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(54) Title: CATHEPSIN CYSTEINE PROTEASE INHIBITORS

(57) Abstract: Provided are a novel class of compounds which are cysteine protease inhibitors, including but not limited to, inhibitors of cathepsins K, L, S and B. These compounds are useful for treating diseases in which inhibition of bone resorption is indicated, such as osteoporosis.

CATHEPSIN CYSTEINE PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, hypercalcemia of malignancy or multiple myeloma. One of the most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic fractures are a major cause of morbidity and mortality in the elderly population. As many as 50% of women and a third of men will experience an osteoporotic fracture. A large segment of the older population already has low bone density and a high risk of fractures. There is a significant need to both prevent and treat osteoporosis and other conditions associated with bone resorption. Because osteoporosis, as well as other disorders associated with bone loss, are generally chronic conditions, it is believed that appropriate therapy will typically require chronic treatment.

Cathepsins belong to the papain superfamily of cysteine proteases. These proteases function in the normal physiological as well as pathological degradation of connective tissue. Cathepsins play a major role in intracellular protein degradation and turnover and remodeling. To date, a number of cathepsin have been identified and sequenced from a number of sources. These cathepsins are naturally found in a wide variety of tissues. For example, cathepsin B, C, F, H, L, K, O, S, V, W, and Z have been cloned. Cathepsin L is implicated in normal lysosomal proteolysis as well as several diseases states, including, but not limited to, metastasis of melanomas. Cathepsin S is implicated in Alzheimer's disease, atherosclerosis, chronic obstructive pulmonary disease and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts. Increased Cathepsin B levels and redistribution of the enzyme are found in tumors, suggesting a role in tumor invasion and metastasis. In addition, aberrant Cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis, pneumocystisis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

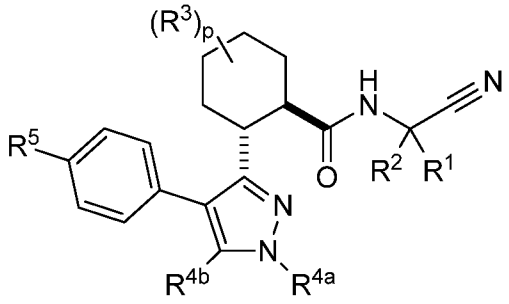
Mammalian cathepsins are related to the papain-like cysteine proteases expressed by disease-causing parasites including those from the families protozoa, platyhelminthes, nematodes and arthropodes. These cysteine proteases play an essential role in the life cycle of these organisms.

Human type I collagen, the major collagen in bone is a good substrate for cathepsin K. *See* Kafienah, W., *et al.*, 1998, *Biochem J*331:727-732, which is hereby incorporated by reference in its entirety. *In vitro* experiments using antisense oligonucleotides to cathepsin K, have shown diminished bone resorption *in vitro*, which is probably due to a reduction in translation of cathepsin K mRNA. *See* Inui, T., *et al.*, 1997, *J Biol Chem*272:8109-8112, which is hereby incorporated by reference in its entirety. The crystal structure of cathepsin K has been resolved. *See* McGrath, M. E., *et al.,* 1997, *Nat Struct Biol*4:105-109; Zhao, B., *et al.*, 1997, *Nat Struct Biol*4: 109-11, which are hereby incorporated by reference in their entirety. Also, selective peptide based inhibitors of cathepsin K have been developed *See* Bromme, D., *et al.*, 1996, *Biochem J*315:85-89; Thompson, S. K., *et al.*, 1997, *Proc Natl Acad Sci U S A*94:14249-14254, which are hereby incorporated by reference in their entirety. Accordingly, inhibitors of Cathepsin K can reduce bone resorption. Such inhibitors would be useful in treating disorders involving bone resorption, such as osteoporosis.

What is needed in the art are therapeutic agents to treat diseases associated with Cathepsin K activity including osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease and cancer including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma.

SUMMARY OF THE INVENTION

The present invention relates to compounds of Formula I, and the pharmaceutically acceptable salts, stereoisomers and N-oxide derivatives thereof:

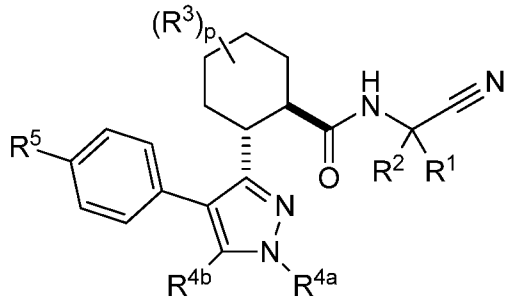


I.

The compounds of formula I are inhibitors of Cathepsin K. As a result, the compounds of Formula I could be useful for method of treating, inhibiting or amelioration of one or more disease states that could benefit from inhibition of Cathepsin K, including osteoporosis. The compounds of this invention coupld further be used in combination with other therapeutically effective agents, including but not limited to, other drugs useful for the treatment of osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma. The invention furthermore relates to processes for preparing compounds of Formula I, and pharmaceutical compositions which comprise compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the following chemical formula:



wherein R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl or heterocyclyl, wherein said alkyl and alkenyl groups are optionally substituted with one to sixsubstituents independently selected from the group consisting of hydroxy, C_{3-6} cycloalkyl, halo andR^8; and wherein said cycloalkyl and heterocyclyl groups are optionally substituted with one or two substituents independently selected from the group consisting of C_{1-6} alkyl, halo, OR^6 and keto;

R^2 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to sixsubstituents independently selected from the group consisting of hydroxy, C_{3-6} cycloalkyl, halo and R^8;

or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-6}cycloalkyl or heterocyclyl ring wherein said cycloalkyl and heterocyclyl rings are optionally substituted with one to two substituents independently selected from the group consisting of R^6, C_{1-6} haloalkyl and halo;

each R^3 is independently selected from the group consisting of halo and C_{1-2} alkyl, wherein said alkyl group is optionally substituted with one to three halo; or two R^3 groups on adjacent carbons can be taken together with the carbon atoms to which they are attached to form a C_{3-4} cycloalkyl ring, wherein said ring is optionally substituted with one to three halo;

R^{4a} is aryl or heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one to four substituents independently selected from the group consisting of halo, hydroxy, cyano, R^6, OR^6 and R^8;

R^{4b} is hydrogen or C_{1-6} alkyl which is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and $O(C_{1-6}$ alkyl);

or R^{4a} and R^{4b} can be taken together with the atoms to which they are attached to form a 4 to 7 membered saturated or unsaturated ring wherein said ring is optionally substituted with one to two substituents independently selected from the group consisting of R^6, C_{1-6} haloalkyl and halo;

R^5 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocycyl, $C(O)NR^6R^8$, $C(O)R^8$, $NR^6C(O)OR^7$ or SO_mR^6, wherein said aryl, heteroaryl, cycloalkyl and heterocycyl groups are optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6} alkyl, halo, oxo, cyano, C_{1-6} haloalkyl, OR^6, $C(O)NR^6R^7$, $C(O)OR^6$, $C(O)R^6$, $=NR^6$, =NCN and SO_mR^6;

R^6 is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to four substituents independently selected from the group consisting of halo, hydroxy, cyano, C_{1-3}haloalkyl, and $O(C_{1-6}$ alkyl);

R^7 is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and $O(C_{1-6}$ alkyl);

R^8 is C_{3-8} cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups are optionally substituted with one to four substituents independently selected from the group consisting of halo, cyano, oxo, R^6, OR^6, NR^6R^7, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, SO_mR^6 and SF_5 ;

m is an integer from zero to two;

p is an integer from zero to two;

or a pharmaceutically acceptable salt thereof.

In an embodiment of the invention, R^1 is hydrogen or C_{1-3} alkyl, wherein said alkyl group is optionally substituted with one to six halo.In a class of the invention, $R^1$is

hydrogen. In another class of the invention, R1is methyl. In another class of the invention, R1is isopropyl. In another class of the invention, R1is trifluoroethyl.

In an embodiment of the invention, R^2 is hydrogen or C_{1-3} alkyl, wherein said alkyl group is optionally substituted with one to six halo.In a class of the invention, $R^2$is hydrogen. In another class of the invention, $R^2$is methyl.

In an embodiment of the invention, R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-4}cycloalkyl ring. In a class of the invention, R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a cyclopropyl ring.

In an embodiment of the invention, each $R^3$is independently selected from the group consisting of hydrogen, halo or methyl, or two R^3 groups on adjacent carbons can be taken together with the carbon atoms to which they are attached to form a C_{3-4} cycloalkyl ring, wherein said ring is optionally substituted with one to three halo. In a class of the invention, $R^3$is hydrogen. In a class of the invention, $R^3$is halo. In a subclass of the invention, $R^3$is fluoro. In another class of the invention, $R^3$is methyl. In another class of the invention, two R^3groups on adjacent carbons can be taken together with the carbon atoms to which they are attached to form a cyclopropyl ring.

In an embodiment of the invention, R^{4a} is aryl, wherein said aryl group is optionally substituted with one to four substituents independently selected from the group consisting of halo, hydroxy, cyano, R^6, $OR^6$and heteroaryl. In a class of the invention, R^{4a} is phenyl, which is optionally substituted with halo. In another embodiment of the invention,R^{4a} is heteroaryl, wherein said heteroaryl group is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, cyano and methyl. In a class of the invention, R^{4a} is pyridinyl, which is optionally substituted with halo.

In an embodiment of the invention, R^{4b} is hydrogen or C_{1-6} alkyl which is optionally substituted with one to three substituents independently selected from the group consisting of halo and hydroxy. In a class of the invention, R^{4b} is hydrogen. In another class of the invention, R^{4b} is methyl. In another class of the invention, R^{4b} is hydroxymethyl.

In an embodiment of the invention, R^{4a} and R^{4b} can be taken together with the atoms to which they are attached to form a 6 membered saturated ring.

In an embodiment of the invention, R^5 is heterocyclyl, $C(O)R^8$ or SO_mR^6, wherein said heterocyclyl group is optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6} alkyl, halo, oxo, cyano, C_{1-6} haloalkyl, OR^6, $C(O)NR^6R^7$, $C(O)OR^6$, $C(O)R^6$, $=NR^6$, =NCN and SO_mR^6. In a class of the

invention, R^5 is heterocyclyl, which is optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6} alkyl, halo, oxo, cyano, $=NR^6$ and =NCN. In a subclass of the invention, R^5 is 1,1-dioxidothiomorphonlinyl. In another subclass of the invention, R^5 is 1-imino-1-oxidothiomorphonlinyl. In another subclass of the invention, R^5 is 1-methylimino-1-oxidothiomorphonlinyl.

In an embodiment of the invention, R^6 is hydrogen. In another embodiment of the invention, R^6 is C_{1-6} alkyl which is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and $O(C_{1-6}$ alkyl). In a class of the invention, R^6 is methyl. In another class of the invention, R^6 is trifluoromethyl.

In an embodiment of the invention, m is two.

In an embodiment of the invention, p is zero. In another embodiment of the invention, p is one. In another embodiment of the invention, p is two.

Reference to the preferred classes and subclasses set forth above is meant to include all combinations of particular and preferred groups unless stated otherwise.

Specific embodiments of the present invention include, but are not limited to the compounds identified herein as Examples 1 to 171, or pharmaceutically acceptable salts thereof.

Also included within the scope of the present invention is a pharmaceutical composition which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The invention is also contemplated to encompass a pharmaceutical composition which is comprised of a pharmaceutically acceptable carrier and any of the compounds specifically disclosed in the present application. The present invention further includes combinations useful for the treatment or prevention of Cathepsin K dependent diseases, such as osteoporosis. These and other aspects of the invention will be apparent from the teachings contained herein.

Utilities

The compounds of the present invention are inhibitors of cathepsins and are may be useful to treat or prevent cathepsin dependent diseases or conditions in mammals, preferably humans. Specifically, the compounds of the present invention are inhibitors of Cathepsin K and are may be useful to treat or prevent Cathepsin K dependent diseases or conditions in mammals, preferably humans.

The compounds of the present invention have advantages over structurally similar compounds known in the art in that they have a marked improved selectivity profiles toward related cathepsins, especially cathepsin F.

"Cathepsin dependent diseases or conditions" refers to pathologic conditions that depend on the activity of one or more cathepsins. "Cathepsin K dependent diseases or conditions" refers to pathologic conditions that depend on the activity of Cathepsin K. Diseases associated with Cathepsin K activities include osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease and cancer, including metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. In treating such conditions with the instantly claimed compounds, the required therapeutic amount will vary according to the specific disease and is readily ascertainable by those skilled in the art. Although both treatment and prevention are contemplated by the scope of the invention, the treatment of these conditions is the preferred use.

An embodiment of the invention is a method of inhibiting cathepsin activity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of treating or preventing cathepsin dependent conditions in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

A class of the embodiment is the method wherein the cathepsin activity is cathepsin K activity.

Another embodiment of the invention is a method of inhibiting bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. Another embodiment of the invention is a method of reducing bone loss in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the inhibition of bone resorption, which includes abnormally increased bone turnover, bone fractures, Paget's disease, osteogenesis imperfecta and

periprosthetic osteolysis, is known in the literature, see Stroup, G.B., Lark, M.W., Veber, DF., Bhattacharrya, A., Blake, S., Dare, L.C., Erhard, K.F., Hoffman, S.J., James, I.E., Marquis, R.w., Ru, Y., Vasko-Moser, J.A., Smith, B.R., Tomaszek, T. and Gowen, M. Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption in vivo in a nonhuman primate. J. Bone Miner. Res., 16:1739-1746; 2001; and Votta, B.J., Levy, M.A., Badger, A., Dodds, R.A., James, I.E., Thompson, S., Bossard, M.J., Carr, T., Connor, J.R., Tomaszek, T.A., Szewczuk, L., Drake, F.H., Veber, D., and Gowen, M. Peptide aldehyde inhibitors of cathepsin K inhibit bone resorption both *in vivo* and *in vitro*. J. Bone Miner. Res. 12:1396-1406; 1997.

Another embodiment of the invention is a method of treating or preventing osteoporosis, including glucocorticoid induced osteoporosis, in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the above pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the treatment or prevention of osteoporosis is known in the literature, see Saftig, P., Hunziker, E., Wehmeyer, O., Jones, S., Boyde, A., Rommerskirch, W., Moritz, J.D., Schu, P., and Vonfigura, K. Impaired osteoclast bone resorption leads to osteopetrosis in cathepsin K-deficient mice. Proc. Natl. Acad. Sci. USA 95:13453-13458; 1998.

Another embodiment of the invention is a method of treating or preventing periodontal disease, including tooth loss, in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the above pharmaceutical compositions described above. The utility of cathepsin K inhibitors in the treatment or prevention of periodontal disease and tooth loss is known in the literature, see Tsuji Y,et al., Expression of cathepsin K mRNA and protein in odontoclasts after experimental tooth movement in the mouse maxilla by in situ hybridization and immunoelectron microscopy.Cell Tissue Res. 2001 Mar;303(3):359-69.

Another embodiment of the invention is a method of treating or preventing rheumatoid arthritic condition in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that progressive destruction of the periarticular bone is a major cause of joint dysfunction and disability in patients with rheumatoid arthritis (RA), see Goldring SR, "Pathogenesis of bone erosions in rheumatoid arthritis". Curr.Opin.Rheumatol.2002; 14: 406-10. Analysis of joint tissues from patients with RA have provided evidence that cathepsin K positive osteoclasts are the cell types that mediate the focal bone resorption associated with rheumatoid synovial lesion, see Hou, W-S, Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallese, EM, Goldring, SR, Bromme, D, "Comparison of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", Arthritis Rheumatism 2002; 46: 663-74. In addition, generalized

bone loss is a major cause of morbidity associated with severe RA. The frequency of hip and spinal fractures is substantially increased in patients with chronic RA, see Gould A, Sambrook, P, Devlin J et al, "Osteoclastic activation is the principal mechanism leading to secondary osteoporosis in rheumatoid arthritis". J. Rheumatol. 1998; 25: 1282-9. The utility of cathepsin K inhibitors in the treatment or prevention of resorption in subarticular bone and of generalized bone loss represent a rational approach for pharmacological intervention on the progression of rheumatoid arthritis.

Another embodiment of the invention is a method of treating or preventing the progression of osteoarthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that osteoarthritis (OA) is accompanied with well-defined changes in the joints, including erosion of the articular cartilage surface, peri-articular endochondral ossification/ osteophytosis, and subchondral bony sclerosis and cyst formation, see Oettmeier R, Abendroth, K, "Osteoarthritis and bone: osteologic types of osteoarthritis of the hip", Skeletal Radiol. 1989; 18: 165-74. Recently, the potential contribution of subchondral bone sclerosis to the initiation and progression of OA have been suggested. Stiffened subchondral bone as the joint responding to repetitive impulsive loading, is less able to attenuate and distribute forces through the joint, subjecting it to greater mechanical stress across the articular cartilage surface. This in turn accelerates cartilage wear and fibrillate, see Radin, EL and Rose RM, "Role of subchondral bone in the initiation and progression of cartilage damage", Clin. Orthop.1986; 213: 34-40. Inhibition of excessive subarticular bone resorption by an anti-resorptive agent such as a cathepsin K inhibitor, will lead to inhibition of subchondral bone turnover, thus may have a favorable impact on OA progression.

In addition to the above hypothesis, cathepsin K protein expression was recently identified in synovial fibroblasts, macrophage-like cells, and chondrocytes from synovium and articular cartilage specimens derived from OA patients, see Hou, W-S, Li, W, Keyszer, G, Weber, E, Levy, R, Klein, MJ, Gravallese, EM, Goldring, SR, Bromme, D, "Comparison of Cathepsin K and S expression within the Rheumatoid and Osteoarthritic Synovium", Arthritis Rheumatism 2002; 46: 663-74; and Dodd, RA, Connor, JR, Drake, FH, Gowen, M, "Expression of Cathepsin K messenger RNA in giant cells and their precursors in human osteoarthritic synovial tissues". Arthritis Rheumatism 1999; 42: 1588-93; and Konttinen, YT, Mandelin, J, Li, T-F, Salo, J, Lassus, J et al. "Acidic cysteine endoproteinase cathepsin K in the degeneration of the superficial articular hyaline cartilage in osteoarthritis", Arthritis Rheumatism 2002; 46: 953-60. These recent studies thus implicated the role of cathepsin K in the destruction of collagen type II in the articular cartilage associated with the progression of osteoarthritis. The utility of cathepsin K inhibitors in the treatment or

prevention of osteoarthritis as described in this invention thus comprise of two different mechanisms, the first is on the inhibition of osteoclast-driven subchondral bone turnover, and the second is on the direct inhibition of collagen type II degeneration in the synovium and cartilage of patients with OA.

Another embodiment of the invention is a method of treating cancer in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K is expressed in human breast carcinoma, prostate cancer and chordoma and has matrix degrading capabilities, seeLittlewood-Evans AJ, Bilbe G, Bowler WB, Farley D, Wlodarski B, Kokubo T, Inaoka T, Sloane J, Evans DB, Gallagher JA, "The osteoclast-associated protease cathepsin K is expressed in human breast carcinoma." Cancer Res 1997 Dec 1; 57(23):5386-90, Brubaker KD, Vessella RL, True LD, Thomas R, Corey E "Cathepsin K mRNA and protein expression in prostate cancer progression." J Bone Miner Res 2003 18, 222-30, Haeckel C, Krueger S, Kuester D, Ostertag H, Samii M, Buehling F, Broemme D, Czerniak B, Roessner A. "Expression of cathepsin K in chordoma." Hum Pathol 2000 Jul; 31(7):834-40.

Another embodiment of the invention is a method of treating atherosclerosis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K is expressed in human atheroma and has significant elastase activity, see Sukhova GK, Shi GP, Simon DI, Chapman HA, Libby P. "Expression of the elastolytic cathepsins S and K in human atheroma and regulation of their production in smooth muscle cells." J Clin Invest 1998 Aug 102, 576-83. It is also known that the Cat K null mouse when crossed with an ApoE null mouse shows reduced atherosclerotic plaque area and increased resistance to plaque rupture, see E. Lutgens, S.P.M. Lutgens, B.C.G. Faber, S. Heeneman, M.M.J. Gijbels, M.P.J. de Winther, P. Frederik, I. van der Made, D. Black, M.J.A.P. Daemen, K.B.J.M. Cleutjens "Disruption of the *Cathepsin K* Gene Reduces Atherosclerosis Progression and Induces Plaque Fibrosis but Accelerates Macrophage Foam Cell Formation." Circulation 2006 113:98-107. Increased plaque stability would lead to a decrease in heart attack and stroke in a patient administered a therapeutically effective amound of any of the compounds or any of the pharmaceutical compositions described above.

Another embodiment of the invention is a method of treating obesity in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K mRNA is increased in adipose tissue in several mouse models of obesity and also in adipose tissue of obese human males, see Chiellini C,

Costa M, Novelli SE, Amri EZ, Benzi L, Bertacca A, Cohen P, Del Prato S, Friedman JM, Maffei M. "Identification of cathepsin K as a novel marker of adiposity in white adipose tissue," J Cell Physiol 2003, 195, 309-21.

Another embodiment of the invention is a method of treating glaucoma in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amound of any of the compounds or any of the pharmaceutical compositions described above. Cathepsin K is highly expressed in the iris, cillary body and retinal pigment epithelium, and as such can be useful in the treatment of glaucoma, see Ortega, J., *et al.*, "Gene Expression of Proteases and Protease Inhibitors in the Human Ciliary Epithelium and ODM-2 cells," Exp. Eye Res (1997) 65, 289-299; International Publication WO 2004/058238 (Alcon, Inc.).

Another embodiment of the invention is a method of treating chronic obstructive pulmonary disease in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K plays a role in lung fibrosis, see Buhling, F., *et al.,* "Pivotal role of cathepsin K in lung fibrosis," Am J Pathol. 2004 Jun; 164(6):2203-16.

Another embodiment of the invention is a method of treating parasitic infections in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that mammalian cathepsins are related to the papain-like cysteine proteases which play an important role in the life cycle of these parasites. Such parasites are involved in the diseases of malaria, American trypanosomiasis, African trypanosomiasis, leishmaniasis, giardiasis, trichomoniasis, amoebiasis, schistosomiasis, fascioliasis, paragonimiasis and intestinal roundworms, see Lecaille F, Kaleta J, Bromme D., Human and parasitic papain-like cysteine proteases: their role in physiology and pathology and recent developments in inhibitor design. Chem Rev 2002 102, 4459-88.

Another embodiment of the invention is a method of treating severe acute respiratory syndrome (SARS) in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above.

Another embodiment of the invention is a method of treating metastatic bone disease in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that osteoclasts are responsible

for bone resorption and that bone destruction and hypercalcemia induced by metastatic tumors are carried out by osteoclasts. Accordingly, the inhibition of osteoclasts can prevent bone destruction and bone metastasis, see Miyamoto, T. and Suda, T., "Differentiation and function of osteoclasts," Keio J Med 2003 Mar; 52(1):1-7.

Another embodiment of the invention is a method of preventing metastatic bone disease in a mammal with a primary tumor that carries a risk of bone metastasis, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is described in the literature that compounds that inhibit osteoclasts function can prevent tumor cell adhesion to bone, see S. Boissier, M. Ferreras, O. Peyruchaud, S. Magnetto, F. H. Ebetino, M. Colombel, P. Delmas, J.-M. Delaissé and P. Clézardin "Bisphosphonates Inhibit Breast and Prostate Carcinoma Cell Invasion, an Early Event in the Formation of Bone Metastases" Cancer Research 60, 2949-2954, 2000

Another embodiment of the invention is a method of treating hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above. It is known in the literature that cathepsin K plays a role in hypercalcemia of malignancy and multiple myeloma, see Faust, J. *et al.,* Multiple myeloma cells and cells of the human osteoclast lineage share morphological and cell surface markers. J Cell Biochem. 1998 Dec 15;71(4):559-68; A. lipton, New therapeutic agents for the treatment of bone diseases. Expert Opin Biol Ther. 2005 Jun;5(6):817-32.

Another embodiment of the invention is administering to a mammal a therapeutically effective amount of any of the compounds or any of the pharmaceutical compositions described above for the treatment of mammalian diseases associated with cathepsin S including Alzheimer's disease, atherosclerosis, chronic obstructive pulmonary disease, cancer and certain autoimmune disorders, including, but not limited to juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, rheumatoid arthritis and Hashimoto's thyroiditis; allergic disorders, including, but not limited to asthma; and allogenic immune responses, including, but not limited to, rejection of organ transplants or tissue grafts. It is known in the literature that cathepsin S activity is associated with the above disease states, see Munger JS, Haass C, Lemere CA, Shi GP, Wong WS, Teplow DB, Selkoe DJ, Chapman HA. Lysosomal processing of amyloid precursor protein to A beta peptides: a distinct role for cathepsin S. Biochem J 1995 311, 299-305, Sukhova GK, Zhang Y, Pan JH, Wada Y, Yamamoto T, Naito M, Kodama T, Tsimikas S, Witztum JL, Lu ML, Sakara Y, Chin MT, Libby P, Shi GP. Deficiency of cathepsin S reduces atherosclerosis in LDL receptor-deficient mice. J Clin Invest 2003 111, 897-906, Zheng T, Zhu Z, Wang Z, Homer RJ, Ma B, Riese RJ Jr, Chapman

HA Jr, Shapiro SD, Elias JA. Inducible targeting of IL-13 to the adult lung causes matrix metalloproteinase- and cathepsin-dependent emphysema. J Clin Invest 2000 106,1081-93, Shi GP, Sukhova GK, Kuzuya M, Ye Q, Du J, Zhang Y, Pan JH, Lu ML, Cheng XW, Iguchi A, Perrey S, Lee AM, Chapman HA, Libby P. Deficiency of the cysteine protease cathepsin S impairs microvessel growth. Circ Res 2003 92, 493-500, Nakagawa TY, Brissette WH, Lira PD, Griffiths RJ, Petrushova N, Stock J, McNeish JD, Eastman SE, Howard ED, Clarke SR, Rosloniec EF, Elliott EA, Rudensky AY. Impaired invariant chain degradation and antigen presentation and diminished collagen-induced arthritis in cathepsin S null mice. Immunity 1999 10, 207-17.

Exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of osteoporosis in a mammal in need thereof. Still further exemplifying the invention is the use of any of the compounds described above in the preparation of a medicament for the treatment and/or prevention of: bone loss, bone resorption, bone fractures, metastatic bone disease and/or disorders related to cathepsin functioning.

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. For oral use of a therapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. For oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate,

sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

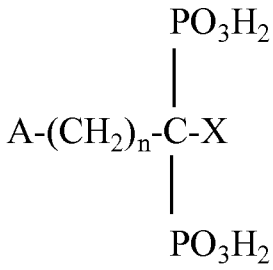
The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

The instant compounds are also useful in combination with known agents useful for treating or preventing osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. Combinations of the presently disclosed compounds with other agents useful in treating or preventing osteoporosis or other bone disorders are within the scope of the invention. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved. Such agents include the following: an organic bisphosphonate; a selective estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; Vitamin D; a synthetic Vitamin D analogue; a Nonsteroidal anti-

inflammatory drug; a selective cyclooxygenase-2 inhibitor; an inhibitor of interleukin-1 beta; a LOX/COX inhibitor; and the pharmaceutically acceptable salts and mixtures thereof. A preferred combination is a compound of the present invention and an organic bisphosphonate. Another preferred combination is a compound of the present invention and a selective estrogen receptor modulator. Another preferred combination is a compound of the present invention and an androgen receptor modulator. Another preferred combination is a compound of the present invention and an osteoblast anabolic agent.

"Organic bisphosphonate" includes, but is not limited to, compounds of the chemical formula



wherein n is an integer from 0 to 7 and wherein A and X are independently selected from the group consisting of H, OH, halogen, NH_2, SH, phenyl, C_1-C_{30} alkyl, C_3-C_{30} branched or cycloalkyl, bicyclic ring structure containing two or three N, C_1-C_{30} substituted alkyl, C_1-C_{10} alkyl substituted NH_2, C_3-C_{10} branched or cycloalkyl substituted NH_2, C_1-C_{10} dialkyl substituted NH_2, C_1-C_{10} alkoxy, C_1-C_{10} alkyl substituted thio, thiophenyl, halophenylthio, C_1-C_{10} alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, imidazopyridinyl, and benzyl, such that both A and X are not selected from H or OH when n is 0; or A and X are taken together with the carbon atom or atoms to which they are attached to form a C_3-C_{10} ring.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C_1-C_{30} substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH_2, C_1-C_{10} alkyl or dialkyl substituted NH_2, OH, SH, and C_1-C_{10} alkoxy.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Non-limiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra- C_1-C_{10} -alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of

sodium, potassium, calcium, magnesium, and ammonium salts. More preferred are sodium salts. Non-limiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 5 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 5 mg of alendronic acid.

Non-limiting examples of bisphosphonates useful herein include the following:

Alendronate, which is also known as alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid, alendronate sodium or alendronate monosodium trihydrate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronate is described in U.S. Patents 4,922,007, to Kieczykowski *et al.*, issued May 1, 1990; 5,019,651, to Kieczykowski *et al.*, issued May 28, 1991; 5,510,517, to Dauer *et al.*, issued April 23, 1996; 5,648,491, to Dauer *et al.*, issued July 15, 1997, all of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (incadronate, formerly known as cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem 32*, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

1-hydroxy-2-imidazo-(1,2-a)pyridin-3-yethylidene (minodronate).

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Breliere et al., October 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zoledronate).

Nonlimiting examples of bisphosphonates include alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, and zolendronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially a sodium, potassium, calcium, magnesium or ammonium salt of alendronic acid. Exemplifying the preferred bisphosphonate is a sodium salt of alendronic acid, especially a hydrated sodium salt of alendronic acid. The salt can be hydrated with a whole number of moles of water or non whole numbers of moles of water. Further exemplifying the preferred bisphosphonate is a hydrated sodium salt of alendronic acid, especially when the hydrated salt is alendronate monosodium trihydrate.

It is recognized that mixtures of two or more of the bisphosphonate actives can be utilized.

The precise dosage of the organic bisphosphonate will vary with the dosing schedule, the particular bisphosphonate chosen, the age, size, sex and condition of the mammal or human, the nature and severity of the disorder to be treated, and other relevant

medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician. Appropriate amounts can be determined by routine experimentation from animal models and human clinical studies. Generally, an appropriate amount of bisphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the bisphosphonate is administered. For humans, an effective oral dose of bisphosphonate is typically from about 1.5 to about 6000 μg/kg body weight and preferably about 10 to about 2000 μg/kg of body weight. For alendronate monosodium trihydrate, common human doses which are administered are generally in the range of about 2 mg/day to about 40 mg/day, preferably about 5 mg/day to about 40 mg/day. In the U.S. presently approved dosages for alendronate monosodium trihydrate are 5 mg/day for preventing osteoporosis, 10 mg/day for treating osteoporosis, and 40 mg/day for treating Paget's disease.

In alternative dosing regimens, the bisphosphonate can be administered at intervals other than daily, for example once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In a once weekly dosing regimen, alendronate monosodium trihydrate would be administered at dosages of 35 mg/week or 70 mg/week.

