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(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHAPARRO MARTIN, Maria Jesus** [ES/ES]; GlaxoSmithKline, Parque Tecnologico De Madrid, Calle Doctor Severo Ochoa, Tres Cantos, E-28760 Madrid (ES). **COTERON LOPEZ, Jose Miguel** [ES/ES]; GlaxoSmithKline, Parque Tecnologico De Madrid, Calle Doctor Severo Ochoa, Tres Cantos, E-28760 Madrid (ES). **FERNANDEZ VELANDO, Esther Pilar** [ES/ES]; GlaxoSmithKline, Parque Tecnologico De Madrid, Calle Doctor Severo Ochoa, Tres Cantos, E-28760 Madrid (ES). **FIANDOR ROMAN, Jose Maria** [ES/ES]; GlaxoSmithKline, Parque Tecnologico De Madrid, Calle Doctor Severo Ochoa, Tres Cantos, E-28760 Madrid (ES). **MARCO MARTIN, Maria** [ES/ES]; GlaxoSmithKline, Parque Tecnologico De Madrid, Calle Doctor Severo Ochoa, Tres Cantos, Third Avenue, E-28760 Madrid (ES).

(74) Agent: **SARDHARWALA, Fatema**; GlaxoSmithKline, CIP CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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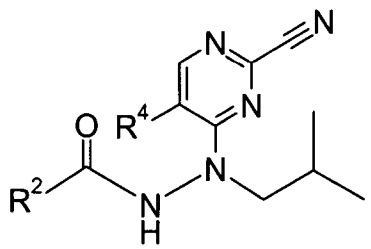

(I)

(57) Abstract: Substituted heteroaryl nitrile derivatives of Formula I, processes for their preparation, pharmaceutical compositions comprising such compounds and use of the compounds as cysteine protease inhibitors are provided.

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NOVEL CYSTEINE PROTEASE INHIBITORS

FIELD OF THE INVENTION

The invention is directed to certain substituted heteroaryl nitrile derivatives, which are protease inhibitors. More specifically, the compounds are inhibitors of cysteine proteases. In particular, the compounds inhibit cysteine proteases of the papain superfamily, more specifically those of the falcipain family, which are cysteine proteases found in the malaria parasite *Plasmodium falciparum*, and also cysteine proteases of the cathepsin family such as cathepsins K, L, S and B.

BACKGROUND OF THE INVENTION

Malaria is one of the major disease problems of the developing world. The most virulent malaria-causing parasite in humans is *Plasmodium falciparum*, which is the cause of hundreds of millions of cases of malaria per annum, and is thought to cause over 1 million deaths each year, Breman, J. G., et al., (2001) Am. Trop. Med. Hyg. 64, 1-11. One problem encountered in the treatment of malaria is the build-up of resistance by the parasite to available drugs. Thus there is a need to develop new antimalarial drugs.

One way of identifying a potential new drug with antimalarial activity is to study biological targets found in the *Plasmodium falciparum* parasite, in turn by investigating biological pathways in which particular targets might be identified. In *Plasmodium falciparum*, haemoglobin is transported to an acidic food vacuole, where it is degraded. It appears that multiple enzymes, including food vacuole cysteine, aspartic, and metalloproteases, and a cytosolic aminopeptidase, contribute to haemoglobin hydrolysis, Francis S.E. et al., (1997) Annu. Rev. Microbiol. 51, 97-123; Rosenthal P.J. Protease inhibitors. In: Rosenthal P.J., ed. Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery, Totowa, N.J.: Humana Press, (2001) 325-345. Plasmodial haemoglobinases are therefore potential therapeutic targets.

Cysteine protease inhibitors were shown some years ago to block haemoglobin degradation by erythrocytic parasites, causing a characteristic morphological abnormality in which the food vacuole fills with undegraded haemoglobin and parasite development is blocked, · Rosenthal P. J., et al., (1998) J. Clin. Invest. 82, 1560-6; Gamboa de Dominguez N.D. and Rosenthal P.J., (1996) Blood 87, 4448-54. Efforts to identify enzymes responsible for haemoglobin degradation led to the characterization of "falcipain" as a trophozoite food vacuole cysteine protease, Rosenthal P.J. and Nelson R.G., (1992) Mol Biochem Parasitol 51, 143-52; Salas F. et al., (1995) Infect. Immun. 63 2120-5. It has more recently been found that "falcipain" actually constitutes three related papain-family cysteine proteases which share a number of unusual features, known as falcipain-1, falcipain-2 and falcipain-3, Rosenthal, P. J., et al., (2002) Curr. Pharm. Des. 8, 1659-1672. Falcipain-2 is the principal cysteine protease of *Plasmodium falciparum* trophozoites,

Shenai B.R. et. al., (2000) J Biol Chem 275, 29000-10. Importantly, cysteine protease inhibitors that inhibit falcipain-2 consistently block haemoglobin hydrolysis and parasite development. These data suggest that falcipain-2 is a key target enzyme, but it is likely that the other two falcipains are also appropriate targets and that, in many cases, they are inhibited by the same compounds that are active against falcipain-2. Like falcipain-2, falcipain-3 readily hydrolyzes native haemoglobin under mildly reducing conditions that are similar to those found in physiological systems, Shenai B.R. et al., (2000) J. Biol. Chem. 275, 29000-10; Sijwali P.S. et al., (2001) Biochem. J. 360, 481-9; Shenai B.R. and Rosenthal P.J., (2002) Mol. Biochem. Parasitol. 122, 99-104. Falcipain-2 and falcipain-3 are similar in structure but falcipain-1 is a more distant relative; it is thought that this enzyme plays a key role in the invasion of erythrocytes by *Plasmodium falciparum* merozoites but that it is not essential for normal development during the erythrocytic stage, Sijwali, P. S., et al., Proceedings of the National Academy of Sciences of the United States of America 101, 8721-8726. Whether falcipain-1 also plays a role in haemoglobin processing is unknown. Very recently, a fourth papain-family cysteine protease has been found, now known as falcipain-2'. Falcipain-2' is nearly identical in sequence to falcipain-2, differing by only 3 amino acids, none of which are located at the active site. The structure of falcipain-2' is not known, but is likely to be very similar to that of falcipain-2. The biological role of falcipain-2' is also expected to be very similar, although probably not identical, to that of falcipain-2. In any event, cysteine protease inhibition, in particular the inhibition of falcipain-2, blocks parasite development. Falcipain-2 and related plasmodial cysteine proteases are thus logical targets for antimalarial chemotherapy and therefore there is a need for compounds which are inhibitors of these targets.

P. vivax is the second most important human malaria parasite, after *P. falciparum*. Although less virulent than *P. falciparum*, *P. vivax* is the most widely distributed human malaria parasite, and it causes extensive morbidity (Mendis, K., Sina, B. J., Marchesini, P. and Carter, R. (2001) "The neglected burden of *Plasmodium vivax* malaria" *Am. J. Trop. Med. Hyg.* **64**, 97-106). These two parasites are responsible for more than 90% of episodes of human malaria, totalling several hundred million cases annually. However, comprehensive studies of *P. vivax* have been limited due to technical shortcomings. Notably, unlike the case with *P. falciparum*, routine *in vitro* culture of *P. vivax* is not available, and animal models are limited to primates. Very recently (Na, B.K., Shenai, B. R., Sijwali, P. S., Choe, Y., Pandey, K. C., Singh, A., Craik, C. S., Rosenthal, P. J. (2004) identification and biochemical characterization of vivapains, cysteine proteases of the malaria parasite *Plasmodium vivax*. *Biochem. J.* **378**, 529-538), two cysteine protease genes (vivapain-2 and vivapain-3) from *P. vivax* have been identified and cloned and the heterologously expressed gene products have been characterized biochemically. It was found that these cysteine proteases are apparent orthologues of falcipain-2 and falcipain-3, but key differences in the biochemical properties of the plasmodial proteases warrant

attention to the inhibition of each enzyme in the evaluation of antimalarial protease inhibitors.

Cathepsins are a family of enzymes which are part of the papain superfamily of cysteine proteases. Certain cathepsins, for example cathepsins K, B, L, and S have been described in the literature. Cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Patent No. 5,501,969. Cathepsin K has also been variously denoted as cathepsin O or cathepsin O2 in the literature. The designation cathepsin K is considered to be the most appropriate and is used herein. Cathepsin K has been expressed, purified, and characterised, Bossard, M. J., et al., (1996) J. Biol. Chem. 271, 12517-12524; Drake, F.H., et al., (1996) J. Biol. Chem. 271, 12511-12516; Bromme, D., et al., (1996) J. Biol. Chem. 271, 2126-2132.

Cathepsins function in the normal physiological process of protein degradation in animals, including humans, e.g. in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated as causative agents in various disease states, including but not limited to, infections by *Pneumocystis Carinii*, *Trypsanoma cruzi*, *Trypsanoma brucei*, and *Crithidia fusiculata*; as well as in schistosomiasis, malaria, cancer, for example pancreatic cancer (see Joyce J. A. *et al.*, Cancer Cell (2004) 5, 443-453 and Gocheva V., Genes & Development (2006) 20, 543-556), tumour invasion and tumour metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, inflammation, rheumatoid arthritis, osteoarthritis, osteoporosis, coronary disease, atherosclerosis, autoimmune diseases, respiratory diseases such as obstructive pulmonary disorder (COPD), immunologically mediated diseases (for example, transplant rejection), and other related diseases, see: International Publication Number WO 94/04172, published on March 3, 1994, and references cited therein; see also: European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine proteases from *P. gingivallis*, called gingipains, have been implicated in the pathogenesis of gingivitis, Potempa, J., et al., (1994) Perspectives in Drug Discovery and Design 2, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I collagen represents the major structural protein of bone comprising approximately 90% of the protein matrix. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of haematopoietic lineage. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle of resorption and formation. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma. Several published studies have demonstrated that inhibitors of cysteine proteases are effective at inhibiting osteoclast-mediated bone resorption, thus indicating an essential role for cysteine proteases in bone resorption. For example, Delaisse, et al., (1980) Biochem. J., 192, 365, suggests that inhibitors of cysteine proteases (e.g., leupeptin, Z-Phe-Ala-CHN_2) prevent bone resorption, while serine protease inhibitors were ineffective. Delaisse et. al., (1984) Biochem. Biophys. Res. Commun. *125*, 441, discloses that E-64 (L-trans-epoxysuccinyl-leucinamido-(4-guanidino)butane) and leupeptin are also effective at preventing bone resorption *in vivo* in rats. Lerner, et al., (1992) J. Bone Min. Res. 7, 433, discloses that cystatin, an endogenous cysteine protease inhibitor, inhibits PTH stimulated bone resorption in mouse calvariae. Other studies report a correlation between inhibition of cysteine protease activity and bone resorption. Tezuka, et al., (1994) J. Biol. Chem. 269, 1106; Inaoka, et al., (1995) Biochem. Biophys. Res. Commun., 206, 89 and Shi, et al., (1995) FEBS Lett. 357, 129 disclose that under normal conditions cathepsin K is abundantly expressed in osteoclasts and may be the major cysteine protease present in these cells.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Cathepsin K is also expressed in synovial giant cells taken from osteoarthritic patients (Dodds, et al., (1999) Arthritis & Rheumatism, 42, 1588, and Hou, et al., (2002), American Journal of Pathology 159, 2167). Cathepsin K staining is observed in osteoarthritic as well as rheumatoid arthritic samples (Hou, et al., (2002), American Journal of Pathology 159, 2167). The expression of cathepsin K has also been localized to cartilage tissue and a decrease in pH in cartilage correlated with severity of damage (Konttinen, et al., (2002), Arthritis & Rheumatism, 46, 953). This observation, combined with the fact that cathepsin K is an acidic lysosomal protease, strongly suggests a physiological role of cathepsin K in cartilage turnover in addition to bone resorption. These researchers also demonstrated that cathepsin K can degrade aggrecan and type II collagen, the two major protein components of the cartilage matrix. Thus, inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Cathepsin K has been shown to be abnormally or

overexpressed in numerous tumors and in prostate cancer (Littlewood-Evans, et al., (1997), Cancer Res., 57, 5386 and Brubaker, et al., (2003), J. Bone Miner. Res., 18, 222). Furthermore, increased levels of bone resorption marker have been detected in bone metastases of prostate cancer suggesting that cathepsin K inhibitor may have utility in preventing metastasis of tumors to bone (Ishikawa, et al., (2001), Mol. Carcinog., 32, 84 and Brubaker, et al., (2003), J. Bone Miner. Res., 18, 222). Metastatic neoplastic cells also typically express high levels of other proteolytic enzymes such as cathepsin B, S and L that degrade the surrounding matrix. Thus, inhibition of cathepsin K may also be useful for treating certain tumors and neoplastic diseases.

Cathepsin L has been implicated in several diseases including osteoporosis, osteoarthritis, rheumatoid arthritis, lymphoproliferative diseases, cancer, for example pancreatic cancer, metastasis, atherosclerosis (Lecaille, et al., (2002) Chem. Rev. 102, 4459 and Liu, et al., (2004), Arterioscler Throm Vasc Biol. 24, 1359). Cathepsin L-deficient mice have also been shown to have increased resistance to osteoporosis following ovariectomy suggesting its potential for osteoporosis (Potts, et al., (2004) Int. J. Exp. Path. 85, 85). Cathepsin L is required for endothelial progenitor cell-induced neovascularization (Urbich, et al., (2005) Nat. Med. 11, 206). Similarly, targeting cathepsin L by specific ribozymes decreases cathepsin L protein synthesis and cartilage destruction in rheumatoid arthritis (Schedel, et al., (2004) Gene Ther. 11, 1040) suggesting its potential role in rheumatoid arthritis.

Cathepsin S has been implicated in several diseases including immune and auto-immune disorders, rheumatoid arthritis, inflammation, inflammatory bowel disease, myesthania gravis, atherosclerosis, lymphoproliferative diseases, cancer, for example pancreatic cancer, metastasis (Lecaille, et al., (2002) Chem. Rev. 102, 4459 and Liu, et al., (2004), Arterioscler Throm Vasc Biol. 24, 1359). Cathepsin S is thought to play a role in invariant chain degradation and antigen presentation and cathepsin S null mice have been shown to have a diminished collagen-induced arthritis (Nakagawa, et al., (1999) Immunity, 10, 207) suggesting its potential role in rheumatoid arthritis.

Cathepsin B has been implicated in immune and auto-immune disorders, rheumatoid arthritis, inflammation, inflammatory bowel disease, myesthania gravis, osteoarthritis, lymphoproliferative diseases, cancer, for example pancreatic cancer, metastasis (Lecaille, et al., (2002) Chem. Rev. 102, 4459 and Lang, et al., (2000), J. Rheumatol. 27, 1970). Cathepsin B has been implicated in the processing of invariant chain (Zhang, et al., (2000) Immunology, 100, 13) suggesting its role in immune disorders such as those listed above. Cathepsin B is one of the most highly expressed cysteine protease in cartilage and inhibitors of cathepsin B has been shown to inhibit cartilage degradation. Cathepsin B may contribute to matrix degradation through cleavage of aggrecan and collagen, two components of cartilage matrix (Mort et al., (1998), Biochem. J., 335, 491). Additionally,

cathepsin B could contribute to the mechanical loading component of osteoarthritis by cleaving lubricin, an abundant lubricating protein in synovial fluid. Cleavage of lubricin by cathepsin B has been shown to increase the coefficient of friction in synovial fluid and intact joints (Elsaid, K.A. et al. (2005), Transactions of the Orthopedic Research Society, 51st Annual Meeting, Abstract 924). These data suggest potential for cathepsin B inhibitors in osteoarthritis.

In view of the number of pathological responses and conditions that are mediated by cathepsins K, L, S and B, there is a need for inhibitors of these cathepsins which can be used in the treatment of a variety of conditions.

WO 2005/085210 A1 discloses certain fused bicyclic pyrimidine compounds as inhibitors of cathepsin K, useful in the treatment of bone diseases such as osteoporosis and the like. WO 2005/103012 A1 discloses certain hydrazine-heterocyclic nitrile compounds as inhibitors of cathepsin K, useful in the treatment of bone diseases such as osteoporosis and the like.

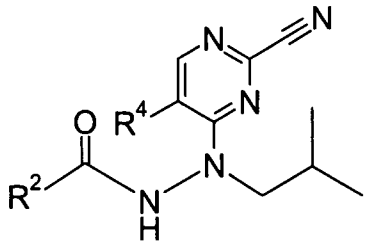
SUMMARY OF THE INVENTION

The invention is directed to novel heteroaryl nitrile derivatives and their use as protease inhibitors, more specifically inhibitors of cysteine protease, even more specifically inhibitors of cysteine proteases of the papain superfamily. In one aspect of the invention the cysteine proteases are those of the falcipain family, for example falcipain-2 and falcipain-3, which are examples of cysteine proteases indicated in malaria. In another aspect of the invention the cysteine proteases are those of the cathepsin family for example cathepsins K, L, S and B, which is a cysteine protease indicated for example in conditions characterised by excessive bone loss such as osteoporosis and bone metastasis, and other bone and joint diseases such as osteoarthritis. The compounds of the invention may also have utility as serine protease inhibitors.

The invention involves the compounds represented hereinbelow, pharmaceutical compositions comprising such compounds and use of the compounds as protease inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides at least one chemical entity selected from compounds of Formula I:



I

Wherein:

R^4 represents halogen;

R^2 represents

i) -phenyl-C_{1-3}alkylene-X, -pyridyl-phenyl-C_{1-3}alkylene-X or -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3; or

ii) -Y-C_{1-3}alkylene-X or -Y-C_{1-3}alkylene-X-R^J;

Y represents an aromatic group comprising a 5-membered ring having one to four heteroatoms selected from N, O and S, the ring being optionally fused to a phenyl ring;

R^J represents Z, -C_{1-4}alkylene-Z or -C(O)Z;

X and Z independently represent:

i) a monocyclic 4-membered, saturated hydrocarbon group containing one nitrogen atom;

ii) a monocyclic 5-membered, saturated or partially saturated hydrocarbon group containing one nitrogen atom; or

iii) a monocyclic 6-membered, saturated, partially saturated or aromatic hydrocarbon group containing one or two nitrogen atoms and optionally an oxygen atom;

wherein X and Z are independently optionally substituted with a) one group selected from: C_{1-4}alkyl, C_{1-4}alkylOH, -C_{1-4}alkylOC_{1-4}alkylOH, OH, -C_{1-4}alkylC(O)OC_{1-4}alkyl, -C(O)OC_{1-4}alkyl, NR^ER^F, -C_{1-4}alkylNR^ER^F, -NC(O)C_{1-3}alkyl, -NC(O)OC_{1-4}alkyl and -C(O)NR^ER^F and b) optionally an additional group which is C_{1-4}alkyl;

R^E and R^F independently represent hydrogen or C_{1-4}alkyl or C_{1-4}alkenyl;

and pharmaceutically acceptable derivatives thereof.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention, R^4 represents chlorine, bromine or iodine. In another embodiment, R^4 represents chlorine or bromine. In a further embodiment, R^4 represents bromine.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention R^2 represents -phenyl-C_{1-3}alkylene-X, -pyridyl-phenyl-C_{1-3}alkylene-X or -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3. In another embodiment, R^2 represents -pyridyl-phenyl-C_{1-3}alkylene-X or -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3. In a further embodiment, R^2 represents -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3. In a further embodiment, R^2 represents -pyridyl-phenyl-C_{1-3}alkylene-X, wherein phenyl is optionally substituted with one group selected from halogen or CF_3. In a yet further embodiment, R^2 represents -phenyl-C_{1-3}alkylene-X, wherein phenyl is optionally substituted with one group selected from halogen or CF_3. In one embodiment, wherein a phenyl group in R^2 is optionally substituted, the optional substituent is fluorine. In another embodiment, the phenyl group in R^2 is unsubstituted. In one embodiment, the groups directly bonded to the phenyl group in R^2 (excluding optional substituents) are in *para* orientation relative to one another. In another embodiment, the groups directly bonded to the phenyl group in R^2 (excluding optional substituents) are in *meta* orientation relative to one another. In one embodiment, where R^2 contains a pyridyl group, the groups directly bonded to the pyridyl group (excluding optional substituents) are in *para* orientation relative to one another. In another embodiment, where R^2 contains a pyridyl group, the groups directly bonded to the pyridyl group (excluding optional substituents) are in *meta* orientation relative to one another. In one embodiment of the invention, R^2 represents -Y-C_{1-3}alkylene-X or -Y-C_{1-3}alkylene-X-R^J. In another embodiment, R^2 represents -Y-C_{1-3}alkylene-X. In a further embodiment, R^2 represents -Y-C_{1-3}alkylene-X-R^J. In one embodiment, the alkylene group or groups in R^2 is methylene.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention Y represents furan, thiophene, isoxazole or benzofuran.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention, R^J represents Z. In another aspect, R^J represents -C_{1-3}alkylene-Z. In a further aspect, R^J represents -C(O)Z.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention, X and Z independently represent an

optionally substituted monocyclic 4-membered, saturated hydrocarbon group containing one nitrogen atom. In another embodiment, X and Z independently represent an optionally substituted monocyclic 5-membered, saturated or partially saturated hydrocarbon group containing one nitrogen atom. In a further embodiment, X and Z independently represent an optionally substituted monocyclic 6-membered, saturated, partially saturated or aromatic hydrocarbon group containing one or two nitrogen atoms and optionally an oxygen atom.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention, X represents piperidine, piperazine or morpholine, each of which is optionally substituted. In another embodiment, X represents piperidine or piperazine, each of which is optionally substituted. In a further embodiment, X represents piperidine which is optionally substituted. In one embodiment, X represents pyrrolidine or pyrroline, each of which is optionally substituted. In another embodiment, X respresents pyrrolidine which is optionally substituted. In one embodiment X is unsubstituted.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention, Z represents piperidine, piperazine or morpholine, each of which is optionally substituted. In another embodiment, Z represents piperidine or piperazine, each of which is optionally substituted. In a further embodiment, Z represents piperazine which is optionally substituted. In one embodiment, Z represents pyrrolidine which is optionally substituted. In one embodiment Z is unsubstituted.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention, in one embodiment X is optionally substituted with a) one group selected from: C_{1-4}alkyl, C_{1-4}alkylOH, -C_{1-4}alkylOC_{1-4}alkylOH, OH, -C_{1-4}alkylC(O)OC_{1-4}alkyl, -C(O)OC_{1-4}alkyl, NR^ER^F, -C_{1-4}alkylNR^ER^F, -NC(O)C_{1-3}alkyl, -NC(O)OC_{1-4}alkyl and -C(O)NR^ER^F and b) optionally an additional group which is C_{1-4}alkyl. In another embodiment, X is optionally substituted with a) one group selected from: C_{1-4}alkyl, C_{1-4}alkylOH, -C_{1-4}alkylOC_{1-4}alkylOH, OH, -C_{1-4}alkylC(O)OC_{1-4}alkyl, -C(O)OC_{1-4}alkyl, NR^ER^F, -NC(O)C_{1-3}alkyl, -NC(O)OC_{1-4}alkyl and -C(O)NR^ER^F and b) optionally an additional group which is C_{1-4}alkyl. In a further embodiment, the C_{1-4}alkyl substituent group is selected from methyl and propyl. In yet another embodiment, the C_{1-4}alkyl substituent group is methyl. In a further embodiment, X is substituted with two methyl groups.

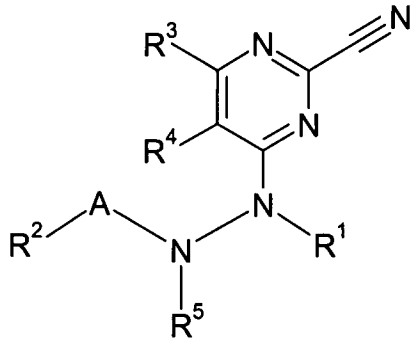
In one embodiment, Z is optionally substituted with C_{1-4}alkyl. In another embodiment, Z is optionally substituted with methyl.

In respect of compounds of Formula I and pharmaceutically acceptable derivatives thereof: in one embodiment of the invention, R^E and R^F represent C_{1-4}alkyl. In another embodiment, R^E and R^F independently represent methyl, ethyl or propyl. In a further embodiment, R^E and R^F represent methyl. In one embodiment of the invention, R^E and R^F represent C_{1-4}alkenyl. In another embodiment, R^E and R^F represent propenyl.

The meaning of any functional group or substituent thereon at any one occurrence in Formula I or any subformula thereof, is independent of its meaning, or any other functional group's or substituent's meaning, at any other occurrence, unless stated otherwise.

It is to be understood that the present invention covers all combinations of the groups according to different aspects of the invention as described hereinabove.

In an alternative embodiment the invention provides at least one chemical entity chosen from compounds of Formula IA:



IA

Wherein:

R^1 represents C_{1-8}alkyl, -C_{1-8}alkyleneNR^{E}R^F, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl, -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl or -C_{1-8}alkylene-cycloalkyl;

R^3 represents hydrogen, C_{1-3}alkyl, alkoxy, or -C(O)Oalkyl;

R^4 represents hydrogen, halogen, alkoxy, -CΞC-aryl, -NHC_{1-3}alkylene-aryl, NO_2, CF_3, or OCF_3;

provided that R^3 and R^4 are not both hydrogen, and when R^3 is C_{1-3}alkyl then R^4 is other than hydrogen;

and

a) A represents C(O) and

i) R^2 represents R^{2a} or R^{2b} wherein

R^{2a} represents $-NR^H$-aryl, $-NR^H$-heteroaryl, $-NR^H$-aryl-heteroaryl or $-NR^H$-heteroaryl-aryl; and

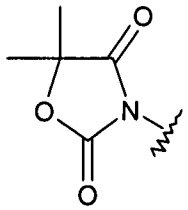
R^{2b} represents $-C_{1-6}$alkyleneR^A, aryl, biaryl, -aryl-heteroaryl, -heteroaryl-aryl, -aryl-heterocyclyl, -aryl-C_{1-3}alkylene-heterocyclyl, -aryl-O-C_{1-3}alkylene-heterocyclyl, aryl-C_{1-3}alkylene-heteroaryl, -aryl-heteraoaryl-C_{1-3}alkylene-heterocyclyl, -heteroaryl-aryl-C_{1-3}alkylene-heterocyclyl, aryloxy, heteroaryl, cycloalkyl, -cycloalkyl-aryl, cycloalkyloxy, heterocyclyl, $-NR^H$-aryl-heterocyclyl, $-NR^H$-cycloalkyl, $-N(R^B)C_{1-6}$alkyleneR^C, -NH-N(C_{1-3}alkyl)-heteroaryl, $-OC_{1-6}$alkyleneR^D, $-OC_{1-6}$alkenyl, -aryl-C_{1-3}alkylene-heterocyclyl-R^J, -aryl-C_{1-3}alkylene-heteroaryl-R^K, C_{1-3}alkylene(NH_2)-aryl, or -aryl-C_{1-3}alkylene-NH-C_{1-3}alkylene-OH;

and

R^5 represents hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, $-C(O)R^{2a}$, $-C_{1-8}$alkylene-heterocyclyl, $-C_{1-8}$alkylene$NR^GC(O)C_{1-6}$alkyl, $-C_{1-8}$alkylene$NR^GC(O)OC_{1-6}$alkyl, $-C_{1-8}$alkyleneNR^ER^F, N-phthalidimido-C_{1-8}alkylene- or $-C(O)C_{1-6}$alkyl;

or

ii) R^2 and R^5 together with the carbon and nitrogen atoms to which they are respectively attached form a group selected from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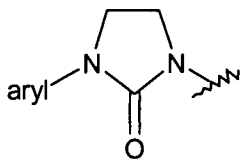

;

or

b) A represents $-SO_2$- and

R^2 represents C_{1-6}alkyl, aryl, C_{1-6}aralkyl or -C_{1-6}alkyleneheterocyclyl;

and

R^5 represents hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, -C_{1-8}alkylene-heterocyclyl, $-C_{1-8}$alkylene$NR^GC(O)C_{1-6}$alkyl, $-C_{1-8}$alkylene$NR^GC(O)OC_{1-6}$alkyl, $-C_{1-8}$alkyleneNR^ER^F, N-phthalidimido-C_{1-8}alkylene- or $-C(O)C_{1-6}$alkyl;

R^A, R^C and R^D independently represent hydrogen, halogen, $-NR^ER^F$, cyano, CCl_3, $-C(O)C_{1-6}$alkyl, C_{1-3}alkyl, cycloalkyl, heterocyclyl, aryl, biaryl, -aryl-heteroaryl, -aryl-C_{1-3}alkylene-heterocyclyl, -aryl-O-C_{1-3}alkylene-heterocyclyl, -C_{1-3}alkenylaryl, heteroaryl, C_{1-6}aralkyl, $-NHC(O)C_{1-6}$alkyl, $-NHC(O)OC_{1-6}$alkyl, $-NHC(O)C_{1-6}$aralkyl or $-NHC(O)OC_{1-6}$aralkyl;

R^B represents hydrogen or C_{1-8}alkyl;

R^E and R^F independently represent hydrogen or C_{1-3}alkyl; or R^E represents cycloalkyl and R^F represents hydrogen; or R^E and R^F together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring;

R^G represents hydrogen or C_{1-3}alkyl;

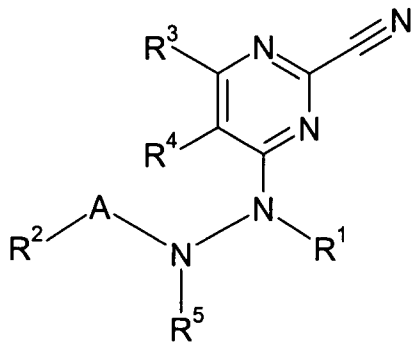
R^H represents hydrogen, C_{1-6}alkyl, $-C_{1-6}$alkyleneNR^{E}R^F, $-C_{1-6}$alkyleneNHC(O)C_{1-4}alkyl, or $-C_{1-6}$alkyleneNHC(O)OC_{1-4}alkyl;

R^J represents aryl, heteroaryl, heterocyclyl, $-C_{1-3}$alkylene$(aryl)_2$, $-C_{1-3}$alkylene-heteroaryl, $-C_{1-3}$aralkyl, $-C_{1-3}$alkylene-C(O)-heterocyclyl, -O-C(O)C_{1-3}alkylene-aryl, or -O-C(O)C_{1-3}alkylene-aryl;

R^K represents one or two aryl substituents;

and salts and solvates thereof.

In another alternative embodiment the invention provides at least one chemical entity chosen from compounds of Formula IB



IB

Wherein:

R^1 represents C_{1-8}alkyl, -C_{1-8}alkyleneNR^{E}R^F, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl, -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl or -C_{1-8}alkylene-cycloalkyl;

R^3 represents hydrogen, C_{1-3}alkyl, alkoxy, or -C(O)Oalkyl;

R^4 represents hydrogen, halogen, alkoxy, -C≡C-aryl, -NHC_{1-3}alkylene-aryl, NO_2, CF_3, or OCF_3;

provided that R^3 and R^4 are not both hydrogen, and when R^3 is C_{1-3}alkyl then R^4 is other than hydrogen;

and

a) A represents C(O) and

i) R^2 represents R^{2a} or R^{2b} wherein

R^{2a} represents -NR^H-aryl, -NR^H-heteroaryl, -NR^H-aryl-heteroaryl or -NR^H-heteroaryl-aryl; and

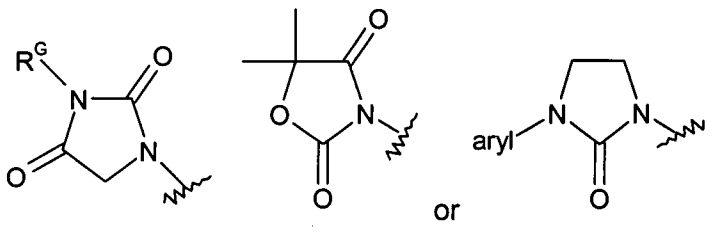
R^{2b} represents -C_{1-6}alkyleneR^A, aryl, biaryl, -aryl-heteroaryl, -heteroaryl-aryl, -aryl-heterocyclyl, -aryl-C_{1-3}alkylene-heterocyclyl, -heteroaryl-C_{1-3}alkylene-heterocyclyl, -aryl-O-C_{1-3}alkylene-heterocyclyl, aryl-C_{1-3}alkylene-heteroaryl, -aryl-heteraoaryl-C_{1-3}alkylene-heterocyclyl, -heteroaryl-aryl-C_{1-3}alkylene-heterocyclyl, aryloxy, heteroaryl, cycloalkyl, -cycloalkyl-aryl, cycloalkyloxy, heterocyclyl, -NR^H-aryl-heterocyclyl, -NR^H-cycloalkyl, -N(R^B)C_{1-6}alkyleneR^C, -NH-N(C_{1-3}alkyl)-heteroaryl, -OC_{1-6}alkyleneR^D, -OC_{1-6}alkenyl, -aryl-C_{1-3}alkylene-heterocyclyl-R^J, -aryl-C_{1-3}alkylene-heteroaryl-R^K, C_{1-3}alkylene(NH_2)-aryl, or -aryl-C_{1-3}alkylene-NH-C_{1-3}alkylene-OH;

and

R^5 represents hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, -C(O)R^{2a}, -C_{1-8}alkylene-heterocyclyl, -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl, -C_{1-8}alkyleneNR^{E}R^F, N-phthalidimido-C_{1-8}alkylene- or -C(O)C_{1-6}alkyl;

or

ii) R^2 and R^5 together with the carbon and nitrogen atoms to which they are respectively attached form a group selected from



or

b) A represents $-SO_2-$ and
R^2 represents C_{1-6}alkyl, aryl, C_{1-6}aralkyl or -C_{1-6}alkyleneheterocyclyl;

and

R^5 represents hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, -C_{1-8}alkylene-heterocyclyl, -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl, -C_{1-8}alkyleneNR^{E}R^F, N-phthalidimido-C_{1-8}alkylene- or -C(O)C_{1-6}alkyl;

R^A, R^C and R^D independently represent hydrogen, halogen, -NR^{E}R^F, cyano, CCl_3, -C(O)C_{1-6}alkyl, C_{1-3}alkyl, cycloalkyl, heterocyclyl, aryl, biaryl, -aryl-heteroaryl, -aryl-C_{1-3}alkylene-heterocyclyl, -aryl-O-C_{1-3}alkylene-heterocyclyl, -C_{1-3}alkenylaryl, heteroaryl, C_{1-6}aralkyl, -NHC(O)C_{1-6}alkyl, -NHC(O)OC_{1-6}alkyl, -NHC(O)C_{1-6}aralkyl or -NHC(O)OC_{1-6}aralkyl;

R^B represents hydrogen or C_{1-8}alkyl;

R^E and R^F independently represent hydrogen or C_{1-3}alkyl; or R^E represents cycloalkyl and R^F represents hydrogen; or R^E and R^F together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring;

R^G represents hydrogen or C_{1-3}alkyl;

R^H represents hydrogen, C_{1-6}alkyl, -C_{1-6}alkyleneNR^{E}R^F, -C_{1-6}alkyleneNHC(O)C_{1-4}alkyl, -C_{1-6}alkyleneNHC(O)OC_{1-4}alkyl, -C_{1-6}alkyleneheterocyclyl, or -C_{1-6}alkyleneheterocyclyl-R^J;

R^J represents aryl, heteroaryl, heterocyclyl, -C_{1-3}alkylene(aryl)$_2$, -C_{1-3}alkylene-heteroaryl, -C_{1-3}aralkyl, -C_{1-3}alkylene-C(O)-heterocyclyl, -O-C(O)C_{1-3}alkylene-aryl, -C(O)-O-C_{1-3}alkylene-aryl or -C_{1-4}alkylene-heterocyclyl

R^K represents one or two aryl substituents;

and salts and solvates thereof.

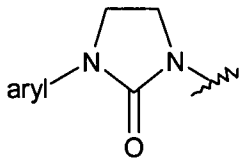
In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention, R^1 represents C_{1-8}alkyl, or -C_{1-8}alkylene-cycloalkyl. In another embodiment, R^1 represents isobutyl (2-methylpropyl). In an alternative embodiment, R^1 represents -methylene-cyclopentyl or -methylenecyclohexyl. In another embodiment, R^1 represents -methylene-cyclopentyl.

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention, R^3 represents hydrogen, C_{1-3}alkyl or -C(O)Oalkyl; in another embodiment R^3 represents hydrogen.

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention, R^4 represents halogen.

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention, A represents C(O) and R^2 represents R^{2a} or R^{2b} wherein R^{2a} represents -NR^H-aryl; and R^{2b} represents -C_{1-6}alkyleneR^A, aryl, biaryl, -aryl-heteroaryl, -heteroaryl-aryl, -aryl-heterocyclyl, -aryl-C_{1-3}alkylene-heterocyclyl, -aryl-O-C_{1-3}alkylene-heterocyclyl, aryl-C_{1-3}alkylene-heteroaryl, heteroaryl, -cycloalkyl-aryl, -$NR^B C_{1-6}$alkyleneR^C, -OC_{1-6}alkyleneR^D, -aryl-C_{1-3}alkylene-heterocyclyl-R^J, -aryl-C_{1-3}alkylene-heteroaryl-R^K, C_{1-3}alkylene(NH_2)-aryl; and R^5 represents hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, or -C_{1-8}alkylene$NR^E R^F$;

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in a further embodiment of the invention A represents C(O) and R^2 and R^5 together with the carbon and nitrogen atoms to which they are respectively attached form the group



In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in a further embodiment of the invention A represents -SO_2-; R^2 represents aryl, C_{1-6}aralkyl or -C_{1-6}alkyleneheterocyclyl; and R^5 represents hydrogen, C_{1-6}alkyl, or C_{1-6}alkenyl.

