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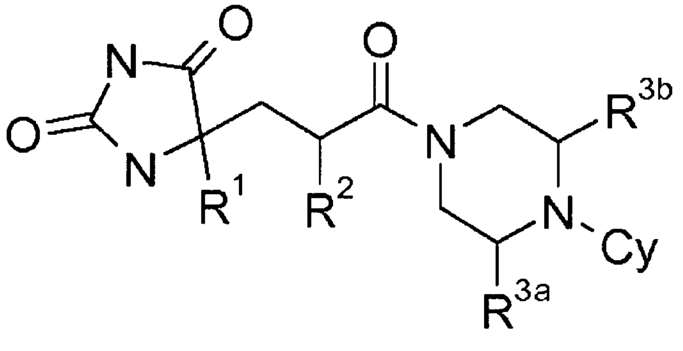
(54) Title: 5-[(PIPERAZIN-1-YL)-3-OXO-PROPYL]-IMIDAZOLIDINE-2,4-DIONE DERIVATIVES AS ADAMTS INHIBITORS FOR THE TREATMENT OF OSTEOARTHRITIS



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(57) **Abstract**: The present invention discloses compounds according to Formula (I), wherein R, R^2, R^{3a}, R^{3b}, and Cy are as defined herein. The present invention discloses compounds inhibiting ADAMTS, methods for their production, pharmaceutical compositions comprising the same and methods for the prophylaxis and/or treatment of inflammatory conditions and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

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5-[(PIPERAZIN-1-YL)-3-OXO-PROPYL]-IMIDAZOLIDINE-2,4-DIONE DERIVATIVES AS ADAMTS INHIBITORS FOR THE TREATMENT OF OSTEOARTHRITIS

FIELD OF THE INVENTION

[0001] The present invention relates to hydantoin compounds, and their use in the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In a particular aspect, the present compounds are ADAMTS inhibitors, and more particularly ADAMTS-5. The present invention also provides methods for the production of a compound of the invention, pharmaceutical compositions comprising a compound of the invention, methods for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis by administering a compound of the invention.

BACKGROUND OF THE INVENTION

[0002] Cartilage is an avascular tissue of which chondrocytes are the main cellular component. One of the functional roles of cartilage in the joint is to allow bones to articulate on each other smoothly. Loss of articular cartilage, therefore, causes the bones to rub against each other leading to pain and loss of mobility, and is the hallmark of various diseases, among which rheumatoid arthritis and osteoarthritis are the most prominent.

[0003] The chondrocytes in normal articular cartilage occupy approximately 5% of the tissue volume, while the extra-cellular matrix makes up the remaining 95% of the tissue. The chondrocytes secrete the components of the matrix, mainly proteoglycans (including aggrecan) and collagens, which in turn supply the chondrocytes with an environment suitable for their survival under mechanical stress. Collagen type II, together with collagen type IX, is arranged in solid fibril-like structures, and provides cartilage with high mechanical strength properties, whereas aggrecan and other proteoglycans can absorb water and provide the resilient and shock-absorbing properties of the cartilage.

[0004] Under physiological conditions, cartilage homeostasis is maintained by a balance between the production (anabolism) and degradation (catabolism) of aggrecan and collagen. However, in OA and other joint disorders, this balance shifts toward catabolism. Loss of aggrecan occurs early in the onset of cartilage destruction, initially at the joint surface then spreading more deeply at more advanced stages (Pond and Nuki, 1973).

[0005] Osteoarthritis (also referred to as OA, or wear-and-tear arthritis) is the most common form of arthritis and is characterized by loss of articular cartilage, often associated with the subchondral bone remodelling and pain. The disease mainly affects hands, spine and weight-bearing joints such as knees, and hips. During the disease process, the cartilage progressively deteriorates, which can be graded. At more advanced stages, the deeper layers of cartilage are affected, leading to calcification and exposure of the subchondral bone (Wieland et al., 2005).

[0006] The clinical manifestations of the development of the osteoarthritis condition include: increased volume of the joint, pain, crepitation and functional disability that lead to pain and reduced mobility of the joints. When disease further develops, pain at rest emerges. If the condition persists without correction and/or therapy, the joint is destroyed leading to disability.

[0007] Osteoarthritis is difficult to treat. At present, no cure is available and treatment focuses on relieving pain and preventing the affected joint from becoming deformed. Common treatments are currently limited to steroidal and non-steroidal anti-inflammatory drugs (NSAIDS), which provide symptomatic relief for pain and inflammation but do not arrest or slow down the progression of the disease (Mobasheri, 2013).

[0008] Therapeutic methods for the correction of the articular cartilage lesions that appear during the osteoarthritic disease have been developed, but so far none of them have been able to slow down the disease progression or to promote the regeneration of articular cartilage *in situ* and *in vivo*.

[0009] Although some dietary supplements as chondroitin and glucosamine sulfate have been advocated as safe and effective options for the treatment of osteoarthritis, a clinical trial revealed that both treatments did not reduce pain associated to osteoarthritis (Clegg et al., 2006).

[0010] In severe cases, joint replacement may be necessary. This is especially true for hips and knees. If a joint is extremely painful and cannot be replaced, it may be fused. This procedure stops the pain, but results in the permanent loss of joint function, making walking and bending difficult.

[0011] Another possible treatment is the transplantation of cultured autologous chondrocytes. Here chondral cellular material is taken from the patient, sent to a laboratory where it is expanded. The material is then implanted in the damaged tissues to cover the tissue's defects.

[0012] Yet another treatment includes the intra-articular instillation of Hylan G-F 20 (Synvisc, Hyalgan, Artz etc.), a substance that improves temporarily the rheology of the synovial fluid, producing an almost immediate sensation of free movement and a marked reduction of pain.

[0013] Other methods include application of tendinous, periosteal, facial, muscular or perichondral grafts; implantation of fibrin or cultured chondrocytes; implantation of synthetic matrices, such as collagen, carbon fiber; and administration of electromagnetic fields. All of these have reported minimal and incomplete effects, resulting in a poor quality tissue that can neither support the weighted load nor allow the restoration of an articular function with normal movement.

[0014] The ADAMTS family of secreted zinc metalloproteinases includes nineteen members that are known to bind and degrade extra cartilage matrix (ECM) components (Shiomi et al., 2010). Several members of the ADAMTS family have been found to cleave aggrecan, the major proteoglycan component of cartilage: ADAMTS-1, -4, -5, -8, -9, -15, -16 and -18. Since the expression and/or aggrecanase degrading activity of ADAMTS-1, -8, -9, -15, -16 and -18 are quite low, ADAMTS-4 (aggrecanase-1) and ADAMTS-5 (aggrecanase-2) are believed to be the two major functional aggrecanases (Tortorella and Malfait, 2008).

[0015] ADAMTS-5 was identified in 1999 (Abbaszade et al., 1999). In 2005 two independent groups identified ADAMTS-5 as the principal aggrecanase in mouse cartilage (Glasson et al., 2005; Stanton et al., 2005). Proteolysis of aggrecan by ADAMTS-5 occurs at different sites: however cleavage at the Glu373-Ala374 bond (aggrecan IGD) is likely more important in the pathogenesis of osteoarthritis and inflammatory arthritis since a loss of integrity at this bond results in the loss of an entire aggrecan molecule, which is highly detrimental to cartilage integrity and function (Little et al., 2007).

[0016] Studies in genetically engineered mouse models (GeMMs) have demonstrated that ADAMTS-5 ablation protects against cartilage damage and aggrecan loss after osteoarthritis induction through surgical instability of the medial meniscus (DMM) (Glasson et al., 2005). Moreover in the DMM model ADAMTS-5 knock-out mice showed reduced subchondral bone changes (Botter et al., 2009) and did not develop osteoarthritis-associated mechanical allodynia (Malfait et al., 2010). Besides preclinical evidence, clinical evidence also indicates the importance of and interest in ADAMTS-5 as a target for osteoarthritis. Recently, studies with an antibody targeting ADAMTS-5 (Chiusaroli et al., 2013) have been reported. ELISA's have been developed allowing the measurement of aggrecanase-derived cartilage neo-epitope levels in the synovial fluid as well as blood from rodents to human. This method revealed increased levels of ADAMTS-5 derived neo-epitope levels in the joints of rats in which cartilage degradation was induced by meniscal tear as well as in joints of osteoarthritis patients, thereby providing further translational evidence for the importance of this protease in the development of osteoarthritis (Chockalingam et al., 2011; Larsson et al., 2014).

[0017] These findings provide strong evidence for a central role of ADAMTS-5 in osteoarthritis pathology as a key target and an ADAMTS-5 inhibitor capable to reach the joint cartilage at sufficient levels is expected to exert a protective effect on cartilage in osteoarthritic patients.

[0018] Matrix metalloproteinases (MMPs) constitute another family of 23 zinc metalloproteinases with many structural elements in common with ADAMTS family members (Georgiadis and Yiotakis, 2008). Clinical studies on broad spectrum MMP inhibitors in oncology revealed that inhibition of particular MMPs was associated with poorer prognosis and undesirable side effects. In particular, MMP8 and MMP12 have been categorized as antitargets based on *in vivo* animal studies (Dufour and Overall, 2013). Therefore, there is a need for selective ADAMTS, and in particular ADAMTS-5 inhibitors without affecting the activity of structurally related MMPs, and more particularly MMP-8 and -12.

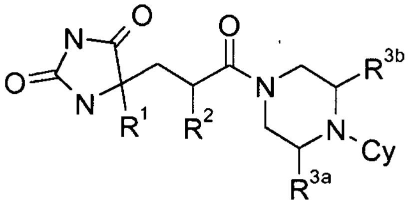
[0019] Therefore the identification of novel inhibitors of ADAMTS, in particular ADAMTS-5, could provide desirable tools for the prophylaxis and/or treatment of diseases involving cartilage degradation, in particular osteoarthritis, and/or rheumatoid arthritis.

[0020] It is therefore an object of the present invention to provide compounds and their use in the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In particular the compounds of the present invention are inhibitors of ADAMTS, and more particularly ADAMTS-5.

SUMMARY OF THE INVENTION

[0021] The present invention is based on the identification of novel hydantoin compounds that may be useful for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In a particular aspect, the compounds of the invention are inhibitors of ADAMTS-5. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for treating inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis by administering the compounds of the invention.

[0022] Accordingly, in a first aspect of the invention, a compound of the invention is provided having a Formula (I):



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wherein

R^1 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^4 groups,
- C_{3-7} monocyclic cycloalkyl optionally substituted with one or more independently selected R^4 groups,
- 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl,
- phenyl optionally substituted with one or more independently selected R^5 groups,
- phenyl fused to a 5-6 membered monocyclic heterocycloalkyl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, which heterocycloalkyl is optionally substituted with one or more =O, or
- 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^5 groups;

R^2 is independently selected from:

- H,
- OH,
- C_{1-4} alkoxy, and

- C_{1-4} alkyl optionally substituted with one
  - OH,
  - CN,
  - C_{1-4} alkoxy optionally substituted with one phenyl, or
  - 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl;

each R^{3a}, and R^{3b} is independently selected from:

- H, and
- C_{1-4} alkyl;

Cy is

- 6-10 membered monocyclic or fused bicyclic aryl optionally substituted with one or more independently selected R^6 groups,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^6 groups;

R^4 is

- halo,
- OH,
- CN,
- C_{1-4} alkyl,
- C_{1-4} alkoxy optionally substituted with one C_{1-4} alkoxy, or phenyl,
- C_{1-4} thioalkoxy,
- 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, optionally substituted with one or more independently selected halo, or $-C(=O)OC_{1-4}$ alkyl,
- phenyl,
- $-S(=O)_2C_{1-4}$ alkyl,
- $-C(=O)OR^{7a}$,
- $-C(=O)NR^{7b}R^{7c}$,
- $-NHC(=O)OR^{7d}$,
- $-NHC(=O)R^{7e}$, or
- $-NR^{8a}R^{8b}$;

each R^5 is

- halo,
- OH,
- CN,

- C_{1-4} alkyl optionally substituted with one or more independently selected halo, $-NR^{9a}R^{9b}$, or $-C(=O)NR^{9c}R^{9d}$,
- C_{1-4} alkoxy optionally substituted with one $-NR^{9e}R^{9f}$, or
- $-S(=O)_2C_{1-4}$ alkyl;

each R^6 is

- halo,
- -CN,
- $-NO_2$,
- $-CH_3$,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or
- $-NR^{9g}R^{9h}$;

each R^{7a}, R^{7b}, R^{7c}, R^{7d}, or R^{7e} is

- H, or
- C_{1-4} alkyl optionally substituted with one OH, C_{1-4} alkoxy;

each R^{8a}, or R^{8b} is independently selected from

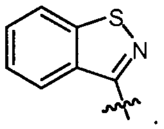
- H, and
- C_{1-4} alkyl optionally substituted with one or more independently selected OH, C_{1-4} alkoxy, or phenyl;

each R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, and R^{9h} is independently selected from H, and C_{1-4} alkyl;

or a pharmaceutically acceptable salt, or a solvate, or a pharmaceutically acceptable salt of a solvate thereof;

provided that:

- R^1 and R^2 are not simultaneously H, and
- when R^1 is Me, then Cy is not



[0023] In a particular aspect, the compounds of the invention may exhibit selectivity towards the ADAMTS protease family, in particular towards the ADAMTS-5. In a further particular aspect, the compounds of the invention may show low activity on MMP family members, in particular MMP8 and/or MMP12. Such selectivity may result in improved drug safety and/or reduce off-target associated risks. In another more particular embodiment, the compounds of the invention surprisingly exhibit activity against ADAMTS-5 compared to structurally related close analogues.

[0024] In a further aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. In a particular aspect, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the invention. In a more particular aspect, the further therapeutically active ingredient is an agent for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

[0025] Moreover, the compounds of the invention, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0026] In a further aspect of the invention, this invention provides a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the invention as described herein.

[0027] The present invention also provides pharmaceutical compositions comprising a compound of the invention, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular aspect, the pharmaceutical composition is for use in the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

[0028] In a particular aspect, the compounds of the invention are provided for use in the prophylaxis and/or treatment of osteoarthritis.

[0029] In additional aspects, this invention provides methods for synthesizing the compounds of the invention, with representative synthetic protocols and pathways disclosed later on herein.

[0030] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0031] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0032] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0033] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein.

[0034] The articles “a” and “an” may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example “an analogue” means one analogue or more than one analogue.

[0035] ‘Alkyl’ means straight or branched aliphatic hydrocarbon with the number of carbon atoms specified. Particular alkyl groups have 1 to 8 carbon atoms. More particular is lower alkyl which has 1 to 6 carbon atoms. A further particular group has 1 to 4 carbon atoms. Exemplary straight chained groups include methyl, ethyl n-propyl, and n-butyl. Branched means that one or more lower alkyl groups such as methyl, ethyl, propyl or butyl is attached to a linear alkyl chain, exemplary branched chain groups include isopropyl, iso-butyl, t-butyl and isoamyl.

[0036] ‘Alkoxy’ refers to the group $-OR^{20}$ where R^{20} is alkyl with the number of carbon atoms specified. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0037] ‘Alkylene’ refers to divalent alkene radical groups having the number of carbon atoms specified, in particular having 1 to 6 carbon atoms and more particularly 1 to 4 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), or $-CH(CH_3)-$ and the like.

[0038] ‘Alkenyl’ refers to monovalent olefinically (unsaturated) hydrocarbon groups with the number of carbon atoms specified. Particular alkenyl has 2 to 8 carbon atoms, and more particularly, from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. Particular alkenyl groups include ethenyl ($-CH=CH_2$), n-propenyl ($-CH_2CH=CH_2$), isopropenyl ($-C(CH_3)=CH_2$) and the like.

[0039] ‘Amino’ refers to the radical $-NH_2$.

[0040] ‘Aryl’ refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an aromatic ring structure, monocyclic or polycyclic, with the number of ring atoms specified. Specifically, the term includes groups that include from 6 to 10 ring members. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Particularly aryl groups include phenyl, and naphthyl.

[0041] ‘Cycloalkyl’refers to a non-aromatic hydrocarbyl ring structure, monocyclic or polycyclic, with the number of ring atoms specified. A cycloalkyl may have from 3 to 10 carbon atoms, and in particular from 3 to 7 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0042] ‘Cyano’ refers to the radical -CN.

[0043] ‘Halo’ or ‘halogen’ refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

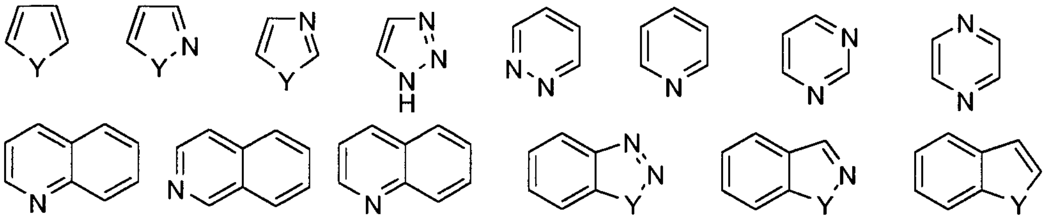
[0044] ‘Hetero’ when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, *e.g.* heteroalkyl, cycloalkyl, *e.g.* heterocycloalkyl, aryl, *e.g.* heteroaryl, and the like having from 1 to 4, and particularly from 1, 2 or 3 heteroatoms, more typically 1 or 2 heteroatoms, for example a single heteroatom.

[0045] ‘Heteroaryl’ means an aromatic ring structure, monocyclic or fused polycyclic, that includes one or more heteroatoms independently selected from O, N and S and the number of ring atoms specified. In particular, the aromatic ring structure may have from 5 to 9 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a fused bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

[0046] Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrolyl, furanyl, thiophenyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

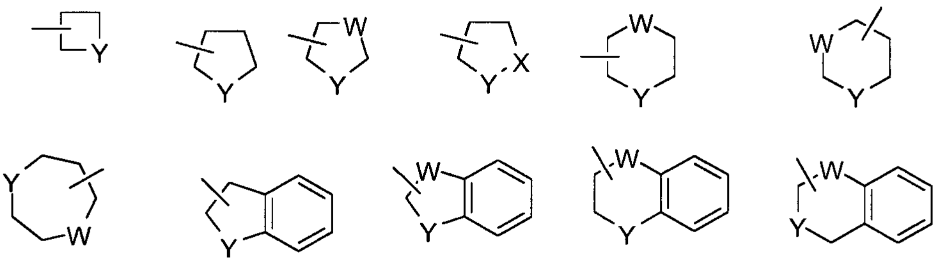
[0047] Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five-membered ring include but are not limited to imidazothiazolyl and imidazoimidazolyl. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuranyl, benzthiophenyl, benzimidazolyl, benzoxazolyl, isobenzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indolizinyl, purinyl (*e.g.* adenine, guanine), indazolyl, pyrazolopyrimidinyl, triazolopyrimidinyl, and pyrazolopyridinyl groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinolinyl, isoquinolinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, and pteridinyl groups. Particular heteroaryl groups are those derived from thiophenyl, pyrrolyl, benzothiophenyl, benzofuranyl, indolyl, pyridinyl, quinolinyl, imidazolyl, oxazolyl and pyrazinyl.

[0048] Examples of representative heteroaryls include the following:



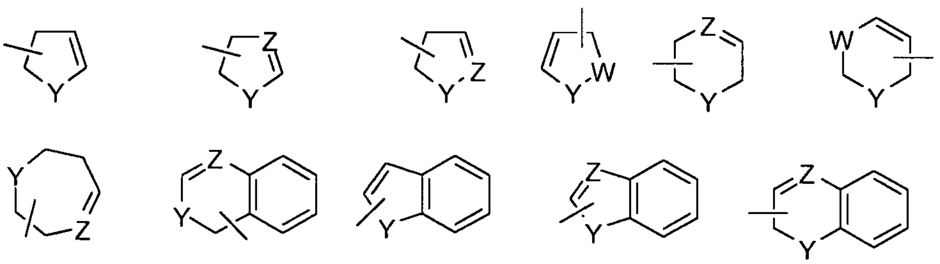
wherein each Y is selected from >C(=O), NH, O and S.

[0049] As used herein, the term 'heterocycloalkyl' means a stable non-aromatic ring structure, mono-cyclic or polycyclic, that includes one or more heteroatoms independently selected from O, N and S and the number of ring atoms specified. The non-aromatic ring structure may have from 4 to 10 ring members, and in particular from 4 to 7 ring members. A fused heterocyclic ring system may include carbocyclic rings and need only to include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran, , tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidone, piperazone, and N-alkyl piperidines such as N-methyl piperidine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:



wherein each W is selected from CH_2, NH, O and S; and each Y is selected from NH, O, C(=O), SO_2, and S.

[0050] As used herein, the term 'heterocycloalkenyl' means a 'heterocycloalkyl, wherein one bond of the ring is reduced, thus the ring comprises a double bond. Particular examples of heterocycloalkenyl groups are shown in the following illustrative examples:



wherein each Z is =CH- or =N-; W is selected from $-CH_2-$, -NH-, -O- and –S-; and each Y is selected from –NH-, -O-, -C(=O)-, $-SO_2-$, and –S-.

[0051] 'Hydroxyl' refers to the radical -OH.

[0052] 'Oxo' refers to the radical =O.

[0053] 'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).

[0054] 'Sulfo' or 'sulfonic acid' refers to a radical such as $-SO_3H$.

[0055] 'Thiol' refers to the group -SH.

[0056] As used herein, term 'substituted with one or more' refers to one to four substituents. In one embodiment it refers to one to three substituents. In further embodiments it refers to one or two substituents. In a yet further embodiment it refers to one substituent.

[0057] 'Thioalkoxy' refers to the group $-SR^{20}$ where R^{20} has the number of carbon atoms specified and particularlyC_1-C_8 alkyl. Particular thioalkoxy groups are thiomethoxy, thioethoxy, n-thiopropoxy, isothiopropoxy, n-thiobutoxy, tert-thiobutoxy, sec-thiobutoxy, n-thiopentoxy, n-thiohexoxy, and 1,2-dimethylthiobutoxy. Particular thioalkoxy groups are lower thioalkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0058] One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

[0059] 'Pharmaceutically acceptable' means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0060] 'Pharmaceutically acceptable salt' refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.* an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term 'pharmaceutically acceptable cation' refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

[0061] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[0062] 'Prodrugs' refers to compounds, including derivatives of the compounds of the invention,which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0063] 'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared *e.g.* in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 'Solvate' encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0064] 'Subject' includes humans. The terms 'human', 'patient' and 'subject' are used interchangeably herein.

[0065] 'Effective amount' means the amount of a compound of the invention that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The "effective amount" can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[0066] 'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease or disorder (*i.e.* causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset.

[0067] The term 'prophylaxis' is related to 'prevention', and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0068] 'Treating' or 'treatment' of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (*i.e.* arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment 'treating' or 'treatment' refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, 'treating' or 'treatment' refers to modulating the disease or disorder, either physically, (*e.g.* stabilization of a discernible symptom), physiologically, (*e.g.* stabilization of a physical parameter), or both. In a further embodiment, "treating" or "treatment" relates to slowing the progression of the disease.

[0069] As used herein the term 'inflammatory diseases' refers to the group of conditions including rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, allergic airway disease (*e.g.* asthma, rhinitis), chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases (*e.g.* Crohn's disease, ulcerative colitis), endotoxin-driven disease states (*e.g.* complications after bypass surgery or chronic endotoxin states contributing to *e.g.* chronic cardiac failure), and related diseases involving cartilage, such as that of the joints. Particularly the term refers to rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma), chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases. More particularly the term refers to rheumatoid arthritis, and osteoarthritis (OA). Most particularly the term refers to osteoarthritis (OA).

[0070] As used herein the term 'diseases involving degradation of cartilage and/or disruption of cartilage homeostasis' includes conditions such as osteoarthritis, psoriatic arthritis, juvenile rheumatoid arthritis, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, achondroplasia, Paget's disease, Tietze syndrome or costal chondritis, fibromyalgia, osteochondritis, neurogenic or neuropathic arthritis, arthropathy, sarcoidosis, amylosis, hydarthrosis, periodical disease, rheumatoid spondylitis, endemic forms of arthritis like osteoarthritis deformans endemica, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis. More particularly, the term refers to osteoarthritis (OA).

[0071] 'Compound(s) of the invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as herein described, which expression includes the pharmaceutically acceptable salts, and the solvates, *e.g.* hydrates, and the solvates of the pharmaceutically acceptable salts where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0072] When ranges are referred to herein, for example but without limitation, C_{1-8} alkyl, the citation of a range should be considered a representation of each member of said range.

[0073] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (Bundgaard, 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particularly useful prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particular such prodrugs are the C_{1-8} alkyl, C_{2-8} alkenyl, C_{6-10} optionally substituted aryl, and (C_{6-10} aryl)-(C_{1-4} alkyl) esters of the compounds of the invention.

[0074] As used herein, the term ‘isotopic variant’ refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an ‘isotopic variant’ of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0075] All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[0076] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed ‘isomers’. Isomers that differ in the arrangement of their atoms in space are termed ‘stereoisomers’.

[0077] Stereoisomers that are not mirror images of one another are termed ‘diastereomers’ and those that are non-superimposable mirror images of each other are termed ‘enantiomers’. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.* as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a ‘racemic mixture’.

[0078] ‘Tautomers’ refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base.

Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

[0079] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0080] The compounds of the invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

[0081] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

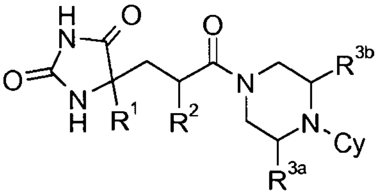
[0082] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

THE INVENTION

[0083] The present invention is based on the identification of novel hydantoin compounds that may be useful for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In a particular aspect, the compounds of the invention are inhibitors of ADAMTS-5.

[0084] The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis by administering the compounds of the invention.

[0085] Accordingly, in a first aspect of the invention, acompound of the invention is provided having a Formula (I):



I

wherein

R^1 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^4 groups,
- C_{3-7} monocyclic cycloalkyl optionally substituted with one or more independently selected R^4 groups,

- 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl,
- phenyl optionally substituted with one or more independently selected R^5 groups,
- phenyl fused to a 5-6 membered monocyclic heterocycloalkyl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, which heterocycloalkyl is optionally substituted with one or more =O, or
- 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^5 groups;

R^2 is independently selected from:

- H,
- OH,
- C_{1-4} alkoxy, and
- C_{1-4} alkyl optionally substituted with one
  - OH,
  - CN,
  - C_{1-4} alkoxy optionally substituted with one phenyl, or
  - 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl;

each R^{3a}, and R^{3b} is independently selected from:

- H, and
- C_{1-4} alkyl;

Cy is

- 6-10 membered monocyclic or fused bicyclic aryl optionally substituted with one or more independently selected R^6 groups,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^6 groups;

R^4 is

- halo,
- OH,
- CN,
- C_{1-4} alkyl,
- C_{1-4} alkoxy optionally substituted with one C_{1-4} alkoxy or phenyl,
- C_{1-4} thioalkoxy,

- 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, optionally substituted with one or more independently selected halo or -C(=O)OC$_{1-4}$ alkyl,
- phenyl,
- -S(=O)$_2$C$_{1-4}$ alkyl,
- -C(=O)OR^{7a},
- -C(=O)NR^{7b}R^{7c},
- -NHC(=O)OR^{7d},
- -NHC(=O)R^{7e}, or
- -NR^{8a}R^{8b};

each R^5 is

- halo,
- OH,
- CN,
- C$_{1-4}$ alkyl optionally substituted with one or more independently selected halo, -NR^{9a}R^{9b}, or -C(=O)NR^{9c}R^{9d},
- C$_{1-4}$ alkoxy optionally substituted with one -NR^{9e}R^{9f}, or
- –S(=O)$_2$C$_{1-4}$ alkyl;

each R^6 is

- halo,
- -CN,
- -NO$_2$,
- -CH$_3$,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected halo, C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, or
- -NR^{9g}R^{9h};

each R^{7a}, R^{7b}, R^{7c}, R^{7d}, or R^{7e} is

- H, or
- C$_{1-4}$ alkyl optionally substituted with one OH, or C$_{1-4}$ alkoxy;

each R^{8a} or R^{8b} is independently selected from:

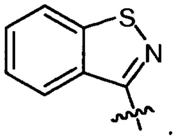
- H, and
- C$_{1-4}$ alkyl optionally substituted with one or more independently selected OH, C$_{1-4}$ alkoxy, or phenyl;

each R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, and R^{9h} is independently selected from H, and C$_{1-4}$ alkyl;

or a pharmaceutically acceptable salt, or a solvate, or a pharmaceutically acceptable salt of a solvate thereof; or a biologically active metabolite thereof;

provided that:

- R^1, and R^2 are not simultaneously H, and
- When R^1 is Me, then Cy is not



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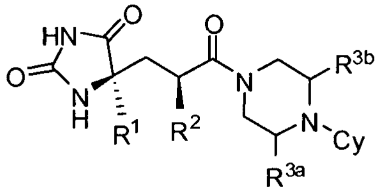
[0086] In one embodiment, a compound of the invention is according to Formula II:



II

wherein R^1, R^2, R^{3a}, R^{3b}, and Cy are as defined above.

[0087] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is H.

[0088] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is C_{1-4} alkyl. In a particular embodiment, R^1 is Me, Et, Pr, iPr, or tBu. In a more particular embodiment, R^1 is Me, or Et.

[0089] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is C_{1-4} alkyl substituted with one or more independently selected R^4 groups. In another embodiment, R^1 is Me, or Et, each of which is substituted with one or more independently selected R^4 groups. In a particular embodiment, R^1 is C_{1-4} alkyl substituted with one, two or three independently selected R^4 groups. In another particular embodiment, R^1 is Me, or Et, each of which is substituted with one, two or three independently selected R^4 groups. In a more particular embodiment, R^1 is C_{1-4} alkyl substituted with one R^4 group. In another more particular embodiment, R^1 is Me, or Et, each of which is substituted with one R^4 group.

[0090] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is C_{3-7} monocyclic cycloalkyl. In a particular embodiment, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In a more particular embodiment, R^1 is cyclopropyl.

[0091] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is C_{3-7} monocyclic cycloalkyl substituted with one or more independently selected R^4 groups. In another embodiment, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is substituted with one or more independently selected R^4 groups. In a particular embodiment, R^1 is C_{3-7} monocyclic cycloalkyl substituted with one, two or three independently selected R^4 groups. In another particular embodiment, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is substituted with one, two or three independently selected R^4 groups. In a more particular embodiment, R^1 is C_{3-7} monocyclic cycloalkyl substituted with one R^4 group. In another more particular embodiment, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is substituted with one R^4 group.

[0092] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is halo, OH, and CN. In a more particular embodiment, each R^4 is independently selected from F, Cl, OH, and CN.

[0093] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is C_{1-4} alkyl. In a particular embodiment, R^4 is $-CH_3$, $-CH_2CH_3$, or $-CH(CH_3)_2$. In a more particular embodiment, R^4 is $-CH_3$.

[0094] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is C_{1-4} alkoxy. In a particular embodiment, R^4 is OMe, OEt, or OiPr. In a more particular embodiment, R^4 is OMe.

[0095] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is C_{1-4} alkoxy substituted with one C_{1-4} alkoxy, or phenyl. In a particular embodiment, R^4 is OMe, OEt, or OiPr, each of which is substituted with one C_{1-4} alkoxy, or phenyl. In a more particular embodiment, R^4 is C_{1-4} alkoxy substituted with one OMe, OEt, or phenyl. In another more particular embodiment, R^4 is OMe, OEt, or OiPr, each of which is substituted with one OMe, OEt, or phenyl. In a most particular embodiment, R^4 is $-OCH_2-CH_2-OCH_3$, $-OCH_2$-Ph.

[0096] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is C_{1-4} thioalkoxy. In a particular embodiment, R^4 is $-SCH_3$, or $-SCH_2CH_3$. In a more particular embodiment, R^4 is $-SCH_3$.

[0097] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O. In a particular embodiment, R^4 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl. In a more particular embodiment, R^4 is azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl.

[0098] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, substituted with one or more halo, $-C(=O)OC_{1-4}$ alkyl. In a particular embodiment, R^4 is 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, substituted with one, two or three independently selected F, Cl, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, or $-C(=O)OC(CH_3)_3$. In another particular embodiment, R^4 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one, two or three independently selected F, Cl, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, or $-C(=O)OC(CH_3)_3$. In a more particular embodiment, R^4 is 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, substituted with one F, Cl, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, or $-C(=O)OC(CH_3)_3$. In another particular embodiment, R^4 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one F, Cl, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, or $-C(=O)OC(CH_3)_3$. In a most particular embodiment, R^4 is azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl, each of which is substituted with one, two or three independently selected F, Cl. In another most particular embodiment, R^4 is azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl, each of which is substituted with one $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, or $-C(=O)OC(CH_3)_3$.

[0099] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is phenyl.

[0100] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is $-S(=O)_2C_{1-4}$ alkyl. In a particular embodiment, R^4 is $-S(=O)_2CH_3$, or $-S(=O)_2CH_2CH_3$.

[0101] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is $-C(=O)OR^{7a}$, and R^{7a} is as previously described. In a particular embodiment, R^{7a} is H. In another particular embodiment, R^{7a} is C_{1-4} alkyl. In yet another particular embodiment, R^{7a} is C_{1-4} alkyl substituted with one OH, C_{1-4} alkoxy. In a more particular embodiment, R^{7a} is Me, Et, iPr or tBu. In another more particular embodiment, R^{7a} is Me, Et, iPr or tBu, each of which is substituted with one OH, C_{1-4} alkoxy. In yet another more particular embodiment, R^{7a} is Me, Et, iPr or tBu, each of which is substituted with one OH, $-OCH_3$. In a most particular embodiment, R^4 is $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, or $-C(=O)OC(CH_3)_3$.

[0102] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is $-C(=O)NR^{7b}R^{7c}$, and each R^{7b} or R^{7c} is as previously described. In a particular embodiment, R^{7b} and R^{7c} are H. In another particular embodiment, one of R^{7b} or R^{7c} is H, and the other is C_{1-4} alkyl. In yet another particular embodiment, one of R^{7b} or R^{7c} is H, and the other is C_{1-4} alkyl substituted with one OH, C_{1-4} alkoxy. In a further particular embodiment, R^{7b} and R^{7c} are C_{1-4} alkyl. In a more particular embodiment, one of R^{7b} or R^{7c} is H, and the other is Me, Et, iPr or tBu. In another more particular embodiment, one of R^{7b} or R^{7c} is H, and the other is Me, Et, iPr or tBu, each of which is substituted with one OH, C_{1-4} alkoxy. In yet another more particular embodiment, one of R^{7b} or R^{7c} is H, and the other is Me, Et, iPr or tBu, each of which is substituted with one OH, $-OCH_3$. In a most particular embodiment, R^4 is $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_2CH_3$, $-C(=O)NHCH_2CH_2\text{-}OH$ or $-C(=O)NHCH_2CH_2\text{-}OCH_3$.

[0103] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is $-NHC(=O)OR^{7d}$, and R^{7d} is as previously described. In a particular embodiment, R^{7d} is H. In another particular embodiment, R^{7d} is C_{1-4} alkyl. In yet another particular embodiment, R^{7d} is C_{1-4} alkyl substituted with one OH, C_{1-4} alkoxy. In a more particular embodiment, R^{7d} is Me, Et, iPr or tBu. In another more particular embodiment, R^{7d} is Me, Et, iPr or tBu, each of which is substituted with one OH, C_{1-4} alkoxy. In yet another more particular embodiment, R^{7d} is Me, Et, iPr or tBu, each of which is substituted with one OH, $-OCH_3$. In a most particular embodiment, R^4 is $-NHC(=O)OCH_3$, $-NHC(=O)OCH_2CH_3$, or $-NHC(=O)OC(CH_3)_3$.

[0104] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is $-NHC(=O)R^{7e}$, and R^{7e} is as previously described. In a particular embodiment, R^{7e} is H. In another particular embodiment, R^{7e} is C_{1-4} alkyl. In yet another particular embodiment, R^{7e} is C_{1-4} alkyl substituted with one OH, C_{1-4} alkoxy. In a more particular embodiment, R^{7e} is Me, Et, iPr or tBu. In another more particular embodiment, R^{7e} is Me, Et, iPr or tBu, each of which is substituted with one OH, C_{1-4} alkoxy. In yet another more particular embodiment, R^{7e} is Me, Et, iPr or tBu, each of which is substituted with one OH, $-OCH_3$. In a most particular embodiment, R^4 is $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, or $-NHC(=O)C(CH_3)_3$.

[0105] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^4 is $-NR^{8a}R^{8b}$, and each R^{8a} or R^{8b} is as previously described. In a particular embodiment, R^{8a} and R^{8b} are H. In another particular embodiment, one of R^{8a} or R^{8b} is H, and the other is C_{1-4} alkyl. In yet another particular embodiment, one of R^{8a} or R^{8b} is H, and the other is C_{1-4} alkyl substituted with one OH, C_{1-4} alkoxy, or phenyl. In a further particular embodiment, R^{8a} and R^{8b} are C_{1-4} alkyl. In a more particular embodiment, one of R^{8a} or R^{8b} is H, and the other is Me, Et, iPr or tBu. In another more particular embodiment, one of R^{8a} or R^{8b} is H, and the other is Me, Et, iPr or tBu, each of which is substituted with one OH, C_{1-4} alkoxy, or phenyl. In yet another more particular embodiment, one of R^{8a} or R^{8b} is H, and the other is Me, Et, iPr or tBu, each of which is substituted with one OH, $-OCH_3$, or phenyl. In a most particular embodiment, R^4 is $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2$Phenyl, or $-NHCH_2CH_2-OCH_3$.

[0106] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S. In a particular embodiment, R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl. In a more particular embodiment, R^1 is azetidinyl.

[0107] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, substituted with one or more independently selected C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl. In another embodiment, R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one or more independently selected C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl. In a particular embodiment, R^1 is 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, substituted with one C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl. In another particular embodiment, R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl. In a more particular embodiment, R^1 is 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from

N, O, and S, substituted with one or more independently selected $-CH_3$, $-C(=O)CH_3$, or $-C(=O)OC(CH_3)_3$. In another more particular embodiment, R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one or more independently selected $-CH_3$, $-C(=O)CH_3$, $-C(=O)OCH_3$, or $-C(=O)OC(CH_3)_3$. In yet another more particular embodiment, R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one $-C(=O)CH_3$, $-C(=O)OCH_3$, or $-C(=O)OC(CH_3)_3$.

[0108] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is phenyl.

[0109] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is phenyl substituted with one or more independently selected R^5 groups. In a particular embodiment, R^1 is phenyl substituted with one, two, or three independently selected R^5 groups. In another particular embodiment, R^1 is phenyl substituted with one R^5 group.

[0110] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S. In a particular embodiment, R^1 is imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

[0111] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^1 is 5-6 membered monocyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S substituted with one or more independently selected R^5 groups. In another embodiment R^1 is imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridinyl, pyrimidinyl or pyrazinyl, each of which is substituted with one or more independently selected R^5 groups. In a particular embodiment, R^1 is 5-6 membered monocyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S substituted with one, two, or three independently selected R^5 groups. In another particular embodiment, R^1 is imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridinyl, pyrimidinyl or pyrazinyl, each of which is substituted with one, two, or three independently selected R^5 groups. In a more particular embodiment, R^1 is 5-6 membered monocyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S substituted with one R^5 group. In another more particular embodiment, R^1 is imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridinyl, pyrimidinyl or pyrazinyl, each of which is substituted with one R^5 group.

[0112] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^5 is halo, OH, or CN. In a particular embodiment, R^5 is F, Cl, OH, or CN.

[0113] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^5 is C_{1-4} alkyl. In a particular embodiment, R^5 is Me, Et, or iPr.

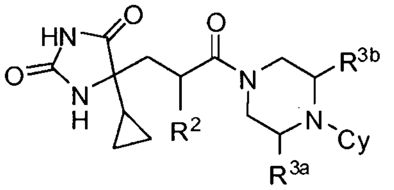
[0114] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^5 is C_{1-4} alkyl substituted with one or more independently selected halo, $-NR^{9a}R^{9b}$, $-C(=O)NR^{9c}R^{9d}$, wherein R^{9a}, R^{9b}, R^{9c}, or R^{9d} is as previously described. In another embodiment, R^5 is Me, or Et, each of which is substituted with one or more independently selected halo, -NR^{9a}R^{9b}, -C(=O)NR^{9c}R^{9d}. In a particular embodiment, R^5 is C$_{1-4}$ alkyl substituted with one, two or three independently selected halo, -NR^{9a}R^{9b}, or -C(=O)NR^{9c}R^{9d}. In another particular embodiment, R^5 is Me, or Et, each of which is substituted with one, two, or three independently selected halo, -NR^{9a}R^{9b}, or -C(=O)NR^{9c}R^{9d}. In a more particular embodiment, R^5 is C$_{1-4}$ alkyl substituted with one halo, -NR^{9a}R^{9b}, or -C(=O)NR^{9c}R^{9d}. In another more particular embodiment, R^5 is Me, or Et, each of which is substituted with one halo, -NR^{9a}R^{9b}, or -C(=O)NR^{9c}R^{9d}. In one embodiment, each R^{9a}, R^{9b}, R^{9c}, or R^{9d} is independently selected from H, Me, and Et. In a most particular embodiment, R^5 is -CF$_3$, -CH$_2$NH$_2$, -CH$_2$NHMe, -CH$_2$NMe$_2$, -CH$_2$C(=O)NH$_2$, -CH$_2$C(=O)NHMe, or -CH$_2$C(=O)NMe$_2$.

[0115] In one embodiment, a compound of the invention is according to Formula I or II, wherein R^5 is C$_{1-4}$ alkoxy. In a particular embodiment, R^5 is -OMe, -OEt, or -OiPr.

[0116] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^5 is C$_{1-4}$ alkoxy substituted with one -NR^{9e}R^{9f}, wherein R^{9e} are R^{9f} as previously described. In another embodiment, R^5 is -OEt, substituted with one -NR^{9e}R^{9f}. In one embodiment, each R^{9e}, and R^{9f}, is independently selected from H, Me, and Et. In a most particular embodiment, R^5 is -OCH$_2$CH$_2$NH$_2$, -OCH$_2$CH$_2$NHMe, or -OCH$_2$CH$_2$NMe$_2$.

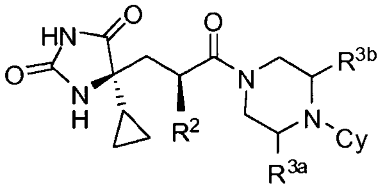
[0117] In another embodiment, a compound of the invention is according to Formula I or II, wherein R^5 is –S(=O)$_2$C$_{1-4}$ alkyl. In a particular embodiment, R^5 is –S(=O)$_2$CH$_3$.

[0118] In one embodiment, a compound of the invention is according to Formula IIIa or IIIb:



IIIa

or



IIIb

wherein R^2, R^{3a}, R^{3b}, and Cy are as described above.

[0119] In one embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is H.

[0120] In one embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is -OH.

[0121] In one embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is C$_{1-4}$ alkoxy. In a particular embodiment, R^2 is –OMe, -OEt, or -OiPr. In a more particular embodiment, R^2 is –OMe.

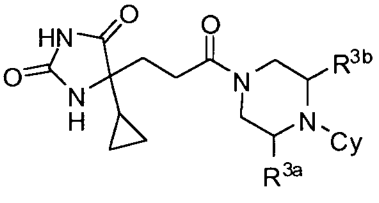
[0122] In one embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is C$_{1-4}$ alkyl. In a particular embodiment, R^2 is Me, Et, or iPr. In a more particular embodiment, R^2 is Me, or Et.

[0123] In one embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is C$_{1-4}$ alkyl substituted with one OH, or CN. In a particular embodiment, R^2 is Me, or Et, each of which is substituted with one OH, or CN. In a more particular embodiment, R^2 is $-CH_2-OH$, or $-CH_2-CN$.

[0124] In one embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one C_{1-4} alkoxy optionally substituted with one phenyl. In another embodiment, R^2 is Me, or Et, each of which is substituted with one C_{1-4} alkoxy optionally substituted with one phenyl. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one -OMe, -OEt, each of which is optionally substituted with one phenyl. In another particular embodiment, R^2 is Me, or Et, each of which is substituted with one –OMe, -OEt, each of which is optionally substituted with one phenyl. In a more particular embodiment, R^2 is $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2OCH_2CH_2OCH_3$, or $-CH_2OCH_2$Phenyl.

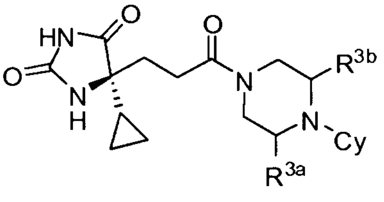
[0125] In one embodiment, a compound of the invention is according to any one of Formulae I-IIIb, wherein R^2 is C_{1-4} alkyl substituted with one 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl. In another embodiment, R^2 is Me, or Et, each of which is substituted with one 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with one imidazolyl, pyrrazolyl, oxazolyl, each of which is optionally substituted with one or more independently selected C_{1-4} alkyl. In another particular embodiment, R^2 is Me or Et, each of which is substituted with one imidazolyl, pyrrazolyl, oxazolyl, each of which is optionally substituted with one or more independently selected C_{1-4} alkyl. In a more particular embodiment, R^2 is C_{1-4} alkyl substituted with one imidazolyl, pyrrazolyl, oxazolyl, each of which is optionally substituted with one or more independently selected Me, or Et. In another particular embodiment, R^2 is Me, or Et, each of which is substituted with one imidazolyl, pyrrazolyl, oxazolyl, each of which is optionally substituted with one or more independently selected Me, or Et.

[0126] In one embodiment, a compound of the invention is according to Formula IVa or IVb:



IVa

or

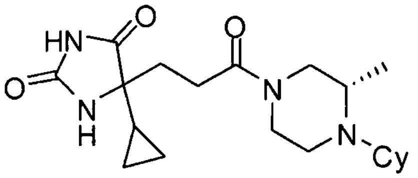


IVb

wherein R^{3a}, R^{3b}, X, and Cy are as described above.

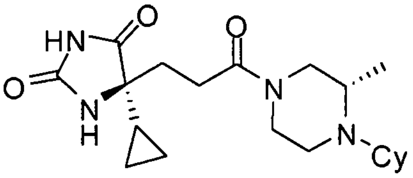
[0127] In one embodiment, a compound of the invention is according to any one of Formulae I-IVb, wherein R^{3a}, and R^{3b} are both H. In another embodiment, one of R^{3a} and R^{3b} is H, and the other is C_{1-4} alkyl. In a particular embodiment, one of R^{3a} and R^{3b} is H, and the other is Me, or Et. In a more particular embodiment, one of R^{3a} and R^{3b} is H, and the other is Me, or Et. In a most particular embodiment, one of R^{3a} and R^{3b} is H, and the other is Me. In another most particular embodiment, R^{3a} and R^{3b} are both Me.

[0128] In one embodiment, a compound of the invention is according to Formula Va, or Vb:



Va

or



Vb

wherein Cy is as described above.

[0129] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein Cy is 6-10 membered monocyclic or fused bicyclic aryl. In a particular embodiment, Cy is phenyl, or naphthyl. In a more particular embodiment, Cy is phenyl.

[0130] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein Cy is 6-10 membered monocyclic or fused bicyclic aryl substituted with one or more independently selected R^6 groups. In another embodiment, Cy is phenyl, or naphthyl, each of which is substituted with one or more independently selected R^6 groups. In a particular embodiment, Cy is 6-10 membered monocyclic or fused bicyclic aryl substituted with one, two or three independently selected R^6 groups. In another embodiment, Cy is phenyl, or naphthyl, each of which is substituted with one, two or three independently selected R^6 groups. In a more particular embodiment, Cy is 6-10 membered monocyclic or fused bicyclic aryl substituted with one R^6 group. In another embodiment, Cy is phenyl, or naphthyl, each of which is substituted with one R^6 group.

[0131] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein Cy is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S. In a particular embodiment, Cy is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, indazolyl, pyrrolopyridinyl, or benzofuranyl. In a more particular embodiment, Cy is pyridinyl.

[0132] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein Cy is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S substituted with one or more independently selected R^6 groups. In another embodiment, Cy is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, indazolyl, pyrrolopyridinyl, or benzofuranyl, each of which is substituted with one or more independently selected R^6 groups. In a particular embodiment, Cy is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S substituted with one, two or three independently selected R^6 groups. In another embodiment, Cy is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, indazolyl, pyrrolopyridinyl, or benzofuranyl, each of which is substituted with one, two or three independently selected R^6 groups. In a more particular embodiment, Cy is 5-10 membered monocyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S substituted with one R^6 group. In another embodiment, Cy is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, indazolyl, pyrrolopyridinyl, or benzofuranyl, each of which is substituted with one R^6 group.

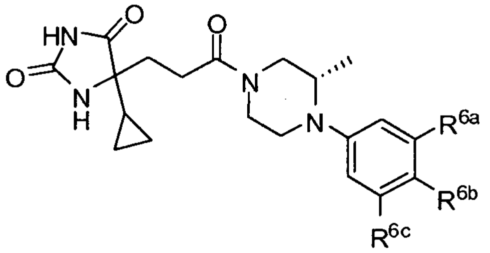
[0133] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein R^6 is halo, -CN, or -NO_2. In a particular embodiment, R^6 is F, Cl, -CN, or -NO_2.

[0134] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein R^6 is -CH_3.

[0135] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein R^6 is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected halo, C_{1-4} alkyl, C_{1-4} alkoxy. In another embodiment, R^6 is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, or pyrimidinyl, each of which is optionally substituted with one or more independently selected halo, C_{1-4} alkyl, C_{1-4} alkoxy. In a particular embodiment, R^6 is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one, two, or three independently selected halo, C_{1-4} alkyl, or C_{1-4} alkoxy. In another particular embodiment, R^6 is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, or pyrimidinyl, each of which is optionally substituted with one, two, or three independently selected halo, C_{1-4} alkyl, or C_{1-4} alkoxy. In a more particular embodiment, R^6 is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one halo, C_{1-4} alkyl, C_{1-4} alkoxy. In another more particular embodiment, R^6 is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, or pyrimidinyl, each of which is optionally substituted with one halo, C_{1-4} alkyl, or C_{1-4} alkoxy. In a most particular embodiment, R^6 is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one, two, or three independently selected F, Cl, Me, Et, -OMe, or -OEt. In another more particular embodiment, R^6 is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, or pyrimidinyl, each of which is optionally substituted with one, two, or three independently selected F, Cl, Me, Et, -OMe, or -OEt.

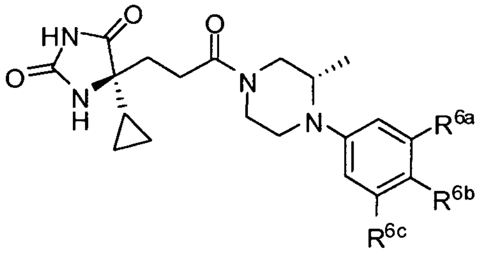
[0136] In one embodiment, a compound of the invention is according to any one of Formulae I-Vb, wherein R^6 is -$NR^{9g}R^{9h}$, wherein R^{9g} and R^{9h} are as previously described. In a particular embodiment, R^{9g} and R^{9h} are both H. In another particular embodiment, R^{9g} and R^{9h} are both C_{1-4} alkyl. In yet another particular embodiment, one of R^{9g} and R^{9h} is H, and the other is C_{1-4} alkyl. In a more particular embodiment, R^6 is –NH_2, -NHMe, or –NMe_2.

[0137] In one embodiment, a compound of the invention is according to Formula VIa or VIb:



VIa

or



VIb

wherein each one of R^{6a}, R^{6b} and R^{6c} is independently selected from H, halo, -CN, and $-CH_3$.

[0138] In one embodiment, a compound of the invention is according to Formula VIa or VIb, wherein each one of R^{6a}, R^{6b} and R^{6c} is independently selected from H, halo, and $-CH_3$. In a more particular embodiment, each one of R^{6a}, R^{6b} and R^{6c} is independently selected from H, F, Cl, and $-CH_3$.

[0139] In another particular embodiment, a compound of the invention is according to Formula VIa or VIb, wherein R^{6b} is H, and each one of R^{6a}, and R^{6c} is independently selected from H, halo, and $-CH_3$. In a particular embodiment, R^{6b} is H, and each one of R^{6a}, and R^{6c} is independently selected from H, F, Cl, and $-CH_3$. In a more particular embodiment, R^{6b} is H, and each one of R^{6a}, and R^{6c} is independently selected from H, F, and Cl.

[0140] In another particular embodiment, a compound of the invention is according to Formula VIa or VIb, wherein R^{6a} is H, and each one of R^{6b}, and R^{6c} is independently selected from H, halo, and $-CH_3$. In a particular embodiment, R^{6a} is H, and each one of R^{6b}, and R^{6c} is independently selected from H, F, Cl, and $-CH_3$. In a more particular embodiment, R^{6a} is H, and each one of R^{6b}, and R^{6c} is independently selected from H, F, and Cl.

[0141] In one embodiment, a compound of the invention is selected from:

Cpd 1 5-methyl-5-[3-oxo-3-(4-phenylpiperazin-1-yl)propyl]imidazolidine-2,4-dione,

Cpd 2 5-[3-[4-(4-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 3 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 4 5-[3-oxo-3-(4-phenylpiperazin-1-yl)propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 5 5-[3-[4-(4-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 6 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 7 5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 8 5-[3-[4-(2,3-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 9 5-[3-[4-(2-naphthyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 10 5-[3-[4-(4-chloro-3-fluoro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 11 5-[3-[4-(2,3-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 12 5-methyl-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 13 5-[3-[4-(4-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione, Cpd 14 5-[3-[4-(6-isoquinolyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 15 5-[3-oxo-3-[4-(2-quinolyl)piperazin-1-yl]propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 16 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 17 5-[3-[4-(4-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 18 5-[3-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 19 5-[3-[4-(2-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 20 5-[3-[4-(2-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 21 5-[3-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 22 5-[3-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 23 5-[3-[4-(3-methyl-4-nitro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 24 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 25 5-[3-[4-(benzofuran-5-yl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 26 5-[3-[4-(1,3-benzothiazol-5-yl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 27 (5S)-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 28 5-[3-[4-(4-bromophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 29 2-[4-[3-(4-methyl-2,5-dioxo-imidazolidin-4-yl)propanoyl]piperazin-1-yl]benzonitrile,

Cpd 30 5-[3-[4-(2-fluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 31 5-[3-[4-(2,4-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 32 5-isopropyl-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 33 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-isopropyl-imidazolidine-2,4-dione,

Cpd 34 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 35 5-cyclopropyl-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 36 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 37 5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 38 5-[3-[4-(2,4-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 39 5-[3-[4-(2,5-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 40 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 41 5-[3-[4-(2,3-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione, Cpd 42 5-methyl-5-[3-oxo-3-[4-(2-pyridyl)piperazin-1-yl]propyl]imidazolidine-2,4-dione,

Cpd 43 5-methyl-5-[3-oxo-3-[4-(3-pyridyl)piperazin-1-yl]propyl]imidazolidine-2,4-dione,

Cpd 44 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-dimethylaminoethyl)imidazolidine-2,4-dione,

Cpd 45 5-[3-oxo-3-[4-(3-pyridyl)piperazin-1-yl]propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 46 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 47 5-[3-[4-(3-fluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 48 5-[3-[4-(3-bromophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 49 5-[3-[4-(4-chloro-3-fluoro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 50 5-[3-[4-[2-(dimethylamino)phenyl]piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 51 5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 52 5-[3-[4-(3-chloro-4-fluoro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 53 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-isopropyl-imidazolidine-2,4-dione,

Cpd 54 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-isopropyl-imidazolidine-2,4-dione,

Cpd 55 5-cyclopropyl-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 56 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 57 5-cyclopropyl-5-[3-[4-(2,3-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 58 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-dimethylaminoethyl)imidazolidine-2,4-dione,

Cpd 59 5-methyl-5-[3-oxo-3-(4-thiazol-2-ylpiperazin-1-yl)propyl]imidazolidine-2,4-dione,

Cpd 60 5-[3-[4-(3-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 61 5-[3-[4-(4-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 62 5-[3-(3-methyl-4-phenyl-piperazin-1-yl)-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 63 5-methyl-5-[3-(3-methyl-4-phenyl-piperazin-1-yl)-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 64 5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 65 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione, Cpd 66 5-[3-[4-(4-fluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 67 5-[3-[4-(3,4-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 68 5-[3-oxo-3-(4-phenylpiperazin-1-yl)propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 69 5-[3-[4-(2,3-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 70 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclobutyl-imidazolidine-2,4-dione,

Cpd 71 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclobutyl-imidazolidine-2,4-dione,

Cpd 72 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclohexyl-imidazolidine-2,4-dione,

Cpd 73 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclohexyl-imidazolidine-2,4-dione,

Cpd 74 5-(4-chlorophenyl)-5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 75 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(4-chlorophenyl)imidazolidine-2,4-dione,

Cpd 76 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(p-tolyl)imidazolidine-2,4-dione,

Cpd 77 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(p-tolyl)imidazolidine-2,4-dione,

Cpd 78 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(4-methoxyphenyl)imidazolidine-2,4-dione,

Cpd 79 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(4-methoxyphenyl)imidazolidine-2,4-dione,

Cpd 80 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-[4-(2-dimethylaminoethyloxy)phenyl]imidazolidine-2,4-dione,

Cpd 81 5-[4-(2-dimethylaminoethyloxy)phenyl]-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 82 5-[4-(dimethylaminomethyl)phenyl]-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 83 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-[4-(dimethylaminomethyl)phenyl]imidazolidine-2,4-dione,

Cpd 84 5-[3-[4-(5-fluoro-3-pyridyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 85 5-[3-[4-(5-chloro-3-pyridyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 86 5-[3-[4-(5-bromo-3-pyridyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 87 5-[3-[4-(2,5-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 88 5-[3-[4-(2,5-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione, Cpd 89 5-cyclopropyl-5-[3-[4-(2,5-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 90 5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 91 5-[3-[4-(3-chloro-4-fluoro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 92 5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 93 5-[3-[4-(4-chloro-5-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 94 5-[3-[4-(4,5-difluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 95 5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 96 5-[3-[4-(3-chloro-4-fluoro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 97 5-[3-[4-(3-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 98 5-[3-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 99 5-cyclopropyl-5-[3-[4-(3-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 100 5-[3-[4-(3-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 101 5-[3-[4-(2,3-dimethylphenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 102 5-[3-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 103 5-[3-[4-(3-fluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 104 5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 105 5-[3-(3-methyl-4-phenyl-piperazin-1-yl)-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 106 5-cyclopropyl-5-[3-(3-methyl-4-phenyl-piperazin-1-yl)-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 107 5-tert-butyl-5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 108 5-tert-butyl-5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 109 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclopentyl-imidazolidine-2,4-dione, Cpd 110 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclopentyl-imidazolidine-2,4-dione,

Cpd 111 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 112 5-[3-[4-(3-fluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 113 5-cyclopropyl-5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 114 5-[3-[4-(3-chloro-4-fluoro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 115 5-cyclopropyl-5-[3-[4-(3-fluorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 116 5-cyclopropyl-5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 117 5-[3-[4-(3-chloro-5-fluoro-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 118 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(dimethylaminomethyl)imidazolidine-2,4-dione,

Cpd 119 5-(dimethylaminomethyl)-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 120 5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-(dimethylaminomethyl)imidazolidine-2,4-dione,

Cpd 121 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 122 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-ethyl-imidazolidine-2,4-dione,

Cpd 123 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(3-methoxyphenyl)imidazolidine-2,4-dione,

Cpd 124 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(4-methylsulfonylphenyl)imidazolidine-2,4-dione,

Cpd 125 4-[4-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]benzonitrile,

Cpd 126 5-[3-[4-(4-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 127 5-[3-[4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 128 5-cyclopropyl-5-[3-[(3R)-3-methyl-4-phenyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 129 5-cyclopropyl-5-[3-[4-(5-fluoro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione, Cpd 130 5-cyclopropyl-5-[3-[4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 131 5-[3-[(3R)-3-methyl-4-phenyl-piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 132 5-(5-chloro-2-methoxy-phenyl)-5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 133 5-(5-chloro-2-methoxy-phenyl)-5-[3-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 134 5-[3-[(3R)-3-methyl-4-phenyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 135 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-phenyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 136 5-[3-[(3S)-3-methyl-4-phenyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 137 5-[3-[(3S)-3-methyl-4-phenyl-piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione,

Cpd 138 5-cyclopropyl-5-[3-oxo-3-(4-phenylpiperazin-1-yl)propyl]imidazolidine-2,4-dione,

Cpd 139 5-[3-[4-(3,5-dichloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 140 5-[3-[4-(3,5-difluorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 141 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(m-tolyl)imidazolidine-2,4-dione,

Cpd 142 5-cyclopropyl-5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 143 5-[3-[(3S)-4-(4-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 144 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 145 5-[3-[(3S)-4-(5-fluoro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 146 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-methoxyphenyl)imidazolidine-2,4-dione,

Cpd 147 5-[3-[(3S)-4-(4-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 148 5-cyclopropyl-5-[3-[(3S)-4-(5-fluoro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 149 5-cyclopropyl-5-[3-[4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 150 5-[3-[4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione, Cpd 151 5-cyclopropyl-5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 152 5-[3-[(3S)-4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 153 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(2-oxoindolin-5-yl)imidazolidine-2,4-dione,

Cpd 154 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-[[2-methoxyethyl(methyl)amino]methyl]imidazolidine-2,4-dione,

Cpd 155 5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(morpholinomethyl)imidazolidine-2,4-dione,

Cpd 156 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 157 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 158 5-[3-[(3S)-4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 159 (5R)-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 160 5-cyclopropyl-5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 161 5-cyclopropyl-5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 162 5-[3-[(3S)-4-(4-chloro-3-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 163 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 164 5-[3-[(3S)-4-(4-chloro-3-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 165 5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 166 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 167 5-cyclopropyl-5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 168 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione, Cpd 169 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 170 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 171 5-(aminomethyl)-5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 172 5-cyclopropyl-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 173 (5S)-5-cyclopropyl-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 174 5-cyclopropyl-5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 175 5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 176 5-[3-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 177 5-cyclopropyl-5-[3-[(3S)-4-(3,5-dichloro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 178 5-[3-[(3S)-4-(3,5-dichloro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 179 5-[3-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 180 5-(aminomethyl)-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 181 5-[(benzylamino)methyl]-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 182 methyl 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetate,

Cpd 183 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetic acid,

Cpd 184 5-[(benzylamino)methyl]-5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 185 5-cyclopropyl-5-[3-[4-[2-(methylamino)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 186 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione, Cpd 187 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]-N-(2-methoxyethyl)acetamide,

Cpd 188 tert-butyl 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetate,

Cpd 189 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]-N-(2-hydroxyethyl)acetamide,

Cpd 190 5-cyclopropyl-5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 191 5-cyclopropyl-5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 192 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 193 5-[3-[(3S)-4-(4-chlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 194 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 195 3-[4-[3-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl)propanoyl]piperazin-1-yl]benzonitrile,

Cpd 196 5-(azetidin-3-yl)-53-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 197 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-methylsulfanylethyl)imidazolidine-2,4-dione,

Cpd 198 tert-butyl 4-[[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]methyl]piperidine-1-carboxylate,

Cpd 199 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-tetrahydropyran-4-yl-imidazolidine-2,4-dione,

Cpd 200 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 201 5-cyclopropyl-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-hydroxy-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 202 5-[3-[(3S)-4-(4-chloro-5-fluoro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 203 (5S)-5-cyclopropyl-5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 204 (5S)-5-cyclopropyl-5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 205 (5S)-5-cyclopropyl-5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione, Cpd 206 5-cyclopropyl-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methoxy-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 207 (5S)-5-cyclopropyl-5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 208 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(4-piperidylmethyl)imidazolidine-2,4-dione,

Cpd 209 5-cyclopropyl-5-[3-[4-[3-(dimethylamino)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 210 5-(2-aminoethyl)-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 211 5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 212 (5S)-5-cyclopropyl-5-[(2S)-3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 213 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 214 5-[3-[(3S)-4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 215 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 216 5-[3-[(3S)-4-(5-fluoro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 217 5-methyl-5-[2-methyl-3-[(3S)-3-methyl-4-phenyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 218 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-methylsulfonylethyl)imidazolidine-2,4-dione,

Cpd 219 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 220 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-(hydroxymethyl)-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 221 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-methoxyethoxymethyl)imidazolidine-2,4-dione,

Cpd 222 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 223 N-[[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]methyl]acetamide,

Cpd 224 5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione, Cpd 225 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 226 5-[3-[(S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 227 5-[3-[(3S)-4-(3,5-dichloro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 228 5-[3-[(3S)-4-(5-fluoro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 229 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 230 5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 231 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 232 5-[3-[(3S)-4-(3-chloro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 233 5-[3-[(3S)-4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 234 tert-butyl 3-[4-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]azetidine-1-carboxylate,

Cpd 235 tert-butyl N-[2-[4-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]ethyl]carbamate,

Cpd 236 5-[2-[4-(3,5-dichlorophenyl)piperazine-1-carbonyl]butyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 237 5-[3-[(3S)-4-(3-chloro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 238 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-[(2,5-dimethylpyrazol-3-yl)methyl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 239 tert-butyl 3-[4-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]azetidine-1-carboxylate,

Cpd 240 5-(azetidin-3-yl)-5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 241 5-(2-aminoethyl)-5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 242 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(morpholinomethyl)imidazolidine-2,4-dione,

Cpd 243 5-[3-[(3R,5S)-4-(3,5-dichlorophenyl)-3,5-dimethyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione, Cpd 244 5-[3-[(3R,5S)-4-(3,5-dichlorophenyl)-3,5-dimethyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 245 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 246 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(morpholinomethyl)imidazolidine-2,4-dione,

Cpd 247 5-(azetidin-3-yl)-5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 248 5-(1-acetylazetidin-3-yl)-5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 249 5-(1-acetylazetidin-3-yl)-5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 250 5-[3-[4-(4,5-dichloro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 251 5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 252 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-[(3,3-difluoropyrrolidin-1-yl)methyl]imidazolidine-2,4-dione,

Cpd 253 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-[(3,3-difluoropyrrolidin-1-yl)methyl]imidazolidine-2,4-dione,

Cpd 254 4-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-[(4-methyl-2,5-dioxo-imidazolidin-4-yl)methyl]-4-oxo-butanenitrile,

Cpd 255 (5S)-cyclopropyl-5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 256 5-[3-[(3S)-4-(6-chloropyrimidin-4-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 257 5-cyclopropyl-5-[3-[(3S)-4-(4,6-dichloro-2-pyridyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 258 5-cyclopropyl-5-[3-[(3S)-4-(2,6-dichloro-4-pyridyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 259 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(3-pyridyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 260 5-[3-[(3S)-4-(5-chloro-3-pyridyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,,

Cpd 261 5-cyclopropyl-5-[3-[(3S)-4-(5-fluoro-3-pyridyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione, Cpd 262 5-[3-[(3S)-4-(4,5-dichloro-2-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 263 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 264 5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 265 (5R)-5-[(2S)-3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 266 5-ethyl-5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 267 5-[3-[4-(4-chloro-2-fluoro-5-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 268 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-(hydroxymethyl)-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 269 5-[3-[(3S)-4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 270 5-[3-[(3S)-4-(3-bromophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 271 5-[3-[(3S,5S)-4-(3,5-dichlorophenyl)-3,5-dimethyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 272 5-[3-[(3S,5S)-4-(3,5-dichlorophenyl)-3,5-dimethyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 273 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(3-pyridyl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 274 5-cyclopropyl-5-[3-[(3S)-4-(1H-indol-5-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 275 5-methyl-5-[2-methyl-3-[(3S)-3-methyl-4-(3-pyridyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 276 5-[3-[(3S)-4-(5-chloro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 277 5-[3-[(3S)-4-(5-fluoro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 278 5-cyclopropyl-5-[3-oxo-3-[4-(4-pyridyl)piperazin-1-yl]propyl]imidazolidine-2,4-dione,

Cpd 279 5-[3-[4-(4-chloro-3,5-difluoro-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 280 5-[3-[(3S)-4-(benzofuran-7-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione, Cpd 281 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(4-pyridyl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 282 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(1H-pyrazol-4-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 283 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(1-methylpyrazol-4-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 284 5-[3-[(3S)-4-(4-chloropyrimidin-2-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 285 5-[3-[(3S)-4-(6-chloropyridazin-3-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 286 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-pyrazin-2-yl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 287 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-3-pyridyl)imidazolidine-2,4-dione,

Cpd 288 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(4-pyridyl)imidazolidine-2,4-dione,

Cpd 289 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(3-quinolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 290 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylindol-5-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 291 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylindol-6-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 292 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-(methoxymethyl)-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 293 5-[3-[4-(3-chloro-5-fluoro-2-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 294 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methoxy-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 295 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methoxy-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 296 5-cyclopropyl-5-[3-[(3S)-4-(1H-indazol-5-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 297 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylindazol-5-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 298 5-cyclopropyl-5-[3-[(3S)-4-(4-fluoro-3-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione, Cpd 299 5-cyclopropyl-5-[3-[(3S)-4-(3-fluoro-4-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 300 5-cyclopropyl-5-[3-[(3S)-4-(4-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 301 5-[3-[(3S)-4-(2-chloropyrimidin-4-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 302 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-pyridazin-3-yl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 303 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(5-methyl-3-pyridyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 304 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-pyrimidin-5-yl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 305 5-[3-[(3S)-4-(1,3-benzothiazol-6-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 306 5-[3-[(3S)-4-(3-chloro-4-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 307 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 308 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 309 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 310 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 311 5-[3-[(3S)-4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 312 5-[3-[(3S)-4-(4-chlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 313 5-cyclopropyl-5-[3-[(3S)-4-(5-fluoro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 314 5-[3-[(3S)-4-(5-chloro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 315 5-[3-[(3S)-4-(4-chloro-3-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 316 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione, Cpd 317 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 318 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 319 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 320 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 321 5-cyclopropyl-5-[3-[(3S)-4-[3-(2-methoxy-4-pyridyl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 322 5-[3-[(3S)-4-[3-(5-chloro-3-pyridyl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 323 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(2-methyl-3-pyridyl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 324 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(6-methyl-3-pyridyl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 325 5-[3-[(3S)-4-(4-chloro-2-pyridyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 326 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrazin-2-yl-imidazolidine-2,4-dione,

Cpd 327 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrazin-2-yl-imidazolidine-2,4-dione,

Cpd 328 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylindol-4-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 329 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(2-methyl-4-pyridyl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 330 5-[(2S)-4-[3-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl)propanoyl]-2-methyl-piperazin-1-yl]pyridine-3-carbonitrile,

Cpd 331 (S)-5-((S)-3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 332 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrimidin-5-yl-imidazolidine-2,4-dione,

Cpd 333 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylindazol-4-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 334 3-[(2S)-4-[3-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl)propanoyl]-2-methyl-piperazin-1-yl]-5-fluoro-benzonitrile, Cpd 335 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-[6-(trifluoromethyl)-3-pyridyl]imidazolidine-2,4-dione,

Cpd 336 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methoxy-2-pyridyl)imidazolidine-2,4-dione,

Cpd 337 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylpyrrolo[3,2-b]pyridin-6-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 338 5-cyclopropyl-5-[3-[(3S)-4-[3-fluoro-5-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 339 5-cyclopropyl-5-[(2S)-2-methyl-3-[(3S)-3-methyl-4-[3-(1H-pyrazol-4-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 340 5-cyclopropyl-5-[3-[(3S)-4-[4-fluoro-3-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 341 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylindazol-6-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 342 5-cyclopropyl-5-[2-methyl-3-[(3S)-3-methyl-4-(5-methyl-3-pyridyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 343 5-cyclopropyl-5-[3-[(3S)-4-(4-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 344 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 345 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 346 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 347 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 348 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 349 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrazin-2-yl-imidazolidine-2,4-dione,

Cpd 350 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrazin-2-yl-imidazolidine-2,4-dione,

Cpd 351 5-cyclopropyl-5-[2-methyl-3-[(3S)-3-methyl-4-(3-pyridyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 352 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(3-methyl-1,2,4-oxadiazol-5-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione, Cpd 353 5-cyclopropyl-5-[3-[(3S)-4-[3-(3,5-dimethyl-1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 354 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-methyl-1H-imidazol-4-yl)imidazolidine-2,4-dione,

Cpd 355 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(3-methyl-1H-pyrazol-4-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 356 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methoxy-3-pyridyl)imidazolidine-2,4-dione,

Cpd 357 (5S)-5-cyclopropyl-5-[3-[(3S)-4-[3-fluoro-5-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 358 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(1H-pyrazol-3-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 359 5-[(2S)-3-[4-(5-chloro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-ethyl-imidazolidine-2,4-dione,

Cpd 360 5-ethyl-5-[3-[(3S)-4-(5-fluoro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 361 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(1-methylimidazol-4-yl)imidazolidine-2,4-dione,

Cpd 362 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-oxazol-4-yl-imidazolidine-2,4-dione,

Cpd 363 5-[3-[(3S)-4-(5-chloro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 364 5-[3-[(3S)-4-(5-fluoro-3-pyridyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 365 5-[3-[(3S)-4-(4-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 366 5-[3-[(3S)-4-(4-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 367 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-methyl-4-pyridyl)imidazolidine-2,4-dione,

Cpd 368 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-[3-(2-methylpyrazol-3-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 369 5-cyclopropyl-5-[3-[(3S)-4-[3-(3,5-dimethylisoxazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 370 5-cyclopropyl-5-[3-[(3S)-4-[3-(1-isopropylpyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione, Cpd 371 5-methyl-5-[(2-methyl-3-[(3S)-3-methyl-4-[3-(1H-pyrazol-4-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 372 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(3-pyrazin-2-ylphenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 373 5-[3-[(3S)-4-(6-chloropyridazin-4-yl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 374 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(1-methylpyrazol-3-yl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 375 5-[3-[(3S)-4-[3-fluoro-5-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 376 5-[3-[(3S)-4-[3-fluoro-5-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 377 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-(3-pyrimidin-5-ylphenyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 378 5-cyclopropyl-5-[3-[(3S)-4-[4-fluoro-3-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 379 5-cyclopropyl-5-[3-[(3S)-4-[3-fluoro-5-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 380 5-(methoxymethyl)-5-[2-methyl-3-[(3S)-3-methyl-4-[3-(1H-pyrazol-4-yl)phenyl]piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 381 5-[3-[(3S)-4-[3-(6-chloropyridazin-3-yl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

Cpd 382 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrimidin-2-yl-imidazolidine-2,4-dione,

Cpd 383 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-3-pyridyl)imidazolidine-2,4-dione,

Cpd 384 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-3-pyridyl)imidazolidine-2,4-dione,

Cpd 385 5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-3-pyridyl)imidazolidine-2,4-dione,

Cpd 386 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-3-pyridyl)imidazolidine-2,4-dione,

Cpd 387 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(5-methylisoxazol-3-yl)imidazolidine-2,4-dione,

Cpd 388 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-oxazol-4-yl-imidazolidine-2,4-dione, Cpd 389 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(1-methylimidazol-4-yl)imidazolidine-2,4-dione,

Cpd 390 (5R)-5-[3-[4-(4-chloro-3-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 391 (5R)-5-[3-[(3S)-4-[4-chloro-3-(dimethylamino)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 392 (5R)-5-[3-[(3S)-4-[4-chloro-3-(methylamino)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 393 (5R)-5-methyl-5-[3-[4-(m-tolyl)piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 394 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(1-methylpyrazol-3-yl)imidazolidine-2,4-dione,

Cpd 395 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-methyloxazol-4-yl)imidazolidine-2,4-dione,

Cpd 396 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2,5-dimethyloxazol-4-yl)imidazolidine-2,4-dione,

Cpd 397 5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(1-methylpyrazol-4-yl)imidazolidine-2,4-dione,

Cpd 398 (5R)-5-[3-[(3S)-4-(2,5-dimethylphenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 399 5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(1-methylazetidin-3-yl)imidazolidine-2,4-dione,

Cpd 400 (5R)-5-[3-[(3S)-4-(4-chloro-3,5-dimethyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 401 (5R)-5-[3-[4-(4-chloro-3,5-dimethyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 402 2-[4-[3-[4-(4-chloro-3-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]-N-(2-hydroxyethyl)acetamide,

Cpd 403 (5S)-5-cyclopropyl-5-[3-[(3R)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

Cpd 404 5-[3-[(3S)-4-(4-chloro-3,5-difluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 405 5-{3-[(S)-4-(3-Chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl}-5-methyl-imidazolidine-2,4-dione, and

Cpd 406 5-{3-[(S)-4-(3-Chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl}-5-methoxymethyl-imidazolidine-2,4-dione.

[0142] In another embodiment, a compound of the invention is selected from:

Cpd 407 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-3-oxopropyl)-5-(pyridin-2-yl)imidazolidine-2,4-dione,

Cpd 408 5-cyclopropyl-5-(3-((S)-4-(3,4-dichlorophenyl)-3-methylpiperazin-1-yl)-3-oxopropyl)imidazolidine-2,4-dione,

Cpd 409 5-cyclopropyl-5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)imidazolidine-2,4-dione,

Cpd 410 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 411 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-cyclopropylimidazolidine-2,4-dione,

Cpd 412 5-(3-((S)-4-(4-chlorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-cyclopropylimidazolidine-2,4-dione,

Cpd 413 5-(3-((S)-4-(3-chloro-5-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-cyclopropylimidazolidine-2,4-dione,

Cpd 414 (R)-5-(3-((S)-4-(3,4-dichlorophenyl)-3-methylpiperazin-1-yl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 415 5-(benzyloxymethyl)-5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)imidazolidine-2,4-dione,

Cpd 416 5-cyclopropyl-5-(3-((S)-4-(3,4-dichlorophenyl)-3-methylpiperazin-1-yl)-3-oxopropyl)imidazolidine-2,4-dione,

Cpd 417 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)-5-(hydroxymethyl)imidazolidine-2,4-dione,

Cpd 418 5-(3-((S)-4-(3-chloro-5-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 419 (R)-5-((S)-3-((S)-4-(3,4-dichlorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 420 5-(3-((S)-4-(3,5-dichlorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 421 5-(3-((S)-4-(3,4-difluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 422 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 423 5-(3-((S)-4-(3,5-dichloro-2-methylphenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 424 5-(2-(benzyloxymethyl)-3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione, Cpd 425 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-(hydroxymethyl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 426 5-(3-((S)-4-(3,5-dichlorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-((2-methoxyethoxy)methyl)imidazolidine-2,4-dione,

Cpd 427 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 428 5-(3-(4-(3,4-difluorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 429 5-(3-((S)-4-(3,5-dichlorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 430 5-(3-((S)-4-(3,5-dichloro-2-methylphenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 431 5-(3-((S)-4-(3-chloro-5-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 432 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 433 5-(3-(4-(3-chloro-2-methylphenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 434 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)-5-(pyridin-2-yl)imidazolidine-2,4-dione,

Cpd 435 5-(2-(4-(3,5-dichlorophenyl)piperazine-1-carbonyl)butyl)-5-methylimidazolidine-2,4-dione,

Cpd 436 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-(methoxymethyl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 437 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(pyridin-2-yl)imidazolidine-2,4-dione,

Cpd 438 5-(2-(4-(3,5-dichlorophenyl)piperazine-1-carbonyl)-3-methylbutyl)-5-methylimidazolidine-2,4-dione,

Cpd 439 5-(3-(4-(3,5-dichlorophenyl)piperazin-1-yl)-2-methoxy-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 440 5-(3-(4-(4,5-dichloro-2-methylphenyl)piperazin-1-yl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 441 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)imidazolidine-2,4-dione,

Cpd 442 5-(3-((S)-4-(3,5-dichlorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(pyridin-2-yl)imidazolidine-2,4-dione,

Cpd 443 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-(hydroxymethyl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione, Cpd 444 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-ethylimidazolidine-2,4-dione,

Cpd 445 5-(3-((S)-4-(3-chloro-5-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-ethylimidazolidine-2,4-dione,

Cpd 446 5-(3-((S)-4-(3-chlorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(pyridin-2-yl)imidazolidine-2,4-dione,

Cpd 447 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 448 5-(3-(4-(4-chloro-3,5-difluorophenyl)piperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

Cpd 449 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-(methoxymethyl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 450 5-(3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methoxy-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 451 5-(3-((S)-4-(3-chloro-5-fluorophenyl)-3-methylpiperazin-1-yl)-2-(methoxymethyl)-3-oxopropyl)-5-methylimidazolidine-2,4-dione,

Cpd 452 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 453 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(3-pyridyl)imidazolidine-2,4-dione,

Cpd 454 5-[3-[(3S)-4-(4-chloro-3-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 455 (S)-5-{(S)-3-[(S)-4-(3-Chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl}-5-methoxymethyl-imidazolidine-2,4-dione,

Cpd 456 5-cyclopropyl-5-(3-((S)-4-(4-fluoro-3-methylphenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)imidazolidine-2,4-dione,

Cpd 457 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 458 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 459 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

Cpd 460 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrazin-2-yl-imidazolidine-2,4-dione,

Cpd 461 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrazin-2-yl-imidazolidine-2,4-dione, Cpd 462 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrimidin-2-yl-imidazolidine-2,4-dione,

Cpd 463 5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-pyrimidin-2-yl-imidazolidine-2,4-dione,

Cpd 464 5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-3-pyridyl)imidazolidine-2,4-dione,

Cpd 465 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-oxazol-4-yl-imidazolidine-2,4-dione,

Cpd 466 5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(1-methylimidazol-4-yl)imidazolidine-2,4-dione,

Cpd 467 5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(1-methylimidazol-4-yl)imidazolidine-2,4-dione,

Cpd 468 (5R)-5-[3-[(3S)-4-(4-chloro-3-isopropyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 469 (5R)-5-[3-[(3S)-4-(4-chloro-3-methyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 470 (5R)-5-[3-[(3S)-4-(4-chloro-3,5-dimethyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 471 2-[4-[3-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetic acid,

Cpd 472 (5R)-5-[3-[(3S)-4-[4-chloro-3-(trifluoromethyl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 473 5-[3-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(6-methyl-2-pyridyl)imidazolidine-2,4-dione,

Cpd 474 (5R)-5-[3-[(3S)-4-[4-chloro-3-(difluoromethyl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 475 tert-butyl 3-[4-[3-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]propanoate,

Cpd 476 (5R)-5-[3-[(3S)-4-[4-chloro-3-(fluoromethyl)phenyl]-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

Cpd 477 3-[4-[3-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]propanoic acid,

Cpd 478 5-{3-[(S)-4-(4-Chloro-3-trifluoromethyl-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl}-5-methoxymethyl-imidazolidine-2,4-dione,

Cpd 479 5-[3-[(3S)-4-(4-chloro-3,5-difluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione, Cpd 480 5-[3-[(3S)-4-(4-chloro-3,5-difluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione, and

Cpd 481 5-[3-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione.

[0143] In one embodiment a compound of the invention is not an isotopic variant.

[0144] In one aspect a compound of the invention according to any one of the embodiments herein described is present as the free base.

[0145] In one aspect a compound of the invention according to any one of the embodiments herein described is a pharmaceutically acceptable salt.

[0146] In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of the compound.

[0147] In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of a pharmaceutically acceptable salt of a compound.

[0148] While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.

[0149] While specified groups for each embodiment have generally been listed above separately, a compound of the invention may be one for which one or more variables (for example, R groups) is selected from one or more embodiments according to any of the Formula(e) listed above. Therefore, the present invention is intended to include all combinations of variables from any of the disclosed embodiments within its scope.

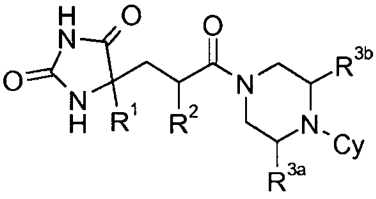
[0150] Alternatively, the exclusion of one or more of the specified variables from a group or an embodiment, or combinations thereof is also contemplated by the present invention.

[0151] In certain aspects, the present invention provides prodrugs and derivatives of the compounds according to the formulae above. Prodrugs are derivatives of the compounds of the invention, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0152] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism(Bundgaard, 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly useful are the C_1 to C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds of the invention.

CLAUSES

1. A compound according to Formula I:



I

wherein

R^1 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^4 groups,
- C_{3-7} monocyclic cycloalkyl optionally substituted with one or more independently selected R^4 groups,
- 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl,
- phenyl optionally substituted with one or more independently selected R^5 groups,
- phenyl fused to a 5-6 membered monocyclic heterocycloalkyl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, which heterocycloalkyl is optionally substituted with one or more =O, or
- 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^5 groups;

R^2 is independently selected from:

- H,
- OH,
- C_{1-4} alkoxy, and
- C_{1-4} alkyl optionally substituted with one
  - OH,
  - CN,
  - C_{1-4} alkoxy optionally substituted with one phenyl, or
  - 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl;

each R^{3a}, and R^{3b} is independently selected from:

- H, and
- C_{1-4} alkyl;

Cy is

- 6-10 membered monocyclic or fused bicyclic aryl optionally substituted with one or more independently selected R^6 groups,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^6 groups;

R^4 is

- halo,
- OH,
- CN,
- C_{1-4} alkyl,
- C_{1-4} alkoxy optionally substituted with one C_{1-4} alkoxy, or phenyl,
- C_{1-4} thioalkoxy,
- 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, optionally substituted with one or more halo, or $-C(=O)OC_{1-4}$ alkyl,
- Phenyl,
- $-S(=O)_2C_{1-4}$ alkyl,
- $-C(=O)OR^{7a}$,
- $-C(=O)NR^{7b}R^{7c}$,
- $-NHC(=O)OR^{7d}$,
- $-NHC(=O)R^{7e}$, or
- $-NR^{8a}R^{8b}$;

each R^5 is

- halo,
- OH,
- CN,
- C_{1-4} alkyl optionally substituted with one or more independently selected halo, $-NR^{9a}R^{9b}$, $-C(=O)NR^{9c}R^{9d}$,
- C_{1-4} alkoxy optionally substituted with one $-NR^{9e}R^{9f}$, or
- $-S(=O)_2C_{1-4}$ alkyl;

each R^6 is

- halo,

- -CN,
- $-NO_2$,
- $-CH_3$,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected halo, C_{1-4} alkyl, C_{1-4} alkoxy, or
- $-NR^{9g}R^{9h}$;

each R^{7a}, R^{7b}, R^{7c}, R^{7d}, or R^{7e}, is

- H, or
- C_{1-4} alkyl optionally substituted with one OH, or C_{1-4} alkoxy;

each R^{8a}, or R^{8b} is independently selected from

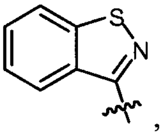
- H, and
- C_{1-4} alkyl optionally substituted with OH, C_{1-4} alkoxy, or phenyl;

each R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, and R^{9h} is independently selected from H, and C_{1-4} alkyl;

or a pharmaceutically acceptable salt, or a solvate, or a pharmaceutically acceptable salt of a solvate thereof; or a biologically active metabolite thereof;

provided that:

- R^1, and R^2 are not simultaneously H, and
- When R^1 is Me, X is N, then Cy is not



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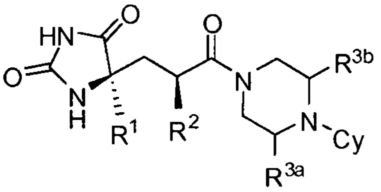
or a pharmaceutically acceptable salt, or a solvate, or the salt of the solvate thereof.

2. A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein the compound is according to Formula II:



II

3. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is H.

4. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is C_{1-4} alkyl.

5. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is Me, Et, Pr, iPr, or tBu.

6. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is C_{1-4} alkyl substituted with one or more independently selected R^4 groups.

7. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is Me, Et, Pr, iPr, or tBu substituted with one or more independently selected R^4 groups.

8. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is C_{1-4} alkyl substituted with one R^4 group.

9. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is Me, Et, Pr, iPr, or tBu substituted with one R^4 group.

10. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is C_{3-7} monocyclic cycloalkyl.

11. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

12. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is cyclopropyl.

13. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is selected from F, Cl, OH, and CN.

14. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is C_{1-4} alkoxy.

15. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is OMe, OEt, or OiPr.

16. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is C_{1-4} alkoxy substituted with one C_{1-4} alkoxy, or phenyl.

17. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is OMe, OEt, or OiPr, each of which is substituted with one C_{1-4} alkoxy, or phenyl.

18. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is OMe, OEt, or OiPr, each of which is substituted with one OMe, OEt, or phenyl.

19. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is C_{1-4} thioalkoxy.

20. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is -SMe.

21. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O.

22. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl.

23. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, substituted with one or more halo, or $-C(=O)OC_{1-4}$ alkyl.

24. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one or more halo, or $-C(=O)OC_{1-4}$ alkyl.

25. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is phenyl.

26. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is $-S(=O)_2C_{1-4}$ alkyl.

27. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is $-S(=O)_2Me$, or $-S(=O)_2Et$.

28. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is $-C(=O)OR^{7a}$.

29. A compound or pharmaceutically acceptable salt thereof, according to clause 28, wherein R^{7a} is H.

30. A compound or pharmaceutically acceptable salt thereof, according to clause 28, wherein R^{7a} is C_{1-4} alkyl.

31. A compound or pharmaceutically acceptable salt thereof, according to clause 28, wherein R^{7a} is Me, Et, iPr or tBu.

32. A compound or pharmaceutically acceptable salt thereof, according to clause 28, wherein R^{7a} is C_{1-4} alkyl substituted with one OH, or C_{1-4} alkoxy.

33. A compound or pharmaceutically acceptable salt thereof, according to clause 28, wherein R^{7a} is Me, Et, iPr or tBu, each of which is substituted with one OH, or C_{1-4} alkoxy.

34. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is $-C(=O)NR^{7b}R^{7c}$.

35. A compound or pharmaceutically acceptable salt thereof, according to clause 34, wherein each R^{7b} or R^{7c} is independently selected from H, Me, and Et.

36. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is $-NHC(=O)OR^{7d}$.

37. A compound or pharmaceutically acceptable salt thereof, according to clause 36, wherein R^{7d} is selected from H, Me, Et, iPr and tBu.

38. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is $-NHC(=O)R^{7e}$.

39. A compound or pharmaceutically acceptable salt thereof, according to clause 38, wherein R^{7e} is selected from H, Me, Et, iPr and tBu.

40. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 6-9, wherein R^4 is $-NR^{8a}R^{8b}$.

41. A compound or pharmaceutically acceptable salt thereof, according to clause 40, wherein each R^{8a} or R^{8b} is independently selected from H, Me, Et, iPr and tBu.

42. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S.

43. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl.

44. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, substituted with one or more independently selected C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl.

45. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or dioxanyl, each of which is substituted with one or more independently selected F, Cl, $-CH_3$, -C(=O)Me, -C(=O)OMe, or -C(=O)OEt.

46. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is phenyl.

47. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is phenyl substituted with one or more independently selected R^5 groups.

48. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is phenyl substituted with one R^5 group.

49. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S.

50. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridinyl, pyrimidinyl or pyrazinyl.

51. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one or more independently selected R^5 groups.

52. A compound or pharmaceutically acceptable salt thereof, according to clause 1 or 2, wherein R^1 is imidazolyl, pyrazolyl, thiazolyl, oxazolyl, pyridinyl, pyrimidinyl or pyrazinyl, each of which is substituted with one or more independently selected R^5 groups.

53. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is F, Cl, OH, or CN.

54. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is C_{1-4} alkyl.

55. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is Me, or Et.

56. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is C_{1-4} alkyl substituted with one or more independently selected halo.

57. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is Me, or Et, each of which is substituted with one or more independently selected F, or Cl.

58. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is C_{1-4} alkyl substituted with one $-NR^{9a}R^{9b}$.

59. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is Me, or Et, each of which is substituted with one $-NR^{9a}R^{9b}$.

60. A compound or pharmaceutically acceptable salt thereof, according to clause 58 or 59, wherein each R^{9a} or R^{9b} is independently selected from H, Me, and Et.

61. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is C_{1-4} alkyl substituted with one $-C(=O)NR^{9c}R^{9d}$.

62. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is Me, or Et, each of which is substituted with one $-C(=O)NR^{9c}R^{9d}$.

63. A compound or pharmaceutically acceptable salt thereof, according to clause 61 or 62, wherein each R^{9c} or R^{9d} is independently selected from H, Me, and Et.

64. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is C_{1-4} alkoxy.

65. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is OMe, or OEt.

66. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is C_{1-4} alkoxy substituted with one $-NR^{9e}R^{9f}$.

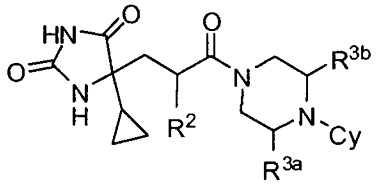
67. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is OMe, or OEt, each of which is substituted with one $-NR^{9e}R^{9f}$.

68. A compound or pharmaceutically acceptable salt thereof, according to clause 66 or 67, wherein each R^{9e} or R^{9f} is independently selected from H, Me, and Et.

69. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is $-S(=O)_2C_{1-4}$ alkyl.

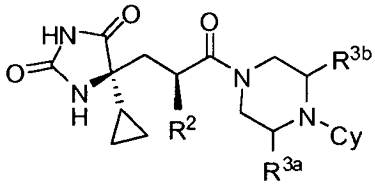
70. A compound or pharmaceutically acceptable salt thereof, according to clause 47, 48, 51 or 52, wherein R^5 is $-S(=O)_2CH_3$.

71. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-70, wherein the compound is according to Formula IIIa or IIIb:



IIIa

or



IIIb

72. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is H.

73. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is -OH.

74. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkoxy.

75. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is –OMe, -OEt, or -OiPr.

76. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl.

77. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is Me, Et, or iPr.

78. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl substituted with one OH, or CN.

79. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is $-CH_2$-OH, or $-CH_2$-CN.

80. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl substituted with one C_{1-4} alkoxy optionally substituted with one phenyl.

81. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is Me, or Et, each of which is substituted with one C_{1-4} alkoxy optionally substituted with one phenyl.

82. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl substituted with one –OMe, -OEt, or $-OCH_2$-Phenyl.

83. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is $-CH_2$-OMe, $-CH_2$-OEt, or $-CH_2$- OCH_2-Phenyl.

84. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl substituted with one 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S.

85. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl substituted with one imidazolyl, pyrazolyl, oxazolyl.

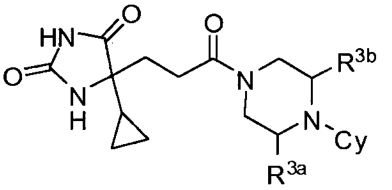
86. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is Me, or Et, each of which is substituted with one imidazolyl, pyrazolyl, oxazolyl.

87. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl substituted with one 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one or more independently selected C_{1-4} alkyl.

88. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is C_{1-4} alkyl substituted with one imidazolyl, pyrrazolyl, oxazolyl, each of which is substituted with one or more independently selected Me, or Et.

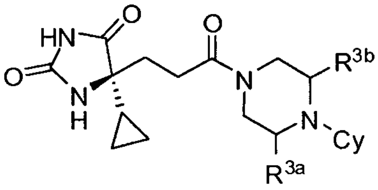
89. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-71, wherein R^2 is Me, or Et, each of which is substituted with one imidazolyl, pyrazolyl, oxazolyl, each of which is substituted with one or more independently selected Me, or Et.

90. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-89, wherein the compound is according to Formula IVa or IVb:



IVa

or



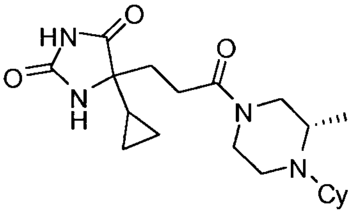
IVb

91. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-90, wherein each R^{3a}, and R^{3b} is independently selected from H, and CH_3.

92. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-90, wherein R^{3a} is H and R^{3b} is selected from CH_3, and CF_3.

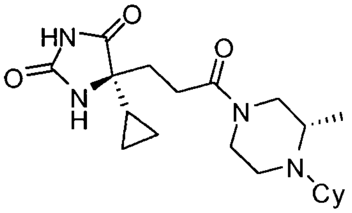
93. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-90, wherein R^{3a} and R^{3b} are H.

94. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-89, wherein the compound is according to Formula Va or Vb:



Va

or



Vb

95. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is 6-10 membered monocyclic or fused bicyclic aryl.

96. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is phenyl, or naphthyl.

97. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is 6-10 membered monocyclic or fused bicyclic aryl, substituted with one or more R^6 groups.

98. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is phenyl, substituted with one or more R^6 groups.

99. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is phenyl, substituted with one, two, or three R^6 groups.

100. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S.

101. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, indazolyl, pyrrolopyridinyl, or benzofuranyl.

102. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, substituted with one or more R^6 groups.

103. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, indazolyl, pyrrolopyridinyl, or benzofuranyl, each of which is substituted with one or more R^6 groups.

104. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-94, wherein Cy is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, indazolyl, pyrrolopyridinyl, or benzofuranyl, each of which is substituted with one, two, or three R^6 groups.

105. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is F, Cl, CN, or NO_2.

106. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is $-CH_3$.

107. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S.

108. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, or pyrimidinyl.

109. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, substituted with one or more independently selected halo, C_{1-4} alkyl, or C_{1-4} alkoxy.

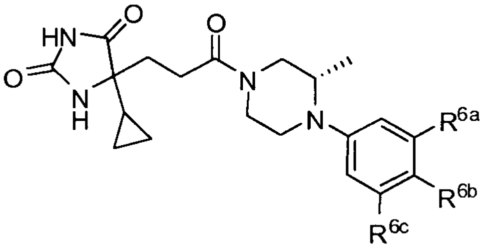
110. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, or pyrimidinyl, each of which is substituted with one or more independently selected halo, C_{1-4} alkyl, or C_{1-4} alkoxy.

111. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is pyrrazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridinyl, pyrazinyl, pyridazinyl, or pyrimidinyl, each of which is substituted with one or more independently selected F, Cl, Me, Et, OMe, or OEt.

112. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 97-99, 102-104, wherein R^6 is $-NR^{9g}R^{9h}$.

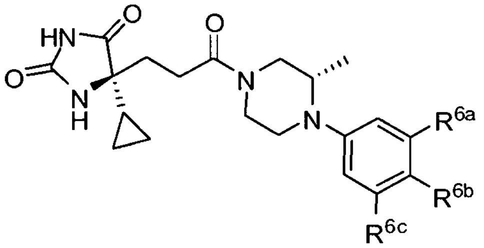
113. A compound or pharmaceutically acceptable salt thereof, according to clause 113, wherein each R^{9g} or R^{9h} is independently selected from H, Me, or Et.

114. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-89, wherein the compound is according to Formula VIa or VIb:



VIa

or



VIb

wherein each one of R^{6a}, R^{6b} and R^{6c} is independently selected from H, F, Cl, and $-CH_3$.

115. A compound or pharmaceutically acceptable salt thereof, according to clause 115, wherein each R^{9g} or R^{9h} is independently selected from H, Me, and Et.

116. A compound or pharmaceutically acceptable salt thereof, according to clause 115, wherein R^{6b} is H, and each one of R^{6a}, and R^{6c} is independently selected from H, halo, and $-CH_3$.

117. A compound or pharmaceutically acceptable salt thereof, according to clause 115, wherein R^{6b} is H, and each one of R^{6a}, and R^{6c} is independently selected from H, F, Cl, and $-CH_3$.

118. A compound or pharmaceutically acceptable salt thereof, according to clause 115, wherein R^{6b} is H, and each one of R^{6a}, and R^{6c} is independently selected from H, F, and Cl.

119. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to any one of clauses 1-119.

120. A pharmaceutical composition according to clause 120 comprising a further therapeutic agent.

121. A compound or pharmaceutically acceptable salt thereof, according to any one of clause 1-119, or a pharmaceutical composition according to clause 120 or 121 for use in medicine.

122. A compound or pharmaceutically acceptable salt thereof, according to any one of clause 1-119, or a pharmaceutical composition according to clause 120 or 121 for use in the prophylaxis and/or treatment of

inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

123. A compound or pharmaceutically acceptable salt thereof, according to any one of clause 1-119, or a pharmaceutical composition according to clause 120 or 121 for use in the prophylaxis and/or treatment of osteoarthritis.

124. A compound or pharmaceutically acceptable salt thereof or a pharmaceutical composition for use according to clause 123 or 124, wherein said compound or pharmaceutical composition is administered in combination with a further therapeutic agent.

125. The pharmaceutical composition according to clause 121, or the use according to clause 125, wherein the further therapeutic agent is an agent for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

126. The pharmaceutical composition according to clause 121, or the use according to clause 125, wherein the further therapeutic agent is an agent for the prophylaxis and/or treatment of osteoarthritis.

PHARMACEUTICAL COMPOSITIONS

[0153] When employed as a pharmaceutical, a compound of the invention is typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound of the invention according to Formula I. Generally, a compound of the invention is administered in a pharmaceutically effective amount. The amount of compound of the invention actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound of the invention administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0154] The pharmaceutical compositions of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intra-articular, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, a compound of the invention is preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[0155] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term 'unit dosage forms' refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient, vehicle or carrier. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound of the invention according to Formula I is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about

40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[0156] Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compound of the inventions of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint or orange flavoring.

[0157] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound of the invention according to Formula I in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[0158] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as an ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

[0159] A compound of the invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[0160] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[0161] A compound of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[0162] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 - Tablets

[0163] A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 240-270 mg tablets (80-90 mg of active compound of the invention according to Formula I per tablet) in a tablet press.

Formulation 2 - Capsules

[0164] A compound of the invention according to Formula I may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture may be filled into 250 mg capsules (125 mg of active compound of the invention according to Formula I per capsule).

Formulation 3 - Liquid

[0165] A compound of the invention according to Formula I (125 mg), may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color may be diluted with water and added with stirring. Sufficient water may then be added with stirring. Further sufficient water may be then added to produce a total volume of 5 mL.

Formulation 4 - Tablets

[0166] A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 450-900 mg tablets (150-300 mg of active compound of the invention according to Formula I) in a tablet press.

Formulation 5 - Injection

[0167] A compound of the invention according to Formula I may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

[0168] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of A compound of the invention according to Formula I (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) may be added and the resulting mixture may be stirred until it congeals.

METHODS OF TREATMENT

[0169] In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in medicine. In a particular embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

[0170] In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

[0171] In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is an agent for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

[0172] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition.

[0173] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition.

[0174] In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of inflammatory diseases. In a particular embodiment, the inflammatory disease is selected from rheumatoid arthritis, and osteoarthritis. More particularly, the inflammatory disease is osteoarthritis.

[0175] In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of inflammatory diseases. In a particular embodiment, the inflammatory disease is selected from rheumatoid arthritis, and osteoarthritis. More particularly, the inflammatory disease is osteoarthritis.

[0176] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with inflammatory diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the inflammatory disease is selected from rheumatoid arthritis, and osteoarthritis. More particularly, the inflammatory disease is osteoarthritis.

[0177] In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In a particular embodiment, the diseases involving degradation of cartilage and/or disruption of cartilage homeostasis is selected from osteoarthritis, psoriatic arthritis, juvenile rheumatoid arthritis, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, achondroplasia, Paget's disease, Tietze syndrome or costal chondritis, fibromyalgia, osteochondritis, neurogenic or neuropathic arthritis, arthropathy, sarcoidosis, amylosis, hydarthrosis, periodical disease, rheumatoid spondylitis, endemic forms of arthritis like osteoarthritis deformans endemica, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis. More particularly, the diseases involving degradation of cartilage and/or disruption of cartilage homeostasis is osteoarthritis (OA).

[0178] In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of diseases involving degradation of cartilage and/or disruption of cartilage homeostasis. In a particular embodiment, the diseases involving degradation of cartilage and/or disruption of cartilage homeostasis is selected from osteoarthritis, psoriatic arthritis, juvenile rheumatoid arthritis, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, achondroplasia, Paget's disease, Tietze syndrome or costal chondritis, fibromyalgia, osteochondritis, neurogenic or neuropathic arthritis, arthropathy, sarcoidosis, amylosis, hydarthrosis, periodical disease, rheumatoid spondylitis, endemic forms of arthritis like osteoarthritis deformans endemica, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis. More particularly, the diseases involving degradation of cartilage and/or disruption of cartilage homeostasis is osteoarthritis (OA).

[0179] In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with diseases involving degradation of cartilage and/or disruption of cartilage homeostasis, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the diseases involving degradation of cartilage and/or disruption of cartilage homeostasis is selected from osteoarthritis, psoriatic arthritis, juvenile rheumatoid arthritis, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, achondroplasia, Paget's disease, Tietze syndrome or costal chondritis, fibromyalgia, osteochondritis, neurogenic or neuropathic arthritis, arthropathy, sarcoidosis, amylosis, hydarthrosis, periodical disease, rheumatoid spondylitis, endemic forms of arthritis like osteoarthritis deformans endemica, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis. More particularly the diseases involving degradation of cartilage and/or disruption of cartilage homeostasis is osteoarthritis (OA).

[0180] Injection dose levels range from about 0.1 mg/kg/h to at least 10 mg/kg/h, all for from about 1 to about 120 h and especially 24 to 96 h. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 1 g/day for a 40 to 80 kg human patient.

[0181] For the prophylaxis and/or treatment of long-term conditions, such as degenerative conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to four (1-4) regular doses daily, especially one to three (1-3) regular doses daily, typically one to two (1-2) regular doses daily, and most typically one (1) regular dose daily are representative regimens. Alternatively for long lasting effect drugs, with oral dosing, once every other week, once weekly, and once a day are representative regimens. In particular, dosage regimen can be every 1-14 days, more particularly 1-10 days, even more particularly 1-7 days, and most particularly 1-3 days.

[0182] Using these dosing patterns, each dose provides from about 1 to about 1000 mg of a compound of the invention, with particular doses each providing from about 10 to about 500 mg and especially about 30 to about 250 mg.

[0183] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[0184] When used to prevent the onset of a condition, a compound of the invention will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[0185] A compound of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other compound of the inventions that demonstrate the same or a similar therapeutic activity and that are determined to be safe and efficacious for such combined administration. In a specific embodiment, co-administration of two (or more) agents allows for significantly lower doses of each to be used, thereby reducing the side effects seen.

[0186] In one embodiment, a compound of the invention or a pharmaceutical composition comprising a compound of the invention is administered as a medicament. In a specific embodiment, said pharmaceutical composition additionally comprises a further active ingredient.

[0187] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of a disease involving inflammation, particular agents include, but are not limited to, immunoregulatory agents *e.g.* azathioprine, corticosteroids (*e.g.* prednisolone or dexamethasone), cyclophosphamide, cyclosporin A, tacrolimus, mycophenolate, mofetil, muromonab-CD3 (OKT3, *e.g.* Orthocolone®), ATG, aspirin, acetaminophen, ibuprofen, naproxen, and piroxicam.

[0188] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of arthritis (*e.g.* rheumatoid arthritis), particular agents include but are not limited to analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, synthetic DMARDS (for example but without limitation methotrexate, leflunomide, sulfasalazine, Auranofin , sodium aurothiomalate, penicillamine, chloroquine, hydroxychloroquine, azathioprine, tofacitinib, baricitinib, fostamatinib, and cyclosporin), and biological DMARDS (for example but without limitation infliximab, etanercept, adalimumab, rituximab, and abatacept).

[0189] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of SLE, particular agents include but are not limited to: human monoclonal antibodies (belimumab (Benlysta)), Disease-modifying antirheumatic drugs (DMARDs) such as antimalarials (*e.g.* plaquenil, hydroxychloroquine), immunosuppressants (*e.g.* methotrexate and azathioprine), cyclophosphamide and mycophenolic acid, immunosuppressive drugs and analgesics, such as nonsteroidal anti-inflammatory drugs, opiates (*e.g.* dextropropoxyphene and co-codamol), opioids (*e.g.* hydrocodone, oxycodone, MS Contin, or methadone) and the fentanyl duragesic transdermal patch.

[0190] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of psoriasis, particular agents include but are not limited to: topical treatments such as bath solutions, moisturizers, medicated creams and ointments containing coal tar, dithranol (anthralin), corticosteroids like desoximetasone (Topicort™), fluocinonide, vitamin D3 analogues (for example, calcipotriol), argan oil and retinoids (etretinate, acitretin, tazarotene), systemic treatments such as methotrexate, cyclosporine, retinoids, tioguanine, hydroxyurea, sulfasalazine, mycophenolate mofetil, azathioprine, tacrolimus, fumaric acid esters or biologics such as Amevive™, Enbrel™, Humira™, Remicade™, Raptiva™ and ustekinumab (a IL-12 and IL-23 blocker). Additionally, a compound of the invention may be administered in combination with other therapies including, but not limited to phototherapy, or photochemotherapy (*e.g.* psoralen and ultraviolet A phototherapy (PUVA)).

[0191] By co-administration is included any means of delivering two or more therapeutic agents to the patient as part of the same treatment regime, as will be apparent to the skilled person. Whilst the two or more agents may be administered simultaneously in a single formulation, *i.e.* as a single pharmaceutical composition, this is not essential. The agents may be administered in different formulations and at different times.

CHEMICAL SYNTHETIC PROCEDURES

General

[0192] The compound of the invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.* reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0193] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art(Wuts and Greene, 2012).

[0194] The following methods are presented with details as to the preparation of a compound of the invention as defined hereinabove and the comparative examples. A compound of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

[0195] All reagents are of commercial grade and are used as received without further purification, unless otherwise stated. Commercially available anhydrous solvents are used for reactions conducted under inert atmosphere. Reagent grade solvents are used in all other cases, unless otherwise specified. Column chromatography is performed on silica gel 60 (35-70 µm). Thin layer chromatography is carried out using pre-coated silica gel 60F-254 plates (thickness 0.25 mm). ^{1}H NMR spectra are recorded on a 400 MHz Avance Bruker spectrometer or a 300 MHz DPX Bruker spectrometer. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or the appropriate residual solvent peak, i.e. $CHCl_3$ (δ 7.27), as internal reference. Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quin), multiplet (m) and broad (br). Electrospray MS spectra are obtained on a Waters platform LC/MS spectrometer or with Waters Acquity UPLC with Waters Acquity PDA detector and SQD mass spectrometer. Columns used: UPLC BEH C18 1.7µm 2.1x5mm VanGuard Pre-column with Acquity UPLC BEH C18 1.7 µm 2.1x30mm Column or Acquity UPLC BEH C18 1.7µm 2.1x50mm Column. All the methods are using MeCN/H_2O gradients. MeCN and H_2O contain either 0.1% Formic Acid or 0.05% NH_3. Preparative LCMS: column used, Waters XBridge Prep C18 5µm ODB 30mm ID x 100mm L (preparative column) and Waters XBridge C18 5µm 4.6mm ID x 100mm L (analytical column). All the methods are using MeCN/H_2O gradients. MeCN and H_2O contain either 0.1% Formic Acid or 0.1% Diethylamine. Chiral HPLC analysis are obtained from a Waters 2690 Alliance HPLC system.Microwave heating is performed with a Biotage Initiator. Optical rotation was determined on a Dr. Kernchen Propol digital automatic polarimeter.

Table I. List of abbreviations used in the experimental section:

Abbreviation	Definition
µL	microliter
AUC	Area Under the Curve
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Bn	Benzyl
br. d	Broad doublet

Abbreviation	Definition
Boc	tert-Butyloxy-carbonyl
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
br. s	Broad singlet
br. t	Broad triplet
Cat.	Catalytic amount
CDI	1,1'-Carbonyldiimidazole
$COCl_2$	Phosgene
Cpd	Compound
d	doublet
DavePhos	2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIPE	Diisopropylether
DIPEA	N,N-diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethylsulfoxide
dppf	1,1'- Bis(diphenylphosphino) ferrocene
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)
EDC.HCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
eq.	Equivalent
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FBS	Fetal bovine serum
g	gram
h	hour
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HPLC/MS	High-performance liquid chromatography / mass-spectrometry
HRMS	High-resolution Mass Spectrometry
HRP	horseradish peroxydase
Int	Intermediate
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
kg	kilogram
L	liter
LCMS	Liquid Chromatography- Mass Spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
m	multiplet

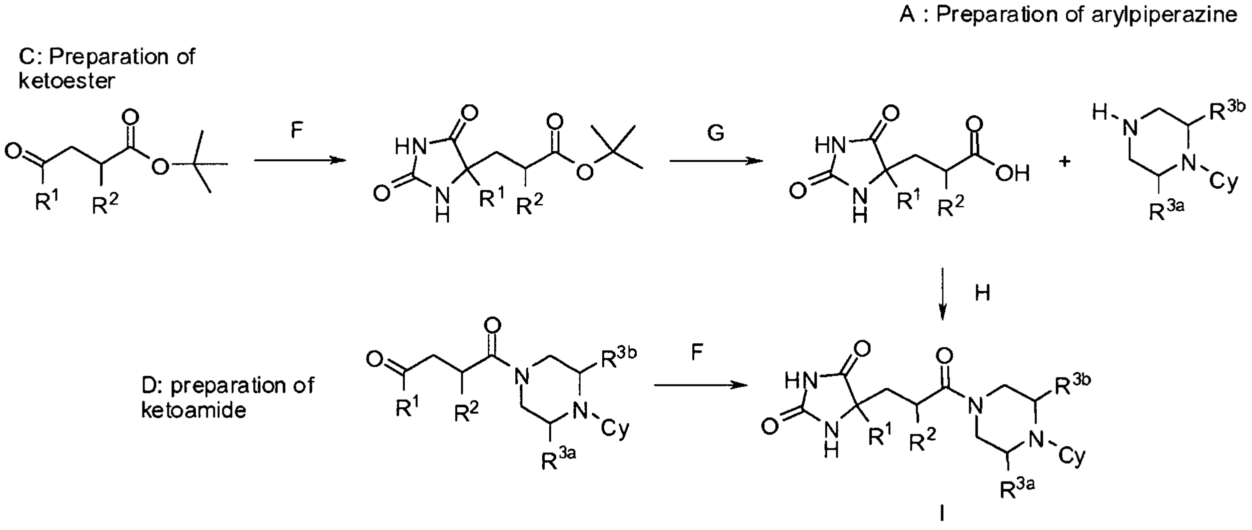
Abbreviation	Definition
m-CPBA	3-Chloroperbenzoic acid
MeCN	Acetonitrile
MEK	Methyl ethyl ketone
Meldrum's acid	2,2-dimethyl-1,3-dioxane-4,6-dione
MeOH	Methanol
mg	milligram
min	minute
mL	millilitre
mmol	millimoles
MMP	Matrix Metallo Proteinase
Ms'd	Mass measured by LCMS
Mtd	Method
Mukaiyama reagent	2-Chloro-1-methylpyridinium iodide
MW	Molecular weight
N.A.	Not available
n/a	No measurable activity
iPrOH	Isopropyl alcohol
nBuOH	n-Butanol
NMR	Nuclear Magnetic Resonance
PBF	phosphate buffered formalin
PBS	Phosphate buffered salin
$P(tBu)_3$	Tristertbutylphosphine
$P(Bu)_3$	Tributylphosphine
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd/C	Palladium on Carbon 10%
$Pd_2(dba)_3$	Tris(dibenzylideneacetone) dipalladium(0)
$PdCl_2(dppf)$	[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)
$PdCl_2[P(o\text{-}Tol)_3]_2$	Dichlorobis(tri-*o*-tolylphosphine)palladium(II)
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(OH)_2/C$	Palladium hydroxide on carbon
PEG	Polyethylene glycol
PEPPSI™-IPr	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl) palladium(II) dichloride
ppm	part-per-million
PS-CDI	Polymer supported 1,1'-Carbonyldiimidazole
PS-Mukaiyama reagent	Polymer supported Mukaiyama reagent
q	quadruplet
r.t.	room temperature
RNA	Ribonucleic acid
Rt	retention time
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	singlet
SCX	Biotage Isolute® SCX(Biotage Part 530)
SCX-2	Biotage Isolute® SCX-2 (Biotage Part 532)
sept	septuplet
SFC	Supercritical fluid chromatography

Abbreviation	Definition
SM	Starting Material
Ster	Stereochemistry
t	triplet
TBAF	Tetra-*n*-butylammonium fluoride
5(6)-TAMRA	5(6)-Carboxytetramethylrhodamine (CAS# 98181-63-6)
5-FAM	5-carboxyfluorescein (CAS# 76823-03-5)
t-BuOH	Tert-butanol
TBDPSCl	Tert-butyldiphenylsilyl chloride
TBSCl	Tert-butyldimethylsilyl chloride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TIPS	triisopropyl silyl
UPLC/MS	Ultra-performance liquid chromatography / mass-spectrometry
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

SYNTHETIC PREPARATION OF THE COMPOUND OF THE INVENTION

Example 1. General synthetic methods

1.1. Synthetic methods overview



General methods A: Preparation of arylpiperazine

Method A1 : NBoc protection

Method A2 : Buchwald reaction with NBoc-piperazine

Method A3 : Suzuki reaction

Method A4 : SNAr with NBoc-piperazine

Method A5 : NBoc deprotection

Method A6 : with TIPS protecting group

Method A7 : Buchwald reaction with NH-piperazine

Method A8 : SNAr with NH-piperazine

General methods C: Preparation of ketoester

Method C1 : from Meldrum's acid

Method C2 : with tert-butyl bromoacetate

Method C3: esterification

Method C4 : Stetter reaction

Method C5 : via epoxide opening

General method D: preparation of ketoamide

Method D1: preparation of acrylamide

Method D2: Stetter reaction

Method D4 : Oxidative cleavage

Method D5 : via furan oxidation

Method D6 : via a-bromo ketone

Method D7 : ketoamide functionalization by Suzuki coupling

General method E: Functionalization of g-ketoamide

General method F: Bucherer Bergs reaction

General method G : Method for preparation of hydantoin propionic acids

General method H : Amide bond formation

Method H1 : EDC/HOBt

Method H2 : HATU

Method H3 : BOP

Method H4 : CDI

Method H5 : Mukaiyama reagent

General method I : Functionalization of final compound

Method I1: acetylation

Method I2 : N-Boc deprotection

Method I3 : alkylation

Method I4 : O-debenzylation

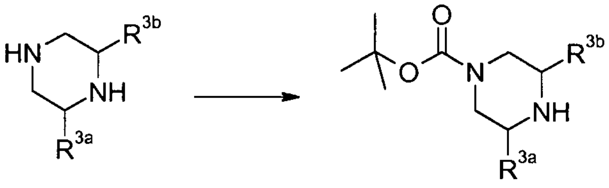
Method I5 : Two-steps functionalization by Suzuki reaction

Method I6 : Suzuki reaction

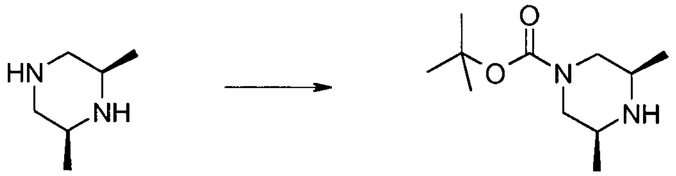
1.2. General methods

1.2.1. General methods A: Preparation of arylpiperazine

1.2.1.1. Method A1 : NBoc protection

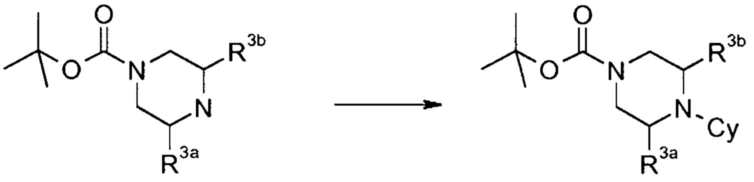


1.2.1.2. Illustrative synthesis of cis-3,5-dimethyl-piperazine-1-carboxylic acid tert-butyl ester



[0196] To a solution of the cis-2,6-dimethyl-piperazine (2 g, 17.515 mmol, 1 eq.) in DCM (200 mL) at 0°C is added dropwise a solution of di-*tert*-butyl dicarbonate in DCM (20 mL). After 3.5h, reaction mixture is quenched by a saturated Na_2CO_3 solution, the organic layer is separated, and the aqueous layer is extracted with DCM. The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 90/10) affords the expected product.

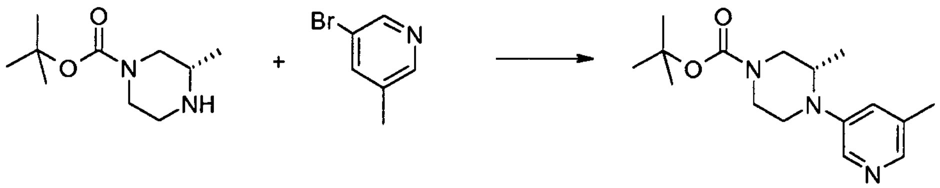
1.2.2. Method A2 : Buchwald reaction with NBoc-piperazine



1.2.2.1. Method A2a ($Pd_2(dba)_3$/BINAP)

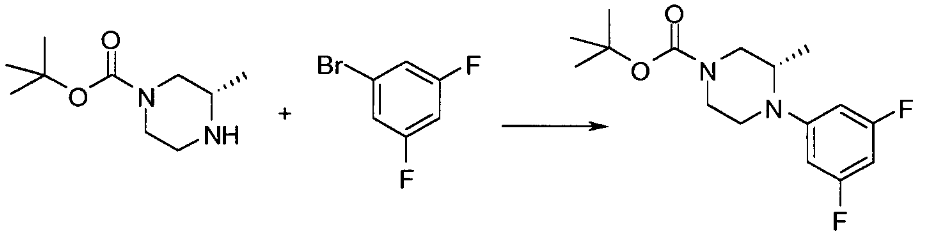
[0197] A flask is charged with N-Boc protected piperazine (1 eq.), bromoderivative (0.5-2 eq.), BINAP (0.042-0.12 eq.), NaOtBu (0.7-1.4 eq.) and toluene. The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (0.021-0.06 eq.) is added. Reaction mixture is heated at 90-110°C for 2h-20h. The reaction mixture is quenched by addition of water or saturated $NaHCO_3$ solution, extracted with DCM or EtOAc. The combined organic layers are washed with water and brine, dried (over anhydrous Na_2SO_4 or $MgSO_4$), filtered and concentrated *in vacuo* to afford the expected arylpiperazine (used as such or purified by flash chromatography on silica gel).

Illustrative synthesis of (S)-3-Methyl-4-(5-methyl-pyridin-3-yl)-piperazine-1-carboxylic acid tert-butyl ester



[0198] A flask is charged with (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (291 mg, 1.453 mmol, 1 eq.), 3-bromo-5-methyl-pyridine (300 mg, 1.744 mmol, 1.2 eq.), BINAP (45 mg, 0.073 mmol, 0.05 eq.), NaOtBu (196 mg, 2.034 mmol, 1.4 eq.) and toluene (2 mL). The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (33 mg, 0.036 mmol, 0.025 eq.) is added. Reaction mixture is heated at 110°C overnight, quenched with water, extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 98/2) affords the expected product. LCMS: MW (calcd): 291; m/z MW (obsd): 292 (M+H).

Illustrative synthesis of (S)-4-(3,5-Difluoro-phenyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester

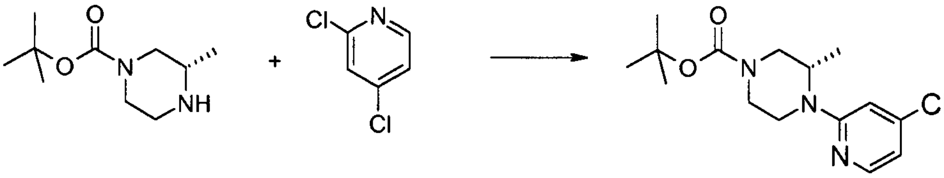


[0199] A flask is loaded with (*S*)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester (75 g, 0.374 mol, 1eq.) and dry toluene (375 mL). The reaction mixture is degassed with N_2, 1-Bromo-3,5-difluoro-benzene (47.3 mL, 0.412 mol, 1.1 eq.), NaO^tBu (50.4 g, 0.524 mol, 1.4 eq.) and BINAP (11.66 g, 0.019 g, 0.05 eq.) are added. The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (5.14g, 0.006 mol, 0.015 eq.) is added. Reaction mixture is stirred at 110°C for 2.5h, quenched with water and EtOAc, extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected N-Boc-arylpiperazine. LCMS: MW (calcd): 312; m/z MW (obsd): 313 (M+H).

1.2.2.1.1 Method A2b ($Pd(OAc)_2$/JohnPhos)

[0200] A flask is charged with N-Boc protected piperazine (1 eq.), halide derivative (1.1-1.2 eq.), JohnPhos (0.1-0.12 eq.), NaOtBu (1.2-1.4 eq.) and toluene. The reaction mixture is degassed with N_2 and $Pd(OAc)_2$ (0.06-0.1 eq.) is added. Reaction mixture is heated at 100°C for 2h-20h, quenched by addition of water or saturated $NaHCO_3$ solution, extracted with DCM or EtOAc. The combined organic layers are washed with water and brine, dried (over anhydrous Na_2SO_4 or $MgSO_4$), filtered and concentrated *in vacuo* to afford the expected arylpiperazine after purification by flash chromatography on silica gel.

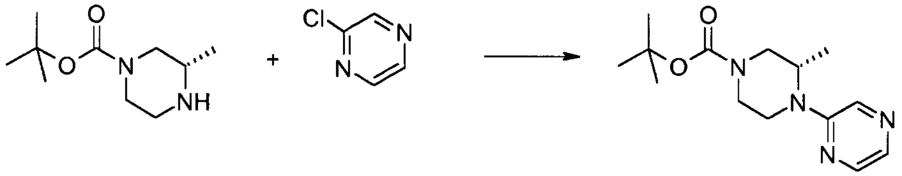
Illustrative synthesis of (S)-4-(4-Chloro-pyridin-2-yl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester



[0201] A flask is charged with (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (1 g, 4.993 mmol, 1 eq.), 2,4-dichloro-pyridine (887 mg, 5.992 mmol, 1.2 eq.), JohnPhos (149 mg, 0.499 mmol, 0.1 eq.), NaOtBu (672 mg, 6.990 mmol, 1.4 eq.) and toluene (5 mL). The reaction mixture is degassed with N_2 and $Pd(OAc)_2$ (112 mg, 0.499 mmol, 0.1 eq.) is added. Reaction mixture is heated at 100°C overnight, quenched by addition of water, extracted with EtOAc. The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel affords the expected product. LCMS: MW (calcd): 312; m/z MW (obsd): 312-314 (M+H).

1.2.2.1.2 *Method A2c (PEPPSI)*

Illustrative synthesis of (S)-2-Methyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester

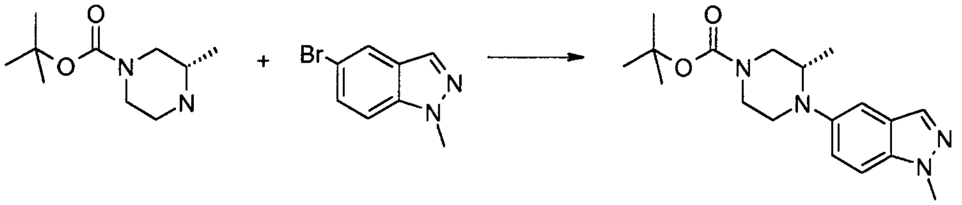


[0202] A flask is charged with (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (3 g, 14.979 mmol, 1 eq.), 2-chloropyrazine (1.71g, 14.979 mmol, 1eq.), Cs_2CO_3 (6.83g, 20.97 mmol, 1.4 eq.) and DME (60 mL). The reaction mixture is degassed with N_2 and PEPPSI™-IPr (0.2g, 0.3 mmol, 0.02 eq.) is added. Reaction mixture is heated at 110°C overnight, quenched with water, extracted with Et_2O. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with Heptane/EtOAc 80/20 to 30/70) affords the expected product. LCMS: MW (calcd): 278; m/z MW (obsd): 279 (M+H).

1.2.2.1.3 *Method A2d ($Pd(OAc)_2/P(tBu)_3$)*

[0203] A flask is charged with N-Boc protected piperazine (1 eq.), bromo derivative (1.1 eq.), $Pd(OAc)_2$ (0.06 eq.), NaOtBu (1.5 eq.) and toluene. The reaction mixture is degassed with N_2 and $P(tBu)_3$ (1M solution in toluene, 0.12 eq.) is added. Reaction mixture is heated at 105°C for 4h-20h, filtered on celpure P65, washed with EtOAc and DCM. The filtrate is concentrated *in vacuo* to afford the expected arylpiperazine after purification by flash chromatography on silica gel.

Illustrative synthesis of (S)-3-Methyl-4-(1-methyl-1H-indazol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester

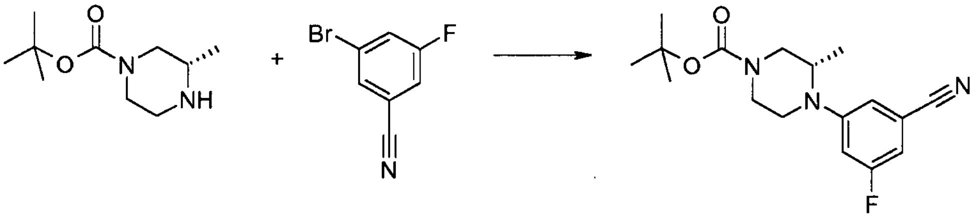


[0204] A flask is charged with (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (50 mg, 0.25 mmol, 1 eq.), 5-bromomethylindazole (58 mg, 0.27 mmol, 1.1 eq.), Pd(OAc)$_2$ (3 mg, 0.015 mmol, 0.06 eq.), NaOtBu (36 mg, 0.38 mmol, 1.5 eq.) and toluene. The reaction mixture is degassed with N$_2$ and P(tBu)$_3$ (1M solution in toluene, 30 µL, 0.03 mmol, 0.12 eq.) is added. Reaction mixture is heated at 105°C overnight, filtered on celpure P65, washed with EtOAc and DCM. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 70/30) to afford the expected product. LCMS: MW (calcd): 330; m/z MW (obsd): 331 (M+H).

1.2.2.1.4 Method A2e (Pd$_2$(dba)$_3$/Xantphos)

[0205] A flask is charged with N-Boc protected piperazine (1 eq.), bromo derivative (0.67 eq. to 1.1 eq.), a base (Cs$_2$CO$_3$, 2eq. or NaOtBu, 1.4 eq.), Xantphos (0.12 eq.) and a solvent (toluene or dioxane). The reaction mixture is degassed with N$_2$ and Pd$_2$(dba)$_3$ (0.06 eq.) is added. Reaction mixture is heated at 115°C for 4.5h and is either filtered on celpure P65 or submitted to water/EtOAc work up. The filtrate is concentrated *in vacuo* to afford the expected arylpiperazine after purification by flash chromatography on silica gel.

Illustrative synthesis of (S)-4-(3-Cyano-5-fluoro-phenyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester

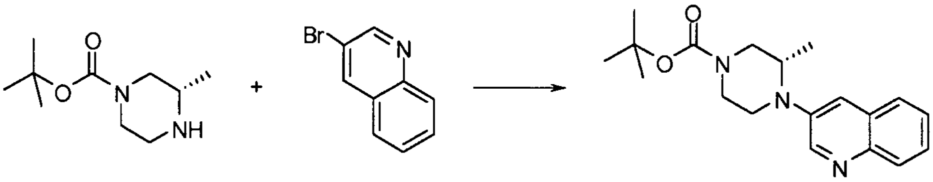


[0206] A flask is charged with (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (100 mg, 0.50 mmol, 1 eq.), 3-bromo-5-fluoro-benzonitrile (110 mg, 0.55 mmol, 1.1 eq.), NaOtBu (67 mg, 0.7 mmol, 1.4 eq.), Xantphos (35 mg, 0.06 mmol, 0.12 eq.) and toluene (2 mL). The reaction mixture is degassed with N$_2$ and Pd$_2$(dba)$_3$ (27 mg, 0.03 mmol, 0.06 eq.) is added. Reaction mixture is heated at 115°C for 4.5h and filtered on celpure P65. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 80/20) to afford the expected product. LCMS: MW (calcd): 319; m/z MW (obsd): 320 (M+H).

1.2.2.1.5 Method A2f ($Pd_2(dba)_3$/DavePhos)

[0207] A flask is charged with N-Boc protected piperazine (1 eq.), bromoderivative (1.1 eq.), DavePhos (0.12 eq.), NaOtBu (1.2 eq.) and toluene. The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (0.06 eq.) is added. Reaction mixture heated at 90-110°C for 2h-20h and filtered on celpure P65. The filtrate is concentrated *in vacuo* to afford the expected arylpiperazine after purification by flash chromatography on silica gel.

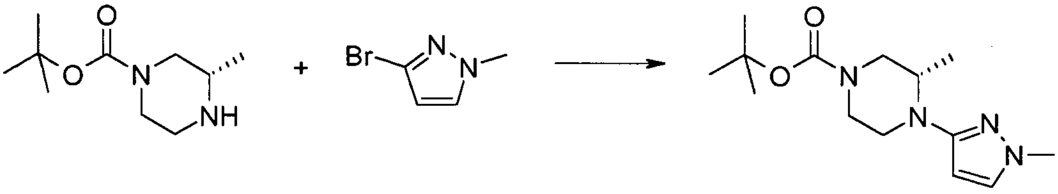
Illustrative synthesis of (S)-3-Methyl-4-quinolin-3-yl-piperazine-1-carboxylic acid tert-butyl ester



[0208] A flask is charged with (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (100 mg, 0.50 mmol, 1 eq.), 3-bromoquinoleine (114 mg, 0.55 mmol, 1.1 eq.), DavePhos (24 mg, 0.06 mmol, 0.12 eq.), NaOtBu (58 mg, 0.60 mmol, 1.2 eq.) and toluene (2 mL). The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (27 mg, 0.03 mmol, 0.06 eq.) is added. Reaction mixture is heated at 95°C overnight and filtered on celpure P65. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 70/30) to afford the expected product. LCMS: MW (calcd): 327; m/z MW (obsd): 328 (M+H).

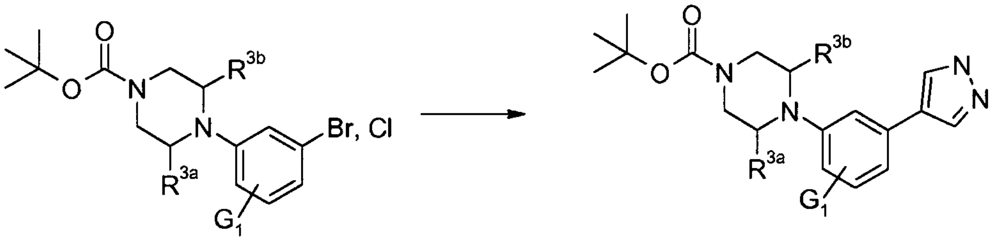
1.2.2.1.6 Method A2g ($Pd_2(dba)_3$/Xphos)

Illustrative synthesis of (S)-3-Methyl-4-(1-methyl-1H-pyrazol-3-yl)-piperazine-1-carboxylic acid tert-butyl ester



[0209] A flask is charged with (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (500 mg, 2.5 mmol, 1 eq.), 3-bromo-1-methyl-1H-pyrazole (442 mg, 2.75 mmol, 1.1 eq.), NaOtBu (288 mg, 3 mmol, 1.2 eq.), XPhos (143 mg, 0.3 mmol, 0.12 eq.) and tolulene (15 mL). The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (137 mg, 0.15 mmol, 0.06 eq.) is added. Reaction mixture is heated at 105°C overnight, quenched with saturated $NaHCO_3$ solution, extracted with EtOAc. The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 50/50) to afford the expected product. LCMS: MW (calcd): 280; m/z MW (obsd): 281 (M+H).

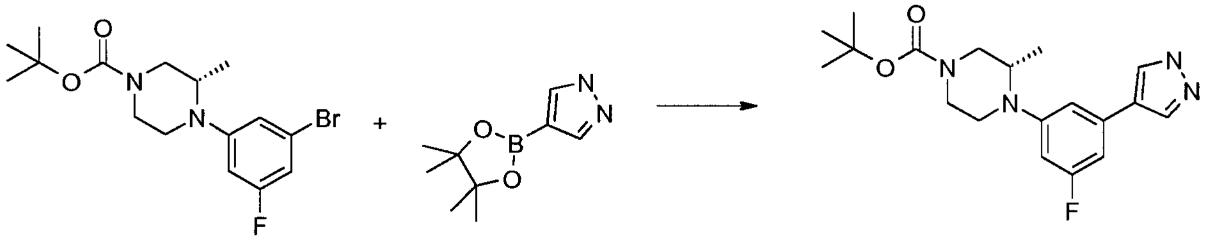
1.2.2.2. Method A3 : Suzuki reaction



G_1=H, C or F

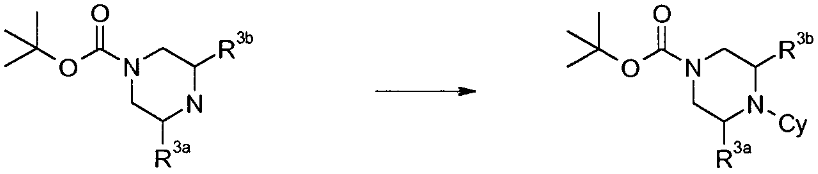
[0210] A solution of Na_2CO_3 (3 eq.) in water is added to a mixture of halogeno derivative (1 eq., obtained by any method A2), boronic ester (2 eq.) and dioxane degassed with argon. $PdCl_2$(dppf) (0.2 eq.) is added, and the reaction is stirred at 140°C in a microwave reactor for 30 min to 45 min. The reaction mixture is poured in water and DCM. The organic layer is washed with water and concentrated *in vacuo* to afford the expected arylpiperazine (used as such or purified by flash chromatography on silica gel).

Illustrative synthesis of (S)-4-[3-Fluoro-5-(1H-pyrazol-4-yl)-phenyl]-3-methyl-piperazine-1-carboxylic acid tert-butyl ester



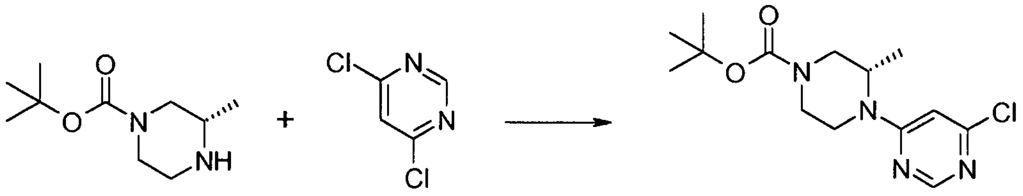
[0211] A solution of Na_2CO_3 (771 mg, 4.02 mmol, 3 eq.) in water (4 mL) is added to a mixture of ((S)-4-(3-Bromo-5-fluoro-phenyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (500 mg, 1.34 mmol, 1 eq.), 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (520 mg, 2.68 mmol, 2 eq.) and dioxane (8 mL) degassed with argon. $PdCl_2$(dppf) (219 mg, 0.27 mmol, 0.2 eq.) is added, and the reaction is stirred at 140°C in a microwave reactor for 40 min. Reaction mixture is poured in 50 mL water and 50 mL DCM and extracted. The organic layer is washed with water and concentrated *in vacuo* to afford the expected product used in next reaction step without further purification. LCMS: MW (calcd): 360; m/z MW (obsd): 361 (M+H).

1.2.2.3. Method A4 : SNAr with NBoc-piperazine



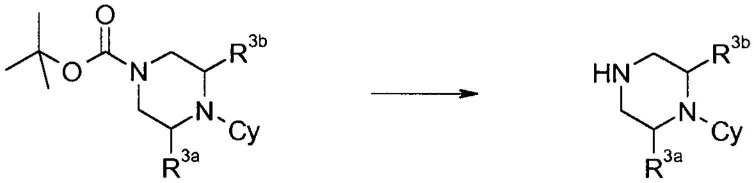
[0212] A vial is charged with arylchloride derivative (1 eq.), (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (1 to 1.6 eq.), a base (Et_3N or DIPEA, 1 to 3 eq.) and a solvant (DCM, DMF, THF or MeCN). The reaction mixture is heated (60°C-120°C) for 1.5h to 5 days. The appropriate work up (concentration in vacuo or aqueous work up extracting with EtOAc) followed by purification by flash chromatography on silica gel affords the expected arylpiperazine.

Illustrative synthesis of (S)-4-(6-Chloro-pyrimidin-4-yl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester



[0213] A vial is charged with 4,6-dichloropyrimidine (3.55 g, 23.83 mmol, 1 eq.), (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (5g, 25.02 mmol, 1.05 eq.), Et_3N (3.35 mL, 23.83 mmol, 1 eq.) and CH_3CN (70 mL). The reaction mixture is heated at 120°C for 1.5h, concentrated *in vacuo* and the residue is taken up in EtOAC, washed with a saturated NH_4Cl solution, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 90/10 to 80/20) to afford the expected product. LCMS: MW (calcd): 323; m/z MW (obsd): 313-315 (M+H).

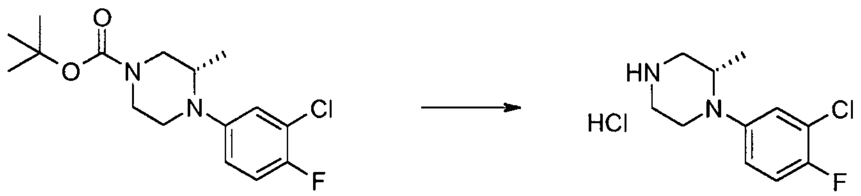
1.2.2.4. Method A5 : NBoc deprotection



1.2.2.4.1 Method A5a (HCl)

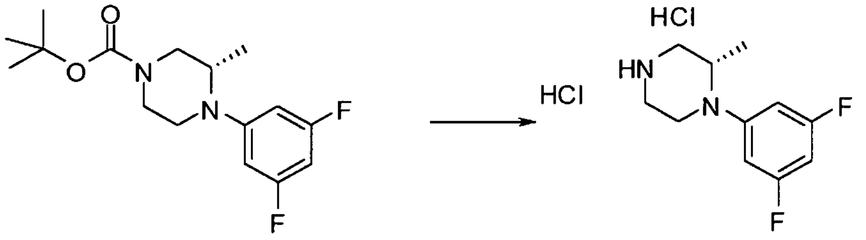
[0214] A flask is charged with N-*tert*-butoxycarbonyl derivative (1 eq.), HCl 4N in dioxane (10 to 40 eq.) is added. The reaction mixture is stirred at r.t. for 1h to 2 days. If a precipitate is formed, it is filtered and washed with Et_2O or CH_3CN, otherwise, the reaction mixture is concentrated *in vacuo*. Both work up afford the expected arylpiperazine as hydrochloride salt.

Illustrative synthesis of ***Int 198***



[0215] A flask is charged with N-*tert*-butoxycarbonyl derivative (4.06g, 12.35 mmol, 1 eq.), HCl 4N in dioxane (100 mL, 400 mmol, 32 eq.) is added. The reaction mixture is stirred at r.t. overnight and concentrated *in vacuo*. The residue is triturated in Et_2O, filtered and dried *in vacuo* to afford the expected product as hydrochloride salt. LCMS: MW (calcd): 229; m/z MW (obsd): 229-231 (M+H).

Illustrative synthesis of (2S)-1-(3,5-difluorophenyl)-2-methyl-piperazine ***(Int 207)***

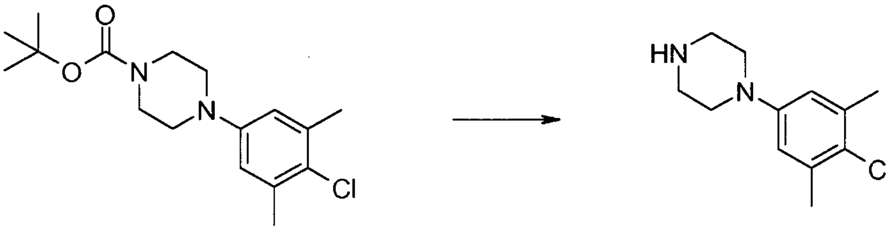


[0216] A flask is loaded with (S)-4-(3,5-Difluoro-phenyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (64g, 0.204 mol, 1eq.) and acetonitrile (191 mL). HCl 4N in dioxane (255 mL, 1.018 mol, 5 eq.) is added at 0°C and the reaction mixture is stirred at 0°C for 1.5h then at r.t. for 3.5h. The precipitate is filtered, washed with acetonitrile and Et_2O, suspended in a mixture acetonitrile/Et_2O (300 mL/100mL) and stirred at r.t. ovenright. The suspension is filtered; the precipitate is washed again with acetonitrile and Et_2O and dried *in vacuo* to afford the expected arylpiperazine hydrochloride salt. LCMS: MW (calcd): 212; m/z MW (obsd): 213 (M+H).

1.2.2.4.2 Method A5b (HCl + basic work up)

[0217] To a solution of N-*tert*-butoxycarbonyl derivative (1 eq.) in acetonitrile or DCM is added HCl 4N in dioxane (10 to 40 eq.). The reaction mixture is stirred at r.t. for 1h to 2 days, concentrated *in vacuo* and the residue is taken up in water and EtOAc or DCM. The aqueous layer is separated and basified (with either NaOH 1N solution or with a saturated Na_2CO_3 or $NaHCO_3$ solution) and extracted with EtOAc or DCM. The combined organic layers are dried over anhydrous Na_2SO_4 (or $MgSO_4$), filtered and concentrated *in vacuo* to afford the expected arylpiperazine.

Illustrative synthesis of ***Int 278***

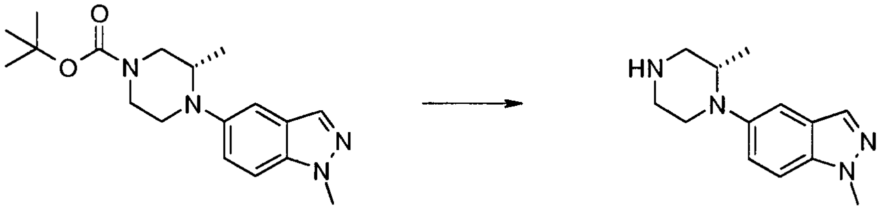


[0218] N-*tert*-butoxycarbonyl derivative (632 mg, 2.88 mmol, 1 eq.) is stirred in HCl 4N in dioxane (6 mL) at room temperature for 3 hours. The reaction mixture is diluted with water, a solution of saturated $NaHCO_3$ is added and the aqueous layer is extracted with DCM several times. The combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 224; m/z MW (obsd): 225-227 (M+H).

1.2.2.4.3 Method A5c (TFA + basic work up)

[0219] A flask is charged with N-tert-butoxycarbonyl derivative (1 eq.) and a mixture DCM/TFA (5/1). The reaction mixture is stirred at r.t. for 2h to 3h, concentrated in vacuo. The residue is taken up in a saturated Na_2CO_3 solution and extracted with EtOAc and/or EtOAc/n-BuOH. The combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected arylpiperazine.

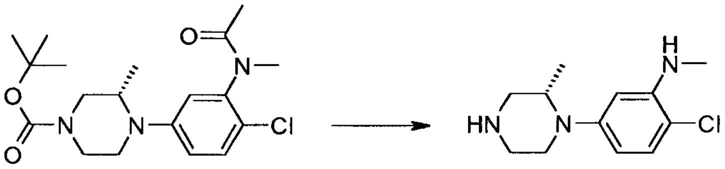
Illustrative synthesis of ***Int 259***



[0220] A flask is charged with N-*tert*-butoxycarbonyl derivative (320 mg, 0.97 mmol, 1 eq.), DCM (5 mL) and TFA (1 mL). The reaction mixture is stirred at r.t. for 2h, concentrated *in vacuo*. The residue is taken up in a saturated Na_2CO_3 solution and extracted with EtOAc and EtOAc/n-BuOH. The combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 230; m/z MW (obsd): 231 (M+H).

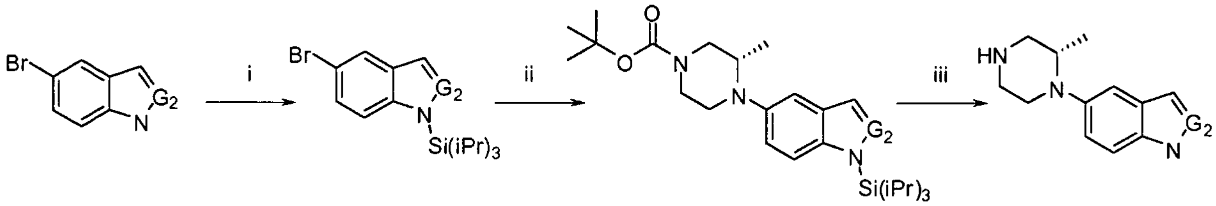
1.2.2.4.4 *Method A5e (H_2SO_4) : Boc and acetamide deprotection*

Illustrative synthesis of ***Int 193***



[0221] A flask is charged with with N-*tert*-butoxycarbonyl derivative (60 mg, 0.16 mmol, 1.0 eq.) and water (1 mL), and concentrated sulfuric acid (0.2 mL) is added. The reaction mixture is stirred at 80°C for 16h. An aqueous NaOH 2N solution is added until pH reaches 13, and the aqueous phase is extracted 3 times with DCM. The combined organic phases are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 239; m/z MW (obsd): 240 (M+H).

1.2.2.5. *Method A6 : with TIPS protecting group*



wherein G_2 = C or N

Step i)

[0222] To a solution of the bromo heteroaryl derivative (1 eq.) in THF at 0°C is added NaH portionwise (50% in oil, 2 eq.). Reaction mixture is stirred at r.t. for 1h, cooled to 0°C and a solution of triisopropylsilyl chloride (1.2 eq.) in THF is added dropwise. The reaction mixture is stirred at r.t. and concentrated *in vacuo.* The residue is partitionned between water and EtOAc, the organic layer is dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* Purification by flash chromatography on silica gel affords the expected triisopropylsilyl derivative.

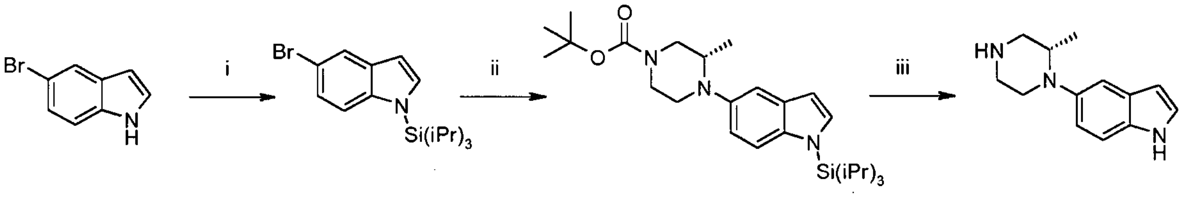
Step ii)

[0223] A flask is charged with bromoderivative (1 eq.), (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (1.15 eq.), NaOtBu (1.7 eq.) and toluene. The reaction mixture is degassed with N_2 and $PdCl_2[P(o\text{-}Tol)_3]_2$ (0.05 eq.) is added. Reaction mixture is heated at 110°C overnight, quenched by addition of water, extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue is purified by flash chromatography on silica gel to afford the expected NBoc-arylpiperazine.

Step iii)

[0224] To a solution of the NBoc-arylpiperazine (1 eq.) in DCM is added TFA (50 eq.). Reaction mixture stirred at r.t. overnight and concentrated *in vacuo.* The residue is taken up in EtOAc and saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected NH-arylpiperazine.

Illustrative synthesis of ***Int 257***



Step i) 5-Bromo-1-(triisopropylsilyl)-1H-indole

[0225] To a solution of 5-bromo-1H-indole (1.96 g, 10 mmol, 1 eq.) in THF (80 mL) at 0°C is added NaH portionwise (50% in oil, 1g, 20 mmol, 2 eq.). Reaction mixture is stirred at r.t. for 1h, cooled to 0°C and a solution of triisopropylsilyl chloride (2.3 g, 12 mmol, 1.2 eq.) in THF (10 mL) is added dropwise. The reaction mixture is stirred at r.t. and concentrated *in vacuo.* The residue is partitionned between water and EtOAc, the organic layer is dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* Purification by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 50/50) affords the expected triisopropylsilyl derivative. LCMS: MW (calcd): 352; m/z MW (obsd): 352-354 (M+H).

Step ii) (S)-3-Methyl-4-(1--(triisopropylsilyl)--1H-indol-5-yl)-piperazine-1-carboxylic acid tert-butyl ester

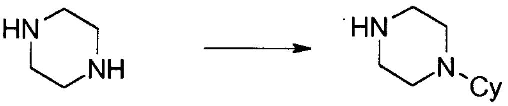
[0226] A flask is charged with bromo triisopropylsilyl derivative (1.4 g, 3.5 mmol, 1 eq.), (S)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (800 mg, 4 mmol, 1.15 eq.), NaOtBu (576 mg, 6 mmol, 1.7 eq.) and toluene (25 mL). The reaction mixture is degassed with N_2 and $PdCl_2[P(o\text{-}Tol)_3]_2$

(160 mg, 0.2 mmol, 0.05 eq.) is added. Reaction mixture is heated at 110°C overnight, quenched by addition of water, extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 50/50) to afford the expected NBoc-arylpiperazine. LCMS: MW (calcd): 472; m/z MW (obsd): 473 (M+H).

Step iii) 5-((S)-2-Methyl-piperazin-1-yl)-1H-indole

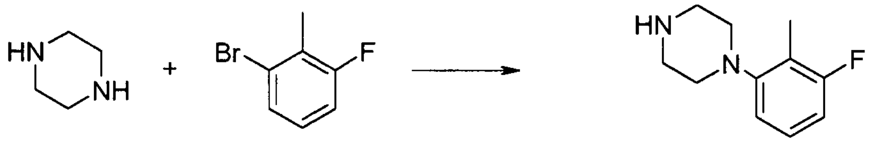
[0227] To a solution of the NBoc-arylpiperazine (370 mg, 0.79 mmol, 1 eq.) in DCM (30 mL) is added TFA (3 mL). Reaction mixture stirred at r.t. overnight and concentrated *in vacuo*. The residue is taken up in EtOAc and saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 215; m/z MW (obsd): 216 (M+H).

1.2.2.6. Method A7 : Buchwald reaction with NH-piperazine



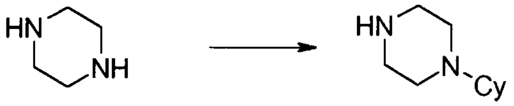
[0228] A flask is charged with bromoaryl derivative (1 eq.), piperazine (4-6 eq.), BINAP (0.06-0.22 eq.), NaOtBu (1.4-2.5 eq.) and toluene. The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (0.03-0.11 eq.) is added. Reaction mixture is heated at 100-110°C for 2h-20h. The reaction mixture is extracted with HCl 1N solution. The aqueous layer is basified with NaOH 2N solution and extracted with EtOAc or DCM. The combined organic layers are washed with water and brine, dried (over anhydrous Na_2SO_4 or $MgSO_4$), filtered and concentrated *in vacuo* to afford the expected arylpiperazine used without further purification.

Illustrative synthesis of ***Int 266***



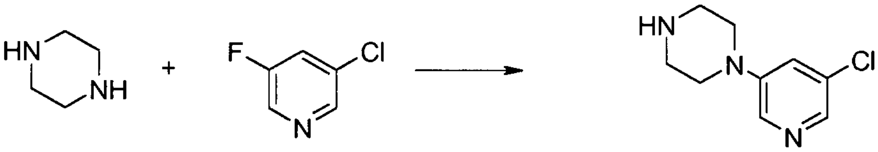
[0229] A flask is charged with 1-bromo-3-fluoro-2-methyl-benzene (189 mg, 1 mmol, 1 eq.), piperazine (517 mg, 6 mmol, 6 eq.), BINAP (37 mg, 0.06 mmol, 0.06 eq.), NaOtBu (135 mg, 1.4 mmol, 1.4 eq.) and toluene (2 mL). The reaction mixture is degassed with N_2 and $Pd_2(dba)_3$ (27 mg, 0.03 mmol, 0.03 eq.) is added. Reaction mixture is heated at 110°C overnight. The reaction mixture is extracted with HCl 1N solution. The aqueous layer is basified with NaOH 2N solution and extracted with DCM. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 194; m/z MW (obsd): 195 (M+H).

1.2.2.7. *Method A8 : SNAr with NH-piperazine*



[0230] A vial is charged with arylfluoride derivative (1 eq.), piperazine (2-8 eq.), K_2CO_3 (1.5-2.6 eq.) and a solvant (dioxane, DMSO). The reaction mixture is heated at 100°C for 1-3 days, diluted with water and extracted with EtOAc or DCM. The combined organic layers are washed with water and brine, dried (over anhydrous Na_2SO_4 or $MgSO_4$), filtered and concentrated *in vacuo* to afford the expected arylpiperazine used without further purification.

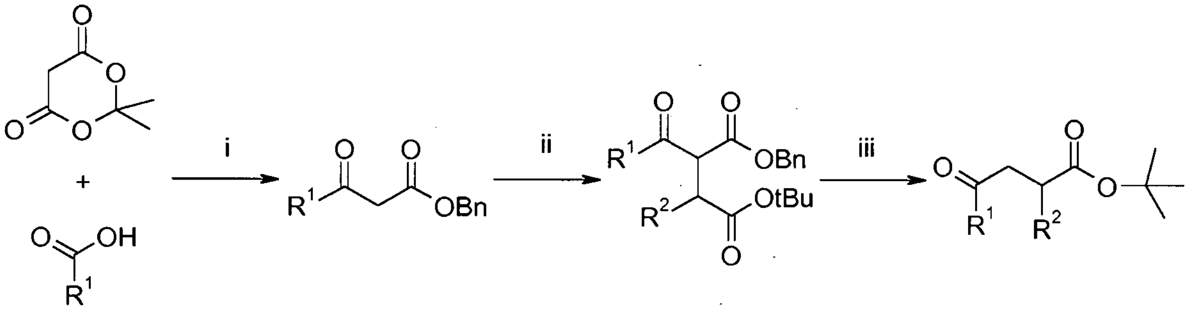
Illustrative synthesis of ***Int 269***



[0231] A vial is charged with 3-chloro-5-fluoro-pyridine (195 mg, 1.5 mmol, 1 eq.), piperazine (1.03 g, 12.0 mmol, 8 eq.), K_2CO_3 (553 mg, 4.0 mmol, 2.6 eq.) and a solvant dry dioxane (5 mL). The reaction mixture is heated at 100°C for 3 days, diluted with water and extracted with DCM. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 198; m/z MW (obsd): 198-200 (M+H).

1.2.3. General methods C: Preparation of ketoester

1.2.3.1. *Method C1 : from Meldrum's acid*



Step i)

[0232] To a solution of the carboxylic acid (1 eq.) in DCM at 0°C under N_2 atmosphere is added portionwise DMAP (1.5 eq.) then 2,2-Dimethyl-[1,3]dioxane-4,6-dione (1.1 eq.) then EDC.HCl (1.2 eq.). After 10min at 0°C, the reaction mixture is warmed to r.t. and stirred for 4h. The reaction mixture is quenched with a solution of $KHSO_4$ 5%. The aqueous phase is extracted with DCM, the combined organic layers are washed with a solution of $KHSO_4$ 5%., water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. This residue is taken up in anhydrous toluene and benzyl alcohol

(1.1 eq.) is added. The reaction mixture is stirred at 120°C for 16h to 20h, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected β-ketoester.

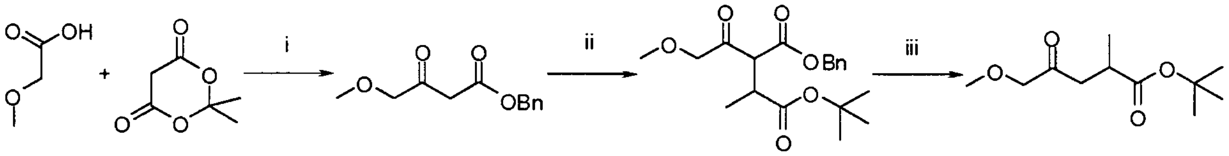
Step ii)

[0233] To a solution of the β-ketoester (1 eq.) in MEK are added K_2CO_3 (2 eq.), NaI (0.1 eq.) and bromoderivative (1 eq.). The reaction mixture is stirred at 90°C for 6h to 16h and cooled to r.t. Water is added, reaction mixture acidified to pH 8 and extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue is purified by flash chromatography on silica gel to afford the expected γ-ketoester.

Step iii)

[0234] To a solution of the γ-ketoester (1 eq.) in MeOH (or EtOH) are added $Pd(OH)_2/C$ (0.01 eq.), and cyclohexene (10-50 eq.). The reaction mixture is stirred at 70-80°C for 19h. The reaction mixture is filtered on celpure P65 and the filtrate is concentrated *in vacuo.* The residue is used as such or is purified by flash chromatography on silica gel to afford the expected γ-ketoester.

*Illustrative synthesis of **Int 158***



Step i) 4-Methoxy-3-oxo-butyric acid benzyl ester

[0235] To a solution of methoxy-acetic acid (5.11 mL, 0.067 mol, 1 eq.) in DCM (160 mL) at 0°C under N_2 atmosphere is added portionwise DMAP (12.21 g, 0.100 mol, 1.5 eq.) then 2,2-Dimethyl-[1,3]dioxane-4,6-dione (10.56 g, 0.073 mol, 1.1 eq.) then EDC.HCl (15.32 g, 0.080 mol, 1.2 eq.). After 10min at 0°C, the reaction mixture is warmed to r.t. and stirred for 4h. The reaction mixture is quenched with a solution of $KHSO_4$ 5%. The aqueous phase is extracted with DCM, the combined organic layers are washed with a solution of $KHSO_4$ 5%, water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* This residue is taken up in anhydrous toluene (220 mL) and benzyl alcohol (7.59 mL, 0.073 mol, 1.1 eq.) is added. The reaction mixture is stirred at 120°C for 16h, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM 100%) to afford the expected β-ketoester. LCMS: MW (calcd): 222; m/z MW (obsd): 245.3 (M+Na)

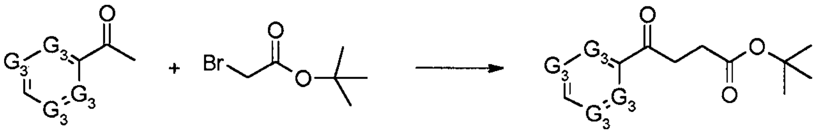
Step ii) 2-(2-Methoxy-acetyl)-3-benzyl-succinic acid 4-tert-butyl ester 1-methyl ester

[0236] To a solution of the β-ketoester (8.96 g, 0.040 mol, 1 eq.) in MEK (120 mL) are added K_2CO_3 (11.14 g, 0.081 mol, 2 eq.), NaI (0.6 g, 0.004 mol, 0.1 eq.) and 2-Bromo-propionic acid tert-butyl ester (6.69 mL, 0.040 mol, 1 eq.). The reaction mixture is stirred at 90°C for 6h and cooled to r.t.. Water is added, reaction mixture is acidified to pH 8 and extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 50/50) to afford the expected γ-ketoester. LCMS: MW (calcd): 350; m/z MW (obsd): 373.4 (M+Na)

Step iii) 5-Methoxy-2-methyl-4-oxo-pentanoic acid tert-butyl ester

[0237] To a solution of the γ-ketoester (6.42 g, 0.018 mol, 1 eq.) in MeOH are added $Pd(OH)_2/C$ (0.642 g, 0.002 mol, 0.01 eq.), and cyclohexene (93 mL, 0.916 mol, 50 eq.). The reaction mixture is stirred at 70°C for 19h. The reaction mixture is filtered on celpure P65, washed with MeOH and the filtrate is concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 70/30) to afford the expectected product. LCMS: MW (calcd): 216; m/z MW (obsd): 239.3 (M+Na).

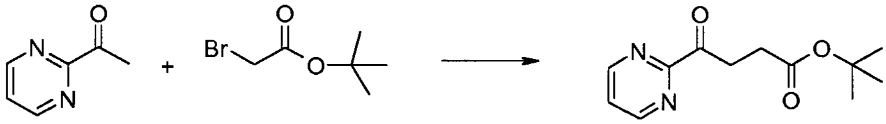
1.2.3.2. Method C2 : with tert-butyl bromoacetate



G_3=C or N

[0238] To a solution of the acetyl derivative (1 eq.) in THF and DMPU at 0°C under N_2 atmosphere is added LiHMDS (1M solution in THF, 1.2 eq.) dropwise. After 15min at 0°C, *tert*-butyl bromoacetate (1.5 eq.) is added dropwise and the reaction mixture is stirred at 0°C for 3h. The reaction mixture is quenched by a saturated NH_4Cl solution, the organic layer is separated, and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel affords the expected γ-ketoester.

Illustrative synthesis of ***Int 141***

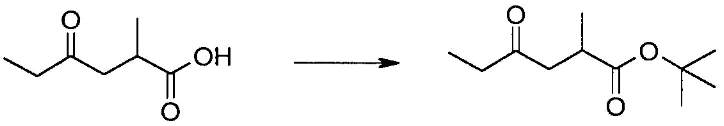


[0239] To a solution of the 2-acetyl pyrimidine (2 g, 16.38 mmol, 1 eq.) in THF and DMPU at 0°C under N_2 atmosphere is added LiHMDS (1M solution in THF, 19.6 mL, 19.65 mmol, 1.2 eq.) dropwise. After 15min at 0°C, tert-butyl bromoacetate (3.96 mL, 24.56 mmol, 1.5 eq.) is added dropwise and the reaction mixture is stirred at 0°C for 3h. The reaction mixture is quenched by a saturated NH_4Cl solution, the organic layer is separated, and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with Heptane/EtOAc 80/20 to 50/50) affords the expected product. LCMS: MW (calcd): 236; m/z MW (obsd): 237 (M+H).

1.2.3.3. Method C3: esterification

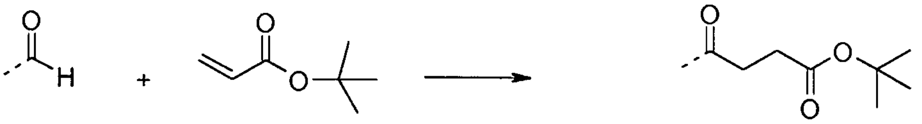
[0240] A glass pressure flask is charged with the carboxylic acid (1 eq.), DCM and concentrated H_2SO_4 (0.1 eq.). It is capped and weighted as such. It is then cooled to -45°C, the flask is opened and isobutene is bubbled through the cold reaction mixture for approximatively 5 min. The flask is capped and weighted. The process is repeated until the expected weigh of isobutene is obained (5 eq.). The reaction mixture is stirred at r.t. for 4 days, then the flask is cooled to -45°C prior to opening. A saturated $NaHCO_3$ solution is added portionwise, and the vigourous stiring kept for 30 min. The organic layer is separated; the aqueous layer is extracted with DCM. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* (with a minimum vaccum of 50 mbar) to afford the expected γ-ketoester.

Illustrative synthesis of ***Int 171***



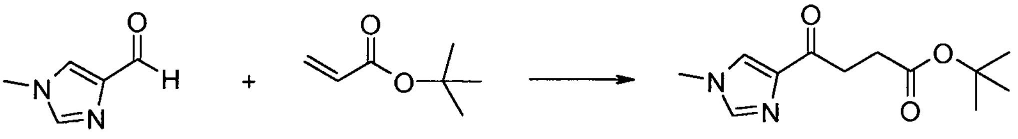
[0241] A glass pressure flask is charged with 2-Methyl-4-oxo-hexanoic acid (Kato et al., 2003) (7.3 g, 50.6 mmol, 1 eq.), DCM (40 mL) and concentrated H_2SO_4 (270 µL, 5.06 mmol, 0.1 eq.). The flask is capped and weighted as such. It is then cooled to -45°C, the flask is opened and isobutene is bubbled through the cold reaction mixture for approximatively 5 min. The flask is capped and weighted (11g of isobutene is condensed). The process is repeated until the expected weight of isobutene is obained (14.2 g, 253.2 mmol, 5 eq.). The reaction mixture is stirred at r.t. for 4 days, then the flask is cooled to -45°C prior to opening. A saturated $NaHCO_3$ solution is added portionwise, and the vigourous stiring kept for 30 min. The organic layer is separated; the aqueous layer is extracted with DCM. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* (with a minimum vaccum of 50 mbar) to afford the expected product.

1.2.3.4. Method C4 : Stetter reaction



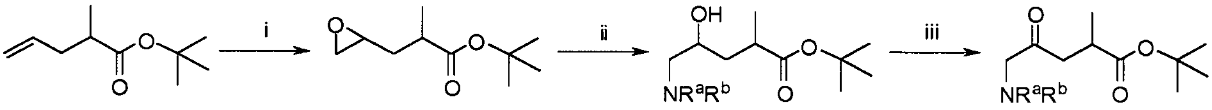
[0242] A vial is charged with aldehyde (1 eq.), *tert*-butyl ester acrylate (1 eq.), $P(Bu)_3$ (1eq.) and dry THF. The vial is capped and heated at 70°C for 2h to 16h. The reaction mixture is partitionned between EtOAc and water. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected γ-ketoester after purification by flash chromatography on silica gel.

*Illustrative synthesis of **Int 181***



[0243] To a solution of 1-methyl-1H-imidazole-4-carbaldehyde (1g, 9.1 mmol, 1.1 eq.) in THF (12 mL) is added $P(Bu)_3$ (2.16 mL, 8.7 mmol, 1.05 eq.) and the reaction mixture is heated at 50°C for 5 min. *tert*-butyl ester acrylate (1.2 mL, 8.3 mmol, 1 eq.) is added and the reaction mixture is stirred at 80°C for 3h. *tert*-butyl ester acrylate (0.3 mL, 0.25 eq.) is added and this process (heating 3h and addition of *tert*-butyl ester acrylate) is repeated until no evolution is observed by TLC (EtOAc) and UPLC/MS. The reaction mixture is concentrated in *vacuo* and the residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 0/100) to afford the expected product. LCMS: MW (calcd): 238; m/z MW (obsd): 239 (M+H).

1.2.3.5. Method C5 : via epoxide opening



Step i)

[0244] To a solution of alkene (1eq.) in DCM at 0°C, is added m-CPBA (1.5 eq.) and the reaction mixture is stirred at r.t. overnight. The white precipitate is filtered and washed with DCM. The filtrate is washed with a saturated $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel to afford the expected epoxide.

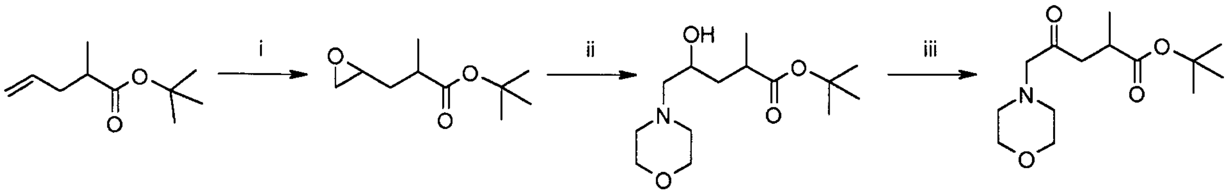
Step ii)

[0245] A sealed tube is charged with the epoxide (1 eq.), EtOH and secondary amine (1.5 eq.). After heating at reflux for 3h30, the reaction mixture is concentrated *in vacuo*. The residue is taken up in DCM, washed with a saturated NH_4Cl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected aminoalcohol used in next step without further purification.

Step iii)

[0246] A two necked flask, under N_2 atmosphere, is charged with dry DCM and $(COCl)_2$ (1.1 eq.). The reaction mixture is cooled to -70°C, a solution of DMSO (2.4 eq.) in dry DCM is added dropwise and the reaction mixture is stirred at -70°C/-60°C for 45 min. A solution of the aminoalcohol (1eq.) in dry DCM is added dropwise and the reaction mixture is stirred for 1h at -60°C. Et_3N (5 eq.) is added dropwise. Reaction mixture stirred at -40°C for 30 min then warmed to r.t. and stirred overnight. Water is added, the organic layer is separated and washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel to afford the expected γ-ketoester.

Illustrative synthesis of ***Int 188***



Step i) 2-Methyl-3-oxiranyl-propionic acid tert-butyl ester

[0247] To a solution of **Int 148** (2 g, 11.8 mmol, 1eq.) in DCM (20 mL) at 0°C, is added m-CPBA (3.05 g, 17.7 mmol, 1.5 eq.) and the reaction mixture is stirred at r.t. overnight. The white precipitate is filtered and washed with DCM. The filtrate is washed with a saturated $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 80/20) to afford the expected epoxide.

Step ii) 4-Hydroxy-2-methyl-5-morpholin-4-yl-pentanoic acid tert-butyl ester

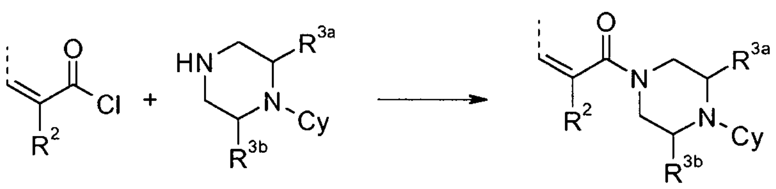
[0248] A sealed tube is charged with the epoxide obtained in the previous step (0.19 g, 1.02 mmol, 1 eq.), EtOH (3 mL) and morpholine (0.134 mL, 1.53 mmol, 1.5 eq.). After heating at reflux for 3h30, the reaction mixture is concentrated *in vacuo*. The residue is taken up in DCM, washed with a saturated NH_4Cl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected aminoalcohol used in next step without further purification.

Step iii) 2-Methyl-5-morpholin-4-yl-4-oxo-pentanoic acid tert-butyl ester

[0249] A two necked flask, under N_2 atmosphere, is charged with dry DCM (5 mL) and $(COCl)_2$ (0.153 mL, 1.81 mmol, 1.1 eq.). The reaction mixture is cooled to -70°C, a solution of DMSO (0.281 mL, 3.96 mmol, 2.4 eq.) in dry DCM (0.5 mL) is added dropwise and the reaction mixture is stirred at -70°C/-60°C for 45 min. A solution of the aminoalcohol obtained in the previous step (0.450 g, 1.65 mmol, 1eq.) in dry DCM (2 mL) is added dropwise and the reaction mixture is stirred for 1h at -60°C. Et_3N (1.19 mL, 8.24 mmol, 5 eq.) is added dropwise. Reaction mixture stirred at -40°C for 30 min then warmed to r.t. and stirred overnight. Water is added, the organic layer is separated and washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with DCM/acteone 90/10) to afford the expected product.

1.2.4. General method D: preparation of ketoamide

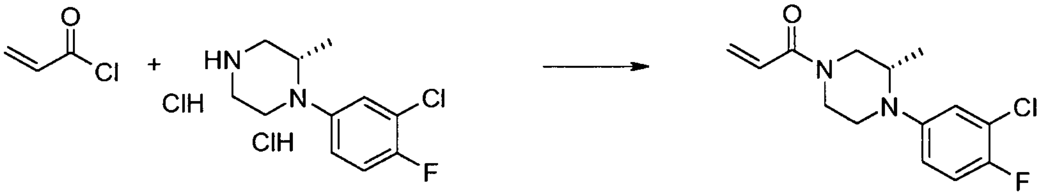
1.2.4.1. Method D1: preparation of acrylamide



1.2.4.1.1 Method D1a:

[0250] To a solution of piperazine (1 eq.) in EtOAc/$NaHCO_3$ sat. aq. (2/1 v/v) at 0°C is added dropwise the acryloyl chloride derivative (1.1 eq.). Reaction mixture is stirred at 0°C for 30 min then r.t. for 1h. The organic layer is separated. The aqueous layer is extracted with EtOAc and the combined organic layers are washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected acrylamide (used as such or purified by flash chromatography on silica gel).

Illustrative synthesis of ***Int 006***

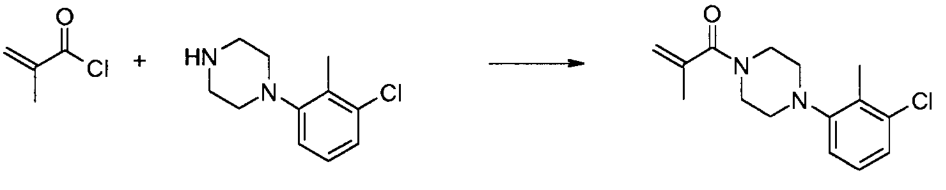


[0251] To a solution of (S)-1-(3-Chloro-4-fluoro-phenyl)-2-methyl-piperazine dihydrochloride (2 g, 6.63 mmol, 1 eq.) in EtOAc/$NaHCO_3$ sat. aq. (60 mL/30mL) at 0°C is added dropwise acryloyl chloride (0.595 mL, 7.29 mmol, 1.1 eq.). Reaction mixture is stirred at 0°C for 30 min then r.t. for 1h. The organic layer is separated. The aqueous layer is extracted with EtOAc and the combined organic layers are washed with water, brine and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 283; m/z MW (obsd): 283-285 (M+H).

1.2.4.1.2 Method D1b

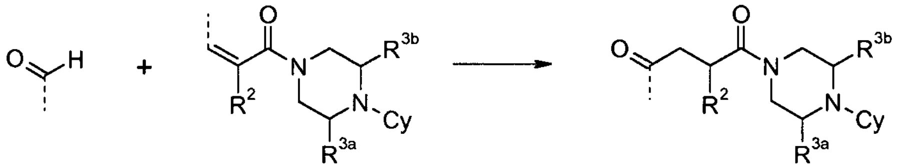
[0252] To a solution of piperazine (1 eq.) and Et3N (1.5 eq.) in DCM at 0°C is added dropwise the acryloyl chloride derivative (1.5 eq.). Reaction mixture is stirred at 0°C for 1h and allowed to reach r.t.. Water and DCM are added, the organic layer is separated. The aqueous layer is extracted with DCM, the combined organic layers are washed with brine and dried over anhydrous Na2SO4, filtered and concentrated in vacuo to afford the expected acrylamide after purification by flash chromatography on silica gel.

Illustrative synthesis of ***Int 009***



[0253] To a solution of 1-(3-Chloro-2-methyl-phenyl)-piperazine (2.06 g, 9.8 mmol, 1 eq.) and Et_3N (1.5 mL, 14.7 mmol, 1.5 eq.) in DCM at 0°C is added dropwise 2-Methyl-acryloyl chloride (2.05 mL, 14.7 mmol, 1.5 eq.). Reaction mixture is stirred at 0°C for 1h and allowed to reach r.t.. Water and DCM are added, the organic layer is separated. The aqueous layer is extracted with DCM, the combined organic layers are washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 90/10) to afford the expected product. LCMS: MW (calcd): 279; m/z MW (obsd): 279-281 (M+H).

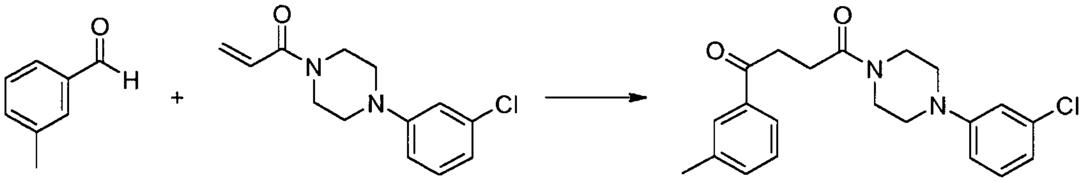
1.2.4.2. Method D2: Stetter reaction



1.2.4.2.1 Method D2a (P(Bu)₃)

[0254] A vial is charged with aldehyde (1 eq.), acrylamide (0.95 eq.), $P(Bu)_3$ (1eq.) and dry THF. The vial is capped and heated at 70°C for 2h to 3h. The reaction mixture is partitionned between EtOAc and water. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected γ-ketoamide after purification by flash chromatography on silica gel.

Illustrative synthesis of ***Int 095***

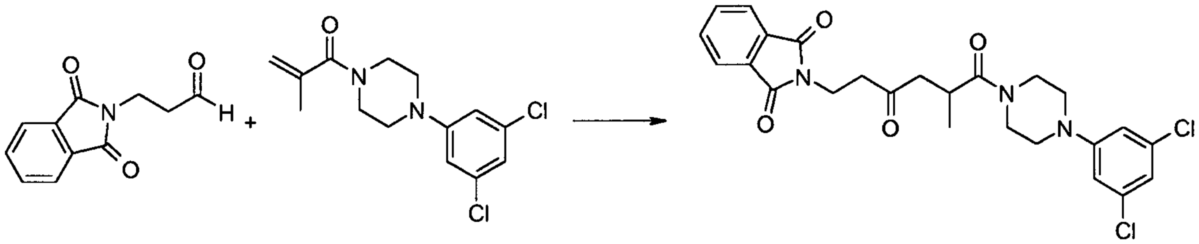


[0255] A vial is charged with 3-Methyl-benzaldehyde (0.141 mL, .1.2 mmol, 1 eq.), **Int 005** (0.300 g, 1.2 mmol, 1 eq.), $P(Bu)_3$ (0.242 mL, 1.2 mmol, 1eq.) and dry THF (2 mL). The vial is capped and heated at 70°C for 2h. Additional $P(Bu)_3$ (15 μL, 0.05eq.) and 3-Methyl-benzaldehyde (10 μL, 0.1 eq.) is added, and the vial is capped and heated at 80°C for 2h. The reaction mixture is partitionned between EtOAc and water. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc, from 100/0 to 0/100) to afford the expected product. LCMS: MW (calcd): 370; m/z MW (obsd): 371-373 (M+H).