"Selective estrogen receptor modulators" refers to compounds which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, estrogen, progestogen, estradiol, droloxifene, raloxifene, lasofoxifene, TSE-424, tamoxifen, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

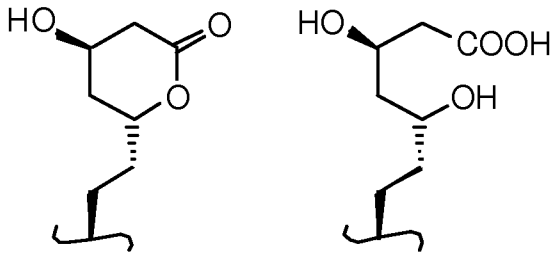
An "estrogen receptor beta modulator" is a compound that selectively agonizes or antagonizes estrogen receptor beta (ERβ Agonizing ERβ increases transcription of the tryptophan hydroxylase gene (TPH, the key enzyme in serotonin synthesis) via an ERβ mediated event. Examples of estrogen receptor beta agonists can be found in PCT International publication WO 01/82923, which published on November 08, 2001, and WO 02/41835, which published on May 20, 2002, both of which are hereby incorporated by reference in their entirety.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"An inhibitor of osteoclast proton ATPase" refers to an inhibitor of the proton ATPase, which is found on the apical membrane of the osteoclast, and has been reported to play a significant role in the bone resorption process. This proton pump represents an attractive target for the design of inhibitors of bone resorption which are potentially useful for the treatment and prevention of osteoporosis and related metabolic diseases. See C. Farina et al., "Selective inhibitors of the osteoclast vacuolar proton ATPase as novel bone antiresorptive agents," DDT, 4: 163-172 (1999)), which is hereby incorporated by reference in its entirety.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



Lactone
I

Open-Acid
II

In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from atorvastatin, rosuvastain, lovastatin and simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenz-imidazole, diethylamine, piperazine, and tris(hydroxymethyl) aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

As used above, "integrin receptor antagonists" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_V\beta_3$

integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the αvβ5 integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_V\beta_3$ integrin and the $\alpha_V\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_V\beta_6$, $\alpha_V\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_V\beta_6$, $\alpha_V\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. H.N. Lode and coworkers in PNAS USA 96: 1591-1596 (1999) have observed synergistic effects between an antiangiogenic αv integrin antagonist and a tumor-specific antibody-cytokine (interleukin-2) fusion protein in the eradication of spontaneous tumor metastases. Their results suggested this combination as having potential for the treatment of cancer and metastatic tumor growth. $\alpha_V\beta_3$ integrin receptor antagonists inhibit bone resorption through a new mechanism distinct from that of all currently available drugs. Integrins are heterodimeric transmembrane adhesion receptors that mediate cell-cell and cell-matrix interactions. The α and β integrin subunits interact non-covalently and bind extracellular matrix ligands in a divalent cation-dependent manner. The most abundant integrin on osteoclasts is $\alpha_V\beta_3$ (>10^7/osteoclast), which appears to play a rate-limiting role in cytoskeletal organization important for cell migration and polarization. The $\alpha_V\beta_3$ antagonizing effect is selected from inhibition of bone resorption, inhibition of restenosis, inhibition of macular degeneration, inhibition of arthritis, and inhibition of cancer and metastatic growth.

"An osteoblast anabolic agent" refers to agents that build bone, such as PTH. The intermittent administration of parathyroid hormone (PTH) or its amino-terminal fragments and analogues have been shown to prevent, arrest, partially reverse bone loss and stimulate bone formation in animals and humans. For a discussion refer to D.W. Dempster et al., "Anabolic actions of parathyroid hormone on bone," Endocr Rev 14: 690-709 (1993). Studies have demonstrated the clinical benefits of parathyroid hormone in stimulating bone formation and thereby increasing bone mass and strength. Results were reported by RM Neer et al., in New Eng J Med 344 1434-1441 (2001).

In addition, parathyroid hormone-related protein fragments or analogues, such as PTHrP-(1-36) have demonstrated potent anticalciuric effects [see M.A. Syed et al., "Parathyroid hormone-related protein-(1-36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy," JCEM 86: 1525-1531 (2001)] and may also have potential as anabolic agents for treating osteoporosis.

"Vitamin D" includes, but is not limited to, vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol), which are naturally occurring, biologically inactive precursors of

the hydroxylated biologically active metabolites of vitamin D: 1α-hydroxy vitamin D; 25-hydroxy vitamin D, and 1α,25-dihydroxy vitamin D. Vitamin D_2 and vitamin D_3 have the same biological efficacy in humans. When either vitamin D_2 or D_3 enters the circulation, it is hydroxylated by cytochrome P_{450}-vitamin D-25-hydroxylase to give 25-hydroxy vitamin D. The 25-hydroxy vitamin D metabolite is biologically inert and is further hydroxylated in thekidney by cytochrome P450-monooxygenase, 25 (OH) D-1α -hydroxylase to give 1,25-dihydroxy vitamin D. When serum calcium decreases, there is an increase in the production of parathyroid hormone (PTH), which regulates calcium homeostasis and increases plasma calcium levels by increasing the conversion of 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D.

1,25-dihydroxy vitamin D is thought to be responsible for the effects of vitamin D on calcium and bone metabolism. The 1,25-dihydroxy metabolite is the active hormone required to maintain calcium absorption and skeletal integrity. Calcium homeostasis is maintained by 1,25-dihydroxy vitamin D by inducing monocytic stem cells to differentiate into osteoclasts and by maintaining calcium in the normal range, which results in bone mineralization by the deposition of calcium hydroxyapatite onto the bone surface, see Holick, MF, Vitamin D photobiology, metabolism, and clinical applications, In: DeGroot L, Besser H, Burger HG, eg al.,eds. *Endocrinology*, 3rd ed., 990-1013 (1995). However, elevated levels of 1α,25-dihydroxy vitamin D_3 can result in an increase of calcium concentration in the blood and in the abnormal control of calcium concentration by bone metabolism, resulting in hypercalcemia. 1α,25-dihydroxy vitamin D_3 also indirectly regulates osteoclastic activity in bone metabolism and elevated levels may be expected to increase excessive bone resorption in osteoporosis.

"Synthetic vitamin D analogues" includes non-naturally occurring compounds that act like vitamin D.

"Nonsteroidal anti-inflammatory drugs" or NSAIDs, inhibit the metabolism of arachidonic acid to proinflammatory prostaglandins via cyclooxygenase (COX)-1 and COX-2. Nonlimiting examples of NSAIDs include: aspirin, ibuprofen, naproxen, diclofenac, etodolac, fenoporfen, flubiprofen, indomethacin, ketoprofen, ketorolac, meloxicam, nabumetone, oxaprozin, piroxicam, sulindac, tolmetin, diflunisal, meclofenamate and phenylbutazone.

A "selective cyclooxygenase-2 inhibitor," or COX-2 inhibitor, refers to a type of nonsteroidal anti-inflammatory drug (NSAID), that inhibit the COX-2 coenzyme, which contributes to pain and inflammation in the body. Nonlimiting examples of COX-2 inhibitos include: celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib and lumiracoxib.

An "inhibitor of interleukin-1 beta" or IL-1β refers to in inhibitors of IL-1, which is a soluble factor produced by monocytes, macrophages, and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. Nonlimiting examples of IL-1B inhibitors include diacerein and rhein.

A "LOX/COX inhibitor" refers to an inhibitor or all three of the major enzymes involved in arachidonic acid pathway - namely, 5-LOX, COX-1 and COX-2. A nonlimiting example of a LOX/COX inhibitor is licofelone.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents. The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985, which is incorporated by reference herein in its entirety. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

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 that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The terms “treating” or “treatment” of a disease as used herein includes: inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

The term “preventing” or “prevention” of a diseases includes causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease.

The term “bone resorption,” as used herein, refers to the process by which osteoclasts degrade bone.

The present invention also encompasses a pharmaceutical composition useful in the treatment of osteoporosis or other bone disorders, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

When a compound according to this invention is administered to a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for a cathepsin dependent condition. Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds of the present invention can be used in combination with other agents useful for treating cathepsin-mediated conditions. The individual components of such combinations can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. It will be understood that the scope of combinations of the compounds of this invention with other agents useful for treating cathepsin-mediated conditions includes in principle any combination with any pharmaceutical composition useful for treating disorders related to estrogen functioning.

The scope of the invention therefore encompasses the use of the instantly claimed compounds in combination with a second agent selected from: an organic bisphosphonate; a selective estrogen receptor modulator; an androgen receptor modulator; an inhibitor of osteoclast proton ATPase; an inhibitor of HMG-CoA reductase; an integrin receptor antagonist; an osteoblast anabolic agent, such as PTH; Vitamin D; a synthetic Vitamin D analogue; a Nonsteroidal anti-inflammatory drug; a selective cyclooxygenase-2 inhibitor; an inhibitor of interleukin-1 beta; a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof.

These and other aspects of the invention will be apparent from the teachings contained herein.

Definitions

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. Unless a specific stereochemistry

is indicated, the present invention is meant to comprehend all such isomeric forms of these compounds.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diasteromeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

In the compounds of Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Tautomers of compounds defined in Formula Iare also included within the scope of the present invention. For example, compounds including carbonyl $-CH_2C(O)-$

groups (keto forms) may undergo tautomerism to form hydroxyl –CH=C(OH)- groups (enol forms). Both keto and enol forms are included within the scope of the present invention.

When any variable (e.g. R^3, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is bicyclic, it is intended that the bond be attached to any of the suitable atoms on either ring of the bicyclic moiety.

It is understood that one or more silicon (Si) atoms can be incorporated into the compounds of the instant invention in place of one or more carbon atoms by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art from readily available starting materials. Carbon and silicon differ in their covalent radius leading to differences in bond distance and the steric arrangement when comparing analogous C-element and Si-element bonds. These differences lead to subtle changes in the size and shape of silicon-containing compounds when compared to carbon. One of ordinary skill in the art would understand that size and shape differences can lead to subtle or dramatic changes in potency, solubility, lack of off-target activity, packaging properties, and so on. (Diass, J. O. *et al.* Organometallics (2006) 5:1188-1198; Showell, G.A. et al. Bioorganic & Medicinal Chemistry Letters (2006) 16:2555-2558).

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be understood as meaning that the group in question is either unsubstituted or may be substituted with one or more substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having one to ten carbon atoms unless otherwise specified.For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10}alkyl" specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

The term "haloalkyl" means an alkyl radical as defined above, unless otherwise specified, that is substituted with one to five, preferably one to three halogen. Representative examples include, but are not limited to trifluoromethyl, dichloroethyl, trichloroethyl and the like.

The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so on.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms and at least 1 carbon to carbon double bond. Preferably 1 carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight or branched portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 12 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydroindolyl, dihydroquinolinyl, methylenedioxybenzene, benzothiazolyl, benzothienyl, quinolinyl, isoquinolinyl, oxazolyl, and tetra-hydroquinoline. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered nonaromatic ring, unless otherwise specified, containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S, SO, or SO_2 and includes bicyclic groups. "Heterocyclyl" therefore includes, but is not limited to the following: piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, dihydropiperidinyl, tetrahydrothiophenyl and the like. If the heterocycle contains a nitrogen, it is understood that the corresponding N-oxides thereof are also emcompassed by this definition.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

"Celite®" (Fluka) diatomite is diatomaceous earth, and can be referred to as "celite".

The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. Also when compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. Salts derived from inorganic bases include aluminum,

ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In one aspect of the invention the salts are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

For purposes of this specification, the following abbreviations have the indicated meanings:

AcOH	=	acetic acid
Ar	=	aryl
BuLi	=	normal butyl lithium
Bn	=	benzyl
Br_2	=	bromine
BINAP	=	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
18-crown-6	=	1,4,7,10,13,16-hexaoxacyclooctadecane
DAST	=	diethylaminosulfur trifluoride
DCE	=	1,2-dichloroethane
DCM	=	dichloromethane
DEA	=	diethylamine
DBU	=	2,3,4,6,7,8,9,10-Octahydropyrimidol[1,2-a]azepine
DIBAL-H	=	diisobutylaluminum hydride
DIPA	=	diisopropanolamine
DIEA	=	diisopropylethylamine

	DIPEA	=	diisopropylethylamine
	DMF	=	N,N-dimethylformamide
	DMSO	=	dimethylsulfoxide
	DTT	=	Dithiothreitol
	EDC	=	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
	EDTA	=	Ethylenediaminetetraacetic acid
	EtOAc	=	ethyl acetate
	Et_3N	=	triethylamine
	EtOH	=	ethanol
	HATU	=	2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (V)
	HBTU	=	*O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (V)
	HCl	=	hydrochloric acid
	Hex	=	hexanes
	H_2O	=	water
	HOAt	=	1-Hydroxy-7-azabenzotriazole
	Hunig's Base	=	diisopropylethylamine
	HPLC	=	high performance liquid chromatography
	IPA	=	isopropyl alcohol
	KOAc	=	potassium acetate
	K_3PO_4 H_2O	=	potassium phosphate tribasic monohydrate
	LG	=	leaving group
	Lawesson's reagent	=	2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide
	h	=	hour

	MeCN	=	acetonitrile
	MeOH	=	methanol
	MgBr	=	magnesium bromide
	$MgSO_4$	=	magnesium sulfate
	MTBE	=	methyl tert-butyl ether
	NaOMe	=	sodium methoxide
	Na_2SO_3	=	sodium sulfite
	Na_2SO_4	=	sodium sulfate
	$Na_2S_2O_3$	=	sodium thiosulfate
	NBS	=	N-Bromosuccinimide
	NMP	=	N-methylpyrrolidinone
	$PdCl_2$	=	palladium (II) chloride
	$PdCl_2$(dppf)	=	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	$Pd_2(dba)_3$	=	Tris(dibenzylideneacetone)dipalladium(0)
	$Pd(dtbpf)Cl_2$	=	[1,1′-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II)
	Pearlman's catalyst	=	palladium hydroxide on carbon
	PG	=	protecting group
	$Pd(OAc)_2$	=	palladium (II) acetate
	Pr_2NEt	=	*N,N*-diisopropylethylamine
	PyBOP	=	benzotriazol-1-yloxytris(pyrrolidino)phosphonium-hexafluorophosphate
	RT or rt	=	room temperature
	sat. aq.	=	saturated aqueous
	SFC	=	Supercritical fluid chromatography
	SiO_2	=	silicon dioxide

	TBAF	=	tetrabutylammonium fluoride
	tert-BuOK	=	potassium *tert*-butoxide
	TEA	=	triethylamine
	TfO	=	trifluoromethanesulfonate
5	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	tlc	=	thin layer chromatography
	TMS	=	trimethylsilyl
	TMSBr	=	bromotrimethylsilane
10	TPPTS	=	3,3′,3″-Phosphanetriyltris(benzenesulfonic acid) trisodium salt
	TsOH	=	4-methylbenzenesulfonic acid
	$SOCl_2$	=	thionyl chloride
	Me	=	methyl
	Et	=	ethyl
15	n-Pr	=	normal propyl
	i-Pr	=	isopropyl
	n-Bu	=	normal butyl
	i-Bu	=	isobutyl
	s-Bu	=	secondary butyl
20	t-Bu	=	tertiary butyl
	XPhos precatalyst	=	chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2- aminoethyl)phenyl)]palladium(II)

The compounds disclosed in the present application exhibited activity in the 25 following assays. In addition, the compounds disclosed in the present application have an enhanced pharmacological profile relative to previously disclosed compounds.

Cathepsin K Assay

Serial dilutions (1/3) from 500 μM down to 0.025 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 0.5 μL of DMSO from each dilution were added to 18.75 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) containing human cathepsin K (0.4 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 6.25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =360 nm; Emλ = 460 nm) for 30 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin L Assay

Serial dilutions (1/3) from 500 μM down to 0.025 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 0.5 μL of DMSO from each dilution were added to 18.75 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) containing human cathepsin L (0.027 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Leu-Arg-AMC (8 μM) in 6.25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =360 nm; Emλ = 460 nm) for 30 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve

Cathepsin B Assay

Serial dilutions (1/3) from 500 μM down to 0.025 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 0.5 μL of DMSO from each dilution were added to 18.75 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) containing human cathepsin B (0.1 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Boc-Leu-Lys-Arg-AMC (8 μM) in 6.25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =360 nm; Emλ = 460 nm) for 30 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin S Assay

Serial dilutions (1/3) from 500 μM down to 0.025 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 0.5 μL of DMSO from each dilution were added to 18.75 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) containing human cathepsin S (0.66 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Val-Val-Arg-AMC (8 μM) in 6.25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =360 nm; Emλ = 460 nm) for 20 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Cathepsin F assay

Serial dilutions (1/3) from 500 μM down to 0.025 μM of test compounds were prepared in dimethyl sulfoxide (DMSO). Then 0.5 μL of DMSO from each dilution were added to 18.75 μL of assay buffer (MES, 50 mM (pH 5.5); EDTA, 2.5 mM; DTT, 2.5 mM and 10% DMSO) containing human cathepsin F (10 nM) in assay buffer solution. The assay solutions were mixed for 5-10 seconds on a shaker plate and incubated for 15 minutes at room temperature. Z-Phe-Arg-AMC (8 μM) in 6.25 μL of assay buffer was added to the assay solutions. Hydrolysis of the coumarin leaving group (AMC) was followed by spectrofluorometry (Exλ =360 nm; Emλ = 460 nm) for 20 minutes. Percent of inhibition were calculated by fitting experimental values to standard mathematical model for dose response curve.

Pharmacokinetics in Rats

Per Os (PO) Pharmacokinetics in Rats

PROCEDURE:

The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

Male Sprague Dawley rats (250-400 g) are fasted overnight prior to each PO blood level study.

The rats are placed in the restrainer one at a time and the box firmly secured. The zero blood sample is obtained by nicking a small (1 mm or less) piece off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top to the bottom to milk out the blood. Approximately 0.5 mL of blood is collected into a heparinized vacutainer tube.

Compounds are prepared as required, in a standard dosing volume of 10 mL/kg, and administered orally by passing a 16 gauge, 3" gavaging needle into the esophagus.

Subsequent blood collections are taken in the same manner as the zero blood sample except that there is no need to nick the tail again. The tail is cleaned with a piece of gauze and milked/stroked as described above into the appropriately labeled tubes.

Immediately after sampling, blood is centrifuged, separated, the plasma put into clearly marked vials and stored in a freezer until analyzed.

Typical time points for determination of rat blood levels after PO dosing are:

0, 15min, 30min, 1h, 2h, 4h, 6h, 8h, 24h

After the 4 hr time point bleed, food is provided to the rats *ad libitum*. Water is provided at all times during the study.

Vehicles:

The following vehicles (with corresponding dose volumes) may be used in PO rat blood level determinations:

PEG 200/300/400 (0-60% in water):	equal or less than 10 mL/kg
Methocel (0.5% - 1.0% in water):	equal or less than 10mL/kg
Tween 80 (1-10% in water):	equal or less than 10mL/kg

Compounds for PO blood levels can be in suspension form. For better homogeneity, the suspension can be placed in a sonicator for approximately 5 minutes.

For analysis, aliquots are diluted with 1.2 to 1.5 volumes of acetonitrile optionally containing an internal standard and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with mass spectrometry (MS) or ultra-violet absorbance (UV) or fluorescence (Fluo) detection. Quantization is done relative to a standard curve prepared using clean blood samples spiked with a known quantities of drug in acetonitrile optionally containing an internal standard. Additional acetonitrile optionally containing internal standard is added to amount 1.2 to 1.5 volumes of the initial blood amount to correspond to what was done in the case of the samples. Bioavailability (F) is assessed by comparing area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUCpo}{AUCiv} \times \frac{DOSEiv}{DOSEpo} \times 100\%$$

and

$$AUC = (C1+C2)*(T2-T1)/2$$

where C is the measured concentration by MS or UV or Fluo at a given time T

Intravenous Pharmacokinetics in Rats

PROCEDURE:

The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

Male Sprague Dawley (325-375 g) non-fasted rats are used in theses studies.

The compound is prepared as required, in a standard dosing volume of 1 mL/kg.

Dosing of the conscious rats for intravenous administration is done via the jugular vein using a 25 gauge needle. This constitutes the zero time point.

The 5 min bleed is taken by nicking a piece (1-2 mm) off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top of the tail to the bottom to milk the blood out of the tail. Approximately 0.5 mL of blood is collected into a heparinized collection vial. Subsequent bleeds are taken in the same fashion, except that there is no need to nick the tail again. The tail is cleaned with a piece of gauze and bled, as described above, into the appropriate labeled tubes.

Typical time points for determination of rat blood levels after I.V. dosing are either:

0, 5 min, 15min, 30min, 1h, 2h, 4h, 6h

or 0, 5 min, 30min, 1h, 2h, 4h, 6h, 8h, 24h

Vehicles:

The following vehicles may be used in IV rat blood level determinations:

Dextrose: 1mL/kg

Moleculosol 25%: 1mL/kg

DMSO (dimethylsulfoxide): Restricted 10% of the dose volume up to 0.1 mL per kilogram of animal

PEG 200: Not more than 80% mixed with 20% sterile water - 1mL/kg

With Dextrose, either sodium bicarbonate can be added if the solution is cloudy.

For analysis, aliquots are diluted with 1.2 to 1.5 volumes of acetonitrile optionally containing an internal standard and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with mass spectrometry (MS) or ultra-violet absorbance (UV) or fluorescence (Fluo) detection. Quantization is done relative to a standard curve prepared using clean blood samples spiked with a known quantities of drug in acetonitrile optionally containing an internal standard. Additional acetonitrile optionally containing internal standard is added to amount 1.2 to 1.5 volumes of the initial blood amount to correspond to what was done in the case of the samples. Bioavailability (F) is assessed by comparing area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUCpo}{AUCiv} \times \frac{DOSEiv}{DOSEpo} \times 100\%$$

and

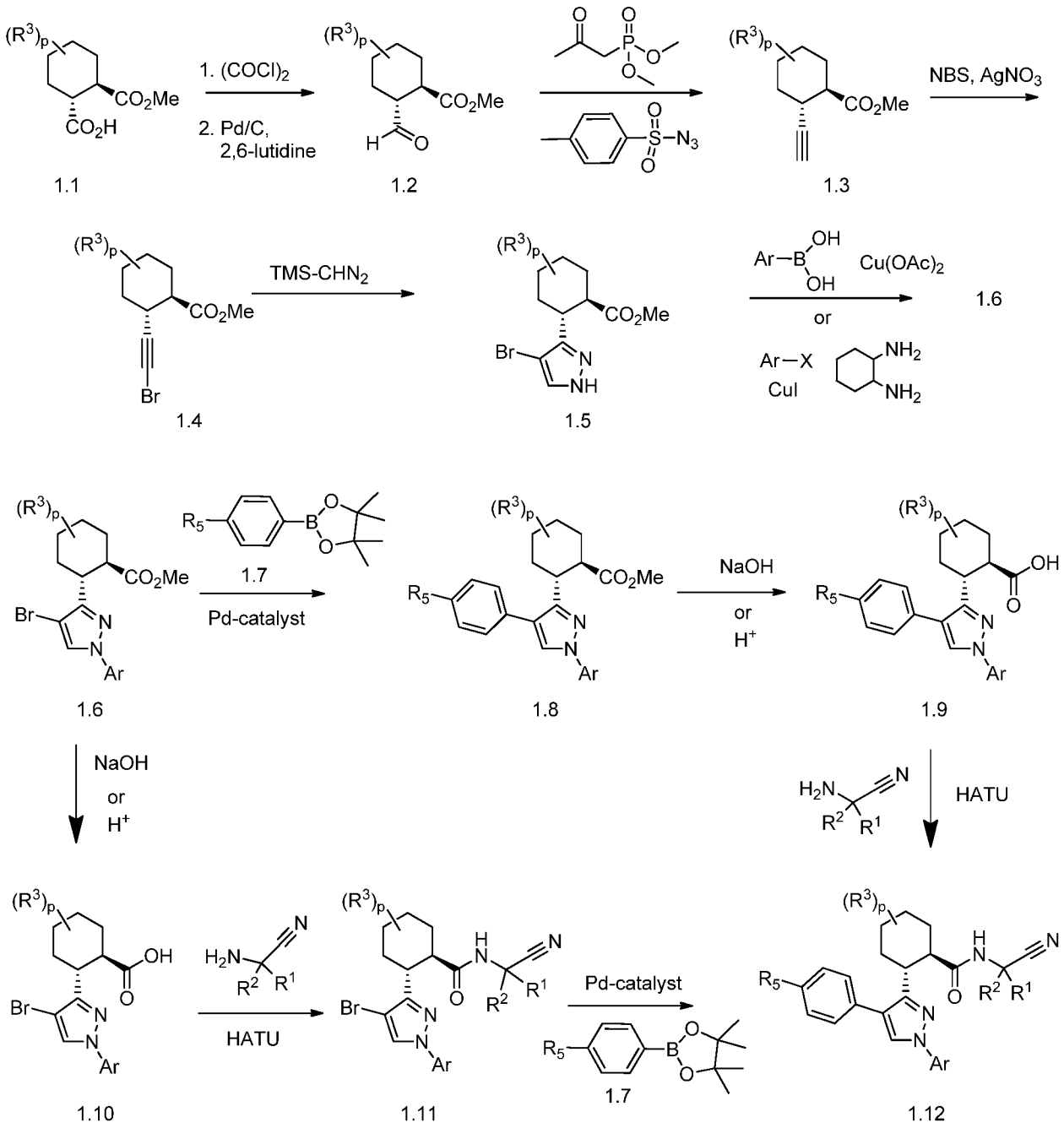
$$AUC = (C1+C2)*(T2-T1)/2$$

where C is the measured concentration by MS or UV or Fluo at a given time T.

Hepatocyte Incubations

For rat hepatocyte incubations, 1 x 10^6 cells diluted in 0.5 mL of Krebs-Henseleit buffer were first prepared at 37°C for 20 min under 95%:5% O_2:CO_2 (BOC gases: Montreal, Canada) in a 48-well plate, and the 5 µL of a 10 mM solution of compound dissolved in acetonitrile were added to each well to a final concentration of 50 µM. After 2 h of incubation at 37°C under 95%:5% O_2:CO_2 atmosphere, one volume of acetonitrile was added in each well. A quenched incubation spiked with the parent compound and a blank were also prepared as controls. Once transferred, samples were centrifuged for 10 min at 14,000 rpm using an Eppendorf 5415C centrifuge (Hamburg, Germany) and the supernatant used for LC/UV/MS analysis.

SCHEME 1



Compounds of the present invention may be prepared according to Scheme 1. Thus, compound 1.1 is converted to an acid chloride by treatment with oxalyl chloride, which undergoes palladium catalyzed hydrogenation in the presence of 2,6-lutidine providing aldehyde 1.2. Ohira-Bestmann homologation of aldehyde 1.2 by dimethyl (1-diazo-2-oxopropyl)phosphonate that is generated in situ from dimethyl (2-oxopropyl)phosphonate and diazo transfer reagent (such as but not limited to Tosyl azide) leads to alkyne 1.3. Bromination of terminal acetylene 1.3 with NBS in the presence of $AgNO_3$ leads to bromide

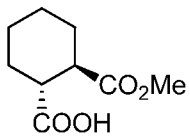
1.4. 1,3-Dipolar cycloaddition of bromo alkyne 1.4 with TMS-diazomethane provides pyrazole 1.5.

N-arylation of pyrazole 1.5 with aryl boronic acids in the presence of $Cu(OAc)_2$ effectively provides compound 1.6. In addition, compound 1.6 may be prepared from pyrazole 1.5 and aryl halides by copper-diamine-catalyzed *N*-arylation. Palladium-catalyzed Suzuki cross-coupling reaction of bromo-pyrazole 1.6 with corresponding organoborane 1.7 or corresponding organoboronic acid affords compound 1.8. Hydrolysis of ester 1.8 with either aqueous base or acid leads to carboxylic acid 1.9 that can be coupled with corresponding amines in the presence of amide coupling reagents (such as, but not limited to, HATU) giving the desired compounds 1.12 of the current invention.

Alternatively, compounds of the present invention may be prepared by hydrolysis of ester 1.6 with either aqueous base or acid leading to 1.10. Resulting carboxylic acid 1.10 can be coupled with corresponding amines in the presence of amide coupling reagents (such as, but not limited to, HATU) giving amides 1.11. Palladium-catalyzed Suzuki cross-coupling reaction of bromo-pyrazole 1.11 with the corresponding organoborane 1.7 or corresponding organoboronic acid affords the desired compounds 1.12 of the current invention.

SYNTHESIS OF INTERMEDIATES

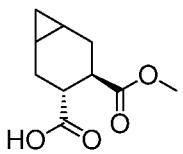
INTERMEDIATE 1



(1*R*,2*R*)-2-(methoxycarbonyl)cyclohexanecarboxylic acid

This compound can be prepared from (1R,2S)-dimethyl cyclohex-4-ene-1,2-dicarboxylate following a similar procedure as described in *J. Am. Chem. SOC.* 1995, 117,10905-10913 and in HELVETICA CHIMICA ACTA- Vol. 70 (1987), p.142.

INTERMEDIATE 2



(3*R*,4*R*)-4-(methoxycarbonyl)bicyclo[4.1.0]heptane-3-carboxylic acid

Step A: (1R,2S)-1-Benzyl 2-methyl cyclohex-4-ene-1,2-dicarboxylate

Into a 50-mL round-bottom flask, was placed a solution of (1R,6S)-6-(methoxycarbonyl)cyclohex-3-enecarboxylic acid(2.40 g, 13.0 mmol, 1.00 equiv) in *N*,*N*-dimethylformamide (30 mL). To this solution was added potassium carbonate (3.59 g, 26.0 mmol, 2.00 equiv). This was followed by the addition of benzyl bromide (3.34 g, 19.5 mmol, 1.50 equiv) dropwise with stirring at ambient temperature. The reaction mixture was stirred for 16 h at ambient temperature. The resulting mixture was diluted with brine (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was applied onto silica gel column chromatography with ethyl acetate/petroleum ether (1:30-1:15). This resulted in of (1*R*,2*S*)-1-benzyl 2-methyl cyclohex-4-ene-1,2-dicarboxylate as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.43-7.30 (m, 5H), 5.69 (s, 2H), 5.14 (s, 2H), 3.58 (s, 3H), 3.14-3.05 (m, 2H), 2.64-2.53 (m, 2H), 2.42-2.34 (m, 2H); MS(ES,*m/z*): 275.1 (M + 1).

Step B: (3R,4S)-3-Benzyl 4-methyl bicyclo[4.1.0]heptane-3,4-dicarboxylate

Into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of diethylzinc (1 M in hexane, 46.8 mL, 4.00 equiv) in anhydrous dichloromethane (150 mL). This was followed by the addition of trifluoroacetic acid (5.34 g, 46.8 mmol, 4.00 equiv) dropwise with stirring at 0 °C. To this solution was added diiodomethane (12.5 g, 46.8 mmol, 4.00 equiv) dropwise with stirring at 0 °C and the mixture was stirred for 15 min at 0 °C. Then a solution of (1*R*,2*S*)-1-benzyl 2-methyl cyclohex-4-ene-1,2-dicarboxylate (3.20 g, 11.7 mmol, 1.00 equiv) in anhydrous dichloromethane (50 mL) was added dropwise with stirring at 0 °C. The reaction solution was stirred and warmed slowly to ambient temperature for 16 h. The reaction solution was quenched by the addition of water (300 mL) and extracted with dichloromethane (3 x 200 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was applied onto silica gel column chromatography with ethyl acetate/petroleum ether (1:20-1:10). This resulted in of (3*R*,4*S*)-3-benzyl 4-methyl bicyclo[4.1.0]heptane-3,4-dicarboxylate as light yellow oil:MS(ES,*m/z*): 289.0 (M + 1).

Step C: (3R,4S)-4-(Methoxycarbonyl)bicyclo[4.1.0]heptane-3-carboxylic acid

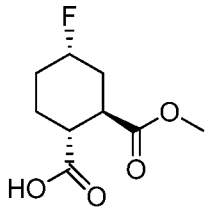
Into a 250-mL round-bottom flask was placed a solution of (3*R*,4*S*)-3-benzyl 4-methyl bicyclo[4.1.0]heptane-3,4-dicarboxylate (3.10 g, 10.8 mmol, 1.00 equiv) in methanol (100 mL), followed by the addition of palladium 10% on carbon (0.300 g, wetted with ca. 55% water). The reaction mixture was degassed with hydrogen for 3 times and stirred under

hydrogen balloon for 16 h at ambient temperature. The solid was filtered out. The filtrate was concentrated under vacuum. This resulted in of crude (3*R*,4*S*)-4-(methoxycarbonyl)bicyclo[4.1.0]heptane-3-carboxylic acid as a colorless oil, which was used directly in next step without further purification: MS(ES,*m/z*): 199.2 (M + 1).