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention R^A, R^C and R^D independently represent hydrogen, aryl, -aryl-C_{1-3}alkylene-heterocyclyl, -aryl-O-C_{1-3}alkylene-heterocyclyl, or -NHC(O)OC_{1-6}alkyl.

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention R^B represents C_{1-8}alkyl;

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention R^E and R^F independently represent hydrogen or C_{1-3}alkyl; or R^E and R^F together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring;

In respect of compounds of Formula IA, Formula IB and salts and solvates thereof: in one embodiment of the invention R^H represents hydrogen, C_{1-6}alkyl, or $-C_{1-6}$alkyleneNR^{E}R^F.

The meaning of any functional group or substituent thereon at any one occurrence in Formula IA or IB or any subformula thereof, is independent of its meaning, or any other functional group's or substituent's meaning, at any other occurrence, unless stated otherwise.

It is to be understood that the present invention covers all combinations of the groups according to different aspects of the invention as described hereinabove.

Terms and Definitions

As used herein, the term "alkyl" as a group or a part of a group refers to a linear or branched alkyl group containing the indicated number of carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl or hexyl, 3,3-dimethylbutyl and the like.

As used herein, the term "alkylene" as a group or a part of a group refers to a linear or branched saturated hydrocarbon linker group containing the indicated number of carbon atoms. Examples of such groups include methylene, ethylene and the like. In one embodiment, alkylene is methylene.

As used herein, the term "alkenyl" as a group or a part of a group refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds and containing the indicated number of carbon atoms. Examples of such groups include ethenyl, propenyl, butenyl, pentenyl or hexenyl and the like.

As used herein, the term "alkoxy" as a group or a part of a group refers to an -O-alkyl group wherein alkyl is as herein defined. Examples of such groups include methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy, pentoxy, hexoxy and the like.

As used herein, the term "aralkyl" as a group or a part of a group refers to an alkyl group as herein defined which contains the indicated number of carbon atoms, the alkyl group being substituted with an aryl group as herein defined.

As used herein, the term "aryl" as a group or a part of a group refers to an optionally substituted hydrocarbon aromatic group containing one, two or three conjugated or fused rings with at least one ring having a conjugated pi-electron system. Examples of such groups include optionally substituted phenyl, naphthyl or tetrahydronaphthalenyl and the like. In one embodiment aryl represents phenyl. In another embodiment aryl represents naphthyl. In one embodiment aryl moieties are unsubstituted. In another embodiment aryl moieties are monosubstituted, disubstituted or trisubstituted. In a further embodiment aryl moieties are monosubstituted or disubstituted. Optional aryl substituents include C_{1-4}alkyl, C_{1-4}alkoxy, halogen, nitro, trihalomethyl, trihalomethoxy, $-C(O)CH_3$, $-N(C_{1-3}alkyl)_2$ and $-SO_2-C_{1-4}$alkyl.

As used herein, the term "aryloxy" as a group or a part of a group refers to an -O-aryl group wherein aryl is as herein defined.

As used herein, the term "biaryl" as a group or a part of a group refers to an aryl group which is directly substituted with a second aryl group, wherein aryl is as herein defined.

As used herein, the term "heteroaryl" as a group or a part of a group refers to an optionally substituted aromatic group comprising one to four heteroatoms selected from N, O and S, the aromatic group containing one, two or three 5- or 6- membered conjugated or fused rings with at least one ring having a conjugated pi-electron system. Examples of monocyclic heteroaryl groups (one ring) include optionally substituted thienyl, furyl, furazanyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyranyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, triazinyl, tetrazinyl and the like. Examples of fused aromatic rings include quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pteridinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolyl, isoindolyl, azaindolyl, indolizinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, benzofuranyl, isobenzofuranyl, benzothienyl, benzoimidazolyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl, dibenzofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzo[1,3]-dioxole and the like. In one embodiment heteroaryl moieties are pyridyl, imidazolyl, oxazolyl, benzofuranyl, dibenzofuranyl, benzothiazolyl, indolyl or indazolyl. In a further embodiment heteroaryl moieties are pyridyl, imidazolyl, isoxazolyl, benzofuranyl, dibenzofuranyl, benzothiazolyl, indolyl or indazolyl. In a yet further embodiment optionally substituted heteroaryl moieties are benzofuranyl, pyridyl, dibenzofuranyl, imidazolyl and isoxazolyl. In one embodiment heteroaryl moieties are unsubstituted. In another embodiment

heteroaryl moieties are monosubstituted, disubstituted or trisubstituted. In a further embodiment heteroaryl moieties are monosubstituted or disubstituted. Optional heteroaryl substituents include C_{1-4}alkyl, C_{1-4}alkoxy and halogen.

As used herein, the term "cycloalkyl" as a group or a part of a group refers to a saturated cyclic hydrocarbon group of 3 to 7 carbon atoms. Examples of such groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

As used herein, the term "cycloalkyloxy" as a group or a part of a group refers to an -O-cycloalkyl group wherein cycloalkyl is as herein defined.

As used herein, the terms "heterocyclyl" or "heterocyclic ring" as a group or a part of a group refer to i) an optionally substituted, monocyclic 3- to 7-membered, saturated or partially saturated hydrocarbon group containing one to four heteroatoms selected from N, O and S and also ii) to polycyclic groups, e.g. bicyclic and tricyclic groups, which are fused rings of optionally substituted, 3- to 7-membered, saturated or partially saturated hydrocarbon groups containing one to four heteroatoms selected from N, O and S. Examples of monocyclic groups include include pyrrolidinyl, azetidinyl, imidazolidinyl, oxoimidazolidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and the like. Examples of bicyclic groups include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine, tetrahydroisoquinolinyl, hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl and the like. In one embodiment heterocyclyl is an optionally substituted 5- or 6-membered monocyclic group, or a 9-membered bicyclic group. In another embodiment heterocyclyl is an optionally substituted 5- or 6- membered monocyclic group. In a further embodiment heterocyclyl moieties are optionally substituted pyrrolidnyl, imidazolidinyl, piperidinyl, piperazinyl or morpholinyl. In a yet further embodiment heterocyclyl moieties are optionally substituted piperazinyl. In one embodiment heterocyclyl moieties are unsubstituted. In another embodiment heterocyclyl moieties are monosubstituted, disubstituted or trisubstituted or tetrasubstituted. In a further embodiment heterocyclyl moieties are monosubstituted. Optional heterocyclyl substituents include C_{1-6}alkyl, -C(O)C_{1-4}alkyl, -C(O)OC_{1-4}alkyl, -NC(O)C_{1-4}alkyl, -NC(O)OC_{1-4}alkyl, -C(O)NR^BC_{1-4}alkyl, -C_{1-6}alkyleneOH, -C_{1-3}alkyleneC(O)OC_{1-3}alkyl, -C_{1-3}alkylene-O-C_{1-3}alkyleneOH, -C_{1-3}alkylene-NH-C_{1-3}alkyleneOH, -C_{1-6}alkyleneNR^ER^F, cyano, hydroxy, - NR^ER^F, spiroacetal, and oxo.

As used herein, the term "halogen" or "halo" refers to a fluorine (fluoro), chlorine (chloro), bromine (bromo) or iodine (iodo) atom. In one embodiment halogen substituents are a fluorine or chlorine atom.

As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient such as an active ingredient, a salt thereof or an excipient) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

As used herein, the term "N-phthalimido" refers to a phthalimide group which is bonded through the nitrogen atom.

As used herein, the term "proteases" are enzymes that catalyze the cleavage of amide bonds of peptides and proteins by nucleophilic substitution at the amide bond, ultimately resulting in hydrolysis. Proteases include: cysteine proteases, serine proteases, aspartic proteases, and metalloproteases. Protease "inhibitors" bind more strongly to the enzyme than the substrate and in general are not subject to cleavage after enzyme catalyzed attack by the nucleophile. They therefore competitively prevent proteases from recognizing and hydrolysing natural substrates and thereby act as inhibitors.

In one aspect of the invention there is provided at least one chemical entity selected from the list:

N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;

N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;

N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;

N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;

4-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide;

N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-piperidinylmethyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-pyrrolidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(2,6-dimethyl-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
ethyl 1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-4-piperidinecarboxylate;
N-{(3R)-1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-pyrrolidinyl}acetamide;
1,1-dimethylethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-pyrrolidinyl}carbamate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(4-{2-[(2-hydroxyethyl)oxy]ethyl}-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-piperidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[(2R)-2-(hydroxymethyl)-1-pyrrolidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-pyrrolidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-(2,5-dihydro-1H-pyrrol-1-ylmethyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(2,5-dimethyl-2,5-dihydro-1H-pyrrol-1-yl)methyl]-N'-(2-methylpropyl)benzohydrazide;
1,1-dimethylethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-4-piperidinyl}carbamate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(dimethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[3-(4-morpholinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(diethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(dipropylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(di-2-propen-1-ylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[(1-methyl-4-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(1-methyl-4-piperidinyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;

ethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-piperidinyl}acetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(diethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(di-2-propen-1-ylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(dipropylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-[(2,6-dimethyl-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
3-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-(1-piperidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[3-(dipropylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[3-(diethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(4-hydroxy-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-N,N-dimethyl-L-prolinamide;
4-(1-azetidinylmethyl)-N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[(2S)-2-(1-pyrrolidinylcarbonyl)-1-pyrrolidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[(1-methyl-3-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(diethylamino)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-pyridinyl)-1-piperazinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(dimethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-(1-pyrrolidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(diethylamino)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[2-(diethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(1-methyl-4-piperidinyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[3-(4-morpholinyl)propyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[(1-methyl-4-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;

3-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-3-isoxazolecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-7-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-1-benzofuran-2-carbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-2-furancarbohydrazide 4-methylbenzenesulfonate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-6-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-6-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-1-benzofuran-2-carbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-2-thiophenecarbohydrazide;
and pharmaceutically acceptable derivatives thereof.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate of a compound of Formula I, IA or IB, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of Formula I, IA or IB, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives. In one aspect of the invention pharmaceutically acceptable derivatives are salts, solvates, esters and carbamates. In another aspect of the invention pharmaceutically acceptable derivatives are salts, solvates and esters. In a further aspect, pharmaceutically acceptable derivatives are salts and solvates.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. Indeed, in certain embodiments of

the invention, pharmaceutically acceptable salts of the compounds according to Formula I, IA or IB, IA or IB may be preferred over the respective free base or free acid because such salts impart greater stability or solubility to the molecule thereby facilitating formulation into a dosage form. Accordingly, the invention is further directed to pharmaceutically acceptable salts of the compounds according to Formula I, IA or IB.

As used herein, the term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. For a review on suitable salts see Berge et al, J. Pharm. Sci., 1977, 66, 1-19. The term "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts. These pharmaceutically acceptable salts may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of Formula I, IA or IB with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulfuric, sulfamic, nitric, phosphoric, succinic, maleic, hydroxymaleic, acrylic, formic, acetic, hydroxyacetic, phenylacetic, butyric, isobutyric, propionic, fumaric, citric, tartaric, lactic, mandelic, benzoic, o-acetoxybenzoic, chlorobenzoic, methylbenzoic, dinitrobenzoic, hydroxybenzoic, methoxybenzoic salicylic, glutamaic, stearic, ascorbic, palmitic, oleic, pyruvic, pamoic, malonic, lauric, glutaric aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, naphthalenesulfonic (e.g. 2-naphthalenesulfonic), p-aminobenzenesulfonic (i.e. sulfanilic), hexanoic, heptanoic, or phthalic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, hydroiodide, sulfate, bisulfate, nitrate, phosphate, hydrogen phosphate, succinate, maleate, malate, formate, acetate, trifluoroacetate, saccharate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2- naphthalenesulfonate), methanesulphonic, ethanesulphonic, p-toluenesulphonic, isethionate or hexanoate salt. In one embodiment there is provided the trifluoroacetic acid salts of the compounds of the invention. In another embodiment there is provided the hydrochloric acid salts of the compounds of the invention.

A pharmaceutically acceptable base addition salt can be formed by reaction of a compound of Formula I, IA or IB with a suitable inorganic or organic base (e.g. ammonia, triethylamine, ethanolamine, triethanolamine, choline, arginine, lysine or histidine), optionally in a suitable solvent such as an organic solvent, to give the base addition salt which is usually isolated for example by crystallisation and filtration. Pharmaceutically acceptable base salts include ammonium salts and salts with organic bases, including salts of primary, secondary and tertiary amines, including aliphatic amines, aromatic amines, aliphatic diamines, and hydroxy alkylamines, such as methylamine, ethylamine, isopropylamine, diethylamine, ethylenediamine, ethanolamine, trimethylamine, dicyclohexyl amine, diethanolamine, cyclohexylamine and N-methyl-D-glucamine. Other suitable pharmaceutically acceptable base salts include pharmaceutically acceptable metal salts, for example pharmaceutically acceptable alkali-metal or alkaline-earth-metal salts such as hydroxides, carbonates and bicarbonates of sodium, potassium, lithium, calcium, magnesium, aluminium, and zinc; in particular pharmaceutically acceptable metal salts of one or more carboxylic acid moieties that may be present in the compound of Formula I, IA or IB.

Other non-pharmaceutically acceptable salts, for example oxalates may be used, for example in the isolation of compounds of the invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of Formula I, IA or IB.

As used herein, the term "compounds of the invention" means the compounds according to Formula I, IA or IB and the pharmaceutically acceptable derivatives thereof. The term "a compound of the invention" means any one of the compounds of the invention as defined above.

As used herein the term “at least one chemical entity” means at least one chemical substance chosen from the group of compounds consisting of compounds of Formula I, IA or IB and pharmaceutically acceptable derivatives thereof.

The compounds of the invention may exist as solids or liquids, both of which are included in the invention. In the solid state, the compounds of the invention may exist as either amorphous material or in crystalline form, or as a mixture thereof. It will be appreciated that solvates of the compounds of the invention may be formed wherein solvent molecules are incorporated into the crystalline lattice during crystallisation. Solvates may involve non-aqueous solvents such as ethanol, isopropanol, DMSO, acetic acid, ethanolamine, and ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent that is incorporated into the

crystalline lattice are typically referred to as "hydrates." The invention includes all such solvates.

It will be further appreciated that all crystalline forms, polymorphs, geometric isomers, stereoisomers (including enantiomers and diastereomers) and tautomers of the compounds of the invention, or mixtures thereof, are contemplated to be within the scope of the present invention.

According to another aspect of the invention there is provided at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof for use in human or veterinary medical therapy.

The compounds of the invention are cysteine protease inhibitors, such as inhibitors of cysteine proteases of the papain superfamily, for example of the falcipain family, including falcipain-2 or falcipain-3. The compounds of the invention are also inhibitors of cysteine proteases of the papain superfamily, for example those of the cathepsin family such as cathepsins K, L, S and B.

The compounds of the invention may be useful for treating conditions in which cysteine proteases are implicated, including infections by *Plasmodium falciparum* which is the most virulent malaria-causing parasite, and by *Plasmodium vivax*, *Pneumocystis carinii*, *Trypsanoma cruzi*, *Trypsanoma brucei*, and *Crithidia fusiculata*; as well as in treating conditions such as schistosomiasis, malaria, cancer, for example pancreatic cancer, tumour invasion and tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, chronic obstructive pulmonary disorder (COPD), atherosclerosis; and especially conditions in which cathepsin K is implicated, including diseases of excessive bone or cartilage loss and other bone and joint diseases such as osteoporosis, bone metastasis, gingival disease (including gingivitis and periodontitis), arthritis (including osteoarthritis and rheumatoid arthritis), Paget's disease; hypercalcemia of malignancy, and metabolic bone disease. In addition, metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of the invention. Accordingly, the invention is directed to methods of treating such conditions.

In one aspect of the invention, there is provided at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof, for use in the treatment of a condition mediated by inhibition of a cysteine protease, particularly inhibition of a cysteine protease of the papain superfamily such as those of the falcipain family, including falcipain-2 or falcipain-3, for example malaria.

In another aspect of the invention, there is provided at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition mediated by inhibition of a cysteine protease, particularly inhibition of a cysteine protease of the papain superfamily, such as those of the cathepsin family for example cathepsins K, L, S and B, i) in one embodiment cathepsin K, for example conditions characterised by excessive bone loss such as osteoporosis and bone metastasis, and other bone and joint diseases such as osteoarthritis, or ii) in another embodiment cathepsin L or S, for example pancreatic cancer.

In another aspect of the invention there is provided the use of at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a condition mediated by inhibition of a cysteine protease, particularly inhibition of a cysteine protease of the papain superfamily such as those of the falcipain family, including falcipain-2 or falcipain-3, for example malaria.

In a further aspect of the invention there is provided the use of at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof in the manufacture of a medicament for the treatment of a condition mediated by inhibition of a cysteine protease, particularly inhibition of a cysteine protease of the papain superfamily, such as those of the cathepsin family, for example cathepsins K, L, S and B, i) in one embodiment cathepsin K, for example conditions characterised by excessive bone loss such as osteoporosis and bone metastasis, and other bone and joint diseases such as osteoarthritis, or ii) in another embodiment cathepsin L or S, for example pancreatic cancer.

In another aspect of the invention there is provided a method for the treatment of a human or animal subject suffering from a condition mediated by inhibition of a cysteine protease, particularly inhibition of a cysteine protease of the papain superfamily such as those of the falcipain family, including falcipain-2 or falcipain-3, for example malaria, which method comprises administering an effective amount of at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof or a pharmaceutical composition comprising at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof.

In another aspect of the invention there is provided a method for the treatment of a human or animal subject suffering from a condition mediated by inhibition of a cysteine protease, particularly inhibition of a cysteine protease of the papain superfamily, such as those of the cathepsin family, for example cathepsins K, L, S and B, i) in one embodiment cathepsin K, for example conditions characterised by excessive bone loss such as

osteoporosis and bone metastasis, and other bone and joint diseases such as osteoarthritis, or ii) in another embodiment cathepsin L or S, for example pancreatic cancer, which method comprises administering an effective amount of at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof or a pharmaceutical composition comprising at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof.

The compounds of the invention are cysteine protease inhibitors and can be useful in the treatment of a condition mediated by inhibition of a cysteine protease, particularly inhibition of a cysteine protease of the papain superfamily such as those of the falcipain family, including falcipain-2 or falcipain-3, for example in the treatment of malaria, or those of the cathepsin family for example cathepsins K, L, S and B, i) in one embodiment cathepsin K, for example conditions characterised by excessive bone loss such as osteoporosis and bone metastasis, and other bone and joint diseases such as osteoarthritis, or ii) in another embodiment cathepsin L or S, for example pancreatic cancer. Accordingly, the invention is further directed to pharmaceutical compositions comprising at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof.

As used herein "excessive bone loss" is a disease state in which the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Diseases which are characterised by excessive bone loss include, but are not limited to, osteoporosis and gingival diseases, excessive cartilage or matrix degradation including osteoarthritis and rheumatoid arthritis.

The methods of treatment of the invention comprise administering a safe and effective amount of at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof, or a pharmaceutical composition containing at least one chemical entity selected from a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof, to a patient in need thereof.

As used herein, "treatment" means: (1) the amelioration or prevention of the condition being treated or one or more of the biological manifestations of the condition being treated, (2) the interference with (a) one or more points in the biological cascade that leads to or is responsible for the condition being treated or (b) one or more of the biological manifestations of the condition being treated, or (3) the alleviation of one or more of the symptoms or effects associated with the condition being treated. The skilled artisan will appreciate that "prevention" is not an absolute term. In medicine, "prevention" is understood to refer to the prophylactic administration of a drug to substantially diminish

the likelihood or severity of a condition or biological manifestation thereof, or to delay the onset of such condition or biological manifestation thereof.

As used herein, "safe and effective amount" means an amount of the compound sufficient to significantly induce a positive modification in the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio) within the scope of sound medical judgment. A safe and effective amount of a compound of the invention will vary with the particular compound chosen (e.g. depending on the potency, efficacy, and half-life of the compound); the route of administration chosen; the condition being treated; the severity of the condition being treated; the age, size, weight, and physical condition of the patient being treated; the medical history of the patient to be treated; the duration of the treatment; the nature of concurrent therapy; the desired therapeutic effect; and like factors, but can nevertheless be routinely determined by the skilled artisan.

As used herein, "patient" refers to a human or other animal.

The compounds of the invention may be administered by any suitable route of administration, including both systemic administration and topical administration. Systemic administration includes oral administration, parenteral administration, transdermal administration, rectal administration, and administration by inhalation. Parenteral administration refers to routes of administration other than enteral, transdermal, or by inhalation, and is typically by injection or infusion. Parenteral administration includes intravenous, intramuscular, and subcutaneous injection or infusion. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. Topical administration includes application to the skin as well as intraocular, optic, intravaginal, and intranasal administration.

The compounds of the invention may be administered once or according to a dosing regimen wherein a number of doses are administered at varying intervals of time for a given period of time. For example, doses may be administered one, two, three, or four times per day. Doses may be administered until the desired therapeutic effect is achieved or indefinitely to maintain the desired therapeutic effect. Suitable dosing regimens for a compound of the invention depend on the pharmacokinetic properties of that compound, such as absorption, distribution, and half-life, which can be determined by the skilled artisan. In addition, suitable dosing regimens, including the duration such regimens are administered, for a compound of the invention depend on the condition being treated, the severity of the condition being treated, the age and physical condition of the patient being treated, the medical history of the patient to be treated, the nature of concurrent therapy, the desired therapeutic effect, and like factors within the knowledge and expertise of the skilled artisan. It will be further understood by such skilled artisans that suitable dosing

regimens may require adjustment given an individual patient's response to the dosing regimen or over time as individual patient needs change.

Typical daily dosages may vary depending upon the particular route of administration chosen. Typical daily dosages for oral administration range from about 0.01 to about 25 mg/kg, in one embodiment from about 0.1 to about 14 mg/kg. Typical daily dosages for parenteral administration range from about 0.001 to about 10 mg/kg; in one embodiment from about 0.01 to about 6 mg/kg .The compounds of Formula I, IA or IB may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent. When a compound of Formula I, IA or IB or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

The compounds of the present invention may be used alone or in combination with one or more additional active agents, such as other inhibitors of cysteine and serine proteases, antimalarial drugs or drugs to treat excessive bone loss.

Such other active agents include inhibitors of bone resorption or other bone diseases, for example bisphosphonates (i.e., allendronate, risedronate, etidronate, and ibandronate), hormone replacement therapy, anti-estrogens, calcitonin, and anabolic agents such as bone morphogenic protein, iproflavone, and PTH. In the alternative, such other active agents include antimalarial drugs, such as folates (e.g. chloroquine, mefloquine, primaquine pyrimethamine, quinine artemisinin, halofantrine, doxycycline, amodiquine, atovaquine [atovaquone], tafenoquine) and antifolates (e.g. dapsone, proguanil, sulfadoxine, pyrimethamine, chlorcycloguanil, cycloguanil) or antibacterial drugs such as azithromycin, doxycycline, ciprofloxacin and clindamycin. In another alternative, such other active agents include anti-cancer agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

When administration is sequential, either the compound of the present invention or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition. When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

Compositions

The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient. In one aspect, the invention is directed to pharmaceutical compositions comprising a compound of the invention. In another aspect the invention is directed to pharmaceutical compositions comprising a compound of the invention and a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the receipient thereof.

The pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of the invention can be extracted and then given to the patient such as with powders or syrups. Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged in unit dosage form wherein each physically discrete unit contains a safe and effective amount of a compound of the invention. When prepared in unit dosage form, the pharmaceutical compositions of the invention typically contain from about 0.5 mg to about 1750 mg, e.g. from about 5 mg to about 1000 mg for oral dosage forms and from about 0.05 mg to about 700 mg, e.g. from about 0.5 mg to about 500 mg for parenteral dosage forms.

The pharmaceutical compositions of the invention typically contain one compound of the invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. For example, in certain embodiments the pharmaceutical compositions of the invention contain two compounds of the invention. In addition, the pharmaceutical compositions of the invention may optionally further comprise one or more additional pharmaceutically active compounds. Conversely, the pharmaceutical compositions of the invention typically contain more than one pharmaceutically acceptable excipient. However, in certain embodiments, the pharmaceutical compositions of the invention contain one pharmaceutically acceptable excipient.

As used herein, the term "pharmaceutically acceptable" means suitable for pharmaceutical use.

The compound of the invention and the pharmaceutically acceptable excipient or excipients will typically be formulated into a dosage form adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral administration such as tablets, capsules, caplets, pills, troches, powders, syrups, elixers, suspensions, solutions, emulsions, sachets, and cachets; (2) parenteral administration such as sterile solutions, suspensions, and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal administration such as suppositories; (5) inhalation such as aerosols and solutions; and (6) topical administration such as creams, ointments, lotions, solutions, pastes, sprays, foams, and gels.

Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the carrying or transporting the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically acceptable excipients may be chosen for their ability to enhance patient compliance.

Suitable pharmaceutically acceptable excipients include the following types of excipients: binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavoring agents, flavor masking agents, coloring agents, anticaking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, antioxidants, preservatives, stabilizers, surfactants, and buffering agents. The skilled artisan will appreciate that certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to select suitable pharmaceutically acceptable excipients in appropriate amounts for use in the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically acceptable excipients and may be useful in selecting suitable pharmaceutically acceptable excipients. Examples include Remington's

Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press).

The pharmaceutical compositions of the invention are prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

In one aspect, the invention is directed to a solid or liquid oral dosage form such as a liquid, tablet, lozenge or a capsule, comprising a safe and effective amount of a compound of the invention and a carrier. The carrier may be in the form of a diluent or filler. Suitable diluents and fillers in general include lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. corn starch, potato starch, and pre-gelatinized starch), cellulose and its derivatives (e.g. microcrystalline cellulose), calcium sulfate, and dibasic calcium phosphate. A liquid dosage form will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, olive oil, glycerine, glucose (syrup) or water (e.g. with an added flavouring, suspending, or colouring agent). Where the composition is in the form of a tablet or lozenge, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers or a semi solid e.g. mono di-glycerides of capric acid, Gelucire™ and Labrasol™, or a hard capsule shell e.g gelatin. Where the composition is in the form of a soft shell capsule e.g. gelatin, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums or oils, and may be incorporated in a soft capsule shell.

An oral solid dosage form may further comprise an excipient in the form of a binder. Suitable binders include starch (e.g. corn starch, potato starch, and pre-gelatinized starch), gelatin, acacia, sodium alginate, alginic acid, tragacanth, guar gum, povidone, and cellulose and its derivatives (e.g. microcrystalline cellulose). The oral solid dosage form may further comprise an excipient in the form of a disintegrant. Suitable disintegrants include crospovidone, sodium starch glycolate, croscarmelose, alginic acid, and sodium carboxymethyl cellulose. The oral solid dosage form may further comprise an excipient in the form of a lubricant. Suitable lubricants include stearic acid, magnesium stearate, calcium stearate, and talc.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of Formula I, IA or

IB or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier and/or excipient.

Preparations for oral administration may be suitably formulated to give controlled/extended release of the active compound.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

Abbreviations

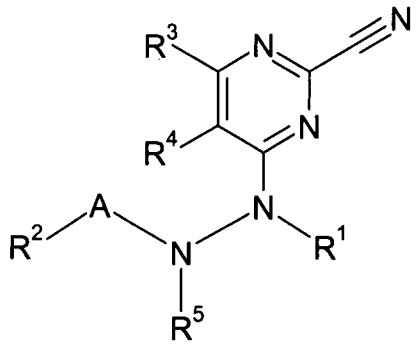
In describing the invention, chemical elements are identified in accordance with the Periodic Table of the Elements. Abbreviations and symbols utilized herein are in accordance with the common usage of such abbreviations and symbols by those skilled in the chemical arts. The following abbreviations are used herein:

ACN	acetonitrile
AcOEt	ethyl acetate
AFC	7-amido-4-trifluoromethylcoumarin
AMC	7-amido-4-methylcoumarin
$CDCl_3$	deuterated chloroform
CHAPS	3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate
CYS	cysteine
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DIPEA	diisopropylamine
DMAP	4-dimethylamino pyridine
DMSO-d6	deuterated dimethylsulfoxide
DMSO	dimethylsulfoxide
DTT	dithiothreitol
E64	*trans*-epoxysuccinyl-L-leucylamido(4-guanidino)butane
EDCI	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
EDTA	(ethylenedinitrilo)tetraacetic acid
ES+ MS	Positive Electrospray mass spectrometry
ES- MS	Negative Electrospray mass spectrometry
EtOH	ethanol
h	hours
H-D-VLR-AFC	HD-Valyl-Leucyl-Arginyl-7-Amido-4-trifluoromethylcoumarin
Hex	hexane
HOBt	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography

i-PrOH	isopropanol
kg	kilogram(s)
KQKLR-AMC	N-Acetyl-Lysyl-Glutaminyl-Lysyl-Leucyl-Arginyl-7-Amido-4-methylcoumarin
MeOH	methanol
MES	2-(N-morpholino)ethanesulfonic acid
$MgSO_4$	magnesium sulfate
min	minutes
mg	miligram(s)
$NaHCO_3$	sodium bicarbonate
Na_2SO_4	sodium sulfate
nM	Nanomolar
NMR	Nuclear Magnetic Resonance spectroscopy
PtO_2	platinum oxide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Z-LR-AMC	benzyloxycarbonyl-leucyl-arginyl-7-amido-4-methylcoumarin

Compound Preparation

The general procedures used to synthesise the compounds of Formula IA are described in reaction Schemes 1-15 and are illustrated in the Examples. It will be readily apparent to those skilled in the art that compounds of Formula IB and compounds of Formula I may be synthesised according to the same as, or analogous procedures to those described hereinbelow for Formula IA.



IA

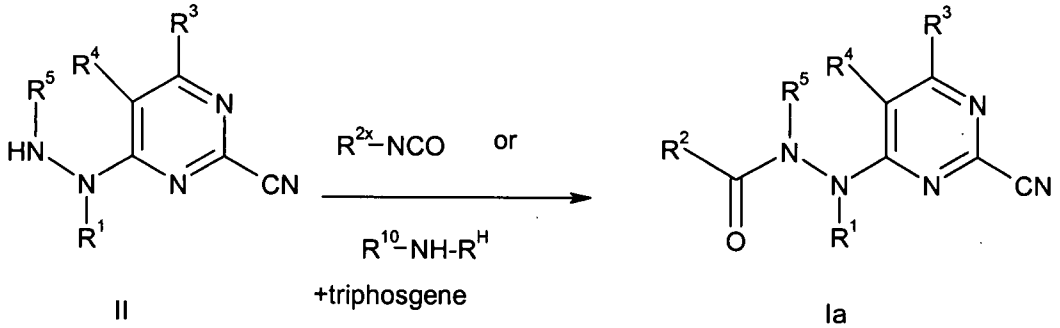
Throughout the specification, general formulae are designated by Roman numerals IA, II, III, IV etc. Subsets of compounds of Formula IA are defined as Ia, Ib, Ib(i), Ib(ii), Ib(iii), Ib(iv), Ic, Ic(i), and Id.

The semicarbazide compounds of Formula Ia, which are compounds of Formula IA wherein, R^3 and R^4 are as defined above for Formula IA, R^1 is C_{1-8}alkyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^GC(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^GC(O)C_{1-6}alkyl, A is C(O), R^5 is

hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl, and R^2 is -NR^H-aryl-heterocyclyl, -NR^H-cycloalkyl, -NR^BC_{1-6}alkyleneR^C, -NH-N(C_{1-3}alkyl)-heteroaryl, -NR^H-aryl, -NR^H-heteroaryl, -NR^H-aryl-heteroaryl or -NR^H-heteroaryl-aryl; in which R^H is as defined above for Formula IA, may be prepared from the corresponding hydrazine compounds of Formula II, wherein R^3 and R^4 are as defined above for Formula IA, R^1 is C_{1-8}alkyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl and R^5 is hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl, according to Scheme 1. This transformation may be carried out following one of two different procedures, procedure A or procedure B.

Procedure A: Compounds of Formula IIa, which are compounds of Formula II, wherein R^5 is hydrogen, are reacted with one equivalent of the isocyanate, R^{2x}NCO, wherein R^{2x}N is as defined above for R^2 in Formula Ia, in the presence of a suitable base such as triethylamine in a suitable solvent such as DCM to give compounds of Formula Ia wherein R^5 is hydrogen and R^H is hydrogen.

Procedure B: A primary amine R^{10}-NH_2, or a secondary amine R^{10}-NH-R^H, wherein and R^H is as defined as above for Formula Ia, and R^{10} is aryl, heteroaryl, aryl-heteroaryl, heteroaryl-aryl, aryl-heterocyclyl, N(C_{1-3}alkyl)-heteroaryl, cycloalkyl or -C_{1-6}alkyleneR^C, wherein R^C is hydrogen, C_{1-3}alkyl, aryl or halogen is dissolved in a suitable solvent such as dry THF and cooled to a suitable temperature, e.g. -10°C to 10°C, then reacted with triphosgene, and the resulting mixture is added to compounds of Formula II in the presence of a suitable base such as caesium carbonate or triethylamine. This mixture may be stirred at a suitable temperature for a suitable length of time for complete reaction, for example at room temperature for 6 h, to give compounds of Formula Ia wherein R^5, R^{10} and R^H are as defined above for Formula Ia.

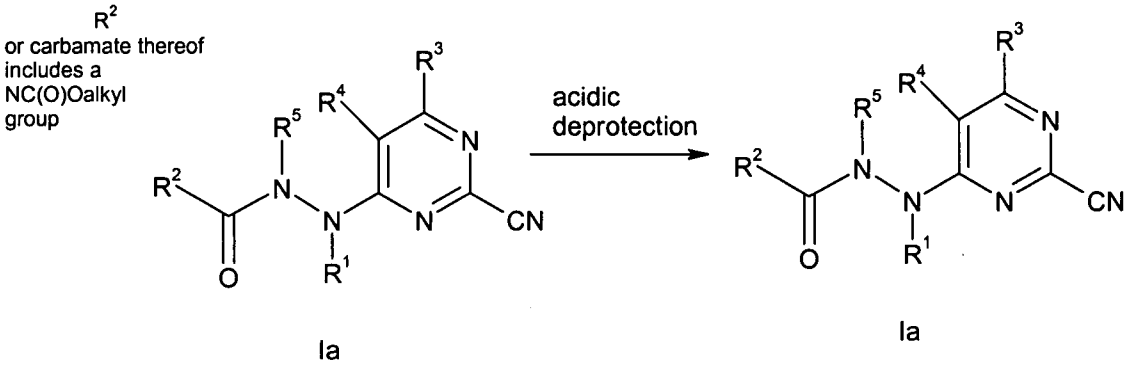


II Ia

Scheme 1

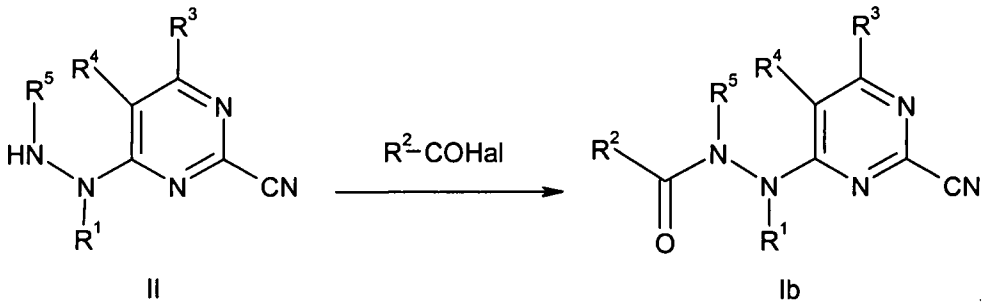
Compounds of Formula Ia wherein R^1, R^3 and R^4 are as defined above for Formula IA, R^2 is aryl, C_{1-8}alkyleneR^A, N(R^H)aryl, R^H is C_{1-6}alkyleneNR^{E}R^F and R^E and R^F are both hydrogen, R^5 is hydrogen, or alkylene-heterocyclyl may be prepared from other compounds of Formula Ia, wherein R^1, R^3 and R^4 are as defined above for Formula IA, R^2

is $N(R^H)$aryl, R^H is C_{1-6}alkyleneNHC(O)OC_{1-4}alkyl, R^5 is hydrogen, or a carbamate derivative of a compound of Formula Ia in which R^2 is C_{1-3}alkylene(NH_2)-aryl, according to Scheme 2 by deprotection in the presence of a suitable acid such as trifluoroacetic acid or *p*-toluenesulfonic acid.



