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(54) Titre : INHIBITEURS HETEROAROMATIQUES DE PROTEINASES DE LA FAMILLE DES ASTACINES
(54) Title: HETEROAROMATIC INHIBITORS OF ASTACIN PROTEINASES

(57) Abrégé/Abstract:
The present invention relates to novel hydroxamic acid derivatives useful as inhibitors of astacin metalloproteinases, in particular procollagen C-proteinase (PCP) enzymes, meprins, ovastacin and/or nematode astacins; more particularly human or mammalian meprin α, meprin β, BMP-1, ovastacin and/or DPY-31 from nematodes; pharmaceutical compositions comprising such compounds; methods for treatment or prophylaxis of diseases or conditions, especially such that are related to said metalloproteinases; and compounds and pharmaceutical compositions for use in such methods.

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(57) Abstract: The present invention relates to novel hydroxamic acid derivatives useful as inhibitors of astacin metalloproteinases, in particular procollagen C-proteinase (PCP) enzymes, meprins, ovastacin and/or nematode astacins; more particularly human or mammalian meprin α, meprin β, BMP-1, ovastacin and/or DPY-31 from nematodes; pharmaceutical compositions comprising such compounds; methods for treatment or prophylaxis of diseases or conditions, especially such that are related to said metalloproteinases; and compounds and pharmaceutical compositions for use in such methods.

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HETEROAROMATIC INHIBITORS OF ASTACIN PROTEINASES

FIELD OF THE INVENTION

The present invention relates to novel hydroxamic acid derivatives useful as inhibitors of astacin metalloproteinases, in particular procollagen C-proteinase (PCP) enzymes, meprins, ovastacin and/or nematode astacins; more particularly human or mammalian meprin α, meprin β, BMP-1, ovastacin and/or DPY-31 from nematodes; pharmaceutical compositions comprising such compounds; methods for treatment or prophylaxis of diseases or conditions, especially such that are related to said metalloproteinases; and compounds and pharmaceutical compositions for use in such methods.

BACKGROUND ART

Proteinases from the astacin family represent a widespread group of metalloproteinases occurring in lower as well as in higher organisms. The astacins are a subfamily of the metzincin superfamily of proteinases, all of which share the conserved zinc binding sequence in their active site, a conserved methionine-containing turn (Met-turn) backing the zinc site and strikingly similar three-dimensional structures of their catalytic domains (Sterchi et al., *Mol Aspects Med.* (2008), 29(5): 309–328). In the human organism, there are at least four enzymes of the astacin family: the bone morphogenetic protein 1 (BMP-1), the two meprins (meprin α and meprin β), as well as ovastacin. Additionally, nematode parasites such as trichina and hookworms secrete a variety of astacins which are found throughout the entire taxon *Nemathelminthes*.

BMP-1 and the meprins participate in collagen formation and thus play a role in various diseases associated with pathological formation of connective tissue, such as fibrotic conditions including pulmonary fibrosis and keloids. Furthermore, meprins have been described as being associated with various types of cancer, Morbus Alzheimer, acute renal failure and chronic inflammatory bowel diseases. Meprin inhibitors, therefore, represent novel candidates for the treatment of such diseases.

In turn, ovastacin plays a role in reproduction. Upon fertilization of the oocyte, hardening of the zona pellucida (ZPH) takes place which is induced by the ovastacin activity and provides mechanical protection to the fertilized egg by establishing a block against polyspermy and ensuring normal development of the embryo. However, if such hardening occurs too early, or even in the absence of fertilization, infertility can arise. Inhibition of ovastacin can therefore represent a novel approach for addressing an unfulfilled desire to have a child and/or in the context of *in vitro* fertilization and reproductive medicine.

Furthermore, multiple astacin proteases have been identified in nematodes. These play an important role in the formation of the collagen-containing cuticula. Nematode infections represent a major issue, in particular in livestock farming. Furthermore, nematode parasites are responsible for multiple tropical diseases. Inhibition of these enzymes interferes with the formation of an external protective layer and leads to mitigated growth or death of the worms. Inhibitors of such nematode astacins, therefore, represent novel anthelmintic agents for the treatment of parasite infections.

Metzincins and the Astacin Family

As noted above, the astacins are a family of multi-domain metallopeptidases with manifold functions in the metabolism. They are either secreted or membrane-anchored and are regulated by being synthesized as inactive zymogens and by co-localizing protein inhibitors. The distinct family members consist of N-terminal signal peptides and pro-segments, zinc-dependent catalytic domains, further downstream extracellular domains, transmembrane anchors, and cytosolic domains. The catalytic domains of four astacins and the zymogen of one of these have been structurally characterized and shown to comprise compact ~200-residue zinc-dependent moieties divided into an N-terminal and a C-terminal sub-domain by an active-site cleft. Astacins include an extended zinc-binding motif (HEXXHXXGXXH) which includes three metal ligands and groups them into the metzincin clan of metallopeptidases. In mature, unbound astacins, a conserved tyrosine acts as an additional zinc ligand, which is swung out upon substrate or inhibitor binding in a 'tyrosine switch' motion. Other characteristic structural elements of astacin catalytic domains are three large α-helices and a five-stranded β-sheet, as well as two or three disulfide bonds. The N-terminal pro-segments are variable in length and rather unstructured. They inhibit the catalytic zinc following an 'aspartate-switch' mechanism mediated by an aspartate embedded in a conserved motif (FXGD). Removal of the pro-segment uncovers a deep and extended active-site cleft, which in general shows preference for aspartate residues in the specificity pocket (S_1') (Gomis-Rüth et al., *Biol. Chem.* (2012), 393: 1027–1041).

Besides the family of astacins, further metalloproteinase families within the metzincin superfamily include ADAMs ("A Disintegrin And Metalloproteinase", such as ADAM metallopeptidase domain 17 (ADAM17), also called TACE (tumor necrosis factor-α-converting enzyme); and ADAM10, i.e. α secretase) and MMPs ("Matrix Metalloproteinases", such as MMP1 collagenase; MMP2 gelatinase; MMP9; and MMP13), as shown in Fig. 1 of Sterchi et al., *Mol Aspects Med.* (2008), 29(5): 309–328.

For instance, TACE (ADAM17) inhibitors are known. However, many of these compounds display non-selectivity, being potent inhibitors of matrix metalloproteases, and in particular MMP-1, inhibition of which has been postulated to cause joint pain in clinical trials of metalloproteases inhibitors, as described in WO 2008/142376 A1. Therein, bicyclosulfonyl acid (BCSA) compounds are disclosed, all of which share as a common structural motif 2-(1,1-dioxo-2-phenyl-2,3-dihvdro-1H-benzo[d]isothiazol-3-yl)acetic acid, (1,1-dioxo-2-phenyl-2,3-dihydro-1H-isothiazolo[4,5-b]pyridin-3-yl)acetic acid, 2-(1,1-Dioxo-2-phenyl-2,3-dihydro-1H-benzo[b]thiophen-3-yl)acetic acid or substituted derivatives thereof. In other words, all the compounds therein have a SO_2 group at the 1-position within the 5-membered ring of the bicyclic system. Furthermore, all of the 5-membered rings forming part of the bicyclic systems described therein a partially saturated, i.e. puckered. Finally, the compounds disclosed therein are inhibitors of TACE (an ADAM metalloprotease) rather than astacin metalloproteinases.

In the human and mouse genomes, genes encoding astacin proteases include *BMP-1*, *tll1*, *tll2*, *mep1a*, *mep1b*, and *astl*. The first three code for the so-called tolloid subgroup, which includes the protein BMP-1 and its major splice variant, mammalian tolloid. These two are also known as procollagen C-proteases and are important for extracellular matrix assembly. Genes *mep1a* and *mep1b* encode the multi-domain proteins meprin α and meprin β, respectively. A further subgroup of astacins in vertebrates comprises the so-called hatching enzymes, represented by just one member in mammals termed ovastacin which plays a role in sperm-egg interaction. Finally, the genomes of

lower invertebrates, and in particular nematodes, contain more astacin genes than mammalian genomes (up to about 40 in nematodes such as *Caenorhabditis elegans* (Gomis-Rüth et al., *Biol. Chem.* (2012), 393: 1027–1041).

Meprins

Specifically, meprin α and β both represent zinc-dependent metalloproteases of the astacin family and the metzincin superfamily. They show a similar domain structure and the human enzymes are of 45% sequence homology to each other. Meprin β is a type 1 transmembrane protein with extracellular protease activity whereas meprin α is shed during the secretory pathway and secreted into extracellular space. Both enzymes are expressed as zymogens with high expression rates in epithelial cells of the kidney and intestine, and they have been demonstrated in intestinal leukocytes, skin and certain cancer cells.

The meprins show distinct substrate specificity with a preference of acidic amino acids in the P1´-position (Becker-Pauly et al. *Mol.Cell Proteomics* (2011), doi: 10.1074/mcp.M111.009233). Several *in vitro* substrates have been identified, including extracellular matrix proteins, peptide hormones and cytokines. Known *in vitro* substrates of meprin β comprise orcokinin, gastrin 17, Peptide YY, kinetensin, osteopontin, interleukin 1β, APP, MUC 2 mucin, and cystic fibrosis transmembrane conductance regulator E-cadherin, whereas known *in vitro* substrates of meprin α comprise bombesin, neurotensin, Substance P, angiotensin I, luteinizing hormone releasing hormone, valosin, vasoactive intestinal peptide, bradykinin, α-melanocyte stimulating hormone, MCP-1, and occludin. Known *in vitro* substrates of both meprin β and α are, e.g., the Gastrin-releasing peptide, and Cholecystokinin. Although the function of meprins *in vivo* still remains to be elucidated, there is increasing evidence for their role in collagen assembly, inflammation, intestinal immune response and neurodegeneration.

The lack of meprin β and α in mouse or the use of Actinonin (a meprin inhibitor) have been shown to protect against renal injury and bladder inflammation (Bylander et al., *American journal of physiology. Renal physiology* (2008), 294(3): F480-90; Yura et al., *American journal of physiology. Renal physiology* (2009), 296(1): F135-44). Accordingly, meprin β and α appear to be involved in the pathogenesis and/or disease progression of, e.g., nephritis, renal injury, renal ischemic injury, ischemic acute tubular necrosis, acute renal failure, and bladder inflammation.

Both enzymes have been demonstrated to be C- and N-procollagen proteinases and to induce collagen maturation and assembly (Biasin et al., *The Journal of pathology* (2014), 233(1): 7–17; Prox et al., *Matrix biology* (2015), 44–46: 7–13). Under fibrotic conditions (keloids, pulmonary hypertension), overexpression of the enzymes has been found in these studies. Accordingly, meprin β and α appear be involved in the pathogenesis and/or disease progression of, e.g., fibrosis and fibrotic conditions (keloids, pulmonary hypertension) and interstitial lung disease (ILD).

Meprin β has been shown to act as β-secretase of amyloid precursor protein to form amyloid β (Aβ) peptides *in vitro* (Bien et al., *The Journal of biological chemistry* (2012), 287(40): 33304–33313). The Aβ peptide, which is abundantly found in the brains of patients suffering from Alzheimer's disease, is central in the pathogenesis of this disease. Said study showed that, in contrast to BACE I, meprin β is capable of formation of N- terminally truncated Aβ and therefore might be involved in the generation of potentially more toxic species of Aβ. Accordingly, meprin β appears to be involved in the pathogenesis and/or disease progression of, e.g., Alzheimer's disease.

Meprin α has been shown to be a susceptibility gene for IBD (Crohn´s disease, ulcerative colitis) and that its absence increases chronic inflammation, while meprin β has pro-inflammatory activity and its lack results in some protection from injury (Banerjee et al., *Am. J. Physiol. Gastrointest. Liver Physiol.* (2011), 300(2): G273-82). Accordingly, meprin β and α appear to be involved in the pathogenesis and/or disease progression of, e.g., chronic inflammation, Crohn´s disease, ulcerative colitis, and inflammatory bowel disease (IBD). Pro-angiogenetic activity and non-polarized secretion have been described for meprin α, thereby increasing invasiveness of colorectal cancer (Lottaz et al., *PloS one* (2011), 6(11): e26450). Accordingly, meprin α is relevant to the pathogenesis and/or disease progression of cancer, especially colorectal cancer.

Several broad-spectrum metalloproteases and MMP inhibitors have been elucidated concerning their inhibitory activity towards meprin α and β (Broder et al., *The Biochemical Journal* (2013), 450: 253-264). Although some compounds showed inhibition of meprin α, for all the compounds, the inhibition of Meprin β was much lower (exhibiting inhibition constants in the micromolar range) or were lacking acceptable drug-like properties (Madoux et al., *Biopolymers* (2014), 102(5): 396-406). A phosphinic inhibitor of meprin β (PMI) is described in Broder C., Characterization of the metalloproteases meprin α and meprin β within the protease web (August 2013; Doctoral dissertation; Universitätsbibliothek Kiel; Accession No. urn:nbn:de:gbv:8-diss-146034; pp. 29, 53).

PCP Enzymes; BMP-1

The bone morphogenetic protein BMP-1 belongs to the procollagen C-proteinase (PCP) enzymes, which are a small group of closely-related zinc metalloproteinases with the ability to specifically cleave the carboxyl pro-domains of fibrillar collagens (Turtle et al., *Expert Opin., Ther. Patents* (2004), 14(8): 1185-1197). The PCPs are part of the astacin family of zinc metalloproteinases. Astacin, a digestive enzyme from crayfish, is one of the smallest members in this family of diverse proteases. BMP-1 has a 39% sequence homology with astacin, and, like all members of this family contains a conserved zinc-binding motif, HEXXHXXGXXH. The astacin active-site domain is contained within a cleft between large N- and C-terminal domains. The active-site zinc is coordinated by the three histidine residues of the consensus sequence, a tyrosine sequence and a water molecule. The glutamic acid of the consensus sequence acts as a general base on the zinc bound water molecule, the nucleophile attacking the scissile amide bond of the substrate.

BMP-1 is the smallest of the PCP isoforms. In addition to BMP-1, four closely related mammalian PCPs have been discovered: mTLD, TLL-1 and -2 and BMP-1/His enzymes. All five enzymes share a high sequence homology in the catalytic astacin-like domain, and also appear to have redundancy in some functions. The PCPs have been primarily noted for their procollagen possessing ability, a process required for fibrosis and wound healing, and their relation to conditions that promote collagen remodeling. The concept of PCP inhibition as an antifibrotic approach is based on the presumption that blockade of PCP activity does not in itself reduce formation of procollagen but prevents the formation of highly structured collagen fibrils. Without cleaving by PCP, procollagen remains soluble to 0.5–1.0 mg/ml and is not as readily incorporated into collagen fibrils. Inhibition of PCP has been associated with the deposition of collagen which is more susceptible to rapid degradation by matrix metalloproteinases (MMP). Therefore, inhibition of PCP enzymes,

and in particular BMP-1, has been established as a therapeutic approach for the treatment of fibrosis/scarring as well as diseases and conditions associated therewith (Turtle et al., *Expert Opin. Ther. Patents* (2004), 14(8): 1185-1197).

Scar formation is part of the natural healing response to tissue or organ damage. The wound healing process consists of blood coagulation, inflammatory response, tissue formation, and tissue remodeling, with the remodeled tissue becoming the scar or fibrotic tissue. Under ideal wound healing conditions, the fibrotic response produces minimal scar tissue, leaving most of the functional tissue intact, thereby preserving organ function. Fibrotic diseases are characterized by fibroblast over-proliferation and excessive deposition of collagen, which presents itself as dense fibers running through the tissue. The resulting fibrotic tissue blocks arteries, immobilizes joints and stiffens internal organs, obstructing the body's ability to maintain normal functions. Fibrotic diseases remain the number one killer in the world, accounting for more than 45% of the entire mortality in the United States, but there are currently no adequate therapies for most fibrotic conditions (Turtle et al., *Expert Opin. Ther. Patents* (2004), 14(8): 1185-1197).

Although, fibrosis is usually not a primary pathological event but follows trauma, infection, inflammation or surgical procedures, it may occur for unknown reasons, and may also have genetic and autoimmune components. Therefore, fibrosis can occur in any organ and accompanies many disease states, such as hepatitis (liver cirrhosis), hypertension and myocardial infarction (heart failure), asthma and pulmonary hypertension (pulmonary fibrosis), scleroderma (fibrotic skin and internal organs), diabetes (nephropathy), atherosclerosis (fibrotic blood vessels). In addition, hypertrophic dermal scarring and keloids can result in disability and disfigurement, and acute CNS scarring following traumatic injuries, such as strokes and spinal cord injuries, presents a major barrier for neuronal regeneration. Development of obliterative fibrosis of the hollow structures within grafts is the common denominator of the chronic allograft rejection. The process of fibrosis and wound healing, regardless of its etiology, actually recapitulates the major event commonly associated with embryogenesis. However, the underlying mechanisms are quite different; in adults, healing of wounds is often accompanied by scar formation, whilst fetal wounds heal with minimal or no scar formation. In addition to the serious, often life-threatening, chronic fibrotic disorders, acute fibrotic conditions, such as post-surgical scarring and dermal scarring, represent an important potential market for antifibrotics. Millions of surgical procedures are performed annually. Surgical scarring can complicate medical procedures and limit recovery, and the therapeutic need goes far beyond cosmetic applications: fibrosis resulting from gynecological procedures can cause infertility; fibrosis after eye surgery can result in blindness; fibrosis following angioplasty can result in restenosis; and fibrosis following surgery on joints can severely limit range of motion. Finally, PCP inhibitors have also been postulated to be useful in preventing local invasion, recurrence and metastasis of squamous cell carcinoma (SCCs), malignant keratinocytes, which are a common form of cancer, particularly in skin cancers. In summary, inhibitors that are selective for PCPs, such as BMP-1, are thought to be optimal for halting the excess collagen deposition associated with pathological fibrotic conditions and related diseases (Turtle et al., *Expert Opin. Ther. Patents* (2004), 14(8): 1185-1197).

However, it has also been noted that the non-specific inhibition of MMPs has been associated with muscular skeleton-stiffening side effects seen in human clinical trials (Turtle et al., *Expert Opin. Ther. Patents* (2004) 14(8): 1185-1197, p. 1190). Therefore, there is a demand for selective PCP, in particular BMP-1 inhibitors, which are preferably selective over MMPs such as MMP2, MMP9, etc.

Hatching Enzymes; Ovastacin

Inhibition of ovastacin has been reported to be directly related to mammalian gamete fusion and is thus of high relevance to reproductive biology and fertility control (Stöcker et al., *Biol. Chem.* (2014), 395(10): 1195-1199). The zona pellucida, a glycoprotein matrix surrounding the mammalian oocyte, hardens after intrusion of the first spermatozoon, thus protecting the embryo until implantation and preventing multiple fertilizations (polyspermy). Definitive zona hardening is mediated by the metalloprotease ovastacin, which is released from cortical granules of the oocyte upon sperm penetration. However, traces of ovastacin seep from unfertilized eggs to cause zona hardening even in the absence of sperm. These small amounts of protease are inactivated by the plasma protein fetuin-B, thus keeping eggs fertilizable. Once a sperm has penetrated the egg, ovastacin from cortical vesicles overrides fetuin-B and initiates zona hardening. The molecular mechanism of fertilization control was discovered in the highly specific interaction of fetuin-B and the cortical granule protease ovastacin. A proposed mechanism for the interaction of ovastacin and fetuin-B at the egg cell surface is based on an observation that in wild-type mouse oocytes, small amounts of ovastacin seeping from unfertilized eggs are inhibited by fetuin-B. Invading sperm will trigger the cortical degranulation reaction. Massive ovastacin release from cortical granules will override fetuin-B inhibition in the zona pellucida. Ovastacin will cleave ZP2 and the zona pellucida will harden. Thus, a mechanic protection of the fertilized egg and a block against polyspermy will be established. In contrast, in *fetuB*$^{-/-}$ mice without fetuin-B, small amounts of ovastacin seeping from unfertilized eggs are not inhibited by fetuin-B. Thus, zona pellucida hardening (ZPH) will occur even in the absence of fertilization, and premature ZPH renders oocytes non-fertilizable (Stöcker et al., *Biol. Chem.* (2014), 395(10): 1195-1199; see Figure 1 therein).

Pre-mature release of ovastacin has also been suggested to be the reason for infertility of fetuin-B deficient female mice. Also, addition of fetuin-B (the naturally occurring ovastacin inhibitor) during IVF partially prevented ZPH and improved the fertilization rate (Körschgen et al., *Molecular Human Reproduction* (2017), 23(9): 607–616).

Therefore, the development of novel inhibitors of ovastacin can contribute to the treatment of mammal infertility and improving *in vitro* fertilization.

Nematode Astacins

Nematode astacins are crucial for the development of nematodes (roundworms) and have specific roles in hatching, moulting and cuticle synthesis, as described by Stepek et al. (*International Journal for Parasitology* (2015), 45: 345-355). As noted therein, gastrointestinal (GI) nematodes cause chronic debilitating infections in livestock and humans worldwide, having a major economic impact on sheep farming resulting in a loss of appetite, weight loss, decreased wool, meat and milk production, as well as death. Current treatment is by use of anthelmintic drugs; however, multiple resistance to anthelmintics of the three major classes has now developed in veterinary parasites. Only a limited number of new drugs with novel modes of action have become available in recent years, thereby limiting prospects for effective control.

All nematodes are surrounded by an external protective structure called the cuticle. The cuticle functions as an exoskeleton and provides protection from the external environment during development, hence its importance for nematode survival. Synthesis of this structure is a complex, multi-step process, involving numerous enzymes. The

cuticle is largely composed of collagens, which are homologous between the free-living nematode, *C. elegans*, and parasitic nematodes such as the major GI nematodes of sheep, *Teladorsagia circumcincta* and *Haemonchus contortus*. The process of cuticle biosynthesis has been studied in detail in *C. elegans*, with many of the crucial cuticle synthesizing enzymes and proteases also present in parasitic nematodes, suggesting that the cuticle biosynthesis process may be similar between *C. elegans* and its parasitic counterparts. Protease enzymes are essential for the continued development and survival of nematodes in the host and fall into the following main classes: aspartic, cysteine, metallo-, threonine and serine proteases. The astacin metalloprotease enzymes play an essential role in cuticle biosynthesis in *C. elegans*. These enzymes are zinc metallo-endopeptidases that are characterised by two conserved motifs in the N-terminal astacin domain: the zinc-binding active site and the methionine-turn (SxMHY). Binding of the zinc in the active site is essential for the catalytic activity of the enzyme; this zinc is pentacoordinated in a trigonal-bipyramidal geometry between the three histidine residues in the binding motif, the tyrosine in the methionine-turn and a water molecule. Functional roles for astacin proteases in parasitic nematodes include host tissue penetration by infective L3s (Williamson et al., *Infect. Immun.* (2006), 74: 961-967), cuticle formation and ecdysis (Gamble et al., *J. Parasitol.* (1989), 82: 197-202; Stepek et al., *Int. J. Parasitol.* (2010), 40: 533-542; Stepek at al., *Parasitology* (2011), 138: 237-248) and digestion (Gallego et al., *Parasitol. Int.* (2005), 54: 123-133).

There are 39 nematode astacin (NAS) metalloproteinases expressed in *C. elegans* (Stepek et al., *International Journal for Parasitology* (2015), 45: 345-355). All the *C. elegans* NAS have a similar domain arrangement. Among these, DPY-31 (also known as NAS-35) has similarities to the vertebrate procollagen C-proteinase bone morphogenetic protein 1 (BMP-1) mentioned above, which is critical for the assembly of collagen fibrils during cartilage and bone formation through its excision of the C-terminal domain of procollagen to form mature collagen. In *C. elegans*, DPY-31 is expressed throughout the life-cycle, particularly in the embryonic and larval stages, in most hypodermal cells, as well as rectal and vulvar epithelial cells (Novelli et al., *Genetics* (2004) 168, 1259–1273). The procollagens in DPY-31(e2770) mutants remain partially processed and cannot form mature collagens (Novelli et al., *Genetics* (2006), 172, 2253–2267.) Thus, DPY-31 plays a crucial role in cuticle formation and moulting process in *C. elegans*.

Identity of 74% has been noted between DPY-31 from *C. elegans* and *T. circumcincta*, as well as of 70% between *C. elegans* and *H. contortus* and of 89% between the proteins from *T. circumcincta* and *H. contortus*. The presence of DPY-31 orthologues throughout the entire nematode phylum supports a conserved, crucial role for this protease during nematode development. It has been further found that multiple compounds specifically developed to target procollagen C-proteinases (PCP) were important inhibitors also of recombinant nematodic DPY-31, thus being promising for development of new drugs to combat important nematode infections (Stepek et al., *International Journal for Parasitology* (2015), 45: 345-355). Finally, France et al. (*Bioorganic & Medicinal Chemistry Letters* (2015), 25: 5752-5755) reported several inhibitors of DPY-31 from the human filarial nematode *Brugia malayi* which are also active against DPY-31 from the parasitic gastrointestinal nematode of sheep *T. circumcincta*.

Thus, the zinc-dependent metzincin metalloproteases of the astacin family, more specifically procollagen C-proteinase (PCP) enzymes, meprins, ovastacin and/or nematode proteins, and even more specifically human or mammalian BMP-1, meprin α, meprin β and/or ovastacin as well as nematode DPY-31, can be considered highly

relevant therapeutic targets, and there is a high demand for the development of new treatments of diseases and conditions associated therewith.

Compounds

US 4,146,721 discloses pyrazol-4-acetic acid compounds, such as substituted pyrazol-4-acetic acid, its esters, amides, nitrites and their pharmaceutically acceptable salts and method for the preparation of these compounds are disclosed. These compounds are useful analgesics, anti-inflammatory, and antipyretics.

WO 2006114263 A1 discloses imidazo [1, 2-a] pyridine derivatives, which are are a novel type of peptide deformylase (PDF) inhibitors, and are therefore of great interest especially as new antibiotics.

E. Adiguzel et. al. (JOURNAL OF MOLECULAR STRUCTURE. vol. 1127, pages 403-412) discloses the synthesis and characterization of two new hydroxamic acid derivatives and their metal complexes, in particular the investigation on the keto/enol E/Z and hydroxamate/hydroximate forms thereof.

PROBLEMS TO BE SOLVED BY THE INVENTION

In view of the above, the present invention aims at the object of providing compounds and/or pharmaceutical compositions capable of inhibiting metalloproteinases of the astacin family; in particular procollagen C-proteinase (PCP) enzymes, meprins, ovastacin and/or nematode astacins; more particularly human or mammalian meprin α (such as human meprin α, hMeprin α), meprin β (such as human meprin β, hMeprin β), BMP-1 (such as human BMP-1, hBMP-1), ovastacin (such as human ovastacin, hOvastacin) and/or DPY-31 from nematodes (such as DPY-31 from *T. circumcincta* (tcDPY-31), *H. contortus* (hcDPY-31) and *B. malayi* (bmDPY-31).

Preferably, in order to mitigate potential side effects, the inhibitors and/or pharmaceutical compositions should be selective over further members of the metzincin superfamily including ADAMs (such as ADAM10 and ADAM17 (TACE)) and MMPs (such as MMP2, MMP9 and MMP13). Preferably, the inhibitors should selectively inhibit one or more of the enzymes selected from hMeprin α, hMeprin β, hBMP-1, hOvastacin, tcDPY-31, hcDPY-31 and bmDPY-31. Further preferably, the inhibitors should have acceptable drug-like properties.

A further object is to provide a pharmaceutical composition comprising an inhibitor according to any of the aforementioned objects that is suitable for administration to a subject in need thereof.

A further object is to provide methods for producing such compounds.

A further object is to provide a method for treatment or prophylaxis of the human or animal body, and a compound or a pharmaceutical composition for use in such a method.

A further object is to provide a method for treatment or prophylaxis of a subject suffering from or having risk of developing a disease or condition related to one or more of the above-mentioned metalloproteinases of the astacin family. Preferably, the disease or condition is associated with one or more of the enzymes selected from hMeprin α, hMeprin β, hBMP-1, hOvastacin, tcDPY-31, hcDPY-31 and bmDPY-31.

A further object is to provide a method for treatment or prophylaxis of a subject suffering from or having risk of developing a disease or condition selected from Alzheimer's disease; nephritis; renal injury; renal ischemic injury;

ischemic acute tubular necrosis; acute renal failure; bladder inflammation; inflammatory bowel disease (IBD); Crohn's disease; ulcerative colitis; chronic inflammation; colitis; fibrosis; fibrotic conditions; keloids; pulmonary hypertension; interstitial lung disease (ILD); cancer; and colorectal cancer, and/or a compound for use in such a method.

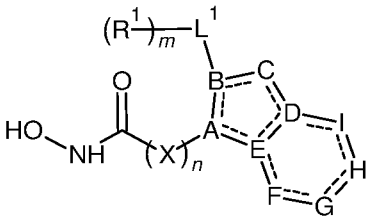
A further object is to provide a method for treatment or prophylaxis of a subject suffering from or having risk of developing a disease or condition selected from fibrosis; acute fibrotic disorders and conditions; chronical fibrotic disorders and conditions; fibrosis occurring in organs and/or accompanying diseases and conditions selected from hepatitis, liver cirrhosis, hypertension, myocardial infarction, heart failure, asthma, pulmonary hypertension, scleroderma, fibrotic skin and internal organs, diabetes, diabetes nephropathy, atherosclerosis and fibrotic blood vessels; hypertrophic dermal scarring; keloids; pulmonary fibrosis; acute CNS scarring following traumatic injury; neuronal regeneration following stroke or spinal cord injury; obliterative fibrosis of the hollow structures within grafts; chronic allograft rejection; wound healing disorders; post-surgical scarring; dermal scarring; fibrosis resulting from gynecological procedures; fibrosis after eye surgery; fibrosis following angioplasty; fibrosis following surgery on joints; preventing local invasion, recurrence and metastasis of malignant keratinocytes or squamous cell carcinomas (SCCs), and/or a compound for use in such a method.

A further object is to provide a method for treatment or prophylaxis of mammalian infertility and for therapeutic use for *in vitro* fertilization (IVF) treatment of a mammal, and/or a compound for use in such a method.

A further object is to provide a method for treatment or prophylaxis of a subject suffering from or having risk of developing a disease or condition selected from nematode infections; infections caused by *Teladorsagia circumcincta*; infections caused by *Haemonchus contortus*; and infections caused by *Brugia malayi*, and and/or a compound for use in such a method.

SUMMARY OF THE INVENTION

As a solution to the above-formulated problems, the present invention provides a compound according to the following Formula I,

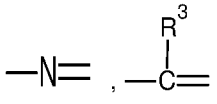


I

its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein:

A is independently selected from  and  ;

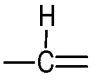
B is independently selected from  and  ;

C is independently selected from  ;

F, if present, is independently selected from  and ;

G, if present, is independently selected from  and ;

H, if present, is independently selected from  and ;

I, if present, is independently selected from  and ;

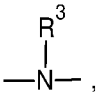
wherein if F, G, H and I are present, then:

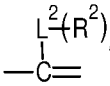
D is  ,

E is independently selected from  and , and

the ring formed by D, E, F, G, H and I is substituted by *p* substituents represented by R^2, wherein *p* is 0, 1, 2, 3 or 4;

otherwise if F, G, H and I are absent, then:

D is independently selected from  , and , and

E is independently selected from  and , wherein *p* is 0, 1, 2, 3, 4 or 5;

L^1 and L^2 are each independently selected from the group consisting of alkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring;

each X is independently selected form $C(R^a)R^b$, NR^a and O;

X and L^2 can be joined together to form a ring, wherein said ring can be optionally fused to aryl;

n is 1, 2, 3 or 4;

m is 0, 1, 2, 3, 4 or 5;

each R^1 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy;

each R^2 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy, hydroxyl and heteroaryl;

each R^3 is independently selected from hydrogen and the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heterocyclyl fused to aryl, heteroaryl and heteroarylalkyl, each of which can be substituted by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy; and

R^a and R^b are each independently selected from hydrogen, deuterium and C_{1-3} alkyl.

The present invention further provides a pharmaceutical composition comprising the compound as defined above and a pharmaceutically acceptable excipient.

The present invention also provides methods for producing the above compounds.

The present invention further provides a compound or a pharmaceutical composition as defined above for use in a method for treatment or prophylaxis of the human or animal body by surgery or therapy, as well as methods for treatment or prophylaxis of the human or animal body by surgery or therapy comprising administering a therapeutically effective amount of the above compound or pharmaceutical composition to a subject in need thereof.

The present invention further provides a compound or a pharmaceutical as defined above for use in a method for therapy or prevention of diseases and conditions selected from:

(a) Alzheimer's disease; nephritis; renal injury; renal ischemic injury; ischemic acute tubular necrosis; acute renal failure; bladder inflammation; inflammatory bowel disease (IBD); Crohn's disease; ulcerative colitis; chronic inflammation; colitis; fibrosis; fibrotic conditions; keloids; pulmonary hypertension; interstitial lung disease (ILD); cancer; colorectal cancer;

(b) fibrosis; acute fibrotic disorders and conditions; chronical fibrotic disorders and conditions; fibrosis occurring in organs and/or accompanying diseases and conditions selected from hepatitis, liver cirrhosis, hypertension, myocardial infarction, heart failure, asthma, pulmonary hypertension, scleroderma, fibrotic skin and internal organs, diabetes, diabetes nephropathy, atherosclerosis and fibrotic blood vessels; hypertrophic dermal scarring; keloids; pulmonary fibrosis; acute CNS scarring following traumatic injury; neuronal regeneration following stroke or spinal cord injury; obliterative fibrosis of the hollow structures within grafts; chronic allograft rejection; wound healing disorders; post-surgical scarring; dermal scarring; fibrosis resulting from gynecological procedures; fibrosis after eye surgery; fibrosis following angioplasty; fibrosis following surgery on joints; preventing local

invasion, recurrence and metastasis of malignant keratinocytes or squamous cell carcinomas (SCCs);

(c) mammalian infertility; therapeutic use for *in vitro* fertilization (IVF) treatment of a mammal;

(d) nematode infections; infections caused by *Teladorsagia circumcincta*; infections caused by *Haemonchus contortus*; and infections caused by *Brugia malayi,*

as well as, and/or methods for therapy or prevention of any of the preceding diseases or conditions, the method comprising administering a therapeutically effective amount of the above compound or pharmaceutical composition to a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows structural alignment of Astacin-proteinases. hMeprin α (homology model, template pdb:4GWN), hMeprin β (X-ray, pdb: 4GWN), hOvastacin (homology model, template pdb: 3LQB), *Teladorsagia circumcincta* DPY-31 (tcDPY-31, homology model, template pdb: 6BTO), *Haemonchus contortus* DPY-31 (hcDPY-31, homology model, template pdb:6BTO), hBMP-1 (X-ray, pdb:6BTO).

Fig. 2 shows an active site view of aligned proteinases (hMeprin α (homology model, template pdb:4GWN), hMeprin β (X-ray, pdb: 4GWN), hOvastacin (homology model, template pdb: 3LQB). Essential side chains for inhibitor binding are shown.

Fig. 3 shows an active site view of aligned proteinases (hMeprin α (homology model, template pdb:4GWN), hMeprin β (X-ray, pdb: 4GWN)), *Teladorsagia circumcincta* DPY-31 (tcDPY-31, homology model, template pdb: 6BTO), *Haemonchus contortus* DPY-31 (hcDPY-31, homology model, template pdb:6BTO). Essential side chains for inhibitor binding are shown.

Fig. 4 shows an active site view of aligned proteinases (hMeprin α (homology model, template pdb:4GWN), hMeprin β (X-ray, pdb: 4GWN), hBMP-1 (X-ray, pdb:6BTO). Essential side chain for inhibitor binding are shown.

Fig. 5 shows a CLUSTAL O(1.2.4) multiple sequence alignment of hMeprin α, hMeprin β, hOvastacin, tcDPY-31 and hcDPY-31.

DETAILED DESCRIPTION OF THE INVENTION

Therapeutic Targets, Inhibitory Activity and Effects Achieved by the Invention

The present inventors have found that the compounds according to Formula I exhibit high inhibitory activity against various astacin metalloproteinases, in particular against hMeprin α and hMeprin β as evidenced by the experimental results shown herein (see Table 2). Additionally, as evidenced by the results shown in Table 3, the compounds also exhibit selectivity for astacin metalloproteinases while at the same time being significantly less active on further members of the metzincin superfamily including ADAMs (such as ADAM10 and ADAM17 (TACE)) and MMPs (such as MMP2, MMP9 and MMP13), thereby reducing the risk for potential side effects

Additionally, further enzymes among the same family such as hOvastacin, tcDPY-31 and hcDPY-31 share an identical Zn^{2+} binding sequence in their respective active sites, an identical specificity pocket (S_1'), and a highly conserved methionine-containing turn (Met-turn, SxMHY) backing the zinc site, as can be seen from the sequence alignment shown in Fig. 5. Moreover, hMeprin α, hMeprin β, as hOvastacin, tcDPY-31 and hcDPY-31 strikingly similar overall three-dimensional structures (as shown in Fig. 1) and in particular of their active sites also responsible for inhibitor binding (as shown in Fig. 2–4).

Furthermore, earlier work has indicated that compounds that were known as highly effective inhibitors of procollagen C-proteinases (e.g., BMP-1) or meprins (actinonin) are also effective against nematode DPY-31 enzymes, such as tcDPY-31 and hcDPY-31 (Stepek et al., *International Journal for Parasitology* (2015), 45: 345-355) as well as tcDPY-31 and bmDPY-31 (France et al., *Bioorganic & Medicinal Chemistry Letters* (2015), 25: 5752-5755).

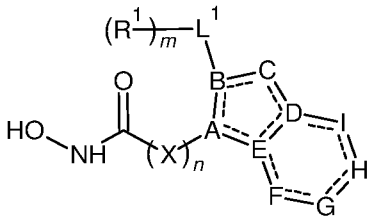
In view of the above evidence and the experimental results shown herein, all of the present compounds are useful as inhibitors of metalloproteinases of the astacin family; in particular procollagen C-proteinase (PCP) enzymes, meprins, ovastacin and/or nematode astacins; more particularly human or mammalian meprin α (such as human meprin α, hMeprin α), meprin β (such as human meprin β, hMeprin β), BMP-1 (such as human BMP-1, hBMP-1), ovastacin (such as human ovastacin, hOvastacin) and/or DPY-31 from nematodes (such as DPY-31 from *T. circumcincta* (tcDPY-31), *H. contortus* (hcDPY-31) and *B. malayi* (bmDPY-31).

The present invention provides a new class of inhibitors different in its physical chemical properties from compounds known from the prior art, such as tertiary amine inhibitors. Also, the pharmacokinetic and pharmacodynamic properties of the new molecules are influenced thereby, which leads, e.g., to an improved activity against the target enzymes. Additionally, the present compounds are characterized by the presence of a flat aromatic or heteroaromatic central cyclic system. The structural features of the presently described compounds are clearly distinct from any previously described inhibitors of astacin metalloproteases or related enzymes.

Compounds

Specifically, the present disclosure provides compounds to any one of the following aspects <1>–<31>.

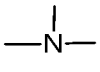
<1> A compound according to the following Formula I,

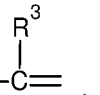


I

its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein:

A is independently selected from  and  ;

B is independently selected from  and  ;

C is independently selected from  ,  ,  , –O– and –S–;

F, if present, is independently selected from  and  ;

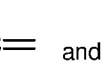
G, if present, is independently selected from  and  ;

H, if present, is independently selected from  and  ;

I, if present, is independently selected from  and  ;

wherein if F, G, H and I are present, then:

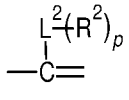
D is  ,

E is independently selected from  and  , and

the ring formed by D, E, F, G, H and I is substituted by *p* substituents represented by R^2, wherein *p* is 0, 1, 2, 3 or 4;

otherwise if F, G, H and I are absent, then:

D is independently selected from  ,  and  , and

E is independently selected from  and  , wherein *p* is 0, 1, 2, 3, 4 or 5;

L^1 and L^2 are each independently selected from the group consisting of alkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring; preferably L^1 and L^2 are each independently selected from the group consisting of aryl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring;

each X is independently selected form $C(R^a)R^b$, NR^a and O;

n is 1, 2, 3 or 4;

m is 0, 1, 2, 3, 4 or 5;

each R^1 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy;

each R^2 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy hydroxyl and heteroaryl;

each R^3 is independently selected from hydrogen and the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heterocyclyl fused to aryl, heteroaryl and heteroarylalkyl, each of which can be substituted by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy; and

R^a and R^b are each independently selected from hydrogen, deuterium and C_{1-3} alkyl.

