- or -5-pyrazolyl, 2-, 4- or -5-pyrimidinyl, 2-pyrazinyl, 3- or 4-pyridazinyl, 4*H*-1,2,4-triazolyl, 1*H*-1,2,3-triazolyl, 2*H*-1,2,3-triazolyl, 1*H*-tetrazolyl, 2*H*-tetrazolyl, oxazolyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, thiazolyl, 3-, 4- or 5-isothiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl etc.; fused ring systems such as 3-, 4- or 7-indolyl, isoindolyl, indoliziny, benzimidazolyl, 2-, 3-, 4- or 8-quinolinyl, 1-, 3- or 4-isoquinolinyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-*b*]pyridazinyl, etc.), etc.; benzothiazolyl, benzothiadiazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, 1-[(C₁-C₆)-alkyl]benzimidazolyl, 1-, 3- or 4-isoquinolinyl, 1-phthalazinyl, 3- or 4-cinnolinyl, 2- or 4-quinazolinyl, 2-pyrazinyl, 2-quinoxaliny, 2-quinoxaliny etc.

Examples of unsaturated heterocyclyl radicals within the scope of the invention include, besides the heteroaryl ring systems described as above, other partially saturated heterocyclic systems such as pyrrolinyl, imidazoliny, oxazoliny, 3,4-dihydroquinolinyl, 5-oxo-2,5-dihydrofuran-3yl, 2,3,6,7-tetrahydro-1*H*-azepin-4-yl, 3,6-dihydro-2*H*-thiopyran-4-yl, 2*H*-thiochromen-3-yl, 2*H*-benzo[1,4]thiazine-3-yl etc.

The term lower haloalkyl means at least one halogen, as defined herein, appended to the lower alkyl group, as defined herein. Representative examples of lower haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl.

With the groups of preferred compounds of formula I and *N*-oxides thereof mentioned hereinafter, definitions of substituents from the general definitions mentioned hereinbefore may reasonably be used, e.g. to replace more general definitions with more specific definitions or especially with definitions characterized as being preferred.

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

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

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.

Salts of compounds of formula I are the physiologically acceptable salts. Physiologically acceptable salts are particularly suitable for medical applications, due to their greater solubility in water compared with the starting or base compounds. Suitable physiologically acceptable acid addition salts of the compounds of the

invention may be salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, and the like or of organic acids such as, for example, acetic acid, benzenesulfonic acid, methanesulfonic acid, benzoic acid, citric acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartartic acid, amino acids, such as glutamic acid or aspartic acid, and the like. Examples of suitable physiologically acceptable basic salts are ammonium salts, or suitable organic amines, such as tertiary monoamines, e.g. triethylamine or tris(2-hydroxyethyl)amine etc., alkali metal salts such as sodium salts and potassium salts and alkaline earth metal salts such as magnesium salts and calcium salts.

When a basic group and an acid group are present in the same molecule, a compound of formula I may also form internal salts.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, e.g. picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed 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 and that can be used as intermediates, e.g. 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.

In one embodiment, the preferred compounds of formula I are selected from the compounds wherein P is a 5 or 6 membered heteroaryl and R₁ represents a heteroaryl ring. The heteroaryl ring may contain one or more hetero atoms selected from O, S and N. Preferably the heteroaryl is a nitrogen and/ or sulfur containing heteroaryl. Preferably the heteroaryl ring P is selected from the group consisting of pyrimidine and thiazole.

Preferably the heteroaryl radical R₁ is selected from the group consisting of pyridinyl, pyrazinyl, thiophenyl, furanyl, pyrrolyl, quinolinyl, pyrimidinyl, thiazolyl, which may be substituted or unsubstituted.

In one preferred embodiment P is pyrimidine and R₁ is 2-pyridinyl.

In one embodiment the compounds of formula I are selected from the compounds wherein X represents NH, and Y represents C=O.

In one preferred embodiment P is pyrimidine, X= NH, Y = C=O and R₁ is pyridine.

In one embodiment the compounds of formula I are selected from the compounds wherein R₂ represents lower alkyl.

In one embodiment the compounds of formula I are selected from the compounds wherein R₃ represents hydrogen.

In one embodiment the compounds of formula I are selected from the compounds wherein R₄ represents C(O)-aryl.

In one embodiment the compounds of formula I are selected from the compounds wherein R₄ represents SO₂-aryl.

In one embodiment the compounds of formula I are selected from the compounds wherein Y represents C=O and R₄ represents C(O)-aryl.

In one embodiment the compounds of formula I are selected from the compounds wherein Y represents C=O and R₄ represents SO₂-aryl.

In one embodiment the compounds of formula I wherein R₃ & R₄ together form a cyclic system represented as in the moiety IA; L & M represent C=O.

In one embodiment the present invention provides a compound of formula I and an N-oxide derivative thereof.

In one embodiment the present invention provides a compound of formula I and physiologically acceptable salt, thereof.

The compounds of the present invention can be exemplified by the following non-limiting examples:

Example No.	Chemical Name
I.1	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-fluorobenzoyl)hydrazide
I.2	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -4-[[4-methyl-1-piperazinyl)methyl]benzoyl]hydrazide
I.3	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[[3-methyl-5-(4-methyl-imidazol-1-yl)]benzoyl]hydrazide
I.4	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(5- <i>tert</i> -butyl-1-phenyl-1 <i>H</i> -pyrazol-3-carbonyl)hydrazide

Example No.	Chemical Name
I.5	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5- <i>tert</i> -butyl-1-(pyridin-2-yl)-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.6	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[(4-trifluoromethoxy)benzoyl]hydrazide
I.7	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[3,5-bis(trifluoromethyl)benzoyl]hydrazide
I.8	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-hydroxybenzoyl)hydrazide
I.9	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5-(4-chlorophenyl)-1-(4-sulfonamido)phenyl-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.10	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5-(4-methoxyphenyl)-1-(4-sulfonamido)phenyl-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.11	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5- <i>tert</i> -butyl-1-(4-fluorophenyl)-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.12	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5- <i>tert</i> -butyl-1-(2,4-dichlorophenyl)-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.13	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,4-dichlorophenyl)-5-(pyridin-2-yl)-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.14	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5- <i>tert</i> -butyl-1-(3-trifluoromethyl)phenyl-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.15	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(4-fluorophenyl)-5-(pyridin-2-yl)-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.16	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1,5-bis(pyridin-2-yl)-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.17	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5-(pyridin-2-yl)-1-(4-sulfonamido)phenyl-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.18	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.19	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[2-(trifluoromethyl)benzoyl]hydrazide
I.20	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(pyridin-3-carbonyl)hydrazide
I.21	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(5-methylpyrazin-2-carbonyl)hydrazide
I.22	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(4-fluorobenzoyl)hydrazide
I.23	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(1 <i>H</i> -indol-5-carbonyl)hydrazide
I.24	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(pyridin-2-carbonyl)hydrazide
I.25	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -1-(1 <i>H</i> -benzimidazol-5-carbonyl)hydrazide
I.26	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[(3-trifluoromethyl)benzoyl]hydrazide
I.27	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[(<i>E</i>)-3-phenylacryloyl]hydrazide
I.28	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[(<i>E</i>)-3-(3-trifluoromethyl)phenylacryloyl]hydrazide

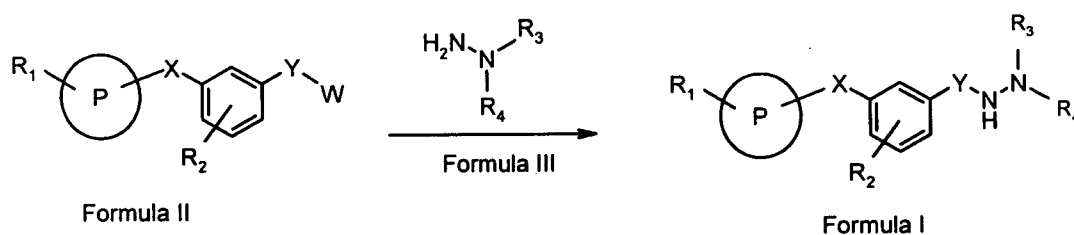
Example No.	Chemical Name
I.29	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5- <i>tert</i> -butyl-1-(4-chlorophenyl)-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.30	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(4-sulfonamido)phenyl-5-(4-trifluoromethyl)phenyl-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.31	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[(<i>E</i>)-3-(3-hydroxyphenyl)acryloyl]hydrazide
I.32	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[5- <i>tert</i> -butyl-1-(4-sulfonamido)phenyl-1 <i>H</i> -pyrazol-3-carbonyl]hydrazide
I.33	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(3,3,3-trifluoropropanoyl)hydrazide
I.34	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzoyl)hydrazide
I.35	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[2-(3-trifluoromethyl)phenylacetyl]hydrazide
I.36	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,5-difluorobenzoyl)hydrazide
I.37	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(3,5-difluorobenzoyl)hydrazide
I.38	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[3,5-bis(trifluoromethyl)benzoyl]hydrazide
I.39	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[4-(trifluoromethyl)benzoyl]hydrazide
I.40	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[(<i>E</i>)-3-fluoro-5-(trifluoromethyl)acryloyl]hydrazide
I.41	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-chlorobenzoyl)hydrazide
I.42	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-difluorobenzoyl)hydrazide
I.43	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,3-dichlorobenzoyl)hydrazide
I.44	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4-dichlorobenzoyl)hydrazide
I.45	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[(<i>E</i>)-3-(2,6-dichlorophenyl)acryloyl]hydrazide
I.46	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[2,6-bis(trifluoromethyl)benzoyl]hydrazide
I.47	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-bromobenzoyl)hydrazide
I.48	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-6-methylbenzoyl)hydrazide
I.49	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-6-fluorobenzoyl)hydrazide
I.50	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-nitrobenzoyl)hydrazide
I.51	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(3-chlorothiophene-2-carbonyl)hydrazide
I.52	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzenesulfonyl)hydrazide

Example No.	Chemical Name
I.53	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(4-chlorobenzoyl)hydrazide
I.54	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(5-chlorothiophene-2-carbonyl)hydrazide
I.55	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trimethoxybenzoyl)hydrazide
I.56	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trifluorobenzoyl)hydrazide
I.57	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trichlorobenzoyl)hydrazide
I.58	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[[[2-(trifluoromethyl)phenyl]amino]carbonyl]hydrazide
I.59	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[[[4- <i>tert</i> -butylphenyl]amino]carbonyl]hydrazide
I.60	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[[[2,6-dichlorophenyl]amino]carbonyl]hydrazide
I.61	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzoyl)hydrazide
I.62	4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzoyl)hydrazide
I.63	4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-fluorobenzoyl)hydrazide
I.64	4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trichlorobenzoyl)hydrazide
I.65	4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzoyl)hydrazide
I.66	4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-fluorobenzoyl)hydrazide
I.67	4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trichlorobenzoyl)hydrazide
I.68	4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-6-methylbenzoyl)hydrazide
I.69	4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-chloro-6-methylbenzoyl)hydrazide
I.70	4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzoyl)hydrazide
I.71	4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzoyl)hydrazide
I.72	4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trichlorobenzoyl)hydrazide
I.73	4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-chloro-6-methylbenzoyl)hydrazide
I.74	4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trichlorobenzoyl)hydrazide
I.75	4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,6-dichlorobenzoyl)hydrazide
I.76	4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2-chloro-6-methylbenzoyl)hydrazide

Example No.	Chemical Name
I.77	4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trifluorobenzoyl)hydrazide
I.78	4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -(2,4,6-trichlorobenzoyl)hydrazide
I.79	4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichlorophenyl)]hydrazide
I.80	4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-6-methylbenzoyl)]hydrazide
I.81	4-Methyl-3-[[4-(2-thiazolyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-6-methylbenzoyl)]hydrazide
I.82	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichloro-pyridin-4-yl)]hydrazide
I.83	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,4,6-trimethylphenyl)]hydrazide
I.84	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(4-methanesulfonylbenzoyl)]hydrazide
I.85	4-Methyl-3-[[4-(6-chloro-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichlorobenzoyl)]hydrazide
I.86	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-pyridin-3-yl)benzoyl]hydrazide
I.87	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichloro-pyridin-3-yl)benzoyl]hydrazide
I.88	4-Methyl-3-[[4-(6-methoxy-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichlorobenzoyl)]hydrazide
I.89	4-Methyl-3-[[4-(3-dimethylamino)phenyl]-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichlorobenzoyl)]hydrazide.
I.90	4-Methyl-3-[[4-(6-methyl-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-iodobenzoyl)]hydrazide
I.91	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-4-methyl-pyridin-3-yl)benzoyl]hydrazide
I.92	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-5-methoxybenzoyl)]hydrazide
I.93	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -benzoylhydrazide
I.94	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,4,6-triisopropylbenzoyl)]hydrazide
I.95	4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,4,6-trimethylbenzoyl)]hydrazide
I.96	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-amino-6-methylbenzoyl)]hydrazide
I.97	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-4-fluorobenzoyl)]hydrazide
I.98	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-[2-chloro-4-(4-methyl-1-piperazinyl)benzoyl]]hydrazide
I.99	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-[2-chloro-4-(5-methyl-3-imidazolyl)benzoyl]]hydrazide
I.100	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-iodo-6-methylbenzoyl)]hydrazide
I.101	4-Methyl-3-[[4-(2-methyl-5-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-

Example No.	Chemical Name
	iodobenzoyl)]hydrazide
I.102	4-Methyl-3-[[4-(3-quinoliny)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-6-methylbenzoyl)]hydrazide
I.103	4-Methyl-3-[[4-(5-pyrimidinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-iodobenzoyl)]hydrazide
I.104	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-hydroxy-6-methylbenzoyl)]hydrazide
I.105	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-fluoro-6-iodobenzoyl)]hydrazide
I.106	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-4-iodobenzoyl)]hydrazide
I.107	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -benzylhydrazide
I.108	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(3-trifluoromethyl-4-methylbenzoyl)]hydrazide
I.109	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichloro-4-methoxybenzoyl)]hydrazide
I.110	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2,6-dichlorobenzenesulfonyl)]hydrazide
I.111	4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenesulfonic acid <i>N'</i> -[1-(2,4,6-trichlorobenzoyl)]hydrazide
I.112	4-Methyl-3-[[4-(3-pyridinyl)-2-thiazolyl]amino]benzoic acid <i>N'</i> -[1-(2,4,6-trichlorobenzoyl)]hydrazide
I.113	4-Methyl-3-[[4-(5-pyrimidinyl)-2-pyrimidinyl]amino]benzoic acid <i>N'</i> -[1-(2-chloro-6-methylbenzoyl)]hydrazide
IA.1	<i>N</i> -(4-Hydroxy-1,3-dioxo-isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide
IA.2	<i>N</i> -(1,3-Dioxo-isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide
IA.3	<i>N</i> -(4-Chloro-1-oxo-1 <i>H</i> -isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide

The present invention provides a process for the preparation of compounds of formula I by reacting the compounds of formula II with compounds of formula III, Scheme 1,



Scheme 1

wherein P, R₁, R₂, R₃, R₄, X and Y are as defined for compound of formula I, and W is a leaving group. Preferably the reaction is carried out in the presence of an inert base and/or a suitable catalyst in an inert

solvent. The compound of formula II, which is in activated form, can alternatively be generated *in situ* from the corresponding acid ($W=OH$) and then condensed with the compound of formula III to generate the compound of formula I.

A derivative of the formula II in activated form (i.e. $-YW$) is especially an acid halide, a reactive ester, a reactive anhydride or a reactive cyclic amide.

Formula II wherein $Y-W$ is an acid halide group, can be obtained, for example, by treatment of the corresponding acid ($W=OH$) with a halogenating agent such as thionyl chloride, phosphorus pentachloride or oxalyl chloride.

Reactive esters of formula II are especially for example vinyl esters obtainable, for example, by transesterification of a corresponding ester with vinyl acetate, carbamoylvinyl esters or by treatment of the with a lower alkoxyacetylene. Other active esters are of the amidino type, such as N,N' -disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with a suitable N,N' -disubstituted carbodiimide, for example, N,N' -dicyclohexylcarbodiimide), or N,N' -disubstituted amidino esters (obtainable, for example, treatment of the corresponding acid with N,N' -disubstituted cyanamide), suitable aryl esters, especially phenyl esters suitably substituted by electron-attracting substituents (obtainable, for example, by treatment of the corresponding acid with a suitably substituted phenol, for example, 4-nitrophenol, 2,4,5-trichlorophenol, or 2,3,4,5,6-pentachloro-phenol in the presence of a condensation agent, such as N,N' -dicyclohexylcarbodiimide). Other suitable active esters include cyanomethyl esters (obtainable, for example, by treatment of the corresponding acid with chloroacetonitrile in the presence of a base), thio esters, especially unsubstituted or substituted, for example nitro-substituted, phenylthio esters (obtainable, for example, by treatment of the corresponding acid with unsubstituted or substituted, for example nitro-substituted, thiophenols, *inter alia* by the anhydride or carbodiimide method), amino or amido esters (obtainable, for example, by treatment of the corresponding acid with an N -hydroxyamino or N -hydroxyamido compound, for example, N -hydroxysuccinimide, N -hydroxypiperidine, N -hydroxyphthalimide or 1-hydroxybenzotriazole, for example by the anhydride or carbodiimide method).

Other activated forms of formula II of may be anhydrides. Anhydrides may be with carbonic acid semiderivatives, such as corresponding esters, for example carbonic acid lower alkyl semiesters (obtainable, for example, by treatment of the corresponding acid with haloformic, such as chloroformic, acid); lower alkyl esters or with a 1-lower alkoxy-carbonyl-2-lower alkoxy-1,2-dihydroquinoline, for example 1-lower alkoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline; anhydrides with dihalogenated, especially dichlorinated phosphoric acid (obtainable, for example, by treatment of the corresponding acid with phosphorus

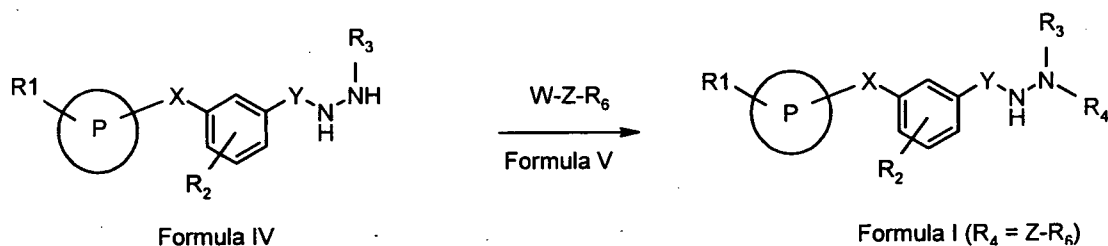
oxychloride), or anhydrides with organic acids, such as mixed anhydrides with organic carboxylic acids (obtainable, for example, by treatment of the corresponding acid with an unsubstituted or substituted lower alkane acid halide, for example, pivalic acid chloride or trifluoroacetyl chloride). Anhydrides may also be with organic sulfonic acids (obtainable, for example, by treatment of a salt, such as an alkali metal salt, of the corresponding acid, with a suitable organic sulfonic acid halide, such as lower alkane- or aryl-, for example methane- or *p*-toluenesulfonyl chloride), or with organic phosphonic acids (obtainable, for example, by treatment of the corresponding acid with a suitable organic phosphonic anhydride or phosphonic cyanide).