Step D: (3R,4R)-4-(Methoxycarbonyl)bicyclo[4.1.0]heptane-3-carboxylic acid

Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed anhydrous methanol (130 mL). This was followed by the addition of sodium (2.00 g, 87.0 mmol, 8.21 equiv) in portions at 0 °C. The resulting mixture was stirred for 30 min at ambient temperature until sodium disappeared. To this solution was added a solution of (3*R*,4*S*)-4-(methoxycarbonyl)bicyclo[4.1.0]heptane-3-carboxylic acid (2.10 g, 10.6 mmol, 1.00 equiv) in methanol (20 mL). The resulting solution was refluxed for 16 h. The reaction mixture was cooled to 0 °C. The pH value was adjusted to 4 with aqueous hydrochloricacid solution (1 M). The resulting mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under vacuum. The residue was applied onto silica gel column chromatography with ethyl acetate/petroleum ether (1:5-1:3). This resulted in of (3*R*,4*R*)-4-(methoxycarbonyl)bicyclo[4.1.0]heptane-3-carboxylic acid as a light yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.30-12.10 (brs, 1H), 3.55 (s, 3H), 2.36-2.25 (m, 3H), 2.12-2.04 (m, 1H), 1.79-1.74 (m, 1H), 1.36-1.34 (m, 1H), 0.99-0.95 (m, 2H), 0.63-0.60 (m, 1H), 0.10-0.08 (m, 1H); MS(ES,*m/z*): 199.2 (M + 1).

INTERMEDIATE 3



(1R,2R,4S)-4-fluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid

Step A: (7R,8R)-dimethyl 1,4-dioxaspiro[4.5]decane-7,8-dicarboxylate

The solution of (1R,2R)-dimethyl 4-oxocyclohexane-1,2-dicarboxylate (300 g, 1.4 mol) in toluene (6 L) was added ethylene glycol (117 ml, 2.1 mol) and TsOH (5.29 g, 0.028 mol). The resulted solution was refluxed for 6 hours. The reaction mixture was cool to 23 °C and washed with saturated $NaHCO_3$ (2 x 5 L) and water once. The organic phase was concentrated giving (7R,8R)-dimethyl 1,4-dioxaspiro[4.5]decane-7,8-dicarboxylateas a yellow oil.

Step B: (7R,8R)-7-(methoxycarbonyl)-1,4-dioxaspiro[4.5]decane-8-carboxylic acid

*In a 50 L round buttom flask equipped with overhead stirring and pH Stat, NZL-102 enzyme(*available from Codexis, Inc., *200 Penobscot* Drive, Redwood City, CA 94063, *www.codexis.com, tel. 1-650-421-8100) (60 g (5 g/L)) was dissolved in 24 L of phosphate buffer pH 7. (7R,8R)-Dimethyl 1,4-dioxaspiro[4.5]decane-7,8-dicarboxylate (300 g, 1.16 mol) in 300 mL of DMSO solution was added dropwise and aged at 23 °C overnight. The reaction mixtures was dissolved in 3:1=EtOAc: IPA, extracted and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated giving (7R,8R)-7-(methoxycarbonyl)-1,4-dioxaspiro[4.5]decane-8-carboxylic acid as a yellow solid.*

Step C: (7R,8R)-8-benzyl 7-methyl 1,4-dioxaspiro[4.5]decane-7,8-dicarboxylate

To the solution of (7R,8R)-7-(methoxycarbonyl)-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (2.9 g, 11.87 mmol) in DMF (20 ml) was added K_2CO_3 (2.461 g, 17.81 mmol) and then (bromomethyl)benzene (3.05 g, 17.81 mmol) and KI (394 mg, 2.375 mmol). The resulting suspension was stirred at RT overnight. The reaction mixture was extracted with EtOAc and purified by flash chromatography on silica gel giving (7R,8R)-8-benzyl 7-methyl 1,4-dioxaspiro[4.5]decane-7,8-dicarboxylate as oil.

Step D: (1R,2R)-1-benzyl 2-methyl 4-oxocyclohexane-1,2-dicarboxylate

To the solution of of (7R,8R)-8-benzyl 7-methyl 1,4-dioxaspiro[4.5]decane-7,8-dicarboxylate (2.95 g, 8.82 mmol) in acetone (40 ml) was added 1N HCl (40 mL) and the resulting mixture was heated at 60 °C for 1 hour. The reaction mixture was diluted with EtOAc/water, organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel giving (1R,2R)-1-benzyl 2-methyl 4-oxocyclohexane-1,2-dicarboxylate as a clear oil.

Step E: (1R,2R,4R)-1-benzyl 2-methyl 4-hydroxycyclohexane-1,2-dicarboxylate

The solution of (1R,2R)-1-benzyl 2-methyl 4-oxocyclohexane-1,2-dicarboxylate (2.6 g, 8.96 mmol) in THF (45 ml) was cooled with salt ice bath (~ -5 °C) and $NaBH_4$ (0.678 g, 17.91 mmol) was added. The resulted solution was stirred at 0 °C for 2 hours. The reaction mixture was quenched carefully with water and EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel giving the desired alcohol (1R,2R,4R)-1-benzyl 2-methyl 4-hydroxycyclohexane-1,2-dicarboxylate.

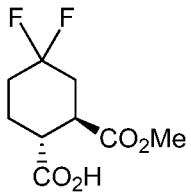
Step F: (1R,2R,4S)-1-benzyl 2-methyl 4-fluorocyclohexane-1,2-dicarboxylate

To a solution of morpholinodifluorosulfinium tetrafluoroborate(1.704 g, 7.01 mmol) in DCM (4 mL) was added triethylamine trihydrofluoride (2.261 g, 14.03 mmol). The resulting suspension was stirred for 10 min at RT and cooled to -78 °C. (1R,2R,4R)-1-Benzyl 2-methyl 4-hydroxycyclohexane-1,2-dicarboxylate (2.05 g, 7.01 mmol) solution in DCM (10 mL) was added with internal temp kept < -40 °C. The mixture was stirred at -40 °C for ~ 30 min. The reaction was quenched at low temperature with water. The isolated organic phase was washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (ISCO column, 12 g silica gel, 0-20% EtOAc/heptane) giving of (1R,2R,4S)-1-benzyl 2-methyl 4-fluorocyclohexane-1,2-dicarboxylate as a colorless oil.

Step G: (1R,2R,4S)-4-fluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid

The suspension of Pd/C (10%) (122 mg, 0.115 mmol) in EtOAc (1 ml) was added to (1R,2R,4S)-1-benzyl 2-methyl 4-fluorocyclohexane-1,2-dicarboxylate (675 mg, 2.293 mmol). The resulted suspension was stirred at 1 atm H_2 balloon for 5 hour. The reaction mixture was filtered and concentrated to give the desired (1R,2R,4S)-4-fluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid as a colorless oil.

INTERMEDIATE 4



(1R,2R)-4,4-difluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid

Step A: (1R,2R)-dimethyl 4-oxocyclohexane-1,2-dicarboxylate

Racemic dimethyl 4-oxocyclohexane-1,2-dicarboxylate (660 g) was chaged into 11 L of 50 mM phosphate buffer, pH =6.8. Esterase K310-903 (available from Dow Chemical Company, www.dow.com) (25 mL) was added to the solution and the resulting mixture was stirred at 30 °C overnight. SFC shows the reaction was done. 1N NaOH was added to pH=7 and the solution was extracted with MTBE (4 x 8 L). The combined organic fraction was washed with brine, dry (Na_2SO_4), and filtered. Removal the solvent by evaporation gave (1R,2R)-dimethyl 4-oxocyclohexane-1,2-dicarboxylate as oil.

Step B: (1R,2R)-dimethyl 4,4-difluorocyclohexane-1,2-dicarboxylate

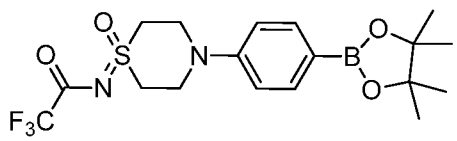
To a solution of $Et_3N.3HF$ (224 g, 1.38 mol) in DCE (2.8 L) was added $DAST.BF_3$ (630 g, 2.74 mol). The resultant suspension was stirred for 10 min and then (1R,2R)-

dimethyl 4-oxocyclohexane-1,2-dicarboxylate (280 g, 1.31 mol) was added. The mixture was heated at 55 °C overnight. The reaction mixture was poured into sat. $NaHCO_3$ (5.6 L) and then extracted with DCM (2 L x 3). The organic layer was dried (Na_2SO_4), concentrated and purified by flash chromatography (petrolium ether/EtOAc=15:1) to afford of pale yellow oil.The yellow oil was dissolved in 4 L DCM. 3 L of 5% KMnO4 aq. solution was added. The mixture was stirred at 23 °C overnight. The organic layer was separated, washed with 3 L of 5% $KMnO_4$ for another 3 hour. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to dryness giving (1R,2R)-dimethyl 4,4-difluorocyclohexane-1,2-dicarboxylateas white solid (230 g, 74.5%). ^1H NMR 400MHz ($CDCl_3$):δ 8.19-8.22 (m, 2H), 7.83 (d, *J*=8.1 Hz, 1H), 7.65-7.69 (m, 1H), 7.52-7.55 (m, 2H), 7.37 (s, 1H), 7.22 (dd, *J*=8.1 Hz, *J*=2.0 Hz, 1H), 3.17-3.20 (m, 2H), 2.73-2.76 (m, 2H).

Step C: (1R,2R)-4,4-difluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid

Cal B enzyme(available from Novozymes North America, 77 Perry Chapel Church Road Franklinton, NC 27525, United States, Phone: 919-494-3000) (26.5 mL) was dissolved in 0.1M phosphate buffer at pH 7.0 (6.8 L). (1R,2R)-dimethyl 4,4-difluorocyclohexane-1,2-dicarboxylate (100 g) in DMSO (300 mL) was added into the reaction mixture and stirred at 25 °C for 6 hours. The solution was washed with brine (1 L) and extracted with MTBE (3 L* 4). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to dryness giving (1R,2R)-4,4-difluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid as white solid. ^1H NMR 400MHz $CDCl_3$:δ 3.65 (S, 3H), 2.93 (m, 1H), 2.68 (m, 1H), 2.39 (m, 1H), 2.12 (m, 2H), 1.74 (m, 3H).

INTERMEDIATE 5



2,2,2-Trifluoro-N-(1-oxido-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholin-1-ylidene)acetamide

Step A: 4-(4-Bromophenyl)thiomorpholine

To the solution of thiomorpholine (7 g, 67.8 mmol) in toluene (170 mL) in 500 mL round bottom flask under N_2 were added 1,4-dibromobenzene (20.8 g, 88 mmol), $Pd_2(dba)_3$ (1.55 g, 1.7 mmol), BINAP (2.112 g, 3.39 mmol), and *tert*-BuOK (16.3 g, 170 mmol). The reaction mixture was heated at 86 °C for 1.5-2 h. The reaction mixture was quenched with

water (600 mL). The resulting mixture was extracted with EtOAc (3 x 600 mL). The combined organic fractions were washed with brine (600 mL), dried ($MgSO_4$), filtered, and solvent was removed under reduced pressure. The residue was purified by flash chromatography on ISCO silica gel column (Hexane/EtOAc (0-10%) giving 4-(4-bromophenyl)thiomorpholine as light yellow solid.

Step B: 4-(4-Bromophenyl)thiomorpholine 1-oxide

4-(4-bromophenyl)thiomorpholine (200 mg, 0.775 mmol) was dissolved in CH_3CN (5 mL) in a round bottom flask. $FeCl_3$ hydride (7.9 mg, 0.029 mmol) and periodic acid (194 mg, 0.852 mmol) were added to the solution at 23 °C, and the resulting mixture was stirred over night at room temperature. EtOAc (60-70 mL) was added to the reaction mixture and the solution was washed with brine (3 x 50 mL). Most of the solid gets dissolved during work up. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO, CH_2Cl_2/MeOH = 0-10%) giving 4-(4-bromophenyl)thiomorpholine-1-oxideas an off-white solid.

Step C: N-(4-(4-Bromophenyl)-1-oxidothiomorpholin-1-ylidene)-2,2,2-trifluoroacetamide

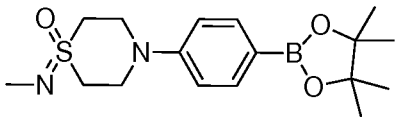
To the solution of 4-(4-bromophenyl)thiomorpholine 1-oxide (11 g, 40.1 mmol) in CH_2Cl_2 (150 mL) in 250 mL round bottom flask under N_2 was added 2,2,2-trifluoroacetamide (11.46 g, 101 mmol), iodobenzene diacetate (20 g, 1.55 eq, 62.1 mmol), magnesium oxide (6.63 g, 4 eq, 160 mmol), and Rhodium(II) acetate dimer (1.67 g, 3.78 mmol). The reaction mixture was stirred at 40 °C under N_2 for overnight. The solids were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO, Hexanes/EtOAc (0-50%) giving N-(4-(4-bromophenyl)-1-oxidothiomorpholin-1-ylidene)-2,2,2-trifluoroacetamide as a light yellow solid.

Step D: 2,2,2-Trifluoro-N-(1-oxido-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholin-1-ylidene)acetamide

To the solution of N-(4-(4-bromophenyl)-1-oxidothiomorpholin-1-ylidene)-2,2,2-trifluoroacetamide (0.5 g, 1.3 mmol) in anhydrous DMSO (6.5 mL) were added bis(pinacolato)diboron (1.1 g, 4.33 mmol), $Pd(dppf)Cl_2$ (100 mg, 0.137 mmol), and KOAc (0.637 g, 6.49 mmol). The resulting mixture was heated at 100 °C for 6 h, then left at RT for overnight. The reaction mixture was diluted with water (60 mL) and the resulting mixture was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO, Hexanes/EtOAc (0-45%)) giving

2,2,2-Trifluoro-N-(1-oxido-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholin-1-ylidene)acetamide as a white solid.

INTERMEDIATE 6



1-(Methylimino)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1-oxide

Step A: 4-(4-Bromophenyl)-1-iminothiomorpholine 1-oxide

N-(4-(4-bromophenyl)-1-oxidothiomorpholin-1-ylidene)-2,2,2-trifluoroacetamide from Step C of INTERMEDEATE 5 (1 g, 2.6 mmol) was dissolved in MeOH (15 mL) and THF (4 mL). K_2CO_3 (2.2 g, 12.41 mmol) was added to the solution and the reaction mixture was stirred at 23 °C for 1 hour and filtered through a celite/silica gel short layer. The solvent was removed under reduced pressure giving orange residue that was dissolved in water, added 1 N HCl until solution got pH 3-4. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure giving 4-(4-bromophenyl)-1-iminothiomorpholine 1-oxide. The product was used in the next step without further purification.

Step B: 4-(4-Bromophenyl)-1-(methylimino)thiomorpholine 1-oxide

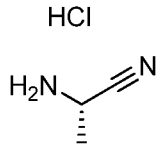
4-(4-Bromophenyl)-1-iminothiomorpholine 1-oxide (620 mg, 2.14 mmol) was dissolved in MeOH (17 mL). Added 37% solution of formaldehyde (1.6 mL, 21.44 mmol) and bromocresol green as an internal pH indicator. 1 N NaOH was added until solution turned dark green-blue. The resulting mixture was stirred for 5 min. AcOH was added to the solution until it became dark yellow color followed by the addition of $NaCNBH_3$ (148 mg, 2.36 mmol). The reaction mixture was stirred for 5 min, AcOH was used to adjust pH of the reaction and more $NaCNBH_3$ (240 mg) was added. The addition of AcOH and $NaCNBH_3$had to be repeated until all starting material was consumed. The reaction mixture was quenched with water (keeping reaction flask in the cold water bath), then with saturated $NaHCO_3$ until the solution turned light blue and stopped bubbling. The resulting mixture was extracted with CH_2Cl_2 (4 x 10 mL). Combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by Reverse Phase HPLC (Gilson, water/CH_3CN (0.1% TFA)=10-80%, 20 min. Fractions with the product were combined, quenched with saturated $NaHCO_3$ solution, and extracted with

CH_2Cl_2 (3 x 50 mL). Combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated, giving 4-(4-bromophenyl)-1-(methylimino)thiomorpholine-1-oxide.

Step C: 1-(Methylimino)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1-oxide

To the solution of 4-(4-bromophenyl)-1-(methylimino)thiomorpholine 1-oxide (0.2 g, 0.66 mmol) in anhydrous DMSO (4 mL) were added bis(pinacolato)diboron (670 g, 2.64 mmol), $Pd(dppf)Cl_2$ (96 mg, 0.132 mmol), and KOAc (0.450 g, 4.63 mmol). The reaction mixture was heated at 100 °C for 1 hour. The reaction mixture was diluted with water (60 mL) and the resulting mixture was extracted with EtOAc (4 x 60 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO, EtOAc) giving 1-(methylimino)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1-oxide as an off white solid.

INTERMEDIATE 7



(S)-2-aminopropanenitrile hydrochloride

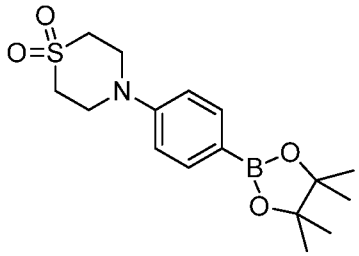
Step A: (S)-Benzyl (1-cyanoethyl)carbamate

To a solution of (S)-benzyl (1-amino-1-oxopropan-2-yl)carbamate (7.070 g, 31.8 mmol) in DMF (70.7 ml) was added 2,4,6-trichloro-1,3,5-triazine (2.93 g, 15.91 mmol) and the resulting mixture was stirred at RT for 1 hour. The reaction mixture was then added slowly to 500 mL stirring ice water (not much ice). The resulting thick suspension stirred for 30 min, filtered, washed with water, and dried on filter overnight giving (S)-benzyl (1-cyanoethyl)carbamate as a white solid: MS(ES,*m/z*): 205.2 (M + 1).

Step B: (S)-2-aminopropanenitrile hydrochloride (INTERMEDIATE 5)

To a solution of (S)-benzyl (1-cyanoethyl)carbamate (6.042 g, 29.6 mmol) in EtOAc (296 ml) was added Pearlman's catalyst (1g, 1.424 mmol) and the resulting mixture was pressurized to 1atm under H_2 balloon. The reaction mixture was stirred under H_2 at 1 atm for overnight. Palladium catalyst was filtered away and 4M HCl in dioxane (16.27 ml, 65.1 mmol) was added to the solution leading to formation of white suspension. The mixture was concentrated under reduced pressure giving crude (S)-2-aminopropanenitrile hydrochloride as an off white solid. The material was used without further purification.

INTEMEDIATE 8



4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide

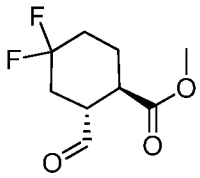
Step A: 4-(4-Bromophenyl)thiomorpholine 1,1-dioxide

Dissolved a mixture of 1,4-dibromobenzene (10.014 g, 42.4 mmol) and thiomorpholine 1,1-dioxide (5.16 g, 38.2 mmol) in dioxane (150 mL), then added $Pd(OAc)_2$ (959 mg, 4.24 mmol), BINAP (racemic) (2.64 g, 4.24 mmol), and Cs_2CO_3 (41.48 g, 127 mmol). The reaction mixture was degassed several times then connected to a reflux condensor under nitrogen and heated to 100 °C for overnight. The reaction was cooled to RT then filtered through celite, and washed with EtOAc. The resulting solution was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (0-50% EtOAc in hexanes) to yield the desired 4-(4-Bromophenyl)thiomorpholine 1,1-dioxideas a light yellow solid. MS (ES, *m/z*): 292.1(M + 1).

Step B: 4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide

Dissolved 4-(4-Bromophenyl)thiomorpholine 1,1-dioxide (4.93 g, 16.99 mmol) in dioxane (24 mL) then added bis(pinacolato)diboron (5.18 g, 20.39 mmol), $PdCl_2(dppf)$-CH_2Cl_2 Adduct (1.39 g, 1.7 mmol), and KOAc (5 g, 51 mmol). The reaction flask was topped with a reflux condensor and degassed by pulling a vacuum on the mixture then backfilling with nitrogen several times. The mixture was heated to 80 °C for 12 hours. the rxn was added to brine then extracted w/ EtOAc. The combined organic extracts were dried over Na_2SO_4 then filtered, concentrated, and purified on silica (0-40% EtOAc in hexanes) to yield the desired product as a light yellow solid.

INTERMEDIATE 9



(1R,2R)-Methyl 4,4-difluoro-2-formylcyclohexanecarboxylate

Step A: (1R,2R)-2-((Benzyloxy)methyl)-4,4-difluorocyclohexanecarbaldehyde

Into a 100-mL round-bottom flask purged and maintained under nitrogen, were added oxalyl chloride (2.10 g, 16.7 mmol, 1.50 equiv) and DCM (10 mL). The flask was degassed and back-filled with nitrogen 3 times. This was followed by the dropwise addition of the solution of DMSO (1.73 g, 22.2 mmol, 2.00 equiv) in DCM (10 mL) at -78 °C for 30 min followed by the addition of the solution of ((1*R*,2*R*)-2-((benzyloxy)methyl)-4,4-difluorocyclohexyl)methanol (3.00 g, 11.1 mmol, 1.00 equiv) in DCM (5 mL). The reaction mixture was stirred at -78 °C for 2 hours followed by the addition of TEA (10 mL). The solution was stirred at -78 °C for 3 hours, and diluted with water (20 mL). The resulting mixture was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine (3 x 50 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:10) giving (1*R*, 2*R*)-2-((benzyloxy)methyl)-4, 4-difluorocyclohexanecarbaldehyde as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.59 (s, 1H), 7.61 - 7.05 (m, 5H), 4.41 (s, 2H), 3.62 - 3.31 (m, 2H), 2.40 - 2.16 (m, 4H), 2.05 - 1.44 (m, 4H).

Step B: (1R,2R)-2-((Benzyloxy)methyl)-4,4-difluorocyclohexanecarboxylic acid

Into a 250-mL round-bottom flask, were added (1*R*, 2*R*)-2-((benzyloxy)methyl)-4, 4-difluorocyclohexanecarbaldehyde (8.00 g, 29.8 mmol, 1.00 equiv), sodium chlorite (10.7 g, 1.19 mol, 4.00 equiv), KH_2PO_4 (32.0 g, 2.38 mol, 8.00 equiv), THF (40 mL), water (40 mL), BuOH (10 mL), and 2-methylbut-2-ene (30 mL). The reaction mixture was stirred at 25 °C for 3 hours and water (50 mL) was added to the reaction. The resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried giving (1R,2R)-2-((benzyloxy)methyl)-4,4-difluorocyclohexanecarboxylic acid as a colorless oil. MS (ES, *m/z*): 283.2 (M-1).

Step C: (1R,2R)-Methyl 2-((benzyloxy)methyl)-4,4-difluorocyclohexanecarboxylate

Into a 50-mL round-bottom flask, were added (1R,2R)-2-((benzyloxy)methyl)-4,4-difluorocyclohexanecarboxylic acid (3.50 g, 12.3 mmol, 1.00 equiv), DBU (2.10 g, 13.8 mmol, 1.12 equiv), toluene (20 mL) and MeI (3.50 g, 24.6 mmol, 2.00 equiv). The reaction mixture was stirred at 25 °C for 16 hours, and then concentrated under reduced pressure. The residue was applied purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:10) giving (1R,2R)-methyl 2-((benzyloxy)methyl)-4,4-difluorocyclohexanecarboxylate as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.36-

7.26 (m, 5H), 4.50-4.41 (m, 2H), 3.61 (s, 3H), 3.41-3.35 (m, 2H), 2.41-2.04 (m, 4H), 1.95-1.58 (m, 4H); MS (ES, *m/z*): 299.1 (M + 1).

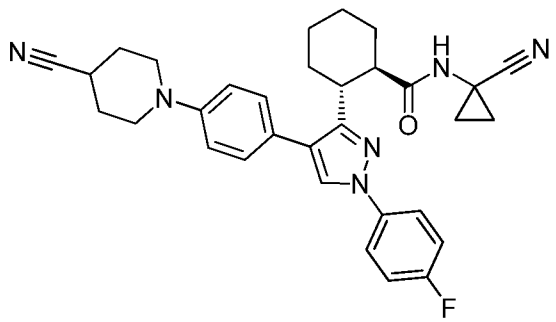
Step D: (1R,2R)-Methyl 4,4-difluoro-2-(hydroxymethyl)cyclohexanecarboxylate

Into a 100-mL round-bottom flask were added (1R,2R)-methyl 2-((benzyloxy)methyl)-4,4-difluorocyclohexanecarboxylate (7.00 g, 23.5 mmol, 1.00 equiv), MeOH (50 mL), $Pd(OH)_2/C$(10%, 2.00 g, 16.7 mmol, 0.700 equiv). The flask was degassed with hydrogen for 3 times and stirred under H_2 balloon for 16 hours. The solids were filtered out and the filtrate was concentrated under reduced pressure giving (1R,2R)-methyl 4,4-difluoro-2-(hydroxymethyl)cyclohexanecarboxylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.05 (s ,3H), 3.71-3.51 (m, 2H), 2.43-2.39 (m, 2H), 2.36-2.17 (m, 2H), 2.16-1.92 (m, 2H), 1.88-1.45 (m, 2H).

Step E: (1R,2R)-Methyl 4,4-difluoro-2-formylcyclohexanecarboxylate

Into a 100-mL round-bottom flask purged and maintained under nitrogen, were added oxalyl chloride (2.00 g, 15.8 mmol, 1.64 equiv) and DCM (15 mL). The flask was degassed and back-filled with nitrogen 3 times followed by the dropwise addition of the solution of DMSO (1.45 g, 18.6 mmol, 1.93 equiv) in DCM (10 mL) with stirring at -78 °C for 30 min. (1R,2R)-Methyl 4,4-difluoro-2-(hydroxymethyl)cyclohexanecarboxylate (2.00 g, 9.61 mmol, 1.00 equiv) in DCM (5 mL) was added dropwise to this solution -78 °C. The reaction mixture was stirred at -78 °C for 30 min followed by the addition of TEA (10 mL). The reaction mixture was stirred at -78 °C for 3 hours, diluted with water (20 mL), and the resulting mixture was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine (3 x 50 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:4) giving (1R,2R)-methyl 4,4-difluoro-2-formylcyclohexanecarboxylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.68 (s, 1H), 3.72 (s, 3H), 3.19-3.06 (m, 1H), 2.82-2.60 (m, 1H), 2.39-1.74 (m, 6H).

EXAMPLE 1



(1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(4-cyanopiperidin-1-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 1)

Step A: (1R,2R)-Methyl 2-formylcyclohexanecarboxylate

Oxalyl chloride (25.3 g, 201 mmol, 1.50 equiv) was added dropwise to a solution of (1*R*,2*R*)-2-(methoxycarbonyl)cyclohexanecarboxylic acid (25.0 g, 134 mmol, 1.00 equiv) in dichloromethane (30.0 mL) followed by the addition of one drop of DMF at 0 °C. The resulting solution was stirred for 3 h at ambient temperature. The solution was concentrated under reduced pressure to give (1R,2R)-methyl 2-(chlorocarbonyl)cyclohexanecarboxylate as a semi-solid that was dissolved in THF (30.0 mL). To the above solution were added 2,6-dimethylpyridine (21.5 g, 201 mmol, 1.50 equiv) and palladium on carbon (10%, 2.00 g, 16.7 mmol, 0.125 equiv). The flask was degassed and back-filled with hydrogen 3 times and stirred under hydrogen balloon for 16 h at ambient temperature. The solids were filtered out. The filtrate was diluted with ethyl acetate (100 mL), washed with aqueous HCl solution (1.0 M, 100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:50) giving (1*R*,2*R*)-methyl 2-formylcyclohexanecarboxylate as a light yellow oil.^{1}HNMR (300 MHz, $CDCl_3$) δ ppm 9.66 (s, 1H), 3.71 (s, 3H), 2.77-2.52 (m, 2H), 2.18-2.02 (m, 2H), 1.91-1.78 (m, 2H), 2.51-1.17 (m, 4H).

Step B: (1R,2R)-Methyl 2-ethynylcyclohexanecarboxylate

A mixture of dimethyl (2-oxopropyl)phosphonate (10.2 g, 61.1 mmol, 1.30 equiv), 4-methylbenzene-1-sulfonyl azide (12.3 g, 62.5 mmol, 1.33 equiv) and K_2CO_3 (19.5 g, 141 mmol, 3.00 equiv) in acetonitrile (300 mL) was stirred under N_2 for 3 h at ambient temperature followed by the dropwise addition of the solution of (1*R*,2*R*)-methyl 2-formylcyclohexanecarboxylate (8.00 g, 47.0 mmol, 1.00 equiv) in methanol (100 mL). The resulting mixture was stirred at ambient temperature for 16 h. The mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:25) giving (1*R*,2*R*)-methyl 2-ethynylcyclohexanecarboxylate as a yellow oil.^{1}HNMR (300 MHz, $CDCl_3$) δ ppm 3.74 (s, 3H), 2.71-2.58 (m, 1H), 2.49-2.39 (m, 1H), 2.11-2.01 (m, 1H), 2.09 (s, 1H), 2.01-1.89 (m, 1H), 1.81-1.68 (m, 2H), 1.52-1.39 (m, 2H), 1.38-1.26 (m, 2H).

Step C: (1R,2R)-Methyl 2-(bromoethynyl)cyclohexanecarboxylate

A mixture of methyl (1*R*,2*R*)-methyl 2-ethynylcyclohexanecarboxylate (5.00 g, 30.0 mmol, 1.00 equiv), NBS (6.14 g, 34.5 mmol, 1.15 equiv) and $AgNO_3$ (507 mg, 3.00 mmol, 0.100 equiv) in acetone (150 mL) was stirred at 20 °C for 2 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:25) giving (1*R*,2*R*)-methyl 2-(bromoethynyl)cyclohexanecarboxylate as a yellow oil. ^{1}HNMR (300 MHz, $CDCl_3$) δ ppm 3.73 (s, 3H), 2.69-2.56 (m, 1H), 2.47-2.32 (m, 1H), 2.06-1.88 (m, 2H), 1.82-1.62 (m, 2H), 1.53-1.18 (m, 4H).

Step D: (1R,2R)-Methyl 2-(4-bromo-1H-pyrazol-3-yl)cyclohexanecarboxylate

To a solution of (1*R*,2*R*)-methyl 2-(bromoethynyl)cyclohexanecarboxylate (4.00 g, 16.3 mmol, 1.00 equiv) in THF (200 mL) was added (diazomethyl)trimethylsilane (49.0 mL, 2.00 M in hexanes, 6.00 equiv) under N_2. The resulting mixture was stirred in an oil bath at 75 °C for 48 hours. The solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:1) giving (1*R*,2*R*)-methyl 2-(4-bromo-1H-pyrazol-3-yl)cyclohexanecarboxylate as a light yellow oil. MS(ES,*m/z*): 287.0 (M + 1), 289.1 (M + 1).

Step E: (1R,2R)-methyl 2-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

(1*R*,2*R*)-Methyl 2-(4-bromo-1H-pyrazol-3-yl)cyclohexanecarboxylate (0.670 g, 2.33 mmol, 1.00 equiv), (4-fluorophenyl)boronic acid (0.655 g, 4.68 mmol, 2.00 equiv), pyridine (0.370 g, 4.68 mmol, 2.00 equiv), and $Cu(OAc)_2$ (0.634 g, 3.49 mmol, 1.50 equiv) were disolved in CH_2Cl_2 (20.0 mL) in a 50-mL round-bottom flask. The resulting mixture was stirred at room temperature for 16 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:10) giving (1R,2R)-methyl 2-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate as a light yellow oil. MS(ES,*m/z*): 380.9 (M + 1), 383.0 (M + 1).

Step F: (1R,2R)-2-(4-Bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid

Lithium hydroxide (0.215 g, 8.98 mmol, 3.00 equiv) was added to the solution of (1R,2R)-methyl 2-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate (0.680 g, 1.78 mmol, 1.00 equiv) in methanol (10.0 mL) and water (2.00 mL). The resulting mixture was stirred at 80 °C for 18 h. The pH of the solution was adjusted to pH 3.0 by addition of aqueous hydrochloric acid (2.00 mol/L). The resulting solution wasextracted with EtOAc (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure giving (1R,2R)-2-(4-bromo-1-(4-

fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid as a light yellow solid. MS(ES,*m/z*): 367.0 (M + 1), 368.9 (M + 1).