<2> The compound according to aspect 1, wherein, unless otherwise specified:

said aryl is independently selected from the group consisting of a monocyclic C_{6-10}, bicyclic C_{6-10}, monocyclic, C_6 and bicyclic C_6 aryl group;

said heterocyclyl is independently selected from the group consisting of a monocyclic C_{2-11}, monocyclic C_{2-8}, monocyclic C_{3-5}, bicyclic C_{2-11}, bicyclic C_{2-8} and bicyclic C_{3-5} heterocyclic group, each comprising 1 to 4 ring heteroatoms selected from N, S and O;

said heteroaryl is independently selected from the group consisting of a monocyclic C_{2-11}, monocyclic C_{2-8}, monocyclic C_{3-5}, bicyclic C_{2-11}, bicyclic C_{2-8} and bicyclic C_{3-5} aromatic heterocyclic group, each comprising 1 to 3 ring heteroatoms selected from N, S and O;

said alkyl or alk is independently selected from the group consisting of a C_{1-12}, C_{1-6}, C_{1-3}, C_{1-2} and C_1alkyl group, each of which can be linear or branched, open-chained or cyclic;

said alkenyl is independently selected from the group consisting of a C_{2-12}, C_{2-4}, C_{2-3} and C_2 group comprising at least one C=C bond, each of which can be linear or branched, open-chained or cyclic;

said alkynyl is independently selected from the group consisting of a C_{2-12}, C_{2-6}, C_{2-4}, C_{2-3} and C_2 group comprising at least one C≡C bond, each of which can be linear or branched, open-chained or cyclic;

said cycloalkyl is independently selected from the group consisting of a monocyclic C_{3-12}, monocyclic C_{3-6}, bicyclic C_{3-12} and bicyclic C_{3-6} alkyl group;

said cycloalkenyl is independently selected from the group consisting of C_{3-12}, C_{4-6} and C_{5-6} carbocyclic group comprising at least one C=C bond;

wherein each of the above groups can be substituted by one or more groups selected from halogen, carboxy, cyano, methoxy and hydroxy.

<3> The compound according to aspect 1 or 2, wherein, unless otherwise specified:

said aryl is independently a monocyclic or bicyclic C_{6-10}, preferably C_6 aryl group;

said heterocyclyl is independently a monocyclic or bicyclic C_{2-11}, preferably C_{2-8}, more preferably C_{3-5} heterocyclic group comprising 1 to 4 ring heteroatoms selected from N, S and O;

said heteroaryl is independently a monocyclic or bicyclic C_{2-11} preferably C_{2-8}, more preferably C_{3-5} aromatic heterocyclic group comprising 1 to 3 ring heteroatoms selected from N, S and O;

said alkyl or alk is independently a linear or branched, open-chained or cyclic C_{1-12}, preferably C_{1-6}, more preferably C_{1-3}, even more preferably C_{1-2} alkyl group;

said alkenyl is independently a linear or branched, open-chained or cyclic C_{2-12}, preferably C_{2-4}, more preferably C_{2-3}, even more preferably C_2 group comprising at least one C=C bond;

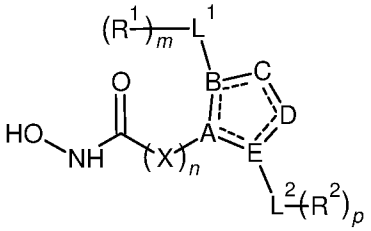
said alkynyl is independently a linear or branched, open-chained or cyclic C_{2-12}, preferably C_{2-6}, more preferably C_{2-4}, even more preferably C_{2-3} group comprising at least one C≡C bond;

said cycloalkyl is independently a C_{3-12}, preferably C_{3-6}, monocyclic or bicyclic alkyl group;

said cycloalkenyl is independently C_{3-12}, preferably C_{4-6}, more preferably C_{5-6} carbocyclic group comprising at least one C=C bond;

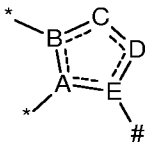
wherein each of the above groups can be substituted by one or more groups selected from halogen, carboxy, cyano, methoxy and hydroxy.

<4> The compound according to any one of aspects 1 to 3, which is represented by the following Formula Ia:

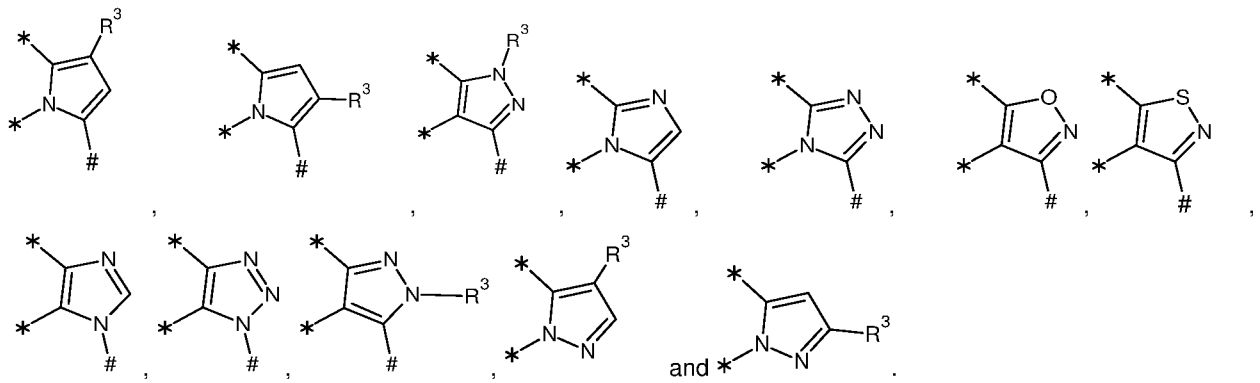


Ia

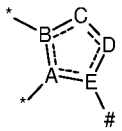
<5> The compound according to any one of aspects 1 to 4, wherein if F, G, H and I are absent, the ring fragment



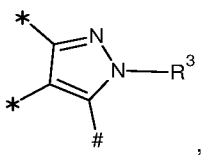
is represented by one of the following structures:



<6> The compound according to any one of aspects 1 to 5, wherein when the ring fragment



is represented by



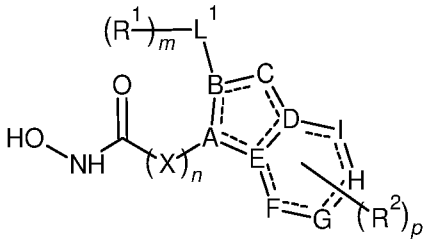
then:

R^3 is selected from hydrogen and the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, substituted aryl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl wherein optionally substituted or substituted refers, respectively, to optional substitution or substitution by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -$C(O)NH_2$, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy,

alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy.

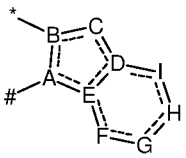
<7> The compound according to any one of aspects 1 to 6, wherein R^3 is aryl substituted by one or more groups independently selected from amino, chloro, fluoro, bromo, iodo, cyano, hydroxy, carboxy, C_{1-6} alkyl, C_1-C_6 alkoxy and hydroxy.

<8> The compound according to any one of aspects 1 to 7, which is represented by the following Formula Ib:

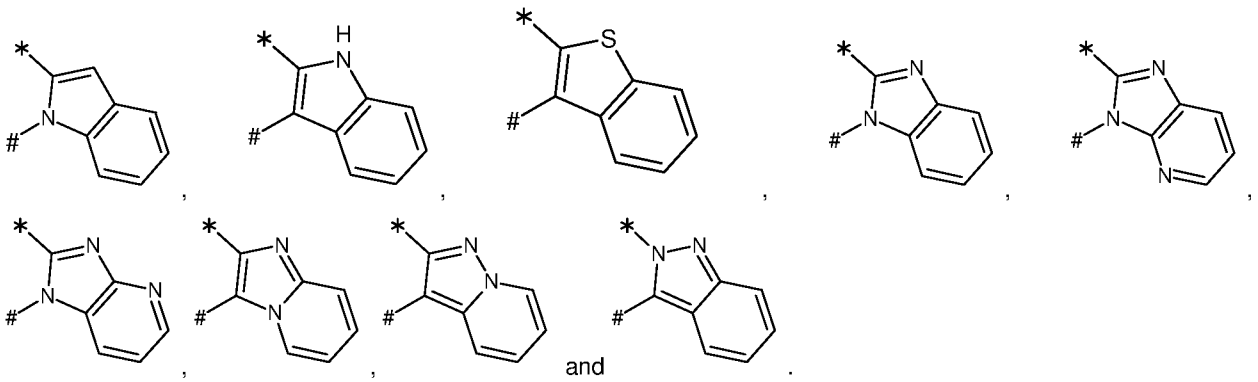


Ib.

<9> The compound according to any one of aspects 1 to 8, wherein if F, G, H and I are present, the ring fragment

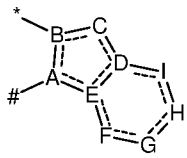


is represented by one of the following structures:

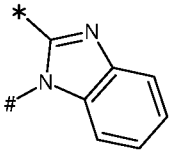


and .

<10> The compound according to any one of aspects 1 to 9, wherein when the ring fragment



is represented by



,

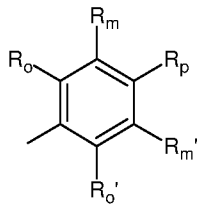
then at least one of *m* and *p* is larger than 0.

<11> The compound according to any of aspects 8 to 10, wherein *n* = 1.

<12> The compound according to any of aspects 1 to 11, wherein at least one or each of *m* and *p* is larger than 0.

<13> The compound according to any of aspects 1 to 12, wherein R^1 and R^2 are the same or different and are each independently selected from the group consisting of chloro, fluoro, bromo, iodo, cyano, C_1-C_6 alkoxy, C_1-C_6 alkyl, fluoro(C_{1-6} alkyl), fluoro(C_{1-6} alkoxy), and a functional group having an acidic hydrogen selected from hydroxy, carboxy, -SO_3H, -$P(O)(OH)_2$, -C(O)-NH-OH tetrazol-5-yl, -SO_3H, -$P(O)(OH)_2$, -C(O)-NH-OH and tetrazol-5-yl.

<14> The compound according to any of aspects 1 to 13, wherein $L^1(R^1)_m$ and $L^2(R^2)_p$ are the same or different and each independently represented by the following structure:



wherein:

(i) at least one of R_o, R_o', R_m, R_m' and R_p, is a functional group having an acidic hydrogen selected from hydroxy, carboxy, -SO_3H, -$P(O)(OH)_2$, -C(O)-NH-OH and tetrazol-5-yl, and the remaining ones are either H or as defined for R^1 or R^2 according to any one of the preceding aspects; and/or

(ii) at least two of R_o, R_o', R_m, R_m' and R_p are alkoxy groups that are joined together as a part of a 5- to 8-membered heterocycle, and the remaining ones are H or as defined for R^1 or R^2 according to any one of the preceding aspects; and/or

<15> The compound according to any of aspects 1 to 14, wherein $L^1(R^1)_m$ and $L^2(R^2)_p$ are the same or different and are each independently selected from the group consisting of 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 3-chlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-methylphenyl, 4-carboxyphenyl, 4-chlorophenyl, 4-cyanophenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-methylphenyl, 3-carboxy-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-chloro-2-fluoro-3-hydroxyphenyl, 5-chloro-3-fluoro-4-hydroxyphenyl, 3-chloro-5-fluoro-4-hydroxyphenyl, 3,5-dichloro-4-hydroxyphenyl, 2,6-difluoro-4-methoxyphenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxol-5-yl, 3-(trifluoromethyl)-1H-pyrazol-4-yl, 3-(1H-tetrazol-5-yl)phenyl, 2-carboxycyclohexyl, 3-carboxycyclohexyl, 3-carboxycyclohexyl and (1,3-benzodioxol-5-yl)methyl; preferably from the group consisting of 3-carboxyphenyl, 3-chlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-methylphenyl, 4-carboxyphenyl, 4-

chlorophenyl, 4-cyanophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-methylphenyl, 3-carboxy-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-chloro-2-fluoro-3-hydroxyphenyl, 3-chloro-5-fluoro-4-hydroxyphenyl, 3,5-dichloro-4-hydroxyphenyl, 2,6-difluoro-4-methoxyphenyl, 2,3-dihydro-1,4-benzodioxin-6-yl and 1,3-benzodioxol-5-yl

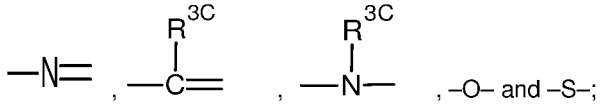
<16> The compound according to any of aspects 1 to 15, wherein $L^1(R^1)_m$ and $L^2(R^2)_p$ are the same.

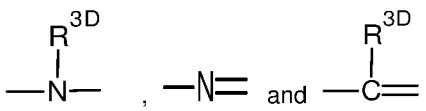
<17> The compound according to any of aspects 1 to 15, wherein $L^1(R^1)_m$ and $L^2(R^2)_p$ are the different.

<18> The compound according to any of aspects 1 to 17, wherein each R^3 is independently selected from hydrogen and the group consisting of C_{1-6} alkyl, carboxy(C_{1-6} alkyl), amino(C_{1-6} alkyl), cyano(C_{1-6} alkyl), C_{2-6} alkynyl, C_{3-6} cycloalkyl, carboxy(C_{6-10} aryl), C_{1-6} alkoxy(C_{6-10} aryl), cyano(C_{6-10} aryl), halo(C_{6-10} aryl), hydroxy(C_{6-10} aryl), C_{1-6} alkoxy(C_{2-8} heteroaryl), cyano(C_{2-8} heteroaryl), halo(C_{2-8} heteroaryl), C_{3-5} heteroaryl(C_{6-10} aryl), hydroxy(C_{2-8} heteroaryl), carboxy(C_{2-8} heteroaryl), (C_{6-10} aryl)methyl, (C_{1-6} alkoxy(C_{6-10} aryl))methyl, (hydroxy(C_{6-10} aryl))methyl, (carboxy(C_{6-10} aryl))methyl, (C_{1-6} alkoxy(C_{2-8} heteroaryl))methyl, (C_{2-8} heteroaryl-(C_{6-10}aryl))methyl, (hydroxy(C_{2-8} heteroaryl))methyl and (carboxy(C_{2-8} heteroaryl))methyl, each of which can be further substituted by one or more groups independently selected from chloro, fluoro, bromo, iodo, carboxy cyano, C_{1-6} alkyl, C_1-C_6 alkoxy and hydroxy.

<19> The compound according to any of aspects 1 to 18, wherein each R^3 is independently selected from hydrogen and the group consisting of methyl, ethyl, 2-propyl, 1-propyl, phenyl, 2-aminoethyl, propargyl, cyclopropyl, $-CH_2COOH$, $-CH_2CN$, phenyl, 3-carboxyphenyl, 3-chlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-methylphenyl, 4-carboxyphenyl, 4-chlorophenyl, 4-cyanophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-methylphenyl, 3-carboxy-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-chloro-2-fluoro-3-hydroxyphenyl, 3-chloro-5-fluoro-4-hydroxyphenyl, 3,5-dichloro-4-hydroxyphenyl, 2,6-difluoro-4-methoxyphenyl, 1,3-benzodioxol-5-yl, benzyl, (3-carboxyphenyl)methyl, (3-chlorophenyl)methyl, (3-cyanophenyl)methyl, (3-fluorophenyl)methyl, (3-methoxyphenyl)methyl, (3-methylphenyl)methyl, (4-carboxyphenyl)methyl, (4-chlorophenyl)methyl, (4-cyanophenyl)methyl, (4-fluorophenyl)methyl, (4-methoxyphenyl)methyl, (4-methylphenyl)methyl, (3-carboxy-4-methoxyphenyl)methyl, (3-fluoro-4-methoxyphenyl)methyl, (4-chloro-2-fluoro-3-hydroxyphenyl)methyl, (3-chloro-5-fluoro-4-hydroxyphenyl)methyl, (3,5-dichloro-4-hydroxyphenyl)methyl, (2,6-difluoro-4-methoxyphenyl)methyl, (2,3-dihydro-1,4-benzodioxin-6-yl)methyl and (1,3-benzodioxol-5-yl)methyl and/or from the group consisting of *para*-methyl-benzoic acid, and *meta*-methyl-benzoic acid

<20> The compound according to any of aspects 1 to 19, wherein

C is selected from  , –O– and –S–;

D is selected from  , and

R^{3C} and R^{3D} are the same or different from each other and each independently selected from the groups defined for R^3 according to any one of the preceding aspects.

<21> The compound according to aspect 20, wherein R^{3C} and R^{3D} are different from each other.

<22> The compound according to any of aspects 1 to 21, wherein: each X is $C(R^a)R^b$, wherein one of the $C(R^a)R^b$ groups can be replaced by a NR^a group; *n* is 1 or 2; *m* is 0, 1, 2 or 3; *p* is 0, 1, 2 or 3; L^1 is phenyl; L^2 is phenyl; R^1 is independently selected from Cl, F, OH, CN, OCH_3 and COOH, and/or two R^1 groups together form part of a 1,3-benzodioxol ring or a 2,3-dihydro-1,4-benzodioxin ring; R^2 is independently selected from Cl, F, OH, CN, OCH_3 and COOH, and/or two R^2 groups together form part of a 1,3-benzodioxol ring or a 2,3-dihydro-1,4-benzodioxin ring; R^3 is selected from hydrogen, methyl, ethyl, propargyl, cyclopropyl, 2-aminoethyl, $-CH_2COOH$, $-CH_2CN$, benzyl, unsubstituted phenyl, and substituted phenyl selected from 3-carboxyphenyl and 4-carboxyphenyl; and R^a and R^b are hydrogen.

<23> The compound according to any of aspects 1 to 22, wherein X is $C(R^a)R^b$; *n* is 1; and at least one of *m* and *p* is larger than 0.

<24> The compound according to any of according to any of aspects 1 to 21, wherein each X is $C(R^a)R^b$; *n* is 1 or 2; *m* is 0, 1, 2 or 3; *p* is 0, 1, 2 or 3; L^1 is phenyl; L^2 is cyclohexyl; R^1 is COOH, R^2 is COOH; R^3 is hydrogen; and R^a and R^b are hydrogen.

<25> The compound according to any of according to any of aspects 1 to 21, wherein each X is $C(R^a)R^b$, wherein one of the $C(R^a)R^b$ groups can be replaced by a NR^a group; *n* is 1 or 2; *m* is 0, 1, 2 or 3; *p* is 0, 1, 2 or 3; L^1 is phenyl; L^2 is phenyl; R^1 is independently selected from Cl, F, OH, CN, OCH_3 and COOH, and/or two R^1 groups together form part of a 1,3-benzodioxol ring or a 2,3-dihydro-1,4-benzodioxin ring; preferably R^1 is hydrogen; R^2 is a bioisosteric replacement of an acidic group, preferably R^3 is tetrazole; R^3 is selected from hydrogen, methyl, ethyl, propargyl, cyclopropyl, 2-aminoethyl, $-CH_2COOH$, $-CH_2CN$, benzyl, unsubstituted phenyl, and substituted phenyl selected from 3-carboxyphenyl and 4-carboxyphenyl; preferably R^3 is hydrogen; and R^a and R^b are hydrogen.

<26> A compound having a structure selected from Table 2, its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof.

<27> A pharmaceutical composition comprising the compound according to any of aspects 1 to 25 and a pharmaceutically acceptable excipient.

<28> A compound according to any of aspects 1 to 26 or a pharmaceutical composition according to aspect 26 for use in a method for treatment of the human or animal body.

<29> A compound according to any of aspects 1 to 26 or a pharmaceutical composition according to aspect 26 for use in a method for therapy or prevention of diseases and conditions selected from Alzheimer's disease; nephritis; renal injury; renal ischemic injury; ischemic acute tubular necrosis; acute renal failure; bladder inflammation;

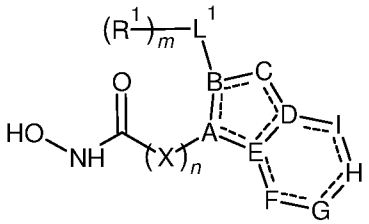
inflammatory bowel disease (IBD); Crohn's disease; ulcerative colitis; chronic inflammation; colitis; fibrosis; fibrotic conditions; keloids; pulmonary hypertension; interstitial lung disease (ILD); cancer; and colorectal cancer.

<30> A compound according to any of aspects 1 to 26 or a pharmaceutical composition according to aspect 27 for use in a method for therapy or prevention of diseases and conditions selected from fibrosis; acute fibrotic disorders and conditions; chronical fibrotic disorders and conditions; fibrosis occurring in organs and/or accompanying diseases and conditions selected from hepatitis, liver cirrhosis, hypertension, myocardial infarction, heart failure, asthma, pulmonary hypertension, scleroderma, fibrotic skin and internal organs, diabetes, diabetes nephropathy, atherosclerosis and fibrotic blood vessels; hypertrophic dermal scarring; keloids; pulmonary fibrosis; acute CNS scarring following traumatic injury; neuronal regeneration following stroke or spinal cord injury; obliterative fibrosis of the hollow structures within grafts; chronic allograft rejection; wound healing disorders; post-surgical scarring; dermal scarring; fibrosis resulting from gynecological procedures; fibrosis after eye surgery; fibrosis following angioplasty; fibrosis following surgery on joints; preventing local invasion, recurrence and metastasis of malignant keratinocytes or squamous cell carcinomas (SCCs);

<31> A compound according to any of aspects 1 to 26 or a pharmaceutical composition according to aspect 27 for use in a method for therapy or prevention of diseases and conditions selected from mammalian infertility and therapeutic use for *in vitro* fertilization (IVF) treatment of a mammal.

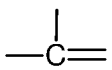
<32> A compound according to any of aspects 1 to 26 or a pharmaceutical composition according to aspect 27 for use in a method for therapy or prevention of diseases and conditions selected from nematode infections; infections caused by *Teladorsagia circumcincta*; infections caused by *Haemonchus contortus*; and infections caused by *Brugia malayi*.

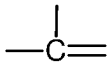
In a preferred embodiment of aspect <1>, the present disclosure provides compounds of the following Formula I,

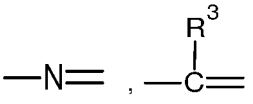


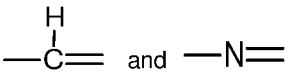
I

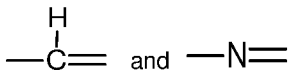
its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein:

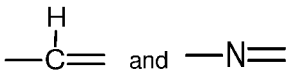
A is independently selected from  and  ;

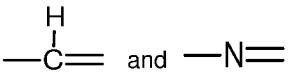
B is independently selected from  and  ;

C is independently selected from  ;

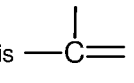
F, if present, is independently selected from  ;

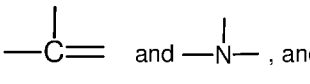
G, if present, is independently selected from  ;

H, if present, is independently selected from  ;

I, if present, is independently selected from  ;

wherein if F, G, H and I are present, then:

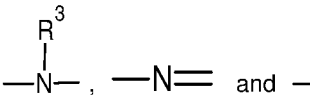
D is  ,

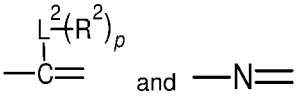
E is s independently elected from  , and

the ring formed by D, E, F, G, H and I is substituted by *p* substituents represented by R^2,

wherein *p* is 0, 1, 2, 3 or 4;

otherwise if F, G, H and I are absent, then:

D is independently selected from  , and

E is independently selected from  , wherein *p* is 0, 1, 2, 3, 4 or 5;

L^1 and L^2 are each independently selected from the group consisting of alkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring;

each X is independently selected form $C(R^a)R^b$, NR^a and O;

X and L^2 can be joined together to form a ring, wherein said ring can be optionally fused to aryl;

n is 1, 2, 3 or 4;

m is 0, 1, 2, 3, 4 or 5;

each R^1 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy;

each R^2 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy, hydroxy and heteroaryl;

each R^3 is independently selected from hydrogen and the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heterocyclyl fused to aryl, heteroaryl and heteroarylalkyl, each of which can be substituted by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy; and

R^a and R^b are each independently selected from hydrogen, deuterium and C_{1-3} alkyl,

wherein, unless otherwise specified:

said aryl is independently a monocyclic or bicyclic C_{6-10}, preferably C_6 aryl group;

said heterocyclyl is independently a monocyclic or bicyclic C_{2-11}, preferably C_{2-8}, more preferably C_{3-5} heterocyclic group comprising 1 to 4 ring heteroatoms selected from N, S and O;

said heteroaryl is independently a monocyclic or bicyclic C_{2-11} preferably C_{2-8}, more preferably C_{3-5} aromatic heterocyclic group comprising 1 to 3 ring heteroatoms selected from N, S and O;

said alkyl or alk is independently a linear or branched, open-chained or cyclic C_{1-12}, preferably C_{1-6}, more preferably C_{1-3}, even more preferably C_{1-2} alkyl group;

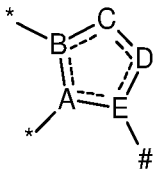
said alkenyl is independently a linear or branched, open-chained or cyclic C_{2-12}, preferably C_{2-4}, more preferably C_{2-3}, even more preferably C_2 group comprising at least one C=C bond;

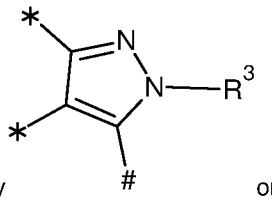
said alkynyl is independently a linear or branched, open-chained or cyclic C_{2-12}, preferably C_{2-6}, more preferably C_{2-4}, even more preferably C_{2-3} group comprising at least one C≡C bond;

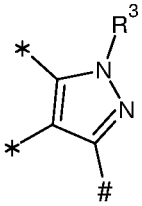
said cycloalkyl is independently a C_{3-12}, preferably C_{3-6}, monocyclic or bicyclic alkyl group;

said cycloalkenyl is independently C_{3-12}, preferably C_{4-6}, more preferably C_{5-6} carbocyclic group comprising at least one C=C bond;

wherein each of the above groups can be substituted by one or more groups selected from halogen, carboxy, cyano, methoxy and hydroxy,

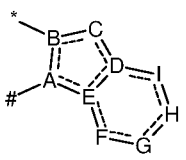
wherein when the ring fragment 

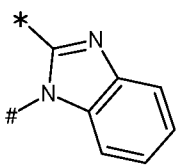
is represented by 

or 

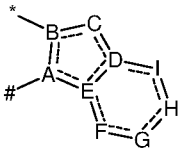
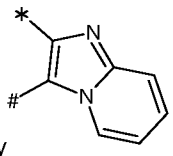
, then:

R^3 is selected from hydrogen and the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, substituted aryl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl wherein optionally substituted or substituted refers, respectively, to optional substitution or substitution by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), $-C(O)NH_2$, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy;

when the ring fragment 

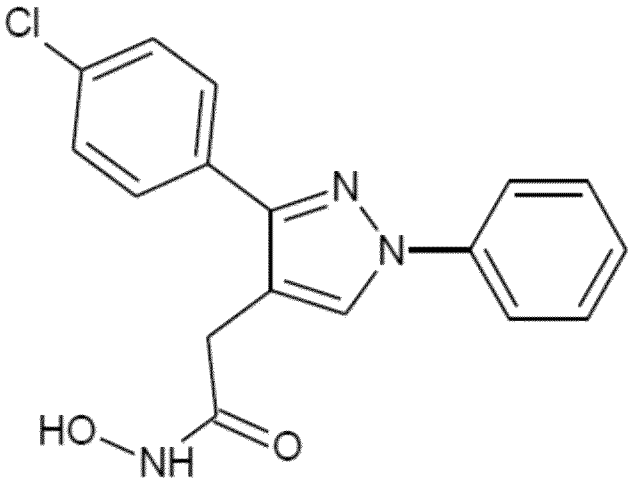
is represented by 

, then at least one of *m* and *p* is larger than 0; and

when the ring fragment  is represented by  , then *m* is larger than 0.

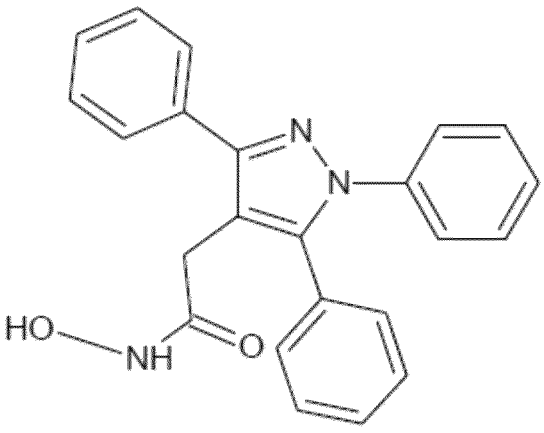
In a further preferred embodiment, the following compounds a) to d) are excluded from the scope of the compounds of Formula (I):

Compound a):



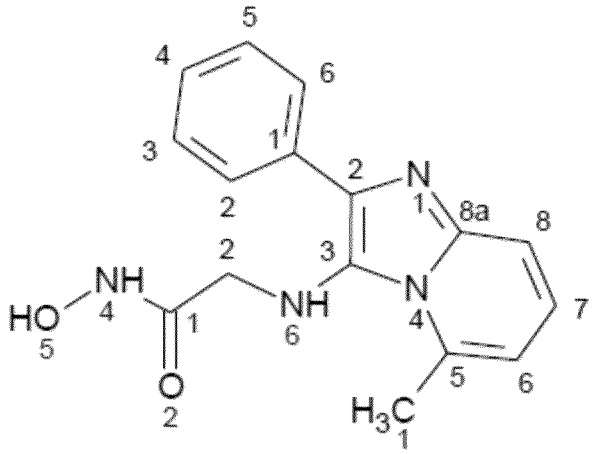
1-phenyl-3-(*p*-chlorophenyl)-pyrazol-4-yl-methylhydroxamic acid;

Compound b):



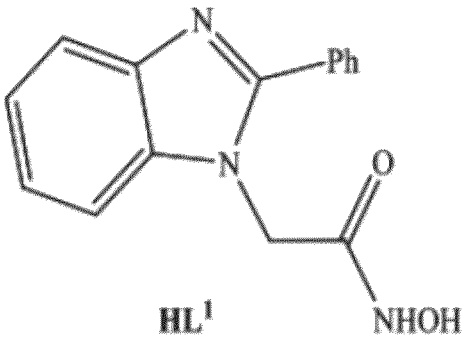
1,3,5-triphenyl-pyrazol-4-yl-methyl-hydroxamic acid;

Compound c):



N-hydroxy-2-(5-methyl-2-phenyl-imidazo[1,2-a]pyridine-3-yl-amino)-acetamide; and

Compound d):



(2-phenyl-benzimidazol-1-yl)-methylhydroxamic acid.

Compounds a) and b) are disclosed in US 4,146,721.

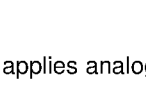
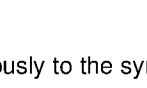
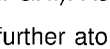
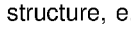
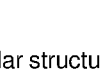
Compound c) is disclosed in WO 2006114263 A1.

Compound d) is disclosed in E. Adiguzel et. al. (JOURNAL OF MOLECULAR STRUCTURE. vol. 1127, pages 403-412).

More preferably, compounds a) to d) are not excluded from the scope of the compounds of formula (I) as far as their use in a method for therapy or prevention of diseases and conditions as described herein is concerned.

Definitions

As used herein, the symbol —C= represents an sp^2 carbon atom capable of being connected with three further atoms, and should be understood to denote any orientation within the respective molecular structure, e.g., also =C— , with the proviso that the double bond must be part of the respective planar ring system (ABCDE or

ABCDEFGHI). This applies analogously to the symbols  ,  and , the only difference in these cases being that the respective sp^2 carbon atom is capable of being connected with two further atoms of the respective planar ring system, whereas the group H, $L^2(R^2)_p$ and R^3, respectively, are substituents of the respective planar ring system (ABCDE or ABCDEFGHI). As used herein, the symbol  represents an sp^2 nitrogen atom capable of being connected with two further atoms, and should be understood to denote any orientation within the respective molecular structure, e.g., also  , with the proviso that the double bond must be part of the respective planar ring system (ABCDE or ABCDEFGHI). As used herein, the symbol represents an sp^3 nitrogen atom capable of being connected with three further atoms, and should be understood to comprise any orientation within the respective molecular structure. This applies analogously to the symbol  , the only difference in this cases being that the sp^3 nitrogen atom is capable of being connected with two further atoms of the respective planar ring system, whereas the group R^3 is a substituent of the respective planar ring system.

The expression "alkyl" as used herein, unless specifically limited, denotes a C_{1-12} alkyl group, suitably a C_{1-8} alkyl group, e.g. C_{1-6} alkyl group, e.g. C_{1-4} alkyl group. Alkyl groups may be straight chain or branched. Suitable alkyl groups include, for example, methyl, ethyl, propyl (e.g. n-propyl and isopropyl), butyl (e.g. n-butyl, iso-butyl, sec-butyl and tert-butyl), pentyl (e.g. n-pentyl), hexyl (e.g. n-hexyl), heptyl (e.g. n-heptyl) and octyl (e.g. n-octyl). The term "alkyl" also comprises cycloalkyl groups. The expression "cycloalkyl", unless specifically limited, denotes a C_{3-10} cycloalkyl group (i.e. 3 to 10 ring carbon atoms), more suitably a C_{3-8} cycloalkyl group, e.g. a C_{3-6} cycloalkyl group. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. A most suitable number of ring carbon atoms is three to six.

The expression "heteroalkyl", unless specifically limited, refers to an alkyl group wherein one or more carbon atoms, preferably 1, 2 or 3, are replaced by heteroatoms selected from N, S and O.

The expressions "carbocyclyl" and “carbocyclic”, unless specifically limited, denote any ring system in which all the ring atoms are carbon, and which contains between three and twelve ring carbon atoms, suitably between three and ten carbon atoms and more suitably between three and eight carbon atoms. Carbocyclyl groups may be saturated or partially unsaturated, but do not include aromatic rings. Examples of carbocyclyl groups include monocyclic, bicyclic, and tricyclic ring systems, in particular monocyclic and bicyclic ring systems. Other carbocyclic groups include bridged ring systems (e.g. bicyclo[2.2.1]heptenyl). A specific example of a carbocyclyl group is a cycloalkyl group. A further example of a carbocyclyl group is a cycloalkenyl group.

The expression "aryl", unless specifically limited, denotes a C_{6-12} aryl group, suitably a C_{6-10} aryl group, more suitably a C_{6-8} aryl group. Aryl groups will contain at least one aromatic ring (e.g. one, two or three rings). An example of a typical aryl group with one aromatic ring is phenyl. An example of a typical aryl group with two aromatic rings is naphthyl.

The expressions "heterocyclyl" and “heterocyclyc", unless specifically limited, refer to a carbocyclyl group wherein one or more (e.g. 1, 2 or 3) ring atoms are replaced by heteroatoms selected from N, S and O. A specific example of a heterocyclyl group is a cycloalkyl group (e.g. cyclopentyl or more particularly cyclohexyl) wherein one or more (e.g. 1, 2 or 3, particularly 1 or 2, especially 1) ring atoms are replaced by heteroatoms selected from N, S or O. Exemplary heterocyclyl groups containing one hetero atom include pyrrolidine, tetrahydrofuran and piperidine, and exemplary heterocyclyl groups containing two hetero atoms include morpholine and piperazine. A further specific example of a heterocyclyl group is a cycloalkenyl group (e.g. a cyclohexenyl group) wherein one or more (e.g. 1, 2 or 3, particularly 1 or 2, especially 1) ring atoms are replaced by heteroatoms selected from N, S and O. An example of such a group is dihydropyranyl (e.g. 3,4-dihydro-2H-pyran-2-yl-).

The expression "heteroaryl", unless specifically limited, denotes an aryl residue, wherein one or more (e.g. 1, 2, 3, or 4, suitably 1 , 2 or 3) ring atoms are replaced by heteroatoms selected from N, S and O, or else a 5-membered aromatic ring containing one or more (e.g. 1 , 2, 3, or 4, suitably 1 , 2 or 3) ring atoms selected from N, S and O. Heteroaryl groups represent a particular subtype within the general class of "heterocyclyl" or “heterocyclyc" groups. Exemplary monocyclic heteroaryl groups having one heteroatom include: five membered rings (e.g. pyrrole, furan, thiophene); and six membered rings (e.g. pyridine, such as pyridin-2-yl, pyridin-3-yl and pyridin-4-yl). Exemplary monocyclic heteroaryl groups having two heteroatoms include: five membered rings (e.g. pyrazole, oxazole, isoxazole, thiazole, isothiazole, imidazole, such as imidazol-1-yl, imidazol-2-yl imidazol-4-yl); six membered rings (e.g. pyridazine, pyrimidine, pyrazine). Exemplary monocyclic heteroaryl groups having three heteroatoms include: 1,2,3-triazole and 1,2,4-triazole. Exemplary monocyclic heteroaryl groups having four heteroatoms include tetrazole. Exemplary bicyclic heteroaryl groups include: indole (e.g. indol-6-yl), benzofuran, benzthiophene, quinoline, isoquinoline, indazole, benzimidazole, benzothiazole, quinazoline and purine.

The expressions “alkoxyaryl”, “carboxyaryl”, “cyanoaryl”, “haloaryl”, “hydroxyaryl” and “heteroarylaryl”, unless specifically limited, denote an aryl residue which is substituted by at least one alkoxy, carboxy, cyano, halo, hydroxy and heteroaryl group, respectively.

The expressions “alkoxyheteroaryl”, “carboxyheteroaryl”, “cyanoheteroaryl”, “haloheteroaryl” and “hydroxyheteroaryl”, unless specifically limited, denote a heteroaryl residue which is substituted by at least one alkoxy, carboxy, cyano, halo, and hydroxy group, respectively.

The expression "alk", for example in the expressions "alkoxy", "haloalkyl" should be interpreted in accordance with the definition of "alkyl". Exemplary alkoxy groups include methoxy, ethoxy, propoxy (e.g. n-propoxy), butoxy (e.g. n-butoxy), pentoxy (e.g. n-pentoxy), hexoxy (e.g. n-hexoxy), heptoxy (e.g. n-heptoxy) and octoxy (e.g. n-octoxy). Exemplary haloalkyl groups include fluoroalkyl e.g. CF_3; exemplary haloalkoxy groups include fluoroalkyl e.g. OCF_3.

The term "halogen" or "halo" comprises fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

The terms “hydrogen” or “H” as used herein encompass all isotopes of hydrogen, in particular protium (^1H) and deuterium (^2H, also denoted as D).

The term ”optionally substituted” refers to optional substitution by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional

group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy; wherein *preferably*, at each occurrence, said aryl is a C_6 aryl group; said heterocyclyl is a heterocyclic group comprising 1 to 4 ring heteroatoms selected from N, S and O; said heteroaryl is a C_{3-5} aromatic heterocyclic group comprising 1 to 3 ring heteroatoms selected from N, S and O; said alkyl or alk is a C_{1-2} alkyl group; said alkenyl is a C_2 group comprising at least one C=C bond; said alkynyl is a C_{2-3} group comprising at least one C≡C bond; said cycloalkyl is a C_{3-6}, monocyclic or bicyclic alkyl group; said cycloalkenyl is a C_{5-6} carbocyclic group comprising at least one C=C bond.

As used herein, the meaning of the term "comprising" encompasses three alternatives, namely "comprising", "consisting of" and "consisting essentially of".

Stereoisomers

All possible stereoisomers of the claimed compounds are included in the present invention. Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Where the processes for the preparation of the compounds according to the invention give rise to a mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their components enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base, or by salt formation with an optically active base, such as quinine, quinidine, quinotoxine, cinkotoxine, (*S*)-phenylethylamine, (1*R*,2*S*)-ephedrine, (*R*)-phenylglycinol, (*S*)-2-aminobutanol, followed by fractional crystallization and regeneration of the free acid. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

Polymorph Crystal Forms, Solvates, Hydrates

Furthermore, some of the individual crystalline forms of the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e. hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention. The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. In view of the close relationship between the free compounds and the compounds in the form of their salts, hydrates or solvates, whenever a compound is referred to in this context, a corresponding salt, solvate or polymorph is also intended, provided such is possible or appropriate under the circumstances.

Tautomers

As used herein, the term “tautomer” refers to the migration of protons between adjacent single and double bonds. The tautomerization process is reversible. Compounds described herein can undergo any possible tautomerization that is within the physical characteristics of the compound.

Pharmaceutically Acceptable Salts

As used herein, the term "pharmaceutically acceptable" embraces both human and veterinary use. For example, the term "pharmaceutically acceptable" embraces a veterinarily acceptable compound or a compound acceptable in human medicine and health care.

Salts, hydrates and solvates of the compounds of Formula I and physiologically functional derivatives thereof which are suitable for use in medicine are those wherein the counter-ion or associated solvent is pharmaceutically acceptable. However, salts, hydrates and solvates having non-pharmaceutically acceptable counter-ions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds and their pharmaceutically acceptable salts, hydrates and solvates.

Suitable salts according to the invention include those formed with either organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulfuric, nitric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulfamic, sulfanilic, succinic, oxalic, fumaric, maleic, malic, mandelic, glutamic, aspartic, oxaloacetic, methanesulfonic, ethanesulfonic, arylsulfonic (for example p-toluenesulfonic, benzenesulfonic, naphthalenesulfonic or naphthalenedisulfonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalenes-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic), isethionic acids, perchloric, propionic, glycolic, hydroxyethanesulfonic, pamoic, cyclohexanesulfamic, salicylic, saccharinic and trifluoroacetic acid. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexylamine and *N*-methyl-*D*-glucamine.

All pharmaceutically acceptable acid addition salt forms of the compounds of the present invention are intended to be embraced by the scope of the present invention.

Pharmaceutical Compositions

The pharmaceutical composition according to the present invention comprises a compound as described above and a pharmaceutically acceptable excipient.

As used herein, the term "pharmaceutical composition" is intended to encompass a product comprising the claimed compounds in the therapeutically effective amounts, as well as any product that results, directly or indirectly, from combinations of the claimed compounds. As used herein, the term “excipient” refers to a carrier, a binder, a disintegrator and/or a further suitable additive for galenic formulations, for instance, for liquid oral preparations, such

as suspensions, elixirs and solutions; and/or for solid oral preparations, such as, for example, powders, capsules, gelcaps and tablets. Carriers, which can be added to the mixture, include necessary and inert pharmaceutical excipients, including, but not limited to, suitable suspending agents, lubricants, flavorants, sweeteners, preservatives, coatings, granulating agents, dyes, and coloring agents.