Suitable cyclic amides are especially amides with five-membered diazacycles of aromatic character, such as with imidazoles (obtainable, for example, by treatment of the corresponding acid with *N,N'*-carbonyldiimidazole; imidazolid method), or pyrazoles, for example 3,5-dimethylpyrazole.

Formula II in activated form is preferably generated *in situ* from the corresponding acid ($W=OH$). For example, *N,N'*-disubstituted amidino esters can be formed *in situ* by reacting a mixture of the acid of formula II ($W=OH$) and the compound of formula III in the presence of a suitable condensating agent for example *N,N'*-dicyclohexylcarbodiimide. Reactive mixed anhydrides of the acid of formula IV may also be generated with an organic phosphonic acid *in situ* by reaction with propylphosphonic anhydride or diethylcyanophosphonate in the presence of suitable base for e.g. triethylamine or 4-(*N,N*-dimethylamino)pyridine.

The reaction can be carried out in a manner known *per se*, the reaction conditions being dependent especially on how the acid group of formula II has been activated, usually in the presence of a suitable solvent or diluent or of a mixture thereof and, if necessary, in the presence of a condensation agent. Customary condensation agents are, for example, carbodiimides such as *N,N'*-diethyl-, *N,N'*-diisopropyl-, *N,N'*-dicyclohexyl- or *N*-ethyl-*N'*-(3-diethylaminopropyl)-carbodiimide; suitable carbonyl compounds, for example carbonyldiimidazole, or 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium 3'-sulfonate and 2-*tert*-butyl-5-methyl-isoxazolium perchlorate, or a suitable acylamino compound, for example, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline. The bases normally used for aiding the condensation are either inorganic bases such as sodium or potassium carbonate, or organic bases, such as pyridine, triethylamine, *N,N'*-diisopropyl-*N*-ethylamine or 4-(*N,N*-dimethylamino)pyridine.

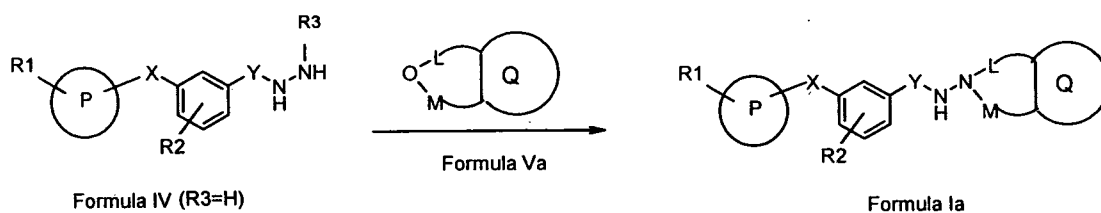
Alternatively, the preparation of compounds of formula I in the present invention can be performed by reacting compounds of formula IV with the compounds of formula V, Scheme 2, using similar condensation methods as described above (for Scheme 1).



Scheme 2

wherein P , R_1 , R_2 , R_3 , R_4 , R_6 , W , X , Y & Z are as previously defined.

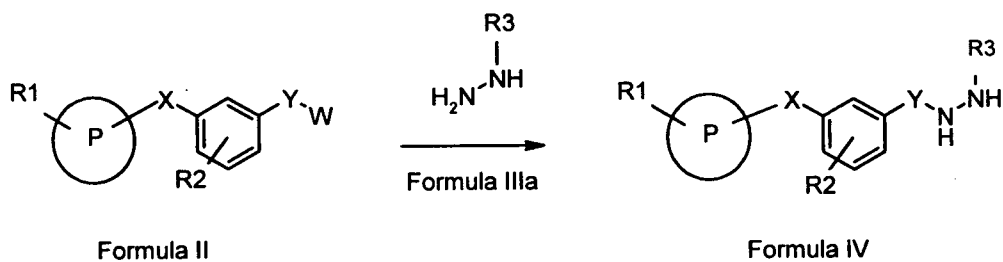
Scheme 2a represents a reaction sequence for the preparation of compounds of formula Ia in which the moiety of formula IA is incorporated into formula I. These compounds are prepared by direct condensation of compounds of formula IV with compounds of formula Va (O represents oxygen).



Scheme 2a

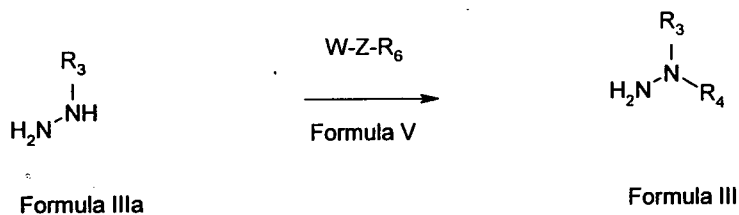
wherein L , M , P , Q , R_1 , R_2 , R_3 , X and Y are as defined for a compound of formula I.

Compounds of formula IV can be prepared from compounds of formula II and hydrazine of formula IIIa, scheme 3, utilizing the coupling procedures as described for scheme 1, *vide supra*.



Scheme 3

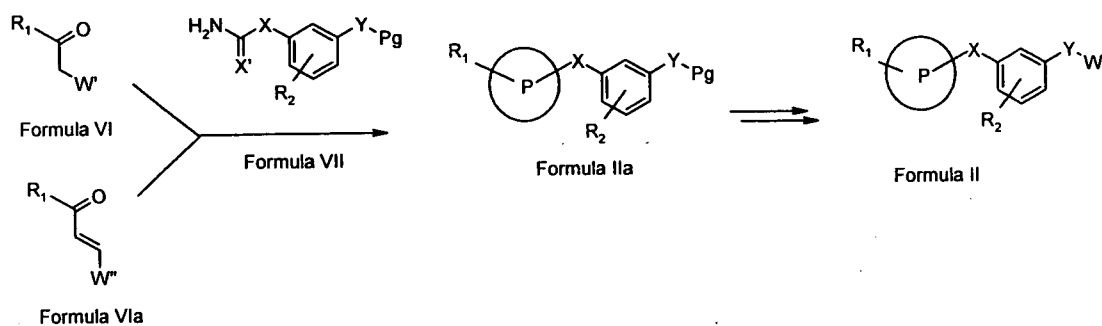
In a similar manner the compound of formula III can be prepared from formula IIIa and formula V, Scheme 4.



Scheme 4

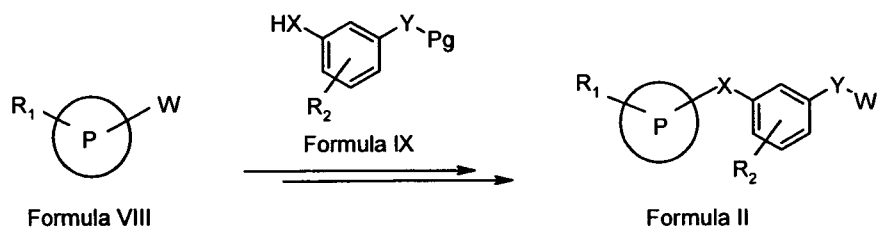
Where the above starting compounds II, IIIa and IV contain functional groups that may interfere with the coupling reaction, they are preferably protected using suitable protecting groups that can be conveniently removed later.

The compounds of formula II can be prepared by methods well reported in literature. For example, as illustrated in Scheme 5, when ring P represents a five membered heterocyclic ring such as thiazole, imidazole or an oxazole, reaction of the corresponding thiourea ($\text{X}'=\text{S}$ & $\text{X}=\text{NH}$), guanidine ($\text{X}=\text{X}'=\text{NH}$) or urea ($\text{X}'=\text{O}$ & $\text{X}=\text{NH}$) of formula VII (Pg represents a suitable protecting group) with a ketone of formula VI (wherein W' is a halogen or a suitable leaving group such as a tosylate, mesylate, triflate, trifluoroacetate etc), followed by deprotection affords compound of formula II. Similarly, condensation of compound of formula VII ($\text{X}=\text{X}'=\text{NH}$) with a compound of formula VIa (wherein W'' is a suitable leaving group such as *N,N*-dialkylamino, -O-lower alkyl, -S-lower alkyl or a halogen) affords formula II wherein P represents a six membered heterocyclic ring for example a pyrimidin-2-yl moiety.



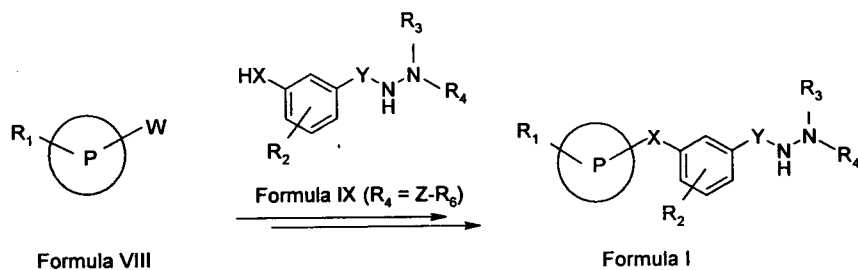
Scheme 5

Alternatively, compound of formula II can also be prepared by *ipso* substitution of the leaving group in compound of formula VIII with a compound of formula IX and subsequent deprotection, wherein P, Pg, R₁, R₂, W, X, Y are as defined above, Scheme 5a



Scheme 5a

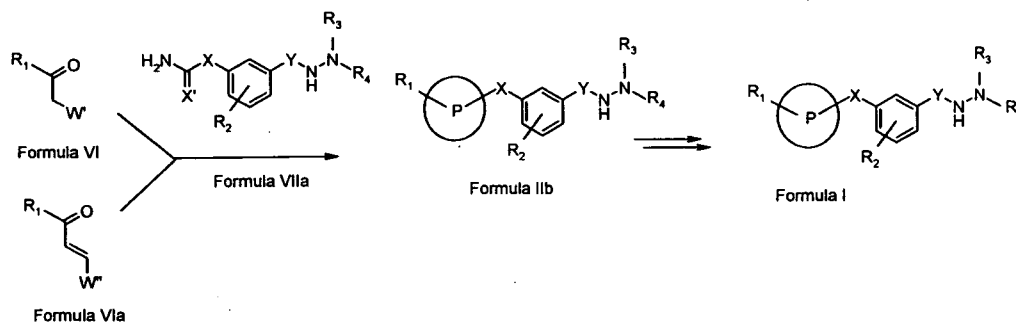
The above method can also be utilized for the synthesis of compounds of formula I as shown in Scheme 6, i.e. by *ipso* substitution at the leaving group in compound of formula VIII with a preformed hydrazide derivative of formula IX when R₄ represents Z-R₆; and wherein P, R₁, R₂, R₃, R₄, R₆, W, X, Y & Z are as previously defined.



Scheme 6

wherein P, R₁, R₂, R₃, R₄, R₆, W, X, Y & Z are as previously defined.

An alternate approach to the compounds of formula I utilizes the construction of the P ring in the final step using a compound of formula VIIa as shown in Scheme 6a.



Scheme 6a

wherein P, R₁, R₂, R₃, R₄, W, W', W'', X and Y are as previously defined.

If so desired, an obtainable compound of formula I is converted into another compound of formula I or a *N*-oxide thereof, a free compound of formula I is converted into a salt, an obtainable salt of a compound of formula I is converted into the free compound or another salt, and/or a mixture of isomeric compounds of formula I is separated into the individual isomers.

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

Stereoisomeric mixtures can be separated into their corresponding individual stereoisomers by means of suitable well known separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution and other known procedures. This separation may be conducted either in a compound of formula I itself or at the level of a precursor compound. Enantiomers may be resolved by well known techniques for example through the formation of diastereomeric salts with enantiomer-pure chiral acid or a base; by derivatization with a suitable chiral derivatizing agent and separation such as by fractional crystallization, fractional distillation or by kinetic resolution such as enzymatic or chemical hydrolysis of the derivatized. Alternatively, the enantiomers may be resolved of by means of chromatography, for example by chiral HPLC, using a chiral chromatographic stationary phase.

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

Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

At all reaction stages, isomeric mixtures that occur can be separated into their individual isomers, e.g. diastereomers or enantiomers, or into any mixtures of isomers, e.g. racemates or diastereomeric mixtures.

In the preferred embodiment, a compound of formula I is prepared according to or in analogy to the processes and process steps defined in the Examples.

The compounds of formula I, including their salts, are also obtainable in the form of hydrates.

The compounds of formula I including their salts and *N*-oxides thereof wherever applicable, have valuable pharmacological properties, as described hereinbefore and hereinafter.

In one embodiment the present invention provides a method for treatment of disorders dependent on tyrosine kinases comprising administering to a mammal in need of such treatment an effective amount of compound of formula I or salt thereof.

A compound of formula I including their salts or an *N*-oxide thereof inhibits to varying degrees receptor and non receptor tyrosine kinases all of which play a role in growth regulation and transformation in mammalian cells, including human cells. The receptor tyrosine kinase may be kinases of the EGF family, e.g. ErbB2 kinase (HER-2), ErbB3 kinase, ErbB4 kinase; insulin-like growth factor receptor kinase (IGF-1 kinase), especially members of the PDGF-receptor tyrosine kinase family, such as PDGF- α & PDGF- β receptor kinase, JAK-2, CSF-1-receptor kinase, Kit-receptor kinase, Flt-3, Flt-4, FGFR-1, FGFR-3, FGFR-4, c-Met, RON, c-Ret, ALK and VEGF-receptor kinase. The non receptor tyrosine kinase may be kinases such as e.g. Bcr-Abl and Abl kinase, ARG, kinases from the Src family, especially c-Src kinase, c-Yes, Lck, and Fyn.

Especially the compounds of the present invention have been found to inhibit Abl kinase, PDGF- α & PDGF- β kinases, Kit-receptor kinase, Src kinase, Flt-3, Lyn, Fyn, Hck, Lck and Yes.

The compounds of the present invention can be used to treat disorders dependent on tyrosine kinases especially CML, CLL, ALL, AML, myelodysplastic syndrome, melanoma, germ cell tumors, GIST, NSCLC, mastocytosis, neuroblastoma, glioblastoma, astrocytoma, hepatocellular carcinoma, renal cell cancer, breast cancer and other solid tumors, diabetes remission.

On the basis of these studies, a compound of formula I according to the invention shows therapeutic efficacy especially against disorders dependent on TK, especially in proliferative diseases.

The present invention relates furthermore to a method for the treatment of a neoplastic disease which responds to an inhibition of a protein kinase activity, which comprises administering a compound of formula I or a *N*-oxide or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above for formula I, in a quantity effective against said disease, to a warm-blooded animal requiring such treatment.

In particular the invention relates to a method for the treatment of proliferative disorders especially leukemia, irrespective of etiology of the disorder, which respond to inhibition of the aforementioned tyrosine kinases, particularly the Abl tyrosine kinase and one or more of its several mutated forms. The treatment comprises administering a compound of formula I or an *N*-oxide or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above for formula I, in a quantity effective against the particular disorder, to a warm-blooded animal requiring such treatment.

A compound of formula I can be administered alone or in combination with one or more other therapeutic agents, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic agents being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic agents. A compound of formula I can, besides or in addition, be administered especially for cancer therapy, such as leukemia or tumor therapy, in combination with chemotherapy, radiotherapy, immunotherapy, surgical intervention or a combination of these. Long-term therapy is equally possible as adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, e.g. in patients at risk.

Therapeutic agents for possible combination are especially another tyrosine kinase inhibitors such as imatinib, nilotinib, dasatinib, sorafenib, lapatinib, sunitinib, gefitinib, erlotinib, one or more cytostatic or cytotoxic compounds, e.g. a chemotherapeutic agent or several selected from the group comprising indarubicin, cytarabine, interferon, hydroxyurea, busulfan, DNA alkylating/ intercalating agent, an inhibitor of polyamine biosynthesis, antifolate agent, inhibitor of microtubule depolymerization, topoisomerase I & II inhibitor, proteasome inhibitor, an inhibitor of protein kinase, especially of serine/threonine protein kinase, such as protein kinase C, or of tyrosine protein kinase, such as epidermal growth factor receptor tyrosine

kinase, a cytokine, a negative growth regulator, such as TGF- β or IFN- β , an aromatase inhibitor, classical cytostatic, and an inhibitor of the interaction of an SH2 domain with a phosphorylated protein.

A compound according to the invention is not only for the (prophylactic and preferably therapeutic) management of humans, but also for the treatment of other warm-blooded animals, e.g. of commercially useful animals, e.g. rodents, such as mice, rabbits or rats, or guinea pigs. Such a compound may also be used as a reference standard in the test systems described above to permit a comparison with other compounds.

In general, the invention relates also to the use of a compound of formula I or an *N*-oxide thereof for the inhibition of tyrosine kinase activity, either *in vitro* or *in vivo*.

The present invention relates also to pharmaceutical compositions that comprise a compound of formula I or an *N*-oxide thereof as active ingredient and that can be used especially in the treatment of diseases mentioned at the beginning. Compositions for enteral administration, such as nasal, buccal, rectal or especially oral administration, and for parental administration, such as intravenous, intramuscular or subcutaneous administration, to warm-blooded animals, especially humans, are especially preferred. The compositions comprise the active ingredient alone or preferably together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the disease to be treated and upon the species, its age, weight and individual condition, the individual pharmacokinetic data and the mode of administration.

The present invention relates especially to pharmaceutical compositions that comprise a compound of formula I, a tautomer, an *N*-oxide or a pharmaceutically acceptable salt, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable carrier.

The invention relates also to pharmaceutical compositions for use in a method for the prophylactic or especially therapeutic management of the human or animal body, to a process for the preparation thereof (especially in the form of compositions for the treatment of tumors) and to a method of treating diseases, especially those mentioned hereinabove.

The invention relates also to processes and to the use of compounds of formula I or *N*-oxides thereof for the preparation of pharmaceutical preparations which comprise compounds of formula I or *N*-oxides thereof as active component (active ingredient).

In the preferred embodiment, a pharmaceutical preparation is suitable for administration to warm-blooded animals, especially humans or commercially useful mammals suffering from disease responsive to inhibition of tyrosine kinase(s), for example inhibition of the Abl tyrosine kinase for chronic myelogenous leukemia (CML), and comprises an effective quantity of a compound of formula I or *N*-oxides thereof for the inhibition of the Bcr-Abl fusion protein, or a pharmaceutically acceptable salt thereof, if salt-forming groups are present, together with at least one pharmaceutically acceptable carrier.