Step G: (1R,2R)-2-(4-Bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide

To the mixture of (1R,2R)-2-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid (0.550 g, 1.50 mmol, 1.00 equiv), 1-aminocyclopropanecarbonitrile hydrochloride (1.30 g, 11.0 mmol, 7.30 equiv), and HATU (0.915 g, 2.41 mmol, 1.60 equiv) in DMF (10.0 mL) was added DIPEA (1.80 g, 13.9 mmol, 10.0 equiv). The resulting mixture was stirred at 80 °C for 16 h. The reaction was diluted with EtOAc (30.0 mL) and the solution was then washed with water (3 x 10.0 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:3) giving (1R,2R)-2-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide as a light yellow solid. MS(ES,*m/z*): 431.1 (M + 1), 433.1 (M + 1).

Step H: 1-(4-Bromophenyl)piperidine-4-carbonitrile

Piperidine-4-carbonitrile (2.00 g, 18.2 mmol, 1.00 equiv), 1,4-dibromobenzene (6.40 g, 27.1 mmol, 1.49 equiv), sodium-*tert*-butoxide (5.20 g, 54.1 mmol, 2.98 equiv), toluene (50.0 mL), Xantphos (1.60 g, 2.77 mmol, 0.150 equiv) and $Pd_2(dba)_3 \cdot CHCl_3$(0.940 g) were placed into a 100-mL round-bottom flask. The flask was degassed and back-filled with N_2 for three times. The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to ambient temperature and quenched with water (100 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (Na_2SO_4), and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (5% - 50%) giving 1-(4-bromophenyl)piperidine-4-carbonitrile as a yellow solid: MS(ES,*m/z*): 264.8 (M + 1), 266.8 (M + 1).

Step I: 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-4-carbonitrile

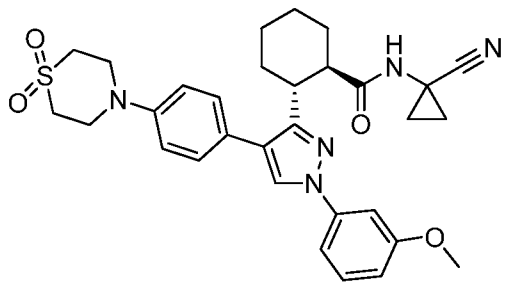
1-(4-Bromophenyl)piperidine-4-carbonitrile (0.500 g, 1.89 mmol, 1.00 equiv), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.958 g, 3.77 mmol, 2.00 equiv), KOAc (0.554 g, 5.65 mmol, 3.00 equiv), dioxane (20.0 mL) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.231 g, 0.280 mmol, 0.150 equiv) were placed into a 100-mL round-bottom flask. The flask was degassed and back-filled with nitrogen for three times. The resulting mixture was stirred at 90 °C for 16 h. The reaction mixture was cooled to ambient temperature and quenched with water (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined

organic layers were washed with brine (2 x 50 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc /petroleum ether (30% - 40%) giving 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-4-carbonitrile as a yellow solid: ^{1}HNMR (300 MHz, $CDCl_3$) δ ppm 7.71 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 3.56-3.48 (m, 2H), 3.22-3.14 (m, 2H), 2.81-2.80 (m, 1H), 2.04-1.95 (m, 4H),1.33 (s, 12H);MS(ES,*m/z*): 313.2 (M + 1).

Step J: (1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(4-cyanopiperidin-1-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine-4-carbonitrile (36.2 mg, 0.120 mmol, 1.00 equiv), (1R,2R)-2-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide (50.0 mg, 0.120 mmol, 1.00 equiv), K_2CO_3 (48.1 mg, 0.350 mmol, 3.00 equiv), DMF (5.00 mL), water (1.00 mL) and Pd(dtbpf)Cl_2 (7.60 mg, 0.0100 mmol, 0.100 equiv) were placed into a 10-mL round-bottom flask. The flask was degassed and back-filled with nitrogen for three times. The resulting mixture was stirred at 80 °C for 2 hours. The solution was diluted with EtOAc (20.0 mL) and the mixture was washed with water (3 x 15 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The crude productwas purified by Prep-HPLC with the following conditions: Column, Sunfire C^{18}, 5 μm, 19 x 150 mm; Mobile phase: Water (0.05% NH_4HCO_3) and acetonitrile (68% acetonitrile up to 85% in 10 min, hold 100% for 3 min, down to 68% in 1 min); Detector, UV 220 and 254 nm. This resulted in (1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(4-cyanopiperidin-1-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 1) as a white solid: ^{1}HNMR (400 MHz, CD_3OD) δ ppm 8.09 (s, 1H), 7.82-7.79 (m, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.25-7.20 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 3.50-3.46 (m, 2H), 3.40-3.32 (m, 1H), 3.22-3.11 (m, 2H), 3.03-2.95 (m, 1H), 2.89-2.80 (m, 1H), 2.13-2.10 (m, 2H), 2.00-1.78 (m, 6H), 1.44-1.31 (m, 6H), 0.95-0.88 (m, 1H), 0.74-0.69 (m, 1H);MS(ES,*m/z*): 537.4 (M + 1).

EXAMPLE 2



(1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 2)

Step A: (1R,2R)-Methyl 2-(4-bromo-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

(1*R*,2*R*)- Methyl 2-(4-bromo-1-(3-methoxyphenyl)-1*H*-pyrazol-3-yl)cyclohexanecarboxylate was synthesized following the same procedure as in Step E of Example 1 using pyridine (32.0 mg, 0.440 mmol, 2.00 equiv), (1*R*,2*R*)- methyl 2-(4-bromo-1*H*-pyrazol-3-yl)cyclohexanecarboxylate (62.0 mg, 0.220 mmol, 1.00 equiv), (3-methoxyphenyl)boronic acid (65.6 mg, 0.440 mmol, 2.00 equiv), CH_2Cl_2 (2.0 mL) and $Cu(OAc)_2$ (59.0 mg, 0.330 mmol, 1.50 equiv). This resulted in (1R,2R)-methyl 2-(4-bromo-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate as a yellow oil. MS (ES, *m/z*): 578.3 (M + 1).

Step B: (1R,2R)-Methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

(1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate was synthesized following the same procedure as in Step J of Example 1 using K_2CO_3 (58.0 mg,0.420 mmol, 3.00 equiv), (1R,2R)-methyl 2-(4-bromo-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate (55.0 mg, 0.140 mmol, 1.00 equiv), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide (71.0 mg, 0.210 mmol, 1.50 equiv), DMF (2.5 mL), water (0.50 mL) and $Pd(dtbpf)Cl_2$ (7.50 mg, 0.10 equiv). This resulted in (1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate as a colorless oil. MS(ES,*m/z*): 524.2 (M+1).

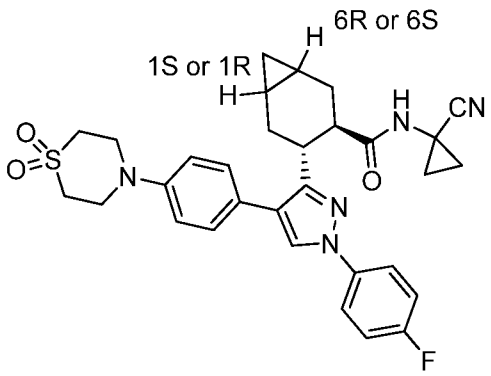
Step C: (1R,2R)-2-(4-(4-(1,1-Dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid

(1*R*,2*R*)-2-(1-(3-Methoxyphenyl)-4-(4-thiomorpholino-1,1-dioxide-phenyl)-1*H*-pyrazol-3-yl)cyclohexanecarboxylic acid was synthesized following the same procedure as in Step F of Example 1 using LiOH (9.0 mg, 3.00 equiv), (1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate (65.0 mg, 0.120 mmol, 1.00 equiv), water (1.0 mL) and EtOH (10 mL). This resulted in crude (1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid as a yellow oil: MS (ES, *m/z*): 510.1 (M + 1).

Step D: (1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamidewas synthesized following the same procedure as in Step G of Example 1 using crude (1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid (40.0 mg, 80.0 μmol, 1.00 equiv), 1-aminocyclopropanecarbonitrile hydrochloride (23.0 mg, 0.200 mmol, 2.50 equiv), DMF (2.0 mL),HATU(48.0 mg, 0.130 mmol, 1.60 equiv) and DIPEA(56.0 mg, 0.430 mmol, 5.50 equiv). This resulted in 6.5 mg (14%) of (1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 2) as a white solid: ^{1}HNMR (300 MHz, $CDCl_3$) δ ppm 8.13 (s, 1H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.41-7.32 (m, 3H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.88-6.86 (m, 1H), 3.94-3.90 (m, 4H), 3.90 (s, 3H), 3.25-3.15 (m, 5H), 2.92-2.81 (m, 1H), 2.00-1.75 (m, 4H), 1.69-1.28 (m, 6H), 1.01-0.88 (m, 1H), 0.78-0.68 (m, 1H);MS(ES,*m/z*): 574.2 (M+1).

EXAMPLE 3 and EXAMPLE 4



(1S or 1R,3R,4R,6R or 6S)-N-(1-Cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide (Compound 3)

(1R or 1S,3R,4R,6S or 6R)-N-(1-Cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide (Compound 4)

Step A: (3R,4R)-Methyl 4-formylbicyclo[4.1.0]heptane-3-carboxylate

Oxalyl chloride (1.91 g, 15.1 mmol, 1.50 equiv) was added dropwise into a stirring solution of (3*R*,4*R*)-4-(methoxycarbonyl)bicyclo[4.1.0]heptane-3-carboxylic acid (2.00 g, 10.0 mmol, 1.00 equiv) in DCM (30 mL) and DMF (5.00 mg, cat.) at 0 °C. The resulting mixture was stirred at RT for 3 h. The mixture was concentrated under reduced pressure. The residue was dissolved in THF (30 mL), and 2,6-lutidine (1.62 g, 15.1 mmol, 1.50 equiv) and

Pd/C (10%) (0.200 g, cat.) were added to the solution. The resulting mixture was degassed with N_2 for 3 times and stirred under H_2 for 16 hours. The solids were filtered out, the filtrate was diluted with EtOAc (100 mL), washed with aqueous HCl (1.0 M, 100 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:50) giving crude (3R,4R)-methyl 4-formylbicyclo[4.1.0]heptane-3-carboxylate as a yellow oil.

Step B: (3R,4R)-Methyl 4-ethynylbicyclo[4.1.0]heptane-3-carboxylate

A mixture of dimethyl (2-oxopropyl)phosphonate (1.72 g, 10.3 mmol, 1.30 equiv), 4-methylbenzenesulfonyl azide (2.09 g, 10.6 mmol, 1.33 equiv) and K_2CO_3 (3.30 g, 23.8 mmol, 3.00 equiv) in CH_3CN (100 mL) was stirred at RT for 3 hours under N_2 followed by the dropwise addition of the solution of (3R,4R)-methyl 4-formylbicyclo[4.1.0]heptane-3-carboxylate (1.45 g, 7.96 mmol, 1.00 equiv) in MeOH (50 mL) at RT. The resulting mixture was stirred at RT for 16 hours. The mixture was concentrated under vacuum. The residue was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:25) giving crude (3R,4R)-methyl 4-ethynylbicyclo[4.1.0]heptane-3-carboxylate as a light yellow oil.

Step C: (3R,4R)-methyl 4-(bromoethynyl)bicyclo[4.1.0]heptane-3-carboxylate

A mixture of (3R,4R)-methyl 4-ethynylbicyclo[4.1.0]heptane-3-carboxylate (0.648 g, 3.64 mmol, 1.00 equiv), NBS (0.744 g, 4.18 mmol, 1.15 equiv) and $AgNO_3$ (62.0 mg, 0.360 mmol, 0.0100 equiv) in acetone (40 mL) was stirred at RT for 70 min. The mixture was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:25) giving (3R,4R)-methyl 4-(bromoethynyl)bicyclo[4.1.0]heptane-3-carboxylate as a light yellow oil.

Step D: (3R,4R)-Methyl 4-(4-bromo-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate

The solution of (3R,4R)-methyl 4-(bromoethynyl)bicyclo[4.1.0]heptane-3-carboxylate (0.895 g, 3.48 mmol, 1.00 equiv) and (diazomethyl)trimethylsilane (10.5 mL, 20.9 mmol 6.00 equiv) in THF (30 mL) was stirred at 75 °C for 48 hours under N_2 atmosphere. The mixture was concentrated under vacuum and the residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:1) giving (3R,4R)-methyl 4-(4-bromo-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate as yellow oil: ^{1}HNMR (300 MHz, $CDCl_3$) *δppm*: 9.00-8.40 (brs, 1H), 7.47 (d, J = 4.2 Hz, 1H), 3.48 (s, 3H), 3.00-2.65 (m, 2H), 2.45-2.37 (m, 1H), 2.29-2.15 (m, 1H), 2.14-2.05 (m, 1H), 1.78-1.58 (m, 1H),

1.15-1.00 (m, 2H), 0.75-0.65 (m, 1H), 0.23-0.12 (m, 1H);MS(ES,*m/z*):299.0 (M + 1), 301.0 (M + 1).

Step E: (3R,4R)-methyl 4-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate

(3*R*,4*R*)-Methyl 4-(4-bromo-1-(4-fluorophenyl)-1*H*-pyrazol-3-yl]bicyclo[4.1.0]heptane-3-carboxylate was synthesized following the same procedure as Step E of Example 1using(3R,4R)-methyl 4-(4-bromo-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate (0.150 g, 0.500 mmol, 1.00 equiv), (4-fluorophenyl)boronic acid (0.211 g, 1.51 mmol, 3.00 equiv),$Cu(OAc)_2$ (0.274 g, 1.51 mmol, 3.00 equiv) andpyridine (0.189 g, 1.51 mmol, 3.00 equiv) in DCM (10.0 mL). This resulted in (3R,4R)-methyl 4-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate: MS (ES, *m/z*): 393.0 (M + 1), 395.0 (M + 1).

Step F: (3R,4R)-methyl 4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate

(3R,4R)-methyl 4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate was synthesized following the same procedure as Step J of Example 1using (3R,4R)-methyl 4-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate (0.150 g, 0.380 mmol, 1.00 equiv), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide (0.257 g, 0.760 mmol, 2.00 equiv), $Pd(dtbpf)Cl_2$ (25.0 mg, 0.0400 mmol, 0.10 equiv) and K_2CO_3 (0.158 g, 1.14 mmol, 3.00 equiv) in THF/water (5:1, 6 mL). This resulted in (3R,4R)-methyl 4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate: MS (ES, *m/z*): 527.0 (M + 1).

Step G: (3R,4R)-4-(4-(4-(1,1-Dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylic acid

(3R,4R)-4-(4-(4-(1,1-Dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylic acid was synthesized following the same procedure as Step F of Example 1using (3R,4R)-methyl 4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylate (0.150 g, 0.290 mmol, 1.00 equiv) and LiOH (0.100 g, 2.51 mmol, 8.00 equiv) in MeOH/water (3:1, 8 mL). This resulted in (3R,4R)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylic acid: MS (ES, *m/z*): 510.1 (M + 1).

Step H: (3R,4R)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide

(3R,4R)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide was synthesized following the same procedure as Step G of Example 1using (3R,4R)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxylic acid (0.100 g, 0.200 mmol, 1.00 equiv), 1-aminocyclopropanecarbonitrile hydrochloride (0.120 g, 1.01 mmol, 5.00 equiv), DIPEA (0.250 g, 1.93 mmol, 10.00 equiv) and HATU (0.190 g, 0.500 mmol, 2.50 equiv) in NMP (1 mL). This resulted in (3R,4R)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide as a colorless solid: MS (ES, *m/z*): 574.2 (M + 1).

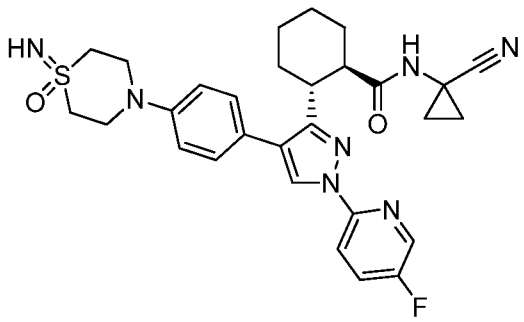
Step I: Chiral separation of (1S or 1R,3R,4R,6R or 6S)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide (Compound 3) and

(1R or 1S,3R,4R,6S or 6R)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide (Compound 4)

Racemic (3R,4R)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide(50.0 mg) was separated by CHIRAL-Prep-HPLC with the following conditions: Instrument, 2#-Prep-HPLC-001(SHIMADZU); Column, Chiralpak IBO. 46 x 25 cm, 5 um; Chiral-A(IB)001IB00CE-LA026; mobile phase: Phase A: Hex and Phase B:EtOH(0.2%DEA)-HPLC (hold 40% Phase B for 10 min); Detector, UV254 nm. It gave (1S or 1R,3R,4R,6R or 6S)-*N*-(1-cyanocyclopropyl)-4-(1-(4-fluorophenyl)-4-(4-(1,1-dioxo)thiomorpholinophenyl)-1*H*-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide (Compound 3): ^{1}H NMR (300 MHz, DMSO-d_6)δ*ppm*: 8.65 (s, 1H), 8.30 (s,1H), 7.78-7.73 (m, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.25 (t, J = 8.7 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 3.82-3.76 (m, 4H), 3.10-3.01 (m, 4H), 2.83-2.80 (m, 1H), 2.43-2.38 (m, 1H), 2.25-2.17 (m, 1H), 1.96-1.85 (m, 2H), 1.42-1.25 (m, 1H), 1.22-1.15 (m, 1H), 0.97-0.58 (m, 5H), 0.24-0.18 (m, 1H), 0.05- -0.02 (m, 1H); MS (ES, *m/z*): 574.0 (M + 1) and

(1R or 1S,3R,4R,6S or 6R)-*N*-(1-cyanocyclopropyl)-4-(1-(4-fluorophenyl)-4-(4-(1,1-dioxo)thiomorpholinophenyl)-1*H*-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide (Compound 4): ^{1}H NMR (300 MHz, DMSO-d_6)δ*ppm*: 8.63 (s, 1H), 8.34 (s,1H), 7.81-7.76 (m, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.29 (t, J = 8.7 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 3.75-3.79 (m, 4H), 3.05-3.09 (m, 4H), 2.80-2.72 (m, 1H), 2.45-2.55 (m, 1H), 2.12-2.22 (m, 1H), 2.03-1.95 (m, 1H), 1.84-1.70 (m, 1H), 1.55-1.45 (m, 1H), 1.30-1.10 (m, 1H), 1.00-0.50 (m, 5H), 0.24-0.18 (m, 1H), 0.05- -0.02 (m, 1H); MS (ES, *m/z*): 574.0 (M + 1).

EXAMPLE 5



(1R,2R)-N-(1-Cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 5)

Step A: (1R,2R)-2-(4-Bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid

The solution of (1*R*,2*R*)- methyl 2-(4-bromo-1*H*-pyrazol-3-yl)cyclohexanecarboxylate (0.600 g, 2.09 mmol, 1.00 equiv), 2,5-difluoropyridine (0.483 g, 4.20 mmol, 2.00 equiv), 18-crown-6 (0.554 g, 2.10 mmol, 1.00 equiv) and KOH (0.352 g, 6.27 mmol, 3.00 equiv) in DMSO (10 mL) was stirred at 40 °C in an oil bath for 24 hours. The resulting solution was cooled and diluted with water (70 mL). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel with EtOAc /petroleum ether (1:100-1:5) to give (1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid as a yellow solid: MS (ES, *m/z*): 367.9 (M + 1), 369.9 (M + 1).

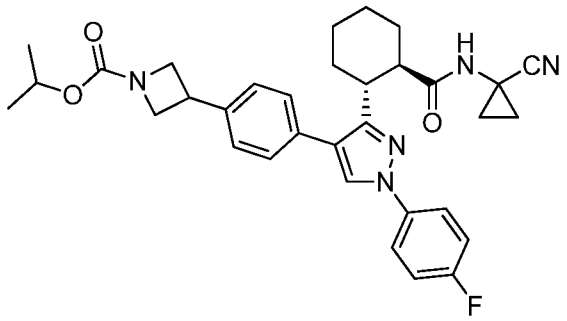
Step B: (1R,2R)-2-(4-Bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide

(1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide was synthesized following the same procedure as Step G of Example 1using of (1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid (90.0 mg, 0.240 mmol, 1.00 equiv), 1-aminocyclopropanecarbonitrile hydrochloride (0.140 g, 1.18 mmol, 5.00 equiv), HATU (0.225 g, 0.590 mmol, 2.50 equiv) and DIPEA (0.300 g, 2.32 mmol, 10.0 equiv) in NMP (2 mL). This resulted in (1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide as a yellow solid: MS (ES, *m/z*): 432.0 (M + 1), 434.0 (M + 1).

Step C: (1R,2R)-N-(1-Cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 5)

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide was synthesized following the same procedure as in Step J of Example 1using (1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide (35.0 mg, 0.0810 mmol, 1.00 equiv) 2,2,2-trifluoro-N-(1-oxido-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholin-1-ylidene)acetamide (Intermediate 3) (35.0 mg, 0.0810 mmol, 1.00 equiv), $Pd(dtbpf)Cl_2$ (5.00 mg, 0.0100 mmol, 0.100 equiv) and K_2CO_3 (65.0 mg, 0.470 mmol, 6.00 equiv) in dioxane/water (5:1, 2.4 mL). This resulted in (1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 5) as a white solid: ^1H NMR (400 MHz, CD_3OD) δ *ppm*: 8.41(s.1H), 8.32(s.1H), 8.04-8.01 (m, 1H), 7.76-7.73 (m, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 4.01-3.98 (m, 2H), 3.82-3.79 (m, 2H), 3.28-3.22 (m, 5H), 2.90-2.85 (m, 1H), 1.97-1.79 (m, 4H), 1.61-1.58 (m, 1H), 1.42-1.29 (m, 5H), 0.96-0.93 (m, 1H), 0.76-0.73 (m, 1H);MS (ES, *m/z*): 562.2 (M + 1).

EXAMPLE 6



Isopropyl 3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate (Compound 6)

Step A: *tert*-Butyl 3-(4-(1-(4-fluorophenyl)-3-((1R,2R)-2-(methoxycarbonyl)cyclohexyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate

(1R,2R)-Methyl 2-(4-bromo-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate from Example 1 Step E (0.400 g, 1.05 mmol, 1.00 equiv), *tert*-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine-1-carboxylate (0.567 g, 1.58 mmol, 1.50 equiv), $Pd(dppf)Cl_2$ (85.9 mg, 0.120 mmol, 0.110 equiv), $Pd(dtbpf)Cl_2$ (65.6 mg, 0.100 mmol, 0.100 equiv), K_2CO_3 (0.290 g, 2.10 mmol, 2.00 equiv), DMF (6.00 mL), and water (2.00 mL) were placed into a 50-mL round-bottom flask. The flask was degassed and back-filled with N_2 for three times. The reaction mixture was stirred

at 85 °C in an oil bath for 3 hours. The resulting mixture was cooled to RT, diluted with EtOAc (15.0 mL), and washed with water (3 x 10.0 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:6) giving *tert*-butyl 3-(4-(1-(4-fluorophenyl)-3-((1R,2R)-2-(methoxycarbonyl)cyclohexyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate: MS (ES, *m/z*): 534.4 (M + 1).

Step B: (1R,2R)-2-(4-(4-(1-(*tert*-Butoxycarbonyl)azetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid

Lithium hydroxide (0.205 g, 8.56 mmol, 8.01 equiv) was added to the solution of *tert*-butyl 3-(4-(1-(4-fluorophenyl)-3-((1R,2R)-2-(methoxycarbonyl)cyclohexyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate (0.570 g, 1.07 mmol, 1.00 equiv) in EtOH (5.00 mL) and water (1.00 mL). The reaction mixture was stirred at 50 °C in an oil bath for 16 hours. The resulting mixture was concentrated under reduced pressure and the pH of the solution was adjusted to pH 2 with aqueous HCl (3.0 M). The resulting mixture was extracted with EtOAc (3 x 10.0 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure giving (1R,2R)-2-(4-(4-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid: MS (ES, *m/z*): 520.3 (M + 1).

Step C: *tert*-Butyl 3-(4-(3-((1R,2R)-2-((benzyloxy)carbonyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate

Benzyl bromide (0.252 g, 1.47 mmol, 1.50 equiv), and potassium carbonate (0.271 g, 1.96 mmol, 2.00 equiv) were added to the solution of (1R,2R)-2-(4-(4-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid (0.510 g, 0.980 mmol, 1.00 equiv) in DMF (4.00 mL). The reaction mixture was stirred at RT for 16 hours. The mixture was diluted with EtOAc (15.0 mL) and the resulting solution was washed with water (3 x 5.0 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:8) giving *tert*-butyl 3-(4-(3-((1R,2R)-2-((benzyloxy)carbonyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate: MS (ES, *m/z*): 610.2 (M + 1).

Step D: (1R,2R)-Benzyl 2-(4-(4-(azetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

Trifluoroacetic acid (3.00 mL) was added to the solution of *tert*-butyl 3-(4-(3-((1R,2R)-2-((benzyloxy)carbonyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate (0.540 g, 0.890 mmol, 1.00 equiv) in DCM (5.00 mL.) The

resulting mixture was stirred at RT for 3 hours, quenched with saturated aqueous $NaHCO_3$ (10.0 mL), and extracted with DCM (3 x 10.0 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure giving (1R,2R)-benzyl 2-(4-(4-(azetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate: MS (ES, *m/z*): 510.3 (M + 1).

Step E: Isopropyl 3-(4-(3-((1R,2R)-2-((benzyloxy)carbonyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate

Triethylamine (79.4 mg, 0.780 mmol, 4.00 equiv) and isopropyl chloroformate (47.9 mg, 0.390 mmol, 1.99 equiv) were added to the solution of (1R,2R)-benzyl 2-(4-(4-(azetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate (0.100 g, 0.200 mmol, 1.00 equiv) in DCM (3.00 mL). The resulting mixture was stirred at RT for 5 hours and extracted with DCM (3 x 5.0 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (3:2) giving isopropyl 3-(4-(3-((1R,2R)-2-((benzyloxy)carbonyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate: MS (ES, *m/z*): 596.2 (M + 1).

Step F: (1R,2R)-2-(1-(4-Fluorophenyl)-4-(4-(1-(isopropoxycarbonyl)azetidin-3-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid

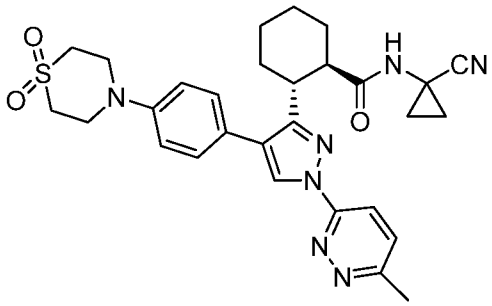
Palladium on carbon (10%, 20.0 mg, 0.0833 mmol, 0.694 equiv) was added to the solution of isopropyl 3-(4-(3-((1R,2R)-2-((benzyloxy)carbonyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate (70.0 mg, 0.120 mmol, 1.00 equiv) in MeOH (10.0 mL). The flask was degassed and back-filled with H_2 three times. The resulting mixture was stirred at RT for 16 hours. The solids were filtered out and the filtrate was concentrated under reduced pressure giving the crude (1R,2R)-2-(1-(4-fluorophenyl)-4-(4-(1-(isopropoxycarbonyl)azetidin-3-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid: (ES, *m/z*): 506.2 (M + 1).

Step G: Isopropyl 3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate (Compound 6)

DIPEA (61.3 mg, 0.480 mmol, 8.01 equiv) was added to the mixture of (1R,2R)-2-(1-(4-fluorophenyl)-4-(4-(1-(isopropoxycarbonyl)azetidin-3-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid (30.0 mg, 0.0600 mmol, 1.00 equiv), 1-aminocyclopropanecarbonitrile hydrochloride (35.1 mg, 0.300 mmol, 4.98 equiv), and HATU (33.9 mg, 0.0900 mmol, 1.50 equiv) in DMF(2.00 mL). The reaction mixture was stirred at RT for 16 hours, diluted with EtOAc (15.0 mL) and washed with water (3 x 5.0 mL). The organic layer was concentrated under reduced pressure. The residue was purified by Prep-

HPLC with the following conditions: Column, Sunfire C_{18} 19 x 150 mm; mobile phase: Water (0.05% NH_4HCO_3) and acetonitrile (47.0% acetonitrile up to 65% in 15 min, hold 100% for 3 min down to 65% in 1 min); Detector, UV 220 and 254 nm. This resulted in isopropyl 3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate (Compound 6) as a white solid. ^{1}H NMR (300 MHz,DMSO): δ ppm 8.70 (s, 1H), 8.51 (s, 1H), 7.99-7.79 (m, 2H), 7.60-7.23 (m, 6H), 4.87-4.71 (m, 1H), 4.42-4.18 (m, 2H), 4.03-3.79 (m, 3H), 3.20-3.04 (m, 1H), 2.84-2.68 (m, 1H), 1.93-1.62 (m, 4H), 1.44-1.26 (m, 6H), 1.20 (d, *J* = 6.0 Hz, 6H), 0.91-0.78 (m, 1H), 0.54-0.41 (m, 1H); MS (ES, *m/z*): 570.4 (M + 1).

EXAMPLE 7



(1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 7)

Step A: 3-Iodo-6-methylpyridazine

3-Chloro-6-methylpyridazine (0.500 g, 3.89 mmol, 1.00 equiv), HI(3 mL), and NaI (0.581 g, 3.88 mmol, 1.00 equiv) were placed to a 10-mL round-bottom flask purged and maintained under N_2. The resulting mixture was stirred at 120 °C in an oil bath for 16 hours. The reaction mixture was cooled, diluted with water (10 mL), and the pH was adjusted to pH 8 by addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (10.0 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (30% - 100%) giving 3-iodo-6-methylpyridazine as a light yellow solid: MS (ES, *m/z*) 220.9 (M + 1).

Step B: (1R,2R)-Methyl 2-(4-bromo-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

(1*R*,2*R*)-Methyl 2-(4-bromo-1H-pyrazol-3-yl)cyclohexanecarboxylate from Step D of Example 1 (0.100 g, 0.35 mmol, 1.00 equiv), 3-iodo-6-methylpyridazine (0.230 g, 1.05 mmol, 3.00 equiv), Cs_2CO_3 (0.340 g, 1.05 mmol, 3.00 equiv), cyclohexane-1,2-diamine (24.7 mg, 0.17 mmol, 0.50 equiv), and CuI (33.1 mg, 0.17 mmol, 0.50 equiv), in DMF (2 mL) were

placed into a 10-mL round-bottom flask purged and maintained under N_2. The reaction mixture was degassed with N_2 three times and stirred at 80 °C in an oil bath for 18 hours. The reaction mixture was cooled to RT, diluted with EtOAc (20 mL), and the resulting mixture was washed with water (3 x 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (20% - 50%) giving (1*R*,2*R*)-methyl 2-(4-bromo-1-(6-methylpyridazin-3-yl)-1*H*-pyrazol-3-yl]cyclohexanecarboxylate as a light yellow solid: MS (ES, *m/z*) 378.9 (M + 1), 380.9 (M + 1).

Step C: (1R,2R)-Methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

(1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylate was synthesized following the same procedure as in Step A of Example 6 using (1*R*,2*R*)-methyl 2-(4-bromo-1-(6-methylpyridazin-3-yl)-1*H*-pyrazol-3-yl]cyclohexanecarboxylate (0.160 g, 0.42 mmol, 1.00 equiv), 4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide (Intermediate 6) (0.170 g, 0.51 mmol, 1.20 equiv), K_2CO_3 (0.175 g, 1.26 mmol, 3.00 equiv), Pd(dtbpf)Cl_2(36.4 mg, 0.04 mmol, 0.10 equiv), Pd(dppf)Cl_2(27.5 mg, 0.04 mmol, 0.10 equiv), and DMF/water (10:1, 2 mL). This resulted in (1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylate: MS (ES, *m/z*) 510.3 (M + 1).