Therapeutic Applications

The present disclosure provides a compound, e.g., a compound of any one of the above aspects <1>-<24>, and/or a pharmaceutical composition as described above for use in a method for treatment of the human or animal body. The present disclosure also provides a method for treatment of the human or animal body wherein the method comprises administration of a therapeutically effective amount of said compound or composition to a subject in need thereof.

The present disclosure further provides a compound and/or a pharmaceutical composition as described herein, e.g., a compound of any one of the above aspects <1>-<24>, for use in a method for therapy or prophylaxis of diseases and conditions associated with Meprin α and/or Meprin β; as well as a method for therapy or prophylaxis of such diseases and conditions wherein the method comprises administration of a therapeutically effective amount of said compound or composition to a subject in need thereof. As explained in the background section above, such diseases and conditions associated with Meprin α and/or Meprin β include Alzheimer's disease; nephritis; renal injury; renal ischemic injury; ischemic acute tubular necrosis; acute renal failure; bladder inflammation; inflammatory bowel disease (IBD); Crohn's disease; ulcerative colitis; chronic inflammation; colitis; fibrosis; fibrotic conditions; keloids; pulmonary hypertension; interstitial lung disease (ILD); cancer; and colorectal cancer.

The present disclosure further provides a compound and/or a pharmaceutical composition as described herein, e.g., a compound of any one of the above aspects <1>-<24>, for use in a method for therapy or prophylaxis of diseases and conditions associated with BMP-1; as well as a method for therapy or prophylaxis of such diseases and conditions wherein the method comprises administration of a therapeutically effective amount of said compound or composition to a subject in need thereof. As explained in the background section above, such diseases and conditions associated with associated with BMP-1 include fibrosis; acute fibrotic disorders and conditions; chronical fibrotic disorders and conditions; fibrosis occurring in organs and/or accompanying diseases and conditions selected from hepatitis, liver cirrhosis, hypertension, myocardial infarction, heart failure, asthma, pulmonary hypertension, scleroderma, fibrotic skin and internal organs, diabetes, diabetes nephropathy, atherosclerosis and fibrotic blood vessels; hypertrophic dermal scarring; keloids; pulmonary fibrosis; acute CNS scarring following traumatic injury; neuronal regeneration following stroke or spinal cord injury; obliterative fibrosis of the hollow structures within grafts; chronic allograft rejection; wound healing disorders; post-surgical scarring; dermal scarring; fibrosis resulting from gynaecological procedures; fibrosis after eye surgery; fibrosis following angioplasty; fibrosis following surgery on joints; and preventing local invasion, recurrence and metastasis of malignant keratinocytes or squamous cell carcinomas (SCCs).

The present disclosure further provides a compound and/or a pharmaceutical composition as described herein, e.g., a compound of any one of the above aspects <1>-<24>, for use in a method for therapy or prophylaxis of

diseases and conditions associated with ovastacin; as well as a method for therapy or prophylaxis of such diseases and conditions wherein the method comprises administration of a therapeutically effective amount of said compound or composition to a subject in need thereof. As explained in the background section above, such diseases and conditions associated with ovastacin include mammalian infertility; and therapeutic use for *in vitro* fertilization (IVF) treatment of a mammal. Typical candidates for such treatment can be subjects (mammals) suffering from or suspected of suffering from infertility. Preferably, the subject is a female. Further preferably, the subject is a female human. According to the WHO-ICMART revised glossary, infertility in the case of humans can be defined as "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse." Additionally, the present compounds can be administered to females undergoing assisted reproductive treatments such as *in vitro* fertilization, e.g., for stimulating fertilization. Additionally, the present compounds can be used as a method for improving the fertilization rate for a subject undergoing assisted reproduction treatment or procedure, e.g., by administering a therapeutically effective amount of said compound or composition to a subject undergoing such treatment, and/or by contacting an oocyte *in vitro* with a composition comprising a compound as described herein.

The term "*in vitro* fertilization (IVF)" may refer to a method comprising collecting an ovum, fertilizing the ovum *in vitro* with a spermatozoon and, when cleavage has progressed to a certain degree, inserting the ovum into the uterine cavity, i.e. it may include the processes of ovulation induction, ovum collection, *in vitro* fertilization and culture, and embryo transfer.

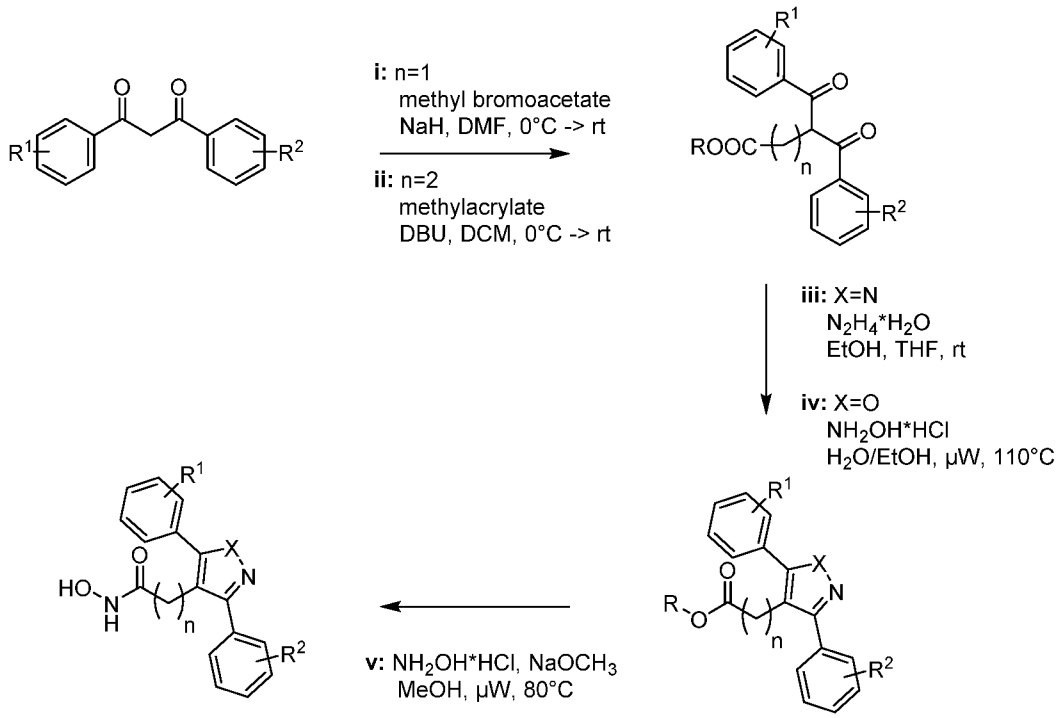
The term "subject" as used herein refers to an animal, preferably a mammal, most preferably a human.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

EXAMPLES

Description of Synthetic Methods

Scheme 1



Method i:

The respective 1,3-diaryl-1,3-propanedione or azole derivative or benzo-fused N-heterocycle (1 eq) was dissolved in DMF (c=0.5 M), cooled to 0°C and treated with sodium hydride (1.2 eq). After 30 min, methyl bromoacetate or another suitable alkyl halide (1.1 eq) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for 12 hours. The reaction was stopped by addition of water and extracted with EtOAc (3x30 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Method ii:

The respective 1,3-diaryl-1,3-propanedione (1 eq) was dissolved in dichloromethane (c=0.2 M), cooled to 0°C and treated with 1,8-diazabicyclo[5.4.0]undec-7-en (DBU, 0.2 eq). After 15 min, methyl acrylate (2 eq) dissolved in DCM was added dropwise over 15 min. After complete addition, the reaction was warmed to room temperature and stirred for 48 hours. The reaction was stopped by addition of saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Method iii:

A compound obtained either by method I or ii (1 eq) was dissolved in an EtOH/THF mixture (2:1, v/v, c=0.07 M). Hydrazine monohydrate (5 eq) was added and the mixture was stirred at room temperature. Upon complete consumption of the starting material (~4-5 hours), the volatiles were evaporated. The remains were taken up with water, acidified by means of diluted aqueous HCl and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Method iv:

A compound obtained either by method i or ii (1 eq) was dissolved in an EtOH/water mixture (3:2, v/v, c=0.4 M). Hydroxylamine hydrochloride (1 eq) was added and the mixture was heated in a microwave at 110°C for 20 minutes. After cooling, the mixture was poured into iced water and extracted with DCM (2x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Method v:

The respective ester derivative (1 eq) was dissolved in MeOH (5 ml), treated with $NaOCH_3$ (6 eq) and hydroxylamine hydrochloride (3 eq). The mixture was heated in a microwave at 80°C for 10 minutes. The volatiles were evaporated. The remains were taken up in water, acidified by means of diluted aqueous HCl and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by semi-preparative HPLC.

Example 1: 2-(3,5-Diphenyl-1H-pyrazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods i, iii and v as described above. Yield (last step): 83 mg (40%); ESI-MS: m/z 294.5 $[M+H]^+$; HPLC (gradient 1): rt 12.03 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.32 (s, 1.8H), 3.63 (s, 0.2H), 7.38-7.42 (m, 2H), 7.46-7.49 (m, 4H), 7.64-7.66 (m, 4H), 10.09 (br s, 0.1H), 10.62 (br s, 0.9H) mixture of cis-trans isomers.

Example 2: 2-(3,5-Diphenylisoxazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods i, iv and v as described above. Yield (last step): 32 mg (35%); ESI-MS: m/z 295.1 $[M+H]^+$, 317.2 $[M+Na]^+$; HPLC (gradient 1): rt 14.56 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.41 (s, 2H), 7.55-7.62 (m, 6H), 7.68-7.70 (m, 2H), 7.79-7.82 (m, 2H), 10.77 (s, 1H).

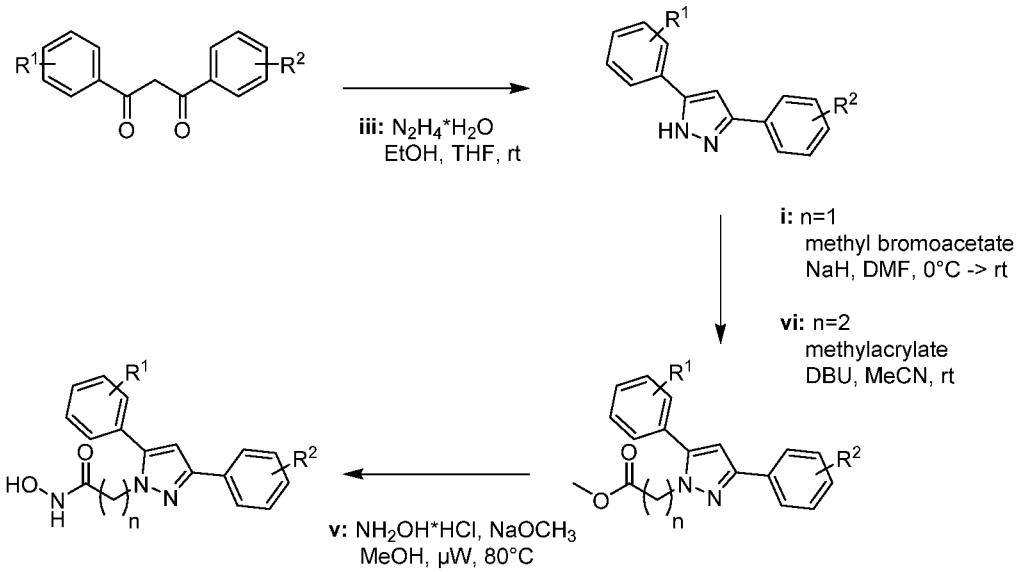
Example 3: 3-(3,5-Diphenyl-1H-pyrazol-4-yl)propanehydroxamic acid

The compound was synthesized according to methods ii, iii and v as described above. Yield (last step): 58 mg (19%); ESI-MS: m/z 308.4 $[M+H]^+$; HPLC (gradient 1): rt 15.52 min (96.8%); ^1H NMR, 400 MHz, DMSO d_6: δ 2.06-2.11 (m, 2H), 2.93-2.97 (m, 2H), 7.41 (t, 2H, ^3J = 7.3 Hz), 7.50 (t, 4H, ^3J = 7.6 Hz), 7.64 (d, 4H, ^3J = 7.8 Hz), 10.33 (br s, 1H).

Example 4: 3-(3,5-Diphenylisoxazol-4-yl)propanehydroxamic acid

The compound was synthesized according to methods ii, iv and v as described above. Yield (last step): 11 mg (22%); ESI-MS: m/z 309.4 $[M+H]^+$, 331.4 $[M+Na]^+$; HPLC (gradient 1): rt 14.93 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 2.09-2.13 (m, 2H), 2.95-2.99 (m, 2H), 7.57-7.63 (m, 2H), 7.69-7.71 (m, 2H), 7.81-7.84 (m, 2H), 10.36 (br s, 1H).

Scheme 2



Method vi:

The respective diarylpyrazole (1 eq) obtained by method iii as described above, or another suitable azole derivative, was dissolved in acetonitrile (c=1.7 M) and treated with DBU (0.5 eq) and methyl acrylate (1.5 eq). The mixture was stirred at room temperature overnight. The volatiles were evaporated, and the remains were dissolved in EtOAc. Water was added, and the aqueous layer was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue could be used without further purification.

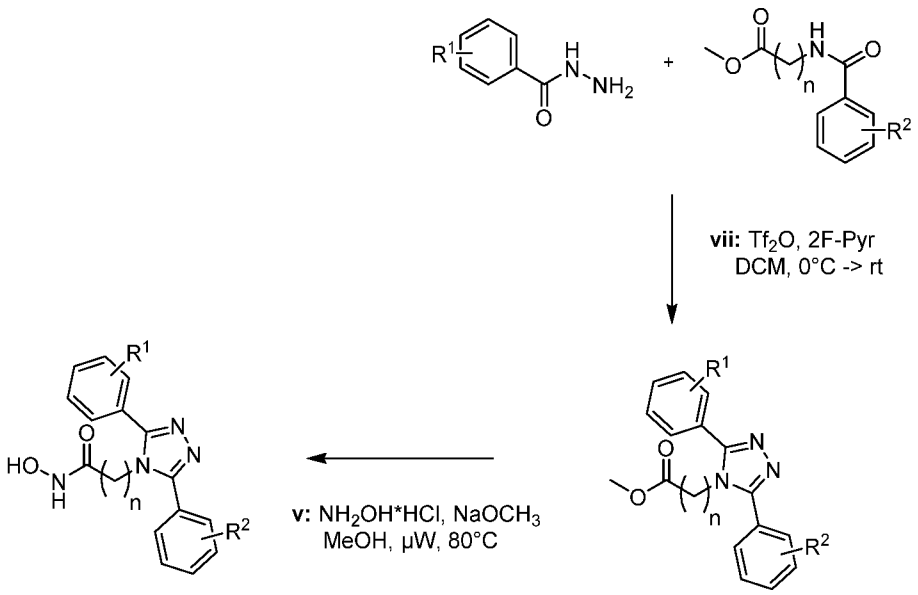
Example 5: 2-(3,5-Diphenylpyrazol-1-yl)ethanehydroxamic acid

The compound was synthesized according to methods iii, i and v as described above. Yield (last step): 141 mg (57%); ESI-MS: m/z 294.4 $[M+H]^+$; HPLC (gradient 1): rt 15.63 min (97.5%); ^1H NMR, 400 MHz, DMSO d_6: δ 4.68 (s, 1.8H), 5.04 (br s, 0.2H), 6.91 (s, 1H), 7.31-7.35 (m, 1H), 7.41-7.55 (m, 5H), 7.65-7.68 (m, 2H), 7.83-7.85 (m, 2H), 9.12 (br s, 0.9H), 9.36 (br s, 0.1H), 10.35 (br s, 0.1H), 10.93 (br s, 0.9H) mixture of cis-trans isomers.

Example 6: 3-(3,5-Diphenylpyrazol-1-yl)propanehydroxamic acid

The compound was synthesized according to methods iii, vi and v as described above. Yield (last step): 171 mg (66%); ESI-MS: m/z 308.4 $[M+H]^+$; HPLC (gradient 1): rt 17.68 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 2.66 (t, 2H, ^3J = 7.2 Hz), 4.32 (t, 2H, ^3J = 7.2 Hz), 6.84 (s, 1H), 7.30-7.34 (m, 1H), 7.41-7.45 (m, 2H), 7.47-7.57 (m, 3H), 7.60-7.63 (m, 2H), 7.84-7.86 (m, 2H), 9.97 (br s, 0.1H), 10.53 (br s, 0.9H) mixture of cis-trans isomers.

Scheme 3



Method vii:

The respective benzamide derivative (1 eq) and 2-fluoro-pyridine (1.1 eq) were dissolved in DCM (3 ml) in a sealed tube under argon atmosphere. The mixture was chilled on an ice bath and trifluoromethanesulfonic anhydride (1.1 eq) was added slowly via syringe. After further stirring at 0°C for 45 minutes, the respective benzhydrazide was added. After 45 minutes at room temperature, the mixture was heated in a microwave at 140°C for 2 hours. After cooling, saturated aqueous $NaHCO_3$ was added and extracted with DCM (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$/MeOH gradient).

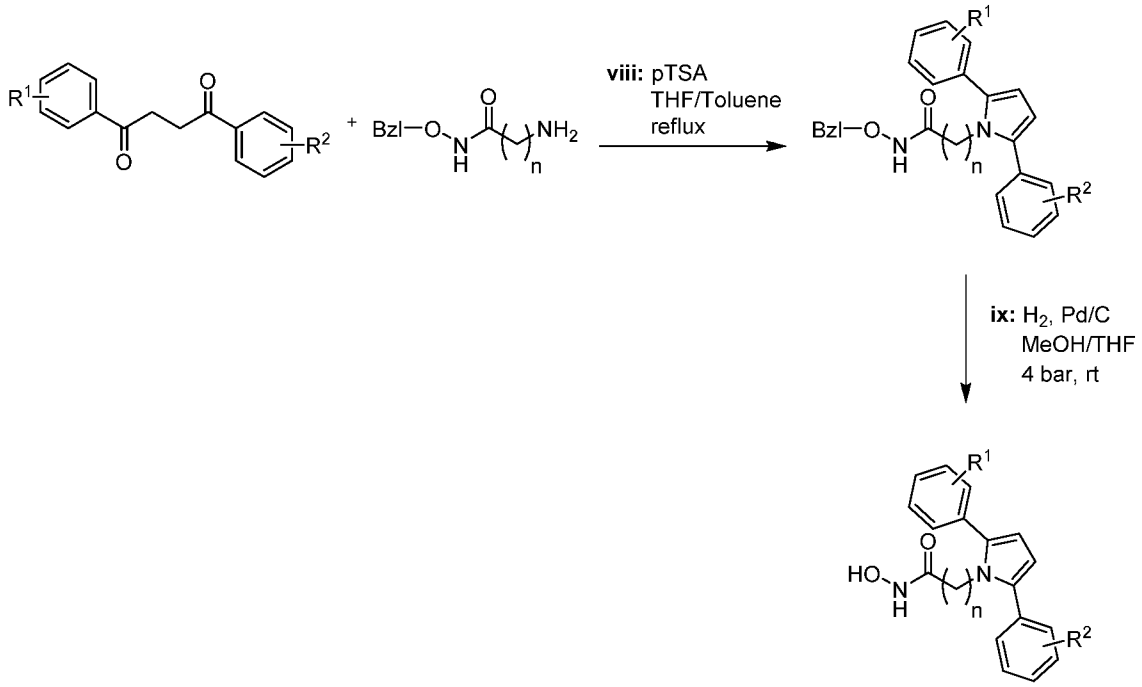
Example 7: 2-(3,5-Diphenyl-1,2,4-triazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods vii and v as described above. Yield (last step): 45 mg (53%); ESI-MS: m/z 295.3 $[M+H]^+$; HPLC (gradient 1): rt 7.73 min (98.2%); ^1H NMR, 400 MHz, DMSO d_6: δ 4.56 (s, 1.5 H), 4.85 (s, 0.5 H), 7.58-7.70 (m, 10 H), 10.50 (br s, 0.3 H), 10.81 (br s, 0.7 H) mixture of cis-trans isomers.

Example 8: 3-(3,5-Diphenyl-1,2,4-triazol-4-yl)propanehydroxamic acid

The compound was synthesized according to methods vii and v as described above. Yield (last step): 39 mg (37%); ESI-MS: m/z 309.4 $[M+H]^+$; HPLC (gradient 1): rt 8.59 min (97.0%); ^1H NMR, 400 MHz, DMSO d_6: δ 2.10 (t, 2H, ^3J = 7.6 Hz), 4.39 (t, 2H, ^3J = 7.5 Hz), 7.61-7.63 (m, 6H), 7.75-7.78 (m, 4H), 9.89 (br s, 0.1H), 10.28 (br s, 0.9H) mixture of cis-trans isomers.

Scheme 4



Method viii:

The respective 1,4-butanedione (1 eq) was dissolved in THF/Toluene (1:1 v/v, c=0.1 M). A suitable benzyl-protected amino acid derivative (1.5 eq) and para-toluenesulfonic acid (0.07 eq) were added and the mixture was heated to reflux for 48 hours. The volatiles were evaporated, and the remains were re-dissolved in water, slightly basified by means of aqueous $NaHCO_3$ and extracted with EtOAc (3x25 ml). The combined organic layers were evaporated and purified by flash chromatography (silica, heptane/EtOAc gradient).

Method ix:

The respective benzyl-protected hydroxamic acid derivative was dissolved in MeOH/THF (1:1 v/v, 10 ml). Palladium on charcoal was added and the vial was purged with hydrogen. After 4 hours at 4 bar, the mixture was filtered through Celite and evaporated. The residue was purified by semi-preparative HPLC.

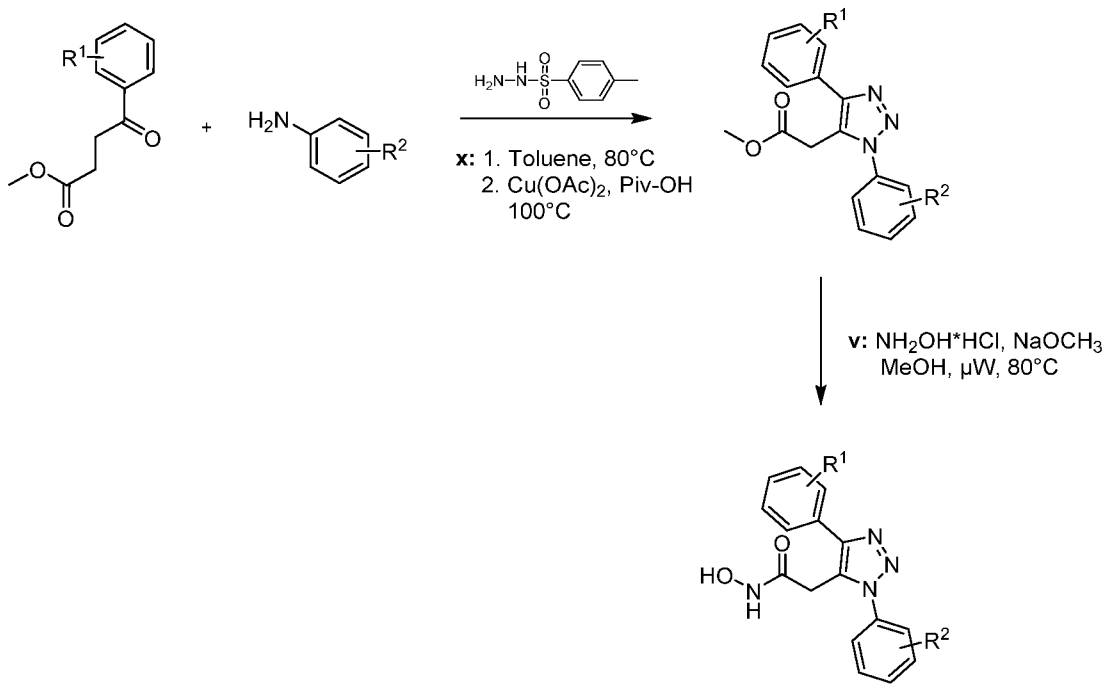
Example 9: 2-(2,5-Diphenylpyrrol-1-yl)ethanehydroxamic acid

The compound was synthesized according to methods viii and ix as described above. Yield (last step): 25 mg (37%); ESI-MS: m/z 293.2 $[M+H]^+$; HPLC (gradient 1): rt 15.84 min (97.7%); ^1H NMR, 400 MHz, DMSO d_6: δ 4.34 (s, 1.5H), 4.65 (s, 0.5H), 6.27 (s, 2H), 7.33-7.36 (m, 2H), 7.41-7.47 (m, 8H), 8.99 (br s, 0.6H), 9.19 (br s, 0.2H), 10.26 (br s, 0.2H), 10.54 (br s, 0.8H) mixture of cis-trans isomers.

Example 10: 3-(2,5-Diphenylpyrrol-1-yl)propanehydroxamic acid

The compound was synthesized according to methods viii and ix as described above. Yield (last step): 9 mg (4%); ESI-MS: m/z 307.4 $[M+H]^+$, 329.4 $[M+Na]^+$; HPLC (gradient 1): rt 16.27 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 1.83-1.87 (m, 1.8H), 2.09-2.13 (m, 0.2H), 4.28-4.32 (m, 2H), 6.23 (s, 2H), 7.34-7.38 (m, 2H), 7.44-7.51 (m, 8H), 8.57 (br s, 0.6H), 8.81 (br s, 0.1H), 9.76 (br s, 0.1H), 10.16 (br s, 0.9H) mixture of cis-trans isomers.

Scheme 5



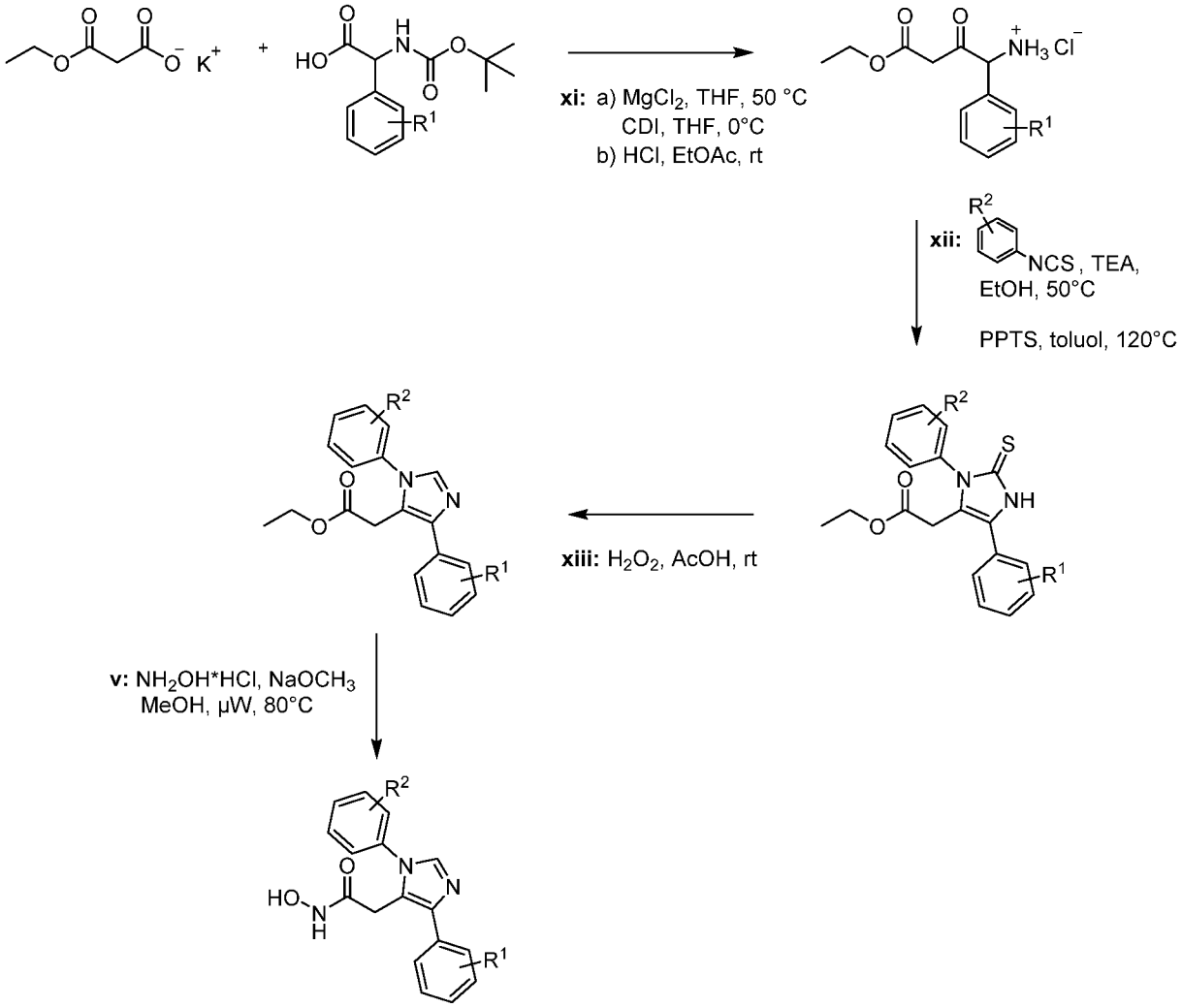
Method x:

The respective 4-oxo-4-phenylbutanoate (1 eq) was dissolved in toluene (c=0.2 M). Tosylhydrazide (1 eq) was added and the mixture was stirred at 80°C for 2 hours. The aniline derivative (2 eq), $Cu(OAc)_2$ (1 eq) and pivalic acid (2 eq) were added and the mixture was heated to 100°C overnight. The volatiles were evaporated, and the residue was purified by flash chromatography (silica, heptane/diethylether gradient).

Example 11: 2-(3,5-Diphenyltriazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods x and v as described above. Yield (last step): 23 mg (32%); ESI-MS: m/z 295.1 $[M+H]^+$; HPLC (gradient 1): rt 10.43 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.63 (s, 1.7H), 3.92 (s, 0.3H), 7.42-7.45 (m, 1H), 7.52 (t, 2H, ^3J = 7.8 Hz), 7.57-7.69 (m, 5H), 7.75-7.77 (m, 2H), 9.04 (br s, 0.6H), 9.39 (br s, 0.2H), 10.33 (s, 0.1H), 10.76 (s, 0.9H) mixture of cis-trans isomers.

Scheme 6



Method xi:

A suspension of ethyl potassium malonate (1.5 eq), $MgCl_2$ (anhydrous, 1 eq) in THF (c=0.6 M) was stirred at 50°C for 6 hours under argon atmosphere. In another flask, *N,N'*-carbonyldiimidazole (1.5 eq) was added portionwise to a solution of Boc-Phg-OH (1 eq) in THF (c=0.6 M) at 0°C under argon atmosphere and the mixture was stirred at room temperature for 2 hours. To the suspension, the above-mentioned Boc-phenylglycine solution was added via syringe and the mixture was stirred vigorously at room temperature overnight. The volatiles were evaporated, the remains were taken up in water and adjusted to pH 3 by means of diluted aqueous HCl. The aqueous layer was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient). The residue was treated with HCl in EtOAc (20 ml) and the mixture was stirred at room temperature until TLC showed full conversion of the starting material. The volatiles were evaporated and the residue was used without further purification.

Method xii:

The compound obtained from method xi was dissolved in EtOH (c=0.4 M). Triethylamine (1.5 eq) and phenyl isothiocyanate (1.2 eq) were added to the solution and the mixture was heated to 50°C for 4 hours. The reaction mixture

was then concentrated in vacuo to dryness. The residue was suspended in toluol (c= 0.4 M) and treated with PPTS (0.1 eq). The mixture was heated to 120°C for 4 hours. After cooling to room temperature, the volatiles were evaporated and the remains were taken up in water. The aqueous layer was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

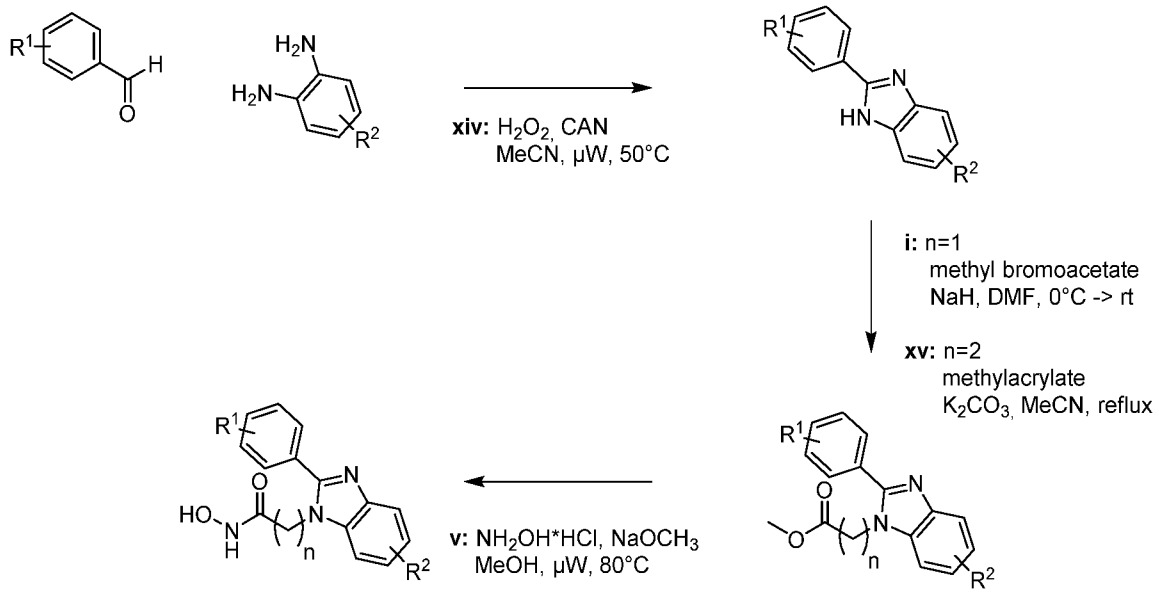
Method xiii:

The cyclic thiourea obtained from method xii was suspended in glacial acetic acid (c=0.3 M). H_2O_2 (30%, 4 eq) was added dropwise and the mixture was stirred at room temperature for 5 minutes. The reaction was cooled to 0°C and quenched with 10% K_2CO_3 solution (10 ml). The pH of the mixture was adjusted to pH 9 with 1 N NaOH solution. The mixture was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Example 12: 2-(3,5-Diphenylimidazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods xi, xii, xiii and v as described above. Yield (last step): 34 mg (39%); ESI-MS: m/z 294.1 $[M+H]^+$; HPLC (gradient 1): rt 6.51 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.47 (s, 1.7H), 3.77 (s, 0.3H), 7.44-7.47 (m, 1H), 7.51-7.69 (m, 9H), 8.88 (br s, 0.1H), 9.32 (br s, 0.1H), 10.25 (s, 0.2H), 10.61 (s, 0.8H) mixture of cis-trans isomers.

Scheme 7



Method xiv:

Ortho-phenylendiamine, or a substituted analogue, (1 eq) was dissolved in acetonitrile (c=0.2 M). The respective aldehyde (1 eq), 30% hydrogen peroxide (4 eq) and ceric ammonium nitrate (0.1 eq) were added and the mixture was heated to 50°C for 12 minutes under microwave irradiation. The volatiles were evaporated, the remains were taken up with water and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$/MeOH gradient).

Method xv:

The respective 2-phenylbenzimimidazole obtained by method xiv (1 eq) was dissolved in acetonitrile (2 ml). Methyl acrylate (1.1 eq) and K_2CO_3 (1 eq) were added and the mixture was heated under reflux for 6 hours. The volatiles were evaporated and taken up with a small amount of EtOAc. Water was added, and the mixture was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Example 13: 2-(2-Phenylbenzimidazol-1-yl)ethanehydroxamic acid

The compound was synthesized according to methods xiv, i and v as described above. Yield (last step): 88 mg (66%); ESI-MS: m/z 268.3 $[M+H]^+$; HPLC (gradient 1): rt 5.96 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 4.95 (s, 1.6 H), 5.29 (s, 0.4 H), 7.44-7.51 (m, 2H), 7.64-7.71 (m, 4H), 7.78-7.84 (m, 1H), 7.88-7.90 (m, 2H), 10.62 (br s, 0.2 H), 11.10 (br s, 0.8 H) mixture of cis-trans isomers.

Example 14: 3-(2-Phenylbenzimidazol-1-yl)propanehydroxamic acid

The compound was synthesized according to methods xiv, xv and v as described above. Yield (last step): 33 mg (37%); ESI-MS: m/z 282.4 $[M+H]^+$; HPLC (gradient 1): rt 6.61 min (95.7%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 2.59 (t, 2H, ^3J = 7.4 Hz), 4.60 (t, 2H, ^3J = 7.7 Hz), 7.49-7.57 (m, 2H), 7.67-7.74 (m, 3H), 7.80-7.83 (m, 1H), 7.87-7.89 (m, 2H), 7.93-7.95 (m, 1H), 10.05 (br s, 0.1H), 10.50 (br s, 0.9H) mixture of cis-trans isomers.

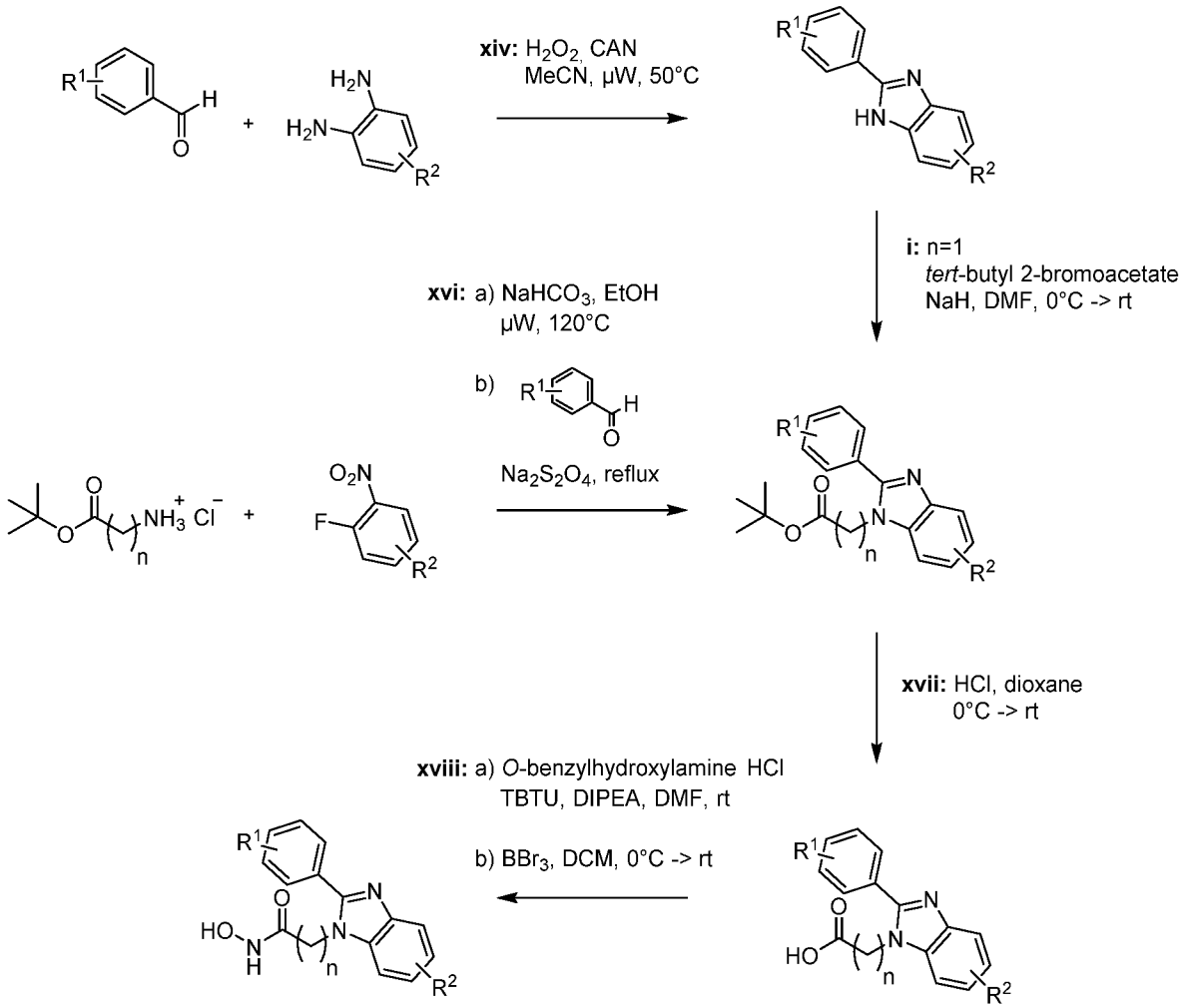
Example 15: 2-[2-(4-Methoxyphenyl)benzimidazol-1-yl]ethanehydroxamic acid

The compound was synthesized according to methods xiv, i and v as described above. Yield (last step): 55 mg (36%); ESI-MS: m/z 298.1 $[M+H]^+$; HPLC (gradient 1): rt 6.88 min (98.2%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.90 (s, 3H), 4.97 (s, 1.6H), 5.32 (s, 0.4H), 7.22-7.26 (m, 2H), 7.72-7.87 (m, 4H), 10.67 (s, 0.2H), 11.15 (s, 0.8H) mixture of cis-trans isomers.