A pharmaceutical composition for the prophylactic or especially therapeutic management of neoplastic and other proliferative diseases of a warm-blooded animal, especially a human or a commercially useful mammal requiring such treatment, especially suffering from such a disease, comprising as active ingredient in a quantity that is prophylactically or especially therapeutically active against the said diseases a novel compound of formula I or *N*-oxides thereof, is likewise preferred.

The pharmaceutical compositions comprise from approximately 1% to a approximately 95% active ingredient, single-dose administration forms comprising in the preferred embodiment from approximately 20% to approximately 90% active ingredient and forms that are not of single-dose type comprising in the preferred embodiment from approximately 5% to approximately 20% active ingredient. Unit dose forms are, for example, coated and uncoated tablets, ampoules, vials, suppositories or capsules. Further dosage forms are, for example, ointments, creams, pastes, foams, tinctures, sprays, etc. Examples are capsules containing from about 0.005 g to about 1.0 g active ingredient.

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 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 or solubilizers.

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 of a long-chained fatty acid having from 8 to 22 carbon atoms. 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, especially glycol and glycerol.

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, cellulose preparations, and/or calcium phosphates, also binders such as starches, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators. Additional excipients are especially flow conditioners and lubricants.

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.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, also soft sealed capsules consisting of gelatin and a plasticizer. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, binders, and/or glidants, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, to which stabilizers and detergents 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.

For parental 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 parental administration by the addition of suitable solvents. Solutions that are used, for example, for parental administration can also be employed as infusion solutions.

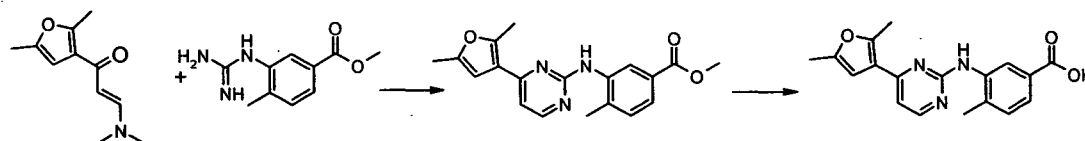
The invention relates likewise to a process or a method for the treatment of one of the pathological conditions mentioned hereinabove, especially a disease which responds to an inhibition of a tyrosine kinase, especially a corresponding neoplastic disease. The compounds of formula I or *N*-oxides thereof can be administrated as such or especially in the form of pharmaceutical compositions, prophylactically or therapeutically, preferably in an amount effective against the said disease, to a warm-blooded animal, for example a human, requiring such treatment. In the case of an individual having a bodyweight of about 70 kg the daily dose administrated is from approximately 0.005 g to approximately 5 g, preferably from approximately 0.05 g to approximately 1.0 g, of a compound of a compound of the present investigation.

The present invention relates especially also to the use of a compound of formula I or *N*-oxides thereof, or a pharmaceutically acceptable salt thereof, as such or in the form of a pharmaceutical formulation with at least one pharmaceutically acceptable carrier for the therapeutic and also prophylactic management of one or more of the diseases mentioned hereinabove, preferably a disease which responds to an inhibition of a tyrosine kinase, especially a neoplastic disease.

The preferred dose quantity, composition and preparation of pharmaceutical dosage forms (medicines) which are to be used in each case are described above.

The following examples serve to illustrate the invention without limiting the invention in its scope. The methods of preparing some of the starting compounds used in the examples are described as reference examples.

EXAMPLES

Reference Example 1**4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid**

A mixture of 3-guanidino-4-methylbenzoic acid methyl ester (3g, 0.011mol), 3-dimethylamino-1-(2,5-dimethylfuran-3-yl)-propenone (2.14g, 0.011mol) and powdered sodium hydroxide (0.532g, 0.013mol) in 2-propanol (25ml) was heated under reflux for 68hrs. The solvent was evaporated off under reduced pressure and the residue filtered off to give a residue. Purification by column chromatography with 5% methanol in dichloromethane to gave 2.1g of 4-methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid methyl ester which was used as such in the next step.

An aqueous solution of sodium hydroxide (0.622g, 0.015mol) and water, 2ml) was added to a mixture of the methyl ester obtained as above in tetrahydrofuran-methanol (1:1, 60ml) and stirred at 60°C for 6hrs and then concentrated *in vacuo*. Water (10ml) was added to the mixture and acidified with citric acid until pH was about 4.0-4.5. The solid obtained was filtered, washed successively with water and diethyl ether and dried at room temperature to get 4-methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid.

¹H NMR (400 MHz in DMSO-d₆), δ 2.29 (s, 3H), 2.35 (s, 3H), 2.47 (s, 3H), 6.60 (s, 1H), 6.98 (d, J = 5.2 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.66 (dd, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1H), 8.22 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H), 8.85 (s, 1H).

Similarly were prepared the following acids from the appropriate 3-dimethylamino-1-aryl-2-propen-1-ones and 3-guanidino-4-substituted benzoic acid esters

4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid

4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid

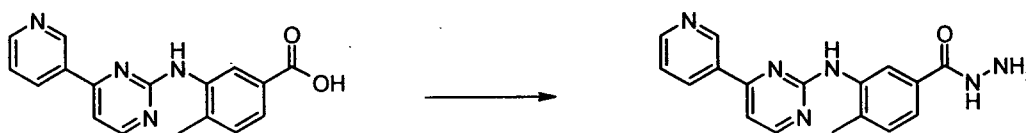
4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid

4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid

4-Methyl-3-[[4-(2-thiazolyl)-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[4-(6-chloro-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[4-(6-methoxy-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[[4-(3-dimethylamino)phenyl]-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[4-(6-methyl-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[4-(2-methyl-5-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[4-(3-quinolinyl)-2-pyrimidinyl]amino]benzoic acid
 4-Methyl-3-[[4-(5-pyrimidinyl)-2-pyrimidinyl]amino]benzoic acid

Reference Example 2

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide



A mixture of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid (5.0g, 0.016mol), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (4.69g, 0.024mol) and 1-hydroxybenzotriazole (3.3g, 0.024mol) in *N,N*-dimethylformamide (75ml) was stirred at room temperature for 1hr. Hydrazine hydrate (1.52ml, 0.048mol) was then added and the mixture stirred for another 2hrs. Concentration and trituration of the residue with water produced a solid product which was filtered, washed with water and finally dried in *vacuo* to get the hydrazide as a pale yellow solid.

¹H NMR (400 MHz in CDCl₃), δ 2.34 (s, 3H), 4.57 (s, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 5.1 Hz, 1H), 7.57-7.61 (m, 2H), 8.15 (s, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.57 (d, *J* = 5.2 Hz, 1H), 8.74 (d, *J* = 3.5 Hz, 1H), 9.13 (s, 1H), 9.31 (d, *J* = 1.5 Hz, 1H), 9.76 (s, 1H).

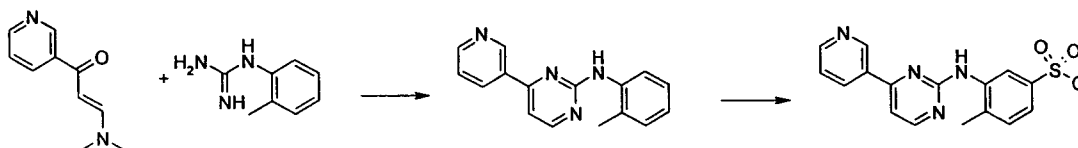
Similarly were prepared the following hydrazides from the appropriate aryl carboxylic acids:

4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide

4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(2-thiazolyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(6-chloro-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(6-methoxy-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[[4-(3-dimethylamino)phenyl]-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(6-methyl-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(2-methyl-5-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(3-quinolinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide
 4-Methyl-3-[[4-(5-pyrimidinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide

Reference Example 3

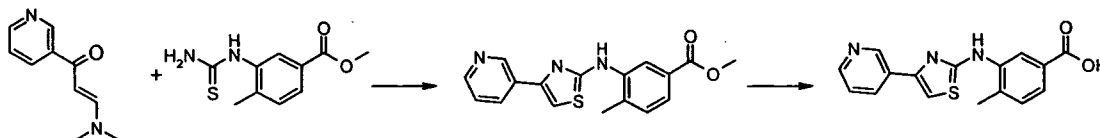
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenesulfonyl chloride



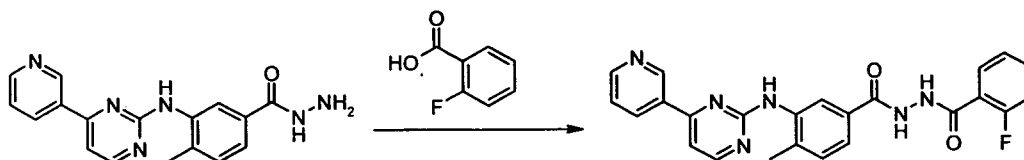
A mixture of *N*-2-tolyl guanidine (16.0g, 0.075mol), 3-dimethylamino-1-(pyridin-3-yl)-propanone (13.2g, 0.075mol) and potassium carbonate (12.5g, 0.090mol) in *N,N*-dimethylacetamide (40ml) was heated to 111°C for 12hrs. Water was added to the reaction mixture and stirred at room temperature for 15min. The solid product obtained was filtered, washed with water and dried to give 10.8g of (4-(3-pyridinyl)-2-pyrimidinyl)-2-tolylamine which was used as such in the next step.

Chlorosulfonic acid (2.5ml) was added at 0°C to the (4-(3-pyridinyl)-2-pyrimidinyl)-2-tolylamine obtained from the previous step. The thick reaction mixture was stirred for 90 min, quenched with chilled sodium bicarbonate solution and extracted with ethyl acetate. The organic layer is washed with sodium bicarbonate solution and concentrated to gave a pale yellow solid of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzene-sulfonyl chloride.

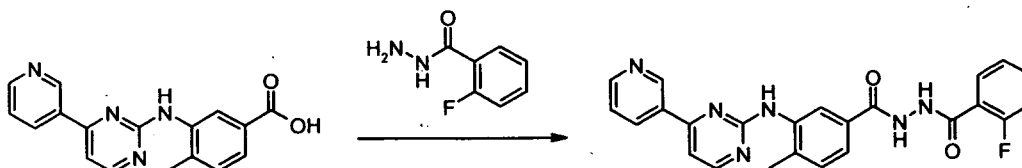
¹H NMR (400 MHz in DMSO-*d*₆), δ 2.31 (s, 3H), 7.58-7.61 (m, 3H), 7.65 (d, *J* = 5.1 Hz, 1H), 8.20 (dd, *J*₁ = 7.8 Hz, *J*₂ = 5.8 Hz, 1H), 8.69 (d, *J* = 5.1 Hz, 1H), 9.05 (d, *J* = 5.2 Hz, 1H), 9.10 (d, *J* = 8.1 Hz, 1H), 9.34 (s, 1H), 9.43 (s, 1H).

Reference Example 4**4-Methyl-3-[[4-(3-pyridinyl)-2-thiazolyl]amino]benzoic acid**

The preparation was carried out as per reference Example 1 by using 3-thioureido-4-methylbenzoic acid methyl ester in place of 3-guanidino-4-methylbenzoic acid methyl ester.

Example 1.1**4-Methyl-3-[[4-(3-pyridin-yl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-fluorobenzoyl)hydrazide****Method A:**

A mixture of 2-fluorobenzoyl hydrazide (1.05g, 0.0047mol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.34g, 0.007mol) and 1-hydroxybenzotriazole (0.95g, 0.007mol) in *N,N*-dimethylformamide (15ml) was stirred at room temperature for 0.5hrs. 4-Methyl-3-[[4-(3-pyridin-yl)-2-pyrimidinyl]amino]benzoic acid hydrazide (1.5g, 0.0047mol) was added, the reaction mixture stirred for further 12hrs, then quenched with water and extracted with ethyl acetate. The organic extract was concentrated, degassed and the residue purified by flash chromatography on silica gel (eluant 3% methanol in dichloromethane) to obtain the title compound.

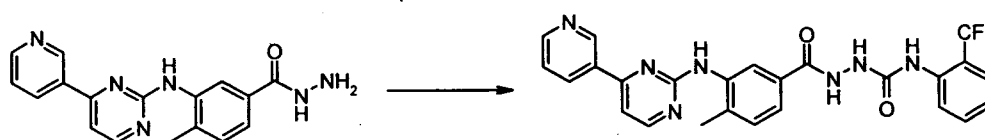
Method B

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-fluorobenzoyl)hydrazide was also prepared by the reaction of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid with 2-fluorobenzoic acid hydrazide. The coupling was performed in a manner similar to that described in Example 2.

The compounds I.2 to I.57; I.62 to I.106, I.108 to I.110 & I.113 were prepared in a manner similar to example I.1, by following either method A or method B, using the appropriate substrates (compound of formulas II & IIIa for method A; compound of formula IV & V for method B).

Example I.58

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[[[2-(trifluoromethyl)phenyl]amino]carbonyl]hydrazide

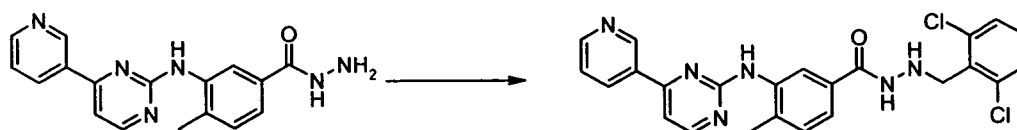


To a solution of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide (0.1g, 0.3mmol) in dimethylformamide (10ml) was added 2-(trifluoromethyl)phenylisocyanate (0.1ml, 0.6mmol) and the mixture stirred at ambient temperature for 3hrs. The mixture was concentrated under *vacuo*, and 2-propanol (20ml) was added to the residue and re-concentrated to half of the volume. Diisopropylether (10ml) was then added, stirred and the solid obtained was filtered and dried to obtain a pale yellow solid.

The compounds I.59 & I.60 were prepared in an analogous manner using appropriate isocyanates.

Example I.61

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzyl)hydrazide



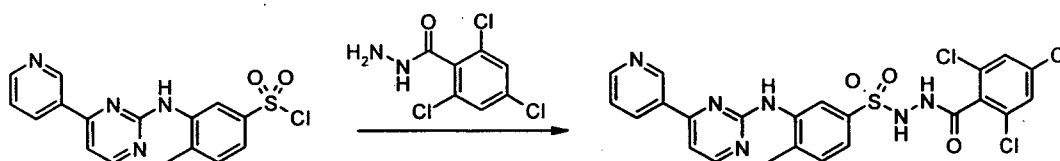
A mixture of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide (0.15g, 0.46mmol), anhydrous potassium carbonate (0.077g, 0.5mmol), 2,6-dichlorobenzyl chloride (0.091g, 0.4mmol) and

sodium iodide (0.04mmol) in dimethylformamide (5ml) was stirred for 12hrs at ambient temperature. The mixture was concentrated under *vacuo*, the residue treated with saturated sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. Concentration, degassing and trituration of the residue sequentially with methanol, dichloromethane-methanol (2:8), and finally with ether gave the product as a white solid.

The compound I.107 was prepared in an analogous manner using appropriate substrate.

Example I.111

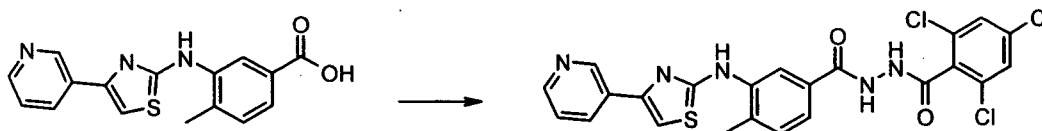
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenesulfonic acid *N'*-(2,4,6-trichlorobenzoyl)hydrazide



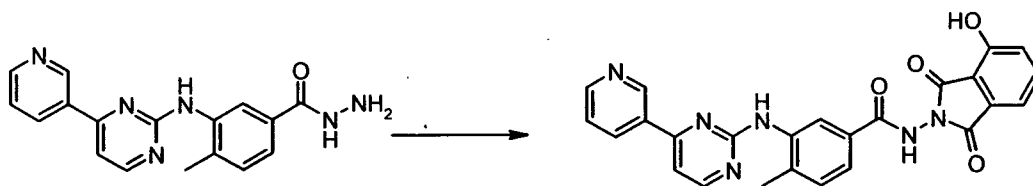
A mixture of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenesulfonyl chloride (122mg, 0.038mmol), 2,4,6-trichlorobenzoyl hydrazide (100mg, 0.038mmol) and triethylamine (0.08ml, 0.057mmol) in *N,N*-dimethylformamide (5ml) was stirred at 70°C for 3hrs. The reaction mixture was concentrated under *vacuo*, water and ethyl acetate was added, stirred and the organic layer separated. Concentration of the organic extract and purification of the residue by flash column chromatography on silica gel (eluant 4% methanol in dichloromethane) gave the product as an almost white solid.

Example I.112

4-Methyl-3-[[4-(3-pyridinyl)-2-thiazolyl]amino]benzoic acid *N'*-(2,4,6-trichlorobenzoyl)hydrazide

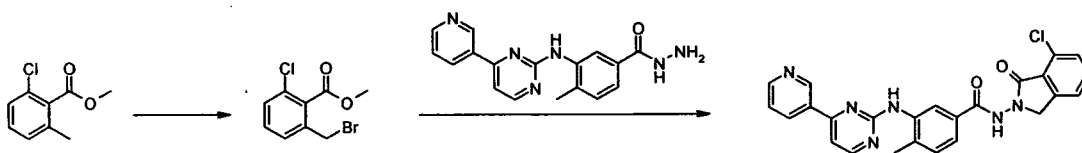


The preparation of this compound was similar to Example I.1, 4-methyl-3-[[4-(3-pyridinyl)-2-thiazolyl]amino]benzoic acid (Reference Example 4) was used in place of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid.

Example IA.1***N*-(4-hydroxy-1,3-dioxo-isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide**

A mixture of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide (0.1g, 0.3mmol) and 3-hydroxyphthalic anhydride (0.05g, 0.3mmol) was refluxed in glacial acetic acid (3ml) for 0.5hr. The mixture was cooled to room temperature; the solid product was filtered, washed successively with methanol and ether to obtain the product as an off-white solid.

Compound IA.2 was prepared in the same manner using phthalic anhydride in the place of 3-hydroxyphthalic anhydride.

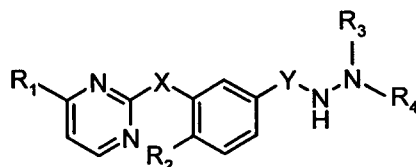
Example IA.3***N*-(4-chloro-1-oxo-2,3-dihydro-isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide**

A mixture of *N*-bromosuccinimide (0.44g, 0.24mmol), methyl 2-chloro-6-methylbenzoate (0.42g, 0.22mmol) in carbon tetrachloride (10ml) and catalytic amount of benzoyl peroxide (22mg) was refluxed for 5hrs. The reaction mixture was diluted with dichloromethane, washed successively with water and brine, dried and concentrated to dryness. The residue was purified by flash chromatography on silica gel (eluant 2-4% ethyl acetate in hexane) to get 2-chloro-6-bromomethylbenzoate as a yellow liquid.