Step D: (1R,2R)-2-(4-(4-(1,1-Dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid

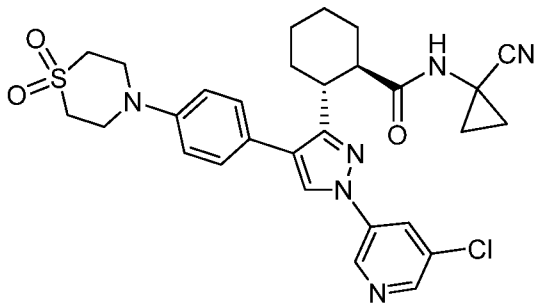
(1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid was synthesized following the same procedure as in Step F of Example 1 using(1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylate (0.100 g, 0.20 mmol, 1.00 equiv), LiOH (41.2 mg, 0.98 mmol, 5.00 equiv) and MeOH/water (10:1, 11 mL) giving crude (1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid as yellow solid: MS (ES, *m/z*) 496.3 (M + 1).

Step E: (1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide was synthesized following the same procedure as in Step G of Example 1 using (1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-

yl)cyclohexanecarboxylic acid (0.100 g, 0.20 mmol, 1.00 equiv), HATU (0.153 g, 0.40 mmol, 2.00 equiv), 1-aminocyclopropanecarbonitrile hydrochloride (0.120 g, 1.01 mmol, 5.00 equiv), DIPEA(0.260 g, 2.01 mmol, 10.00 equiv) andDMF(2 mL) giving (1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 7): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (s, 1H), 8.69 (s, 1H),8.15 (d, *J*= 8.8 Hz, 1H),7.81 (d, *J*= 9.2 Hz, 1H),7.47(d, *J*=8.8 Hz, 2H),7.13(d, *J*=8.8 Hz, 2H),3.90-3.80(m, 4H),3.22-3.10 (m, 5H),2.86-2.71 (m, 1H),2.71(s, 3H),1.90-1.67 (m, 4H),1.57-1.40 (m, 1H),1.40-1.20(m, 5H),0.88-0.75 (m, 1H),0.59-0.43 (m,1H); MS (ES, *m/z*) 560.4 (M + 1).

EXAMPLE 8



(1R,2R)-2-(1-(5-Chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide (Compound 8)

Step A: (1R,2R)-Methyl 2-(4-bromo-1-(5-chloropyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

Potassium hydroxide (97.5 mg, 1.74 mmol, 5.00 equiv) was added to a mixture of(1*R*,2*R*)-methyl 2-(4-bromo-1H-pyrazol-3-yl)cyclohexanecarboxylate from Step D of Example 1 (0.100 g, 0.350 mmol, 1.00 equiv), 3-chloro-5-fluoropyridine (0.240 g, 1.82 mmol, 5.00 equiv) and 18-crown-6 ether (0.100 g, 0.380 mmol, 1.00 equiv) in DMSO (10 mL). The reaction mixture was stirred at 50 °C for 16 hours, diluted with water (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), brine (2 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:5) giving (1*R*,2*R*)-methyl 2-(4-bromo-1-(5-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)cyclohexanecarboxylate as a light brown solid:MS (ES, *m/z*) 398.0 (M + 1), 400.0(M + 1).

Step B: (1R,2R)-Methyl 2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate

(1R,2R)-methyl 2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate was synthesized following the same procedure as in Step J of Example 1 using K_2CO_3 (0.125 g, 0.900 mmol, 3.00 equiv),(1*R*,2*R*)-methyl 2-(4-bromo-1-(5-chloropyridin-3-yl)-1*H*-pyrazol-3-yl)cyclohexanecarboxylate (0.120 g, 0.300 mmol, 1.00 equiv), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine-1,1-dioxide (Intermediate 6) (0.122 g, 0.360 mmol, 1.20 equiv), DMF (10 mL), water (0.30 mL) and Pd(dtbpf)Cl_2(24.6 mg, 30.0 μmol, 0.100 equiv). This resulted in crude (1R,2R)-methyl 2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate as a brown solid: MS (ES, *m/z*): 529.2 (M + 1), 531.2 (M + 1).

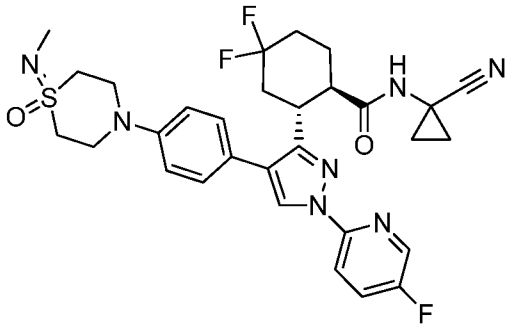
Step C: (1R,2R)-2-(1-(5-Chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid

(1R,2R)-2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid was synthesized following the same procedure as in Step F of Example 1 using LiOH (59.7 mg, 2.49 mmol, 5.00 equiv),(1R,2R)-methyl 2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylate (0.150 g, 0.284 mmol, 1.00 equiv), in water (1.0 mL) and EtOH (10 mL). This resulted in (1R,2R)-2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxylic acid as a brown solid: MS (ES, *m/z*) 515.1 (M + 1), 517.1 (M + 1).

Step D: (1R,2R)-2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide

(1R,2R)-2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide was synthesized following the same procedure as in Step G of Example 1 using (1*R*,2*R*)-2-(1-(5-chloropyridin-3-yl)-4-(4-thiomorpholino-1,1-dioxide-phenyl)-1*H*-pyrazol-3-yl)cyclohexanecarboxylic acid (98.0 mg, 0.190 mmol, 1.00 equiv),1-aminocyclopropanecarbonitrile hydrochloride (0.119 g, 1.00 mmol, 5.00 equiv), DMF (10 mL), HATU (0.145 g, 0.380 mmol, 2.00 equiv) and DIPEA (0.246 g, 1.90 mmol, 10.0 equiv). This resulted in (1R,2R)-2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide (Compound 8) as an off-white solid:^{1}HNMR(300MHz, $CDCl_3$)δppm8.89(s,1H),8.47(s,1H) ,8.02(s,1H) ,7.85(s,1H) ,7.39 (d,*J*=8.4Hz,2H) ,6.99 (d, *J*= 8.7 Hz,2H) ,5.94 (s,1H) ,3.88 (m,4H) ,3.25-3.11 (m,5H) ,2.80-2.67 (m,1H) ,1.94-1.85 (m,3H) ,1.54-1.35 (m, 7H), 0.95-0.92(m, 2H); MS (ES, *m/z*) 579.3 (M + 1), 581.3 (M + 1).

EXAMPLE 9



(1R,2R)-N-(1-Cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 9)

Step A: (1R,2R)-Methyl 2-ethynyl-4,4-difluorocyclohexanecarboxylate

(1R,2R)-Methyl 2-ethynyl-4,4-difluorocyclohexanecarboxylate was synthesized following the same procedure as in Step B of Example 1 using K_2CO_3 (1.30 g, 9.45 mmol, 3.00 equiv), 4-methylbenzene-1-sulfonyl azide (0.827 g, 4.19 mmol, 1.33 equiv), dimethyl (2-oxopropyl)phosphonate (0.673 g, 4.05 mmol, 1.29 equiv), CH_3CN (20 mL), and (1*R*, 2*R*)-methyl 4, 4-difluoro-2-formylcyclohexanecarboxylate (0.650 g, 3.15 mmol, 1.00 equiv) and MeOH (5 mL). This resulted in (1R,2R)-methyl 2-ethynyl-4,4-difluorocyclohexanecarboxylate as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.74 (s, 3H), 2.98-2.91 (m, 1H), 2.49-2.43 (m, 1H), 2.04 (s, 1H), 2.25-2.01 (m, 3H), 1.94-1.47 (m, 3H).

Step B: (1R,2R)-Methyl 2-(bromoethynyl)-4,4-difluorocyclohexanecarboxylate

(1R,2R)-methyl 2-(bromoethynyl)-4,4-difluorocyclohexanecarboxylate was synthesized following the same procedure as in Step C of Example 1 (1R,2R)-methyl 2-ethynyl-4,4-difluorocyclohexanecarboxylate (0.300 g, 1.48 mmol, 1.00 equiv), NBS (0.302 g, 1.70 mmol, 1.14 equiv), $AgNO_3$ (25.0 mg, 0.15 mmol, 0.100 equiv) and acetone (15 mL). This resulted in (1R,2R)-methyl 2-(bromoethynyl)-4,4-difluorocyclohexanecarboxylate. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.99 (s, 3H), 3.14-2.72 (m, 1H), 2.49-2.41 (m, 1H), 2.17-1.47 (m, 6H).

Step C: (1R,2R)-Methyl 2-(4-bromo-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylate

(1R,2R)-Methyl 2-(4-bromo-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylate was synthesized following the same procedure as in Step D of Example 1 using (1R,2R)-

methyl 2-(bromoethynyl)-4,4-difluorocyclohexanecarboxylate (0.370 g, 1.32 mmol, 1.00 equiv), (trimethylsilyl) diazomethane (4 mL, 2 M in hexanes) and THF (5 mL). This resulted in (1R,2R)-methyl 2-(4-bromo-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylate as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.53 (s, 1H), 3.61 (s, 3H), 3.47-3.39 (m, 1H), 3.05-2.88 (m, 1H), 2.41-1.76 (m, 6H); MS (ES, *m/z*): 323.1 (M + 1), 325.0 (M + 1).

Step D: (1R,2R)-Methyl 2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylate

2,5-Difluoropyridine (0.463 g, 4.02 mmol, 2.00 equiv), (1*R*,2*R*)- methyl 2-(4-bromo-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylate (0.650 g, 2.01 mmol, 1.00 equiv), and K_2CO_3 (0.835 g, 6.04 mmol, 3.00 equiv) in DMF (15 mL) were placed into a 50-mL round-bottom flask purged and maintained under N_2. The reaction mixture was stirred at 100 °C for 16 hours, diluted with EtOAc (200 mL), and washed with water (3 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:8) giving (1R,2R)-methyl 2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylate: MS (ES, m/z): 418.1 (M + 1), 420.1 (M + 1).

Step E: (1R,2R)-2-(4-Bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylic acid

(1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylic acid was synthesized following the same procedure as in Step F of Example 1 using (1R,2R)-methyl 2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylate (0.280 g, 0.67 mmol, 1.00 equiv), aqueous LiOH (2 mol/L, 10 mL), THF (10 mL) and 1,4-dioxane (2 mL). This resulted in crude (1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylic acid as a light yellow solid: MS (ES, *m/z*): 404.1 (M + 1), 406.1 (M + 1).

Step F: (1R,2R)-2-(4-Bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)-4,4-difluorocyclohexanecarboxamide

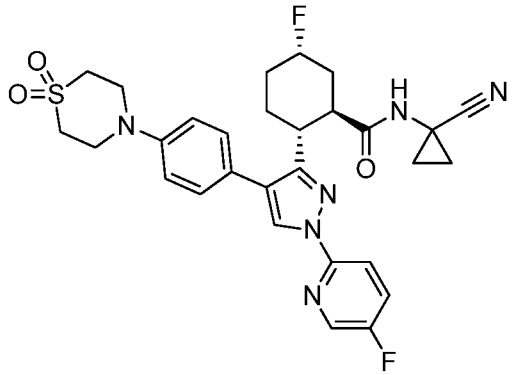
(1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)-4,4-difluorocyclohexanecarboxamide was synthesized following the same procedure as in Step G of Example 1 using (1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxylic acid (0.300 g, 0.740 mmol, 1.00 equiv), DMF (5 mL), 1-aminocyclopropanecarbonitrile hydrochloride (0.173 g, 1.47 mmol, 2.00 equiv), HATU (0.564 g, 1.48 mmol, 2.00 equiv), DIPEA (0.480 g, 3.71 mmol, 5.00 equiv). This resulted in (1R,2R)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-N-(1-

cyanocyclopropyl)-4,4-difluorocyclohexanecarboxamide: MS (ES, *m/z*): 468.1 (M + 1), 470.1 (M + 1).

Step G: (1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide

(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide was synthesized following the same procedure as in Step J of Example 1 using(1*R*,2*R*)-2-(4-bromo-1-(5-fluoropyridin-2-yl)-1*H*-pyrazol-3-yl)-*N*-(1-cyanocyclopropyl)-4,4-difluorocyclohexanecarboxamide (52.0 mg, 0.110 mmol, 1.00 equiv), 1,4-dioxane (1.5 mL), Pd(dtbpf)Cl_2 (14.3 mg, 0.020 mmol, 0.200 equiv), K_2CO_3 (91.0 mg, 0.660 mmol, 6.00 equiv), water (0.3 mL), 1-(methylimino)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1-oxide (Intermediate 4) (0.143 g, 0.330 mmol, 3.00 equiv). This resulted in (1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide (Compound 9) as a colorless solid: ^{1}H NMR: (300 MHz, CD_3OD) δ ppm 8.41 (s, 1H), 8.30-8.28 (m, 1H), 8.02-7.97 (m, 1H), 7.77-7.70 (m, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 3.98-3.93 (m, 2H), 3.78-3.75 (m, 2H), 3.61-3.49 (m, 1H), 3.39-3.15 (m, 4H), 2.93-2.85 (m, 1H), 2.78 (s, 3H), 2.27-2.10 (m, 2H), 1.99-1.79 (m, 4H), 1.32-1.24 (m, 2H), 0.92-0.71 (m, 2H); MS (ES, *m/z*): 612.3 (M + 1).

EXAMPLE 10



(1R,2R,5S)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide (Compound 10)

Step A: (1R,2R,5S)-Methyl 5-fluoro-2-formylcyclohexanecarboxylate

(1R,2R,4S)-4-Fluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid (INTERMEDIATE 3) (4 g, 19.59 mmol) was dried by azeotroping twice from toluene. Oxalyl chloride (2.058 ml, 23.51 mmol) was added to a solution of dry (1R,2R,4S)-4-fluoro-

2-(methoxycarbonyl)cyclohexanecarboxylic acid (4 g, 19.59 mmol) in toluene (61.2 ml). The resulting mixture was stirred under N_2 at 23 °C for 24 hours. N_2 was bubbled through the reaction for ~15 min to remove HCl. Toluene was removed under reduced pressure. The residue was dissolved in THF (60 mL) followed by the addition of 2,6-lutidine (2.5 mL, 21.55 mmol) and Pd/C-10% (1.2 g, 1.128 mmol). The resulting mixture was hydrogenated under 40 psi H_2 for 16 hours. The reaction mixture was filtered through celite, washing with EtOAc. The combined filtrate was washed with 1 N HCl (1 x), saturated $NaHCO_3$ (1x), brine, dried ($MgSO_4$), and concentrated under reduced pressure to give (1R,2R,5S)-methyl 5-fluoro-2-formylcyclohexanecarboxylate as a colorless oil. The crude material was used without further purification.

Step B: (1R,2R,5S)-Methyl 2-ethynyl-5-fluorocyclohexanecarboxylate

Sodium methoxide 25% solution (3.77 ml, 16.47 mmol) was added to a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (3.80 g, 19.77 mmol) in dry MeOH (30 mL), and the resulting mixture was stirred at 0 °C for 10 min. A solution of (1R,2R,5S)-methyl 5-fluoro-2-formylcyclohexanecarboxylate (3.1 g, 16.47 mmol) in MeOH (12 mL) was added to the reaction mixture and stirred in the cooling bath for 15 min, and then at RT for 16 hours under N_2.

The reaction mixture was diluted with DCM (200 mL), washed with water (1 x 150 mL), and aqueous layer was extracted with DCM (2 x 150 mL). Combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude yellow oil was purified flash chromatography on silica gel (ISCO, 5-30% EtOAc/Hexanes) giving (1R,2R,5S)-methyl 2-ethynyl-5-fluorocyclohexanecarboxylate as oil (stains with $KMnO_4$).

Step C: (1R,2R,5S)-Methyl 2-(bromoethynyl)-5-fluorocyclohexanecarboxylate

NBS (2.151 g, 12.08 mmol) and silver nitrate (0.178 g, 1.051 mmol) were added to a solution of (1R,2R,5S)-methyl 2-ethynyl-5-fluorocyclohexanecarboxylate (1.9355g, 10.51 mmol) in acetone (52.5 ml). The resulting mixture was stirred at 23 °C for 1 hour, then filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO, 0-25% EtOAc/hexanes) giving 1R,2R,5S)-methyl 2-(bromoethynyl)-5-fluorocyclohexanecarboxylate as oil.

Step D: (1R,2R,5S)-Methyl 2-(4-bromo-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate

(Diazomethyl)trimethylsilane (2 M solution in hexanes, 29.2 ml, 58.4 mmol) was added to a solution of (1R,2R,5S)-methyl 2-(bromoethynyl)-5-fluorocyclohexanecarboxylate (2.56 g, 9.73 mmol) in THF (100 ml), and the resulting mixture was heated to 70 °C for 40 hours.

The reaction mixture was cooled to RT and concentrated under reduced pressure to give crude oil that was purifeid by flash chromatography on silica gel (ISCO, 0-75% EtOAc/hexanes) giving (1R,2R,5S)-methyl 2-(4-bromo-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate as oil.

Step E: (1R,2R,5S)-Methyl 2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate

A flask was flushed with N_2 and charged with copper (I) iodide (0.374 g, 1.966 mmol) and DMF (65.5 ml). 1,2-Diaminocyclohexane (0.241 ml, 1.966 mmol) was added to the CuI solution, and the resulting mixture was stirred at RT for 20min. This mixture was added via syringe to a N_2-flushed flask containing (1R,2R,5S)-methyl 2-(4-bromo-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate (2 g, 6.55 mmol), Cs_2CO_3 (10.68 g, 32.8 mmol) and 5-fluoro-2-iodopyridine (3.9 g, 17.49 mmol). The resulting mixture was heated to 80 °C for 1.5 hour. The reaction mixture was cooled, filtered, concentrated under reduced pressure, and purified by flash chromatography on silica gel (ISCO, 0-20% EtOAc/hexanes) giving (1R,2R,5S)-methyl 2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate as white solid.

Step F: (1R,2R,5S)-Methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate

A vial was charged with (1R,2R,5S)-methyl 2-(4-bromo-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate (2.168 g, 5.42 mmol), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide (2.284 g, 6.77 mmol), $PdOAc_2$ (0.061 g, 0.271 mmol), TPPTS (0.477 g, 0.813 mmol), water (5.42 ml), DMF (16.25 ml), and DIPA (1.930 ml, 13.54 mmol). The resulting mixture was heated to 80 °C for 30 min. The reaction was cooled, and brine was added to the reaction. The resulting mixture was diluted with water and extracted with EtOAc (3 x 100 mL). Combined organic phase was washed with water (3 x 100 mL), brine (100 mL), dried ($MgSO_4$), filtered, and solvent was removed under reduced pressure to give crude foam. The residue was purified by flash chromatography on silica gel (ISCO, 0-100% EtOAc/hexanes) giving more than (1R,2R,5S)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate as white foam contaminated with residual boronic ester. The product was used without further purification.

Step G: (1R,2R,5S)-2-(4-(4-(1,1-Dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylic acid

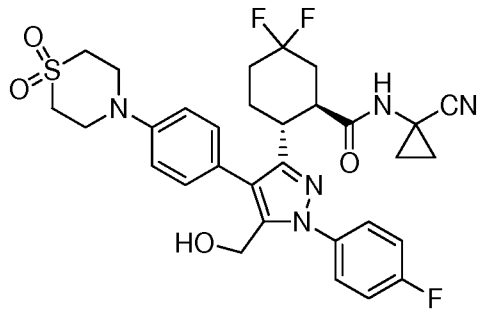
To a solution of (1R,2R,5S)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate (2.88 g, 5.42 mmol) in

THF (54.2 ml) was added MeOH (54.2 ml) and 1 N NaOH (54.2 ml, 54.2 mmol) The resuting mixture was heated at 65 °C for 2.5 hours, cooled to rt, and 1M HCl was added to quench the reaction. The resulting mixture was diluted with EtOAc/water. EtOAc layer was separated, and the aqueous phase was extracted with EtOAc (3 x). The combined organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated on a rotovapto give crude (1R,2R,5S)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylic acid as white foam. The product was used without further purification.

Step H: (1R,2R,5S)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide

To a solution of (1R,2R,5S)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylic acid (2.80 g, 5.42 mmol) in DCM (21.68 ml) was added DIPEA (1.041 ml, 5.96 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (1.806 g, 5.96 mmol). The resulting mixture was stirred at RT for 15 min follwed by the addition of 1-aminocyclopropanecarbonitrile hydrochloride (0.964 g, 8.13 mmol), DIPEA (2.84 ml, 16.26 mmol), and DMAP (0.132 g, 1.084 mmol). The resulting yellow suspension was stirred at room temperature for 45min and then diluted with saturated $NaHCO_3$/DCM. The resulting mixture was extracted with DCM (2 x). The combined organic phases were washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and solvent was removed under reduced pressure to give crude white solid. The residue was purifed, first, by flash chromatography on silica gel (ISCO, 10-75% EtOAc/DCM) using $CHCl_3$ to aid solubility. Second, the combined fractions with the desired product were concentrated on a rotovap, and the resulting residue was purified by reverse phase preparative HPLC (GILSON, 20-95% MECN/H_2O, 0.1% TFA, 20 min) giving (1R,2R,5S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide as white solid.^{1}H NMR (500 MHz, *CDCl$_3$*): δ ppm 0.80-0.70 (m; 2 H); 1.36-1.30 (m; 2 H); 1.67-1.50 (m; 1 H); 1.80-1.75 (m; 1 H); 2.15-1.90 (br m; 3 H); 2.28-2.19 (m; 1 H); 3.19-3.09 (m; 6 H); 3.94-3.88 (m; 4 H); 5.01 (d; J = 47.71 Hz; 1 H); 5.95 (s; 1 H); 6.97 (d; J = 8.35 Hz; 2 H); 7.35 (d; J = 8.35 Hz; 2 H); 7.61-7.55 (m; 1 H); 7.93 (dd; J = 9.00; 3.82 Hz; 1 H); 8.27 (d; J = 2.89 Hz; 1 H); 8.40 (s; 1 H); MS (ES, *m/z*): 581.2(M + 1).

EXAMPLE 11



(1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide (Compound 11)

Step A: (1R,2R)-methyl 2-(chlorocarbonyl)-5,5-difluorocyclohexanecarboxylate

Oxalyl chloride (2 mL) was added to the solution of (1R,2R)-4,4-difluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid (1.50 g, 6.75 mmol, 1.00 equiv) in DCM (20 mL) followed by the addition of DMF (0.1 mL). The reaction mixture was stirred under N_2 at RT for 2 hours. The resulting solution was concentrated under reduced pressure giving crude (1R,2R)-methyl 2-(chlorocarbonyl)-5,5-difluorocyclohexanecarboxylate as yellow oil. The crude product was used directly in the next step.

Step B: (1R,2R)-Methyl 2-(2-((benzyloxy)carbonyl)-3-oxobutanoyl)-5,5-difluorocyclohexanecarboxylate

Benzyl 3-oxobutanoate (1.30 g, 6.76 mmol, 1.01 equiv) was added to a suspension of $MgCl_2$ (0.630 g, 6.70 mmol, 1.00 equiv) in DCM (30 mL). The reaction mixture was kept under N_2 and cooled to 0 °C. Pyridine (1.10 mL, 13.7 mmol, 2.00 equiv) was added via a syringe to the suspension. The resulting mixture was stirred at 0 °C for 15 min. To this mixture, (1R,2R)-methyl 2-(chlorocarbonyl)-5,5-difluorocyclohexanecarboxylate (1.60 g, 6.65 mmol, 1.00 equiv) was added. The resulting mixture was further stirred at 0 °C for 15 min. The suspension was allowed to warm to RT and stirred for 5 hours. The reaction mixture was then quenched by the addition of aqueous HCl (3 M, 30 mL). The resulting solution was extracted with DCM (3 x 30 mL). The combined organic layers were washedwith water (30 mL),brine (30 mL), dried (Na_2SO_4), filtrate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1/20) giving (1R,2R)-methyl 2-(2-((benzyloxy)carbonyl)-3-oxobutanoyl)-5,5-difluorocyclohexanecarboxylate: MS (ES, *m/z*): 460.2 (M+ 23 + 41).

Step C: (1R,2R)-Methyl 5,5-difluoro-2-(3-oxobutanoyl)cyclohexanecarboxylate

Palladium hydroxideon activated carbon (0.500 g) was added to a mixture of (1R,2R)-methyl 2-(2-((benzyloxy)carbonyl)-3-oxobutanoyl)-5,5-difluorocyclohexanecarboxylate (1.70 g, 4.29 mmol, 1.00 equiv) in ethanol (30 mL). The reaction mixture was degassed with hydrogen 3 times and stirred under H_2 balloon for 16 hours. The solids were filtered out and the filtrate was concentrated under reduced pressure. This resulted in (1R,2R)-methyl 5,5-difluoro-2-(3-oxobutanoyl)cyclohexanecarboxylate: MS (ES, *m/z*): 263.1 (M+ 1).

Step D: (1R,2R)-Methyl 5,5-difluoro-2-(5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxylate

Hydrazine hydrochloride (1.98 g, 18.9mmol, 5.00 equiv) was added to a mixture of (1R,2R)-methyl 5,5-difluoro-2-(3-oxobutanoyl)cyclohexanecarboxylate (1.00 g, 3.81 mmol, 1.00 equiv) in isopropanol (30 mL). The reaction mixture was stirred under N_2 at 80 °C for 16 hours, and diluted with DCM (50 mL). The solids were filtered and the filtrate was concentrated under reduced pressure giving crude (1R,2R)-methyl 5,5-difluoro-2-(5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxylate: MS (ES, *m/z*): 259.1 (M+ 1).

Step E: (1R,2R)-Methyl 5,5-difluoro-2-(1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxylate

(1R,2R)-Methyl 5,5-difluoro-2-(1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxylate was synthesized following the same procedure as in Step E of Example 1 using(4-fluorophenyl)boronic acid (26.0 mg, 0.190 mmol, 1.20 equiv) , (1R,2R)-methyl 5,5-difluoro-2-(5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxylate (40.0 mg, 0.150 mmol, 1.00 equiv), DCM (4 mL), $Cu(OAc)_2$ (56.0 mg, 0.300 mmol, 2.00 equiv) and pyridine (24.4 mg, 0.310 mmol, 2.00 equiv). This resulted in (1R,2R)-methyl 5,5-difluoro-2-(1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxylate: MS (ES, *m/z*): 353.1 (M+ 1).

Step F: (1R,2R)-Methyl 2-(4-bromo-1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate

Bromine in $CHCl_3$ (0.8 M, 0.4 mL, 2.50 equiv) was added to the solution of (1R,2R)-methyl 5,5-difluoro-2-(1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxylate (44.0 mg, 0.120 mmol, 1.00 equiv) in $CHCl_3$ (1.5 mL). The reaction mixture was stirred at RT for 1.5 hours, quenched with saturated aqueous Na_2SO_3 (5 mL), and extracted with DCM (3 x 6 mL). The combined organic layers were washed with water (1 x 6 mL), brine (1 x 6 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure giving crude (1R,2R)-methyl 2-(4-bromo-1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate: MS (ES, *m/z*): 431.1 (M+1), 433.1 (M+1).

Step G: (1R,2R)-Methyl 2-(4-bromo-5-(bromomethyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate

NBS (61.9 mg, 0.348 mmol) was added to a mixture of (1R,2R)-methyl 2-(4-bromo-1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate (0.100 g, 0.232 mmol) in CCl_4 (2 mL) followed by the addition of benzoyl peroxide (22.5 mg, 0.0930 mmol) at RT. The resulting solution was stirred at 85 °C for 6 hours, cooled to RT, diluted with water (10 mL), and extracted with DCM (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), brine (2 x 10 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure giving (1R,2R)-methyl 2-(4-bromo-5-(bromomethyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate: MS (ES, *m/z*): 508.7(M + 1), 510.7 (M + 1), 512.7 (M + 1).

Step H: (1R,2R)-Methyl 2-(4-bromo-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate

Copper(I) oxide (50.5 mg, 0.353 mmol) was added to a mixture of (1R,2R)-methyl 2-(4-bromo-5-(bromomethyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate (90.0 mg, 0.176 mmol) in DMSO (2 mL) and water (0.6 mL).The resulting mixture was stirred at60 °C for 1 hour. The mixture was cooled, diluted with water (10 mL,) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), brine (2 x 10 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:10-1:5) giving (1R,2R)-methyl 2-(4-bromo-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate: MS (ES, *m/z*): 447.2 (M + 1), 449.2 (M + 1).

Step I: (1R,2R)-Methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate

(1R,2R)-Methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate was synthesized following the same procedure as in Step A of Example 6 using (1R,2R)-methyl 2-(4-bromo-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate (25.0 mg, 0.0560 mmol) , 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide (28.3 mg, 0.0840 mmol), DMF (1 mL), water (0.3 mL), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (4.56 mg, 5.59 μmol), $Pd(dtbpf)Cl_2$ (7.29 mg, 0.0110 mmol) and K_2CO_3 (23.2 mg, 0.168 mmol) giving (1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate: MS (ES, *m/z*): 578.3 (M + 1).

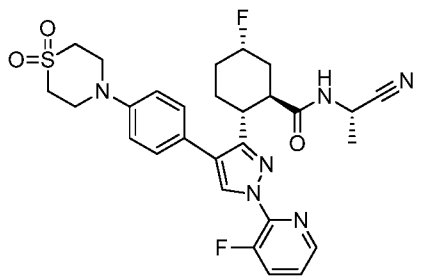
Step J: (1R,2R)-2-(4-(4-(1,1-Dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylic acid

(1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylic acid was synthesized following the same procedure as in Step F of Example 1 using LiOH (10.4 mg, 0.433 mmol), (1R,2R)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylate (25.0 mg, 43.0μmol), EtOH (1.0 mL) and water (1.0 mL). This resulted in(1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylic acid: MS (ES, *m/z*): 564.2 (M + 1).

Step K: (1R,2R)-N-(1-Cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide was synthesized following the same procedure as in Step G of Example 1 using (1R,2R)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxylic acid (40.0 mg, 0.0710 mmol), 1-aminocyclopropanecarbonitrile hydrochloride (42.1 mg, 0.355 mmol), DMF (1 mL), HATU (43.2 mg, 0.114 mmol), andDIPEA(0.124 ml, 0.710 mmol). This resulted in (1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide as off-white solid:^{1}H NMR (300 MHz, DMSO-d_6) δ ppm8.88 (s, 1H), 7.85-7.80 (m, 2H), 7.44-7.35 (m, 4H), 7.13 (d, J = 8.4 Hz, 2H), 5.51-5.48 (m, 1H), 4.23 (d, J =3.6 Hz, 2H), 3.91-3.79 (m, 4H), 3.20-2.98 (m, 6H), 2.30-1.82 (m, 5H), 1.70-1.53 (m, 1H), 1.35-1.32 (m, 2H), 0.91-0.82 (m, 1H), 0.62-0.61 (m, 1H);MS (ES, *m/z*): 628.2 (M + 1).