Example 16: 2-[2-(4-Chloro-2-fluoro-3-hydroxy-phenyl)benz-imidazol-1-yl]ethanehydroxamic acid

The compound was synthesized according to methods xiv, i and v as described above, final deprotection of the phenol was accomplished by treatment with BBr_3 (1M in DCM, 5 eq). Yield (last step): 24 mg (51%); ESI-MS: m/z 336.5 $[M+H]^+$; HPLC (gradient 1): rt 7.31 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 4.80 (s, 1.6H), 5.13 (s, 0.4H), 7.06-7.46 (m, 3H), 7.62 (d, 1H, ^3J = 7.7 Hz), 7.77 (d, 1H, ^3J = 7.7 Hz), 10.43 (br s, 0.2 H), 10.91 (br s, 0.8H) mixture of cis-trans isomers.

Scheme 8



Method xvi:

The respective 1-fluoro-2-nitrobenzene derivative (1 eq), amino acid *tert*-butyl ester (1 eq) and $NaHCO_3$ (2 eq) were suspended in EtOH (c=0.3 M). The mixture was heated to 120°C for 20 minutes under microwave irradiation. After cooling to room temperature, the mixture was transferred into a flask and diluted with EtOH (5 ml). The respective aldehyde and $Na_2S_2O_4$ were added in portions. The mixture was heated to reflux overnight. The volatiles were evaporated. The remains were taken up with a small amount of water, saturated aqueous $NaHCO_3$ were added and the mixture was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Method xvii:

The compound obtained either by method i or xvi (1 eq) was treated with 5M HCl in dioxane (50 eq) and cooled with ice. The mixture was allowed to warm up to room temperature and stirred overnight. The volatiles were evaporated and used without further purification.

Method xviii:

The respective 2-(2-phenyl-1H-benzimidazol-1-yl)acetic acid (1 eq) obtained by method xvii was dissolved in dimethylformamide (c=0.2 M). TBTU (1 eq) and DIPEA (2 eq) were added and the mixture was stirred at room temperature. After several minutes, O-benzylhydroxylamine hydrochloride (1 eq) and DIPEA (2 eq) were added and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with water and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$/MeOH gradient). The purified product was dissolved in DCM (c=0.1 M) in a sealed flask under argon atmosphere. The mixture was cooled down to 0°C and treated with BBr_3 (1 M in DCM, 10-13 eq) for final deprotection. The mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with water and cooled with ice. The aqueous layer was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by semi-preparative HPLC.

Example 17: 2-[1-[2-(Hydroxyamino)-2-oxo-ethyl]benzimidazol-2-yl]benzoic acid

The compound was synthesized according to methods xiv, i, xvii and xviii as described above. Yield (last step): 1.5 mg (2%); ESI-MS: m/z 312.1 $[M+H]^+$; HPLC (gradient 1): rt 5.17 min (>99%); ^1H NMR, 400 MHz, MeOH d_4: δ 5.21 (br s, 0.4H), 7.61-7.67 (m, 2H), 7.72-7.82 (m, 3H), 7.86-7.92 (m, 2H), 8.34-8.37 (m, 1H) mixture of cis-trans isomers.

Example 18: 3-[1-[2-(Hydroxyamino)-2-oxo-ethyl]benzimidazol-2-yl]benzoic acid

The compound was synthesized according to methods xiv, i, xvii and xviii as described above. Yield (last step): 5 mg (3%); ESI-MS: m/z 312 $[M+H]^+$; HPLC (gradient 1): rt 6.13 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 4.92 (s, 1.6H), 5.25 (s, 0.4H), 7.39-7.46 (m, 2H), 7.63-7.66 (m, 1H), 7.74-7.80 (m, 2H), 7.99-8.01 (m, 0.2H), 8.11-8.13 (m, 0.8H), 8.17-8.19 (m, 1H), 8.35 (s, 0.2H), 8.46 (s, 0.8H), 10.60 (s, 0.2H), 11.05 (s, 0.8H), 13.31 (br s, 1H) mixture of cis-trans isomers.

Example 19: 4-[1-[2-(Hydroxyamino)-2-oxo-ethyl]benzimidazol-2-yl]benzoic acid

The compound was synthesized according to methods xiv, i, xvii and xviii as described above. Yield (last step): 4 mg (4%); ESI-MS: m/z 312 $[M+H]^+$; HPLC (gradient 1): rt 6.37 min (>99%); ^1H NMR, 400 MHz, MeOH d_4: δ 5.09 (s, 1.5H), 5.47 (s, 0.5H), 7.61-7.66 (m, 2H), 7.76-7.78 (m, 1H), 7.84-7.86 (m, 1H), 7.92-7.94 (m 0.4H), 7.99-8.01 (m, 1.6H), 8.29-8.33 (m, 2H) mixture of cis-trans isomers.

Example 20: 2-(4-Chloro-2-fluoro-3-hydroxy-phenyl)-1-[2-(hydroxyamino)-2-oxo-ethyl]benzimidazole-4-carboxylic acid

The compound was synthesized according to methods xvi, xvii and xiii as described above. Yield (last step): 32 mg (39%); ESI-MS: m/z 380 $[M+H]^+$; HPLC (gradient 1): rt 7.44 min (91.4%); ^1H NMR, 400 MHz, DMSO d_6: δ 4.88 (s, 1.6H), 5.20 (br s, 0.4H), 7.08-7.11 (m, 0.2H), 7.15-7.19 (m, 0.8H), 7.43-7.45 (m, 1H), 7.53 (t, 1H, ^3J = 7.5 Hz), 7.91-7.95 (m, 2H), 10.48 (br s, 0.2H), 10.90 (s, 0.8H), 10.95 (br s, 1H) mixture of cis-trans isomers.

Example 21: 2-(4-Chloro-2-fluoro-3-hydroxy-phenyl)-1-[2-(hydroxyamino)-2-oxo-ethyl]benzimidazole-5-carboxylic acid

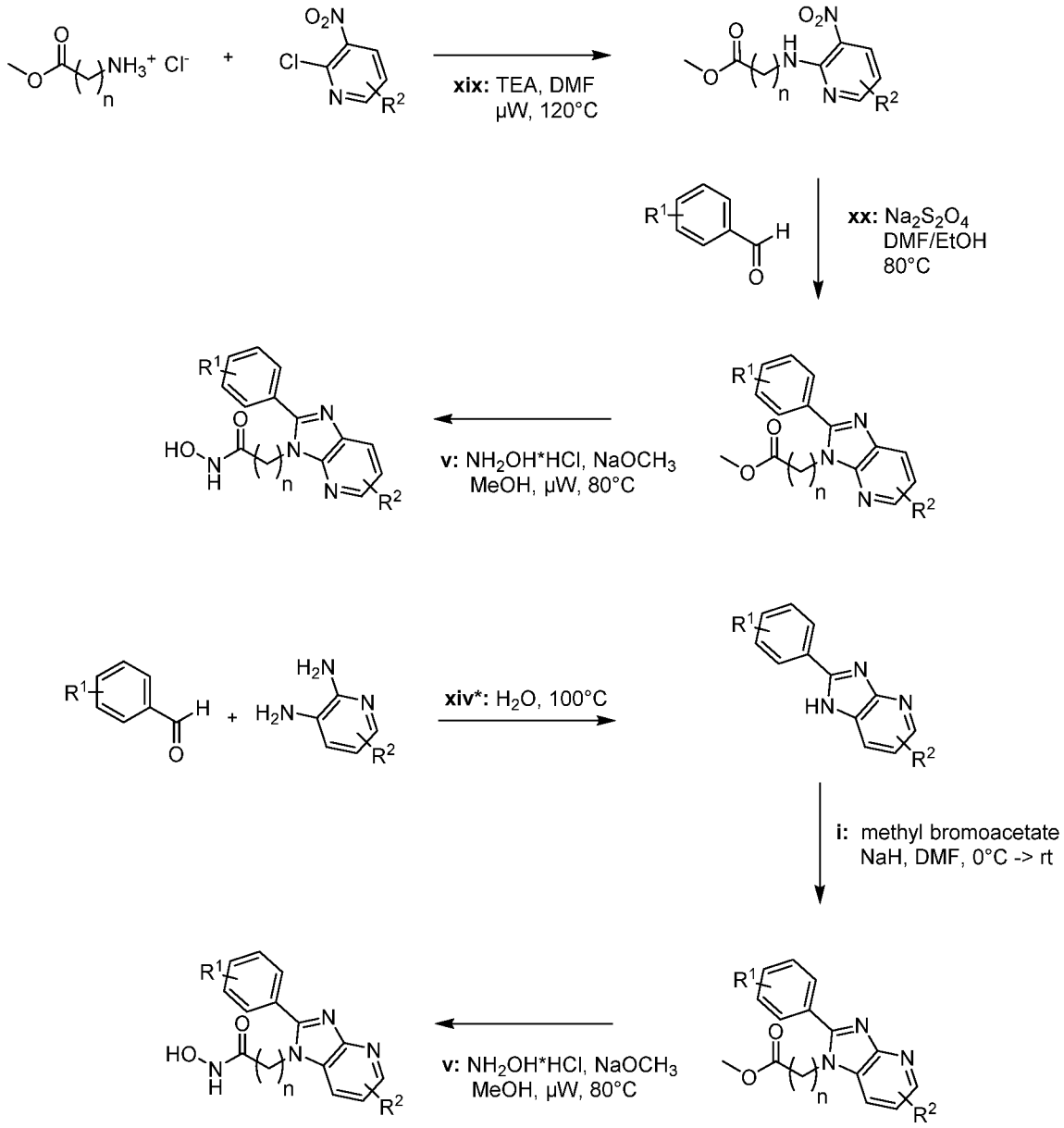
The compound was synthesized according to methods xvi, xvii and xiii as described above. Yield (last step): 35 mg (26%); ESI-MS: m/z 380 $[M+H]^+$; HPLC (gradient 1): rt 8.48 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 4.79 (s, 1.6H), 5.10 (s, 0.4H), 7.02-7.06 (m, 0.2H), 7.10-7.14 (m, 0.8H), 7.40-7.42 (m, 1H), 7.58-7.60 (m, 0.2H), 7.63-7.65

(m, 0.8H), 7.93-7.97 (m, 1H), 8.29 (s, 1H), 10.39 (br s, 0.2H), 10.83 (br s, 0.7H), 10.87 (s, 1H), 12.83 (br s, 0.8H) mixture of cis-trans isomers.

Example 22: 2-(4-Chloro-2-fluoro-3-hydroxy-phenyl)-3-[2-(hydroxyamino)-2-oxo-ethyl]benzimidazole-5-carboxylic acid

The compound was synthesized according to methods xvi, xvii and xiii as described above. Yield (last step): 49 mg (43%); ESI-MS: m/z 379.9 $[M+H]^+$; HPLC (gradient 1): rt 8.75 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 4.83 (s, 1.6H), 5.14 (s, 0.4H), 7.03-7.06 (m, 0.2H), 7.12-7.16 (m, 0.8H), 7.40-7.43 (m, 1H), 7.78-7.81 (m, 1H), 7.90-7.93 (m, 1H), 8.12 (s, 0.2H), 8.21 (s, 0.8H), 10.42 (s, 0.2H), 10.84 (br s, 0.8H), 10.90 (s, 1H) mixture of cis-trans isomers.

Scheme 9



Method xiv*:

Pyridine-2,3-diamine or a substituted analogue (1 eq) was dissolved in water (1 M), treated with the respective aldehyde (1 eq) and heated to reflux overnight. After cooling the mixture was basified with aqueous $NaHCO_3$ and

extracted with EtOAc (3x 25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$/MeOH gradient).

Method xix:

The respective amino acid ester (1 eq) was dissolved in dimethylformamide (c=1.0 M). 2-Chloro-3-nitropyridine derivative (1 eq) and triethylamine (2.5 eq) were added and the mixture was heated in a microwave to 120°C for 20 min. After cooling, water was added and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was used without further purification.

Method xx:

The nitropyridine derivative obtained by method xix was dissolved in DMF/EtOH (1:1 v/v, c=0.15M). The respective aldehyde (1 eq) and $Na_2S_2O_4$ (3 eq) were added and the mixture was stirred at 80°C for 22h. The volatiles were evaporated, and the remains were taken up with a small amount of water. The mixture was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc 1:1)

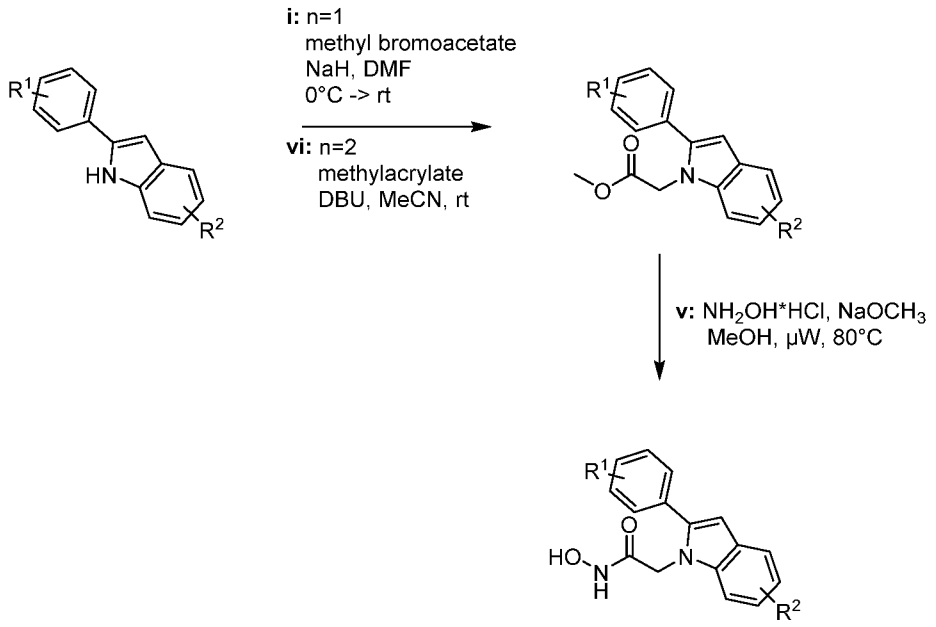
Example 23: 2-(2-Phenylimidazo[4,5-b]pyridin-3-yl)ethane-hydroxamic acid

The compound was synthesized according to methods xix, xx and v as described above. Yield (last step): 35 mg (39%); ESI-MS: m/z 269.1 $[M+H]^+$; HPLC (gradient 1): rt 6.75 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 4.92 (s, 1.6H), 5.26 (s, 0.4H), 7.36-7.39 (m, 1H), 7.58-7.61 (m, 3H), 7.78-7.80 (m, 0.5H), 7.87-7.89 (m, 1.5H), 8.14-8.16 (dd, 1H, ^3J = 7.8 Hz, ^{4}J=1.2 Hz), 8.38-8.89 (m, 1H), 9.53 (br s, 0.2H), 10.45 (s, 0.2H), 11.01 (s, 0.8H) mixture of cis-trans isomers.

Example 24: 2-(2-phenylimidazo[4,5-b]pyridin-1-yl)ethane-hydroxamic acid

The compound was synthesized according to methods xiv*, i and v as described above. Yield (last step): 38 mg (20%); ESI-MS: m/z 269.1 $[M+H]^+$; HPLC (gradient 1): rt 6.61 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 5.54 (s, 1.4H), 5.86 (s, 0.6H), 7.69-7.71 (m, 3H), 7.98 (t, 1H, ^3J = 7.1 Hz), 8.32-8.34 (m, 2H), 8.73-8.79 (m, 2H), 9.32 (br s, 0.7H), 9.84 (br s, 0.3H), 10.80 (s, 0.3H), 11.27 (s, 0.7H) mixture of cis-trans isomers.

Scheme 10



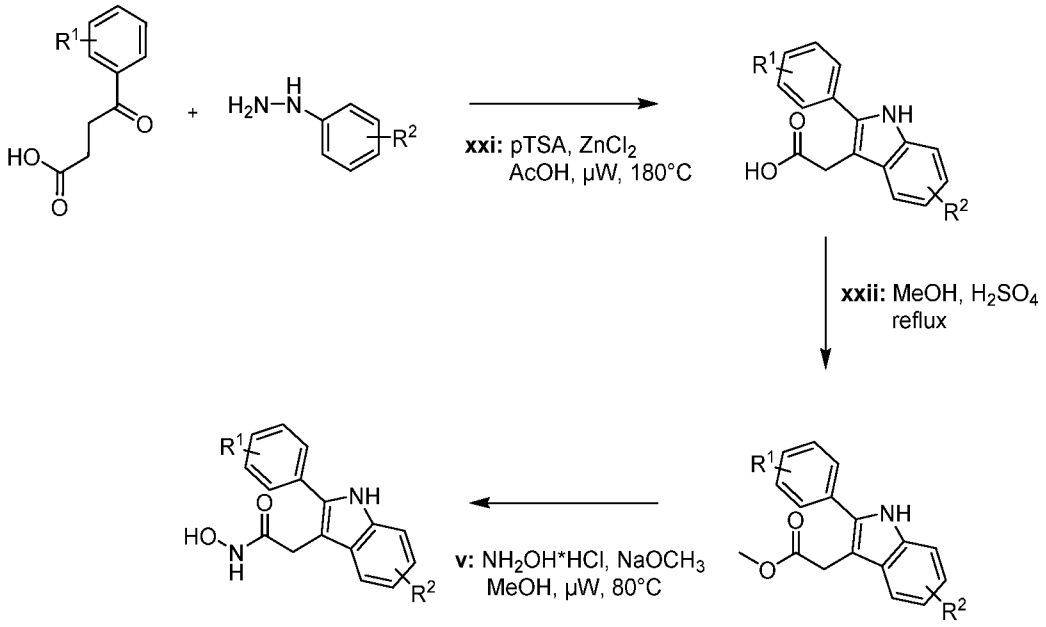
Example 25: 2-(2-Phenylindol-1-yl)ethanehydroxamic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 91 mg (34%); ESI-MS: m/z 267.3 $[M+H]^+$; HPLC (gradient 1): rt 15.81 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 4.66 (s, 1.7H), 4.99 (s, 0.3H), 6.58 (s,1H), 7.08-7.12 (m, 1H), 7.16-7.20 (m, 1H), 7.36-7.38 (m, 1H), 7.43-7.47 (m, 1H), 7.49-7.53 (m, 2H), 7.58-7.64 (m, 3H), 10.34 (s, 0.1H), 10.93 (s, 0.9H) mixture of cis-trans isomers.

Example 26: 3-(2-Phenylindol-1-yl)propanehydroxamic acid

The compound was synthesized according to methods vi and v as described above. Yield (last step): 33 mg (18%); ESI-MS: m/z 281.2 $[M+H]^+$; HPLC (gradient 1): rt 15.22 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 2.34-2.38 (m, 2H), 4.36-4.40 (m, 2H), 6.54 (s, 1H), 7.07-7.10 (m, 1H), 7.18-7.22 (m, 1H), 7.45-7.49 (m, 1H), 7.51-7.58 (m, 6H), 9.97 (br s, 0.1H), 10.46 (br s, 0.9H) mixture of cis-trans isomers.

Scheme 11



Method xxi:

The respective benzoylpropionic acid (1 eq) was dissolved in acetic acid (c=0.33 M). Phenylhydrazine (1.2 eq), para-toluenesulfonic acid (1.1 eq) and $ZnCl_2$ (1 eq) were added and the mixture was heated to 180°C in a microwave for 40 minutes. After cooling, water was added, and the mixture was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

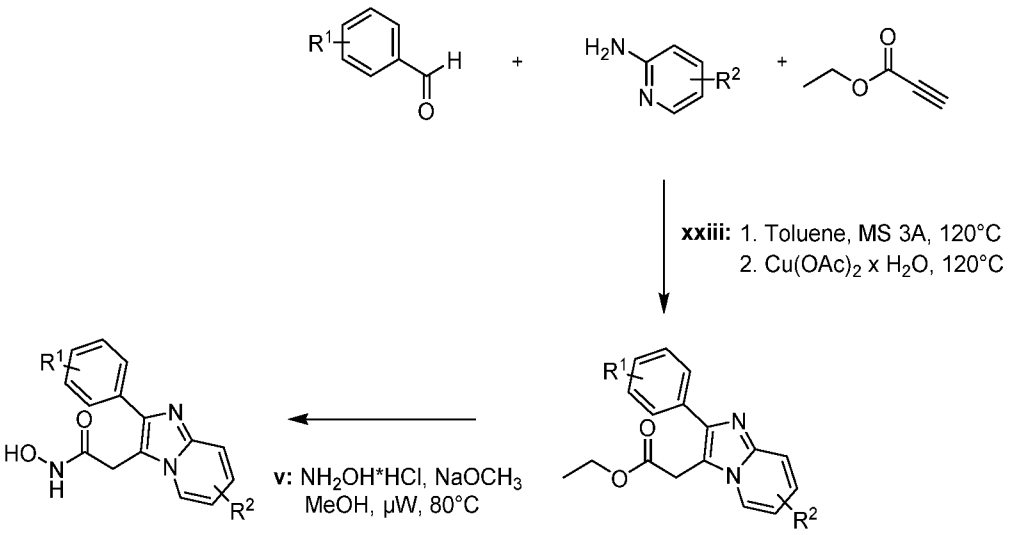
Method xxii:

The respective indole derivative obtained by method xxi was dissolved in methanol (5 ml) and treated with conc. H_2SO_4. The mixture was heated to reflux for 4 hours. The volatiles were evaporated, re-dissolved in dichloromethane and washed carefully with saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated. The residue was used without further purification.

Example 27: 2-(2-Phenyl-1H-indol-3-yl)ethanehydroxamic acid

The compound was synthesized according to methods xxi, xxii and v as described above. Yield (last step): 14 mg (15%); ESI-MS: m/z 267.2 $[M+H]^+$, 206.1 $[M-CH_2NO_2]^+$; HPLC (gradient 1): rt 11.97 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.51 (s, 1.9H), 3.85 (s, 0.1H), 7.02 (t, 1H, ^3J = 7.6 Hz), 7.12 (t, 1H, ^3J = 7.5 Hz), 7.36-7.42 (m, 2H), 7.51 (t, 2H, ^3J = 7.7 Hz), 7.61 (d, 1H, ^3J = 7.8 Hz), 7.87 (d, 2H, ^3J = 7.8 Hz), 10.77 (s, 1H), 11.26 (s, 1H) mixture of cis-trans isomers.

Scheme 12



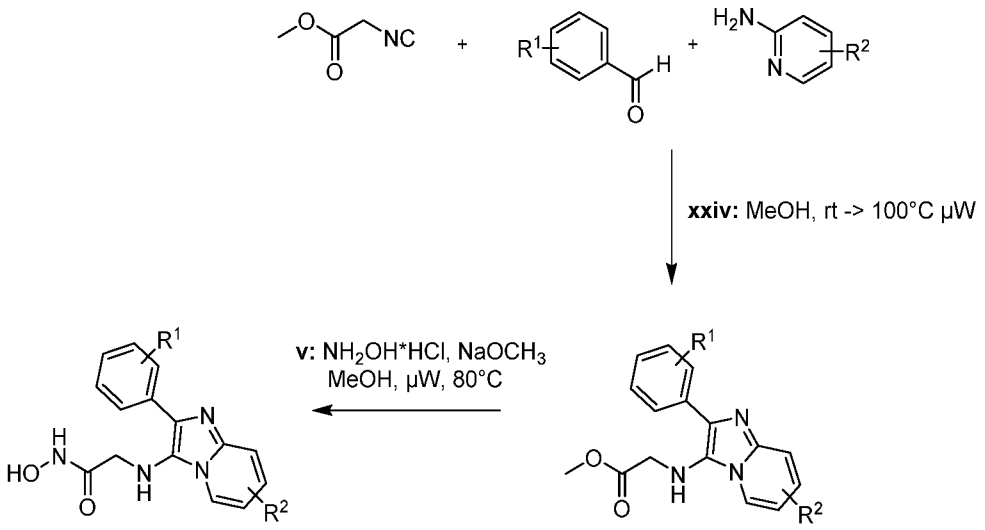
Method xxiii:

Aminopyridine (1 eq) and the respective aldehyde (1.2 eq) were dissolved in toluene (c=0.2 M). Molecular sieves (3Å, 200 mg) were added and the mixture was heated to 120°C for 14 hours. After cooling to room temperature, $Cu(OAc)_2$ x H_2O (0.1 eq) and ethyl propiolate (1 eq) were added and heated to 120°C for 3 hours. Afterwards, the mixture was filtered through Celite and the volatiles were evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$/MeOH gradient).

Example 28: 2-[2-(4-Chloro-2-fluoro-3-hydroxy-phenyl)imidazo-[1,2-a]pyridin-3-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxiii and v as described above, final deprotection of the phenol was accomplished by treatment with BBr_3 (1M in DCM, 5 eq). Yield (last step): 7 mg (13%); ESI-MS: m/z 336.2 $[M+H]^+$; HPLC (gradient 1): rt 6.75 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.90 (s, 1.7H), 4.19 (s, 0.3H), 7.05-7.14 (m, 1H), 7.42-7.44 (m, 2H), 7.81-7.93 (m, 2H), 8.62-8.74 (m, 1H), 9.01 (br s, 0.3H), 9.45 (br s, 0.1H), 10.37 und 10.84 (br s, 1H), 10.80 (s, 1H) mixture of cis-trans isomers.

Scheme 13



Method xxiv:

2-Aminopyridine, or a substituted analogue, (1 eq) was dissolved in MeOH (c=0.4 M). The respective aldehyde (1 eq) was added and the mixture was stirred at ambient temperature for 10 minutes. After addition of methyl isocyanoacetate (1 eq), the reaction was heated at 100°C for 30 minutes under microwave irradiation. After cooling, cold diethylether was added. The resulting precipitate was collected by filtration and used without further purification.

Example 29: 2-[(2-Phenylimidazo[1,2-a]pyridin-3-yl)amino]-ethanehydroxamic acid

The compound was synthesized according to methods xxiv and v as described above. Yield (last step): 32 mg (6%); ESI-MS: m/z 283.2 $[M+H]^+$; HPLC (gradient 2): rt 6.91 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.56 (s, 1.8H), 3.90 (s, 0.2H), 5.86 (br s, 1H), 7.44-7.53 (m, 2H), 7.61 (t, 2H, ^3J = 7.8 Hz), 7.83-7.84 (m, 2H), 8.01-8.03 (m, 2H), 8.91-8.93 (m, 2H), 10.10 (br s, 0.3H), 10.54 (br s, 0.7H) mixture of cis-trans isomers.

Example 30: 4-[3-[[2-(Hydroxyamino)-2-oxo-ethyl]amino]-imidazo[1,2-a]pyridin-2-yl]benzoic acid

The compound was synthesized according to methods xxiv and v as described above. Yield (last step): 67 mg (11%); ESI-MS: m/z 327.2 $[M+H]^+$; HPLC (gradient 2): rt 6.69 min (93.4%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.91 (s, 2H), 5.92 (br s, 1H), 7.35-7.41 (m, 1H), 7.71-7.79 (m, 2H), 8.11-8.17 (m, 4H), 8.84-8.90 (m, 2H), 10.51 (s, 1H), 13.13 (br s, 1H).

Example 31: 3-[3-[[2-(Hydroxyamino)-2-oxo-ethyl]amino]-imidazo[1,2-a]pyridin-2-yl]benzoic acid

The compound was synthesized according to methods xxiv and v as described above. Yield (last step): 39 mg (10%); ESI-MS: m/z 327.2 $[M+H]^+$; HPLC (gradient 2): rt 7.15 min (98.9%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.90 (s, 2H), 5.93 (br s, 1H), 7.41-7.45 (m, 1H), 7.72 (t, 1H, ^3J = 7.8 Hz), 7.80-7.84 (m, 2H), 8.03-8.05 (m, 1H), 8.29-8.31 (m, 1H), 8.59 (br s, 1H), 8.89-8.96 (m, 2H), 10.52 (br s, 1H).

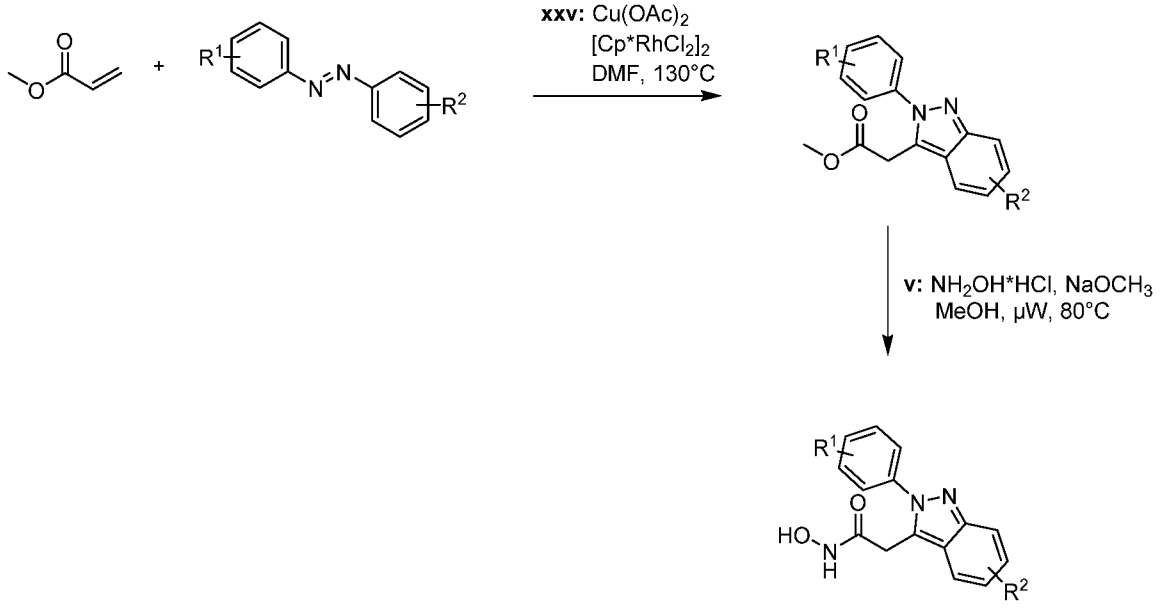
Example 32: 2-[[2-(2,3-Dihydro-1,4-benzodioxin-6-yl)imidazo-[1,2-a]pyridin-3-yl]amino]ethanehydroxamic acid

The compound was synthesized according to methods xxiv and v as described above. Yield (last step): 36 mg (10%); ESI-MS: m/z 327.2 $[M+H]^+$; HPLC (gradient 2): rt 8.19 min (96.8%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.55 (s, 2H), 4.34 (s, 4H), 5.81 (br s, 1H), 7.09-7.11 (m, 1H), 7.46-7.55 (m, 3H), 7.81-7.88 (m, 2H), 8.92-8.94 (m, 2H), 10.11 (br s, 0.3H), 10.53 (br s, 0.7H) mixture of cis-trans isomers.

Example 33: 3-[[2-(Hydroxyamino)-2-oxo-ethyl]amino]-2-phenyl-imidazo[1,2-a]pyridine-8-carboxylic acid

The compound was synthesized according to methods xxiv and v as described above. Yield (last step): 16 mg (11%); ESI-MS: m/z 327.4 $[M+H]^+$; HPLC (gradient 1): rt 5.81 min (98.0%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.51 (s, 2H), 5.78 (br s, 1H), 7.36-7.63 (m, 6H), 7.98-8.04 (m, 2H), 8.17-8.29 (m, 1H), 10.50 (s, 1H).

Scheme 14



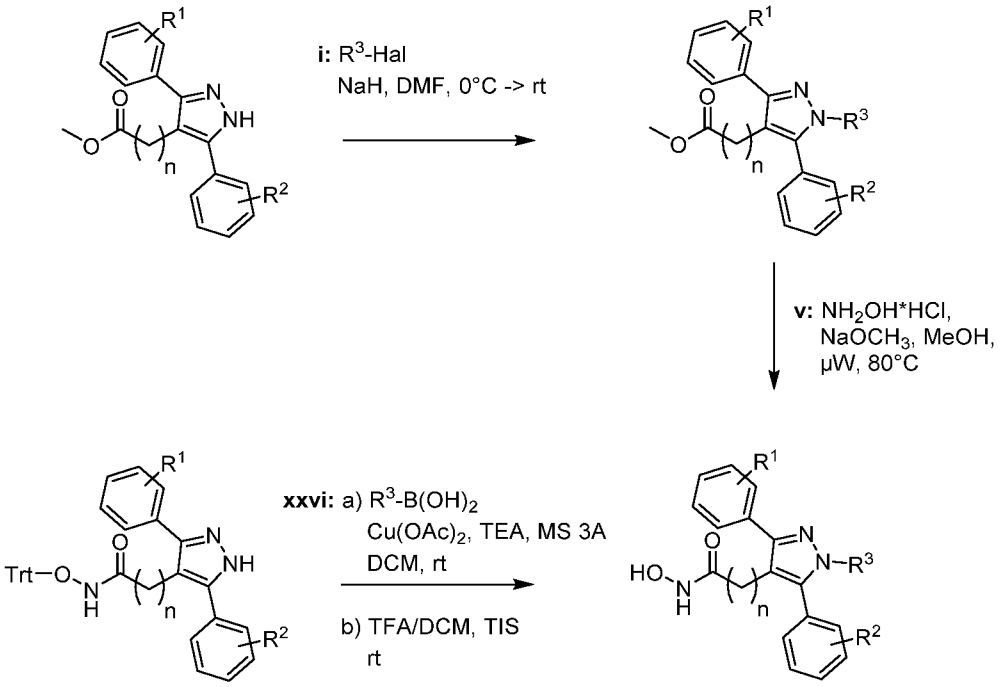
Method xxv:

A vial containing the respective azabenzene (1 eq), $[Cp^*RhCl_2]_2$ (0.05 eq) and $Cu(OAc)_2$ (2 eq) was sealed and purged with argon. Dimethylformamide (c=0.2 M) and methyl acrylate (1.2 eq) were added and the mixture was stirred at 130°C overnight. The reaction was quenched with water and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Example 34: 2-(2-Phenylindazol-3-yl)ethanehydroxamic acid

The compound was synthesized according to methods xxv and v as described above. Yield (last step): 18 mg (56%); ESI-MS: m/z 268.1 $[M+H]^+$; HPLC (gradient 1): rt 9.49 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.83 (s, 1.8H), 4.15 (s, 0.2H), 7.08-7.11 (m, 1H), 7.30-7.34 (m, 1H), 7.55-7.66 (m, 4H), 7.72-7.78 (m, 3H), 10.21 (s, 0.1H), 10.86 (s, 0.9H) mixture of cis-trans isomers.

Scheme 15



Method xxvi:

2-(3,5-Diphenyl-1H-pyrazol-4-yl)-N-trityloxy-acetamide (1 eq) was dissolved in dichloromethane (c=0.1 M). The respective boronic acid (2 eq), triethylamine (2 eq), $Cu(OAc)_2$ (1.5 eq) and molecular sieves were added, and the mixture was vigorously stirred at room temperature until TLC showed full conversion of the starting materials. The mixture was filtered through Celite and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient). The purified product was treated with TFA/DCM (1:1 v/v, 10 ml) and triisopropylsilane (180 µl) and stirred at room temperature for 1-2 hours. The volatiles were evaporated, and the remains were purified by semi-preparative HPLC.

Example 35: 2-(1-Methyl-3,5-diphenyl-pyrazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 96 mg (45%); ESI-MS: m/z 308.2 $[M+H]^+$; HPLC (gradient 1): rt 11.55 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.14 (s, 1.8H), 3.45 (s, 0.2H), 3.77 (s, 3H), 7.33-7.37 (m, 1H), 7.41-7.58 (m, 7H), 7.64-7.67 (m, 2H), 10.00 (s, 0.1H), 10.45 (s, 0.9H) mixture of cis-trans isomers.

Example 36: 2-(1,3,5-Triphenylpyrazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods xxvi as described above. Yield (last step): 50 mg (14%); ESI-MS: m/z 370.3 $[M+H]^+$; HPLC (gradient 1): rt 15.63 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.24 (s, 1.8H), 3.54 (s, 0.2H), 7.28-7.50 (m, 13H), 7.66-7.77 (m, 2H), 10.06 (s, 0.1H), 10.53 (s, 0.9H) mixture of cis-trans isomers.

Example 37: 4-[4-[2-(Hydroxyamino)-2-oxo-ethyl]-3,5-diphenyl-pyrazol-1-yl]benzoic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 55 mg (13%); ESI-MS: m/z 414.2 $[M+H]^+$; HPLC (gradient 1): rt 13.08 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.24 (s,

1.8H), 3.55 (s, 0.2H), 7.28-7.52 (m, 10H), 7.68-7.79 (m, 2H), 7.90-7.92 (m, 2H), 10.09 (s, 0.1H), 10.55 (s, 0.9H), 13.06 (br s, 1H) mixture of cis-trans isomers.

Example 38: 3-[4-[2-(Hydroxyamino)-2-oxo-ethyl]-3,5-diphenyl-pyrazol-1-yl]benzoic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 45 mg (11%); ESI-MS: m/z 414.3 $[M+H]^+$; HPLC (gradient 1): rt 13.09 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.25 (s, 1.8H), 3.55 (s, 0.2H), 7.27-7.51 (m, 10H), 7.67-7.78 (m, 2H), 7.83-7.91 (m, 2H), 10.08 (s, 0.1H), 10.53 (s, 0.9H), 13.13 (br s, 1H) mixture of cis-trans isomers.

Example 39: 2-(1-Benzyl-3,5-diphenyl-pyrazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 81 mg (35%); ESI-MS: m/z 383.4 $[M+H]^+$; HPLC (gradient 1): rt 15.63 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.18 (s, 1.8H), 3.47 (s, 0.2H), 5.28 (s, 2H), 7.01-7.04 (m, 2H), 7.22-7.31 (m, 3H), 7.34-7.52 (m, 8H), 7.58-7.70 (m, 2H), 9.97 (s, 0.1H), 10.45 (S, 0.9H) mixture of cis-trans isomers.

Example 40: 4-[[4-(2-(Hydroxyamino)-2-oxo-ethyl]-3,5-diphenyl-1H-pyrazol-1-yl]methyl]benzoic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 130 mg (32%); ESI-MS: m/z 428.2 $[M+H]^+$; HPLC (gradient 1): rt 12.69 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.18 (s, 1.8H), 3.48 (s, 0.2H), 5.35 (s, 2H), 7.13-7.15 (m, 2H), 7.35-7.49 (m, 8H), 7.60-7.70 (m, 2H), 7.85-7.87 (m, 2H), 9.98 (s, 0.1H), 10.45 (s, 0.9H), 12.90 (br s, 1H) mixture of cis-trans isomers.

Example 41: 3-[[4-[2-(Hydroxyamino)-2-oxo-ethyl]-3,5-diphenyl-1H-pyrazol-1-yl]methyl]benzoic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 16 mg (5%); ESI-MS: m/z 428.2 $[M+H]^+$; HPLC (gradient 1): rt 12.88 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.17 (s, 1.8H), 3.47 (s, 0.2H), 5.34 (s, 2H), 7.23-7.25 (m, 1H), 7.35-7.50 (m, 9H), 7.59-7.70 (m, 3H), 7.81-7.83 (m, 1H), 9.96 (s, 0.1H), 10.45 (s, 0.9H) mixture of cis-trans isomers.

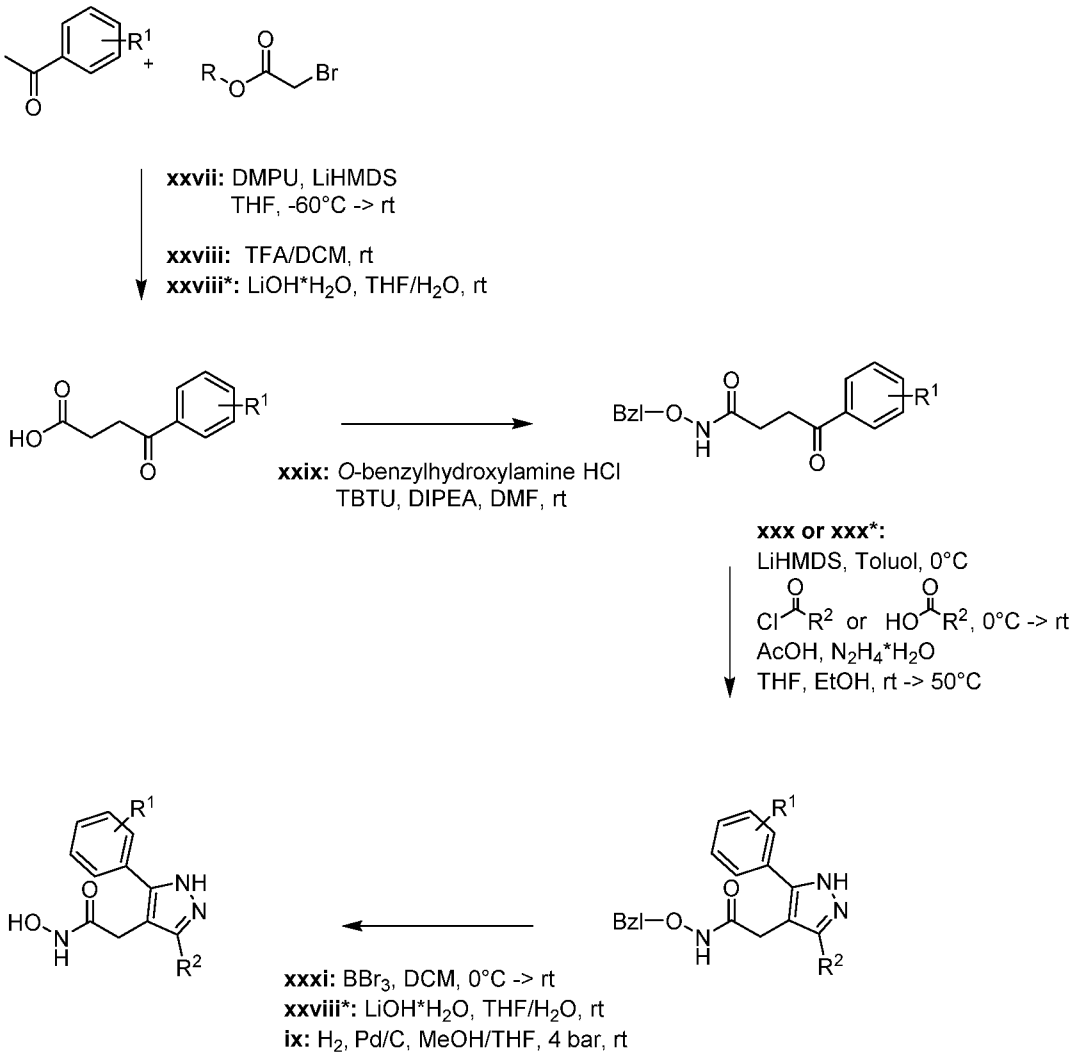
Example 42: 2-[1-(4-Chloro-2-fluoro-3-hydroxybenzyl)-3,5-diphenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods i and v as described above, followed by phenol deprotection using 3 eq BBr_3 in DCM (5 ml). Yield (last step): 142 mg (54%); ESI-MS: m/z 452.2 $[M+H]^+$; HPLC (gradient 1): rt 14.75 min (98.4%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.15 (s, 1.8H), 3.46 (s, 0.2H), 5.27 (s, 2H), 6.42-6.46 (m, 1H), 7.11-7.13 (m, 1H), 7.34-7.53 (m, 8H), 7.57-7.67 (m, 2H), 9.97 (s, 0.1H), 10.36-10.44 (m, 1.7H) mixture of cis-trans isomers.