1.2.4.2.2 Method D2b (Rh catalyst)

[0256] A vial is charged with bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (0.10 eq.), 1,4-bis(diphenylphosphino)butane (0.10 eq.), dry DCM and sealed with a septum. The flask is evacuated and refilled with H_2 (3 times) and the reaction mixture is stirred under an atmosphere of H_2. After 3h, volatiles are removed under a nitrogen stream. The residue is combined with acrylamide (1 eq.), aldehyde (1.5 equiv.) and 1,2-dichloroethane in a vial under a N_2 atmosphere. The vial is sealed with a cap and heated at 100°C. After 16h, the mixture is concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected γ-ketoamide.

Illustrative synthesis of ***Int 021***

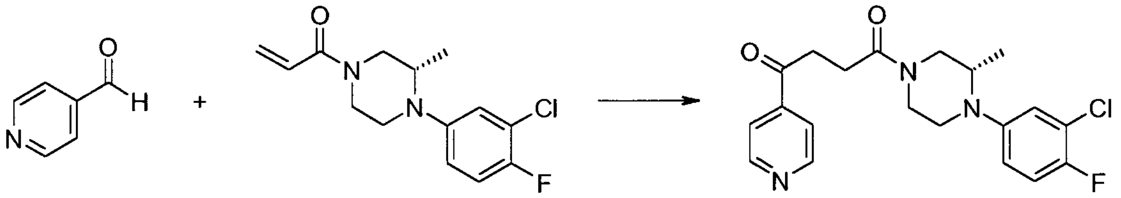


[0257] A vial is charged with bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (0.054 g, 0.132 mmol, 0.10 eq.), 1,4-bis(diphenylphosphino)butane (0.056 g, 0.132 mmol, 0.10 eq.), dry DCM (2mL) and sealed with a septum. The flask is evacuated and refilled with H_2 (3 times) and the reaction mixture is stirred under an atmosphere of H_2. After 3h, volatiles are removed under a nitrogen stream. The residue is combined with **Int 001** (0.397 g, 1.328 mmol, 1 eq.), 3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-propionaldehyde (0.406 g, 2.00 mmol, 1.5 equiv.) and 1,2-dichloroethane (2 mL) in a vial under a N_2 atmosphere. The vial is sealed with a cap and heated at 100°C. After 2 days, the mixture is concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 0/100, then DCM/MeOH 90/10) to afford **Int 021**. LCMS: MW (calcd): 502; m/z MW (obsd): 502-504 (M+H).

1.2.4.2.3 *Method D2c (NaCN)*

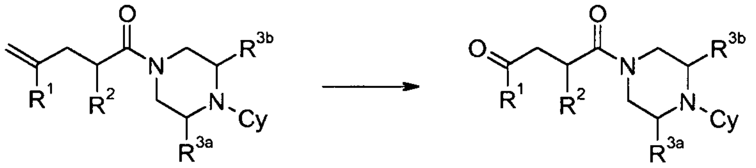
[0258] A vial is charged with aldehyde (3 eq.) and dry DMF. NaCN (1.5 eq) is added and the reaction mixture is stirred at r.t. for 5 min. A solution of acrylamide (1 eq.) in dry DMF is added, the vial is sealed and heated at 120°C for 3h30 and cooled to r.t.. A saturated $NaHCO_3$ solution and water are added to the reaction mixture followed by extraction with EtOAc. The combined organic layer are washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected γ-ketoamide.

Illustrative synthesis of ***Int 060***



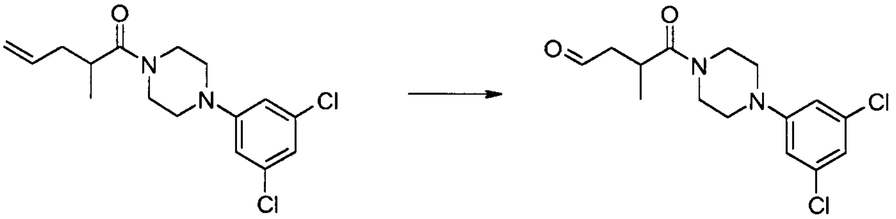
[0259] A vial is charged with pyridine-4-carbaldehyde (0.227 g, 2.12 mmol, 3 eq.) and dry DMF (4 mL). NaCN (0.052 g, 1.06 mmol, 1.5 eq) is added and the reaction mixture is stirred at r.t. for 5 min. A solution of **Int 006** (0.200 g, 0.71 mmol, 1 eq.) in dry DMF (2 mL) is added, the vial is sealed and heated at 120°C for 3h30 and cooled to r.t.. A saturated $NaHCO_3$ solution and water are added to the reaction mixture followed by extraction with EtOAc. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 98/2) to afford the expected product. LCMS: MW (calcd): 390; m/z MW (obsd): 390-392 (M+H).

1.2.4.3. Method D4 : Oxidative cleavage



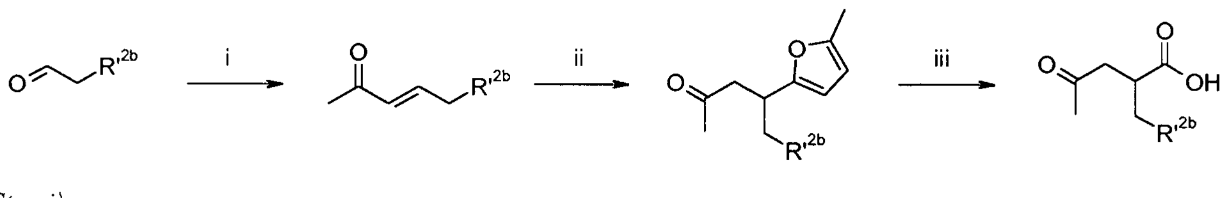
[0260] A vial is charged with alkene (1 eq.), a mixture of dioxane/water or THF/water and OsO_4 (0.01-0.06 eq.). After 15 min, $NaIO_4$ (2-4 eq.) is added and the reaction mixture is strirred at r.t. for 2h to 20h, combined with water or a solution of $NaHSO_3$ and extracted with DCM. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected γ-ketoamide.

Illustrative synthesis of ***Int 055***



[0261] A vial is charged with alkene **Int 124** (4.95 g, 15.1 mmol, 1 eq.), a mixture of dioxane (100 mL) and water (20 mL), and OsO_4 (2.5 wt% in t-BuOH, 2.8 mL, 223 mmol, 0.015 eq.). After 15min, a solution of $NaIO_4$ (6.61 g, 30.9 mmol, 2 eq.) in water (150 mL) is added dropwise over 10 minutes, and the reaction mixture is strirred at r.t. overnight, combined with water (600 mL) and extracted with $CHCl_3$ (250mL). The organic layer is washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with EtOAc/DCM 20/80) to afford the expected the expected product. LCMS: MW (calcd): 329; m/z MW (obsd): 329-331 (M+H).

1.2.4.4. Method D5 : via furan oxidation



Step i)

[0262] To a solution of phosphonate (1.1 eq.) in EtOH is added K_2CO_3 (1.2 eq.). The reaction mixture is stirred at r.t. for 2h prior to addition of the aldehyde (1 eq.). The reaction mixture is stirred at r.t. (1h to 3h), diluted with EtOAc and filtered on celpure P65. The filtrate is concentrated *in vacuo*. The residue is taken up in EtOAc and washed with a saturated NH_4Cl solution, a saturated $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected α,β-unsaturated ketone.

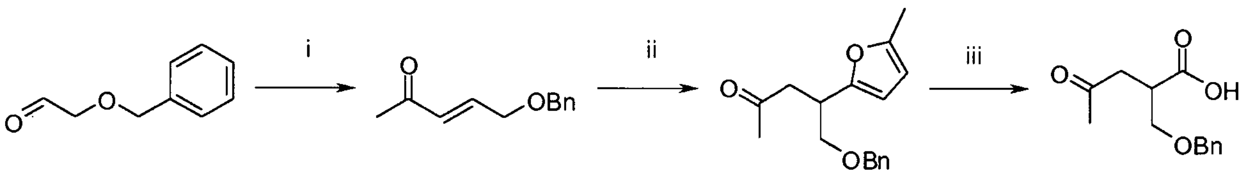
Step ii)

[0263] To a solution of the α,β-unsaturated ketone obtained in the previous step (1 eq.) in dry MeOH are added $PdCl_2$ (0.1 eq.) and 2-methylfuran (2 eq.). The reaction mixture is stirred at r.t. for 3h to 24h, diluted with EtOAc and filtered on celpure P65. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected ketone.

Step iii)

[0264] To a solution of ketone obtained in the previous step (1 eq.) in Heptane/EtOAc/water (1/3/4) is added $NaIO_4$ (7 eq.). The reaction mixture is stirred for 10 min then $RuCl_3 \cdot 3H_2O$ (0.02 eq.) is added. The reaction mixture is stirred for 30 min to 1h30, filtered on celpure P65, washed with MeCN and the filtrate is concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel to afford the expected γ-ketoacid.

Illustrative synthesis of ***Int 138***



Step i)

[0265] To a solution of phosphonate (14.22 g, 73.24 mmol, 1.1 eq.) in EtOH (150 mL) is added K_2CO_3 (11 g, 79.90 mmol, 1.2 eq.). The reaction mixture is stirred at r.t. for 2h prior to addition of benzyloxy-acetaldehyde (10 g, 66.59 mmol, 1 eq.). The reaction mixture is stirred at r.t. for 3h, diluted with EtOAc and filtered on celpure P65. The filtrate is concentrated *in vacuo*. The residue is taken up in EtOAc and washed with a saturated NH_4Cl solution , a saturated $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 80/20) to afford the expected α,β-unsaturated ketone.

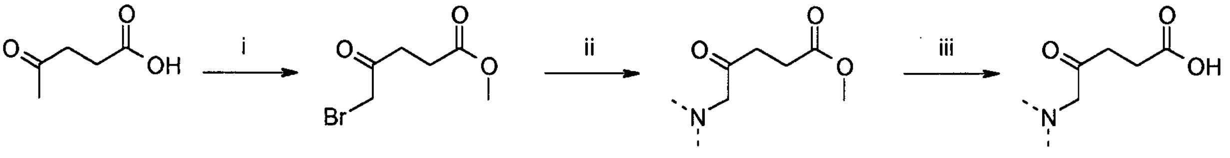
Step ii)

[0266] To a solution of the α,β-unsaturated ketone obtained in the previous step (8.7 g, 45.73 mmol, 1 eq.) in dry MeOH (183 mL) are added $PdCl_2$ (0.811 g, 0.457 mmol, 0.1 eq.) and 2-methylfuran (8.25 mL, 91.46 mmol, 2 eq.). The reaction mixture is stirred at r.t. for 3h, diluted with EtOAc and filtered on celpure P65. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with Heptane/EtOAc 100/0 to 85/15) to afford the expected ketone.

Step iii)

[0267] To a solution of ketone obtained in the previous step (1g, 3.67 mmol, 1 eq.) in Heptane/EtOAc/water (6 mL/18 mL/24 mL) is added $NaIO_4$ (5.48 g, 25.69 mmol, 7 eq.). The reaction mixture is stirred for 10 min then $RuCl_3 \cdot 3H_2O$ (0.019 g, 0.073 mmol, 0.02 eq.) is added. The reaction mixture is stirred for 1h15, filtered on celpure P65, washed with MeCN and the filtrate is concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with DCM/MeOH 98/2 to 95/5) to afford the expected product (stored at 4°C).

1.2.4.5. Method D6 : via α-bromo ketone



Step i)

[0268] To a solution of levulinic acid (1 eq.) in MeOH, bromine (1 eq.) is added dropwise. The reaction mixture is stirred at r.t. overnight and concentrated *in vacuo*. The residue is partitioned between water and Et_2O, the pH is adjusted to 8 using a saturated $NaHCO_3$ solution. After extraction with Et_2O, the combined organic layer are dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected bromo derivative as a methylester.

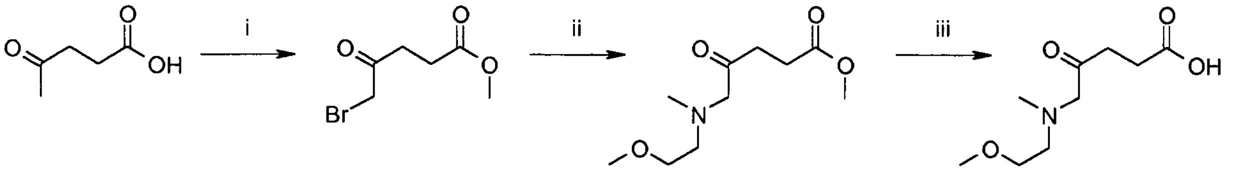
Step ii)

[0269] To a solution of the bromo derivative obtained in the previous step (1 eq.) in MeOH is added Et_3N (0 or 1 eq.) and secondary amine (1 to 2 eq.). Reaction mixture is stirred at r.t. for 30 to 120 min and concentrated *in vacuo*. The residue is used as such or purified by flash chromatography on silica gel to afford the expected amino ester derivative.

Step iii)

[0270] Amino ester obtained in the previous step (1 eq.) is heated at 80°C with an excess of 1M solution of NaOH for 2 to 3h. After complete hydrolysis (followed by HPLC/MS), the reaction mixture is acidified and evaporated to dryness and the crude amino acid is used as such in next step or triturated in DMF to remove salts.

Illustrative synthesis of ***Int 130***



Step i) 5-Bromo-4-oxo-pentanoic acid methyl ester

[0271] To a solution of levulinic acid (5 g, 43.1 mmol, 1 eq.) in MeOH (103 mL) under N_2 atmosphere, bromine (2.2 mL, 43.1 mmol, 1 eq.) is added dropwise. The resultant solution is stirred at r.t. overnight and concentrated *in vacuo*. The residue is partitioned between water and Et_2O, the pH is adjusted to 8 using a saturated $NaHCO_3$ solution. After extraction with Et_2O, the combined organic layers are dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with iso-Hexane/EtOAc 100/0 to 50/50) to afford the expected bromo derivative as a methylester.

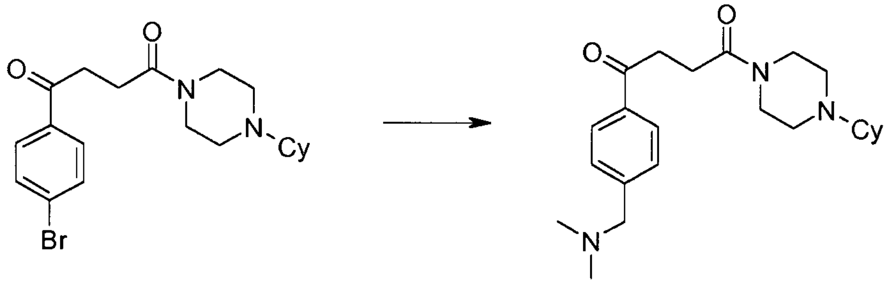
Step ii) 5-[(2-Methoxy-ethyl)-methyl-amino]-4-oxo-pentanoic acid methyl ester

[0272] To a solution of the bromo derivative obtained in the previous step (1g, 4.78 mmol, 1 eq.) in MeOH (12.5 mL) is added Et_3N (0.670 mL, 4.82 mmol, 1 eq.) and (2-methoxy-ethyl)-methyl-amine (0.420mL, 4.83 mmol, 1 eq.). Reaction mixture is stirred at r.t. for 2h and concentrated *in vacuo*. The expected amino ester derivative is used as such in next step.

Step iii) 5-[(2-Methoxy-ethyl)-methyl-amino]-4-oxo-pentanoic acid

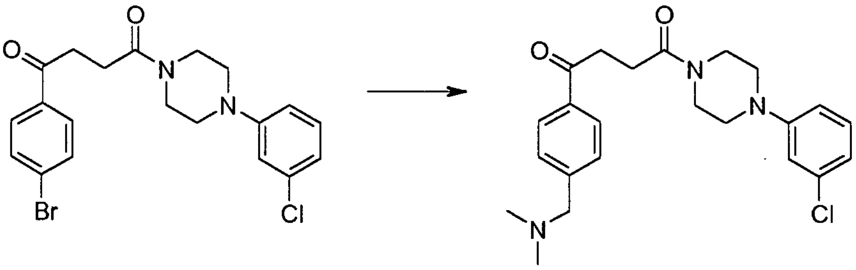
[0273] Amino ester obtained in the previous step (1.75g crude assumed as 4.78 mmol, 1 eq.) is heated at 80°C with an excess of 1M solution of NaOH (15 mL, 15 mmol, 3eq.) for 2h. After complete hydrolysis (followed by HPLC/MS), the reaction mixture is acidified and evaporated to dryness and the crude amino acid is used as such.

1.2.4.6. *Method D7 : ketoamide functionalization by Suzuki coupling*



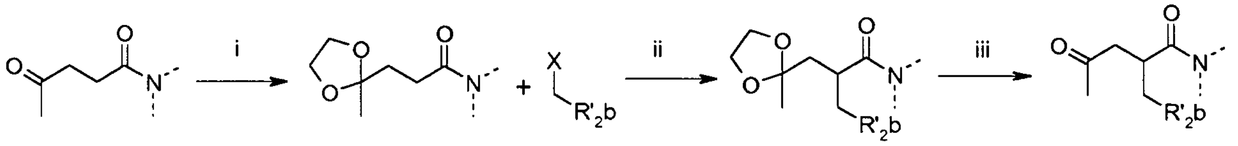
[0274] A vial is charged with bromide derivative (1 eq.), Xphos (0.06-0.018 eq.), $Pd(OAc)_2$ (0.03-0.09 eq.), Cs_2CO_3 (4-5 eq.), [(Dimethylammonium)methyl]trifluoroborate internal salt (3 eq.), THF and water. The reaction mixture is heated at 80°C until completion is observed by UPLC/MS (6-8 days). Additions of Xphos, $Pd(OAc)_2$, Cs_2CO_3 and [(Dimethylammonium)methyl]trifluoroborate internal salt are performed every 24h to reach a good level of conversion. A saturated $NaHCO_3$ solution is added to the reaction mixture followed by extraction with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected functionalized γ-ketoamide.

Illustrative synthesis of ***Int 090***



[0275] A vial is charged with **Int 118** (300 mg, 0.69 mmol, 1 eq.), Xphos (59 mg, 0.0124 mmol, 0.018 eq.), $Pd(OAc)_2$ (14 mg, 0.062 mmol, 0.09 eq.), Cs_2CO_3 (1.12g, 3.44 mmol, 5 eq.), [(Dimethylammonium)methyl]trifluoroborate internal salt (262 mg, 2.07 mmol, 3 eq.), THF (2.3 mL) and water (0.6 mL). The reaction mixture is heated at 80°C for 2 days. Xphos (30 mg, 0.0062 mmol, 0.009 eq.), $Pd(OAc)_2$ (7 mg, 0.031 mmol, 0.045 eq.) and [(Dimethylammonium)methyl]trifluoroborate internal salt (66 mg, 0.52 mmol, 0.75 eq.) are added and the reaction mixture is heated at 80°C for 24h. Cs_2CO_3 (440 mg, 1.35 mmol, 2 eq.), and [(Dimethylammonium)methyl]trifluoroborate internal salt (80 mg, 0.63 mmol, 1 eq.) are added and the reaction mixture is heated at 80°C for 2 days. Xphos (30 mg, 0.0062 mmol, 0.009 eq.) and $Pd(OAc)_2$ (7 mg, 0.031 mmol, 0.045 eq.) are added and the reaction mixture is stirred at r.t. for 3 days. A saturated $NaHCO_3$ solution is added to the reaction mixture followed by extraction with EtOAc. The combined organic layer are washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with heptane/DCM 1/0 to 0/1 then DCM/MeOH 100/0 to 90/10) to afford the expected product. LCMS: MW (calcd): 414; m/z MW (obsd): 414-416 (M+H).

1.2.5. General method E: Functionalization of γ-ketoamide



Step i)

[0276] A Dean-Starck apparatus is loaded with γ-ketoamide (1 eq.) in toluene, ethylene glycol (1.2 to 1.4 eq.) and *p*-toluenesulfonic acid (0.06 to 0.2 eq.). The reaction mixture is heated at reflux for 2h to 4h. A solution of NaOH 0.1N and EtOAc are added, the organic layer is separated, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to afford the expected dioxolane. This residue is either purified by flash chromatography on silica gel or used as such in next step.

Step ii)

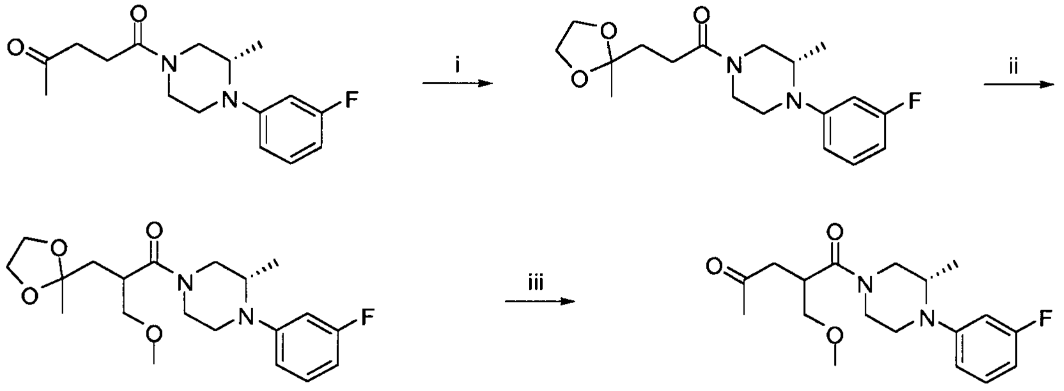
[0277] To a solution of the dioxolane obtained in the previous step (1 eq.) in dry THF at -78°C is added dropwise LDA or LiHMDS (2M solution in THF, 1.1 eq.). The reaction mixture is stirred at -78°C for 30 min, then 0°C for 10 min then cooled to -78°C for dropwise addition of a solution of alkyl halide (1.4 eq.) in dry THF. The reaction mixture is allowed to warm to r.t. and quenched with a saturated

NH_4Cl solution. After evaporation of the THF, the aqueous layer is extracted with EtOAc, the combined organic layer are washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected functionalized dioxolane.

Step iii)

[0278] To a solution of the functionalized dioxolane obtained in the previous step (1 eq.) in MeOH is added an aqueous solution of HCl 6N (6 eq.). The reaction mixture is stirred at r.t. for 3h, a saturated $NaHCO_3$ solution is added to the reaction mixture followed by extraction with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected functionalized γ-ketoamide.

Illustrative synthesis of ***Int 066***



Step i) 1-[(S)-4-(3-Fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-(2-methyl-[1,3]dioxolan-2-yl)-propan-1-one

[0279] A Dean-Starck apparatus is loaded with **Int 122** (1 g, 3.4 mmol, 1 eq.), toluene (50 mL), ethylene glycol (220 μL, 3.9 mmol, 1.2 eq.) and *p*-toluenesulfonic acid (100 mg, 0.58 mmol, 0.17 eq.). The reaction mixture is heated at reflux for 2h. A solution of NaOH 0.1N and EtOAc are added, the organic layer is separated, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to afford the expected dioxolane used as such in next step. LCMS: MW (calcd): 336; m/z MW (obsd): 337 (M+H).

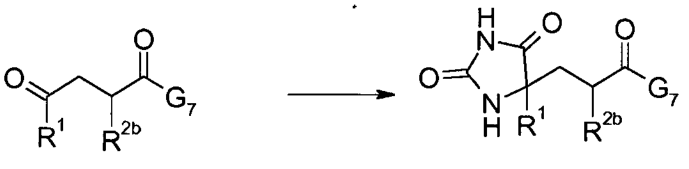
Step ii) 1-[(S)-4-(3-Fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methoxymethyl-3-(2-methyl-[1,3]dioxolan-2-yl)-propan-1-one

[0280] To a solution of the dioxolane obtained in the previous step (380 mg, 1.13 mmol, 1 eq.) in dry THF (30 mL) at -78°C is added dropwise LDA (2M solution in THF, 0.6 mL, 1.2 mmol, 1.1 eq.). The reaction mixture is stirred at -78°C for 30 min, then 0°C for 10 min then cooled to -78°C for dropwise addition of a solution of bromomethylether (137 μL, 1.5 mmol, 1.4 eq.) in dry THF (5 mL). The reaction mixture is allowed to warm to r.t. and quenched with a saturated NH_4Cl solution. After evaporation of the THF, the aqueous layer is extracted with EtOAc, the combined organic layer are washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with Heptane/EtOAc 100/0 to 50/50) to afford the expected functionalized dioxolane. LCMS: MW (calcd): 380; m/z MW (obsd): 381 (M+H).

Step iii) 1-[(S)-4-(3-Fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methoxymethyl-pentane-1,4-dione

[0281] To a solution of the functionalized dioxolane obtained in the previous step (190 mg, 0.5 mmol, 1 eq.) in MeOH (5 mL) is added an aqueous solution of HCl 6N (0.5 mL, 3 mmol, 6 eq.). The reaction mixture is stirred at r.t. for 3h, a saturated $NaHCO_3$ solution is added to the reaction mixture followed by extraction with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/acetone 100/0 to 90/10) to afford the expected product. LCMS: MW (calcd): 336; m/z MW (obsd): 337 (M+H).

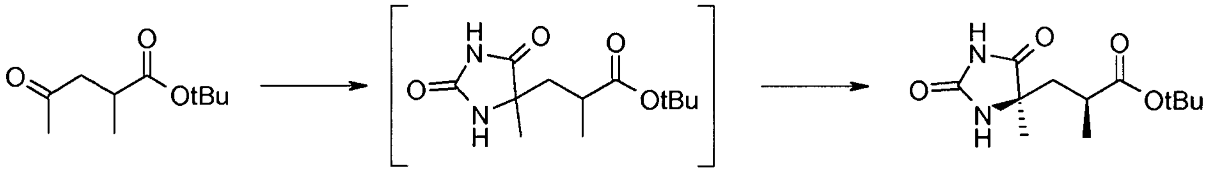
1.2.6. General method F: Bucherer Bergs reaction



G_7=O-Alk_1, Alk_2-N-Alk_3

[0282] A pressure reactor or an open round bottom flask equipped with a condenser is charged with a solution of $(NH_4)_2CO_3$ or $(NH_4)HCO_3$ (8-12 eq.) in water. KCN (2 to 4 eq.) is added portionwise then a solution of γ-ketoester or γ-ketoamide (1eq.) in EtOH is added. The vessel is sealed and heated at 60-90°C for 1h to 2 days. The reaction mixture is cooled to r.t., combined with water and extracted with AcOEt or $CHCl_3$/nBuOH 10%. The combined organic layers are washed with water and brine, dried (over anhydrous Na_2SO_4 or $MgSO_4$), filtered and concentrated *in vacuo*. The residue is either recrystallized or purified by flash chromatography on silica gel to afford the expected hydantoin derivative.

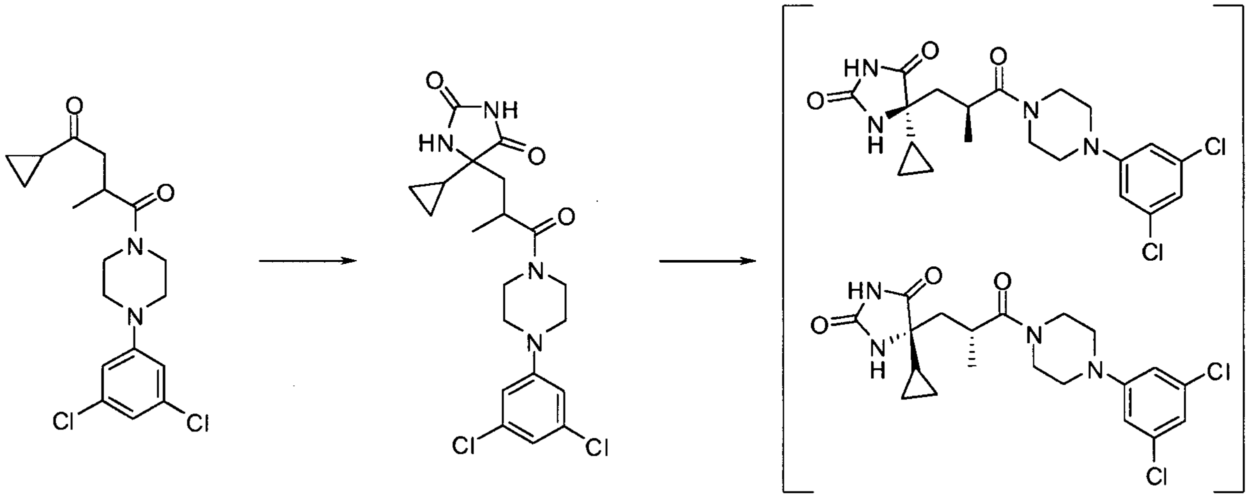
Illustrative synthesis of (R)-5-Methyl-5-((S)-2-methyl-3-oxo-butyl)-imidazolidine-2,4-dione + (S)-5-Methyl-5-((R)-2-methyl-3-oxo-butyl)-imidazolidine-2,4-dione



[0283] A pressure reactor is charged with a solution of $(NH_4)_2CO_3$ (79.4g, 0.826 mol, 8 eq.) in water (400 mL). KCN (20g, 0.307 mol, 3 eq.) is added portionwise then a solution of γ-ketoester (19.15 g, 0.103 mol, 1eq.) in EtOH (400 mL) is added. The vessel is sealed and heated at 90°C overnight. The reaction mixture is cooled to r.t., combined with water and extracted with $CHCl_3$/nBuOH 10%. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*.

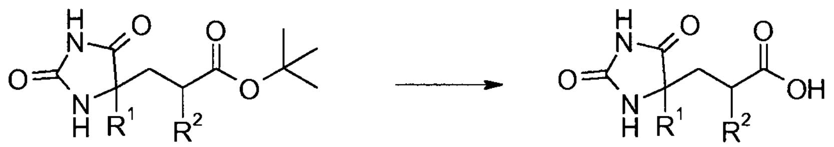
[0284] The above reaction is performed twice and the two crude residues are gathered for recrystallization. A flask is charged with the two crude residues, EtOH (250 mL) is added and the reaction mixture is heated at reflux. Upon complete dissolution, the reaction mixture is allowed to cool to r.t. for 2 days, it is filtered and the crystalline solid is combined with EtOH (200 mL), heated to reflux, cooled to r.t. overnight and filtered to afford the expected hydantoin as a *trans*-Me racemic mixture (LCMS: > 99% de, MW (calcd): 256; m/z MW (obsd): 257 (M+H)).

Illustrative synthesis of ***Cpd 172***



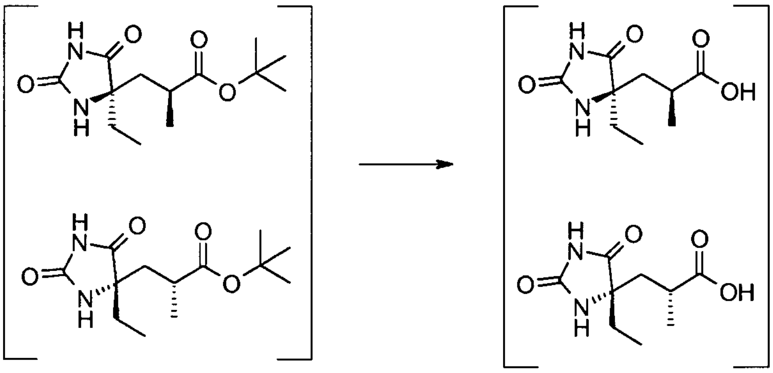
[0285] A pressure reactor is charged with $(NH_4)_2CO_3$ (0.645 g, 6.71 mmol, 10 eq.), KCN (0.175 g, 2.69 mmol, 4 eq.), **Int 046** (0.248g, 0.671 mmol, 1eq.), EtOH (4 mL) and water (4 mL). The vessel is sealed and heated at 60°C for 40h. The reaction mixture is cooled to r.t., combined with water and extracted with DCM. The combined organic layers are washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*. Purification by flash chromatography on silica gel (eluting with DCM/iPrOH 20/1) afforded the two diastereoisomers, of which the faster eluting compound is the expected product. (LCMS: MW (calcd): 439-441; m/z MW (obsd): 439-441 (M+H)).

1.2.7. General method G : Method for preparation of hydantoin propionic acids



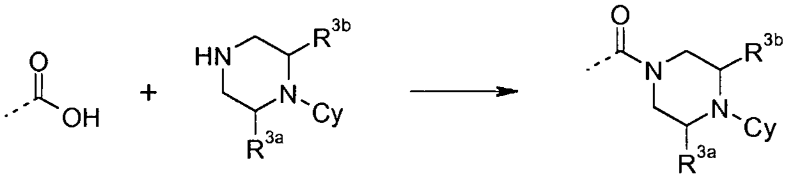
[0286] A flask is charged with *tert*-butyl ester (1 eq.) and HCl 4N in dioxane (5 to 40 eq.). In some cases, an additionnal solvent such as DCM, dioxane or water is added to increase solubilty. The reaction mixture is stirred at r.t. for 1h to 4 days until complete conversion. The reaction mixture is either concentrated *in vacuo* or filtered and washed with Et_2O to afford the expected carboxylic acid.

Illustrative synthesis of ***Int 169***



[0287] A flask is charged with **Int 170** (3.6g, 13.32 mmol, 1 eq.) and HCl 4N in dioxane (33.3 mL, 133 mmol, 10 eq.). The reaction mixture is stirred at r.t. for 2 days and concentrated *in vacuo* to afford the expected product.

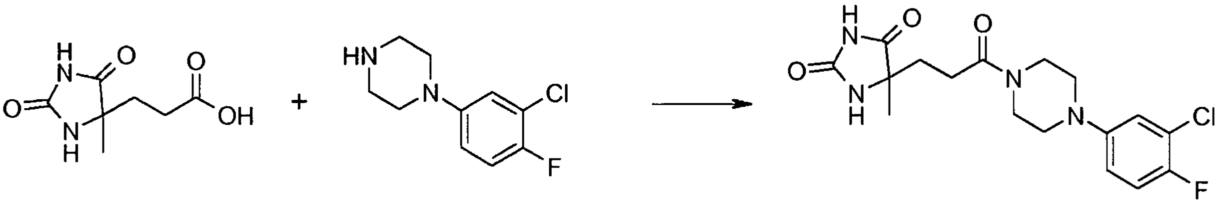
1.2.8. General method H : Amide bond formation



1.2.8.1. Method H1 : EDC/HOBt

[0288] A solution of acid (1 eq.), Et_3N (3 to 4 eq.), HOBt (0.1 to 1.1 eq.) in DMF (or DCM) is stirred at r.t.. EDC.HCl (1 to 1.2 eq.) is added, then amine (0.95 to 2 eq.) is added and the reaction mixture is stirred at r.t. for 5h to 2 days. The reaction mixture is partitioned between DCM (or EtOAC) and water, extracted with DCM (or EtOAc). The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4 (or $MgSO_4$), filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel or preparative LCMS to afford the expected amide.

Illustrative synthesis of ***Cpd 052***

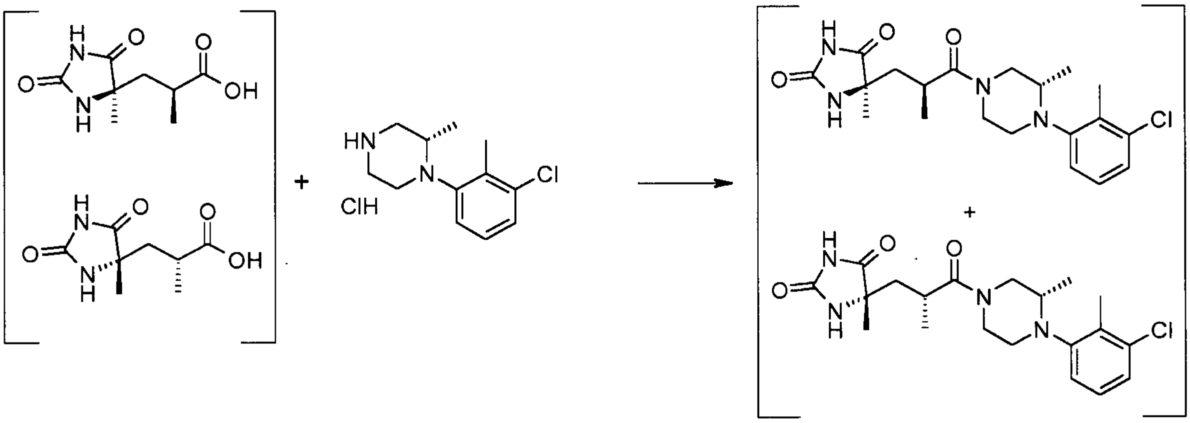


[0289] A solution of 3-(4-methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid (64 mg, 0.34 mmol, 1 eq.), Et_3N (142 μL, 1.02 mmol, 3 eq.), HOBt (46 mg, 0.34 mmol, 1 eq.) in DMF (2 mL) is stirred at r.t.. EDC.HCl (78 mg, 0.41 mmol, 1.2 eq.) is added, then 1-(3-chloro-4-fluorophenyl)piperazine dihydrochloride (150 mg, 0.52 mmol, 1.5 2 eq.) is added and the reaction mixture is stirred at r.t. overnight.The reaction mixture is partitioned between DCM and water, extracted with DCM. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by preparative LCMS to afford the expected product. LCMS: MW (calcd): 383; m/z MW (obsd): 383-385 (M+H).

1.2.8.2. Method H2 : HATU

[0290] A flask is charged with acid (1 eq.), amine (0.85 to 1.1 eq.), HATU (0.85 to 1.1 eq.) and DMF (or THF). DIPEA (2 to 6 eq.) is added and the reaction mixture is stirred at r.t. for 5h to 2 days.The reaction mixture is partitioned between EtOAc and water, extracted with EtOAc. The combined organic layers are washed with water and brine, dried (over anhydrous Na_2SO_4, $MgSO_4$, or hydrophobic column), filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel or preparative LCMS to afford the expected amide.

Illustrative synthesis of Cpd 237 (mixture of trans isomers)

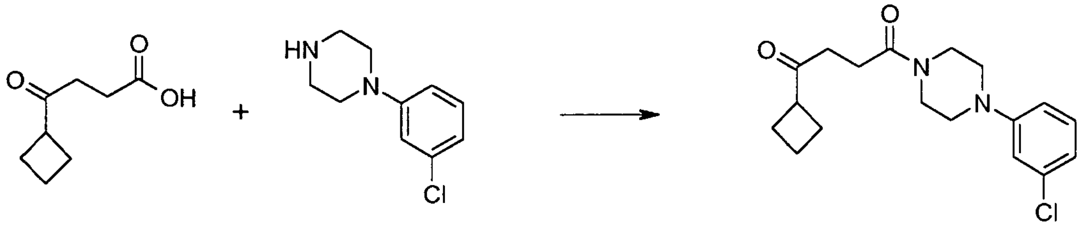


[0291] A flask is charged with **Int 165** (70 mg, 0.35 mmol, 1.1 eq.), **Int 216** (95 mg, 0.32 mmol, 1 eq.), HATU (127 mg, 0.34 mmol, 1.05 eq) and DMF (3 mL). DIPEA (167 µL, 0.96 mmol, 3 eq.) is added and the reaction mixture is stirred at r.t. overnight.The reaction mixture is partitioned between EtOAc and water, extracted with EtOAc. The combined organic layers are washed with water and brine, dried over hydrophobic column, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 96/4) to afford the expected product. LCMS: MW (calcd): 407; m/z MW (obsd): 407-409 (M+H).

1.2.8.3. Method H3 : BOP

[0292] A flask is charged with acid (1 eq.), DMF (or DCM), DIPEA or Et_3N (2 to 6 eq.) and BOP (0.77 to 1.1 eq.). After 5-15 min, amine (0.77 to 1.5 eq.) is added and the reaction mixture is stirred at r.t. for 5h to 2 days.The reaction mixture is partitioned between EtOAc (or DCM) and water, extracted with EtOAc (or DCM). The combined organic layers are washed with water and brine, dried (over anhydrous Na_2SO_4, $MgSO_4$, or hydrophobic column), filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel or preparative LCMS to afford the expected amide.

*Illustrative synthesis of **Int 034***

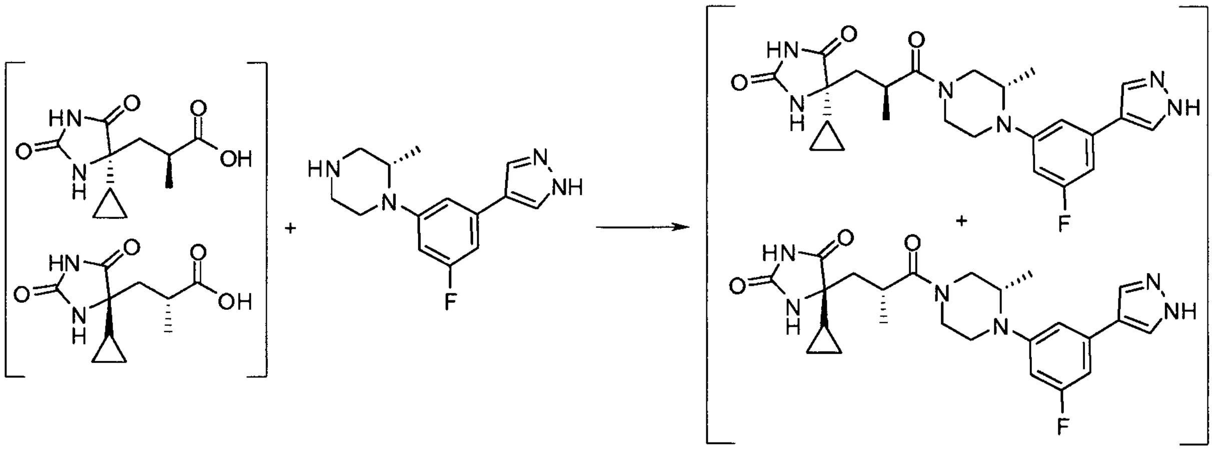


[0293] A flask is charged with 4-cyclobutyl-4-oxo-butyric acid (104 mg, 0.67 mmol, 1 eq.), DMF (2 mL), Et_3N (0.4 mL, 2.88 mmol, 4.3 eq.) and BOP (320 mg, 0.72 mmol, 1.1 eq.). After 5-15 min, 1-(3-chlorophenyl)piperazine (157 mg, 0.67 mmol, 1 eq.) is added and the reaction mixture is stirred at r.t. overnight. The reaction mixture is partitioned between DCM and water, extracted with DCM. The combined organic layers are washed with water and brine, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/EtOAc 90/10) afford the expected product. LCMS: MW (calcd): 335; m/z MW (obsd): 335-337 (M+H).

1.2.8.4. Method H4 : CDI

[0294] A flask is charged with acid (1 eq.), amine (1 eq.) and DMF. HOBt (0.8 eq.), DIPEA (1.5 eq.) and PS-CDI (load 1.25 mmol/g, 1.3 eq.) are added and the reaction mixture is stirred in a microwave reactor at 60°C for 30-60 min. Reaction mixture is filtered to remove PS-CDI, washed with EtOAc and the filtrate is extracted with EtOAc and brine. The combined organic layers concentrated *in vacuo* and purified by flash chromatography on silica gel or preparative LCMS to afford the expected amide.

*Illustrative synthesis of **Cpd 379***

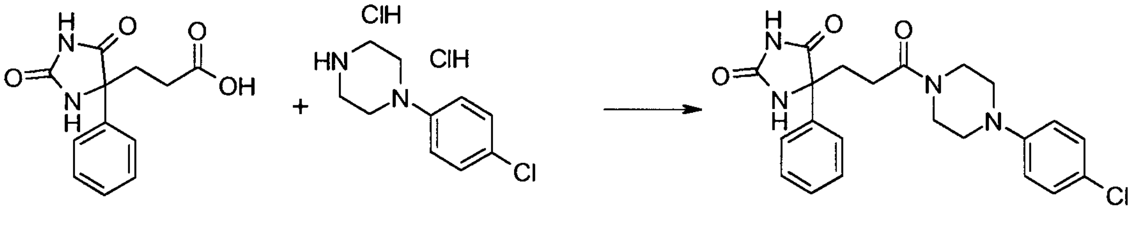


[0295] A flask is charged with **Int 164** (41 mg, 0.23 mmol, 1 eq.), **Int 232** (60 mg, 0.23 mmol, 1 eq.) and DMF (5 mL). HOBt (28 mg, 0.18 mmol, 0.8 eq.), DIPEA (60 µL, 0.34 mmol, 1.5 eq.) and PS-CDI (load 1.25 mmol/g, 237 mg, 0.29 mmol, 1.3 eq.) are added and the reaction mixture is stirred in a microwave reactor at 60°C for 30 min. Reaction mixture is filtered to remove PS-CDI, washed with EtOAc and the filtrate is extracted with EtOAc and brine. The combined organic layers concentrated *in vacuo* and purified by flash chromatography (eluting with DCM/MeOH 100/0 to 90/10) to afford the expected product. LCMS: MW (calcd): 468; m/z MW (obsd): 469 (M+H).

1.2.8.5. Method H5 : Mukaiyama reagent

[0296] A flask is charged with acide (1 eq.), amine (1.5 eq.) and DMF/DCM. Et_3N (4 eq.) and PS-Mukaiyama reagent (load 1.17 mmol/g, 2 eq.) are added and the reaction mixture is stirred at r.t. for 24h. Reaction mixture is filtered, washed with DCM and the filtrate is concentrated *in vacuo* and purified by preparative LCMS to afford the expected amide.

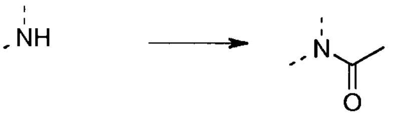
Illustrative synthesis of ***Cpd 005***



[0297] A flask is charged with 3-(2,5-dioxo-4-phenyl-imidazolidin-4-yl)propionic acid (77 mg, 0.31 mmol, 1 eq.), 1-(4-chloro-phenyl)-piperazine dihydrochloride (126 mg, 0.47 mmol, 1.5 eq.) and DMF/DCM (1mL/4mL). Et_3N (169 µL, 1.25 mmol, 4 eq.) and PS-Mukaiyama reagent (load 1.17 mmol/g, 540 mmg, 0.63 mmol, 2 eq.) are added and the reaction mixture is stirred at r.t. for 24h. Reaction mixture is filtered, washed with DCM and the filtrate is concentrated *in vacuo* and purified by preparative LCMS to afford the expected product. LCMS: MW (calcd): 427; m/z MW (obsd): 427-429 (M+H).

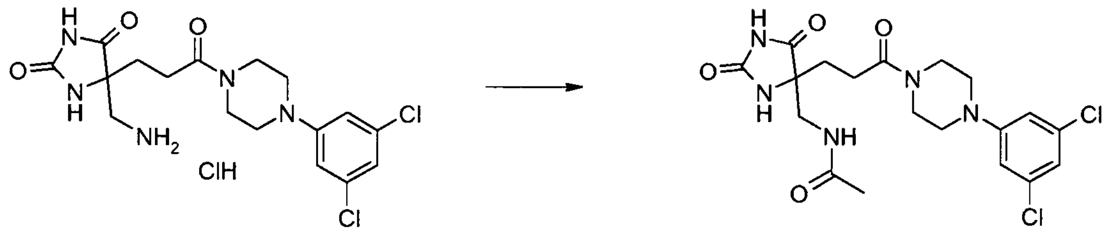
1.2.9. General method I : Functionalization of final compound

1.2.9.1. Method I1: acetylation



[0298] To a solution of amino derivative (1 eq.) in pyridine is added acetic anhydride (1.02 eq.). The reaction mixture is stirred at r.t. for 4h to 16h, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected acetamide.

Illustrative synthesis of ***Cpd 223***

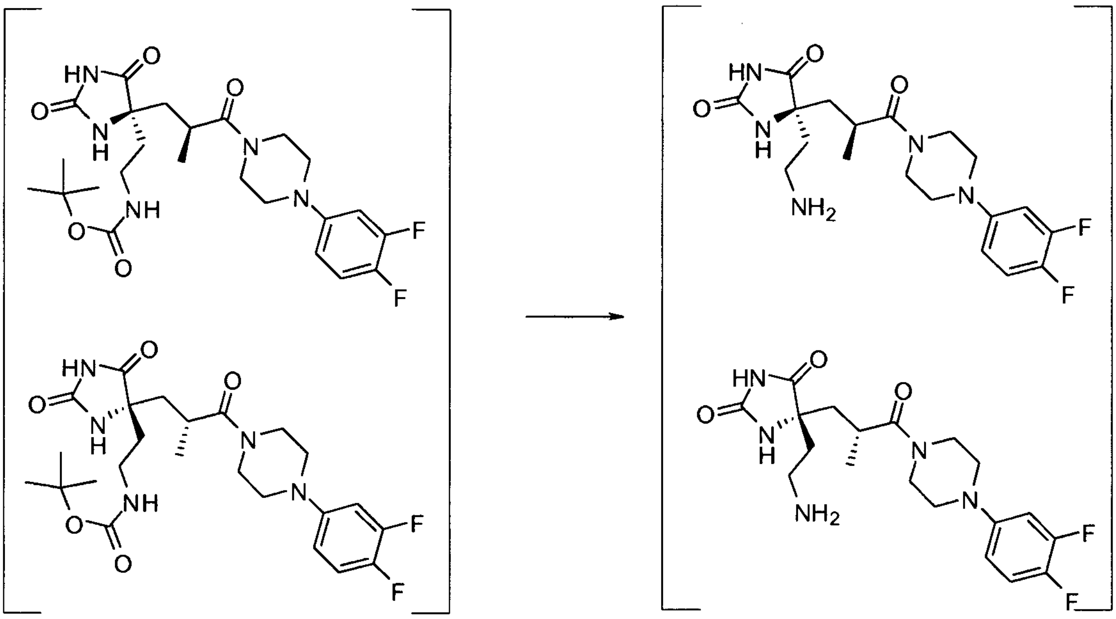


[0299] To a solution of **Cpd 180** (150 mg, 0.33 mmol, 1 eq.) in pyridine (2 mL) is added acetic anhydride (32 µL, 0.34 mmol, 1.02 eq.). The reaction mixture is stirred at r.t. for 4h, concentrated *in* *vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 90/10) to afford the expected product. LCMS: MW (calcd): 456; m/z MW (obsd): 456-458 (M+H).

1.2.9.2. Method I2 : NBoc deprotection

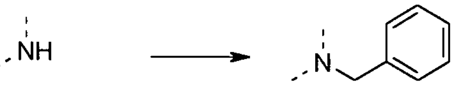
[0300] To a solution of N-*tert*-butoxycarbonyl derivative (1 eq.) in a mixture DCM/MeOH is added HCl 4N in dioxane (10 to 20 eq.). The reaction mixture is stirred at r.t. for 4h to 2 days and concentrated *in vacuo*.The residue is either purified by preparative HPLC or dissolved in DCM/MeOH, neutralized by addition of a base (NH_3 in MeOH (7N) or $NaHCO_3$) and purified by SCX column or flash chromatography on silica gel to afford the expected amine.

*Illustrative synthesis of **Cpd 241***



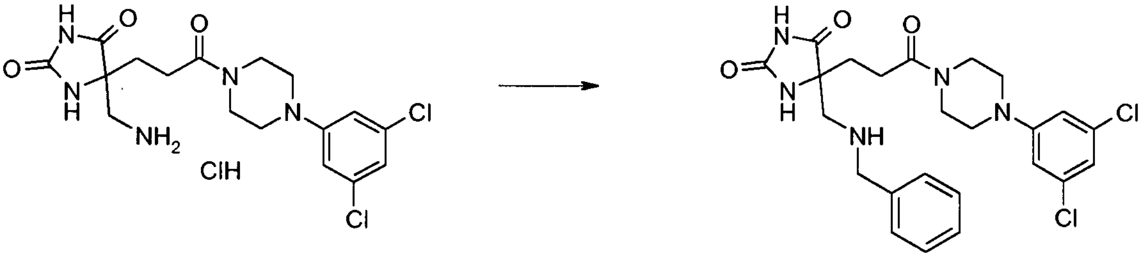
[0301] To a solution of **Cpd 235**(39 mg, 0.076 mmol, 1 eq.) in a mixture DCM/MeOH (1.5mL/1mL) is added HCl 4N in dioxane (0.37 mL, 1.51 mmol, 20 eq.). The reaction mixture is stirred at r.t. for 16h and concentrated *in vacuo*. The residue is dissolved in DCM/MeOH, neutralized by addition of NH_3 in MeOH (7N, 110 µL, 0.75 mmol, 10 eq.) and purified by SCX-2 column (eluting successively with $DCM/MeOH/NH_3$: 8/1/1, 6/3/1 and 0/9/1) to afford the expected product. LCMS: MW (calcd): 409; m/z MW (obsd): 410 (M+H).

1.2.9.3. Method I3 : alkylation



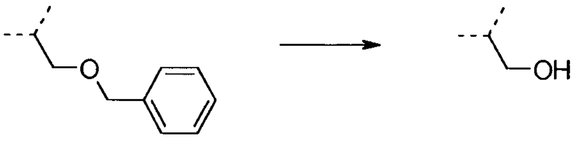
[0302] To a solution of amino derivative (1 eq.) in DMF is added K_2CO_3 (3 eq.) then benzyl bromide (1 eq.). The reaction mixture is stirred at r.t. for 16h to 4 days, quenched by addition of water and extracted with EtOAc. The organic layers are combined, washed with brine, dried by filtration over hydrophobic column, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected benzylamine.

Illustrative synthesis of ***Cpd 181***



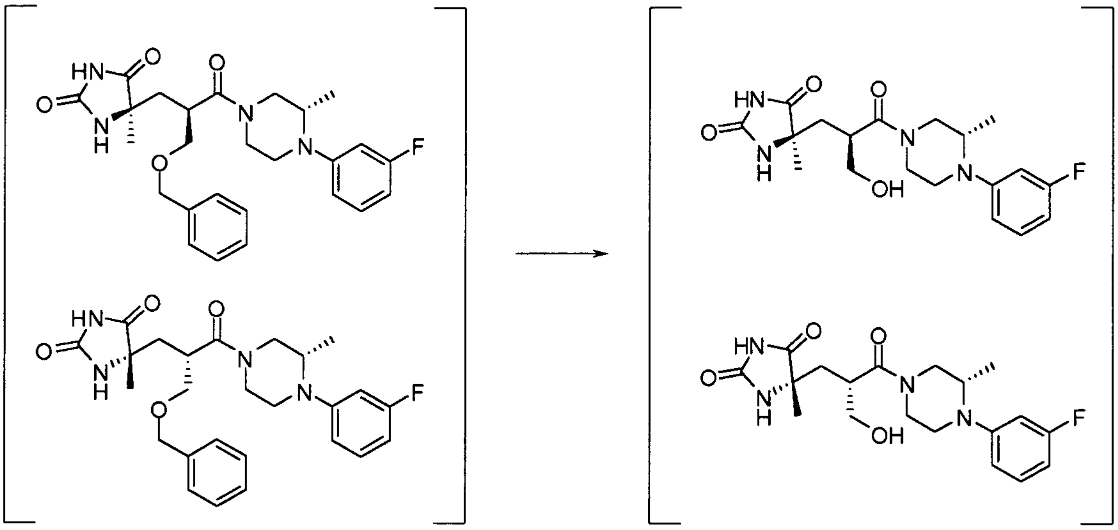
[0303] To a solution of **Cpd 180**(200 mg, 0.444 mmol, 1 eq.) in DMF (2 mL) is added K_2CO_3 (184 mg, 1.331 mmol, 3 eq.) then benzyl bromide (76 mg, 0. 444 mmol, 1 eq.). The reaction mixture is stirred at r.t. overnight, quenched by addition of water and extracted with EtOAc. The organic layers are combined, washed with brine, dried by filtration over hydrophobic column, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/isopropyl alcohol 100/0 to 90/10) to afford the expected product. LCMS: MW (calcd): 504; m/z MW (obsd): 504-506 (M+H).

1.2.9.4. Method I4 : O-debenzylation



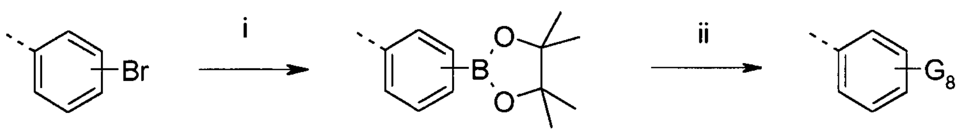
[0304] To a solution of benzyloxy derivative (1 eq.) in dry THF or MeOH under argon atmosphere is added $Pd(OH)_2/C$. The reaction mixture is stirred under H_2 atmosphere at r.t. for 5h to 2 days then filtered on celpure P65. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected alcohol.

*Illustrative synthesis of **Cpd 268** (Mixture of trans isomers)*



[0305] To a solution of **Int 062** (70 mg, 0.15mmol, 1 eq.) in dry THF (75 mL) under argon atmosphere is added $Pd(OH)_2/C$ (35 mg, 50%w/w). The reaction mixture is degassed by 3 vacuum/hydrogen filling cycles, and stirred under H_2 atmosphere at r.t. for 2 days then filtered on celpure P65. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 95/5) to afford the expected product. LCMS: MW (calcd): 392; m/z MW (obsd): 429-431 (M+H).

1.2.9.5. Method I5 : Two-steps functionalization by Suzuki reaction



G_8=Ar, HetAr

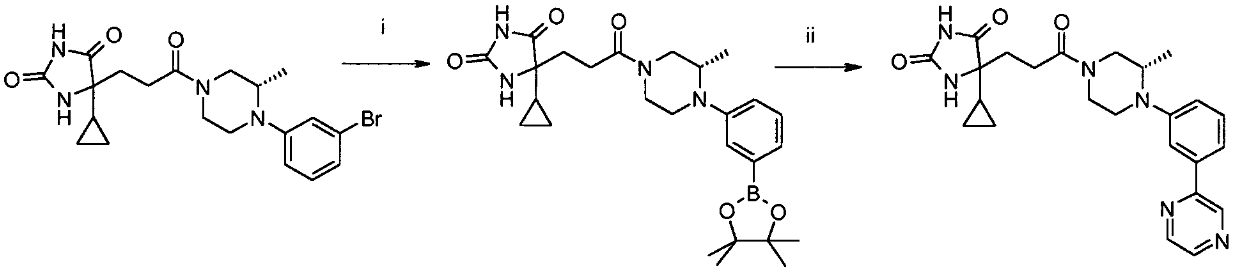
Step i)

[0306] A vial is loaded with bromo derivative (1 eq.), bis(pinacolato)diboron (1.2 eq.), KOAc (3 eq.) and dioxane degassed with N_2. $PdCl_2(dppf)$ (0.05 eq.) is added, the vial is sealed and stirred at 90°C overnight. The reaction mixture is filtered on celpure P65, washed with EtOAc. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected boronic ester.

Step ii)

[0307] A vial is loaded with the boronic ester obtained in the previous step (1 eq.), aryl halide (1.1 to 1.2 eq.), Na_2CO_3 (3 eq.) and a mixture dioxane/water (9/1) degassed with N_2. $PdCl_2(dppf)$ (0.05 to 0.2 eq.) is added, the vial is sealed and stirred at 90°C overnight. The reaction mixture is filtered on celpure P65, washed with EtOAc. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel or preparative HPLC to afford the expected compound.

Illustrative synthesis of ***Cpd 372***



Step i) 5-Cyclopropyl-5-(3-{(S)-3-methyl-4-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-piperazin-1-yl}-3-oxo-propyl)-imidazolidine-2,4-dione

[0308] A vial is loaded with **Cpd 270** (90 mg, 0.200 mmol, 1 eq.), bis(pinacolato)diboron (61 mg, 0.240 mmol, 1.2 eq.), KOAc (59 mg, 0.601 mmol, 3 eq.) and dioxane (2 mL) degassed with N_2. $PdCl_2$(dppf) (7 mg, 0.010 mmol, 0.05 eq.) is added, the vial is sealed and stirred at 90°C overnight. The reaction mixture is filtered on celpure P65, washed with EtOAc. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 97/3) to afford the expected boronic ester. LCMS: MW (calcd): 496; m/z MW (obsd): 497 (M+H).

Step ii) 5-Cyclopropyl-5-{3-[(S)-3-methyl-4-(3-pyrazin-2-yl-phenyl)-piperazin-1-yl]-3-oxo-propyl}-imidazolidine-2,4-dione

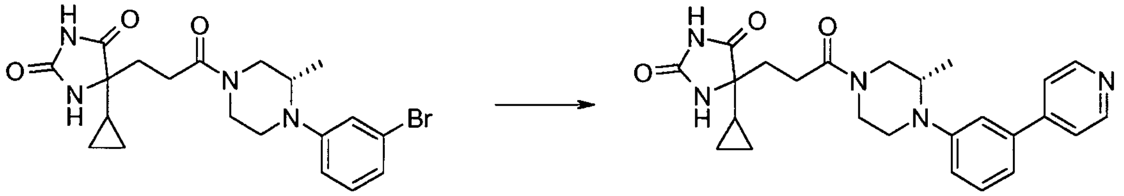
[0309] A vial is loaded with the boronic ester obtained in the previous step (86 mg, 0.173 mmol, 1 eq.), iodopyrazine (39 mg, 0.191 mmol, 1.1 eq.), Na_2CO_3 (100 mg, 0.520 mmol, 3 eq.) and a mixture dioxane/water (2.5 mL, 9/1) degassed with N_2. $PdCl_2$(dppf) (7 mg, 0.009 mmol, 0.05 eq.) is added, the vial is sealed and stirred at 90°C overnight. The reaction mixture is filtered on celpure P65, washed with EtOAc. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 95/5) to afford the expected product. LCMS: MW (calcd): 449; m/z MW (obsd): 450 (M+H).

1.2.9.6. Method I6 : Suzuki reaction

G_8=Ar, HetAr

[0310] A vial is loaded with bromo derivative (1 eq.), boronic acid or boronic ester (1.3 to 2 eq.), Na_2CO_3 (3 eq.) and a mixture dioxane/water (9/1) degassed with N_2. $PdCl_2$(dppf) (0.05 to 0.2 eq.) is added, the vial is sealed and stirred at 90°C for 3h to 20h. The reaction mixture is quenched with water and extracted with EtOAc. The combined organic layers are washed with brine, dried (filtration over hydrophobic column or anhydrous $MgSO_4$), concentrated *in vacuo* and purified by flash chromatography on silica gel or preparative HPLC to afford the expected compound.

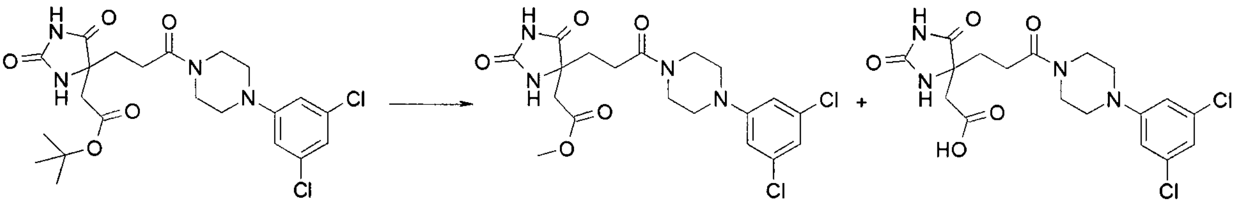
*Illustrative synthesis of **Cpd 281***



[0311] A vial is loaded with **Cpd 270** (100 mg, 0.223 mmol, 1 eq.), pyridine-4-boronic acid (55 mg, 0.445 mmol, 2 eq.), Na_2CO_3 (128 mg, 0.668 mmol, 3 eq.) and a mixture dioxane/water (2 mL, 9/1) degassed with N_2. $PdCl_2$(dppf) (36 mg, 0.045 mmol, 0.2 eq.) is added, the vial is sealed and stirred at 90°C for 3h. The reaction mixture is quenched with water and extracted with EtOAc. The combined organic layers are washed with a saturated $NaHCO_3$ solution, brine, dried by filtration over hydrophobic column, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 94/6) to afford the expected product. LCMS: MW (calcd): 448; m/z MW (obsd): 449 (M+H).

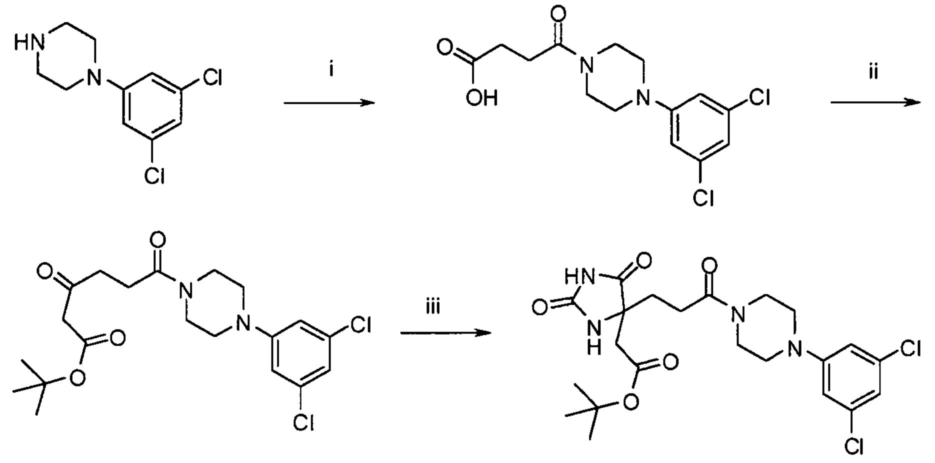
Example 2. Preparation of the compounds of the invention.

2.1. *Methyl 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetate (Cpd 182) and 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetic acid (Cpd 183)*



[0312] A vial is charged with **Cpd 188** (1.61 g, 3.2 mmol, 1eq.), dioxane (5 mL) and HCl 4N in dioxane (5 mL). The reaction is heated at 80°C for 20h, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/EtOAc 60/40 to 10/90, then DCM/MeOH 90/10) to afford **Cpd 182** (LCMS: MW (calcd): 457; m/z MW (obsd): 457-459 (M+H)) and **Cpd 183** (LCMS: MW (calcd): 443; m/z MW (obsd): 443-445 (M+H)).

2.2. tert-butyl 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetate (Cpd 188)



Step i) 4-[4-(3,5-Dichloro-phenyl)-piperazin-1-yl]-4-oxo-butyric acid

[0313] A flask is charged with succinic anhydride (2.38g, 24 mmol, 1.1 eq.) and 1-(3,5-dichloro-phenyl)-piperazine (5g, 22 mmol, 1eq.) and toluene (100 mL). The reaction mixture is heated at reflux overnight, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 80/20) to afford the carboxylic acid derivative.

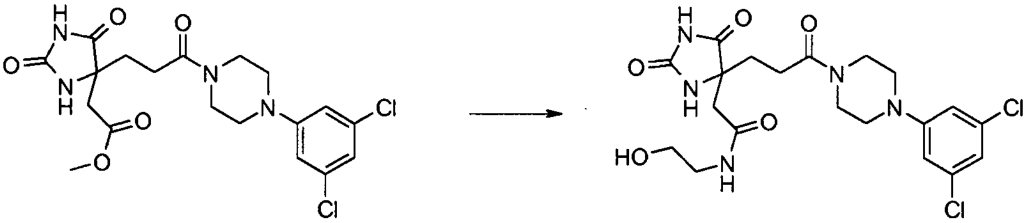
Step ii) 6-[4-(3,5-Dichloro-phenyl)-piperazin-1-yl]-3,6-dioxo-hexanoic acid tert-butyl ester

[0314] To a solution of the carboxylic acid obtained in the previous step (7.29g, 22 mmol, 1 eq.) in DCM (125 mL) are added DMAP (0.537 g, 4.4 mmol, 0.2 eq.), EDC.HCl (5.06 g, 26.4 mmol, 1.2 eq.) and Et_3N (9.2 mL, 66 mmol, 3 eq). The reaction mixture is stirred at r.t. for 15 min then a solution of 2,2-dimethyl-[1,3]dioxane-4,6-dione (3.8 g, 26.4 mmol, 1.2 eq.) in DCM (25 mL) is added and the reaction mixture is stirred at r.t. overnight. DMAP (1 g) and EDC.HCl (1.5g) are added and the RM is stirred at 40°C for 2h, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 90/10). The residue is taken up in toluene (100 mL) and t-BuOH (5.8 mL, 61 mmol) is added. The reaction mixture is heated at reflux for 4h, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with Hexanes/EtOAc 70/30 to 30/70) to afford the expected β-ketoester.

Step iii) tert-butyl 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetate

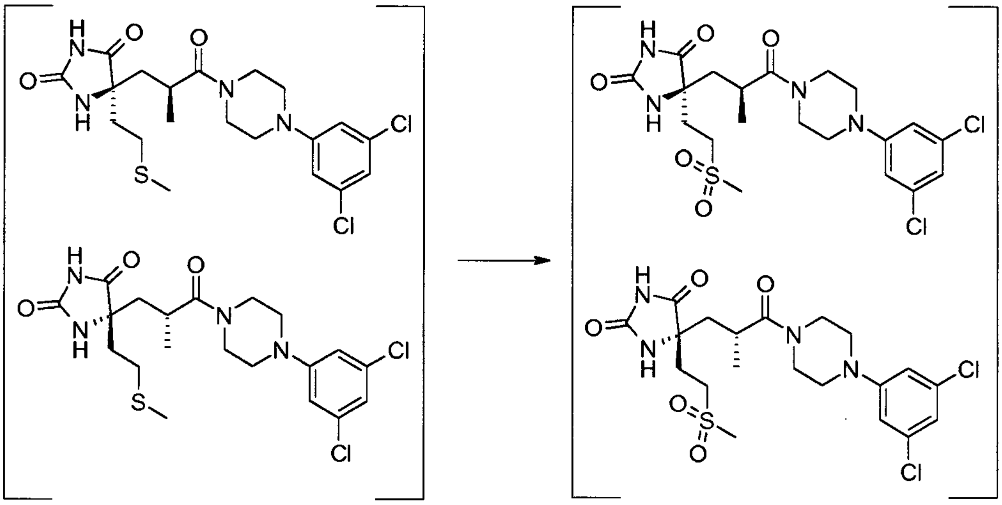
[0315] Starting from the above β-ketoester, the expected product is obtained according to Method F. LCMS: MW (calcd): 499; m/z MW (obsd): 499-501 (M+H).

2.3. 2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]-N-(2-hydroxyethyl)acetamide (Cpd 189)



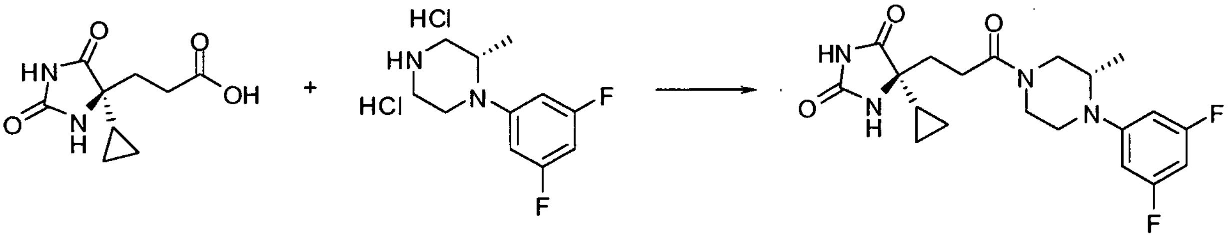
[0316] A vial is charged with **Cpd 182** (150 mg, 0.32 mmol, 1 eq.), 2-amino-ethanol (193 µL, 3.2 mmol, 10 eq.) and EtOH (2 mL). The reaction mixture is heated at 160°C for 1h in microwave reactor, concentrated *in vacuo* and purified by preparative LCMS to afford the expected product. LCMS: MW (calcd): 486; m/z MW (obsd): 486-488 (M+H).

2.4. 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-methylsulfonylethyl)imidazolidine-2,4-dione (Cpd 218)



[0317] To a solution of **Cpd 197** (40 mg, 0.084 mmol, 1 eq.) in DCM (2 mL) at 0°C is added *meta*-chloroperoxybenzoic acid (32 mg, 0.186 mmol, 2.2 eq.). The reaction mixture is stirred at 0°C for 45min then at r.t. for 24h, quenched with a saturated $NaHCO_3$ solution, extracted with DCM. The combined organic layers are washed with brine, dried by filtration over hydrophobic column and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with DCM/MeOH 100/0 to 98/2) to afford the expected product. LCMS: MW (calcd): 505; m/z MW (obsd): 505-507 (M+H).

2.5. (5S)-cyclopropyl-5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione (Cpd 255)

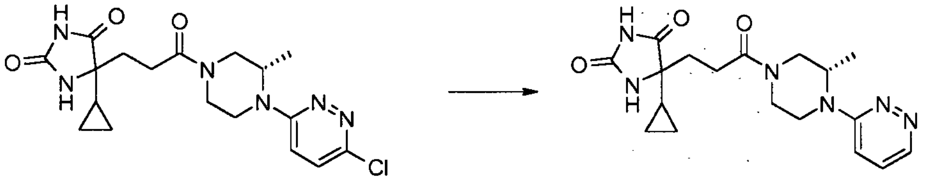


[0318] (S)-Hydantoin propionic acid (Int 163, 50 g, 0.24 mol, 1.1 eq.) is dissolved in DMF (360 mL). Amine hydrochloride (61 g, 0.21 mol, 1 eq.), DIPEA (148 mL, 0.84 mol, 4 eq., added through glass funnel over 2min), EDC.HCl (45 g, 0.24 mol, 1.1 eq.) and HOBt hydrate (4.95 g, 0.032 mol, 0.15 eq.) are added and reaction mixture is stirred at r.t. for 18h. Reaction mixture is poured into cold stirring water (1.8 L) and stirred for 45 min. A small precipitate is formed, filtered off through black ribbon. Filtrate is extracted with EtOAc (2x650 mL and 300 mL). Combined organic layers are washed with sat. aq. $NaHCO_3$ (2x800 mL and 500 mL), brine (2x500 mL), dried over Na_2SO_4 and concentrated *in vacuo.* This residue is purified by flash chromatography on silica gel (eluting with DCM/MeOH/NH_3 100/0/0 to 90/5/0.5) to afford the desired compound.

[0319] Chiral HPLC: ee ≥ 99.4%; Condition used to determine the enantiomeric excess are the following:

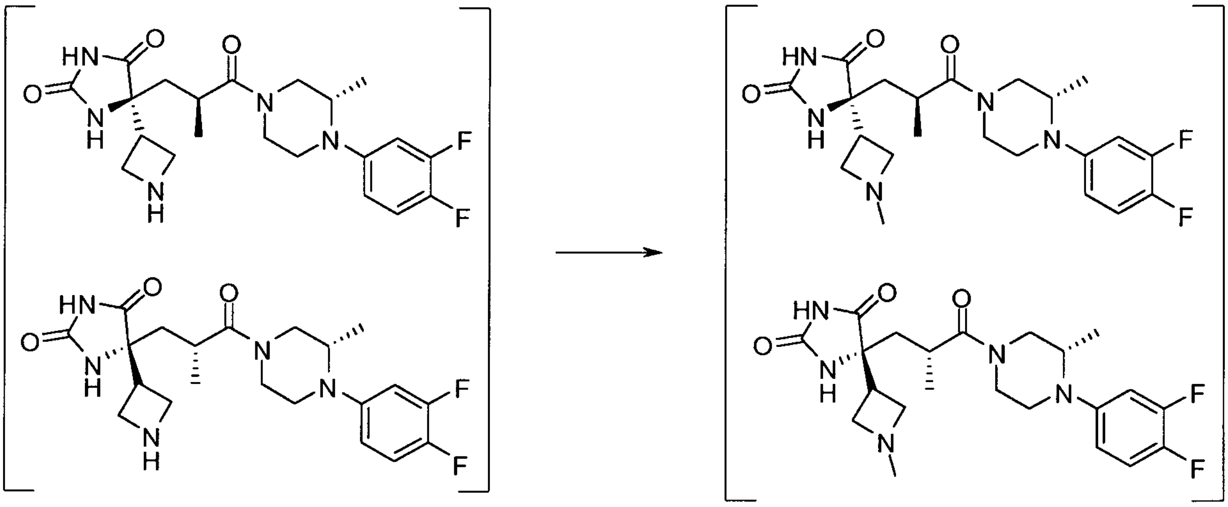
- column: Chiralpak IC (250 x 4.6 mm), 5μm, at room temperature
- mobile phase: Heptane/Ethanol/DEA (70/30/0.1, v/v/v)
- flow rate of 1 mL/min

2.7. 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-pyridazin-3-yl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione (Cpd 302)



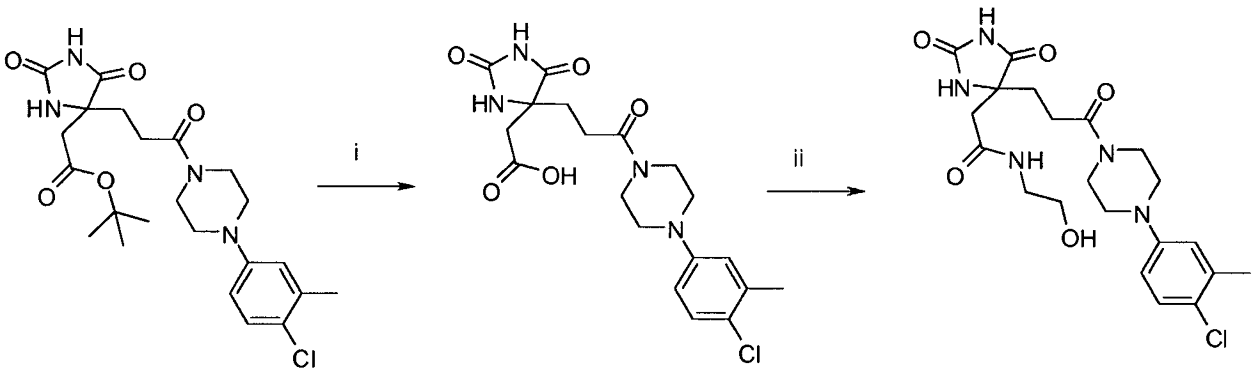
[0320] To a solution of **Cpd 285** (72 mg, 0.177 mmol, 1 eq.) in EtOH (3.7 mL) and DMF (0.7 mL) is added Et_3N (0.2 mL, 1.44 mmol, 8 eq.) and the reaction mixture is heated at 40°C to increase solubility. Pd/C 10% (14 mg) is added and the reaction mixture is stirred at r.t. overnight and filtered. The filtrate is concentrated *in vacuo* and purified by flash chromatography on silica gel (DCM/MeOH 100/0 to 94/6) to afford the expected product. LCMS: MW (calcd): 372; m/z MW (obsd): 373 (M+H).

2.8. 5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(1-methylazetidin-3-yl)imidazolidine-2,4-dione (Cpd 399)



[0321] To a suspension of **Cpd 247** (55 mg, 0.13 mmol, 1.0 eq.) in MeCN (1 mL) is added a formaldehyde in water solution (37%wt, 37 µL, 0.51 mmol, 4.0 eq.) and the mixture is stirred at r.t. for 10 min. Sodium cyanoborohydride is added (16 mg, 0.25 mmol, 2.0 eq.) and the reaction mixture is stirred at r.t. for 1h. Sodium triacetoxyborohydride is added (53 mg, 0.25 mmol, 2.0 eq.) and the reaction mixture is stirred at r.t. for 2h. An aqueous $NaHCO_3$ solution (1 mL) is added and the mixture is concentrated to dryness. The residue is purified by flash chromatography on KP-NH type silica gel (eluting with DCM/MeOH 100/0 to 95/5) to afford the expected product. LCMS: MW (calcd): 449; m/z MW (obsd): 450 (M+H).

2.9. 2-[4-[3-[4-(4-chloro-3-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]-N-(2-hydroxyethyl)acetamide (Cpd 402)



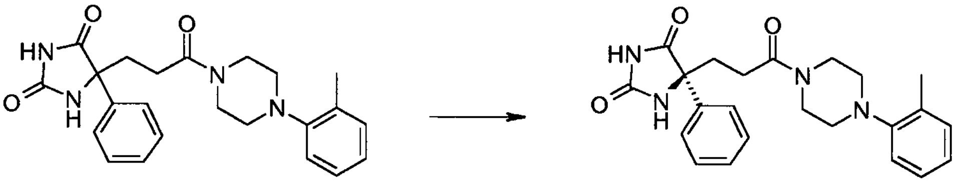
Step i) (4-{3-[4-(4-Chloro-3-methyl-phenyl)-piperazin-1-yl]-3-oxo-propyl}-2,5-dioxo-imidazolidin-4-yl)-acetic acid

[0322] A flask is charged with **Int 116** (30 mg, 0.06 mmol 1.0 eq.) and a solution of HCl in dioxane (4.0M, 630 µL, 40 mmol, 2.5 eq.). The reaction mixture is stirred at r.t. for 2h, and then diltuted with water and extracted 3 times with DCM. The combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 422; m/z MW (obsd): 423 (M+H).

Step ii)

[0323] The carboxylic acid (18 mg, 0.04 mmol, 1.0 eq.) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo-[4,5-b]pyridinium-3-oxyde hexafluorophosphate (18 mg, 0.05 mmol, 1.1 eq.) are stirred in DMF (0.5 mL) at r.t.. After 30 min, ethanolamine (2.6 µL, 0.04 mmol, 1.0 eq.) is added; the reaction mixture is stirred at r.t. for 2h, then diluted with water and extracted 3 times with DCM. The combined organic layers are dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and purified by preparative HPLC to afford the expected product. LCMS: MW (calcd): 465; m/z MW (obsd): 466 (M+H).

2.10. (5S)-5-[3-[4-(o-tolyl)piperazin-1-yl]-3-oxo-propyl]-5-phenyl-imidazolidine-2,4-dione (Cpd 027): chiral separation by chiral HPLC

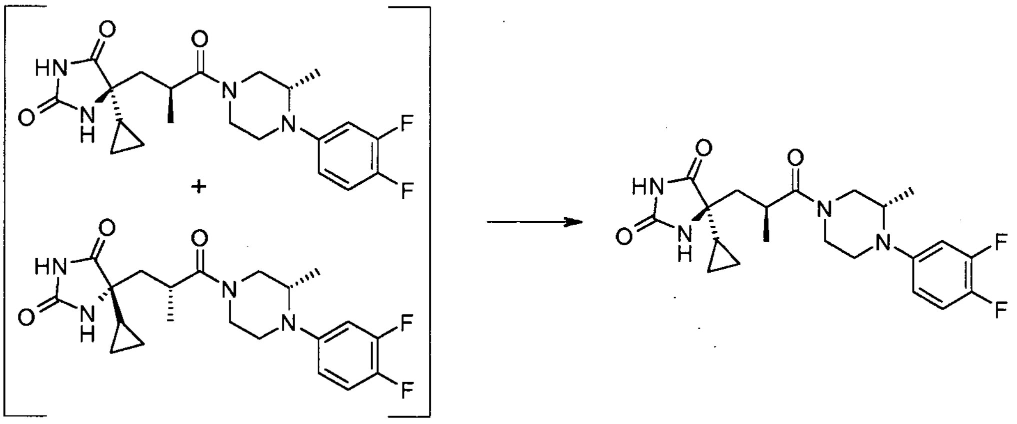


[0324] **Cpd 007** is purified by chiral HPLC using the following conditions:

- Column: Chiralpak AD 20 µm 250 x 21.7mm,
- Mobile phase: 100% EtOH,
- Flow rate: 20 mL/min.

[0325] This purification affords the expected product as a single enantiomer.

2.11. (5S)-5-cyclopropyl-5-[(2S)-3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione (Cpd 212): chiral separation by SFC



[0326] **Cpd 191** is purified by SFC using the following conditions:

- Instrument: Waters Thar SFC prep100

- Column: Chiralpak IA (30 x 250mm), 5 µM
- Mobile phase: Isocratic 25% iPrOH/DCM (80/20) and 75% CO_2,
- Flow rate: 100 mL/min

[0327] **Cpd 191** is dissolved in iPrOH (7 vol) and DCM (3 vol) (approximately 50mg/mL), Injection volume 1500 µl which equates to loading of 75 mg on column per injection. This purification affords the expected product as a single enantiomer.

2.12. (5R)-5-[(2S)-3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione (Cpd 265): chiral separation by SFC

[0328] **Cpd 405** is purified by SFC the following conditions:

- Instrument: Waters Thar SFC prep100
- Column: Chiralpak IA (30 x 250mm), 5uM
- Mobile phase: Isocratic 20% iPrOH and 80% CO_2,.
- Flow rate: 100 mL/min

[0329] **Cpd 405** is dissolved in iPrOH (2 vol) and acetonitrile (1 vol) (approximately 4.5mg/mL), Injection volume 1500µL which equates to loading of 6.75mg on column per injection. This purification affords the expected product **Cpd 265** as a single enantiomer.

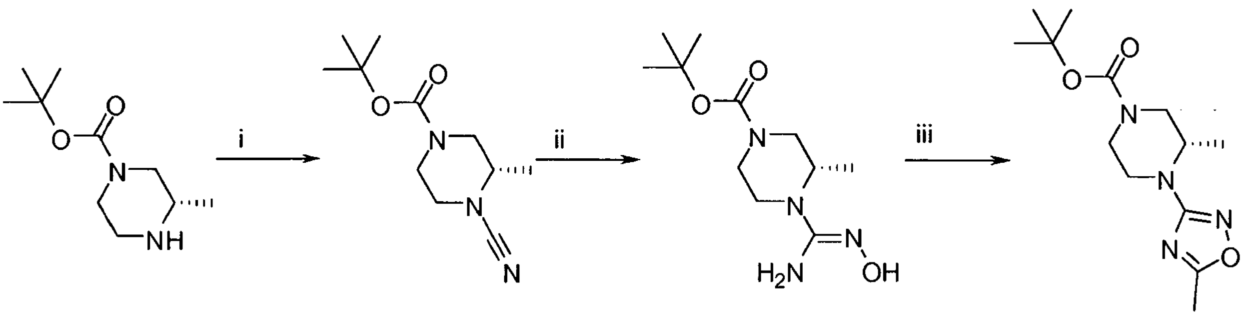
2.13. (S)-5-((S)-3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione (Cpd 331): chiral separation by SFC

[0330] **Cpd 406** is purified by SFC using the following conditions:

- Instrument: Waters Thar SFC prep100
- Column: Chiralpak IA (20 x 250mm), 5uM
- Mobile phase: Isocratic 35% EtOH and 65% CO_2,
- Flow rate: 100 mL/min

[0331] Cpd 406 is dissolved in EtOH (70 mL) (approximately 20 mg/mL), Injection volume 1500µL which equates to loading of 30mg on column per injection, total number of stacks: 49. This purification affords the expected product **Cpd 331** as a single enantiomer.

2.14. (S)-3-Methyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-piperazine-1-carboxylic acid tert-butyl ester-precursor of Int 237



Step i) (S)-4-Cyano-3-methyl-piperazine-1-carboxylic acid tert-butyl ester

[0332] (S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester (1g, 4.99 mmol, 1eq.) is suspended in acetonitrile (20 mL), K_2CO_3 (1.851 g, 13.4 mmol, 2.7 eq.) is added and the suspension is stirred for 10 min before the addition of BrCN (5.0M in acetonitrile, 1.248 mL, 6.24 mmol, 1.25 eq.). The reaction is stirred at r.t. for 3h and filtered; the solid is washed with EtOAc and the filtrate is concentrated *in vacuo* to afford the expected cyano derivative. LCMS: MW (calcd): 225; m/z MW (obsd): 226 (M+H).

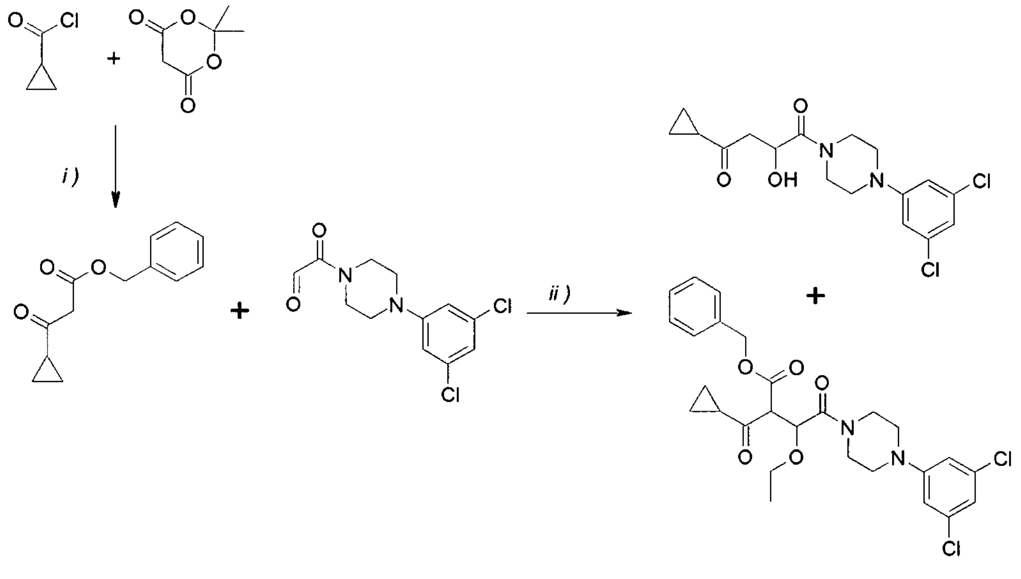
Step ii) (S)-4-(N-Hydroxycarbamimidoyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester

[0333] To a solution of (S)-4-Cyano-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (500 mg, 2.22 nmol, 1 eq.) in EtOH (10 mL), hydroxylamine hydrochloride (261 mg, 3.75 mmol, 1.5 eq.) and Et_3N (869 µL, 6.25 mmol, 2.5 eq.) are added and reaction mixture is refluxed for 2h concentrated *in vacuo* to afford the expected N-hydroxy amidine derivative used as such in the next reaction step.

Step iii) (S)-3-Methyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-piperazine-1-carboxylic acid tert-butyl ester

[0334] Crude N-hydroxy amidine derivative (2.22 mmol, 1eq.) is dissolved in pyridine (10 mL) and acetylchloride (266 µL, 3.75mmol, 1.5 eq.) is added. Reaction mixture is stirred at 120°C for 1h, poured into water, extracted with EtOAc. The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected product (precursor of **Int 237**). LCMS: MW (calcd): 282; m/z MW (obsd): 283 (M+H).