EXAMPLE 12



(1R,2R,5S)-N-((S)-1-Cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide

Step A: (1R,2R,5S)-Methyl 2-(4-bromo-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate

CuI (37.4 mg, 0.197 mmol) and 1,2-diaminocyclohexane (0.024 mL, 0.197 mmol) were mixed together in anhidrous DMF (4.5 mL) at RT, and the resulting solution was stirred at rt for 20 min. In a separate vial (1R,2R,5S)-methyl 2-(4-bromo-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate (200 mg, 0.655 mmol), Cs_2CO_3 (1.068 g, 3.28 mmol) and 3-fluoro-2-iodopyridine (438 mg, 1.97 mmol) were mixed together. The first solution with copper complex was added to the second solution through a syringe at 23 °C. The color of the solution turned deep blue after mixing everything together. The resulting mixture was heated at 80 °C for 3 hours. The reaction mixture was diluted with water (45-50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by reversed phase preparative HPLC (H_2O/MeCN (30-95%) with 0.1%TFA, 20 min) getting (1R,2R,5S)-methyl 2-(4-bromo-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate.

Step B: (1R,2R,5S)-Methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate

A vial was charged with (1R,2R,5S)-methyl 2-(4-bromo-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate (35 mg, 0.087 mmol), sodium 4,4',4''-phosphinetriyltribenzenesulfonate (15 mg, 0.026 mmol), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thiomorpholine 1,1-dioxide (88 mg, 0.262 mmol), $PdOAc_2$ (2 mg, 8.91 μmol), DMF (700 mL), water (230 μl), and DIPA (38 μl, 0.267 mmol). The resulting mixture was heated at 80 °C for 1 h 30 min, then cooled to RT. The reaction mixture was filtered through a 0.45 μm syringe filter and purified via reverse phase preparative HPLC (H_2O/MeCN (20-95%) with 0.1%TFA, 20 min). Fractions with the desired product were treated with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x). Combined oranic phases were washed with brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure giving (1R,2R,5S)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate.

Step C: (1R,2R,5S)-2-(4-(4-(1,1-Dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylic acid

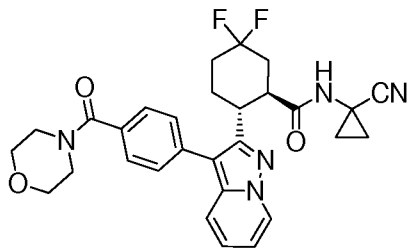
To a solution of (1R,2R,5S)-methyl 2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylate (34 mg, 0.064 mmol) in THF (1 ml)/MeOH (1 ml) was added 1 N NaOH (1.3 mL, 1.3 mmol) and the resulting mixture was heated to 65 °C for 2 hours 20 min leading to fully hydrolyze the ester. The

reaction mixture was cooled to rt and 1M HCl (1.301 mL) was added to quench the reaction. The resulting mixture was diluted with EtOAc (10 mL) and water (10 mL). The mixture was extracted with EtOAc (3 x 10 mL). Combined organic phases were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude (1R,2R,5S)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylic acid as white solid that was used without further purification.

Step D: (1R,2R,5S)-N-((S)-1-Cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide (Compound 12)

To the vial containing starting material (1R,2R,5S)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxylic acid (15 mg, 0.029 mmol) in NMP (500 μL) was added (S)-2-aminopropanenitrile hydrochloride (19 mg, 0.178 mmol), DIPEA (61 μL, 0.348 mmol), and HATU (17 mg, 0.044 mmol) at room temperature.The resulting mixture was heated at 65 °C for 2 hours. The crude mixture was purified directly via reverse phase Gilson HPLC (water/MeCN(10 to 85%) with 0.1% TFA, 20 min). Fractions with the desired product were treated with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure giving (1R,2R,5S)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide (Compound 12) as white solid. ^1H NMR (500 MHz, *CDCl₃*): δ ppm 1.07 (d; J = 7.12 Hz; 3 H); 2.12-1.49 (m; 5 H); 2.32-2.23 (m; 1H); 3.16-3.11 (m, 4H); 3.19-3.16 (m; 1 H); 3.39 (td; J = 11.95; 3.35 Hz; 1H); 3.94-3.87 (m; 4H); 4.83-4.77 (m; 1H); 5.00 (d; J = 47.79 Hz; 1H); 6.58 (d; J = 8.55 Hz; 1H); 6.96 (d; J = 8.37 Hz; 2 H); 7.32 (m, 1H); 7.34 (d; 2 H); 7.71-7.67 (m; 1H); 8.18 (s; 1 H); 8.37 (dd; J = 4.67; 1.25 Hz; 1H).

EXAMPLE 13



(1R,2R)-N-(1-cyanocyclopropyl)-5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide (Compound 13)

Step A: (1R,2R)-Methyl 5,5-difluoro-2-formylcyclohexanecarboxylate

(1R,2R)-Methyl 5,5-difluoro-2-formylcyclohexanecarboxylate was synthesized following the same procedure as in Step A of Example 1 using (1*R*,2*R*)-4,4-difluoro-2-(methoxycarbonyl)cyclohexanecarboxylic acid (2.00 g, 9.00 mmol, 1.00 equiv) in DCM (40 mL), in the present of DMF (one drop), oxalyl chloride (1.70 g, 13.39 mmol, 1.50 equiv), THF (50 mL), Pd/C 10 % (0.500 g), and 2,6-lutidine (1.60 g, 14.93 mmol, 1.50 equiv). This resulted in (1R,2R)-methyl 5,5-difluoro-2-formylcyclohexanecarboxylate as a colorless oil:^{1}HNMR: (300 MHz, DMSO-d_6) δ ppm 9.56 (s, 1H), 3.56 (s, 3H), 2.91-2.65 (m, 2H), 2.35-2.13 (m, 1H), 2.12-1.79 (m, 4H), 1.55-1.30 (m, 1H).

Step B: (1R,2R)-Methyl 2-ethynyl-5,5-difluorocyclohexanecarboxylate

(1R,2R)-Methyl 2-ethynyl-5,5-difluorocyclohexanecarboxylate was synthesized following the same procedure as in Step B of Example 1 using 4-methylbenzene-1-sulfonyl azide (1.20g, 6.08 mmol, 1.33 equiv), dimethyl (2-oxopropyl)phosphonate (0.943g, 5.68 mmol, 1.30 equiv), K_2CO_3 (1.80g, 13.02 mmol, 3.00 equiv), and (1R,2R)-methyl 5,5-difluoro-2-formylcyclohexanecarboxylate (0.900 g, 4.36 mmol, 1.00 equiv) in CH_3CN (20 mL) and MeOH (10 mL). This resulted in (1R,2R)-methyl 2-ethynyl-5,5-difluorocyclohexanecarboxylate as colorless oil:^{1}HNMR: (300 MHz, DMSO-d_6) δ ppm 3.65 (s, 3H), 3.00 (m, 1H), 2.79-2.60 (m, 1H), 2.59-2.50 (m, 1H), 2.30-2.10 (m, 1H), 2.09-1.78 (m, 4H), 1.65-1.40 (m, 1H).

Step C: (1R,2R)-Methyl 5,5-difluoro-2-(pyridin-2-ylethynyl)cyclohexanecarboxylate

(1R,2R)-Methyl 2-ethynyl-5,5-difluorocyclohexanecarboxylate (0.500 g, 2.47 mmol, 1.00 equiv), $Pd(PPh_3)_2Cl_2$ (0.173 g, 0.250 mmol, 0.10 equiv), DIPEA (1.60 g, 12.4 mmol, 5.00 equiv), 2-bromopyridine (0.430 g, 2.72 mmol, 1.10 equiv), and CuI (50.0 mg, 0.260 mmol, 0.10 equiv) in CH_3CN (15 mL) were placed into a 50-mL round-bottom flask purged and maintained under N_2. The reaction mixture was degassed with nitrogen 3 times and stirred at ambient temperature for 3 hours. The solids were filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1/3). This resulted in (1R,2R)-methyl 5,5-difluoro-2-(pyridin-2-ylethynyl)cyclohexanecarboxylate as yellow solid: MS (ES, *m/z*) 280.3 (M + 1).

Step D: 1-Amino-2-(((1R,2R)-4,4-difluoro-2-(methoxycarbonyl)cyclohexyl)ethynyl)pyridin-1-ium

(1R,2R)-Methyl 5,5-difluoro-2-(pyridin-2-ylethynyl)cyclohexanecarboxylate (50.0 mg, 0.180 mmol, 1.00 equiv) in DCM (5 mL) was placed into a 25-mL round-bottom flask. To this solution, O-(mesitylsulfonyl)hydroxylamine (0.116 g, 0.540 mmol, 3.00 equiv) was added with stirring at 0 °C. The reaction mixture was stirred at an ice bath temperature for 6 hours, filtered, and the filtrate was concentrated under reduced pressure providing the crude

1-amino-2-[2-[(1*R*,2*R*)-4,4-difluoro-2-(methoxycarbonyl)cyclohexyl]ethynyl]pyridin-1-ium as a yellow solid: MS (ES, *m/z*) 295.3 (M + 1).

Step E: (1R,2R)-Methyl 5,5-difluoro-2-(pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylate

Into a 25-mL round-bottom flask, were placed 1-amino-2-[2-[(1*R*,2*R*)-4,4-difluoro-2-(methoxycarbonyl)cyclohexyl]ethynyl]pyridin-1-ium (0.400 g, 0.540 mmol, 1.00 equiv, 40%) and K_2CO_3 (0.280 g, 2.03 mmol, 3.00 equiv) in DMF (10 mL). The resulting mixture was stirred at 10 °C for 16 hours, diluted with EtOAc (200 mL,) and washed with brine (3 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:4) giving (1R,2R)-methyl 5,5-difluoro-2-(pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylate: MS (ES, *m/z*) 295.4 (M + 1).

Step F: (1R,2R)-Methyl 2-(3-bromopyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxylate

Bromine (53.0 mg, 0.330 mmol, 1.50 equiv) was added to the solution of (1R,2R)-methyl 5,5-difluoro-2-(pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylate (65.0 mg, 0.220 mmol, 1.00 equiv) in $CHCl_3$ (5 mL) at 0 °C. The resulting mixture was stirred at 10 °C for 1 hour. The reaction mixture was diluted with chloroform (20 mL) and washed with saturated aqueous Na_2SO_3 (25 mL). The organic layer was dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1/5) giving 1R,2R)-methyl 2-(3-bromopyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxylate: MS (ES, *m/z*) 373.3 (M + 1), 375.2 (M + 1).

Step G: Morpholino(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone

Into a 50-mL round-bottom flask, were placed morpholine (5.27 g, 60.5 mmol, 3.00 equiv), HATU (23.0 g, 60.5 mmol, 3.00 equiv), DIPEA (17.6 ml, 101 mmol, 5.00 equiv), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (5.00 g, 20.2 mmol, 1.00 equiv) in DMF (20 ml). The resulting mixture was stirred at ambient temperature for 16 hours, quenched with water (50 mL,) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (5 x 30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc /hexanes (1:3) giving morpholino(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.85 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 3.78-3.33 (m, 8H), 1.38 (s, 12H).

Step H: (1R,2R)-Methyl 5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylate

Into a 10-mL microwave vial were placed morpholino(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone from Step G (76.0 mg, 0.241 mmol, 1.50 equiv), $Pd(PPh_3)_4$(37.2 mg, 0.0320 mmol, 0.20 equiv), Cs_2CO_3 (0.262 g, 0.804 mmol, 5.00 equiv), (1R,2R)-methyl 2-(3-bromopyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxylate from Step F (60.0 mg, 0.161 mmol, 1.00 equiv), water (0.5 ml), and DMF (2.00 ml). The reaction mixture was irradiated with microwave radiation at 100 °C for 1 hour, quenched with water (10 mL,) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1: 6) giving (1R,2R)-methyl 5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylate: MS (ES, *m/z*): 484.5 (M + 1).

Step I: (1R,2R)-5,5-Difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylic acid

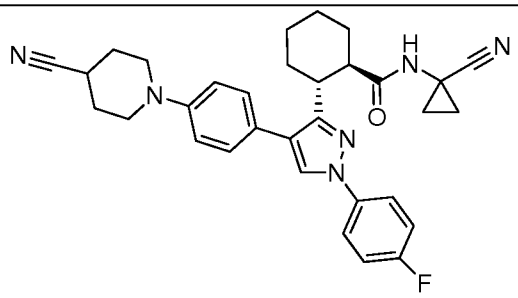
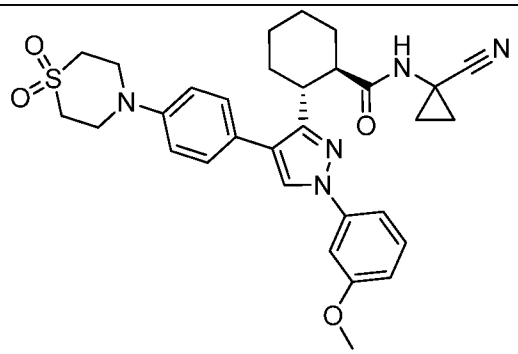
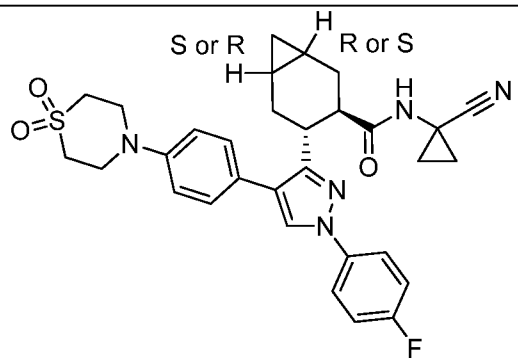
The solution of (1R,2R)-methyl 5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylate (55.0 mg, 0.114 mmol, 1.00 equiv) and 3M sulfuric acid (6.06 ml) in THF (1.00 ml) and water (1ml) was heated at 60 °C for 2 hours in a 25 mL round bottom flask. The reaction mixture was cooled, diluted with water (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 25 mL), dried (Na_2SO_4), filtered, and the filtrate was concentrated under reduced pressure giving (1R,2R)-5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylic acid: MS (ES, m/z): 470.4 (M + 1).

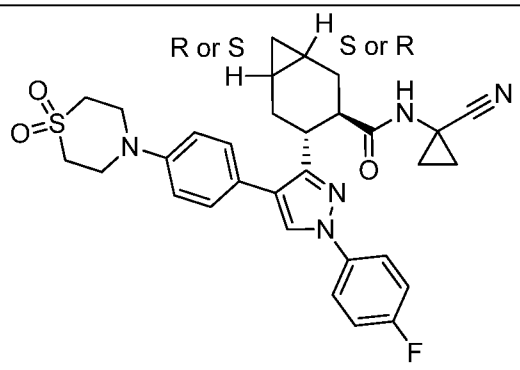
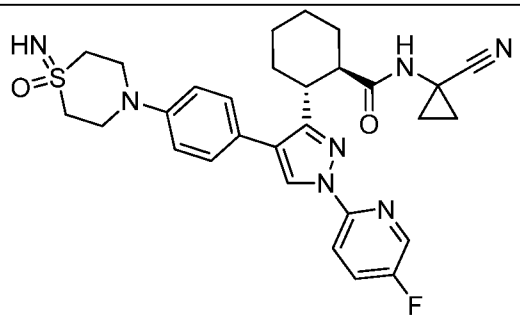
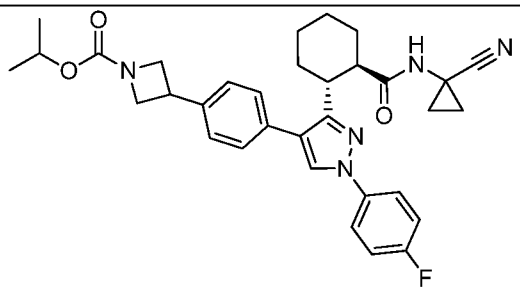
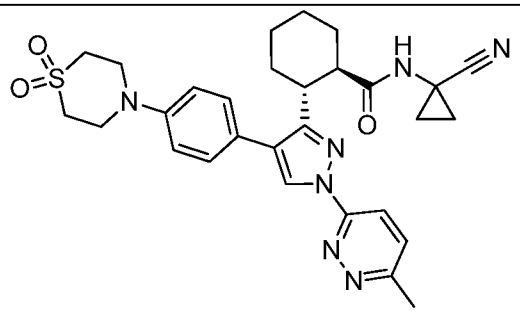
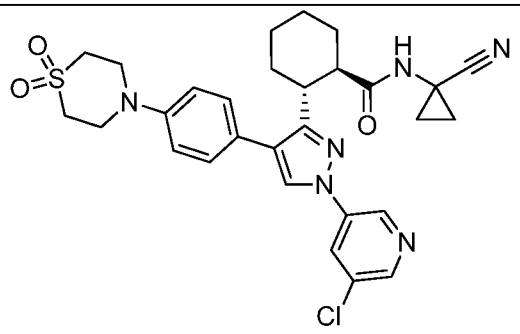
Step J: (1R,2R)-N-(1-Cyanocyclopropyl)-5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide

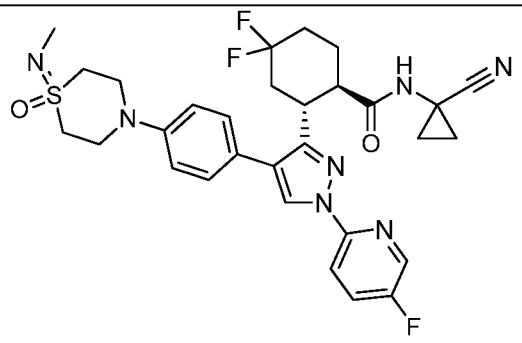
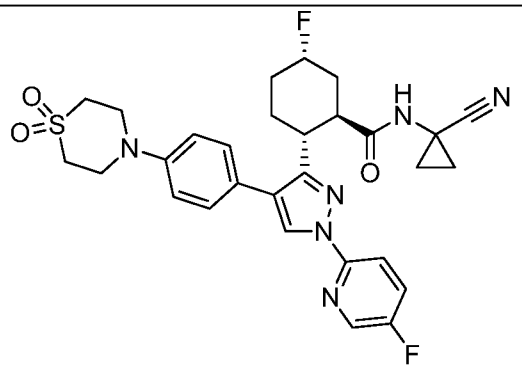
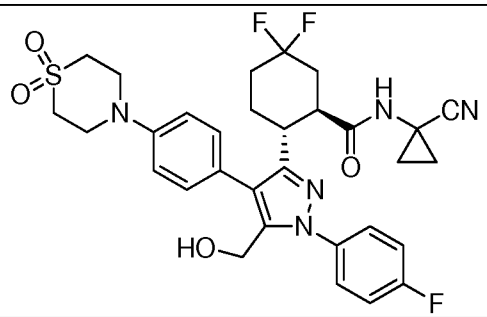
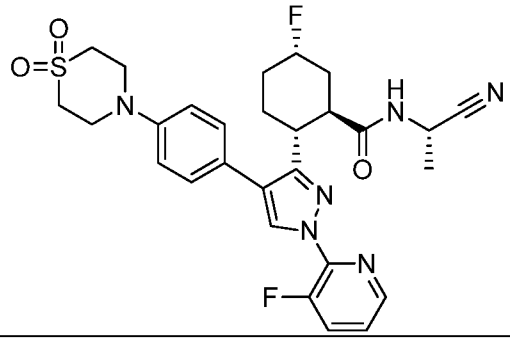
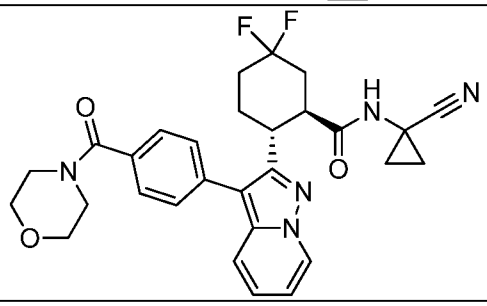
(1*R*,2*R*)-*N*-(1-Cyanocyclopropyl)-5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide was synthesized following the same procedure as in Step G of Example 1 using1-aminocyclopropanecarbonitrile hidrochloride (21.0 mg, 0.256 mmol, 3.00 equiv), HATU (97 mg, 0.256 mmol, 3.00 equiv), DIPEA (0.074 ml, 0.426 mmol, 5.00 equiv), (1*R*,2*R*)-5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxylic acid (40 mg, 0.085 mmol, 1.00 equiv) in DMF (1.00 ml).This resulted in (1R,2R)-N-(1-cyanocyclopropyl)-5,5-difluoro-2-(3-(4-(morpholine-4-

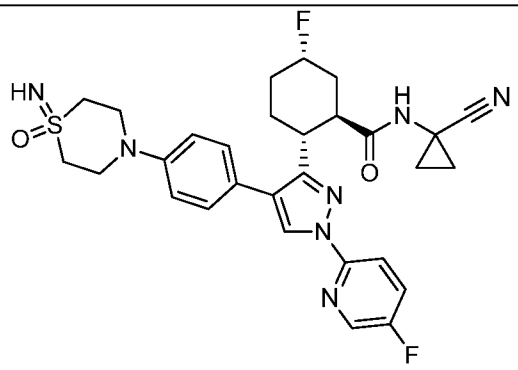
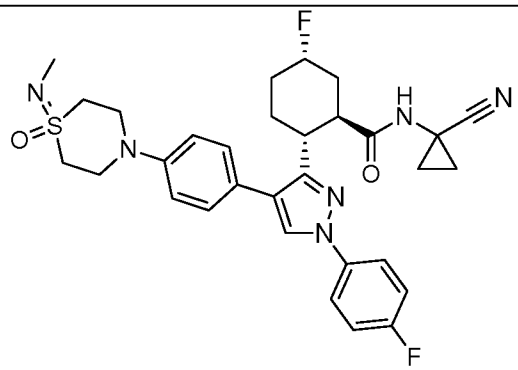
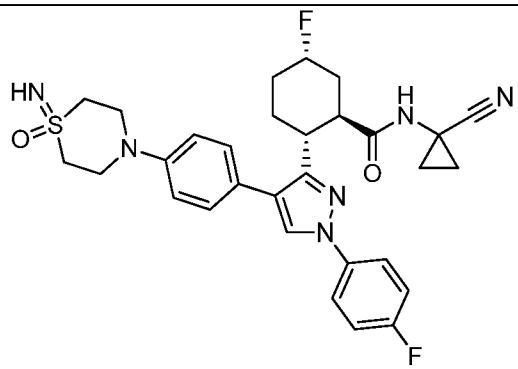
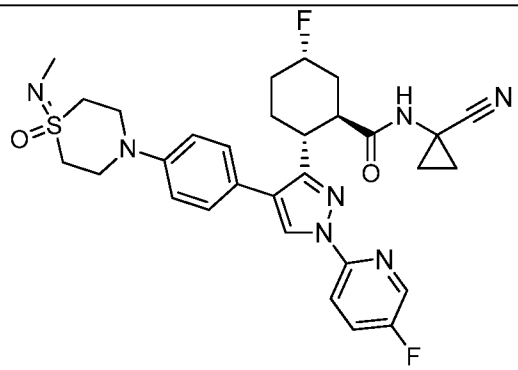
carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide (Compound 13) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 8.76 (s, 1H), 8.60 (d, J = 6.9 Hz, 1H), 7.61-7.52 (m, 5H), 7.26-7.21 (m, 1H), 6.95-6.90 (m, 1H), 3.65 3.31 (m, 9H), 3.12-3.05 (m, 1H), 2.17-1.78 (m, 5H), 1.77-1.62 (m, 1H), 1.27-1.23 (m, 2H), 0.65-0.60 (m, 1H), 0.45-0.40 (m, 1H); MS (ES, *m/z*): 534.2 (M + 1).

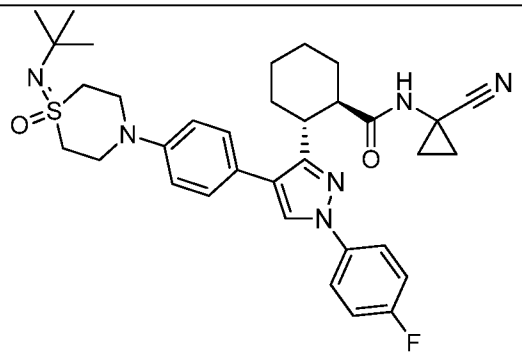
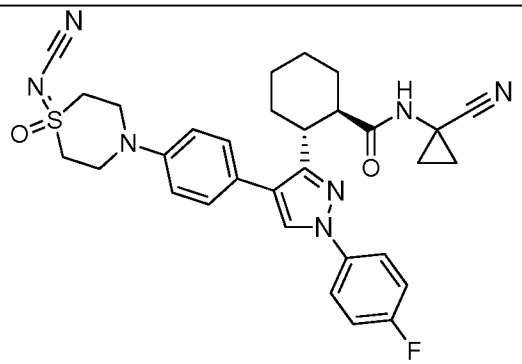
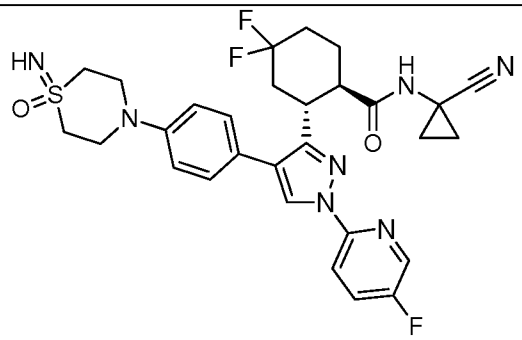
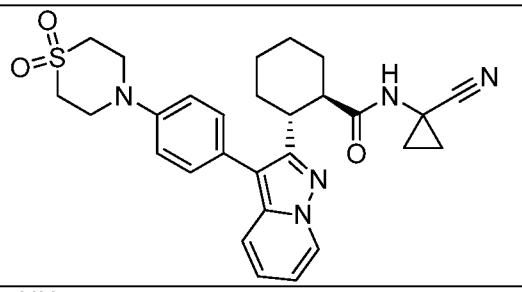
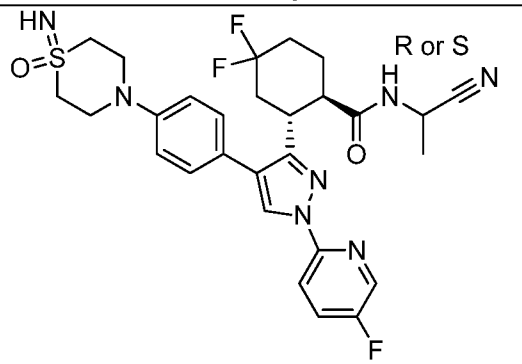
The following compounds were prepared using methods analogous to those described in the preceding examples:

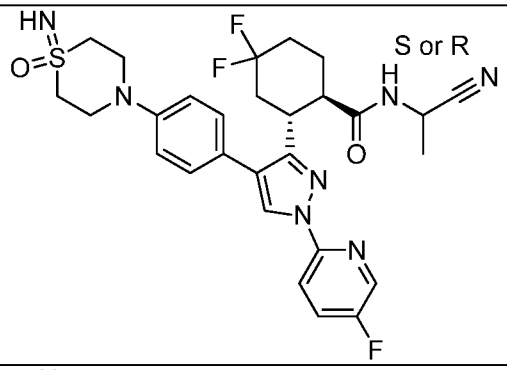
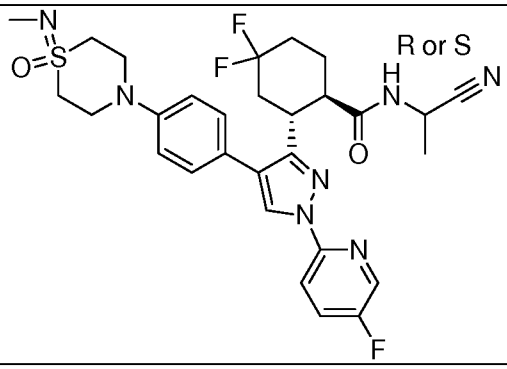
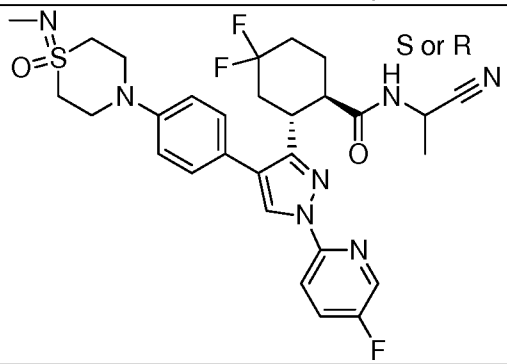
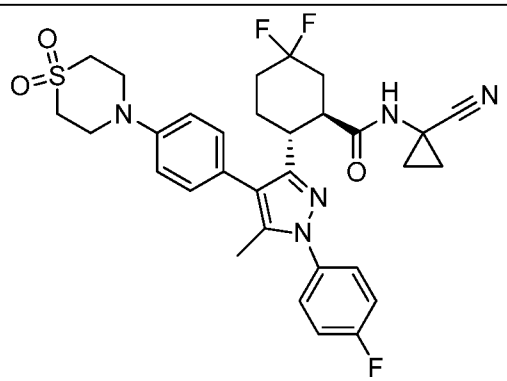
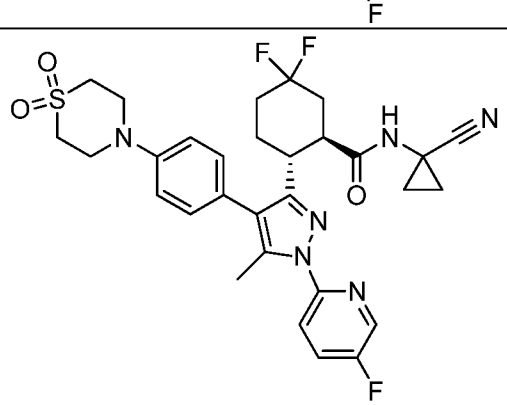
	Structure	Name	LC-MS m/z (M+H)	hrbCat K (IP (nM))	hCat F (IP (nM))
1		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(4-cyanopiperidin-1-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	537.4	2.72	698
2		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	574.2	0.99	494
3		(1S,3R,4R,6R) or (1R,3R,4R,6S)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide	574.0	0.84	333

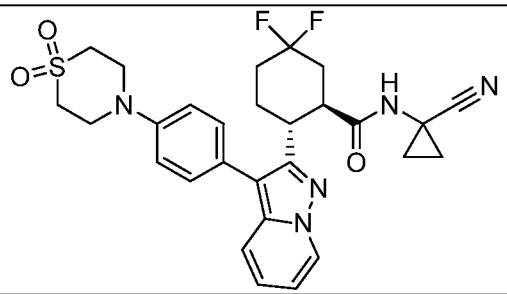
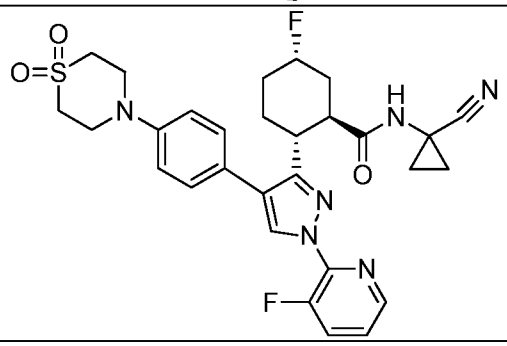
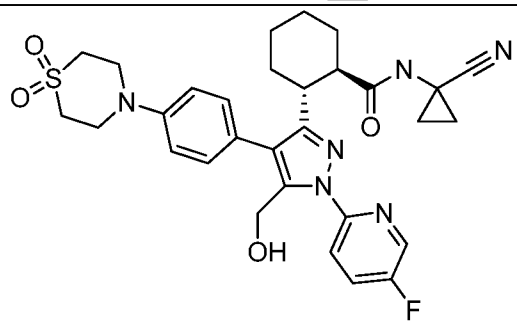
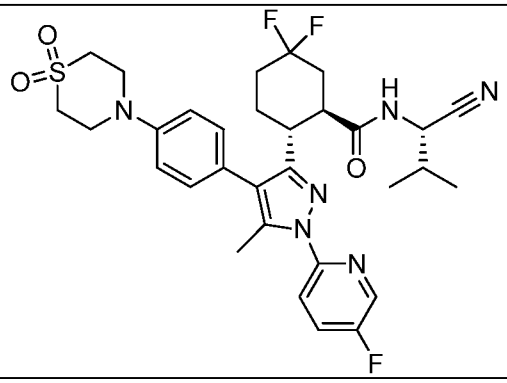
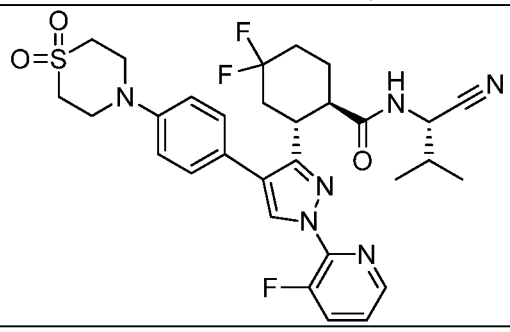
4		(1R,3R,4R,6S)or (1S,3R,4R,6R) -N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide	574.0	0.93	258
5		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	562.2	1.53	877
6		isopropyl 3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate	570.4	0.53	49
7		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	560.4	1.54	517
8		(1R,2R)-2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	579.3	0.75	215