Example 43: 2-[1-(1,3-Benzodioxol-5-ylmethyl)-3,5-diphenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods i and v as described above. Yield (last step): 161 mg (53%); ESI-MS: m/z 428.4 $[M+H]^+$; HPLC (gradient 1): rt 15.33 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.15 (s, 1.8H), 3.46 (s, 0.2H), 5.17 (s, 2H), 5.97 (s, 2H), 6.47-6.49 (m, 1H), 6.56-6.57 (M, 1H), 6.79-6.81 (m, 1H), 7.34-7.51 (m, 8H), 7.58-7.69 (m, 2H), 9.96 (s, 0.1H), 10.44 (s, 0.9H) mixture of cis-trans isomers.

Scheme 16



Method xxvii:

The respective acetophenone derivative (1 eq) was dissolved in dry toluol (c=1 M) in a flask sealed with a septum. The solution was cooled to -60°C. DMPU (3.6 eq) and LiHMDS (1 M in THF, 1.2 eq) were added via syringe at -60°C under argon atmosphere. After 30 minutes of stirring, methyl bromoacetate or another suitable alkyl halide (1.5 eq) was added dropwise. The mixture was stirred for an additional 10 minutes, then allowed to warm up to room temperature and stirred for further 5 hours. The volatiles were evaporated and the remains were taken up with a small amount of water. The aqueous layer was slightly acidified by means of diluted aqueous HCl and was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/diethyl ether gradient)

Method xxviii:

The respective *tert*-butyl ester derivative obtained by method xxvii was treated with TFA/DCM (1:1, 10 ml) at 0°C and stirred for 2 hours. The volatiles were evaporated, and the remains were purified by flash chromatography (silica, heptane/EtOAc gradient).

Method xxviii*:

The respective methyl ester derivative was dissolved in THF/water (3:1, c=0.4 M). $LiOH^*H_2O$ (2 eq) was added and the mixture was stirred overnight at room temperature. The volatiles were evaporated and the remains were taken up in water, acidified by means of diluted aqueous HCl and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was used without further purification.

Method xxix:

The respective 4-oxo-4-phenylbutanoic acid derivative (1 eq) was dissolved in dimethylformamide (c=0.2 M). TBTU (1 eq) and DIPEA (2 eq) were added and the mixture was stirred at room temperature. After several minutes, *O*-benzylhydroxylamine hydrochloride (1 eq) and DIPEA (2 eq) were added and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with water and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, heptane/EtOAc gradient).

Method xxx:

The respective N-benzyloxy-4-oxo-4-phenylbutanamide derivative (1 eq) obtained by method xxix was dissolved in dry toluol (c=0.4 M) in a flask sealed with a septum. The solution was cooled to 0°C under argon. LiHMDS (1 M in THF, 2.1 eq) was added quickly via syringe and the mixture was stirred for 5 minutes. The respective acyl chloride derivative (0.5 eq) was added in one portion and the mixture was allowed to warm up to room temperature. The mixture was stirred vigorously until TLC showed full conversion of the acyl chloride. AcOH (2 ml) was added to the mixture. EtOH (10 ml) and THF (5 ml) were added to form a homogeneous mixture, then $N_2H_4^*H_2O$ (34.3 eq) was added. The mixture was heated to 50°C and the reaction was monitored via TLC. The volatiles were evaporated and the remains were taken up in water, acidified by means of diluted aqueous HCl and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$/MeOH gradient).

Method xxx*:

The respective carboxylic acid derivative (0.5 eq) was dissolved in dry THF (c=0.3 M). Under argon atmosphere CDI was added to the solution. The mixture was stirred for 1 hour at room temperature. In a separate flask the respective N-benzyloxy-4-oxo-4-phenylbutanamide derivative (1 eq) obtained by method xxix was dissolved in dry toluol (c=0.4 M) and sealed with a septum. The solution was cooled to 0°C under argon. LiHMDS (1 M in THF, 2.1 eq) was added quickly via syringe and the mixture was stirred for 5 minutes. The respective activated carboxylic acid derivative (0.5 eq) was added in one portion and the mixture was allowed to warm up to room temperature. The mixture was stirred vigorously until TLC showed full conversion of the carboxylic acid derivative. AcOH (2 ml) was added to the mixture. EtOH (10 ml) and THF (5 ml) were added to form a homogeneous mixture, then hydrazine monohydrate (34.3 eq) was added. The mixture was heated to 50°C and the reaction was monitored via TLC. The volatiles were evaporated and the remains were taken up in water, acidified by means of diluted aqueous HCl and extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (silica, $CHCl_3$/MeOH gradient).

Method xxxi:

The compound obtained by method xxx or xxx* was dissolved in DCM (c=0.1 M). in a sealed flask under argon atmosphere. The mixture was cooled down to 0°C and treated with BBr_3 (1 M in DCM, 3-15 eq) for final deprotection. The mixture was allowed to warm up to room temperature and stirred overnight. The reaction was quenched with water and cooled with ice. The aqueous layer was extracted with EtOAc (3x25 ml). The combined organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by semi-preparative HPLC.

Example 44: 2-(3-Methyl-5-phenyl-1H-pyrazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 22 mg (27%); ESI-MS: m/z 232.2 $[M+H]^+$; HPLC (gradient 1): rt 6.56 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 2.20 (s, 3H), 3.21 (s, 1.9H), 3.55 (br s, 0.1H), 7.34-7.38 (m, 1H), 7.44 (t, 2H, ^3J = 7.3 Hz), 7.65-7.67 (m, 2H), 10.58 (br s, 1H) mixture of cis-trans isomers.

Example 45: 2-(3-Cyclopentyl-5-phenyl-1H-pyrazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 49 mg (31%); ESI-MS: m/z 286.2 $[M+H]^+$; HPLC (gradient 1): rt 9.07 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 1.60-1.71 (m, 4H), 1.74-1.78 (m, 2H), 1.93-2.00 (m, 2H), 3.05-3.13 (m, 1H), 3.22 (s, 1.9H), 3.56 (br s, 0.1H), 7.34-7.38 (m, 1H), 7.43 (t, 2H, ^3J = 7.3 Hz), 7.67 (d, 2H, ^3J = 7.3 Hz), 9.96 (br s, 0.1H), 10.56 (br s, 0.9H) mixture of cis-trans isomers.

Example 46: 2-(3-Benzyl-5-phenyl-1H-pyrazol-4-yl)ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 24 mg (30%); ESI-MS: m/z 308.3 $[M+H]^+$; HPLC (gradient 1): rt 10.43 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.21 (s, 1.8H), 3.54 (br s, 0.2H), 3.96 (s, 2H), 7.17-7.22 (m, 1H), 7.26-7.29 (m, 4H), 7.34-7.37 (m, 1H), 7.43 (t, 2H, ^3J = 7.6 Hz), 7.66-7.68 (m, 2H), 9.98 (br s, 0.1H), 10.61 (br s, 0.9H) mixture of cis-trans isomers.

Example 47: 2-[3-(3-Methoxyphenyl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method ix. Yield (last step): 145 mg (82%); ESI-MS: m/z 324.3 $[M+H]^+$; HPLC (gradient 1): rt 10.69 min (98.1%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.32 (s, 1.8H), 3.63 (br s, 0.2H), 3.81 (s, 3H), 6.95-6.98 (m, 1H), 7.20-7.22 (m, 2H), 7.36-7.42 (m, 2H), 7.47 (t, 2H, ^3J = 7.5 Hz), 7.64-7.65 (m, 2H), 10.12 (br s, 0.1H), 10.63 (s, 0.9H) mixture of cis-trans isomers.

Example 48: 2-[3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method ix. Yield (last step): 114 mg (48%); ESI-MS: m/z 324.3 $[M+H]^+$; HPLC (gradient 1): rt 10.37 min (97.8%); ^1H NMR, 400 MHz, DMSO d_6: δ 3.29 (s, 1.8H), 3.60

(s, 0.2H), 3.81 (s, 3H), 7.03 (d, 2H, ^3J = 8.7 Hz), 7.37-7.41 (m, 1H), 7.46 (t, 2H, ^3J = 7.6 Hz), 7.57 (d, 2H, ^3J = 8.7 Hz), 7.63-7.65 (m, 2H), 10.08 (br, 0.1H), 10.60 (s, 0.9H) mixture of cis-trans isomers.

Example 49: 2-[3-(3,4-Dimethoxyphenyl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method ix. Yield (last step): 49 mg (52%); ESI-MS: m/z 354.3 $[M+H]^+$; HPLC (gradient 1): rt 9.95 min (98.6%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.30 (s, 1.8H), 3.61 (br s, 0.2H), 3.80-3.81 (m, 6H), 7.03-7.06 (m, 1H), 7.15-7.17 (m, 1H), 7.23-7.24 (m, 1H), 7.37-7.41 (m, 1H), 7.47 (t, 2H, ^3J = 7.6 Hz), 7.66 (d, 2H, ^3J = 7.6 Hz), 10.13 (br s, 0.1H), 10.63 (s, 0.9H) mixture of cis-trans isomers.

Example 50: 2-[3-(1,3-Benzodioxol-5-yl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method ix. Yield (last step): 45 mg (41%); ESI-MS: m/z 338.2 $[M+H]^+$; HPLC (gradient 1): rt 10.40 min (98.1%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.29 (s, 1.8H), 3.59 (s, 0.2H), 6.08 (s, 2H), 7.00-7.02 (m, 1H), 7.11-7.14 (m, 1H), 7.20-7.21 (m, 1H), 7.37-7.41 (m, 1H), 7.47 (t, 2H, ^3J = 7.6 Hz), 7.61-7.63 (m, 2H), 10.11 (br s, 0.1H), 10.62 (s, 0.9H) mixture of cis-trans isomers.

Example 51: 3-[4-[2-(Hydroxyamino)-2-oxo-ethyl]-5-phenyl-1H-pyrazol-3-yl]benzoic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 5 mg (6%); ESI-MS: m/z 338.2 $[M+H]^+$; HPLC (gradient 1): rt 9.39 min (95.8%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.35 (s, 1.7H), 3.65 (br s, 0.3H), 7.40-7.43 (m, 1H), 7.49 (t, 2H, ^3J = 7.6 Hz), 7.57-7.65 (m, 3H), 7.89 (d, 1H, ^3J = 7.8 Hz), 7.96 (d, 1H, ^3J = 7.8 Hz), 8.27 (s, 1H), 10.12 (br s, 0.1H), 10.61 (s, 0.9H) mixture of cis-trans isomers.

Example 52: 4-[4-[2-(Hydroxyamino)-2-oxo-ethyl]-5-phenyl-1H-pyrazol-3-yl]benzoic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 16 mg (5%); ESI-MS: m/z 338.3 $[M+H]^+$; HPLC (gradient 1): rt 9.41 min (95.5%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.67 (br s, 0.2H), 7.41-7.44 (m, 1H), 7.49 (t, 2H, 3J = 7.5 Hz), 7.65 (d, 2H, 3J = 7.6 Hz), 7.79 (d, 2H, 3J = 8.1 Hz), 8.01-8.05 (m, 2H), 8.91 (br s, 0.7H), 9.26 (br s, 0.1H), 10.13 (br s, 0.1H), 10.66 (s, 0.9H), 13.16 (br s, 1H) mixture of cis-trans isomers.

Example 53: 2-[3-(4-Chloro-2-fluoro-3-hydroxy-phenyl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the phenol and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 28 mg (45%); ESI-MS: m/z 362.2 $[M+H]^+$; HPLC (gradient 1): rt 10.32 min (97.0%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.24 (s, 1.8H), 3.55 (br s, 0.2H), 7.00 (t, 1H, ^3J = 7.8 Hz), 7.26-7.29 (m, 1H), 7.38-7.42 (m, 1H), 7.47 (t, 2H, ^3J = 7.3 Hz), 7.66 (d, 2H, ^3J = 7.3 Hz), 9.92 (br s, 0.1H), 10.45 (br s, 1.9H) mixture of cis-trans isomers.

Example 54: 2-[3-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the phenol and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 13 mg (17%); ESI-MS: m/z 362.3 $[M+H]^+$; HPLC (gradient 1): rt 10.51 min (95.9%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.30 (s, 1.8H), 3.61 (s, 0.2H), 7.39-7.44 (m, 1H), 7.46-7.52 (m, 4H), 7.60 (d, 2H, ^{3}J = 7.3 Hz), 10.57 (br s, 1H), 10.69 (s, 0.9H), 10.92 (s, 0.1H) mixture of cis-trans isomers.

Example 55: 2-[3-(3-Cyanophenyl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 25 mg (39%); ESI-MS: m/z 319.2 $[M+H]^+$; HPLC (gradient 1): rt 10.48 min (95.6%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.36 (s, 1.8H), 3.66 (br s, 0.2H), 7.42-7.45 (m, 1H), 7.50 (t, 2H, ^{3}J = 7.6 Hz), 7.61-7.64 (m, 2H), 7.66-7.71 (m, 1H), 7.86 (d, 1H, ^{3}J = 7.7 Hz), 8.02 (d, 1H, ^{3}J = 7.8 Hz), 8.12 (s, 1H), 10.69 (s, 0.9H), 10.92 (s, 0.1H) mixture of cis-trans isomers.

Example 56: 2-[3-(4-Cyanophenyl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 27 mg (42%); ESI-MS: m/z 74.1 $C_2H_4NO_2^{\bullet}$ fragment, 319.2 $[M+H]^+$; HPLC (gradient 1): rt 10.56 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.36 (s, 1.8H), 3.67 (br s, 0.2H), 7.42-7.45 (m, 1H), 7.50 (t, 2H, ^{3}J = 7.6 Hz), 7.62 (d, 2H, ^{3}J = 7.7 Hz), 7.88-7.94 (m, 4H), 10.15 (br s, 0.1H), 10.68 (s, 0.9H) mixture of cis-trans isomers.

Example 57: 2-[3,5-Bis(1,3-benzodioxol-5-yl)-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxvii, xxviii*, xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method ix. Yield (last step): 29 mg (13%); ESI-MS: m/z 382.3 $[M+H]^+$; HPLC (gradient 1): rt 10.72 min (95.4%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.26 (s, 1.9H), 3.56 (br s, 0.1H), 6.08 (s, 4H), 6.99-7.01 (m, 2H), 7.08-7.10 (m, 2H), 7.16-7.17 (m, 2H), 10.12 (br s, 0.1H), 10.63 (s, 0.9H) mixture of cis-trans isomers.

Example 58: 3-[3-(3-Carboxyphenyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-5-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the methyl esters and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 3 mg (3%); ESI-MS: m/z 382.3 $[M+H]^+$; HPLC (gradient 1): rt 8.67 min (93.0%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.37 (s, 1.3H), 3.66 (s, 0.1H), 7.61 (t, 2H, ^{3}J = 7.8 Hz), 7.87-7.89 (m, 2H), 7.96-7.98 (m, 2H), 8.20-8.25 (m, 2H), 10.13 (br s, 0.1H), 10.61 (s, 0.9H) mixture of cis-trans isomers.

Example 59: 4-[3-(4-Carboxyphenyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-5-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the methyl esters and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 3 mg (5%); ESI-MS: m/z 382.2 $[M+H]^+$; HPLC (gradient 1): rt 8.43 min (90.2%); ^{1}H NMR, 400 MHz, MeOH d_4: δ 3.49 (s, 2H), 7.74-7.76 (m, 4H), 8.09-8.14 (m, 4H).

Example 60: 2-[3,5-Bis(4-chloro-2-fluoro-3-hydroxy-phenyl)-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the phenols and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 4 mg (11%); ESI-MS: m/z 430.3 $[M+H]^+$; HPLC (gradient 1): rt 10.40 min (96.8%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.15 (s, 1.8H), 3.47 (br s, 0.2H), 6.99-7.03 (m, 2H), 7.26-7.29 (m, 2H), 9.76 (br s, 0.1H), 10.31 (s, 0.9H), 10.50 (br s, 2H) mixture of cis-trans isomers.

Example 61: 3-[3-(1,3-Benzodioxol-5-yl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-5-yl)benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the methyl ester and benzyl-protected hydroxamic acid was accomplished according to methods xxviii* and ix. Yield (last step): 90 mg (69%); ESI-MS: m/z 382.3 $[M+H]^+$, 404.3 $[M+Na]^+$; HPLC (gradient 1): rt 9.63 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.32 (s, 1.8H), 3.61 (br s, 0.2H), 6.09 (s, 2H), 7.02-7.04 (m, 1H), 7.10-7.13 (m, 1H), 7.19-7.20 (m, 1H), 7.58 (t, 1H, ^{3}J = 7.7 Hz), 7.84-7.86 (m, 1H), 7.94-7.96 (m, 1H), 8.18-8.24 (m, 1H), 10.13 (br s, 0.1H), 10.62 (s, 0.9H) mixture of cis-trans isomers.

Example 62: 4-[3-(1,3-Benzodioxol-5-yl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-5-yl)benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the methyl esters and benzyl-protected hydroxamic acid was accomplished according to methods xxviii* and ix. Yield (last step): 8 mg (10%); ESI-MS: m/z 382.2 $[M+H]^+$; HPLC (gradient 1): rt 9.68 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.33 (s, 1.7H), 3.63 (br s, 0.3H), 6.09 (s, 2H), 7.02-7.04 (m, 1H), 7.12-7.14 (m, 1H), 7.21-7.22 (m, 1H), 7.75-7.77 (m, 2H), 8.00-8.02 (m, 2H), 10.14 (br s, 0.1H), 10.66 (s, 0.9H) mixture of cis-trans isomers.

Example 63: 3-[5-(4-Chloro-2-fluoro-3-hydroxy-phenyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-3-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the phenol, methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 4 mg (16%); ESI-MS: m/z 406.3 $[M+H]^+$; HPLC (gradient 1): rt 9.55 min (95.3%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.26 (s, 2H), 6.97-7.01 (m, 1H), 7.28-7.30 (m, 1H), 7.57-7.61 (m, 1H), 7.90-7.92 (m, 1H), 7.95-7.97 (m, 1H), 8.21-8.27 (m, 1H), 9.95 (br s, 0.1H), 10.45 (s, 0.7H), 10.53 (br s, 0.5H) mixture of cis-trans isomers.

Example 64: 3-[5-(3-Chloro-5-fluoro-4-hydroxy-phenyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-3-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the phenol, methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 18 mg (26%); ESI-MS: m/z 406.3 $[M+H]^+$; HPLC (gradient 1): rt 9.55 min (97.6%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.33 (s, 1.8H), 3.63 (br s, 0.2H), 7.47-7.52 (m, 2H), 7.60 (t, 1H, ^{3}J = 7.8 Hz), 7.83-7.84 (m, 1H), 7.96-7.98 (m, 1H), 8.16-8.22 (m, 1H), 10.19 (br s, 0.1H), 10.62-10.68 (m, 2H) mixture of cis-trans isomers.

Example 65: 4-[5-(4-Chloro-2-fluoro-3-hydroxy-phenyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-3-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the phenol, methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 4 mg (5%); ESI-MS: m/z 406.3 $[M+H]^+$; HPLC (gradient 1): rt 9.63 min (>99%); ^{1}H NMR, 400

MHz, MeOH d_4: δ 3.40 (s, 1.9H), 3.74 (br s, 0.1H), 6.97-7.01 (m, 1H), 7.21-7.24 (m, 1H), 7.76-7.78 (m, 2H), 8.11-8.13 (m, 2H) mixture of cis-trans isomers.

Example 66: 3-[3-(4-Carboxyphenyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-5-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the methyl esters and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 3 mg (7%); ESI-MS: m/z 382.3 $[M+H]^+$; HPLC (gradient 1): rt 8.64 min (>99%); ^{1}H NMR, 400 MHz, MeOH d_4: δ 3.49 (s, 1.9H), 3.82 (br s, 0.1H), 7.60 (t, 1H, ^3J = 7.8 Hz), 7.75-7.77 (m, 2H), 7.87-7.89 (m, 1H), 8.07-8.14 (m, 3H), 8.30 (s, 1H) mixture of cis-trans isomers.

Example 67: 3-Phenyl-1,4-dihydroindeno[1,2-c]pyrazole-4-carbohydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 37 mg (11%); ESI-MS: m/z 292.3 $[M+H]^+$; HPLC (gradient 1): rt 9.92 min (96.5%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 4.66 (s, 1H), 7.30-7.34 (m, 1H), 7.36-7.43 (m, 2H), 7.47-7.56 (m, 3H), 7.65-7.66 (m, 1H), 7.72-7.74 (m, 2H), 10.51 (br s, 0.1H), 11.07 (br s, 0.9H) mixture of cis-trans isomers.

Example 68: 3-Phenyl-4,5-dihydro-1H-benzo[g]indazole-4-carbohydroxamic acid

The compound was synthesized according to methods xxix and xxx as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 4 mg (11%); ESI-MS: m/z 306.2 $[M+H]^+$; HPLC (gradient 1): rt 10.59 min (97.9%); ^{1}H NMR, 400 MHz, MeCN d_3: δ 3.22-3.35 (m, 2H), 3.91-3.94 (m, 1H), 7.25-7.35 (m, 3H), 7.41-7.45 (m, 1H), 7.48-7.52 (m, 2H), 7.60-7.62 (m, 2H), 7.74-7.76 (m, 1H).

Example 69: 2-[3-(3-Hydroxyisoxazol-5-yl)-5-phenyl-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the benzyl-protected hydroxy isoxazole and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 10 mg (16%); ESI-MS: m/z 301.3 $[M+H]^+$; HPLC (gradient 1): rt 8.37 min (>99%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.44 (s, 1.8H), 3.76 (s, 0.2H), 6.16-6.25 (m, 1H), 7.43-7.47 (m, 1H), 7.49-7.53 (m, 2H), 7.61-7.63 (m, 2H), 10.08 (br s, 0.1H), 10.63 (s, 0.9H), 11.37 (br s, 1H) mixture of cis-trans isomers.

Example 70: 2-[5-Phenyl-3-[3-(trifluoromethyl)-1H-pyrazol-4-yl]-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the *tert*-butyl-protected pyrazole and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 26 mg (31%); ESI-MS: m/z 352.2 $[M+H]^+$; HPLC (gradient 1): rt 9.84 min (97.9%); ^{1}H NMR, 400 MHz, DMSO d_6: δ 3.21 (s, 1.8H), 3.52 (br s, 0.2H), 7.39-7.42 (m, 1H), 7.48 (t, 2H, ^3J = 7.7 Hz), 7.64-7.66 (m, 2H), 8.07 (s, 1H), 10.00 (br s, 0.1H), 10.55 (s, 0.9H), 13.77 (br s, 0.7H) mixture of cis-trans isomers.

Example 71: 2-[5-Phenyl-3-[3-(1H-tetrazol-5-yl)phenyl]-1H-pyrazol-4-yl]ethanehydroxamic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the PMB-protected tetrazole and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 38 mg (32%); ESI-MS: m/z 362.1 $[M+H]^+$; HPLC (gradient 1): rt 9.47 min (>99%); ^{1}H NMR, 400 MHz,

DMSO d_6: δ 3.40 (s, 1.7H), 3.66 (br s, 0.3H), 7.41-7.45 (m, 1H), 7.51 (t, 2H, ^3J = 7.5 Hz), 7.64-7.72 (m, 3H), 7.86-7.88 (m, 1H), 8.04-8.06 (m, 1H), 8.37 (s, 1H), 10.11 (br s, 0.1H), 10.62 (s, 0.9H) mixture of cis-trans isomers.

Example 72: 3-[1-[(4-chloro-2-fluoro-3-hydroxy-phenyl)methyl]-3,5-diphenyl-pyrazol-4-yl]propanehydroxamic acid

The compound was synthesized according to methods i and v as described above, final deprotection of the phenol was accomplished by treatment with BBr_3 (1M in DCM, 3 eq). Yield (last step): 56 mg (21%); ESI-MS: m/z 466.2 $[M+H]^+$; HPLC (gradient 1): rt 15.28 min (>99%); ^1H NMR, 400 MHz, DMSO d_6: δ 1.95-1.97 (m, 2H), 2.72-2.75 (m, 2H), 5.21 (s, 2H), 6.36 (t, 1H, ^3J=7.9 Hz), 7.10 (d, 1H, ^3J=8.6 Hz), 7.36-7.38 (m, 3H), 7.45 (t, 2H, ^3J=7.5 Hz), 7.49-7.53 (m, 3H), 7.68 (d, 2H, ^3J=7.5 Hz), 10.26 (s, 1H), 10.36 (s, 1H).

Example 73: (1S,2R)-2-[4-[2-(Hydroxyamino)-2-oxoethyl]-5-phenyl-1H-pyrazol-3-yl]cyclohexanecarboxylic acid

The compound was synthesized according to methods xxix and xxx* with a respective anhydride as described above, final deprotection of the benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 2 mg (2%); ESI-MS: m/z 344.2 $[M+H]^+$; HPLC (gradient 1): rt 9.01 min (91.8%); ^1H NMR, 400 MHz, DMSO d_6: δ 1.35-1.40 (m, 3H), 1.60-1.63 (m, 0.8H), 1.70-1.75 (m, 2.7H), 1.78-1.79 (m, 0.2H), 1.85-1.87 (m, 0.3H), 1.99-2.07 (m, 1H), 2.18 (br s, 1H), 2.67-2.74 (m, 1H), 3.17-3.30 (m, 2H), 7.33-7.37 (m, 1H), 7.41-7.45 (m, 2H), 7.48-7.50 (m, 0.2H), 7.61-7.62 (m, 1.8H), 10.52 (br sm, 0.2H), 10.50 (s, 0.7H) mixture of cis-trans isomers.

Example 74: 3-[4-[2-(Hydroxyamino)-2-oxo-ethyl]-5-phenyl-1H-pyrazol-3-yl]cyclohexanecarboxylic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 10 mg (8%); ESI-MS: m/z 344.3 $[M+H]^+$; HPLC (gradient 1): rt 8.64 min (96.5%); ^1H NMR, 400 MHz, DMSO d_6: δ 1.26-1.49 (m, 3H), 1.55-1.64 (m, 1H), 1.79-1.85 (m, 2H), 1.92-2.01 (m, 2H), 2.32-2.38 (m, 1H), 2.74-2.78 (m, 1H), 3.22 (s, 2H), 7.33-7.37 (m, 1H), 7.43 (t, 2H, ^3J=7.4 Hz), 7.65-7.67 (m, 2H), 9.99 (br s, 0.1H), 10.67 (s, 0.9H) mixture of cis-trans isomers.

Example 75: *cis*-4-[4-[2-(Hydroxyamino)-2-oxo-ethyl)-5-phenyl-1H-pyrazol-3-yl]cyclohexanecarboxylic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 10 mg (13%); ESI-MS: m/z 344.2 $[M+H]^+$; HPLC (gradient 1): rt 8.67 min (26.4%) and 8.80 min (73.6%) double peak; ^1H NMR, 400 MHz, DMSO d_6: δ 1.40-1.66 (m, 5H), 1.83-1.87 (m, 1H), 1.95-2.01 (m, 1H), 2.10-2.13 (m, 1H), 2.19-2.25 (m, 0.5H), 2.60-2.71 (m, 1.5H), 3.19 (s, 1.8H), 3.53 (br s, 0.2H), 7.33-7.36 (m, 1H), 7.40-7.44 (m, 2H), 7.50-7.53 (m, 0.2H), 7.64-7.68 (m, 1.8H), 9.98 (br s, 0.1H), 10.59-10.62 (m, 0.9H) mixture of cis-trans isomers.

Example 76: *trans*-4-[4-[2-(Hydroxyamino)-2-oxo-ethyl]-5-phenyl-1H-pyrazol-3-yl]cyclohexanecarboxylic acid

The compound was synthesized according to methods xxix and xxx* as described above, final deprotection of the methyl ester and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 8 mg (12%); ESI-MS: m/z 344.3 $[M+H]^+$; HPLC (gradient 1): rt 8.69 min (>99%); ^1H NMR, 400 MHz, MeOH d_4: δ 1.52-

1.73 (m, 4H), 2.07-2.17 (m, 4H), 2.39-2.45 (m, 1H), 2.81-2.87 (m, 1H), 3.42 (s, 1.8H), 3.79 (s, 0.2H), 7.45-7.54 (m, 3H), 7.58-7.59 (m, 0.2H), 7.63-7.66 (m, 1.8H) mixture of cis-trans isomers.

Example 77: *cis*-3-[3-(4-carboxycyclohexyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-5-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the methyl esters and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 2 mg (1%); ESI-MS: m/z 388.4 $[M+H]^+$; HPLC (gradient 1): rt 8.00 min (95.2%); ^{1}H NMR, 400 MHz, MeOH d_4: 1.57-1.73 (m, 4H), 2.04-2.15 (m, 4H), 2.38-2.48 (m, 1H), 2.77-2.83 (m, 1H), 3.41 (s, 1.7H), 3.66 (s, 0.3H), 7.58 (t, 1H, ^{3}J=7.6 Hz), 7.88-7.90 (m, 1H), 8.06-8.08 (m, 1H), 8.29 (s, 1H) mixture of cis-trans isomers.

Example 78: *trans*-3-[3-(4-Carboxycyclohexyl)-4-[2-(hydroxyamino)-2-oxo-ethyl]-1H-pyrazol-5-yl]benzoic acid

The compound was synthesized according to methods xxvii, xxviii, xxix and xxx* as described above, final deprotection of the methyl esters and benzyl-protected hydroxamic acid was accomplished according to method xxxi. Yield (last step): 2 mg (1%); ESI-MS: m/z 388.3 $[M+H]^+$; HPLC (gradient 1): rt 7.95 min (>99%); ^{1}H NMR, 400 MHz, MeOH d_4: δ δ 1.43-1.73 (m, 4H), 2.04-2.16 (m, 4H), 2.38-2.44 (m, 1H), 2.78-2.83 (m, 1H), 3.41 (s, 1.4H), 3.67 (s, 0.6H), 7.59 (t, 1H, ^{3}J=7.6 Hz), 7.88-7.93 (m, 1H), 8.07-8.09 (m, 1H), 8.29 (s, 1H) mixture of cis-trans isomers.

Analytical methods

HPLC: The analytical HPLC-system consisted of a Merck-Hitachi device (model LaChrom) utilizing a LUNA RP 18 (5 µm), analytical column (length: 125 mm, diameter: 4 mm), and a diode array detector (DAD) with λ = 214 nm as the reporting wavelength. The compounds were analysed using a gradient at a flow rate of 1 mL/min; whereby eluent (A) was acetonitrile, eluent (B) was water, both containing 0.04 % (v/v) trifluoroacetic acid applying one of the following gradients:

Gradient 1: 0 min - 5 min -> 5% (A), 5 min - 15 min -> 5 - 60% (A), 15 min - 20 min 60 - 95% (A) 20 min - 30 min 95% (A)

Gradient 2: 0 min - 15 min 5 - 50 % (A), 15 min - 20 min -> 50 - 95 % (A), 20 min - 23 min 95 % (A)

The purities of all reported compounds were determined by the percentage of the peak area at 214 nm.

Mass-spectrometry, NMR-spectroscopy: ESI-Mass spectra were obtained with a SCIEX API 1200 spectrometer (Perkin Elmer) or an expressionCMS (Advion). The ^{1}H NMR-Spectra were recorded at an Agilent DD2 400-MHz spectrometer. Chemical shifts (δ) are expressed as parts per million (ppm) downfield from tetramethylsilane. Splitting patterns have been designated as follows: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet) and br (broad signal).

I. Enzymatic assays

The determination of enzymatic activity was based on the cleavage of internally quenched peptide substrates. A typical assay of 250 µl total volume measured in black 96 well plates consisted of 100 µl buffer, 50 µl enzyme at a final concentration of 5e-8 M to 2e-10 M, 50 µl substrate (0.15 to 80 µM, in buffer, 0.5% DMSO) and 50 µl inhibitor solution (in buffer, 1% DMSO). In case of 125 µl assay volume (black 96 half area well plates) all volumes were cut in

half. Enzymatic activity of ADAMs was measured in 384 well plates with 60 µl total assay volume consisting of 20 µl inhibitor, 20 µl buffer, 10 µl enzyme and 10 µl substrate.

Table 1. Peptide substrates and assay conditions used for determination of enzymatic activity (Abz = 2-aminobenzoyl; Dnp = 2,4-dinitrophenyl; Mca = 7-methoxy coumarin; Dap = 2,3-diaminopropionic acid; hMeprin = human meprin; hMMPs = human Matrix Metalloproteases, hADAMs = human A Desintegrin and Metalloproteases)

Enzyme		Substrate	Buffer	Assay volume
Method A	hMeprin β	Abz-YVAEAPK(Dnp)G-OH	40 mM Tris pH 8.0	250 µl
	hMeprin α	Abz-YVADAPK(Dnp)G-OH	40 mM HEPES pH 7.4, 100 mM NaCl	250 µl
Method B	hMeprin β	Ac-R-E(EDANS)-DR-Nle-VGDDPY-K(Dabcyl)-NH_2	50 mM HEPES, 150 nM NaCl, pH 7.4	250 µl
	hMeprin α	Ac-R-E(EDANS)-DR-Nle-VGDDPY-K(Dabcyl)-NH_2	50 mM HEPES, 150 nM NaCl, pH 7.4	250 µl
hMMP 2 (Abnova)		Mca-PLGL-(DapDnp)-AR-NH_2	50 mM Tris, 2 µM $ZnCl_2$, 150 mM NaCl, pH 8.5	125 µl
hMMPs 9 and 13 (R&D systems)		Mca-PLGL-(DapDnp)-AR-NH_2	50 mM Tris, 2 µM $ZnCl_2$, 150 mM NaCl, pH 7.5	125 µl
hADAMs 10 and 17 (R&D systems)		Abz-LANAVRSSSR-(DapDnp)-NH_2	25 mM Tris, 2 µM $ZnCl_2$, 150 mM NaCl, pH 9.0	60 µl

IC_{50} values were determined by method A or/and B. For IC_{50} values in method A the influence of 12 inhibitor concentrations ranging from 0 to 5e-5 M on the enzymatic activity was investigated in the presence of one standard substrate concentration (10 µM). For IC_{50} values in method B the influence of 14 inhibitor concentrations ranging from 0 to 1e-5 M on enzymatic activity was investigated in the presence of 8 µM substrate concentration for hMeprin α and 20 µM substrate concentration for hMeprin β. Initial velocities were determined and converted into concentration units applying a standard curve obtained after complete conversion of different substrate concentrations under assay conditions. Based on method B $Ki^{(app)}$ values were determined using Morrison's equation. All measurements were performed using a fluorescence plate reader (FLUOstar OPTIMA, BMG Labtech) at 30°C. The kinetic parameters were determined at least in duplicates on separate days. The excitation/emission wavelength was 340/420 nm. The kinetic data was evaluated using GraFit software (version 7.0.3, Erithacus Software).

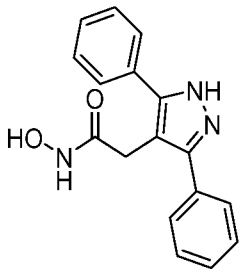
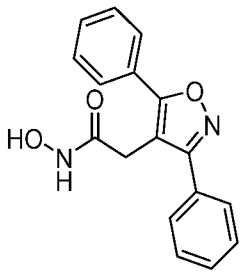
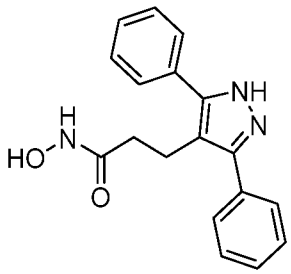
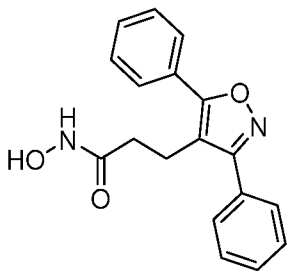
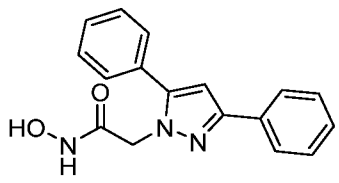
MMPs were activated prior to measurement by APMA (p-aminophenylmercuric acetate) treatment according to manufacturer´s instructions (R&D systems).

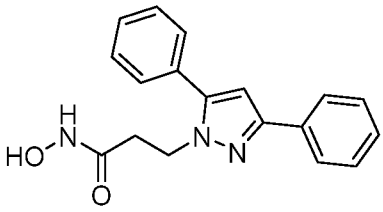
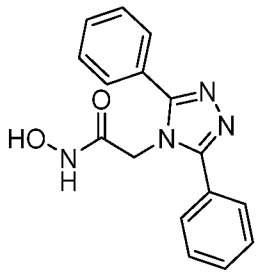
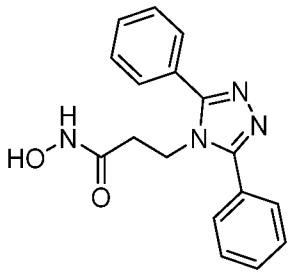
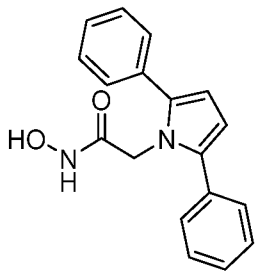
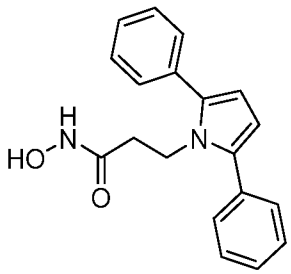
II. Inhibition of Meprin α and β

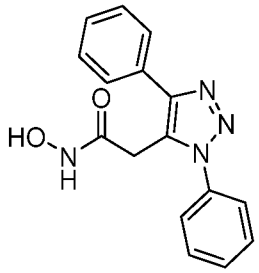
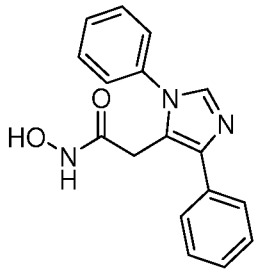
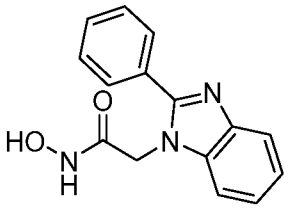
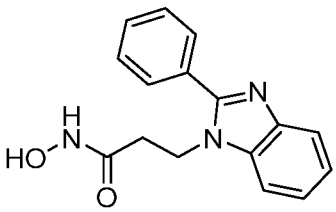
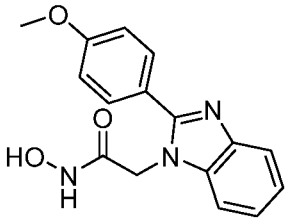
The following compounds according to the present invention were synthesized using the above general procedures. IC_{50} values for the inhibition of hMeprin β and α measured using the above enzyme assays are shown in

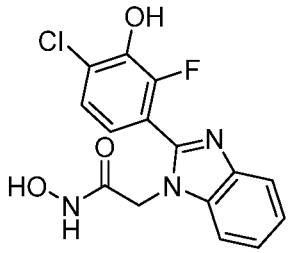
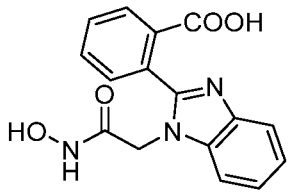
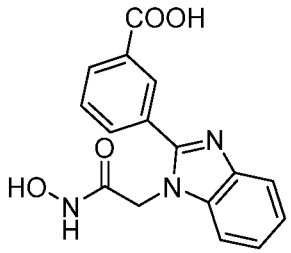
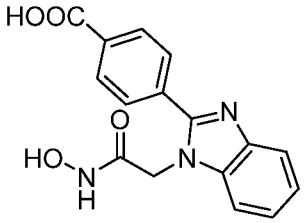
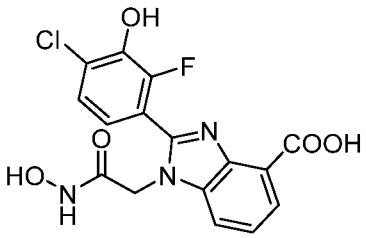
the following Tables. IC_{50} refers to the average IC_{50} values (geometric mean of independent experiments; geometric SD factor is given in parentheses) measured as described above.