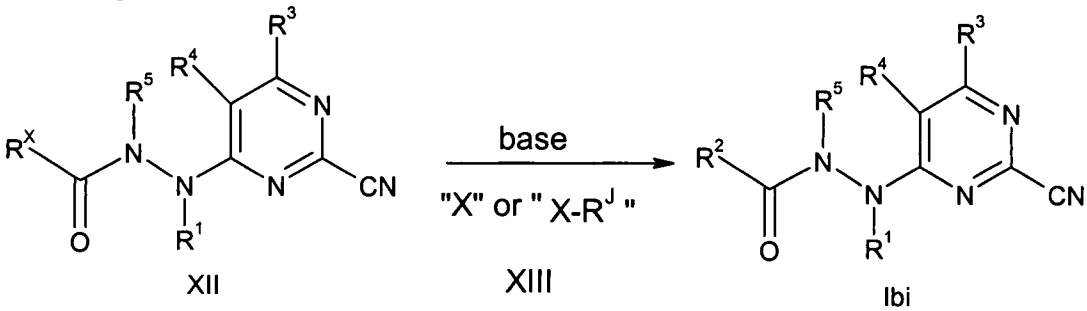
Scheme 2

The acylhydrazide compounds of Formula Ib, which are compounds of Formula IA wherein R^1, R^3, R^4 are as hereinbefore defined for Formula IA (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl, R^3 represents hydrogen and R^4 represents halogen), A is C(O), R^5 is hydrogen, C_{1-6}alkyl, -C_{1-8}alkylene-heterocyclyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl, -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl; (for example, R^5 is hydrogen); and R^2 is aryl, heteroaryl, cycloalkyl, heterocyclyl, -aryl-heterocyclyl, biaryl, aryl-heteroaryl, -heteroaryl-aryl, -aryl-C_{1-3}alkylene-heterocyclyl, -heteroaryl-aryl-C_{1-3}alkylene-heterocyclyl, -aryl-C_{1-3}alkylene-heterocyclyl-R^J, -aryl-O-C_{1-3}alkylene-heterocyclyl or C_{1-6}alkyleneR^A, wherein R^A is hydrogen, C_{1-3}alkyl, halogen, -N(C_{1-3}alkyl)$_2$, aryl, biaryl, cycloalkyl, -aryl-C_{1-3}alkylene-heterocyclyl or -aryl-O-C_{1-3}alkylene-heterocyclyl; (for example, R^2 is -phenyl-C_{1-3}alkylene-X, -pyridyl-phenyl-C_{1-3}alkylene-X or -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3); may be prepared from the corresponding hydrazine compounds of Formula II, wherein R^1, R^3 and R^4 are as hereinbefore defined for Formula IA, (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl, R^3 represents hydrogen and R^4 represents halogen), and R^5 is hydrogen, C_{1-8}alkyl, -C_{1-8}alkylene-heterocyclyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl; (for example, R^5 is hydrogen); according to Scheme 3. Compounds of Formula II are reacted with an acid chloride R^2COHal, wherein R^2 is as defined above for Formula Ib, and Hal is Cl or Br, in a suitable solvent such as pyridine to give compounds of Formula Ib.



Scheme 3

The acylhydrazide compounds of Formula Ibi, which are compounds of Formula Ib (and therefore of Formula IA) wherein R^1, R^3, R^4 are as hereinbefore defined for Formula IA, (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl, R^3 represents hydrogen and R^4 represents halogen), A is C(O), R^5 is hydrogen, C_{1-6}alkyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl, or -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl, (for example, R^5 is hydrogen); and R^2 is -aryl-C_{1-3}alkylene-heterocyclyl, -aryl-C_{1-3}alkylene-heterocyclyl-R^J, -heteroaryl-aryl-C_{1-3}alkylene-heterocyclyl, (for example, R^2 is -phenyl-C_{1-3}alkylene-X, -pyridyl-phenyl-C_{1-3}alkylene-X or -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3); may be prepared from the corresponding acylhydrazide compounds of Formula XII, wherein R^1, R^3 and R^4 are as hereinbefore defined for Formula IA, (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl, R^3 represents hydrogen and R^4 represents halogen), R^5 is hydrogen, C_{1-8}alkyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl; (for example, R^5 is hydrogen); and R^X is -arylhaloC_{1-3}alkylene or -heteroaryl-arylhaloC_{1-3}alkylene, by reaction with compounds of Formula XIII, which compounds are heterocyclyl or heterocyclyl-R^J, for example compounds XIII are "X" or "X-R^J", wherein "X" and "R^J" are as defined hereinabove for Formula I, in the presence of a base, for example an inorganic base such as potassium carbonate, or an organic base such as an amine, e.g. DIPEA, and optionally in the presence of iodide, for example by addition of NaI, according to Scheme 4.

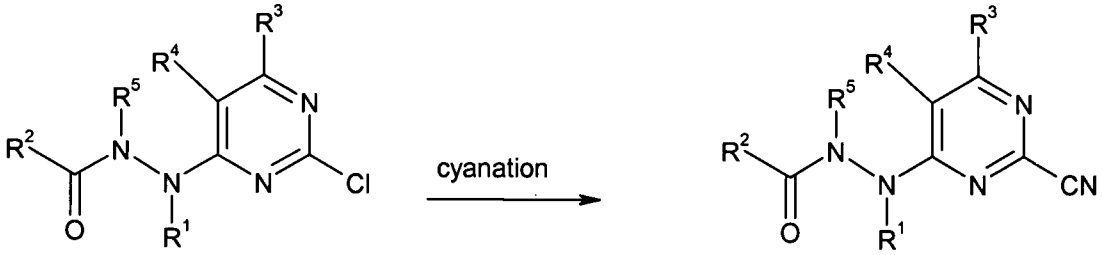


Scheme 4

Compounds of Formula XII may be prepared using an analogous procedure to that described for Scheme 3, by a reaction between compounds of Formula II and R^XCHal, wherein R^X is R^X is -arylhaloC_{1-3}alkylene or -heteroaryl-arylhaloC_{1-3}alkylene, and Hal is Cl

or Br, in the presence of a base, for example an inorganic base such as potassium carbonate, or an organic base such as an amine, e.g. DIPEA.

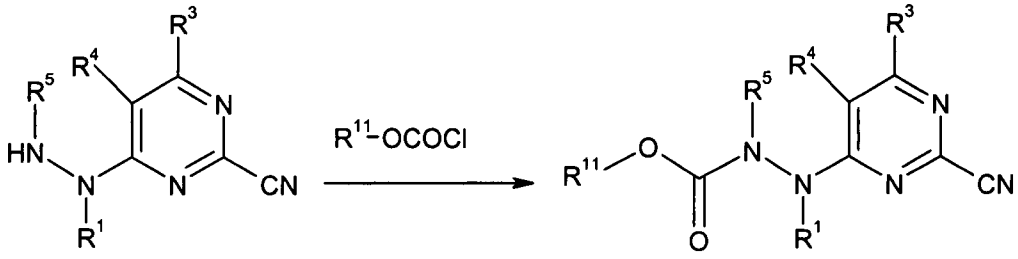
Compounds of Formula IA may be prepared from compounds of Formula III, wherein R^1, R^2, R^3, R^4 and R^5 are as defined above for Formula IA, according to Scheme 5 by cyanation, by displacement of the chloro substituent of compounds of Formula III using a variety of conditions, for example by treatment with potassium or sodium cyanide in the presence of a suitable base such as DABCO in a suitable solvent such as DMSO.



III I

Scheme 5

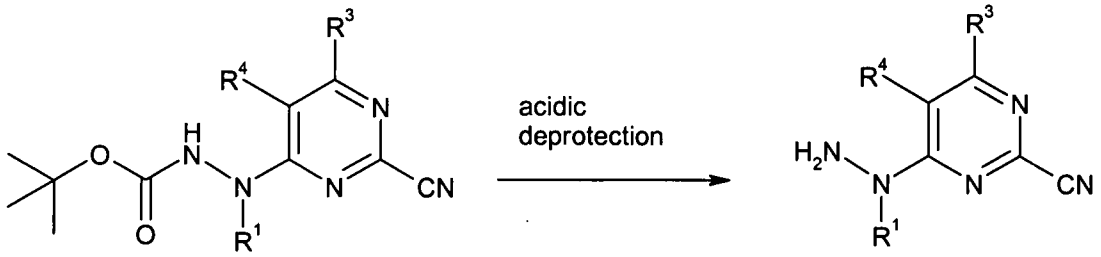
The alkoxycarbonyl hydrazine compounds of Formula Ic, which are compounds of Formula IA wherein R^1 , R^3 and R^4 are as defined above for Formula IA, A is C(O), and R^5 is hydrogen, C_{1-6}alkyl, C_{1-6}alkenyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^GC(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^GC(O)C_{1-6}alkyl and R^2 is OR^{11} in which R^{11} is C_{1-6}alkenyl, or -C_{1-6}alkyleneR^D, wherein R^D is hydrogen, C_{1-3}alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclyl, CCl_3, cyano, -NHC(O)C_{1-6}alkyl, -NHC(O)OC_{1-6}alkyl, or -C(O)C_{1-6}alkyl, may be prepared from the corresponding hydrazine compounds of Formula II, wherein R^5 is hydrogen, C_{1-8}alkyl, C_{1-6}alkenyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkyleneNR^GC(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^GC(O)C_{1-6}alkyl and R^1, R^3 and R^4 are as defined above for Formula IA, according to Scheme 6. Compounds of Formula II are reacted with a chloroformate R^{11}OCOCl, wherein R^{11} is as defined above for Formula Ic, in a suitable solvent such as DCM in the presence of a suitable base such as a mixture of diisopropylethylamine and DMAP to give compounds of Formula Ic. Chloroformates R^{11}OCOCl are either commercially available, or they may be obtained by reaction between the corresponding commercially available alcohol R^{11}OH, wherein R^{11} is as defined above for Formula Ic, and triphosgene in a suitable solvent such as THF, which may be directly reacted with compounds of Formula II in the presence of a suitable base such as triethylamine in a suitable solvent, for example pyridine, to give compounds of Formula Ic.



II Ic

Scheme 6

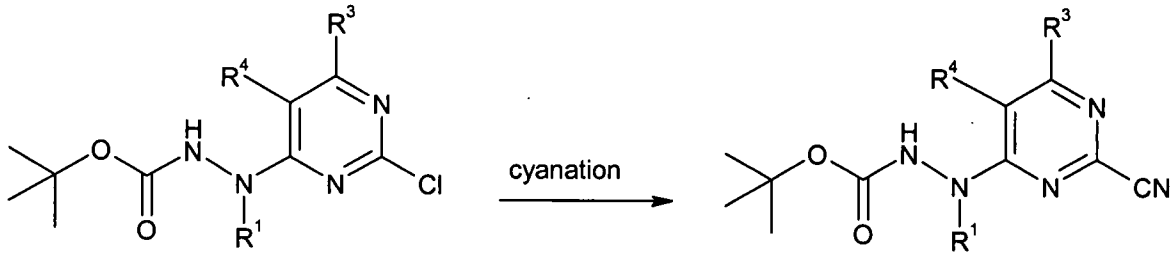
Compounds of Formula IIa which are compounds of Formula II wherein R^5 is hydrogen, may be prepared from compounds of Formula IV, wherein R^1, R^3 and R^4 are as defined above for Formula II (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl, R^3 represents hydrogen and R^4 represents halogen), according to Scheme 7 by deprotection in the presence of a suitable acid such as trifluoroacetic acid.



IV IIa

Scheme 7

Compounds of Formula IV may be prepared from compounds of Formula V, wherein R^1, R^3 and R^4 are as defined above for Formula IV (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl, e.g. cycloalkylmethyl, R^3 represents hydrogen and R^4 represents halogen), according to Scheme 8 by cyanation, by displacement of the chloro substituent of compounds of Formula V using a variety of conditions, for example by treatment with potassium or sodium cyanide in the presence of a suitable base such as DABCO in a suitable solvent such as DMSO.

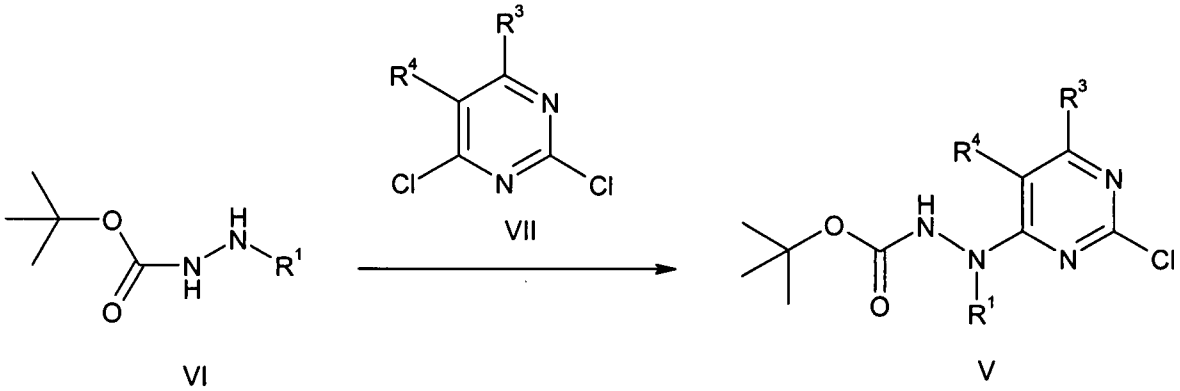


V IV

Scheme 8

Compounds of Formula V may be prepared from compounds of Formula VI, wherein R^1 is as defined above for Formula V (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl, e.g.

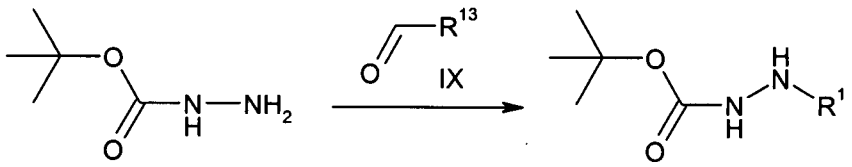
cycloalkylmethyl), according to Scheme 9 by reaction of compounds of Formula VI with a compound of Formula VII, wherein R^3 and R^4 are as described for Formula V, (for example, R^3 represents hydrogen and R^4 represents halogen), (commercially available from FLUKA or SIGMA) in a suitable solvent such as EtOH, for example at room temperature for 3-4 days, for example according to the literature procedure given in Bagley J. R. et al., (1989) J. Med. Chem. 32, 663-671.



VI VII V

Scheme 9

Compounds of Formula VI may be prepared from the compound of Formula VIII by a reductive amination reaction with an aldehyde IX, wherein R^{13} is one carbon shorter in chain length than R^1, wherein R^1 is C_{1-8}alkyl, -C_{1-8}alkyleneNR^{E}R^F, -C_{1-8}alkyleneNR^{G}C(O)OC_{1-6}alkyl, -C_{1-8}alkyleneNR^{G}C(O)C_{1-6}alkyl or -C_{1-8}alkylene-cycloalkyl, (for example, R^1 represents C_{1-8}alkyl, e.g. isobutyl), according to Scheme 10. The compound of Formula VIII, *tert*-butyl carbazate, is commercially available (ALDRICH). Reductive amination of the compound of Formula VIII with aldehydes of Formula IX is carried out in the presence of a suitable reducing agent such as hydrogen, and a suitable catalyst such as platinum or palladium or platinum oxide, in a suitable solvent such as i-PrOH, EtOH or a mixture thereof, for example according to the literature procedures given in Hilpert, H. (2001) Tetrahedron, 57, 7675-7683 or Dyker, H. et al, (2001) J. Org. Chem. 66, 3760-3766).

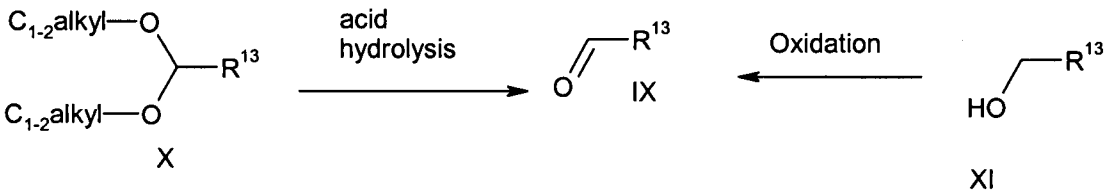


VIII VI

Scheme 10

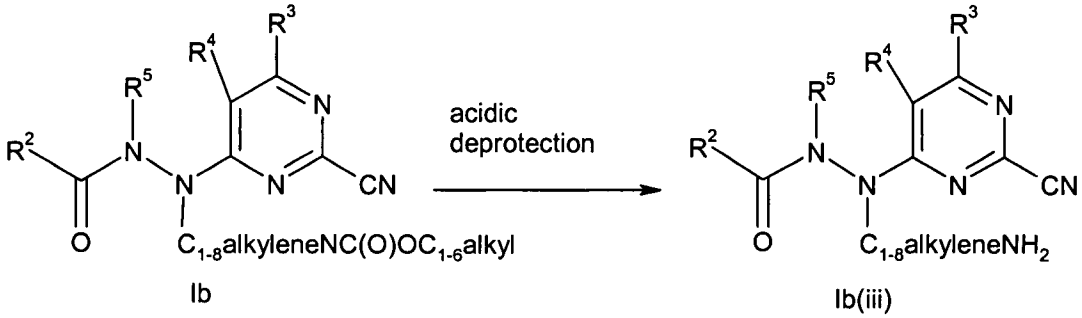
Aldehydes of Formula IX are either commercially available, e.g. isobutylaldehyde, or they may be prepared according to Scheme 11 i) from the corresponding commercially available dimethyl or diethyl acetal compound of Formula X wherein R^{13} is as defined above for compounds of Formula IX, by acid hydrolysis using a suitable acid such as hydrochloric acid, or ii) by oxidation of the commercially available alcohol compound of

Formula XI, wherein R^{13} is as defined above for compounds of Formula IX, following standard procedures as the Swern oxidation or Dess-Martin oxidation.



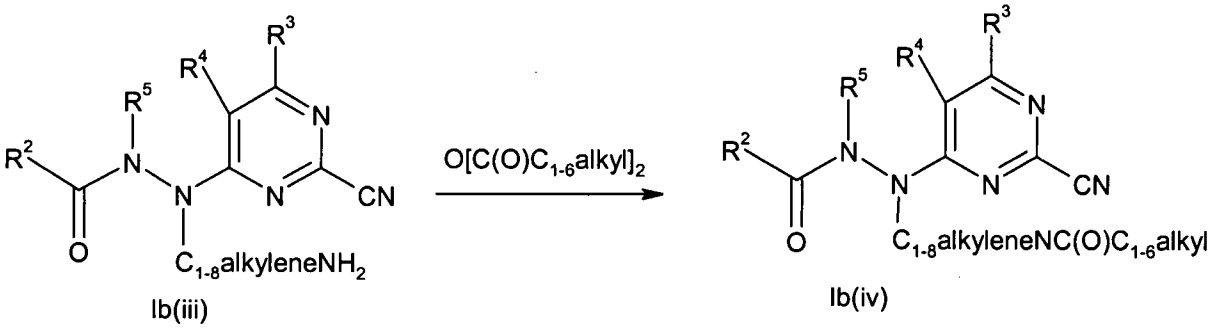
Scheme 11

Compounds of Formula Ib(iii), which are compounds of Formula IA which are compounds of Formula IA wherein R^2, R^3, R^4 and R^5 are as defined above for Formula IA, R^1 is $C_{1-8}alkyleneNH_2$, and A is C(O), may be prepared from a compound of Formula Ib wherein R^2, R^3, R^4 and R^5 are as defined for Formula Ib(iii), and R^1 is $-C_{1-8}alkyleneNC(O)OC_{1-6}alkyl$, by a deprotection reaction in the presence of a suitable acid such as trifluoroacetic acid, in a suitable solvent such as dichloromethane, or alternatively hydrobromic acid in a suitable solvent such as acetic acid according to Scheme 12.



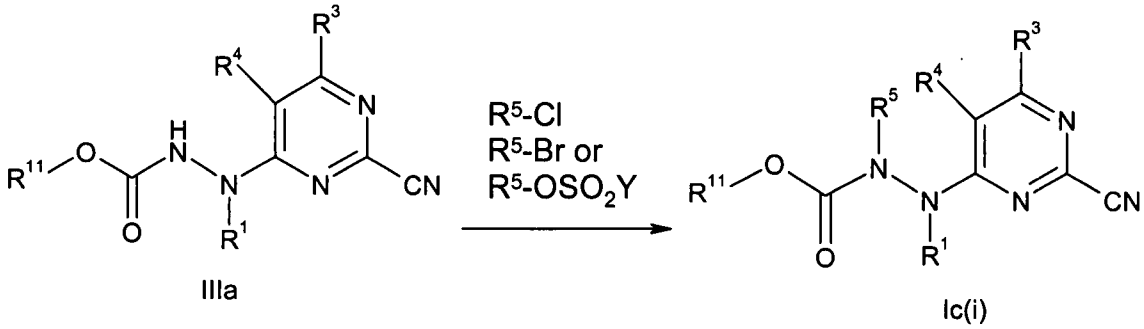
Scheme 12

Compounds of Formula Ib(iv) which are compounds of Formula IA wherein R^2, R^3, R^4 and R^5 are as defined for Formula Ib(iii), R^1 is $-C_{1-8}alkyleneNC(O)C_{1-6}alkyl$, and A is C(O), may be prepared from compounds of Formula Ib(iii) as defined above, according to Scheme 13, by treatment of Ib(i) with an anhydride of Formula $O[C(O)C_{1-6}alkyl]_2$ in a suitable solvent such as dichloromethane, at a suitable temperature, e.g. -10°C to 10°C.



Scheme 13

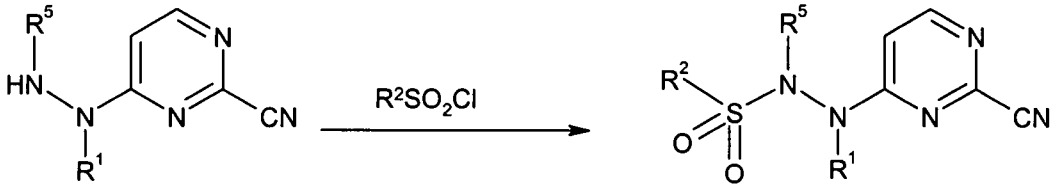
Compounds of Formula Ic(i), which are compounds of Formula IA wherein R^3 and R^4 are as defined above for Formula IA, R^1 is C_{1-8}alkyl, A is C(O), R^5 is C_{1-6}alkyl, C_{1-6}alkenyl, -C_{1-8}alkyleneN(C_{1-3}alkyl)$_2$, -C_{1-8}alkylene-heterocyclyl, -C(O)C_{1-6}alkyl, -C(O)R^{2a}, -C_{1-8}alkyleneNR^GC(O)OC_{1-6}alkyl or -C_{1-8}alkyleneNR^GC(O)C_{1-6}alkyl wherein R^G is as defined for Formula IA, or N-phthalidimido-C1-8alkylene-, and R^2 is OR^{11} in which R^{11} is C_{1-6}alkenyl or -C_{1-6}alkyleneNR^D, wherein R^D is hydrogen, C_{1-3}alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclyl, CCl_3, cyano, -NHC(O)C_{1-6}alkyl, -NHC(O)OC_{1-6}alkyl, or -C(O)C_{1-6}alkyl, may be prepared from compounds of Formula IIIa wherein R^3 and R^4 are as defined above for Formula IA, R^1 is C_{1-8}alkyl, and R^5 is hydrogen and R^2 is OR^{11} in which R^{11} is as defined for Ic(i), according to Scheme 14 by treatment of IIIa with an alkylating agent of Formula R^5-Cl, R^5-Br or R^5-OSO_2Y, wherein R^5 is as defined for Formula Ic(i) and Y is methyl or p-tolyl, in the presence of a suitable catalyst such as tetrabutylammonium hydrogensulfate and optionally sodium iodide in the presence of a base such as a mixture of potassium carbonate and sodium hydroxide, in a suitable solvent such as toluene, optionally at elevated temperature, e.g. 90-170°C.



IIIa Ic(i)

Scheme 14

Compounds of Formula Id, which are compounds of Formula IA wherein R^1, R^2, R^3, R^4 and R^5 are as defined above for Formula IA, A is -SO_2-, may be prepared from compounds of Formula II wherein R^1, R^3, R^4 and R^5 are as defined above for Formula IA according to Scheme 15, by treatment of compounds II with a sulfonyl chloride R^2SO_2Cl, wherein R^2 is as defined above for Formula I; in a suitable solvent such as pyridine. Sulfonyl chlorides R^2SO_2Cl may be commercially available or they may be prepared from the corresponding sulfonic acids R^2SO_2OH by treatment of the sulfonic acids with thionyl chloride in a suitable solvent such as toluene at elevated temperatures such as 90-170°C.



II Id

Scheme 15

It will be appreciated by those skilled in the art that R^3 and R^4 groups in compounds of Formula IA may be converted into other R^3 and R^4 groups in order to provide further compounds of Formula IA. For example, when R^4 is bromo, it may be converted to R^4 is –C≡C-aryl by reaction with H–C≡C-aryl in the presence of copper (I) iodide and bis(triphenylphosphine)palladium(II) chloride. For example, when R^4 is bromo, it may be converted to R^4 is NHC_{1-3}alkylene-aryl by reaction with a suitable amine H-NHC_{1-3}alkylene-aryl in the presence of palladium acetate and a suitable base, for example a mixture of BINAP and potassium carbonate. For example, when R^4 is bromo, it may be converted to R^4 is CF_3 by reaction with 2,2-difluoro-2-(fluorosulfonyl)acetate, hexamethylphosphoramide and copper (I) iodide, optionally heating at a suitable temperature, for example 80°C. Similarly, conversions may be carried out on compounds of Formula III, for example when R^3 is chloro, it may be converted to R^3 is methoxy by reaction with sodium methoxide in a suitable solvent, for example methanol.

It will be readily apparent to those skilled in the art that other compounds of Formula IA may be prepared using methods analogous to those outlined above, or by reference to the experimental procedures detailed in the Examples provided herein.

Those skilled in the art will also appreciate that in the preparation of the compound of Formula IA or a solvate thereof, it may be necessary and/or desirable to protect one or more sensitive groups in the molecule or the appropriate intermediate to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl or aralkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl). Examples of suitable oxygen protecting groups may include for example alky silyl groups, such as trimethylsilyl or *tert*-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or *tert*-butyl; or esters such as acetate.

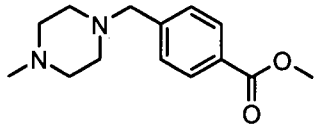
Examples

The following examples illustrate the invention. These examples are not intended to limit the scope of the invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the invention. While particular embodiments of the invention are described, the skilled artisan will appreciate that various

changes and modifications can be made without departing from the spirit and scope of the invention.

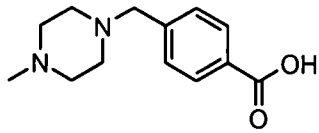
Intermediates

Intermediate 1: **methyl 4-[(4-methyl-1-piperazinyl)methyl]benzoate.**



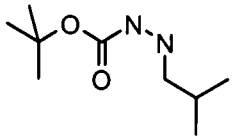
A solution of N-methylpiperazine (ALDRICH, 1.46 ml, 13.1 mmol) in dimethylformamide (5 ml) was cooled to 0° C and, then, potassium carbonate (1.81 g, 13.1 mmol) was added. This mixture was stirred at 0° C for 30 min. Then, methyl 4-(bromomethyl) benzoate (ALDRICH, 3 g, 13.1 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 17 h. The mixture was concentrated under reduce pressure. The residue was dissolved in DCM and washed with water, the aqueous layer was extracted with DCM. The organic layers were combined, washed with water, dried over $MgSO_4$ filtered and the solvent removed under reduce pressure to give the title compound. ^1H RMN (300 MHz, CDCl3-d6): 7.97 (d, 2H), 7 40 (d, 2H), 3.90 (s, 3H), 3.55 (s, 2H), 2.47 (br. m, 8H), 2.28 (s, 3H).

Intermediate 2: **4-[(4-methyl-1-piperazinyl)methyl]benzoic acid.**



A solution of lithium hydroxide (ALDRICH, 337 mg, 14.1 mmol) in H_2O (10 ml) was added to a solution of Intermediate 1 (1.4 g, 5.63 mmol) in MeOH (20 ml) and the mixture was refluxed for 2h. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM and 2N hydrochloric acid was added to give pH 5. The aqueous layer was partitioned with n-Butanol (5 times) and the fractions were combined, dried over $MgSO_4$, filtered and evaporated under reduce pressure to give the title compound as a white solid. ^1H RMN (300 MHz, DMSO-d6): 12.83 (br. m, 1H), 11.05 (br. m, 1H), 7.90 (d, 2H), 7.43 (d, 2H), 4.36 (m, 1H), 3.60 (s, 2H), 3.38-2.80 (br. m, 8H), 2.68 (s, 3H). [ES+ MS] m/z 235 $(MH)^+$.

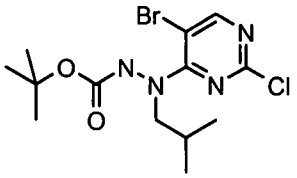
Intermediate 3: **1,1-dimethylethyl 2-(2-methylpropyl)hydrazinecarboxylate.**



A solution of 1,1-dimethylethyl hydrazinecarboxylate (ALDRICH, 9.2 g, 70 mmol) in i-PrOH (50 ml) was treated at 0°C with *i*-butylaldehyde (ALDRICH; 6.4 ml, 70 mmol) over 15 min and stirring at 0°C for 2 h, then the mixture was stirred 5 h at room temperature. To

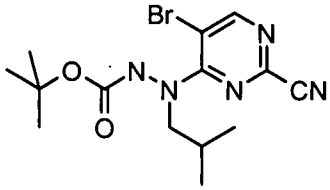
this solution containing the intermediate hydrazone was added PtO_2 and the suspension was hydrogenated at room temperature and 2.6 bar for 48 h. The suspension was filtered and the solvent was removed under reduced pressure to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 6.02 (br.s, 1H), 3.92 (br.s, 1H), 2.66 (d, 2H), 1.73 (m, 1H), 1.46 (s, 9H), 0.93 (d, 6H). [ES+ MS] m/z 189 $(MH)^+$.

Intermediate 4: **1,1-dimethylethyl 2-(5-bromo-2-chloro-4-pyrimidinyl)-2-(2-methyl propyl)hydrazinecarboxylate.**



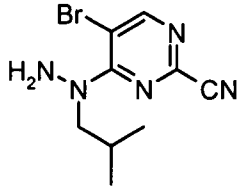
To a solution of 5-bromo-2,4-dichloropyrimidine (ALDRICH, 3.0 g, 13 mmol) and Intermediate 3 (2.5 g, 13 mmol) in *i*-PrOH (80 mL), N,N-diisopropylethylamine (3 mL, 17 mmol) was added and the resulting reaction mixture was refluxed for 5 h. The mixture was concentrated under reduced pressure and the residue partitioned between DCM and 1M ammonium chloride. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography (eluant: Hex/EtOAc 9:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.27 (br.s, 1H), 6.85-6.40 (br.m, 1H), 4.15-3.00 (br.m, 2H), 2.06 (m, 1H), 1.55-1.30 (br.m, 9H), 0.97 (d, 6H) [ES+ MS] m/z 379 $(M)^+$, [ES- MS] m/z 377 $(M-2H)^-$.

Intermediate 5: **1,1-dimethylethyl 2-(5-bromo-2-cyano-4-pyrimidinyl)-2-(2-methyl propyl)hydrazinecarboxylate.**



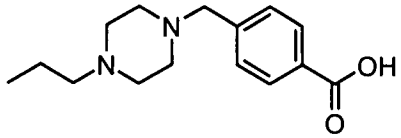
Potassium cyanide (0.9 g, 13 mmol) was added to a suspension of Intermediate 4 (4.1 g, 11 mmol) and DABCO (1.2 g, 11 mmol) in a mixture of $DMSO/H_2O$ 9:1 at room temperature. The reaction mixture was stirred at room temperature for 3 h, and then, poured into iced water. The cream colour solid that precipitated was filtered off, washed abundantly with water and dried under air. The compound was purified by flash chromatography (eluant: Hex/EtOAC 19:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.46 (br.s, 1H), 6.85-6.45 (br.m, 1H), 4.15-3.0 (br.m, 2H), 2.06 (m, 1H), 1.52-1.31 (br.m, 9H), 0.97 (d, 6H); ^1H NMR (300 MHz, d_6-DMSO, 80°C) δ ppm: 9.77 (br.s, 1H), 8.59 (s, 1H), 3.59 (br.s, 2H), 2.04 (m, 1H), 1.41 (br.s, 9H), 0.92 (d, 6H); ^{13}C NMR (90 MHz, d_6-DMSO) δ ppm: 160.7, 159.6, 153.6, 140.6, 115.7, 104.7, 80.4, 58.6, 27.7, 25.5, 20.0. [ES+ MS] m/z 370 $(M)^+$.

Intermediate 6: **5-bromo-4-[1-(2-methylpropyl)hydrazino]-2-pyrimidine carbonitrile.**



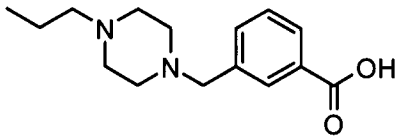
To a solution of Intermediate 5 (3.5 g, 9.4 mmol) in dry acetonitrile (70 mL), *p*-toluensulfonic acid (4.07 g, 23.6 mmol) was added and the resulting reaction mixture was stirred at room temperature for 24 h. The mixture was then concentrated *in vacuo* and the residue partitioned between DCM and sat. sodium bicarbonate. The residue was purified by preparative HPLC (X-TERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.39 (s, 1H), 3.75 (d, 2H), 2.22 (m, 1H), 0.96 (d, 6H). [ES+ MS] m/z 270 $(M)^+$.

Intermediate 7: **4-[(4-propyl-1-piperazinyl)methyl]benzoic acid.**



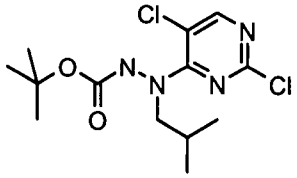
A mixture of 4-(bromomethyl)benzoic acid (ALDRICH, 5 g., 23.2 mmol), 1-N-propylpiperazine dihydrobromide (ALDRICH, 6.74 g., 23.2 mmol) and finely pulverized anhydrous potassium carbonate (ALDRICH, 6.4 g., 46.5 mmol) in dry acetonitrile was stirred at room temperature for 17 hours. Then, 1N HCl was added until pH 2. The mixture was concentrated under reduced pressure. The crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 0-30%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 7.94 (d, 2H), 7.49 (d, 2H), 3.89 (br, 2H), 3.02 (m ,2H), 3.70-2.50 (m , 8H), 1.62 (m, 2H), 0.88 (t, 3H). [ES+ MS] m/z 263 $(MH)^+$.

Intermediate 8: **3-[(4-propyl-1-piperazinyl)methyl]benzoic acid.**



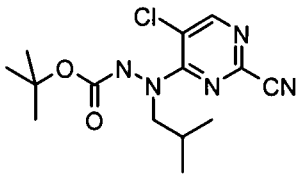
To a solution of 3-(chloromethyl)-benzoic acid (ALDRICH, 0.5 g, 3 mmol) in dry acetonitrile (10 mL), 1-N-propylpiperazine dihydrobromide (ALDRICH, 0.86 g, 3 mmol) and potassium carbonate (0.83 g, 6 mmol) were added and the resulting reaction mixture was stirred at room temperature. After 22 h, the reaction reached completion and hence, solvent was evaporated *in vacuo*. The residue was partitioned between 1-butanol and 1N NH_4Cl, and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the title compound. ^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 7.81 (br., 1H), 7.79-7.71 (br., 1H), 7.84-7.21 (br., 2H), 3.81-2.99 (br., 6H), 2.44-2.22 (br., 4H), 2.18 (m, 2H), 1.38 (m, 2H), 0.82 (m, 3H). [ES+ MS] m/z 263 $(MH)^+$, [ES- MS] m/z 261 $(M-H)^-$.

Intermediate 9: **1,1-dimethylethyl 2-(2,5-dichloro-4-pyrimidinyl)-2-(2-methyl propyl)hydrazinecarboxylate.**



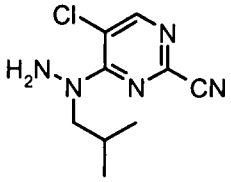
To a solution of 2,4,5-trichloropyrimidine (LANCASTER, 0.5 g, 2.7 mmol) and Intermediate 3 (0.6 g, 3.1 mmol) in *i*-PrOH (15 mL), N,N-diisopropylethylamine (0.7 mL, 3.7 mmol) was added and the resulting reaction mixture was refluxed for 3 h. The mixture was concentrated under reduced pressure and the residue partitioned between DCM and 1M ammonium chloride. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography (eluant: Hex/EtOAc 19:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.11 (br.s, 1H), 6.85-6.70 (br.m, 1H), 3.80-3.50 (br.m, 2H), 2.06 (m, 1H), 1.46 (br.s, 9H), 0.96 (d, 6H). [ES+ MS] m/z 335 $(MH)^+$.

Intermediate 10: **1,1-dimethylethyl 2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methyl propyl)hydrazinecarboxylate.**



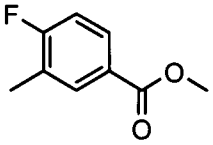
Potassium cyanide (0.2 g, 2.7 mmol) was added to a suspension of Intermediate 9 (0.7 g, 2.2 mmol) and DABCO (1.2 g, 11 mmol) in a mixture of DMSO/H_2O 9:1 (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 9 h, and then, poured into iced water. The light yellow solid that precipitated was filtered off, washed abundantly with water and dried under air. The compound was purified by flash chromatography (eluant: Hex/EtOAC mixtures 19:1 to 9:1) to give the title compound. ^{1}H NMR (300 MHz, d_6-DMSO) δ ppm: 10.09 (br.s, 1H), 8.51 (br.s, 1H), 3.98-3.71 (br.m, 1H), 3.30-3.07 (br.m, 1H), 1.98 (m, 1H), 1.41 (br.s, 9H), 0.99-0.79 (br.m, 6H); ^{1}H NMR (300 MHz, d_6-DMSO, 80°C) δ ppm: 9.81 (br.s, 1H), 8.47 (s, 1H), 3.80-3.34 (br.m, 2H), 2.03 (m, 1H), 1.41 (br.s, 9H), 0.93 (d, 6H). [ES+ MS] m/z 326 $(MH)^+$.