2.15. 4-Cyclopropyl-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-hydroxy-butane-1,4-dione (Int 053) and benzyl 2-(cyclopropanecarbonyl)-4-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-ethoxy-4-oxo-butanoate (Int 054)



Step i) 3-Cyclopropyl-3-oxo-propionic acid benzyl ester and [4-(3,5-Dichloro-phenyl)-piperazin-1-yl]-oxo-acetaldehyde

[0335] A flask is charged with Meldrum's acid (50.3 g, 349 mmol, 1.0 eq.), DCM (300 mL) and pyridine (90 mL, 1.1 mol, 3.2 eq), and cooled in an ice bath. To the resulting solution, is added dropwise cyclopropane carbonyl chloride (35.0 mL, 386 mmol, 1.1 eq). After 2h, the cold bath is removed. After 16h, the mixture is combined with aqueous HCl (2N, 700 mL) and DCM (200 mL) in a separatory funnel and agitated. The organic phase is collected and washed with aqueous HCl (2N) (500 mL), brine (500 mL), and dried over $MgSO_4$ and activated charcoal. After filtration, volatiles are removed via rotary evaporation. The residue is combined with toluene (100 mL) and benzyl alcohol (37 mL, 356 mmol, 1.02 eq) in a round bottomed flask equipped with a reflux condenser, and heated at reflux. After 16h, the mixture is allowed to cool to room temperature. Volatiles are removed via rotary evaporation to give the crude product.

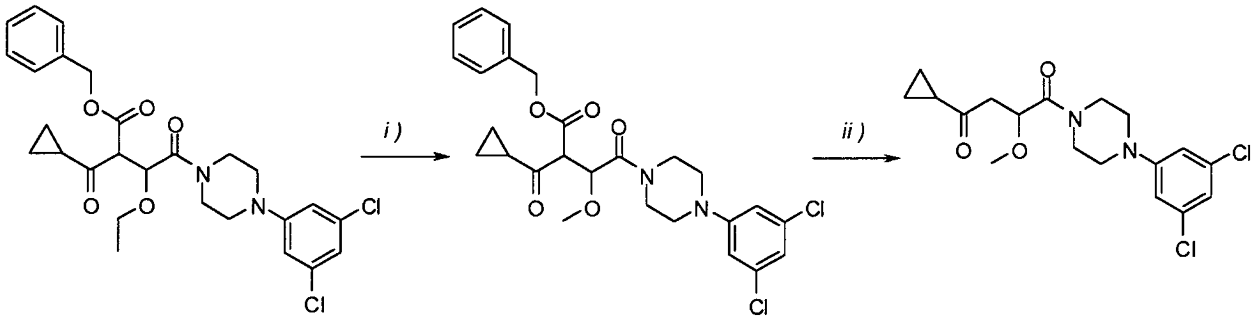
Step ii) 4-Cyclopropyl-1-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-2-hydroxy-butane-1,4-dione and 2-Cyclopropanecarbonyl-4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-3-ethoxy-4-oxo-butyric acid benzyl ester

[0336] A vial is charged with **Int 149** (127 mg, 0.44 mmol, 1.0 eq), the β-keto ester from step i) (189 mg, 0.90 mmol, 2.0 eq), and DCM (2 mL). After 16h, volatiles are removed via rotary evaporation. The residue is combined with $Pd(OH)_2/C$ (20%) (81 mg, 0.12 mmol, 0.26 eq), ethanol (8 mL), and cyclohexene (2.0 mL, 20 mmol, 45eq.) in a round bottomed flask, and heated at reflux. After 1h, the mixture is filtered through a plug of clarcel on a fritted funnel. Volatiles are removed via rotary evaporation. The residue is charged onto a column of silica gel and eluted with EtOAc/DCM (1:9), to afford compound **Int 053**.

[0337] By-product **Int 054** is obtained when step iv) is done in higher scale and concentration:

[0338] A round bottom flask is charged with the aldehyde synthesized in step iii) (3.72 g, 12.9 mmol, 1.0 eq), the β-keto ester from step i) (7.10 g, 32.5 mmol, 2.5 eq), and DCM (10 mL) and left open to the air. After 16h, volatiles were removed via rotary evaporation. The residue is combined with $Pd(OH)_2/C$ (10%) (2.06 g, 1.47 mmol, 0.11 eq), ethanol (100 mL), and cyclohexene (25 mL, 250 mmol, 19 eq.) in a round bottomed flask, and heated at reflux for 16h, and then allowed to cool to room temperature. The mixture is filtered through filter paper, and volatiles are removed via rotary evaporation. The residue is charged onto a column of silica gel and eluted with EtOAc/DCM (1/20), to afford **Int 054** (3.55 g).

2.16. 4-Cyclopropyl-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methoxy-butane-1,4-dione (Int 056)



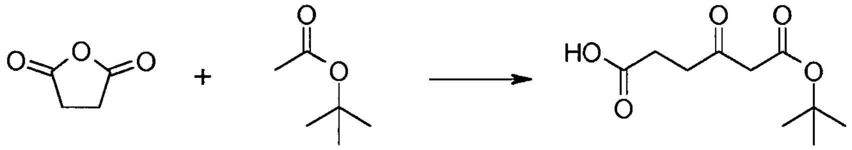
Step i) 2-Cyclopropanecarbonyl-4-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-3-methoxy-4-oxo-butyric acid benzyl ester

[0339] A flask is charged with **Int 054** (289 mg, 0.54 mmol, 1.0 eq.), and MeOH (8mL), and heated at 60°C. After 16h, volatiles are removed from the filtrate via rotary evaporation.The residue is charged onto a column of silica gel, and eluted with EtOAc/DCM (1:20) to afford the expected intermediate.

Step ii) 4-Cyclopropyl-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methoxy-butane-1,4-dione (Int 056)

[0340] The intermediate from *step i)* is stirred with MeOH (20 mL), $Pd(OH)_2/C$ (10%) (45 mg, 0.032 mmol, 0.10 eq), and cyclohexene (4 mL, 39.5 mmol, 120 eq.) in a round bottom flask, and heated to reflux. After 2h, the mixture is filtered through filter paper. Volatiles are removed from the filtrate via rotary evaporation. The residue is charged onto a column of silica gel, and eluted with EtOAc/DCM (1:9) to afford ***Int 056***.

2.17. 6-tert-butoxy-4,6-dioxo-hexanoic acid (Int 129)

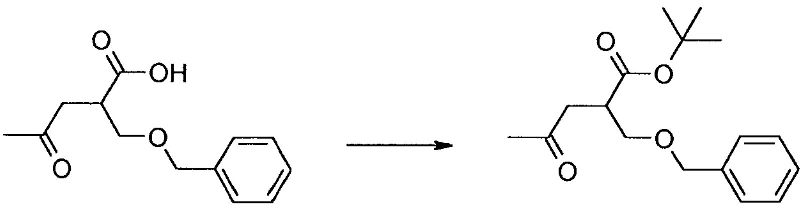


[0341] A solution of n-Butyl lithium (1.6M in hexane) (25mL, 40 mmol, 2.0 eq) is added at 0°C to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (8.5 mL, 41 mmol, 2.04 eq) in anhydrous THF (17 mL). After cooling to -78°C, tertbutyl acetate (5.44 mL, 40 mmol, 2.0 eq) is added within 20min to the solution and stirring is continued for 45min. The resulting α-lithio acetic ester solution is added dropwise over 30 minutes to a solution of succinic anhydride (2g, 20 mmol, 1.0 eq) in THF (24 mL). The resulting mixture is stirred for 3h in a methanol/dry ice bath while the temperature is allowed to increase to -20°C.

[0342] The reaction mixture is warmed up to room temperature, then concentrated HCl (4mL) and water (25 mL) are added. The organic solvent is evaporated, and the resulting aqueous solution is adjusted to pH = 2, and extraction with ethyl acetate followed. Organic layers are combined, dried over

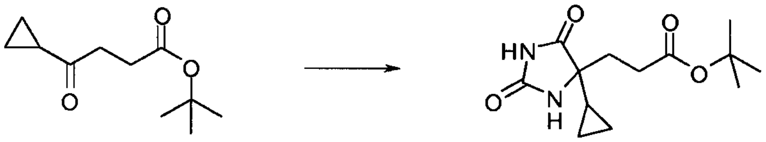
Na_2SO_4, filtered, and concentrated under reduced pressure to give the expected product (used in the next step without further purification).

2.18. tert-butyl 2-(benzyloxymethyl)-4-oxo-pentanoate (Int 137)



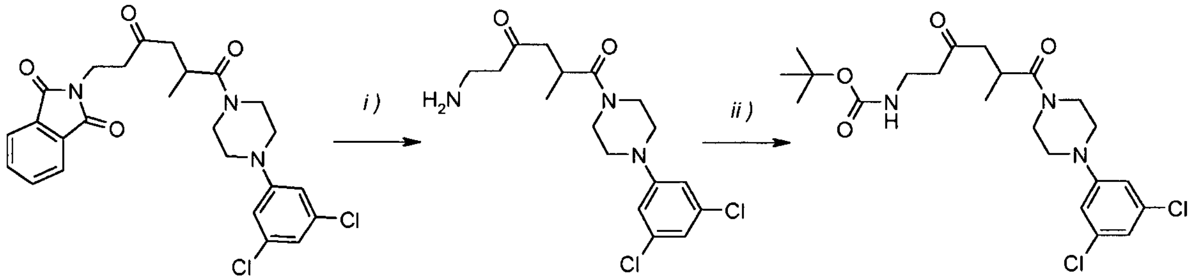
[0343] To a solution of **Int 138** (530 mg, 2.24 mmol, 1 eq.) in toluene (7 mL) is added *N,N*-dimethylformamide di-*tert*-butyl acetal (2.69 mL, 11.2 mmol, 5 eq.). Reaction mixture is heated at 100°C in a sealed tube for 4.5h, quenched by addition of a saturated $NaHCO_3$ solution at 0°C, extracted with EtOAc. The combined organic layers are washed with saturated $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (Heptane/EtOAc 100/0 to 60/40) to afford the expected product. LCMS: MW (calcd): 292; m/z MW (obsd): 315 (M+Na)

2.19. (S)-4-(3,5-Difluoro-phenyl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (Int 110)



[0344] A mixture of γ-ketoester 4-Cyclopropyl-4-oxo-butyric acid tert-butyl ester (120g, 605 mmol, 1 eq.), $(NH_4)_2CO_3$ (494g, 5.15 mol, 8.5 eq.), NaCN (60g, 1.45 mol, 2.4 eq.), H_2O (600mL) and ethanol (600mL) is heated at 60°C for 18h in the sealed reactor. The reaction mixture is poured in a mixture of EtOAc (900mL) and water (900mL), and the aqueous layer is additionally extracted with EtOAc (3x600mL). The organic layer is concentrated until only about 100 mL EtOAc left, and added 500 mL petroleum ether dropwise to afford the expected hydantoin derivative **Int 110**.

2.20. tert-butyl N-[6-[4-(3,5-dichlorophenyl)piperazin-1-yl]-5-methyl-3,6-dioxo-hexyl]carbamate (Int 150)



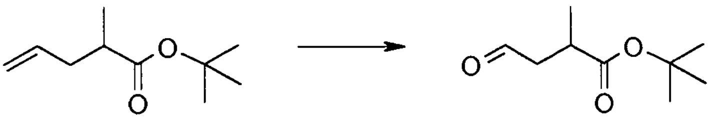
Step i) 6-Amino-1-[4-(3,5-dichloro-phenyl)-piperazin-1-yl]-2-methyl-hexane-1,4-dione

[0345] To a solution of **Int 021** (341 mg, 0.68 mmol, 1.0 eq) in ethanol (27 mL) is added methylamine (40% in water) (845 µL). Stirring is then kept at room temperature overnight. The organic solvent is then removed under reduced pressure, and the aqueous residue is diluted with water and K_2CO_3 (10%), and extracted with ethyl acetate several times. The combined organic layer is washed with water and brine, before being dried, filtered, and concentrated under reduced pressure, to afford crude compound used directly in the next step.

Step ii) tert-butyl N-[6-[4-(3,5-dichlorophenyl)piperazin-1-yl]-5-methyl-3,6-dioxo-hexyl]carbamate (Int 150)

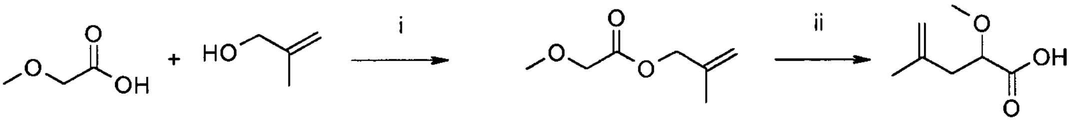
[0346] The crude from *step i)* is stirred in THF/MeOH (1/1) (14 mL). Di-tert-butyl dicarbonate (445 mg, 2.04 mmol, 3 eq) is added, and the mixture is stirred under reflux for 18h. The organic solvents are removed, and the crude is purified by flash chromatography (DCM/Et_2O 100/0 to 0/100 and then DCM/MeOH 100/0 to 90/10) to afford the expectedintermediate. LCMS: MW (calcd): 472; m/z MW (obsd): 472-474-476 (M+H).

2.21. *tert-butyl 2-methyl-4-oxo-butanoate (Int 153)*



[0347] A three neck flask is charged with a solution of alkene **Int 148** (6.3 g, 37 mmol, 1 eq.) and suddan III (cat.) in DCM and cooled at -78°C. O_3 is bubbled trough the reaction mixture until the color became deep blue. The reaction mixture is purged with N_2 for 30 min, Me_2S is added and the reaction mixture is allowed to warm to r.t. overnight. The reaction mixture is washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (Heptane/EtOAc 100/0 to 80/20) affords the expected product.

2.22. *2-methoxy-4-methyl-pent-4-enoic acid (Int 154)*



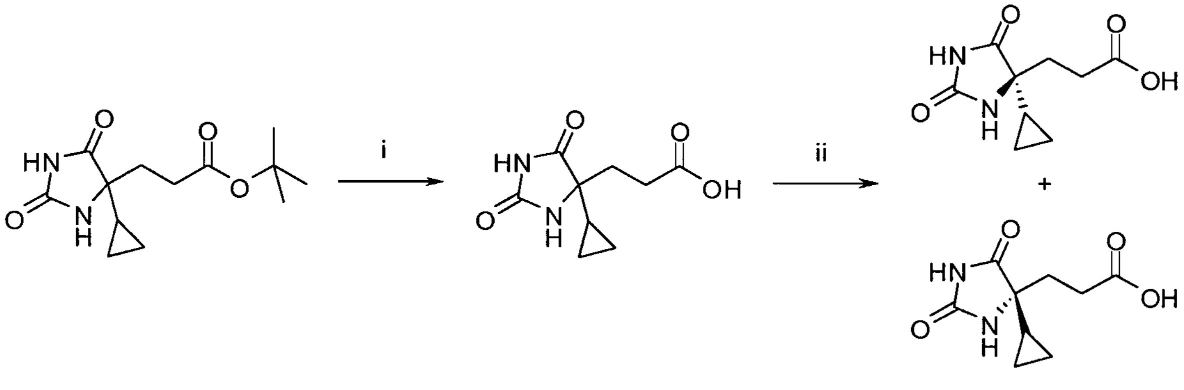
Step i) Methoxy-acetic acid 2-methyl-allyl ester

[0348] To a solution of methoxy-acetic acid (15.54 g, 173 mmol, 1.1 eq.) and 2-methyl-prop-2-en-1-ol (14.5 mL, 172 mmol, 1 eq.) in pyridine (100 mL) at 0°C, is added *p*-toluenesulfonyl chloride (33.08 g, 173 mmol, 1eq.). After 1h, the cold bath is removed and the reaction mixture is stirred at r.t. overnight. The reaction mixture is concentrated *in vacuo* and combined with a EtOAc and a saturated $NaHCO_3$ solution is added. The organic layer is collected, washed with a solution of HCl 1N, water, brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected ester used as such in next step. LCMS: MW (calcd): 144; m/z MW (obsd): 145 (M+H); 167 (M+Na)

Step ii) 2-methoxy-4-methyl-pent-4-enoic acid (Int 154)

[0349] To a solution of the ester (1 g, 6.94 mmol, 1eq.) in dry Et_2O (10 mL) is added Et_3N (1 mL, 7.17 mmol, 1.03 eq.) and trimethylsilyl trifluoromethanesulfonate (1.3 mL, 7.18 mmol, 1.03 eq.). The reaction mixture is stirred at r.t. overnight, a solution of K_2CO_3 (5.45 g, 39.4 mmol, 5.68 eq.) in water (20 mL) is added. After 30min, the reaction mixture is combined with Et_2O, the aqueous layer is collected, cooled in an ice bath and the pH adjusted to pH=2 with H_3PO_4 (85%). The solution is saturated with NaCl and extracted with Et_2O. The combined organic layers are dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to afford the expected product used as such in next step. LCMS: MW (calcd): 144; m/z MW (obsd): 143 (M-H).

2.23. 3-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl)propanoic acid (Int 162), and 3-[(4S)-4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl]propanoic acid (Int 163)



Step i) 3-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl)propanoic acid (Int 162)

[0350] A flask is charged with a solution of hydantoin (200 g, 746 mmol, 1 eq.) in dioxane (100 mL) and is cooled in an ice bath, HCl 6N in dioxane (1 L) is added slowly. The reaction mixture is stirred at r.t. for 4h and concentrated *in vacuo*. The resulting solid is suspended in 240 mL of acetonitrile, then stirred at reflux for 1h, and allowed to cool down to r.t. under stirring. The resulting solid is separated by filtration, washed twice with acetonitrile (2 x 30 mL), and finally dried under vacuum at 45°C to afford the expected carboxylic acid.

Step ii) 3-[(4S)-4- cyclopropyl-2,5-dioxo-imidazolidin-4-yl]propanoic acid (Int 163)

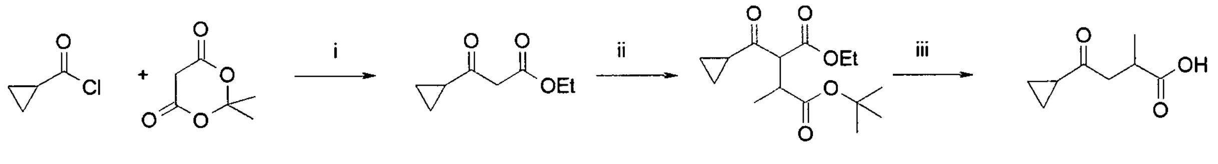
[0351] The racemic hydantoin propionic acid is separated by SFC to afford a fast eluting isomer ((R)-enantiomer) and a slow eluting isomer ((S)-enantiomer).

[0352] The purification is done in 2 stages.

[0353] Conditions of the first separation: preparative SFC, Column: ChiralPak AD-10µm, 300×50mmI.D., Mobile phase: A for CO_2 and B for Ethanol, Gradient: B 45% , Flow rate: 200mL /min, Back pressure: 100 bar, Column temperature: 38°C, Wavelength: 220nm, Cycletime: ~10.0min. The compound is dissolved in methanol to ~120mg/mL, and loaded on the column (16mL per injection). After separation, the fractions are dried off via rotary evaporator to get the desired isomers.

[0354] Conditions of the second separation: Prep HPLC, Column: C18, 250×50mm I.D., Mobile phase: A for H_2O and B for Acetonitrile, Gradient: B 5%-20% in 15min linearly, Flow rate: 80 mL/min, Wavelength: 220nm. The compound is dissolved in methanol (~100mg/mL) and loaded on the column (10mL per injection). After separation, the fraction is concentrated via rotary evaporator and the remaining aqueous layer is lyophilized.

2.24. 4-cyclopropyl-2-methyl-4-oxo-butanoic acid (Int 155)



Step i) 3-Cyclopropyl-3-oxo-propionic acid ethyl ester

[0355] To a solution of Meldrum's acid (2,2-dimethyl-[1,3]dioxane-4,6-dione, 50.10 g, 0.347 mol, 1 eq.) in DCM (500 mL) and pyridine (90 mL, 1.11 mol, 3.2 eq.) at 0°C, cyclopropanecarbonyl chloride (35 mL, 0.386 mol, 1.1 eq.) is added dropwise. After 2h, the cold bath is removed and the reaction mixture is stirred at r.t. overnight and combined with a solution of HCl 2N. The organic layer is collected, washed with brine, dried over anhydrous $MgSO_4$, filtered over activated charcoal and concentrated *in vacuo*. This residue is taken up in ethanol (300 mL) and stirred at reflux overnight, concentrated *in vacuo* and purified by flash chromatography on silica gel (Heptane/EtOAc 80/20) to afford the expected β-ketoester. LCMS: MW (calcd): 156; m/z MW (obsd): 157 (M+H); 179 (M+Na)

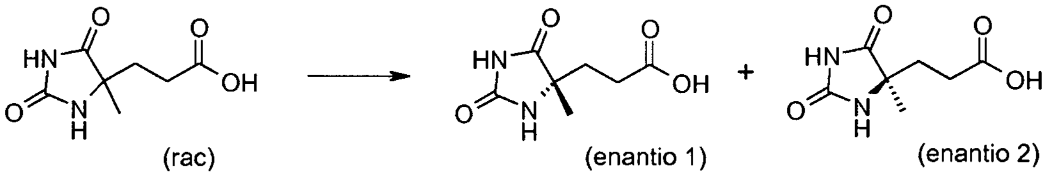
Step ii) 2-Cyclopropanecarbonyl-3-methyl-succinic acid 4-tert-butyl ester 1-ethyl ester

[0356] To a solution of the β-ketoester (16.09 g, 0.103 mol, 1 eq.) in MEK (200 mL) are added K_2CO_3 (28.56 g, 0.207 mol, 2 eq.), NaI (1.65 g, 0.011 mol, 0.1 eq.) and 2-Bromo-propionic acid tert-butyl ester (18 mL, 0.108 mol, 1.04 eq.). The reaction mixture is heated at reflux for 40h and cooled to r.t.. Water is added, reaction mixture acidified to pH 8 and extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected γ-ketoester used as such in next step. LCMS: MW (calcd): 284; m/z MW (obsd): 307 (M+Na)

Step iii) 4-cyclopropyl-2-methyl-4-oxo-butanoic acid (Int 155)

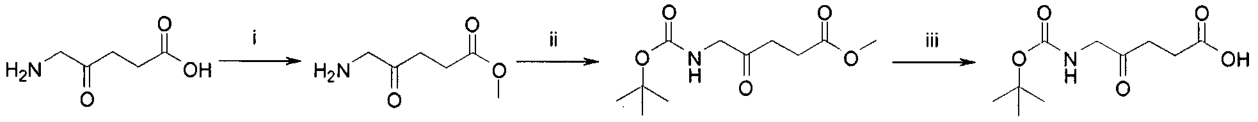
[0357] To a solution of the γ-ketoester (29.2 g, 0.103 mol, 1 eq.) in EtOH (100 mL) is added a solution of NaOH (12.6 g, 0.315 mol, 3 eq.) in water (100 mL). The reaction mixture is heated at reflux for 16h, cooled to r.t., diluted with water (500 mL) and cooled in an ice bath. To this is added dropwise H_3PO_4 (85%, 4 mL, 0.059 mol) and conc. HCl (24 mL, 0.288 mol), the ice bath is removed and reaction mixture is stirred at r.t. for 30min. The reaction mixture is cooled in an ice bath and a solution of NaOH (17g, 0.425 mol) in water (50 mL) is added to adjust the pH to 8. The solution is combined with DCM, the aqueous layer is collected, cooled in an ice bath and the pH adjusted to pH=2 with conc. HCl. The solution is saturated with NaCl and extracted with DCM. The combined organic layers are dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 156; m/z MW (obsd): 157 (M+H); 179 (M+Na).

2.25. 3-[(4R)-4-methyl-2,5-dioxo-imidazolidin-4-yl]propanoic acid (Int 172)



[0358] The racemic 3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid (805 g) is separated by SFC to afford 384 g of the faster eluting isomer and 388 g of the slower eluting isomer. Conditions of the separation : Instrument: Thar350 preparative SFC, Column: ChiralPak AD-10µm, 300×50mmI.D., Mobile phase: A for CO_2 and B for iPrOH (0.1%TFA), Gradient: B 25% , Flow rate: 220mL /min, Back pressure: 100bar, Column temperature: 38°C, Wavelength: 210nm, Cycletime: ~3.8min, Sample preparation: Compound is dissolved in methanol to ~80mg/mL, Injection: 1.0 mL per injection, Work up: After separation, the fractions are dried off via rotary evaporator at bath temperature 40°C to get the desired isomers.

2.26. 5-(tert-butoxycarbonylamino)-4-oxo-pentanoic acid (Int 173)



Step i) 5-Amino-4-oxo-pentanoic acid methyl ester

[0359] To a solution of 5-amino-4-oxo-pentanoic acid hydrochloride (0.5 g, 2.98 mmol, 1 eq.) in MeOH (3 mL) at 0°C is added thionyl chloride (0.7 mL, 8.95 mmol, 3 eq.). The reaction mixture is stirred at r.t. overnight and concentrated *in vacuo* to afford the expected methyl ester (hydrochloride salt) used as such in next step.

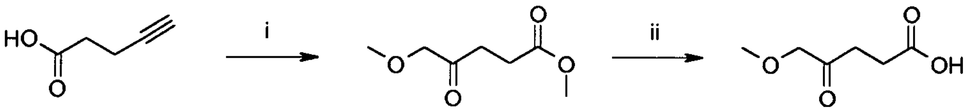
Step ii) 5-tert-Butoxycarbonylamino-4-oxo-pentanoic acid methyl ester

[0360] To a solution of the methyl ester (0.54 g, 2.98 mmol, 1 eq.) and di-*tert*-butyl dicarbonate (1.3 g, 5.97 mmol, 2 eq.) in dry DMF (5 mL) at 0°C is added Et_3N (0.8 mL, 5.97 mmol, 2 eq.). Reaction mixture is stirred at 0°C for 2h then at r.t. overnight, concentrated *in vacuo*. The residue is taken up in water, extracted with EtOAc. The combined organic layers are dried by filtration over hydrophobic column and concentrated *in vacuo* to afford the expected NBoc derivative.

Step iii) 5-(tert-butoxycarbonylamino)-4-oxo-pentanoic acid (Int 173)

[0361] To a solution of the methyl ester (0.495 g, 2.02 mmol, 1 eq.) in THF (4 mL) is added a solution of LiOH 1M (4 mL, 4 mmol, 2 eq.). Reaction mixture is stirred at r.t. for 3h, neutralised to pH 5 and concentrated *in vacuo* (toluene azeotrope) to afford the expected product used as such in next step.

2.27. 5-methoxy-4-oxo-pentanoic acid (Int 177)



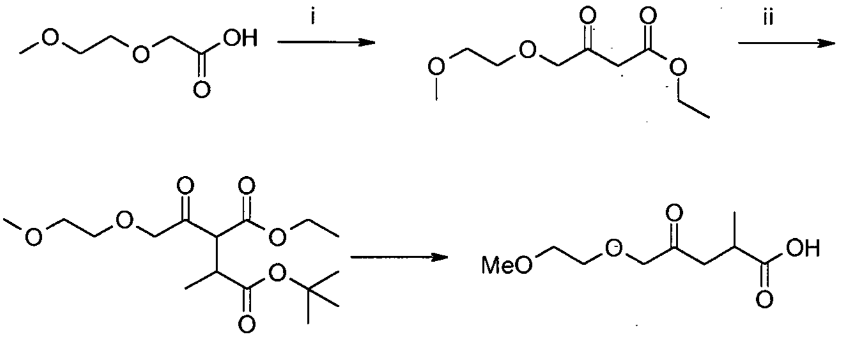
Step i) 5-Methoxy-4-oxo-pentanoic acid methyl ester

[0362] To a solution of iodosylbenzene (4.75 g, 21.6 mmol, 1.5 eq.) in DCM (200 mL) at 0°C under N_2 atmosphere is added pent-4-ynoic acid (1.41 g, 14.4 mmol, 1eq.) portionwise. BF_3.OEt (3.65 mL, 28.8 mmol, 2 eq.) is added dropwise and the reaction mixture is stirred at r.t. for 30 min. The resulting precipitate is separated by filtration,and dried under N_2. MeOH (100 mL) is added, the reaction mixture is stirred at r.t. overnight, concentrated *in vacuo* and purified by flash chromatography on silica gel (Hexanes/EtOAc 700/30 to 400/60) to afford the expected methoxy methyl ester derivative used as such in the next step.

Step ii) 5-methoxy-4-oxo-pentanoic acid (Int 177)

[0363] A solution of the methyl ester (500 mg, 3.1 mmol, 1 eq.) and NaOH (625 mg, 15 mmol, 5 eq.) in THF (6.6 mL), water (4.4 mL) and MeOH (11 mL) is stirred at r.t. for 2h. Then the pH is adjusted to 3.3 with conc. HCl. Reaction mixture is extracted with EtOAc, the combined organic layers are dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected product used as such in next step.

2.28. 5-(2-methoxyethoxy)-2-methyl-4-oxo-pentanoic acid (Int 185)



Step i) 4-(2-Methoxy-ethoxy)-3-oxo-butyric acid ethyl ester

[0364] To a solution of monoethyl malonic acid (5.9 mL, 50 mmol, 1.25 eq.) in dry THF (200 mL), is added magnesium ethoxide (2.86 g, 25 mmol, 0.625 eq.). The reaction mixture is stirred for 1.5h and concentrated *in vacuo*. In another flask, CDI (7.13 g, 44 mmol, 1.1 eq.) is added to a solution of (2-methoxy-ethoxy)-acetic acid (4.6 mL, 40 mmol, 1eq.) in THF (200 mL) . After 4h at r.t., this reaction mixture is added to the magnesium salt prepared above. This new mixture is heated at reflux for 4h, stirred at r.t. for 2 days and concentrated *in vacuo*. The residue is taken up in water and EtOAc, a solution of HCl 0.5N is added, the organic layer is collected, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (Heptane/EtOAc 100/0 to 50/50) affords the expected β–ketoester. LCMS: MW (calcd): 204; m/z MW (obsd): 205 (M+H); 227 (M+Na)

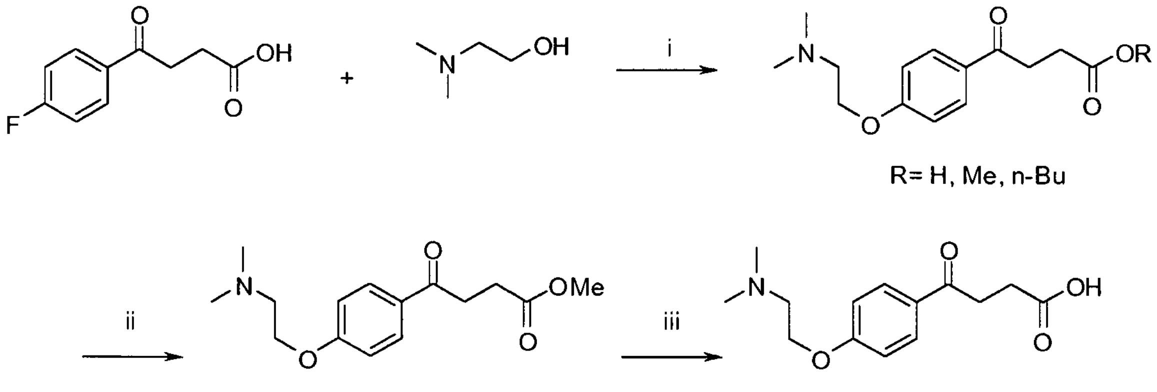
Step ii) 2-[2-(2-Methoxy-ethoxy)-acetyl]-3-methyl-succinic acid 4-tert-butyl ester 1-ethyl ester

[0365] To a solution of the β–ketoester (3 g, 14.7 mmol, 1 eq.) in MEK (60 mL) are added K_2CO_3 (4.1 g, 29.5 mmol, 2 eq.), KI (0.32 g, 1.5 mmol, 0.1 eq.) and 2-bromo-propionic acid tert-butyl ester (2.4 mL, 14.7 mmol, 1 eq.). The reaction mixture is heated at reflux overnight and concentrated *in vacuo*. The residue is taken up in water and EtOAc, extracted with EtOAc. The combined organic layers are dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (Heptane/EtOAc 100/0 to 0/100) to afford the expected γ–ketoester. LCMS: MW (calcd): 332; m/z MW (obsd): 333 (M+H), 355 (M+Na).

Step iii)

[0366] To a solution of the γ–ketoester (332 mg, 1 mmol, 1 eq.) in EtOH (1.5 mL) is added a solution of NaOH 2N (1.5 mL). Reaction mixtureis heated at reflux for 16h, cooled to r.t., diluted with water (2 mL) and cooled in an ice bath. To this is added dropwise H_3PO_4 (85%, 16 µL) and conc. HCl (180 µL), the ice bath is removed and reaction mixture is stirred at r.t. for 30min. The reaction mixture is cooled in an ice bath, a solution of NaOH 2N is added to adjust the pH to 8. The solution is combined with DCM, the aqueous layer is collected, cooled in an ice bath and the pH adjusted to pH=2 with conc. HCl. The solution is saturated with NaCl and extracted with DCM. The combined organic layers are dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 248; m/z MW (obsd): 249 (M+H); 271 (M+Na).

2.29. 4-[4-(2-dimethylaminoethyloxy)phenyl]-4-oxo-butanoic acid (Int 189)



Step i)

[0367] To a solution of 4-(4-fluoro-phenyl)-4-oxo-butyric acid (1g, 5.1 mmol, 1 eq.) in DMA (20 mL) are added 2-dimethylamino-ethanol (1.02 mL, 10.2 mmol, 2 eq.) and KOH (1.43g, 25.5 mmol, 5 eq.). Reaction mixture is heated at 120°C for 1h, 2-dimethylamino-ethanol (1.02 mL, 2 eq.) is added, heating is pursued for 2h, 2-dimethylamino-ethanol (4.08 mL, 8 eq.) is added, heating is pursued for 3h. A solution of 2N HCl is added and reaction mixture is extracted with EtOAc and n-BuOH. The combined organic layers are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is taken up in MeOH and the precipitate is filtered. Analysis of the precipitate shows a mixture of expected carboxylic acid contaminated with methyl ester and n-butyl ester. The mixture is used as such for next step. LCMS: MW (calcd): 265 (R=H); 279 (R=Me); 321 (R=n-Bu); m/z MW (obsd): 266 (M+H, R=H), 280 (M+H, R=Me), 322 (M+H, R=n-Bu).

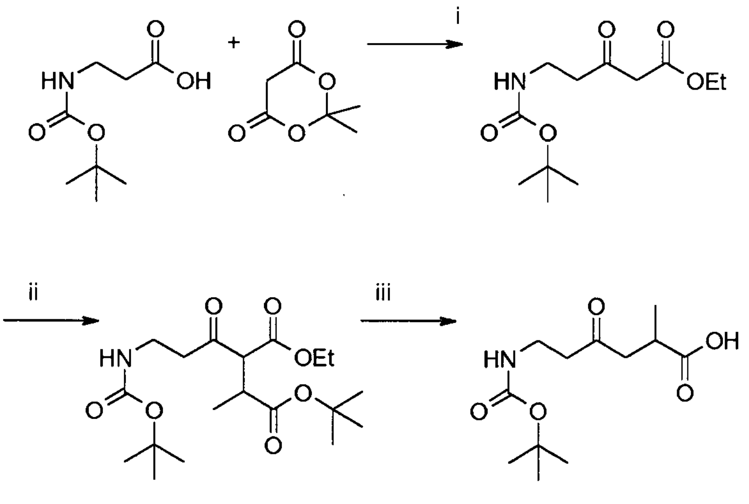
Step ii)

[0368] To a solution of the above mixture of carboxylic acid, methyl ester and n-butyl ester in MeOH (100 mL) is added conc. HCl (4 mL). Reaction mixture is heated at 70°C overnight and concentrated *in vacuo*. The residue is taken up with saturated $NaHCO_3$ solution, extracted with EtOAc, the combined organic layers are washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (DCM/MeOH 100/0 to 80/20) affords the expected methyl ester derivative. LCMS: MW (calcd): 279; m/z MW (obsd): 280 (M+H).

Step iii)

[0369] To a solution of the methyl ester (535 mg, 1.92 mmol, 1 eq.) in MeOH (16 mL) is added a solution of NaOH 2N (1.15 mL, 2.3 mmol, 1.2 eq.). Reaction mixture is heated at 70°C for 2h and concentrated *in vacuo* to afford the expected product used as such in next step. LCMS: MW (calcd): 265; m/z MW (obsd): 266 (M+H).

2.30. 6-(tert-butoxycarbonylamino)-2-methyl-4-oxo-hexanoic acid (Int 191



Step i) 5-tert-Butoxycarbonylamino-3-oxo-pentanoic acid ethyl ester

[0370] To a solution of 3-*tert*-butoxycarbonylamino-propionic acid (1g, 5.29 mmol, 1 eq.) in DCM (30 mL) at 0°C under N_2 atmosphere are added portionwise DMAP (969 mg, 7.93 mmol, 1.5 eq.) and 2,2-dimethyl-[1,3]dioxane-4,6-dione (838 mg, 5.81 mmol, 1.1 eq.) and finally EDC.HCl (1.22g, 6.34 mmol, 1.2 eq.). The reaction mixture is stirred at r.t. overnight, diluted with DCM and washed with a solution of $KHSO_4$ 5%, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. This residue is taken up in dry Ethanol (20 mL) and the reaction mixture is stirred at reflux overnight, concentrated *in vacuo* and purified by flash chromatography on silica gel (eluting with DCM/EtOAc 100/0 to 50/50) to afford the expected β–ketoester. LCMS: MW (calcd): 259; m/z MW (obsd): 282 (M+Na).

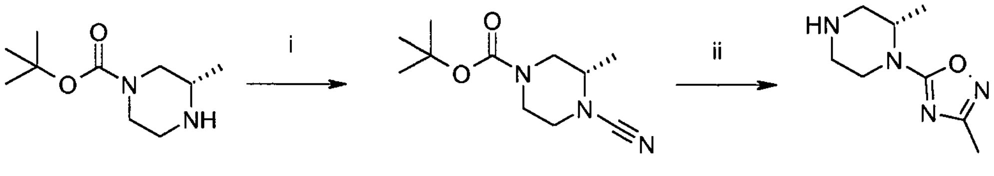
Step ii) 2-(3-tert-Butoxycarbonylamino-propionyl)-3-methyl-succinic acid 4-tert-butyl ester 1-ethyl ester

[0371] To a solution of the β–ketoester (919 mg, 3.54 mmol, 1 eq.) in MEK are added K_2CO_3 (980 mg, 7.09 mmol, 2 eq.), NaI (53 mg, 0.35 mmol, 0.1 eq.) and 2-bromo-propionic acid tert-butyl ester (588 µL, 3.54 mmol, 1 eq.). The reaction mixture is stirred at 95°C for 24h and cooled to r.t. Water is added, reaction mixture acidified to pH 8 and extracted with EtOAc. The combined organic layers are washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by flash chromatography on silica gel (eluting with heptane/EtOAc 100/0 to 80/20) to afford the expected γ–ketoester. LCMS: MW (calcd): 387; m/z MW (obsd): 388 (M+H).

Step iii) 6-(tert-butoxycarbonylamino)-2-methyl-4-oxo-hexanoic acid (Int 191)

[0372] To a solution of the γ–ketoester (1.2 g, 3.1 mmol, 1 eq.) in EtOH (4.7 mL) is added a solution of NaOH 2N (4.65 mL, 9.29 mmol, 3 eq.). The reaction mixture is heated at reflux for 16h, cooled to r.t., diluted with water (500 mL) and cooled in an ice bath. To this is added dropwise H_3PO_4 (85%, 48 µL) and conc. HCl (3.4 mL), the ice bath is removed and reaction mixture stirred at r.t. for 2 days. The reaction mixture is cooled in an ice bath, a solution of NaOH 2N is added to adjust the pH to 8. The solution is combined with DCM, the aqueous layer is collected, cooled in an ice bath and the pH adjusted to pH=3-4 with HCl 2N. The solution is extracted with DCM. The combined organic layers are dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to afford the expected product. LCMS: MW (calcd): 259; m/z MW (obsd): 260 (M+H).

2.31. 3-methyl-5-[(2S)-2-methylpiperazin-1-yl]-1,2,4-oxadiazole (Int 238)



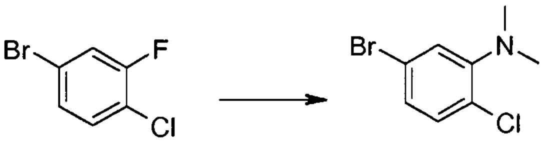
Step i) (S)-4-Cyano-3-methyl-piperazine-1-carboxylic acid tert-butyl ester

[0373] Same as 2.13, step i)

Step ii) 3-methyl-5-[(2S)-2-methylpiperazin-1-yl]-1,2,4-oxadiazole (Int 238)

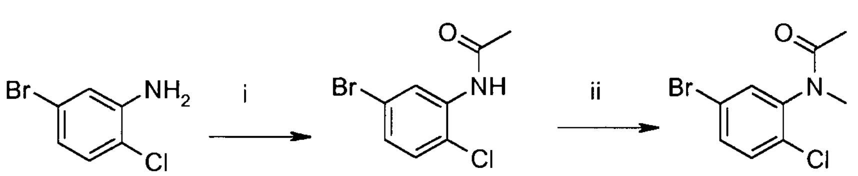
[0374] To a solution of (S)-4-cyano-3-methyl-piperazine-1-carboxylic acid tert-butyl ester (617 mg, 2.74 nmol, 1 eq.) and N-hydroxy-acetamidine (304 mg, 4.11 mmol, 1.5 eq.) in THF (10 mL) and EtOAc (10 mL) under argon, is slowly added $ZnCl_2$ (1M in Et_2O, 6.85 mL, 6.85 mmol, 2.5eq.) and the reaction mixture is stirred at r.t. for 3h and concentrated *in vacuo*. The residue is dissolved in ethanol (20 mL) and conc. HCl is added (2.5 mL). The resulting solution is stirred at 100°C for 4h, cooled and concentrated *in vacuo*. The residue is dissolved in water and pH adjusted to 12 with 2M NaOH. The white precipitate is filtered off and the water filtrate extracted with 10% MeOH in DCM. The combined organic layers are evaporated *in vacuo* to afford the expected product. LCMS: MW (calcd): 182; m/z MW (obsd): 183 (M+H).

2.32. 5-bromo-2-chloro-N,N-dimethyl-aniline (Int 285)



[0375] 1-bromo-4-chloro-3-fluoro-benzene (367 µL, 3.0 mmol, 1.0 eq.), dimethylamine hydrochloride (489 mg, 6.0 mmol, 2.0 eq.) and DIPEA (1.6 mL, 9.0 mmol, 3.0 eq.) are heated in DMA (5 mL) in a sealed microwave vial at 115°C for 18h, then 125°C for 2days. Dimethylamine hydrochloride (400 mg, 4.9 mmol, 1.6 eq.) is added to the reaction mixture and the vial is heated at 130°C for 2days. The reaction mixture is then poured into water and brine. The aqueous layer is extracted 3 times with EtOAc. The combined organic phases are washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected product. LCMS: MW (calcd): 233; m/z MW (obsd): 234-236 (M+H).

2.33. N-(5-bromo-2-chloro-phenyl)-N-methyl-acetamide (Int 286)



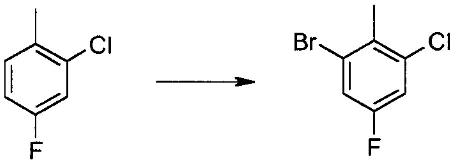
Step i) N-(5-Bromo-2-chloro-phenyl)-acetamide

[0376] To a solution of 3-bromo-6-chloroaniline (2.0 g, 9.7 mmol, 1.0 eq.) in DCM (30 mL) is added acetic anhydride (1.1 mL, 11.6 mmol, 1.2 eq.). The reaction mixture is stirred at r.t. for 22h. The reaction mixture is washed successively with water and a saturated $NaHCO_3$ solution. The organic layer is dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue is stirred in DCM and Et_2O is added. The resulting suspension is filtered and the solid is dried under suction to afford the expected acetamide. MW (calcd): 247; m/z MW (obsd): 248-250 (M+H).

Step ii) N-(5-bromo-2-chloro-phenyl)-N-methyl-acetamide (Int 286)

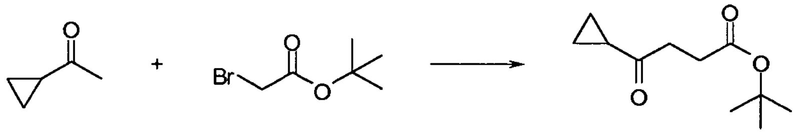
[0377] To a solution of 3-bromo-6-chloroacetanilide (1.53 g, 6.2 mmol, 1.0 eq.) in DMF (17 mL) is added sodium hydride (322 mg, 8.1 mmol, 1.3 eq.) under nitrogen atmosphere. After 10 min stirring at r.t., methyl iodide (502 µL, 8.1 mmol, 1.3 eq.) is added. The reaction mixture is allowed to stir at r.t. under nitrogen atmosphere for 18h. The mixture is poured into water and brine and extracted 3 times with EtOAc. The combined organic phases are washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected product. LCMS: MW (calcd): 261; m/z MW (obsd): 262-264 (M+H).

2.34. 1-bromo-3-chloro-5-fluoro-2-methyl-benzene (Int 287)



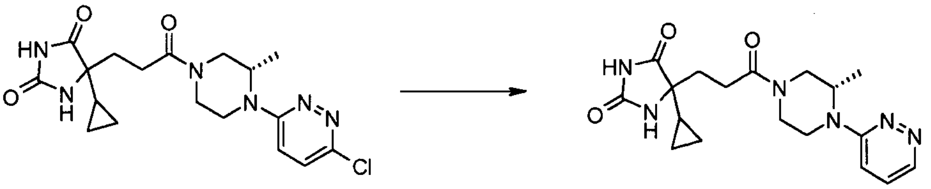
[0378] Sulfuric acid (0.9 mL) and NBS (1.0 g, 6.0 mmol, 1.2 eq.) are added to a solution of 2-chloro-4-fluorotoluene (604 µL, 5.0 mmol, 1.0 eq.) in TFA (3 mL). The reaction mixture is allowed to stir at r.t. for 18h. The reaction is quenched with brine at 0°C, then extracted twice with DCM. The combined organic phases are washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel to afford the expected product as a mixture, which is used as such in the next step.

2.35. 4-Cyclo propyl-4-oxo-butyric acid tert-butyl ester (Int 290)



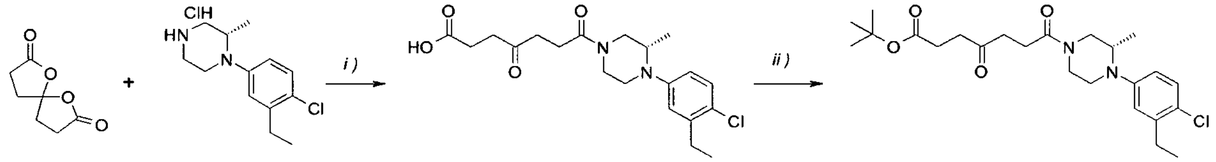
[0379] A solution of LDA (3.0 L, 5.98 mol, 1.17 eq.) in THF (2.5 L) is cooled to -78°C. A solution of 1-cyclopropylethanone (460 g, 5.11 mol, 1 eq.) in THF (0.5 L) is added dropwise, then warmed to -20°C and stirred for 30 min. The reaction mixture is cooled to -78°C and *tert*-butyl bromoacetate (997 g, 5.11 mol, 1 eq.) in THF (0.5 L) is added slowly. The reaction is stirred at 0°C overnight, quenched with saturated NH_4Cl aq. (3.3 L), extracted with EtOAc (0.5 L x 3), washed with water (0.5 L x 2), saturated NH_4Cl aq. (1L), and brine (1 L), dried over anhydrous Na_2SO_4. Purifcation by distillation under reduced pressure (5 mbar, 95°C) affords the expected γ-ketoester.

2.36. 5-cyclopropyl-5-[3-[(3S)-3-methyl-4-pyridazin-3-yl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione (Cpd 302)



[0380] To a suspension of Cpd 285 (72 mg, 0.177 mmol, 1.0 eq.) in EtOH (1.7 mL) and DMF (0.7 mL) is added Et_3N (0.2 mL, 1.44 mmol, 8 eq.). The mixture is heated at 40-50°C and Pd/C (14 mg) is added. The reaction mixture is stirred at room temperature for 21 hours. The mixture is filtered through diatonite and evaporated under vaccum. The crude residue is purified by flash chromatography on silica gel to afford the expected product.

2.37. Int 317



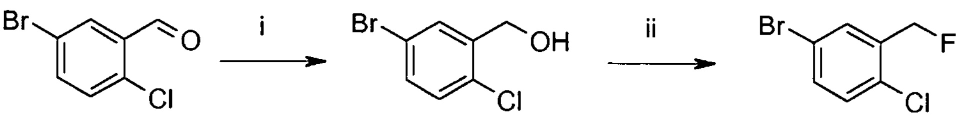
Step i)

[0381] A vial is charged with 1,6-dioxaspiro[4.4]nonane-2,7-dione (47.4 mg, 0.30 mmol, 1 eq), **Int 313** (79 mg, 0.29 mmol, 0.95 eq) , dry dioxane (2 mL), and triethyl amine (0.2 mL, 1.4 mmol, 4.7 eq). After 16h, the mixture is combined with DCM (100 mL) and aqueous H_3PO_4/NaH_2PO_4 (1M, 100 mL) in a separation funnel. The organic phase is collected, washed with brine (100 mL), and dried over $MgSO_4$. After filtration, volatiles are removed via rotary evaporation to give the expected product which is used in the following step without further purification.

Step ii)

[0382] A pressure vessel is charged with the acid synthesized in *step i)* (0.92 mol), DCM (10 mL), and cooled in a NaCl/ice bath (-20°C). Isobutene (3.06 g, 54.5 mmol, 59 eq) is condensed into the cold solution, and concentrated H_2SO_4 (0.1 mL, 1.8 mmol, 2.0 eq) is added. The vessel is hermetically sealed, and then the cold bath is removed. After 16h, the vessel is cooled in a NaCl/ice bath (-20°C), and opened. Et_3N (1.0 mL, 7.2 mmol, 7.8 eq) is added, and the cold bath is removed. Once all volatiles had evaporated, the mixture is combined with H_2O (100 mL) and DCM (100 mL) in a separatory funnel, and agitated. The organic phase is collected, washed with brine (100 mL) and dried over $MgSO_4$. After filtration, volatiles are removed from the filtrate via rotary evaporation. The residue is purified by flash chromatography on silica gel (EtOAc/DCM 1:4), to afford the expected compound **Int 317**.

2.38. Int 318



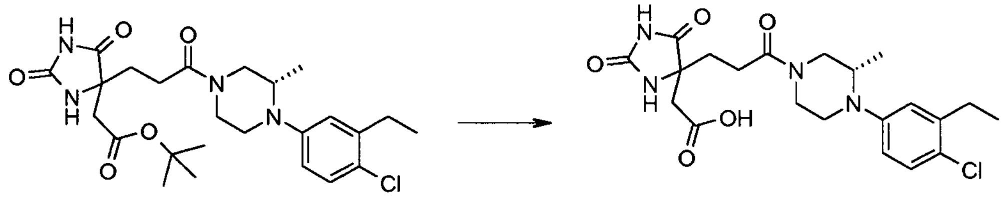
Step i)

[0383] Sodium tetraborohydride (345 mg, 9.1 mmol, 2.0 eq.) is added portionwise to a solution of 5-bromo-2-chloro-benzaldehyde (1.0 g, 4.6 mmol, 1.0 eq.) in EtOH (12.5 mL). The reaction mixture is allowed to stir at r.t. for 40min. Water and EtOAc are added and the reaction mixture is extracted 3 times with EtOAc. The organic phases are combined, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected intermediate.

Step ii)

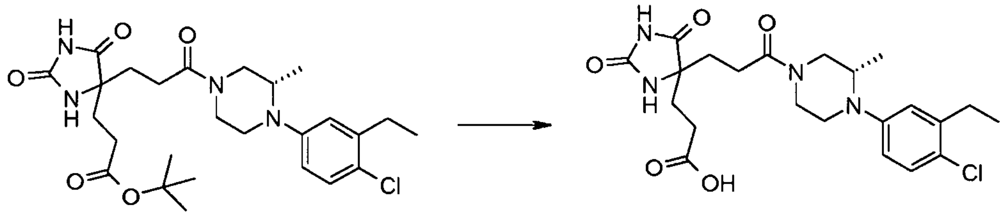
[0384] Diethylaminosulfur trifluoride (393 µL, 2.7 mmol, 2.0 eq.) is added slowly to a solution of 5-bromo-2-chlorobenzyl alcohol (200 mg, 1.4 mmol, 1.0 eq.) in DCM (2 mL) at 0°C. The reaction mixture is allowed to warm to r.t. for 1h45. The reaction mixture is concentrated to dryness and taken up in DCM. A saturated $NaHCO_3$ solution is cautiously added and the layers are separated. The combined organic layers are washed 3 times with water, dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* to afford the expected product which is used as such in the next step.

2.39. Cpd 471



[0385] A flask is charged with **Int 315** (28mg, 0.06 mmol, 1.0 eq.) and a solution of HCl in dioxane (4N) (1mL) is added, and stirring is kept at room temperature for 3h. Reaction mixure is diluted with water, a solution of $NaHCO_3$ is added and extracted with DCM. Organic layers are combined and evaporated under reduced pressure to obtain crude product which is purified by flash chromatography on silica gel (DCM/MeOH 100/0 to 92/8) to afford the expected carboxylic acid. LCMS: MW (calcd): 450; m/z MW (obsd): 451-453 (M+H).

2.40. Cpd 477



[0386] A flask is charged with **Cpd 475** (68 mg, 0.013 mmol, 1.0 eq.) and a solution of HCl in dioxane (4.0M, 10 mL, 40 mmol, 300 eq.). The flask is capped with an oil bubbler and slowly flushed with a stream of N_2. After 64 h, volatiles are removed via rotary evaporation, and the residue is dissolved in a solution of HCl in dioxane (4.0M, 10 mL, 40 mmol, 300 eq.). The reaction mixture is allowed to stir at r.t. for 40h. Volatiles are removed via rotary evaporation. The residue is dissolved in DMSO and purified by preparative LC-MS to afford the expected product. LCMS: MW (calcd): 464; m/z MW (obsd): 465 (M+H).

2.41. (5S)-5-[(2S)-3-[(3S)-4-(3-Chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methoxymethyl-imidazolidine-2,4-dione (Cpd 455): chiral separation by SFC

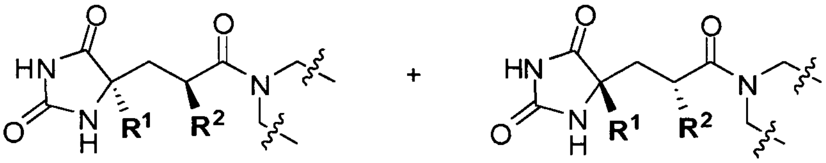
[0387] **Cpd 432** is purified by SFC using the following conditions:

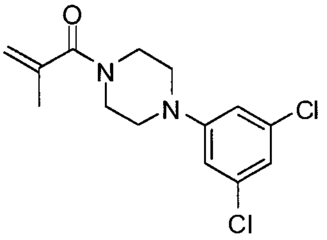
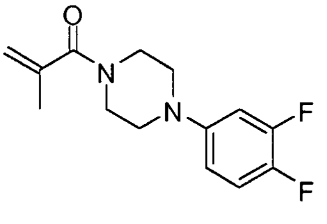
- Instrument: Waters Thar SFC prep100
- Column: Chiralpak IA (20 x 250mm), 5uM
- Mobile phase: Isocratic 35% EtOH and 65% CO_2,
- Flow rate: 100 mL/min

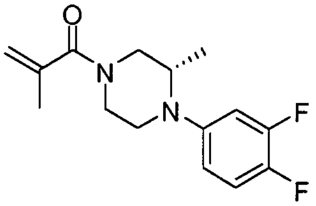
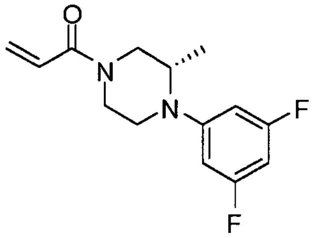
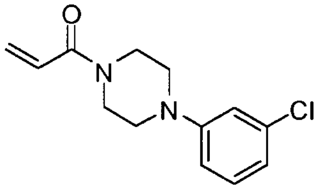
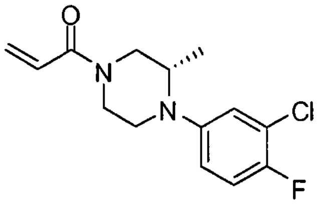
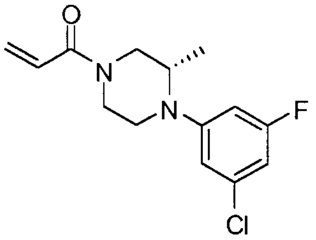
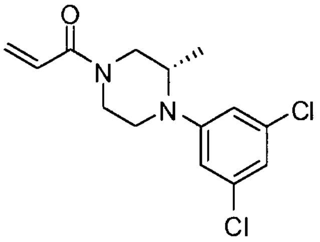
[0388] **Cpd 432** (1.372 g) is dissolved in EtOH (70 mL) (approximately 20 mg/mL), Injection volume 1500µL which equates to loading of 30mg on column per injection, total number of stacks: 49. This purification affords the expected product **Cpd 455** as a single enantiomer.

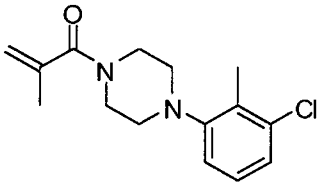
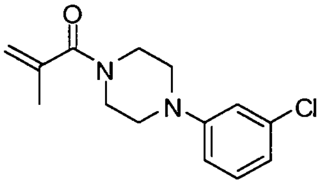
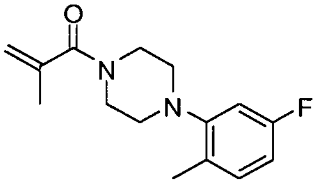
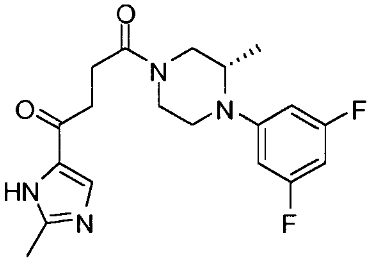
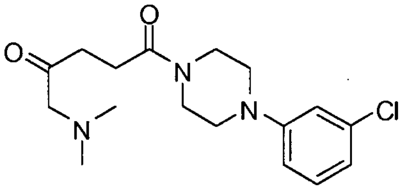
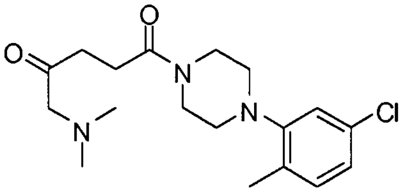
Table II. Illustrative intermediate for the synthesis of illustrative compounds of the invention

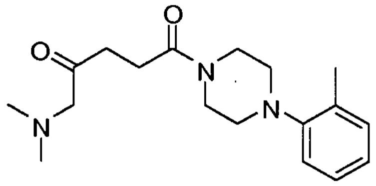
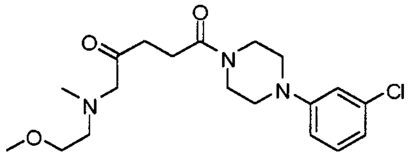
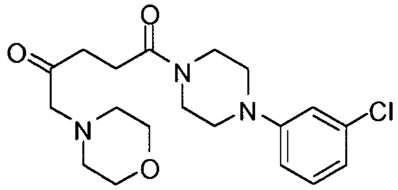
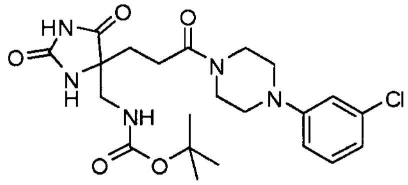
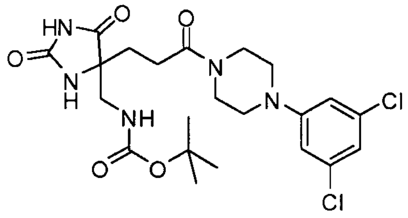
trans:

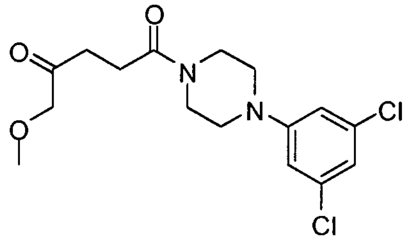
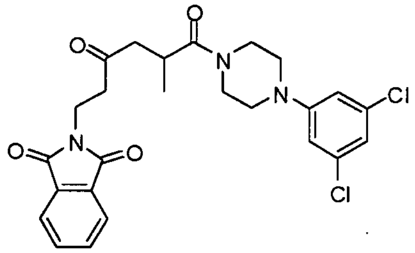
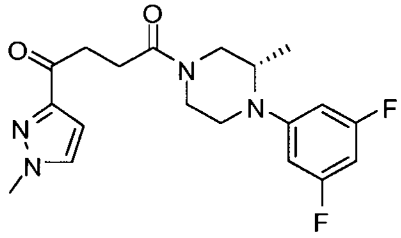
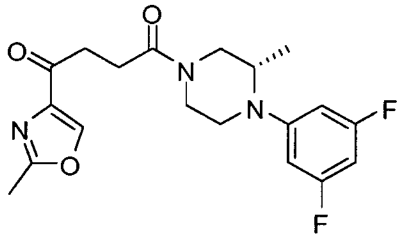
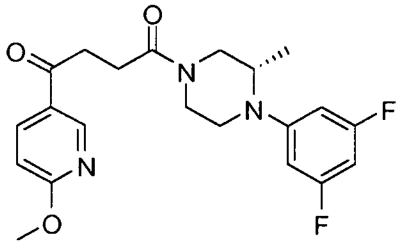


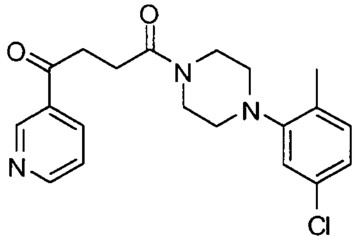
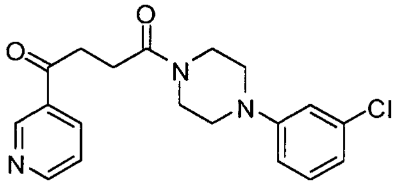
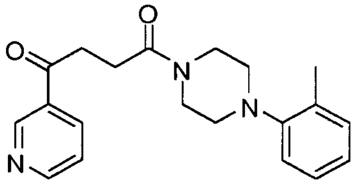
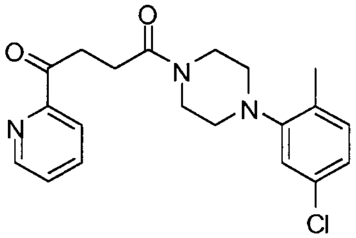
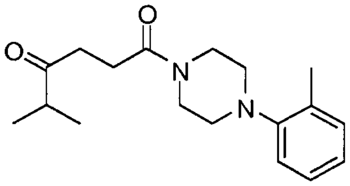
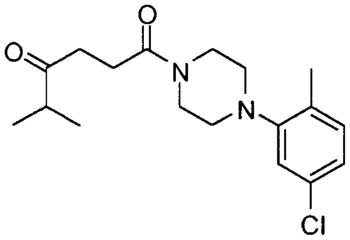
Int	Structure	Name	Mtd	SM	MW	Ms'd
001		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-prop-2-en-1-one	D1a	2-Methyl-acryloyl chloride + 1-(3,5-dichlorophenyl)piperazine	299	299 - 301
002		1-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-prop-2-en-1-one	D1a	2-Methyl-acryloyl chloride + 1-(3,4-difluorophenyl)piperazine	266	267

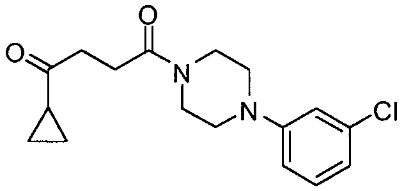
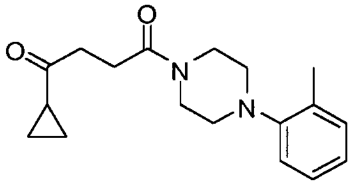
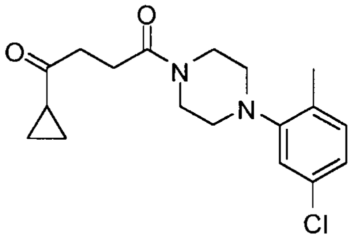
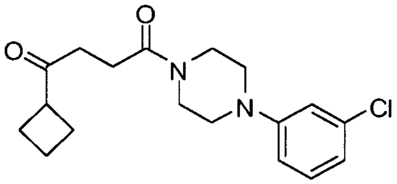
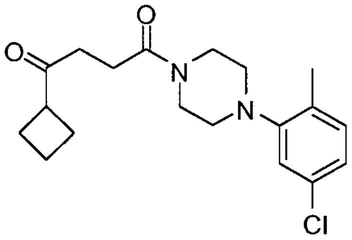
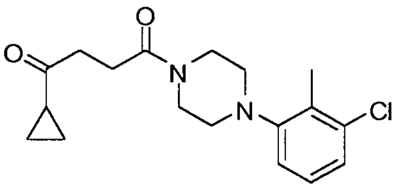
Int	Structure	Name	Mtd	SM	MW	Ms'd
003		1-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-prop-2-en-1-one	D1a	2-Methyl-acryloyl chloride + Int 199	280	281
004		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]prop-2-en-1-one	D1a	Acryloyl chloride + Int 207	266	267
005		1-[4-(3-chlorophenyl)piperazin-1-yl]prop-2-en-1-one	D1a	Acryloyl chloride + 1-(3-Chlorophenyl)piperazine	251	N.A.
006		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]prop-2-en-1-one	D1a	Acryloyl chloride + Int 198	283	283-285
007		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]prop-2-en-1-one	D1a	Acryloyl chloride + Int 206	283	283-285
008		1-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]prop-2-en-1-one	D1a	Acryloyl chloride + Int 197	299	299-301

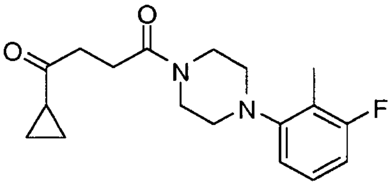
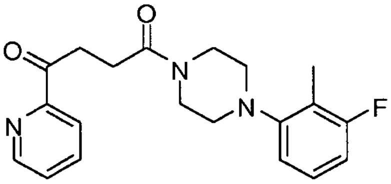
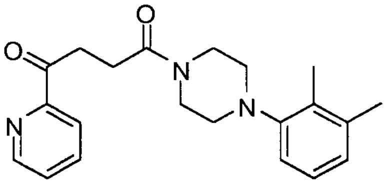
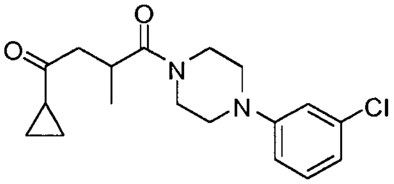
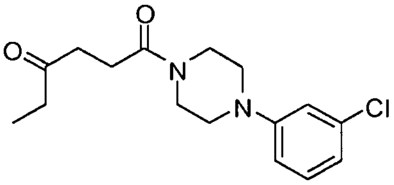
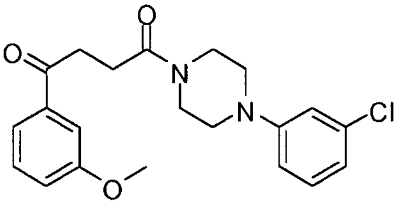
Int	Structure	Name	Mtd	SM	MW	Ms'd
009		1-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-prop-2-en-1-one	D1b	2-Methyl-acryloyl chloride + Int 196	279	279-281
010		1-[4-(3-chlorophenyl)piperazin-1-yl]-2-methyl-prop-2-en-1-one	D1a	2-Methyl-acryloyl chloride + 1-(3-Chloro phenyl) piperazine	265	N.A.
011		1-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-prop-2-en-1-one	D1a	2-Methyl-acryloyl chloride + Int 204	262	N.A.
012		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(2-methyl-1H-imidazol-5-yl)butane-1,4-dione	D2a	2-methyl-1H-imidazole-4-carbal dehyde + Int 004	376	377
013		1-[4-(3-chlorophenyl)piperazin-1-yl]-5-(dimethylamino)pentane-1,4-dione	H2	Int 178 + 1-(3-chloro phenyl) piperazine	338	N.A.
014		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-5-(dimethylamino)pentane-1,4-dione	H2	Int 178 + 1-(5-chloro-2-methyl phenyl)-piperazine	352	N.A.

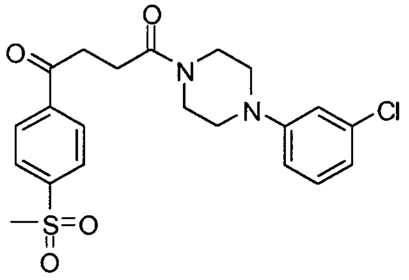
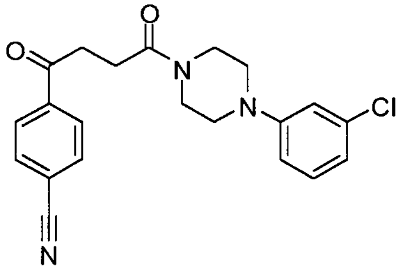
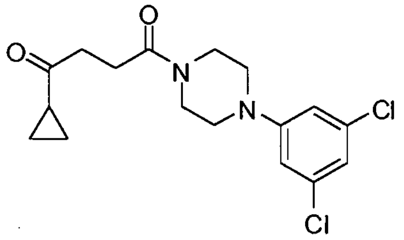
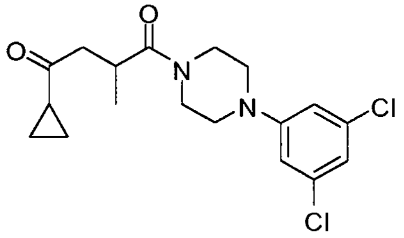
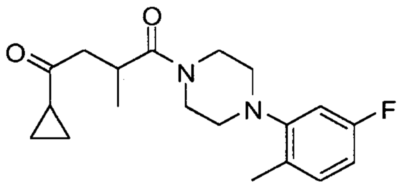
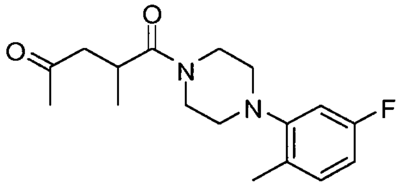
Int	Structure	Name	Mtd	SM	MW	Ms'd
015		5-(dimethylamino)-1-[4-(o-tolyl)piperazin-1-yl]pentane-1,4-dione	H2	Int 178 + 1-(o-tolyl) piperazine dihydrochloride	317	N.A.
016		1-[4-(3-chlorophenyl)piperazin-1-yl]-5-[2-methoxyethyl(methyl)amino]pentane-1,4-dione	H2	Int 130 + 1-(3-chloro phenyl) piperazine	382	N.A.
017		1-[4-(3-chlorophenyl)piperazin-1-yl]-5-morpholino-pentane-1,4-dione	H2	Int 131 + 1-(3-chloro phenyl) piperazine	380	N.A.
018		tert-butyl N-[[4-[3-[4-(3-chlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]methyl]carbamate	F	Int 127	480	N.A.
019		tert-butyl N-[[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]methyl]carbamate	F	Int 128	514	N.A.

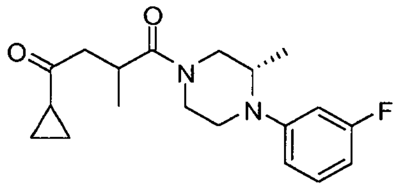
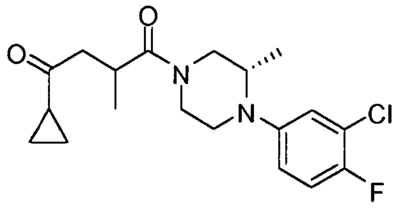
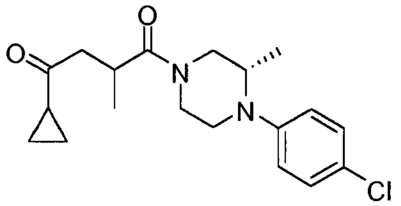
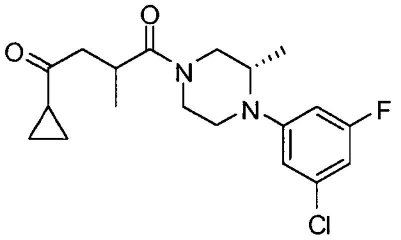
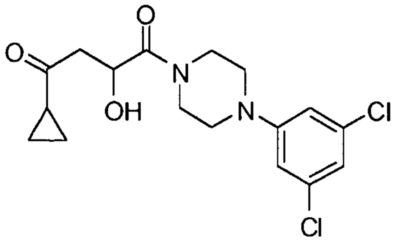
Int	Structure	Name	Mtd	SM	MW	Ms'd
020		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-5-methoxy-pentane-1,4-dione	H2	Int 177 + 1-(3,5-dichlorophenyl)piperazine	359	359-361
021		2-[6-[4-(3,5-dichlorophenyl)piperazin-1-yl]-5-methyl-3,6-dioxo-hexyl]isoindoline-1,3-dione	D2a	Int 001 + 3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-propionaldehyde	502	502-504-506
022		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(1-methylpyrazol-3-yl)butane-1,4-dione	D2a	Int 004 + 1-Methyl-1H-pyrazole-3-carbaldehyde	376	377
023		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(2-methyloxazol-4-yl)butane-1,4-dione	D2a	Int 004 + 2-Methyl-oxazole-4-carbaldehyde	377	378
024		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(6-methoxy-3-pyridyl)butane-1,4-dione	D2a	Int 004 + 6-Methoxy-pyridine-3-carbaldehyde	403	404

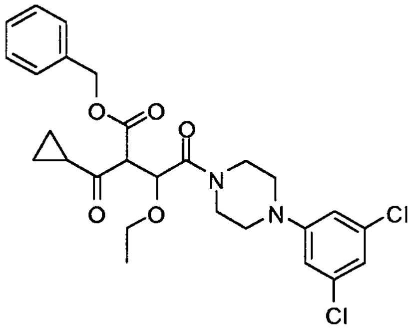
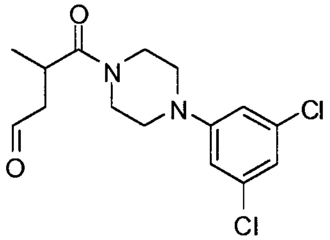
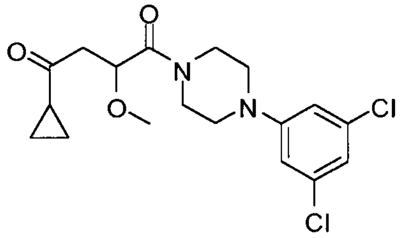
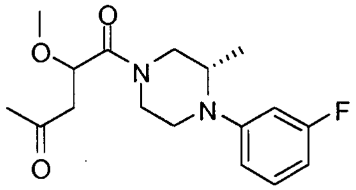
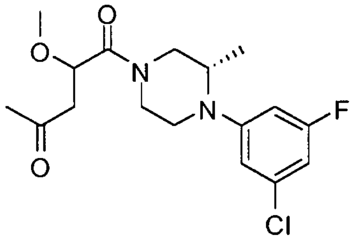
Int	Structure	Name	Mtd	SM	MW	Ms'd
025		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-4-(3-pyridyl)butane-1,4-dione	H1	4-Oxo-4-pyridin-3-yl-butyric acid + 1-(5-Chloro-2-methylphenyl)-piperazine	372	372-374
026		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-(3-pyridyl)butane-1,4-dione	H1	4-Oxo-4-pyridin-3-yl-butyric acid + 1-(3-chlorophenyl)piperazine	358	358-360
027		1-[4-(o-tolyl) piperazin-1-yl]-4-(3-pyridyl)butane-1,4-dione	H1	4-Oxo-4-pyridin-3-yl-butyric acid + 1-(o-tolyl)piperazine dihydrochloride	337	338
028		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H1	4-Oxo-4-pyridin-2-yl-butyric acid + 1-(5-Chloro-2-methylphenyl)-piperazine	372	372-374
029		5-methyl-1-[4-(o-tolyl) piperazin-1-yl]hexane-1,4-dione	H3	5-Methyl-4-oxohexanoic acid + 1-(o-tolyl)piperazine dihydrochloride	302	N.A.
030		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-5-methyl-hexane-1,4-dione	H3	5-Methyl-4-oxohexanoic acid + 1-(5-chloro-2-methylphenyl)-piperazine	337	N.A.

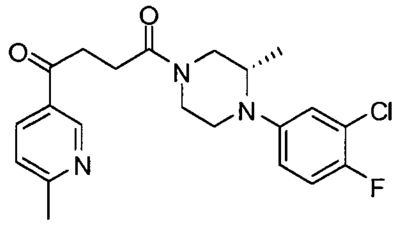
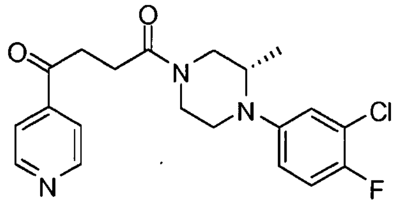
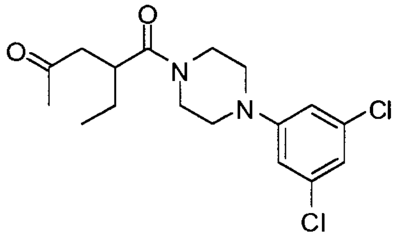
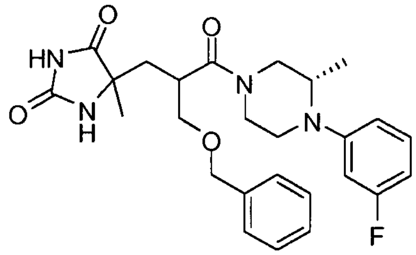
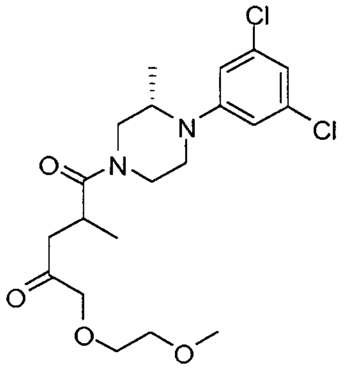
Int	Structure	Name	Mtd	SM	MW	Ms'd
031		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-cyclopropyl-butane-1,4-dione	H3	4-Cyclopropyl-4-oxobutyric acid + 1-(3-chlorophenyl)piperazine	321	N.A.
032		1-cyclopropyl-4-[4-(o-tolyl)piperazin-1-yl]butane-1,4-dione	H3	4-Cyclopropyl-4-oxobutyric acid + 1-(o-tolyl)piperazine dihydrochloride	300	N.A.
033		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-4-cyclopropyl-butane-1,4-dione	H3	4-Cyclopropyl-4-oxobutyric acid + 1-(5-chloro-2-methylphenyl)-piperazine	335	N.A.
034		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-cyclobutyl-butane-1,4-dione	H3	4-Cyclobutyl-4-oxo-butyric acid + 1-(3-chlorophenyl)piperazine	335	335-337
035		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-4-cyclobutyl-butane-1,4-dione	H3	4-Cyclobutyl-4-oxo-butyric acid + 1-(5-chloro-2-methylphenyl)-piperazine	349	349-351
036		1-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-4-cyclopropyl-butane-1,4-dione	H3	4-Cyclopropyl-4-oxobutyric acid + 1-(3-chloro-2-methylphenyl)-piperazine	335	N.A.

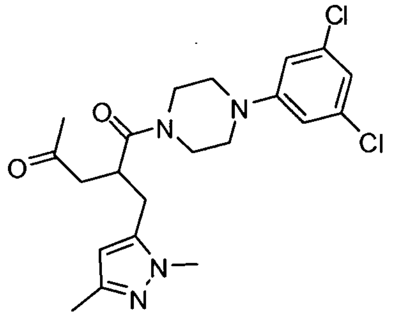
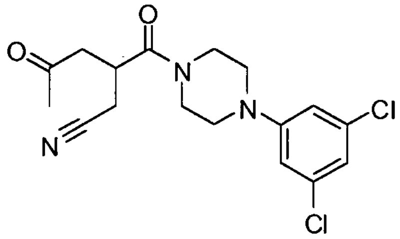
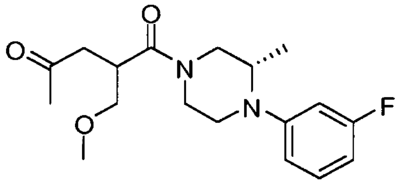
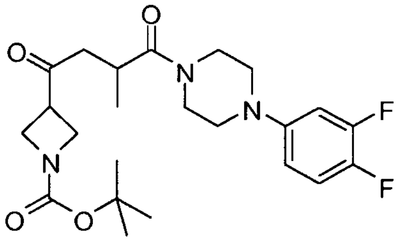
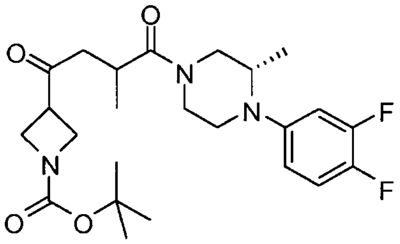
Int	Structure	Name	Mtd	SM	MW	Ms'd
037		1-cyclopropyl-4-[4-(3-fluoro-2-methyl-phenyl)piperazin-1-yl]butane-1,4-dione	H3	4-Cyclopropyl-4-oxobutyric acid + 1-(3-fluoro-2-methylphenyl)-piperazine	318	N.A.
038		1-[4-(3-fluoro-2-methyl-phenyl)piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-Oxo-4-pyridin-2-yl-butyric acid + 1-(3-fluoro-2-methylphenyl)-piperazine	355	N.A.
039		1-[4-(2,3-dimethylphenyl)piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-Oxo-4-pyridin-2-yl-butyric acid + 1-(2,3-Dimethyl-phenyl)-piperazine	351	N.A.
040		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-cyclopropyl-2-methyl-butane-1,4-dione	D2b	Int 010 + cyclopropanecarboxaldehyde	335	335-337
041		1-[4-(3-chlorophenyl)piperazin-1-yl]hexane-1,4-dione	D2b	Int 005 + propanal	309	N.A.
042		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-(3-methoxyphenyl)butane-1,4-dione	D2b	Int 005 + 3-Methoxy benzaldehyde	387	387-389

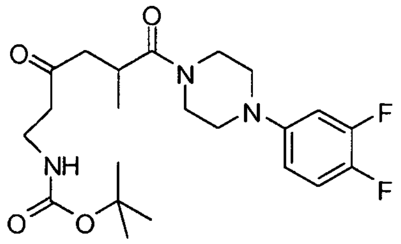
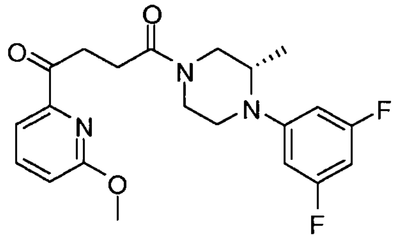
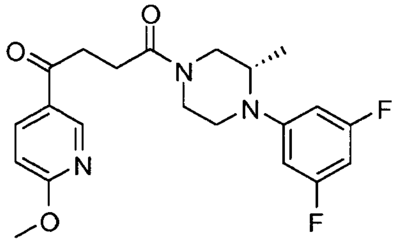
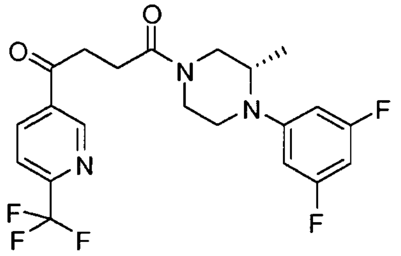
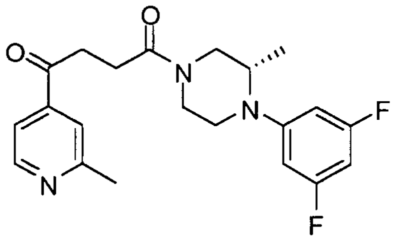
Int	Structure	Name	Mtd	SM	MW	Ms'd
043		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-(4-methylsulfonylphenyl)butane-1,4-dione	D2b	Int 005 + 4-Methylsulphonyl benz aldehyde	435	435-437
044		4-[4-[4-(3-chlorophenyl)piperazin-1-yl]-4-oxo-butanoyl]benzonitrile	D2a	Int 005 + 4-cyano benzaldehyde	382	382-384
045		1-cyclopropyl-4-[4-(3,5-dichlorophenyl)piperazin-1-yl]butane-1,4-dione	H3	4-Cyclopropyl-4-oxobutyric acid + 1-(3,5-dichlorophenyl)piperazine	355	N.A.
046		4-cyclopropyl-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-butane-1,4-dione	D2b	Int 001 + cyclopropanecarb oxaldehyde	369	369-371
047		4-cyclopropyl-1-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-butane-1,4-dione	D2b	Int 011 + cyclopropanecarb oxaldehyde	332	333
048		1-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-pentane-1,4-dione	D2b	Int 011 + acetalde hyde	306	307

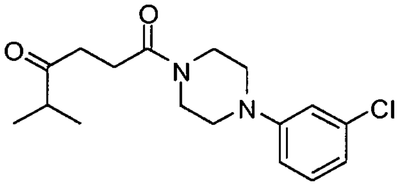
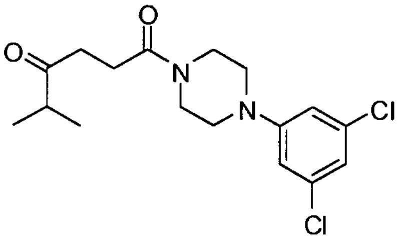
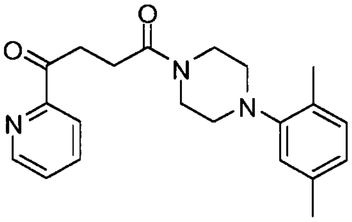
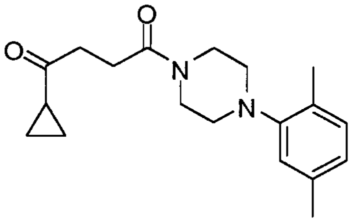
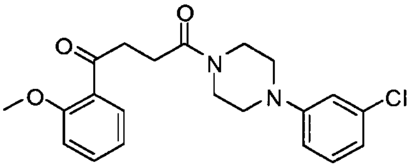
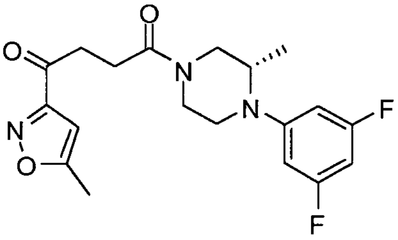
Int	Structure	Name	Mtd	SM	MW	Ms'd
049		4-cyclopropyl-1-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-butane-1,4-dione	H3	Int 155 + Int 202	332	333
050		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-cyclopropyl-2-methyl-butane-1,4-dione	H3	Int 155 + Int 198	367	367-369
051		1-[(3S)-4-(4-chlorophenyl)-3-methyl-piperazin-1-yl]-4-cyclopropyl-2-methyl-butane-1,4-dione	H3	Int 155 + Int 205	349	349-351
052		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-cyclopropyl-2-methyl-butane-1,4-dione	H3	Int 155 + Int 206	367	367-369
053		4-cyclopropyl-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-hydroxy-butane-1,4-dione	2.14	Cyclopropane carbonyl chloride + Meldrum's acid + benzyl alcohol + crotonyl chloride + 3,5-dichlorophenyl piperazine	371	N.A.

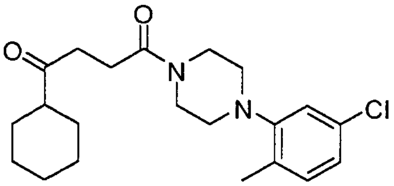
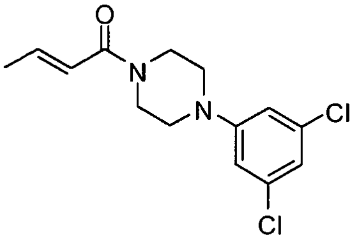
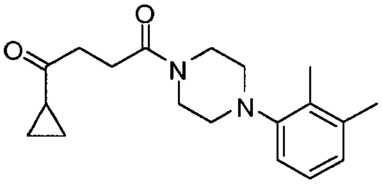
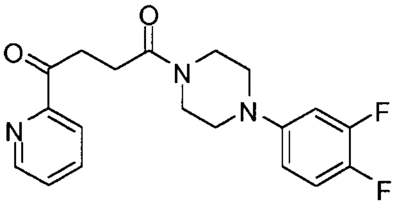
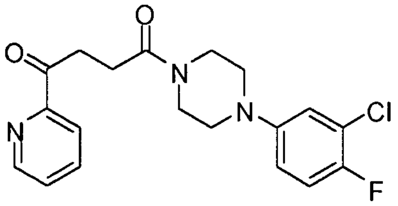
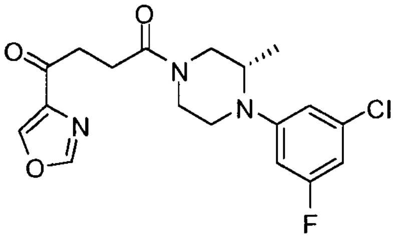
Int	Structure	Name	Mtd	SM	MW	Ms'd
054		benzyl 2-(cyclopropanecarbonyl)-4-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-ethoxy-4-oxo-butanoate	2.14	Cyclopropane carbonyl chloride + Meldrum's acid + benzyl alcohol + crotonyl chloride + 3,5-dichlorophenyl piperazine	533	N.A.
055		4-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-methyl-4-oxo-butanal	D4	Int 124	329	329-331
056		4-cyclopropyl-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methoxy-butane-1,4-dione	2.15	Int 054	385	N.A.
057		1-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methoxy-pentane-1,4-dione	D4	Int 125	322	N.A.
058		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methoxy-pentane-1,4-dione	D4	Int 126	357	N.A.