A mixture of 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid hydrazide (122mg, 0.00038mol), methyl 2-chloro-6-bromomethylbenzoate (100mg, 0.038mmol) and triethylamine (0.08ml, 0.057mmol) in *N,N*-dimethylformamide (5ml) was stirred at 110°C for 3hrs. The reaction mixture was

concentrated, water and ethyl acetate was added, stirred and the organic layer separated. Concentration and purification of the residue by flash column chromatography on silica gel (eluant 4% methanol in dichloromethane) gave the product as a pale yellow solid.

Table 1 illustrates the chemical structures wherein the ring P in compounds of formula I is pyrimidine

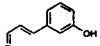
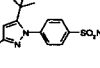
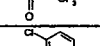
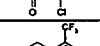
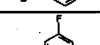
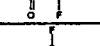
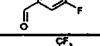
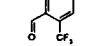
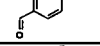
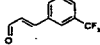
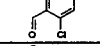
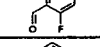
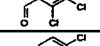
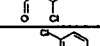
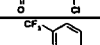
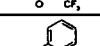
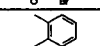
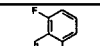
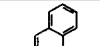
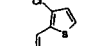
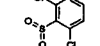
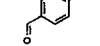


Formula I (wherein P represents Pyrimidine)

Table 1

No.	R ₁	X	R ₂	Y	R ₃	R ₄
I.1	3-Pyridinyl	NH	CH ₃	C=O	H	
I.2	3-Pyridinyl	NH	CH ₃	C=O	H	
I.3	3-Pyridinyl	NH	CH ₃	C=O	H	
I.4	3-Pyridinyl	NH	CH ₃	C=O	H	
I.5	3-Pyridinyl	NH	CH ₃	C=O	H	
I.6	3-Pyridinyl	NH	CH ₃	C=O	H	
I.7	3-Pyridinyl	NH	CH ₃	C=O	H	
I.8	3-Pyridinyl	NH	CH ₃	C=O	H	
I.9	3-Pyridinyl	NH	CH ₃	C=O	H	
I.10	3-Pyridinyl	NH	CH ₃	C=O	H	
I.11	3-Pyridinyl	NH	CH ₃	C=O	H	

No.	R ₁	X	R ₂	Y	R ₃	R ₄
I.12	3-Pyridinyl	NH	CH ₃	C=O	H	
I.13	3-Pyridinyl	NH	CH ₃	C=O	H	
I.14	3-Pyridinyl	NH	CH ₃	C=O	H	
I.15	3-Pyridinyl	NH	CH ₃	C=O	H	
I.16	3-Pyridinyl	NH	CH ₃	C=O	H	
I.17	3-Pyridinyl	NH	CH ₃	C=O	H	
I.18	3-Pyridinyl	NH	CH ₃	C=O	H	
I.19	3-Pyridinyl	NH	CH ₃	C=O	H	
I.20	3-Pyridinyl	NH	CH ₃	C=O	H	
I.21	3-Pyridinyl	NH	CH ₃	C=O	H	
I.22	3-Pyridinyl	NH	CH ₃	C=O	H	
I.23	3-Pyridinyl	NH	CH ₃	C=O	H	
I.24	3-Pyridinyl	NH	CH ₃	C=O	H	
I.25	3-Pyridinyl	NH	CH ₃	C=O	H	
I.26	3-Pyridinyl	NH	CH ₃	C=O	H	
I.27	3-Pyridinyl	NH	CH ₃	C=O	H	
I.28	3-Pyridinyl	NH	CH ₃	C=O	H	
I.29	3-Pyridinyl	NH	CH ₃	C=O	H	
I.30	3-Pyridinyl	NH	CH ₃	C=O	H	

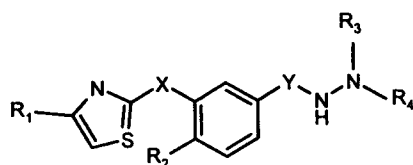
No.	R ₁	X	R ₂	Y	R ₃	R ₄
I.31	3-Pyridinyl	NH	CH ₃	C=O	H	
I.32	3-Pyridinyl	NH	CH ₃	C=O	H	
I.33	3-Pyridinyl	NH	CH ₃	C=O	H	
I.34	3-Pyridinyl	NH	CH ₃	C=O	H	
I.35	3-Pyridinyl	NH	CH ₃	C=O	H	
I.36	3-Pyridinyl	NH	CH ₃	C=O	H	
I.37	3-Pyridinyl	NH	CH ₃	C=O	H	
I.38	3-Pyridinyl	NH	CH ₃	C=O	H	
I.39	3-Pyridinyl	NH	CH ₃	C=O	H	
I.40	3-Pyridinyl	NH	CH ₃	C=O	H	
I.41	3-Pyridinyl	NH	CH ₃	C=O	H	
I.42	3-Pyridinyl	NH	CH ₃	C=O	H	
I.43	3-Pyridinyl	NH	CH ₃	C=O	H	
I.44	3-Pyridinyl	NH	CH ₃	C=O	H	
I.45	3-Pyridinyl	NH	CH ₃	C=O	H	
I.46	3-Pyridinyl	NH	CH ₃	C=O	H	
I.47	3-Pyridinyl	NH	CH ₃	C=O	H	
I.48	3-Pyridinyl	NH	CH ₃	C=O	H	
I.49	3-Pyridinyl	NH	CH ₃	C=O	H	
I.50	3-Pyridinyl	NH	CH ₃	C=O	H	
I.51	3-Pyridinyl	NH	CH ₃	C=O	H	
I.52	3-Pyridinyl	NH	CH ₃	C=O	H	
I.53	3-Pyridinyl	NH	CH ₃	C=O	H	

No.	R ₁	X	R ₂	Y	R ₃	R ₄
I.54	3-Pyridinyl	NH	CH ₃	C=O	H	
I.55	3-Pyridinyl	NH	CH ₃	C=O	H	
I.56	3-Pyridinyl	NH	CH ₃	C=O	H	
I.57	3-Pyridinyl	NH	CH ₃	C=O	H	
I.58	3-Pyridinyl	NH	CH ₃	C=O	H	
I.59	3-Pyridinyl	NH	CH ₃	C=O	H	
I.60	3-Pyridinyl	NH	CH ₃	C=O	H	
I.61	3-Pyridinyl	NH	CH ₃	C=O	H	
I.62	3-Pyridinyl	NH	OCH ₃	C=O	H	
I.63	3-Pyridinyl	NH	OCH ₃	C=O	H	
I.64	3-Pyridinyl	NH	OCH ₃	C=O	H	
I.65	3-Pyridinyl	NH	Cl	C=O	H	
I.66	3-Pyridinyl	NH	Cl	C=O	H	
I.67	3-Pyridinyl	NH	Cl	C=O	H	
I.68	3-Pyridinyl	NH	Cl	C=O	H	
I.69	2-Pyrazinyl	NH	methyl	C=O	H	
I.70	2-Pyrazinyl	NH	methyl	C=O	H	
I.71	2-Thiophenyl	NH	methyl	C=O	H	
I.72	2-Thiophenyl	NH	methyl	C=O	H	
I.73	2-Thiophenyl	NH	methyl	C=O	H	
I.74	2,5-Dimethyl-3-furanyl	NH	methyl	C=O	H	
I.75	2,5-Dimethyl-3-furanyl	NH	methyl	C=O	H	
I.76	2,5-Dimethyl-3-furanyl	NH	methyl	C=O	H	
I.77	2,5-Dimethyl-3-furanyl	NH	methyl	C=O	H	

No.	R ₁	X	R ₂	Y	R ₃	R ₄
I.78	2-pyrrolyl	NH	methyl	C=O	H	
I.79	2-pyrrolyl	NH	methyl	C=O	H	
I.80	2-pyrrolyl	NH	methyl	C=O	H	
I.81	2-thiazolyl	NH	methyl	C=O	H	
I.82	3-Pyridinyl	NH	methyl	C=O	H	
I.83	3-Pyridinyl	NH	methyl	C=O	H	
I.84	3-Pyridinyl	NH	methyl	C=O	H	
I.85	6-Chloro-3-pyridinyl	NH	methyl	C=O	H	
I.86	3-Pyridinyl	NH	methyl	C=O	H	
I.87	3-Pyridinyl	NH	methyl	C=O	H	
I.88	6-Methoxy-3-pyridinyl	NH	methyl	C=O	H	
I.89	3-(Dimethylamino)phenyl	NH	methyl	C=O	H	
I.90	6-Methyl-3-pyridinyl	NH	methyl	C=O	H	
I.91	3-Pyridinyl	NH	methyl	C=O	H	
I.92	3-Pyridinyl	NH	methyl	C=O	H	
I.93	3-Pyridinyl	NH	methyl	C=O	H	
I.94	3-Pyridinyl	NH	methyl	C=O	H	
I.95	2-Pyrazinyl	NH	methyl	C=O	H	
I.96	3-Pyridinyl	NH	methyl	C=O	H	
I.97	3-Pyridinyl	NH	methyl	C=O	H	
I.98	3-Pyridinyl	NH	methyl	C=O	H	
I.99	3-Pyridinyl	NH	methyl	C=O	H	

No.	R ₁	X	R ₂	Y	R ₃	R ₄
I.100	3-Pyridinyl	NH	methyl	C=O	H	
I.101	2-Methyl-5-pyrazinyl	NH	methyl	C=O	H	
I.102	3-Quinolyl	NH	methyl	C=O	H	
I.103	5-Pyrimidinyl	NH	methyl	C=O	H	
I.104	3-Pyridinyl	NH	methyl	C=O	H	
I.105	3-Pyridinyl	NH	methyl	C=O	H	
I.106	3-Pyridinyl	NH	methyl	C=O	H	
I.107	3-Pyridinyl	NH	CH ₃	C=O	H	
I.108	3-Pyridinyl	NH	CH ₃	C=O	H	
I.109	3-Pyridinyl	NH	CH ₃	C=O	H	
I.110	3-Pyridinyl	NH	CH ₃	C=O	H	
I.111	3-Pyridinyl	NH	CH ₃	SO ₂	H	
I.113	5-Pyrimidinyl	NH	methyl	C=O	H	
IA.1	3-Pyridinyl	NH	methyl	C=O		
IA.2	3-Pyridinyl	NH	methyl	C=O		
IA.3	3-Pyridinyl	NH	methyl	C=O		

Table 2 illustrates the chemical structure wherein ring P in compound of formula I is thiazole



Formula I (wherein P represents thiazole)