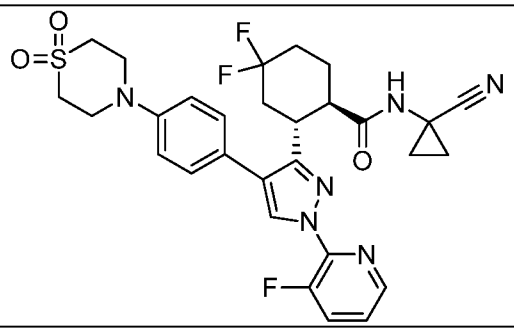
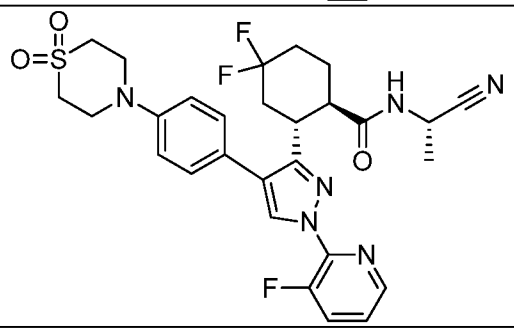
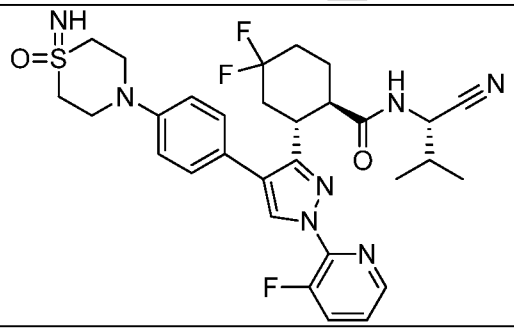
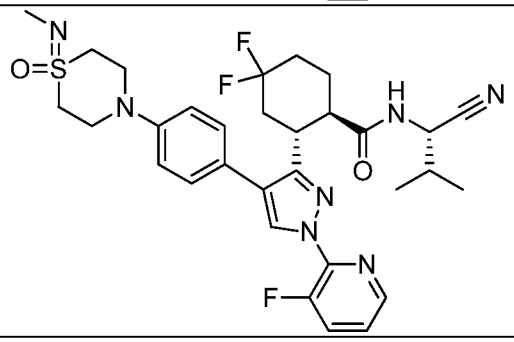
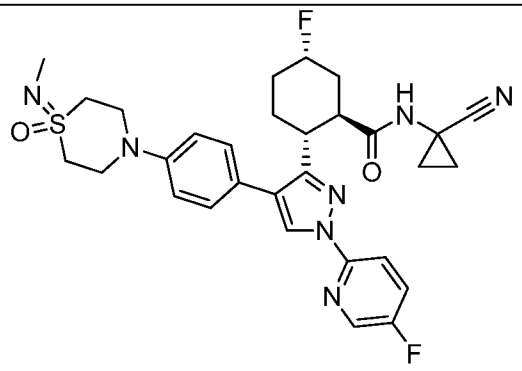
9		(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	612.1	2.56	3,669
10		(1R,2R,5S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide	581.2	0.89	1,048
11		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	628.2	1.41	125
12		(1R,2R,5S)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide	569.4	6.89	10,000
13		(1R,2R)-N-(1-cyanocyclopropyl)-5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide	534.2	4.84	339

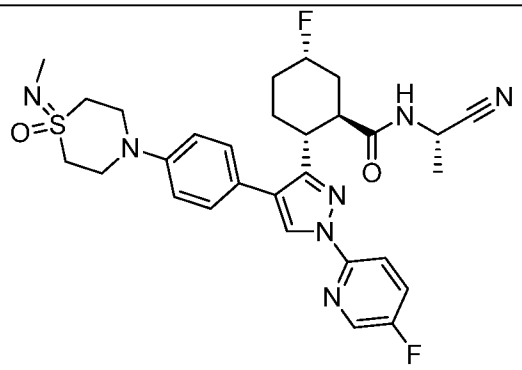
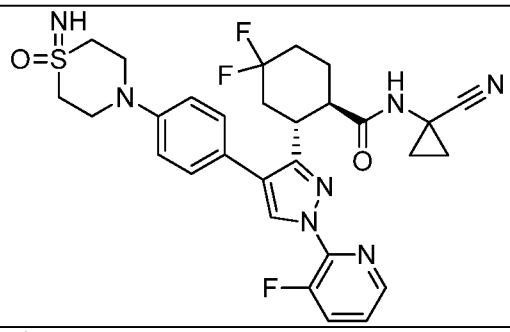
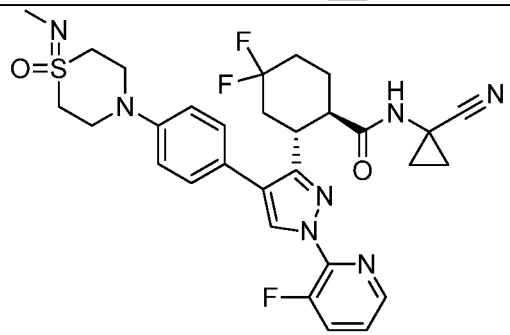
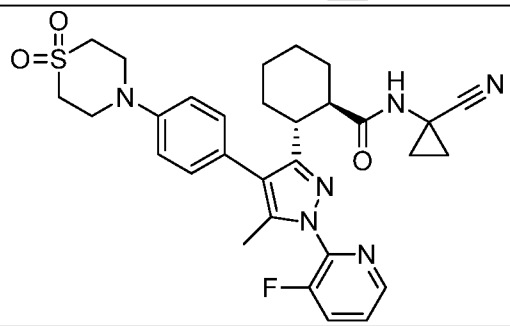
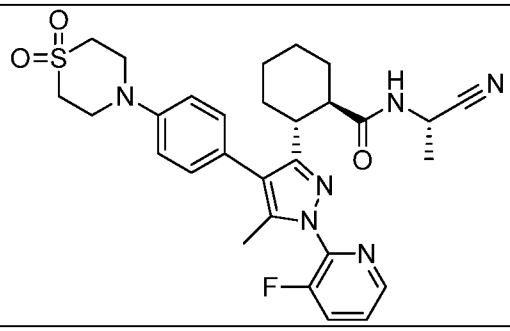
14		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.1	2.00	2,018
15		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(4-fluorophenyl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	593.1	3.00	1,782
16		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(4-fluorophenyl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	579.1	2.83	2,596
17		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	594.1	3.22	1,407

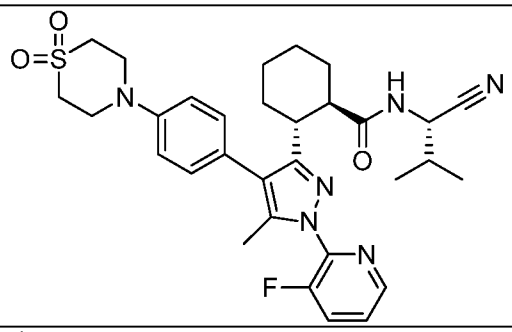
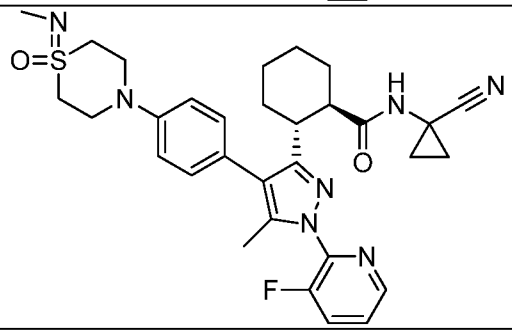
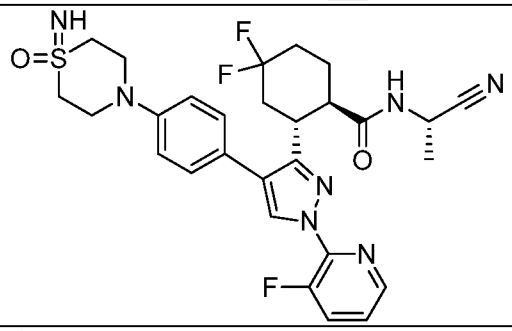
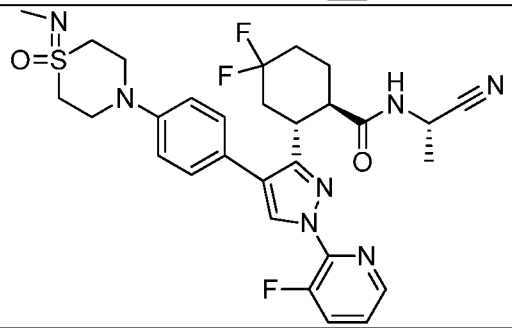
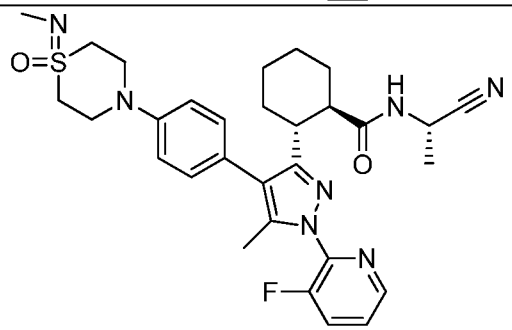
18		(1R,2R)-2-(4-(4-(1-(tert-butylimino)-1-oxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	617.5	5.00	1,289
19		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1-(cyanoimino)-1-oxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	586.3	2.20	809
20		(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	612.5	6.81	1,820
21		(1R,2R)-N-(1-cyanocyclopropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide	518.3	9.56	6,910
22		(1R,2R)-N-((R or S)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	586.3	263.70	10,000

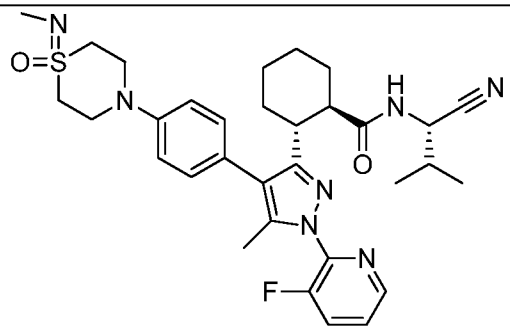
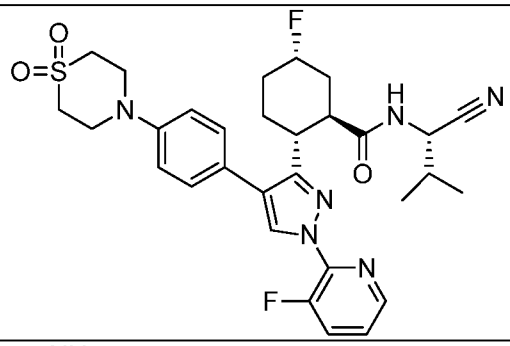
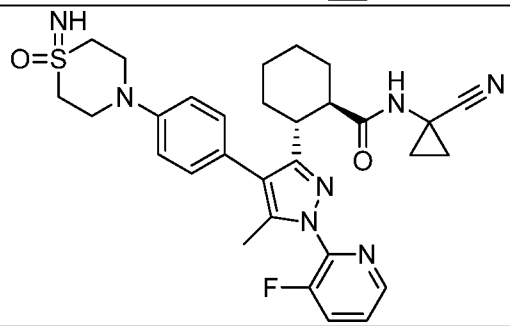
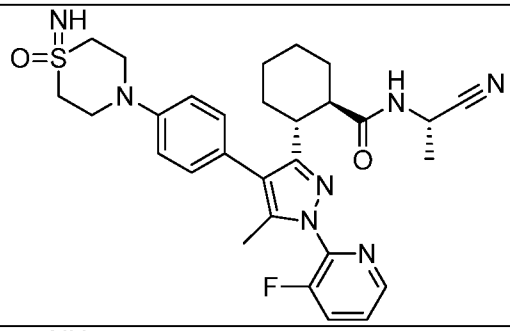
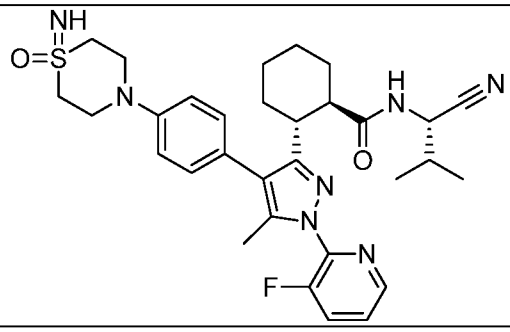
23		(1R,2R)-N-((S or R)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	586.3	1.07	348
24		(1R,2R)-N-((R or S)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	600.4	168.90	10,000
25		(1R,2R)-N-((S or R)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	600.4	0.52	431
26		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	612.2	0.67	168
27		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	613.2	1.28	170

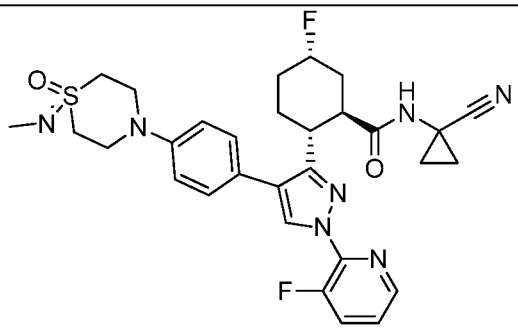
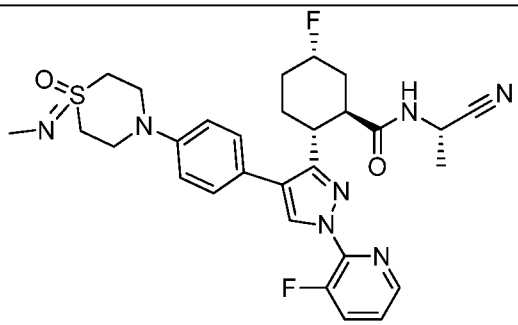
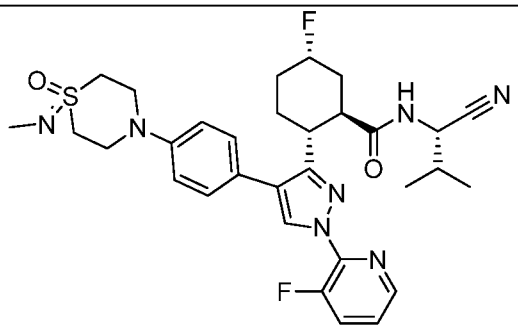
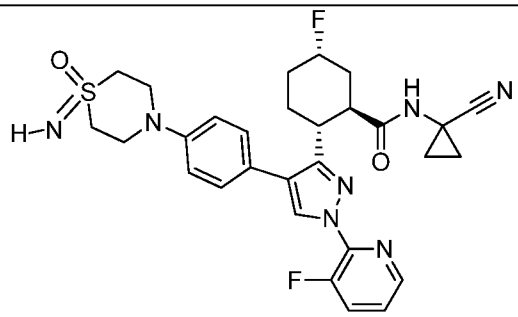
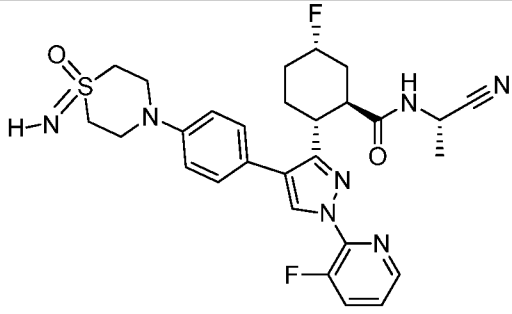
28		(1R,2R)-N-(1-cyanocyclopropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide	554.5	1.94	363
29		(1R,2R,5S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide	581.4	6.20	6,775
30		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	593.4	11.03	5,874
31		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	629.2	1.63	115
32		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide	615.1	7.11	2,777

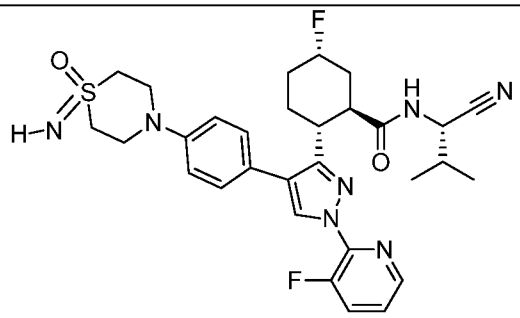
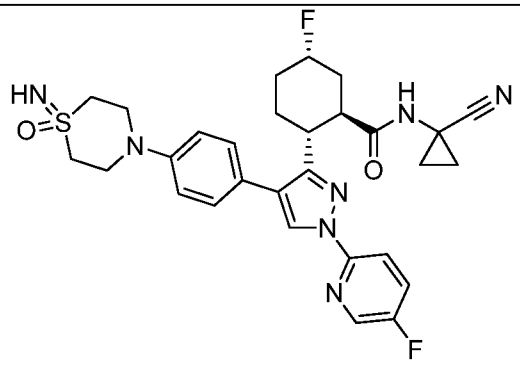
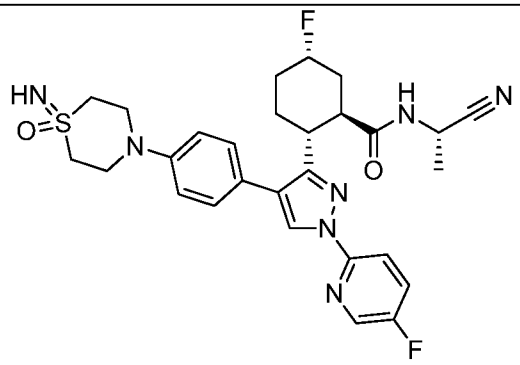
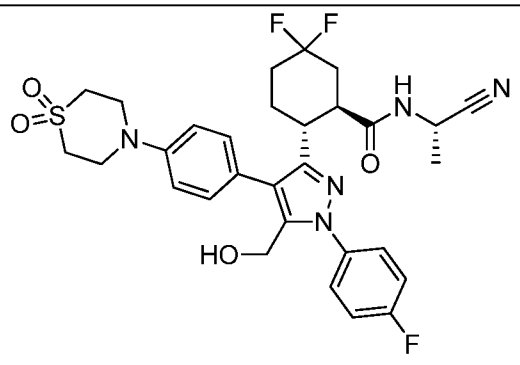
33		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide	599.5	13.62	9,539
34		(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide	587.4	5.40	2,835
35		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	614.1	9.69	4,888
36		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	628.1	8.79	8,183
37		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	594.2	1.76	1,660

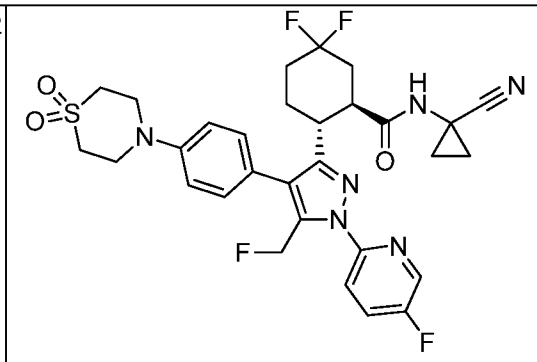
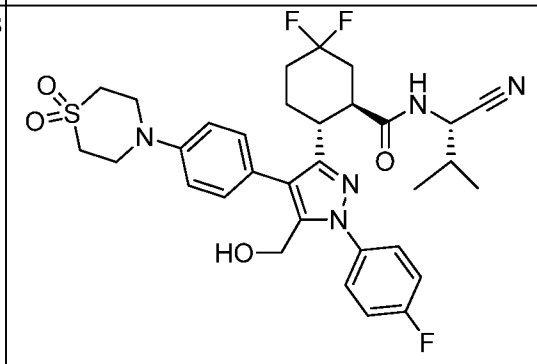
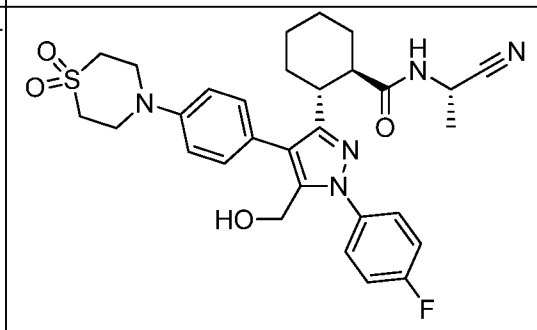
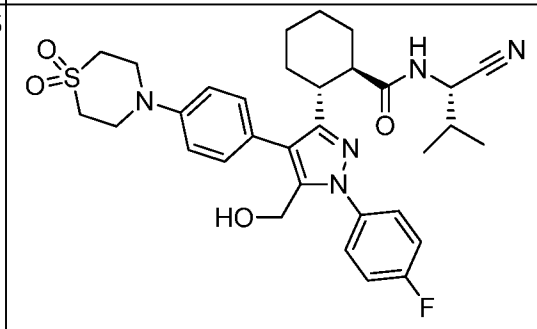
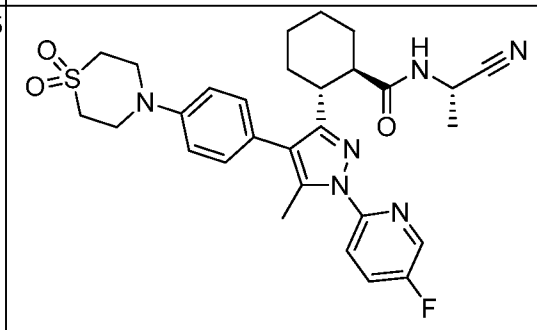
38		(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	582.3	1.14	855
39		(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	598.4	48.66	10,000
40		(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	612.5	22.02	10,000
41		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	577.1	8.50	5,391
42		(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	565.1	3.62	1,989

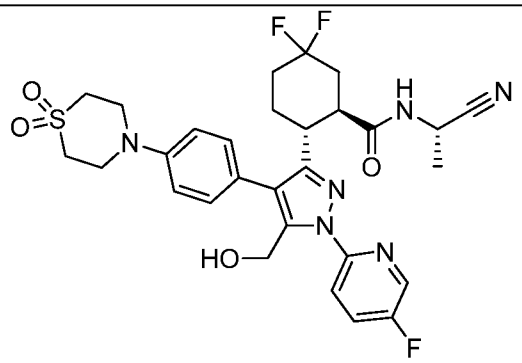
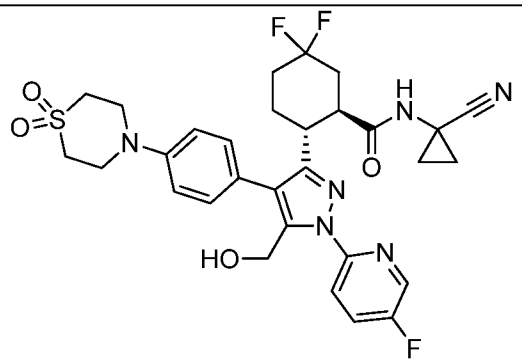
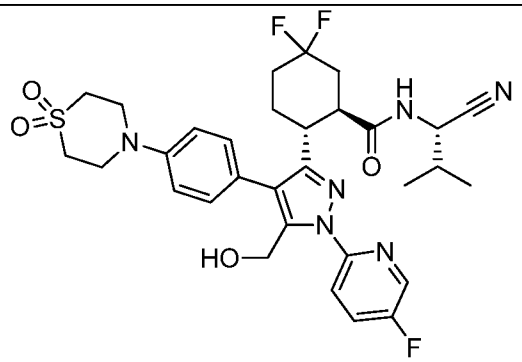
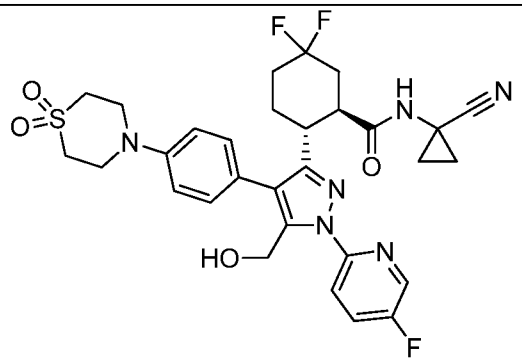
43		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide Molecular Weight: 592.73	593.1	12.08	4,551
44		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3-fluoropyridin-2-yl)-5-methyl-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	590.3	13.87	8,837
45		(1R,2R)-N-((S)-1-cyanoethyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	586.4	6.61	5,477
46		(1R,2R)-N-((S)-1-cyanoethyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	600.5	5.78	6,615
47		(1R,2R)-N-((S)-1-cyanoethyl)-2-(1-(3-fluoropyridin-2-yl)-5-methyl-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	578.5	5.48	3,236

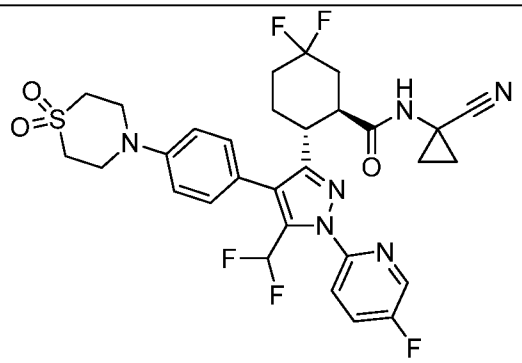
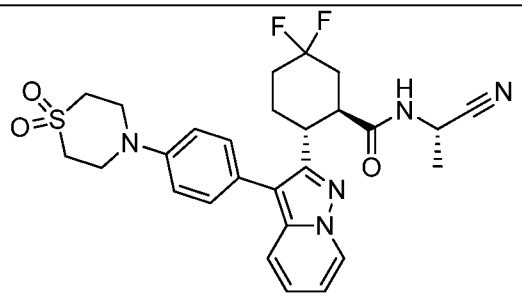
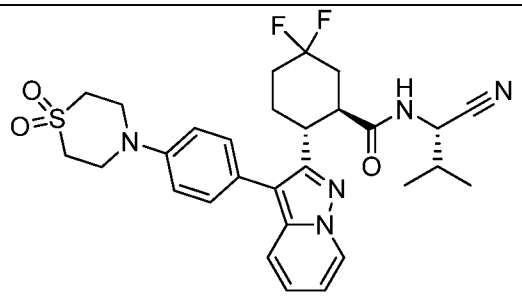
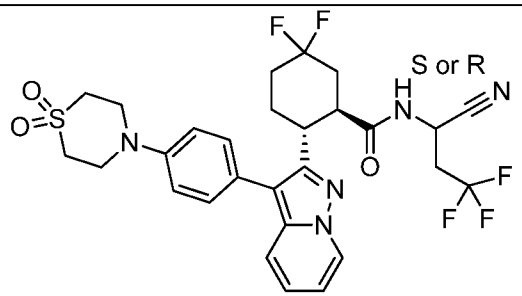
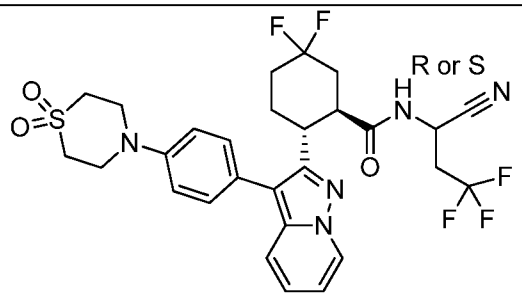
48		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(1-(3-fluoropyridin-2-yl)-5-methyl-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	606.5	19.24	7,348
49		(1R,2R,5S)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide	597.3	8.35	10,000
50		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	576.3	14.04	7,793
51		(1R,2R)-N-((S)-1-cyanoethyl)-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	564.3	7.41	3,870
52		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	592.3	22.47	9,319

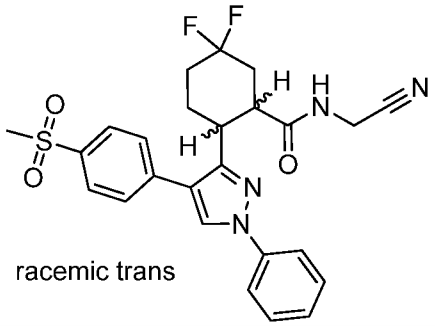
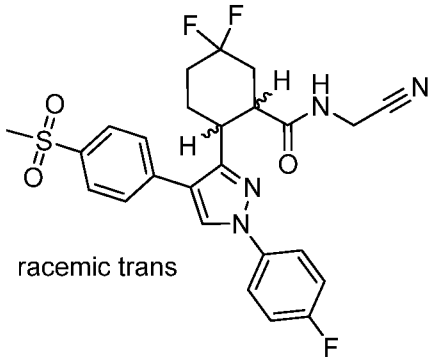
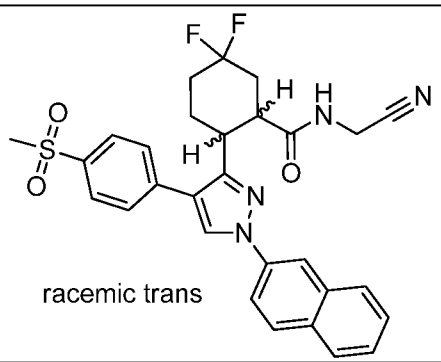
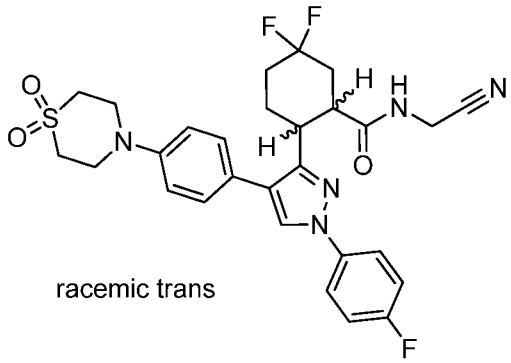
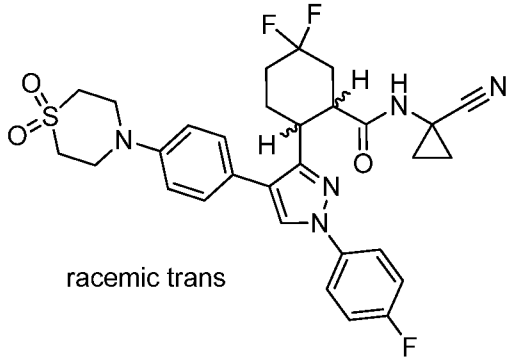
53		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	594.3	6.54	10,000
54		(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	582.3	7.89	10,000
55		(1R,2R,5S)-N-((S)-1-cyano-2-methylpropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	610.3	14.30	10,000
56		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.3	5.69	10,000
57		(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	568.4	8.30	7,772