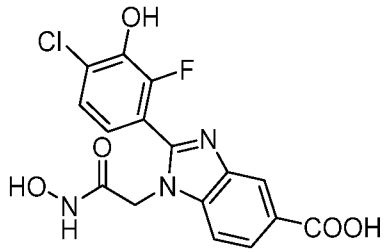
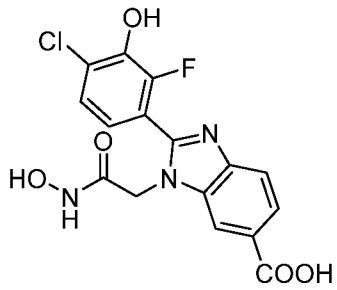
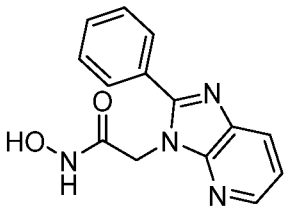
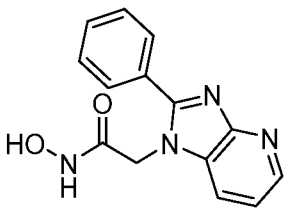
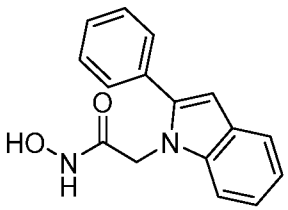
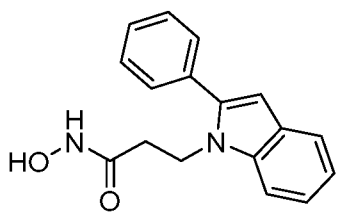
Table 2. Compounds and Inhibitory Activities against Meprin α and β

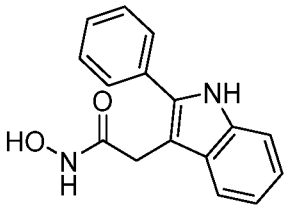
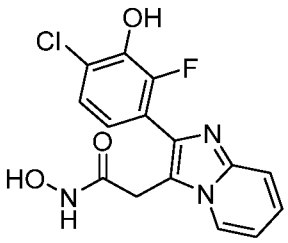
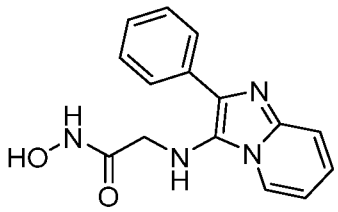
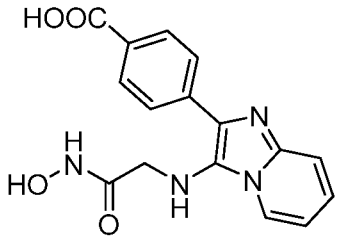
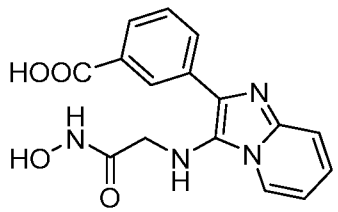
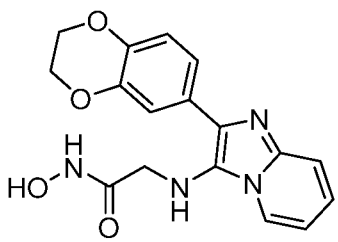
Structure	Compound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 1	4 (1.05)	1 (1.15)	1 (1.19)	204 (1.06)	119 (1.04)	116 (1.08)
	Example 2	7 (1.05)	4 (1.10)	4 (1.08)	831 (1.12)	586 (1.06)	584 (1.06)
	Example 3	108 (1.02)	80 (1.09)	78 (1.12)	8075 (1.07)	9660 (1.07)	9349 (1.02)
	Example 4	32 (1.002)	n.d.	n.d.	13691 (1.05)	n.d.	n.d.
	Example 5	292 (1.13)	n.d.	n.d.	10492 (1.06)	n.d.	n.d.

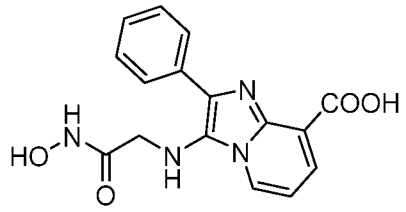
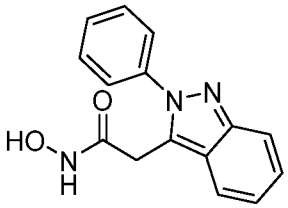
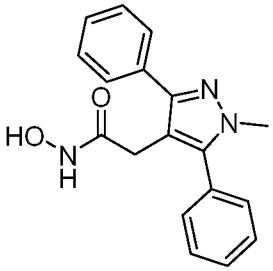
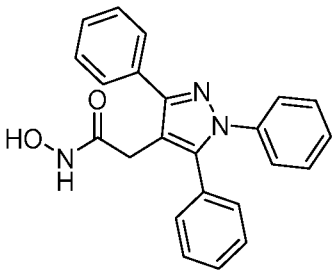
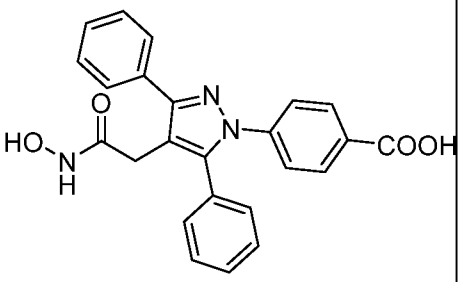
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 6	457 (1.03)	n.d.	n.d.	15445 (1.13)	n.d.	n.d.
	Example 7	69 (1.004)	n.d.	n.d.	8712 (1.04)	n.d.	n.d.
	Example 8	353 (1.09)	n.d.	n.d.	42320 (1.09)	n.d.	n.d.
	Example 9	34 (1.12)	n.d.	n.d.	4317 (1.09)	n.d.	n.d.
	Example 10	727 (1.09)	n.d.	n.d.	15026 (1.08)	n.d.	n.d.

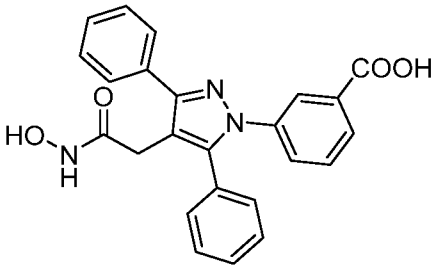
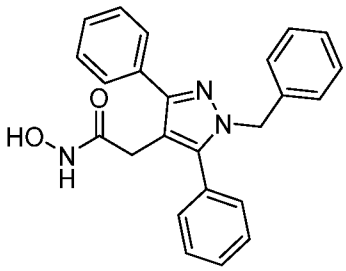
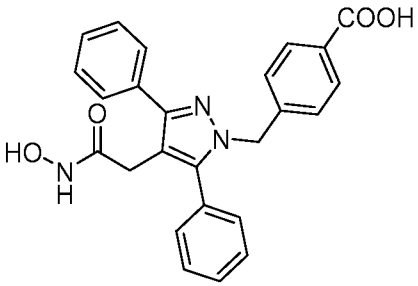
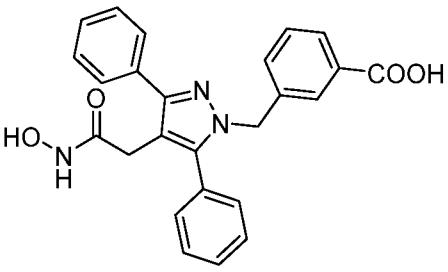
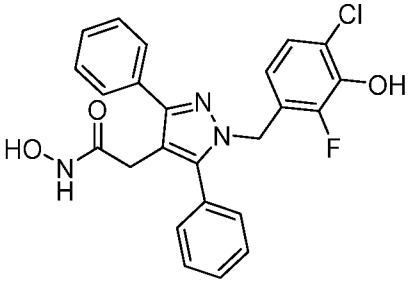
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 11	11 (1.09)	n.d.	n.d.	1450 (1.03)	n.d.	n.d.
	Example 12	2 (1.18)	n.d.	n.d.	486 (1.08)	n.d.	n.d.
	Example 13	173 (1.13)	141 (1.17)	128 (1.23)	1628 (1.08)	1139 (1.05)	1134 (1.05)
	Example 14	1130 (1.04)	708 (1.002)	701 (1.001)	28037 (1.04)	32432 (1.22)	31749 (1.13)
	Example 15	n.d.	95 (1.07)	94 (1.06)	n.d.	257 (1.11)	252 (1.11)

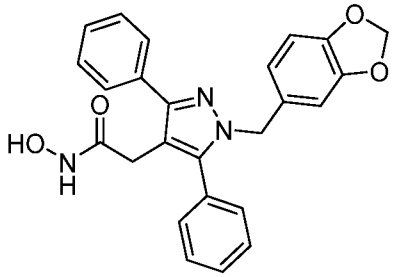
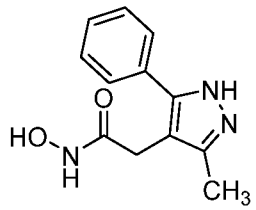
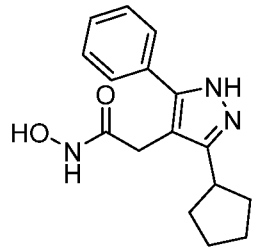
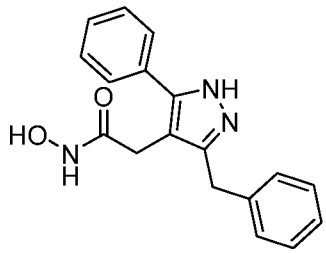
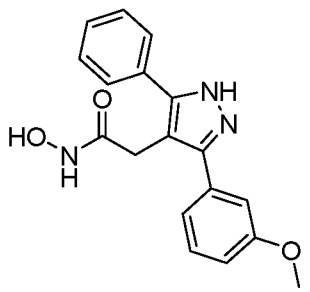
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 16	199 (1.03)	258 (1.03)	263 (1.01)	46 (1.09)	258 (1.16)	254 (1.15)
	Example 17	n.d.	1428 (1.13)	1390 (1.16)	n.d.	13701 (1.21)	13219 (1.18)
	Example 18	n.d.	63 (1.15)	62 (1.16)	n.d.	164 (1.14)	160 (1.14)
	Example 19	n.d.	75 (1.17)	71 (1.23)	n.d.	127 (1.09)	119 (1.15)
	Example 20	n.d.	908 (1.12)	903 (1.11)	n.d.	1187 (1.12)	1159 (1.15)

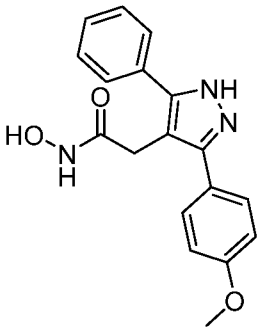
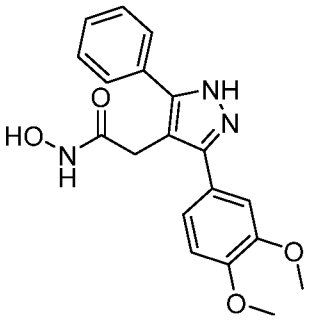
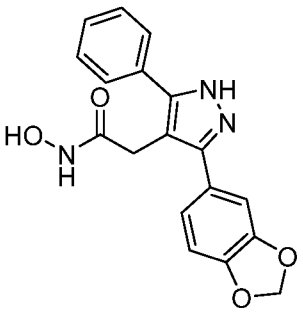
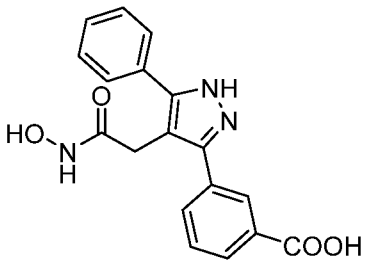
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 21	n.d.	443 (1.18)	435 (1.19)	n.d.	125 (1.15)	119 (1.17)
	Example 22	n.d.	6 (1.16)	6 (1.14)	n.d.	8 (1.19)	7 (1.20)
	Example 23	273 (1.03)	n.d.	n.d.	4556 (1.12)	n.d.	n.d.
	Example 24	1535 (1.29)	n.d.	n.d.	4174 (1.08)	n.d.	n.d.
	Example 25	72 (1.03)	n.d.	n.d.	1136 (1.13)	n.d.	n.d.
	Example 26	475 (1.06)	n.d.	n.d.	13372 (1.17)	n.d.	n.d.

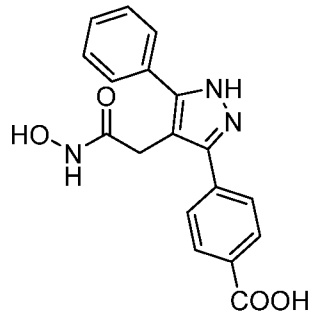
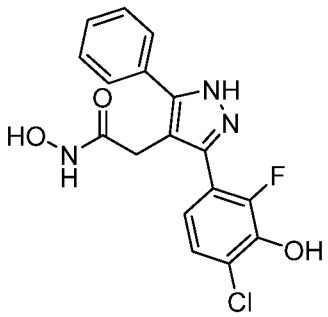
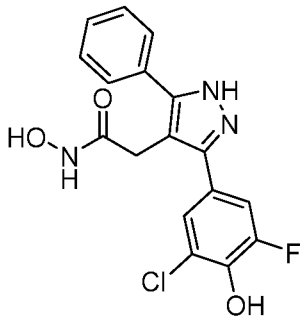
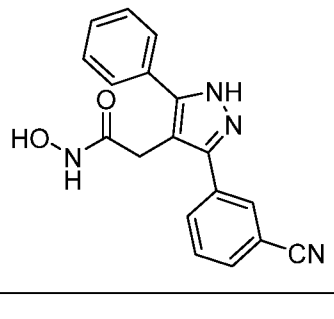
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 27	105 (1.13)	n.d.	n.d.	1205 (1.04)	n.d.	n.d.
	Example 28	135 (1.01)	92 (1.004)	90 (1.002)	23 (1.02)	81 (1.09)	80 (1.10)
	Example 29	793 (1.01)	n.d.	n.d.	7117 (1.07)	n.d.	n.d.
	Example 30	2284 (1.18)	n.d.	n.d.	176 (1.004)	n.d.	n.d.
	Example 31	693 (1.02)	n.d.	n.d.	214 (1.04)	n.d.	n.d.
	Example 32	655 (1.01)	n.d.	n.d.	3139 (1.04)	n.d.	n.d.

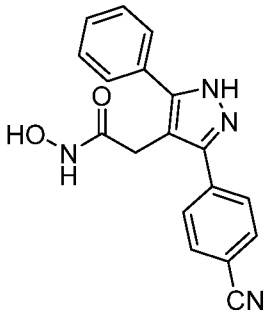
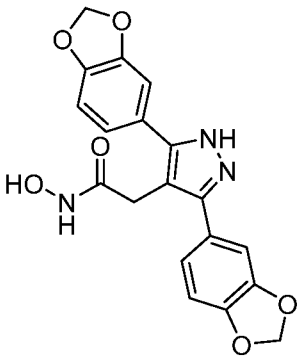
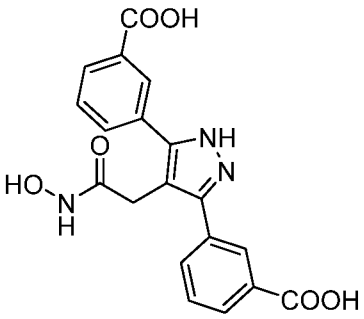
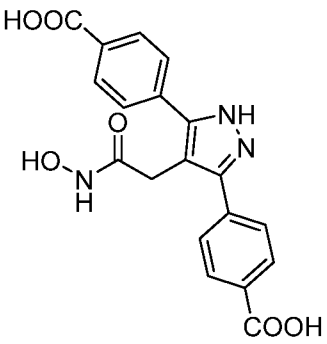
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 33	6745 (1.005)	n.d.	n.d.	3104 (1.09)	n.d.	n.d.
	Example 34	244 (1.06)	n.d.	n.d.	3365 (1.08)	n.d.	n.d.
	Example 35	9 (1.04)	n.d.	n.d.	1220 (1.00)	n.d.	n.d.
	Example 36	17 (1.06)	n.d.	n.d.	2378 (1.27)	n.d.	n.d.
	Example 37	21 (1.04)	n.d.	n.d.	154 (1.21)	n.d.	n.d.

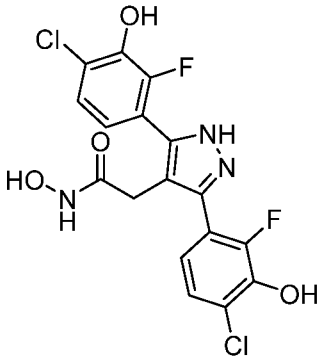
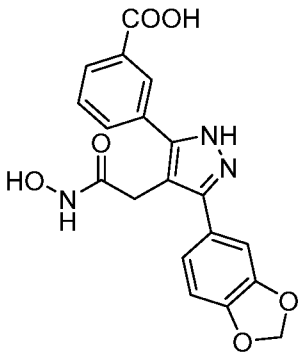
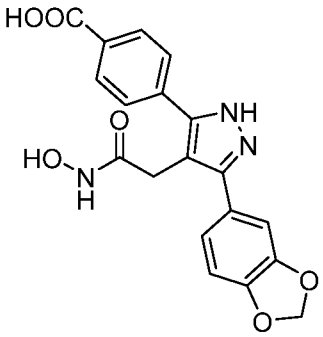
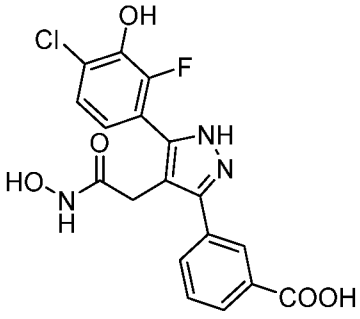
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 38	16 (1.04)	n.d.	n.d.	100 (1.05)	n.d.	n.d.
	Example 39	2 (1.04)	n.d.	n.d.	254 (1.15)	n.d.	n.d.
	Example 40	n.d.	0.45 (1.09)	0.38 (1.36)	n.d.	9 (1.04)	9 (1.16)
	Example 41	n.d.	0.39 (1.08)	0.33 (1.12)	n.d.	10 (1.12)	11 (1.14)
	Example 42	n.d.	0.16 (1.17)	0.08 (1.30)	n.d.	10 (1.10)	9 (1.04)

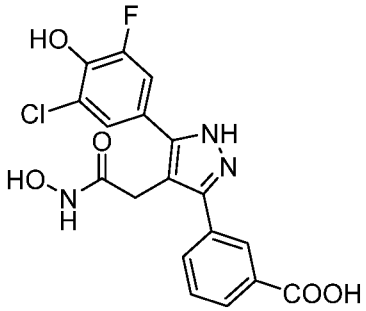
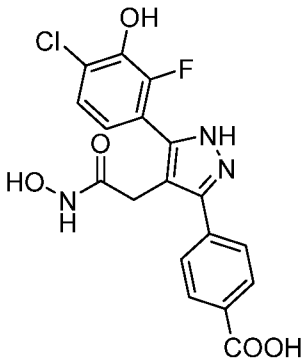
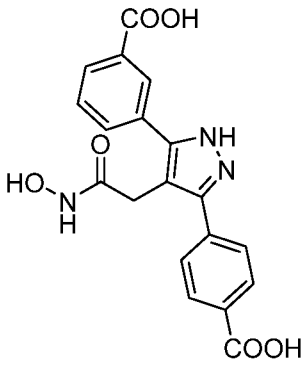
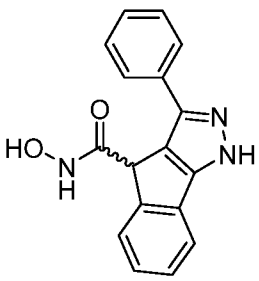
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 43	n.d.	0.75 (1.12)	0.59 (1.23)	n.d.	310 (1.03)	305 (1.02)
	Example 44	n.d.	310 (1.11)	302 (1.12)	n.d.	2165 (1.09)	2111 (1.10)
	Example 45	n.d.	6 (1.05)	6 (1.11)	n.d.	327 (1.05)	320 (1.06)
	Example 46	n.d.	71 (1.05)	70 (1.05)	n.d.	1784 (1.10)	1733 (1.11)
	Example 47	n.d.	1 (1.06)	1 (1.10)	n.d.	123 (1.15)	116 (1.14)

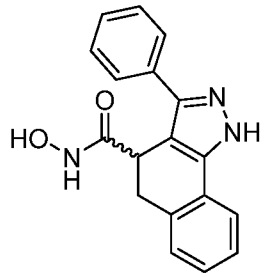
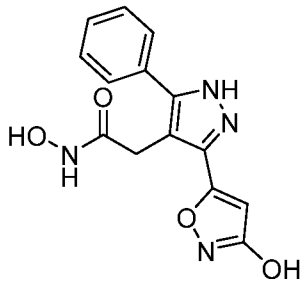
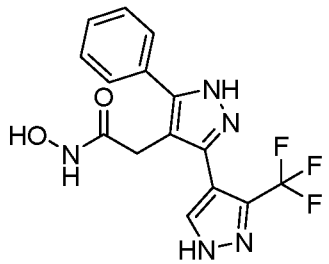
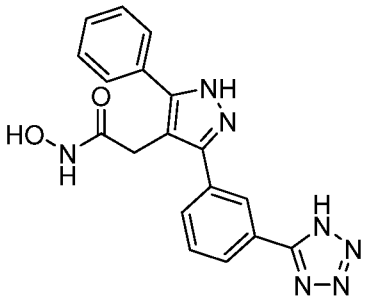
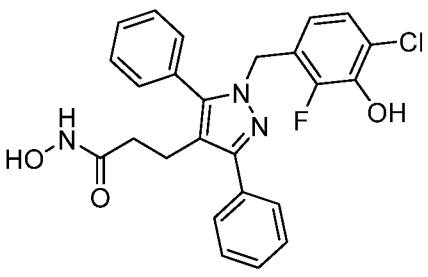
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 48	n.d.	1 (1.15)	1 (1.14)	n.d.	64 (1.07)	62 (1.04)
	Example 49	n.d.	0.79 (1.09)	0.71 (1.31)	n.d.	84 (1.04)	83 (1.05)
	Example 50	n.d.	1 (1.11)	1 (1.09)	n.d.	118 (1.11)	109 (1.09)
	Example 51	n.d.	8 (1.07)	8 (1.33)	n.d.	52 (1.09)	47 (1.16)

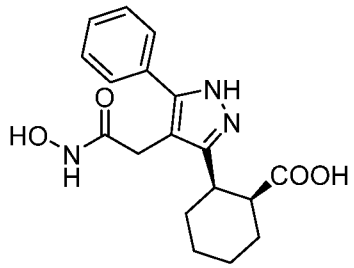
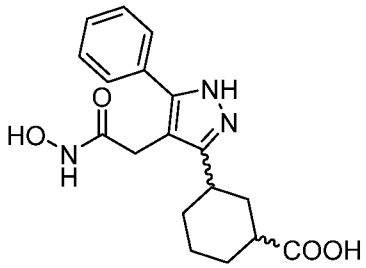
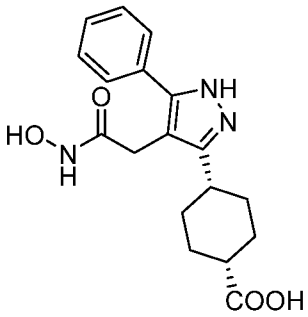
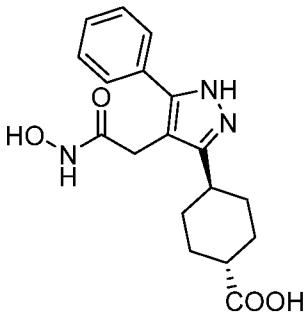
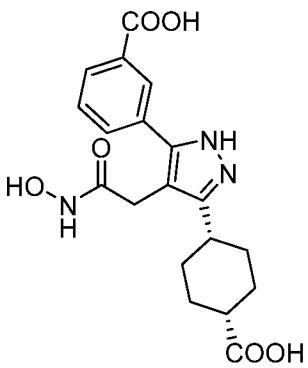
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 52	n.d.	18 (1.11)	17 (1.16)	n.d.	130 (1.05)	116 (1.15)
	Example 53	n.d.	3 (1.13)	2 (1.25)	n.d.	61 (1.10)	61 (1.10)
	Example 54	n.d.	0.21 (1.23)	0.14 (1.62)	n.d.	0.44 (1.12)	0.42 (1.14)
	Example 55	n.d.	5 (1.09)	5 (1.10)	n.d.	346 (1.05)	335 (1.06)

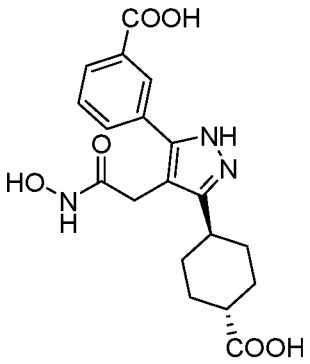
Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 56	n.d.	14 (1.04)	14 (1.04)	n.d.	1022 (1.15)	995 (1.14)
	Example 57	n.d.	0.72 (1.05)	0.64 (1.08)	n.d.	119 (1.10)	113 (1.12)
	Example 58	n.d.	11 (1.06)	10 (1.002)	n.d.	17 (1.07)	14 (1.22)
	Example 59	n.d.	56 (1.03)	56 (1.03)	n.d.	128 (1.11)	116 (1.01)

Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 60	n.d.	4 (1.08)	4 (1.08)	n.d.	14 (1.10)	14 (1.12)
	Example 61	n.d.	3 (1.09)	3 (1.14)	n.d.	45 (1.05)	44 (1.04)
	Example 62	n.d.	11 (1.03)	10 (1.05)	n.d.	94 (1.03)	93 (1.02)
	Example 63	n.d.	5 (1.01)	5 (1.02)	n.d.	4 (1.09)	4 (1.51)

Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 64	n.d.	0.24 (1.14)	0.14 (1.35)	n.d.	0.26 (1.10)	0.24 (1.13)
	Example 65	n.d.	10 (1.08)	10 (1.05)	n.d.	12 (1.09)	11 (1.06)
	Example 66	n.d.	21 (1.04)	20 (1.02)	n.d.	32 (1.09)	32 (1.17)
	Example 67	n.d.	40 (1.03)	39 (1.02)	n.d.	1789 (1.17)	1678 (1.18)

Structure	Com-pound ID	Meprin alpha			Meprin beta		
		IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*	IC_{50} [nM]*A	IC_{50} [nM]*B	K_i(app) [nM]*
	Example 68	n.d.	62 (1.04)	61 (1.07)	n.d.	2599 (1.12)	2530 (1.15)
	Example 69	n.d.	17 (1.16)	16 (1.26)	n.d.	14 (1.08)	14 (1.08)
	Example 70	n.d.	2 (1.13)	2 (1.14)	n.d.	89 (1.12)	88 (1.12)
	Example 71	n.d.	0.71 (1.12)	0.71 (1.09)	n.d.	7 (1.14)	7 (1.15)
	Example 72	n.d.	0.22 (1.07)	0.15 (1.21)	n.d.	1215 (1.10)	1184 (1.07)

	Example 73	n.d.	0.34 (1.14)	0.26 (1.27)	n.d.	33 (1.13)	33 (1.13)
	Example 74	n.d.	1 (1.09)	1 (1.11)	n.d.	55 (1.12)	55 (1.12)
	Example 75	n.d.	10 (1.13)	10 (1.14)	n.d.	35 (1.11)	35 (1.12)
	Example 76	n.d.	12 (1.13)	12 (1.12)	n.d.	98 (1.08)	98 (1.07)
	Example 77	n.d.	24 (1.15)	23 (1.18)	n.d.	15 (1.03)	15 (1.03)

	Example 78	n.d.	20 (1.11)	20 (1.10)	n.d.	21 (1.14)	21 (1.15)

** Geometric mean of independent experiments (geometric SD factor in parentheses).*

[A] IC_{50} values determined by using method A

[B] IC_{50} values determined by using method B

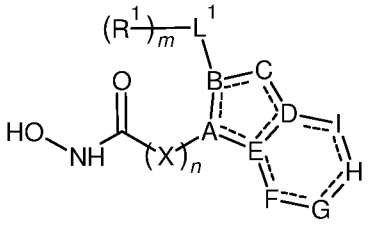
III. Inhibition of selected other metalloproteases

Table 3. Residual enzyme activity of other metalloproteases in the presence of 10 & 200 µM of selected inhibitor compounds.

	Residual enzyme activity [%] @ 10 & 200 µM inhibitor									
Compound ID	MMP2		MMP9		MMP13		ADAM10		ADAM17	
[µM]	10	200	10	200	10	200	10	200	10	200
Example 1	104	61	81	27	75	67	73	23	61	7
Example 2	87	34	86	16	80	31	80	22	62	9
Example 3	97	77	93	65	93	68	66	12	76	27
Example 4	98	74	89	39	79	66	75	21	75	24
Example 7	95	70	99	54	93	76	89	83	90	56
Example 9	83	1	92	1	79	5	83	29	82	25
Example 13	89	46	96	68	102	72	87	76	92	56
Example 16	93	83	94	50	105	84	86	78	92	82
Example 25	85	41	90	53	77	54	89	68	88	56
Example 40	85	24	80	30	86	22	91	43	67	9
Example 41	89	34	83	36	83	34	92	66	84	25
Example 42	69	18	70	14	84	9	85	34	72	14
Example 43	77	60	74	60	78	51	69	39	21	4
Example 47	78	17	80	33	85	28	68	8	52	6
Example 49	83	26	90	44	101	18	87	13	65	6
Example 50	41	8	72	16	71	10	59	5	51	5
Example 54	66	17	86	39	88	28	104	61	68	5
Example 57	29	3	63	10	56	6	62	0	57	4
Example 63	95	81	94	71	105	73	90	74	99	91

Claims

1. A compound according to the following Formula I,



I

its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein:

A is independently selected from and ;

B is independently selected from and ;

C is independently selected from ,  ,  , –O– and –S–;

F, if present, is independently selected from  ;

G, if present, is independently selected from  ;

H, if present, is independently selected from  ;

I, if present, is independently selected from  ;

wherein if F, G, H and I are present, then:

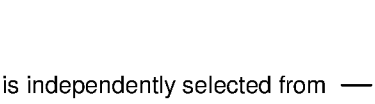
D is ,

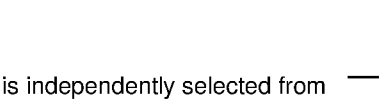
E is s independently elected from and , and

the ring formed by D, E, F, G, H and I is substituted by *p* substituents represented by R^2,

wherein *p* is 0, 1, 2, 3 or 4;

otherwise if F, G, H and I are absent, then:

D is independently selected from  , and

E is independently selected from  , wherein *p* is 0, 1, 2, 3, 4 or 5;

L^1 and L^2 are each independently selected from the group consisting of alkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring;

each X is independently selected form $C(R^a)R^b$, NR^a and O;

X and L^2 can be joined together to form a ring, wherein said ring can be optionally fused to aryl;

n is 1, 2, 3 or 4;

m is 0, 1, 2, 3, 4 or 5;

each R^1 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy;

each R^2 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy, hydroxy and heteroaryl;

each R^3 is independently selected from hydrogen and the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heterocyclyl fused to aryl, heteroaryl and heteroarylalkyl, each of which can be substituted by one or more groups independently selected from amino, halogen,

cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy; and

R^a and R^b are each independently selected from hydrogen, deuterium and C_{1-3} alkyl,

wherein, unless otherwise specified:

said aryl is independently a monocyclic or bicyclic C_{6-10}, preferably C_6 aryl group;

said heterocyclyl is independently a monocyclic or bicyclic C_{2-11}, preferably C_{2-8}, more preferably C_{3-5} heterocyclic group comprising 1 to 4 ring heteroatoms selected from N, S and O;

said heteroaryl is independently a monocyclic or bicyclic C_{2-11} preferably C_{2-8}, more preferably C_{3-5} aromatic heterocyclic group comprising 1 to 3 ring heteroatoms selected from N, S and O;

said alkyl or alk is independently a linear or branched, open-chained or cyclic C_{1-12}, preferably C_{1-6}, more preferably C_{1-3}, even more preferably C_{1-2} alkyl group;

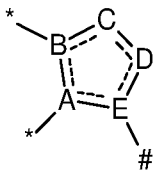
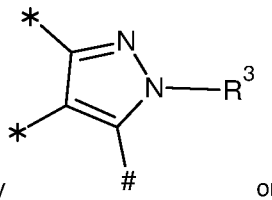
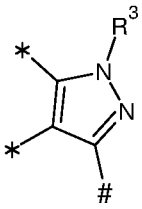
said alkenyl is independently a linear or branched, open-chained or cyclic C_{2-12}, preferably C_{2-4}, more preferably C_{2-3}, even more preferably C_2 group comprising at least one C=C bond;

said alkynyl is independently a linear or branched, open-chained or cyclic C_{2-12}, preferably C_{2-6}, more preferably C_{2-4}, even more preferably C_{2-3} group comprising at least one C≡C bond;

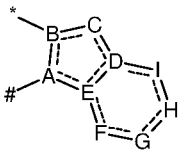
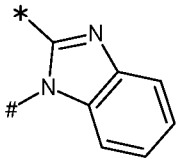
said cycloalkyl is independently a C_{3-12}, preferably C_{3-6}, monocyclic or bicyclic alkyl group;

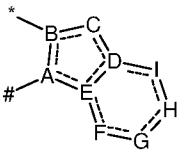
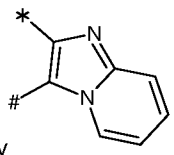
said cycloalkenyl is independently C_{3-12}, preferably C_{4-6}, more preferably C_{5-6} carbocyclic group comprising at least one C=C bond;

wherein each of the above groups can be substituted by one or more groups selected from halogen, carboxy, cyano, methoxy and hydroxy,

wherein when the ring fragment  is represented by  or  ,
then:

R^3 is selected from hydrogen and the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, substituted aryl, optionally substituted arylalkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl wherein optionally substituted or substituted refers, respectively, to optional substitution or substitution by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), $-C(O)NH_2$, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy;

when the ring fragment  is represented by  , then at least one of *m* and *p* is larger than 0; and

when the ring fragment  is represented by  , then *m* is larger than 0.

2. The compound according to claim 1, wherein L^1 and L^2 are each independently selected from the group consisting of aryl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring;

each X is independently selected form $C(R^a)R^b$, NR^a and O;

n is 1, 2, 3 or 4;

m is 0, 1, 2, 3, 4 or 5;

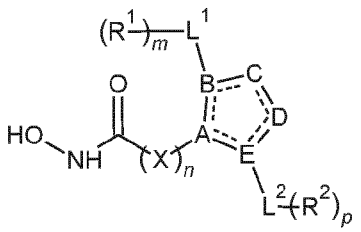
R^1 is selected from the group consisting of halogen, cyano, hydroxy,
carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), $-C(O)-NH_2$, alkylsulfono, a functional group having an acidic

hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy;

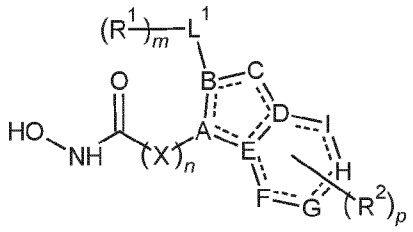
each R^2 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy.

each R^3 is independently selected from hydrogen and the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be substituted by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy.

3. The compound according to claim 1 or 2, which is represented by one the following Formulae Ia and Ib:

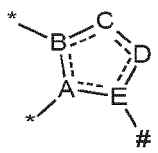


Ia

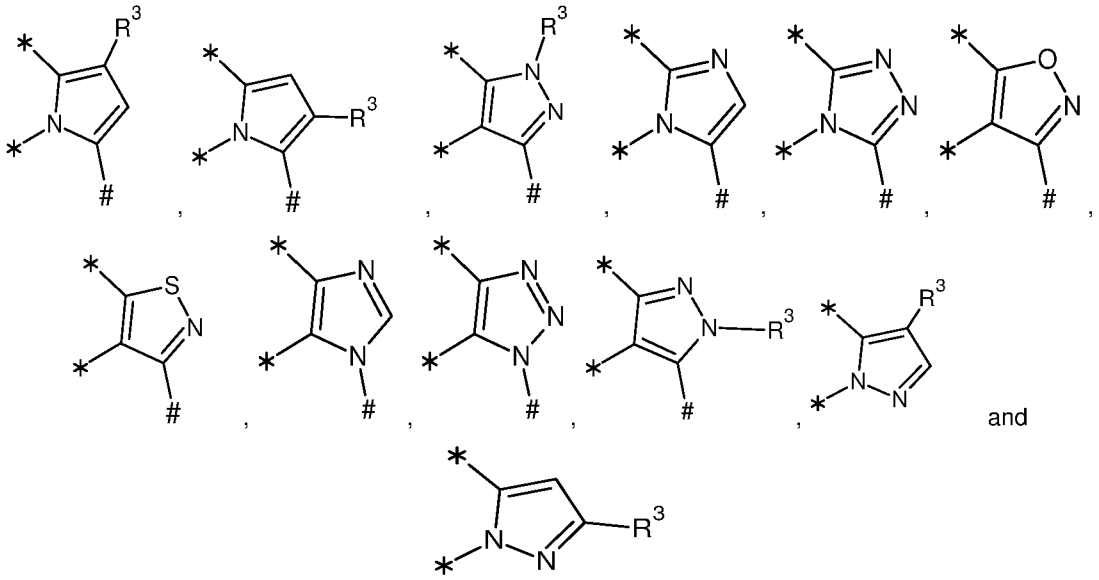


Ib.

4. The compound according to any one of claims 1, 2 or 3, wherein if F, G, H and I are absent, the ring fragment



is represented by one of the following structures:



and

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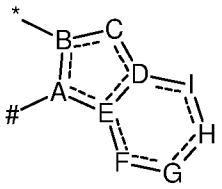
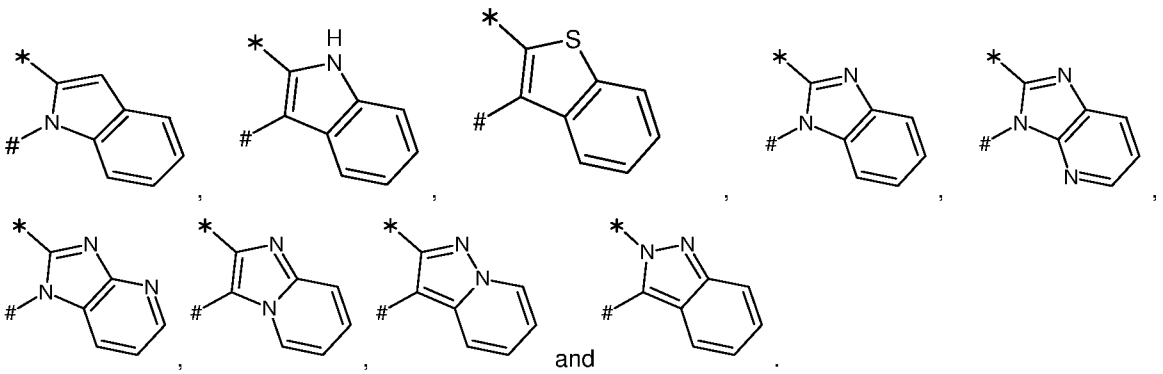
5. The compound according to any one of claims 1 to 4, wherein if F, G, H and I are present, the ring fragment



is represented by one of the following structures:



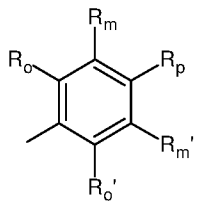
and

.

6. The compound according to any of claims 1 to 5, wherein R^1 and R^2 are the same or different and are each independently selected from the group consisting of chloro, fluoro, bromo, iodo, cyano, C_1-C_6 alkoxy, C_1-C_6 alkyl, fluoro(C_{1-6} alkyl), fluoro(C_{1-6} alkoxy), and a functional group having an acidic hydrogen selected from hydroxy, carboxy, -SO_3H, -$P(O)(OH)_2$, -C(O)-NH-OH tetrazol-5-yl, -SO_3H, -$P(O)(OH)_2$, -C(O)-NH-OH and tetrazol-5-yl.