Table 2

No.	R ₁	X	R ₂	Y	R ₃	R ₄
I.112	3-Pyridinyl	NH	CH ₃	C=O	H	

Table 3 provides spectral data for the compounds of Formula I

Table 3

Compound No.	¹ H NMR (DMSO-d ₆), δ
I.1	2.39 (s, 3H), 7.38-7.45 (m, 3H), 7.52 (d, 1H, $J = 4.1$ Hz), 7.61-7.64 (m, 2H), 7.72 (d, 2H, $J = 6.7$ Hz), 8.26 (s, 1H), 8.51 (d, 1H, $J = 6.9$ Hz), 8.59 (d, 1H, $J = 6.4$ Hz), 8.75 (m, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.38 (s, 1H), 10.58 (s, 1H).
I.2	2.20 (s, 3H), 2.39 (m, 11H), 3.57 (s, 2H), 7.44 (d, 1H, $J = 8.0$ Hz), 7.48 (d, 2H, $J = 8.0$ Hz), 7.52 (d, 1H, $J = 5.1$ Hz), 7.61 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz), 7.72 (d, 1H, $J = 7.7$ Hz), 7.93 (d, 2H, $J = 8.0$ Hz), 8.25 (s, 1H), 8.50 (d, 1H, $J = 7.9$ Hz), 8.60 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 4.0$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.49 (s, 1H).
I.3	2.24 (s, 3H), 2.40 (s, 3H), 7.47 (d, 1H, $J = 8.0$ Hz), 7.53 (d, 1H, $J = 5.0$ Hz), 7.61 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 4.8$ Hz), 7.73-7.75 (m, 2H), 8.21 (s, 1H), 8.27 (s, 1H), 8.33 (s, 1H), 8.45 (d, 1H, $J = 7.0$ Hz), 8.50 (d, 1H, $J = 7.9$ Hz), 8.60 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 3.9$ Hz), 9.20 (s, 1H), 9.32 (s, 1H), 10.70 (s, 1H), 10.92 (s, 1H).
I.4	1.22 (s, 9H), 2.37 (s, 3H), 6.78 (s, 1H), 7.43 (d, 1H, $J = 7.9$ Hz), 7.51 (d, 1H, $J = 5.0$ Hz), 7.57-7.64 (m, 5H), 7.70 (d, 1H, $J = 7.7$ Hz), 8.22 (s, 1H), 8.49 (d, 1H, $J = 7.9$ Hz), 8.58 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 3.8$ Hz), 9.17 (s, 1H), 9.31 (s, 1H), 10.15 (s, 1H), 10.38 (s, 1H).
I.5	1.30 (s, 9H), 2.38 (s, 3H), 6.83 (s, 1H), 7.43 (d, 1H, $J = 7.8$ Hz), 7.53 (d, 1H, $J = 5.1$ Hz), 7.61 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 4.7$ Hz), 7.67 (d, 1H, $J = 5.2$ Hz), 7.69 (d, 1H, $J = 7.1$ Hz), 7.74 (d, 1H, $J = 8.3$ Hz), 8.16 (t, 1H, $J_1 = 15.2$ Hz, $J_2 = 7.6$ Hz), 8.23 (s, 1H), 8.50 (d, 1H, $J = 7.9$ Hz), 8.59 (d, 1H, $J = 5.1$ Hz), 8.69 (d, 1H, $J = 3.8$ Hz), 8.75 (d, 1H, $J = 3.9$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.24 (s, 1H), 10.43 (s, 1H).
I.6	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.6$ Hz), 7.52 (d, 1H, $J = 4.5$ Hz), 7.59-7.60 (m, 2H), 7.72 (d, 1H, $J = 7.1$ Hz), 8.11 (d, 2H, $J = 8.2$ Hz), 8.26 (s, 1H), 8.51 (d, 1H, $J = 6.9$ Hz), 8.59 (d, 1H, $J = 4.4$ Hz), 8.75 (m, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.55 (s, 1H), 10.68 (s, 1H).
I.7	2.39 (s, 3H), 7.46 (d, 1H, $J = 7.5$ Hz), 7.53 (d, 1H, $J = 4.3$ Hz), 7.60 (s, 1H), 7.73 (d, 1H, $J = 7.0$ Hz), 8.27 (s, 1H), 8.48 (m, 2H), 8.59-8.63 (m, 3H), 8.74 (m, 1H), 9.20 (s, 1H), 9.32 (s, 1H), 10.72 (s, 1H), 11.10 (s, 1H).
I.8	2.39 (s, 3H), 7.00 (d, 1H, $J = 7.6$ Hz), 7.03 (d, 1H, $J = 8.0$ Hz), 7.45 (d, 1H, $J = 7.7$ Hz), 7.52-7.54 (m, 2H), 7.58-7.61 (m, 1H), 7.72 (d, 1H, $J = 7.3$ Hz), 7.99 (d, 1H, $J = 7.5$ Hz), 8.27 (s, 1H), 8.50 (d, 1H, $J = 7.5$ Hz), 8.59 (d, 1H, $J = 4.3$ Hz), 8.75 (m, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.66 (s, 1H), 10.76 (s, 1H), 12.05 (s, 1H).
I.9	2.39 (s, 3H), 7.23 (s, 1H), 7.40-7.46 (m, 3H), 7.52-7.59 (m, 5H), 7.63-7.65 (m, 3H), 7.73 (d, 1H, $J = 7.3$ Hz), 7.95 (d, 1H, $J = 8.2$ Hz), 8.26 (s, 1H), 8.50 (d, 1H, $J = 7.6$ Hz), 8.59 (d, 1H, $J = 4.8$ Hz), 8.74 (m, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.45 (s, 1H), 10.51 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
I.10	2.39 (s, 3H), 3.83 (s, 3H), 7.04 (d, 2H, $J = 8.5$ Hz), 7.12 (s, 1H), 7.31 (d, 2H, $J = 8.5$ Hz), 7.45 (d, 1H, $J = 7.9$ Hz), 7.52 (d, 1H, $J = 5.1$ Hz), 7.60 (s, 2H), 7.62-7.64 (m, 3H), 7.73 (d, 1H, $J = 7.8$ Hz), 7.94 (d, 2H, $J = 8.4$ Hz), 8.26 (s, 1H), 8.50 (d, 1H, $J = 7.8$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.74 (m, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.41 (s, 1H), 10.51 (s, 1H).
I.11	1.22 (s, 9H), 2.37 (s, 3H), 7.42-7.48 (m, 3H), 7.52 (d, 1H, $J = 5.0$ Hz), 7.59-7.62 (m, 1H), 7.65-7.71 (m, 3H), 8.22 (s, 1H), 8.49 (d, 1H, $J = 7.8$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.74 (m, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.17 (s, 1H), 10.38 (s, 1H).
I.12	1.23 (s, 9H), 2.37 (s, 3H), 6.84 (s, 1H), 7.43 (d, 1H, $J = 7.9$ Hz), 7.52 (d, 1H, $J = 5.0$ Hz), 7.59-7.62 (m, 1H), 7.68-7.74 (m, 2H), 7.84-7.90 (m, 1H), 8.02 (s, 1H), 8.21 (s, 1H), 8.49 (d, 1H, $J = 7.8$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.74 (d, 1H, $J = 3.7$ Hz), 9.18 (s, 1H), 9.31 (s, 1H), 10.22 (s, 1H), 10.37 (s, 1H).
I.13	2.38 (s, 3H), 7.35-7.38 (m, 1H), 7.44 (d, 1H, $J = 7.9$ Hz), 7.52 (d, 1H, $J = 5.1$ Hz), 7.60-7.63 (m, 2H), 7.66-7.73 (m, 2H), 7.77 (d, 1H, $J = 8.5$ Hz), 7.86-7.95 (m, 3H), 8.24 (s, 1H), 8.38 (m, 1H), 8.50 (d, 1H, $J = 7.9$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 3.9$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.44 (s, 1H), 10.45 (s, 1H).
I.14	1.22 (s, 9H), 2.37 (s, 3H), 6.83 (s, 1H), 7.43 (d, 1H, $J = 7.9$ Hz), 7.51 (d, 1H, $J = 5.0$ Hz), 7.59-7.62 (m, 1H), 7.70 (d, 1H, $J = 7.7$ Hz), 7.86-7.90 (m, 1H), 7.97 (d, 1H, $J = 7.8$ Hz), 8.04-8.06 (m, 2H), 8.22 (s, 1H), 8.49 (d, 1H, $J = 7.8$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.74 (m, 1H), 9.17 (s, 1H), 9.31 (s, 1H), 10.19 (s, 1H), 10.39 (s, 1H).
I.15	2.39 (s, 3H), 7.34-7.39 (m, 2H), 7.41-7.53 (m, 6H), 7.60-7.63 (m, 1H), 7.67 (d, 1H, $J = 7.8$ Hz), 7.72 (d, 1H, $J = 7.7$ Hz), 7.91-7.95 (m, 1H), 8.25 (s, 1H), 8.49-8.54 (m, 1H), 8.59 (d, 1H, $J = 5.0$ Hz), 8.74 (d, 1H, $J = 3.9$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.26 (s, 1H), 10.50 (s, 1H).
I.16	2.39 (s, 3H), 7.39-7.41 (m, 2H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.51-7.54 (m, 2H), 7.60-7.63 (m, 1H), 7.70-7.74 (m, 2H), 7.86 (d, 1H, $J = 8.0$ Hz), 7.90-7.94 (m, 1H), 8.11-8.13 (m, 1H), 8.26 (s, 1H), 8.36 (m, 1H), 8.45 (m, 1H), 8.51 (d, 2H, $J = 7.9$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.75 (m, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.49 (s, 1H), 10.51 (s, 1H).
I.17	2.39 (s, 3H), 7.44-7.48 (m, 3H), 7.52-7.56 (m, 3H), 7.61-7.63 (m, 3H), 7.73 (d, 1H, $J = 7.9$ Hz), 7.80 (d, 1H, $J = 7.7$ Hz), 7.92 (d, 1H, $J = 8.5$ Hz), 7.97-8.01 (m, 1H), 8.26 (s, 1H), 8.50-8.55 (m, 2H), 8.59 (d, 1H, $J = 5.0$ Hz), 8.74 (d, 1H, $J = 3.8$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.48 (s, 1H), 10.52 (s, 1H).
I.18	2.32 (s, 3H), 2.38 (s, 3H), 7.44 (d, 1H, $J = 7.8$ Hz), 7.52-7.54 (m, 3H), 7.60-7.61 (m, 1H), 7.63-7.72 (m, 2H), 7.85 (d, 2H, $J = 9.0$ Hz), 8.24 (s, 1H), 8.50 (d, 1H, $J = 7.7$ Hz), 8.59 (d, 1H, $J = 4.9$ Hz), 8.74-8.75 (m, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.26 (s, 1H), 10.40 (s, 1H).
I.19	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.8$ Hz), 7.53 (d, 1H, $J = 4.9$ Hz), 7.61 (dd, 1H, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz), 7.73-7.79 (m, 3H), 7.86 (d, 1H, $J = 7.3$ Hz), 7.90 (d, 1H, $J = 7.9$ Hz), 8.28 (s, 1H), 8.51 (d, 1H, $J = 7.7$ Hz), 8.60 (d, 1H, $J = 4.9$ Hz), 8.74 (s, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.50 (s, 1H), 10.63 (s, 1H).
I.20	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.6$ Hz), 7.53 (d, 1H, $J = 4.6$ Hz), 7.62 (m, 2H), 7.72 (d, 1H, $J = 7.3$ Hz), 8.26 (s, 1H), 8.32 (d, 1H, $J = 7.2$ Hz), 8.50 (d, 1H, $J = 7.3$ Hz), 8.59 (d, 1H, $J = 4.5$ Hz), 8.75 (s, 1H), 8.83 (s, 1H), 9.13 (s, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.59 (s, 1H), 10.77 (s, 1H).
I.21	2.37 (s, 3H), 2.66 (s, 3H), 7.40 (d, 1H, $J = 7.8$ Hz), 7.51 (d, 1H, $J = 5.1$ Hz), 7.61 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 4.8$ Hz), 7.72 (d, 1H, $J = 7.6$ Hz), 8.22 (s, 1H), 8.50 (d, 1H, $J = 7.8$ Hz), 8.58 (d, 1H, $J = 4.9$ Hz), 8.71 (s, 1H), 8.74 (d, 1H, $J = 3.8$ Hz), 9.11 (s, 1H), 9.15 (s, 1H), 9.31 (s, 1H), 10.76 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
I.22	2.39 (s, 3H), 7.42-7.44 (m, 3H), 7.51 (d, 1H, $J = 5.1$ Hz), 7.60 (m, 1H), 7.72 (d, 1H, $J = 6.7$ Hz), 8.06 (m, 2H), 8.26 (s, 1H), 8.50 (d, 1H, $J = 8.4$ Hz), 8.58 (d, 1H, $J = 4.9$ Hz), 8.75 (s, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.55 (s, 1H).
I.23	2.39 (s, 3H), 6.68 (s, 1H), 7.45 (d, 1H, $J = 7.8$ Hz), 7.51-7.53 (m, 3H), 7.62 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 4.8$ Hz), 7.73-7.76 (m, 2H), 8.27 (d, 2H, $J = 7.3$ Hz), 8.51 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 4.0$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.36 (s, 1H), 10.43 (s, 1H), 11.45 (s, 1H).
I.24	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.52 (d, 1H, $J = 5.1$ Hz), 7.62 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 4.8$ Hz), 7.73 (d, 2H, $J = 6.4$ Hz), 8.09 (d, 1H, $J = 7.6$ Hz), 8.12 (d, 1H, $J = 7.0$ Hz), 8.25 (s, 1H), 8.50 (d, 1H, $J = 7.9$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75-8.77 (m, 2H), 9.19 (s, 1H), 9.32 (s, 1H), 10.54 (s, 1H), 10.68 (s, 1H).
I.25	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.53 (d, 1H, $J = 5.0$ Hz), 7.62 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 4.8$ Hz), 7.73-7.75 (m, 2H), 7.87-7.88 (m, 1H), 8.27 (s, 1H), 8.35-8.43 (m, 2H), 8.51 (d, 1H, $J = 7.9$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 3.8$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.48 (m, 2H), 12.72 (s, 1H).
I.26	2.39 (s, 3H), 7.46 (d, 1H, $J = 7.9$ Hz), 7.53 (d, 1H, $J = 5.1$ Hz), 7.61 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz), 7.73 (d, 1H, $J = 7.7$ Hz), 7.85 (t, 1H, $J_1 = 13.5$ Hz, $J_2 = 7.8$ Hz), 8.05 (d, 1H, $J = 7.6$ Hz), 8.26 (s, 1H), 8.29 (d, 1H, $J = 8.1$ Hz), 8.32 (s, 1H), 8.5 (d, 1H, $J = 7.9$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 4.2$ Hz), 9.20 (s, 1H), 9.32 (s, 1H), 10.61 (m, 1H), 10.84 (s, 1H).
I.27	2.38 (s, 3H), 6.80 (d, 1H, $J = 15.5$ Hz), 7.45-7.50 (m, 5H), 7.61-7.69 (m, 5H), 8.24 (s, 1H), 8.49-8.59 (m, 2H), 8.75 (s, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.25 (s, 1H), 10.52 (s, 1H).
I.28	2.38 (s, 3H), 6.94 (d, 1H, $J = 15.7$ Hz), 7.44 (d, 1H, $J = 6.8$ Hz), 7.52-7.61 (m, 2H), 7.71-7.82 (m, 4H), 8.01 (d, 1H, $J = 6.5$ Hz), 8.05 (s, 1H), 8.25 (s, 1H), 8.50 (d, 1H, $J = 6.1$ Hz), 8.59 (s, 1H), 8.75 (s, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.30 (s, 1H), 10.56 (s, 1H).
I.29	1.23 (s, 9H), 2.37 (s, 3H), 6.80 (s, 1H), 7.43 (d, 1H, $J = 7.9$ Hz), 7.51 (d, 1H, $J = 5.0$ Hz), 7.59-7.64 (m, 3H), 7.69-7.71 (m, 2H), 8.22 (s, 1H), 8.49 (d, 1H, $J = 7.8$ Hz), 8.58 (d, 1H, $J = 5.0$ Hz), 8.74 (m, 1H), 9.17 (s, 1H), 9.31 (s, 1H), 10.16 (s, 1H), 10.38 (s, 1H).
I.30	2.39 (s, 3H), 7.34 (s, 1H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.53 (d, 1H, $J = 5.0$ Hz), 7.57 (s, 2H), 7.59-7.69 (m, 5H), 7.73 (d, 1H, $J = 7.8$ Hz), 7.86 (d, 1H, $J = 8.0$ Hz), 7.96 (d, 1H, $J = 8.4$ Hz), 8.26 (s, 1H), 8.50 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.74 (m, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.48 (s, 1H), 10.52 (s, 1H).
I.31	2.38 (s, 3H), 6.71 (d, 1H, $J = 15.6$ Hz), 6.87 (d, 1H, $J = 5.9$ Hz), 7.05 (s, 1H), 7.09 (d, 1H, $J = 5.7$ Hz), 7.29 (m, 1H), 7.44 (d, 1H, $J = 6.4$ Hz), 7.50-7.53 (m, 2H), 7.60 (m, 1H), 7.69 (m, 1H), 8.24 (s, 1H), 8.49 (m, 1H), 8.59 (s, 1H), 8.75 (s, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 9.70 (s, 1H), 10.24 (s, 1H), 10.51 (s, 1H).
I.32	1.24 (s, 9H), 2.37 (s, 3H), 6.83 (s, 1H), 7.43 (d, 1H, $J = 7.9$ Hz), 7.52 (d, 1H, $J = 5.0$ Hz), 7.59-7.64 (m, 3H), 7.70 (d, 1H, $J = 7.8$ Hz), 7.82 (d, 2H, $J = 8.3$ Hz), 8.05 (d, 2H, $J = 8.2$ Hz), 8.22 (s, 1H), 8.49 (d, 1H, $J = 7.9$ Hz), 8.58 (d, 1H, $J = 5.0$ Hz), 8.74 (d, 1H, $J = 4.1$ Hz), 9.17 (s, 1H), 9.31 (s, 1H), 10.17 (s, 1H), 10.39 (s, 1H).
I.33	2.37 (s, 3H), 3.46-3.49 (m, 2H), 7.42 (d, 1H, $J = 7.6$ Hz), 7.52 (d, 1H, $J = 4.6$ Hz), 7.58-7.60 (m, 1H), 7.67 (d, 1H, $J = 7.2$ Hz), 8.22 (s, 1H), 8.49 (d, 1H, $J = 7.3$ Hz), 8.59 (d, 1H, $J = 4.5$ Hz), 8.74 (s, 1H), 9.17 (s, 1H), 9.31 (s, 1H), 10.40 (s, 1H), 10.51 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
I.34	2.39 (s, 3H), 7.44 (d, 1H, $J = 7.8$ Hz), 7.53 (d, 1H, $J = 5.0$ Hz), 7.55-7.61 (m, 4H), 7.74 (d, 1H, $J = 7.5$ Hz), 8.29 (s, 1H), 8.51 (d, 1H, $J = 7.7$ Hz), 8.61 (d, 1H, $J = 4.9$ Hz), 8.75 (d, 1H, $J = 3.7$ Hz), 9.17 (s, 1H), 9.32 (s, 1H), 10.68 (s, 1H), 10.75 (s, 1H).
I.35	2.37 (s, 3H), 3.83 (s, 2H), 7.42 (d, 1H, $J = 6.5$ Hz), 7.53-7.55 (m, 3H), 7.67 (m, 3H), 7.77 (d, 1H, $J = 6.4$ Hz), 8.23 (s, 1H), 8.48 (m, 1H), 8.58 (m, 1H), 8.73 (m, 1H), 9.16 (s, 1H), 9.31 (s, 1H), 10.25 (s, 1H), 10.40 (s, 1H).
I.36	2.39 (s, 3H), 7.44 (d, 1H, $J = 8.0$ Hz), 7.49-7.53 (m, 4H), 7.61 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz), 7.71 (d, 1H, $J = 7.6$ Hz), 8.26 (s, 1H), 8.50 (d, 1H, $J = 7.9$ Hz), 8.59 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 3.8$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.49 (s, 1H), 10.62 (s, 1H).
I.37	2.19 (s, 3H), 7.62-7.67 (m, 5H), 7.84 (s, 1H), 8.00 (d, 1H, $J = 7.5$ Hz), 8.07 (d, 1H, $J = 5.0$ Hz), 8.58 (d, 1H, $J = 7.7$ Hz), 8.81 (d, 1H, $J = 4.4$ Hz), 8.83 (d, 1H, $J = 5.2$ Hz), 9.37 (s, 1H), 10.15 (s, 1H), 10.71 (s, 1H), 10.77 (s, 1H).
I.38	2.39 (s, 3H), 7.46 (d, 1H, $J = 7.7$ Hz), 7.54 (d, 1H, $J = 4.7$ Hz), 7.58-7.61 (m, 1H), 7.74 (d, 1H, $J = 7.3$ Hz), 8.05 (s, 1H), 8.20 (s, 2H), 8.30 (s, 1H), 8.51 (d, 1H, $J = 7.4$ Hz), 8.60 (d, 1H, $J = 4.5$ Hz), 8.75 (d, 1H, $J = 3.2$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.73 (s, 1H), 10.74 (s, 1H).
I.39	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.53 (d, 1H, $J = 5.0$ Hz), 7.61 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 4.8$ Hz), 7.73 (d, 1H, $J = 7.6$ Hz), 7.98 (d, 2H, $J = 8.0$ Hz), 8.17 (d, 2H, $J = 7.9$ Hz), 8.27 (s, 1H), 8.50 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 3.7$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.60 (s, 1H), 10.81 (s, 1H).
I.40	2.38 (s, 3H), 6.98 (d, 1H, $J = 15.9$ Hz), 7.44 (d, 1H, $J = 7.8$ Hz), 7.52 (d, 1H, $J = 4.8$ Hz), 7.59-7.62 (m, 1H), 7.69-7.73 (m, 2H), 7.79 (d, 1H, $J = 8.3$ Hz), 7.92-7.94 (m, 2H), 8.25 (s, 1H), 8.50 (d, 1H, $J = 7.5$ Hz), 8.59 (d, 1H, $J = 4.9$ Hz), 8.75 (d, 1H, $J = 3.3$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.30 (s, 1H), 10.57 (s, 1H).
I.41	2.39 (s, 3H), 7.44 (d, 1H, $J = 7.7$ Hz), 7.52-7.61 (m, 6H), 7.73 (d, 1H, $J = 7.3$ Hz), 8.27 (s, 1H), 8.51 (d, 1H, $J = 7.1$ Hz), 8.59 (d, 1H, $J = 4.5$ Hz), 8.75 (d, 1H, $J = 3.1$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.45 (s, 1H), 10.62 (s, 1H).
I.42	2.38 (s, 3H), 7.26-7.32 (m, 2H), 7.44 (d, 1H, $J = 8.0$ Hz), 7.53 (d, 1H, $J = 5.2$ Hz), 7.58-7.68 (m, 2H), 7.72 (d, 1H, $J = 7.5$ Hz), 8.27 (s, 1H), 8.51 (d, 1H, $J = 8.0$ Hz), 8.60 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 3.7$ Hz), 9.18 (s, 1H), 9.32 (d, 1H, $J = 1.3$ Hz), 10.68 (s, 1H), 10.73 (s, 1H).
I.43	2.39 (s, 3H), 7.44 (d, 1H, $J = 7.9$ Hz), 7.53-7.62 (m, 4H), 7.73 (d, 1H, $J = 7.6$ Hz), 7.84 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 4.1$ Hz), 8.27 (s, 1H), 8.51 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.74 (d, 1H, $J = 4.1$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.56 (s, 1H), 10.66 (s, 1H).
I.44	2.38 (s, 3H), 7.43-7.81 (m, 7H), 8.27 (s, 1H), 8.51 (d, 1H, $J = 5.9$ Hz), 8.60 (m, 1H), 8.75 (m, 1H), 9.19 (s, 1H), 9.32 (s, 1H), 10.52 (s, 1H), 10.65 (s, 1H).
I.45	2.38 (s, 3H), 6.86 (d, 1H, $J = 16.2$ Hz), 7.43-7.49 (m, 2H), 7.53 (d, 1H, $J = 5.0$ Hz), 7.59-7.70 (m, 5H), 8.24 (s, 1H), 8.50 (d, 1H, $J = 7.9$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 3.9$ Hz), 9.20 (s, 1H), 9.32 (s, 1H), 10.50 (s, 1H), 10.56 (s, 1H).
I.46	2.38 (s, 3H), 7.44 (d, 1H, $J = 7.7$ Hz), 7.52 (d, 1H, $J = 5.0$ Hz), 7.59 (m, 1H), 7.75 (d, 1H, $J = 7.6$ Hz), 7.96 (d, 1H, $J = 7.9$ Hz), 8.21 (d, 2H, $J = 7.9$ Hz), 8.28 (s, 1H), 8.51 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 7.8$ Hz), 8.74 (d, 1H, $J = 4.1$ Hz), 9.19 (s, 1H), 9.30 (s, 1H), 10.70 (s, 1H), 10.87 (s, 1H).
I.47	2.39 (s, 3H), 7.42-7.48 (m, 2H), 7.52-7.64 (m, 4H), 7.72-7.79 (m, 2H), 8.27 (s, 1H), 8.51 (d, 1H, $J = 8.3$ Hz), 8.60 (d, 1H, $J = 5.2$ Hz), 8.75 (d, 1H, $J = 3.3$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.43 (s, 1H), 10.63 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
I.48	2.39 (s, 3H), 2.55-2.56 (m, 3H), 7.31-7.34 (m, 1H), 7.39-7.42 (m, 2H), 7.44 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 5.2 Hz), 7.58-7.62 (m, 1H), 7.74 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 8.30 (d, 1H, J = 1.2 Hz), 8.51-8.54 (m, 1H), 8.60 (d, 1H, J = 5.0 Hz), 8.75 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.5 Hz), 9.18 (s, 1H), 9.32 (d, 1H, J = 2.2 Hz), 10.47 (s, 1H), 10.59 (s, 1H).
I.49	2.38 (s, 3H), 7.40-7.48 (m, 3H), 7.53 (d, 1H, J = 5.1 Hz), 7.57-7.61 (m, 2H), 7.73 (d, 1H, J = 7.7 Hz), 8.28 (s, 1H), 8.51 (d, 1H, J = 8.1 Hz), 8.60 (d, 1H, J = 5.1 Hz), 8.75 (d, 1H, J = 3.5 Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.69 (s, 1H), 10.74 (s, 1H).
I.50	2.39 (s, 3H), 7.44 (d, 1H, J = 7.8 Hz), 7.53 (d, 1H, J = 5.0 Hz), 7.58-7.61 (m, 1H), 7.74 (d, 1H, J = 7.5 Hz), 7.83-7.85 (m, 2H), 7.92-7.96 (m, 1H), 8.15 (d, 1H, J = 8.0 Hz), 8.28 (s, 1H), 8.51 (d, 1H, J = 7.7 Hz), 8.60 (d, 1H, J = 4.9 Hz), 8.75 (d, 1H, J = 4.1 Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.73 (s, 2H).
I.51	2.38 (s, 3H), 7.27 (d, 1H, J = 5.2 Hz), 7.44 (d, 1H, J = 7.9 Hz), 7.53 (d, 1H, J = 5.1 Hz), 7.61 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.8 Hz), 7.70 (d, 1H, J = 7.9 Hz), 7.96 (d, 1H, J = 5.2 Hz), 8.25 (s, 1H), 8.50 (d, 1H, J = 8.0 Hz), 8.60 (d, 1H, J = 5.1 Hz), 8.75 (d, 1H, J = 3.6 Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.27 (s, 1H), 10.59 (s, 1H).
I.52	2.33 (s, 3H), 7.37 (d, 1H, J = 7.9 Hz), 7.50-7.52 (m, 2H), 7.55-7.59 (m, 2H), 7.61-7.63 (m, 2H), 8.00 (s, 1H), 8.46 (d, 1H, J = 7.8 Hz), 8.56 (d, 1H, J = 5.1 Hz), 8.76 (d, 1H, J = 3.8 Hz), 9.14 (s, 1H), 9.28 (s, 1H), 10.33 (s, 1H), 10.78 (s, 1H).
I.53	2.39 (s, 3H), 7.45 (d, 1H, J = 7.9 Hz), 7.53 (d, 1H, J = 5.1 Hz), 7.61 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.8 Hz), 7.67 (d, 2H, J = 8.4 Hz), 7.72 (d, 1H, J = 7.7 Hz), 8.00 (d, 2H, J = 8.4 Hz), 8.25 (s, 1H), 8.50 (d, 1H, J = 7.9 Hz), 8.59 (d, 1H, J = 5.1 Hz), 8.75 (d, 1H, J = 4.0 Hz), 9.20 (s, 1H), 9.32 (s, 1H), 10.54 (s, 1H), 10.66 (s, 1H).
I.54	2.38 (s, 3H), 7.33 (d, 1H, J = 3.9 Hz), 7.45 (d, 1H, J = 7.9 Hz), 7.53 (d, 1H, J = 5.0 Hz), 7.60 (dd, 1H, J_1 = 7.8 Hz, J_2 = 4.9 Hz), 7.69 (d, 1H, J = 7.6 Hz), 7.83 (d, 1H, J = 3.9 Hz), 8.24 (s, 1H), 8.49 (d, 1H, J = 7.9 Hz), 8.59 (d, 1H, J = 5.1 Hz), 8.75 (d, 1H, J = 3.9 Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.54 (s, 1H), 10.70 (s, 1H).
I.55	2.37 (s, 3H), 3.80 (s, 6H), 3.86 (s, 3H), 6.31 (s, 2H), 7.40 (d, 1H, J = 7.9 Hz), 7.52 (d, 1H, J = 5.0 Hz), 7.59-7.62 (m, 1H), 7.73 (d, 1H, J = 7.8 Hz), 8.26 (s, 1H), 8.50-8.52 (m, 1H), 8.59 (d, 1H, J = 5.0 Hz), 8.74-8.76 (dd, 1H, J_1 = 4.6 Hz, J_2 = 1.4 Hz), 9.14 (s, 1H), 9.32 (s, 1H), 9.96 (s, 1H), 10.46 (s, 1H).
I.56	2.37 (s, 3H), 6.70 (s, 1H), 7.31-7.41 (m, 3H), 7.51-7.63 (m, 3H), 8.20 (s, 1H), 8.52 (d, 1H, J = 7.9 Hz), 8.59 (d, 1H, J = 5.3 Hz), 8.75 (d, 1H, J = 4.1 Hz), 9.16 (s, 1H), 9.31 (s, 1H), 10.61 (s, 1H).
I.57	2.39 (s, 3H), 7.44 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 5.2 Hz), 7.60 (dd, 1H, J_1 = 7.9 Hz, J_2 = 4.8 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.85 (s, 2H), 8.28 (s, 1H), 8.51 (d, 1H, J = 8.0 Hz), 8.60 (d, 1H, J = 5.1 Hz), 8.75 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.3 Hz), 9.18 (s, 1H), 9.32 (d, 1H, J = 1.6 Hz), 10.73 (s, 1H), 10.81 (s, 1H).
I.58	2.38 (s, 3H), 7.32 (t, 1H, J = 7.4 Hz), 7.43 (d, 1H, J = 7.8 Hz), 7.52 (d, 1H, J = 5.0 Hz), 7.56-7.59 (m, 1H), 7.67-7.73 (m, 3H), 8.00 (d, 1H, J = 8.1 Hz), 8.15 (s, 1H), 8.24 (s, 1H), 8.49 (d, 1H, J = 7.8 Hz), 8.59 (d, 1H, J = 5.0 Hz), 8.74 (m, 1H), 8.94 (s, 1H), 9.17 (s, 1H), 9.32 (s, 1H), 10.42 (s, 1H).
I.59	1.30 (s, 9H), 2.37 (s, 3H), 7.32 (d, 1H, J = 8.3 Hz), 7.39-7.43 (m, 3H), 7.52 (d, 1H, J = 5.0 Hz), 7.57-7.60 (m, 1H), 7.71 (d, 1H, J = 7.5 Hz), 8.16 (s, 1H), 8.23 (s, 1H), 8.49 (d, 1H, J = 7.8 Hz), 8.58 (d, 1H, J = 5.0 Hz), 8.74-8.75 (m, 1H), 8.82 (s, 1H), 9.17 (s, 1H), 9.32 (s, 1H), 10.27 (s, 1H).
I.60	2.36 (s, 3H), 7.32-7.36 (m, 1H), 7.41 (d, 1H, J = 7.9 Hz), 7.52 (d, 1H, J = 5.1 Hz), 7.55-7.59 (m, 3H), 7.72 (br, 1H), 8.23 (s, 1H), 8.49-8.55 (m, 3H), 8.58 (d, 1H, J = 5.0 Hz), 8.73 (m, 1H), 9.17 (s, 1H), 10.36 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
I.61	2.33 (s, 3H), 4.62 (s, 2H), 7.30-7.36 (m, 3H), 7.43-7.45 (m, 3H), 7.50 (m, 2H), 7.58 (t, 1H, $J_1 = 12.1$ Hz, $J_2 = 5.1$ Hz), 8.07 (s, 1H), 8.48 (d, 1H, $J = 7.5$ Hz), 8.56 (d, 1H, $J = 4.9$ Hz), 8.74 (d, 1H, $J = 3.8$ Hz), 9.10 (s, 1H), 9.31 (d, 1H, $J = 1.3$ Hz), 9.88 (s, 1H).
I.62	4.00 (s, 3H), 7.25 (d, 1H, $J = 8.6$ Hz), 7.48-7.64 (m, 5H), 7.80 (d, 1H, $J = 8.3$ Hz), 8.50 (s, 1H), 8.64-8.69 (m, 2H), 8.77-8.79 (dd, 1H, $J_1 = 4.6$ Hz, $J_2 = 1.4$ Hz), 8.88 (m, 1H), 9.41 (m, 1H), 10.64 (s, 1H), 10.74 (s, 1H).
I.63	4.00 (s, 3H), 7.25 (d, 1H, $J = 8.6$ Hz), 7.39-7.43 (m, 2H), 7.72-7.78 (m, 2H), 8.50 (s, 1H), 8.61-8.66 (m, 1H), 8.67 (d, 1H, $J = 5.2$ Hz), 8.77-8.78 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 1.6$ Hz), 8.86 (m, 1H), 9.41 (m, 1H), 10.38 (s, 1H), 10.53 (s, 1H).
I.64	4.00 (s, 3H), 7.25 (d, 1H, $J = 8.6$ Hz), 7.60-7.65 (m, 2H), 7.74-7.80 (m, 3H), 8.50 (s, 1H), 8.63-8.66 (m, 1H), 8.68 (d, 1H, $J = 5.2$ Hz), 8.77-8.78 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 1.4$ Hz), 8.88 (m, 1H), 9.41 (m, 1H), 10.68 (s, 1H), 10.80 (s, 1H).
I.65	7.47-7.64 (m, 5H), 7.75 (d, 1H, $J = 8.3$ Hz), 7.81 (d, 1H, $J = 8.3$ Hz), 8.56 (s, 2H), 8.66 (d, 1H, $J = 5.1$ Hz), 8.76 (d, 1H, $J = 3.9$ Hz), 9.28 (s, 1H), 9.35 (s, 1H), 10.84 (s, 1H), 10.87 (s, 1H).
I.66	7.40-7.43 (m, 2H), 7.60-7.69 (m, 3H), 7.72-7.78 (m, 3H), 8.53 (s, 1H), 8.66 (d, 1H, $J = 5.0$ Hz), 8.76 (d, 1H, $J = 4.5$ Hz), 9.30 (s, 1H), 9.35 (s, 1H), 10.48 (s, 1H), 10.77 (s, 1H).
I.67	7.59-7.64 (m, 2H), 7.75 (d, 1H, $J = 8.3$ Hz), 7.80 (d, 1H, $J = 8.4$ Hz), 7.86 (s, 1H), 8.55 (s, 2H), 8.66 (d, 1H, $J = 5.1$ Hz), 8.76 (d, 1H, $J = 4.5$ Hz), 9.27 (s, 1H), 9.34 (s, 1H), 10.90 (s, 2H).
I.68	2.53 (s, 3H), 7.32-7.34 (m, 1H), 7.40-7.41 (m, 2H), 7.60-7.64 (m, 2H), 7.75 (d, 1H, $J = 8.3$ Hz), 7.80-7.83 (dd, 1H, $J_1 = 8.3$ Hz, $J_2 = 1.7$ Hz), 8.55-8.57 (m, 2H), 8.66 (d, 1H, $J = 5.1$ Hz), 8.76 (d, 1H, $J = 3.5$ Hz), 9.27 (s, 1H), 9.35 (s, 1H), 10.55 (s, 1H), 10.77 (s, 2H).
I.69	2.40 (s, 3H), 2.52 (s, 3H), 7.30-7.32 (m, 1H), 7.37-7.40 (m, 2H), 7.46 (d, 1H, $J = 8.0$ Hz), 7.69 (d, 1H, $J = 5.0$ Hz), 7.78 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.5$ Hz), 8.26 (s, 1H), 8.69 (d, 1H, $J = 5.0$ Hz), 8.85 (s, 2H), 9.32 (s, 1H), 9.46 (s, 1H), 10.48 (s, 1H), 10.60 (s, 1H).
I.70	2.40 (s, 3H), 7.46 (d, 1H, $J = 7.80$ Hz), 7.51-7.55 (m, 1H), 7.59 (s, 1H), 7.60 (s, 1H), 7.69 (d, 1H, $J = 4.85$ Hz), 7.77 (d, 1H, $J = 7.73$ Hz), 8.26 (s, 1H), 8.69 (d, 1H, $J = 4.84$ Hz), 8.85 (s, 2H), 9.31 (s, 1H), 9.46 (s, 1H), 10.70 (s, 1H), 10.77 (s, 1H).
I.71	2.36 (s, 3H), 7.25-7.27 (m, 1H), 7.33 (d, 1H, $J = 5.2$ Hz), 7.42 (d, 1H, $J = 8.0$ Hz), 7.46-7.55 (m, 1H), 7.59 (s, 1H), 7.60-7.61 (m, 1H), 7.71-7.74 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz), 7.79-7.80 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 0.8$ Hz), 8.01-8.02 (m, 1H), 8.17 (s, 1H), 8.45 (d, 1H, $J = 5.1$ Hz), 9.06 (s, 1H), 10.66 (s, 1H), 10.74 (s, 1H).
I.72	2.36 (s, 3H), 7.25-7.27 (m, 1H), 7.33 (d, 1H, $J = 5.1$ Hz), 7.42 (d, 1H, $J = 8.0$ Hz), 7.70-7.73 (m, 1H), 7.79-7.80 (m, 1H), 7.85 (s, 2H), 8.01-8.02 (dd, 1H, $J_1 = 3.7$ Hz, $J_2 = 1.0$ Hz), 8.16 (s, 1H), 8.45 (d, 1H, $J = 5.1$ Hz), 9.06 (s, 1H), 10.70 (s, 1H), 10.79 (s, 1H).
I.73	2.37 (s, 3H), 2.55 (s, 3H), 7.25-7.27 (m, 1H), 7.31-7.34 (m, 2H), 7.38-7.43 (m, 3H), 7.71-7.74 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 7.79-7.80 (dd, 1H, $J_1 = 4.9$ Hz, $J_2 = 0.9$ Hz), 8.01-8.02 (m, 1H), 8.17 (m, 1H), 8.45 (d, 1H, $J = 5.2$ Hz), 9.06 (s, 1H), 10.45 (s, 1H), 10.56 (s, 1H).
I.74	2.28 (s, 3H), 2.36 (s, 3H), 2.47 (s, 3H), 6.60 (s, 1H), 6.97 (d, 1H, $J = 5.2$ Hz), 7.40 (d, 1H, $J = 8.0$ Hz), 7.69-7.71 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 7.85 (s, 2H), 8.19 (m, 1H), 8.41 (d, 1H, $J = 5.1$ Hz), 8.89 (s, 1H), 10.69 (s, 1H), 10.77 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
1.75	2.28 (s, 3H), 2.36 (s, 3H), 2.48 (s, 3H), 6.60 (s, 1H), 6.97 (d, 1H, $J = 5.2$ Hz), 7.40 (d, 1H, $J = 8.0$ Hz), 7.43-7.55 (m, 1H), 7.59 (s, 1H), 7.60-7.61 (m, 1H), 7.69-7.71 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.6$ Hz), 8.19 (m, 1H), 8.41 (d, 1H, $J = 5.1$ Hz), 8.89 (s, 1H), 10.65 (s, 1H), 10.72 (s, 1H).
1.76	2.28 (s, 3H), 2.36 (s, 3H), 2.48 (s, 3H), 2.52 (s, 3H), 6.60 (s, 1H), 6.97 (d, 1H, $J = 5.2$ Hz), 7.30-7.34 (m, 1H), 7.38-7.42 (m, 3H), 7.66-7.69 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz), 8.19 (m, 1H), 8.42 (d, 1H, $J = 5.2$ Hz), 8.89 (s, 1H), 10.44 (s, 1H), 10.55 (s, 1H).
1.77	2.47 (s, 3H), 2.55 (s, 3H), 6.60 (s, 1H), 6.97 (d, 1H, $J = 5.2$ Hz), 7.39-7.44 (m, 3H), 7.66-7.69 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz), 8.17 (m, 1H), 8.41 (d, 1H, $J = 5.2$ Hz), 8.90 (s, 1H), 10.66 (s, 1H), 10.72 (s, 1H).
1.78	2.37 (s, 3H), 6.25 (s, 1H), 6.99 (s, 1H), 7.06 (s, 1H), 7.13 (d, 1H, $J = 5.25$ Hz), 7.40 (d, 1H, $J = 7.95$ Hz), 7.67 (d, 1H, $J = 7.86$ Hz), 7.86 (s, 2H), 8.35 (s, 1H), 8.36 (s, 1H), 8.61 (s, 1H), 10.72 (s, 1H), 10.80 (s, 1H), 11.48 (s, 1H).
1.79	2.38 (s, 3H), 6.24-6.26 (m, 1H), 7.00-7.05 (m, 1H), 7.06 (m, 1H), 7.13 (d, 1H, $J = 5.3$ Hz), 7.31-7.33 (m, 1H), 7.39-7.41 (m, 3H), 7.67-7.69 (dd, 1H, $J_1 = 7.84$ Hz, $J_2 = 1.65$ Hz), 8.36 (d, 1H, $J = 5.26$ Hz), 8.39 (m, 1H), 8.61 (s, 1H), 10.48 (s, 1H), 10.71 (s, 1H), 11.47 (s, 1H).
1.80	2.38 (s, 3H), 2.53 (s, 3H), 6.24-6.26 (m, 1H), 7.00-7.05 (m, 1H), 7.06 (m, 1H), 7.13 (d, 1H, $J = 5.3$ Hz), 7.31-7.33 (m, 1H), 7.39-7.41 (m, 3H), 7.67-7.69 (dd, 1H, $J_1 = 7.84$ Hz, $J_2 = 1.65$ Hz), 8.36 (d, 1H, $J = 5.26$ Hz), 8.39 (m, 1H), 8.61 (s, 1H), 10.48 (s, 1H), 10.71 (s, 1H), 11.47 (s, 1H).
1.81	2.38 (s, 3H), 2.52 (s, 3H), 7.32-7.48 (m, 5H), 7.76 (d, 1H, $J = 7.67$ Hz), 8.01 (s, 1H), 8.12-8.18 (m, 2H), 8.62 (d, 1H, $J = 4.39$ Hz), 9.33 (s, 1H), 10.45 (s, 1H), 10.57 (s, 1H).
1.82	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.95$ Hz), 7.53 (d, 1H, $J = 5.08$ Hz), 7.58-7.61 (m, 1H), 7.73 (d, 1H, $J = 7.62$ Hz), 8.29 (s, 1H), 8.51 (d, 1H, $J = 7.88$ Hz), 8.60 (d, 1H, $J = 5.04$ Hz), 8.74 (m, 1H), 8.82 (s, 1H), 9.19 (s, 1H), 9.32 (m, 1H), 10.82 (s, 1H), 11.00 (s, 1H).
1.83	2.30 (s, 3H), 2.37 (s, 6H), 2.39 (s, 3H), 6.93 (s, 2H), 7.45 (d, 1H, $J = 8.1$ Hz), 7.53 (d, 1H, $J = 5.2$ Hz), 7.58-7.61 (m, 1H), 7.72 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.6$ Hz), 8.28 (d, 1H, $J = 1.3$ Hz), 8.51-8.54 (m, 1H), 8.61 (d, 1H, $J = 5.1$ Hz), 8.75 (dd, 1H, $J_1 = 4.8$ Hz, $J_2 = 1.6$ Hz), 9.19 (s, 1H), 9.32 (d, 1H, $J = 1.9$ Hz), 10.15 (s, 1H), 10.44 (s, 1H).
1.84	2.39 (s, 3H), 3.35 (s, 3H), 7.45-7.73 (m, 4H), 8.15-8.27 (m, 5H), 8.51 (d, 1H, $J = 6.6$ Hz), 8.60 (d, 1H, $J = 3.5$ Hz), 8.75 (s, 1H), 9.20 (s, 1H), 9.32 (s, 1H), 10.62 (s, 1H), 10.84 (s, 1H).
1.85	2.38 (s, 3H), 7.44 (d, 1H, $J = 8.0$ Hz), 7.54 (d, 2H, $J = 5.5$ Hz), 7.60 (d, 2H, $J = 7.1$ Hz), 7.72-7.75 (m, 2H), 8.30 (s, 1H), 8.58 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 2.3$ Hz), 8.62 (d, 1H, $J = 5.2$ Hz), 9.17 (d, 1H, $J = 2.0$ Hz), 9.22 (s, 1H), 10.69 (s, 1H), 10.75 (s, 1H).
1.86	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.7$ Hz), 7.53 (d, 1H, $J = 4.7$ Hz), 7.62-7.65 (m, 2H), 7.73 (d, 1H, $J = 7.4$ Hz), 8.04 (d, 1H, $J = 7.0$ Hz), 8.28 (s, 1H), 8.51 (d, 1H, $J = 7.4$ Hz), 8.61 (d, 2H, $J = 4.1$ Hz), 8.75 (d, 1H, $J = 2.9$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.64 (s, 1H), 10.70 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
1.87	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.8$ Hz), 7.53 (d, 1H, $J = 5.0$ Hz), 7.60-7.61 (m, 1H), 7.72 (d, 1H, $J = 7.7$ Hz), 7.79 (d, 1H, $J = 7.9$ Hz), 8.10 (d, 1H, $J = 7.9$ Hz), 8.27 (s, 1H), 8.50 (d, 1H, $J = 7.7$ Hz), 8.60 (d, 1H, $J = 4.8$ Hz), 8.75 (d, 1H, $J = 3.5$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.71 (s, 1H), 10.73 (s, 1H).
1.88	2.38 (s, 3H), 3.97 (s, 3H), 7.00 (d, 1H, $J = 8.7$ Hz), 7.42-7.45 (m, 2H), 7.52-7.56 (m, 1H), 7.59-7.61 (m, 2H), 7.73 (d, 1H, $J = 7.87$ Hz), 8.31 (s, 1H), 8.44-8.47 (dd, 1H, $J_1 = 8.73$ Hz, $J_2 = 2.24$ Hz), 8.53 (d, 1H, $J = 5.14$ Hz), 8.96 (m, 1H), 9.07 (s, 1H), 10.68 (s, 1H), 10.74 (s, 1H).
1.89	2.39 (s, 3H), 2.97 (s, 6H), 6.90-6.92 (m, 1H), 7.32-7.36 (m, 1H), 7.39-7.43 (m, 3H), 7.48 (s, 1H), 7.51-7.55 (m, 1H), 7.59 (s, 1H), 7.60 (m, 1H), 7.73 (d, 1H, $J = 7.44$ Hz), 8.26 (s, 1H), 8.51 (d, 1H, $J = 5.13$ Hz), 9.02 (s, 1H), 10.68 (s, 1H), 10.73 (s, 1H).
1.90	2.38 (s, 3H), 2.58 (s, 3H), 7.27-7.31 (m, 1H), 7.42-7.49 (m, 3H), 7.57 (m, 2H), 7.74 (d, 1H, $J = 7.8$ Hz), 8.00 (d, 1H, $J = 7.8$ Hz), 8.28 (s, 1H), 8.39-8.42 (dd, 1H, $J_1 = 8.1$ Hz, $J_2 = 2.1$ Hz), 8.56 (d, 1H, $J = 5.1$ Hz), 9.13 (s, 1H), 9.20 (m, 1H), 10.37 (s, 1H), 10.61 (s, 1H).
1.91	2.39 (s, 3H), 2.43 (s, 3H), 7.43-7.48 (m, 2H), 7.53 (d, 1H, $J = 5.0$ Hz), 7.59-7.62 (m, 1H), 7.72 (d, 1H, $J = 7.5$ Hz), 7.92 (d, 1H, $J = 7.6$ Hz), 8.27 (s, 1H), 8.51 (d, 1H, $J = 7.9$ Hz), 8.59 (d, 1H, $J = 5.0$ Hz), 8.74 (m, 1H), 9.18 (s, 1H), 9.32 (s, 1H), 10.55 (s, 1H), 10.66 (s, 1H).
1.92	2.39 (s, 3H), 3.87 (s, 3H), 7.13-7.16 (m, 2H), 7.44 (d, 1H, $J = 7.9$ Hz), 7.50-7.54 (m, 2H), 7.59-7.62 (dd, 1H, $J_1 = 7.7$ Hz, $J_2 = 4.8$ Hz), 7.73 (d, 1H, $J = 7.8$ Hz), 8.27 (s, 1H), 8.51 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 4.4$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.43 (s, 1H), 10.61 (s, 1H).
1.93	2.39 (s, 3H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.52 (d, 1H, $J = 5.0$ Hz), 7.56-7.67 (m, 4H), 7.73 (d, 1H, $J = 7.6$ Hz), 7.99 (d, 1H, $J = 7.4$ Hz), 8.26 (s, 1H), 8.51 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 4.0$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.50 (s, 1H), 10.54 (s, 1H).
1.94	1.19 (d, 6H, $J = 6.8$ Hz), 1.26 (d, 6H, $J = 6.9$ Hz), 1.33 (d, 6H, $J = 6.7$ Hz), 2.39 (s, 3H), 2.91-2.98 (m, 1H), 3.29-3.44 (m, 2H), 7.11 (s, 2H), 7.44 (d, 1H, $J = 8.0$ Hz), 7.53 (d, 1H, $J = 5.1$ Hz), 7.61 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 4.8$ Hz), 7.74 (d, 1H, $J = 7.9$ Hz), 8.29 (s, 1H), 8.53 (d, 1H, $J = 8.0$ Hz), 8.60 (d, 1H, $J = 5.2$ Hz), 8.75 (d, 1H, $J = 4.7$ Hz), 9.16 (s, 1H), 9.32 (s, 1H), 10.08 (s, 1H), 10.40 (s, 1H).
1.95	2.30 (s, 3H), 2.37 (s, 6H), 2.40 (s, 3H), 6.93 (s, 2H), 7.47 (d, 1H, $J = 8.0$ Hz), 7.69 (d, 1H, $J = 5.0$ Hz), 7.76 (d, 1H, $J = 7.8$ Hz), 8.24 (s, 1H), 8.69 (d, 1H, $J = 5.0$ Hz), 8.85 (s, 2H), 9.30 (s, 1H), 9.45 (s, 1H), 10.14 (s, 1H), 10.44 (s, 1H).
1.96	2.26 (s, 3H), 2.39 (s, 3H), 5.61 (s, 2H), 6.44 (d, 1H, $J = 6.7$ Hz), 6.58 (d, 1H, $J = 7.5$ Hz), 7.03 (t, 1H, $J_1 = 14.1$ Hz, $J_2 = 7.0$ Hz), 7.44 (d, 1H, $J = 7.3$ Hz), 7.54 (d, 1H, $J = 3.9$ Hz), 7.61 (m, 1H), 7.73 (d, 1H, $J = 7.1$ Hz), 8.32 (s, 1H), 8.53 (d, 1H, $J = 6.7$ Hz), 8.61 (d, 1H, $J = 3.8$ Hz), 8.76 (s, 1H), 9.17 (s, 1H), 9.33 (s, 1H), 10.22 (s, 1H), 10.61 (s, 1H).
1.97	2.39 (s, 3H), 7.44 (d, 2H, $J = 8.2$ Hz), 7.53 (d, 1H, $J = 5.2$ Hz), 7.59-7.73 (m, 4H), 8.27 (s, 1H), 8.51 (d, 1H, $J = 7.9$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (d, 1H, $J = 4.0$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.49 (s, 1H), 10.64 (s, 1H).