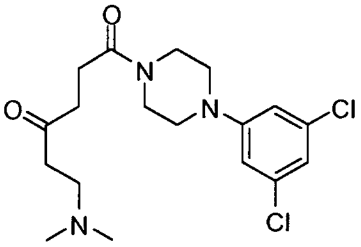
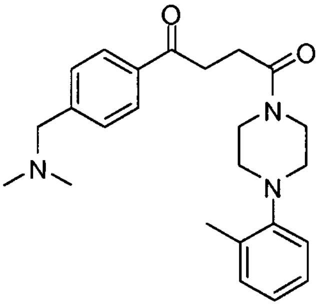
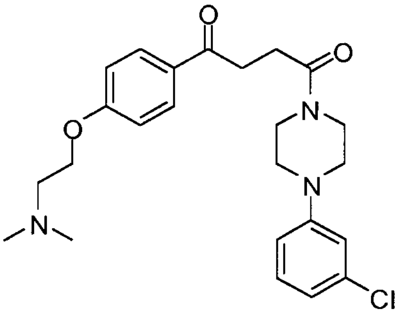
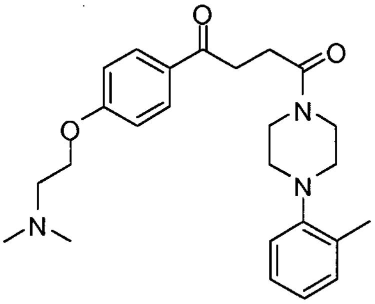
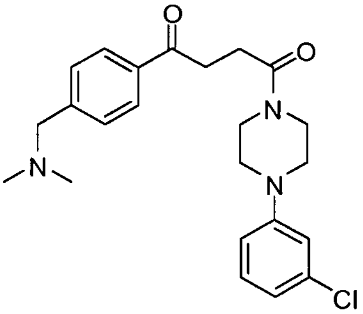
Int	Structure	Name	Mtd	SM	MW	Ms'd
059		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-(6-methyl-3-pyridyl)butane-1,4-dione	D2c	Int 006 + 6-Methyl-pyridine-3-carbaldehyde	404	404-406
060		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-(4-pyridyl)butane-1,4-dione	D2c	Int 006 + Pyridine-4-carbaldehyde	390	390-392
061		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-ethyl-pentane-1,4-dione	H2	Int 190 + 1-(3,5-dichlorophenyl)piperazine	357	357-359
062	 *trans*	5-[2-(benzyloxymethyl)-3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione	H2	Int 135 + Int 202	483	N.A.
063		1-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-5-(2-methoxyethoxy)-2-methyl-pentane-1,4-dione	H2	Int 185 + Int 197	431	431-433

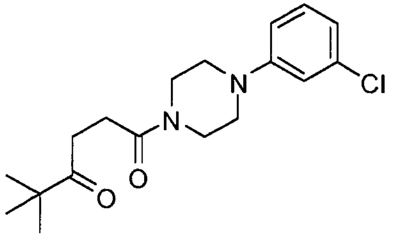
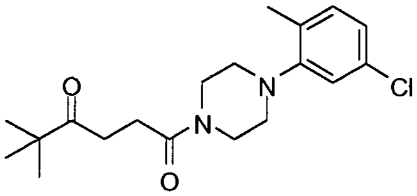
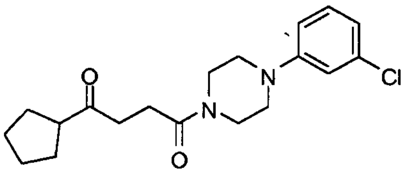
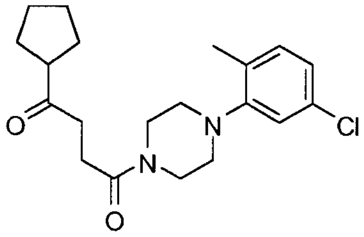
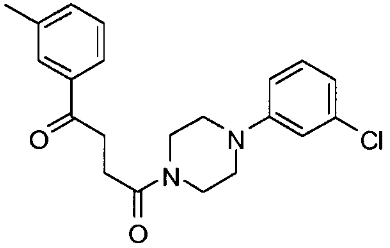
Int	Structure	Name	Mtd	SM	MW	Ms'd
064		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-[(2,5-dimethylpyrazol-3-yl)methyl]pentane-1,4-dione	E	Int 121 + 5-Chloromethyl-1,3-dimethyl-1H-pyrazole	437	437-439
065		3-[4-(3,5-dichlorophenyl)piperazine-1-carbonyl]-5-oxo-hexanenitrile	E	Int 121 + Bromo-acetonitrile	368	368-370
066		1-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-(methoxymethyl)pentane-1,4-dione	E	Int 122 + Bromo-methoxy-methane	336	337
067		tert-butyl 3-[4-[4-(3,4-difluorophenyl)piperazin-1-yl]-3-methyl-4-oxo-butanoyl]azetidine-1-carboxylate	D2b	Int 002 + 1-Boc-3-azetidinecarboxaldehyde	452	453
068		tert-butyl 3-[4-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-3-methyl-4-oxo-butanoyl]azetidine-1-carboxylate	D2b	Int 003 + 1-Boc-3-azetidinecarboxaldehyde	466	467

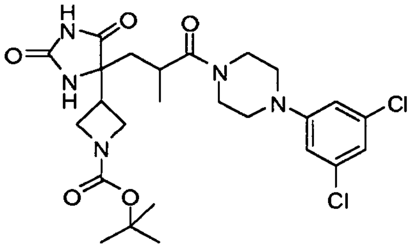
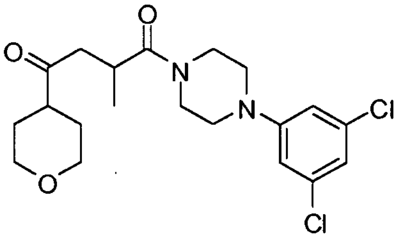
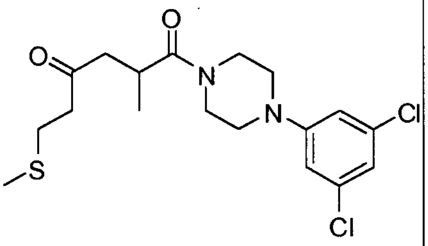
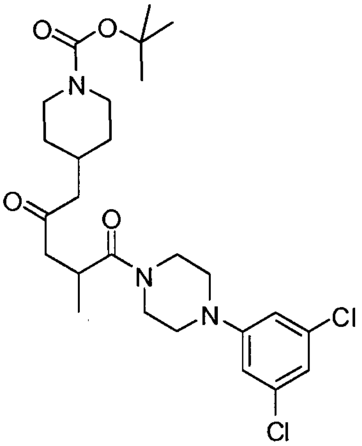
Int	Structure	Name	Mtd	SM	MW	Ms'd
069		tert-butyl N-[6-[4-(3,4-difluorophenyl)piperazin-1-yl]-5-methyl-3,6-dioxo-hexyl]carbamate	H2	Int 191 + 1-(3,4-difluoro phenyl) piperazine	440	441
070		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(6-methoxy-2-pyridyl)butane-1,4-dione	D2a	Int 004 + 6-Methoxy-pyridine-2-carbaldehyde	403	404
071		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(6-methoxy-3-pyridyl)butane-1,4-dione	D2a	Int 004 + 6-Methoxy-pyridine-3-carbaldehyde	403	404
072		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-[6-(trifluoromethyl)-3-pyridyl]butane-1,4-dione	D2a	Int 004 + 6-Trifluoromethyl-pyridine-3-carbaldehyde	441	442
073		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(2-methyl-4-pyridyl)butane-1,4-dione	D2a	Int 004 + 2-Methyl-pyridine-4-carbaldehyde	387	388

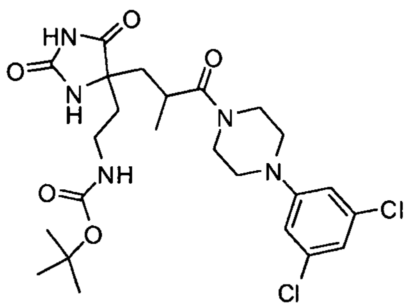
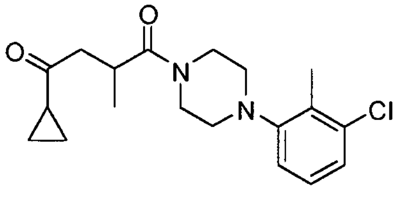
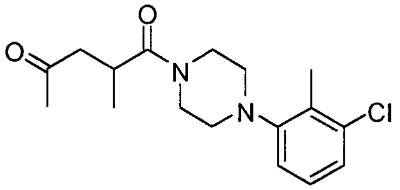
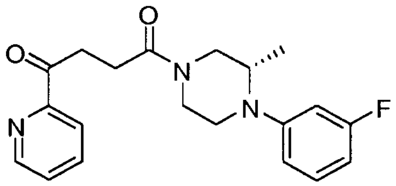
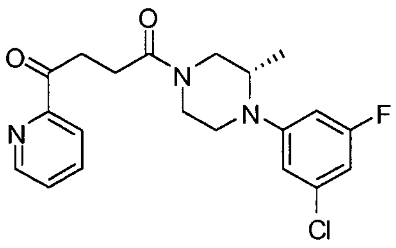
Int	Structure	Name	Mtd	SM	MW	Ms'd
074		1-[4-(3-chlorophenyl)piperazin-1-yl]-5-methyl-hexane-1,4-dione	H3	5-Methyl-4-oxohexanoic acid + 1-(3-chlorophenyl)piperazine	323	323-325
075		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-5-methyl-hexane-1,4-dione	H3	5-Methyl-4-oxohexanoic acid + 1-(3,5-dichlorophenyl)piperazine	357	357-359
076		1-[4-(2,5-dimethylphenyl)piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H1	4-Oxo-4-pyridin-2-yl-butyric acid + 1-(2,5-Dimethylphenyl)piperazine	351	352
077		1-cyclopropyl-4-[4-(2,5-dimethylphenyl)piperazin-1-yl]butane-1,4-dione	H1	4-Cyclopropyl-4-oxo-butyric acid + 1-(2,5-Dimethylphenyl)piperazine	314	315
078		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-(2-methoxyphenyl)butane-1,4-dione	H2	4-(2-methoxyphenyl)-4-oxobutyric acid + 1-(3-chlorophenyl)piperazine	387	387-389
079		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(5-methylisoxazol-3-yl)butane-1,4-dione	D2a	Int 004 + 5-Methylisoxazole-3-carboxaldehyde	377	378

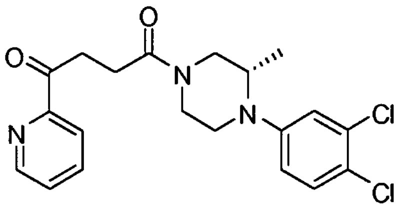
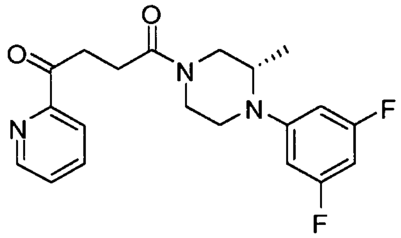
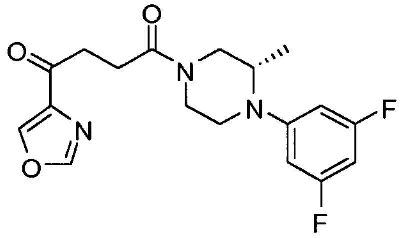
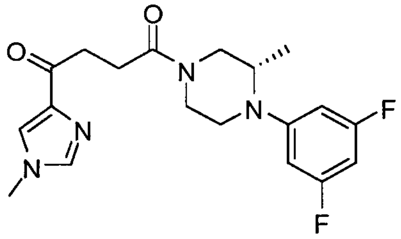
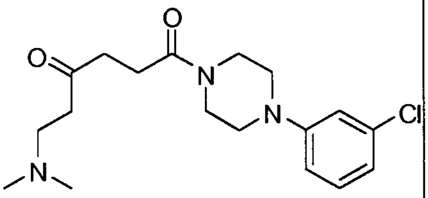
Int	Structure	Name	Mtd	SM	MW	Ms'd
080		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-4-cyclohexyl-butane-1,4-dione	H3	4-cyclohexyl-4-oxobutyric acid + 1-(5-chloro-2-methylphenyl)-piperazine	377	377-379
081		(E)-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]but-2-en-1-one	D1	crotonyl chloride + 3,5-dichloro phenyl piperazine	299	N.A.
082		1-cyclopropyl-4-[4-(2,3-dimethyl phenyl)piperazin-1-yl]butane-1,4-dione	H1	4-Cyclopropyl-4-oxo-butyric acid + 1-(2,3-Dimethylphenyl) piperazine	314	N.A.
083		1-[4-(3,4-difluorophenyl) piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H1	4-Oxo-4-pyridin-2-yl-butyric acid + 1-(3,4-difluorophenyl)piperazine	359	360
084		1-[4-(3-chloro-4-fluoro-phenyl) piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H1	4-Oxo-4-pyridin-2-yl-butyric acid + 1-(3-Chloro-4-fluorophenyl)pipe razine dihydrochloride	376	376-378
085		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-oxazol-4-yl-butane-1,4-dione	D2a	Int 007 + Oxazole-4-carbaldehyde	380	380-382

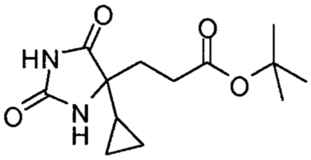
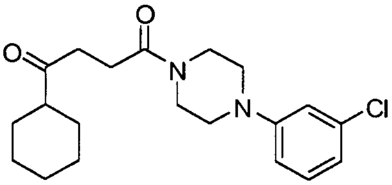
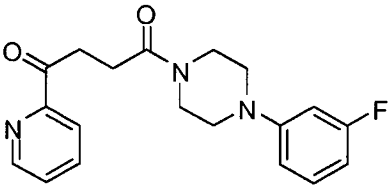
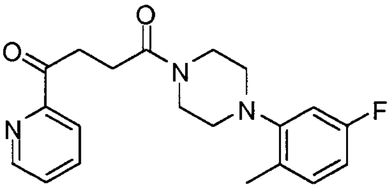
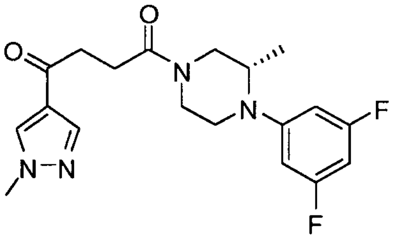
Int	Structure	Name	Mtd	SM	MW	Ms'd
086		1-[4-(3,5-dichlorophenyl) piperazin-1-yl]-6-(dimethylamino)hexane-1,4-dione	H1	6-dimethylamino-4-ketohexanoic acid hydrochloride + 1-(3,5-dichlorophenyl)piperazine	386	386-388-390
087		1-[4-(dimethylamino methyl)phenyl]-4-[4-(o-tolyl) piperazin-1-yl] butane-1,4-dione	D7	Int 117	394	395
088		1-[4-(3-chloro phenyl)piperazin-1-yl]-4-[4-(2-dimethylamino ethyloxy)phenyl] butane-1,4-dione	H1	Int 189 + 1-(3-chlorophenyl)piperazine	444	444-446
089		1-[4-(2-dimethylaminoethyloxy)phenyl]-4-[4-(o-tolyl)piperazin-1-yl]butane-1,4-dione	H1	Int 189 + 1-(o-tolyl)piperazine dihydrochloride	424	425
090		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-[4-(dimethylaminomethyl)phenyl]butane-1,4-dione	D7	Int 118	414	414-416

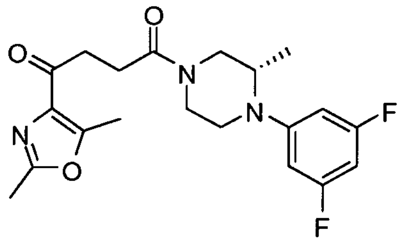
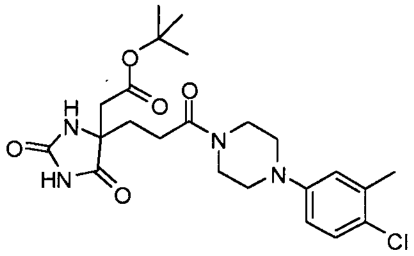
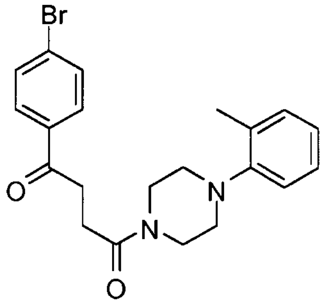
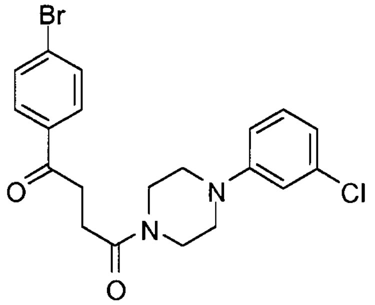
Int	Structure	Name	Mtd	SM	MW	Ms'd
091		1-[4-(3-chlorophenyl)piperazin-1-yl]-5,5-dimethyl-hexane-1,4-dione	H1	5,5-Dimethyl-4-oxo-hexanoic acid + 1-(3-chlorophenyl)piperazine	337	337-339
092		1-[4-(5-chloro-2-methyl-phenyl) piperazin-1-yl]-5,5-dimethyl-hexane-1,4-dione	H1	5,5-Dimethyl-4-oxo-hexanoic acid + 1-(5-chloro-2-methylphenyl)-piperazine	351	351-353
093		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-cyclopentyl-butane-1,4-dione	H1	4-Cyclopentyl-4-oxo-butyric acid + 1-(3-chlorophenyl)piperazine	349	349-351
094		1-[4-(5-chloro-2-methyl-phenyl)piperazin-1-yl]-4-cyclopentyl-butane-1,4-dione	H1	4-Cyclopentyl-4-oxo-butyric acid + 1-(5-chloro-2-methylphenyl)-piperazine	363	363-365
095		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-(m-tolyl)butane-1,4-dione	D2a	Int 005 + 3-Methyl-benzaldehyde	371	371-373

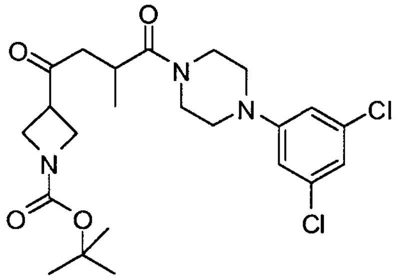
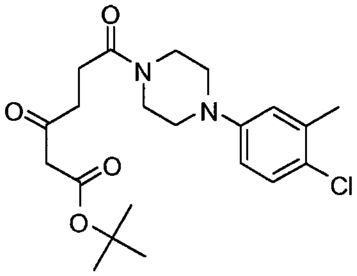
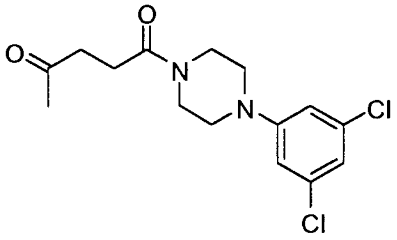
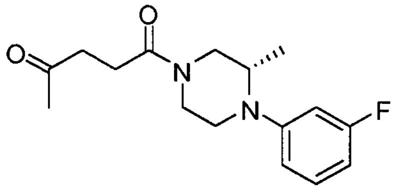
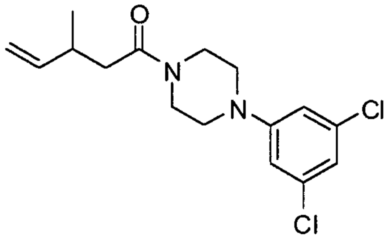
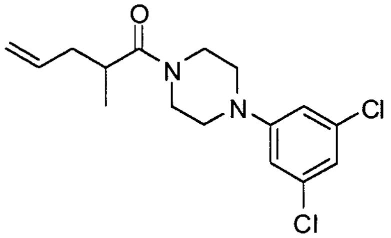
Int	Structure	Name	Mtd	SM	MW	Ms'd
096	 trans	tert-butyl 3-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]azetidine-1-carboxylate	F	Int 119	554	554-556
097		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-4-tetrahydropyran-4-yl-butane-1,4-dione	D2b	Int 001 + Tetrahydro-pyran-4-carbaldehyde	413	413-415
098		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-6-methylsulfanyl-hexane-1,4-dione	D2b	Int 001 + 3-(Methylthio)propionaldehyde	403	403-405
099		tert-butyl 4-[5-[4-(3,5-dichlorophenyl)piperazin-1-yl]-4-methyl-2,5-dioxo-pentyl]piperidine-1-carboxylate	D2b	Int 001 + 4-(2-Oxo-ethyl)-piperidine-1-carboxylic acid tert-butyl ester	527	527-529

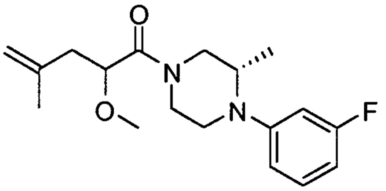
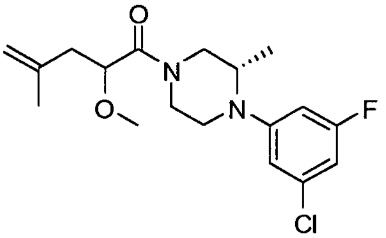
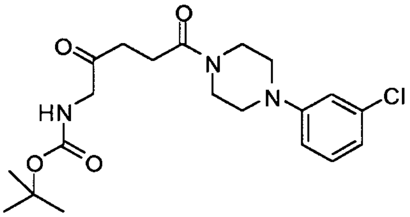
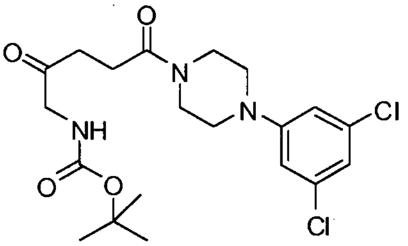
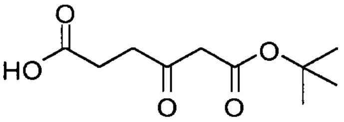
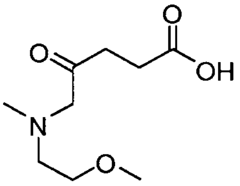
Int	Structure	Name	Mtd	SM	MW	Ms'd
100	 trans	tert-butyl N-[2-[4-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]ethyl] carbamate	F	Int 150	542	542-544
101		1-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-4-cyclopropyl-2-methyl-butane-1,4-dione	D2b	Int 009 + cyclopropanecarboxaldehyde	349	349-351
102		1-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-pentane-1,4-dione	D2b	Int 009 + Acetaldehyde	323	323-325
103		1-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-oxo-4-pyridin-2ylbutyric acid + Int 202	355	356
104		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-oxo-4-pyridin-2ylbutyric acid + Int 206	390	309-392

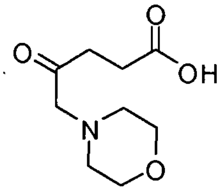
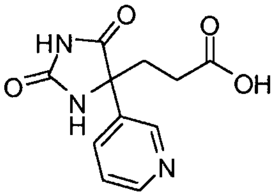
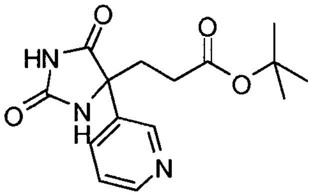
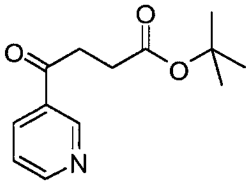
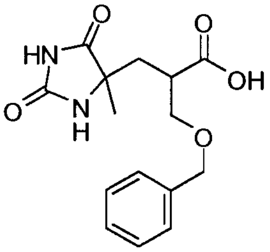
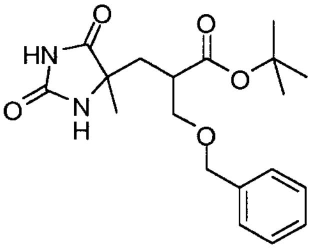
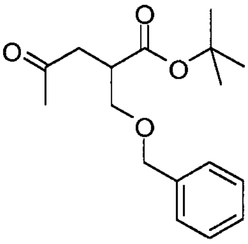
Int	Structure	Name	Mtd	SM	MW	Ms'd
105		1-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-oxo-4-pyridin-2ylbutyric acid + Int 201	406	406-408
106		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-oxo-4-pyridin-2ylbutyric acid + Int 207	373	374
107		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-oxazol-4-yl-butane-1,4-dione	D2a	Int 004 + Oxazole-4-carbaldehyde	363	364
108		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(1-methylimidazol-4-yl)butane-1,4-dione	D2a	Int 004 + 1-Methyl-1H-imidazole-4-carbaldehyde	376	377
109		1-[4-(3-chlorophenyl)piperazin-1-yl]-6-(dimethylamino)hexane-1,4-dione	H1	6-dimethylamino-4-ketohexanoic acid hydrochloride + 1-(3-chlorophenyl)piperazine	352	352-354

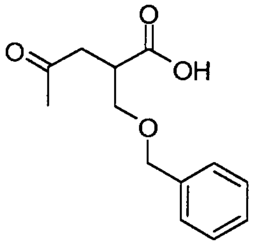
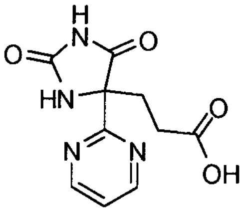
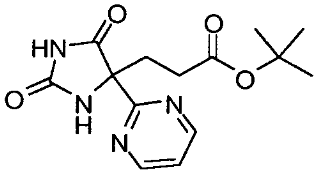
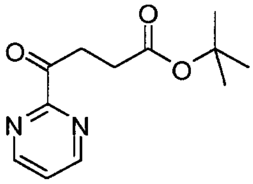
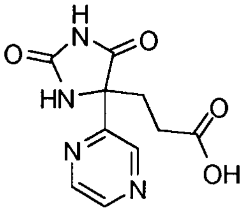
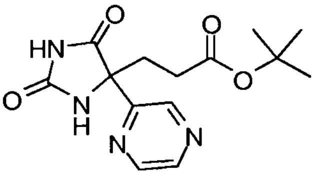
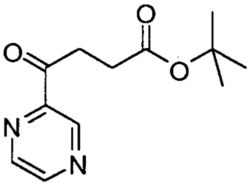
Int	Structure	Name	Mtd	SM	MW	Ms'd
110		(S)-4-(3,5-Di fluoro-phenyl) -3-methyl-pi perazine-1-car boxylic acid tert-butyl ester	2.18	Int 290	268	N.A.
111		1-[4-(3-chlorophenyl)piperazin-1-yl]-4-cyclohexyl-butane-1,4-dione	H3	4-cyclohexyl-4-oxobutyric acid + 1-(3-chlorophenyl)piperazine	363	363-365
112		1-[4-(3-fluorophenyl)piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H1	4-oxo-4-pyridin-2ylbutyric acid + 1-(3-Fluorophenyl)piperazine	341	342
113		1-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H1	4-oxo-4-pyridin-2ylbutyric acid + Int 204	355	356
114		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(1-methylpyrazol-4-yl)butane-1,4-dione	D2a	Int 004 + 1-Methyl-1H-pyrazole-4-carbaldehyde	376	377

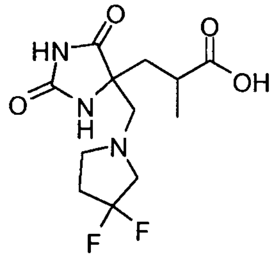
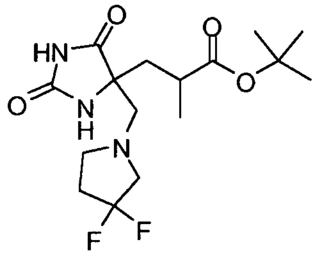
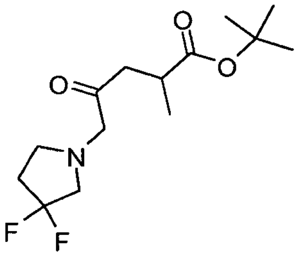
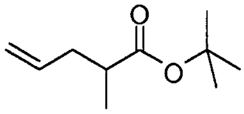
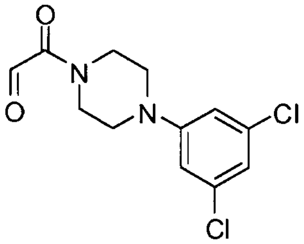
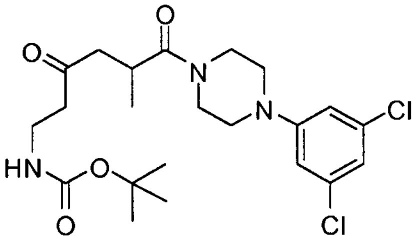
Int	Structure	Name	Mtd	SM	MW	Ms'd
115		1-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-4-(2,5-dimethyloxazol-4-yl)butane-1,4-dione	D2a	Int 004 + 2,5-Dimethyl-oxazole-4-carbaldehyde	391	392
116		tert-butyl 2-[4-[3-[4-(4-chloro-3-methyl-phenyl)piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetate	F	Int 120	479	479
117		1-(4-bromophenyl)-4-[4-(o-tolyl)piperazin-1-yl]butane-1,4-dione	H1	4-(4-Bromo-phenyl)-4-oxo-butyric acid + 1-(o-tolyl)piperazine dihydrochloride	415	415-417
118		1-(4-bromophenyl)-4-[4-(3-chlorophenyl)piperazin-1-yl]butane-1,4-dione	H1	4-(4-Bromo-phenyl)-4-oxo-butyric acid + 1-(3-chlorophenyl)piperazine	436	435-437

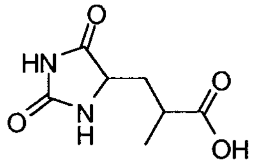
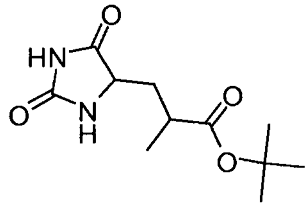
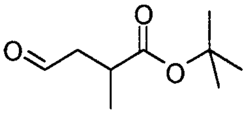
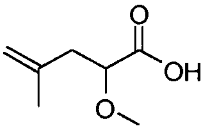
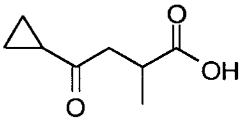
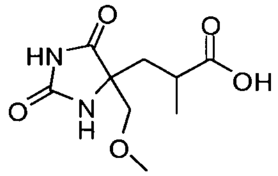
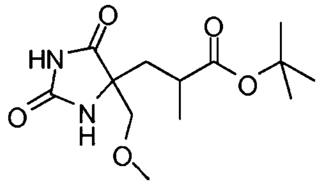
Int	Structure	Name	Mtd	SM	MW	Ms'd
119		tert-butyl 3-[4-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-methyl-4-oxo-butanoyl]azetidine-1-carboxylate	D2b	Int 001 + 3-Formyl-azetidine-1-carboxylic acid tert-butyl ester	484	484-486
120		tert-butyl 6-[4-(4-chloro-3-methyl-phenyl)piperazin-1-yl]-3,6-dioxo-hexanoate	H2	Int 129 + Int 284	409	409
121		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]pentane-1,4-dione	H2	levulinic acid + 1-(3,5-dichlorophenyl)piperazine	329	329-331
122		1-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]pentane-1,4-dione	H2	levulinic acid + Int 202	292	293
123		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-3-methyl-pent-4-en-1-one	H3	3-Methyl-4-pentenoic acid + 1-(3,5-dichlorophenyl)piperazine	327	N.A.
124		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-pent-4-en-1-one	H3	2-Methyl-4-pentenoic acid + 1-(3,5-dichlorophenyl)piperazine	327	327-329

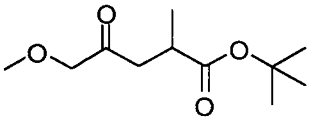
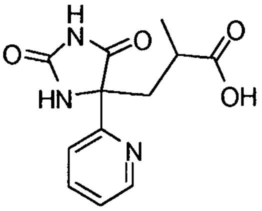
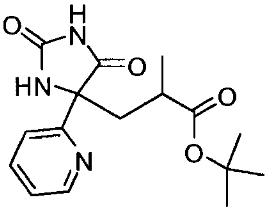
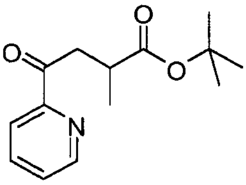
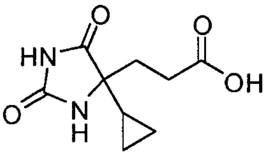
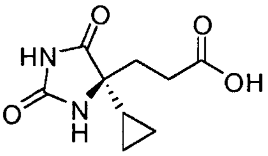
Int	Structure	Name	Mtd	SM	MW	Ms'd
125		1-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methoxy-4-methyl-pent-4-en-1-one	H3	Int 154 + Int 202	320	321
126		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methoxy-4-methyl-pent-4-en-1-one	H3	Int 154 + Int 206	355	355-357
127		tert-butyl N-[5-[4-(3-chlorophenyl)piperazin-1-yl]-2,5-dioxo-pentyl]carbamate	H2	Int 173 + 1-(3-chlorophenyl)piperazine	410	N.A.
128		tert-butyl N-[5-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2,5-dioxo-pentyl]carbamate	H2	Int 173 + 1-(3,5-dichlorophenyl)piperazine	444	N.A.
129		6-tert-butoxy-4,6-dioxo-hexanoic acid	2.16	Succinic anhydride + tertbutyl acetate	216	N.A.
130		5-[2-methoxyethyl(methyl)amino]-4-oxo-pentanoic acid	D6	levulinic acid + (2-methoxy-ethyl)-methyl-amine	203	N.A.

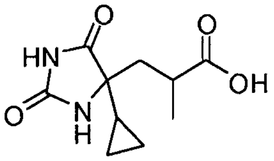
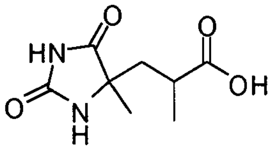
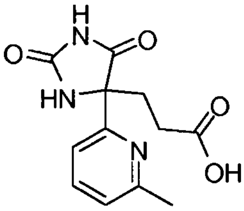
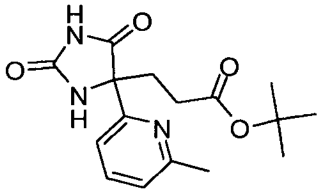
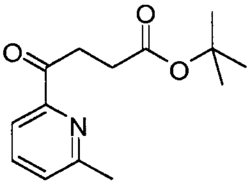
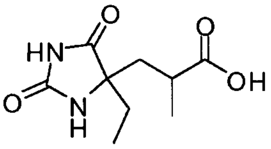
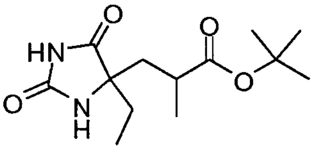
Int	Structure	Name	Mtd	SM	MW	Ms'd
131		5-morpholino-4-oxo-pentanoic acid	D6	levulinic acid + morpholine	201	N.A.
132		3-[2,5-dioxo-4-(3-pyridyl)imidazolidin-4-yl]propanoic acid	G	Int 133	249	N.A.
133		tert-butyl 3-[2,5-dioxo-4-(3-pyridyl)imidazolidin-4-yl]propanoate	F	Int 134	305	306
134		tert-butyl 4-oxo-4-(3-pyridyl)butanoate	C4	Pyridine-3-carbaldehyde + Acrylic acid tert-butyl ester	235	236
135	 trans	2-(benzyloxymethyl)-3-(4-methyl-2,5-dioxo-imidazolidin-4-yl)propanoic acid	G	Int 136	306	307
136	 trans	tert-butyl 2-(benzyloxymethyl)-3-(4-methyl-2,5-dioxo-imidazolidin-4-yl)propanoate	F	Int 137	362	N.A.
137		tert-butyl 2-(benzyloxy methyl)-4-oxo-pentanoate	2.17	Int 138	292	315 (M+ Na)

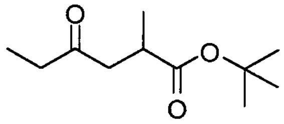
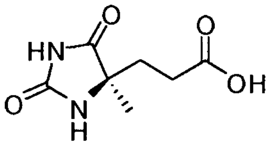
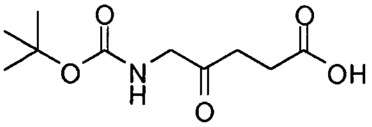
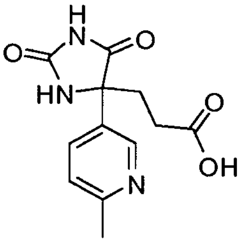
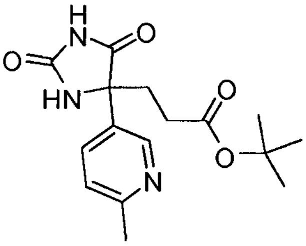
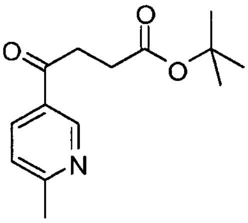
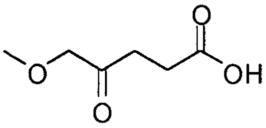
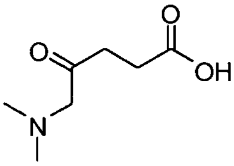
Int	Structure	Name	Mtd	SM	MW	Ms'd
138		2-(benzyloxymethyl)-4-oxo-pentanoic acid	D5	benzyloxy-acetaldehyde	236	N.A.
139		3-(2,5-dioxo-4-pyrimidin-2-yl-imidazolidin-4-yl)propanoic acid	G + H_2O	Int 140	250	251
140		tert-butyl 3-(2,5-dioxo-4-pyrimidin-2-yl-imidazolidin-4-yl)propanoate	F	Int 141	306	307
141		tert-butyl 4-oxo-4-pyrimidin-2-yl-butanoate	C2	1-Pyrimidin-2-yl-ethanone + Bromo-acetic acid tert-butyl ester	236	237
142		3-(2,5-dioxo-4-pyrazin-2-yl-imidazolidin-4-yl)propanoic acid	G	Int 143	250	249 (M-H)
143		tert-butyl 3-(2,5-dioxo-4-pyrazin-2-yl-imidazolidin-4-yl)propanoate	F	Int 144	306	307
144		tert-butyl 4-oxo-4-pyrazin-2-yl-butanoate	C2	1-Pyrazin-2-yl-ethanone + Bromo-acetic acid tert-butyl ester	236	237

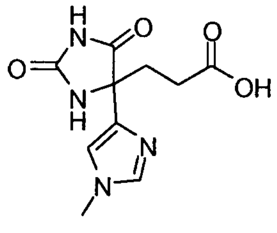
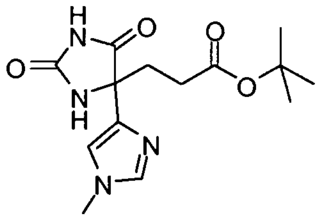
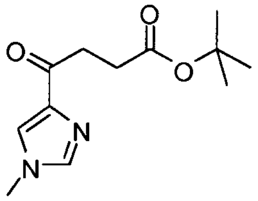
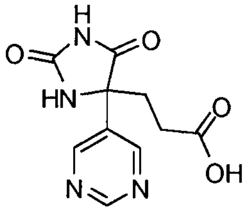
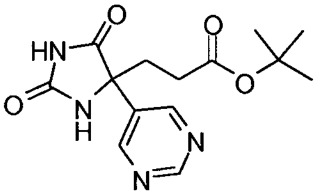
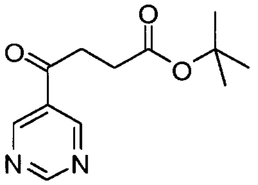
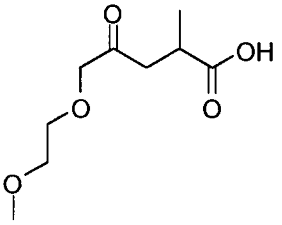
Int	Structure	Name	Mtd	SM	MW	Ms'd
145	 trans	3-[4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2,5-dioxo-imidazolidin-4-yl]-2-methyl-propanoic acid	G	Int 146	305	N.A.
146	 trans	tert-butyl 3-[4-[(3,3-difluoropyrrolidin-1-yl)methyl]-2,5-dioxo-imidazolidin-4-yl]-2-methyl-propanoate	F	Int 147	361	N.A.
147		tert-butyl 5-(3,3-difluoropyrrolidin-1-yl)-2-methyl-4-oxo-pentanoate	C5	Int 148 + 2,2-Difluoro-pyrrolidine hydrochloride	291	292
148		tert-butyl 2-methylpent-4-enoate	C3	2-Methyl-pent-4-enoic acid	170	N.A.
149		2-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-oxo-acetaldehyde	D4	Int 081	287	N.A.
150		tert-butyl N-[6-[4-(3,5-dichlorophenyl)piperazin-1-yl]-5-methyl-3,6-dioxo-hexyl]carbamate	2.19	Int 021	472	472-474-476

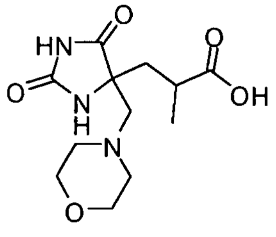
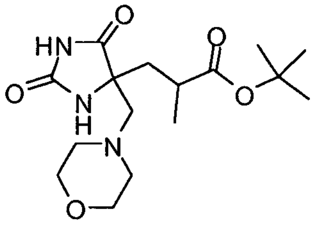
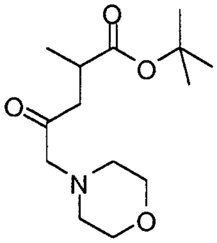
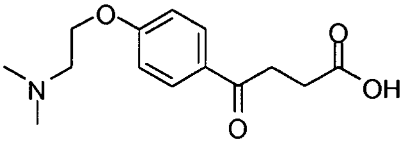
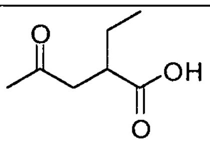
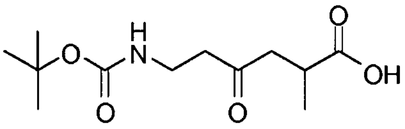
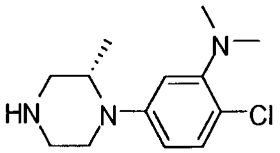
Int	Structure	Name	Mtd	SM	MW	Ms'd
151	 trans	3-(2,5-dioxoimidazolidin-4-yl)-2-methyl-propanoic acid	G	Int 152	186	N.A.
152	 trans	tert-butyl 3-(2,5-dioxoimidazolidin-4-yl)-2-methyl-propanoate	F	Int 153	242	N.A.
153		tert-butyl 2-methyl-4-oxo-butanoate	2.20	Int 148	172	N.A.
154		2-methoxy-4-methyl-pent-4-enoic acid	2.21	Methoxy-acetic acid + 2-Methyl-prop-2-en-1-ol	144	143 (M-H)
155		4-cyclopropyl-2-methyl-4-oxo-butanoic acid	2.23	cyclopropanecarbonyl chloride + 2,2-Dimethyl-[1,3]dioxane-4,6-dione	156	155 (M-H)
156	 trans	3-[4-(methoxymethyl)-2,5-dioxo-imidazolidin-4-yl]-2-methyl-propanoic acid	G	Int 157	230	231
157	 trans	tert-butyl 3-[4-(methoxymethyl)-2,5-dioxo-imidazolidin-4-yl]-2-methyl-propanoate	F	Int 158	286	309 (M+Na)

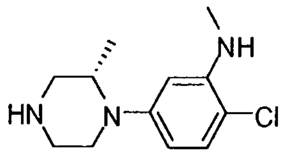
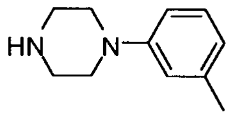
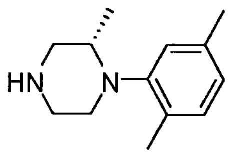
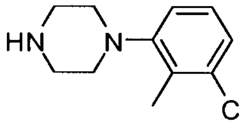
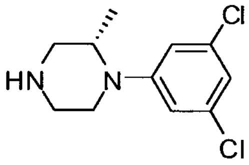
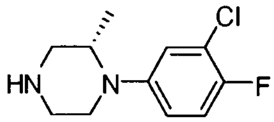
Int	Structure	Name	Mtd	SM	MW	Ms'd
158		tert-butyl 5-methoxy-2-methyl-4-oxo-pentanoate	C1	Methoxy-acetic acid + 2,2-Dimethyl-[1,3]dioxane-4,6-dione	216	239 (M+Na)
159	 trans	3-[2,5-dioxo-4-(2-pyridyl)imidazolidin-4-yl]-2-methyl-propanoic acid	G	Int 160	263	264
160	 trans	tert-butyl 3-[2,5-dioxo-4-(2-pyridyl)imidazolidin-4-yl]-2-methyl-propanoate	F	Int 161	319	320
161		tert-butyl 2-methyl-4-oxo-4-(2-pyridyl)butanoate	C1 step ii + step iii	3-Oxo-3-pyridin-2-yl-propionic acid benzyl ester + Bromo-acetic acid tert-butyl ester	249	272 (M+Na)
162		3-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl)propanoic acid	2.22	Int 110	212	211 (M-H)
163		3-[(4S)-4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl]propanoic acid	2.22	Int 162	212	N.A.

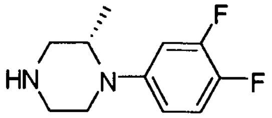
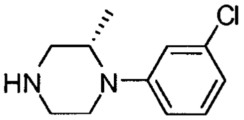
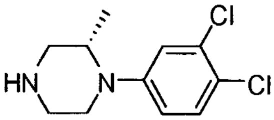
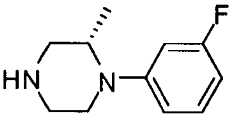
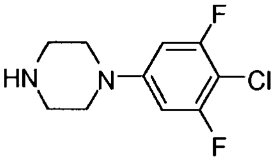
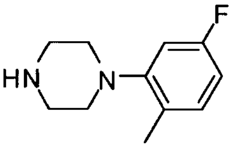
Int	Structure	Name	Mtd	SM	MW	Ms'd
164	 trans	3-(4-cyclopropyl-2,5-dioxo-imidazolidin-4-yl)-2-methyl-propanoic acid	C3 + F + G	Int 155	226	225 (M-H)
165	 trans	2-methyl-3-(4-methyl-2,5-dioxo-imidazolidin-4-yl)propanoic acid	G	Int 289	200	201
166		3-[4-(6-methyl-2-pyridyl)-2,5-dioxo-imidazolidin-4-yl]propanoic acid	G	Int 167	263	264
167		tert-butyl 3-[4-(6-methyl-2-pyridyl)-2,5-dioxo-imidazolidin-4-yl]propanoate	F	Int 168	319	320
168		tert-butyl 4-(6-methyl-2-pyridyl)-4-oxo-butanoate	C4	6-Methyl-pyridine-2-carbaldehyde + Acrylic acid tert-butyl ester	249	250
169	 trans	3-(4-ethyl-2,5-dioxo-imidazolidin-4-yl)-2-methyl-propanoic acid	G	Int 170	214	215
170	 trans	tert-butyl 3-(4-ethyl-2,5-dioxo-imidazolidin-4-yl)-2-methyl-propanoate	F	Int 171	270	271

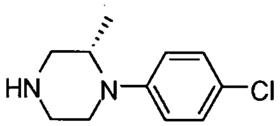
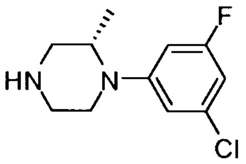
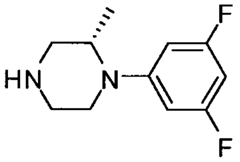
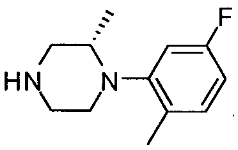
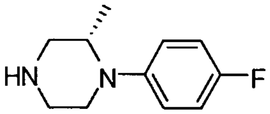
Int	Structure	Name	Mtd	SM	MW	Ms'd
171		tert-butyl 2-methyl-4-oxo-hexanoate	C3	2-Methyl-4-oxo-hexanoic acid [ref J. Org. Chem. 2003, 68, 7983-7989]	200	N.A.
172		3-[(4R)-4-methyl-2,5-dioxo-imidazolidin-4-yl]propanoic acid	2.24	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid	186	373 (2M+H)
173		5-(tert-butoxycarbonylamino)-4-oxo-pentanoic acid	2.25	5-Amino-4-oxo-pentanoic acid	231	N.A.
174		3-[4-(6-methyl-3-pyridyl)-2,5-dioxo-imidazolidin-4-yl]propanoic acid	G	Int 175	263	264
175		tert-butyl 3-[4-(6-methyl-3-pyridyl)-2,5-dioxo-imidazolidin-4-yl]propanoate	F	Int 176	319	320
176		tert-butyl 4-(6-methyl-3-pyridyl)-4-oxo-butanoate	D2c	6-Methyl-pyridine-3-carbaldehyde + Acrylic acid tert-butyl ester	249	250
177		5-methoxy-4-oxo-pentanoic acid	2.26	pent-4-ynoic acid	146	N.A.
178		5-(dimethylamino)-4-oxo-pentanoic acid	D6	levulinic acid + dimethylamine	159	N.A.

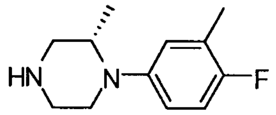
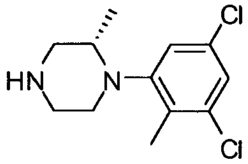
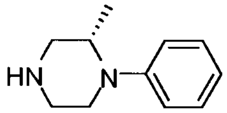
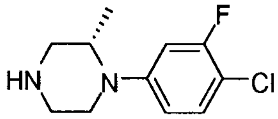
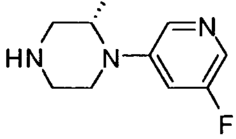
Int	Structure	Name	Mtd	SM	MW	Ms'd
179		3-[4-(1-methylimidazol-4-yl)-2,5-dioxo-imidazolidin-4-yl]propanoic acid	G	Int 180	252	253
180		tert-butyl 3-[4-(1-methylimidazol-4-yl)-2,5-dioxo-imidazolidin-4-yl]propanoate	F	Int 181	308	309
181		tert-butyl 4-(1-methylimidazol-4-yl)-4-oxo-butanoate	C4	1-Methyl-1H-imidazole-4-carbaldehyde + Acrylic acid tert-butyl ester	238	239
182		3-(2,5-dioxo-4-pyrimidin-5-yl-imidazolidin-4-yl)propanoic acid	G	Int 183	250	N.A.
183		tert-butyl 3-(2,5-dioxo-4-pyrimidin-5-yl-imidazolidin-4-yl)propanoate	F	Int 184	306	307
184		tert-butyl 4-oxo-4-pyrimidin-5-yl-butanoate	C2	1-Pyrimidin-5-yl-ethanone + Bromo-acetic acid tert-butyl ester	236	237
185		5-(2-methoxyethoxy)-2-methyl-4-oxo-pentanoic acid	2.27	(2-methoxy-ethoxy)-acetic acid	204	203 (M-H)

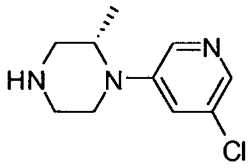
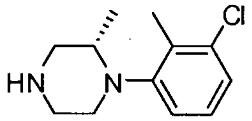
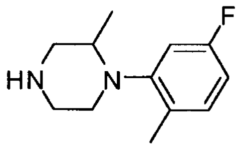
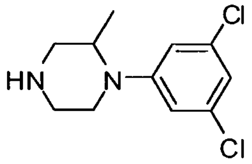
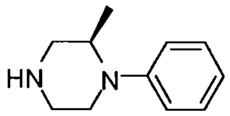
Int	Structure	Name	Mtd	SM	MW	Ms'd
186	 trans	2-methyl-3-[4-(morpholinomethyl)-2,5-dioxo-imidazolidin-4-yl]propanoic acid	G	Int 187	285	N.A.
187	 trans	tert-butyl 2-methyl-3-[4-(morpholinomethyl)-2,5-dioxo-imidazolidin-4-yl]propanoate	F	Int 188	341	342
188		tert-butyl 2-methyl-5-morpholino-4-oxo-pentanoate	C5	Int 148 + morpholine	271	N.A.
189		4-[4-(2-dimethylaminoethyloxy)phenyl]-4-oxo-butanoic acid	2.28	4-(4-fluoro-phenyl)-4-oxo-butyric acid + 2-dimethylamino-ethanol	265	266
190		2-ethyl-4-oxo-pentanoic acid	D5	propionaldehyde	144	N.A.
191		6-(tert-butoxycarbonylamino)-2-methyl-4-oxo-hexanoic acid	2.29	3-tert-butoxycarbonylamino-propionic acid + Meldrum's acid	259	260
192		2-chloro-N,N-dimethyl-5-[(2S)-2-methylpiperazin-1-yl]aniline	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + Int 285	254	254

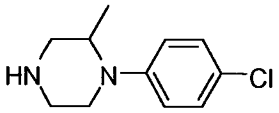
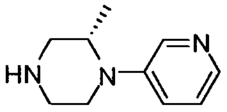
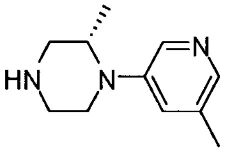
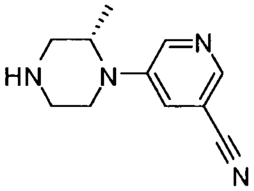
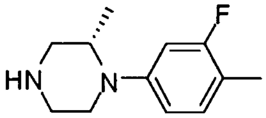
Int	Structure	Name	Mtd	SM	MW	Ms'd
193		2-chloro-N-methyl-5-[(2S)-2-methylpiperazin-1-yl]aniline	A2a + A5e	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + Int 286	240	240
194		1-(m-tolyl) piperazine	A2a + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 3-bromo toluene	176	177
195		(2S)-1-(2,5-dimethylphenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 2-bromo-1,4-dimethyl benzene	204	205
196		1-(3-chloro-2-methyl-phenyl)piperazine	A7	Piperazine + 1-Bromo-3-chloro-2-methyl-benzene	211	211
197		(2S)-1-(3,5-dichlorophenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3,5-dichloro-benzene	245	245-247
198		(2S)-1-(3-chloro-4-fluoro-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-Bromo-2-chloro-1-fluoro-benzene	229	229

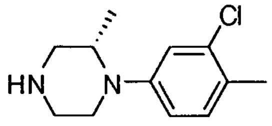
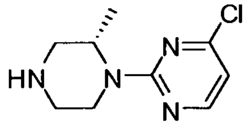
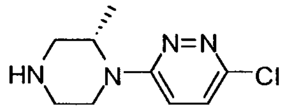
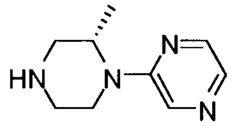
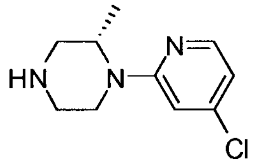
Int	Structure	Name	Mtd	SM	MW	Ms'd
199		(2S)-1-(3,4-difluorophenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-Bromo-1,2-difluoro-benzene	212	214
200		(2S)-1-(3-chlorophenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3-chloro-benzene	211	211
201		(2S)-1-(3,4-dichlorophenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1,2-Dichloro-4-iodo-benzene	245	245
202		(2S)-1-(3-fluorophenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3-fluoro-benzene	194	195
203		1-(4-chloro-3,5-difluoro-phenyl)piperazine	A7	Piperazine + 5-Bromo-2-chloro-1,3-difluoro-benzene	233	233
204		1-(5-fluoro-2-methyl-phenyl)piperazine	A7	Piperazine + 4-Fluoro-2-bromo-1-methyl-benzene	194	195

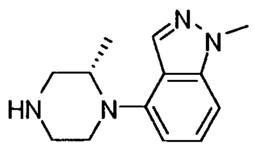
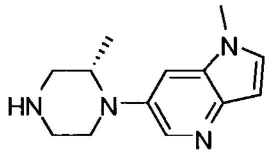
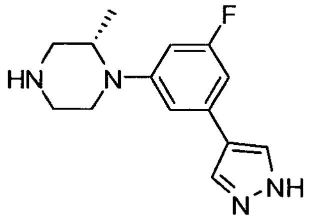
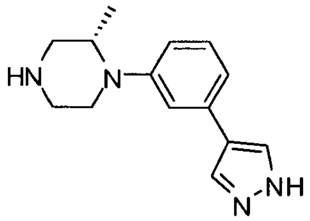
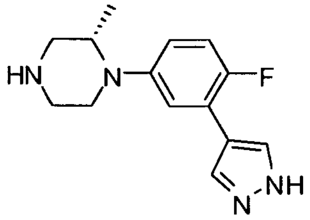
Int	Structure	Name	Mtd	SM	MW	Ms'd
205		(2S)-1-(4-chlorophenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-4-chloro-benzene	211	211
206		(2S)-1-(3-chloro-5-fluoro-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3-chloro-5-fluoro-benzene	229	229-231
207		(2S)-1-(3,5-di fluorophenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3,5-difluoro-benzene	212	213
208		(2S)-1-(5-fluoro-2-methyl-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxy lic acid tert-butyl ester + 2-Bromo-4-fluoro-1-methyl-benzene	208	N.A.
209		(2S)-1-(4-fluorophenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-4-fluoro-benzene	194	195

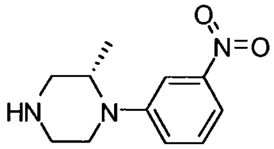
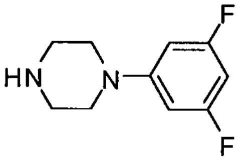
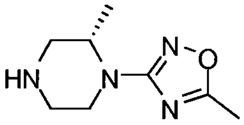
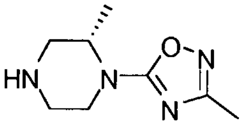
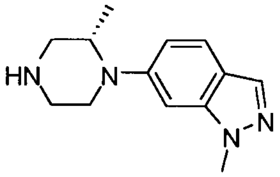
Int	Structure	Name	Mtd	SM	MW	Ms'd
210		(2S)-1-(4-fluoro-3-methyl-phenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxy lic acid tert-butyl ester + 4-Bromo-1-fluoro-2-methyl-benzene	208	209
211		(2S)-1-(3,5-dichloro-2-methyl-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxy lic acid tert-butyl ester + 1-Bromo-3,5-dichloro-2-methyl-benzene	259	261
212		(2S)-2-methyl-1-phenyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxy lic acid tert-butyl ester + Bromo-benzene	176	177
213		(2S)-1-(4-chloro-3-fluoro-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxy lic acid tert-butyl ester + 4-Bromo-1-chloro-2-fluoro-benzene	229	229
214		(2S)-1-(5-fluoro-3-pyridyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-5-fluoro-pyridine	195	196

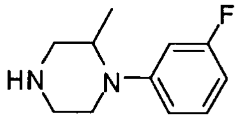
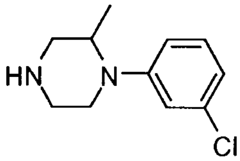
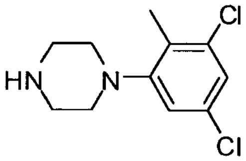
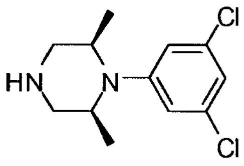
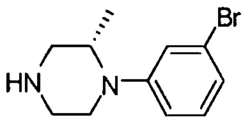
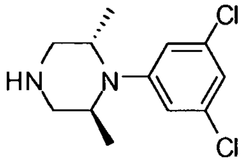
Int	Structure	Name	Mtd	SM	MW	Ms'd
215		(2S)-1-(5-chloro-3-pyridyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-5-chloro-pyridine	212	212
216		(2S)-1-(3-chloro-2-methyl-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3-chloro-2-methyl-benzene	225	225
217		1-(5-fluoro-2-methyl-phenyl)-2-methyl-piperazine	A2a + A5b	3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 2-Bromo-4-fluoro-1-methyl-benzene	208	209
218		1-(3,5-dichlorophenyl)-2-methyl-piperazine	A2a + A5a	3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3,5-dichloro-benzene	245	245-247
219		(2R)-2-methyl-1-phenyl-piperazine	A2a + A5b	(R)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + Bromo-benzene	176	177

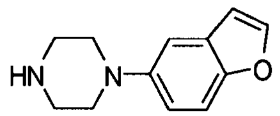
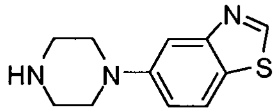
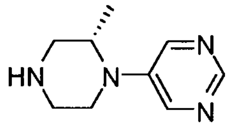
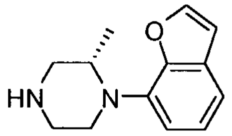
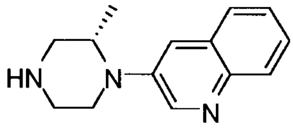
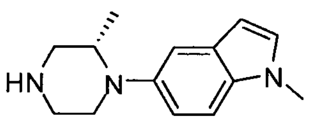
Int	Structure	Name	Mtd	SM	MW	Ms'd
220		1-(4-chlorophenyl)-2-methyl-piperazine	A2a + A5b	3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-4-chloro-benzene	211	211
221		(2S)-2-methyl-1-(3-pyridyl)piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-pyridine	177	178
222		(2S)-2-methyl-1-(5-methyl-3-pyridyl)piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-5-methyl-pyridine	191	N.A.
223		5-[(2S)-2-methylpiperazin-1-yl]pyridine-3-carbonitrile	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 5-Bromo-nicotinonitrile	202	203
224		(2S)-1-(3-fluoro-4-methyl-phenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-Bromo-2-fluoro-1-methyl-benzene	208	209

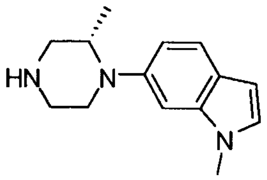
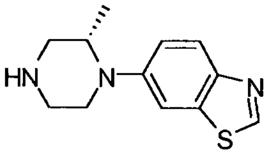
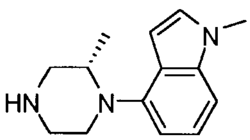
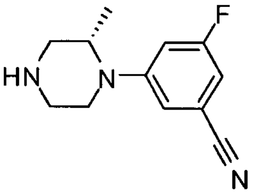
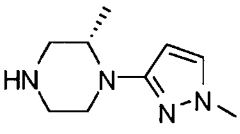
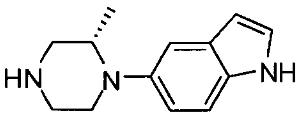
Int	Structure	Name	Mtd	SM	MW	Ms'd
225		(2S)-1-(3-chloro-4-methyl-phenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-Bromo-2-chloro-1-methyl-benzene	225	225-227
226		4-chloro-2-[(2S)-2-methylpiperazin-1-yl]pyrimidine	A4 + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 2,4-Dichloro-pyrimidine	213	213
227		3-chloro-6-[(2S)-2-methylpiperazin-1-yl]pyridazine	A4 + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3,6-Dichloro-pyridazine	213	213
228		2-[(2S)-2-methylpiperazin-1-yl]pyrazine	A2c + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 2-Chloro-pyrazine	178	179
229		(2S)-1-(4-chloro-2-pyridyl)-2-methyl-piperazine	A2b + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 2,4-Dichloro-pyridine	212	N.A.

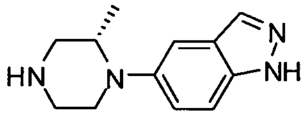
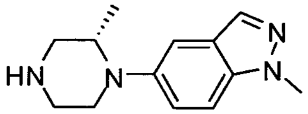
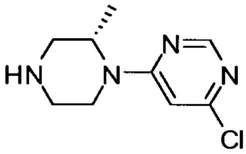
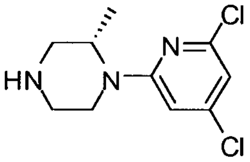
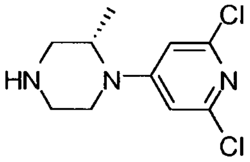
Int	Structure	Name	Mtd	SM	MW	Ms'd
230		1-methyl-4-[(2S)-2-methylpiperazin-1-yl]indazole	A2d + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-Bromo-1-methyl-1H-indazole	230	231
231		1-methyl-6-[(2S)-2-methylpiperazin-1-yl]pyrrolo[3,2-b]pyridine	A2d + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 6-Bromo-1-methyl-1H-pyrrolo[3,2-b]pyridine	230	231
232		(2S)-1-[3-fluoro-5-(1H-pyrazol-4-yl)phenyl]-2-methyl-piperazine	A2a + A3 + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1,3-Dibromo-5-fluoro-benzene	260	261
233		(2S)-2-methyl-1-[3-(1H-pyrazol-4-yl)phenyl]piperazine	A2a + A3 + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1,3-Dibromo-benzene	242	243
234		(2S)-1-[4-fluoro-3-(1H-pyrazol-4-yl)phenyl]-2-methyl-piperazine	A2a + A3 + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-Bromo-2-chloro-1-fluoro-benzene	260	261

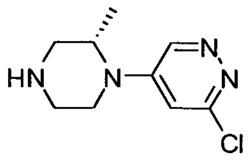
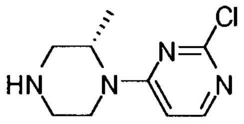
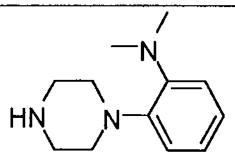
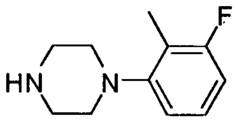
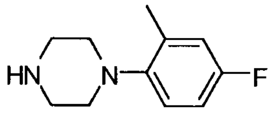
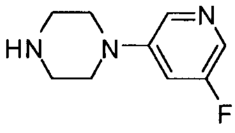
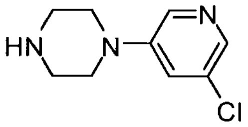
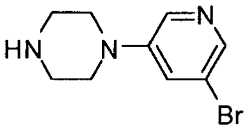
Int	Structure	Name	Mtd	SM	MW	Ms'd
235		(2S)-2-methyl-1-(3-nitrophenyl)piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3-nitro-benzene	221	222
236		1-(3,5-difluorophenyl)piperazine	A2a + A5b	Piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3,5-difluoro-benzene	198	199
237		5-methyl-3-[(2S)-2-methylpiperazin-1-yl]-1,2,4-oxadiazole	2.13 + A5a	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + BrCN	182	N.A.
238		3-methyl-5-[(2S)-2-methylpiperazin-1-yl]-1,2,4-oxadiazole	2.30	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + BrCN	182	183
239		1-methyl-6-[(2S)-2-methylpiperazin-1-yl]indazole	A2d + A5c	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 6-Bromo-1-methyl-1H-indazole	230	231

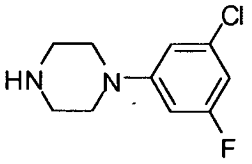
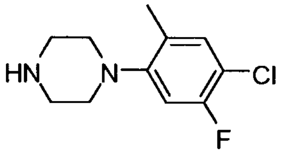
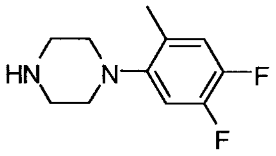
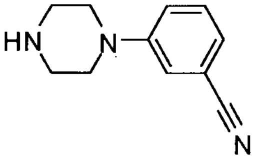
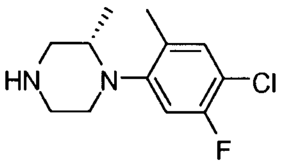
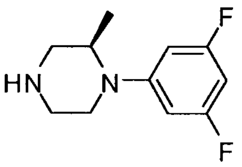
Int	Structure	Name	Mtd	SM	MW	Ms'd
240		1-(3-fluorophenyl)-2-methyl-piperazine	A2a + A5a	3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 1-Bromo-3-fluoro-benzene	194	195
241		1-(3-chlorophenyl)-2-methyl-piperazine	A2a + A5a	3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 1-Bromo-3-chloro-benzene	211	211-213
242		1-(3,5-dichloro-2-methyl-phenyl)piperazine	A7	Piperazine + 1-Bromo-3,5-dichloro-2-methyl-benzene	245	245-247
243		(2S,6R)-1-(3,5-dichlorophenyl)-2,6-dimethyl-piperazine	A1 + A2a + A5a	cis-2,6-Dimethyl-piperazine + 3,5-dichloro bromobenzene	259	259-261
244		(2S)-1-(3-bromophenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1,3-Dibromo-benzene	255	255-257
245		(2S,6S)-1-(3,5-dichlorophenyl)-2,6-dimethyl-piperazine	A2a + A5a	(3S,5S)-3,5-Dimethyl-piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3,5-dichloro-benzene	259	259-261

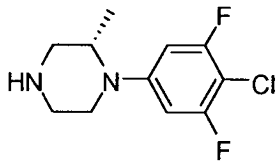
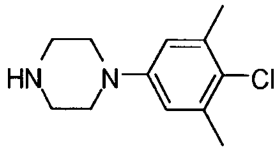
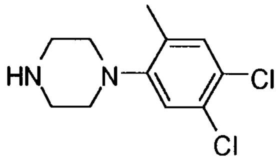
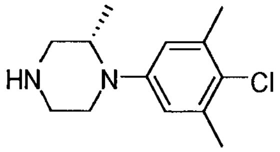
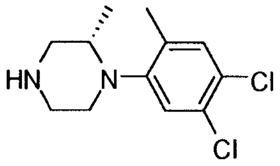
Int	Structure	Name	Mtd	SM	MW	Ms'd
246		1-(benzofuran-5-yl)piperazine	A2e + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 5-Bromo-benzofuran	202	N.A.
247		5-piperazin-1-yl-1,3-benzothiazole	A2e + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 5-Bromo-benzothiazole	219	N.A.
248		5-[(2S)-2-methylpiperazin-1-yl]pyrimidine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 5-Bromo-pyrimidine	178	N.A.
249		(2S)-1-(benzofuran-7-yl)-2-methyl-piperazine	A2f + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 7-Bromo-benzofuran	216	217
250		3-[(2S)-2-methylpiperazin-1-yl]quinoline	A2f + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-quinoline	227	228
251		1-methyl-5-[(2S)-2-methylpiperazin-1-yl]indole	A2b + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 5-Bromo-1-methyl-1H-indole	229	230

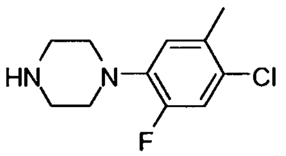
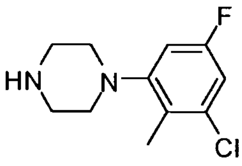
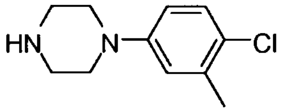
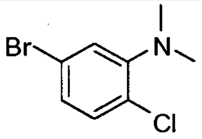
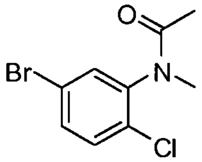
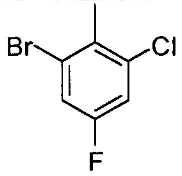
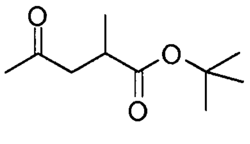
Int	Structure	Name	Mtd	SM	MW	Ms'd
252		1-methyl-6-[(2S)-2-methylpiperazin-1-yl]indole	A2d + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 6-Bromo-1-methyl-1H-indole	229	230
253		6-[(2S)-2-methylpiperazin-1-yl]-1,3-benzothiazole	A2d + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 6-Bromo-benzothiazole	233	234
254		1-methyl-4-[(2S)-2-methylpiperazin-1-yl]indole	A2d + A5c	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-Bromo-1-methyl-1H-indole	229	230
255		3-fluoro-5-[(2S)-2-methylpiperazin-1-yl]benzonitrile	A2e + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-5-fluoro-benzonitrile	219	220
256		(2S)-2-methyl-1-(1-methylpyrazol-3-yl)piperazine	A2g + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-1-methyl-1H-pyrazole	180	181
257		5-[(2S)-2-methylpiperazin-1-yl]-1H-indole	A6	5-Bromo-1H-indole	215	216

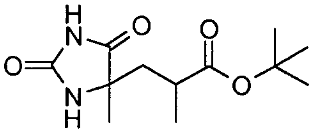
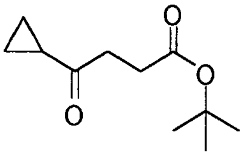
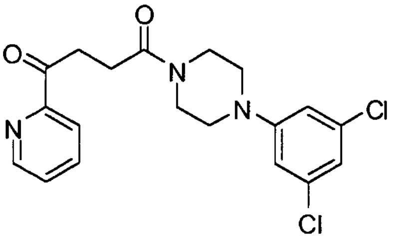
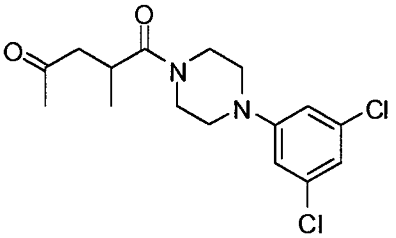
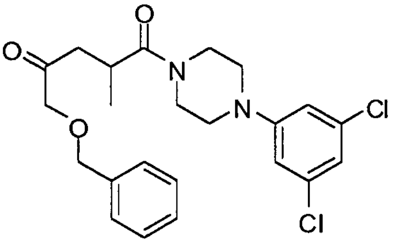
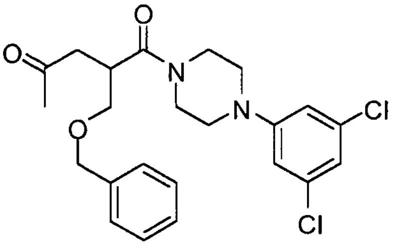
Int	Structure	Name	Mtd	SM	MW	Ms'd
258		5-[(2S)-2-methylpiperazin-1-yl]-1H-indazole	A6	5-Bromo-1H-indazole	216	N.A.
259		1-methyl-5-[(2S)-2-methylpiperazin-1-yl] indazole	A2d + A5c	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 5-Bromo-1-methyl-1H-indazole	230	231
260		4-chloro-6-[(2S)-2-methylpiperazin-1-yl] pyrimidine	A4 + A5a	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 4,6-Dichloro-pyrimidine	213	213
261		(2S)-1-(4,6-dichloro-2-pyridyl)-2-methyl-piperazine	A4 + A5a	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 2,4,6-Trichloro-pyridine	246	246
262		(2S)-1-(2,6-dichloro-4-pyridyl)-2-methyl-piperazine	A4 + A5a	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 2,4,6-Trichloro-pyridine	246	246

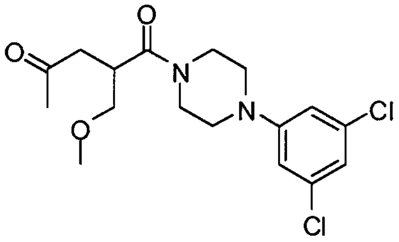
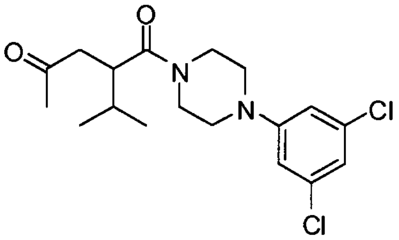
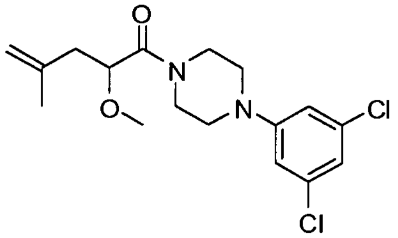
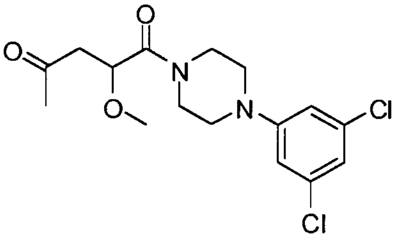
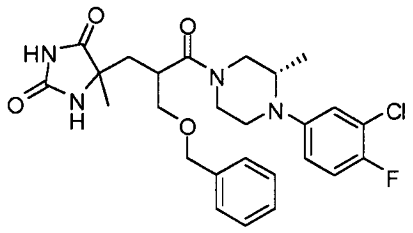
Int	Structure	Name	Mtd	SM	MW	Ms'd
263		3-chloro-5-[(2S)-2-methylpiperazin-1-yl] pyridazine	A4 + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3,5-Dichloro-pyridazine	213	213
264		2-chloro-4-[(2S)-2-methylpiperazin-1-yl] pyrimidine	A4 + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 2,4-Dichloro-pyrimidine	213	213
265		N,N-dimethyl-2-piperazin-1-yl-aniline	A7	piperazine + (2-Bromo-phenyl)-dimethyl-amine	205	N.A.
266		1-(3-fluoro-2-methyl-phenyl)piperazine	A7	piperazine + 1-Bromo-3-fluoro-2-methyl-benzene	194	195
267		1-(4-fluoro-2-methyl-phenyl)piperazine	A7	piperazine + 1-Bromo-4-fluoro-2-methyl-benzene	194	195
268		1-(5-fluoro-3-pyridyl)piperazine	A2a + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 3-Bromo-5-fluoro-pyridine	181	N.A.
269		1-(5-chloro-3-pyridyl)piperazine	A8	piperazine + 3-Chloro-5-fluoro-pyridine	198	198-200
270		1-(5-bromo-3-pyridyl)piperazine	A8	piperazine + 3-Bromo-5-fluoro-pyridine	242	242-244

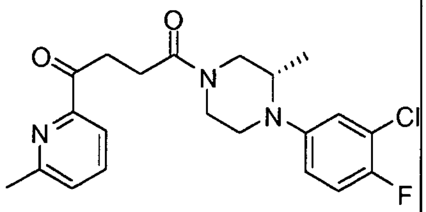
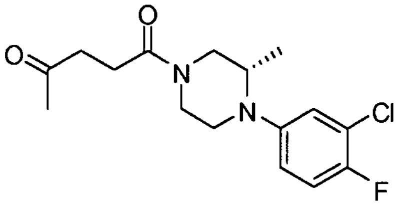
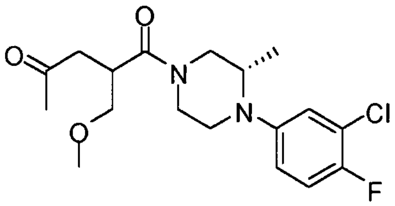
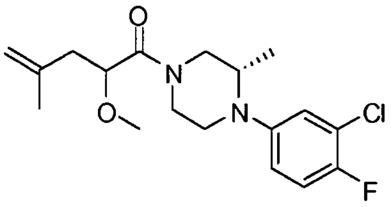
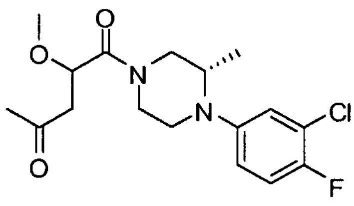
Int	Structure	Name	Mtd	SM	MW	Ms'd
271		1-(3-chloro-5-fluoro-phenyl)piperazine	A2a + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 1-Bromo-3-chloro-5-fluoro-benzene	215	215-217
272		1-(4-chloro-5-fluoro-2-methyl-phenyl)piperazine	A7	Piperazine + 1-Bromo-4-chloro-5-fluoro-2-methyl-benzene	229	229-231
273		1-(4,5-difluoro-2-methyl-phenyl)piperazine	A7	Piperazine + 1-Bromo-4,5-difluoro-2-methyl-benzene	212	213
274		3-piperazin-1-ylbenzonitrile	A8	Piperazine + 3-Fluoro-benzonitrile	187	N.A.
275		(2S)-1-(4-chloro-5-fluoro-2-methyl-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-bromo-2-methyl-4-chloro-5-fluoro benzene	243	N.A.
276		(2R)-1-(3,5-difluorophenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-bromo-3,5-difluoro benzene	212	213

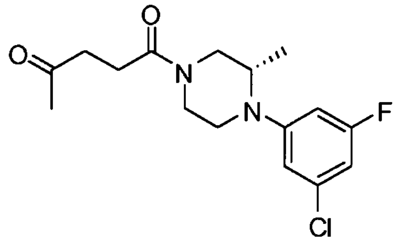
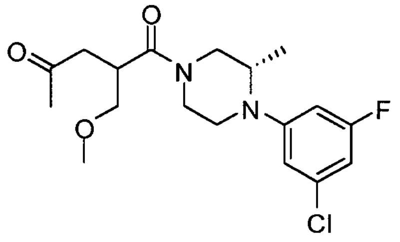
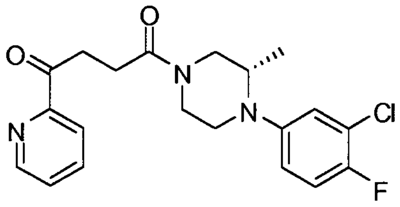
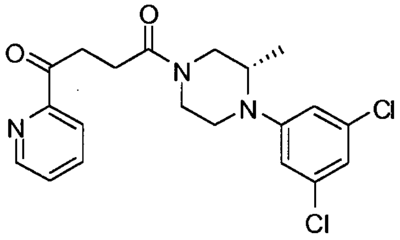
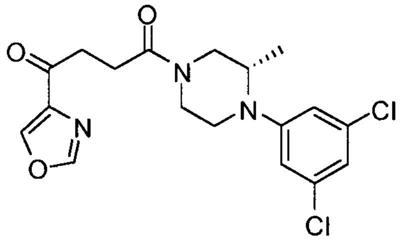
Int	Structure	Name	Mtd	SM	MW	Ms'd
277		(2S)-1-(4-chloro-3,5-difluoro-phenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carbo xylic acid tert-butyl ester + 1-bromo-3,5-difluoro-4-chlorobenzene	247	N.A.
278		1-(4-chloro-3,5-dimethyl-phenyl)piperazine	A2a + A5b	Piperazine-1-carboxylic acid tert-butyl ester + 5-bromo-2-chloro-1,4-dimethyl benzene	225	225-227
279		1-(4,5-dichloro-2-methyl-phenyl)piperazine	A2a + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 3,4-dichloro-6-bromotoluene	245	N.A
280		(2S)-1-(4-chloro-3,5-dimethyl-phenyl)-2-methyl-piperazine	A2a + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 5-bromo-2-chloro-1,3-dimethyl benzene	239	239
281		(2S)-1-(4,5-dichloro-2-methyl-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 3,4-dichloro-6-bromotoluene	259	N.A.

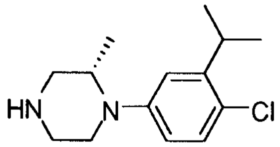
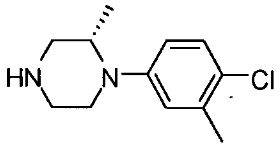
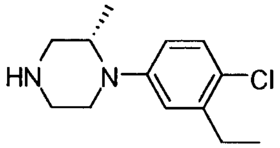
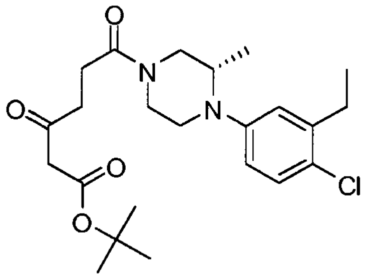
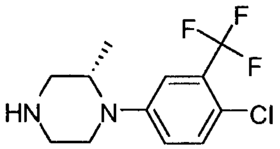
Int	Structure	Name	Mtd	SM	MW	Ms'd
282		1-(4-chloro-2-fluoro-5-methyl-phenyl) piperazine	A2a + A5a	Piperazine-1-carbo xylic acid tert-butyl ester + 1-Bromo-4-chloro-2-fluoro-5-methylbenzene	229	N.A.
283		1-(3-chloro-5-fluoro-2-methyl-phenyl)piperazine	A2a + A5c	Piperazine-1-carboxylic acid tert-butyl ester + Int 287	229	N.A.
284		1-(4-chloro-3-methyl-phenyl)piperazine	A2a + A5a	Piperazine-1-carboxylic acid tert-butyl ester + 5-bromo-2-chloro toluene	211	211-213
285		5-bromo-2-chloro-N,N-dimethyl-aniline	2.31	1-bromo-4-chloro-3-fluoro-benzene	235	234-236
286		N-(5-bromo-2-chloro-phenyl)-N-methyl-acetamide	2.32	3-bromo-6-chloroaniline	263	262-264
287		1-bromo-3-chloro-5-fluoro-2-methyl-benzene	2.33	2-chloro-4-fluorotoluene	223	N.A.
288		2-Methyl-4-oxo-pentanoic acid tert-butyl ester	C1 step ii + step iii	3-Oxo-butyric acid benzyl ester	186	N.A.

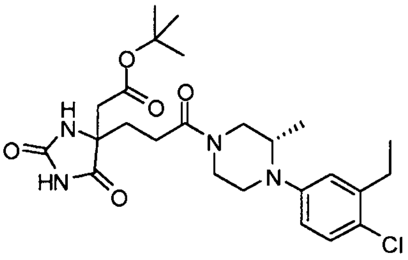
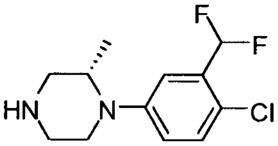
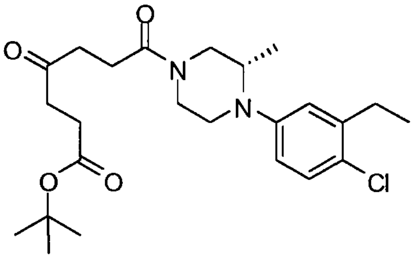
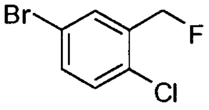
Int	Structure	Name	Mtd	SM	MW	Ms'd
289	 trans	2-Methyl-3-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-propionic acid tert-butyl ester	F	Int 288	256	N.A.
290		4-Cyclopropyl-4-oxo-butyric acid tert-butyl ester	2.34	1-cyclopropylethanone	198	N.A.
291		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-oxo-4-pyridin-2ylbutyric acid + 1-(3,5-dichlorophenyl)piperazine	392	392-394
292		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-pentane-1,4-dione	D2b	Int 001 + acetaldehyde	343	343-345
293		5-benzyloxy-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-pentane-1,4-dione	D2b	Int 001 + Benzyloxyacetaldehyde	449	449-451
294		2-(benzyloxymethyl)-1-[4-(3,5-dichlorophenyl)piperazin-1-yl]pentane-1,4-dione	H2	Int 138 + 1-(3,5-dichlorophenyl)piperazine	449	449-451

Int	Structure	Name	Mtd	SM	MW	Ms'd
295		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-(methoxymethyl)pentane-1,4-dione	E	Int 121 + Bromo-methoxy-methane	373	373-375
296		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-isopropyl-pentane-1,4-dione	E	Int 121 + 2-Chloro-propane	371	371-373
297		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methoxy-4-methyl-pent-4-en-1-one	H3	Int 154 + 1-(3,5-dichlorophenyl)piperazine	357	357-359
298		1-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methoxy-pentane-1,4-dione	D4	Int 297	359	359-361
299	 Trans	5-[2-(benzyloxymethyl)-3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione	H2	Int 135 + Int 198	517	N.A.

Int	Structure	Name	Mtd	SM	MW	Ms'd
300		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-(6-methyl-2-pyridyl)butane-1,4-dione	D2a	Int 006 + 6-Methyl-pyridine-2-carbaldehyde	404	404-406
301		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]pentane-1,4-dione	H2	levulinic acid + Int 198	327	
302		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-(methoxymethyl) pentane-1,4-dione	E	Int 301 + Bromo-methoxy-methane	371	371-373
303		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methoxy-4-methyl-pent-4-en-1-one	H3	Int 154 + Int 198	355	355-357
304		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methoxy-pentane-1,4-dione	D4	Int 303	357	N.A.