7. The compound according to any of claims 1 to 6, wherein $L^1(R^1)_m$ and $L^2(R^2)_p$ are the same or different and:

(a) each independently represented by the following structure:



wherein:

(i) at least one of R_o, R_o', R_m, R_m' and R_p, is a functional group having an acidic hydrogen selected from hydroxy, carboxy, $-SO_3H$, $-P(O)(OH)_2$, -C(O)-NH-OH and tetrazol-5-yl, and the remaining ones are either H or as defined for R^1 or R^2 according to any one of the preceding claims; and/or

(ii) at least two of R_o, R_o', R_m, R_m' and R_p are alkoxy groups that are joined together as a part of a 5- to 8-membered heterocycle, and the remaining ones are H or as defined for R^1 or R^2 according to any one of the preceding claims; and/or

(b) each independently selected from the group consisting of 2-carboxyphenyl, 3-carboxyphenyl, 4-carboxyphenyl, 3-chlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-methylphenyl, 4-carboxyphenyl, 4-chlorophenyl, 4-cyanophenyl, 4-fluorophenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 4-methylphenyl, 3-carboxy-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-chloro-2-fluoro-3-hydroxyphenyl, 5-chloro-3-fluoro-4-hydroxyphenyl, 3-chloro-5-fluoro-4-hydroxyphenyl, 3,5-dichloro-4-hydroxyphenyl, 2,6-difluoro-4-methoxyphenyl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzodioxol-5-yl, 3-(trifluoromethyl)-1H-pyrazol-4-yl, 3-(1H-tetrazol-5-yl)phenyl, 2-carboxycyclohexyl, 3-carboxycyclohexyl, 3-carboxycyclohexyl and (1,3-benzodioxol-5-yl)methyl.

8. The compound according to any of claims 1 to 7, wherein each R^3 is independently selected from:

(a) hydrogen and the group consisting of C_{1-6} alkyl, carboxy(C_{1-6} alkyl), amino(C_{1-6} alkyl), cyano(C_{1-6} alkyl), C_{2-6} alkynyl, C_{3-6} cycloalkyl, carboxy(C_{6-10} aryl), C_{1-6} alkoxy(C_{6-10} aryl), cyano(C_{6-10} aryl), halo(C_{6-10} aryl), hydroxy(C_{6-10} aryl), C_{1-6} alkoxy(C_{2-8} heteroaryl), cyano(C_{2-8} heteroaryl), halo(C_{2-8} heteroaryl), C_{3-5} heteroaryl(C_{6-10} aryl), hydroxy(C_{2-8} heteroaryl), carboxy(C_{2-8}

heteroaryl), (C_{6-10} aryl)methyl, (C_{1-6} alkoxy(C_{6-10} aryl))methyl, (hydroxy(C_{6-10} aryl))methyl, (carboxy(C_{6-10} aryl))methyl, (C_{1-6} alkoxy(C_{2-8} heteroaryl))methyl, (C_{2-8} heteroaryl-(C_{6-10}aryl))methyl, (hydroxy(C_{2-8} heteroaryl))methyl and (carboxy(C_{2-8} heteroaryl))methyl, each of which can be further substituted by one or more groups independently selected from chloro, fluoro, bromo, iodo, carboxy cyano, C_{1-6} alkyl, C_1-C_6 alkoxy and hydroxy; and/or

(b) hydrogen and the group consisting of methyl, ethyl, 2-propyl, 1-propyl, phenyl, 2-aminoethyl, propargyl, cyclopropyl, $-CH_2COOH$, $-CH_2CN$, phenyl, 3-carboxyphenyl, 3-chlorophenyl, 3-cyanophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-methylphenyl, 4-carboxyphenyl, 4-chlorophenyl, 4-cyanophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-methylphenyl, 3-carboxy-4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-chloro-2-fluoro-3-hydroxyphenyl, 3-chloro-5-fluoro-4-hydroxyphenyl, 3,5-dichloro-4-hydroxyphenyl, 2,6-difluoro-4-methoxyphenyl, 1,3-benzodioxol-5-yl, benzyl, (3-carboxyphenyl)methyl, (3-chlorophenyl)methyl, (3-cyanophenyl)methyl, (3-fluorophenyl)methyl, (3-methoxyphenyl)methyl, (3-methylphenyl)methyl, (4-carboxyphenyl)methyl, (4-chlorophenyl)methyl, (4-cyanophenyl)methyl, (4-fluorophenyl)methyl, (4-methoxyphenyl)methyl, (4-methylphenyl)methyl, (3-carboxy-4-methoxyphenyl)methyl, (3-fluoro-4-methoxyphenyl)methyl, (4-chloro-2-fluoro-3-hydroxyphenyl)methyl, (3-chloro-5-fluoro-4-hydroxyphenyl)methyl, (3,5-dichloro-4-hydroxyphenyl)methyl, (2,6-difluoro-4-methoxyphenyl)methyl, (2,3-dihydro-1,4-benzodioxin-6-yl)methyl, (1,3-benzodioxol-5-yl)methyl, *para*-methyl-benzoic acid, and *meta*-methyl-benzoic acid.

9. The compound according to any of claims 1 to 8, wherein:

each X is $C(R^a)R^b$, wherein one of the $C(R^a)R^b$ groups can be replaced by a NR^a group;

n is 1 or 2;

m is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

L^1 is phenyl;

L^2 is phenyl;

R^1 is independently selected from Cl, F, OH, CN, OCH_3 and COOH, and/or two R^1 groups together form part of a 1,3-benzodioxol ring or a 2,3-dihydro-1,4-benzodioxin ring;

R^2 is independently selected from Cl, F, OH, CN, OCH_3 and COOH, and/or two R^2 groups together form part of a 1,3-benzodioxol ring or a 2,3-dihydro-1,4-benzodioxin ring;

R^3 is selected from hydrogen, methyl, ethyl, propargyl, cyclopropyl, 2-aminoethyl, $-CH_2COOH$, $-CH_2CN$, benzyl, unsubstituted phenyl, and substituted phenyl selected from 3-carboxyphenyl and 4-carboxyphenyl; and

R^a and R^b are hydrogen.

10. The compound according to any of claims 1 to 19, wherein

X is $C(R^a)R^b$;

n is 1; and

at least one of *m* and *p* is larger than 0.

11. The compound according to any of claims 1 to 8, wherein:

each X is $C(R^a)R^b$;

n is 1 or 2;

m is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

L^1 is phenyl;

L^2 is cyclohexyl;

R^1 is COOH,

R^2 is COOH;

R^3 is hydrogen; and

R^a and R^b are hydrogen.

12. The compound according to any of claims 1 to 8, wherein:

each X is $C(R^a)R^b$, wherein one of the $C(R^a)R^b$ groups can be replaced by a NR^a group;

n is 1 or 2;

m is 0, 1, 2 or 3;

p is 0, 1, 2 or 3;

L^1 is phenyl;

L^2 is phenyl;

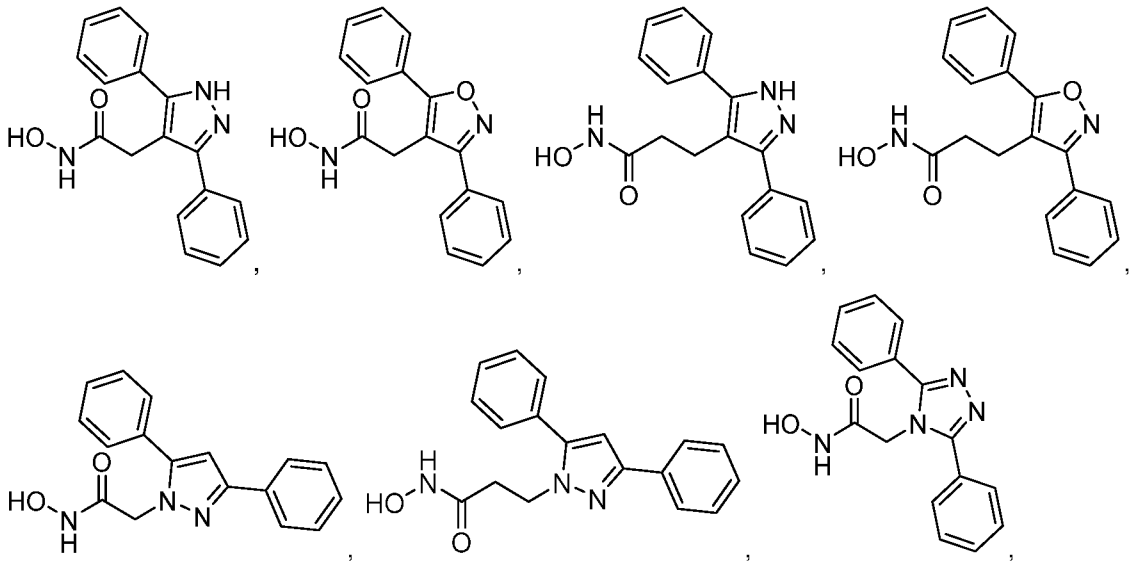
R^1 is independently selected from Cl, F, OH, CN, OCH_3 and COOH, and/or two R^1 groups together form part of a 1,3-benzodioxol ring or a 2,3-dihydro-1,4-benzodioxin ring; preferably R^1 is hydrogen;

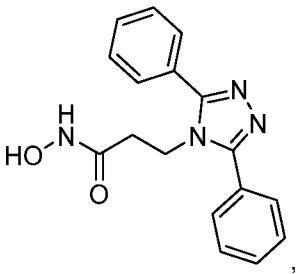
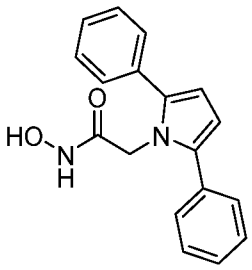
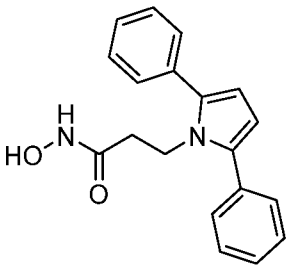
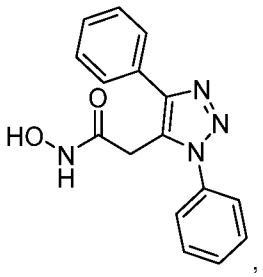
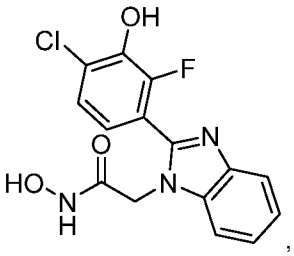
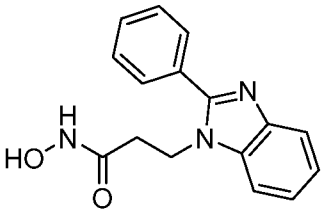
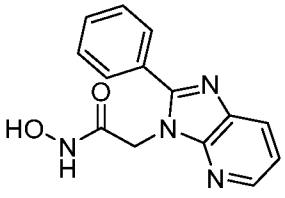
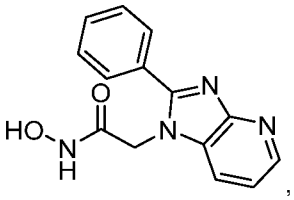
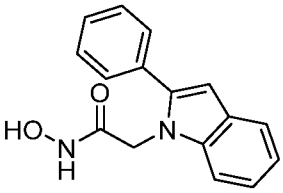
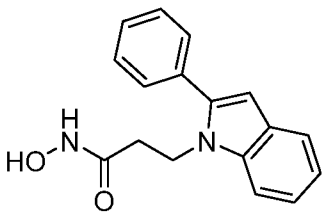
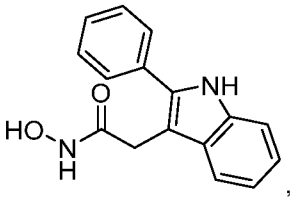
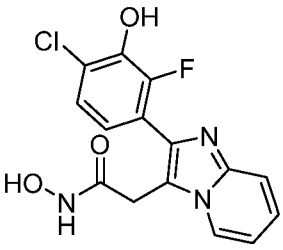
R^2 is a bioisosteric replacement of an acidic group, preferably R^3 is tetrazole;

R^3 is selected from hydrogen, methyl, ethyl, propargyl, cyclopropyl, 2-aminoethyl, $-CH_2COOH$, $-CH_2CN$, benzyl, unsubstituted phenyl, and substituted phenyl selected from 3-carboxyphenyl and 4-carboxyphenyl; preferably R^3 is hydrogen; and

R^a and R^b are hydrogen.

13. The compound according to any of claims 1 to 12 selected from the group consisting of:



 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
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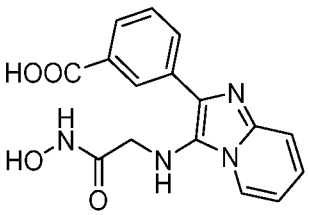
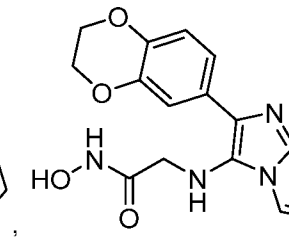
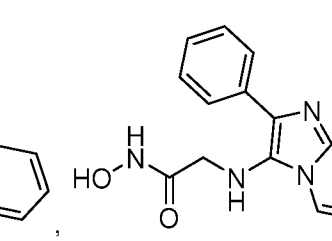
 ,
 ,
 ,
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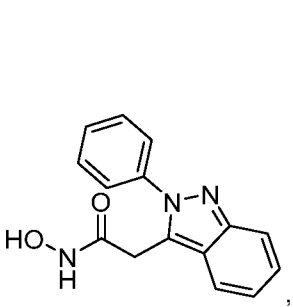
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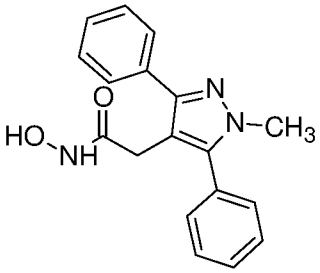
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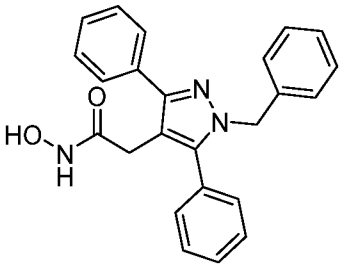
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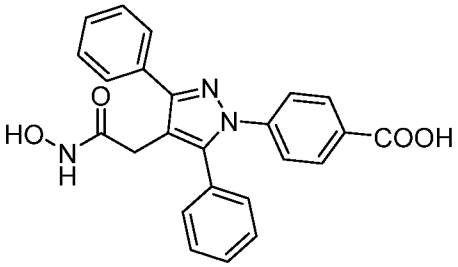
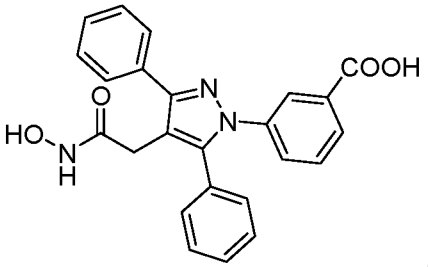
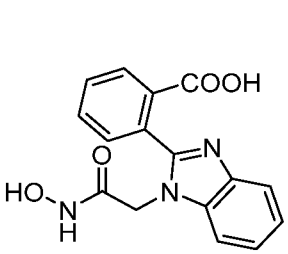


and .

14. The compound according to any of claims 1 to 12 selected from the group consisting of: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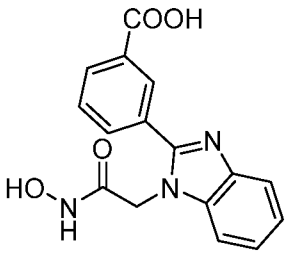
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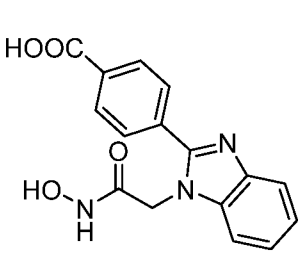
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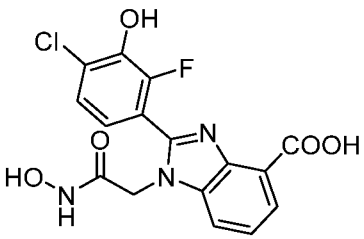
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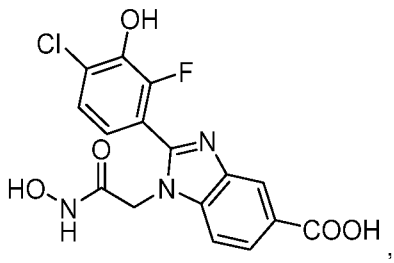
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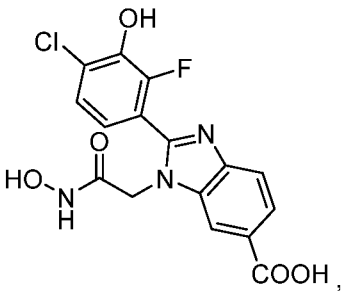
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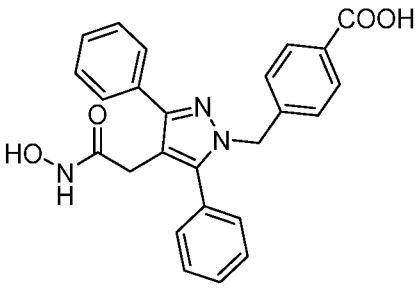
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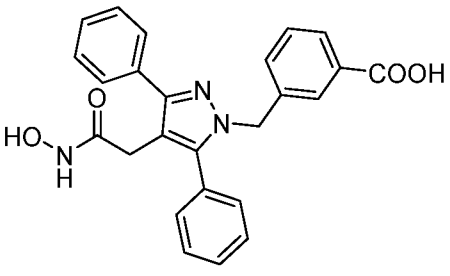
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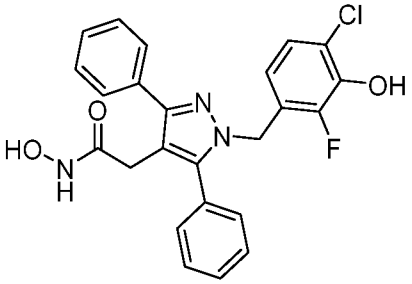
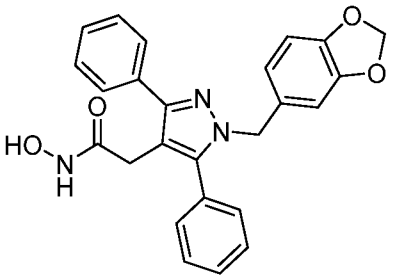
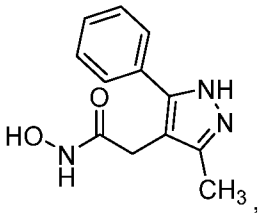
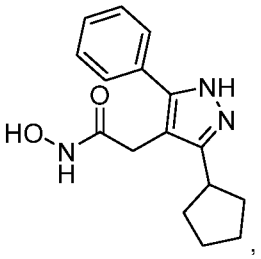
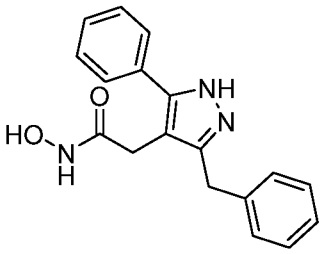
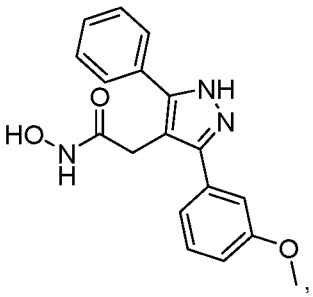
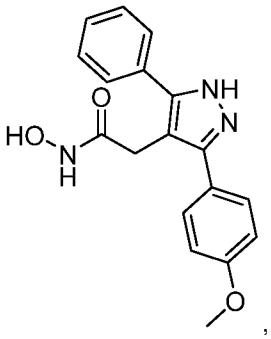
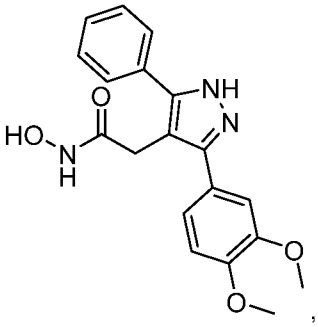
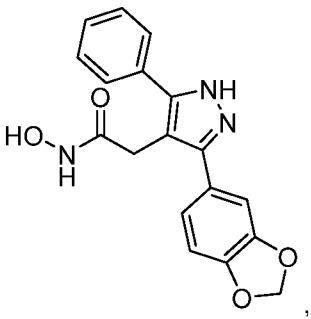
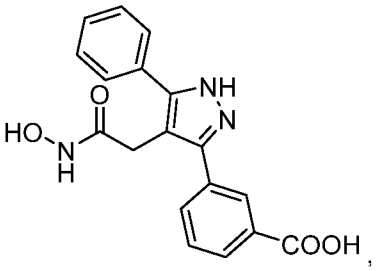
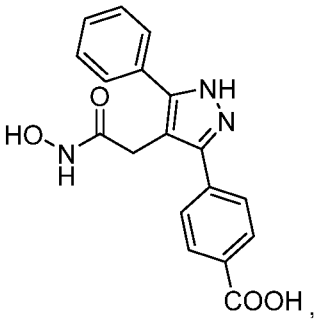
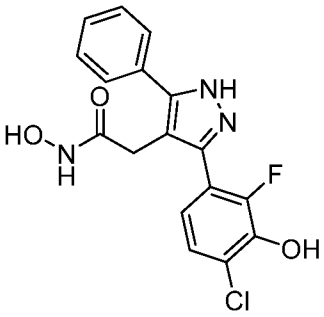
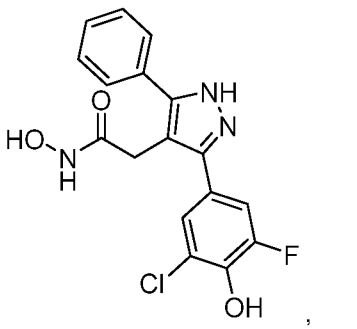
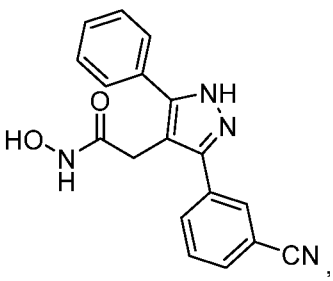
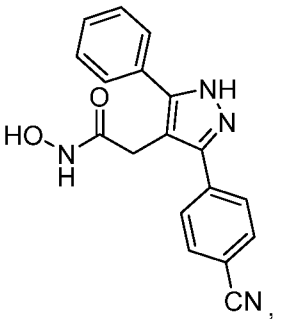
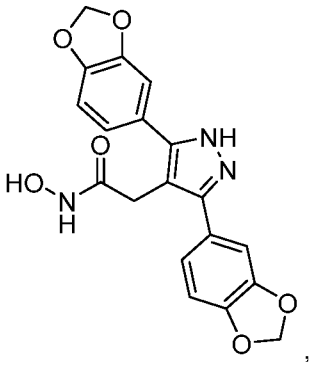

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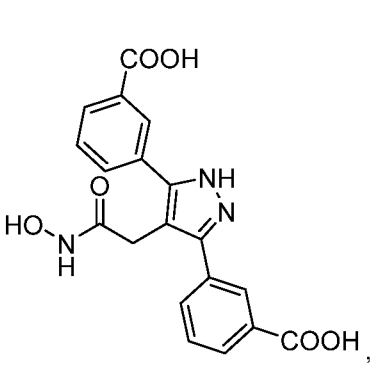
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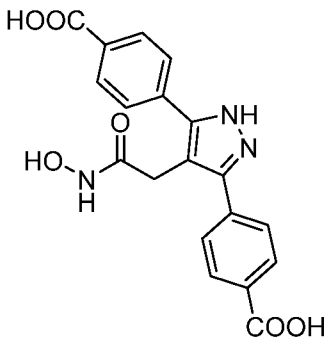
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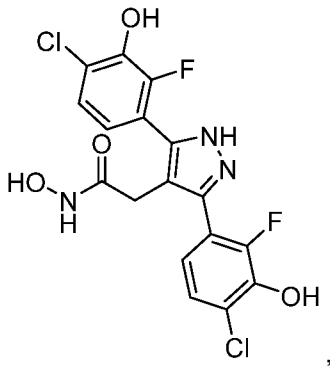
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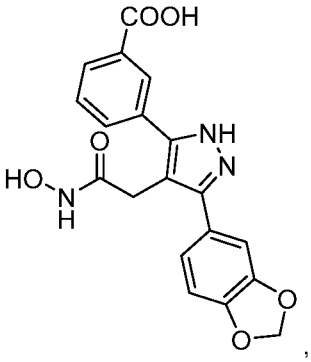
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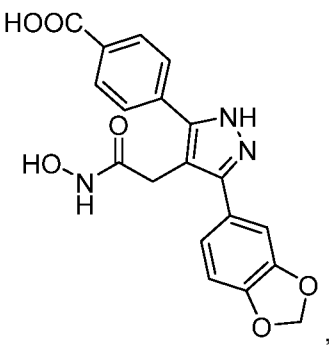
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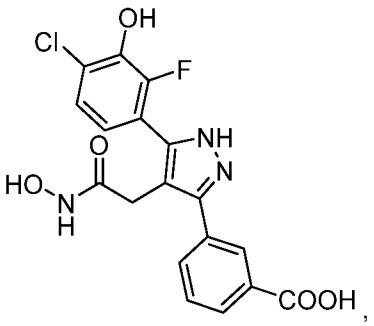
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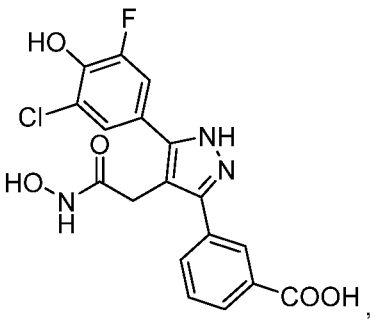
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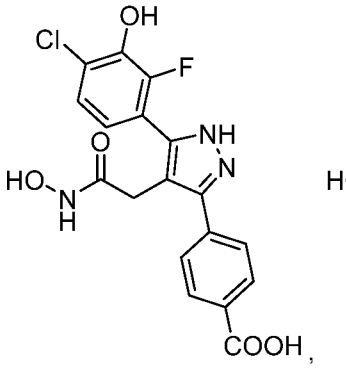
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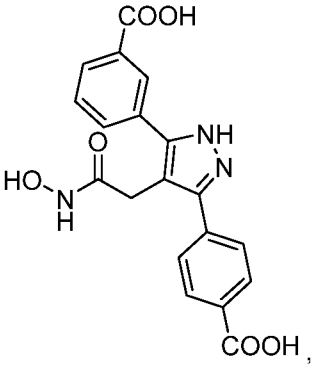
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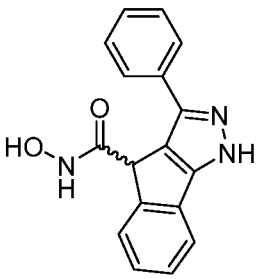
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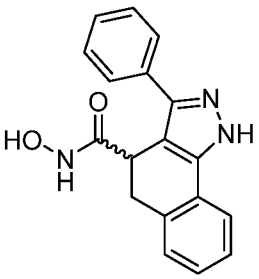
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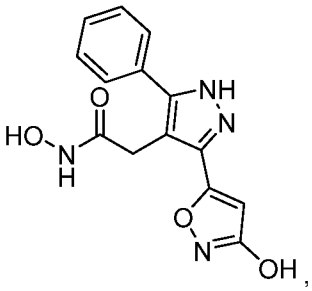
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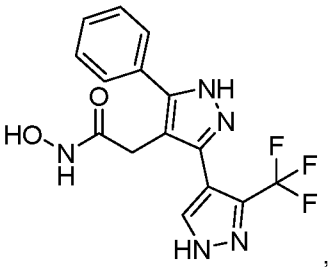
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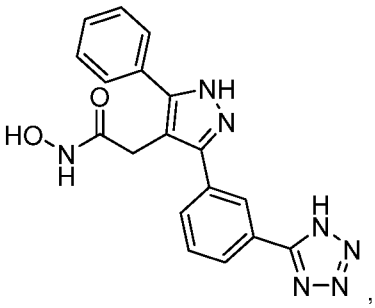
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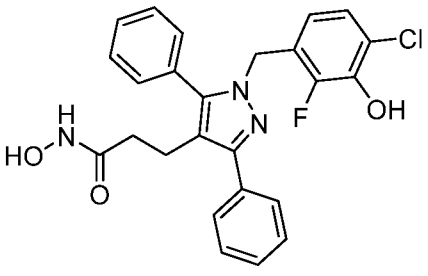
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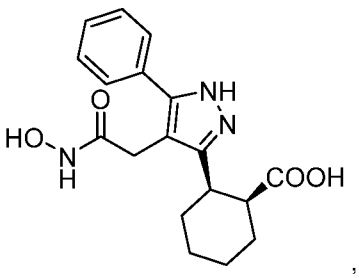
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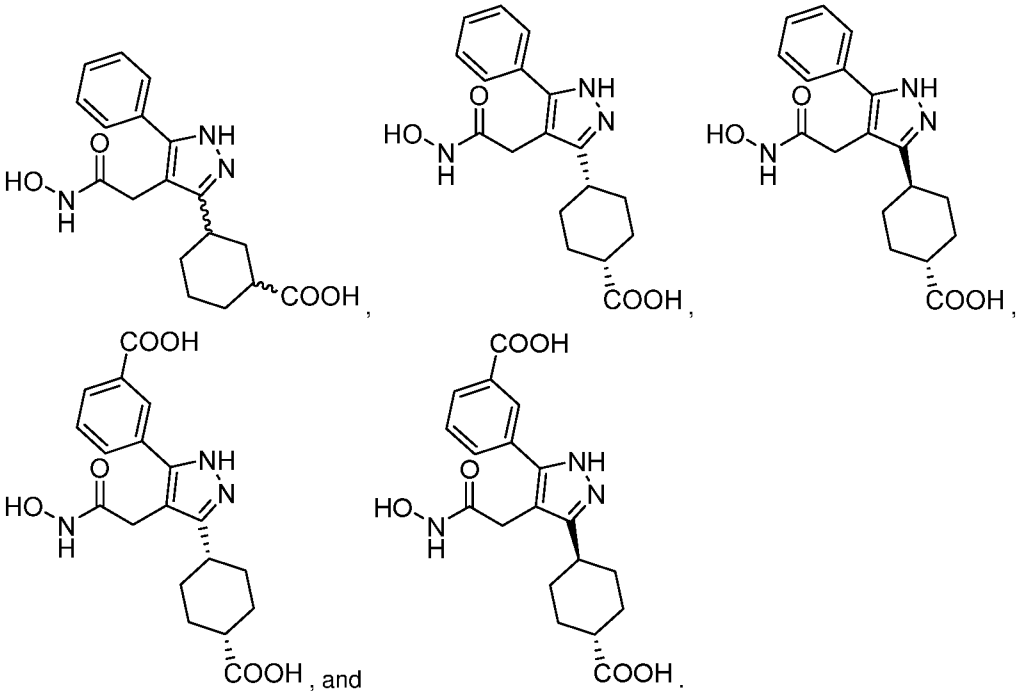
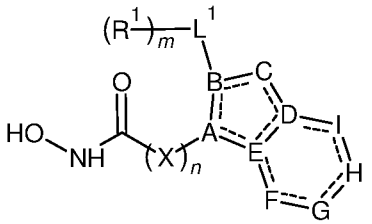


15. A pharmaceutical composition comprising the compound according to any of claims 1 to 14 and a pharmaceutically acceptable excipient.

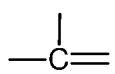
16. A compound according to any of claims 1 to 14 or a pharmaceutical composition according to claim 15 for use in a method for treatment of the human or animal body.

17. A compound according to the following Formula I,



I

its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, wherein:

A is independently selected from  and ;

B is independently selected from and ;

C is independently selected from , , , –O– and –S–;

F, if present, is independently selected from and ;

G, if present, is independently selected from and ;

H, if present, is independently selected from and ;

I, if present, is independently selected from and ;

wherein if F, G, H and I are present, then:

D is ,

E is s independently elected from and , and

the ring formed by D, E, F, G, H and I is substituted by *p* substituents represented by R^2,

wherein *p* is 0, 1, 2, 3 or 4;

otherwise if F, G, H and I are absent, then:

D is independently selected from , and , and

E is independently selected from and , wherein *p* is 0, 1, 2, 3, 4 or 5;

L^1 and L^2 are each independently selected from the group consisting of alkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring;

each X is independently selected form $C(R^a)R^b$, NR^a and O;

X and L^2 can be joined together to form a ring, wherein said ring can be optionally fused to aryl;

n is 1, 2, 3 or 4;

m is 0, 1, 2, 3, 4 or 5;

each R^1 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy;

each R^2 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy, hydroxyl and heteroaryl;

each R^3 is independently selected from hydrogen and the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heterocyclyl fused to aryl, heteroaryl and heteroarylalkyl, each of which can be substituted by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy; and

R^a and R^b are each independently selected from hydrogen, deuterium and C_{1-3} alkyl,

or a pharmaceutical composition comprising said compound according and a pharmaceutically acceptable excipient for use in a method for therapy or prevention of diseases and conditions selected from:

(a) Alzheimer's disease; nephritis; renal injury; renal ischemic injury; ischemic acute tubular necrosis; acute renal failure; bladder inflammation; inflammatory bowel disease (IBD); Crohn's disease; ulcerative colitis; chronic inflammation; colitis; fibrosis; fibrotic conditions; keloids; pulmonary hypertension; interstitial lung disease (ILD); cancer; colorectal cancer;

(b) fibrosis; acute fibrotic disorders and conditions; chronical fibrotic disorders and conditions; fibrosis occurring in organs and/or accompanying diseases and conditions selected from hepatitis, liver cirrhosis, hypertension, myocardial infarction, heart failure, asthma, pulmonary hypertension, scleroderma, fibrotic skin and internal organs, diabetes, diabetes nephropathy, atherosclerosis and fibrotic blood vessels; hypertrophic dermal scarring; keloids; pulmonary fibrosis; acute CNS scarring following traumatic injury; neuronal regeneration following stroke or spinal cord injury; obliterative fibrosis of the hollow structures within grafts; chronic allograft rejection; wound healing disorders; post-surgical scarring; dermal scarring; fibrosis resulting from gynecological procedures; fibrosis after eye surgery; fibrosis following angioplasty; fibrosis following surgery on joints; preventing local invasion, recurrence and metastasis of malignant keratinocytes or squamous cell carcinomas (SCCs);

(c) mammalian infertility; therapeutic use for *in vitro* fertilization (IVF) treatment of a mammal;

(d) nematode infections; infections caused by *Teladorsagia circumcincta*; infections caused by *Haemonchus contortus*; and infections caused by *Brugia malayi*.

18. The compound or pharmaceutical composition for use according to claim 17, wherein

L^1 and L^2 are each independently selected from the group consisting of aryl, heterocyclyl, heteroaryl, cycloalkyl and cycloalkenyl, wherein L^1 and L^2 can be joined together to form a ring;

each X is independently selected form $C(R^a)R^b$, NR^a and O;

n is 1, 2, 3 or 4;

m is 0, 1, 2, 3, 4 or 5;

each R^1 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxy;

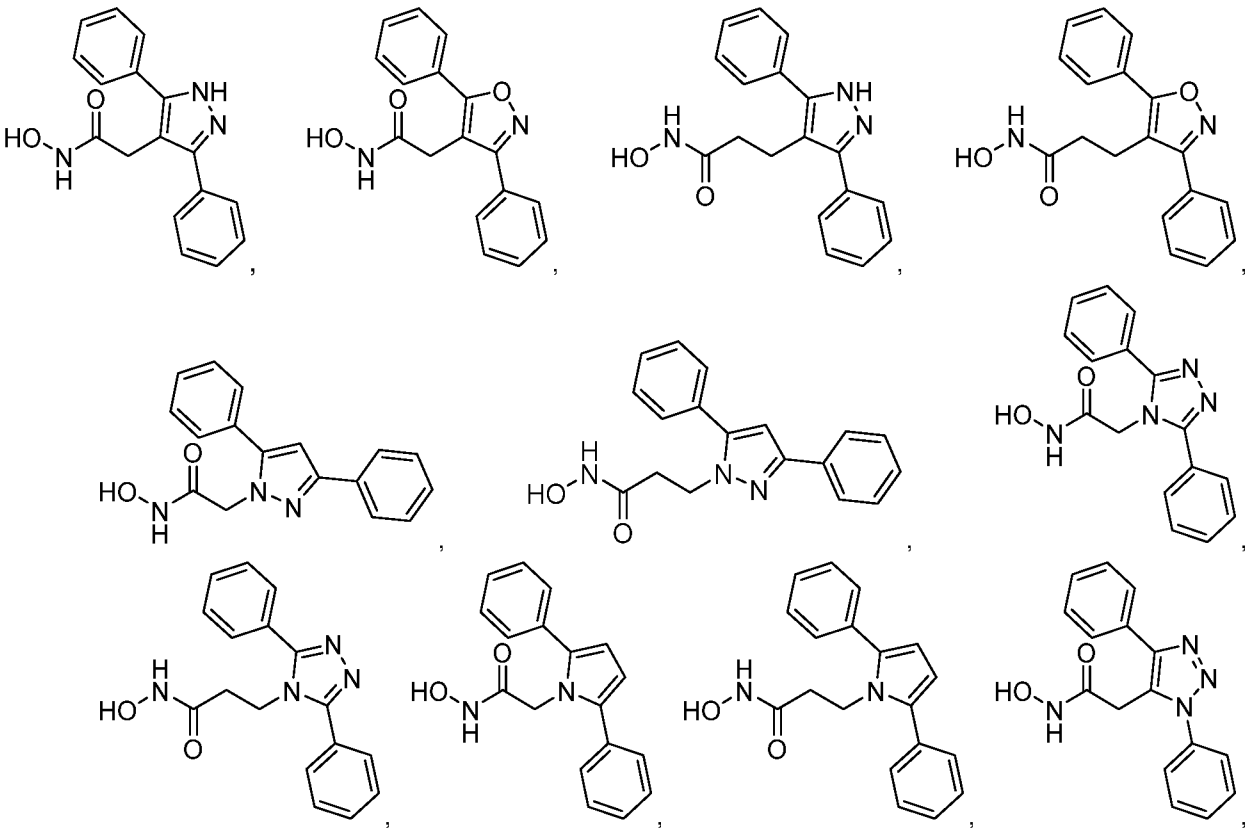
each R^2 is independently selected from the group consisting of halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH(alkyl), -C(O)-NH_2, alkylsulfono, a functional group having an acidic

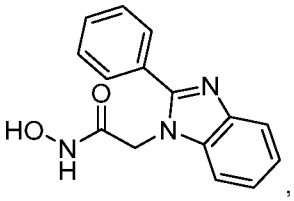
hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl group, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkoxy and hydroxyl;

each R^3 is independently selected from hydrogen and the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be substituted by one or more groups independently selected from amino, halogen, cyano, hydroxy, carboxy, -C(O)O(alkyl), -C(O)NH_2, -C(O)NH(alkyl), alkylsulfono, a functional group having an acidic hydrogen, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, heterocyclyl, heteroaryl and heteroarylalkyl, each of which can be further substituted by one or more groups independently selected from halogen, carboxy, cyano, alkyl, alkoxy and hydroxy; and

R^a and R^b are each independently selected from hydrogen, deuterium and C_{1-3} alkyl.