Compound. No.	¹ H NMR (DMSO-d ₆), δ
I.98	2.29 (s, 3H), 2.38 (s, 3H), 2.51 (m, 4H), 3.32 (m, 4H), 7.02-7.05 (m, 2H), 7.43 (d, 1H, $J = 8.0$ Hz), 7.50-7.53 (m, 2H), 7.61 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 4.8$ Hz), 7.72 (d, 1H, $J = 7.7$ Hz), 8.25 (s, 1H), 8.51 (d, 1H, $J = 8.0$ Hz), 8.60 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 3.7$ Hz), 9.17 (s, 1H), 9.32 (s, 1H), 10.17 (s, 1H), 10.50 (s, 1H).
I.99	2.22 (s, 3H), 2.39 (s, 3H), 7.45 (d, 1H, $J = 7.8$ Hz), 7.53 (d, 1H, $J = 4.9$ Hz), 7.61 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 4.9$ Hz), 7.66 (s, 1H), 7.70-7.72 (m, 2H), 7.81 (d, 1H, $J = 8.0$ Hz), 7.98 (s, 1H), 8.28 (s, 1H), 8.38 (s, 1H), 8.51 (d, 1H, $J = 7.7$ Hz), 8.61 (d, 1H, $J = 4.9$ Hz), 8.75 (d, 1H, $J = 3.8$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.51 (s, 1H), 10.64 (s, 1H).
I.100	2.39 (s, 3H), 2.55 (s, 3H), 7.13 (t, 1H, $J_1 = 15.7$ Hz, $J_2 = 7.8$ Hz), 7.34 (d, 1H, $J = 7.6$ Hz), 7.44 (d, 1H, $J = 8.0$ Hz), 7.52 (d, 1H, $J = 5.1$ Hz), 7.61 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 4.8$ Hz), 7.74-7.76 (m, 2H), 8.31 (s, 1H), 8.52 (d, 1H, $J = 8.0$ Hz), 8.61 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 3.6$ Hz), 9.16 (s, 1H), 9.32 (s, 1H), 10.39 (s, 1H), 10.57 (s, 1H).
I.101	2.40 (s, 3H), 2.64 (s, 3H), 7.27-7.33 (m, 1H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.55 (s, 1H), 7.58 (s, 1H), 7.67 (d, 1H, $J = 5.0$ Hz), 7.77 (d, 1H, $J = 7.9$ Hz), 8.00 (d, 1H, $J = 7.7$ Hz), 8.28 (s, 1H), 8.66 (d, 1H, $J = 5.0$ Hz), 8.74 (s, 1H), 9.25 (s, 1H), 9.35 (s, 1H), 10.38 (s, 1H), 10.62 (s, 1H).
I.102	2.43 (s, 3H), 2.48 (s, 3H), 7.32-7.33 (m, 1H), 7.39-7.41 (m, 1H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.62-7.72 (m, 2H), 7.73-7.77 (m, 2H), 7.91 (d, 1H, $J = 7.4$ Hz), 8.14 (d, 1H, $J = 8.3$ Hz), 8.23 (d, 1H, $J = 8.0$ Hz), 8.49 (s, 1H), 8.66 (d, 1H, $J = 5.1$ Hz), 9.17 (s, 1H), 9.23 (s, 1H), 9.64 (m, 1H), 10.49 (s, 1H), 10.61 (s, 1H).
I.103	2.39 (s, 3H), 7.28-7.31 (m, 1H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.56-7.61 (m, 3H), 7.77 (d, 1H, $J = 7.6$ Hz), 7.99 (d, 1H, $J = 7.8$ Hz), 8.24 (s, 1H), 8.65 (d, 1H, $J = 5.0$ Hz), 9.28 (s, 1H), 9.36 (s, 1H), 9.48 (s, 2H), 10.38 (s, 1H), 10.62 (s, 1H).
I.104	2.39 (s, 3H), 2.41 (s, 3H), 6.73-6.76 (m, 2H), 7.16 (t, 1H, $J_1 = 15.6$ Hz, $J_2 = 7.8$ Hz), 7.43 (d, 1H, $J = 7.9$ Hz), 7.53 (d, 1H, $J = 5.2$ Hz), 7.61 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz), 7.75 (d, 1H, $J = 7.0$ Hz), 8.31 (s, 1H), 8.53 (d, 1H, $J = 8.0$ Hz), 8.60 (d, 1H, $J = 5.2$ Hz), 8.75 (d, 1H, $J = 4.7$ Hz), 9.15 (s, 1H), 9.32 (s, 1H), 9.64 (s, 1H), 10.12 (s, 1H), 10.59 (s, 1H).
I.105	2.39 (s, 3H), 7.34 (m, 1H), 7.40-7.45 (m, 2H), 7.53 (d, 1H, $J = 5.1$ Hz), 7.61 (m, 1H), 7.75 (d, 1H, $J = 7.7$ Hz), 7.80 (d, 1H, $J = 7.7$ Hz), 8.29 (s, 1H), 8.51 (d, 1H, $J = 7.9$ Hz), 8.59-8.61 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 4.2$ Hz), 9.16 (s, 1H), 9.32 (s, 1H), 10.68 (s, 2H).
I.106	2.39 (s, 3H), 7.44 (d, 1H, $J = 8.0$ Hz), 7.45 (m, 2H), 7.62 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz), 7.68 (dd, 1H, $J_1 = 8.2$ Hz, $J_2 = 2.2$ Hz), 7.74 (d, 1H, $J = 7.2$ Hz), 8.09 (d, 1H, $J = 1.8$ Hz), 8.28 (s, 1H), 8.50-8.57 (m, 1H), 8.59-8.61 (d, 1H, $J = 5.1$ Hz), 8.75 (d, 1H, $J = 3.6$ Hz), 9.18 (s, 1H), 9.32 (s, 1H), 10.44 (s, 1H), 10.65 (s, 1H).
I.107	2.34 (s, 3H), 4.02 (d, 2H, $J = 5.2$ Hz), 5.46-5.47 (m, 1H), 7.30-7.44 (m, 6H), 7.51 (d, 1H, $J = 4.9$ Hz), 7.56-7.58 (m, 2H), 8.14 (s, 1H), 8.48 (d, 1H, $J = 7.8$ Hz), 8.58 (d, 1H, $J = 4.9$ Hz), 8.75 (d, 1H, $J = 3.9$ Hz), 9.12 (s, 1H), 9.31 (s, 1H), 10.05 (d, 1H, $J = 6.0$ Hz).
I.108	2.39 (s, 3H), 2.55 (s, 3H), 7.45 (d, 1H, $J = 7.8$ Hz), 7.52 (d, 1H, $J = 4.8$ Hz), 7.61 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 4.9$ Hz), 7.67-7.73 (m, 2H), 8.17 (d, 1H, $J = 7.6$ Hz), 8.27 (d, 2H, $J = 9.1$ Hz), 8.50 (d, 1H, $J = 7.5$ Hz), 8.60 (d, 1H, $J = 4.8$ Hz), 8.75 (d, 1H, $J = 3.6$ Hz), 9.19 (s, 1H), 9.32 (s, 1H), 10.57 (s, 1H), 10.77 (s, 1H).