Int	Structure	Name	Mtd	SM	MW	Ms'd
305		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]pentane-1,4-dione	H2	levulinic acid + Int 206	327	327-329
306		1-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-(methoxymethyl) pentane-1,4-dione	E	Int 305 + Bromo-methoxy-methane	371	371-373
307		1-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-oxo-4-pyridin-2ylbutyric acid + Int 198	390	390-392
308		1-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-4-(2-pyridyl)butane-1,4-dione	H3	4-oxo-4-pyridin-2ylbutyric acid + Int 197	406	406-408
309		1-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-4-oxazol-4-yl-butane-1,4-dione	D2a	Int 008 + Oxazole-4-carbaldehyde	396	396-398

Int	Structure	Name	Mtd	SM	MW	Ms'd
310		(2S)-1-(4-chloro-3-isopropyl-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-bromo-3-isopropyl-4-chlorobenzene	253	253
311		(2S)-1-(4-chloro-3-methyl-phenyl)-2-methyl-piperazine	A2a + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 5-bromo-2-chloro toluene	225	225-227
312		(2S)-1-(4-chloro-3-ethyl-phenyl)-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-bromo-3-ethyl-4-chloro benzene	239	239
313		tert-butyl 6-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-3,6-dioxo-hexanoate	H2	Int 129 + Int 312	437	437-439
314		(2S)-1-[4-chloro-3-(trifluoromethyl)phenyl]-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-bromo-1-chloro-2-trifluoromethyl benzene	279	279

Int	Structure	Name	Mtd	SM	MW	Ms'd
315		tert-butyl 2-[4-[3-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]acetate	F	Int 313	507	507-509
316		(2S)-1-[4-chloro-3-(difluoromethyl)phenyl]-2-methyl-piperazine	A2a + A5a	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-bromo-1-chloro-2-(difluoromethyl)benzene (CAS 627527-07-5)	261	261-263
317		tert-butyl 7-[(3S)-4-(4-chloro-3-ethyl-phenyl)-3-methyl-piperazin-1-yl]-4,7-dioxo-heptanoate	2.36	1,6-dioxaspiro[4.4]nonane-2,7-dione + Int 313	451	451-453
318		4-bromo-1-chloro-2-(fluoromethyl)benzene	2.37	5-bromo-2-chloro-benzaldehyde	223	N.A

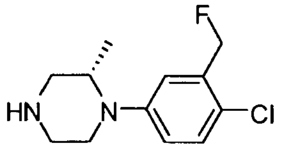
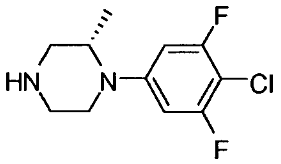
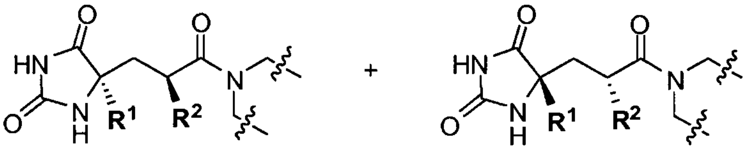
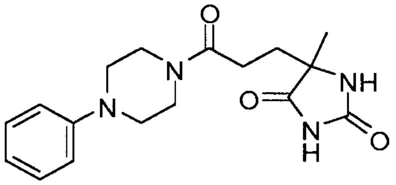
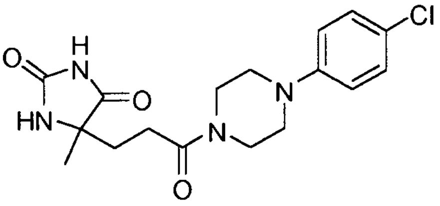
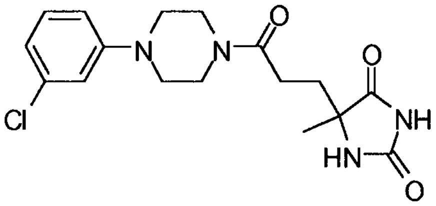
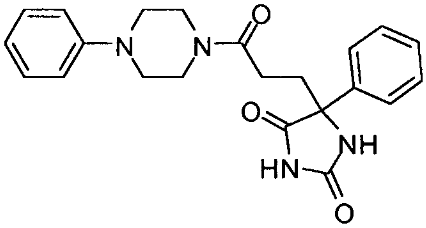
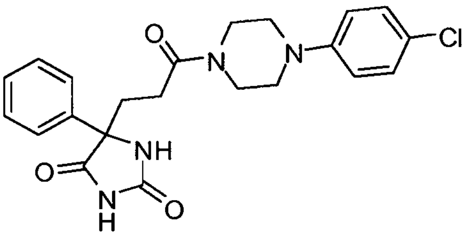
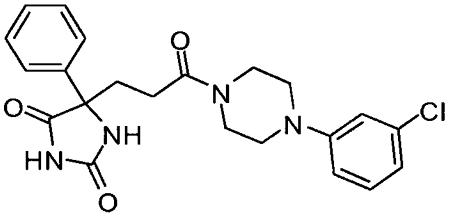
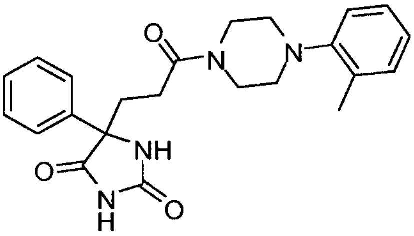
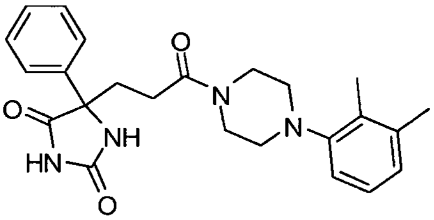
Int	Structure	Name	Mtd	SM	MW	Ms'd
319		(2S)-1-[4-chloro-3-(fluoromethyl)phenyl]-2-methyl-piperazine	A2A + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 4-bromo-1-chloro-2-(fluoromethyl)benzene Int 318	243	243
320		(2S)-1-(4-chloro-3,5-difluoro-phenyl)-2-methyl-piperazine	A2A + A5b	(S)-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester + 1-bromo-3,5-difluoro-4-chlorobenzene	247	N.A.

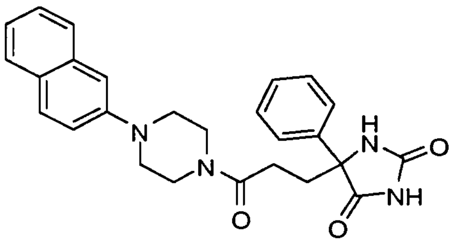
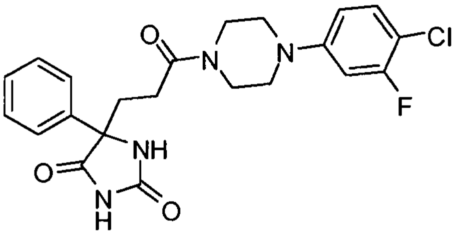
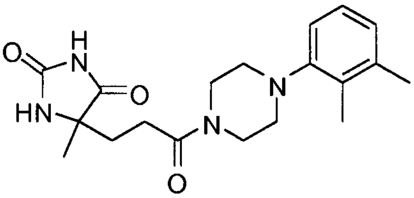
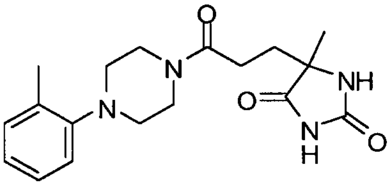
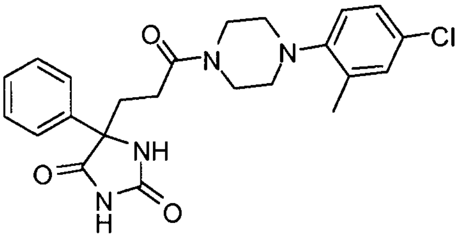
Table III.Illustrative compounds of the invention

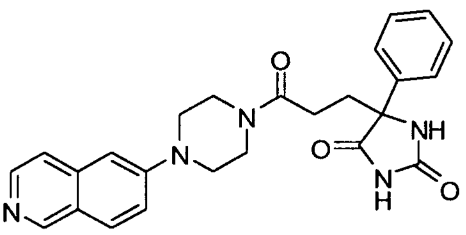
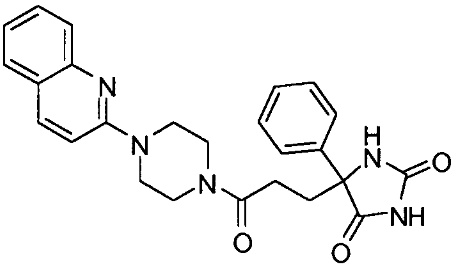
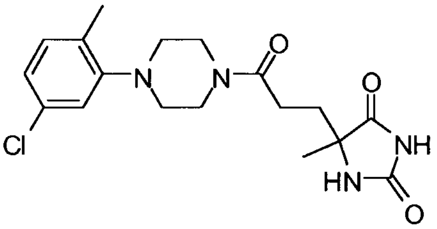
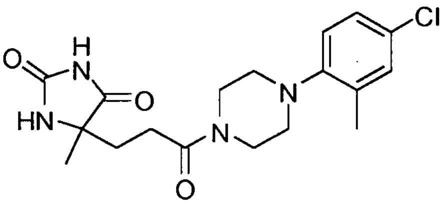
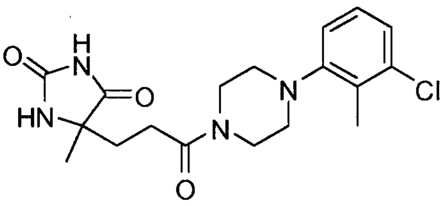
trans:

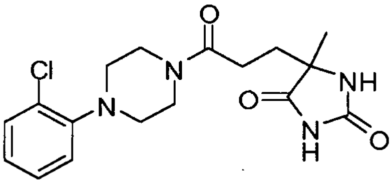
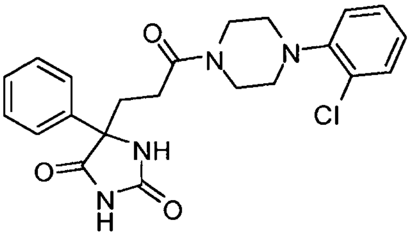
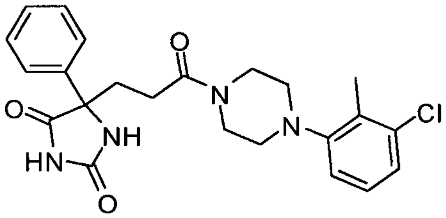
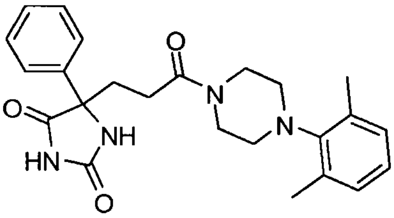
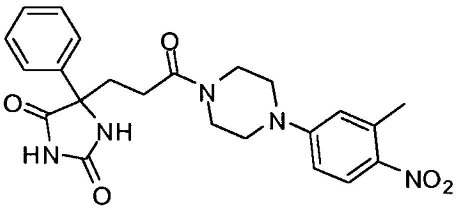
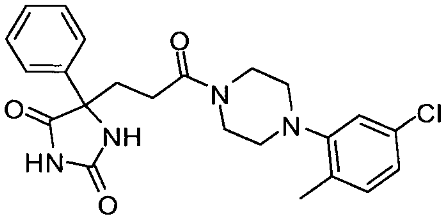


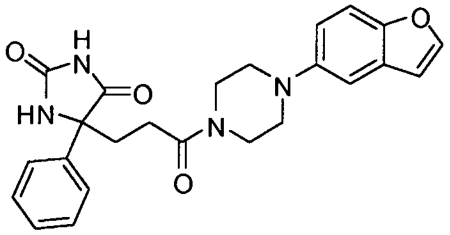
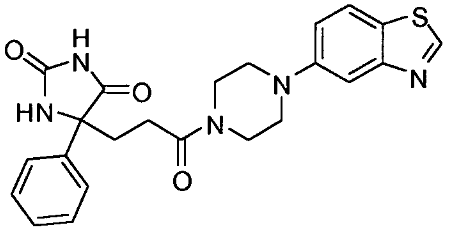
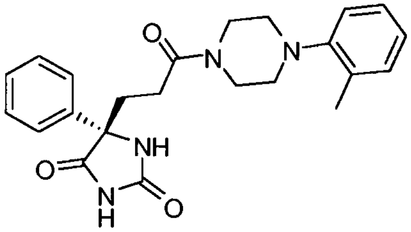
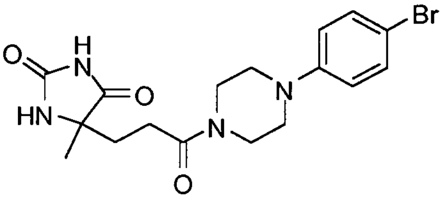
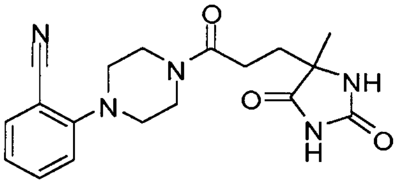
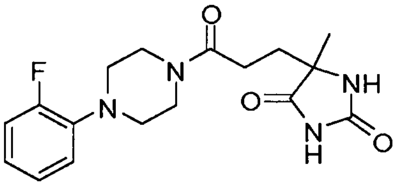
Cpd	Structure	MW	Ms'd	Mtd	SM
001		330	331	H5	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-Phenyl-piperazine
002		365	365	H5	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(4-Chloro-phenyl)-piperazine

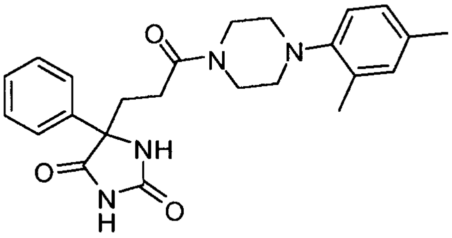
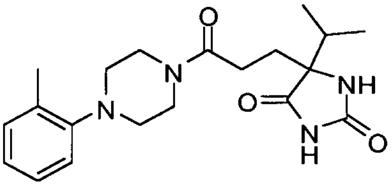
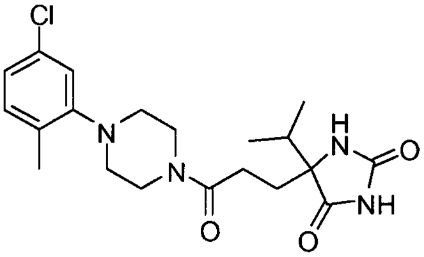
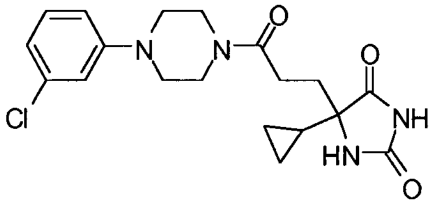
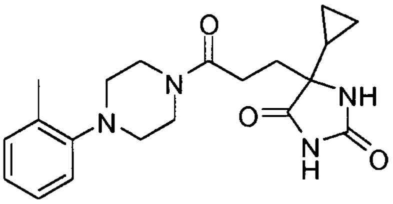
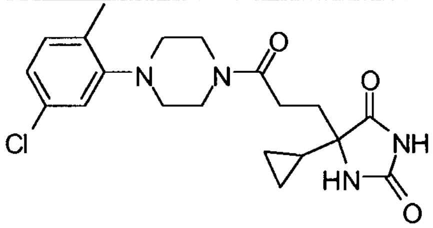
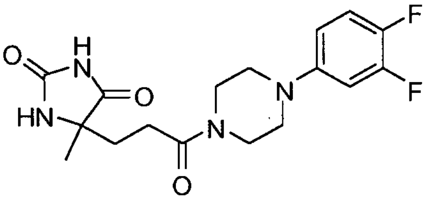
Cpd	Structure	MW	Ms'd	Mtd	SM
003		365	365 - 367	H5	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3-chlorophenyl) piperazine
004		392	393	H5	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-Phenyl-piperazine
005		427	427 - 429	H5	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(4-Chloro-phenyl)-piperazine
006		427	427 - 429	H3	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(3-chlorophenyl) piperazine
007		406	407	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(o-tolyl)piperazine dihydrochloride
008		421	421	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(2,3-Dimethylphenyl) piperazine

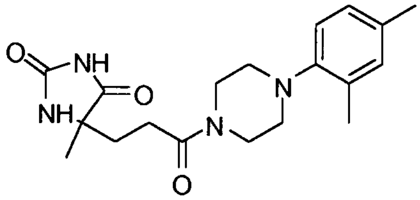
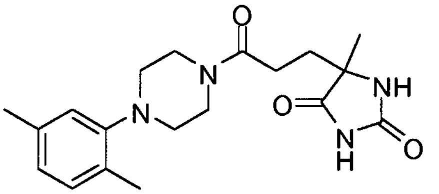
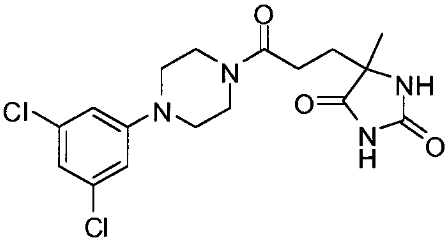
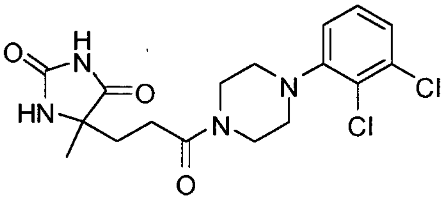
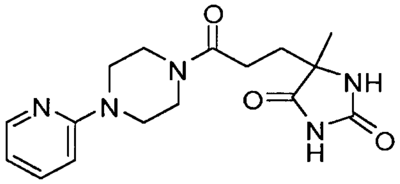
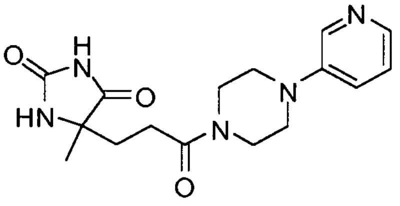
Cpd	Structure	MW	Ms'd	Mtd	SM
009		443	443	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(2-naphthyl) piperazine dihydrochloride
010		445	445	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(4-Chloro-3-fluorophenyl) piperazine
011		358	359	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2,3-Dimethyl phenyl)piperazine
012		344	345	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(o-tolyl)piperazine dihydrochloride
013		441	441 - 443	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(4-chloro-2-methylphenyl)piperazine hydrochloride

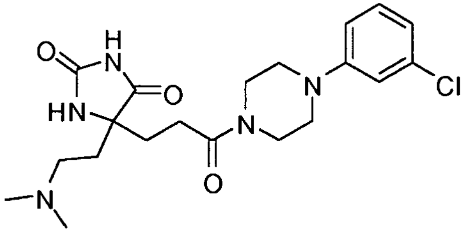
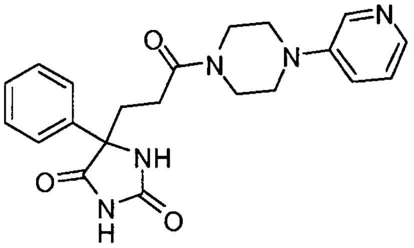
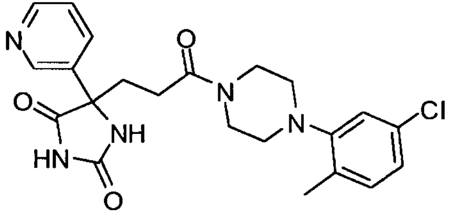
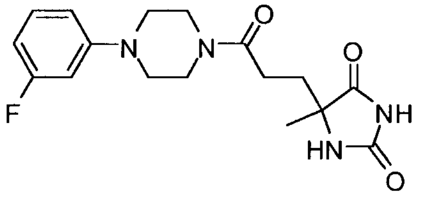
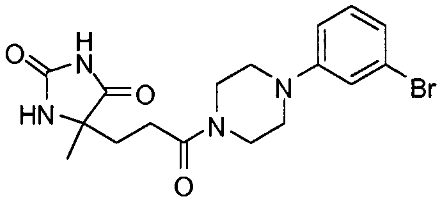
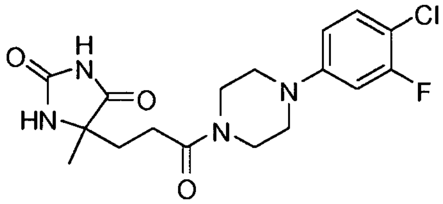
Cpd	Structure	MW	Ms'd	Mtd	SM
014		444	444	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 6-(1-piperazinyl)-isoquinoline hydrochloride
015		444	444	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 2-piperazin-1-yl-quinoline
016		379	379 - 381	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(5-chloro-2-methyl-phenyl) piperazine
017		379	379 - 381	H2	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(4-chloro-2-methyl phenyl)piperazine hydrochloride
018		379	379 - 381	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3-chloro-2-methylphenyl)-piperazine

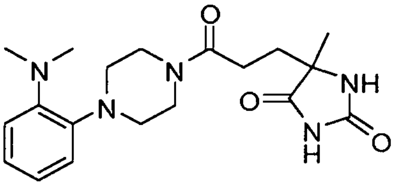
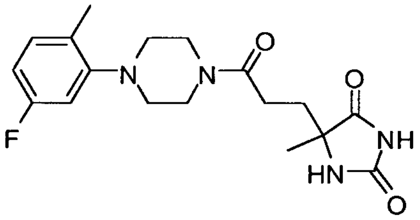
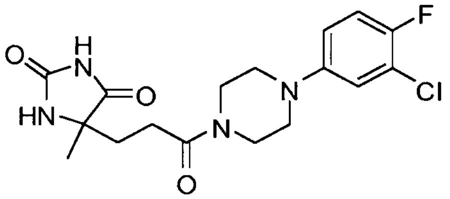
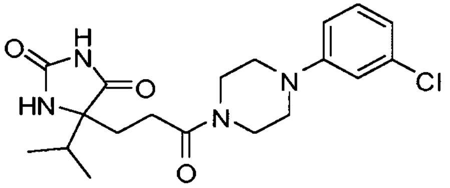
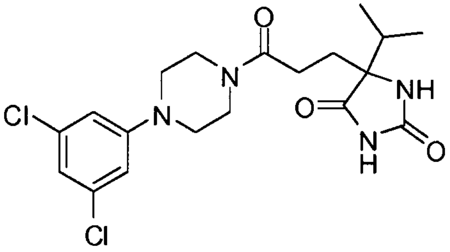
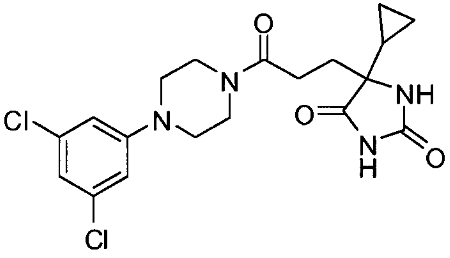
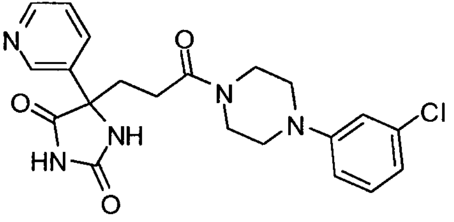
Cpd	Structure	MW	Ms'd	Mtd	SM
019		365	365	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2-chlorophenyl) piperazine hydrochloride
020		427	427	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(2-chlorophenyl) piperazine hydrochloride
021		441	441 - 443	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + Int 196
022		421	421	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(2,6-Dimethyl phenyl)piperazine
023		451	452	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(3-methyl-4-nitro phenyl)piperazine
024		441	441 - 443	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(5-chloro-2-methyl phenyl)-piperazine

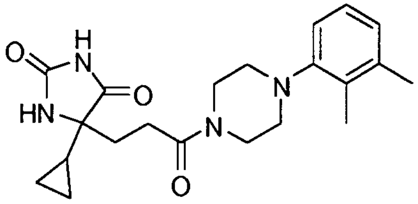
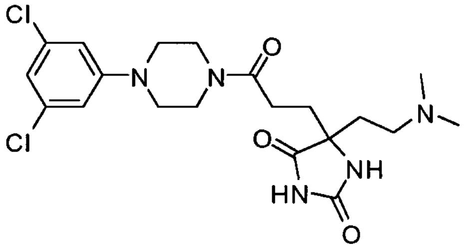
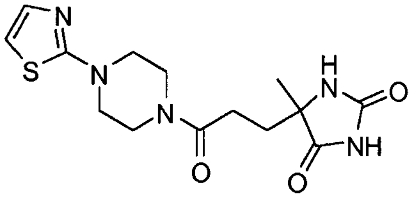
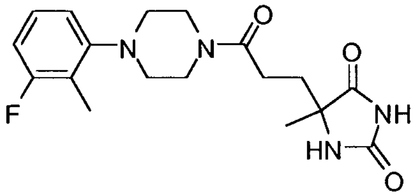
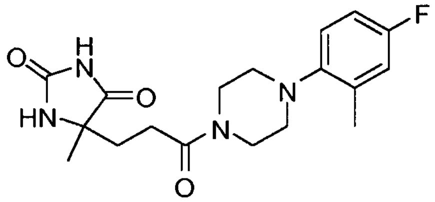
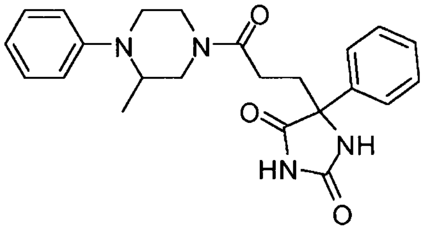
Cpd	Structure	MW	Ms'd	Mtd	SM
025		432	433	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + Int 246
026		450	450	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + Int 247
027		406	407	2.9	Cpd 007
028		409	409 - 411	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(4-bromophenyl) piperazine
029		355	356	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2-cyanophenyl) piperazine
030		348	349	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2-fluorophenyl) piperazine

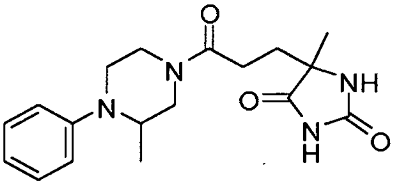
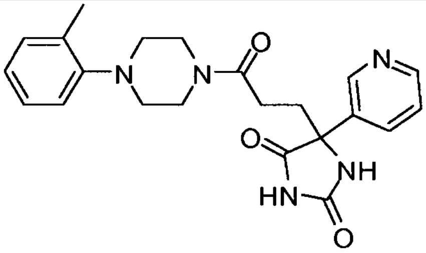
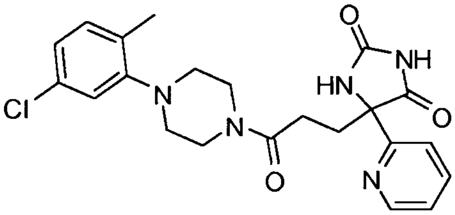
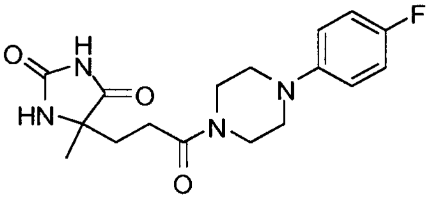
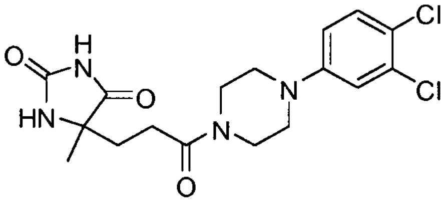
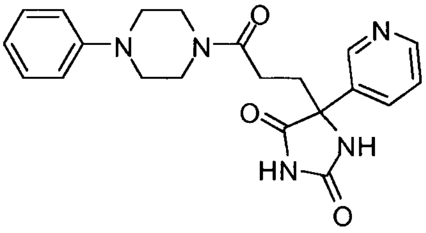
Cpd	Structure	MW	Ms'd	Mtd	SM
031		421	421	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-(2,4-Dimethylphenyl) piperazine
032		372	373	F	Int 029
033		407	407 - 409	F	Int 030
034		391	391 - 393	F	Int 031
035		370	371	F	Int 032
036		405	405 - 407	F	Int 033
037		366	367	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3,4-difluorophenyl) piperazine

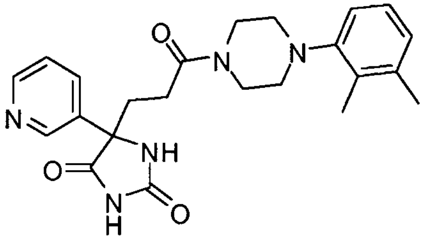
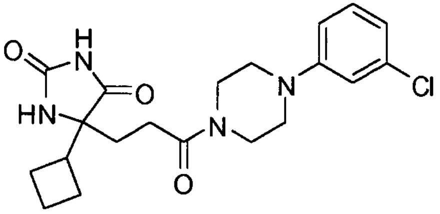
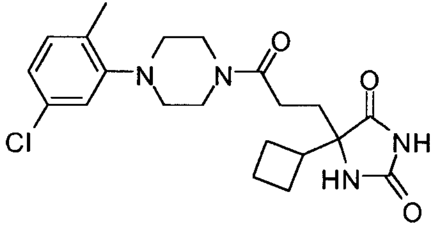
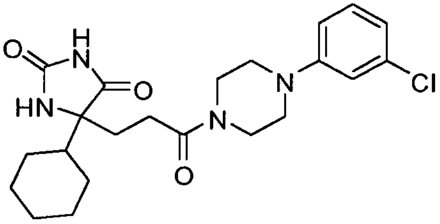
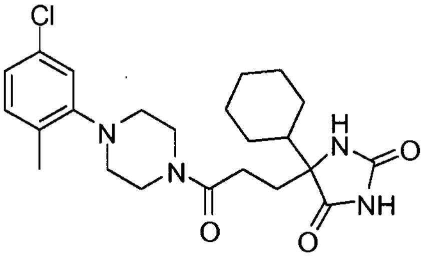
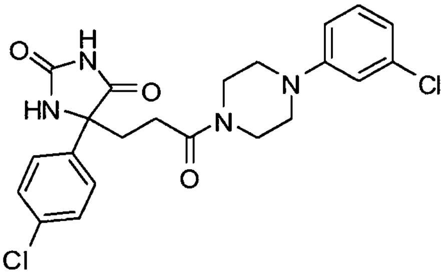
Cpd	Structure	MW	Ms'd	Mtd	SM
038		358	359	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2,4-Dimethyl phenyl)piperazine
039		358	359	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2,5-Dimethyl phenyl)piperazine
040		399	399 - 401	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3,5-dichloro phenyl)piperazine
041		399	399 - 401	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2,3-dichloro phenyl)-piperazine
042		331	332	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(2-pyridyl) piperazine
043		331	332	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-Pyridin-3-yl-piperazine

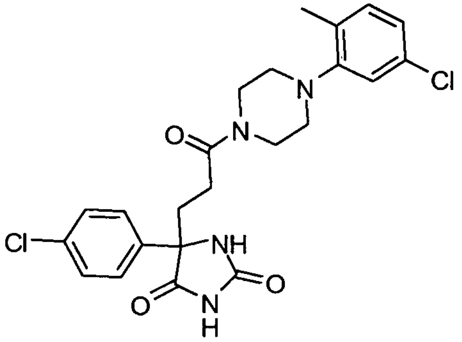
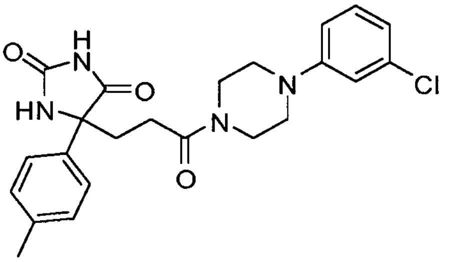
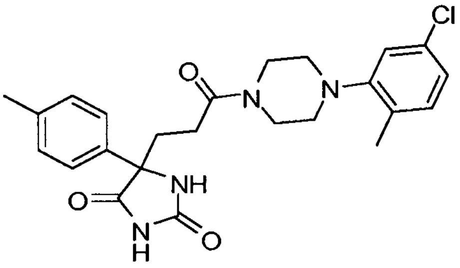
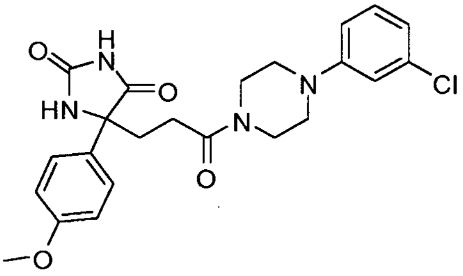
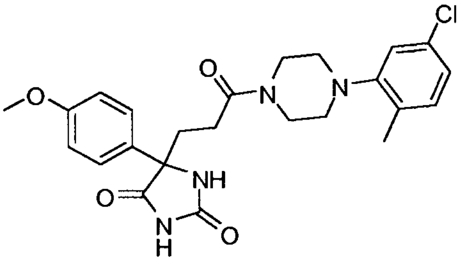
Cpd	Structure	MW	Ms'd	Mtd	SM
044		422	422 - 424	F	Int 109
045		393	394	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 1-Pyridin-3-yl-piperazine
046		442	442 - 44	F	Int 025
047		348	349	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3-fluorophenyl) piperazine
048		409	409 - 411	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3-bromophenyl) piperazine
049		383	383 - 385	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(4-Chloro-3-fluorophenyl) piperazine

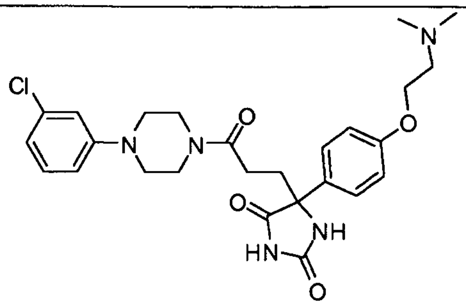
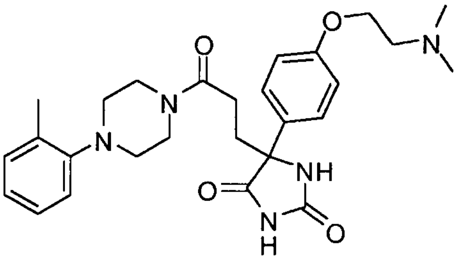
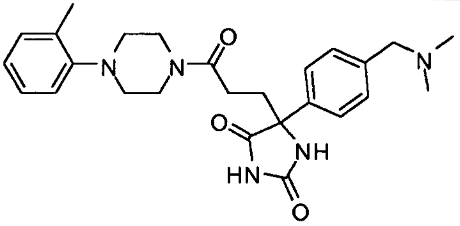
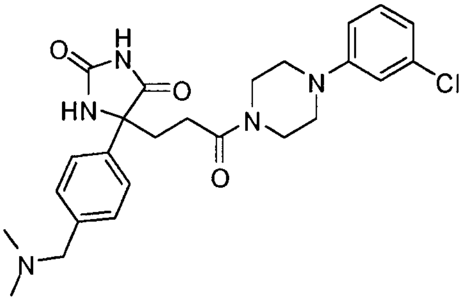
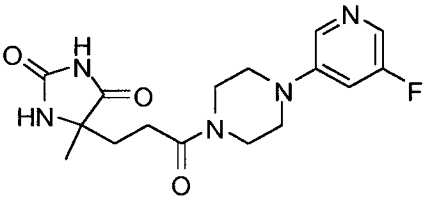
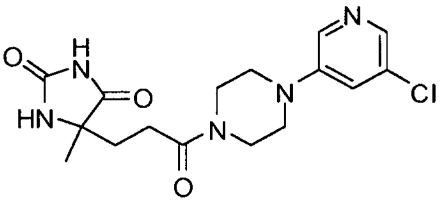
Cpd	Structure	MW	Ms'd	Mtd	SM
050		373	375	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 265
051		362	363	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 204
052		383	383 - 385	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3-Chloro-4-fluoro phenyl)piperazine dihydrochloride
053		393	393 - 395	F	Int 074
054		427	427 - 429	F	Int 075
055		425	425 - 427	F	Int 045
056		428	428 - 430	F	Int 026

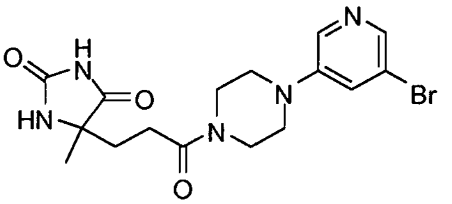
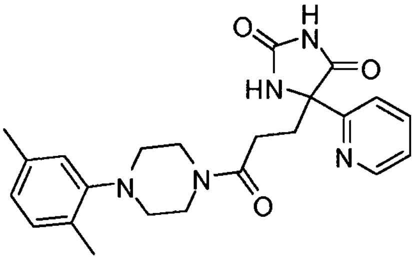
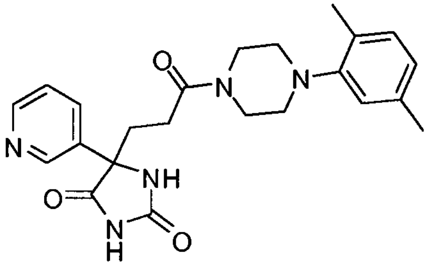
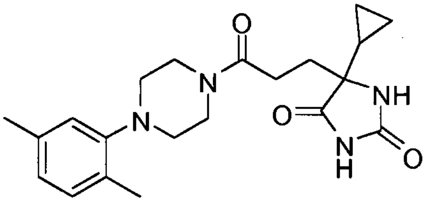
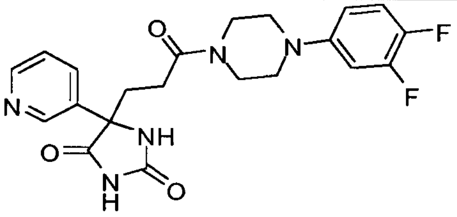
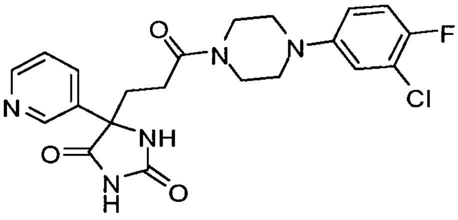
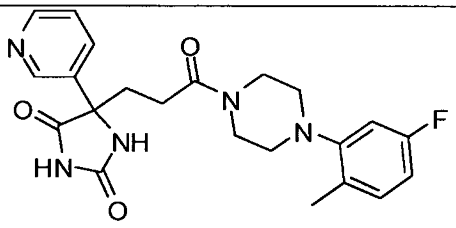
Cpd	Structure	MW	Ms'd	Mtd	SM
057		384	385	F	Int 082
058		456	456 - 458	F	Int 086
059		337	338	H3	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-Thiazol-2-yl-piperazine
060		362	363	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 266
061		362	363	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 267
062		406	407	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + 2-Methyl-1-phenyl piperazine

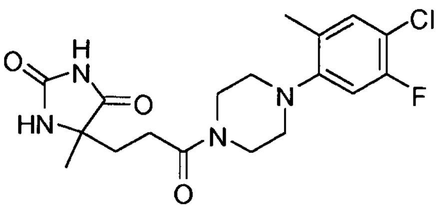
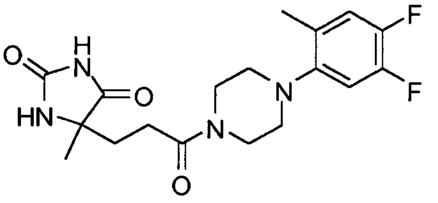
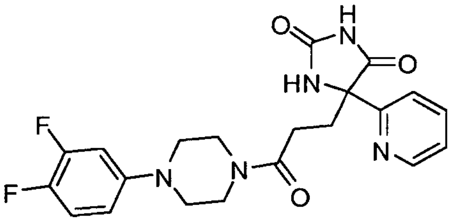
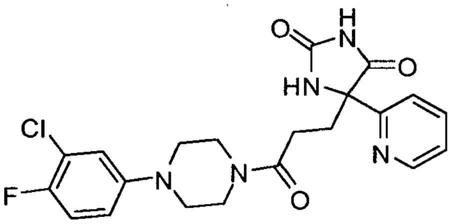
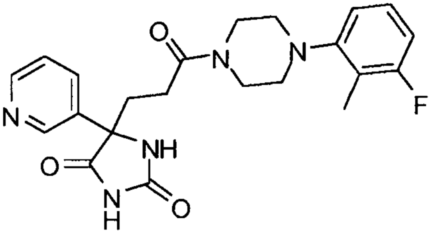
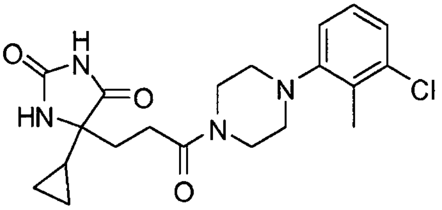
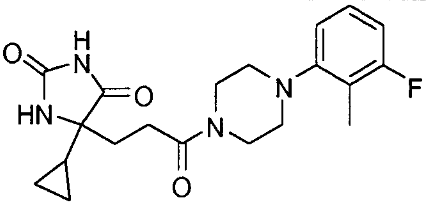
Cpd	Structure	MW	Ms'd	Mtd	SM
063		344	345	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 2-Methyl-1-phenyl piperazine
064		407	408	F	Int 027
065		442	442 - 444	F	Int 028
066		348	349	H3	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(4-fluorophenyl) piperazine
067		399	399 - 401	H3	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + 1-(3,4-dichloro phenyl)piperazine hydrochloride
068		393	394	H1	Int 132 + 1-Phenyl-piperazine

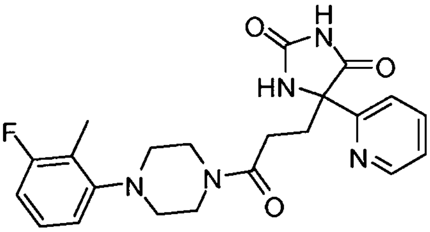
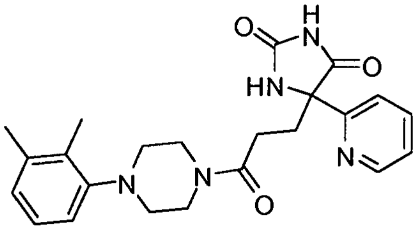
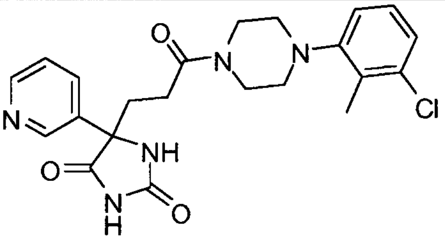
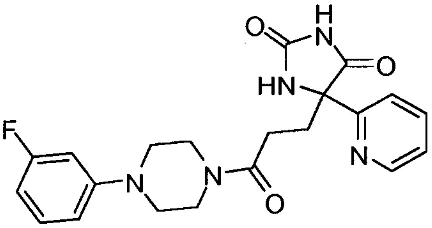
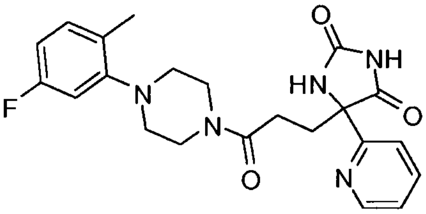
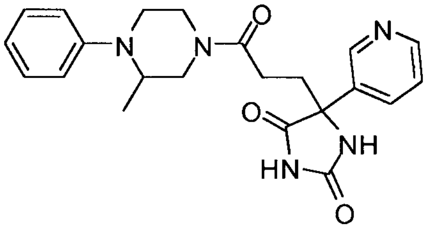
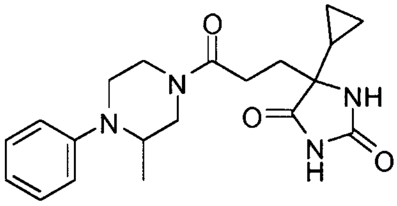
Cpd	Structure	MW	Ms'd	Mtd	SM
069		422	422	H1	Int 132 + 1-(2,3-Dimethyl-phenyl)-piperazine
070		405	405 - 407	F	Int 034
071		419	419 - 421	F	Int 035
072		433	433 - 435	F	Int 111
073		447	393	F	Int 080
074		461	461 - 463	H1	3-[4-(4-Chloro-phenyl)-2,5-dioxo-imidazolidin-4-yl] propionic acid + 1-(3-chlorophenyl) piperazine

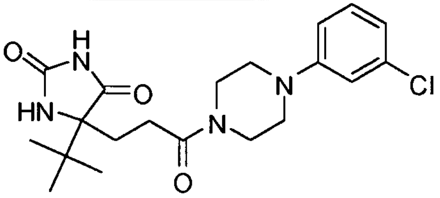
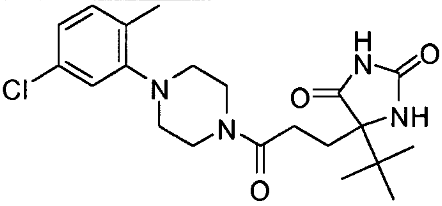
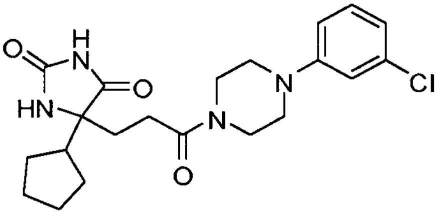
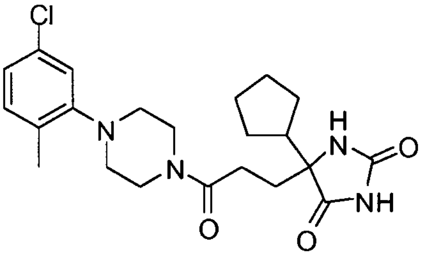
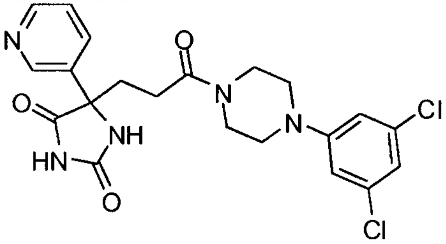
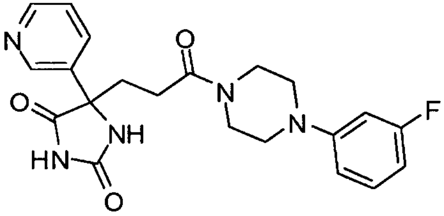
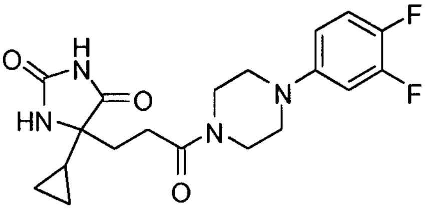
Cpd	Structure	MW	Ms'd	Mtd	SM
075		475	475 - 477	H1	3-[4-(4-Chloro-phenyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid + 1-(5-chloro-2-methylphenyl)-piperazine
076		441	441 - 443	H1	3-(2,5-Dioxo-4-p-tolyl-imidazolidin-4-yl)propionic acid + 1-(3-chloro phenyl)piperazine
077		455	455	H1	3-(2,5-Dioxo-4-p-tolyl-imidazolidin-4-yl)-propionic acid + 1-(5-chloro-2-methylphenyl)-piperazine
078		457	457	H1	3-[4-(4-Methoxy-phenyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid + 1-(3-chlorophenyl) piperazine
079		471	471 - 473	H1	3-[4-(4-Methoxy-phenyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid + 1-(5-chloro-2-methylphenyl)-piperazine

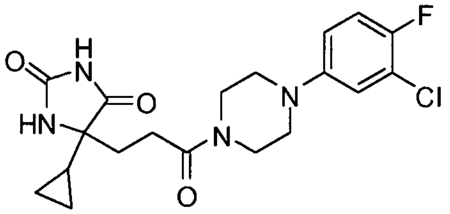
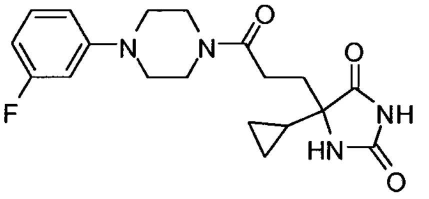
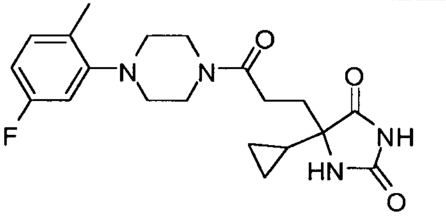
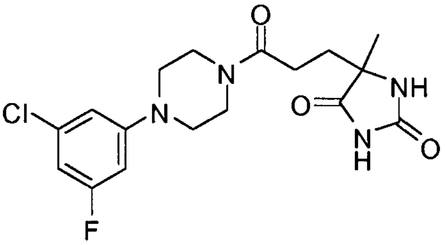
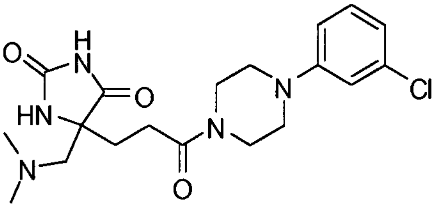
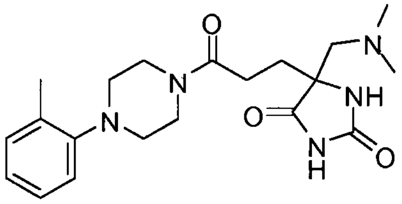
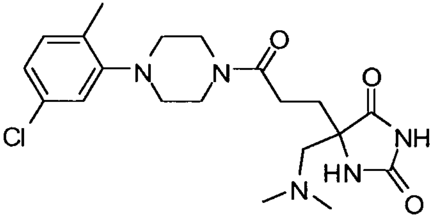
Cpd	Structure	MW	Ms'd	Mtd	SM
080		514	514	F	Int 088
081		494	494	F	Int 089
082		464	464	F	Int 087
083		484	484	F	Int 090
084		349	350	H3	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 268
085		366	366 - 368	H3	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 269

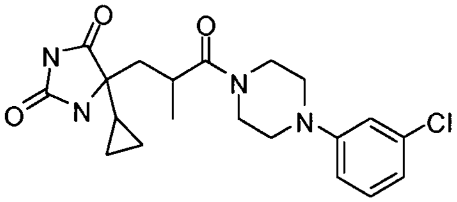
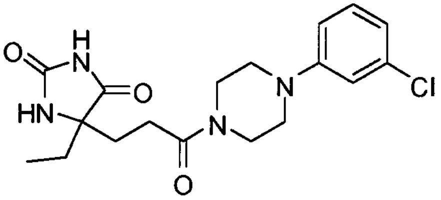
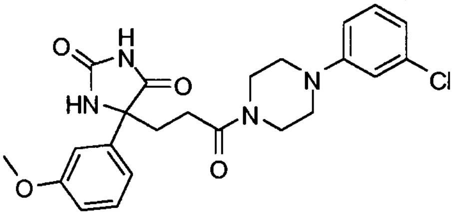
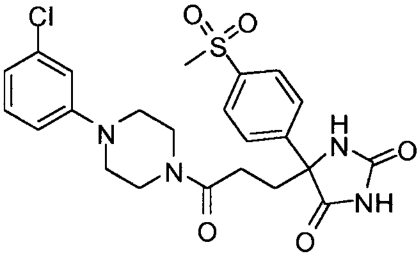
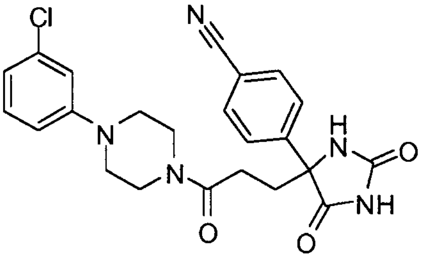
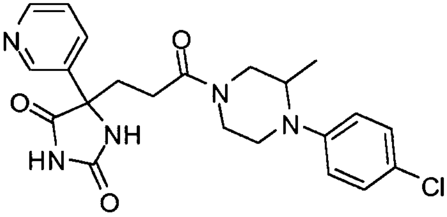
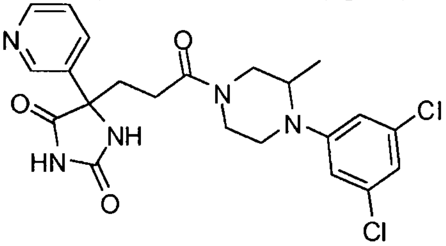
Cpd	Structure	MW	Ms'd	Mtd	SM
086		410	410 - 412	H3	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 270
087		422	422	F	Int 076
088		422	422	H3	Int 132 + 1-(2,5-Dimethylphenyl) piperazine
089		384	386	F	Int 077
090		429	430	H1	Int 132 + 1-(3,4-difluoro phenyl)piperazine
091		446	446 - 448	H1	Int 132 + 1-(3-Chloro-4-fluorophenyl)piperazine dihydrochloride
092		425	426	H1	Int 132 + Int 204

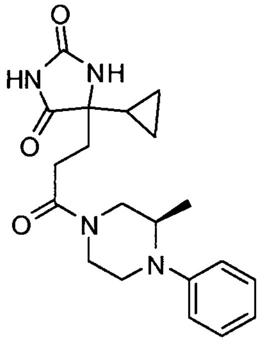
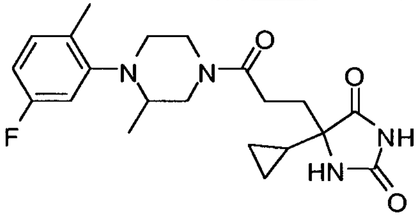
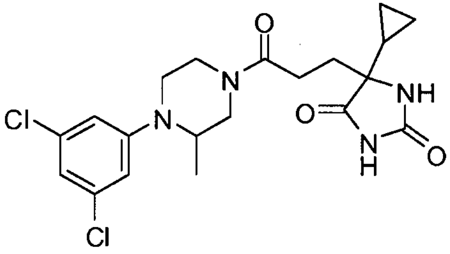
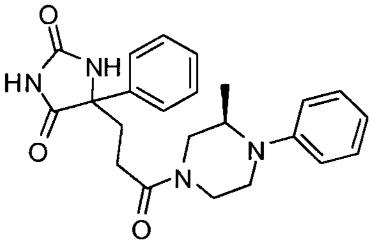
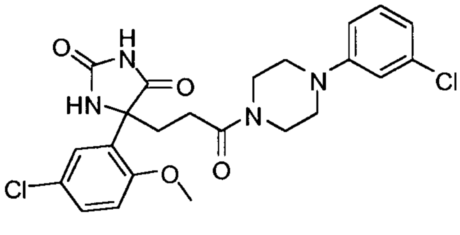
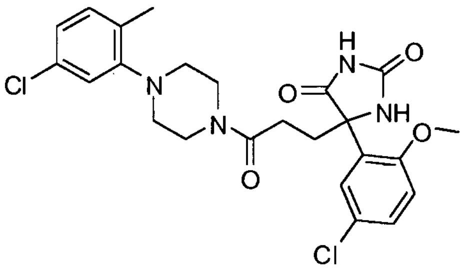
Cpd	Structure	MW	Ms'd	Mtd	SM
093		397	397	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 272
094		380	381	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 273
095		429	430	F	Int 083
096		446	446 - 448	F	Int 084
097		425	426	H3	Int 132 + 1-(3-fluoro-2-methylphenyl)-piperazine
098		405	405 - 407	F	Int 036
099		388	389	F	Int 037

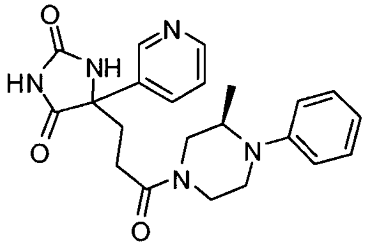
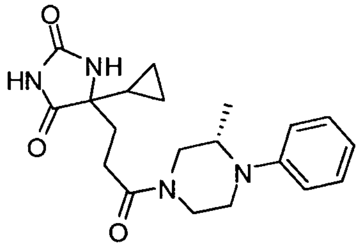
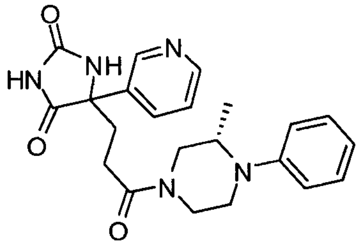
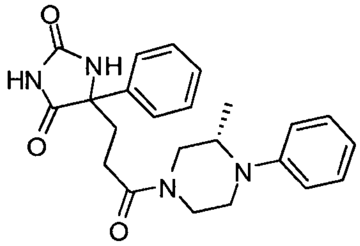
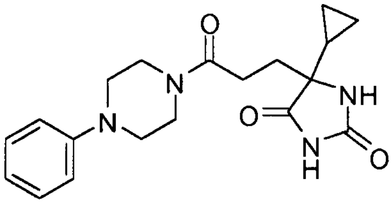
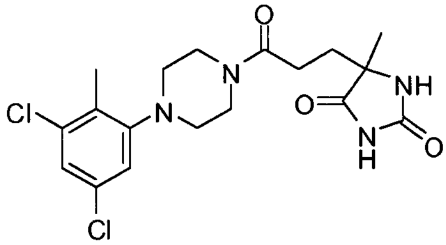
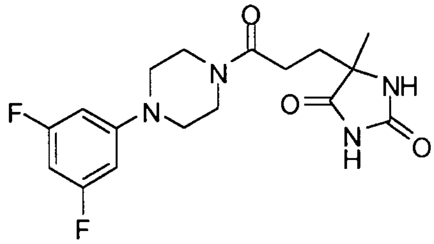
Cpd	Structure	MW	Ms'd	Mtd	SM
100		425	426	F	Int 038
101		422	422	F	Int 039
102		442	442 - 444	H3	Int 132 + 1-(3-chloro-2-methylphenyl)-piperazine
103		411	412	F	Int 112
104		425	426	F	Int 113
105		407	408	H3	Int 132 + 2-methyl-1-phenyl piperazine
106		370	371	H1	Int 162 + 2-methyl-1-phenylpiperazine

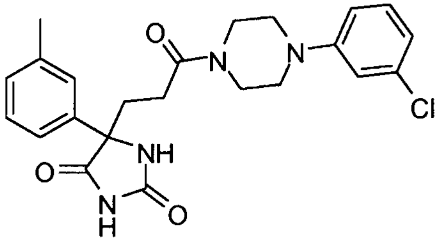
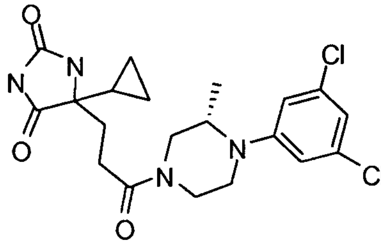
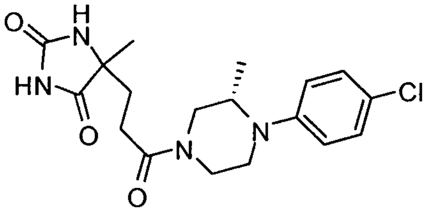
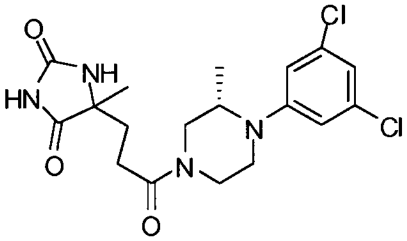
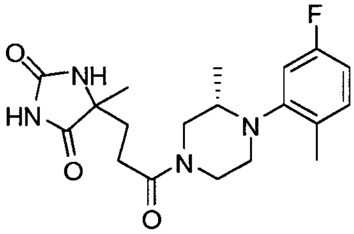
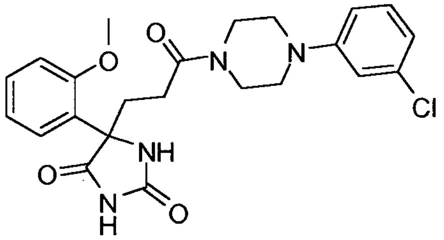
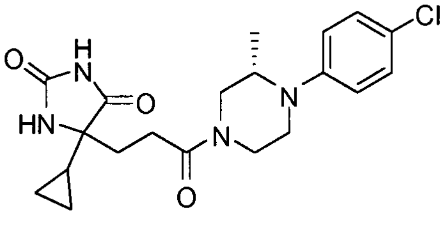
Cpd	Structure	MW	Ms'd	Mtd	SM
107		407	407	F	Int 091
108		421	421	F	Int 092
109		419	419	F	Int 093
110		433	433	F	Int 094
111		462	462 - 464	H1	Int 132 + 1-(3,5-dichloro phenyl)piperazine
112		411	412	H1	Int 132 + 1-(3-fluoro phenyl)piperazine
113		392	393	H1	Int 162 + 1-(3,4-difluoro phenyl)piperazine

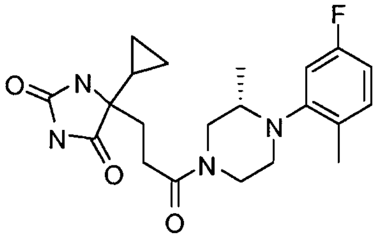
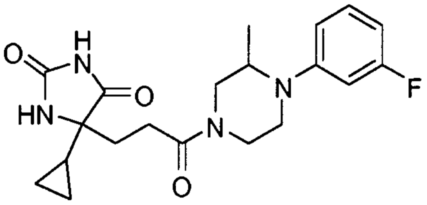
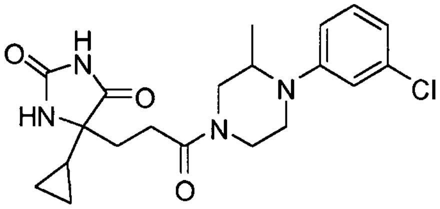
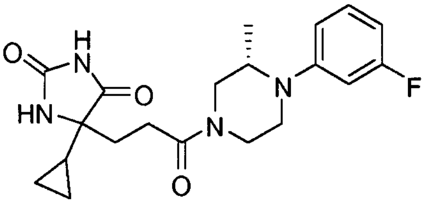
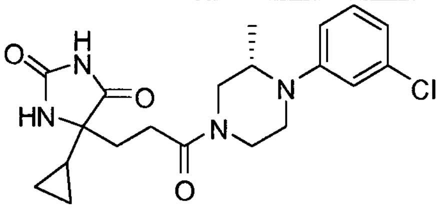
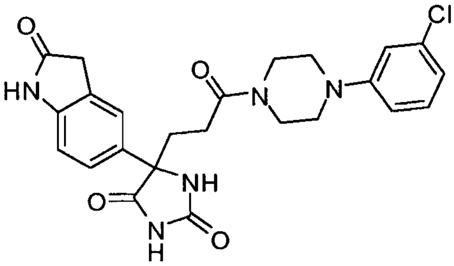
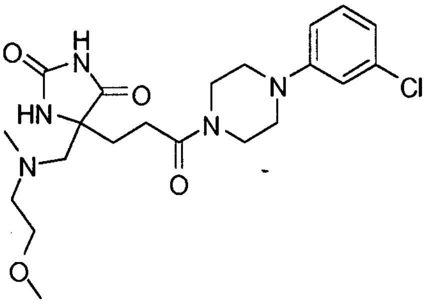
Cpd	Structure	MW	Ms'd	Mtd	SM
114		409	409 - 411	H1	Int 162 + 1-(3-Chloro-4-fluorophenyl) piperazine dihydrochloride
115		374	375	H1	Int 162 + 1-(3-fluorophenyl) piperazine
116		388	389	H1	Int 162 + Int 204
117		383	383 - 385	H3	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 271
118		408	408	F	Int 013
119		387	388	F	Int 015
120		422	422 - 424	F	Int 014

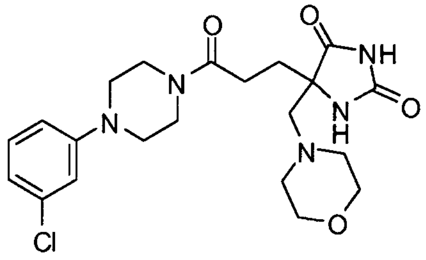
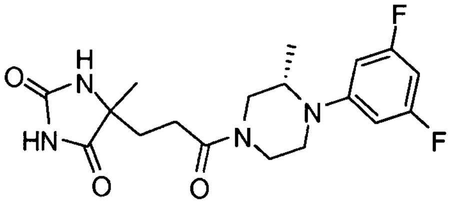
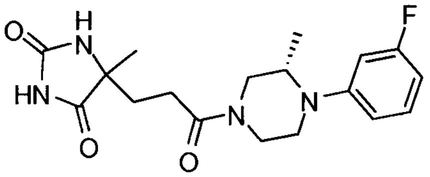
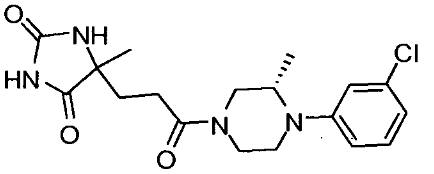
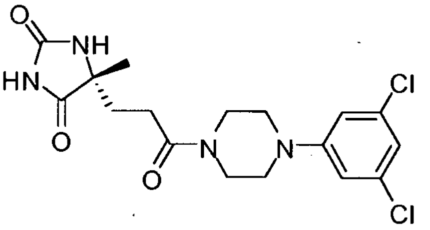
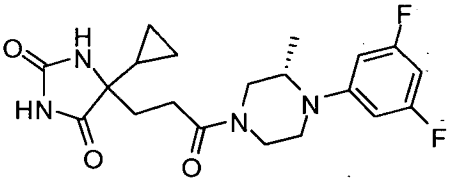
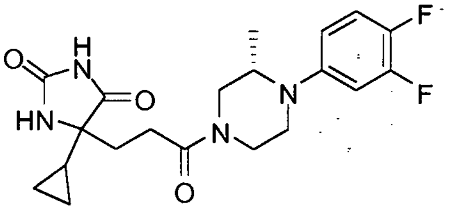
Cpd	Structure	MW	Ms'd	Mtd	SM
121	 trans	405	405 - 407	F	Int 040
122		379	379 - 381	F	Int 041
123		457	457 - 459	F	Int 042
124		505	505 - 507	F	Int 043
125		452	452 - 454	F	Int 044
126		442	442 - 444	H1	Int 132 + Int 220
127		476	476 - 478	H1	Int 132 + Int 218

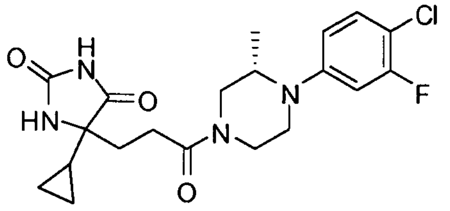
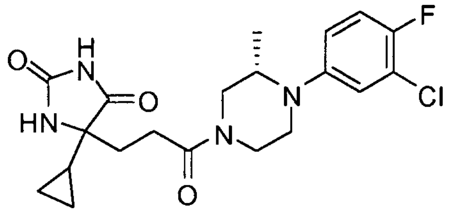
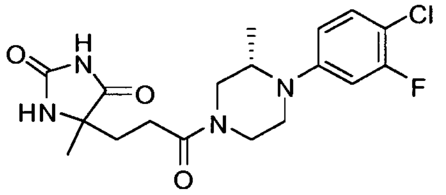
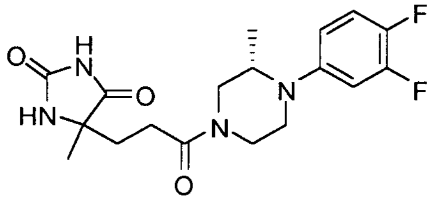
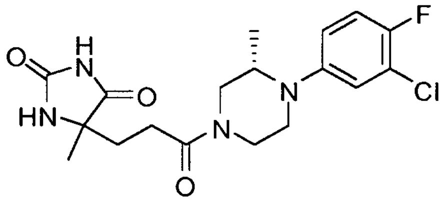
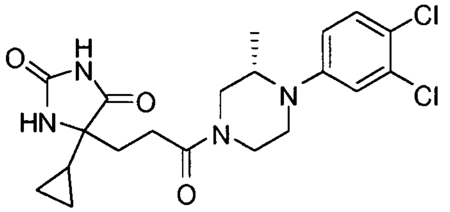
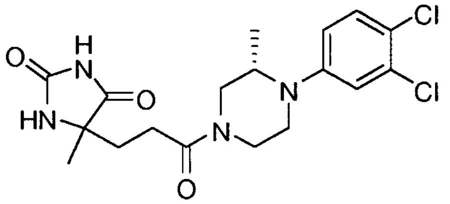
Cpd	Structure	MW	Ms'd	Mtd	SM
128		370	371	H1	Int 162 + Int 219
129		402	403	H1	Int 162 + Int 217
130		439	439 - 441	H1	Int 162 + Int 218
131		406	407	H1	3-(2,5-Dioxo-4-phenylimidazolidin-4-yl)propanoic acid + Int 219
132		491	491 - 493	H1	3-[4-(5-Chloro-2-methoxy-phenyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid + 1-(3-chlorophenyl)piperazine
133		505	505 - 507	H1	3-[4-(5-Chloro-2-methoxy-phenyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid + 1-(5-chloro-2-methylphenyl)-piperazine

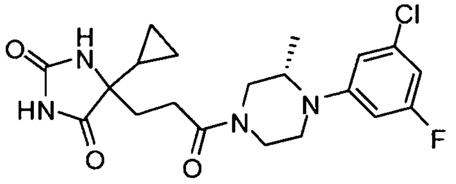
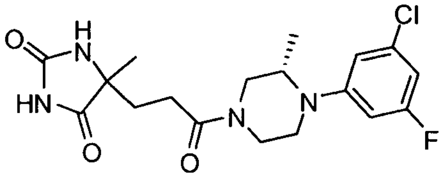
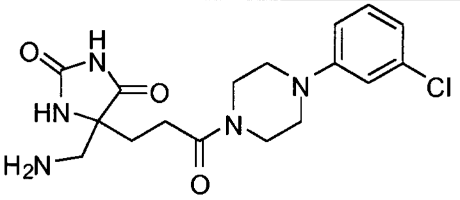
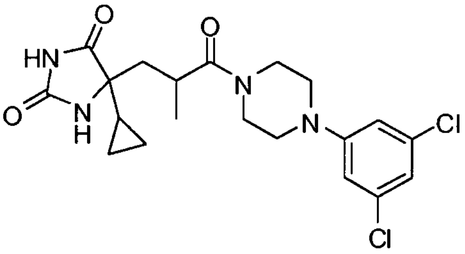
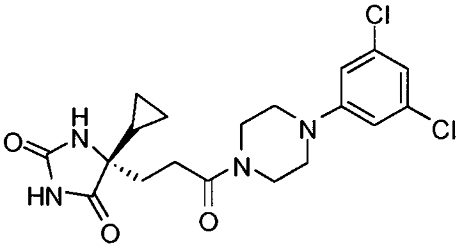
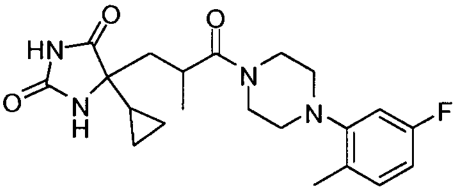
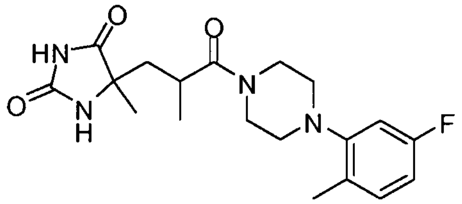
Cpd	Structure	MW	Ms'd	Mtd	SM
134		407	408	H1	Int 132 + Int 219
135		370	371	H1	Int 162 + Int 212
136		407	408	H1	Int 132 + Int 212
137		406	407	H1	3-(2,5-Dioxo-4-phenyl-imidazolidin-4-yl)propionic acid + Int 212
138		356	357	H1	Int 162 + 1-Phenyl-piperazine
139		413	413 - 415	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 242
140		366	367	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 236

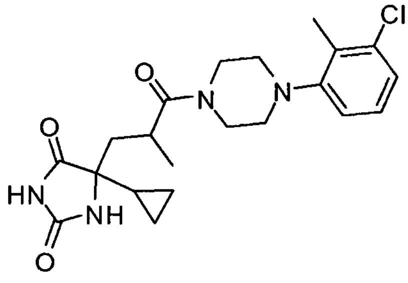
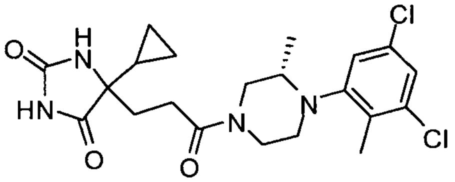
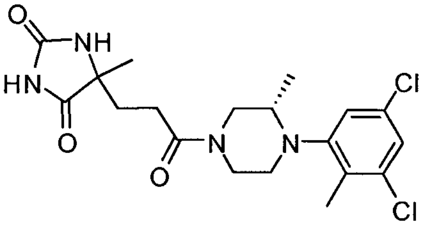
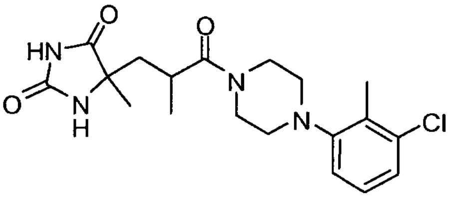
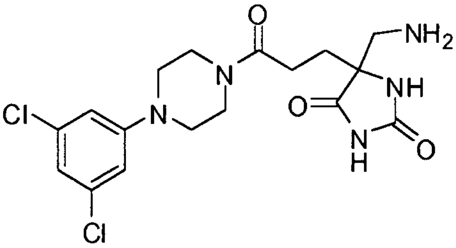
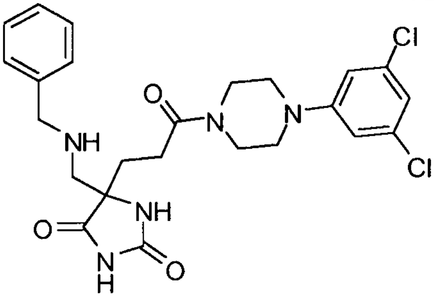
Cpd	Structure	MW	Ms'd	Mtd	SM
141		441	441	F	Int 095
142		439	439 - 441	H1	Int 162 + Int 197
143		379	379 - 381	H1	3-(4-Methyl-2,5-dioxo-imidazolidin- 4-yl)propionic acid + Int 205
144		413	413 - 415	H1	3-(4-Methyl-2,5-dioxo-imidazolidin- 4-yl)propionic acid + Int 197
145		376	377	H1	3-(4-Methyl-2,5-dioxo-imidazolidin- 4-yl)propionic acid + Int 208
146		457	457 - 459	F	Int 078
147		405	405 - 407	H1	Int 162 + Int 205

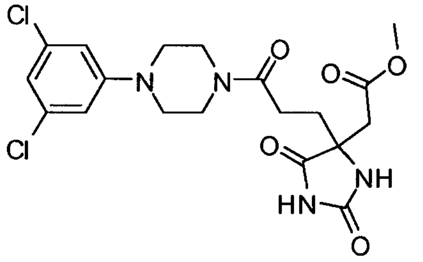
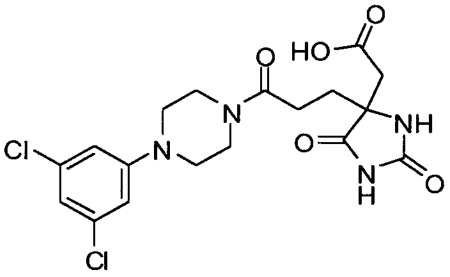
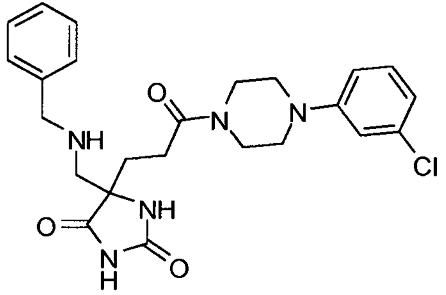
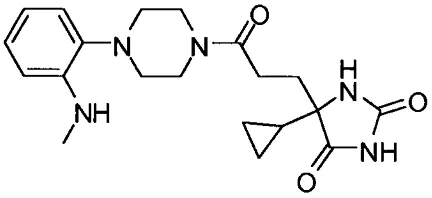
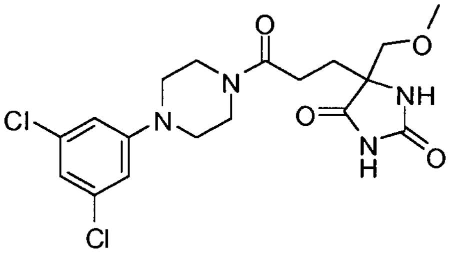
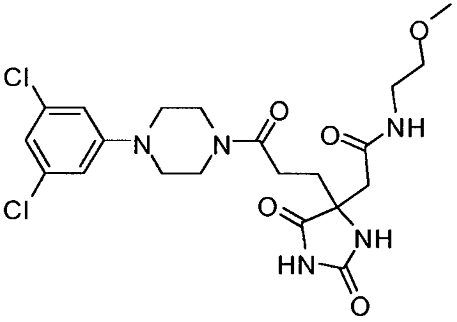
Cpd	Structure	MW	Ms'd	Mtd	SM
148		402	403	H1	Int 162 + Int 208
149		388	389	H1	Int 162 + Int 240
150		405	405 - 407	H1	Int 162 + Int 241
151		388	389	H1	Int 162 + Int 202
152		405	405 - 407	H1	Int 162 + Int 200
153		482	482	H1	3-[2,5-Dioxo-4-(2-oxo-2,3-dihydro-1H-indol-5-yl)-imidazolidin-4-yl]-propionic acid + 1-(3-chlorophenyl)piperazine
154		452	452	F	Int 016

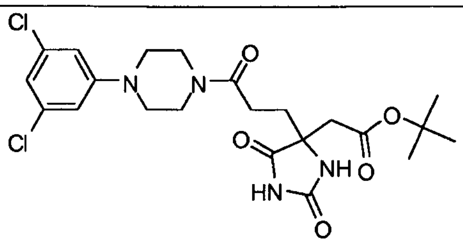
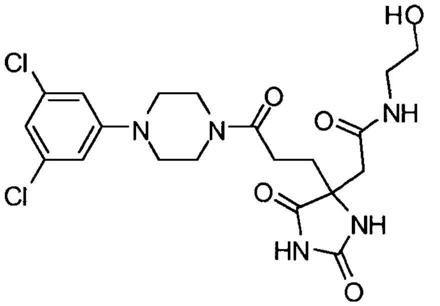
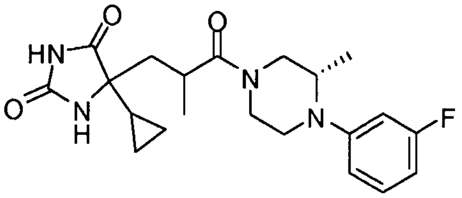
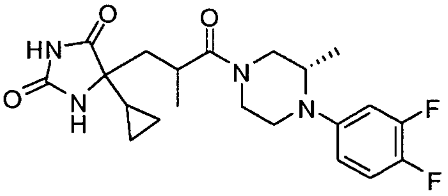
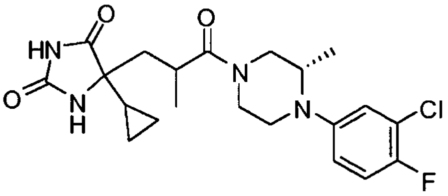
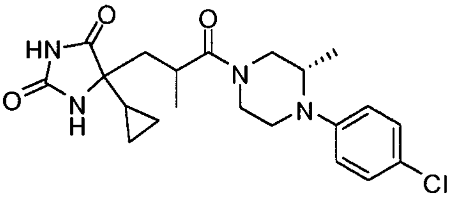
Cpd	Structure	MW	Ms'd	Mtd	SM
155		450	450	F	Int 017
156		380	381	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 207
157		362	363	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 202
158		379	379 - 381	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 200
159		399	399 - 401	H1	Int 172 + 1-(3,5-dichlorophenyl)piperazine
160		406	407	H1	Int 162 + Int 207
161		406	407	H1	Int 162 + Int 199

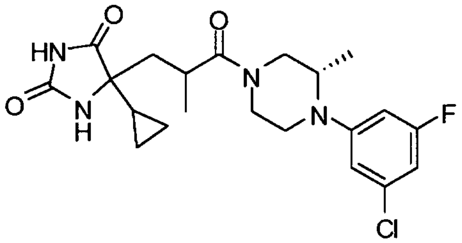
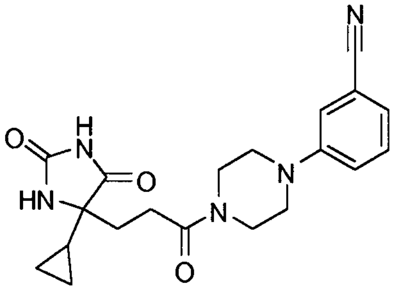
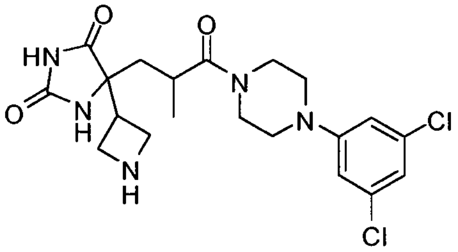
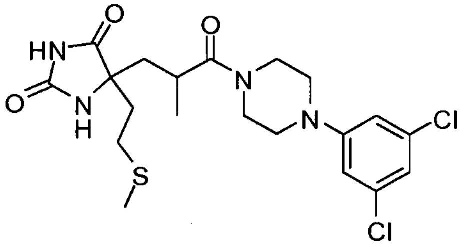
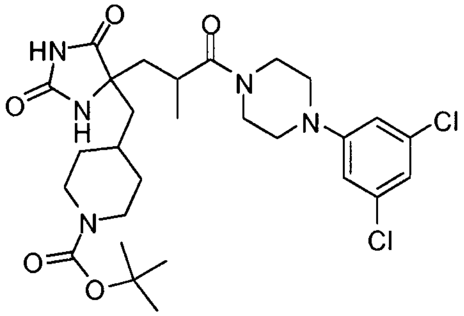
Cpd	Structure	MW	Ms'd	Mtd	SM
162		423	423 - 425	H1	Int 162 + Int 213
163		423	423 - 425	H1	Int 162 + Int 198
164		397	397	H1	3-(4-Methyl-2,5-dioxo-imidazolidin- 4-yl) propionic acid + Int 213
165		380	381	H1	3-(4-Methyl-2,5-dioxo-imidazolidin- 4-yl) propionic acid + Int 199
166		397	397	H1	3-(4-Methyl-2,5-dioxo-imidazolidin- 4-yl) propionic acid + Int 198
167		439	439 - 441	H1	Int 162 + Int 201
168		413	413 - 415	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl) propionic acid + Int 201

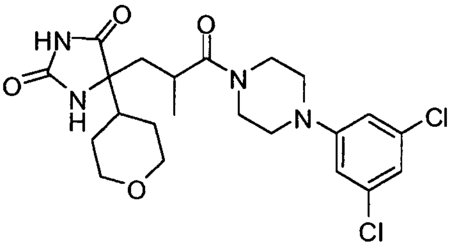
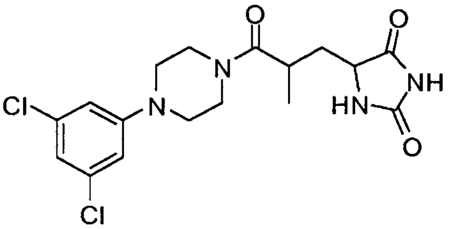
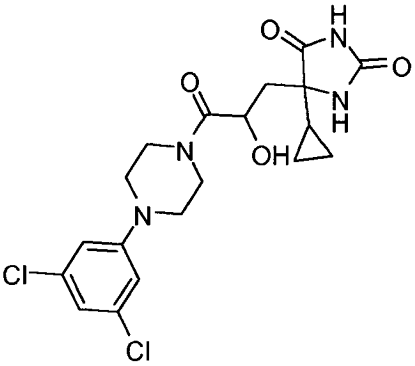
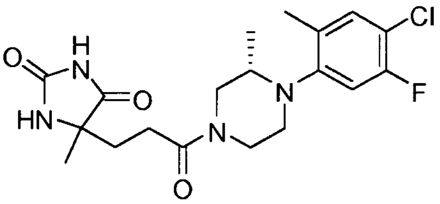
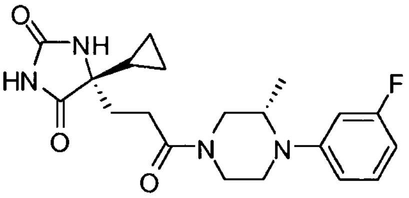
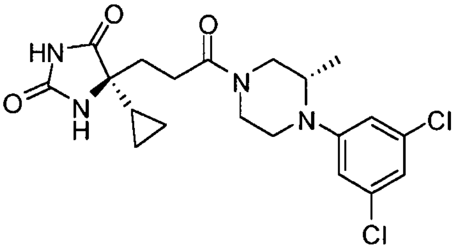
Cpd	Structure	MW	Ms'd	Mtd	SM
169		423	423 - 425	H1	Int 162 + Int 206
170		397	397 - 399	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)-propionic acid + Int 206
171		380	380	I2	Int 018
172	 trans	439	439 - 441	F	Int 046
173		425	425 - 427	H1	Int 163 + 1-(3,5-dichlorophenyl) piperazine
174	 trans	402	403 - 404	F	Int 047
175	 trans	376	377	F	Int 048

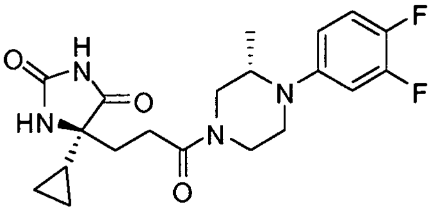
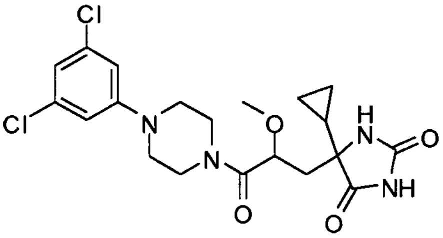
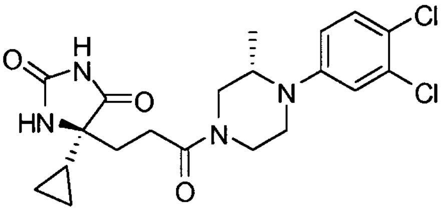
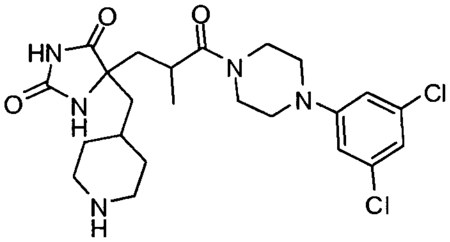
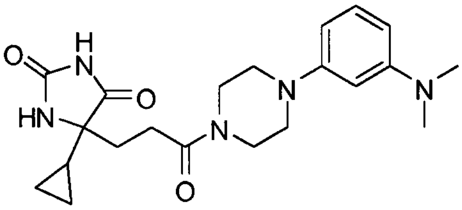
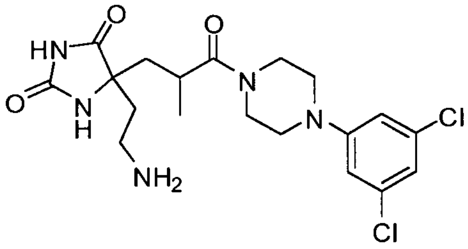
Cpd	Structure	MW	Ms'd	Mtd	SM
176	 trans	419	419 - 421	F	Int 101
177		453	453 - 455	H1	Int 162 + Int 211
178		427	427 - 429	H1	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 211
179	 trans	393	393 - 395	F	Int 102
180		414	414 - 416	I2	Int 019
181		504	504 - 506	I3	Cpd 180

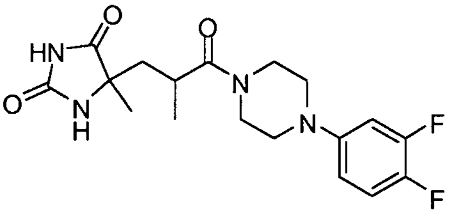
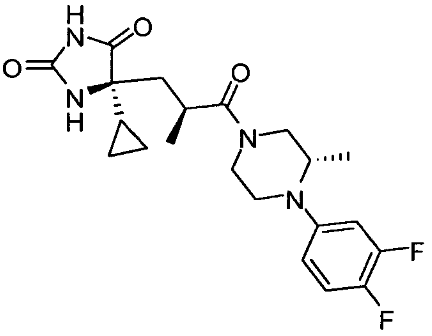
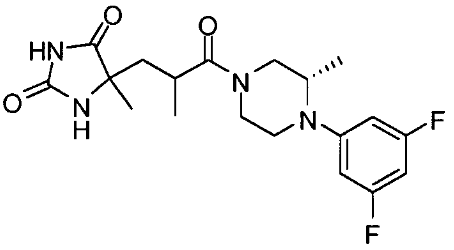
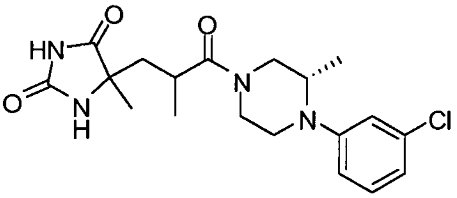
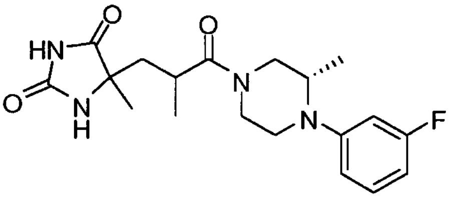
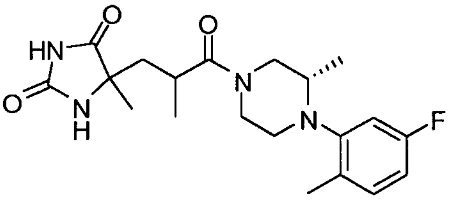
Cpd	Structure	MW	Ms'd	Mtd	SM
182		457	457 - 459	2.1	Cpd 188
183		443	443 - 445	2.1	Cpd 188
184		470	470	I3	Cpd 171
185		385	386	H1	Int 162 + N-methyl-2-piperazin-1-ylaniline
186		429	429 - 431	F	Int 020
187		500	500 - 502	H1	Cpd 183 + 2-Methoxy-ethylamine

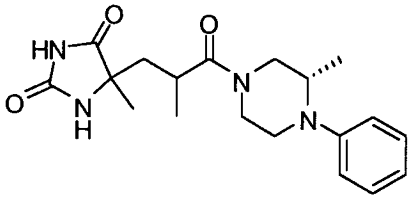
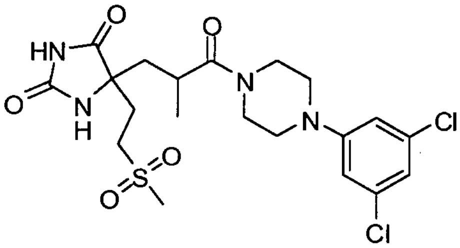
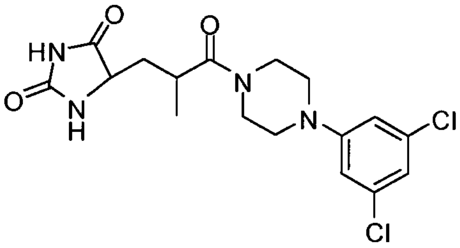
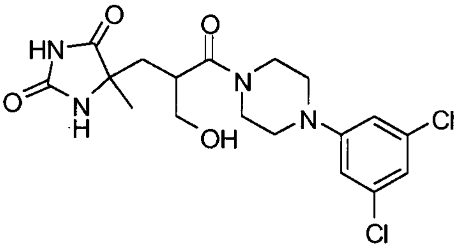
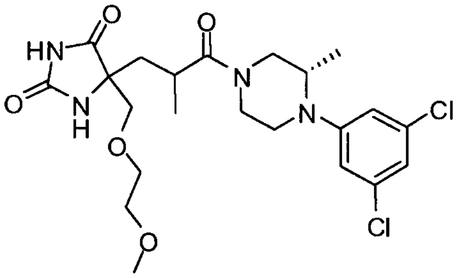
Cpd	Structure	MW	Ms'd	Mtd	SM
188		499	499 - 501	2.2	succininc anhydride + 1-(3,5-dichloro phenyl)piperazine
189		486	486 - 488	2.3	Cpd 182 + 2-Amino-ethanol
190	 trans	402	403	F	Int 049
191	 trans	420	421	H2	Int 164 + Int 199
192	 trans	437	437 - 439	F	Int 050
193	 trans	419	419 - 421	F	Int 051