Intermediate 11: **5-chloro-4-[1-(2-methylpropyl)hydrazino]-2-pyrimidine carbo nitrile.**



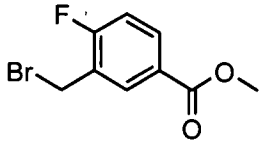
To a solution of Intermediate 10 (0.5 g, 1.5 mmol) in dry acetonitrile (10 mL), *p*-toluenesulfonic acid (0.79 g, 4.6 mmol) was added and the resulting reaction mixture was stirred at room temperature for 20 h. The mixture was then concentrated *in vacuo* and the residue partitioned between DCM and a saturated solution of sodium bicarbonate. The combined organic layers were treated with brine and dried over $MgSO_4$. The residue was purified by flash chromatography (elute: Hex/EtOAc 100:0 to 3:2) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO) δ ppm: 8.30 (s, 1H), 5.09 (br.s, 2H), 3.56 (d, 2H), 2.18 (m, 1H), 0.86 (d, 6H). [ES+ MS] m/z 226 $(MH)^+$.

Intermediate 12: **methyl 4-fluoro-3-methylbenzoate.**



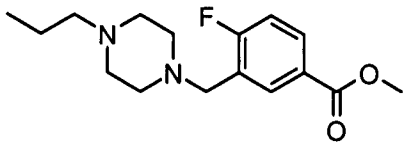
4-Fluoro-3-methylbenzoic acid (ALDRICH, 5.06 g, 32.8 mmol), potassium carbonate (17.9 g, 130 mmol) and methyl iodide (20.2 mL, 324.5 mmol) were dissolved in dry acetone (200 mL). The resulting reaction mixture was stirred at room temperature for 5 minutes before being heated to 50 °C. After 16h, the reaction reached completion and hence, solvent was evaporated *in vacuo*. Excess methyl iodide was removed by dissolving the residue in DCM, followed by solvent removal under reduced pressure. The residue was purified by flash chromatography (elute: Hex/EtOAc 100:0 to 3:2) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.94- 7.82 (m, 2H), 7.08- 7.02 (m, 1H), 3.91 (s, 3H), 2.33- 2.32 (m, 3H).
J. Org. Chem., (1996) 61(12), 4062-4072.

Intermediate 13: **methyl 3-(bromomethyl)-4-fluorobenzoate.**



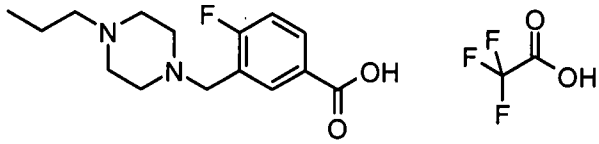
Under Argon atmosphere, Intermediate 12 (1 g, 6 mmol) was dissolved in carbon tetrachloride (25 mL). Argon was bubbled through the resulting solution for several minutes before N-bromosuccinimide previously recrystallised from water (1.27 g, 7.1 mmol) and α, α'- azoisobutyronitrile (0.1 g, 0.6 mmol) were added. The resulting reaction mixture was then heated at 80 °C. After 3h, the reaction reached completion and hence, solids were filtered off and solvent of the filtrate was removed *in vacuo*. The residue was purified by flash chromatography (elute: Hex/EtOAc 100:0 to 1:1) to yield the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.1 (dd, 1H), 8.05- 7.98 (m, 1H), 7.18- 7.09 (m, 1H), 4.53 (m, 2H), 3.93 (s, 3H).

Intermediate 14: **methyl 4-fluoro-3-[(4-propyl-1-piperazinyl)methyl]benzoate.**



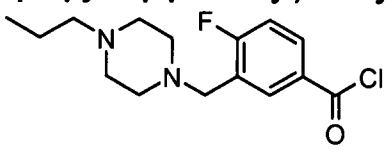
To a solution of Intermediate 13 (0.7 g, 2.7 mmol) in dry ACN (10 mL), 1- N-propylpiperazine dihydrobromide (ALDRICH, 0.9 g, 3.3 mmol), potassium carbonate (0.8 g, 5.7 mmol) and catalytic sodium iodide were added. The resulting reaction mixture was then stirred at room temperature. After 16 h, the reaction reached completion and hence, solvent was removed *in vacuo*. The residue was partitioned between DCM and saturated aqueous ammonium chloride. The aqueous layer was further extracted with DCM and the combined organic layers were washed with brine and dried over anhydrous sodium sulphate. A yellow oil was obtained upon removal of solvent under vacuum, which was then purified by flash chromatography (elute: Hex/EtOAc 100:0 to 1:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.09- 8.03 (dd, 1H), 7.98- 7.90 (m, 1H), 7.11- 7.05 (m, 1H), 3.92 (s, 3H), 3.63 (m, 2H), 2.68- 2.40 (br., 8H), 2.35- 2.30 (m, 2H), 1.58- 1.45 (m, 2H), 0.89 (t, 3H).

Intermediate 15: **4-fluoro-3-[(4-propyl-1-piperazinyl)methyl]benzoic acid trifluoroacetate.**



To a solution of Intermediate 14 (0.3 g, 1.0 mmol) in a 5:1 THF- water mixture (6 mL), lithium hydroxide monohydrate (0.13 g, 3.2 mmol) was added and the resulting reaction mixture was then stirred at room temperature. After 16 h, the reaction reached completion and hence, solvent was removed under reduced pressure. The residue was then dissolved in MeOH and purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 0-30%) to yield the title compound. ^{1}H NMR (300 MHz, d6- DMSO) δ ppm: 9.64- 9.10 (br., 1H), 8.04- 8.01 (dd, 1H), 7.96- 7.89 (m, 1H), 7.36- 7.30 (m, 1H), 3.72 (s, 2H), 3.53- 3.32 (br., 2H), 3.16- 2.80 (br., 6H), 2.52- 2.29 (br., 2H), 1.69- 1.50 (m, 2H), 0.87 (t, 3H).

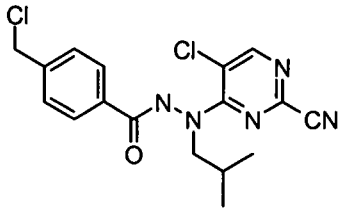
Intermediate 16: **4-fluoro-3-[(4-propyl-1-piperazinyl)methyl]benzoyl chloride.**



Under nitrogen atmosphere, Intermediate 15 (0.3 g, 0.9 mmol) was dissolved in thionyl chloride (10 mL) and the resulting reaction mixture was then stirred at room temperature. After 16h, the reaction had practically reached completion and hence, solvent was removed *in vacuo*. Excess thionyl chloride was removed by dissolving the residue in DCM, followed by solvent removal under reduced pressure, yielding the title compound

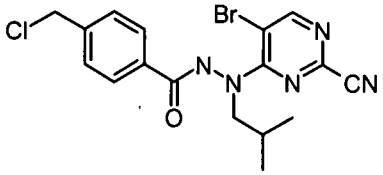
which was used without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.74-8.67 (m, 1H), 8.35- 8.24 (m, 1H), 7.42- 7.34 (m, 1H), 4.41 (br. s, 2H), 4.29- 4.14 (br., 2H), 4.14- 3.96 (br., 2H), 3.66- 3.50 (br., 4H), 3.11- 2.99 (br., 2H), 2.01- 1.84 (br., 2H), 1.08-1.03 (m, 3H).

Intermediate 17: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-(chloromethyl)-*N'*-(2-methyl propyl)benzohydrazide.**



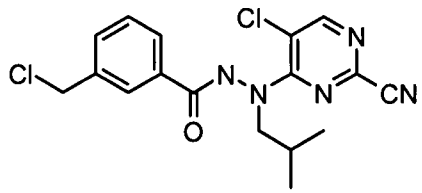
To a stirred solution of Intermediate 11 (2.58 g, 11 mmol) in dry THF (40 mL), 4-(chloromethyl)benzoyl chloride (ALDRICH, 2.17 g, 11 mmol) and potassium carbonate (3.35 g, 24 mmol) were added and the resulting reaction mixture was stirred at room temperature for 2.5 h. The mixture was filtered and the solvent was evaporated *in vacuo*. The crude reaction mixture was purified by flash chromatography (Hex/EtOAc from 100:0 to 1:1) to give the title compound. ^{1}H NMR (300 MHz, CDCl3) δ ppm: 8.31 (s, 1H), 8.25 (br. S, 1H), 7.8 (d, 2H), 7.51 (d, 2H), 4.62 (s, 2H), 3.79 (br.m, 2H), 2.09 (m, 1H), 1.01 (d, 6H).

Intermediate 18: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-4-(chloromethyl)-*N'*-(2-methyl propyl)benzohydrazide.**



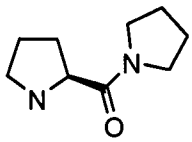
To a stirred mixture of Intermediate 6 (195 mg, 0.72 mmol) and K_2CO_3 (200 mg, 1.44 mmol) in THF (7 mL) was added 4-(chloromethyl)benzoyl chloride (ALDRICH, 164 mg, 0.87 mmol), and the mixture was stirred for 15 hours at room temperature. The mixture was filtered, the filtrate was evaporated to dryness, and the resulting residue was chromatographed (silica gel hexane/ethyl acetate 20%) to obtain the desired product. ^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 11.38 (s, 1H), 8.63 (s, 1H), 7.92 (m, 2H), 7.59 (m, 2H), 4.83 (s, 2H), 4.02 (m, 1H), 3.43 (m, 1H), 2.07 (m, 1H), 0.95 (d, 6H), [ES+ MS] m/z 422 $(M)^+$.

Intermediate 19: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-(chloromethyl)-*N'*-(2-methylpropyl)benzohydrazide.**



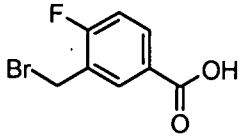
3-(Chloromethyl)-benzoyl chloride (ALDRICH, 0.106 g, 0.56 mmol) was added to a solution of Intermediate 11 (0.13 g, 0.58 mmol) and potassium carbonate (0.160 g, 1.16 mmol) in dry THF (2 mL) and the resultant reaction mixture was stirred at room temperature. After 2 hours, the reaction was complete and the mixture was filtered and the solvent was evaporated. The crude product was purified using silica gel (eluant: hexane/ethyl acetate) to give the title compound. ES+MS m/z 378 $(M)^+$.

Intermediate 20: **1-L-prolylpyrrolidine.**



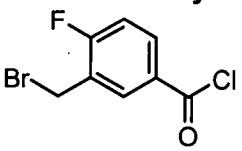
To a solution of benzyl (s)-(-)-2-(1-pyrrolidinylcarbonyl)-1-pyrrolidinecarboxylate (ALDRICH, 300 mg, 1.0 mmol) in methanol/acetic acid (30 mL) was added palladium activated carbon 10% (30 mg). The suspension was hydrogenated at room temperature and 2.46 bar for 150 min. The suspension was filtered and the solvent was evaporated under reduced pressure. The crude was used in next step without further purification. [ES+ MS] m/z 169 $(MH)^+$.

Intermediate 21: **3-(bromomethyl)-4-fluorobenzoic acid.**



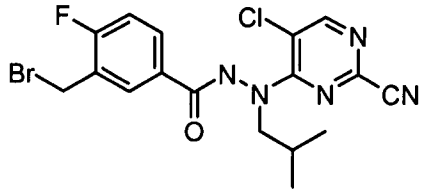
To a solution of 4-fluoro-3-methylbenzoic acid (ALDRICH, 1 g, 6.49 mmol) in carbon tetrachloride (25 mL), N-bromosuccinimide (ALDRICH, 2.54 g, 14.27 mmol) and benzoyl peroxide (ALDRICH, 111 mg) were added, under inert atmosphere. The reaction mixture was refluxed for two hours and stirred at room temperature overnight. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue obtained was purified by preparative HPLC (LUNA 50x250 mm, ACN:H_2O, 0.1%TFA, gradient 30-80%) to give the title compound. ^1H NMR (300 MHz, d6-DMSO) δ ppm: 13.18 (br.s, 1H), 8.17- 8.11 (br.m, 1H), 8.00- 7.91 (br.m, 1H), 7.41- 7.31 (br.m, 1H), 4.77 (s, 2H).

Intermediate 22: **3-(bromomethyl)-4-fluorobenzoyl chloride.**



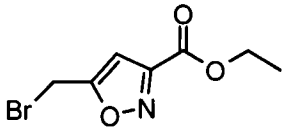
To a solution of Intermediate 21 (500 mg, 2.12 mmol) in DCM (10 mL), thionyl chloride (ALDRICH, 4 mL) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to obtain the title compound. The crude product was used in next step without purification.

Intermediate 23: **3-(bromomethyl)-*N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-*N'*-(2-methylpropyl)benzohydrazide.**



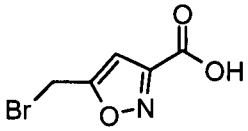
To a solution of Intermediate 22 (531 mg, 2.12 mmol) in dry THF (15 mL), Intermediate 11 (396 mg, 1.76 mmol) and N,N-diisopropylethylamine (FLUKA, 0.613 mL, 3.52 mmol) were added. The reaction mixture was stirred at room temperature overnight to obtain the title compound which was used in next step without further purification.

Intermediate 24: **Ethyl 5-(bromomethyl)-3-isoxazolecarboxylate.**



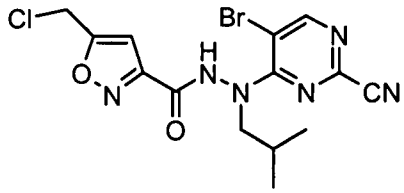
Ethyl 5-methylisoxazole-3-carboxylate (AVOCADO, 1 g, 6.45 mmol) was dissolved in CCl_4 (60 mL). N-bromosuccinimide (ALDRICH, 1.717 g, 9.67 mmol) and a tip of spatula of benzoyl peroxide (ALDRICH) were added and the resultant solution was refluxed for 3 days. The reaction mixture was filtered, evaporated and the residue was purified by preparative-HPLC (LUNA column 50x250 mm, gradient: 30%ACN; 0.1%TFA to 80%ACN, 0.1%TFA) to obtain the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 6.72 (s, 1H), 4.48 (s, 2H), 4.44 (q, 2H, *J*=7.2), 1.41 (t, 3H, *J*=7.2). [ES+ MS] m/z 234 $(M)^+$.

Intermediate 25: **5-(bromomethyl)-3-isoxazolecarboxylic acid.**



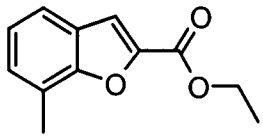
To a solution of Intermediate 24 (242.7 mg, 1.04 mmol) in THF (5 mL), a solution of lithium hydroxide monohydrate (ALDRICH, 62.08 mg, 2.59 mmol) in water (3 mL) was added. The resultant solution was stirred at room temperature for 3.5 hours. Solvents were evaporated to obtain the title compound which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) δ ppm: 6.50 (s, 1H), 4.36 (s, 2H).

Intermediate 26: **N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-(chloromethyl)-N'-(2-methylpropyl)-3-isoxazolecarbohydrazide.**



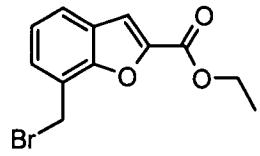
Intermediate 25 (crude product, corresponding to 1.04 mmol) was dissolved in oxalyl chloride (ALDRICH, 5 mL, 2M solution in dichloromethane). The resultant solution was stirred for 24 h, then evaporated, and the residue (418 mg, 1.87 mmol) was added to a solution of Intermediate 6 (252.57 mg, 0.935 mmol) and N,N-diisopropylethylamine (FLUKA, 0.65 mL, 3.74 mmol) in anhydrous THF (10 mL) (previously stirred for 15 minutes). To the resultant solution, potassium tert-butoxide (ALDRICH, 146.9 mg, 1.31 mmol) was added. The mixture was stirred at room temperature overnight. Solvents were evaporated and the residue purified by preparative-HPLC (LUNA column 50x250 mm, gradient: 40% ACN; 0.1%TFA to 80% ACN, 0.1%TFA) to obtain the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.81 (br.s, 1H), 8.49 (s, 1H), 6.79 (s, 1H), 4.67 (s, 2H), 3.77 (m, 2H), 2.10 (m, 1H), 1.00 (d, 6H, *J* = 6 Hz). [ES+ MS] m/z 413 $(M)^+$.

Intermediate 27: **Ethyl 7-methyl-1-benzofuran-2-carboxylate.**



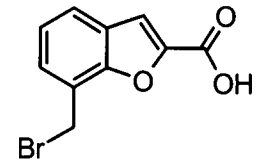
2-Hydroxy-3-methylbenzaldehyde (ALDRICH, 1 g, 7.34 mmol) and diethyl bromomalonate (ALDRICH, 1.82 mL, 11.03 mmol) were dissolved in 2-butanone (ALDRICH, 9 mL) under nitrogen atmosphere. Potassium carbonate (ALDRICH, 2.03 g, 14.69 mmol) was added and the resultant suspension was refluxed until no starting material was left (21 h). The reaction mixture was cooled down to room temperature, potassium carbonate was filtered and the filtrates were diluted with ethyl acetate and washed with NH_4Cl 1N (2x), saturated $NaHCO_3$ (1x) and saturated NaCl (1x). The combined organic phases were dried with $MgSO_4$, filtered and evaporated to dryness. Diethyl-3-hydroxy-7-methyl-1-benzofuran-2, 2-(3*H*)-dicarboxylate was obtained and dissolved in dry THF (50 mL). Sodium hydride, 60% dispersion in mineral oil (ALDRICH, 734 mg, 18.35 mmol) was added portionwise. After 1 h, the reaction was complete. The reaction mixture was poured into ice; saturated $NaHCO_3$ and ethyl acetate were added. The phases were separated and the organic phase was washed with saturated NaCl, dried with $MgSO_4$, filtered and evaporated to dryness. The residue was purified twice in silica (hexane/AcOEt mixtures) to yield the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.50-7.52 (m, 2H), 7.18-7.26 (m, 2H), 4.45 (q, 2H, *J* = 7.2 Hz), 2.60 (s, 3H), 1.44 (t, 3H, *J* = 7.0 Hz). [ES+ MS] m/z 205 $(MH)^+$.

Intermediate 28: **Ethyl 7-(bromomethyl)-1-benzofuran-2-carboxylate.**



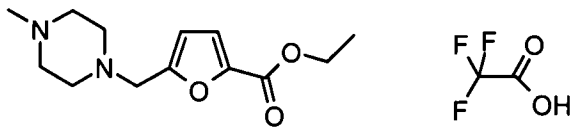
Intermediate 27 (730 mg, 3.57 mmol) was dissolved in carbon tetrachloride (20 mL). N-bromosuccinimide (ALDRICH, 763 mg, 4.29 mmol) and benzoyl peroxide (ALDRICH, 18 mg, cat.) were added and the resultant solution was heated at reflux until no starting material was left (22 h). The reaction was cooled, the solid was filtered and filtrate was evaporated. The residue was purified in silica (hexane/AcOEt mixtures) to yield the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.63-7.66 (m, 1H), 7.54 (s, 1H), 7.48-7.52 (m, 1H), 7.30-7.33 (m, 1H), 4.85 (s, 2H), 4.46 (q, 2H, *J* = 7.0 Hz), 1.44 (t, 3H, *J* = 7.2 Hz). [ES+ MS] m/z 283 $(M)^+$.

Intermediate 29: **7-(bromomethyl)-1-benzofuran-2-carboxylic acid.**



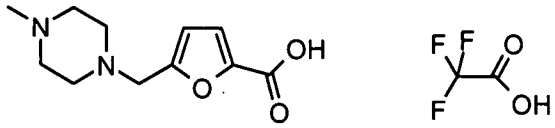
Intermediate 28 (637 mg, 2.25 mmol) was dissolved in THF (45 mL). A solution of 2N lithium hydroxide in water (ALDRICH, 2.8 mL, 5.62 mmol) was added and the reaction was stirred at room temperature for 24 h. Ethyl acetate and water were added and the phases were separated. The aqueous phase was acidified with 2N HCl and extracted with dichloromethane (4x). The organic phase was separated, dried with $MgSO_4$, filtered and evaporated to yield the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.76-7.79 (m, 1H), 7.72 (s, 1H), 7.58-7.61 (m, 1H), 7.32-7.37 (m, 1H), 4.96 (s, 2H). [ES+ MS] m/z 255 $(M)^+$.

Intermediate 30: **Ethyl 5-[(4-methyl-1-piperazinyl)methyl]-2-furancarboxylate trifluoroacetate.**



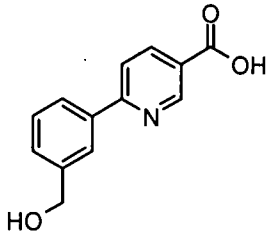
Ethyl 5-(chloromethyl)-2-furancarboxylate (ALDRICH, 1 g, 5.32 mmol) was dissolved in dry ACN (60 mL). Potassium carbonate (ALDRICH, 585.9 mg, 4.24 mmol), N-methyl-piperazine (ALDRICH, 258 uL, 2.33 mmol) and a tip of spatula of sodium iodide (FLUKA) were added and the resultant suspension was stirred at room temperature overnight. The mixture was filtered, evaporated and the residue was purified in preparative-HPLC (XTERRA column 50x250 mm, gradient: 0% ACN; 0.1% TFA to 60% ACN, 0.1% TFA) to obtain the title compound. ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$) δ ppm: 7.10 (d, 1H, *J* = 3.4 Hz), 6.40 (d, 1H, *J* = 3.4 Hz), 4.32 (q, 2H, *J* = 7.1 Hz), 3.73 (s, 2H), 3.24 (br.m, 3H), 2.79-2.95 (m, 8H), 1.34 (t, 3H, *J*=7.1). [ES+ MS] m/z 253 $(MH)^+$.

Intermediate 31: **5-[(4-methyl-1-piperazinyl)methyl]-2-furancarboxylic acid trifluoroacetate.**



To a solution of Intermediate 30 (896.2 mg, 3.552 mmol) in THF (20 mL) was added a solution of lithium hydroxide monohydrate (ALDRICH, 212.68 mg, 8.88 mmol) in water (10 mL). The resultant solution was stirred at room temperature overnight and then, it was refluxed for 24 h. The reaction mixture was cooled, acidified with 2N HCl and concentrated to dryness. The residue was purified by preparative-HPLC (XTERRA column 50x250 mm, gradient: 10%ACN; 0.1%TFA to 100%ACN, 0.1%TFA) to obtain the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.80 (br s, 1H), 7.17 (d, 1H, J = 6 Hz), 6.54 (d, 1H, J = 6 Hz), 3.68 (s, 2H), 3.35-3.38 (m, 2H), 2.95-3.15 (m, 4H), 2.75 (s, 3H), 2.30-2.45 (m, 2H). [ES+ MS] m/z 225 $(MH)^+$.

Intermediate 32: **6-[3-(hydroxymethyl)phenyl]-3-pyridinecarboxylic acid.**



6-chloronicotinic acid (ALDRICH, 300 mg, 1.90 mmol) was dissolved in 1,2-dimethoxyethane (15 mL) under nitrogen. Palladium tetrakistriphenylphosphine (ALDRICH, 440 mg, 0.38 mmol) was added, the resulting reaction mixture was stirred for 15 min. Sodium carbonate (161 mg, 1.52 mmol), water (4 mL) and 3-(Hydroxymethyl)benzeneboronic acid (LANCASTER, 404 mg, 2.66 mmol) were added subsequently. The resulting reaction mixture was refluxed at 95 °C for 16 h and then cooled to r.t. After filtration over celite, the reaction mixture was acidified (2N HCl) to pH 4 but no product could be extracted with DCM. Therefore, the aqueous layer was evaporated to dryness and was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 9.13 (m, 1H), 8.358-8.29 (m, 1H), 8.16-7.96 (m, 3H), 8.02 (m, 1H), 7.51-7.40 (m, 2H), 4.59 (s, 2H).

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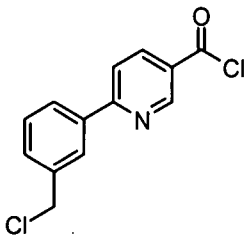
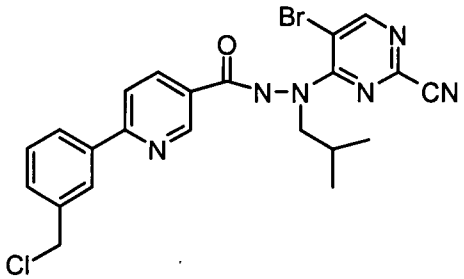
Intermediate 33: **6-[3-(chloromethyl)phenyl]-3-pyridinecarbonyl chloride.**



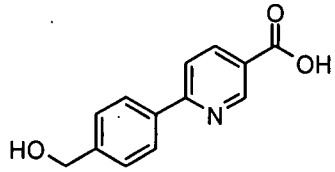
Intermediate 32 (35 mg, 0.15 mmol) and thionyl chloride (ALDRICH, 4 mL) was stirred at room temperature 22 h and then was refluxed 3h. The solvent was evaporated under reduced pressure to obtain intermediate 33. The crude was used in next step without further purification.

Intermediate 34: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-6-[3-(chloromethyl)phenyl]-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide.**



Intermediate 6 (83 mg, 0.31 mmol) and N,N-diisopropylethylamine (FLUKA, 0.107 mL, 0.61 mmol) in dry THF (2 mL) was stirred at room temperature for 30 min. Then, a solution of Intermediate 33 (40 mg, 0.15 mmol) in dry THF (4 mL) was added. The reaction mixture was stirred at room temperature for 17 h. The solvent was evaporated and the crude product was purified by preparative HPLC (Sunfire 19x150 mm, ACN:H2O, 0.1%TFA, gradient 20-100%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 11.59 (s, 1H), 9.17 (m, 1H), 8.67 (s, 1H), 8.41-8.34 (m, 1H), 8.26 (s, 1H), 8.21-8.09 (m, 2H), 7.60-7.55 (m, 2H), 4.88 (s, 2H), 4.68-3.19 (br., 2H), 2.10 (m, 1H), 0.97 (d, 6H).

Intermediate 35: **6-[4-(hydroxymethyl)phenyl]-3-pyridinecarboxylic acid.**



6-chloronicotinic acid (ALDRICH, 500 mg, 2.5 mmol) was dissolved in 1,2-dimethoxyethane (20 mL) under nitrogen. Palladium tetrakistriphenylphosphine (ALDRICH, 733 mg, 0.64 mmol) was added, the resulting reaction mixture was stirred for 15 min. Sodium carbonate (2.7 g, 25.4 mmol), water (20 mL) and 4-(hydroxymethyl) benzene boronic acid (LANCASTER, 674 mg, 4.44 mmol) were added subsequently. The resulting reaction mixture was refluxed at 95 °C for 16 h and then cooled to r.t. After

filtration over celite, the reaction mixture was acidified and was concentrated under reduced pressure. The crude was used in next step without purification.
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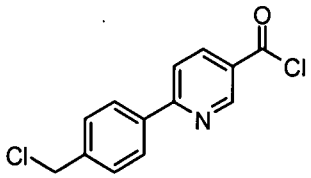
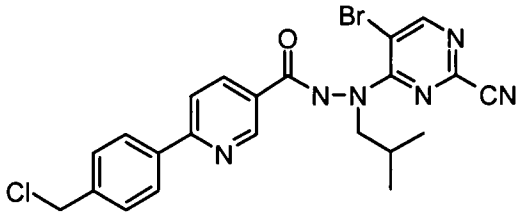
Intermediate 36: **6-[4-(chloromethyl)phenyl]-3-pyridinecarbonyl chloride.**



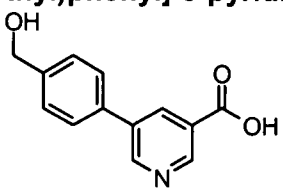
Intermediate 35 and thionyl chloride (ALDRICH, 20 mL) were refluxed for 2h and, then, were stirred at room temperature overnight. The solvent was evaporated under reduced pressure to obtain Intermediate 35. The crude was used in next step without further purification.

Intermediate 37: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-6-[4-(chloromethyl)phenyl]-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide.**



Intermediate 6 (101 mg, 0.37 mmol) and N,N-diisopropylethylamine (FLUKA, 0.097 mL, 0.55 mmol) in dry THF (5 mL) were stirred at room temperature for 30 min. Then, a solution of Intermediate 36 (200 mg, 0.75 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the reaction was diluted with DCM and washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by preparative HPLC (Sunfire 19x150 mm, ACN:H2O, 0.1%TFA, gradient 30-80%) to give the title compound. ^1H NMR (300 MHz, DMSO-d6): 11.58 (s, 1H), 9.15 (m, 1H), 8.66 (s, 1H), 8.40-8.32 (m, 1H), 8.22-8.12 (m, 3H), 7.59 (d, 2H), 4.84 (s, 2H), 4.01 (br., 1H), 3.33 (br., 1H), 2.10 (m, 1H), 0.96 (d, 6H).

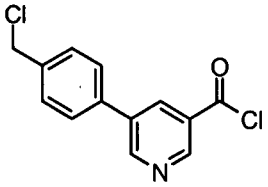
Intermediate 38: **5-[4-(hydroxymethyl)phenyl]-3-pyridinecarboxylic acid.**



5-Bromonicotinic acid (FLUKA, 500 mg, 2.5 mmol) was dissolved in 1,2-dimethoxyethane (25 mL) under nitrogen. Palladium tetrakistriphenylphosphine (ALDRICH, 572 mg, 0.49

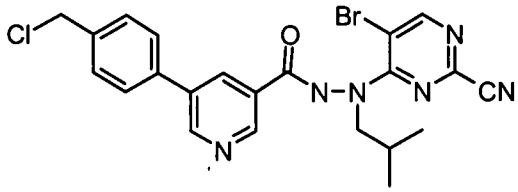
mmol) was added and the resulting reaction mixture was stirred for 15 min. Sodium carbonate (2.1 g, 19.8 mmol), water (20 mL) and 4-(hydroxymethyl) benzene boronic acid (LANCASTER, 525 mg, 3.46 mmol) were added subsequently. The resulting reaction mixture was refluxed at 95 ºC for 16 h and, then, cooled to r.t. After filtration over celite, the reaction mixture was acidified and was concentrated under reduced pressure. The crude was used in next step without further purification. ^{1}H NMR (300 MHz, DMSO-d6) δ ppm: 9.32 (m, 1H), 9.12 (m, 1H), 8.84 (m, 1H), 7.84 (d, 2H), 7.50 (d, 2H), 4.56 (s, 2H). Synthesis (2003), 551-554

Intermediate 39: **5-[4-(chloromethyl)phenyl]-3-pyridinecarbonyl chloride.**



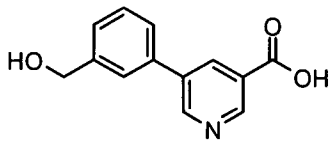
Intermediate 38 and thionyl chloride (ALDRICH, 15 mL) were refluxed for 2 h and, then, stirred at room temperature overnight. The solvent was evaporated under reduced pressure to obtain Intermediate 39 which was used in next step without further purification.

Intermediate 40: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-[4-(chloromethyl)phenyl]-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide.**



Intermediate 6 (100 mg, 0.37 mmol) and N,N-diisopropylethylamine (FLUKA, 0.097 mL, 0.55 mmol) in dry THF (10 mL) was stirred at room temperature 20 min. Then, a solution of Intermediate 39 (300 mg, 1.13 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to obtain Intermediate 40 which was used in the next step without further purification.

Intermediate 41: **5-[3-(hydroxymethyl)phenyl]-3-pyridinecarboxylic acid.**



5-Bromonicotinic acid (FLUKA, 500 mg, 2.5 mmol) was dissolved in 1,2-dimethoxyethano (25 mL) under nitrogen. Palladium tetrakistriphenylphosphine (ALDRICH, 572 mg, 0.49 mmol) was added, the resulting reaction mixture was stirred for 15 min. Sodium carbonate (2.1 g, 19.8 mmol), water (20 mL) and 4-(hydroxymethyl)benzene boronic acid

(LANCASTER, 525 mg, 3.46 mmol) were added subsequently. The resulting reaction mixture was refluxed at 95 °C for 16 h and then cooled to r.t. After filtration over celite, the reaction mixture was acidified and was concentrated under reduced pressure. The crude product was used in next step without purification.

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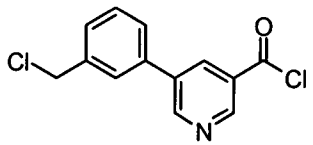
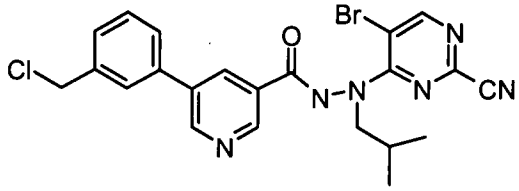
Intermediate 42: **5-[3-(chloromethyl)phenyl]-3-pyridinecarbonyl chloride.**



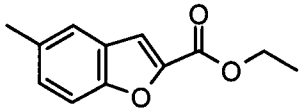
Intermediate 41 and thionyl chloride (ALDRICH, 15 mL) were refluxed for 2h and, then, stirred at room temperature overnight. The solvent was evaporated under reduced pressure to obtain the title intermediate which was used in the next step without further purification.

Intermediate 43: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-[4-(chloromethyl)phenyl]-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide.**



Intermediate 6 (100 mg, 0.37 mmol) and N,N-diisopropylethylamine (FLUKA, 0.097 mL, 0.55 mmol) in dry THF (10 mL) were stirred at room temperature for 20 min. Then, a solution of Intermediate 42 (300 mg, 1.13 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred at room temperature overnight and the crude was used in the next step withour further purification.

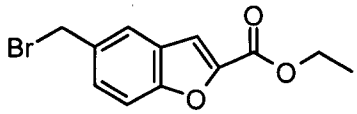
Intermediate 44: **ethyl 5-methyl-1-benzofuran-2-carboxylate.**



To a stirred solution of 2-hydroxy-5-methylbenzaldehyde (ALDRICH; 2g; 14.7mmol; 1eq) and diethyl bromomalonate (ALDRICH; 2.37g; 9.92mmol;1.5eq), in 2-butenona (ALDRICH, 10 mL), K_2CO_3 (ALDRICH; 4.06g; 2eq) was added and the mixture was refluxed for 2h. The crude was filtered, and the filtrate was extracted with EtOAc and NH_4Cl sat (twice), then, the organic layer was washed with sat. $NaHCO_3$, and brine. The combined organic phase was dried (Na_2SO_4), filtered and the solvent was evaporated. NaH (ALDRICH; 60% in oil mineral, 2.5eq) was added to the crude in 50mL of THF; the reaction mixture was stirred 10min and it was dropped onto a mixture of ice and sat. $NaHCO_3$, extracted several times with EtOAc, and washed with brine. The combined

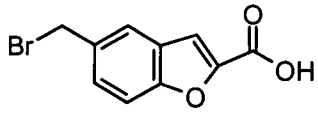
organic phase was dried (Na_2SO_4) and the crude was purified by column chromatography (silica gel; Hexane/ EtOAc) to give the title compound. 1H NMR (d6-DMSO) δ ppm: 7.7-7.5(m; 3H); 7.3(d; 8.5Hz; 1H); 4.3 (q; 7.7Hz; 2H); 2.4 (s; 3H); 1.3 (t; 7.7Hz; 3H).

Intermediate 45: **ethyl 5-(bromomethyl)-1-benzofuran-2-carboxylate.**



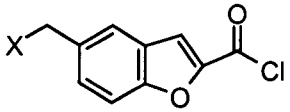
To a refluxing solution of Intermediate 44 (1.3 g, 6.4 mmol; 1 eq) under nitrogen in 20 mL of CCl_4, N-bromosuccinimide (ALDRICH, 1.36 g, 7.63 mmol; 2 eq) and a tip of spatula of benzoyl peroxide (ALDRICH), were added. The mixture was refluxed for 5 days and once it has reached completion the reaction mixture was cooled down to 0 °C, filtered and purified in silica gel (Hexane/EtOAc) to give a mixture of products. ^1H NMR (d6-DMSO) δ ppm: 8-7.4(m; 4H); 4.9(s; 2H); 4.6(s; 0.4H); 4.36(q; 7.2Hz; 2H); 1.35(t; 7.2Hz; 3H).

Intermediate 46: **5-(bromomethyl)-1-benzofuran-2-carboxylic acid.**



To a solution of Intermediate 45 (230mg) in 12mL of THF/H_2O (5/1), 2N lithium hydroxide (ALDRICH; 2.44 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. Once it has reached completion (TLC, eluent: DCM/MeOH 9:1), the solvent was evaporated; water and DCM were added and the aqueous layer extracted and acidified to pH 4. The organic layer was extracted with DCM and AcOEt; the organic combined phase was dried (Na_2SO_4), filtered and the solvent was evaporated giving the title compound that was used in the next step without further purification. ^1H NMR (d4-CD_3OD) δ ppm: 7.7(m; 1H); 7.55(m; 2H); 7.47(m; 1H); 4.7(s; 2H).