Compound No.	¹ H NMR (DMSO-d ₆), δ
I.109	2.38 (s, 3H), 3.89 (s, 3H), 7.19 (s, 2H), 7.43 (d, 1H, $J = 8.1$ Hz), 7.52 (d, 1H, $J = 5.1$ Hz), 7.60 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 4.7$ Hz), 7.74 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.5$ Hz), 8.28 (d, 1H, $J = 0.9$ Hz), 8.51 (d, 1H, $J = 8.1$ Hz), 8.60 (d, 1H, $J = 5.1$ Hz), 8.75 (dd, 1H, $J_1 = 4.8$ Hz, $J_2 = 1.7$ Hz), 9.16 (s, 1H), 9.31 (d, 1H, $J = 1.8$ Hz), 10.63 (s, 2H).
I.110	2.33 (s, 3H), 7.37 (d, 1H, $J = 7.9$ Hz), 7.50-7.52 (m, 2H), 7.55-7.59 (m, 2H), 7.61-7.63 (m, 2H), 8.00 (s, 1H), 8.46 (d, 1H, $J = 7.8$ Hz), 8.56 (d, 1H, $J = 5.1$ Hz), 8.76 (d, 1H, $J = 3.8$ Hz), 9.14 (s, 1H), 9.28 (s, 1H), 10.33 (s, 1H), 10.78 (s, 1H).
I.111	2.41 (s, 3H), 7.58-7.63 (m, 2H), 7.77-7.81 (m, 4H), 8.06 (d, 1H, $J = 8.7$ Hz), 8.52 (d, 1H, $J = 7.8$ Hz), 8.66 (d, 1H, $J = 5.0$ Hz), 8.76 (m, 1H), 9.24 (s, 1H), 9.36 (s, 1H), 10.32 (s, 1H), 10.76 (s, 1H).
I.112	2.42 (s, 3H), 7.41-7.67 (m, 4H), 7.85 (s, 2H), 8.31 (d, 1H, $J = 6.9$ Hz), 8.54 (s, 1H), 8.80 (s, 1H), 9.16 (s, 1H), 9.64 (s, 1H), 10.75 (s, 1H), 10.84 (s, 1H).
I.113	2.39 (s, 3H), 2.52 (s, 3H), 7.30-7.37 (m, 1H), 7.38-7.42 (m, 2H), 7.45 (d, 1H, $J = 7.9$ Hz), 7.59 (d, 1H, $J = 5.0$ Hz), 7.77 (d, 1H, $J = 7.95$ Hz), 8.23 (s, 1H), 8.65 (d, 1H, $J = 5.0$ Hz), 9.28 (s, 1H), 9.36 (s, 1H), 9.48 (s, 2H), 10.46 (s, 1H), 10.58 (s, 1H).
IA.1	2.41 (s, 3H), 7.38 (d, 1H, $J = 8.4$ Hz), 7.46 (d, 1H, $J = 7.1$ Hz), 7.50 (d, 1H, $J = 7.9$ Hz), 7.54 (d, 1H, $J = 4.9$ Hz), 7.61 (dd, 1H, $J_1 = 7.3$ Hz, $J_2 = 4.8$ Hz), 7.74-7.80 (m, 2H), 8.31 (s, 1H), 8.49 (d, 1H, $J = 7.7$ Hz), 8.60 (d, 1H, $J = 4.9$ Hz), 8.75 (d, 1H, $J = 3.4$ Hz), 9.33 (s, 1H), 9.32 (s, 1H), 11.15 (s, 1H), 11.42 (s, 1H).
IA.2	2.42 (s, 3H), 7.52 (d, 1H, $J = 7.9$ Hz), 7.56 (d, 1H, $J = 5.1$ Hz), 7.61 (dd, 1H, $J_1 = 7.8$ Hz, $J_2 = 4.8$ Hz), 7.77 (d, 1H, $J = 7.8$ Hz), 8.02-8.04 (m, 2H), 8.08-8.10 (m, 2H), 8.34 (s, 1H), 8.50 (d, 1H, $J = 7.9$ Hz), 8.61 (d, 1H, $J = 5.1$ Hz), 8.76 (d, 1H, $J = 3.7$ Hz), 9.24 (s, 1H), 9.33 (s, 1H), 11.31 (s, 1H).
IA.3	2.41 (s, 3H), 4.72 (s, 2H), 7.49 (d, 1H, $J = 8.0$ Hz), 7.54 (d, 1H, $J = 5.3$ Hz), 7.61-7.67 (m, 3H), 7.72-7.76 (m, 2H), 8.31 (d, 1H, $J = 1.4$ Hz), 8.50 (d, 1H, $J = 8.0$ Hz), 8.60 (d, 1H, $J = 5.0$ Hz), 8.75 (dd, 1H, $J_1 = 4.7$ Hz, $J_2 = 1.6$ Hz), 9.21 (s, 1H), 9.33 (d, 1H, $J = 1.9$ Hz), 11.04 (s, 1H).