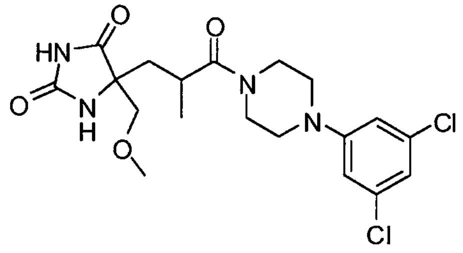
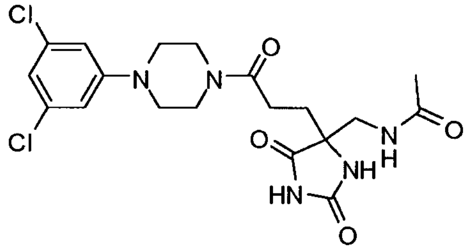
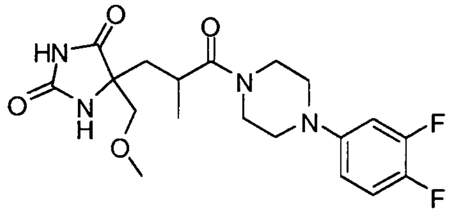
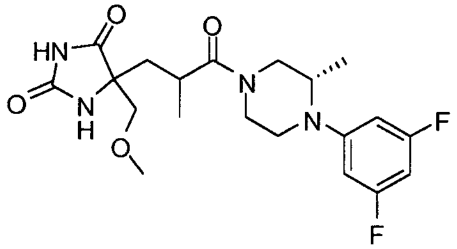
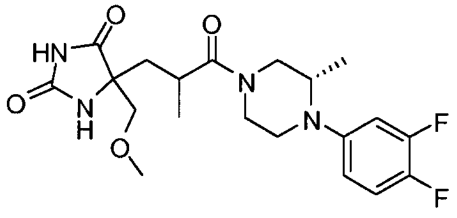
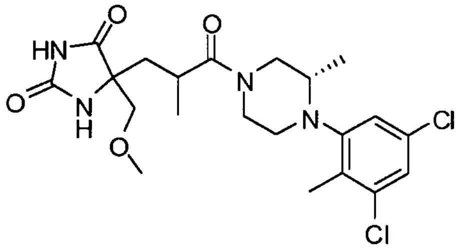
Cpd	Structure	MW	Ms'd	Mtd	SM
194	 trans	437	437 - 439	F	Int 052
195		381	382	H1	Int 162 + Int 274
196	 trans	454	454 - 456	I2	Int 096
197	 trans	473	473 - 475	F	Int 098
198	 trans	597	596 - 598	F	Int 099

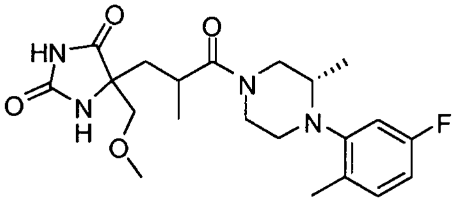
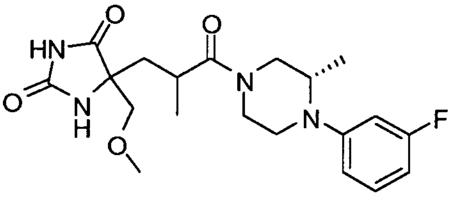
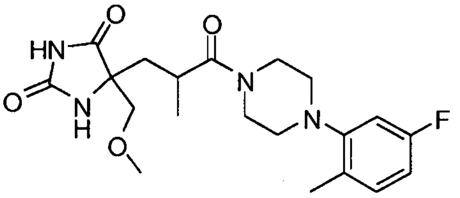
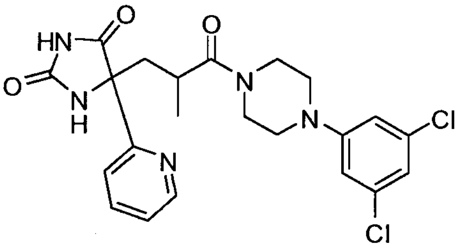
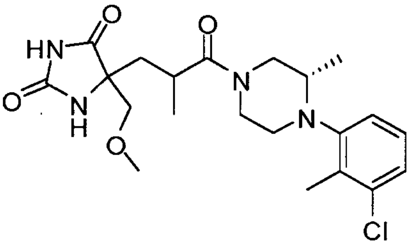
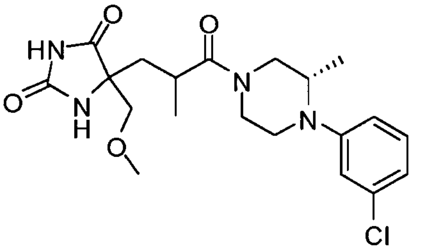
Cpd	Structure	MW	Ms'd	Mtd	SM
199	 trans	483	483 - 485	F	Int 097
200		399	399 - 401	F	Int 055
201		441	441 - 443	F	Int 053
202		411	411	H2	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 275
203		388	389	H2	Int 163 + Int 202
204		439	439 - 441	H3	Int 163 + Int 197

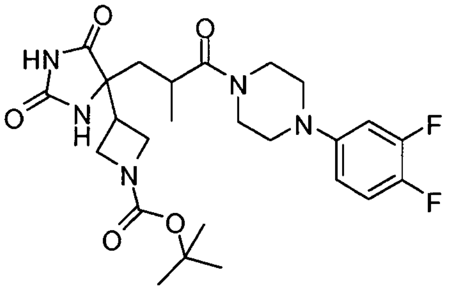
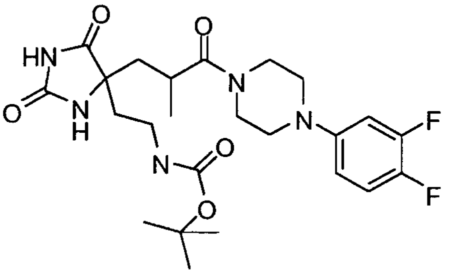
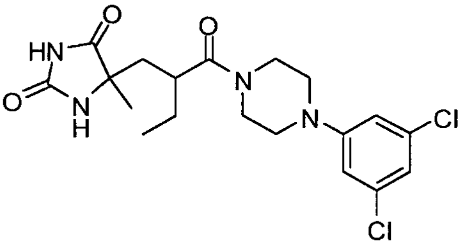
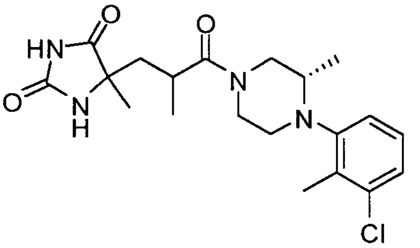
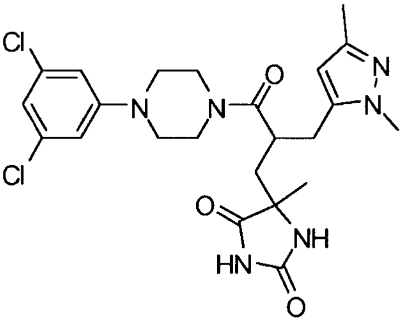
Cpd	Structure	MW	Ms'd	Mtd	SM
205		406	407	H2	Int 163 + Int 199
206		455	455 - 457	F	Int 056
207		439	439 - 441	H2	Int 163 + (S)-1-(3,4-Dichloro-phenyl)-2-methyl-piperazine
208	 trans	496	796 - 798	I2	Cpd 198
209		399	400	H1	Int 162 + N,N-dimethyl-3-piperazine-1-yl aniline trihydrochloride
210	 trans	442	442 - 444	I2	Int 100

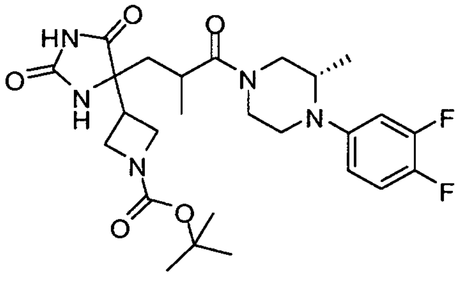
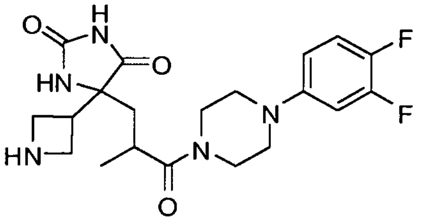
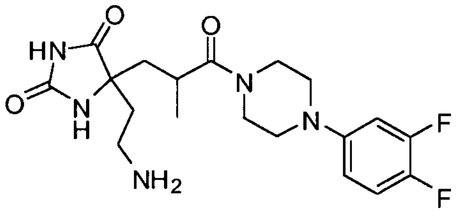
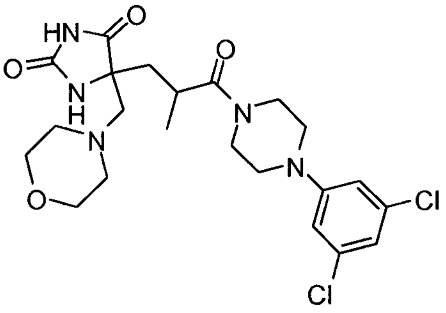
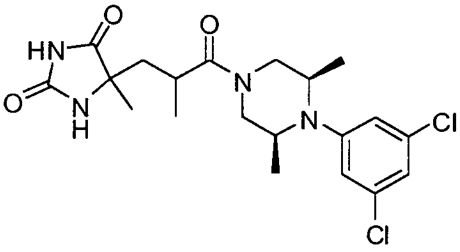
Cpd	Structure	MW	Ms'd	Mtd	SM
211	 trans	380	381	H2	Int 165 + 1-(3,4-difluoro phenyl)piperazine
212		420	421	2.10	Cpd 191
213	 trans	394	395	H2	Int 165 + Int 207
214	 trans	393	393 - 395	H2	Int 165 + Int 200
215	 trans	376	377	H2	Int 165 + Int 202
216	 trans	390	391	H2	Int 165 + Int 208

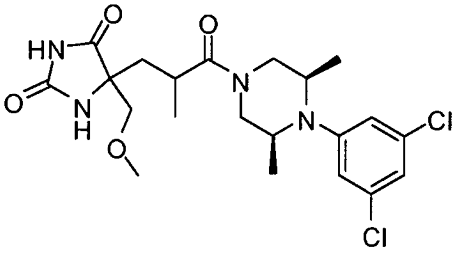
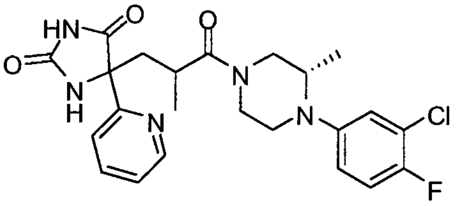
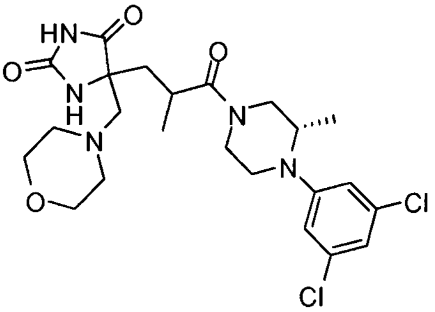
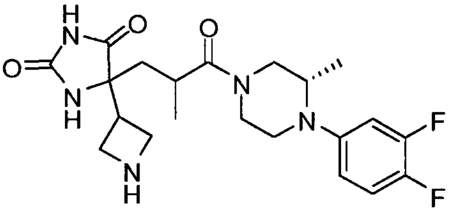
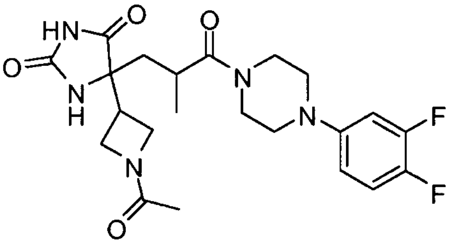
Cpd	Structure	MW	Ms'd	Mtd	SM
217	 trans	358	359	H2	Int 165 + Int 212
218	 trans	505	505 - 507	2.4	Cpd 197
219	 trans	399	399 - 401	H2	Int 151 + 1-(3,5-dichloro phenyl)piperazine
220	 trans	429	429 - 431	H2 + F + I4	Int 138 + 1-(3,5-dichloro phenyl)piperazine
221	 trans	501	501 - 503	F	Int 063

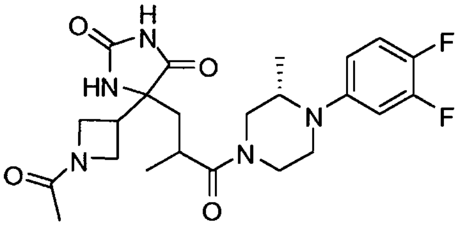
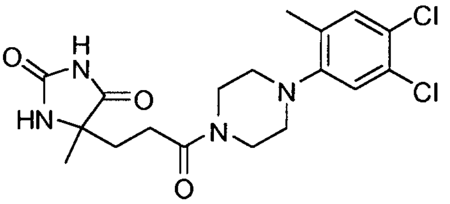
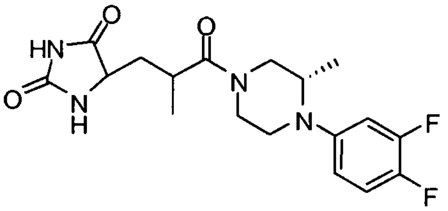
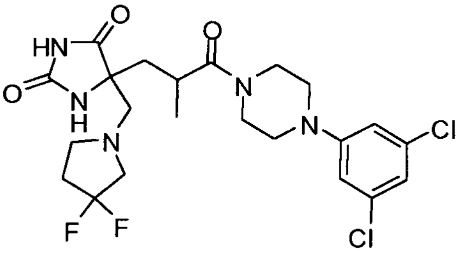
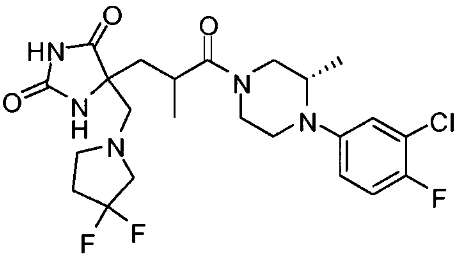
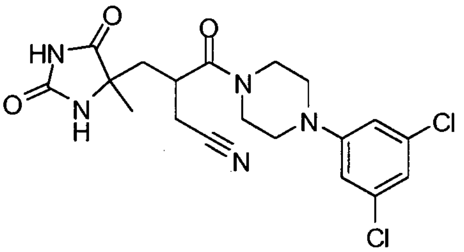
Cpd	Structure	MW	Ms'd	Mtd	SM
222	 trans	443	443 - 445	H2	Int 156 + 1-(3,5-dichlorophenyl)piperazine
223		456	456 - 458	I1	Cpd 180
224	 trans	410	411	H2	Int 156 + 1-(3,4-difluoro phenyl)piperazine
225	 trans	424	425	H2	Int 156 + Int 207
226	 trans	424	425	H2	Int 156 + Int 199
227	 trans	471	471	H2	Int 156 + Int 211

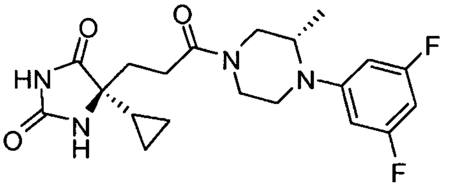
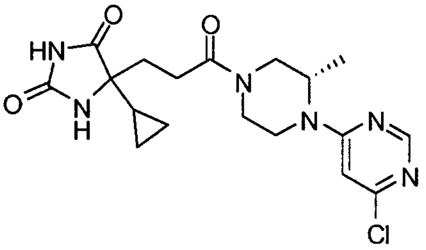
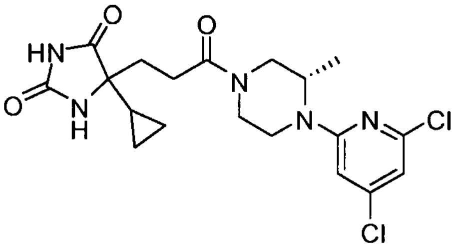
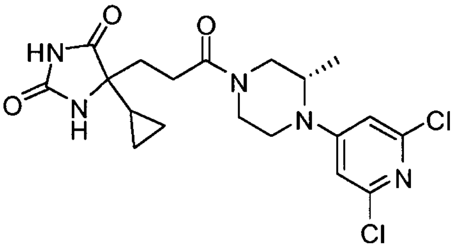
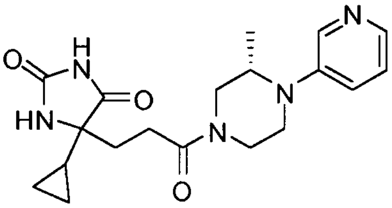
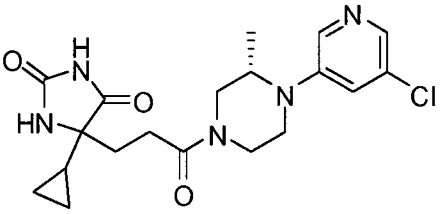
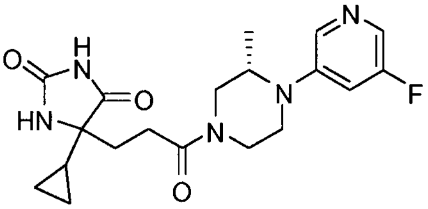
Cpd	Structure	MW	Ms'd	Mtd	SM
228	 trans	420	421	H2	Int 156 + Int 208
229	 trans	406	407	H2	Int 156 + Int 202
230	 trans	406	407	H2	Int 156 + Int 204
231	 trans	476	476 - 478	H2	Int 159 + 1-(3,5-dichloro phenyl)piperazine
232	 trans	437	437 - 439	H2	Int 156 + Int 216
233	 trans	423	423 - 425	H2	Int 156 + Int 200

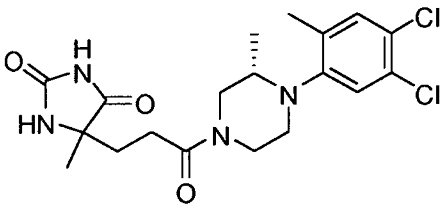
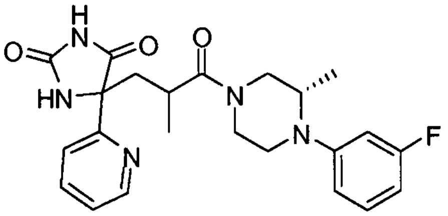
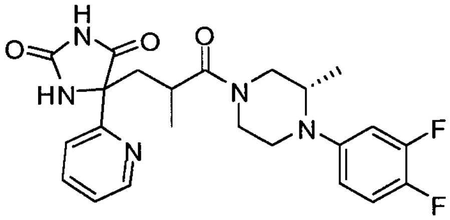
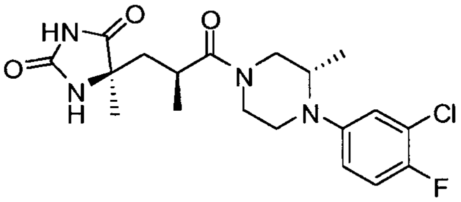
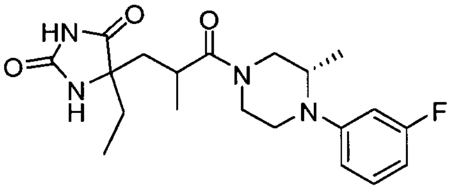
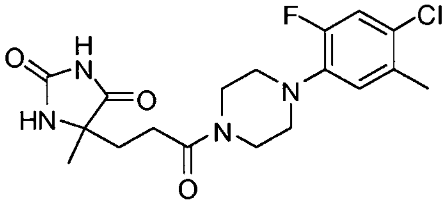
Cpd	Structure	MW	Ms'd	Mtd	SM
234	 trans	522	522	F	Int 067
235	 trans	510	510	F	Int 069
236	 trans	427	427 - 429	F	Int 061
237	 trans	407	407 - 409	H2	Int 165 + Int 216
238	 trans	507	507 - 509	F	Int 064

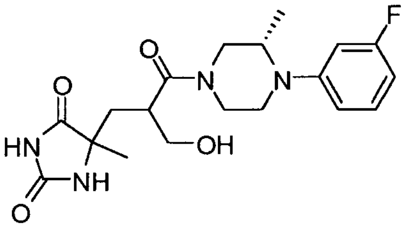
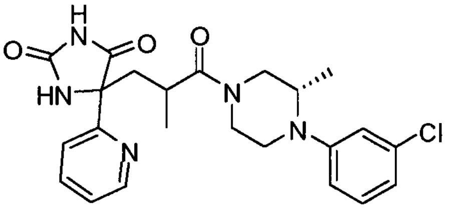
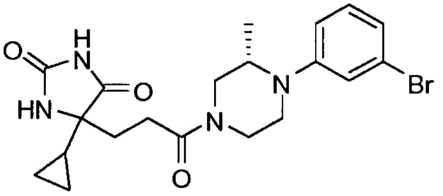
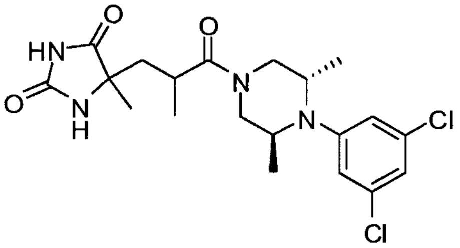
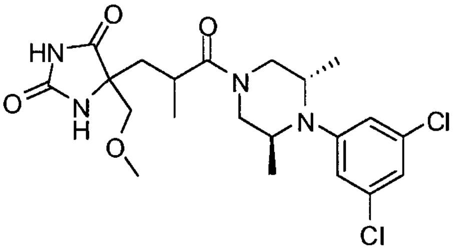
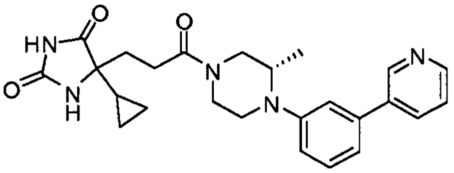
Cpd	Structure	MW	Ms'd	Mtd	SM
239	 trans	536	536	F	Int 068
240	 trans	421	422	I2	Cpd 234
241	 trans	409	410	I2	Cpd 235
242	 trans	498	498 - 500	H2	Int 186 + 1-(3,5-dichloro phenyl)piperazine
243	 trans	441	441	H2	Int 165 + Int 243

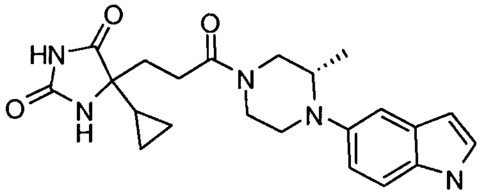
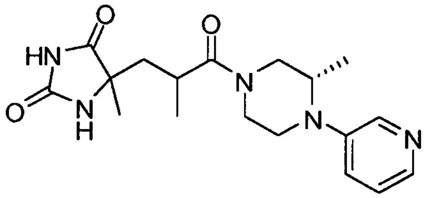
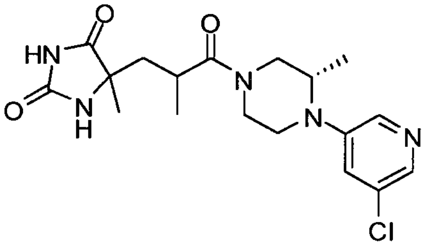
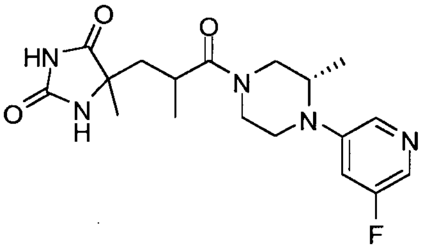
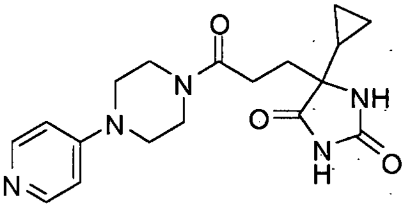
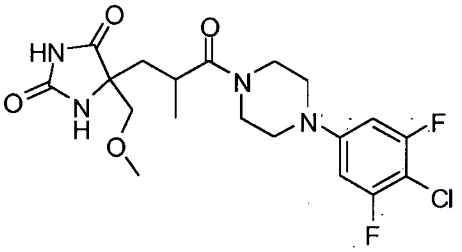
Cpd	Structure	MW	Ms'd	Mtd	SM
244	 trans	471	471	H2	Int 156 + Int 243
245	 trans	474	474	H2	Int 159 + Int 198
246	 trans	512	512 - 514	H2	Int 186 + Int 197
247	 trans	435	436	I2	Cpd 239
248	 trans	463	464	I1	Cpd 240

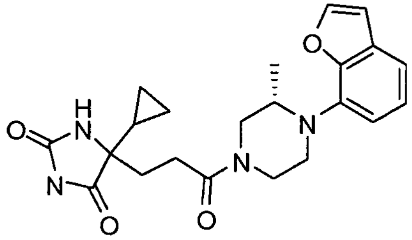
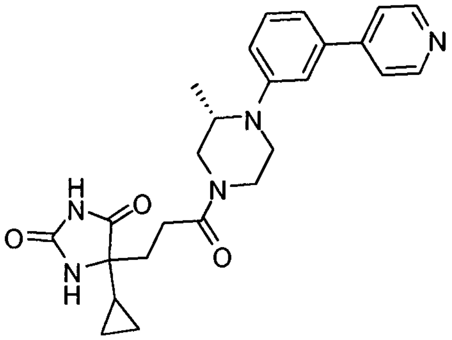
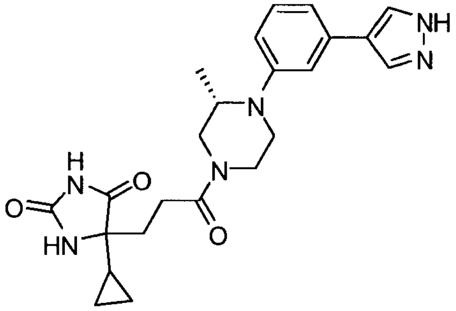
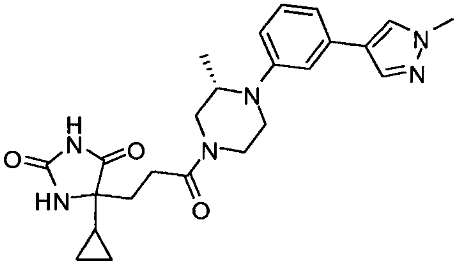
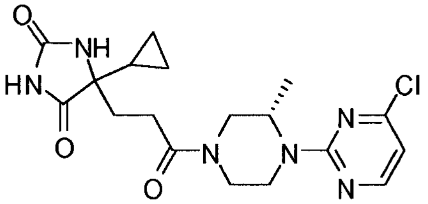
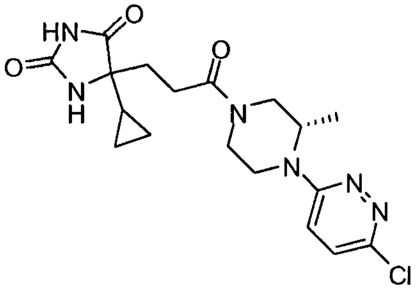
Cpd	Structure	MW	Ms'd	Mtd	SM
249	 trans	478	478	I1	Cpd 247
250		413	412 - 414 - 416	H2	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 279
251	 trans	380	381	H2	Int 151 + Int 199
252	 trans	518	518 - 520	H2	Int 145 + 1-(3,5-dichloro phenyl) piperazine
253	 trans	516	516 - 518	H2	Int 145 + Int 198
254	 trans	438	438 - 440	F	Int 065

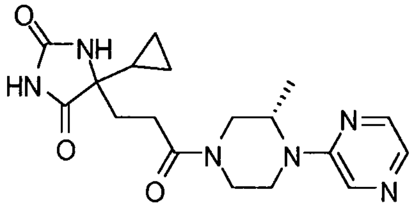
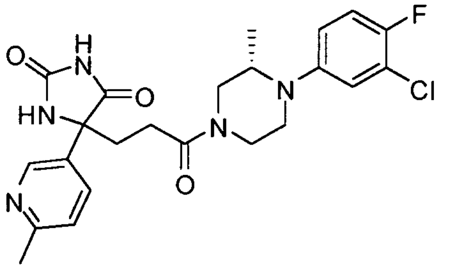
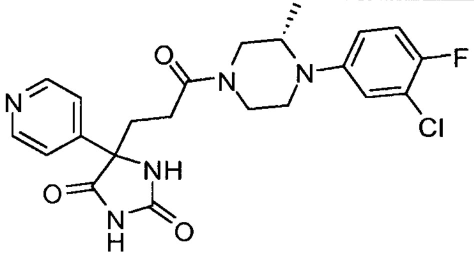
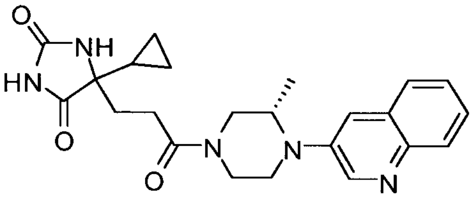
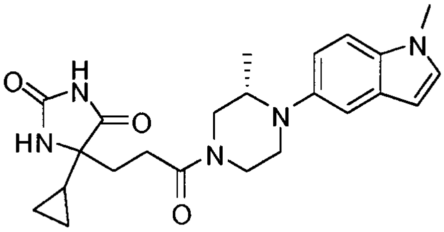
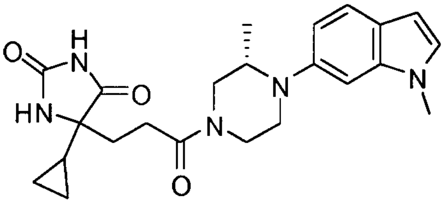
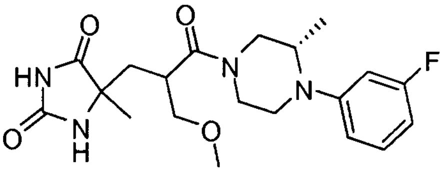
Cpd	Structure	MW	Ms'd	Mtd	SM
255		406	407	2.5	Int 163 + Int 207
256		407	407 - 409	H2	Int 162 + Int 260
257		440	440 - 442	H2	Int 162 + Int 261
258		440	440 - 442	H2	Int 162 + Int 262
259		371	372	H2	Int 162 + Int 221
260		406	406 - 408	H2	Int 162 + Int 215
261		389	390	H2	Int 162 + Int 214

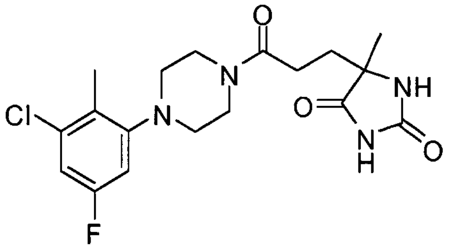
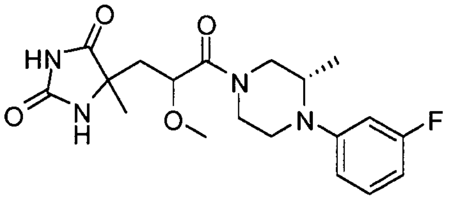
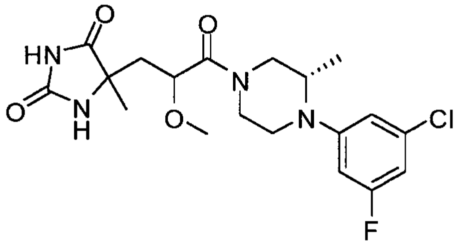
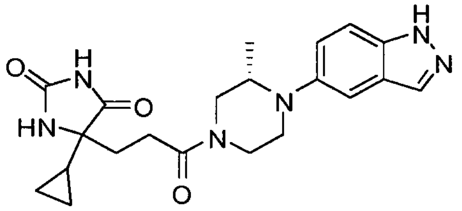
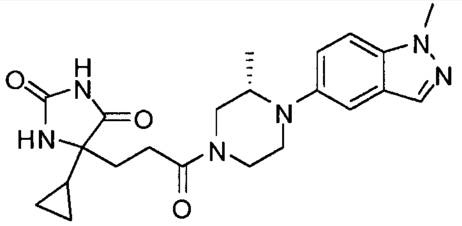
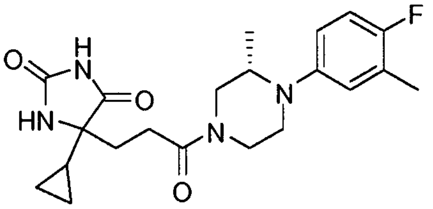
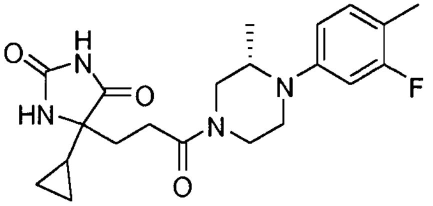
Cpd	Structure	MW	Ms'd	Mtd	SM
262		427	426 - 428 - 430	H2	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 281
263	 trans	439	440	H2	Int 159 + Int 202
264	 trans	457	458	H2	Int 159 + Int 199
265		411	411 - 413	2.11	Cpd 405
266	 trans	390	391	H2	Int 169 + Int 202
267		397	397 - 399	H2	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 282

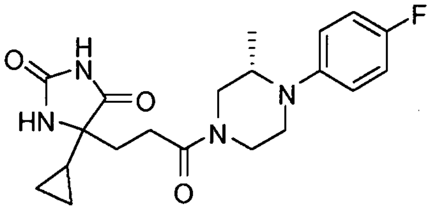
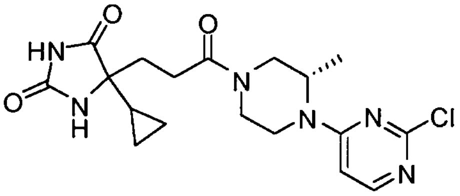
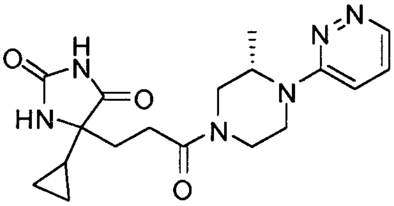
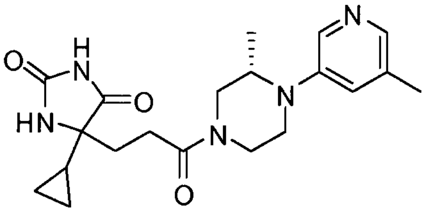
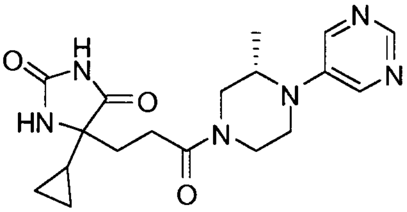
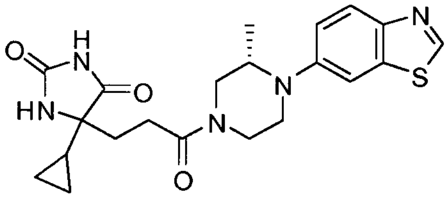
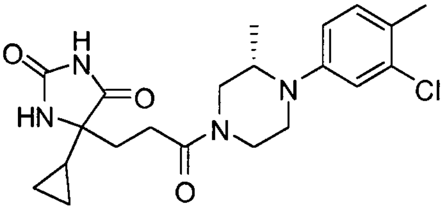
Cpd	Structure	MW	Ms'd	Mtd	SM
268	 trans	392	393	I4	Int 062
269	 trans	456	456 - 458	H2	Int 159 + Int 200
270		449	449 - 451	H2	Int 162 + Int 244
271	 trans	441	441	H2	Int 165 + Int 245
272	 trans	471	471	H2	Int 156 + Int 245
273		448	449	I6	Cpd 270 + Pyridine-3-boronic acid

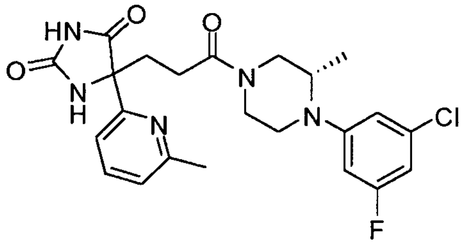
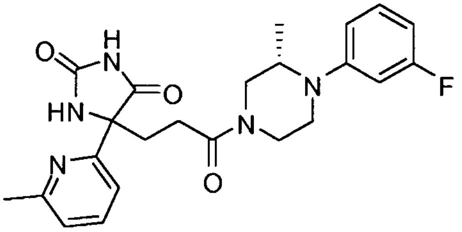
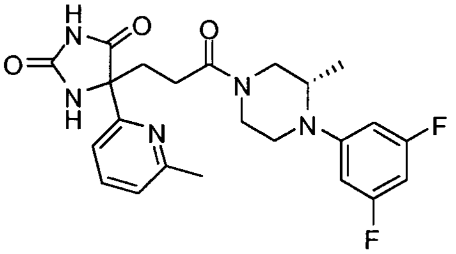
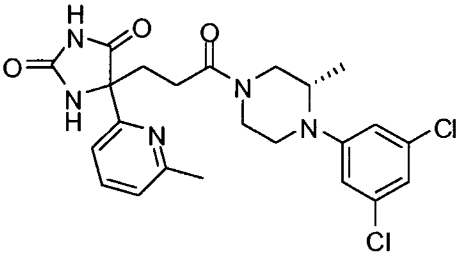
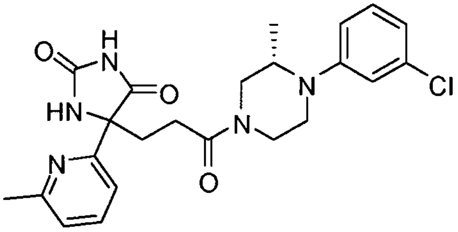
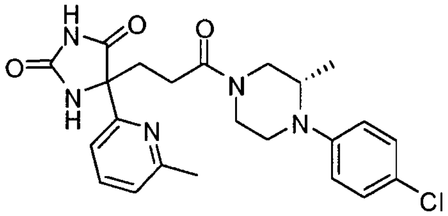
Cpd	Structure	MW	Ms'd	Mtd	SM
274		409	410	H2	Int 162 + Int 257
275	 trans	359	360	H2	Int 165 + Int 221
276	 trans	394	394 - 936	H2	Int 165 + Int 215
277	 trans	377	378	H2	Int 165 + Int 214
278		357	358	H2	Int 162 + 1-(4-pyridyl) piperazine
279	 trans	445	445 - 447	H2	Int 156 + Int 203

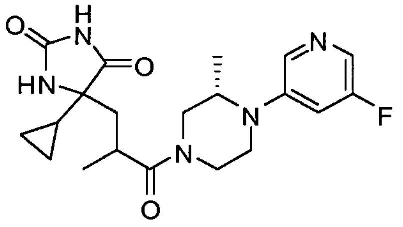
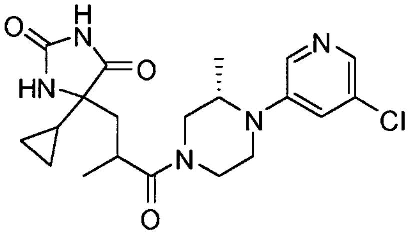
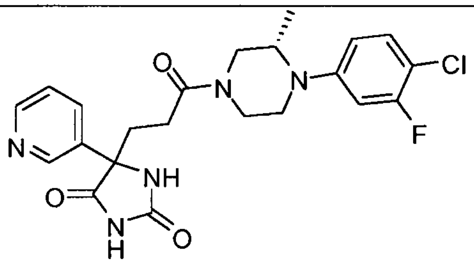
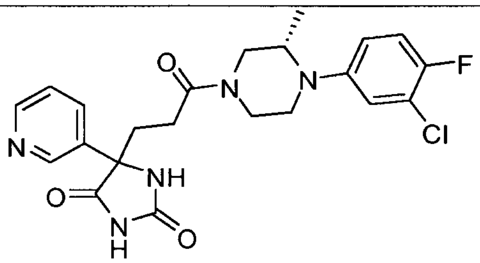
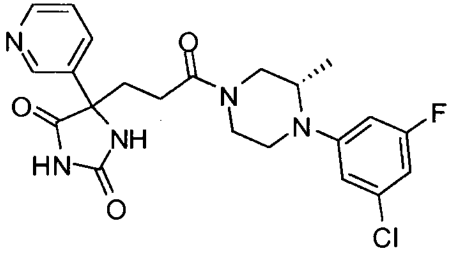
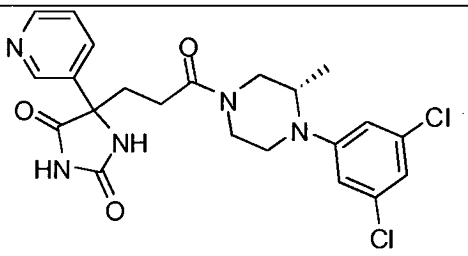
Cpd	Structure	MW	Ms'd	Mtd	SM
280		410	411	H1	Int 162 + Int 249
281		448	449	I6	Cpd 270 + Pyridine-4-boronic acid
282		437	437	I6	Cpd 270 + Pyrazole-4-boronic acid
283		451	451	I6	Cpd 270 + 1-Methyl-1H-pyrazole-4-boronic acid
284		407	407 - 409	H1	Int 162 + Int 226
285		407	407 - 409	H1	Int 162 + Int 227

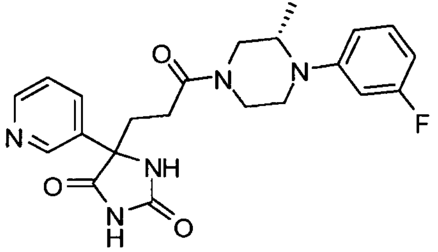
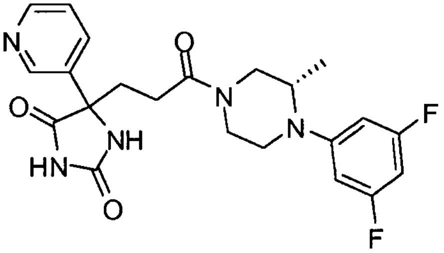
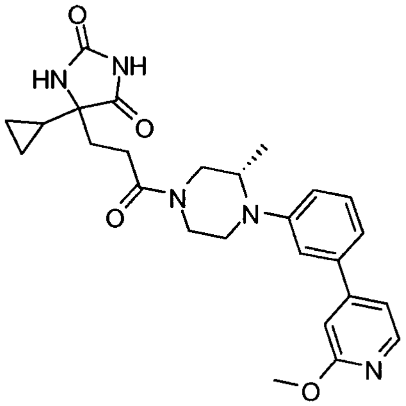
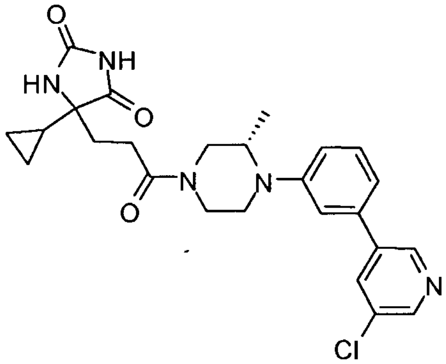
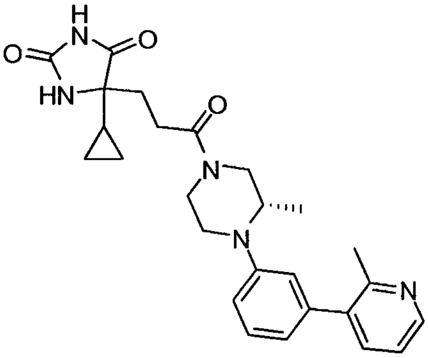
Cpd	Structure	MW	Ms'd	Mtd	SM
286		372	373	H1	Int 162 + Int 228
287		474	474 - 476	F	Int 059
288		460	460 - 462	F	Int 060
289		422	422	H1	Int 162 + Int 250
290		424	425	H1	Int 162 + Int 251
291		424	425	H1	Int 162 + Int 252
292	 trans	406	407	F	Int 066

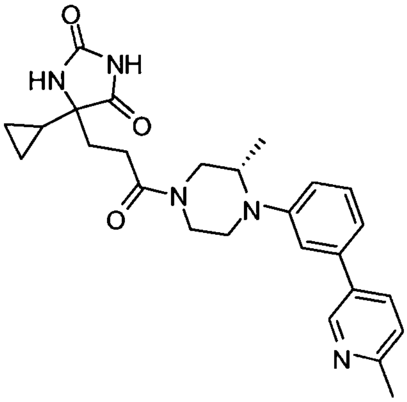
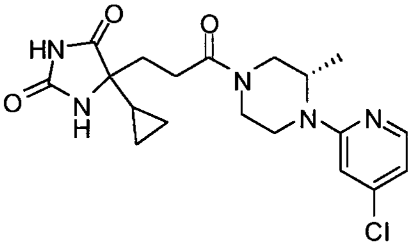
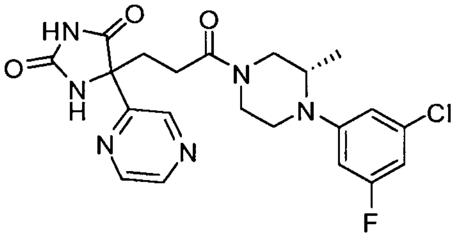
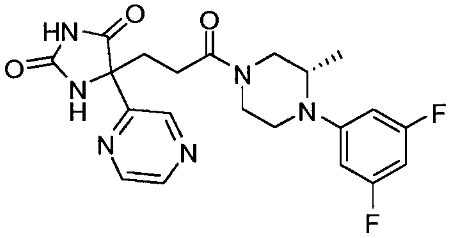
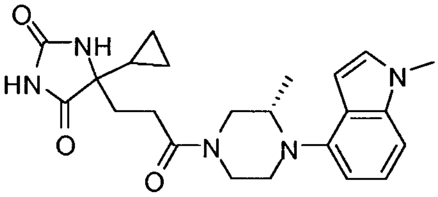
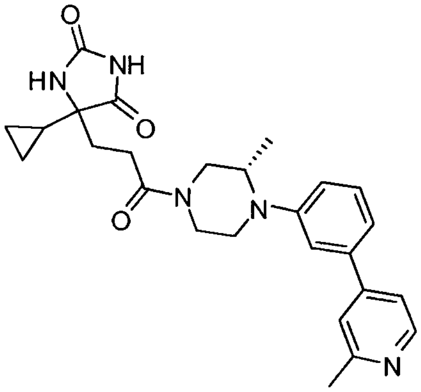
Cpd	Structure	MW	Ms'd	Mtd	SM
293		397	397 - 399	H4	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl)propionic acid + Int 283
294	 trans	392	393	F	Int 057
295	 trans	427	427 - 429	F	Int 058
296		410	411	H2	Int 162 + Int 258
297		425	425	H2	Int 162 + Int 259
298		402	403	H2	Int 162 + Int 210
299		402	403	H2	Int 162 + Int 224

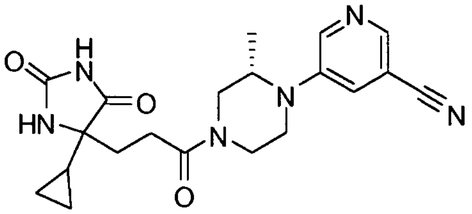
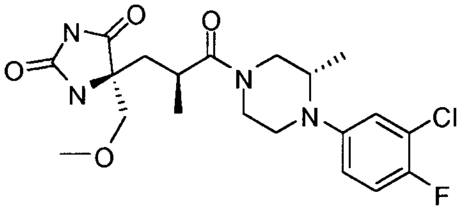
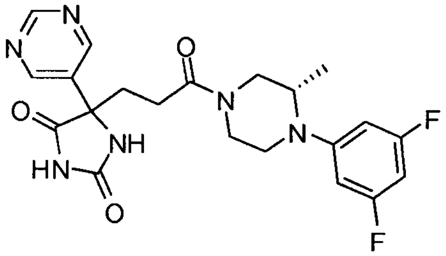
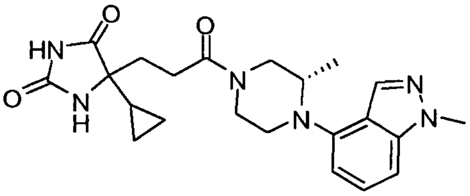
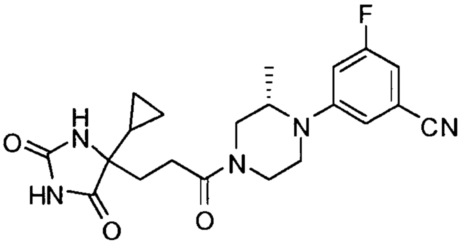
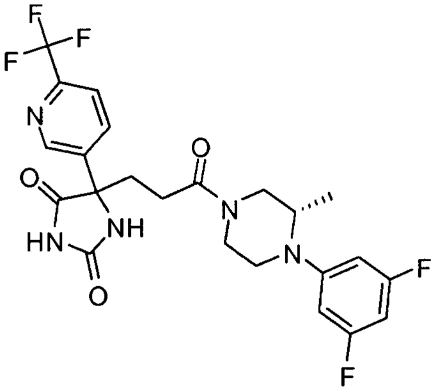
Cpd	Structure	MW	Ms'd	Mtd	SM
300		388	389	H2	Int 162 + Int 209
301		407	407 - 409	H2	Int 162 + Int 264
302		372	373	2.35	Cpd 285
303		385	386	H2	Int 162 + Int 222
304		372	373	H2	Int 162 + Int 248
305		428	428	H1	Int 162 + Int 253
306		419	419 - 421	H2	Int 162 + Int 225

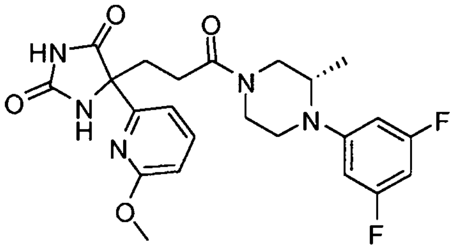
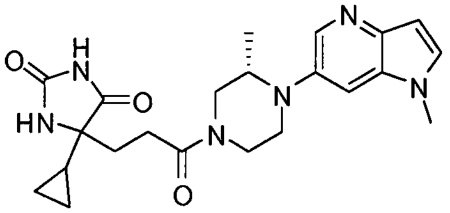
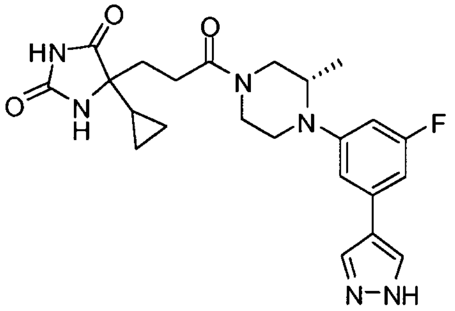
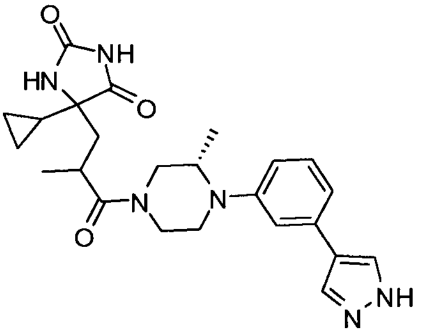
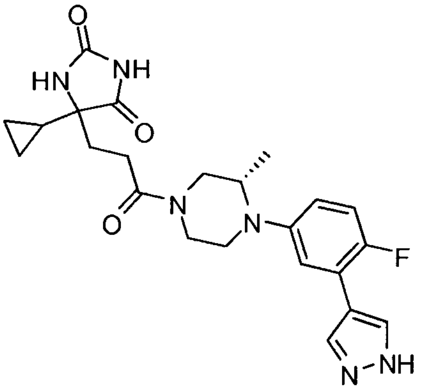
Cpd	Structure	MW	Ms'd	Mtd	SM
307		474	474 - 476	H1	Int 166 + Int 206
308		439	440	H1	Int 166 + Int 202
309		457	458	H1	Int 166 + Int 207
310		490	490 - 492	H1	Int 166 + Int 197
311		456	456 - 458	H1	Int 166 + Int 200
312		456	456 - 458	H1	Int 166 + Int 205

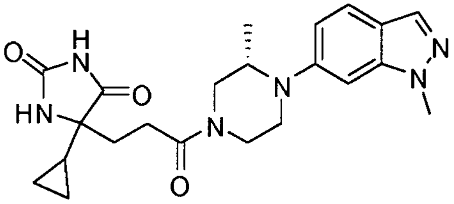
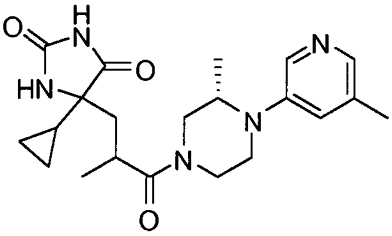
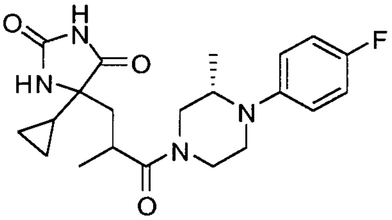
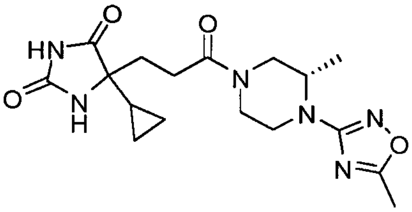
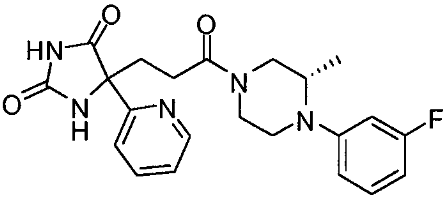
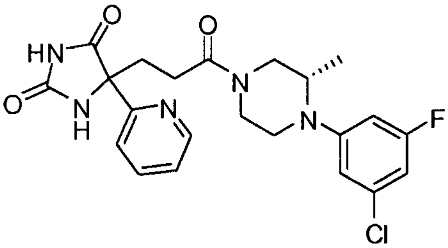
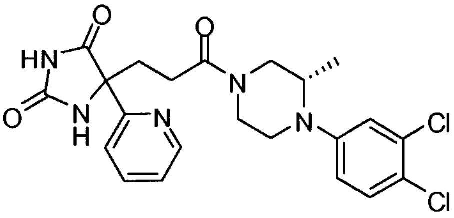
Cpd	Structure	MW	Ms'd	Mtd	SM
313	 trans	403	404	H2	Int 164 + Int 214
314	 trans	420	420 - 422	H2	Int 164 + Int 215
315		460	460 - 462	H2	Int 132 + Int 213
316		460	460 - 462	H2	Int 132 + Int 198
317		460	460 - 462	H2	Int 132 + Int 206
318		476	476 - 478	H2	Int 132 + Int 197

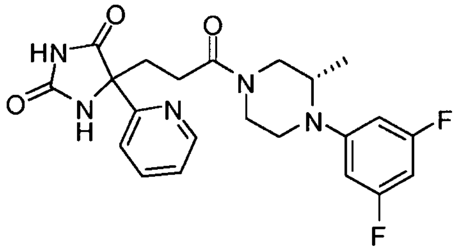
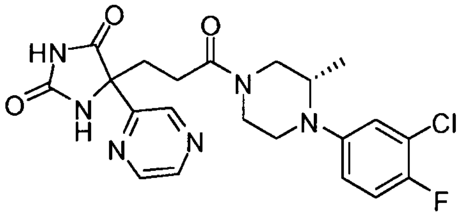
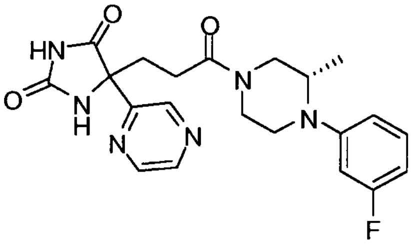
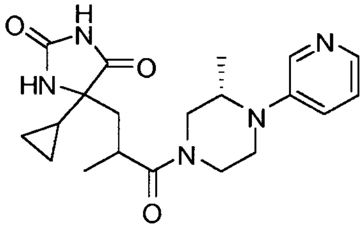
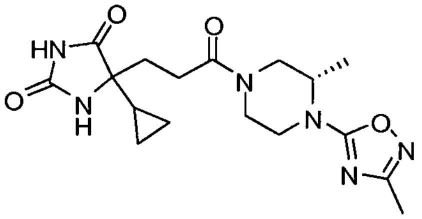
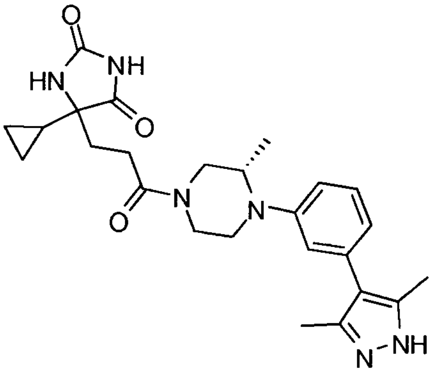
Cpd	Structure	MW	Ms'd	Mtd	SM
319		425	426	H2	Int 132 + Int 202
320		443	444	H2	Int 132 + Int 207
321		478	479	I6	Cpd 270 + 2-Methoxypyridine-4-boronic acid
322		482	482 - 484	I6	Cpd 270 + 5-Chloropyridine-3-boronic acid
323		462	462	I6	Cpd 270 + 2-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine

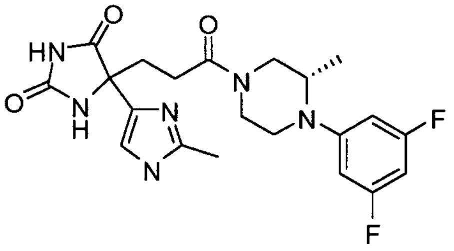
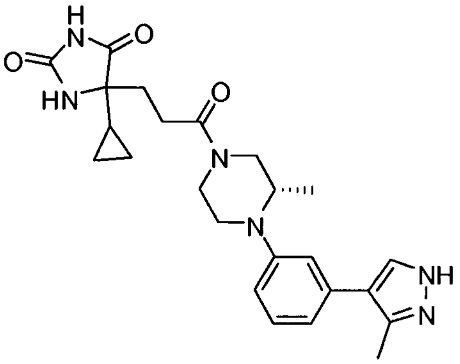
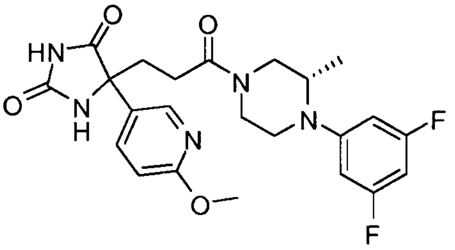
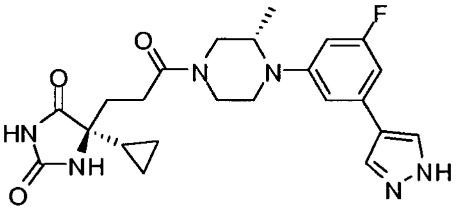
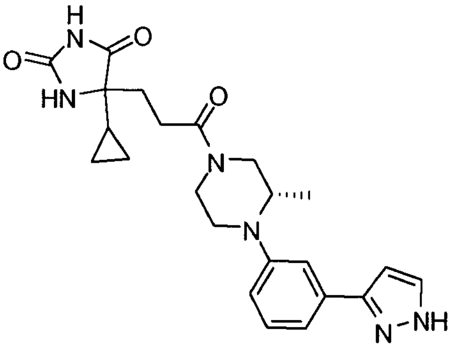
Cpd	Structure	MW	Ms'd	Mtd	SM
324		462	462	I6	Cpd 270 + 2-methyl-5-pyridinylboronic acid
325		406	406 - 408	H2	Int 162 + Int 229
326		461	461 - 463	H2	Int 142 + Int 206
327		444	445	H2	Int 142 + Int 207
328		424	424	H1	Int 162 + Int 254
329		462	462	I6	Cpd 270 + 2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine

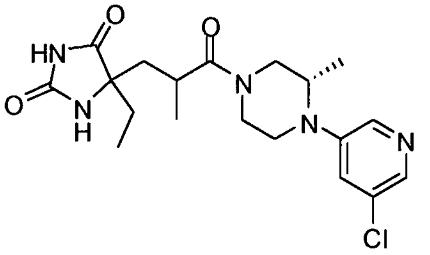
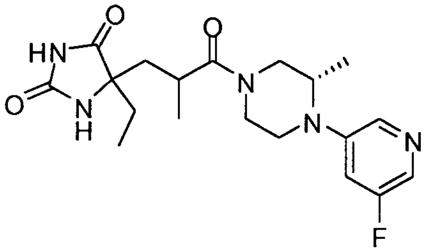
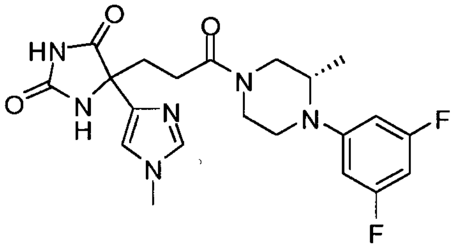
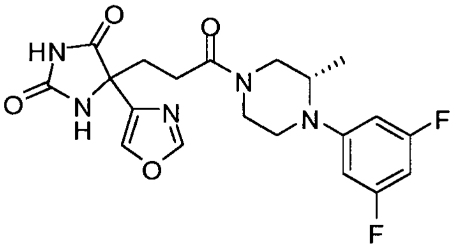
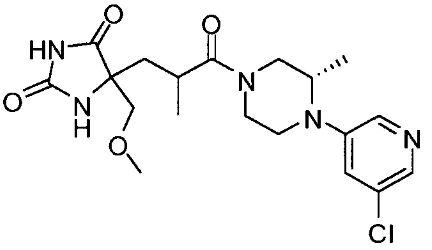
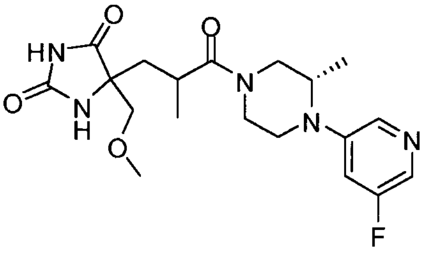
Cpd	Structure	MW	Ms'd	Mtd	SM
330		396	397	H2	Int 162 + Int 223
331		441	441 - 443	2.12	Cpd 406
332		444	445	H2	Int 182 + Int 207
333		425	425	H2	Int 162 + Int 230
334		413	414	H1	Int 162 + Int 255
335		511	512	F	Int 072

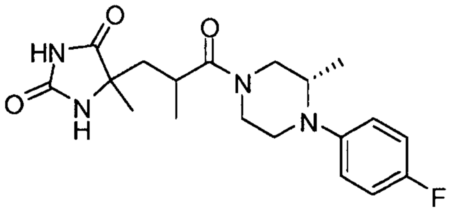
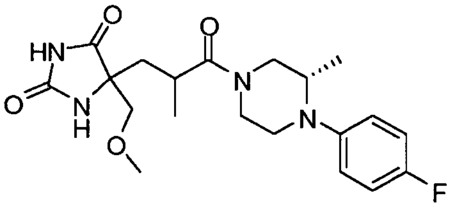
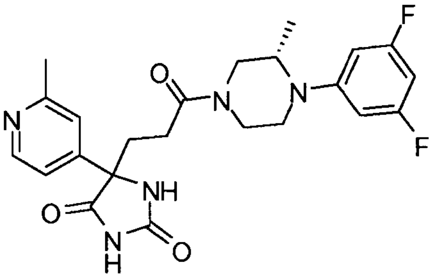
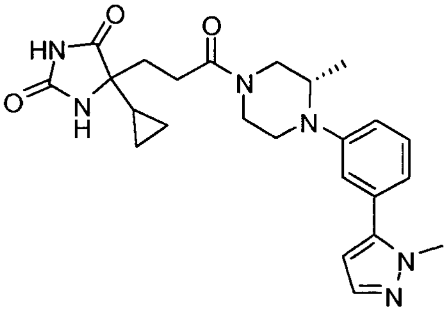
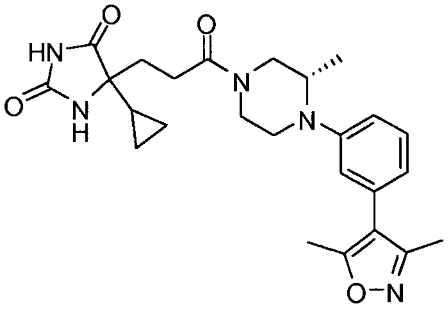
Cpd	Structure	MW	Ms'd	Mtd	SM
336		473	474	F	Int 070
337		425	425	H2	Int 162 + Int 231
338		455	455	H2	Int 162 + Int 232
339	 trans	451	451	H2	Int 164 + Int 233
340		455	455	H2	Int 162 + Int 234

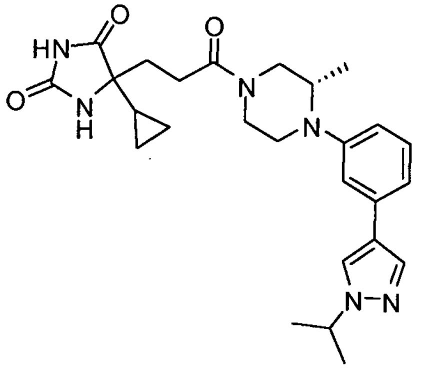
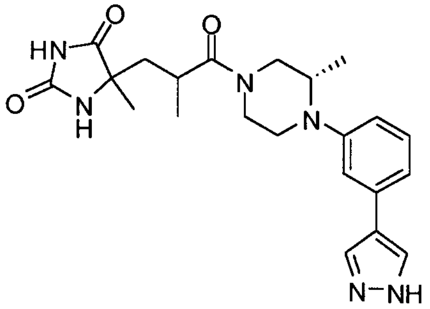
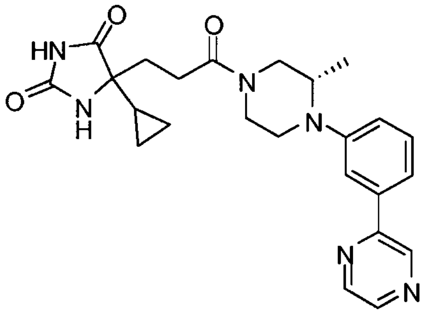
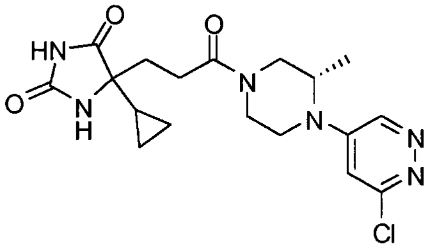
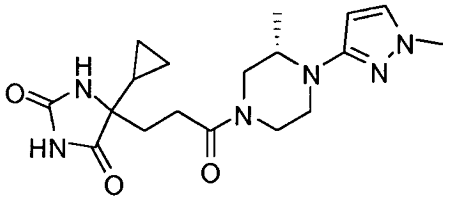
Cpd	Structure	MW	Ms'd	Mtd	SM
341		425	425	H2	Int 162 + Int 239
342	 trans	399	400	H2	Int 164 + Int 222
343	 trans	402	403	H2	Int 164 + Int 209
344		376	377	H2	Int 162 + Int 237
345		425	426	F	Int 103
346		460	460 - 462	F	Int 104
347		476	476 - 478	F	Int 105

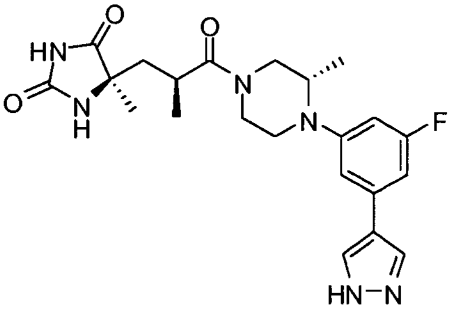
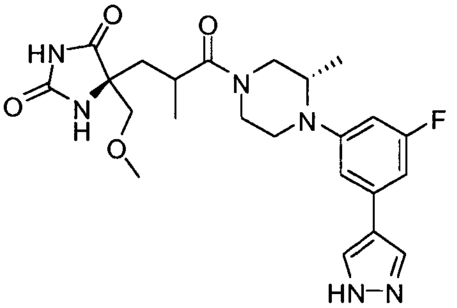
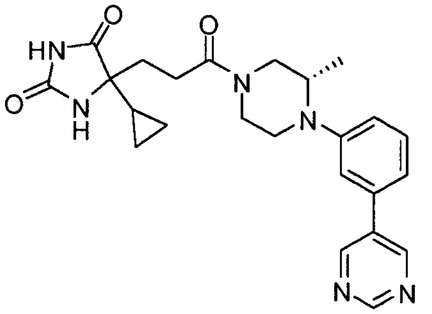
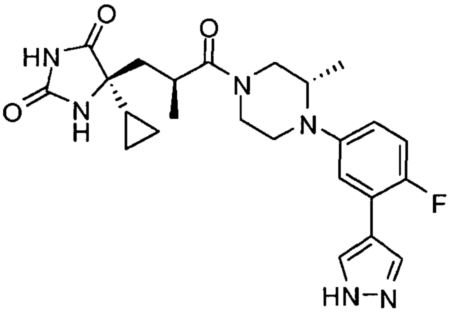
Cpd	Structure	MW	Ms'd	Mtd	SM
348		443	444	F	Int 106
349		461	461 - 463	H2	Int 142 + Int 198
350		426	427	H2	Int 142 + Int 202
351	 trans	385	386	H2	Int 164 + Int 221
352		376	377	H2	Int 162 + Int 238
353		465	466	I6	Cpd 270 + 3,5-dimethylpyrazole-4-boronic acid, pinacol ester

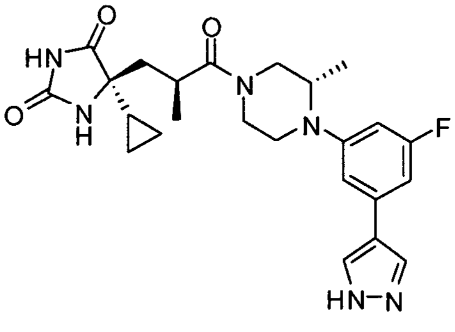
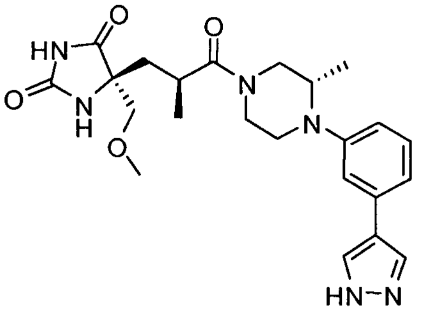
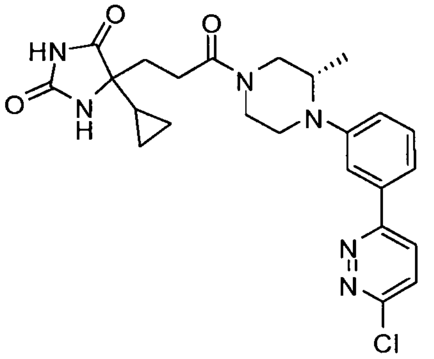
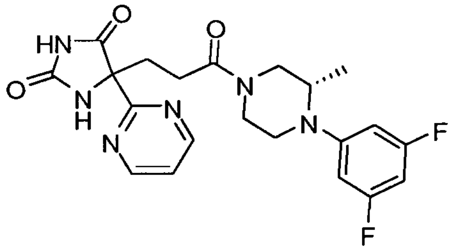
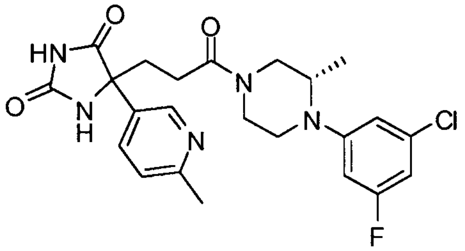
Cpd	Structure	MW	Ms'd	Mtd	SM
354		446	447	F	Int 012
355		451	452	I6	Cpd 270 + 3-methyl-1H-pyrazole-4-boronic acid pinacol ester
356		473	474	F	Int 024
357		455	455	H2	Int 163 + Int 232
358		437	438	I6	Cpd 270 + 1H-pyrazole-3-boronic acid

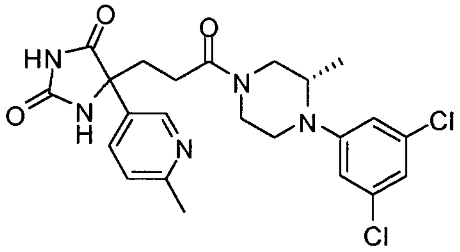
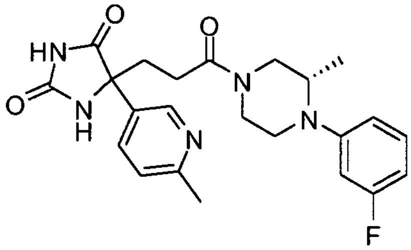
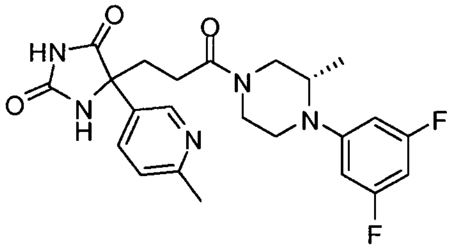
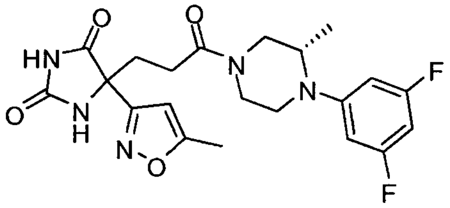
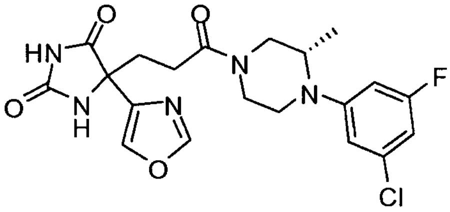
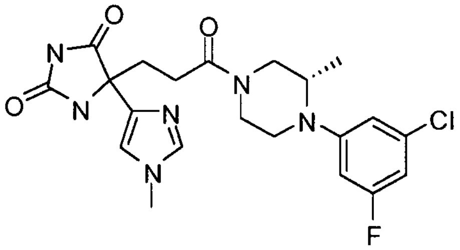
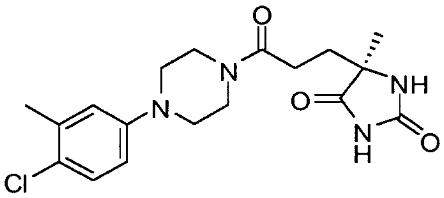
Cpd	Structure	MW	Ms'd	Mtd	SM
359	 trans	408	408	H2	Int 169 + Int 215
360	 trans	391	392	H2	Int 169 + Int 214
361		446	447	F	Int 108
362		433	434	F	Int 107
363	 trans	424	424	H2	Int 156 + Int 215
364	 trans	407	408	H2	Int 156 + Int 214

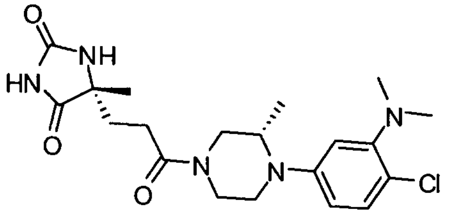
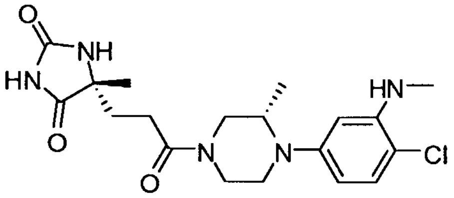
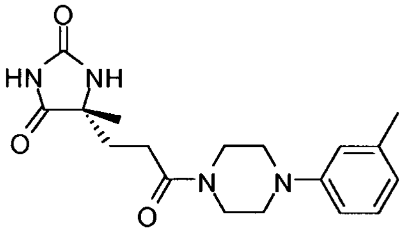
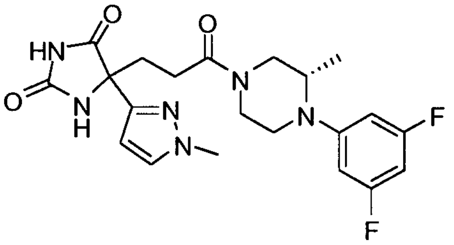
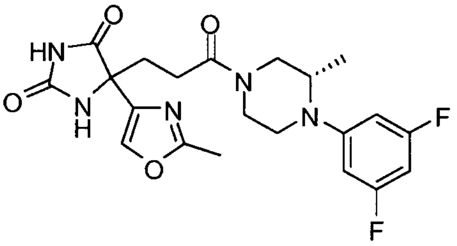
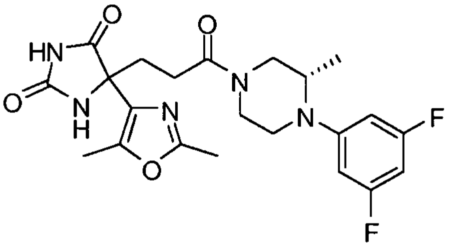
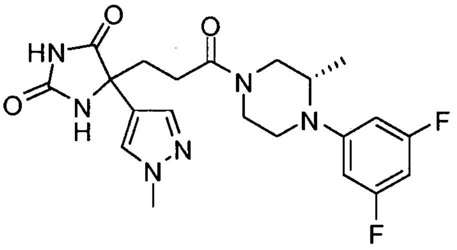
Cpd	Structure	MW	Ms'd	Mtd	SM
365	 trans	376	377	H2	Int 165 + Int 209
366	 trans	406	407	H2	Int 156 + Int 209
367		457	458	F	Int 073
368		451	451	I6	Cpd 270 + 1-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole
369		466	466	I6	Cpd 270 + 3,5-Dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoxazole

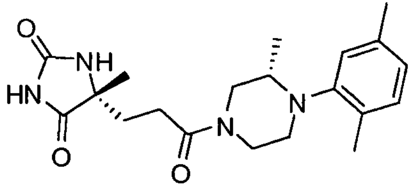
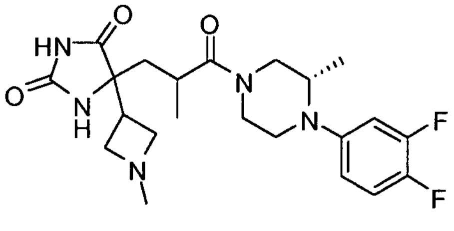
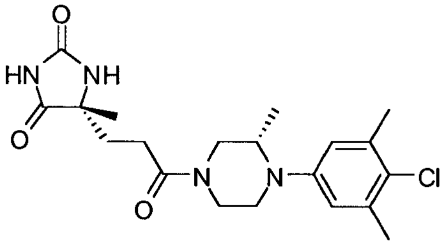
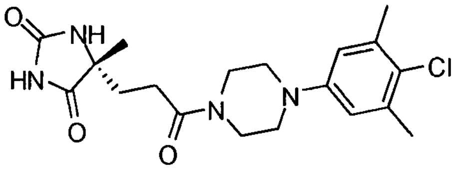
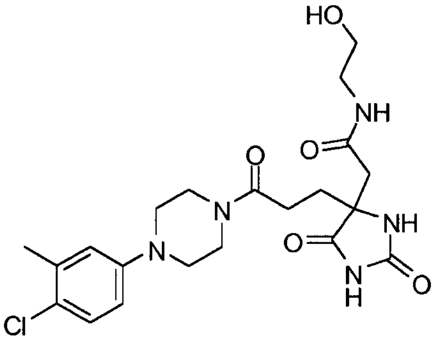
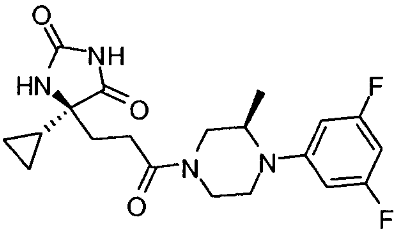
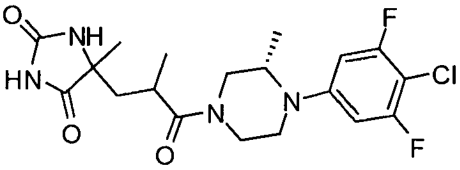
Cpd	Structure	MW	Ms'd	Mtd	SM
370		479	479	I6	Cpd 270 + 1-Isopropyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole
371	 trans	425	425	H2	Int 165 + Int 233
372		449	449	I5	Cpd 270 + 2-Iodo-pyrazine
373		407	407 - 409	H2	Int 162 + Int 263
374		374	375	H1	Int 162 + Int 256

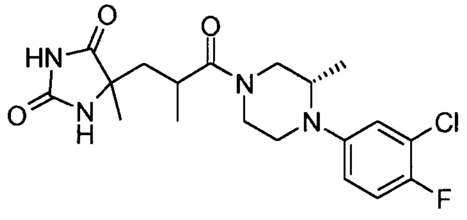
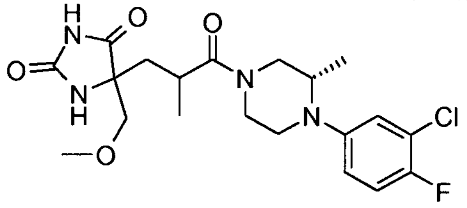
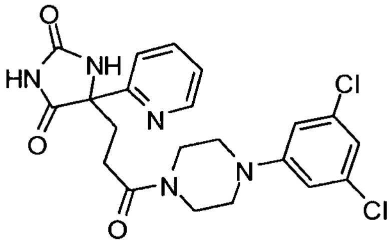
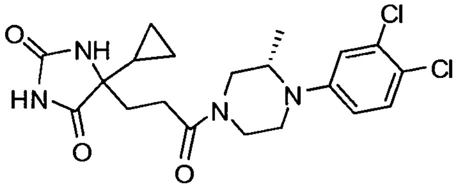
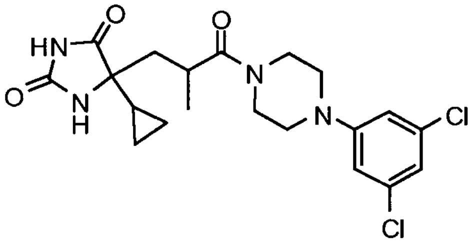
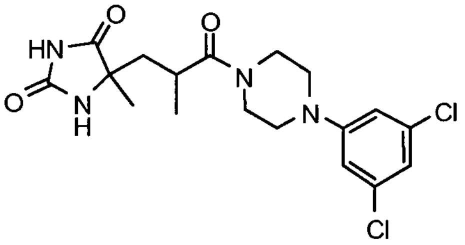
Cpd	Structure	MW	Ms'd	Mtd	SM
375	 trans	442	443	H4	Int 165 + Int 232
376	 trans	473	473	H4	Int 156 + Int 232
377		449	449	I5	Cpd 270 + 5-Bromo-pyrimidine
378	 trans	469	469	H4	Int 164 + Int 234

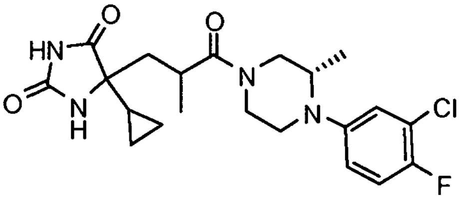
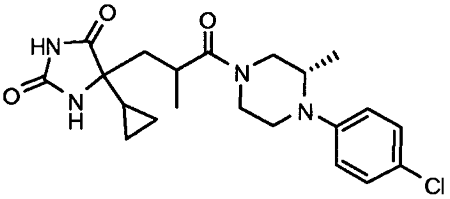
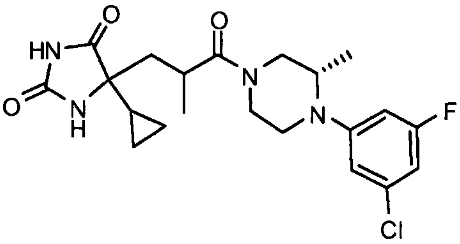
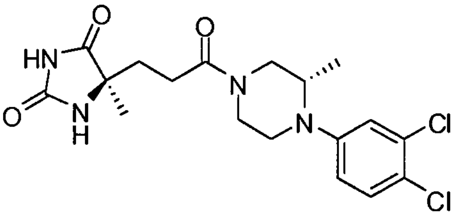
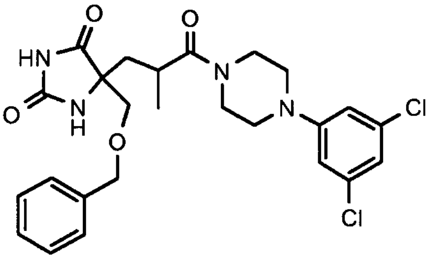
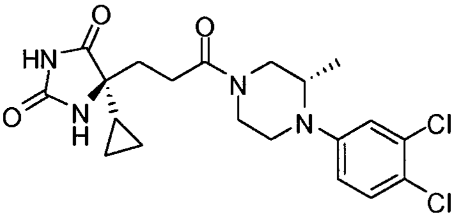
Cpd	Structure	MW	Ms'd	Mtd	SM
379	 trans	469	469	H4	Int 164 + Int 232
380	 trans	455	455	H4	Int 156 + Int 233
381		483	483	I5	Cpd 270 + 3-Chloro-6-iodo-pyridazine
382		444	445	H2	Int 139 + Int 207
383		474	474	H2	Int 174 + Int 206

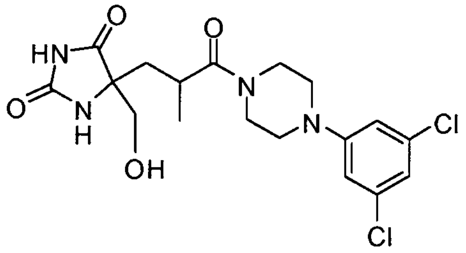
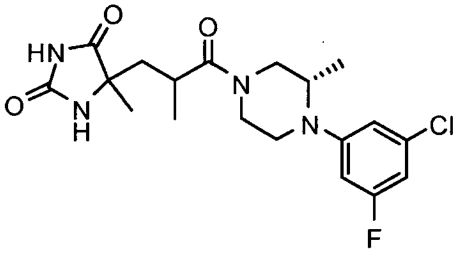
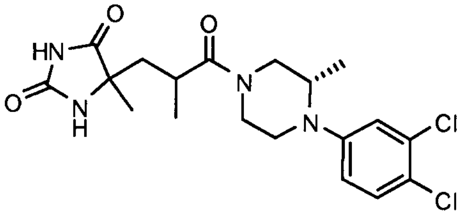
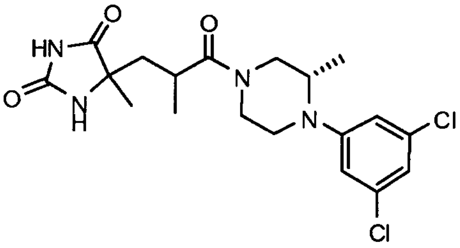
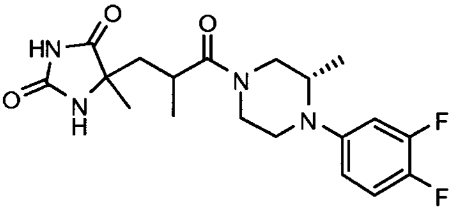
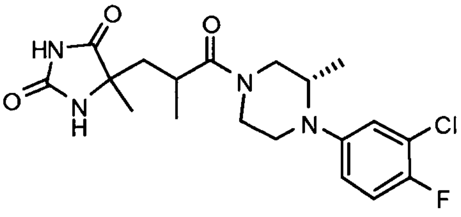
Cpd	Structure	MW	Ms'd	Mtd	SM
384		490	490 - 492	H2	Int 174 + Int 197
385		439	440	H2	Int 174 + Int 202
386		457	458	H2	Int 174 + Int 207
387		447	448	F	Int 079
388		450	450 - 452	F	Int 085
389		463	463 - 465	H1	Int 179 + Int 206
390		379	379 - 381	H2	Int 172 + Int 284

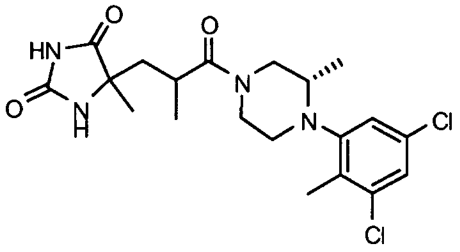
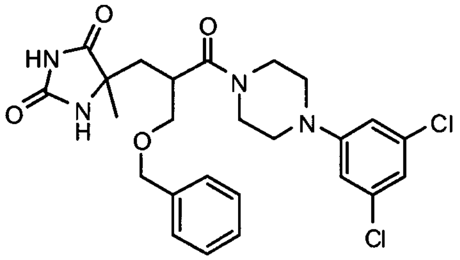
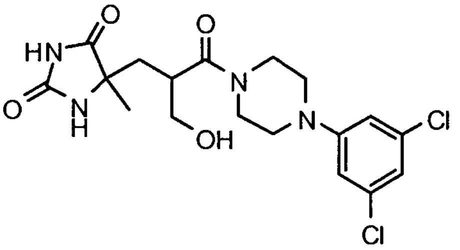
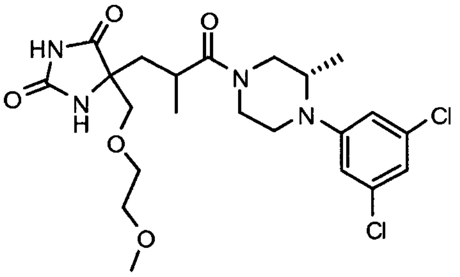
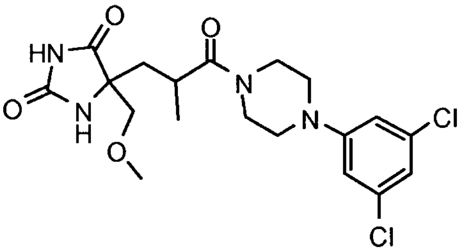
Cpd	Structure	MW	Ms'd	Mtd	SM
391		422	422 - 424	H2	Int 172 + Int 192
392		408	408 - 410	H2	Int 172 + Int 193
393		344	345	H2	Int 172 + Int 194
394		446	447	F	Int 022
395		447	448	F	Int 023
396		461	462	F	Int 115
397		446	447	F	Int 114

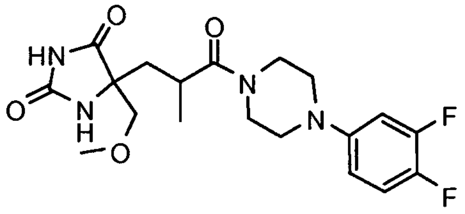
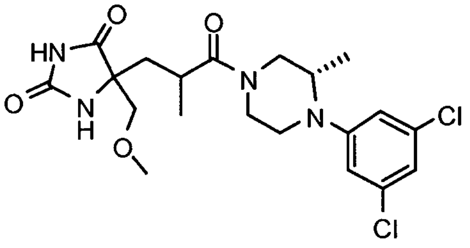
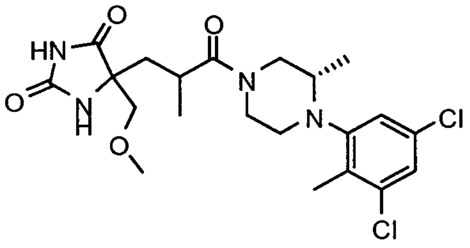
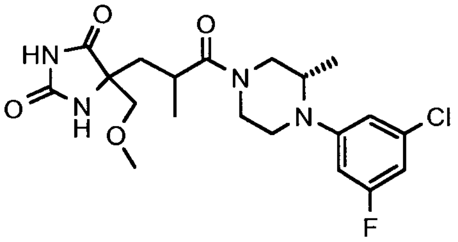
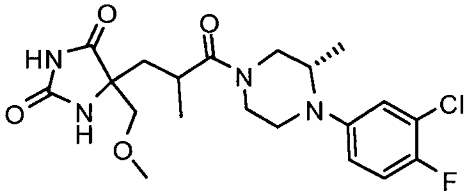
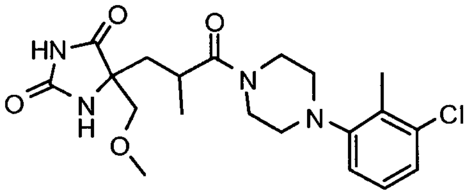
Cpd	Structure	MW	Ms'd	Mtd	SM
398		372	373	H2	Int 172 + Int 195
399	 trans	450	450	2.7	Cpd 247
400		407	407 - 409	H2	Int 172 + Int 280
401		393	393 - 395	H2	Int 172 + Int 278
402		466	466 - 468	2.8	Int 116
403		406	407	H1	Int 163 + Int 276
404	 trans	429	429	H2	Int 165 + Int 277