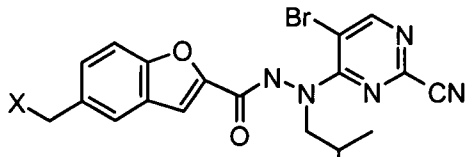
Intermediate 47: **5-(chloro or bromomethyl)-1-benzofuran-2-carbonyl chloride.**



X=Cl or Br

A stirred solution, under N_2, of Intermediate 46 in 1 mL of $SOCl_2$ (ALDRICH) was refluxed during 1 h. Once it had reached completion, solvent was evaporated under reduced pressure giving the title compound that was used in the next step without further purification.

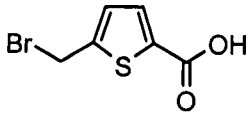
Intermediate 48: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-(chloro or bromomethyl)-*N'*-(2-methylpropyl)-1-benzofuran-2-carbohydrazide.**



X=Cl or Br

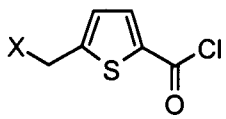
To a cooled solution of Intermediate 47 in 2 mL of dry DCM, a solution of 81 mg of Intermediate 6 (0.30 mmol) with 51 µL of DIPEA (FLUKA; 0.30 mmol) was added dropwise. The reaction was stirred under N_2 overnight and monitorized by HPLC (X-TERRA 4.6X50mm; H_2O: ACN, 0.1%TFA, gradient 25-100%). When the reaction had reached completion, solvent was evaporated and H_2O and DCM were added, the phases were separated and the organic layer was extracted with sat. NH_4Cl (25 mL), then, with Na_2CO_3 (25 mL) and, finally, with 25 mL of brine. The combined organic phase was dried (Na_2SO_4). The crude was purified by chromatography (silica gel, Hexane: EtOAc) to obtain the title compound mixture. ES+MS m/z 462 $(MH)^+$& 507$(M)^+$.

Intermediate 49: **5-(bromomethyl)-2-thiophenecarboxylic acid.**



To a refluxing solution of 5-methyl-2-thiophenecarboxylic acid (ALDRICH; 1 g; 7.03 mmol; 1 eq) in 60 mL of CCl_4 under nitrogen, 1.5 g (8.44 mmol; 1.2 eq) of N-bromosuccinimide and a catalytic amount of benzoyl peroxide were added. The mixture was refluxed for 3 h and once it has reached completion (HPLC: X-TERRA 4.6X50mm; H_2O: ACN, 0.1%TFA, gradient 10-100%; Rt: 4.2'), solvent was evaporated under reduced pressure. The resulting product was purified by preparative HPLC (X-TERRA 50x250mm; H_2O:ACN, 0.1%TFA, gradient 10-100%) giving the title compound. ^1H NMR (DMSO) δ ppm: 7.6(d; 3.81Hz; 2H); 7.26(d; 3.81Hz; 1H); 7 (d; 8.31Hz; 1H); 5 (s; 2H); 4.65(s; 2H).
This product was repurified by preparative HPLC (X-TERRA 50x250mm; H_2O: ACN, 0.1%TFA, gradient 10-100%) giving the title compound. ^1H NMR ($CDCl_3$) δ ppm: 7.8 (d;3.81Hz;0.1H); 7.74 (d;3.81Hz;1H); 7.14 (d;3.81Hz;1H); 7.04 (d;3.81Hz;0.1H); 4.9 (s;0.3H); 4.7 (s; 2H).

Intermediate 50: **5-(bromo or chloromethyl)-2-thiophenecarbonyl chloride.**



X= Cl or Br

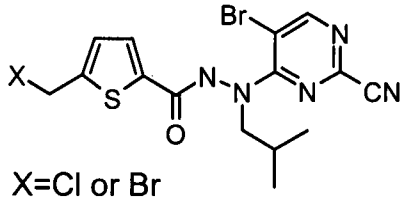
Two methods were used for the synthesis of this intermediate:

a) To a stirred solution, under N_2, of 70 mg of Intermediate 49 (0.317 mmol; 1 eq) in 3 mL of dry THF, oxalyl chloride (0.475 mmol; 1.5 eq) was added. The mixture was stirred at room temperature and monitorized by HPLC (X-TERRA 4.6X50mm; H_2O: ACN, 0.1%TFA,

gradient 10-100%). After 3 h stirring, a second addition of 20 µL of oxalyl chloride made almost complete the reaction. The solvent was evaporated under reduced pressure to obtain a crude mixture that was used in next step without further purification.

b) A stirred solution, under N_2, of 100 mg of Intermediate 49 (0.452 mmol) in 1 mL of $SOCl_2$ was refluxed for 1 h. The solvent was evaporated under reduced pressure giving a crude mixture that was used in the next step without further purification.

Intermediate 51: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-(chloro or bromomethyl)-*N'*-(2-methyl propyl)-2-thiophenecarbohydrazide.**



X=Cl or Br

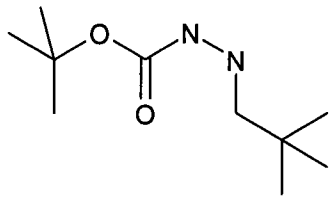
Two methods were used for the synthesis of this intermediate:

a) A solution of 71.36 mg (0.264 mmol) of Intermediate 6 and 150 µL of DIPEA in 3 mL of dry THF was added dropwise to Intermediate 50 a) and then, 35 mg of K^{t}BuO were added. The reaction mixture was stirred at room temperature overnight. Solvent was evaporated under reduced pressure, 25 mL of DCM and 25 mL of sat. NH_4Cl were added, phases were separated, and the organic layer was washed with Na_2CO_3 (25 mL) and then with 25 mL of brine. The combined organic phase was dried (Na_2SO_4). The crude was purified by chromatography (silica gel, Hexane: EtOAc) to give the title product (HPLC X-TERRA 4.6X50mm; H_2O: ACN, 0.1%TFA, gradient 10-100%; Rt: 5.2min). ES+MS m/z 473 & 428 $(MH)^+$.

b) To a cooled solution of Intermediate 50 b) in 1 mL of dry DCM, a solution of 134 mg of Intermediate 6 (0.497 mmol) with 84 µL of DIPEA (0.497 µL), was added dropwise. The reaction was stirred (under N_2) and, fifteen minutes later, 0.249 mmol of DIPEA were added. The mixture was stirred at rt overnight and monitorized by HPLC (X-TERRA 4.6X50mm; H_2O: ACN, 0.1%TFA, gradient 10-100%). When the reaction had reached completion, 20 mL of DCM were added and then the mixture was dropped onto 25 mg of ice-water, the phases were separated and the organic layer was extracted with sat. NH_4Cl (25 mL), then, with Na_2CO_3 (25 mL) and with 25 mL of brine. The combined organic phase was dried (Na_2SO_4). The crude was purified by chromatography (silica gel, Hexane: Teac) to obtain the title product (HPLC X-TERRA 4.6X50mm; H_2O: ACN, 0.1%TFA, gradient 10-100%; Rt: 5.2min). ES+MS m/z 428 & 473 $(MH)^+$.

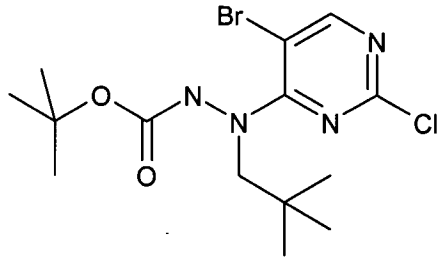
Compounds obtained in the a) and b) sections were mixed and used in the next step as a mixture.

Intermediate 52: **1,1-dimethylethyl 2-(2,2-dimethylpropyl)hydrazinecarboxylate.**



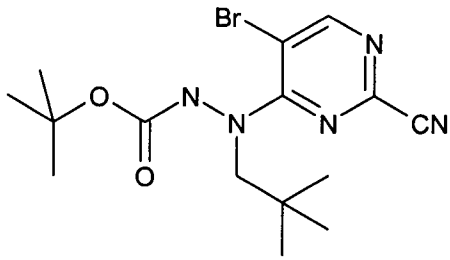
The title compound was prepared by a method analogous to that described for Intermediate 3, replacing *i*-butylaldehyde with trimethylacetaldehyde (ALDRICH). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.19 (s, 1H), 3.34 (br.s, 1H), 2.46 (d, 2H), 1.37 (s, 9H), 0.85 (s, 9H) [ES+ MS] m/z 203 $(MH)^+$.

Intermediate 53: **1,1-dimethylethyl 2-(5-bromo-2-chloro-4-pyrimidinyl)-2-(2,2-dimethylpropyl)hydrazinecarboxylate.**



To a solution of 5-bromo-2,4-dichloropyrimidine (15.4 g, 68 mmol) and Intermediate 52 (12.5 g, 62 mmol) in *i*-PrOH (150 mL), N,N-diisopropylethylamine (14 mL, 80 mmol) was added and the resulting reaction mixture was refluxed for 2.5 h, then stirred at room temperature overnight and again refluxed for further 3h. The mixture was concentrated under reduced pressure and the residue partitioned between DCM and 1M ammonium chloride. The organic layer was treated with brine and dried over anhydrous $MgSO_4$. The residue was purified by flash chromatography (elute: Hex/EtOAc mixtures 95:1 to 1:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.27 (br.s, 1H), 6.85 (br.s, 1H), 4.85-4.63 (br.m, 1H), 2.90-2.65 (br.m, 1H), 1.47 (s, 9H), 0.98 (s, 9H). [ES+ MS] m/z 393 $(M)^+$.

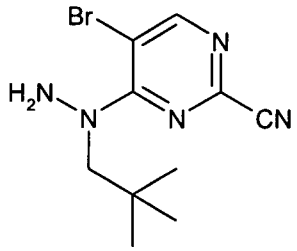
Intermediate 54: **1,1-dimethylethyl 2-(5-bromo-2-cyano-4-pyrimidinyl)-2-(2,2-dimethylpropyl)hydrazinecarboxylate.**



Potassium cyanide (1.6 g, 25 mmol) was added to a suspension of Intermediate 53 (9 g, 23 mmol) and DABCO (2.6 g, 23 mmol) in a mixture of DMSO/H_2O 9:1 (100 mL) at room temperature. The reaction mixture was heated at 80 °C for 1.5 h, and then poured into

iced water. After being stirred for 1.5h, the yellow product that precipitated was filtered off and washed abundantly with water. The compound was redissolved in DCM and the resulting solution was washed with water (twice) and brine and the organic layer was dried over $MgSO_4$. The compound was purified by flash chromatography (eluent: Hex/EtOAC 7:3) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.47 (br.s, 1H), 6.86 (br.s, 1H), 4.85-4.65 (br.m, 1H), 2.90-2.70 (br.m, 1H), 1.47 (s, 9H), 0.99 (s, 9H). [ES+ MS] m/z 384 $(M)^+$.

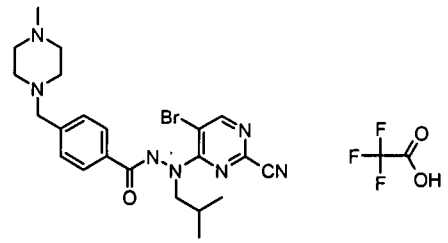
Intermediate 55: **5-bromo-4-[1-(2,2-dimethylpropyl)hydrazino]-2-pyrimidine carbonitrile.**



To a solution of Intermediate 54 (2 g, 5.2 mmol) in dry acetonitrile (100 mL), *p*-toluenesulfonic acid (13 mmol) was added and the resulting reaction mixture was stirred at room temperature overnight. The mixture was then concentrated *in vacuo* and the residue partitioned between DCM and a saturated solution of sodium bicarbonate. The organic layer was washed with brine and dried over anhydrous $NaHCO_3$. The residue was purified by preparative HPLC (X-TERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.39 (s, 1H), 3.85 (s, 2H), 1.00 (s, 9H) [ES+ MS] m/z 284 (M^+).

Examples

Example 1: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-4-[(4-methyl-1-piperazinyl) methyl]-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



Preparation of 4-[(4-methyl-1-piperazinyl)methyl]benzoyl chloride.

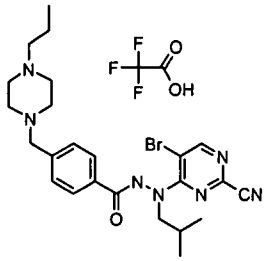
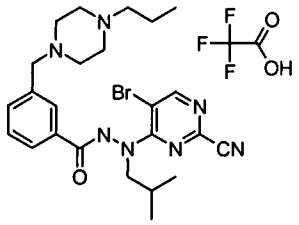
Intermediate 2 (500 mg, 2.13 mmol) was dissolved in thionyl chloride (5 ml). The reaction mixture was refluxed for 6 hours. The solvent was evaporated *in vacuo* and the crude product was used without any further purification.

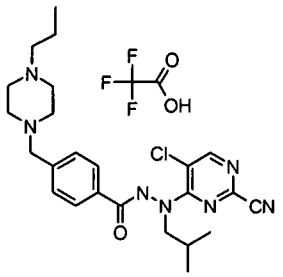
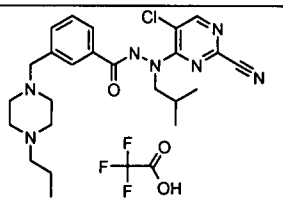
To a stirred solution of Intermediate 6 (200 mg, 0.74 mmol) in pyridine (10 mL), a mixture of the previously prepared acid chloride (539 mg, 2.13 mmol) and DIPEA (0.26 mL, 1.48 mmol) in dry THF (10 mL) was added and the resulting reaction mixture was stirred at

room temperature for 2 hours. The solvent was evaporated *in vacuo* and the crude reaction mixture was purified by flash chromatography (silica gel, dichloromethane:methanol). The solid was repurified by HPLC (H_2O, 0.1%TFA:ACN) to give the title compound. ^1H NMR (300 MHz, DMSO) δ ppm: 11.36 (s, 1H), 8.64 (s, 1H), 7.92 (d, 2H), 7.48 (d, 2H), 3.98 (m, 1H), 3.73 (s 2H), 3.38 (m, 4H), 3.02 (m 4H), 2.78 (s, 3H) 2.42 (m, 1H), 2.05 (m, 1H), 0.94 (d, 6H). [ES+ MS] m/z 486 $(M)^+$.

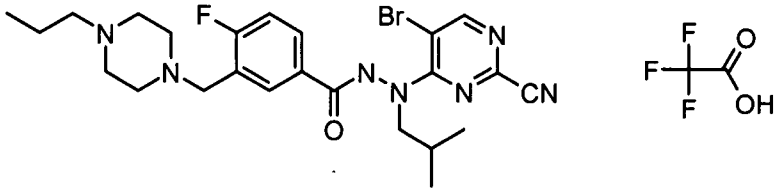
Examples 2-5 were prepared by methods analogous to that described for Example 1 replacing Intermediate 6 and 4-[(4-methyl-1-piperazinyl) methyl]benzoyl chloride with the intermediates and acid/acid chlorides indicated in Table 1.

TABLE 1

Ex	Structure	Acid or Acid chloride	Intermediate	Physical data
2		Intermediate 7	6	1H NMR (300 MHz, DMSO-d6): 11.35 (s, 1H), 8.64 (s, 1H), 7.92 (d, 2H), 7.49 (d, 2H), 3.73 (s, 2H), 3.42 (m, 2H), 3.00 (m, 8H), 2.05 (m, 1H), 1.60 (m, 2H), 0.94 (d, 6H), 0.89 (t, 3H). [ES+ MS] m/z 514 (M)+.
3		Intermediate 8	6	[ES+ MS] m/z 514 $(M)^+$.

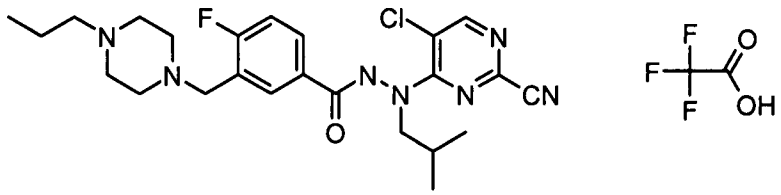
Ex	Structure	Acid or Acid chloride	Intermediate	Physical data
4		Intermediate 7	11	1H NMR (300 MHz, DMSO-d6): 11.38 (s, 1H), 8.52 (s, 1H), 7.90 (d, 2H), 7.50 (d, 2H), 3.75 (s, 2H), 3.55-2.80 (br, 10H), 2.06 (m, 1H), 1.60 (m, 2H), 0.95 (d, 6H), 0.89 (t, 3H). [ES+ MS] m/z 470 (MH)+.
5		Intermediate 8	11	[ES+ MS] m/z 470 (MH)+.

Example 6: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-4-fluoro-*N'*-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate.**



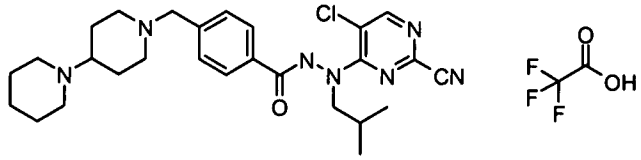
To a solution of Intermediate 6 (5) (0.07 g, 0.3 mmol) in dry THF (5 mL), N, N-diisopropylethylamine (0.2 mL, 1.2 mmol) was added and the resulting reaction mixture was stirred at room temperature for 10 minutes. Then, Intermediate 16 (0.15 g, 0.5 mmol) and potassium *tert*-butoxide (ALDRICH, 0.04 g, 0.4 mmol) were added and the reaction mixture was stirred at room temperature for further 16h. Solvent was removed *in vacuo* and the residue obtained was dissolved in MeOH and purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.77 (s, 1H), 8.43 (s, 1H), 8.29- 8.27 (dd, 1H), 8.08- 8.02 (m, 1H), 7.34- 7.28 (m, 1H), 4.24 (s, 2H), 3.91- 3.72 (br., 2H), 3.66- 3.32 (br., 8H), 3.00- 2.94 (m, 2H), 2.20- 2.07 (m, 1H), 1.85- 1.72 (m, 2H), 1.05- 1.01 (m, 9H); [ES+ MS] m/z 532&534 $(MH)^+$.

Example 7: **N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate**



To a solution of Intermediate 11 (39) (0.06 g, 0.3 mmol) in dry THF (5 mL), N, N-diisopropylethylamine (0.2 mL, 1.2 mmol) was added and the resulting reaction mixture was stirred at room temperature for 10 minutes. Then, Intermediate 16 (0.13 g, 0.44 mmol) and potassium *tert*-butoxide (ALDRICH, 0.04 g, 0.4 mmol) were added and the reaction mixture was stirred at room temperature for further 16h. Solvent was removed *in vacuo* and the residue obtained was dissolved in MeOH and purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.90 (s, 1H), 8.30- 8.24 (m, 2H), 8.11- 8.05 (m, 1H), 7.36- 7.30 (m, 1H), 4.34 (s, 2H), 3.94- 3.76 (br., 2H), 3.76- 3.44 (br., 8H), 3.04- 2.98 (m, 2H), 2.21- 2.06 (m, 1H), 1.87- 1.72 (m, 2H), 1.08- 0.93 (m, 9H); [ES+ MS] m/z 488 $(MH)^+$.

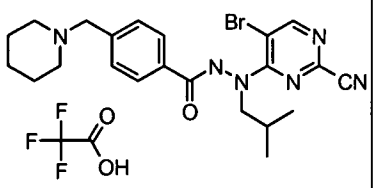
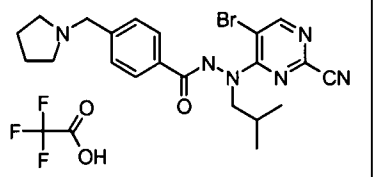
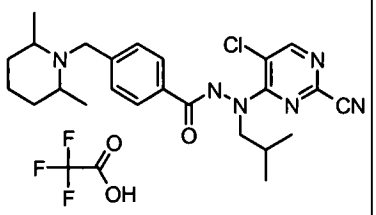
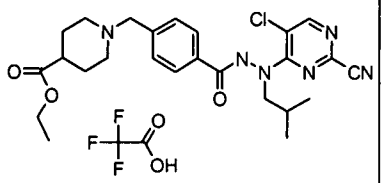
Example 8: **4-(1,4'-bipiperidin-1'-ylmethyl)-*N'*-(5-chloro-2-cyano-4-pyrimidinyl) -*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**

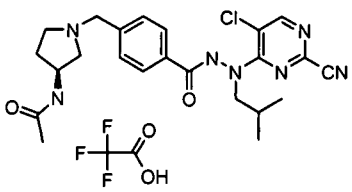
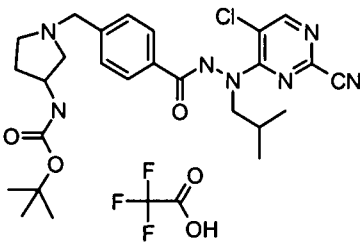
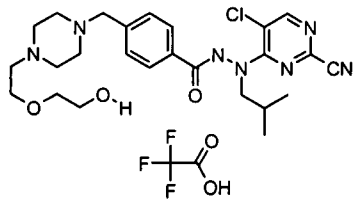


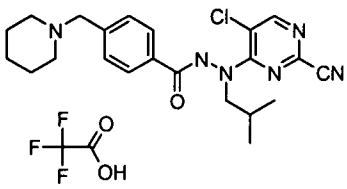
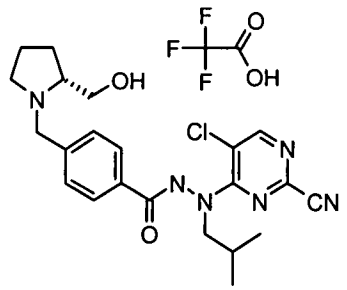
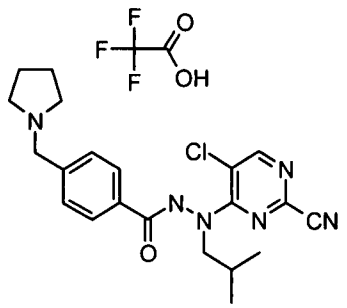
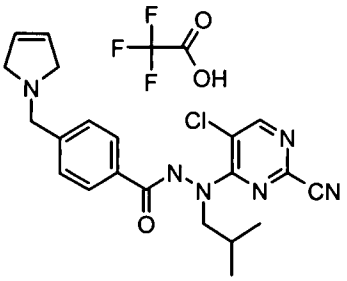
Intermediate 17 (54 mg, 0.14 mmol), 4-Piperidinopiperidine (ALDRICH, 29 mg, 0.17 mmol), potassium carbonate (39 mg, 0.29 mmol) and sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH, filtered and the resulting crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, CDCl3-d6 + CD3OD-d6): 8.24 (s, 1H), 7.89(d, 2H), 7.56 (d, 2H), 4.23 (s, 2H), 3.79-2.72 (br. m, 10H), 2.20-1.89 (br. m, 10H), 1.41 (m, 1H), 0.99 (d, 6H). [ES+ MS] m/z 510 $(MH)^+$.

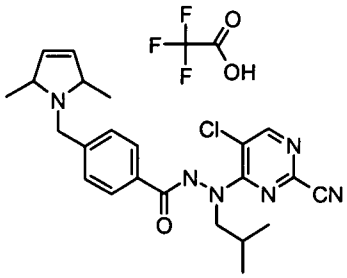
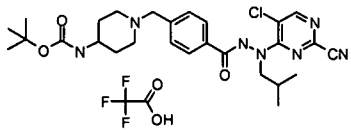
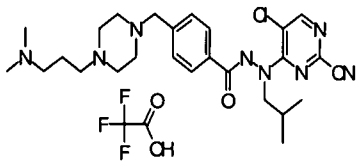
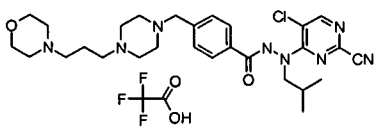
Examples 9-37 were prepared by methods analogous to that described for Example 8 replacing Intermediate 17 and 4-piperidinopiperidine with the Intermediates and amines indicated in Table 2.

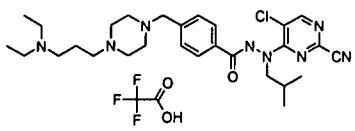
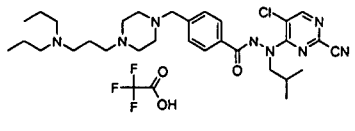
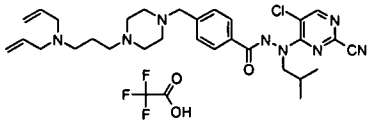
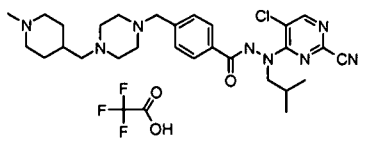
TABLE 2

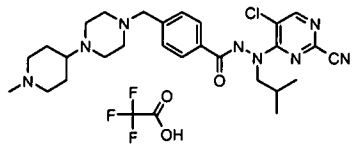
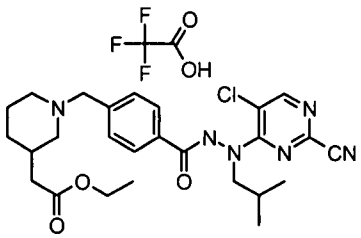
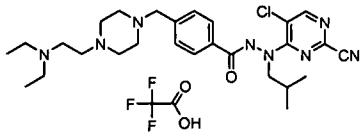
Ex	Structure	Amine	Inter.	Physical data
9		Piperidine (ALDRICH)	18	^{1}H NMR (300 MHz, DMSO-d6) δ ppm:11.45 (s, 1H), 9.61 (br.s, 1H), 8.65 (s, 1H), 8.00 (d, 2H), 7.64 (d, 2H), 4.35 (d, 2H), 3.97 (m, 1H), 3.59 (m, 1H), 3.30 (m, 2H), 2.90 (m, 2H), 2.06 (m, 1H), 1.78 (m, 2H), 1.65 (m, 3H), 1.37 (m, 1H), 0.95 (d, 6H). [ES+ MS] m/z 471 $(M)^+$.
10		Pyrrolidine (ALDRICH)	18	^{1}H NMR (300 MHz, DMSO-d6) δ ppm:11.44 (s, 1H), 10.00 (br.s, 1H), 8.65 (s, 1H), 7.99 (d, 2H), 7.66 (d, 2H), 4.43 (d, 2H), 3.98 (m, 1H), 3.63 (m, 1H), 3.37 (m, 2H), 3.10 (m, 2H), 2.04 (m, 3H), 1.84 (m, 2H), 0.95 (d, 6H). [ES+ MS] m/z 457 $(M)^+$.
11		2,6-dimethylpiperidine (ALDRICH)	17	^{1}H NMR (300 MHz, CDCl3-d6): 11.55-10.94 (br. m, 1H), 9.09 (m, 1H), 8.31-7.53 (br. m, 5H), 4.49-2.96 (m, 6H), 2.17-1.37 (m, 13H), 1.03 (d, 6H). [ES+ MS] m/z 455 $(MH)^+$.
12		ethyl 4-piperidinecarboxylate (ALDRICH)	17	^{1}H NMR (300 MHz, CDCl3-d6): 9.00-8.88 (br. m, 1H), 8.29 (s, 1H), 7.92 (d, 2H), 7.62 (d, 2H), 4.24-2.05 (br. m, 16H), 1.31-1.22 (m, 3H), 1.02 (d, 6H). [ES+ MS] m/z 499 $(MH)^+$.

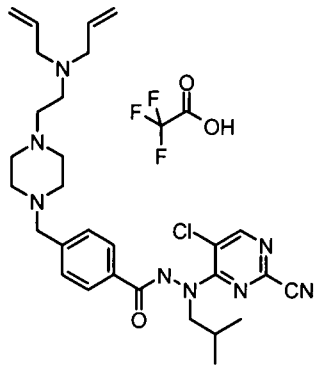
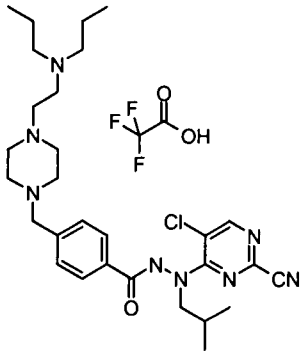
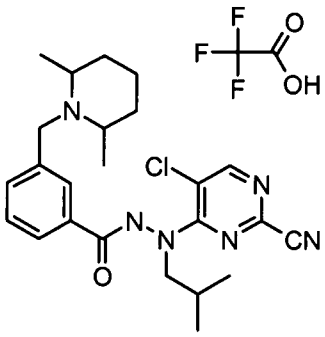
Ex	Structure	Amine	Inter.	Physical data
13		*N*-[(3*S*)-3-pyrrolidinyl]acetamide (TCI)	17	1H NMR (300 MHz, CDCl3):):8.57-8.49 (br.s, 1H), 8.32 (s, 1H), 8.18-8.08 (br.s, 1H), 7.90 (d, 2H), 7.65 (d, 2H), 4.98-4.77 (br.,1H), 4.40- 4.10 (AB system, 2H), 4.00-3.71 (br.m, 3H), 3.46-3.29 (br.m, 1H), 3.21-2.85 (br., 2H), 2.62-2.42 (br.,1H), 2.27-2.04 (br.m, 2H),1.94 (s, 3H), 1.03 (d, 6H). [ES+ MS] m/z 470 $(MH)^+$.
14		3-(*tert*-butoxycarbonylamino)pyrrolidine (TCI FLUOROCHEM)	17	1H NMR (300 MHz, CDCl3):): 8.73-8.59 (br.s, 1H), 8.31 (s,1H), 7.89 (d, 2H), 7.62 (d, 2H), 6.24-5.97 (br.s, 1H), 4.70- 4.46 (br., 1H), 4.41- 4.12 (br., 2H), 3.94- 3.62 (br., 3H), 3.53- 3.36 (br., 1H), 3.18-2.77 (br., 2H), 2.58- 1.92 (br., 3H), 1.41 (s, 9H), 1.02 (d, 6H). [ES+ MS] m/z 528 $(MH)^+$.
15		1-(2-(2-hydroxyethoxy)ethyl)piperazine, (ALDRICH)	17	^{1}H NMR (300 MHz, DMSO): 11.38 (s, 1H), 8.52 (s, 1H), 7.9 (d, 2H), 7.5 (d, 2H), 5.5- 3.87 (br., 6H), 3.85- 3.64 (br., 4H), 3.59- 2.81 (br., 11H), 2.06 (m, 1H), 0.95 (d, 6H). [ES+ MS] m/z 516 $(MH)^+$.

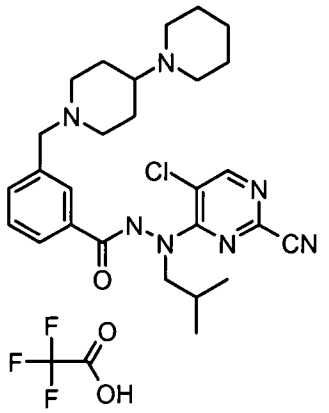
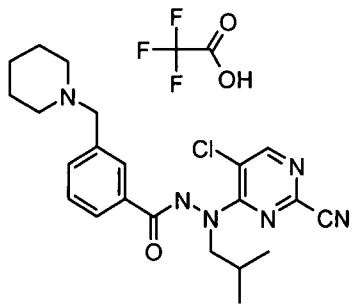
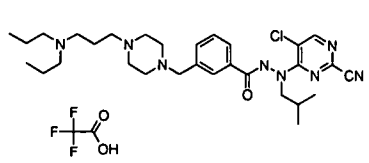
Ex	Structure	Amine	Inter.	Physical data
16		piperidine (ALDRICH)	17	^{1}H NMR (300 MHz, CDCl3-d6): 11.97 (s, 1H), 8.87 (s, 1H), 8.30 (s, 1H), 7.90 (d, 2H), 7.58 (d, 2H), 4.20 (s, 2H), 3.81 (br. m, 2H), 3.56 (m, 2H), 2.64 (m, 2H), 2.11 (m, 1H), 1.99-1.84 (m, 5H), 1.42 (m, 1H), 1.02 (d, 6H). [ES+ MS] m/z 427 $(MH)^+$.
17		(R)-(-)-2-pyrrolidinem ethanol (ALDRICH)	17	1H NMR (300 MHz, CDCl3): 8.94 (br.s, 1H), 8.29 (s, 1H), 7.89 (d, 2H), 7.59 (d, 2H), 4.74 (d, 1H), 4.11 (d,1H), 3.99- 3.46 (br.m, 7H), 3.12- 2.85 (br., 2H), 2.27- 2.00 (br., 3H), 1.90 (m, 1H), 1.01 (d, 6H). [ES+ MS] m/z 443 (MH)+.
18		pyrrolidine (ALDRICH)	17	1H NMR (300 MHz, CDCl3): 9.10 (br.s, 1H), 8.28 (s, 1H), 7.90 (d, 2H), 7.60 (d, 2H) 4.26 (br.s, 2H), 3.91- 3.58 (br.m, 4H), 2.97-2.77 (m, 2H), 2.27- 1.91 (br.m, 5H), 1.01 (d, 6H). [ES+ MS] m/z 413 (MH)+.
19		3-pyrroline (ALDRICH)	17	1H NMR (300 MHz, CDCl3): 9.08 (m,1H), 8.28 (br.s, 1H), 7.92 (m, 2H), 7.67 (m, 2H), 5.90 (br.s, 1H), 4.46- 4.19 (br.,3H), 3.95- 3.53 (br., 4H), 2.58- 1.96 (br.,3H), 1.01 (d, 6H). [ES+ MS] m/z 411 (MH)+.

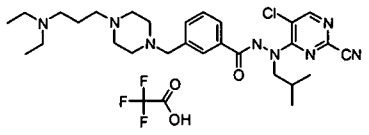
Ex	Structure	Amine	Inter.	Physical data
20		2,5-dimethyl-3-pyrroline (ALDRICH)	17	1H NMR (300 MHz, DMSO):7.59 (br.s, 1H), 7.20 (d, 2H), 6.94 (m, 2H), 5.29- 5.01 (br., 2H), 4.13- 3.97 (br., 2H), 3.87-3.72 (br., 4H), 1.33 (m, 1H), 0.74- 0.35 (br., 6H), 0.23 (d, 6H). [ES+ MS] m/z 439 (MH)+.
21		1,1-Dimethylethyl 4-piperidinylcarbamate (ALDRICH)	17	[ES+ MS] m/z 542 (MH)+.
22		1-(3-dimethylaminopropyl)-piperazine (ALDRICH)	17	1H NMR (300 MHz, CDCl3-d6 + CD3OD-d6): 8.14 (s, 1H), 7.77 (d, 2H), 7.38 (d, 2H), 3.46-2.75 (m, 17H), 2.73 (br. s, 6H), 2.00 (m, 3H), 0.90 (d, 6H). [ES+ MS] m/z 513 (MH+).
23		1-(3-morpholino propyl)-piperazine (FLUOROCHEM)	17	1H NMR (300 MHz, CDCl3-d6 + CD3OD-d6): 8.16 (s, 1H), 7.79 (d, 2H), 7.39 (d, 2H), 3.85 (m, 6H), 3.20-2.73 (m, 19H), 2.02 (m, 3H), 0.92 (d, 6H). [ES+ MS] m/z 555 (MH+).

Ex	Structure	Amine	Inter.	Physical data
24		1-(3-diethylamino-propyl)-piperazine (FLUOROCHEM)	17	1H NMR (300 MHz, DMSO-d6): 11.40 (s, 1H), 9.38 (br., 1H), 8.52 (s, 1H), 7.92 (d, 2H), 7.54 (d, 2H), 3.70-2.72 (m, 20H), 2.06 (m, 1H), 1.92 (m, 2H), 1.18 (t, 6H), 0.95 (d, 6H). [ES+ MS] m/z 541 (MH+).
25		1-(3-dipropylaminopropyl)piperazine (FLUOROCHEM)	17	1H NMR (300 MHz, DMSO-d6): 11.40 (s, 1H), 9.41 (br., 1H), 8.52 (s, 1H), 7.92 (d, 2H), 7.53 (d, 2H), 4.13-2.73 (m, 20H), 2.06 (m, 1H), 1.94 (m, 2H), 1.61 (m, 4H), 1.00-0.83 (m, 12H). [ES+ MS] m/z 569 (MH+).
26		1-(3-diallylamino-propyl)-piperazine (FLUOROCHEM)	17	1H NMR (300 MHz, DMSO-d6): 11.41 (s, 1H), 10.08 (br., 1H), 8.52 (s, 1H), 7.93 (d, 2H), 7.54 (d, 2H), 5.91 (m, 2H), 5.55 (m, 4H), 4.10-2.71 (m, 20H), 2.13-1.88 (m, 3H), 0.96 (d, 6H). [ES+ MS] m/z 565 (MH+).
27		1-(N-methyl-4-piperidin methyl)piperazine (FLUOROCHEM)	17	1H NMR (300 MHz, DMSO-d6): 11.40 (s, 1H), 9.30 (br., 1H), 8.53 (s, 1H), 7.92 (m, 2H), 7.54 (m, 2H), 3.70-2.72 (m, 23H), 2.06 (m, 1H), 1.90 (m, 2H), 1.26 (m, 1H), 0.95 (d, 6H). [ES+ MS] m/z 539 (MH+).