Pharmacological Activity:

Kinase assays

Method A: The kinase assay was performed by MDS Pharma Services at their US pharmacology laboratory.

Bcr-Abl kinase assays were performed in 25 μ L of mixture containing 250 μ M peptide substrate, 740 Bq/ μ L [γ -³³P]ATP and 20 μ M cold adenosine triphosphate by using the SigmaTECT protein tyrosine kinase assay system (Promega, Madison, WI). Each kinase was used at a concentration of >10 nM. Kinase assays for human Abl, c-Kit and PDGF- β were carried out with an enzyme-linked immunosorbent assay (ELISA) kit.

The kinase activity was measured using MDS Pharma Services' proprietary SelectSmart™ technology platform with a modified ELISA procedure.

Method B: The kinase assay was performed by Millipore Pharma Services at their US pharmacology laboratory.

In a final reaction volume of 25 μ L, Abl (human) (5-10 mU) was incubated with 8 mM MOPS pH 7.0, 0.2 mM EDTA, 50 μ M EAIYAAPFAKKK, 10 mM Mg(OAc)₂ and [γ -³³P-ATP] [specific activity approx. 500 cpm/pmol, concentration as required). The reaction was initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction was stopped by the addition of 5 μ L of a 3% phosphoric acid solution. 10 μ L of the reaction was then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

Percent Inhibition Data analysis

Within each kinase assay, percent of control values were calculated for each test compound raw data point based on mean minimum (0%) and maximum (100%) controls ($n = 4$ per control) for that kinase (sample-mean minimum/mean maximum-mean minimum $\times$ 100%). Percent inhibition was calculated from these values (100-mean percent of control).

Table 4 - Abl kinase inhibition (*in vitro*) screening

Compound No.	% Inhibition of cAbl kinase (at 100nM)
I.46	72.0 ^a
I.48	96.0 ^a
I.65	58.5 ^a
I.69	65.5 ^a
I.73	48.0 ^a
I.82	61.6 ^a
I.83	75.0 ^a
I.87	71.1 ^a
I.100	98.5 ^a
I.103	83.0 ^a

I.106	73.5 ^a
I.109	72.0 ^b
Imatinib	33.5 ^a 54.3 ^b

^aMethod A, ^b Method B

Table 5 - c-Kit kinase inhibition (*in vitro*) screening

Compound No.	% Inhibition of c-Kit kinase ^a (at 1 μ M)
I.41	60.0
I.48	55.5
I.51	79.0
I.60	42.0
I.65	59.5
I.69	59.0
I.76	53.0
I.79	42.1
I.82	49.9
I.83	56.9
I.87	86.2
I.88	53.5
I.89	61.0
I.90	83.0
I.91	64.0
I.92	81.5
I.100	60.0
I.101	62.5
I.102	63.5
I.103	79.0
I.106	64.5
Imatinib	31.6

^aMethod A

Table 6 - PDGF- β kinase inhibition (*in vitro*) screening

Compound No.	% Inhibition of PDGF- β kinase ^a (at 100nM)
I.48	78.0
I.65	57.0
I.69	66.0
I.82	63.1
I.83	50.2
I.87	68.1
I.100	54.0
I.103	34.5
I.106	69.0
Imatinib	55.4

^aMethod A**In-vitro Cell Proliferation Assay**

K562/U937 cells (2×10^4 per well) were incubated with the test compounds/vehicle in a total volume of 200 μ L of media at 37°C with 5% CO₂. On day 4, 20 μ L MTT 5mg/ml was added and the cells were incubated for 4-5 hours followed by addition of 100 μ L of 10% SDS prepared in 0.06N HCl. The cells were incubated overnight at 37°C with 5% CO₂. On Day 5 the optical density was measured at 570nm with 630nm as reference wavelength. The optical density in the vehicle treated wells was compared with that of the test compound treated wells.

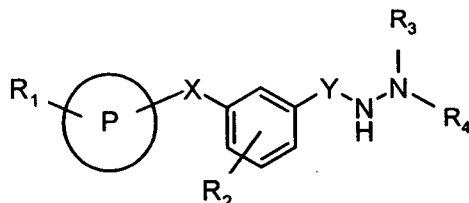
Table 7 –Cell proliferation assay (K562 cells)

Compound No.	Inhibition of cell proliferation (K562 cells), IC ₅₀ (nM)
I.34	134.6
I.109	65.3
I.112	72.4
I.113	39.2
Imatinib	195.5

Compounds of Formula I screened for cell proliferation assay using U937 cells did not show any significant inhibition.

We claim:

- 1 Compounds of formula I, and salts thereof,



Formula I

wherein

P represents a 5 or 6-membered heteroaryl ring;

R₁ is aryl or unsaturated heterocyclyl radical optionally substituted by one or more identical or different radicals R₅;

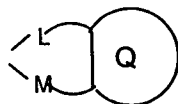
R₂ is selected from the group consisting of hydrogen, halogen, lower alkyl, haloalkyl, -O-lower alkyl, -S-lower alkyl, -S(O)-lower alkyl, -SO₂-lower alkyl, -SO₂NH₂, -SO₂NH-(lower alkyl), -SO₂N(lower alkyl)₂, -NH₂, -NH(lower alkyl), -N(lower alkyl)₂, -CN and -NO₂;

R₃ is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, arylalkyl and a heterocyclyl radical;

R₄ represents the radical R₃ or a radical -Z-R₆, wherein Z is selected from the group consisting of C=O, C=S, SO₂, C(O)NR₃, and C=N(OR₇) and R₆ is selected from the group consisting of C₁-C₁₀-alkyl, aryl and heterocyclyl or optionally in each case can have one or more hydrogen atoms replaced with one or more identical or different radicals R₅;

R₇ represents H or the radical R₆;

or R₃ & R₄ together with the nitrogen atom to which they are attached can form a cyclic system as represented by formula IA



Formula IA

wherein L & M independently or together represent C=O, C=S, SO₂, CH₂, CH(lower alkyl), C(lower alkyl)₂, and Q is an aryl or heterocyclyl system, optionally substituted with one or more identical or different radicals R₅.

R₅ is selected from the group consisting of halogen, -OH, -CN, -NO₂, -lower-alkyl, -cycloalkyl, -O-lower alkyl, -O-cycloalkyl, -O-aryl, -O-heterocyclyl, -lower alkyl-O-lower alkyl, -O-lower alkyl-O-lower alkyl, -O-lower alkyl-NH(lower alkyl), -O-lower alkyl-N(lower alkyl)₂, -O-lower alkyl-(heterocyclyl), -C(O)-lower alkyl, -COOH, -C(O)NH₂, -C(O)NH-lower alkyl, -C(O)N(lower alkyl)₂, -C(O)O-lower alkyl, -lower haloalkyl, -lower alkenyl, -lower alkynyl, -OC(O)-NH₂, -OC(O)-NH(lower alkyl), -OC(O)-N(lower alkyl)₂, -NH₂, -NH(lower alkyl), -N(lower alkyl)₂, -NH-SO₂-lower alkyl, -N(lower alkyl)-SO₂-lower alkyl, -NH-C(O)-(lower alkyl), -N(lower alkyl)-C(O)-(lower alkyl), -NH-C(O)O-lower alkyl, -N(lower alkyl)-C(O)O-lower alkyl, -NH-C(O)-NH₂, -NH-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-NH(lower alkyl), -N(lower alkyl)-C(O)-N(lower alkyl)₂, -NH-C(O)-NH-SO₂-lower alkyl, -N(lower alkyl)-C(O)-NH-SO₂-lower alkyl, -N(lower alkyl)-C(O)-N(lower alkyl)-SO₂-lower alkyl, -S-lower alkyl, -S(O)-lower alkyl, -SO₂-lower alkyl, -S-aryl, -S(O)-aryl, SO₂-aryl, -S-heterocyclyl, -SO-heterocyclyl, -SO₂-heterocyclyl, -SO₂NH₂, -SO₂NH-(lower alkyl), -SO₂N(lower alkyl)₂, heterocyclyl and an aryl group in each case are unsubstituted or mono- or polysubstituted;

X is O, S or NH;

Y is C=O, C=S, SO₂;

with the proviso that when P is a 5 membered heteroaryl ring then it does not contain more than 2 nitrogen atoms

- 2 A compound as claimed in claim 1 wherein P is selected from the group consisting of pyrimidine and thiazole.
- 3 A compound as claimed in claim 1 wherein X is NH.
- 4 A compound as claimed in claim 1 wherein R₁ is selected from the group consisting of pyridinyl, pyrazinyl, thiophenyl, furanyl, pyrrolyl, quinolinyl, pyrimidinyl, thiazolyl which may be optionally substituted by one or more identical or different R₅ radicals wherein R₅ is as defined in claim 1.
5. A compound as claimed in claim 1 selected from the group consisting of
 4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-fluorobenzoyl)hydrazide;
 4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-4-[[4-methyl-1-piperazinyl)methyl]benzoyl]hydrazide;
 4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[[3-methyl

-5-(4-methyl-imidazol-1-yl)]benzoyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid
N'-(5-*tert*-butyl-1-phenyl-1*H*-pyrazol-3-carbonyl)hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-*tert*-butyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[(4-trifluoromethoxy)benzoyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[3,5-bis(trifluoromethyl)benzoyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-hydroxybenzoyl)hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-(4-chlorophenyl)-1-(4-sulfonamido)phenyl-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-(4-methoxyphenyl)-1-(4-sulfonamido)phenyl-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-*tert*-butyl-1-(4-fluorophenyl)-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-*tert*-butyl-1-(2,4-dichlorophenyl)-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,4-dichlorophenyl)-5-(pyridin-2-yl)-1*H*-pyrazol-3-carbonyl] hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-*tert*-butyl-1-(3-trifluoromethyl)phenyl-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(4-fluorophenyl)-5-(pyridin-2-yl)-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1,5-bis(pyridin-2-yl)-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-(pyridin-2-yl)-1-(4-sulfonamido)phenyl-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-carbonyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[2-(trifluoromethyl)benzoyl]hydrazide;
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(pyridin-3-carbonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(5-methylpyrazin-2-carbonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(4-fluorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(1*H*-indol-5-carbonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(pyridin-2-carbonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-1-(1*H*-benzimidazol-5-carbonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[(3-trifluoromethyl)benzoyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[(*E*)-3-phenylacryloyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[(*E*)-3-(3-trifluoromethyl)phenylacryloyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-*tert*-butyl-1-(4-chlorophenyl)-1*H*-pyrazol-3-carbonyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(4-sulfonamido)phenyl-5-(4-trifluoromethyl)phenyl-1*H*-pyrazol-3-carbonyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[(*E*)-3-(3-hydroxyphenyl)acryloyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[5-*tert*-butyl-1-(4-sulfonamido)phenyl-1*H*-pyrazol-3-carbonyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(3,3,3-trifluoropropanoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[2-(3-trifluoromethyl)phenylacetyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,5-difluorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(3,5-difluorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[3,5-bis(trifluoromethyl)benzoyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[4-(trifluoromethyl)benzoyl]hydrazide

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[(*E*)-3-fluoro-5-(trifluoromethyl)acryloyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-chlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-difluorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,3-dichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4-dichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[(*E*)-3-(2,6-dichlorophenyl)acryloyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[2,6-bis(trifluoromethyl)benzoyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-bromobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-6-methylphenyl)hydrazide];

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-6-fluorobenzoyl)hydrazide];

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-nitrobenzoyl)hydrazide];

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(3-chlorothiophene-2-carbonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorophenylsulfonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(4-chlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(5-chlorothiophene-2-carbonyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trimethoxybenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trifluorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[[[2-(trifluoromethyl)phenyl]amino]carbonyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[[[4-*tert*-butylphenyl]amino]carbonyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[[[2,6-dichlorophenyl]amino]carbonyl]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzoyl)hydrazide;

4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzoyl)hydrazide;

4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-fluorobenzoyl)hydrazide;

4-Methoxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trichlorobenzoyl)hydrazide;

4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzoyl)hydrazide;

4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-fluorobenzoyl)hydrazide;

4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trichlorobenzoyl)hydrazide;

4-Chloro-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-6-methylbenzoyl)hydrazide];

4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-chloro-6-methylbenzoyl)hydrazide;

4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(2-thiophenyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-chloro-6-methylbenzoyl)hydrazide;

4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trichlorobenzoyl)hydrazide;

4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,6-dichlorobenzoyl)hydrazide

4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2-chloro-6-methylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(2,5-dimethyl-3-furanyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trifluorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid *N'*-(2,4,6-trichlorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichlorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(2-pyrrolyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-6-benzoyl)]hydrazide;

4-Methyl-3-[[4-(2-thiazolyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-6-benzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichloro-4-pyridinyl)] benzoylhydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,4,6-trimethylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(4-methanesulfonylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(6-chloro-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichlorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-4-pyridinyl)] benzoylhydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichloro-3-pyridinyl)] benzoylhydrazide;

4-Methyl-3-[[4-(6-methoxy-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichlorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-dimethylamino)phenyl]-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichloro-benzoyl)]hydrazide;

4-Methyl-3-[[4-(6-methyl-3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-iodobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-4-methyl-3-pyridinyl)]benzoylhydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-5-methoxybenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-benzoylhydrazide

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,4,6-triisopropylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(2-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,4,6-trimethylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-amino-6-methylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-4-fluorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-[2-chloro-4-(4-methyl-1-piperazinyl) benzoyl]]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-[2-chloro-4-(5-methyl-3-imidazolyl) benzoyl]]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-iodo-6-methylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(2-methyl-5-pyrazinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-iodobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-quinolinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-6-methylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(5-pyrimidinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-iodobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-hydroxy-6-methylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-fluoro-6-iodobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-4-iodobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-benzylhydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(3-trifluoromethyl-4-methylbenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichloro-4-methoxybenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2,6-dichlorobenzenesulfonyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzenesulfonic acid *N'*-[1-(2,4,6-trichlorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(3-pyridinyl)-2-thiazolyl]amino]benzoic acid *N'*-[1-(2,4,6-trichlorobenzoyl)]hydrazide;

4-Methyl-3-[[4-(5-pyrimidinyl)-2-pyrimidinyl]amino]benzoic acid *N'*-[1-(2-chloro-6-methylbenzoyl)]hydrazide;

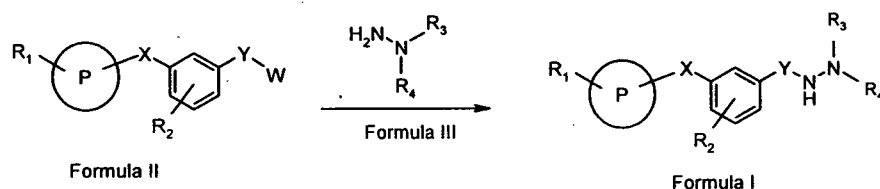
N-(4-Hydroxy-1,3-dioxo-isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide;

N-(1,3-Dioxo-isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide;

N-(4-Chloro-1-oxo-1*H*-isoindol-2-yl)-4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]benzamide.

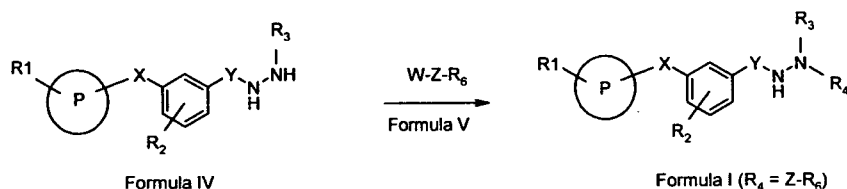
6. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable diluent or carrier.
7. A method for treatment of disorders dependent on tyrosine kinases, comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I or salt thereof.
8. The method of claim 7 wherein the said tyrosine kinase is a receptor tyrosine kinase or a non receptor tyrosine kinase.
9. The method of claim 8 wherein the receptor tyrosine kinase is PDGF- α & PDGF- β receptor kinase, Kit-receptor kinase, Flt-3, Flt-4, FGFR-1, FGFR-3, FGFR-4, Met, RON, Ret or ALK.
10. The method of claim 8 wherein the non- receptor tyrosine kinase is Bcr-Abl, Abl kinase, ARG; kinases from the Src family, Src kinase, Yes, Lck, Lyn or Fyn.
11. The method of claim 7 wherein disorder dependent on tyrosine kinase is a hyperproliferative disorder selected from the group consisting of CML, CLL, ALL, AML, myelodysplastic syndrome, melanoma, germ cell tumors, GIST, NSCLC, mastocytosis, neuroblastoma, glioblastoma, astrocytoma, hepatocellular carcinoma, renal cell cancer, breast cancer and other solid tumors or is diabetes remission.
12. The method for treating cancer comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I.

13. The method of claim 7 wherein the said compound of formula I or salt thereof is administered, simultaneously or sequentially with another tyrosine kinase inhibitor, a chemotherapeutic agent, DNA alkylating/ intercalating agent, an inhibitor of polyamine biosynthesis, antifolate agent, inhibitor of microtubule depolymerization, topoisomerase I & II inhibitor, proteasome inhibitor, an inhibitor of serine/threonine protein kinase, a cytokine, a negative growth regulator, an aromatase inhibitor or classical cytostatic inhibitor.
14. A process for the preparation of compound of formula I comprising reacting the compounds of formula II with compound of formula III,



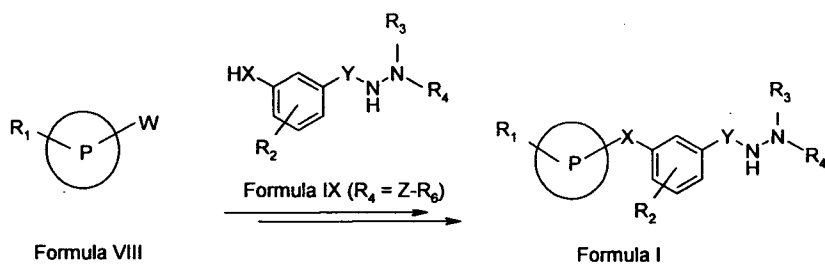
wherein P , R_1 , R_2 , R_3 , R_4 , X and Y are as defined for a compound of formula I and W is a leaving group

15. A process for the preparation of compound of formula I comprising reacting compounds of formula IV with the compounds of formula V,



wherein P , R_1 , R_2 , R_3 , R_4 , R_6 , W , X , Y & Z are as previously defined.

16. A process for the preparation of compound of formula I comprising reacting compounds of formula VIII with the compounds of formula IX,



wherein P, R₁, R₂, R₃, R₄, R₆, W, X, Y & Z are as previously defined.