19. A compound selected from the group consisting of:

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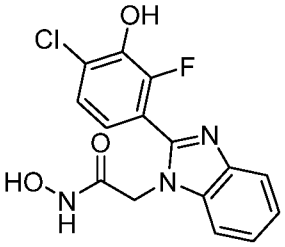
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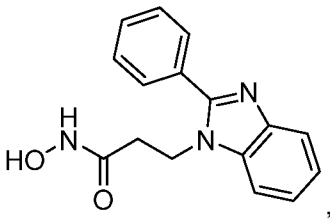
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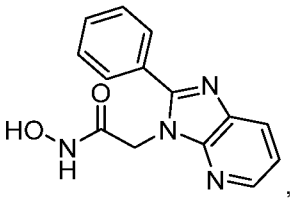
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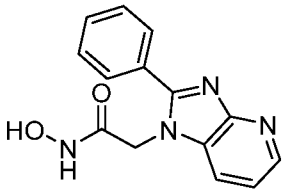
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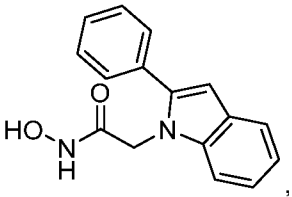
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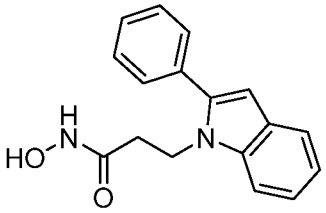
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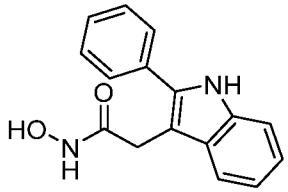
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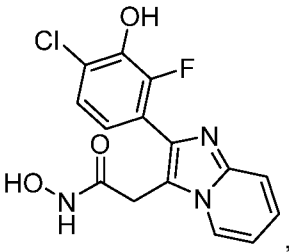
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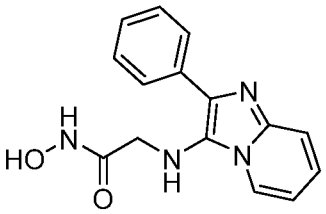
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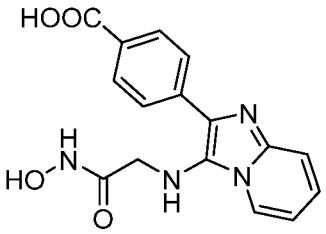
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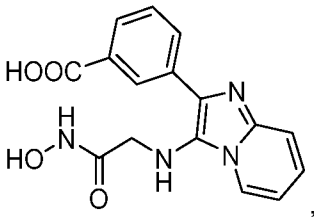
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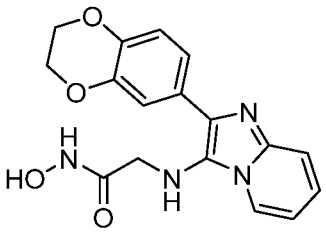
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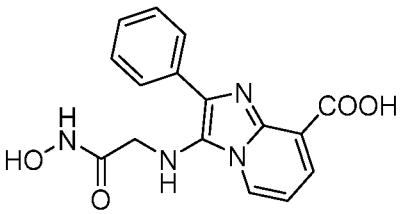
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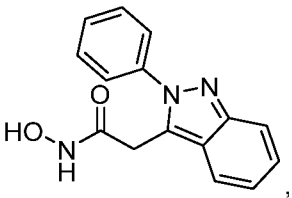
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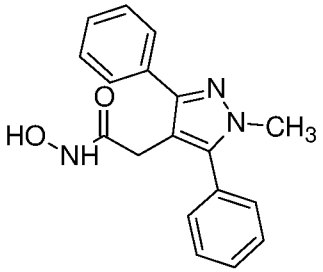
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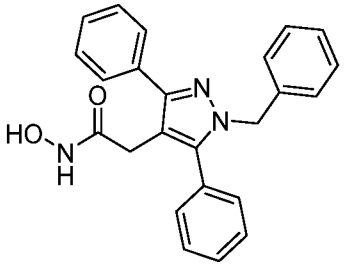
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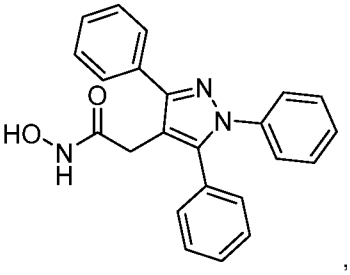
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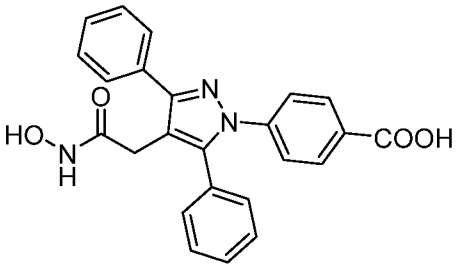
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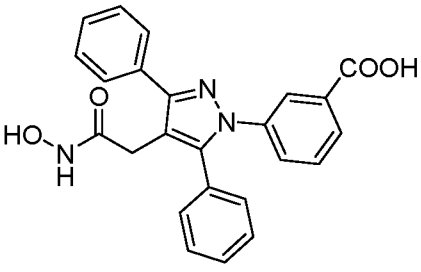
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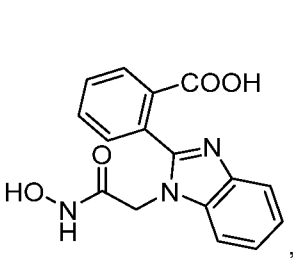
its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising said compound and a pharmaceutically acceptable excipient for use in a method according to claim 17.

20. A compound selected from the group consisting of: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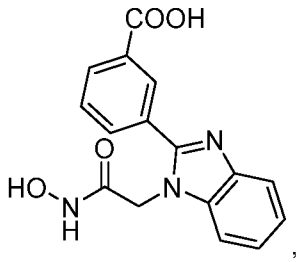
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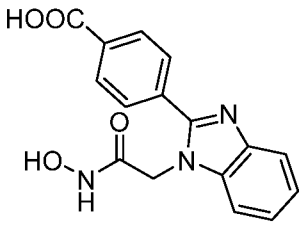
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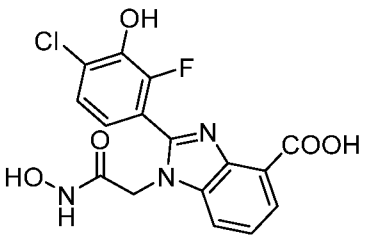
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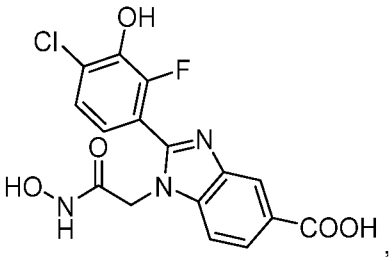
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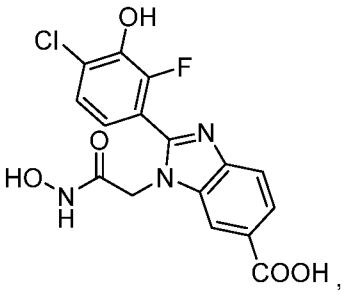
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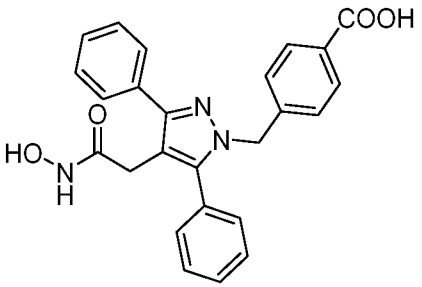
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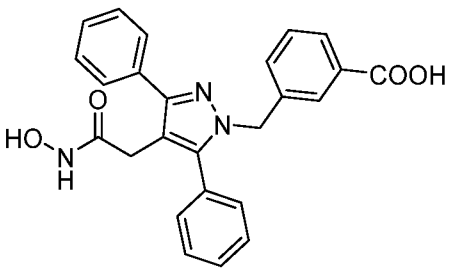
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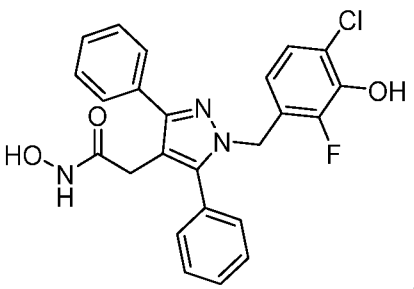
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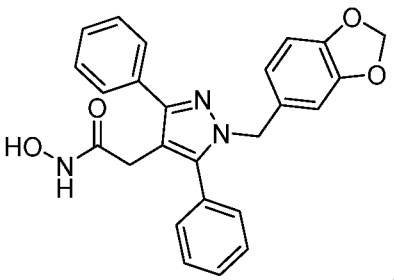
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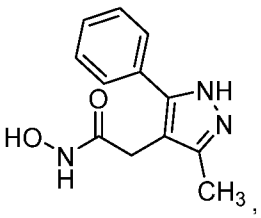
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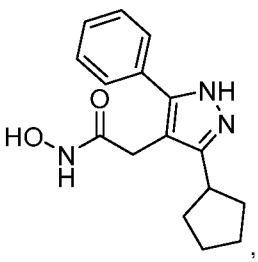
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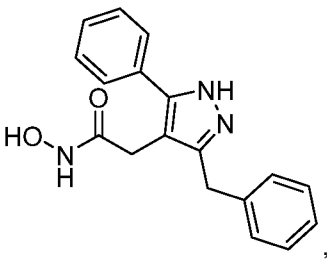
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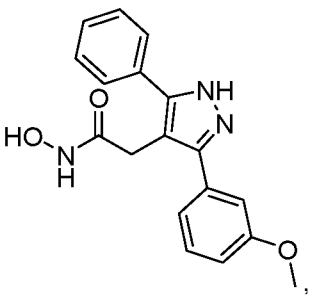
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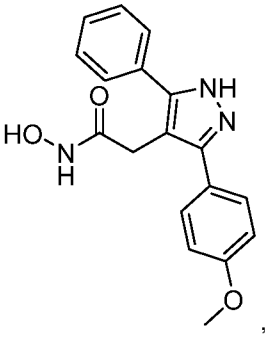
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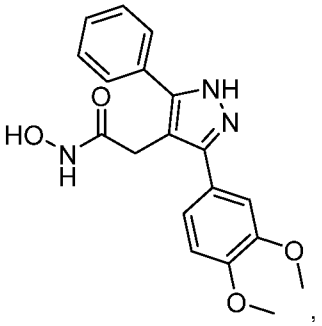
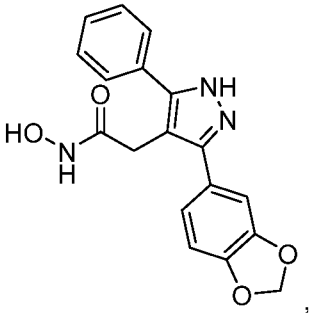
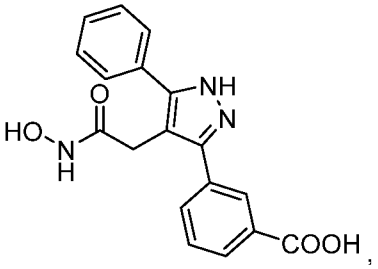
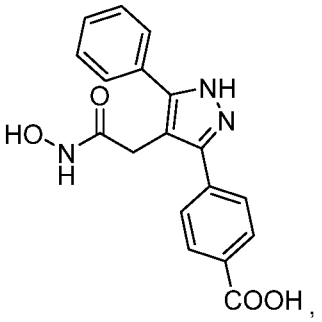
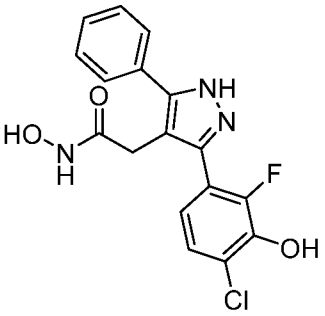
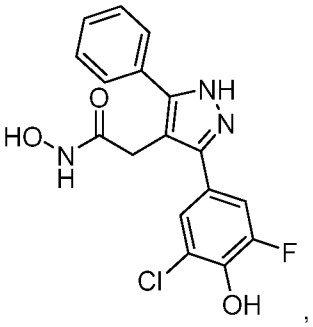
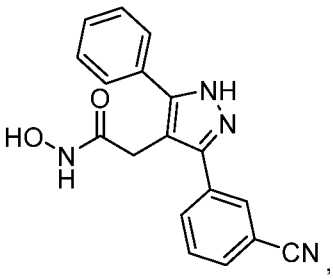
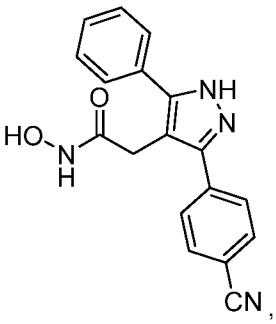
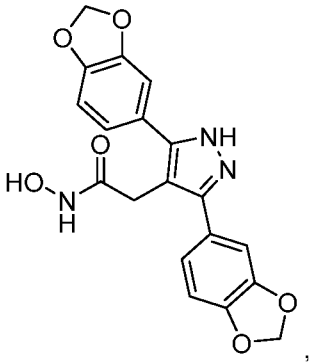
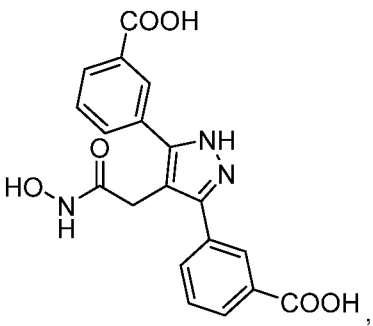
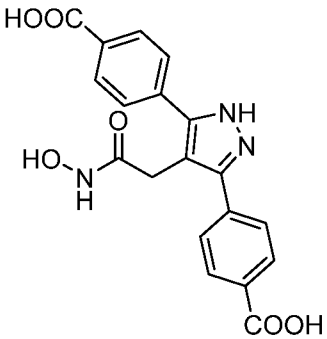
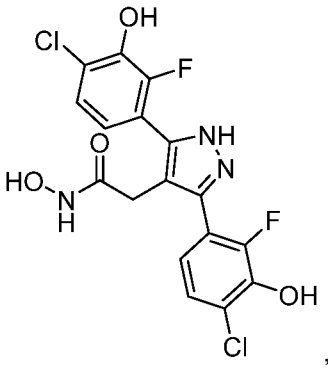
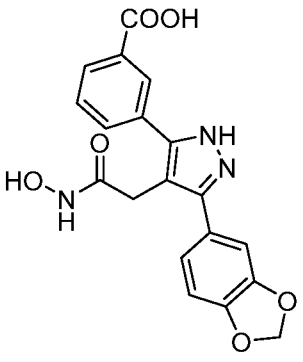
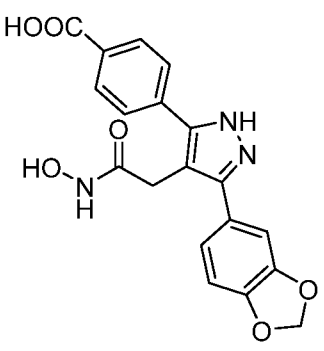
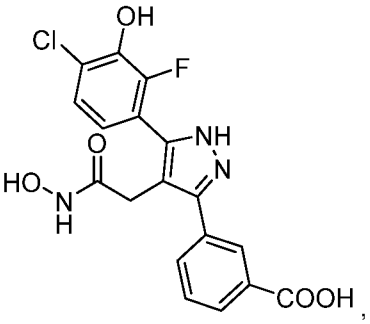

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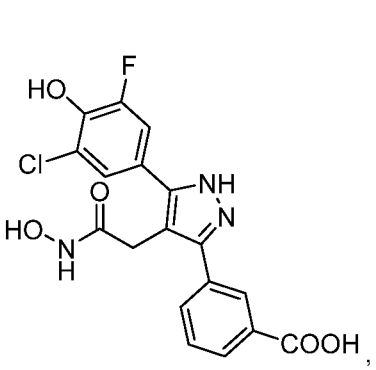
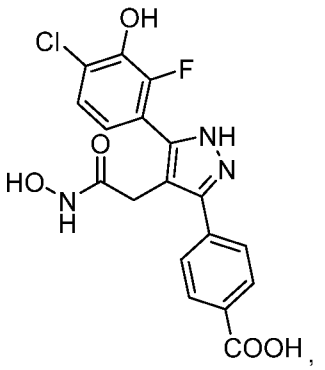
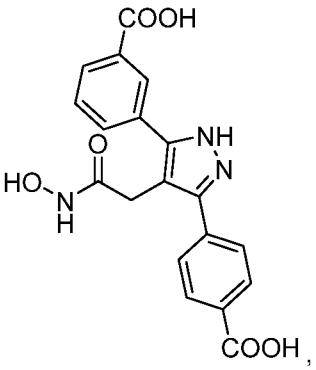
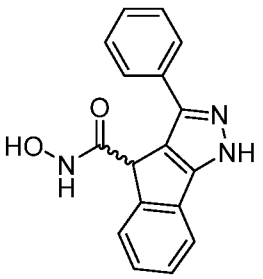
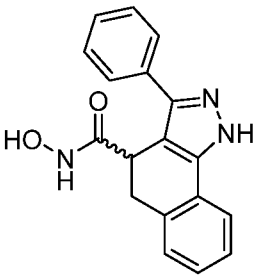
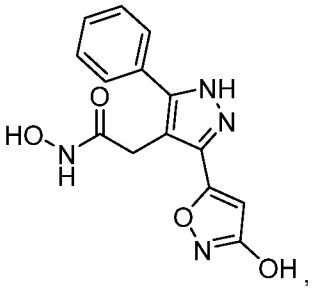
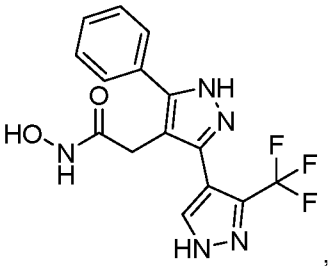
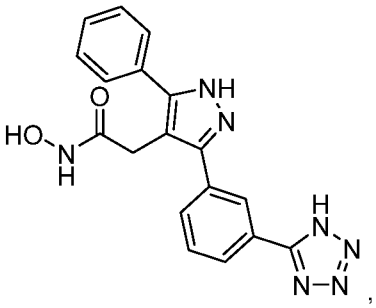
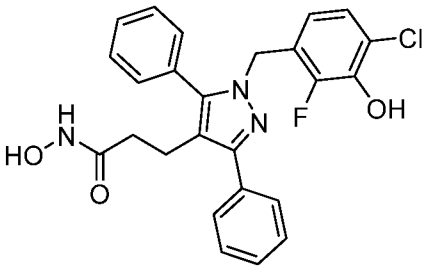
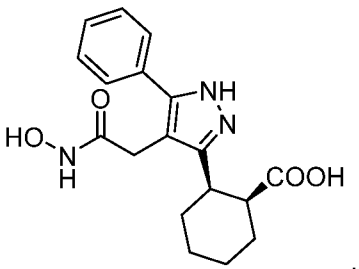
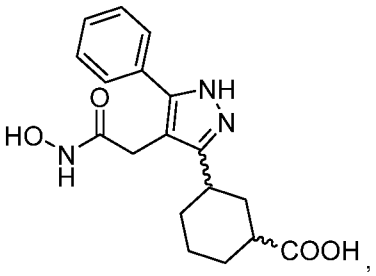
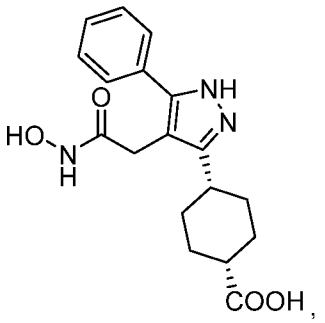
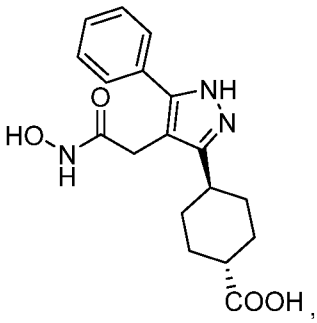
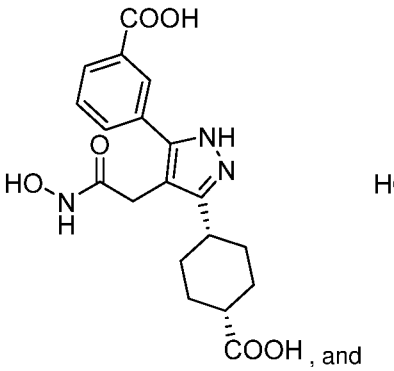
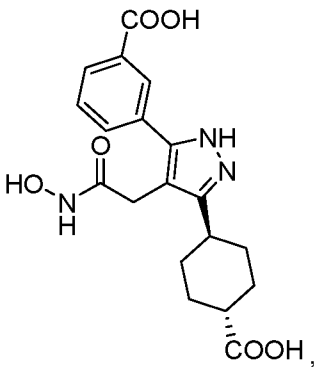

and

its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual tautomers or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition

comprising said compound and a pharmaceutically acceptable excipient for use in a method according to claim 17.

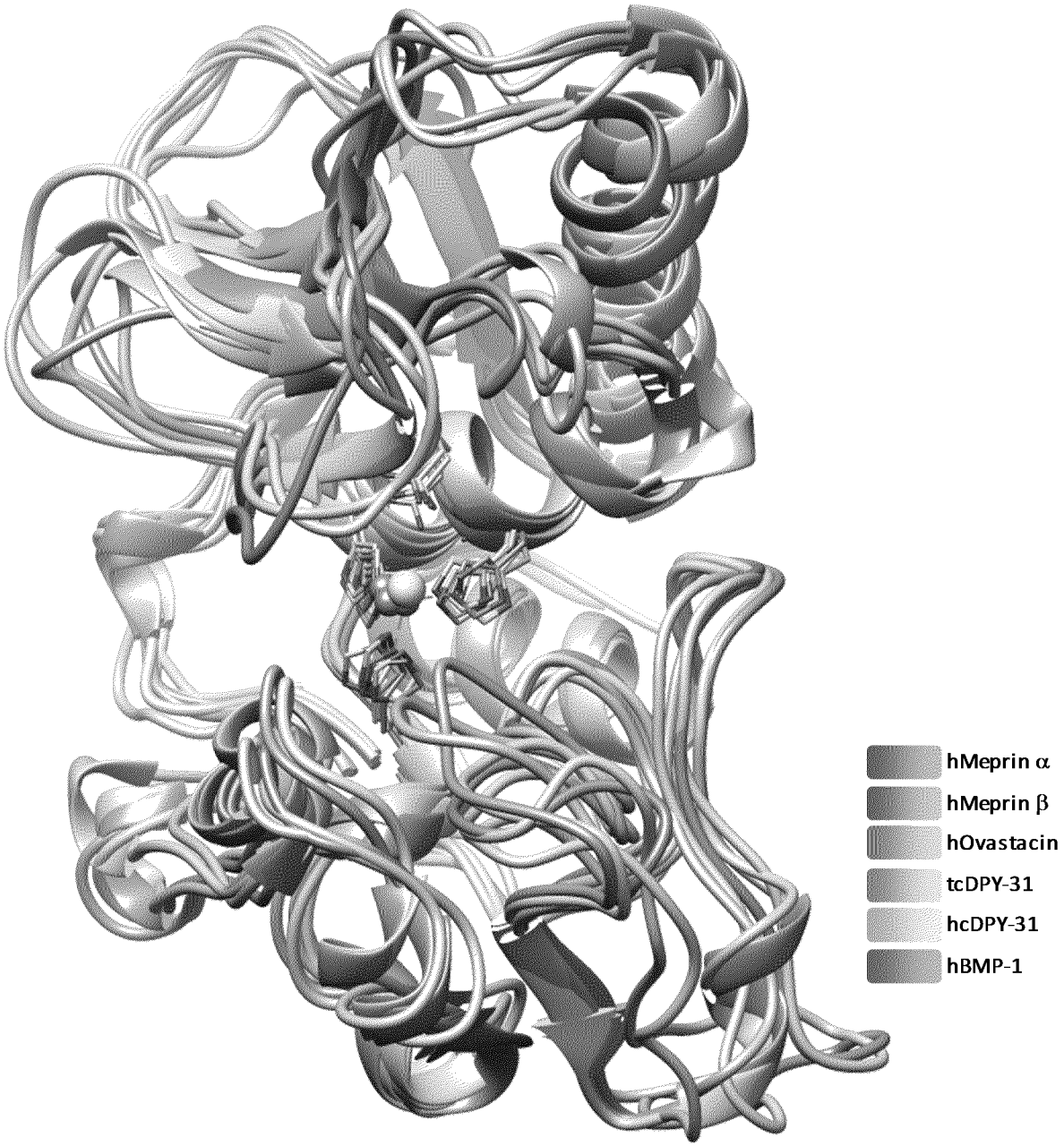

FIG. 1

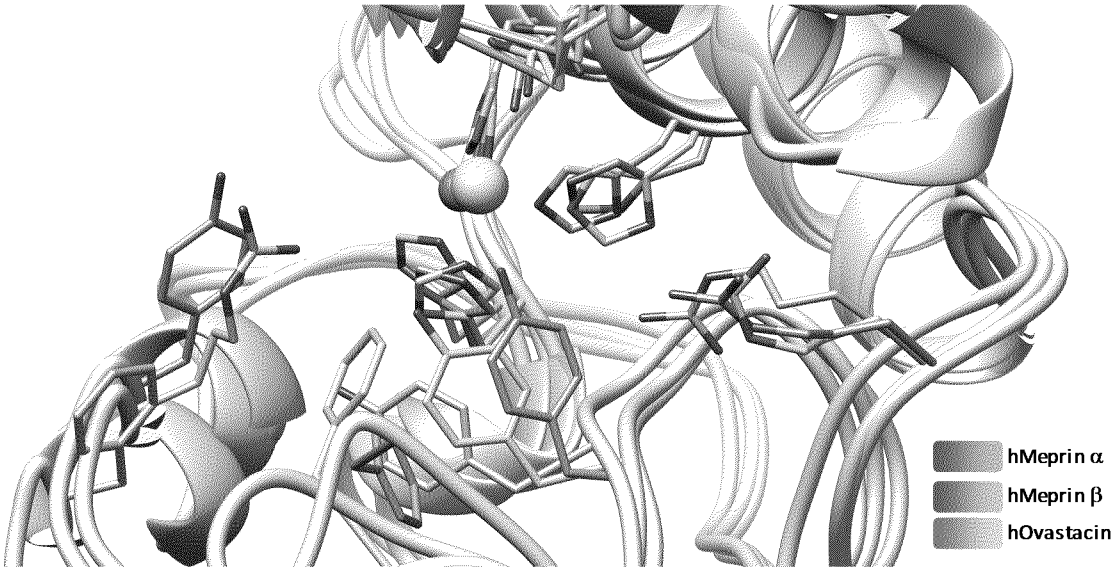

FIG. 2

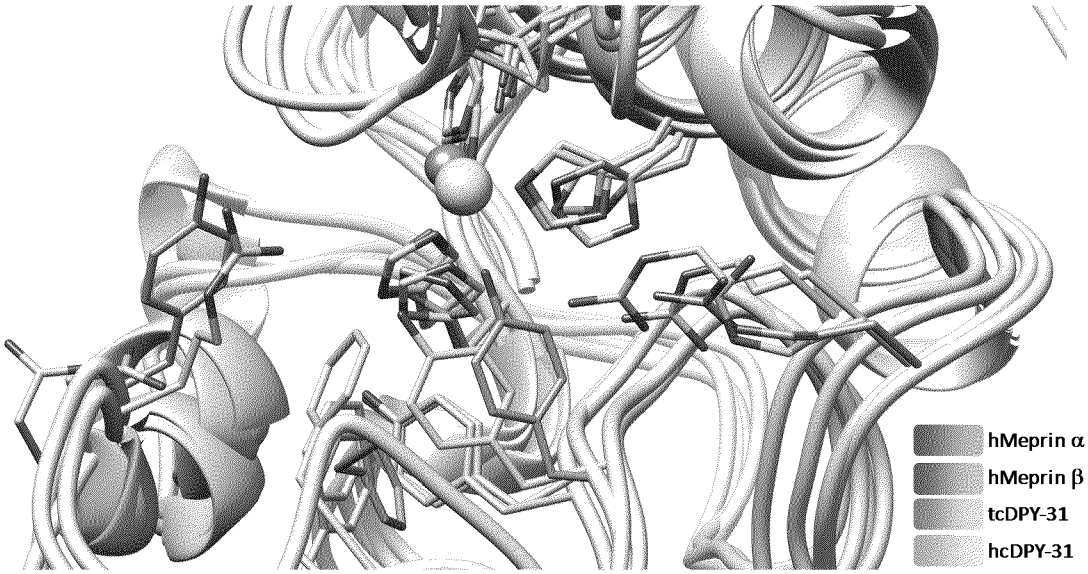

FIG. 3

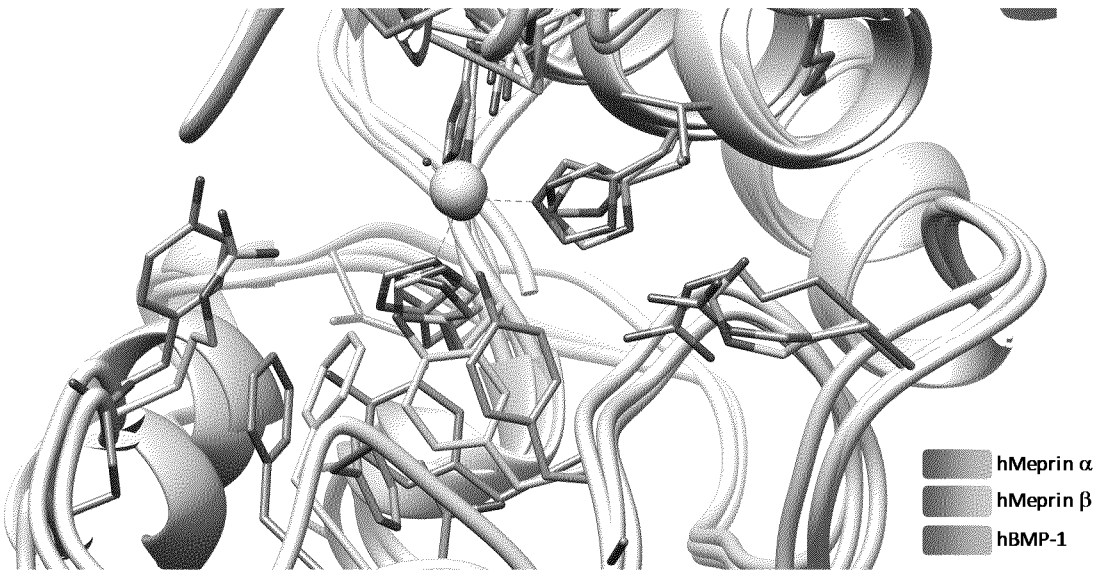

FIG. 4

```
hMeprin_beta          ------------------MDLWNLSW-FLFLDAL----------------------LVISGL 21
hMeprin_alpha         ------------------MAWIRSTCILFFTLLFAHIAA---------------VPIKYL 27
hOvastacin            -----------MEGVGGLWPWVLGLLSLPGVILGAPLAS----------SCAGACGTSFP 39
DPY-31_C.elegans      --------MHKIFIIFGLL------SLCAAHSLRDLSNKDEE-DPPSSAP--GVRKRRMM 43
DPY-31_T.circumcincta MSLLRCTTLLLVVVAIALPPCILGYSLHDGSRLDDFLTESAADRRPRRPTTAAQRRLMGL 60
DPY-31_H.contortus    MSLLRSASLLLVVVTAALPPCTLGYSLHDGSRLDDVIAEFTAERRPRRLATPAQRRLMGL 60
                                                      *

hMeprin_beta          A-------------------TPENFDVDGGM--------DQDIFDINEGLGLD------- 47
hMeprin_alpha         P-------------------EENVHDADFGE--------QKDISEINLAAGLD------- 53
hOvastacin            D-------------------GLTPEGTQASG--------DKDIPAINQGLILEETPESSF 72
DPY-31_C.elegans      SEEDQKTVDYYMDKLNKLADEKHPEEIERHKNP-ELVAWDR-----KRDSVL-NPEEQGK 96
DPY-31_T.circumcincta TEEQYKTVHFYLNKLKELGNQRHPEGYDKDTTKDEADKWRKRMRDDIEGELL-NPEEYGR 119
DPY-31_H.contortus    TEEQHKTVQFYLDKLRELGNRRHPESYNKDSPKNEAYKWRKQMRDDLKTELL-NPEKYGR 119
                                          :           :         *

hMeprin_beta          LFEGDIRLDRAQIR----------------NSIIGEKYRWPH------TIPYVLEDSLEM 85
hMeprin_alpha         LFQGDILLQKS--R----------------NGLRDPNTRWTF------PIPYILADNLGL 89
hOvastacin            LIEGDIIRPSP--F----------------RLLSATSNKWPMGGSGVVEVPFLLSSKYDE 114
DPY-31_C.elegans      FFQGDIVLYPEQAKALYEQALTEGKTRVKRKFIGSNLRRWDA----SRPIIYAFDGSHTQ 152
DPY-31_T.circumcincta HFEGDIILFPEQAKQIYENALKTGQRRVKRKFIGSDLRRWDP----TRPIVYSFDGSHTS 175
DPY-31_H.contortus    HFEGDIILFPEQAKQIYENALKTGQRRVKRKFIGSDLRRWDP----TRPIIYSFDGSHTS 175
                       ::***                      . :     :*         : : : ..

hMeprin_beta          NAKGVILNAFERYRLKTCIDFKPWA--GETNYISVFKGSGCWSSVGNRRVGK-QELSIGA 142
hMeprin_alpha         NAKGAILYAFEMFRLKSCVDFKPYE--GESSYIIFQQFDGCWSEVGDQHVGQ--NISIGQ 145
hOvastacin            PSRQVILEALAEFERSTCIRFVTYQ--DQRDFISIIPMYGCFSSVGRSG-GM-QVVSLAP 170
DPY-31_C.elegans      REQRIIELALEHWHNITCLNFQRNDQANSGNRIVFTDVDGCASNVGRHPLGEEQLVSLAP 212
DPY-31_T.circumcincta REQRIIELALEHWHNITCLNFVRNDNANSGNRIVFTDVDGCASNVGRHPLGEEQLVSLAP 235
DPY-31_H.contortus    REQRIIELALEHRHNITCLNFVRNDNANKGNRIVFTDVDGCASNVGRHPLGEEQLVSLAP 235
                        :  *  *:    .  :*: *      .. . * .    ** *.**    *    :*:.
                          S2'      Zn2+-binding                  S1
hMeprin_beta          NCDR--IATVQHEFLHALGFWHEQSRSDRDDYVRIMWDRILSGREHNFNTYSDDISDSLN 200
hMeprin_alpha         GCAY--KAIIEHEILHALGFYHEQSRTDRDDYVNIWWDQILSGYQHNFDTYDDSLITDLN 203
hOvastacin            TCLQKGRGIVLHELMHVLGFWHEHTRADRDRYIRVNWNEILPGFEINFIKS---QSSNML 227
DPY-31_C.elegans      ECIR--LGVIAHEVAHALGFWHEQSRPDRDQYVTVRWENIDKDSKGQFLKEDPDDVDNAG 270
DPY-31_T.circumcincta ECIR--LGVIAHEVAHALGFWHEQSRPDRDQFVNVRWENIDKDSKGQFLKEDPDDVDNAG 293
DPY-31_H.contortus    ECIR--LGVIAHEVAHALGFWHEQSRPDRDQFVNVRWENIDKDSKGQFLKEDPDDVDNAG 293
                       *     . : **. *.***:**::* *** :: : *:.*  . : :* .       .
                             Met-Turn                  S1'
hMeprin_beta          VPYDYTSVMHYSKTAFQN-GTEPTIVTRISDFEDVIGQRMDFSDSDLLKLNQLYNCS--- 256
hMeprin_alpha         TPYDYESLMHYQPFSFNKNASVPTITAKIPEFNSIIGQRLDFSAIDLERLNRMYNCT--- 260
hOvastacin            TPYDYSSVMHYGRLAFSRRG-LPTITPL-WAPSVHIGQRWNLSASDITRVLKLYGCS--- 282
DPY-31_C.elegans      VPYDYGSIMHYRSKAFSKFDDLYTISTYVTDYQKTIGQRDQLSFNDIRLMNKIYCSAVCP 330
DPY-31_T.circumcincta VPYDYGSIMHYRSKAFSRYDDLYTISTFVTDYQKTIGQRDQLSFNDIRLMNKIYCSNVCS 353
DPY-31_H.contortus    VPYDYGSIMHYRSKAFSRYDDLYTISTFVTDYQKTIGQRDQLSFNDIRLMNKIYCSNVCS 353
                       .**** *:***   :*..     **       .  **** ::*  *:  : ::* .

hMeprin_beta          SSLSFMDSCSFELENVCGMIQSSGDNADWQRV----SQVPRGPESDHS-NMGQCQ--GSG 309
hMeprin_alpha         TTHTLLDHCTFEKANICGMIQGTRDDTDWAHQ----DSAQ-AGEVDHT-LLGQCT--GAG 312
hOvastacin            PSGPRPRGRGSHAH-STGRSPAP-ASLSLQRLLEALSAESRSPDPSGSSAGGQPVPAGPG 340
DPY-31_C.elegans      SKLPCQRG-GYTDPRRCDRCRCP----------------------DGF-TGQYCEQVMPG 366
DPY-31_T.circumcincta RKLPCQRG-GYTDPRRCDRCRCP----------------------DGF-TGQFCEQVMPG 389
DPY-31_H.contortus    RKLPCQRG-GYTDPRRCDRCRCP----------------------DGF-TGQFCEQVMPG 389
                       .          .                              .          *

hMeprin_beta          FFMHFDS---SSVNVGATAVLESRTLYPKRGFQCLQFYL---YNSGSE-SDQLNIYIREY 362
hMeprin_alpha         YFMQFST---SSGSAEEAALLESRILYPKRKQQCLQFFY---KMTGSP-SDRLVVWVRRD 365
hOvastacin            ESPH---------GWESPALKKLSAEASARQPQTLASSPRSRPGAGAPGVAQEQSWLAGV 391
DPY-31_C.elegans      YGATCGGKISLTRSTT----RISSPGYPREF----------------KEGQECSWLLVA 405
DPY-31_T.circumcincta YGAVCGGRIQVNGGWT----KFSSPGYPREF----------------KEGQECSWLLVA 428
DPY-31_H.contortus    YGAVCGGRIQVNSGWT----RFSSPGYPREF----------------KEGQECSWLLVA 428
                                 .           .                      :   ::
```

FIG. 5

```
hMeprin_beta          SADNVDGNLTLVEEIK-----------------------------EIPTGSWQLYHVTL 392
hMeprin_alpha         DSTGNVRKLVKVQTFQ-----------------------------GDDDHNWKIAHVVL 395
hOvastacin            STKP-----------------------------------------TVPSSEAGIQPV-- 407
DPY-31_C.elegans      PPGHIV-EFQFIGEFEMYCKIRHSLCMDYVEVRNSTDFANTGMRYCCYGTPPTRIRSATT 464
DPY-31_T.circumcincta PHGQVV-EMQFIGEFEMYCKVRHSLCMDYVEVRNSTDFANTGMRYCCYGTPSTSIRSATT 487
DPY-31_H.contortus    PPGQVV-EMQFIGEFEMYCKVRHSLCMDYVEVRNSTDFANTGMRYCCYGTPSTSIRSATT 487
                                                                        :  .

hMeprin_beta          KVTKKFRVVFEGRKG--------------------------------------SG-ASL 412
hMeprin_alpha         KEEQKFRYLFQGTKG--------------------------------------DPQNST 416
hOvastacin            --------PVQGSPALPGG---------------------------------CVPRNHF 425
DPY-31_C.elegans      DMVVLFRSFYRGGKGFEARARAVPEAGNWNSWSPWTACSATCGACGSRMRTRTCPPGNAC 524
DPY-31_T.circumcincta DLVVLFRSFYRGGRGFEARARALPANGQWASWSPWTPCTASCGACGSRMRTRVCSHG-AC 546
DPY-31_H.contortus    DLVVLFRSFYRGGRGFEARARALPANGQWASWTPWTPCTASCGACGSRMRTRVCPHG-AC 546
                            .*  .

hMeprin_beta          GGLSIDDINLSETRCPHHIWHIRNFTQFIGS--PNGTLYSPPFYSSKGYAFQIYLNLAHV 470
hMeprin_alpha         GGIYLDDITLTETPCPTGVWTVRNFSQVLENTSKGDKLQSPRFYNSEGYGFGVTLYPNSR 476
hOvastacin            KGMSED---------------------------------------------------- 431
DPY-31_C.elegans      SGEPVETQICNTQACTGMC-----------------------------------AQKR 547
DPY-31_T.circumcincta AGEPVENQVCNTHPCNGLC-----------------------------------AHKK 569
DPY-31_H.contortus    PC---------------------------------------------------------- 548


hMeprin_beta          TN---AGIYFHLISGA---NDDQLQWPCPWQQATMTLLDQNPDIRQRMSNQRSITTDPFM 524
hMeprin_alpha         ESSGYLRLAFHVCSGE---NDAILEWPVENRQVIITILDQEPDVRNRMSSSMVFTTSKSH 533
hOvastacin            ---------------------------------------------------------- 
DPY-31_C.elegans      EEEGQCGGFLSLLRGVRCRQEKTVMAPCENACCPGFTL---------------------- 585
DPY-31_T.circumcincta TEDGECGGFLALLRGVRCKQERTVMEPCENACCPGFSV---------------------- 607
DPY-31_H.contortus    ---------------------------------------------------------- 


hMeprin_beta          --TTDNGNYFWDRPSKVGTVALFSNGTQFRRGGGYGTSAFITHERLKSRDFIKGDDVYIL 582
hMeprin_alpha         TSPAINDTVIWDRPSRVGTYHTD---CNCFRSIDLGWSGFISHQMLKRRSFLKNDDLIIF 590
hOvastacin            ---------------------------------------------------------- 
DPY-31_C.elegans      ---------------------------------------------------------- 
DPY-31_T.circumcincta ---------------------------------------------------------- 
DPY-31_H.contortus    ---------------------------------------------------------- 


hMeprin_beta          LTVEDISHLNSTQIQLTP------------------------------------------ 600
hMeprin_alpha         VDFEDITHLSQTEVPTKGKRLSPQGLILQGQEQQVSEEGSGKAMLEEALPVSLSQGQPSR 650
hOvastacin            ---------------------------------------------------------- 
DPY-31_C.elegans      ---------------------------------------------------------- 
DPY-31_T.circumcincta ---------------------------------------------------------- 
DPY-31_H.contortus    ---------------------------------------------------------- 


hMeprin_beta          ----------------APSVQDLCSKTTCKNDGVCTVRDGKAECRCQSGEDWWYMGERCE 644
hMeprin_alpha         QKRSVENTGPLEDHNWPQYFRDPCDPNPCQNDGICVNVKGMASCRCISGHAFFYTGERCQ 710
hOvastacin            ---------------------------------------------------------- 
DPY-31_C.elegans      ----------------------------------------------------------QRGRCV 591
DPY-31_T.circumcincta ----------------------------------------------------------VGGRCV 613
DPY-31_H.contortus    ---------------------------------------------------------- 


hMeprin_beta          KRGSTRDTIVIAVSSTVAVFALMLIITLVSVYCTRKKYRERMSSNRPNLTPQNQHAF 701
hMeprin_alpha         AVQVHGSVLGMVIGGTAGVIFLTFSI--IAILSQRPRK------------------- 746
hOvastacin            ---------------------------------------------------------- 
DPY-31_C.elegans      R---------------------------------------------------------- 592
DPY-31_T.circumcincta R---------------------------------------------------------- 614
DPY-31_H.contortus    ---------------------------------------------------------- 
```

FIG. 5 (continued)