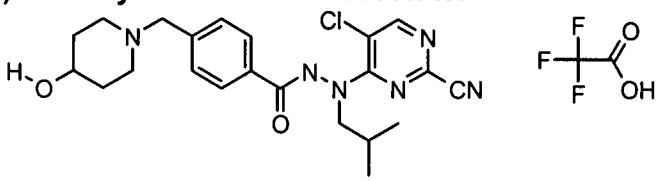
Ex	Structure	Amine	Inter.	Physical data
28		1-(N-methyl-4-piperidyl)-piperazine (ALDRICH)	17	1H NMR (300 MHz, D3OD-d6): 8.38 (br. m, 1H), 7.86 (m, 2H), 7.50 (m, 2H), 3.65 (s, 2H), 3.43 (br. m, 2H), 3.00-2.48 (m, 16H), 2.22-2.02 (m, 4H), 1.74 (m, 2H), 1.02 (d, 6H). [ES+ MS] m/z 525 (MH+).
29		2-(piperidin-4-yl)-acetic acid ethyl ester (FLUOROCHEM)	17	1H NMR($CDCl_3$) δ ppm : 9.09(s;1H);8.28(s;1H);7.90(d;7.91Hz;2H);7.56(d;7.91Hz;2H);4.17(s;2H);4.12(q;7.2Hz;2H);3.80(m;2H);3.55(m;2H);2.67(m;2H);2.29(d;6.3HZ;2H);2.11(m;6.44Hz;1H);1.96(m;3H);1.75(m;2H);1.24(t;7Hz;3H);1.01(d;6.6Hz;6H) ES+MS m/z 513 $(MH)^+$
30		1-(2-diethylamino ethyl)-piperazine (CHEMPUR)	17	1H NMR($CDCl_3$) δ ppm: 9.1(s; 1H); 8.29(s; 1H); 7.86(d; 8.2Hz; 2H); 7.53(d; 8.2Hz; 2H); 4.16(s; 2H); 3.8(m; 2H); 3.35-2.7(m; 16H); 2.11(m;6.6Hz; 1H);1.32(t; 7.3Hz; 6H); 1.01(d; 6.6Hz;6H). ES+MS m/z 527$(MH)^+$

Ex	Structure	Amine	Inter.	Physical data
31		1-(2-diallyl aminoethyl)-piperazine, (FLUOROCHEM)	17	1H NMR (300 MHz, CDCl3): 9.07 (s, 1H), 8.30 (s, 1H), 7.9 (d, 2H), 7.5 (d, 2H), 6.07-5.86 (m, 2H), 5.65- 5.46 (m, 4H), 4.16 (s, 2H), 3.87- 3.75 (br., 2H), 3.7 (d, 4H), 3.36- 3.13 (br., 4H), 3.13- 3.00 (br., 2H), 2.94- 2.71 (br., 6H), 2.19- 2.02 (m, 1H), 1.02 (d, 6H). [ES+ MS] m/z 551 (MH+).
32		1-(2-dipropylamin oethyl)-piperazine (FLUOROCHEM)	17	1H NMR (300 MHz, CDCl3): 8.99 (br.s, 1H), 8.30 (s, 1H), 7.9 (d, 2H), 7.5 (d, 2H), 4.18 (s, 2H), 3.82- 3.63 (br., 2H), 3.23- 2.89 (br., 10H), 2.87- 2.66 (br., 6H), 2.19- 2.05 (m, 1H), 1.76- 1.54 (m, 4H), 1.03- 0.84 (m, 12H). [ES+ MS] m/z 555 (MH+).
33		2,6-dimethylpiperidine (ALDRICH)	19	1H NMR (300 MHz, DMSO-d6): 10.49 (d, 1H), 9.31-8.99 (br. s, 1H), 8.54 (s, 1H), 8.05-7.94 (m, 2H), 7.83-7.57 (m, 2H), 4.60 (m, 1H), 4.39 (m, 1H), 3.55-1.54 (m, 11H), 1.47 (d, 3H), 1.27 (d, 3H), 0.96 (d, 6H). [ES+ MS] m/z 455 (MH+).

Ex	Structure	Amine	Inter.	Physical data
34		4-Piperidinopiperidine (ALDRICH)	19	1H NMR (300 MHz, DMSO-d6): 11.50 (s, 1H), 9.98 (br., 1H), 9.53 (br., 1H), 8.54 (s, 1H), 8.07-7.98 (m, 2H), 7.76-7.61 (m, 2H), 4.36 (br., 2H), 4.08-3.24 (m, 6H), 2.94 (br. m, 4H), 2.20 (br. m, 2H), 2.07 (m, 1H), 1.93-1.53 (m, 8H), 1.40 (m, 1H), 0.96 (d, 6H). [ES+ MS] m/z 510 (MH+).
35		N-methylpiperazine (ALDRICH)	19	1H NMR (300 MHz, DMSO-d6): 11.49 (s, 1H), 9.41 (br. s, 1H), 8.54 (s, 1H), 8.01 (m, 2H), 7.76-7.61 (m, 2H), 4.35 (m, 2H), 3.32 (m, 3H), 2.90 (m, 2 H), 2.07 (m, 1H), 1.88-1.48 (m, 6H), 1.37 (m, 1H), 0.96 (d, 6H). [ES+ MS] m/z 427 (MH+).
36		1-(3-dipropyl aminopropyl) piperazine (FLUOROCHEM)	19	1H NMR (300 MHz, CDCl3-d6): 10.10 (s, 1H), 8.24 (m, 2H), 8.03 (m, 1H), 7.61-7.47 (m, 2H), 4.16 (s, 2H), 3.90-3.35 (m, 10H), 3.31-2.92 (m, 8H), 2.81 (m, 2H), 2.21-2.01 (m, 3H), 1.74 (m, 4H), 1.10-0.93 (m, 12H). [ES+ MS] m/z 569 (MH+).

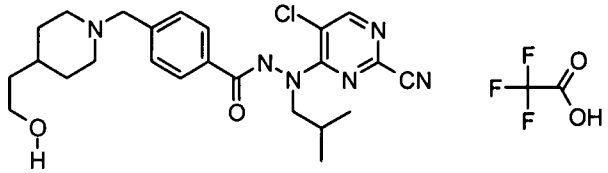
Ex	Structure	Amine	Inter.	Physical data
37		1-(3-diethylamino-propyl)-piperazine (FLUOROCHEM)	19	1H NMR (300 MHz, CDCl3-d6): 10.06 (s, 1H), 8.25 (m, 2H), 8.03 (m, 1H), 7.61-7.47 (m, 2H), 4.17 (s, 2H), 3.82 (br. s, 2H), 3.39-2.97 (m, 14 H), 2.86 (m, 2H), 2.20-2.03 (m, 3H), 1.33 (t, 6H), 1.01 (d, 6H). [ES+ MS] m/z 541 (MH+).

Example 38: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(4-hydroxy-1-piperidinyl) methyl]-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



Intermediate 17 (54 mg, 0.14 mmol), 4-hydroxypiperidine (ALDRICH, 17 mg, 0.17 mmol), potassium carbonate (39 mg, 0.29 mmol) and sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH, filtered and the resulting crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, CDCl3-d6): 8.74 (s, 1H), 8.30 (s, 1H), 7.93 (d, 2H), 7.72 (d, 2H), 4.26-4.20 (m, 3H), 3.82 (m, 2H), 3.37-3.14 (br. m, 4H), 2.42-1.86 (br. m, 5H), 1.03 (d, 6H). [ES+ MS] m/z 443 $(M)^+$.

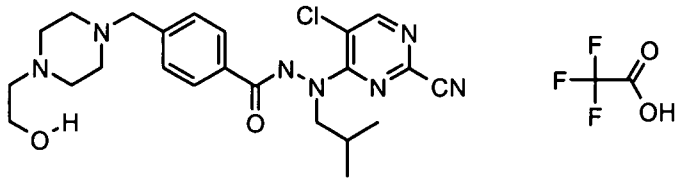
Example 39: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



Intermediate 17 (54 mg, 0.14 mmol), 4-piperidineethanol (ALDRICH, 22 mg, 0.17 mmol), potassium carbonate (39 mg, 0.29 mmol) and sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The residue was dissolved in MeOH, filtered and the resulting crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient

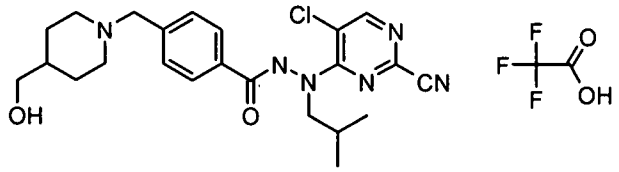
10-100%) to give the title compound. ^{1}H NMR (300 MHz, CDCl3-d6): 8.84 (s, 1H), 8.30 (s, 1H), 7.92 (d, 2H), 7.67 (d, 2H), 4.19 (s, 2H), 3.83-3.35 (br. m, 6H), 2.67 (m, 2H), 2.17-1.56 (m, 8H), 1.02 (d, 6H). [ES+ MS] m/z 471 $(MH)^+$.

Example 40: **N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate.**



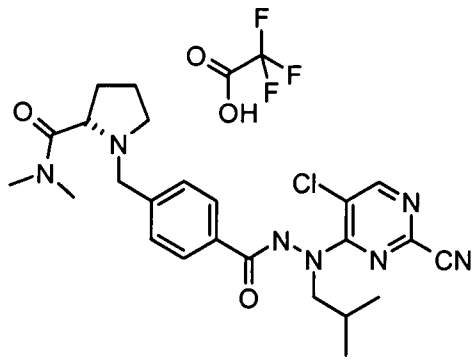
Intermediate 17 (50 mg, 0.13 mmol), 1-(2-hydroxyethyl) piperazine (ALDRICH, 0.02 mL, 0.16 mmol), potassium carbonate (36 mg, 0.26 mmol) and sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH, filtered and the resulting crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO): 11.39 (s, 1H), 8.52 (s, 1H), 7.9 (d, 2H), 7.5 (d, 2H), 5.35- 2.5 (br., 17H), 2.06 (m, 1H), 0.95 (d, 6H). [ES+ MS] m/z 472 $(MH)^+$.

Example 41: **N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate.**



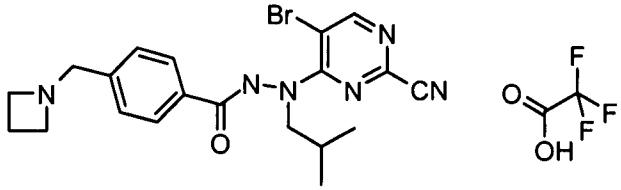
Intermediate 17 (54 mg, 0.14 mmol), 4-(hydroxymethyl)piperidine (ALDRICH, 20 mg, 0.17 mmol), potassium carbonate (39 mg, 0.29 mmol) and sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH, filtered and the resulting crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) and, then, by a second preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 30-100%) to give the title compound. ^{1}H NMR (300 MHz, CDCl3-d6): 8.59 (br., 1H), 8.32 (s, 1H), 7.89 (d, 2H), 7.67 (d, 2H), 4.22 (br. s, 2H), 3.84-3.55 (br. m, 6H), 2.69 (m, 2H), 2.17-1.95 (br. m, 6H), 1.03 (d, 6H). [ES+ MS] m/z 457 $(MH)^+$.

Example 42: **1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl) hydrazino]carbonyl}phenyl)methyl]-N,N-dimethyl-L-prolinamide trifluoroacetate.**



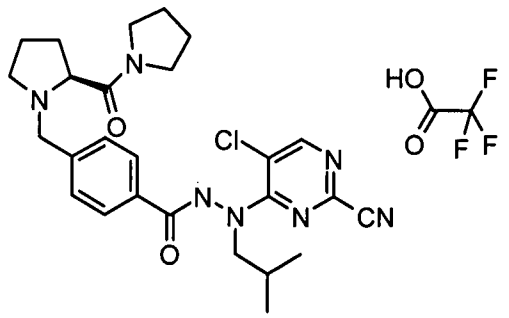
To a solution of Intermediate 17 (50 mg, 0.13 mmol) in dry ACN were added N,N-diisopropylethylamine (FLUKA, 0.046 mL, 0.26 mmol), sodium iodide and *N,N*-dimethyl-L-prolinamide (BACHEM, 23 mg, 0.16 mmol). The solution was stirred at room temperature overnight. After filtration, the solvent was removed under vacuum and the residue was purified by flash chromatography (eluent: DCM/MeOH) then further purified by preparative HPLC (ACN:H2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 11.45 (s, 1H), 9.71 (br., 1H), 8.53 (s, 1H), 7.94 (d, 2H), 7.64 (d, 2H), 4.72-3.18 (m, 6H), 2.87 (br. s, 3H), 2.68 (br. s, 3H), 2.19-1.65 (m, 5H), 0.95 (d, 6H). [ES+ MS] m/z 510 $(MH)^+$.

Example 43: **4-(1-azetidinylmethyl)-*N'*-(5-bromo-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



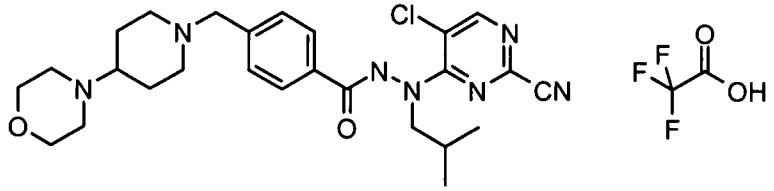
To a stirred solution of Intermediate 18 (50 mg, 0.12 mmol) in THF (2 mL), DIPEA (FLUKA, 0.042 mL, 0.24 mmol) and azetidine hydrochloride (ALDRICH, 22 mg, 0.24 mmol) were added and the resulting reaction mixture was stirred at room temperature for 5 days. The solvent was evaporated *in vacuo* and the crude reaction mixture was purified by HPLC (H_2O, 0.1%TFA:ACN) to give the title compound. ^{1}H NMR (300 MHz, DMSO) δ ppm: 11.42 (s, 1H), 8.65 (s, 1H), 7.97 (d, 2H), 7.58 (d, 2H), 4.42 (m, 2H), 4.35-3.81 (m, 4H), 2.48-2.31 (m, 2H), 2.06 (m, 1H), 0.94 (d, 6H). [ES+ MS] m/z 443 $(MH)^+$.

Example 44: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-4-{[(2*S*)-2-(1-pyrrolidinylcarbonyl)-1-pyrrolidinyl]methyl}benzohydrazide trifluoroacetate.**



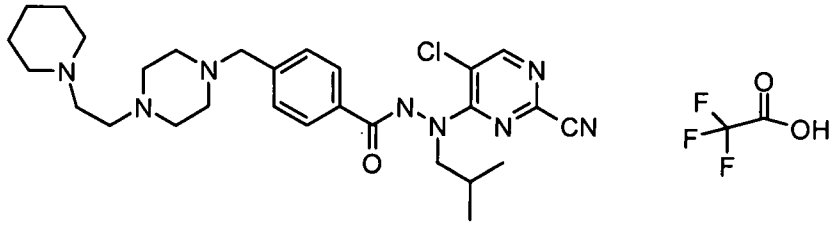
To a solution of Intermediate 20 (300 mg, 0.79 mmol) in dry ACN (5 mL) were added N,N-diisopropylethylamine (FLUKA, 0.382 mL, 2.68 mmol) sodium iodide and Intermediate 17 (270 mg, 1.60 mmol). The solution was stirred at room temperature for 4 h. The residue was purified by flash chromatography (eluent: Hex/AcOEt) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 11.46 (s, 1H), 9.78 (br., 1H), 8.54 (s, 1H), 7.92 (d, 2H), 7.64 (d, 2H), 4.54-2.85 (m, 10H), 2.19-1.50 (m, 9H), 0.95 (d, 6H). [ES+ MS] m/z 510 $(MH)^+$.

Example 45: **N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide trifluoroacetate.**



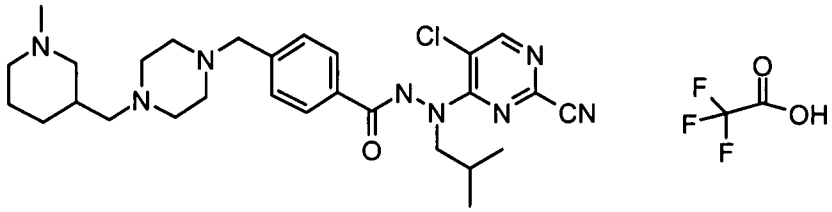
To a mixture of intermediate 17 (50.5 mg, 0.13 mmol) in dry ACN (2 mL), 4-morpholino-piperidine (ALDRICH, 35.6 mg, 0.21 mmol), potassium carbonate (FLUKA, 41.1 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were added. The resultant reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH, filtered and the resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO) δ ppm: 11.5 (s, 1H), 10.7- 10.4 (br, 1H), 8.5 (s, 1H), 7.9 (d, 2H), 7.6 (d, 2H), 4.55- 2.66 (br.m, 16H), 2.35- 2.14 (br.m, 2H), 2.15- 1.95 (m, 2H), 1.96- 1.7 (br.m, 2H), 0.9 (d, 6H). [ES+ MS] m/z 512 $(MH)^+$.

Example 46: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-4-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate.**



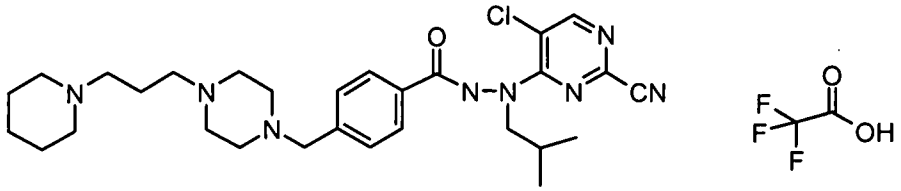
Intermediate 17 (50.0 mg, 0.13 mmol), 1-(2-piperidinoethyl)-piperazine (FLUOROCHEM, 31.0 mg, 0.16 mmol), potassium carbonate (36.0 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (3 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO) δ ppm: 11.48 (s, 1H), 10.07 (br.s, 1H), 8.53 (s, 1H), 7.97 (d, 2H), 7.63 (d, 2H), 4.44- 1.37 (br.m, 27H), 0.96 (d, 6H). [ES+ MS] m/z 539 $(MH)^+$.

Example 47: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[(1-methyl-3-piperidinyl)methyl]-1-piperazinyl}methyl)-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



Intermediate 17 (50.0 mg, 0.13 mmol), 1-(N-methyl-3-piperidylmethyl)-piperazine (FLUOROCHEM, 31.0 mg, 0.16 mmol), potassium carbonate (FLUKA, 36.0 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (3 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO) δ ppm: 11.44 (br.s, 1H), 9.38 (br.s, 1H), 8.53 (s, 1H), 7.95 (d, 2H), 7.59 (m, 2H), 4.13- 1.49 (br.m, 27H), 0.96 (d, 6H). [ES+ MS] m/z 539 $(MH)^+$.

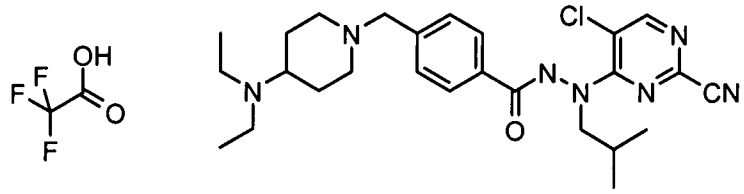
Example 48: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-4-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate.**



Intermediate 17 (50.0 mg, 0.13 mmol), 1-(3-piperidinopropyl)piperazine (FLUOROCHEM, 33.0 mg, 0.16 mmol), potassium carbonate (FLUKA, 36.0 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (3 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O,

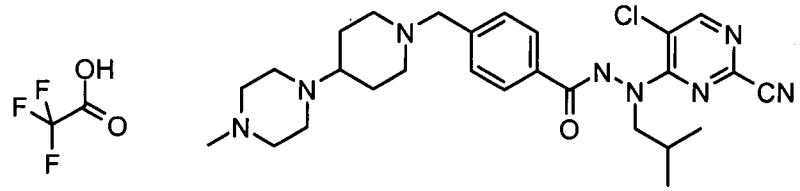
0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO) δ ppm: 11.41 (br.s, 1H), 9.38 (br.s, 1H), 8.52 (s, 1H), 7.92 (d, 2H), 7.53 (d, 2H), 4.39- 1.28 (br.m, 29H), 0.96 (d, 6H). [ES+ MS] m/z 553 $(MH)^+$.

Example 49: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(diethylamino)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



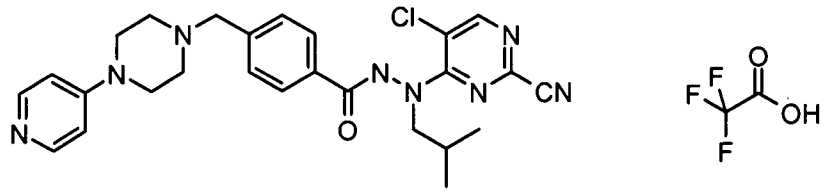
Intermediate 17 (50.0 mg, 0.132 mmol), 4-diethylamino-piperidine (FLUOROCHEM, 24.9 mg, 0.159 mmol), potassium carbonate (FLUKA, 36.0 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. 1H NMR($CDCl_3$+CD_3OD) δ ppm : 8.16(s; 1H); 7.83(d; 8.35Hz; 2H); 7.48(d; 8.35Hz; 2H); 4.17(s ;3H); 3.39(m; 2H); 3.06(m; 6H); 2.12(m; 4H); 2.01(m; 6.44Hz; 1H); 1.26(t; 7.32Hz; 6H); 0.91(d; 6.74Hz; 6H). ES+MS m/z 498 $(MH)^+$.

Example 50: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



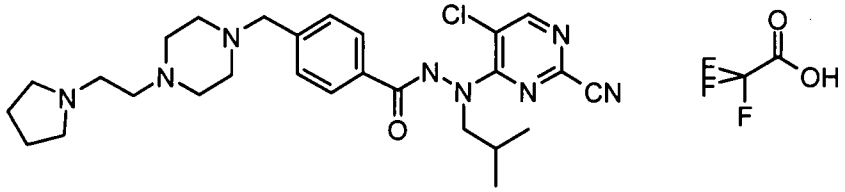
Intermediate 17 (50.0 mg, 0.132 mmol), 1-methyl-4-(piperidin-4-yl)-piperazine (FLUOROCHEM, 27.1 mg, 0.152 mmol), potassium carbonate (FLUKA, 36.0 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. 1H NMR ($CDCl_3$+CD_3OD) δ ppm: 8.18(s; 1H); 7.84(d; 8.35Hz; 2H); 7.47(d; 8.35Hz; 2H); 4.16(s; 2H); 3.42(m; 3H); 3.14(m; 3H); 2.81(m; 5H); 2.73(s; 4H); 2.59(m; 2H); 2.03(m; 7.03Hz; 1H);1.92(m; 4H); 0.93(d; 6.6Hz;6H). [ES+MS] m/z 525 $(MH)^+$.

Example 51: **N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-pyridinyl)-1-piperazinyl]methyl}benzohydrazide trifluoroacetate.**



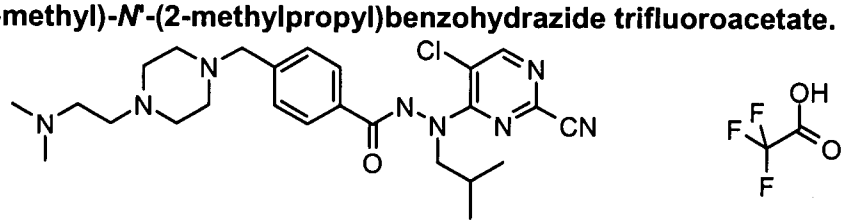
Intermediate 17 (50 mg, 0.13 mmol), 1-(4-pyridyl)-piperazine (LANCASTER, 27.4 mg, 0.17 mmol), potassium carbonate (FLUKA, 36.5 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH, filtered and the resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO) δ ppm: 11.5 (br.s, 1H), 8.5 (s, 1H), 8.34 (d, 2H), 7.97 (d, 2H), 7.6 (d, 2H), 7.24 (d, 2H), 4.59- 2.74 (br.m, 12H), 2.08 (m, 1H), 0.97 (d, 6H). [ES+ MS] m/z 505 $(MH)^+$.

Example 52: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-4-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate.**



Intermediate 17 (50.0 mg, 0.13 mmol), 1-(2-pyrrolidinoethyl)piperazine (FLUOROCHEM, 29.0 mg, 0.16 mmol), potassium carbonate (FLUKA, 36.0 mg, 0.26 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (3 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, d6-DMSO) δ ppm: 11.49 (s, 1H), 10.40- 9.20 (br.s, 1H), 8.53 (s, 1H), 7.98 (d, 2H), 7.64 (d, 2H), 4.59-1.77 (br.m, 25H), 0.96 (d, 6H). [ES+ MS] m/z 525 $(MH)^+$.

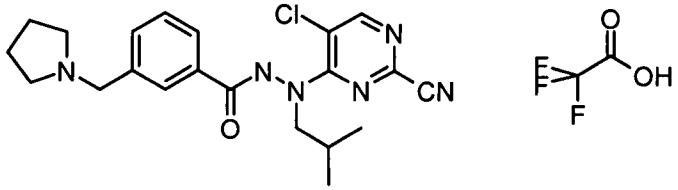
Example 53: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(dimethylamino) ethyl]-1-piperazinyl}methyl)-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



Intermediate 17 (50.0 mg, 0.132 mmol), 1-[2-(Dimethylamino)ethyl]piperazine (ALDRICH, 25 mg, 0.159 mmol), potassium carbonate (FLUKA, 36.5 mg, 0.26 mmol) and a tip of a

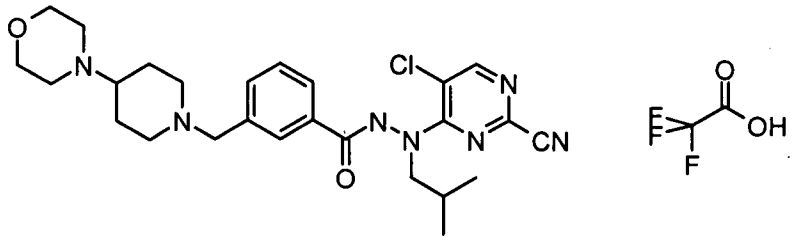
spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. 1H NMR ($CDCl_3$ + CD_3OD) δ ppm: 8.23(s; 1H); 7.86(d; 8.20Hz; 2H); 7.49(d; 8.2Hz; 2H); 4.18(s; 2H); 3.74(m; 2H); 3.22(m; 3H); 3.14(t; 5.4Hz; 2H); 2.83(s; 7H); 2.74(t; 6Hz; 4H); 2.09(m; 6.9Hz;1H); 0.98(d; 6.74Hz; 6H). [ES+MS] m/z 499 $(MH)^+$.

Example 54: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-3-(1-pyrrolidinylmethyl)benzohydrazide trifluoroacetate.**



To a solution of Intermediate 19 (50.0 mg, 0.13 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol), a tip of a spatula of sodium iodide in dry ACN (2 mL), and pyrrolidine (ALDRICH, 13.0 mg, 0.19 mmol) was added. The reaction mixture was stirred at room temperature overnight then, the reaction was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.15 (s, 1H), 8.0 (br.m, 1H), 7.90- 7.85 (br.m, 1H), 7.54- 7.42 (br.m, 2H), 4.24 (s, 2H), 3.48 (br.m, 2H), 3.24 (m, 2H), 2.90 (br.m, 2H), 2.02 (m, 5H), 0.91 (d, 6H). [ES+ MS] m/z 413 $(MH)^+$.

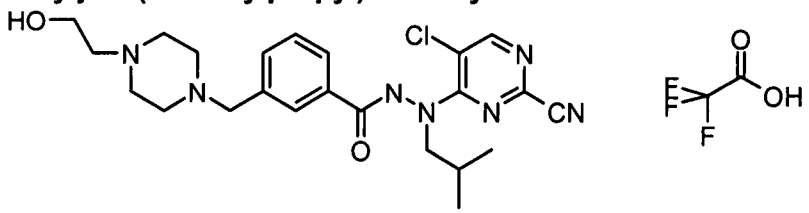
Example 55: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide trifluoroacetate.**



To a solution of intermediate 19 (50.0 mg, 0.13 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol), a tip of a spatula of sodium iodide in dry ACN (2 mL) and 4-morpholinopiperidine (ALDRICH, 32.0 mg, 0.19 mmol) were added. The reaction mixture was stirred at room temperature overnight then, the reaction was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, d6-DMSO) δ ppm: 11.49 (s, 1H), 8.54 (s, 1H),

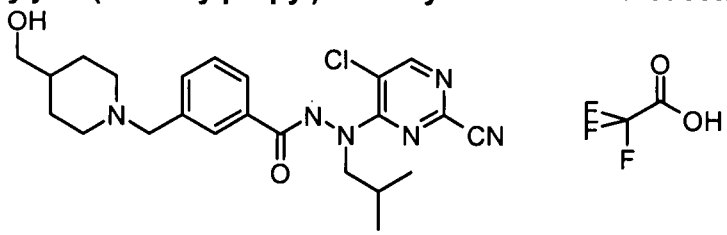
8.04- 7.95 (br.m, 2H), 7.75- 7.59 (br.m, 2H), 4.50- 1.66 (br.m, 22H), 0.96 (d, 6H). [ES+ MS] m/z 512 $(MH)^+$.

Example 56: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



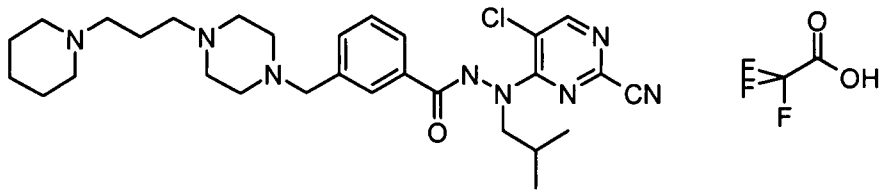
Intermediate 19 (50.0 mg, 0.13 mmol), 1-(2-hydroxyethyl)piperazine (ALDRICH, 24.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 9.78 (s, 1H), 8.31 (s, 1H), 8.27 (s, 1H), 8.06 (m, 1H), 7.64- 7.54 (br.m, 2H), 4.31 (s, 2H), 4.09- 2.83 (br.m, 15H), 2.15 (m, 1H), 1.02 (d, 6H). [ES+ MS] m/z 472 $(MH)^+$.

Example 57: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



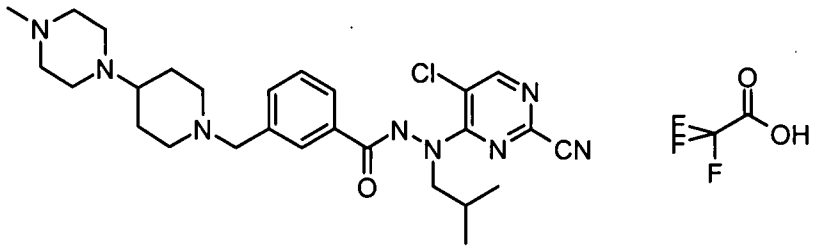
To a solution of Intermediate 19 (50.0 mg, 0.13 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol), a tip of a spatula of sodium iodide in dry ACN (2 mL) and 4-(hydroxymethyl)piperidine (ALDRICH, 21.0 mg, 0.19 mmol) was added. The reaction mixture was stirred at room temperature overnight then, the reaction was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified twice by preparative HPLC (SUNFIRE 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 11.59 (br.s, 1H), 11.53 (br.s, 1H), 8.23 (s, 1H), 8.06 (d, 2H), 7.61- 7.41 (br.m, 2H), 4.29-1.22 (br.m, 17H), 1.01 (d, 6H). [ES+ MS] m/z 457 $(MH)^+$.

Example 58: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-3-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate.**



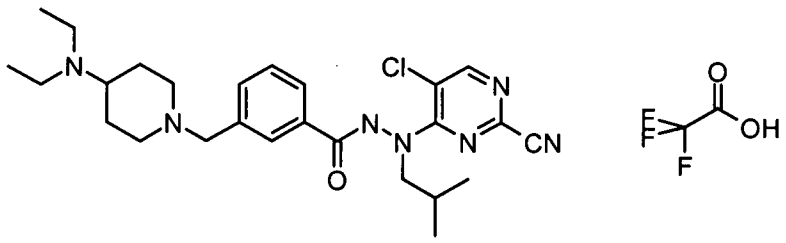
Intermediate 19 (50.0 mg, 0.13 mmol), 1-(3-piperidinopropyl)piperazine (FLUOROCHEM, 39.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 10.14 (s, 1H), 8.24 (s, 1H), 8.07- 8.01 (m, 1H), 7.61- 7.47 (br.m, 2H), 4.17 (s, 2H), 3.89- 1.83 (br.m, 27H), 1.01 (d, 6H). [ES+ MS] m/z 553 $(MH)^+$.

Example 59: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



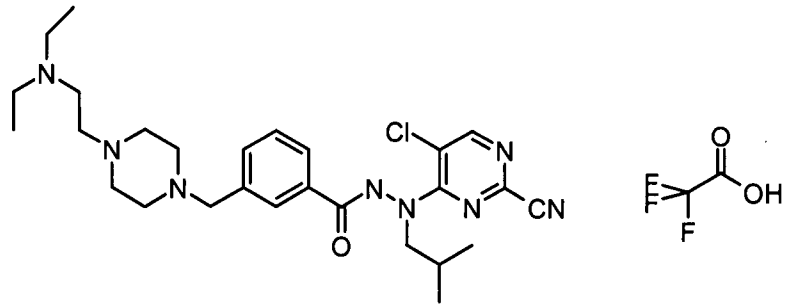
Intermediate 19 (50.0 mg, 0.13 mmol), 1-methyl-4-(piperidin-4-yl)-piperazine (FLUOROCHEM, 34.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ ppm: 8.21 (s, 1H), 8.16 (br.s, 1H), 8.04- 7.99 (m, 1H), 7.57-7.45 (br.m, 2H), 4.21 (s, 2H), 3.87- 1.89 (br.m, 23H), 0.99 (d, 6H). [ES+ MS] m/z 525 $(MH)^+$.

Example 60: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(diethylamino)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



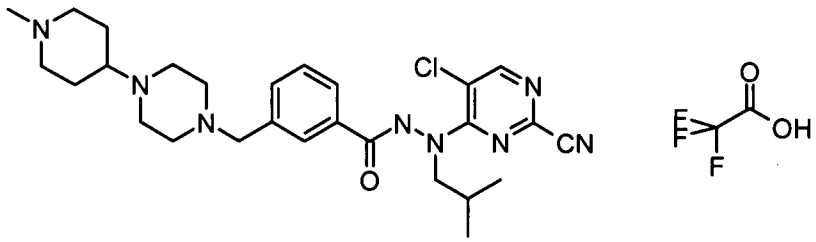
Intermediate 19 (50.0 mg, 0.13 mmol), 4-diethylamino-piperidine (FLUOROCHEM, 29.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 10.45 (br.s, 1H), 8.41 (br.s, 1H), 8.24 (s, 1H), 8.12 (m, 1H), 7.64- 7.39 (br.m, 2H), 4.20 (br.s, 2H), 4.10- 2.06 (br.m, 18H), 1.42 (m, 6H), 1.01 (d, 6H). [ES+ MS] m/z 498 $(MH)^+$.

Example 61: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[2-(diethylamino)ethyl]-1-piperazinyl}methyl)-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



Intermediate 19 (50.0 mg, 0.13 mmol), 1-(2-diethylaminoethyl)-piperazine (CHEMPUR, 34.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 10.63 (s, 1H), 8.35 (br.s, 1H), 8.22 (s, 1H), 8.10- 8.04 (m, 1H), 7.60- 7.44 (m, 2H), 4.19 (s, 2H), 3.94- 1.66 (br.m, 19H), 1.35 (m, 6H), 1.00 (d, 6H). [ES+ MS] m/z 527 $(MH)^+$.

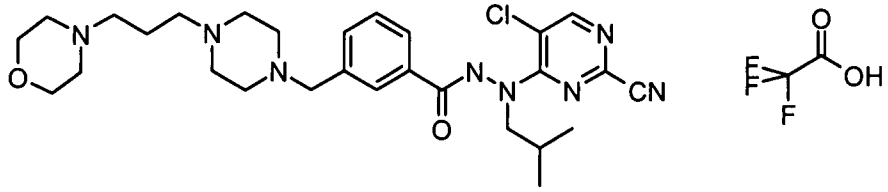
Example 62: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(1-methyl-4-piperidinyl)-1-piperazinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



Intermediate 19 (50.0 mg, 0.13 mmol), 1-(N-methyl-4-piperidyl)-piperazine (ALDRICH, 34.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction

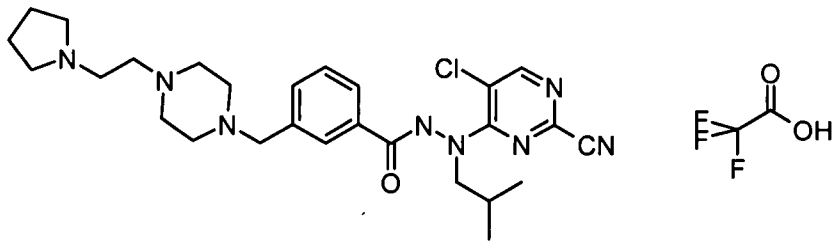
mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ ppm: 8.21 (s, 1H), 8.06 (br.s, 1H), 7.98- 7.92 (m, 1H), 7.55- 7.47 (br.m, 2H), 4.11 (br.s, 2H), 3.86- 1.95 (br.m, 23H), 0.98 (d, 6H). [ES+ MS] m/z 525 $(MH)^+$.