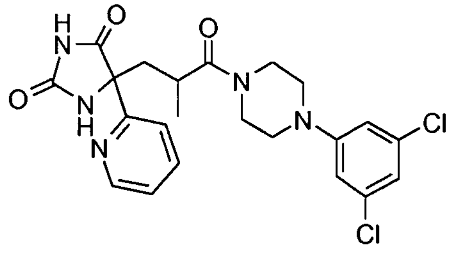
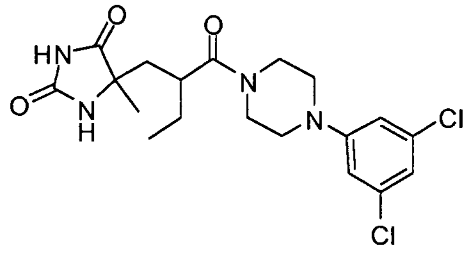
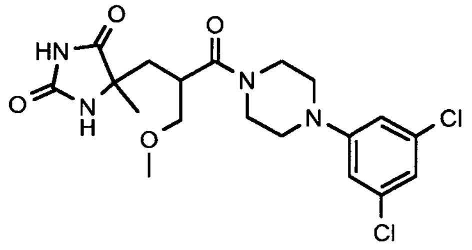
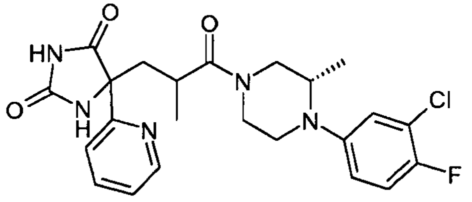
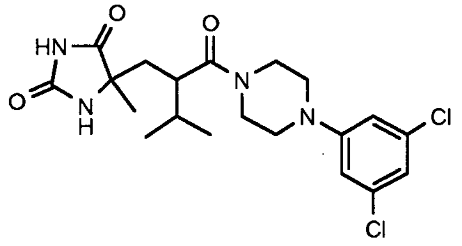
Cpd	Structure	MW	Ms'd	Mtd	SM
405	 trans	410	411	H2	Int 165 + Int 229
406	 trans	441	441 - 443	H2	Int 156 + Int 229
407		462	462- 464	F	Int 291
408		439	439- 441	H1	Int 162 + Int 201
409	 trans	439	439.38- 441.37	F	Int 046
410	 trans	413	413.36- 415.36	F	Int 292

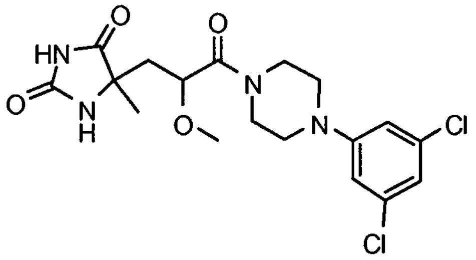
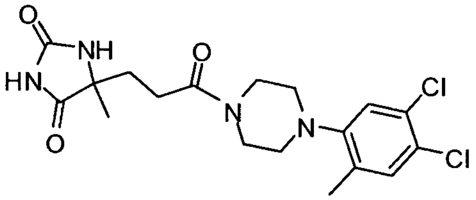
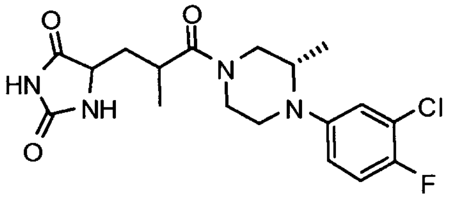
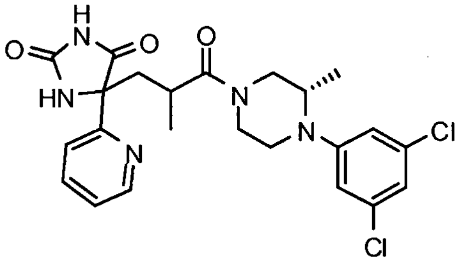
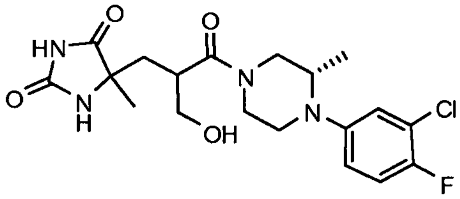
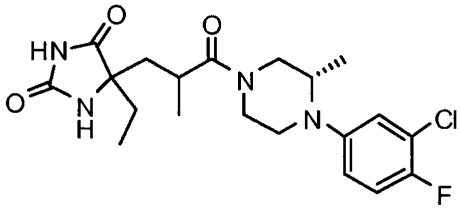
Cpd	Structure	MW	Ms'd	Mtd	SM
411	 trans	437	437- 439	F	Int 050
412	 trans	419	419.45- 421.42	F	Int 051
413	 trans	437	437- 439	F	Int052
414		413	413- 415	H1	Int 172 + Int 201
415	 trans	519	519- 521	F	Int 293
416		439	439- 441	H2	Int 163 + Int 201

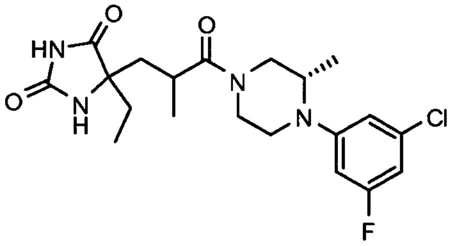
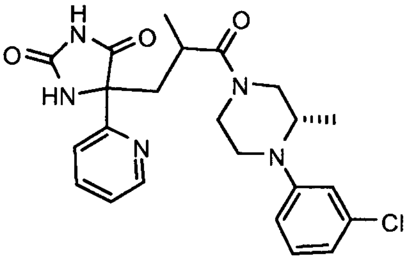
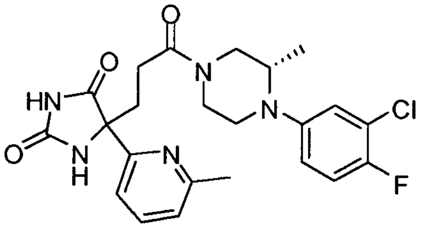
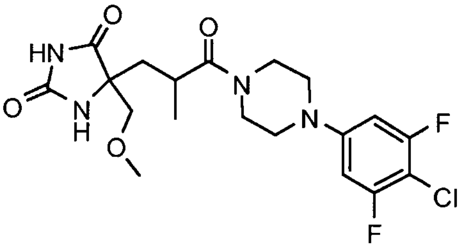
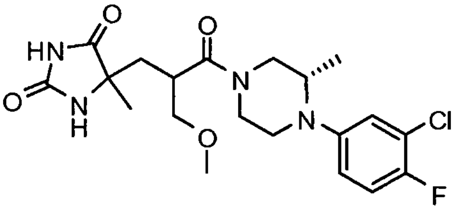
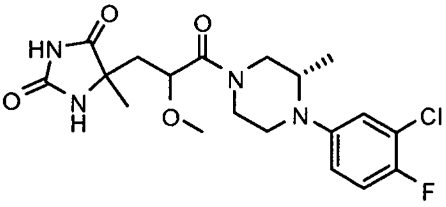
Cpd	Structure	MW	Ms'd	Mtd	SM
417	 trans	429	429- 431	I4	Cpd 415
418	 trans	411	411- 413	H2	Int 165 + Int 206
419	 trans	427	427- 429	H2	Int 165 + Int 201
420	 trans	427	427- 429	H2	Int 165 + Int 197
421	 trans	394	395	H2	Int 165 + Int 199
422	 trans	411	411- 413	H2	Int 165 + Int 198

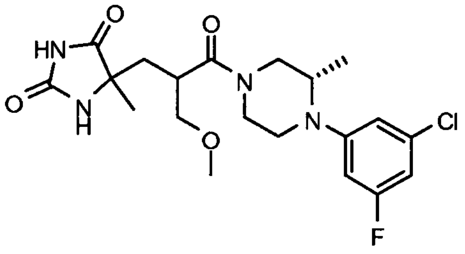
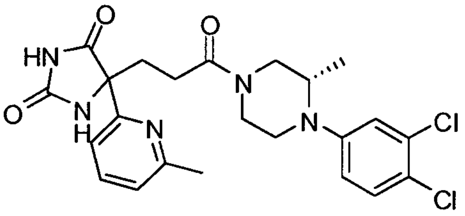
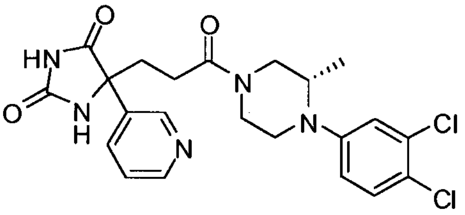
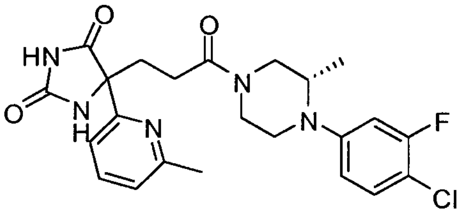
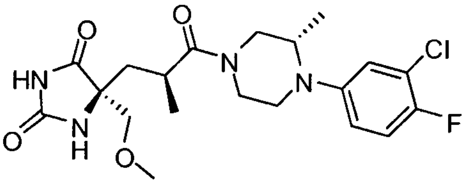
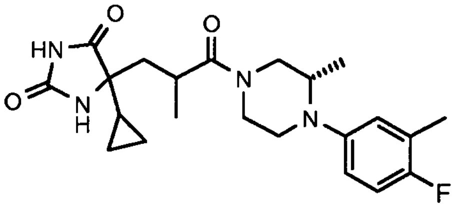
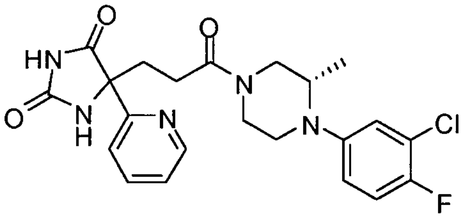
Cpd	Structure	MW	Ms'd	Mtd	SM
423	 trans	441	441- 443	H2	Int 165 + Int 211
424	 trans	519	519- 521	F	Int 294
425	 trans	429	429- 431	I4	Cpd 424
426	 trans	501	501- 503	F	Int 063
427	 trans	443	443- 445	H2	Int 156 + 1-(3,5-dichlorophenyl)piperazine

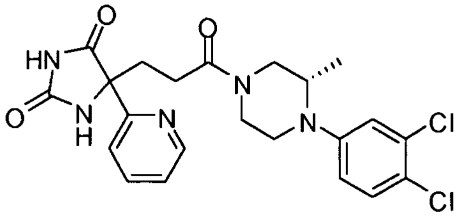
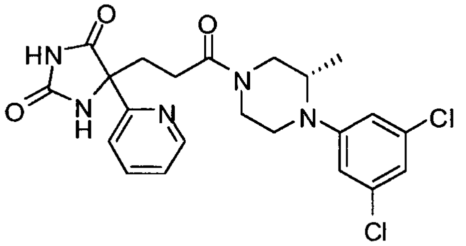
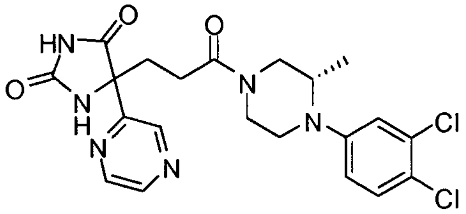
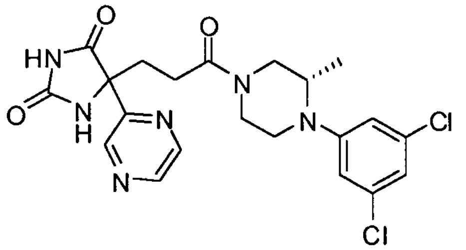
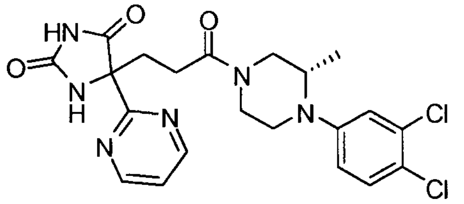
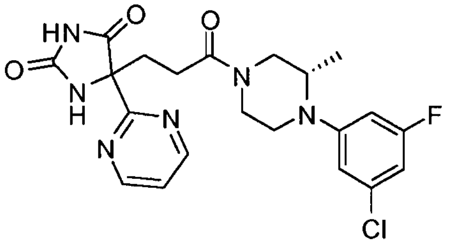
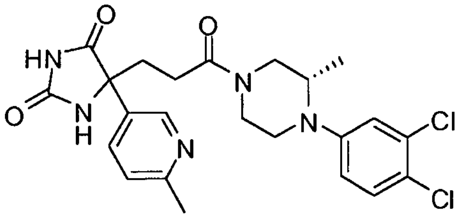
Cpd	Structure	MW	Ms'd	Mtd	SM
428	 trans	410	411	H2	Int 156 + 1-(3,4-difluorophenyl)piperazine
429	 trans	457	457-459	H2	Int 156 + Int 197
430	 trans	471	471	H2	Int 156 + Int 211
431	 trans	441	441-443	H2	Int 156 + Int 206
432	 trans	441	441-443	H2	Int 156 + Int 198
433	 trans	423	423-425	H2	Int 156 + Int 196

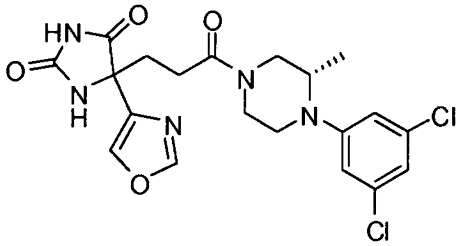
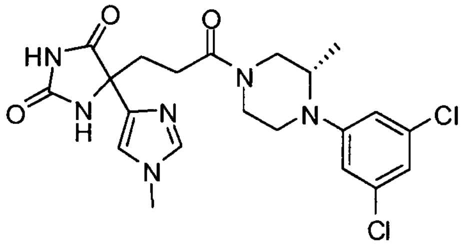
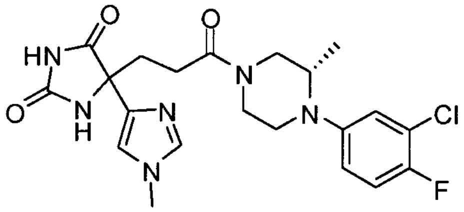
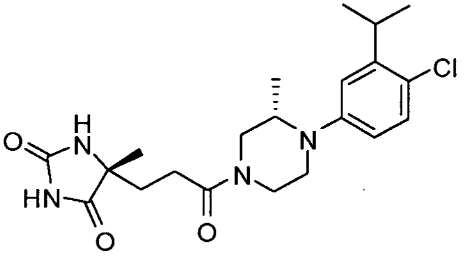
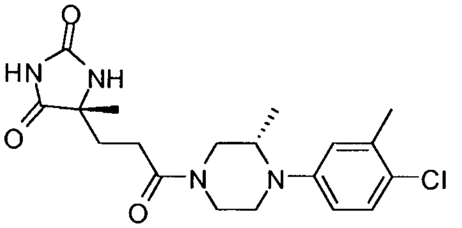
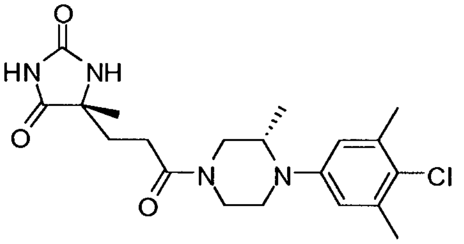
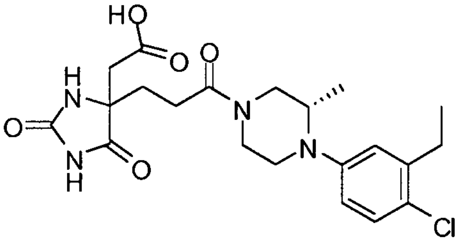
Cpd	Structure	MW	Ms'd	Mtd	SM
434	 trans	476	476- 478	H2	Int 159 + 1-(3,5-dichlorophenyl)piperazine
435	 trans	427	427- 429	F	Int 061
436	 trans	443	443- 445	F	Int 295
437	 trans	474	474	H2	Int 159 + Int 198
438		441	441- 443	F	Int 296

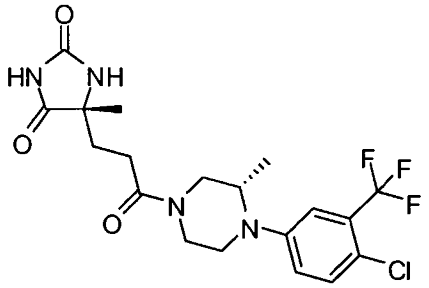
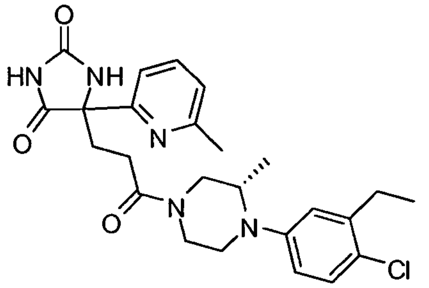
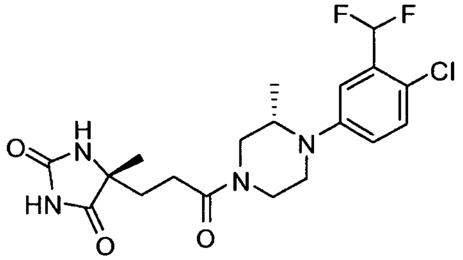
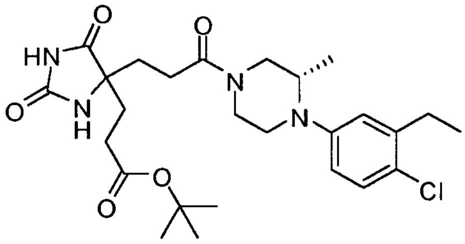
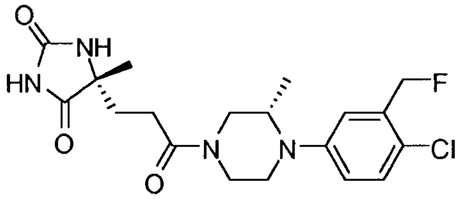
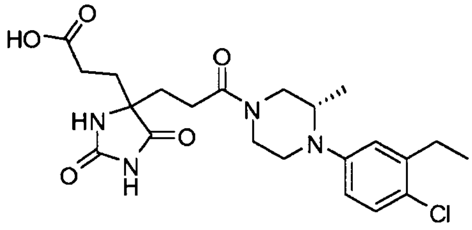
Cpd	Structure	MW	Ms'd	Mtd	SM
439	 trans	429	429- 431	F	Int 298
440		413	412- 414- 416	H2	3-(4-Methyl-2,5-dioxo-imidazolidin-4-yl) propionic acid + Int 279
441	 trans	397	397- 399	H2	Int 151 + Int 198
442	 trans	490	490- 492	H2	Int 159 + Int 197
443	 trans	427	427- 429	I4	Int 299
444	 trans	425	425- 427	H2	Int 169 + Int 198

Cpd	Structure	MW	Ms'd	Mtd	SM
445	 trans	425	425- 427	H2	Int 169 + Int 206
446	 trans	456	456- 458	H2	Int 159 + Int 200
447		474	474- 476	F	Int 300
448	 trans	445	445- 447	H2	Int 156 + Int 203
449	 trans	441	441- 443	F	Int 302
450	 trans	427	427- 429	F	Int 304

Cpd	Structure	MW	Ms'd	Mtd	SM
451	 trans	441	441- 443	F	Int 306
452		490	490- 492	H1	Int 166 + Int 201
453		476	476- 478	H2	Int 132 + Int 201
454		474	474- 476	H1	Int 166 + Int 213
455		441	441- 443	2.40	Cpd 432
456	 trans	417	417	H2	Int 164 + Int 210
457		460	460- 462	F	Int 307

Cpd	Structure	MW	Ms'd	Mtd	SM
458		476	476- 478	F	Int 105
459		476	476- 478	F	Int 308
460		477	477- 479	H2	Int 142 + Int 201
461		477	477	H2	Int 142 + Int 197
462		477	477- 479	H2	Int 139 + Int 201
463		461	461- 463	H2	Int 139 + Int 206
464		490	490- 492	H2	Int 174 + Int 201

Cpd	Structure	MW	Ms'd	Mtd	SM
465		466	466- 468	F	Int 309
466		479	479- 481	H1	Int 179 + Int 197
467		463	463- 465	H1	Int 179 + Int 198
468		421	421- 423	H2	Int 172 + Int 310
469		393	393- 395	H2	Int 172 + Int 311
470		407	407- 409	H2	Int 172 + Int 280
471		451	451- 453	2.38	Int 315

Cpd	Structure	MW	Ms'd	Mtd	SM
472		447	447- 449	H2	Int 172 + Int 314
473		484	484- 486	H2	Int 166 + Int 312
474		429	429- 431	H2	Int 172 + Int 316
475		521	521- 523	F	Int 317
476		411	411	H2	Int 172 + Int 319
477		465	465- 467	2.39	Cpd 475

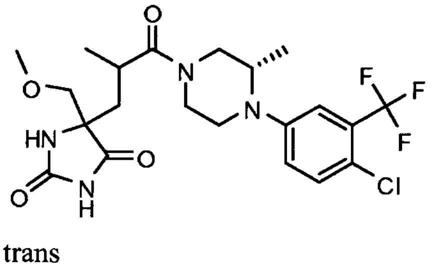
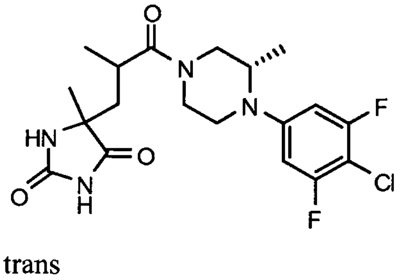
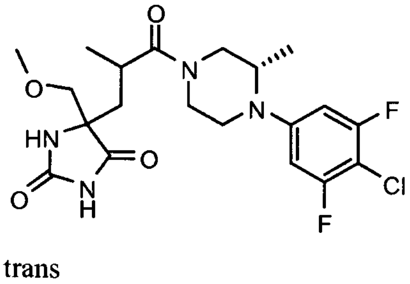
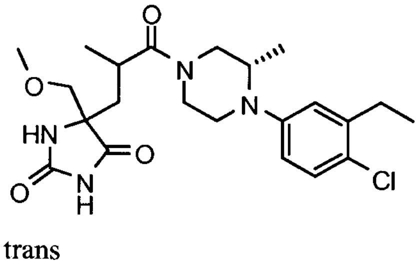
Cpd	Structure	MW	Ms'd	Mtd	SM
478		491	491	H2	Int 156 + Int 314
479		429	429	H2	Int 165 + Int 320
480		459	459	H2	Int 156 + Int 320
481		451	451	H2	Int 156 + Int 312

Table IV. NMR of illustrative compounds of the invention

Cpd	NMR
003	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.61 (1H, s), 7.91 (1H, m), 7.22 (1H, t), 6.97-6.94 (1H, m), 6.90 (1H, dd), 6.80 (1H, dd), 3.60-3.49 (4H, m), 3.24-3.10 (4H, m), 2.42-2.31 (1H, m), 2.27-2.16 (1H, m), 1.82 (2H, t), 1.27 (3H, s)
006	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.81 (1H, s), 8.69 (1H, s), 7.53-7.48 (2H, m), 7.44-7.38 (2H, m), 7.36-7.31 (1H, m), 7.22 (1H, t), 6.96-6.93 -1H, m), 6.89 (1H, dd), 6.80 (1H, dd), 3.58-3.40 (4H, m), 3.21-3.08 (4H, m), 2.40-2.11 (4H, m)

Cpd	NMR
034	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.60 (1H, s), 7.70 (1H, m), 7.22 (1H, t), 6.98-6.94 (1H, m), 6.90 (1H, dd), 6.80 (1H, dd), 3.60-3.49 (4H, m), 3.25-3.10 (4H, m), 2.47-2.36 (1H, m), 2.33-2.21 (1H, m), 2.00-1.89 (2H, m), 1.14-1.05 (1H, m), 0.50-0.41 (1H, m), 0.41-0.27 (2H, m), 0.15-0.06 (1H, m)
049	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.61 (1H, s), 7.91 (1H, m), 7.35 (1H, t), 6.97 (1H, dd), 6.79 (1H, dd), 3.59-3.47 (4H, m), 3.27-3.10 (4H, m), 2.42-2.31 (1H, m), 2.27-2.15 (1H, m), 1.81 (2H, t), 1.27 (3H, s)
052	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40 (1H, s), 7.04 (1H, t), 6.92 (1H, dd), 6.79-6.74 (1H,m), 6.15 (1H, s), 3.82-3.68 (2H, m), 3.64-3.54 (2H, m), 3.12-3.03 (4H, m), 2.41-2.35 (2H, m), 2.25-2.08 (2H, m), 1.48 (3H, s)
054	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.63 (1H, s), 7.85 (1H, s), 6.94 (2H, d), 6.87 (1H, t), 3.58-3.46 (4H, m), 3.30-3.16 (4H, m), 2.36-2.25 (1H, m), 2.20-2.09 (1H, m), 1.96-1.75 (3H, m), 0.89 (3H, d), 0.81 (3H, d)
059	^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.56 (1H, s), 7.22 (1H, d), 6.62 (1H, d), 6.30 (1H, s), 3.83-3.75 (1H, m), 3.75-3.67 (1H, m), 3.63-3.50 (4H, m), 3.48-3.42 (2H, m), 2.39 (2H, t), 2.25-2.08 (2H, m), 1.48 (3H, s)
067	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.61 (1H, s), 7.91 (1H, m), 7.41 (1H, d), 7.14 (1H, d), 6.94 (1H, dd), 3.62-3.46 (4H, m), 3.26-3.10 (4H, m), 2.43-2.30 (1H, m), 2.26-2.15 (1H, m), 1.81 (2H, t), 1.27 (3H, s)
088	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.0 (1H, s), 8.80 (1H, s), 8.71 (1H, d), 8.57 (1H, dd), 7.94-7.89 (1H, m), 7.56 (1H, dd), 7.04 (1H, d), 6.82-6.76 (2H, m), 3.60-3.43 (4H, m), 2.84-2.68 (4H, m), 2.42-2.16 (4H, m), 2.23 (3H, s), 2.20 (3H, s)
113	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.60 (1H, s), 7.70 (1H, s), 7.26 (1H, q), 7.02 (1H, ddd), 6.79-6.69 (1H, m), 3.62-3.47 (4H, m), 3.19-3.01 (4H, m), 2.48-2.34 (1H, m), 2.34-2.19 (1H, m), 2.00-1.87 (2H, m), 1.15-1.03 (1H, m), 0.51-0.25 (3H, m), 0.15-0.03 (1H, m)
181	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.59 (1H, s), 7.72 (1H, s), 7.39-7.12 (5H, m), 6.94 (2H, s), 6.88 (1H, s), 3.74-3.62 (2H, m), 3.59-3.42 (4H, m), 3.29-3.12 (4H, m), 2.75-2.67 (2H, m), 2.40-2.27 (1H, m), 2.25-2.20 (2H, m), 1.88-1.69 (2H, m)
188	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.66 (1H, s), 7.92 (1H, s), 6.95 (2H, d), 6.88 (1H, t), 3.59-3.45 (4H, m), 3.30-3.15 (4H, m), 2.77 (1H, d), 2.48 (1H, d), 2.44-2.32 (1H, m), 2.28-2.16 (1H, m), 1.88-1.72 (2H, m), 1.36 (9H, s)

Cpd	NMR
212	^{1}H NMR (400 MHz, DMSO-d6) δ ppm 10.61 (1H, s), 7.60 (0.4H, s), 7.56 (0.6H, s), 7.25 (1H, q), 7.02-6.91 (1H, m), 6.74-6.65 (1H, m), 4.24-4.16 (0.6H, m), 4.04-3.97 (0.4H, m), 3.97-3.82 (1.4H, m), 3.75-3.67 (0.6H, m), 3.47-3.38 (0.6H, m), 3.37-3.21 (1.4H, m), 3.16-3.08 (0.4H, m), 3.00-2.73 (2.6H, m), 2.42-2.25 (1H, m), 1.70 (1H, dd), 1.10-0.94 (4H, m), 0.90 (3H, dd), 0.47-0.21 (3H, m), 0.12-(-0.03) (1H, m) Rotamers ratio : 6:4
218	^{1}H NMR (400 MHz, CDCl$_3$) δ ppm 8.71 (1H, s), 6.83 (1H, t), 6.74 (2H, d), 6.20 (1H, br.s), 3.90-3.77 (1H, m), 3.70-3.49 (3H, m), 3.26-3.08 (5H, m), 3.07-2.94 (1H, m), 2.91 (3H, s), 2.73-2.49 (2H, m), 2.35-2.13 (2H, m), 1.85 (1H, d), 1.13 (3H, d)
223	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.66 (1H, s), 7.91 (1H, t), 7.67 (1H, m), 6.95 (2H, s), 6.88 (1H, s), 3.60-3.42 (4H, m), 3.42-3.10 (6H, m), 2.44-2.28 (1H, m), 2.26-2.12 (1H, m), 1.88-1.74 (5H, m)
241	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.9-7.4 (1H, br. s), 7.26 (1H, q), 7.00 (1H, ddd), 6.77-6.70 (1H, m), 3.72-3.41 (4H, m), 3.20-3.00 (4H, m), 2.72-2.61 (1H, m), 2.55-2.45 (1H, m), 2.43-2.34 (1H, m), 2.23 (1H, dd), 1.70-1.50 (3H, m), 0.96 (3H, d)
255	^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.06-0.14 (m, 1H), 0.28-0.40 (m, 2H), 0.42-0.49 (m, 1H), 0.91 (d, 1.5H), 0.97 (d, 1.5H), 1.04-1.14 (m, 1H), 1.88-2.03 (m, 2H), 2.20-2.33 (m, 1H), 2.37-2.52 (m, 1H), 2.81-3.05 (m, 2H), 3.21-3.29 (m, 0.5H), 3.40-3.49 (m, 1.5H), 3.65 (d, 0.5H), 3.80 (d, 0.5H), 4.10 (br. s., 1H), 4.17 (d, 0.5H), 4.29 (d, 0.5H), 6.44 (t, 1H), 6.50-6.60 (m, 2H), 7.70 (s, 0.5H), 7.74 (s, 0.5H), 10.61 (br. s., 1H)
281	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.62 (1H, br. s), 8.62 (2H,s), 7.78-7.64 (3H, m), 7.36 (1H, t), 7.24 (1H, s), 7.17 (1H, d), 7.05-6.98 (1H, m), 4.32-4.23 (0.5H, m), 4.20-4.10 (1.5H, m), 3.87-3.78 (0.5H, m), 3.68-3.60 (0.5H, m), 3.54-3.41 (1.5H, m), 3.37-3.30 (0.5H, m), 3.14-2.90 (2H, m), 2.48-2.18 (2H, m), 2.02-1.92 (2H, m), 1.16-1.06 (1H, m), 0.96 (1.5H, d), 0.89 (1.5H, d), 0.50-0.41 (1H, m), 0.41-0.27 (2H, m), 0.15-0.05 (1H, m)
293	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.62 (1H, s), 7.93 (1H, s), 7.11 (1H, dd), 6.89 (1H, dd), 3.63-3.53 (4H, m), 2.88-2.76 (4H, m), 2.42-2.34 (1H, m), 2.26 (3H, s), 2.26-2.16 (1H, m), 1.82 (2H, t), 1.27 (3H, s)
302	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.62 (1H, s), 8.56-8.54 (1H, m), 7.78-7.71 (1H, m), 7.39 (1H, dd), 7.20 (1H, d), 4.66-4.52 (1H, m), 4.37-4.28 (0.5H, m), 4.23 (0.5H, d), 4.18-4.05 (1H, m), 3.90-3.83 (0.5H, m), 3.75-3.67 (0.5H, m), 3.45 (0.5H, dd), 3.32-3.13 (1H, m), 3.12-2.95 (1H, m), 2.91-2.80 (0.5H, m), 2.49-2.21 (2H, m), 2.05-1.88 (2H, m), 1.15-1.05 (1H, m), 1.08 (1.5H, d), 1.00 (1.5H, d), 0.50-0.40 (1H, m), 0.40-0.26 (2H, m), 0.14-0.05 (1H, m)

Cpd	NMR
372	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 10.62 (1H, s), 9.25 (1H, d), 8.71-8.69 (1H, m), 8.60 (1H, d), 7.76-7.70 (1H, t), 7.65-7.61 (1H, m), 7.53 (1H, d), 7.39 (1H, t), 7.09-7.03 (1H, m), 4.33-4.26 (0.5H, m), 4.20-4.11 (1.5H, m), 3.88-3.80 (0.5H, m), 3.70-3.60 (0.5H, m), 3.55-3.36 (2H, m), 3.14-2.90 (2H, m), 2.48-2.20 (2H, m), 2.05-1.91 (2H, m), 1.17-1.03 (1H, m), 0.97 (1.5H, d), 0.90 (1.5H, d), 0.51-0.41 (1H, m), 0.41-0.27 (2H, m), 0.16-0.05 (1H, m)

BIOLOGICAL EXAMPLES

Example 3. In vitro assays

3.1. hADAMTS-1

[0389] The basis for the assay is the cleavage of the substrate 5(6)-Fluorescein-NH-AELQGRPISIAK-5(6)-TAMRA (SEQ ID N°1) by human ADAMTS1

[0390] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM MOPS pH7; 50mM NaCl; 5mM $CaCl_2$; 0.05% CHAPS; 5µM $ZnCl_2$) containing hADAMTS1 (0.38 ng/µL, R&D SYSTEMS INC., Cat# 2197-AD)) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0391] The reaction is initiated by adding to the assay plate 5(6)-Fluorescein-NH-AELQGRPISIAK-5(6)-TAMRA (SEQ ID N°1) (10 µL, 7µM, Anaspec) in the same buffer.

[0392] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 120 min at 37°C (Excitation 485 nm, Emission 535).

3.2. hADAMTS-4

3.2.1. Protocol 1

[0393] The basis for the assay is the cleavage of the substrate TBIS-1 (5-FAM-TEGEARGSVILLK (5TAMRA)K-NH_2) (SEQ ID N°2) by human ADAMTS4

[0394] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM Hepes pH7.5 , 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS, 5% glycerol) containing hADAMTS4 (0.325 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0395] The reaction is initiated by adding to the assay plate TBIS-1 (10 µL, 4.5µM, Anaspec) in the same buffer.

[0396] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 60 min at room temperature (Excitation 485 nm, emission 535).

3.2.2. Protocol 2

[0397] The basis for the assay is the cleavage of the substrate TBIS-1 (5 FAM-TEGEARGSVILLK (5TAMRA)K-NH_2) (SEQ ID N°2) by human ADAMTS4

[0398] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM Hepes pH 7.5 , 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS) containing hADAMTS4 (0.38 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0399] The reaction is initiated by adding to the assay plate TBIS-1 (10 µL, 4.5µM, Anaspec) in the same buffer.

[0400] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 180 min at 37°C (Excitation 485 nm, emission 535).

3.3. Rat ADAMTS-5

[0401] The basis for the assay is the cleavage of the substrate TBIS-1 (5 FAM-TEGEARGSVILLK (5TAMRA)K-NH_2) (SEQ ID N°2) by rnADAMTS-5 (1-564-6H).

[0402] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM TRIS pH7.5, 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS) containing rnADAMTS-5 (0.5 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0403] The reaction is initiated by adding to the assay plate TBIS-1 (10 µL, 4.5µM, Anaspec) in the same buffer.

[0404] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 120 min at 37°C (Excitation 485 nm, emission 535).

[0405] The IC_{50} measured for illustrative compounds of the invention is reported in Table V below.

Table V. Rat ADAMTS-5 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)
1	730
2	361
3	323

Cpd	IC_{50} (nM)
4	66
5	101
6	107

Cpd	IC$_{50}$ (nM)
7	272
8	157
9	331
10	41
11	1170
12	1160
13	966
14	784
15	>4000
16	329
17	>3940
18	930
19	>4000
20	1270
21	162
22	3900
23	158
24	132
27	124
33	178
34	41
35	103
36	29
40	234
46	42
47	236
49	141
51	508
53	179
54	91
55	37
56	72
57	117
64	165
65	65
66	1370
68	200
69	185
70	205
71	198
72	282
73	489
74	106
75	141

Cpd	IC$_{50}$ (nM)
76	102
77	169
78	96
79	53
80	429
81	827
82	2090
83	436
84	637
85	1110
86	1790
87	113
88	119
89	72
90	70
91	69
92	64
93	>4000
94	3020
95	40
96	57
97	148
98	82
99	116
100	163
101	165
102	94
103	24
104	41
105	162
106	222
107	147
108	410
109	182
110	299
111	46
112	39
113	91
114	62
115	38
116	29
121	24
124	37
135	125

Cpd	IC$_{50}$ (nM)
136	242
137	249
138	107
142	54
143	314
144	271
145	563
146	133
147	99
148	97
151	83
152	62
153	114
154	507
156	128
157	284
158	389
159	127
160	36
161	37
162	45
163	45
167	10
168	129
169	27
170	244
172	11
173	21
174	17
175	22
176	7
177	40
178	344
179	34
180	241
181	127
182	87
183	266
184	280
186	136
187	396
188	54

Cpd	IC$_{50}$ (nM)
189	254
190	15
191	11
192	6
193	7
194	5
195	262
196	104
197	21
198	38
199	48
200	135
203	26
204	11
205	27
206	40
207	6
208	79
209	565
210	105
211	23
212	5
213	21
214	30
215	18
216	250
217	49
218	17
219	29
233	20
242	57
249	34
255	23
265	22
294	128
295	71
314	34
388	74
405	18
406	20

3.4. hADAMTS-5

3.4.1. Protocol 1

[0406] The basis for the assay is the cleavage of the substrate TBIS-1 (5 FAM-TEGEARGSVILLK (5TAMRA)K-NH_2) (SEQ ID N°2) by human ADAMTS-5.

[0407] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM Hepes pH7.5 , 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS, 5% glycerol) containing hADAMTS-5 (0.5 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0408] The reaction is initiated by adding to the assay plate TBIS-1 (10 µL, 4.5µM ,Anaspec) in the same buffer.

[0409] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 60 min at Room Temperature (Excitation 485 nm, emission 530).

3.4.2. Protocol 2

[0410] The basis for the assay is the cleavage of the substrate TBIS-1 (5 FAM-TEGEARGSVILLK (5TAMRA)K-NH_2) (SEQ ID N°2) by human ADAMTS-5.

[0411] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM Hepes pH7.5 , 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS l) containing hADAMTS-5 (1 ng/µL, affinity purified, followed by overnight digestion of 6His tag by thrombin and dialysis) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0412] The reaction is initiated by adding to the assay plate TBIS-1 (10 µL, 4.5µM, Anaspec) in the same buffer.

[0413] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 45 min at 37°C (Excitation 485 nm, emission 530).

[0414] The IC_{50} measured for illustrative compounds of the invention is reported in Table VI below.

Table VI. hADAMTS-5 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)
1	694
2	274
3	233
4	114

Cpd	IC_{50} (nM)
5	78
6	79
7	272
8	142

Cpd	IC$_{50}$ (nM)
9	316
10	56
11	988
12	1300
13	836
14	897
15	>4000
16	301
17	2840
18	675
19	>4000
20	1280
21	166
22	>3790
23	157
24	93
25	138
26	706
27	90
28	209
29	>12000
30	>4000
31	1060
32	385
33	134
34	39
35	99
36	34
37	229
38	>4000
39	570
40	186
41	2660
42	>3980
43	1530
44	553
45	204
46	35
47	186

Cpd	IC$_{50}$ (nM)
48	391
49	127
50	>4000
51	282
52	281
53	118
54	61
55	36
56	38
57	93
58	>20000
59	>20000
60	1160
61	2940
62	293
63	1240
64	125
65	50
66	1310
67	152
68	169
69	178
70	253
71	200
72	264
73	382
74	89
75	73
76	91
77	107
78	79
79	53
80	257
81	681
82	1740
83	423
84	815
85	1270
86	1700

Cpd	IC$_{50}$ (nM)
87	137
88	119
89	94
90	85
91	95
92	63
93	>4080
94	2130
95	48
96	49
97	168
98	73
99	160
100	185
101	154
102	104
103	28
104	43
105	226
106	233
107	172
108	320
109	261
110	297
111	42
112	40
113	104
114	67
115	36
116	30
117	211
118	563
119	1740
120	690
121	15
122	341
123	95
124	48

Cpd	IC$_{50}$ (nM)
125	53
126	106
127	96
128	1170
129	150
130	126
131	1260
132	37
133	108
134	1870
135	167
136	187
137	240
138	101
139	231
140	149
141	119
142	39
143	259
144	227
145	505
146	89
147	62
148	63
149	79
150	95
151	68
152	48
153	84
154	430
156	130
157	275
158	351
159	104
160	29
407	33.5

3.4.3. Protocol 3

[0415] The basis for the assay is the cleavage of the substrate TBIS-1 (5 FAM-TEGEARGSVILLK (5TAMRA)K-NH_2) (SEQ ID N°2) by human ADAMTS-5.

[0416] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM Hepes pH7.5 , 100mM NaCl, 5mM $CaCl_2$, 0.1% CHAPS) containing hADAMTS-5 (0.63 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0417] The reaction is initiated by adding to the assay plate TBIS-1 (10 µL, 4.5µM, Anaspec) in the same buffer.

[0418] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 90 min at 37°C (Excitation 485 nm, emission 530).

[0419] The IC_{50} measured for illustrative compounds of the invention is reported in Table VII below.

Table VII. hADAMTS-5 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)
1	1440
3	486
6	86
12	1554
19	>4000
29	>4000
30	>4000
34	73
40	243
50	>4000
51	920
53	148
55	69
75	61
98	127
99	534
102	184
112	58
115	106
116	51
118	711
120	1120
121	15
122	590

Cpd	IC_{50} (nM)
124	35
127	85
135	233
136	286
140	240
142	25
143	443
144	154
145	838
146	70
147	47
148	76
151	32
152	63
153	63
154	742
155	1250
156	188
157	241
158	364
159	126
160	32
161	54
162	39

Cpd	IC$_{50}$ (nM)
163	40
164	236
165	207
166	264
167	19
168	76
169	30
170	170
171	305
172	17
173	22
174	21
175	25
176	16
177	78
178	577
179	94
180	177
181	97
182	104
183	235
184	272
185	>4000
186	110
187	456
188	53
189	256
190	22
191	20
192	11
193	23
194	11
195	318
196	102
197	26
198	52
199	62
200	109
201	307
202	724
203	46
204	16
205	26
206	60
207	12
208	126

Cpd	IC$_{50}$ (nM)
209	836
210	108
211	48
212	12
213	30
214	61
215	37
216	305
217	59
218	20
219	41
220	18
221	110
222	20
223	70
224	14
225	28
226	22
227	105
228	109
229	31
230	24
231	20
232	47
233	27
234	28
235	16
236	15
237	106
238	141
239	46
240	194
241	232
242	66
243	>3890
244	2310
245	17
246	114
247	95
248	49
249	36
250	2150
251	94
252	67
253	35
254	71

Cpd	IC$_{50}$ (nM)
255	20
256	1410
257	1570
258	1530
259	224
260	126
261	165
262	>4000
263	19
264	19
265	18
266	28
267	3080
268	62
269	19
270	76
271	1300
272	623
273	322
274	>4000
275	266
276	115
277	152
278	>20000
279	19
280	275
281	189
282	110
283	1080
284	>12000
285	892
286	>4000
287	52
288	72
289	97
290	2850
291	453
292	48
293	294
294	134
295	115
296	>4000
297	>3620
298	192
299	114
300	140

Cpd	IC$_{50}$ (nM)
301	>20000
302	776
303	266
304	>4000
305	674
306	67
307	44
308	59
309	31
310	50
311	57
312	40
313	34
314	24
315	42
316	61
317	52
318	59
319	94
320	48
321	199
322	237
323	1240
324	407
325	796
326	52
327	45
328	>4000
329	134
330	>4000
331	14
332	61
333	3120
334	430
335	78
336	74
337	764
338	60
339	33
340	155
341	264
342	39
343	22
344	>20000
345	50
346	37

Cpd	IC_{50} (nM)
347	21
348	34
349	62
350	62
351	35
352	>20000
353	1640
354	>20000
355	200
356	40
357	25
358	953
359	83
360	119
361	51
362	50
363	76
364	92
365	72
366	36
367	44
368	257
369	1080
370	532
371	42
372	2390
373	1530
374	3080
375	30
376	52
377	700
378	22
379	18
380	47
381	1970
382	39
383	43
384	60
385	71
386	48
387	37
388	57
389	40
391	>4000
392	567
394	49

Cpd	IC_{50} (nM)
395	39
396	53
397	37
399	163
400	383
401	1120
402	732
403	168
404	19
405	22
406	26
407	25
408	19
409	17
410	22
411	11
412	13
413	11
414	40
415	28
416	12
417	22
418	33
419	23
420	32
421	38
422	21
423	58
424	53
425	18
426	110
427	20
428	14
429	53
430	105
431	30
432	26
433	21
434	20
435	15
436	22
437	17
438	56
439	43
440	2150
441	59

Cpd	IC_{50} (nM)
442	24
443	32
444	25
445	29
446	19
447	56
448	19
449	40
450	58
451	48
452	23
453	36
454	35
455	14
456	27
457	47
458	21
459	46
460	30
461	39

Cpd	IC_{50} (nM)
462	22
463	46
464	26
465	62
466	55
467	42
468	>4000
469	215
470	383
471	852
472	899
474	626
475	307
476	175
477	239
478	61
479	19
480	31
481	29

3.5. hTACE

[0420] The basis for the assay is the cleavage of the substrate 5FAM-LAQAVRSSSRK-5TAMRA (SEQ ID N°3) (Anaspec, custom 34891) by human TACE (R&D SYSTEMS INC., Cat#930-ADB).

[0421] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (25mM Tris pH8.0, 2.5µM $ZnCl_2$, 0.01% CHAPS) containing TACE (0.05 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0422] The reaction is initiated by adding to the assay plate 5FAM-LAQAVRSSSRK-5TAMRA (5 µL, 5µM, Anaspec) in the same buffer.

[0423] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 75 min at room temperature (Excitation 485 nm, Emission 530).

[0424] The IC_{50} measured for illustrative compounds of the invention is reported in Table VIII below.

Table VIII. TACE potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)
1	>20000
2	>17500
3	>5500

Cpd	IC_{50} (nM)
4	>5500
5	>3330
6	2360

Cpd	IC$_{50}$ (nM)
7	>2930
8	>3220
9	2500
10	>2790
11	>20000
12	>4000
13	1170
14	>4000
16	457
17	>4000
18	>4000
20	>4000
21	2060
24	298
25	>2000
26	>10000
27	>2000
28	>20000
32	>4000
33	429
34	>4000
35	>4000
36	670
37	>20000
39	588
40	2720
43	>20000
44	>20000
45	>20000
46	137
47	>20000
49	>20000
51	>3660
52	>20000
53	>4000
54	2270
55	>3310
56	3190
57	>12000
60	>20000
62	>20000
63	>20000
64	3140
65	56

Cpd	IC$_{50}$ (nM)
66	>20000
67	>4000
70	>20000
74	1360
75	550
76	1780
78	2660
79	277
80	>20000
83	2490
85	>4000
86	>4000
87	120
88	211
89	984
90	>4000
91	>4000
92	1050
93	>3530
94	>4000
95	>4000
96	3590
97	>4000
98	>4000
99	>14700
100	>4000
102	3400
103	4100
104	461
105	>20000
106	>20000
107	>4000
109	5260
111	963
112	>4000
113	>20000
114	>20000
115	>20000
116	>4640
117	>4000
118	>4000
120	>4000
121	1100
122	>4000

Cpd	IC_{50} (nM)
123	1640
124	880
125	1800
126	>4000
127	>4000
128	>20000
129	>4000
130	>4000
132	348
133	195
134	>20000
135	>20000
136	>20000
137	>20000
138	>20000
139	1320
140	>20000
142	>4000
143	>20000
144	>4000
145	>4000
146	1580
147	>4000
148	>4000
151	>20000
152	>20000
153	2270
154	>20000
155	>20000
156	>20000
157	>20000
158	>20000
159	1870
160	>20000
161	>20000
162	>20000
163	>20000
164	>20000
165	>20000
166	>20000
167	>4000
168	>20000
169	>20000
170	n/a

Cpd	IC_{50} (nM)
171	>20000
172	311
173	3140
174	321
175	251
176	1230
177	1990
179	785
180	>4000
181	2860
182	>4000
183	>20000
186	4070
187	>20000
188	>4000
189	>4000
190	>20000
191	>20000
192	>4000
193	>20000
194	>4000
196	>3930
197	134
198	817
199	1050
200	1060
201	>20000
203	>20000
204	3870
205	>20000
206	>4000
207	>4000
208	>4000
209	>4000
210	1440
211	3740
212	>4000
213	>20000
214	>4000
215	>12000
216	>4000
217	>4000
218	272
219	441

Cpd	**IC$_{50}$ (nM)**
220	245
221	3200
222	337
223	>4000
224	>4000
225	>20000
226	>4000
227	>3510
228	>4000
229	>4000
230	207
231	106
232	>4000
233	>4000
234	>4000
235	1320
236	225
237	>4000
238	3160
239	>4000
240	>20000
241	>12000
242	2520
243	>19500
244	>19500
245	2130
246	>19500
247	>19600
248	>3780
249	>19600
250	417
251	>12000
252	2690
253	>20000
254	1000
255	>20000
256	>20000
257	>4000
258	>20000
259	>20000
260	>20000
261	>20000
262	>4000
263	2620

Cpd	**IC$_{50}$ (nM)**
264	>4000
265	>4000
266	>4000
267	>4000
268	>4000
269	840
270	>4000
271	>20000
272	>4000
273	>20000
274	>20000
275	>20000
276	>4000
277	>4000
278	>20000
279	2990
280	>20000
281	>20000
282	>20000
283	>20000
284	>20000
285	>4000
286	>20000
287	>4000
288	>4000
289	>4000
290	>20000
291	>20000
292	>4000
294	>20000
295	>20000
296	>20000
297	>20000
298	>20000
299	>20000
300	>20000
301	>20000
302	>20000
303	>20000
304	>20000
305	>20000
306	>4000
307	3590
308	>4000

Cpd	IC$_{50}$ (nM)
309	>4000
310	1320
311	3070
312	3680
313	>20000
314	>4000
315	>4000
316	>4000
317	>4000
318	2190
319	>4000
320	>4000
321	>4000
322	>4000
323	>4000
324	>4000
325	>20000
326	>4000
327	>4000
328	>20000
329	>20000
330	>20000
331	>4000
332	>20000
333	>20000
334	>20000
335	>4000
336	>4000
337	>20000
338	>4000
339	>4000
340	>4000
341	885
342	>4000
343	>20000
344	>20000
345	>4000
346	>4000
347	2380
348	>4000
349	>4000
350	>20000
351	>20000
352	>20000

Cpd	IC$_{50}$ (nM)
353	>20000
354	>20000
355	>20000
356	>4000
357	>4000
358	>20000
359	>12000
360	>20000
361	>20000
362	>20000
363	>12000
364	>20000
365	>9330
366	>4000
367	>4000
368	>20000
369	>20000
370	>20000
371	>3730
372	>20000
373	>20000
374	>20000
375	1130
376	2430
377	>20000
378	>4000
379	1490
380	>4000
381	>20000
382	>20000
383	>4000
384	2230
385	>4000
386	>4000
387	>4000
388	>4000
389	>4000
391	>4000
392	>20000
394	>20000
395	>20000
396	>4000
397	>4000
400	2930

Cpd	IC_{50} (nM)
404	>4000
405	>4000
406	>4000
407	479
408	>4000
409	311
410	170
411	>4000
412	>20000
413	>4000
414	>4000
415	396
416	>4000
417	479
418	>4000
419	>4000
420	2980
421	>4000
422	>4000
423	1470
424	>10800
425	245
426	3200
427	337
428	>4000
429	>3980
430	>3510
431	>4000
432	>4000
433	1250
434	106
435	225
436	368
437	2130
438	1280
439	787
440	417
441	>20000
442	789

Cpd	IC_{50} (nM)
443	>4000
444	>4000
445	>4000
446	840
447	3620
448	2990
449	>20000
450	>20000
451	>12000
452	1780
453	3180
454	2980
455	>4000
456	>4000
457	>4000
458	2380
459	1740
460	>4000
461	2540
462	>4000
463	>4000
464	>4000
465	3500
466	2640
467	>4000
468	>4000
469	>4000
470	2930
472	>4000
474	>4000
475	2650
476	>4000
477	>20000
478	>4000
479	>4000
480	>20000
481	3950

3.6. hMMP1

[0425] Inhibition of the proteases human MMP1 was determined at REACTION BIOLOGY (Reaction Biology Corp. 1 Great Valley Parkway, Suite 2 Malvern, PA 19355, USA) in fluorescent based biochemical assays. The protease activities were monitored as a time-course measurement of the increase in fluorescence signal from fluorescently-labeled peptide substrates, and initial linear portion of slope (signal/min) was analyzed.

[0426] To determine the IC_{50}, a compound is tested starting from 100 nM (highest dilution) with a 1/3 dilution.

[0427] The IC_{50} measured for illustrative compounds of the invention is reported in Table IX below.

Table IX. hMMP-1 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)
27	30000
36	30000
40	>30000
55	>30000
255	>30000

3.7. hMMP2

3.7.1. Protocol 1

[0428] The basis for the assay is the cleavage of the substrate 520 MMP fret substrate XV (Anaspec, Catalog #: AS-60582-01) by human MMP2 (R&D SYSTEMS INC. Systems Inc., Cat# 902-MP).

[0429] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50 mM Tris pH 7.5 , 10mM, $CaCl_2$, 150 mM NaCl, 0.05% Brij35) containing preactivated MMP2 (0.0125 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration). Human MMP2 is preactivated by incubated the enzyme in the same buffer complemented with 1 mM freshly prepared p-Aminophenylmercuric acetate (AMPA) for 1 hour at 37°C.

[0430] The reaction is initiated by adding to the assay plate 520 MMP fret substrate XV (10 µL, 4µM, Anaspec) in the same buffer.

[0431] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 30 min at room temperature (Excitation 485 nm, Emission 530).

[0432] The IC_{50} measured for illustrative compounds of the invention is reported in Table X below.

Table X. hMMP-2 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)	Cpd	IC_{50} (nM)
1	1570	7	>16700
2	250	8	>16700
3	1480	9	271
4	259	10	26
5	44	11	>20000
6	379	12	>20000

Cpd	IC_{50} (nM)
13	>20000
14	38
16	>16700
18	>20000
20	>20000
21	>20000
24	>20000
25	101
26	111
27	>10000
32	>20000
33	>20000
34	220
35	>20000
36	>20000
37	914
39	>20000
40	>4000

Cpd	IC_{50} (nM)
44	2950
45	>4000
46	>20000
47	550
49	83
51	n/a
52	2910
53	3930
54	n/a
55	>20000
56	140
57	n/a
60	>20000
62	>20000
63	>20000
64	>20000
65	>20000

3.7.2. Protocol 2

[0433] The basis for the assay is the cleavage of the substrate 390 MMP FRET substrate I (Anaspec, Catalog n#: AS-27076) by human MMP2 (R&D SYSTEMS INC., Cat#902-MP).

[0434] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (45 mM Tris pH 7.5 , 9mM $CaCl_2$, 135mM NaCl, 0.045% Brij35) containing MMP2 (0.03 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0435] The reaction is initiated by adding to the assay plate 390 MMP FRET substrate I (10 µL, 2.5µM, Anaspec) in the same buffer.

[0436] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 30 min at room temperature (Excitation 485 nm, Emission 530).

[0437] The IC_{50} measured for illustrative compounds of the invention is reported in Table XI below.

Table XI. hMMP-2 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)
3	2560
5	212
17	>20000
28	192
34	489
35	>20000

Cpd	IC_{50} (nM)
36	>20000
40	>20000
43	>20000
46	>20000
47	1410
51	>20000

Cpd	IC$_{50}$ (nM)
53	>4000
54	>20000
55	>20000
57	>20000
60	>20000
64	>20000
65	>20000
66	>4000
67	794
70	1950
74	1410
75	>20000
76	674
78	711
79	>20000
80	452
83	407
85	>20000
86	>20000
87	>20000
88	>20000
89	>20000
90	219
91	745
92	>20000
93	>20000
94	>20000
95	381
96	639
97	>20000
98	>20000
99	>20000
100	>20000
102	>20000
103	123
104	2560
105	212
106	>20000
107	192
109	489
111	>20000
112	>20000
113	>20000
114	>20000
115	>20000
116	1410

Cpd	IC$_{50}$ (nM)
117	>20000
118	>4000
120	>20000
121	>20000
122	>20000
123	>20000
124	>20000
125	>20000
126	>4000
127	794
128	1950
129	1410
130	>20000
132	674
133	711
134	>20000
135	452
136	407
137	>20000
138	>20000
139	>20000
140	>20000
142	>20000
143	219
144	745
145	>20000
146	>20000
147	>20000
148	381
151	639
152	>20000
153	>20000
154	>20000
155	>20000
156	>20000
157	123
158	2560
159	212
160	>20000
161	192
162	489
163	>20000
164	>20000
165	>20000
166	>20000
167	>20000

Cpd	IC_{50} (nM)
168	1410
169	>20000
170	>4000
171	>20000
172	>20000
173	>20000
174	>20000
175	>20000
176	>20000
177	>4000
179	794
180	1950
181	1410
182	>20000
183	674
186	711
187	>20000
188	452
189	407
190	>20000
191	>20000
192	>20000
193	>20000
194	219
196	745
197	>20000
198	>20000
199	>20000
200	381
201	639
203	>20000
204	>20000
205	>20000
206	>20000
207	>20000
208	123
209	2560
210	212
211	>20000
212	192
213	489
214	>20000
215	>20000
216	>20000
217	>20000
218	>20000

Cpd	IC_{50} (nM)
219	1410
220	>20000
221	>4000
222	>20000
223	>20000
224	>20000
225	>20000
226	>20000
227	>20000
228	>4000
229	794
230	1950
231	1410
232	>20000
233	674
234	711
235	>20000
236	452
237	407
238	>20000
239	>20000
240	>20000
241	>20000
242	>20000
243	219
244	745
245	>20000
246	>20000
247	>20000
248	381
249	639
250	>20000
251	>20000
252	>20000
253	>20000
254	>20000
255	123
256	2560
257	212
258	>20000
259	192
260	489
261	>20000
262	>20000
263	>20000
264	>20000

Cpd	IC$_{50}$ (nM)
265	>20000
266	1410
267	>20000
268	>4000
269	>20000
270	>20000
271	>20000
272	>20000
273	>20000
274	>20000
275	>4000
276	794
277	1950
278	1410
279	>20000
280	674
281	711
282	>20000
283	452
284	407
285	>20000
286	>20000
287	>20000
288	>20000
289	>20000
290	219
291	745
292	>20000
294	>20000
295	>20000
296	381
297	639
298	>20000
299	>20000
300	>20000
301	>20000
302	>20000
303	123
304	2560
305	212
306	>20000
307	192
308	489
309	>20000
310	>20000
311	>20000

Cpd	IC$_{50}$ (nM)
312	>20000
313	>20000
314	1410
315	>20000
316	>4000
317	>20000
318	>20000
319	>20000
320	>20000
321	>20000
322	>20000
323	>4000
324	794
325	1950
326	1410
327	>20000
328	674
329	711
330	>20000
331	452
332	407
333	>20000
334	>20000
335	>20000
336	>20000
337	>20000
338	219
339	745
340	>20000
341	>20000
342	>20000
343	381
344	639
345	>20000
346	>20000
347	>20000
348	>20000
349	>20000
350	123
351	2560
352	212
353	>20000
354	192
355	489
356	>20000
357	>20000

Cpd	IC_{50} (nM)
358	>20000
359	>20000
360	>20000
361	1410
362	>20000
363	>4000
364	>20000
365	>20000
366	>20000
367	>20000
368	>20000
369	>20000
370	>4000
371	794
372	1950
373	1410
374	>20000
375	674
376	711
377	>20000
378	452
379	407
380	>20000
381	>20000
382	>20000
383	>20000
384	>20000
385	219
386	745
387	>20000
388	>20000
389	>20000
391	381
392	639
394	>20000
395	>20000
396	>20000
397	>20000
400	>20000
404	123
405	909
406	581
407	>20000
408	1370
409	3020
410	>4000

Cpd	IC_{50} (nM)
411	547
412	63
413	411
414	2053
415	1390
416	990
417	1070
418	740
419	219
420	>14700
421	701
422	879
423	>20000
424	>20000
425	2820
426	>4000
427	>4000
428	38
429	>12000
430	>20000
431	501
432	581
433	>4000
434	1620
435	2590
436	>4000
437	225
438	3420
439	>3890
440	>20000
441	1530
442	>4000
443	1330
444	1440
445	945
446	119
447	>4000
448	2
449	1380
450	>3710
451	1100
452	1860
453	1540
454	449
455	209
456	279

Cpd	IC_{50} (nM)
457	3110
458	846
459	>20000
460	1040
461	>20000
462	946
463	2430
464	848
465	>20000
466	>20000
467	1860
468	>20000

Cpd	IC_{50} (nM)
469	520
470	>4000
472	>4000
474	3260
475	>4000
476	387
477	>20000
478	1020
479	31
480	53
481	3060

3.8. hMMP8

[0438] Inhibition of the human MMP8 protease is determined at REACTION BIOLOGY (Reaction Biology Corp. 1 Great Valley Parkway, Suite 2 Malvern, PA 19355, USA; cat# MMP8) in fluorescence based biochemical assays. The protease activity is monitored as a time-course measurement of the increase in fluorescence signal from fluorescently-labeled peptide substrates, and the slope (signal/min) of the initial linear portion is measured.

[0439] The basis for the assay is the cleavage of the substrate 520 MMP FRET Substrate XIV (Anaspec, cat# AS-60581) by human MMP8 (Enzo®, cat# SE-255) in a buffer solution (50 mM HEPES pH 7.5, 10 mM $CaCl_2$, 0.01% Brij-35, 0.1 mg/mL BSA).

[0440] A 100% DMSO dilution series of test compound (10 final concentrations starting from 30 μM highest concentration, with 1/3 serial dilutions) is added to MMP8 in buffer solution and incubated at room temperature for 5-15 min (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration). The reaction is then initiated by adding 520 MMP FRET Substrate XIV (5 μM final concentration) in the same buffer.

[0441] Fluorescence is read at 5 min intervals for 2 h with an Envision (Perkin Elmer) at room temperature (Excitation 485 nm, Emission 520 nm). The slope of the initial linear portion of the fluorescence signal curve is then calculated by using Excel. Percent protease activity is calculated relative to a no inhibitor DMSO control defined as 100% activity. IC_{50} curve fits are performed using Prism software.

3.9. hMMP12

[0442] Inhibition of the human MMP12 protease is determined at REACTION BIOLOGY (Reaction Biology Corp. 1 Great Valley Parkway, Suite 2 Malvern, PA 19355, USA; cat# MMP12) in fluorescence based biochemical assays. The protease activity is monitored as a time-course measurement of the increase in fluorescence signal from fluorescently-labeled peptide substrates, and the slope (signal/min) of the initial linear portion is measured.

[0443] The basis for the assay is the cleavage of the substrate 520 MMP FRET Substrate XIV (Anaspec, cat# AS 60581) by human MMP12 (Enzo®, cat# SE-138) in a buffer solution (50 mM HEPES pH 7.5, 10 mM CaCl2, 0.01% Brij-35, 0.1 mg/mL BSA).

[0444] A 100% DMSO dilution series of test compound (10 final concentrations starting from 30 µM highest concentration, with 1/3 serial dilutions) is added to MMP12 in buffer solution and incubated at room temperature for 5-15 min (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration). The reaction is then initiated by adding 520 MMP FRET Substrate XIV (5 µM final concentration) in the same buffer.

[0445] Fluorescence is read at 5 min intervals for 2 h with an Envision (Perkin Elmer) at room temperature (Excitation 485 nm, Emission 520 nm). The slope of the initial linear portion of the fluorescence signal curve is then calculated by using Excel. Percent protease activity is calculated relative to a no inhibitor DMSO control defined as 100% activity. IC_{50} curve fits are performed using Prism software.

3.10. hMMP13

3.10.1. Protocol 1

[0446] The basis for the assay is the cleavage of the substrate 390 MMP FRET Substrate I (Anaspec Cat# AS-27076) by human MMP13 (Chemicon, Cat#CC068).

[0447] For the dose response (10 point), 4 µL of a dilution series of compound (20 µM highest concentration, 1/5 dilution in water), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM Tris pH7.5 , 150mM NaCl, 10mM $CaCl_2$, 0.05% CHAPS, 5µM $ZnCl_2$) containing MMP13 (0.01 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration). Human MMP13 is preactivated by incubated the enzyme in the same buffer complemented with 1 mM freshly prepared p-Aminophenylmercuric acetate (AMPA) for 1 hour at 37°C.

[0448] The reaction is initiated by adding to the assay plate 390 MMP FRET Substrate I (10 µL, 2.5 µM) in the same buffer.

[0449] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 45 min at room temperature (Excitation 485 nm, Emission 530).

[0450] The IC_{50} measured for illustrative compounds of the invention is reported in Table XII below.

Table XII. hMMP-13 potency of illustrative compounds of the invention

Cpd#	IC_{50} (nM)
3	>4000
5	794
17	>20000
27	>20000
28	2370
34	3210
35	>20000
36	>20000
40	>20000
43	>20000

Cpd#	IC$_{50}$ (nM)
46	n/a
47	>4000
53	>20000
54	>20000
55	>20000
57	n/a
60	>20000
64	>20000
65	>20000
66	>20000
67	>3500
70	>4000
74	2660
75	>20000
76	2060
78	2100
79	>20000
80	3790
83	>4000
85	>20000
86	>20000
87	>20000
88	>20000
89	>20000
90	1210
91	1680
92	>20000
93	>20000
94	>20000
95	2200
96	1060
97	>20000
98	>20000
99	>20000
100	>20000
102	>20000
103	2000
104	>20000
105	>20000
106	>20000
107	>20000
109	>4000
111	>20000
112	1880

Cpd#	IC$_{50}$ (nM)
113	3620
114	2580
115	>4000
116	>20000
117	>4000
118	>20000
120	>20000
121	70.6
122	>20000
123	919
124	1280
125	2120
126	>4000
127	>20000
128	>20000
129	>20000
130	>20000
132	3290
133	>20000
134	>20000
135	>20000
136	>20000
137	>20000
138	>4000
139	>20000
140	>4000
142	>20000
143	>20000
144	>20000
145	>20000
146	3880
147	>4000
148	>20000
151	>20000
152	>20000
153	>4000
154	>4000
155	>20000
156	>20000
157	>20000
158	>20000
159	>20000
160	>20000
161	>20000

Cpd#	IC_{50} (nM)
162	>4000
163	>20000
164	>20000
165	>20000
166	>20000
167	>4000
168	>20000
169	>20000
170	>20000
171	>4000
172	2740
173	>20000
174	>20000
175	>20000
176	>20000
177	>20000
179	>20000
180	>20000
181	>20000
182	>20000
183	>20000
186	>20000
187	2610
188	2670
189	>20000
190	3060
191	1880
192	865
193	433
194	952
196	>20000
197	>4000
198	1940
199	>20000
200	>20000
201	>20000
203	>20000
204	>12000
205	>20000
206	>4000
207	2880
208	>20000
209	>20000
210	>14700

Cpd#	IC_{50} (nM)
211	377
212	1040
213	>4000
214	>3510
215	>4000
216	>20000
217	>4000
218	2220
219	>4000
220	>4000
221	>4000
222	>4000
223	>20000
224	152
225	3940
226	3270
227	>20000
228	>4000
229	3850
230	>20000
231	766
232	>20000
233	1710
234	5.6
235	21.2
236	1220
242	>20000
247	>20000
249	>4000
250	>20000
255	>20000
262	>20000
405	2333
406	2042
407	>20000
408	>4000
409	2740
410	>4000
411	865
412	433
413	952
414	>4000
415	1300
416	2880

Cpd#	IC_{50} (nM)
417	3130
418	>4000
419	663
420	>14000
421	>4000
422	2330
423	>20000
424	>20000
425	>4000
426	>4000
427	>4000
428	152

Cpd#	IC_{50} (nM)
429	>20000
430	>20000
431	3280
432	2040
433	>20000
434	766
435	1220
436	>4000
438	1850
439	>4000
440	>20000

3.10.2. Protocol 2

[0451] The basis for the assay is the cleavage of the substrate 520 MMP-fret substrate XV (Anaspec, Catalog #: AS-60582-01) by human MMP13 (Chemicon, Cat# CC068).

[0452] For the dose response (10 point), 4 µL of a dilution series of compound (2 mM highest concentration, 1/5 dilution in DMSO further diluted1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM Tris pH7.5, 150mM NaCl, 10mM $CaCl_2$, 0.05% CHAPS, 5µM $ZnCl_2$) containing MMP13 (6.25 10^{-6} µg/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0453] The reaction is initiated by adding to the assay plate 520 MMP-fret substrate XV (10 µL, 4µM) in the same buffer.

[0454] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 60 min at room temperature (Excitation 485 nm, Emission 530).

[0455] The IC_{50} measured for illustrative compounds of the invention is reported in Table XIII below.

Table XIII. hMMP-13 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)
1	>20000
2	2370
3	>4000
4	2520
5	76.4
6	2150
7	>20000
8	>20000
9	1480

Cpd	IC_{50} (nM)
10	285
11	>20000
12	>20000
13	>20000
14	366
16	>20000
18	>20000
20	>20000
21	>20000

3.11. hMMP14

[0456] The basis for the assay is the cleavage of the substrate 390 MMP FRET Substrate I (Anaspec Cat# AS-27076) by human MMP14 (Biomol, Cat#SE-259).

[0457] For the dose response (10 point), 4 µL of a dilution series of compound 2 mM highest concentration, 1/5 dilution in DMSO further diluted 1 in 10 in water, corresponding to a final highest concentration of 20 µM), is transfered to 384 well Fluotrac 200 plate (Greiner, cat# 781076) and incubated at room temperature for 30 min with a 26 µL buffer solution (50mM MOPS pH7 , 5mM $CaCl_2$, 1µM $ZnCl_2$, 0.1% Brij-35) containing MMP14 (0.05 ng/µL) (it will be appreciated by the skilled person that the potency read out is independent of the enzyme concentration).

[0458] The reaction is initiated by adding to the assay plate 390 MMP FRET Substrate I (10 µL, 2.5 µM) in the same buffer.

[0459] Finally, the fluorescence is read on the Envision (Perkin Elmer) after an incubation of 60 min at room temperature (Excitation 485 nm, Emission 530).

[0460] The IC_{50} measured for illustrative compounds of the invention is reported in Table XIV below.

Table XIV. hMMP-14 potency of illustrative compounds of the invention

Cpd	IC_{50} (nM)	Cpd	IC_{50} (nM)
27	>20000	232	>20000
36	>20000	233	384
40	>20000	234	7
51	>20000	235	26
55	>20000	236	1220
173	>20000	242	>20000
192	823	247	>4000
203	>4000	249	1230
204	>20000	251	>4000
205	>4000	255	3230
207	>4000	259	>20000
210	>20000	260	>20000
212	378	261	>20000
214	1230	265	2295
215	2600	266	3640
217	>4000	270	>4000
218	1310	276	>20000
220	3840	277	>20000
223	>20000	282	>20000
226	978	287	>4000
227	>20000	288	>4000
228	>20000	295	3460
229	682	307	>20000
230	>20000	308	>20000
231	549	309	>20000

Cpd	IC$_{50}$ (nM)
313	>20000
314	>20000
316	>20000
317	823
319	>4000
320	>20000
326	>4000
327	>4000
331	>20000
332	378
339	1230
342	2600
346	>4000
350	1310
351	3840
357	>20000
359	978
365	>20000
367	>20000
371	682
375	>20000
388	549
389	>20000
391	384
396	7
397	26
400	1220
404	>20000
405	3817
406	1345
411	547
414	2053
416	990
418	740
420	>14700
421	701
422	879
423	>20000
424	>20000
425	2820
429	>12000
430	>20000
431	501
432	581
433	>4000
434	1620
435	2590
436	>4000
438	3420
439	>3890
441	1530
443	1330
444	1440
445	945
447	>4000
449	1380
450	>3710
451	1100
453	1540
455	209
457	3110
459	>20000
464	848
465	>20000
466	>20000
467	1860
468	>20000
469	520
470	>4000
472	>4000
474	3260
475	>4000
476	387
477	>20000
478	1020
479	31
480	53
481	3060

Example 4. Cellular assays

4.1.1. Mouse explant assay

[0461] In this assay, quantitation of glycosaminoglycans (GAGs) in the form of aggrecan fragments released from cartilage in culture is used to determine the efficacy of a test compound in preventing cartilage catabolism.

[0462] The protocol of mouse cartilage explants is described by Stanton (Stanton et al., 2011). After euthanasia, the femoral head cartilage from the right and left leg of a 3-days-old C57Bl6 male mouse (Janvier, 7-10g), were placed in a 48-wells culture plate. Cell culture medium (400µL) containing human IL1α (1ng/mL) and test compound (3µM) were added to the femoral head cartilage.

[0463] After 3 days of incubation, the supernatant is harvested and stored at -20°C until analysis and the cartilages are digested with a papaïn solution at 60°C for 24h. Using the standard curve performed with a dose range of chondroitin sulfate, the concentration of GAG is determined in the supernatant and on the lysate using dimethylmethylene blue solution (reading at a wavelength of 590nm).

[0464] The percentage of GAG release is calculated as follows:

$$GAG\% = \frac{[\mathrm{GAG}]_{\mathrm{supernatant}}}{[\mathrm{GAG}]_{\mathrm{supernatant}} + [\mathrm{GAG}]_{\mathrm{lysate}}}$$

[0465] The test compound effect is expressed as percent of inhibition (PIN) using the following formula:

$$PIN = \frac{\text{mean }\%[\mathrm{GAG}]_{vehicle+IL1\alpha} - \text{mean }\%[\mathrm{GAG}]_{compound+IL1\alpha}}{\text{mean }\%[\mathrm{GAG}]_{vehicle+IL1\alpha} - \text{mean }\%[\mathrm{GAG}]_{compound}} * 100$$

4.2. Human explant assay

[0466] In this assay, compounds are tested in human articular cartilage explants in order to evaluate their activity on aggrecan degradation induced by IL1β. AGNx1 is the epitope for aggrecanase-mediated aggrecan degradation; on the other hand, AGNx2 is the epitope for MMP-mediated aggrecan degradation. Therefore quantification of AGNx1 and AGNx2 may be used to evaluate the activity of a test compound.

[0467] These studies were conducted in Nordic Bioscience (Herlev Hovedgade 207, DK-2730 Herlev, Denmark).

[0468] Human articular cartilage explants are collected from 3 nearby hospitals under an existing ethical committee application.

[0469] Full-depth cartilage explants from OA cartilage from different patients are cultured for 21 days in culture medium (DMEM/F12 with 0.5% FCS, 1% PS) containing various (positive control, untreated, and test compound at 0.1, 1 and 10 µM).

[0470] The explants from each patient are cultured in a separate 96-well culture plate with 200µL/well PBS, and the 6 replicates of each treatment are distributed in a diagonal pattern on the plate. At each experimental time point (5, 12 and 19 days), supernatants are harvested from the explants cultures, and new treatment-mediums are added. The supernatants are stored at -20°C for later biomarker analysis. The human IL1β (Sigma-Aldrich SRP3083) is used at a concentration of 10 ng/mL.

4.3. Results

[0471] The AGNx1 and AGNx2 concentrations were determined against a standard curve. Mean and SEM were graphed using the excel software. One-way ANOVA plus Dunnett's multiple comparisons post-hoc test are used for the statistical analysis (Prism 3.03 software).

Example 5. In vivo assays

5.1. In vivo menisectomized (MNX) rat model

5.1.1. In vivo efficacy in the rat MNX model

[0472] In vivo efficacy was studied in a female Lewis meniscectomised rat (MNX) model. The MNX rat model is a well-validated disease model of osteoarthritis (Bendele, 2001; Janusz et al., 2002; Pritzker et al., 2006).

5.1.2. Experimental procedures

5.1.2.1. Surgery and dosing

[0473] Osteoarthritis is induced by meniscectomy at day 0 (D0) in the right leg of each rat by a transection of the medial collateral ligament and 4 mm of ligament are removed. Internal part of the meniscus is transected vertically into two flaps which are pushed to the front and the back of the synovial cavity. Sham animals undergo only anaesthesia, skin and muscle incision then suture. On day 1, rats are randomly assigned to a treatment group (n=20 per group) according to their body weight, in order to have a homogenous distribution. From D2 to D21, rats are dosed per os (po) once daily (qd) or twice a day (bid) with compounds formulated in methylcellulose (MC) 0.5% or in HPβCD 10% pH3.0.

5.1.2.2. Steady-state PK determination (ssPK)

[0474] After at least 7 days of treatment, blood is sampled at 4 time points post administration: 0, 1, 3 and 6 h (and assuming 24 h is equal to the pre-dose sample), in order to determine steady-state plasma exposure.

5.1.2.3. Histology

[0475] At sacrifice, the right tibia of each rat is collected and processed for histological analysis. After 48h of fixation in 4% formaldehyde, tibias are decalcified in Osteosoft for 7 days, and cut into 2 half parts prior to embedding face to face in paraffin. Five series of sections are cut at 200 μm intervals, covering about 1.5 mm of the middle part of the bone. One series of slides is stained with Safranin O and light green for morphological evaluation and OARSI scoring. The other series of slides are mounted with DAPI for chondrocyte density measurement.

[0476] The extent of cartilage injury reflecting osteoarthritis in the tibial plateau is evaluated and scored using the OARSI method based on the grading and the staging of cartilage lesion (Pritzker *et al*, 2006). The OARSI scoring is assessed in a blinded manner by two different readers. For each tibia, one score is attributed as the median of the OARSI score of the 5 sections.

[0477] For statistical analysis, medians of groups are compared with a stratified Kruskal-Wallis test followed by Dunnett multiple comparison *post hoc* test.

[0478] Significance levels: ns: not statistically significant; $*p<0.05$; $**p<0.01$; $***p<0.001$ versus MNX-vehicle. Statistical analyses are done on all groups of the studies.

FINAL REMARKS

[0479] It will be appreciated by those skilled in the art that the foregoing descriptions are exemplary and explanatory in nature, and intended to illustrate the invention and its preferred embodiments. Through routine experimentation, an artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. All such modifications coming within the scope of the appended claims are intended to be included therein. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

[0480] 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 are specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[0481] It should be understood that factors such as the differential cell penetration capacity of the various compounds can contribute to discrepancies between the activity of the compounds in the *in vitro* biochemical and cellular assays.

[0482] At least some of the chemical names of compound of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by Open Eye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

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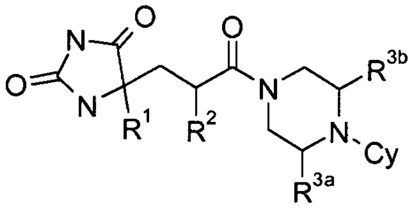
CLAIMS

1) A compound according to Formula I:



I

wherein

R^1 is:

- H,
- C_{1-4} alkyl optionally substituted with one or more independently selected R^4 groups,
- C_{3-7} monocyclic cycloalkyl optionally substituted with one or more independently selected R^4 groups,
- 4-7 membered monocyclic heterocycloalkyl comprising 1 to 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl, $-C(=O)C_{1-4}$ alkyl, or $-C(=O)OC_{1-4}$ alkyl,
- phenyl optionally substituted with one or more independently selected R^5 groups,
- phenyl fused to a 5-6 membered monocyclic heterocycloalkyl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, which heterocycloalkyl is optionally substituted with one or more =O,
- 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^5 groups;

R^2 is independently selected from:

- H,
- OH,
- C_{1-4} alkoxy, and
- C_{1-4} alkyl optionally substituted with one
  - OH,
  - -CN,
  - C_{1-4} alkoxy optionally substituted with one phenyl, and
  - 5-6 membered monocyclic heteroaryl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected C_{1-4} alkyl;

each R^{3a}, and R^{3b} is independently selected from:

- H, and
- C_{1-4} alkyl;

Cy is

- 6-10 membered monocyclic or fused bicyclic aryl optionally substituted with one or more independently selected R^6 groups,
- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected R^6 groups;

R^4 is

- halo,
- OH,
- -CN,
- C_{1-4} alkyl,
- C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy, or phenyl,
- C_{1-4} thioalkoxy,
- 4-7-membered monocyclic heterocycloalkyl comprising one or more heteroatoms independently selected from N, S, and O, optionally substituted with one or more halo, or $-C(=O)OC_{1-4}$ alkyl,
- phenyl,
- $-S(=O)_2C_{1-4}$ alkyl
- $-C(=O)OR^{7a}$
- $-C(=O)NR^{7b}R^{7c}$
- $-NHC(=O)OR^{7d}$
- $-NHC(=O)R^{7e}$
- $-NR^{8a}R^{8b}$;

each R^5 is

- halo,
- OH,
- -CN,
- C_{1-4} alkyl optionally substituted with one or more independently selected halo, $-NR^{9a}R^{9b}$, or $-C(=O)NR^{9c}R^{9d}$,
- C_{1-4} alkoxy optionally substituted with $-NR^{9e}R^{9f}$, or
- $-S(=O)_2C_{1-4}$ alkyl;

each R^6 is

- halo,
- -CN,
- $-NO_2$,
- $-CH_3$,

- 5-10 membered monocyclic or fused bicyclic heteroaryl comprising 1, 2 or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more independently selected halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or
- $-NR^{9g}R^{9h}$;

each R^{7a}, R^{7b}, R^{7c}, R^{7d}, or R^{7e}, is

- H, or
- C_{1-4} alkyl optionally substituted with OH, or C_{1-4} alkoxy;

each R^{8a}, or R^{8b} is independently selected from

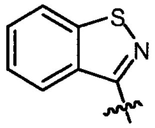
- H, and
- C_{1-4} alkyl optionally substituted with OH, C_{1-4} alkoxy, or phenyl;

each R^{9a}, R^{9b}, R^{9c}, R^{9d}, R^{9e}, R^{9f}, R^{9g}, and R^{9h} is independently selected from H, and C_{1-4} alkyl;

or a pharmaceutically acceptable salt, or a solvate, or a pharmaceutically acceptable salt of a solvate thereof; or a biologically active metabolite thereof;

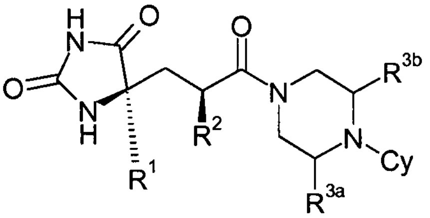
provided that:

- R^1 and R^2 are not simultaneously H, and
- When R^1 is Me, and R^2 is H, then Cy is not



or a pharmaceutically acceptable salt, or a solvate, or the salt of the solvate thereof.

2) A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is according to Formula II:



II

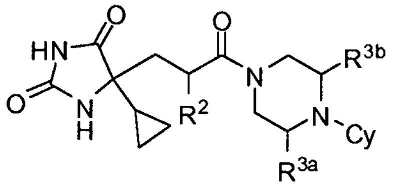
wherein R^1, R^2, R^{3a}, R^{3b}, and Cy are as defined above.

3) A compound or pharmaceutically acceptable salt thereof, according to claim 1 or 2, wherein R^1 is H.

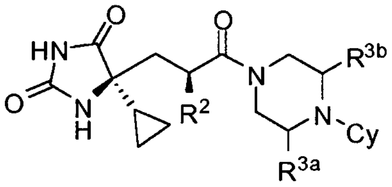
4) A compound or pharmaceutically acceptable salt thereof, according to claim 1 or 2, wherein R^1 is C_{1-4} alkyl.

5) A compound or pharmaceutically acceptable salt thereof, according to claim 1 or 2, wherein R^1 is C_{3-7} monocyclic cycloalkyl.

6) A compound or pharmaceutically acceptable salt thereof, according to any one of claim 1, wherein the compound is according to Formula IIIa or IIIb:



IIIa or

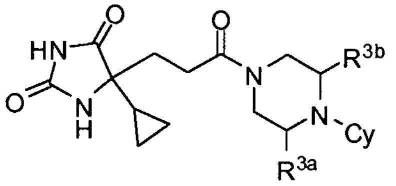


IIIb

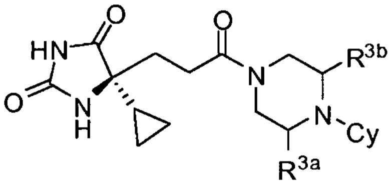
wherein R^2, R^{3a}, R^{3b} and Cy are as described in claim 1.

7) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-6, wherein R^2 is C_{1-4} alkyl.

8) A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is according to Formula IVa or IVb:



IVa or



IVb

wherein R^{3a}, R^{3b} and Cy are as described in claim 1.

9) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein each R^{3a}, and R^{3b} is independently selected from H, and CH_3.

10) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-9, wherein Cy is 6-10 membered aryl, substituted with one or more independently selected R^6 groups.

11) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-9, wherein Cy is phenyl substituted with one or more independently selected R^6 groups.

12) A compound or pharmaceutically acceptable salt thereof, according to claims 10 or 11, wherein each R^6 is F, Cl, CN, $-CH_3$, or NO_2.

13) A compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is selected from

5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

5-[3-[(3S)-4-(3-chloro-5-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

(5S)-5-cyclopropyl-5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

(5S)-5-cyclopropyl-5-[(2S)-3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione, 5-[3-[(3S)-4-(4-chlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

5-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

5-[2-[4-(3,5-dichlorophenyl)piperazine-1-carbonyl]butyl]-5-methyl-imidazolidine-2,4-dione,

(S)-5-((S)-3-((S)-4-(3-chloro-4-fluorophenyl)-3-methylpiperazin-1-yl)-2-methyl-3-oxopropyl)-5-(methoxymethyl)imidazolidine-2,4-dione,

5-[3-[4-(3-chlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

5-[3-[4-(3-chloro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-cyclopropyl-imidazolidine-2,4-dione,

tert-butyl N-[2-[4-[3-[4-(3,4-difluorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-2,5-dioxo-imidazolidin-4-yl]ethyl]carbamate,

(5S)-5-cyclopropyl-5-[3-[(3S)-4-(3,5-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

5-[3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

5-cyclopropyl-5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

(5R)-5-[(2S)-3-[(3S)-4-(3-chloro-4-fluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

5-cyclopropyl-5-[3-[(3S)-4-[3-fluoro-5-(1H-pyrazol-4-yl)phenyl]-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

5-cyclopropyl-5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-(hydroxymethyl)-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

5-[3-[(3S)-4-(3,4-difluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

5-[3-[(3S)-4-(3-chlorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

5-[3-[(3S)-4-(4-chloro-3,5-difluoro-phenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-methyl-imidazolidine-2,4-dione,

5-cyclopropyl-5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-methylsulfonylethyl)imidazolidine-2,4-dione, 5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

(5S)-cyclopropyl-5-[3-[(3S)-4-(3,5-difluorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]imidazolidine-2,4-dione,

5-[3-[(3S)-4-(3-fluorophenyl)-3-methyl-piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione,

5-[3-[4-(4-chloro-3,5-difluoro-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione,

5-cyclopropyl-5-[3-[4-(5-fluoro-2-methyl-phenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]imidazolidine-2,4-dione,

5-[3-[4-(3,5-dichlorophenyl)piperazin-1-yl]-2-methyl-3-oxo-propyl]-5-(methoxymethyl)imidazolidine-2,4-dione, and

5-[3-[(3S)-4-(3,4-dichlorophenyl)-3-methyl-piperazin-1-yl]-3-oxo-propyl]-5-(2-pyridyl)imidazolidine-2,4-dione.

14) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to any one of claims 1-13.

15) A pharmaceutical composition according to claim 14 comprising a further therapeutic agent.

16) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-13, or a pharmaceutical composition according to claims 14 or 15 for use in medicine.

17) A compound or pharmaceutically acceptable salt thereof, according to any one of clause 1-13, or a pharmaceutical composition according to clause 14 or 15 for use in the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

18) The pharmaceutical composition according to claim 15, wherein the further therapeutic agent is an agent for the prophylaxis and/or treatment of inflammatory conditions, and/or diseases involving degradation of cartilage and/or disruption of cartilage homeostasis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/080430

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/06 A61K31/496 A61P19/02 A61P19/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/066151 A1 (LILLY CO ELI [US]) 1 May 2014 (2014-05-01) the whole document examples 1-5 page 24 - page 27; tables 1-4 claims 1-8 -----	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2016	19/02/2016

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Cortés, José

INTERNATIONAL SEARCH REPORT

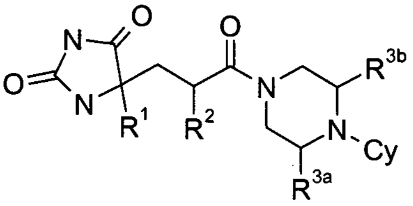
Information on patent family members

International application No
PCT/EP2015/080430

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014066151 A1	01-05-2014	AU 2013334989 A1	23-04-2015
		CA 2886526 A1	01-05-2014
		CN 104755464 A	01-07-2015
		EA 201590621 A1	30-07-2015
		EP 2912021 A1	02-09-2015
		JP 2015535248 A	10-12-2015
		KR 20150058480 A	28-05-2015
		TW 201427955 A	16-07-2014
		US 2015218107 A1	06-08-2015
		WO 2014066151 A1	01-05-2014

说 明 书 摘 要

本发明公开了式(I)化合物，其中R^1、R^2、R^{3a}、R^{3b}和Cy如本文所定义。本发明公开了抑制ADAMTS的化合物、其生产方法、包含其的药物组合物以及预防和/或治疗炎症状况和/或涉及软骨退化和/或软骨稳态破坏的疾病的方法。



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