Example 63: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-3-({4-[3-(4-morpholinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate.**



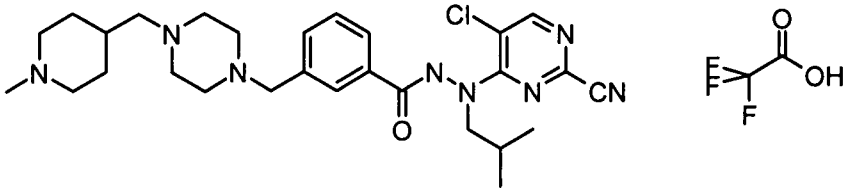
Intermediate 19 (50.0 mg, 0.13 mmol), 1-(3-morpholinopropyl)-piperazine (FLUOROCHEM, 40.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 10.07 (s, 1H), 8.25 (s, 2H), 8.05 (br.s, 1H), 7.63- 7.48 (m, 2H), 4.19 (br.s, 2H), 4.05- 3.05 (br.m, 20H), 2.82 (m, 2H), 2.12 (m, 3H), 1.01 (d, 6H). [ES+ MS] m/z 555 $(MH)^+$.

Example 64: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-3-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate.**



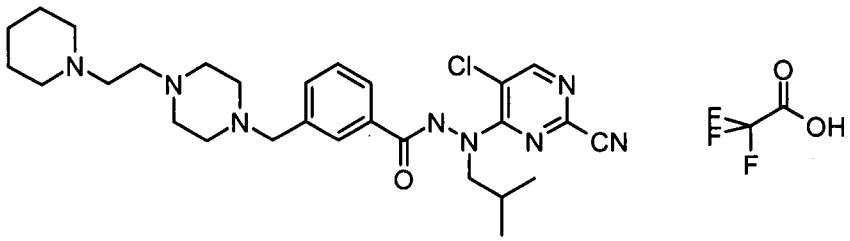
Intermediate 19 (50.0 mg, 0.13 mmol), 1-(2-pyrrolidinoethyl)piperazine (FLUOROCHEM, 34.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 10.51 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 8.11- 8.02 (m, 1H), 7.60- 7.43 (m, 2H), 4.18 (br.s, 2H), 4.01- 2.01 (br.m, 23H), 1.00 (d, 6H). [ES+ MS] m/z 525 $(MH)^+$.

Example 65: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[(1-methyl-4-piperidinyl)methyl]-1-piperazinyl}methyl)-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



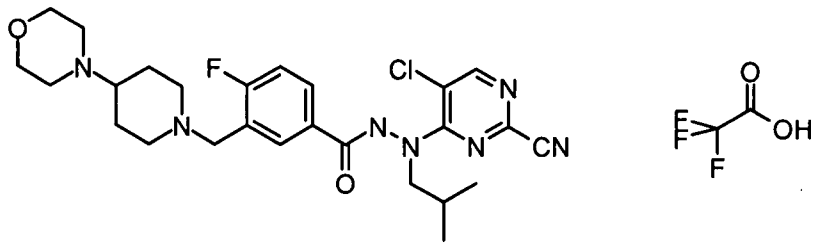
Intermediate 19 (50.0 mg, 0.13 mmol), 1-(N-methyl-4-piperidinmethyl)piperazine (FLUOROCHEM, 37.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 10.23 (s, 1H), 8.34 (br.s, 1H), 8.24 (s, 1H), 8.09- 8.02 (m, 1H), 7.61- 7.45 (m, 2H), 4.18 (br.s, 2H), 3.91- 1.77 (br.m, 27H), 1.01 (d, 6H). [ES+ MS] m/z 539 $(MH)^+$.

Example 66: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-*N'*-(2-methylpropyl)-3-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate.**



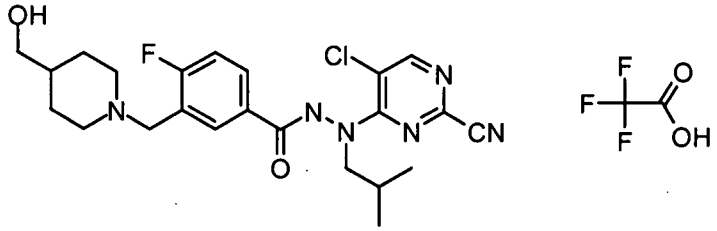
Intermediate 19 (50.0 mg, 0.13 mmol), 1-(2-piperidinoethyl)-piperazine (FLUOROCHEM, 37.0 mg, 0.19 mmol), potassium carbonate (FLUKA, 37.0 mg, 0.27 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (2 mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the reaction mixture was filtered and solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 10.53 (s, 1H), 8.32 (br.s, 1H), 8.22 (s, 1H), 8.10- 8.02 (m, 1H), 7.61- 7.45 (m, 2H), 4.20 (s, 2H), 3.92- 1.78 (br.m, 25H), 1.00 (d, 6H). [ES+ MS] m/z 539 $(MH)^+$.

Example 67: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-*N'*-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide trifluoroacetate.**



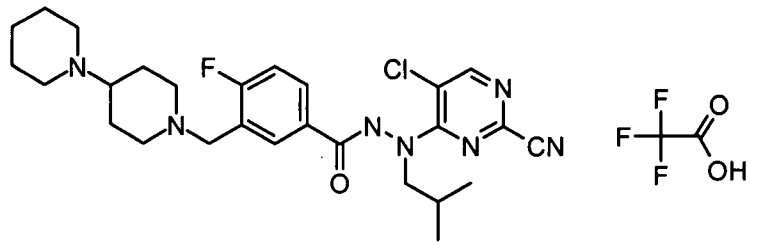
To a solution of Intermediate 23 (90.5 mg, 0.20 mmol) in THF (1.7 mL) 4-morpholinopiperidine (ALDRICH, 70.0 mg, 0.41 mmol) and dry THF (1 mL) were added. The reaction mixture was stirred at room temperature overnight and then, heated 4 hours at 60° C. More 4-morpholinopiperidine (35.0 mg, 0.205 mmol) was added and the reaction mixture was heated at 60° C for 3 hours and, then, it was stirred at room temperature overnight. Once it had reached completion the solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH and was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 10.27 (br.s, 1H), 8.58 (br.m, 1H), 8.25 (s, 1H), 8.11 (br.m, 1H), 7.26 (br.m, 1H), 4.33- 1.22 (br.m, 22H), 1.02 (d, 6H). [ES+ MS] m/z 530 $(MH)^+$.

Example 68: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



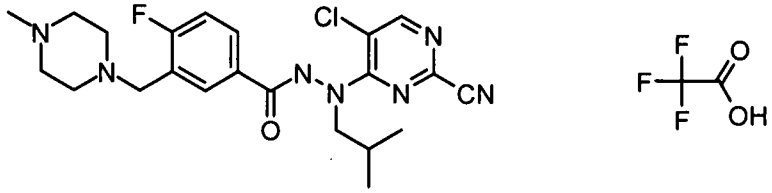
To a solution of Intermediate 23 (90.5 mg, 0.20 mmol) in THF (1.7 mL) 4-(hydroxymethyl)piperidine (ALDRICH, 47.0 mg, 0.41 mmol) in dry THF (1 mL) was added. The reaction mixture was stirred at room temperature overnight and, then, heated at 60° C for 4 hours. More 4-(hydroxymethyl)piperidine (23.5 mg, 0.20 mmol) was added and the reaction mixture was stirred at 60° C for 3 hours and then at room temperature overnight. Once it had reached completion the solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH and was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.29 (br.s, 1H), 10.7 (s, 1H), 8.55 (br.m, 1H), 8.23 (s, 1H), 8.13 (br.m, 1H), 7.26 (br.m, 1H), 4.36- 1.47 (br.m, 17H), 1.01 (d, 6H). [ES+ MS] m/z 475 $(MH)^+$.

Example 69: **3-(1,4'-bipiperidin-1'-ylmethyl)-*N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



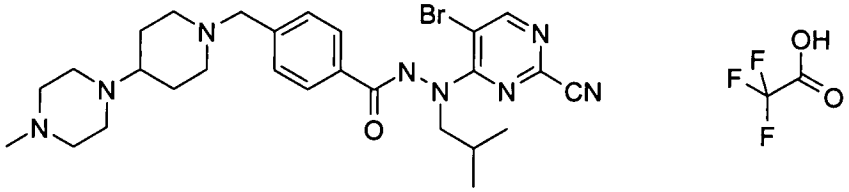
To a solution of Intermediate 23 (90.5 mg, 0.20 mmol) in THF (1.7 mL), 4-piperidinopiperidine (ALDRICH, 69.0 mg, 0.41 mmol) in dry THF (1 mL) was added. The reaction mixture was stirred at room temperature overnight and then, it was heated for 4 hours at 60° C. More 4-piperidinopiperidine (34.5 mg, 0.20 mmol) was added and the mixture was heated at 60° C for 3 hours and at room temperature overnight. Once it had reached completion the solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH and was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 10.45 (s, 1H), 8.50 (br.m, 1H), 8.24 (s, 1H), 8.15 (br.m, 1H), 7.32 (br.m, 1H), 4.27 (s, 2H), 3.96- 1.82 (br.m, 22H), 1.01 (d, 6H). [ES+ MS] m/z 528 $(MH)^+$.

Example 70: ***N'*-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-[(4-methyl-1-piperazinyl)methyl]-*N'*-(2-methylpropyl)benzohydrazide.**



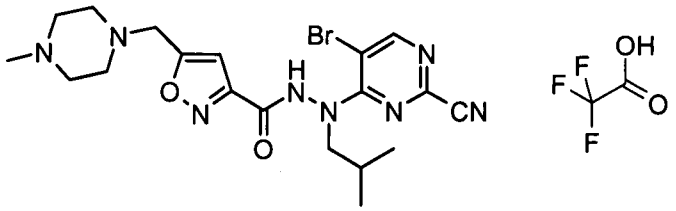
To a solution of Intermediate 23 (90.5 mg, 0.20 mmol) in THF (1.7 mL), N-methylpiperazine (ALDRICH, 41.0 mg, 0.41 mmol) in dry THF (1 mL) was added. The reaction mixture was stirred at room temperature overnight and then, at 60° C for 4 hours. Once it had reached completion the solvent was evaporated under reduced pressure. The crude residue obtained was dissolved in MeOH and was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.67 (s, 1H), 8.30- 8.19 (br.m, 2H), 8.00 (m, 1H), 7.29 (br.m, 1H), 4.19 (s, 2H), 3.92- 3.36 (br.m, 10H), 2.81 (s, 3H), 2.14 (m, 1H), 1.01 (d, 6H). [ES+ MS] m/z 460 $(MH)^+$.

Example 71: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-*N'*-(2-methylpropyl)benzohydrazide trifluoroacetate.**



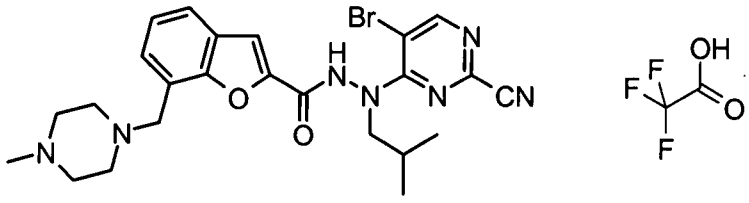
Intermediate 18 (270.0 mg, 0.639 mmol), 1-methyl-4-(piperidin-4-yl)-piperazine (FLUOROCHEM, 183.3 mg, 0.766 mmol), N,N-diisopropylethylamine (ALDRICH, 215µL, 1.278 mmol) and a tip of a spatula of sodium iodide were dissolved in dry ACN (10mL). The reaction mixture was stirred at room temperature overnight. Once it had reached completion, the solvent was evaporated under reduced pressure. The resultant crude product was purified by preparative HPLC (X-TERRA 50x250 mm, ACN:H_2O, 0.1%TFA, gradient 25-100%) to give the title compound. 1H NMR ($CDCl_3$ + CD_3OD) δ ppm: 8.73(s; 1H); 8.03(s; 1H); 7.99(d; 8.2Hz; 2H); 7.54(d; 8.2Hz; 2H); 4.63(s; 3H); 4.14(s; 2H); 3.45(m; 5H); 2.86(m; 6H); 2.73(s; 3H); 2.53(m; 1.9Hz; 3H); 2(m; 8H); 1.2(m; 2H); 0.96(d; 6.6Hz; 6H). [ES+MS] m/z 569 $(M)^+$.

Example 72: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl) methyl]-*N'*-(2-methylpropyl)-3-isoxazolecarbohydrazide trifluoroacetate.**



Intermediate 26 (28.3 mg, 0.068 mmol) was dissolved in dry THF (5 mL). N,N-diisopropylethylamine (FLUKA, 15.2 uL, 0.137 mmol) and N-methylpiperazine (ALDRICH, 23.8 uL, 0.137 mmol) were added and the resultant solution was stirred at room temperature overnight. N,N-diisopropylethylamine (FLUKA, 30.4 uL, 0.274 mmol) and N-methylpiperazine (ALDRICH, 23.8 uL, 0.137 mmol) were added. The solution was stirred at room temperature overnight. More N,N-diisopropylethylamine (FLUKA, 30.4 uL, 0.274 mmol) was added and the reaction was stirred for another 16 hours. The solvent was evaporated and the residue was purified by preparative HPLC (XTERRA column 19 x 150 mm, gradient: 10% ACN; 0.1% TFA to 100% ACN, 0.1% TFA) to obtain the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.88 (br s, 1H), 8.50 (s, 1H), 6.70 (s, 1H), 3.89 (s, 2H), 3.79 (m, 2H), 3.59 (m, 2H), 2.97 (m, 4H), 2.84 (s, 3H), 2.70 (m, 2H), 2.10 (m, 1H),1.02 (d, 6H, J = 6 Hz). [ES+ MS] m/z 477 $(M)^+$.

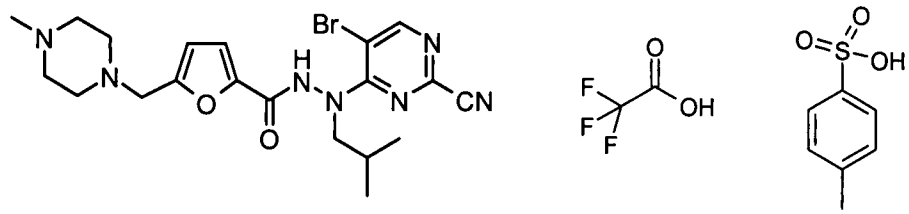
Example 73: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-7-[(4-methyl-1-piperazinyl) methyl]-*N'*-(2-methylpropyl)-1-benzofuran-2-carbohydrazide trifluoroacetate.**



Intermediate 29 (100 mg, 0.39 mmol) was dissolved in dry DCM (6 mL) and dry THF (1.5 mL). Dry DMF (11 uL) was added followed by oxalyl chloride (ALDRICH, 38 uL, 0.43 mmol). Reaction was stirred at room temperature for 1 hour 45 minutes until no starting

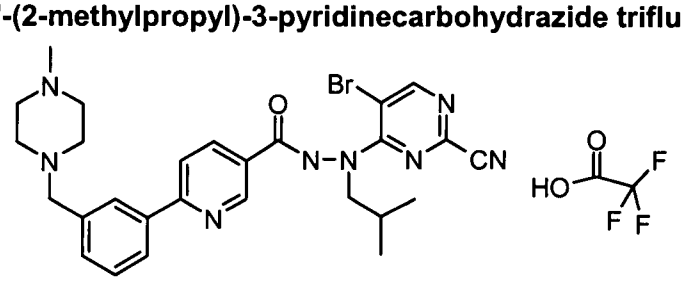
material was left. A solution of Intermediate 6 (127 mg, 0.47 mmol) in anhydrous DCM (3.5 mL) and diisopropylethylamine (FLUKA, 171 uL, 0.98 mmol) was added dropwise to the reaction and the resultant solution was stirred at room temperature for 20 hours. Then, N-methylpiperazine (ALDRICH, 52 uL, 0.47 mmol) and diisopropylethylamine (FLUKA, 82 uL, 0.47 mmol) were added and the reaction was stirred at room temperature for 54 hours. Solvents were evaporated to dryness and the residue was purified using preparative HPLC (XTERRA column 19 x 150 mm, gradient: 25% ACN-water, 0.1%TFA to 100% ACN-water, 0.1%TFA) to yield the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.57 (s, 1H), 9.33 (br s, 1H), 8.69 (s, 1H), 7.82 (s, 1H), 7.75-7.79 (m, 1H), 7.46-7.50 (m, 1H), 7.34-7.40 (m, 1H), 3.99 (m, 4H), 2.98-3.10 (m, 6H), 2.77 (s, 3H), 2.33-2.45 (m, 2H), 2.03-2.14 (m, 1H), 0.97 (d, 6H, J = 6.8 Hz). [ES+ MS] m/z 526 $(M)^+$.

Example 74: **N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl) methyl]-N'-(2-methylpropyl)-3-furancarbohydrazide (0.75 TFA / 0.25 pTsOH salt).**



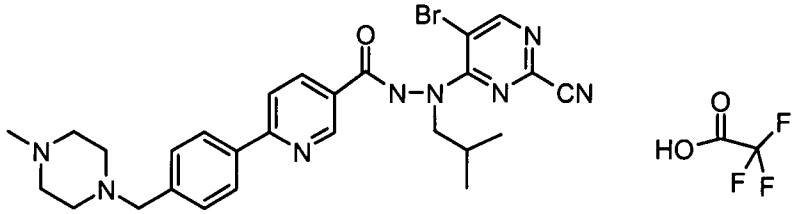
Intermediate 31 (780.7 mg, 3.489 mmol) was dissolved in 40 mL of DCM. Oxalyl chloride (ALDRICH, 513.2 uL, 5.398 mmol) was added slowly and the reaction was stirred at room temperature for 2h and the solvent was evaporated. N,N-diisopropyl-ethylamine (FLUKA, 1.25 mL, 7.198 mmol) was added to a solution of Intermediate 6 (486.1 mg, 1.799 mmol) in anhydrous THF (5 mL). The resultant solution was stirred for 10 min and, then, it was added dropwise over the residue previously obtained (846.78 mg, 3.489 mmol). Potassium tert-butoxide (ALDRICH, 282.7 mg, 2.52 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction was filtered, evaporated and the residue was purified by preparative-HPLC (LUNA column 50x250 mm, gradient: 20% ACN; 0.1% TFA to 100% ACN, 0.1% TFA) to obtain the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.27 (s, 1H), 9.53 (br s, 1H), 8.65 (s, 1H), 7.33 (d, 1H, J = 3.4 Hz), 6.59 (d, 1H, J = 3.5 Hz), 3.73 (s, 2H), 3.38 (m, 3H), 3.01 (m, 5H), 2.78 (s, 3H), 2.39 (m, 2H), 2.06 (m, 1H), 0.94 (d, 6H, J = 6.6 Hz). [ES+ MS] m/z 476 $(M)^+$.

Example 75: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-6-{3-[(4-methyl-1-piperazinyl) methyl]phenyl}-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate.**



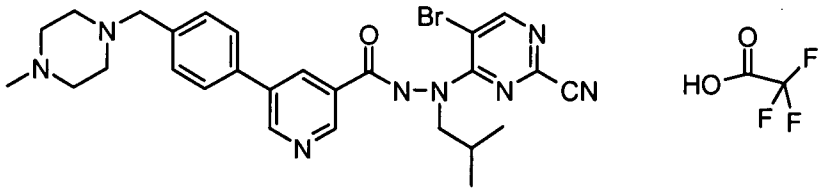
N-methylpiperazine (ALDRICH, 0.007 mL, 0.06 mmol) and N,N-diisopropylethylamine (FLUKA, 0.014 mL, 0.08 mmol) in THF (6 mL) were stirred at room temperature for 5 min. Intermediate 34 (26 mg, 0.05 mmol) was added and the solution was stirred at room temperature for 4 days and, then, it was refluxed for 4 h. The reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H2O, 0.1%TFA, gradient 20-80%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 11.59 (s, 1H), 9.39 (br., 1H), 9.15 (m, 1H), 8.67 (s, 1H), 8.42-8.33 (m, 1H), 8.18-8.04 (m, 3H), 7.57-7.43 (m, 2H), 3.76-2.91 (br. m, 12H), 2.76 (s, 3H), 2.10 (m, 1H), 0.97 (d, 6H). [ES+ MS] m/z 563 $(MH)^+$.

Example 76: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-6-{4-[(4-methyl-1-piperazinyl) methyl]phenyl}-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate.**



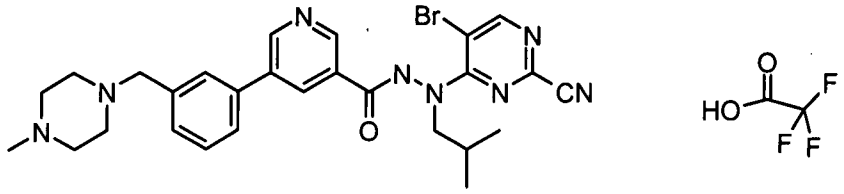
To a solution of Intermediate 37 (37 mg, 0.07 mmol) in THF (5 mL), N,N-DIPEA (FLUKA, 0.019 mL, 0.11 mmol) and N-methylpiperazine (ALDRICH, 0.020 mL, 0.18 mmol) were added. The solution was stirred at room temperature for 2 days and then, it was refluxed for 7 h. The reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 11.57 (s, 1H), 9.42 (br., 1H), 9.15 (m, 1H), 8.40-8.30 (m, 1H), 8.20-8.08 (m, 3H), 7.48 (d, 2H), 4.13-2.84 (br. m, 12H), 2.77 (s, 3H), 2.10 (m, 1H), 0.97 (d, 6H). [ES+ MS] m/z 563 $(MH)^+$.

Example 77: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-{4-[(4-methyl-1-piperazinyl) methyl]phenyl}-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate.**



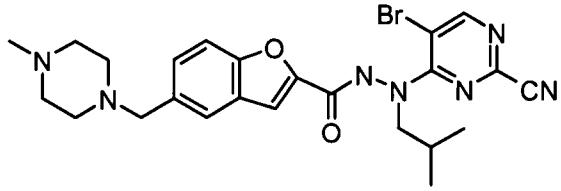
To a solution of Intermediate 40 (crude) in DCM (10 mL), N,N-diisopropylethylamine (Fluka, 0.097 mL, 0.55 mmol), N-methylpiperazine (ALDRICH, 0.049 mL, 0.44 mmol) and sodium iodide were added. The solution was stirred at room temperature for 4 days. The reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H_2O, 0.1%TFA, gradient 20-80%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 11.63 (s, 1H), 9.12 (m, 1H), 9.06 (m, 1H), 8.68 (s, 1H), 8.50 (s, 1H), 7.82 (d, 2H), 7.51 (d, 2H), 4.46-2.88 (m, 13H), 2.77 (s, 3H), 2.11 (m, 1H), 0.96 (d, 6H). [ES+ MS] m/z 563 $(MH)^+$.

Example 78: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-{3-[(4-methyl-1-piperazinyl) methyl]phenyl}-*N'*-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate.**



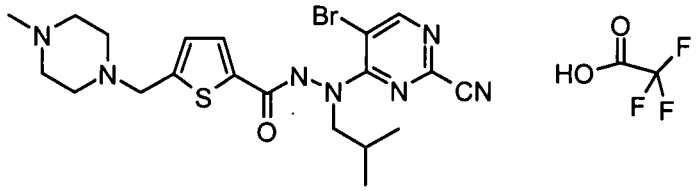
To a solution of Intermediate 43 (crude) in THF (20 mL), DIPEA (FLUKA, 0.097 mL, 0.55 mmol), N-methylpiperazine (ALDRICH, 0.049 mL, 0.44 mmol) and sodium iodide were added. The solution was stirred at room temperature for 4 days and, then, it was refluxed for 3 h. The reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (XTERRA 19x150 mm, ACN:H2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d6): 11.66 (s, 1H), 9.12 (m, 2H), 8.67 (m, 1H), 8.50 (m, 1H), 7.78 (br. s, 1H), 7.60-7.41 (m, 2H), 4.07 (br., 1H), 3.84 (br. s, 2H), 3.53-2.93 (m, 8H), 2.78 (s, 3H), 2.11 (m, 1H), 0.97 (d, 6H). [ES+ MS] m/z 563 $(MH)^+$.

Example 79: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl) methyl]-*N'*-(2-methylpropyl)-1-benzofuran-2-carbohydrazide.**



To a solution of Intermediate 48 (76mg) in 4 mL of dry ACN, DIPEA (FLUKA, 43 µL 0.246 mmol) and N-methyl piperazine (ALDRICH, 22 µL), were added. The reaction mixture was stirred for 5 h and the solvent was evaporated under pressure. The crude product was purified by preparative HPLC (X-TERRA 19x150 mm, ACN: H_2O, 0.1%TFA, gradient 25-100%) giving the title compound. ^{1}H NMR(DMSO) δ ppm: 8.6(s; 1H); 7.8 (s;2H); 7.7(d;8.6Hz;1H); 7.5(d;8.6Hz; 1H);4.6-2.9(m; 12H); 2.78(s; 3H); 2.2-2(m; 6.6Hz;1H);0.96(d;6.6Hz;6H). ES+MS m/z 526 $(MH)^+$.

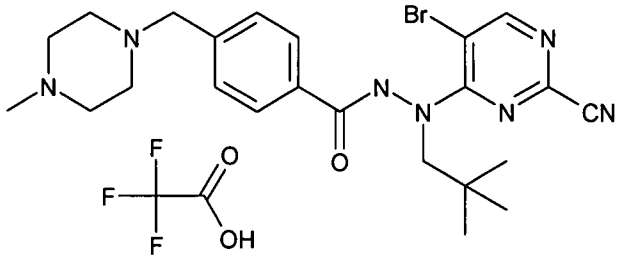
Example 80: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl) methyl]-*N'*-(2-methylpropyl)-2-thiophenecarbohydrazide trifluoroacetate.**



To a stirring solution of Intermediate 51 (100 mg, 0.23 mmol) in 6 mL of dry ACN, 61 µL (0.350 mmol) of DIPEA and 31 µL of N-methyl piperazine, were added. The reaction

mixture was stirred for 4h and the solvent was evaporated under pressure. The resulting crude product was purified by preparative HPLC (X-TERRA 19x150 mm, ACN: H_2O, 0.1%TFA, gradient 10-100%) to give the title compound. ^1H NMR($CDCl_3$) δ ppm: 9.38(s; 1H); 8.43 (s;1H); 7.56 (d;3.81Hz;1H); 7(d;3.81Hz;1H); 3.94 (s;2H); 3.88-3.66(m; 2H); 3.45-3 (m; 4H); 2.82(s; 3H); 2.45-2.1(m; 4H); 2.07 (m; 6.6Hz; 1H); 0.99 (d; 6.6Hz; 6H). ES+MS m/z 492 $(MH)^+$.

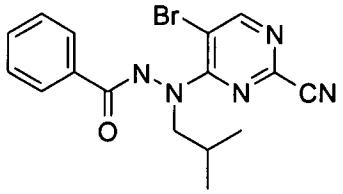
Comparative Example 81: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-*N'*-(2,2-dimethylpropyl)-4-[(4-methyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate.**



Intermediate 2 (1 g, 4.3 mmol) was dissolved in thionyl chloride (5 ml). The reaction mixture was stirred at room temperature for 17 hours. The solvent was evaporated *in vacuo* and the acid chloride was used without any further purification.

To a stirred solution of Intermediate 55 (200 mg, 0.70 mmol) in pyridine (1 mL) and DIPEA (5 mL), potassium carbonate (193 mg, 1.40 mmol) and previously obtained acid chloride (443 mg, 1.75 mmol) were added and the resulting reaction mixture was stirred at room temperature for 17 hours. The solvent was evaporated *in vacuo* and the crude reaction mixture was purified by flash chromatography (silica gel, dichloromethane:methanol). The solid was repurified by HPLC (0.1%TFA, H_2O:ACN) to give the title compound. ^1H NMR (300 MHz, DMSO) δ ppm: 11.33 (s, 1H), 8.64 (s, 1H), 7.91 (d, 2H), 7.49 (d, 2H), 3.72 (s, 2H), 3.37 (m, 2H), 3.25-2.81 (br, 6H), 2.78 (s, 3H) 0.99 (s, 9H). [ES+ MS] m/z 500 (MH^+).

Comparative Example 82: **N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-isobutylbenzohydrazide.**



The title compound was prepared by a method analogous to that described for Example 1, replacing the acid chloide of Intermediate 2 with benzoyl chloride.
^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.47 (s, 1H); 8.18 (s, 1H); 7.85-7.80 (m, 2H); 7.67-7.42 (m, 3H); 3.90-3-70 (m, 2H); 2.20-2.00 (m, 1H); 1.03 (d, J=6.6 Hz, 6H). [ES+ MS] m/z 374 $(M)^+$.

Biological Assays

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

1) Determination of Falcipain-2, Falcipain-3, Vivapain-2, Cathepsin K Cathepsin S, Cathepsin L, and Cathepsin B proteolytic catalytic activity

Assays for Falcipain-2, Falcipain-3, and Vivapain-2 are carried out with parasitic recombinant enzymes. Cathepsins K, S, L, and B are carried out with human recombinant enzymes. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically H-D-VLR-AFC (Falcipain-2, Falcipain-3, Vivapain-2), Z-FR-AFC (Cathepsin K, L, B), or KQKLR-AMC (Cathepsin S) and are determined in 100 mM sodium acetate, pH 5.5, containing 10 mM DTT and 0.5 mM CHAPS (Falcipain-2, Falcipain-3, Vivapain-2), and 100 mM sodium acetate, pH 5.5, containing 5 mM L-cysteine, 1mM CHAPS and 5mM EDTA (Cathepsin K, L, B), or 50mM MES, pH 6.5, containing 0.5mM CHAPS, 10mM L-CYS, 5mM EDTA (Cathepsin S). Stock substrate solutions are prepared at 20 mM in DMSO. The activity assays contained 30 uM substrate (Falcipain-2, Falcipain–3, Vivapain-2), 20 uM substrate (Cathepsin K), 25uM substrate (Cathepsin B), 5uM substrate (Cathepsin L), and 30uM substrate (Cathepsin S). All assays contained 1% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays are conducted at ambient temperature as end point assays being quenched after 60 minutes with the exception of Cathepsin S at 90 minutes, with 16.6 uM E-64 in 1% DMSO. Product formation (AFC or AMC) is determined from fluorescence (excitation at 405nM; emission at 530nM, AFC, or excitation at 360 nM; emission at 460 nM, AMC) monitored with a LJL Aquest (Molecular Devices) fluorescent plate reader. In the case of kinetic reads (used in mechanism of action studies), the reaction is not quenched but is read in the plate reader every 3 minutes for approximately 90 minutes. In addition, the mechanism of action studies for Falcipain-2 utilize Z-LR-AMC as the substrate. Product formation is determined from the fluorescence of AMC, measured with a LJL Acquest (Molecular Devices) fluorescent plate reader (excitation at 360nM; emission at 460nM).

Inhibition studies

Potential inhibitors are evaluated using the quenched read (endpoint) method. Assays are carried out in the presence of variable concentrations of test compound. Reactions are initiated by addition of enzyme and substrate to wells containing inhibitor stamped in 100% DMSO. For endpoint assays, the reaction is quenched with the addition of E64. Dose response data is fit to an IC_{50} curve with preset fitting tools according to equation 1:

$$y = a + (b-a)/(1+(10^{X}/10^{C})^{d}) \qquad (1)$$

where y is the response at a particular inhibitor concentration x, a is the minimum response value, b is the maximum response value, c is the IC_{50}, and d is the slope of the IC_{50} curve. Assuming the compound is a competitive inhibitor, the apparent K_I can be calculated from IC_{50}, as shown in equation 2:

$$IC_{50} = appK_I\,(1+[S]/K_M) \qquad (2)$$

where $appK_I$ is the apparent K_I, S is the concentration of substrate, K_M is the Michaelis binding constant for substrate, and K_I is the binding constant of a competitive inhibitor for free enzyme. For a more direct measurement of the K_I and the binding mechanism, we performed mechanism of action studies that included a titration of substrate and inhibitor with a kinetic read. If the progress curves for each of these kinetic assays are linear, the measured rates (v) were fit to equation 3:

$$v = V_m S / [(K_M\,(1 + [I]/K_I) + [S]\,(1+ [I]/\alpha K_I)] \qquad (3)$$

where V_m is the maximum velocity, S is the concentration of substrate with Michaelis constant of K_M, $[I]$ is the concentration of inhibitor, K_I is the binding constant of inhibitor for free enzyme, and αK_I is the binding constant of inhibitor for a potential enzyme-substrate complex.

For those compounds whose progress curves were nonlinear, with a decrease in enzyme activity over time characteristic of time-dependent inhibition, the progress curves were fit to equation 4 to yield the k_{obs}:

$$[\mathrm{AMC}] = v_S\,t + (v_0 - v_{SS})\,[1 - \exp(-k_{obs}t)] / k_{obs} \qquad (4)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_S is the final steady state rate. The k_{obs} values were fit to equations 5 and 6, describing a one-step and two-step time dependent binding mechansim respectively:

$$k_{obs} = k_{off}(\,1 + [I]/appK_I) \qquad (5)$$

$$k_{obs} = k_{off} + k_{on}(\,[I]/(\,appK_I + [I]\,) \qquad (6)$$

$$appK_I = K_I\,(1+[S]/K_M) \qquad (7)$$

Equation 7 describes the apparent K_I for competitive compounds and was substituted into equations 5 and 6 to generate the relevant binding constants from the fitting routine. In addition, the initial and final velocities were fit to equation 3 to further define the binding

mechanism and potency. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

2) Determination of whole cell activity against the *Plasmodium falciparum* parasite

Compounds can be evaluated for whole cell actvity against the *Plasmodium falciparum* parasite according to the procedure described in Sijwali S. and Rosenthal P. J., (2004) Proceedings of the National Academy of Sciences of the United States of America (PNAS) 101(13), 4384-4389 (see in particular "Measurement of Parasite Growth rates and Inhibitor Sensitivity" on page 4385); IC_{50} values can be calculated as described in Singh A. and Rosenthal P. J., (2001) Antimicrobial Agents and Chemotherapy 45(3), 949-951 (see in particular page 950, first column); synchronised parasites can be prepared as described in Divo A. A. *et al.*, (1985) Protozool. 32, 59-64.

3) *In vitro* models to evaluate activity against bone metastasis

Compounds can be evaluated for their actvity against bone metastasis using published *in vitro* models as follows: prostate cancer bone metastases model in rat (Liepe K. et al., (2005) Anticancer Research 25(2A), 1067-1073 and Neudert M. et al., (2003) International Journal of Cancer 107(3), 468-477); models of prostate and breast cancer metastases to bone in mice (Angelucci A. et al., (2004) International Journal of Oncology 25(6), 1713-1720 and Sasaki A. et al., (1995) Cancer Research 55(16), 3551-3557); and other models in various species for evaluating bone metastasis (Rosol T. J. et al, (2003) Cancer. 97, 748-757).

3) Comparator compounds

Two compounds were employed as comparator compounds. Comparative Example 81, which is a trifluoroacetate salt, and comparative Example 82 which is the free base, were prepared as described hereinabove. The free base of each of these compounds is disclosed in WO 2005/103012 A1 (page 124, Example 15(2) and page 130, Example 17(4) respectively).

Comparative Example 81: ***N'*-(5-bromo-2-cyano-4-pyrimidinyl)-*N'*-(2,2-dimethylpropyl)-4-[(4-methyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate.**

Comparative Example 82: **N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-isobutylbenzohydrazide.**

It will be understood by the skilled artisan that under the ezymatic assay conditions described hereinabove, the assay result obtained for the free base of a given compound is expected to be the same as that obtained when a salt of that compound is tested. This is because the buffer used in the assay determines the pH under which the compound is

tested; the pH determines the relative amounts of free base to salt of the compound being tested. This has been confirmed by testing in the enzymatic assays the free base, the hydrochloride salt and the trifluoroacetate salt of certain compounds of the type exemplified herein.

Results of assays

Cathepsin K

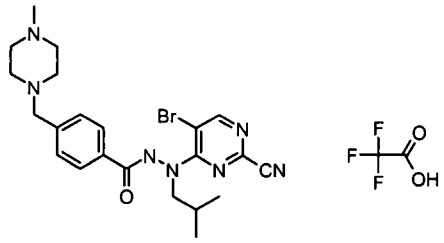
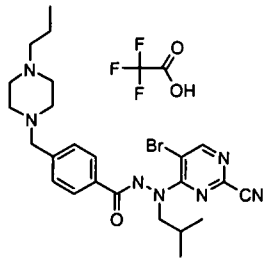
Examples 1-32, 35-54, 57-73, 75-77, 79 and 80 were tested in the enzymatic assay for cathepsin K. Examples 33, 34, 55, 56, 74 and 78 were not tested in this assay. The Examples which were tested were found to have an IC_{50} value of less than 11 nM in the enzymatic assay for cathepsin K.

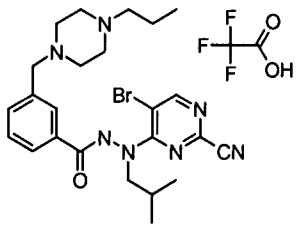
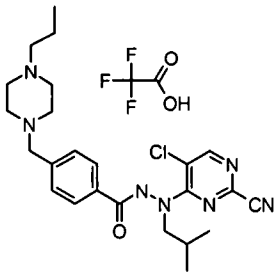
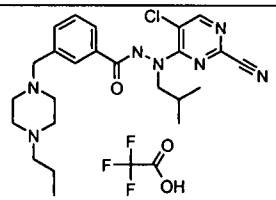
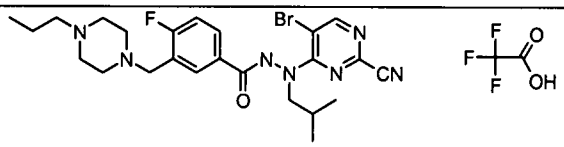
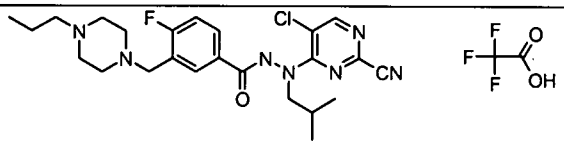
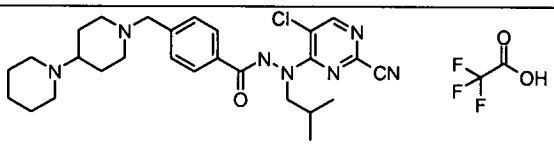
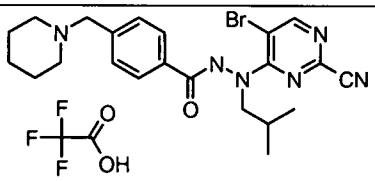
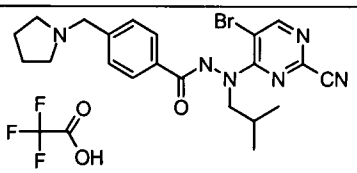
Falcipain-2 and falcipain-3 enzymatic assays, and whole cell assay

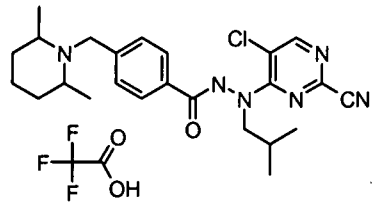
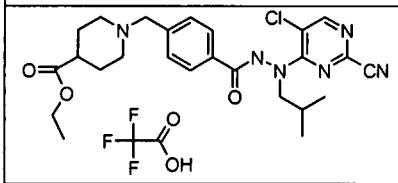
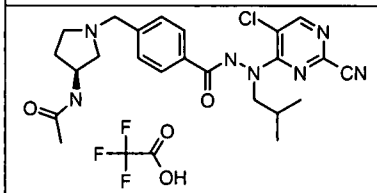
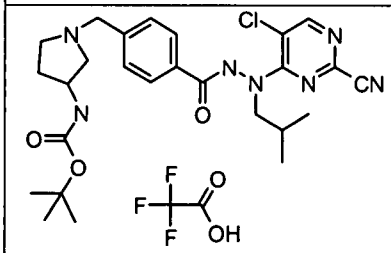
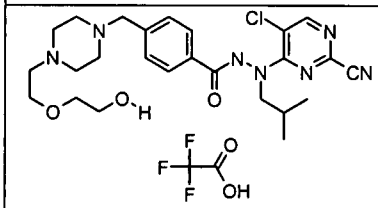
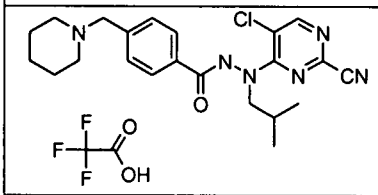
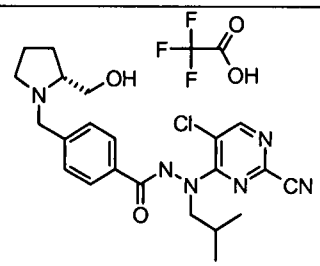
All exemplified compounds (Examples 1-80 and comparative Examples 81 and 82) were tested in the enzymatic assays for falcipain-2 and for falcipain-3, and in the whole cell assay according to the procedures described hereinabove.

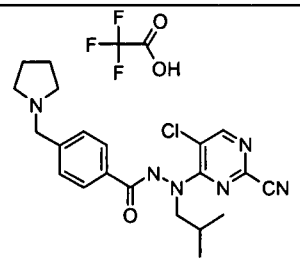
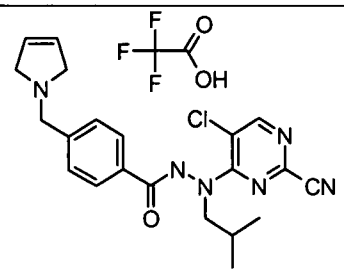
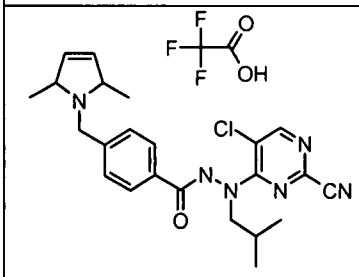
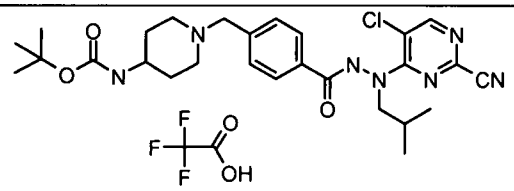
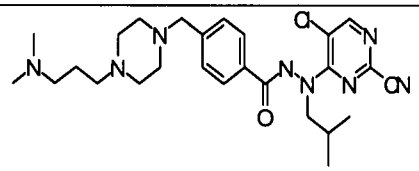
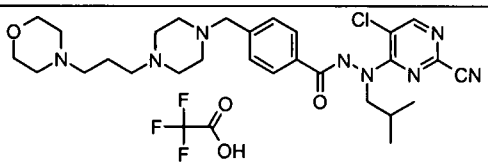
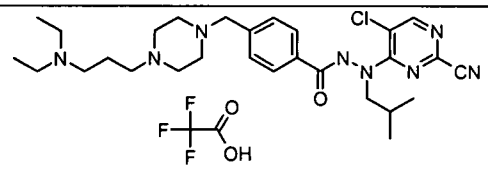
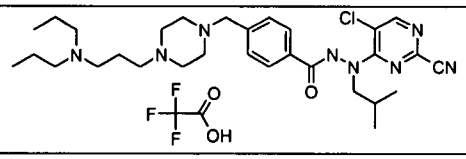
The results of falcipain-2 and falcipain-3 enzymatic assays, and the whole cell assay for all exemplified compounds of the present invention (Examples 1-80) and for comparative Examples 81 and 82 are shown in the table below.

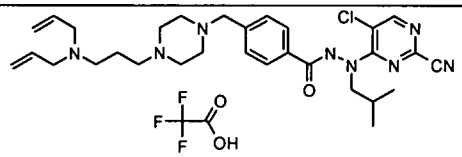
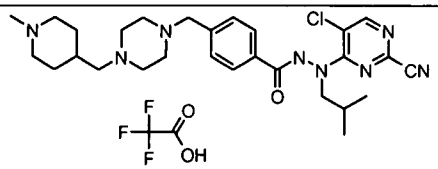
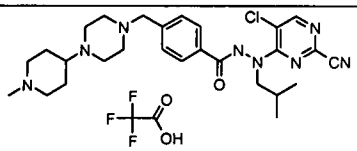
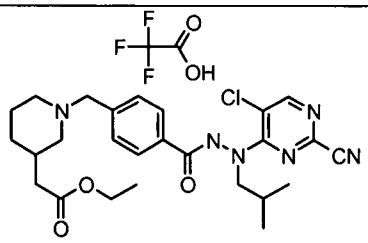
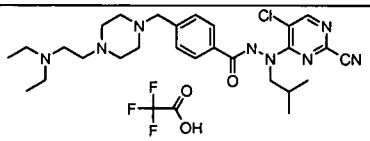
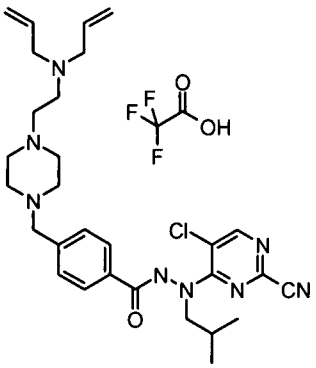
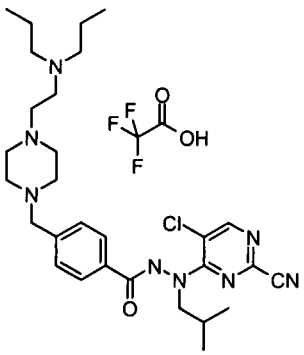
Table of falcipain-2, falcipain-3 and whole cell assay activities

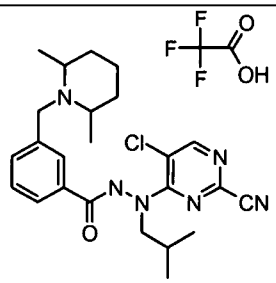
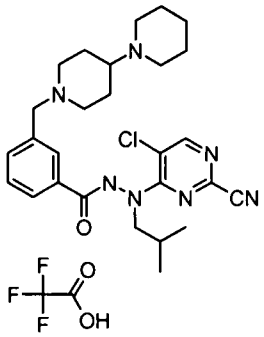
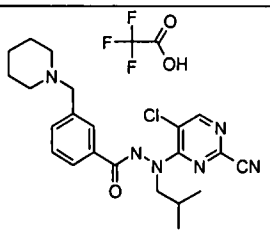
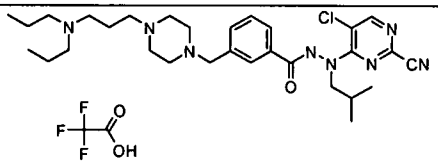
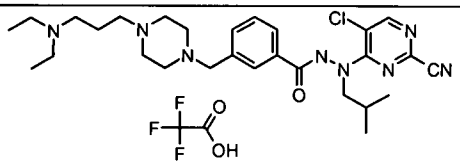
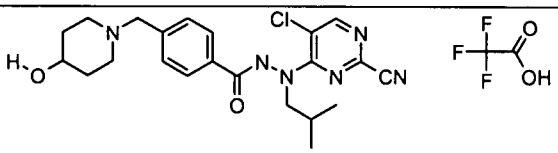
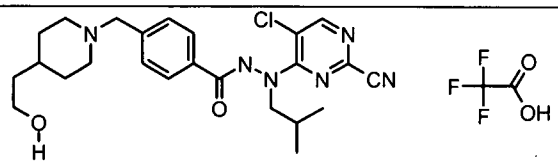
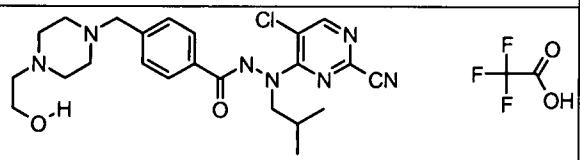
Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	1	*******	****	****
	2	*****	****	***

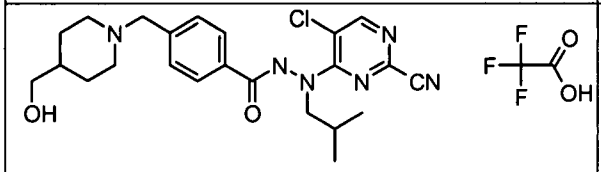
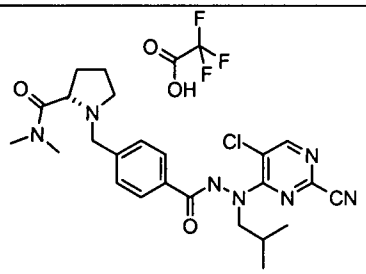
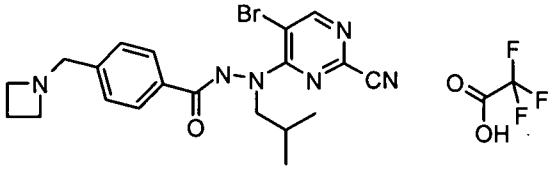
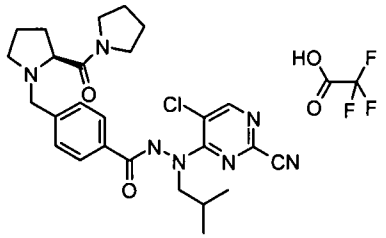
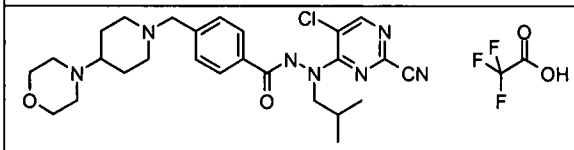
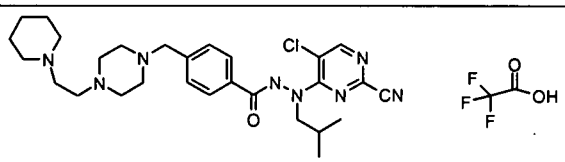
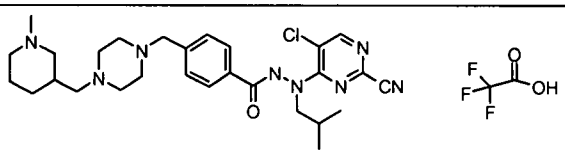
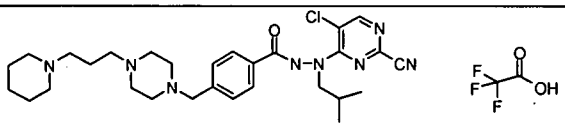
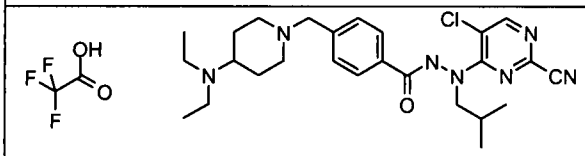
Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	3	*******	****	***
	4	******	****	****
	5	*******	****	****
	6	*******	****	****
	7	*******	****	****
	8	*******	****	****
	9	*****	****	****
	10	*****	****	****

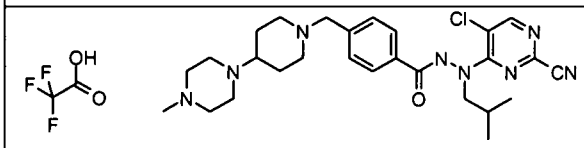
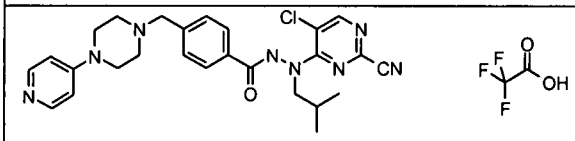
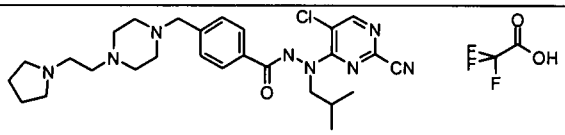
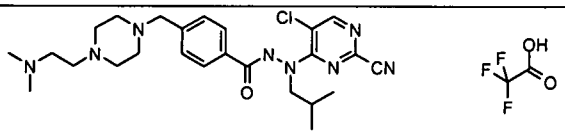
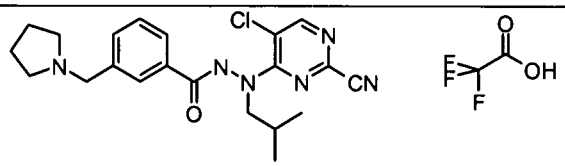
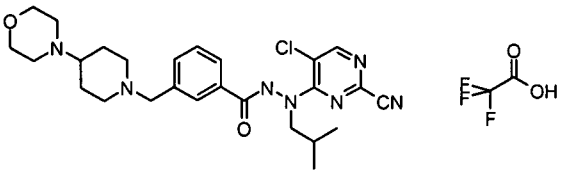
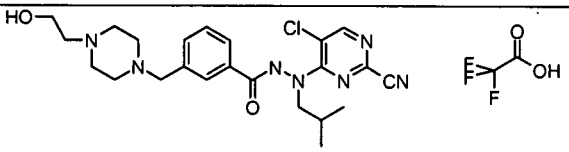
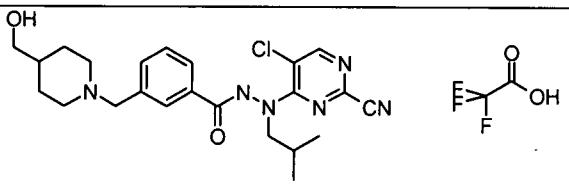
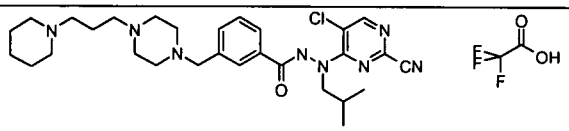
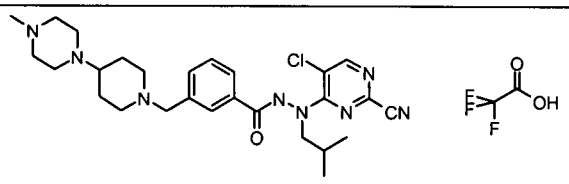
Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	11	*******	****	****
	12	******	****	****
	13	*******	****	****
	14	******	****	****
	15	*******	****	****
	16	*******	****	****
	17	*******	****	****

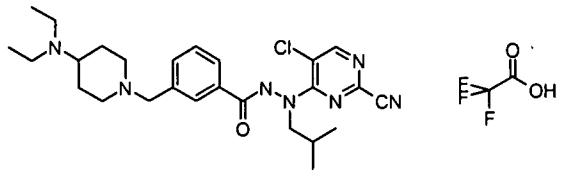
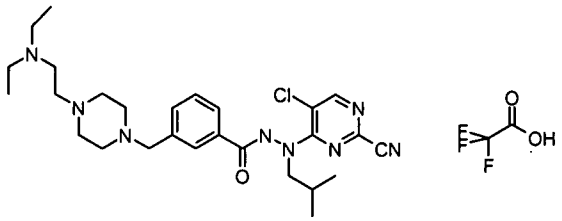
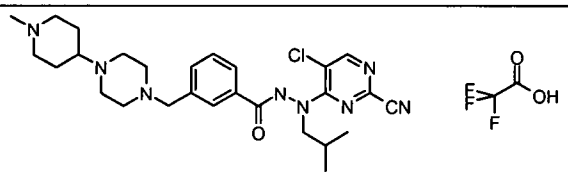
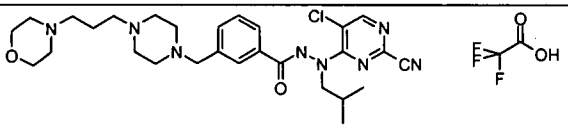
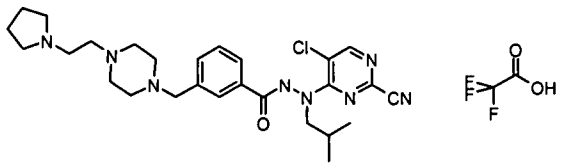
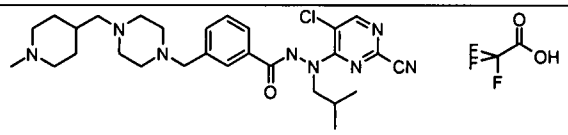
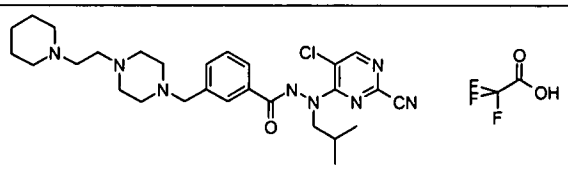
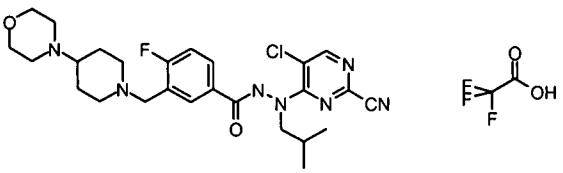
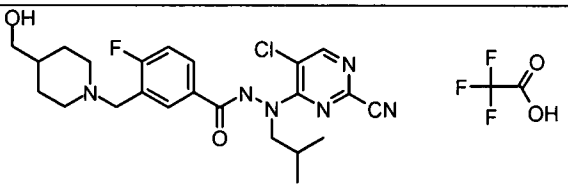
Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	18	*******	****	****
	19	*******	****	****
	20	*******	****	****
	21	*******	****	****
	22	******	****	****
	23	*******	****	****
	24	******	****	****
	25	*******	****	****

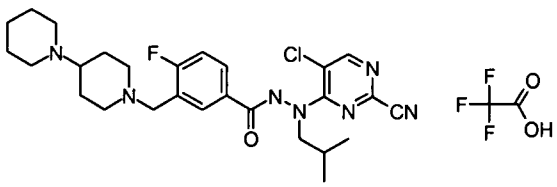
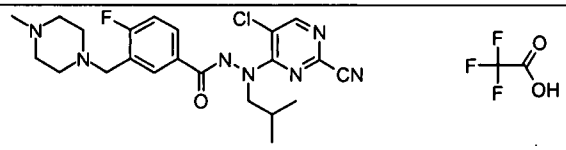
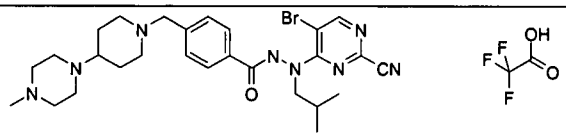
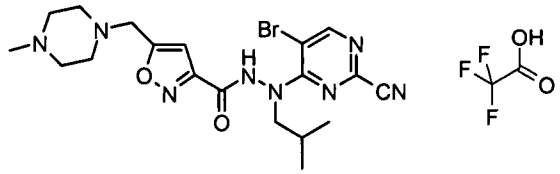
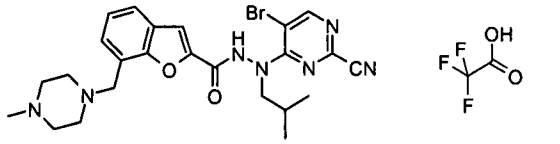
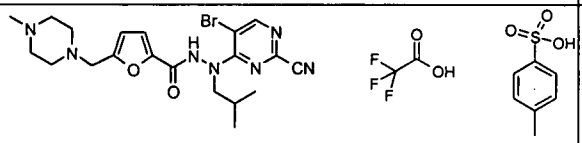
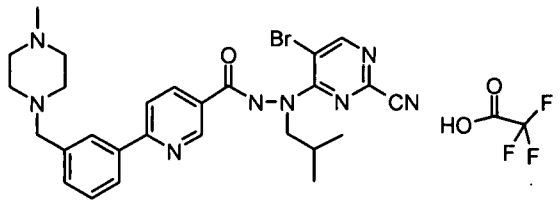
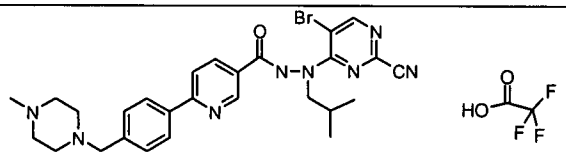
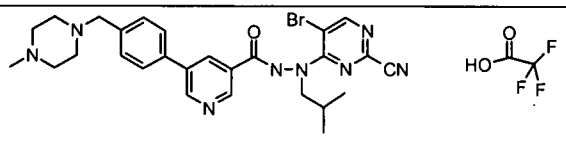
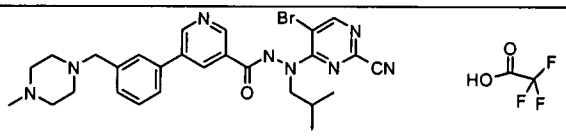
Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	26	*******	*****	****
	27	******	****	***
	28	*******	*****	****
	29	*******	****	****
	30	*****	****	***
	31	******	****	****
	32	*******	*****	****

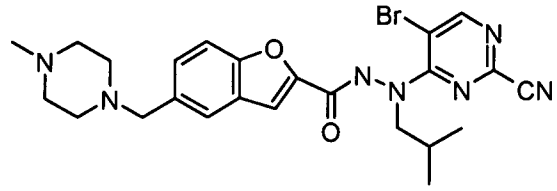
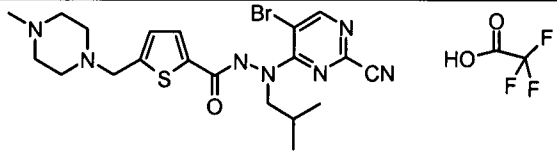
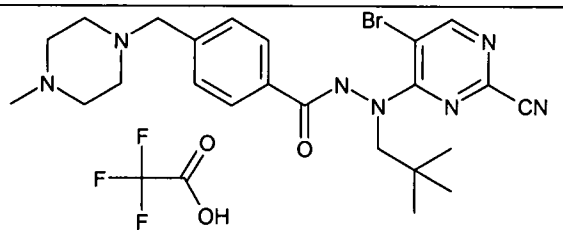
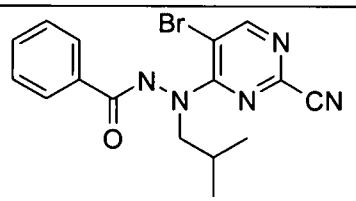
Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	33	*******	****	****
	34	*******	****	****
	35	*******	****	****
	36	*******	*****	****
	37	*******	*****	****
	38	*******	****	****
	39	*******	****	****
	40	*******	****	****

Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	41	*******	****	****
	42	*******	****	****
	43	*******	****	****
	44	*******	****	****
	45	*******	****	****
	46	*******	****	****
	47	*******	****	****
	48	*******	****	****
	49	*******	****	****

Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	50	*******	*****	****
	51	*******	****	****
	52	*******	****	****
	53	*******	****	****
	54	*******	****	****
	55	*******	****	****
	56	*****	****	****
	57	*******	****	****
	58	*******	*****	****
	59	*******	*****	****

Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	60	*******	*****	****
	61	*******	*****	****
	62	*******	*****	****
	63	*******	*****	****
	64	*******	*****	****
	65	*******	*****	****
	66	*******	*****	****
	67	*******	****	****
	68	*******	****	****

Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	69	*******	****	****
	70	*******	****	****
	71	*******	*****	****
	72	******	****	****
	73	*******	****	****
	74	*******	****	*****
	75	*******	****	****
	76	*******	****	****
	77	*******	******	*****
	78	*******	******	*****

Structure	Example No.	Falcipain-2	Falcipain-3	Whole cell
	79	*******	****	****
	80	*******	****	*****
	comparative 81	****	***	*
	comparative 82	*******	****	*

Key to Table

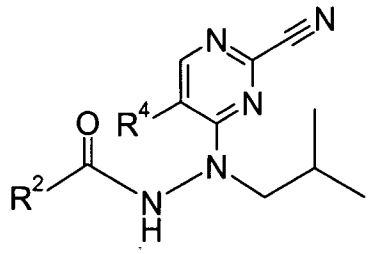
$X = IC_{50}$ in nM

X<1	*******
1<X<2.5	******
2.5<X<15	*****
15<X<150	****
150<X<250	***
250<X<400	**
X≥400	*

The exemplified compounds of the invention exhibit an improved activity in the whole cell assay, as compared with comparative Examples 81 and 82 of the prior art.

Claims

1. At least one chemical entity selected from a compound of Formula I:



I

Wherein:

R^4 represents halogen;

R^2 represents

i) -phenyl-C_{1-3}alkylene-X, -pyridyl-phenyl-C_{1-3}alkylene-X or -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3; or

ii) -Y-C_{1-3}alkylene-X or -Y-C_{1-3}alkylene-X-R^J;

Y represents an aromatic group comprising a 5-membered ring having one to four heteroatoms selected from N, O and S, the ring being optionally fused to a phenyl ring;

R^J represents Z, -C_{1-4}alkylene-Z or -C(O)Z;

X and Z independently represent:

i) a monocyclic 4-membered, saturated hydrocarbon group containing one nitrogen atom;

ii) a monocyclic 5-membered, saturated or partially saturated hydrocarbon group containing one nitrogen atom; or

iii) a monocyclic 6-membered, saturated, partially saturated or aromatic hydrocarbon group containing one or two nitrogen atoms and optionally an oxygen atom;

wherein X and Z are independently optionally substituted with a) one group selected from: C_{1-4}alkyl, C_{1-4}alkylOH, -C_{1-4}alkylOC_{1-4}alkylOH, OH, -C_{1-4}alkylC(O)OC_{1-4}alkyl, -C(O)OC_{1-4}alkyl, NR^ER^F, -C_{1-4}alkylNR^ER^F, -NC(O)C_{1-3}alkyl, -NC(O)OC_{1-4}alkyl and -C(O)NR^ER^F and b) optionally an additional group which is C_{1-4}alkyl;

R^E and R^F independently represent hydrogen or C_{1-4}alkyl or C_{1-4}alkenyl;

and pharmaceutically acceptable derivatives thereof.

2. At least one chemical entity according to claim 1 wherein R^4 represents chlorine, bromine or iodine.

3. At least one chemical entity according to claim 1 or claim 2 wherein R^2 represents -phenyl-C_{1-3}alkylene-X, -pyridyl-phenyl-C_{1-3}alkylene-X or -phenyl-C_{1-3}alkylene-X-R^J, wherein phenyl is optionally substituted with one group selected from halogen or CF_3.

4. At least one chemical entity according to claim 1 or claim 2 wherein R^2 represents -Y-C_{1-3}alkylene-X or -Y-C_{1-3}alkylene-X-R^J.

5. At least one chemical entity according to any one of claims 1, 2 or 4 wherein Y represents furan, thiophene, isoxazole or benzofuran.

6. At least one chemical entity according to any one of claims 1 to 5 wherein the alkylene group or groups in R^2 is methylene.

7. At least one chemical entity according to any one of claims 1 to 6 wherein R^J represents -C_{1-3}alkylene-Z.

8. At least one chemical entity according to any one of claims 1 to 7 wherein X and Z independently represent an optionally substituted monocyclic 6-membered, saturated, partially saturated or aromatic hydrocarbon group containing one or two nitrogen atoms and optionally an oxygen atom.

9. At least one chemical entity selected from:
N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide;
4-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-piperidinylmethyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-pyrrolidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(2,6-dimethyl-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
ethyl 1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-4-piperidinecarboxylate;
N-{(3R)-1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-pyrrolidinyl}acetamide;
1,1-dimethylethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-pyrrolidinyl}carbamate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(4-{2-[(2-hydroxyethyl)oxy]ethyl}-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-piperidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[(2R)-2-(hydroxymethyl)-1-pyrrolidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-pyrrolidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-(2,5-dihydro-1H-pyrrol-1-ylmethyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(2,5-dimethyl-2,5-dihydro-1H-pyrrol-1-yl)methyl]-N'-(2-methylpropyl)benzohydrazide;
1,1-dimethylethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-4-piperidinyl}carbamate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(dimethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[3-(4-morpholinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(diethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(dipropylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(di-2-propen-1-ylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[(1-methyl-4-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(1-methyl-4-piperidinyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
ethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-piperidinyl}acetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(diethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(di-2-propen-1-ylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(dipropylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-[(2,6-dimethyl-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
3-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-(1-piperidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[3-(dipropylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[3-(diethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(4-hydroxy-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-N,N-dimethyl-L-prolinamide;
4-(1-azetidinylmethyl)-N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[(2S)-2-(1-pyrrolidinylcarbonyl)-1-pyrrolidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[(1-methyl-3-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(diethylamino)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-pyridinyl)-1-piperazinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(dimethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-(1-pyrrolidinylmethyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(diethylamino)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[2-(diethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(1-methyl-4-piperidinyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[3-(4-morpholinyl)propyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[(1-methyl-4-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
3-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)benzohydrazide;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-3-isoxazolecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-7-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-1-benzofuran-2-carbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-2-furancarbohydrazide 4-methylbenzenesulfonate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-6-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-6-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-1-benzofuran-2-carbohydrazide;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-2-thiophenecarbohydrazide;
and pharmaceutically acceptable derivatives thereof.

10. At least one chemical entity selected from:
N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate;

N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-[(4-propyl-1-piperazinyl)methyl]benzohydrazide trifluoroacetate;
4-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-piperidinylmethyl)benzohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-pyrrolidinylmethyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(2,6-dimethyl-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
ethyl 1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-4-piperidinecarboxylate trifluoroacetate;
N-{(3R)-1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-pyrrolidinyl}acetamide trifluoroacetate;
1,1-dimethylethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-pyrrolidinyl}carbamate trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(4-{2-[(2-hydroxyethyl)oxy]ethyl}-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-piperidinylmethyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[(2R)-2-(hydroxymethyl)-1-pyrrolidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-(1-pyrrolidinylmethyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-(2,5-dihydro-1H-pyrrol-1-ylmethyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(2,5-dimethyl-2,5-dihydro-1H-pyrrol-1-yl)methyl]-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
1,1-dimethylethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-4-piperidinyl}carbamate trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(dimethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[3-(4-morpholinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(diethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(dipropylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[3-(di-2-propen-1-ylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[(1-methyl-4-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(1-methyl-4-piperidinyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
ethyl {1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-3-piperidinyl}acetate trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(diethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(di-2-propen-1-ylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(dipropylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-[(2,6-dimethyl-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
3-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-(1-piperidinylmethyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[3-(dipropylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[3-(diethylamino)propyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-[(4-hydroxy-1-piperidinyl)methyl]-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
1-[(4-{[2-(5-chloro-2-cyano-4-pyrimidinyl)-2-(2-methylpropyl)hydrazino]carbonyl}phenyl)methyl]-N,N-dimethyl-L-prolinamide trifluoroacetate;
4-(1-azetidinylmethyl)-N'-(5-bromo-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[(2S)-2-(1-pyrrolidinylcarbonyl)-1-pyrrolidinyl]methyl}benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide trifluoroacetate;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[(1-methyl-3-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(diethylamino)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-{[4-(4-pyridinyl)-1-piperazinyl]methyl}benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-4-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-({4-[2-(dimethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-(1-pyrrolidinylmethyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[3-(1-piperidinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(diethylamino)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[2-(diethylamino)ethyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-{[4-(1-methyl-4-piperidinyl)-1-piperazinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[3-(4-morpholinyl)propyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[2-(1-pyrrolidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-3-({4-[(1-methyl-4-piperidinyl)methyl]-1-piperazinyl}methyl)-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;

N'-(5-chloro-2-cyano-4-pyrimidinyl)-N'-(2-methylpropyl)-3-({4-[2-(1-piperidinyl)ethyl]-1-piperazinyl}methyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)-3-{[4-(4-morpholinyl)-1-piperidinyl]methyl}benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-{[4-(hydroxymethyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
3-(1,4'-bipiperidin-1'-ylmethyl)-N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-chloro-2-cyano-4-pyrimidinyl)-4-fluoro-3-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-4-{[4-(4-methyl-1-piperazinyl)-1-piperidinyl]methyl}-N'-(2-methylpropyl)benzohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-3-isoxazolecarbohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-7-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-1-benzofuran-2-carbohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-2-furancarbohydrazide 4-methylbenzenesulfonate trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-6-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-6-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-{4-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-{3-[(4-methyl-1-piperazinyl)methyl]phenyl}-N'-(2-methylpropyl)-3-pyridinecarbohydrazide trifluoroacetate;
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-1-benzofuran-2-carbohydrazide trifluoroacetate;
and
N'-(5-bromo-2-cyano-4-pyrimidinyl)-5-[(4-methyl-1-piperazinyl)methyl]-N'-(2-methylpropyl)-2-thiophenecarbohydrazide trifluoroacetate.

11. At least one chemical entity according to according to any one of claims 1 to 10 for use in medical therapy.

12. Use of at least one chemical entity according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment of a condition susceptible to mediation by a cysteine protease inhibitor.

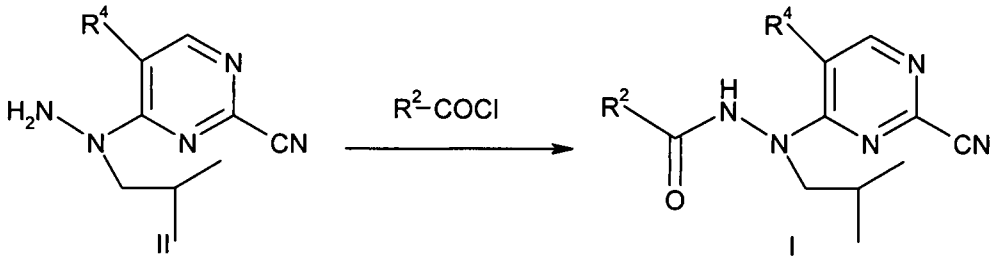
13. Use of at least one chemical entity according to any one of claims 1 to 10 in the manufacture of a medicament for the treatment of malaria.

14. A method for the treatment of a human or animal subject suffering from a condition susceptible to mediation by a cysteine protease inhibitor, comprising administering to said human or animal subject an effective amount of at least one chemical entity according to any one of claims 1 to 10.

15. A method for the treatment of a human or animal subject suffering from malaria, comprising administering to said human or animal subject an effective amount of at least one chemical entity according to any one of claims 1 to 10.

16. A pharmaceutical composition comprising at least one chemical entity according to any one of claims 1 to 10 in admixture with one or more pharmaceutically acceptable carrier and/or excipient.

17. A process for the preparation of compounds of Formula I as defined in claim 1, from a reaction between compounds of Formula II, wherein R^4 is as defined in claim 1 for Formula I, and compounds of Formula R^2COCl, wherein R^2 is as defined in claim 1 for Formula I, according to the Scheme below.



18. A process for the preparation of compounds of Formula I as defined in claim 1, from the corresponding acylhydrazide compounds of Formula XII, wherein R^4 is as defined in claim 1 for Formula I and R^X is -arylhaloC_{1-3}alkylene or -heteroaryl-arylhaloC_{1-3}alkylene, by reaction with compounds of Formula XIII, which compounds are heterocyclyl or heterocyclyl-R^J, for example compounds XIII are "X" or "X-R^{Jn}", wherein "X" and "R^{Jn}" are as defined in claim 1 for Formula I, as depicted in the Scheme below.