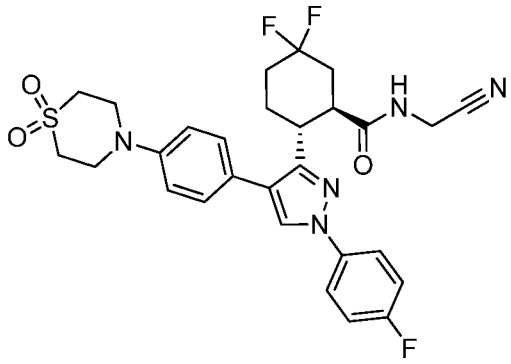
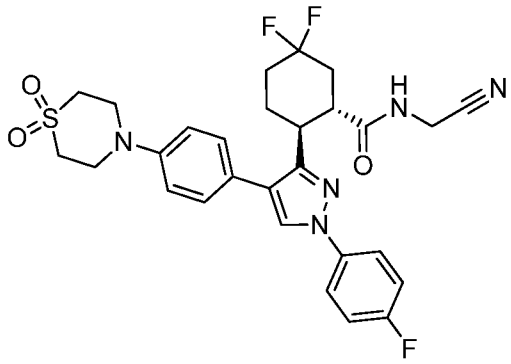
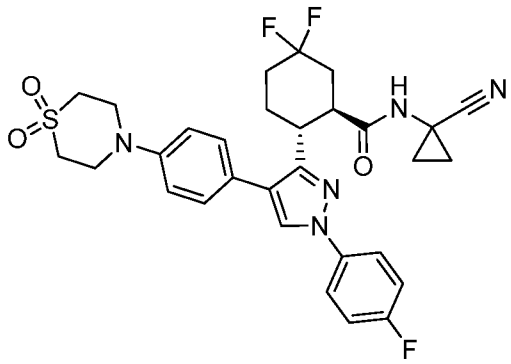
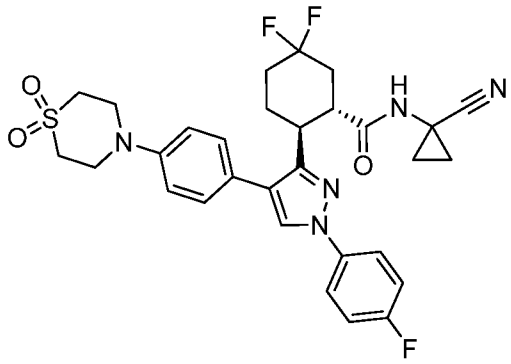
58		(1R,2R,5S)-N-((S)-1-cyano-2-methylpropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	596.4	15.96	10,000
59		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.3	1.29	2,455
60		(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	568.3	1.43	674
61		(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	616.5	1.61	121

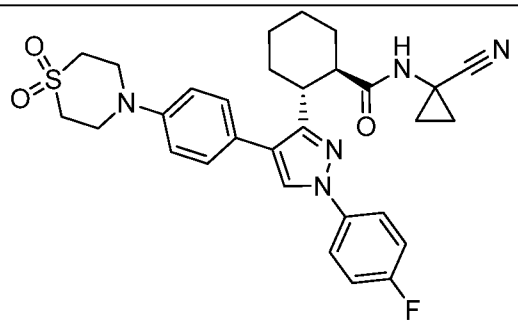
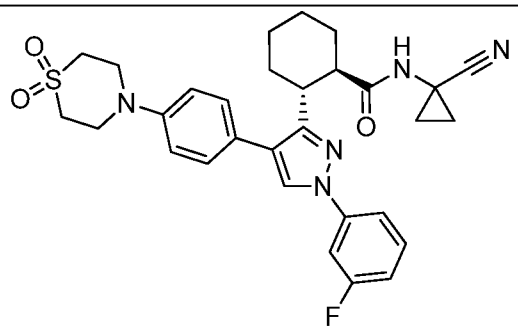
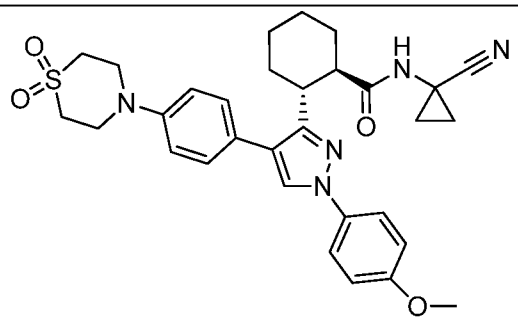
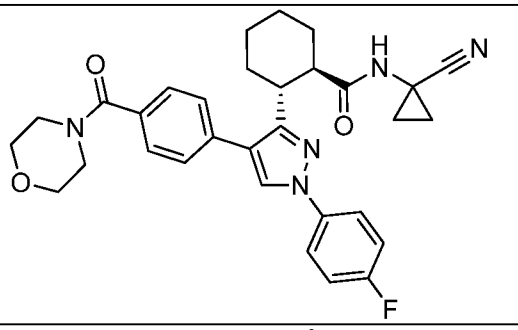
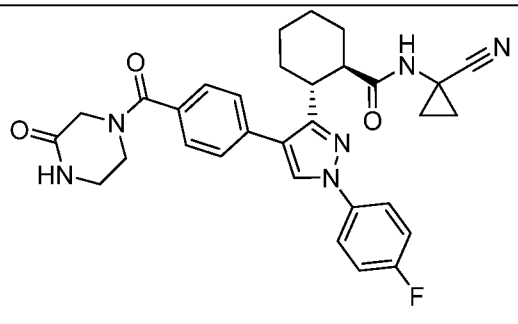
62		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-5-(fluoromethyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	631.2	1.33	151
63		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	644.2	1.98	98
64		(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.2	4.61	565
65		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	608.2	11.01	868
66		(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	565.5	3.60	653

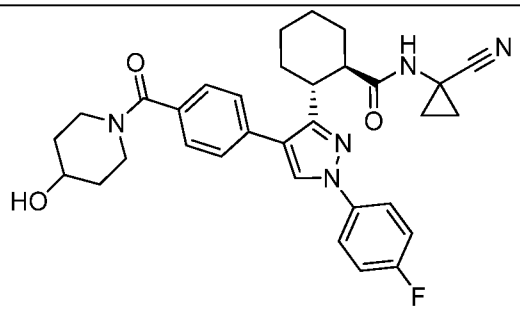
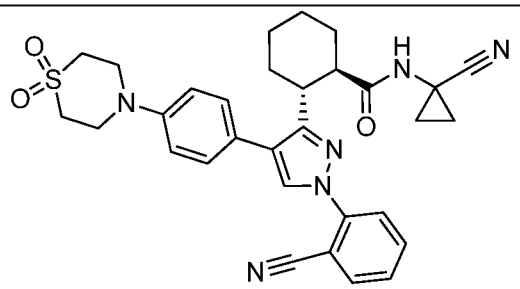
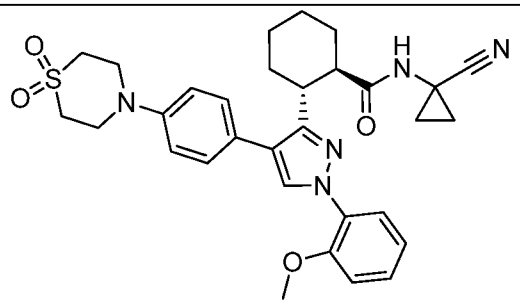
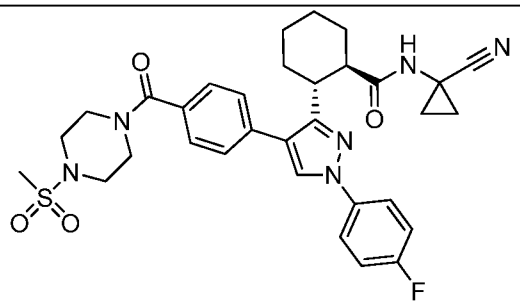
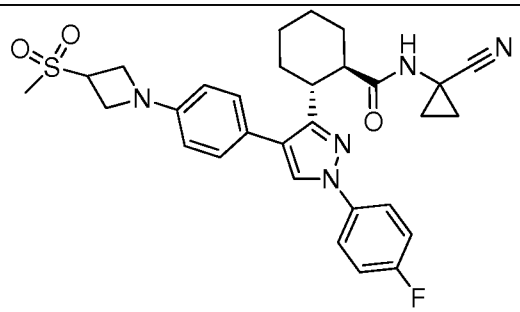
67		(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	617.2	1.24	146
68		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	628.2	1.41	125
69		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	645.2	2.68	225
70		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	629.5	1.90	185

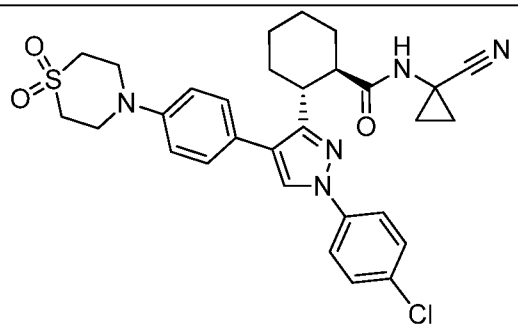
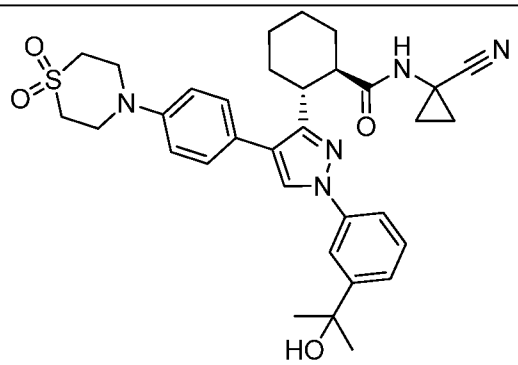
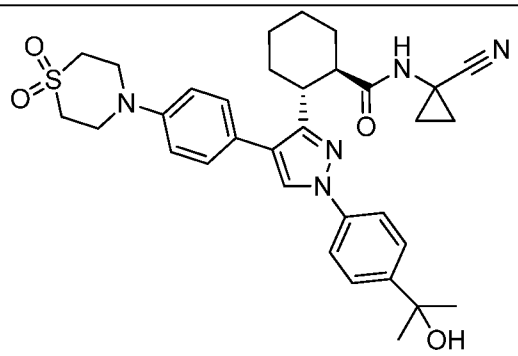
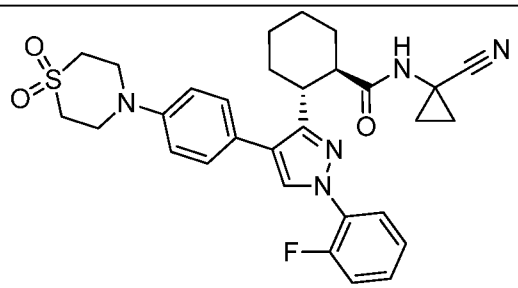
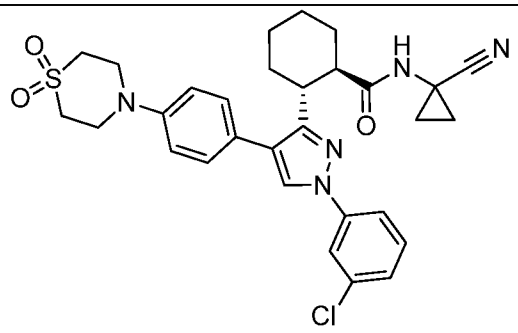
71		(1R,2R)-N-(1-cyanocyclopropyl)-2-(5-(difluoromethyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	649.1	2.35	149
72		(1R,2R)-N-((S)-1-cyanoethyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide	542.5	2.66	230
73		(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide	570.2	5.19	269
74		(1R,2R)-N-((S or R)-1-cyano-3,3,3-trifluoropropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide	610.2	7.69	252
75		(1R,2R)-N-((R or S)-1-cyano-3,3,3-trifluoropropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide	610.2	0.99	21

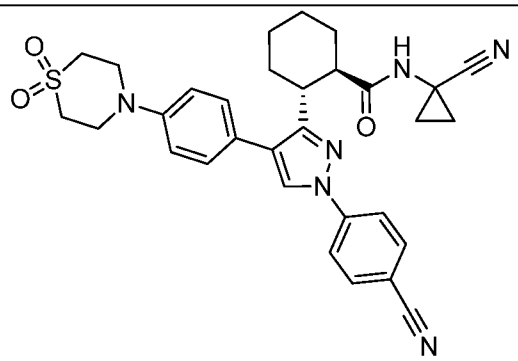
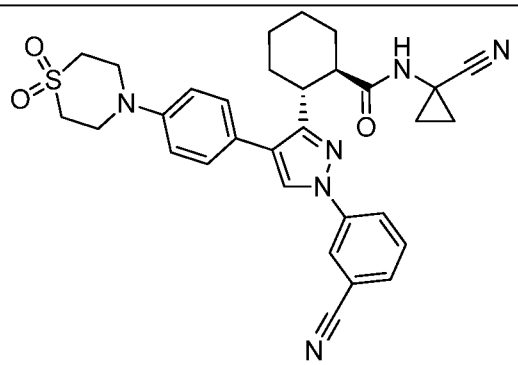
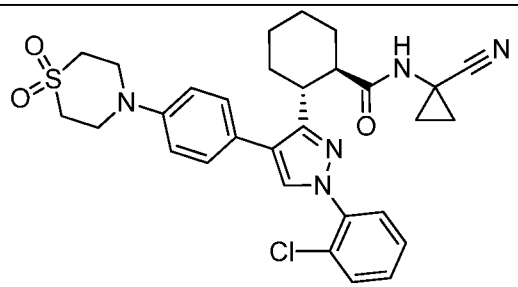
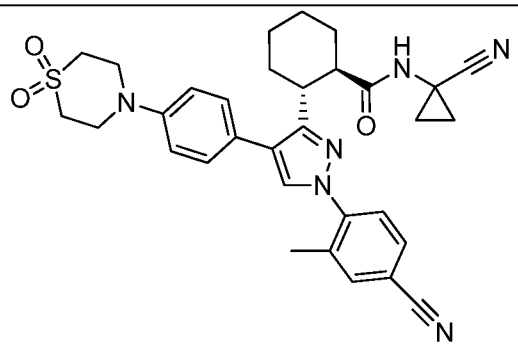
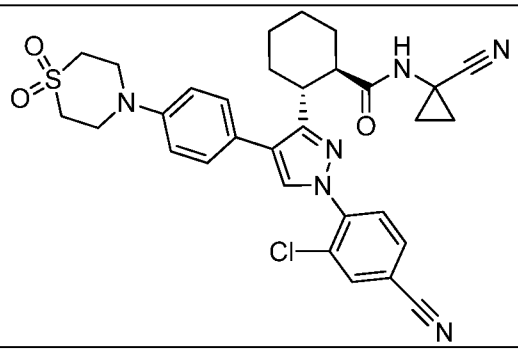
76	 racemic trans	(1R,2R and 1S,2S)-N-(cyanomethyl)-5,5-difluoro-2-(4-(4-(methylsulfonyl)phenyl)-1-phenyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	499.2	0.80	11
77	 racemic trans	(1R,2R and 1S,2S)-N-(cyanomethyl)-5,5-difluoro-2-(1-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	517.2	1.24	9
78	 racemic trans	(1R,2R and 1S,2S)-N-(cyanomethyl)-5,5-difluoro-2-(4-(4-(methylsulfonyl)phenyl)-1-(naphthalen-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	549.2	2.12	4
79	 racemic trans	(1R,2R and 1S,2S)-N-(cyanomethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	572.2	0.81	17
80	 racemic trans	(1R,2R and 1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	598.2	1.00	35

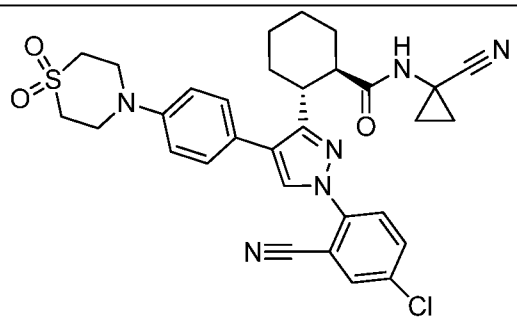
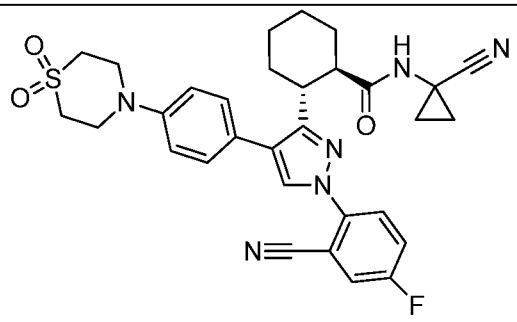
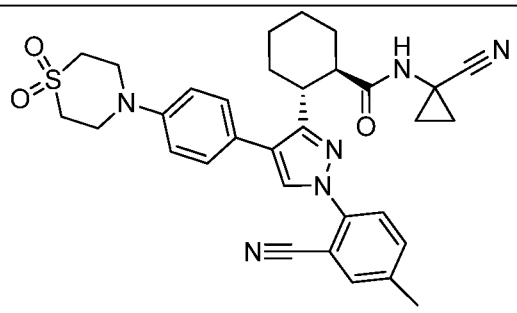
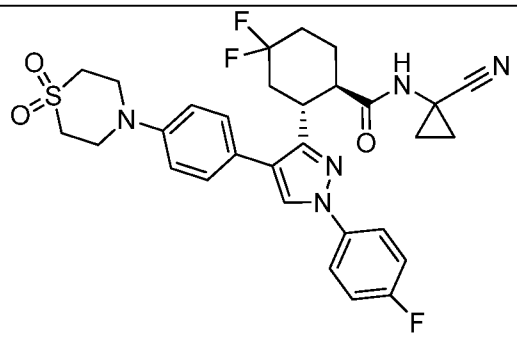
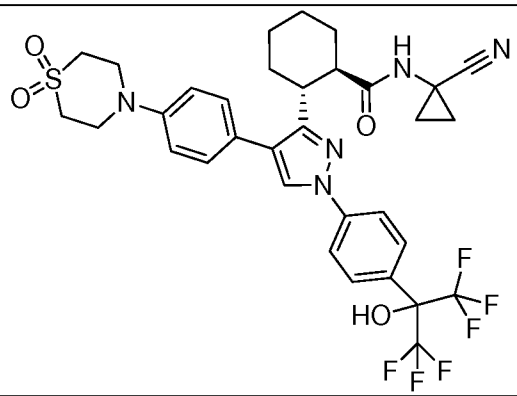
81		(1R,2R)-N-(cyanomethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	572.2	0.37	11
82		(1S,2S)-N-(cyanomethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	572.2	144.20	1,403
83		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	598.2	0.47	28
84		(1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide	598.2	51.63	1,051

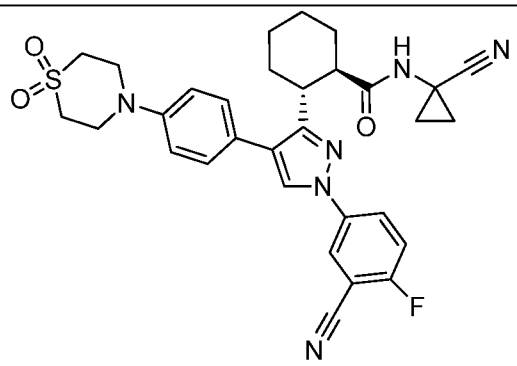
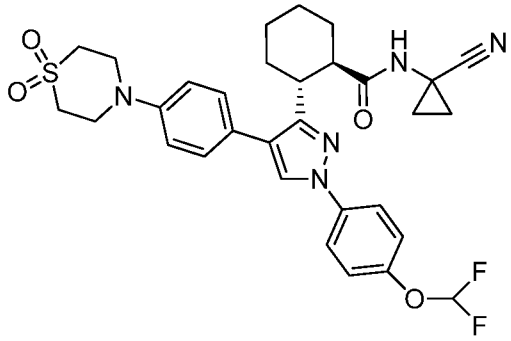
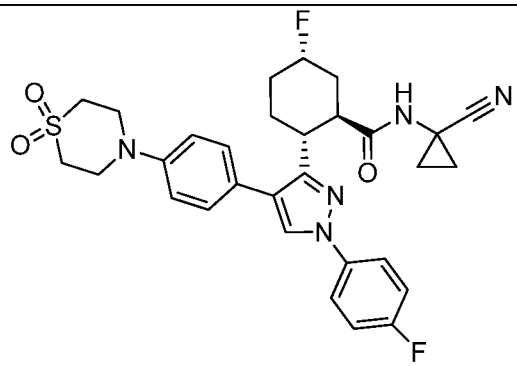
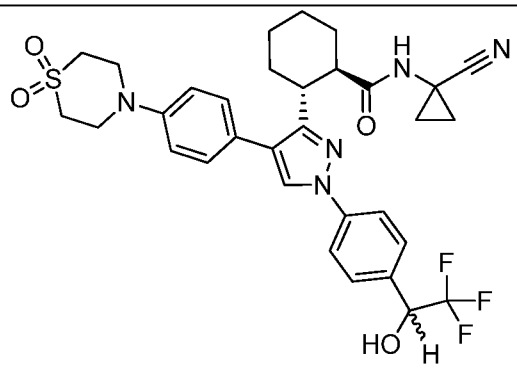
85		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	562.1	0.69	352
86		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	562.1	0.33	268
87		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	574.2	0.99	740
88		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(morpholine-4-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	542.4	6.90	1,010
89		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(3-oxopiperazine-1-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	555.4	9.37	989

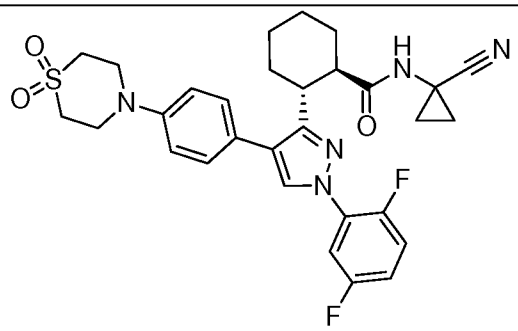
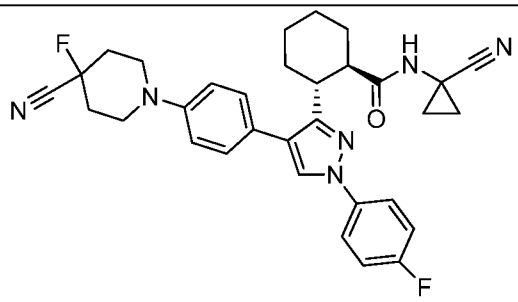
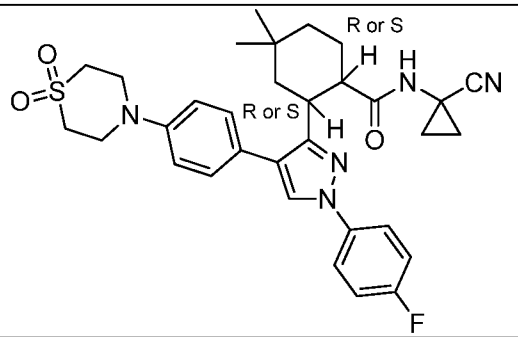
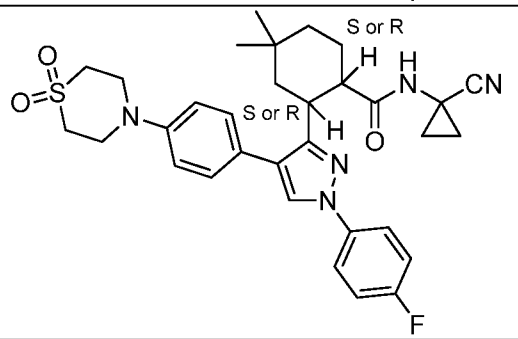
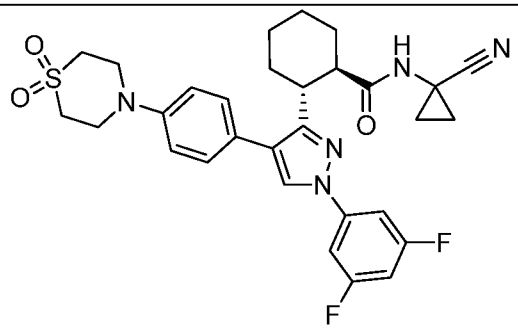
90		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(4-hydroxypiperidine-1-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	556.4	8.01	1,758
91		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	569.2	1.02	1,024
92		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	574.2	0.95	484
93		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(4-(methylsulfonyl)piperazine-1-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	618.9	5.02	2,353
94		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(3-(methylsulfonyl)azetidin-1-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	562.4	2.57	2,784

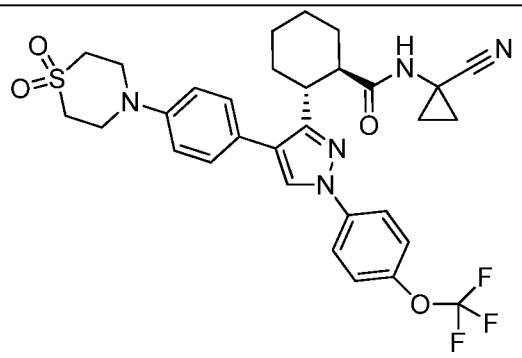
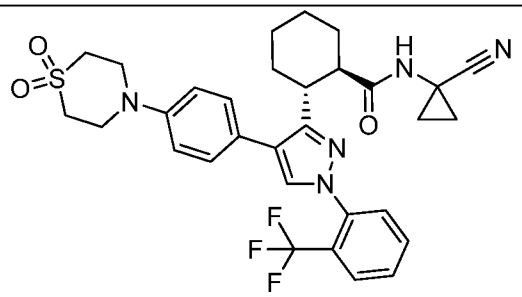
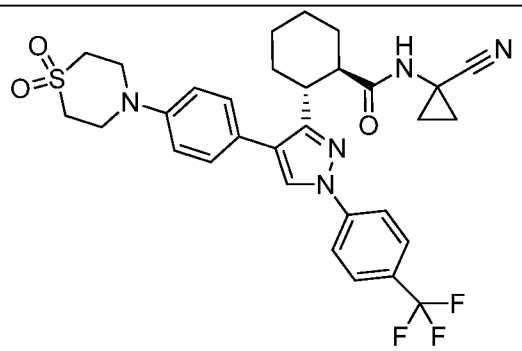
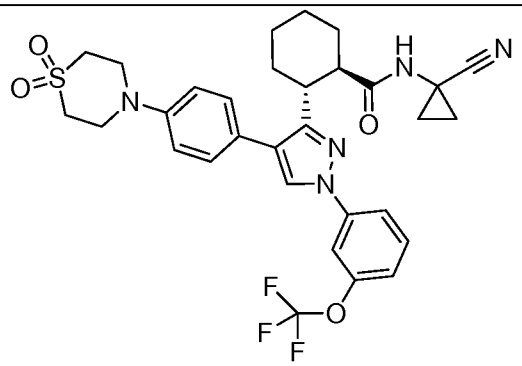
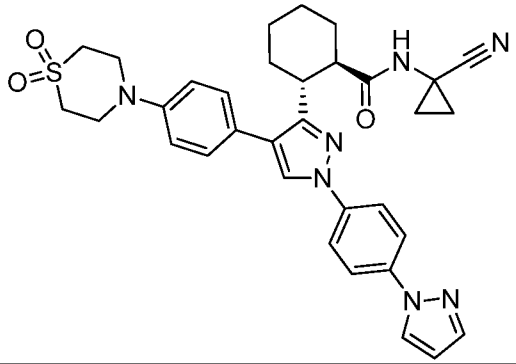
95		(1R,2R)-2-(1-(4-chlorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	578.3	0.73	402
96		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-(2-hydroxypropan-2-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	602.4	1.27	824
97		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(2-hydroxypropan-2-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	602.4	0.80	764
98		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	562.2	0.91	946
99		(1R,2R)-2-(1-(3-chlorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	578.2	0.48	379

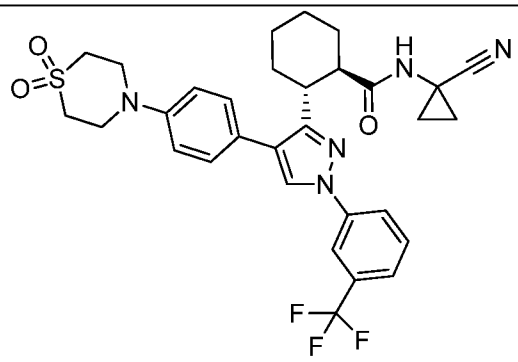
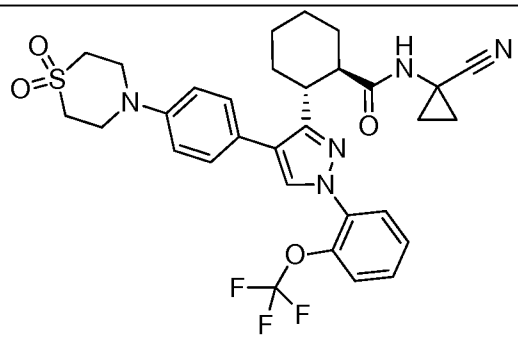
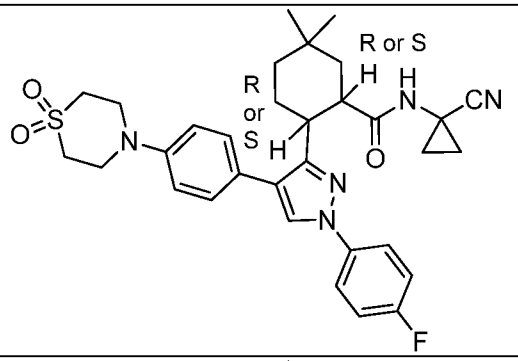
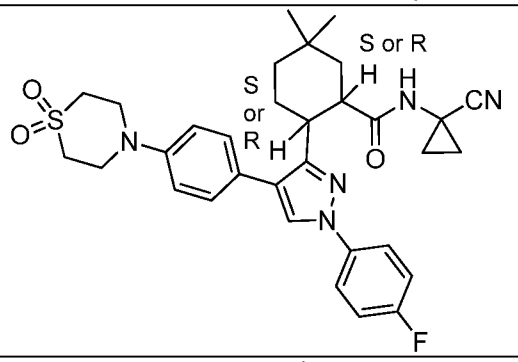
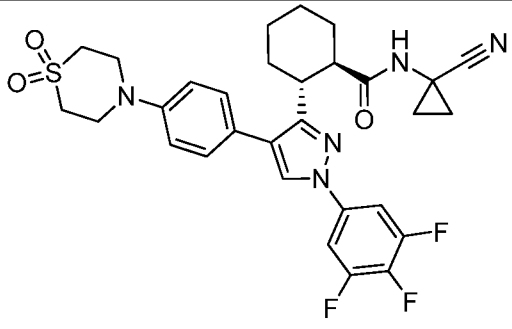
100		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	569.2	0.87	212
101		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	569.2	0.99	452
102		(1R,2R)-2-(1-(2-chlorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	578.2	2.90	643
103		(1R,2R)-2-(1-(4-cyano-2-methylphenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	583.2	2.17	622
104		(1R,2R)-2-(1-(2-chloro-4-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	603.3	2.02	411

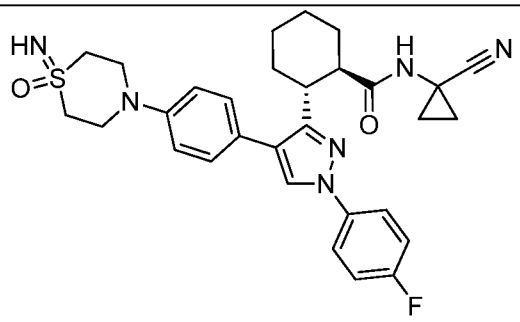
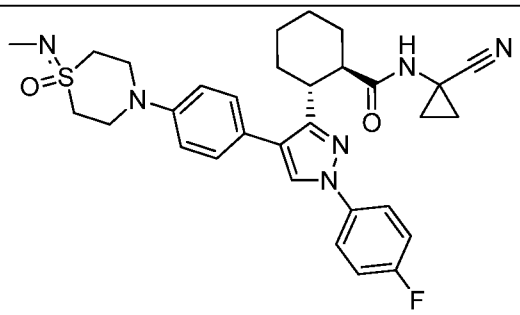
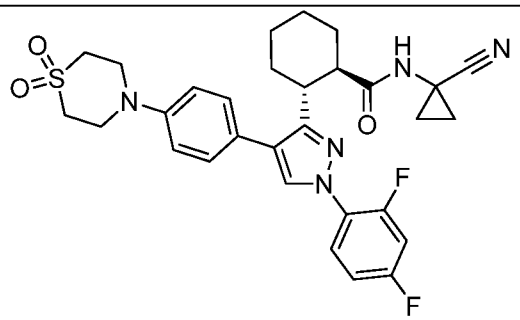
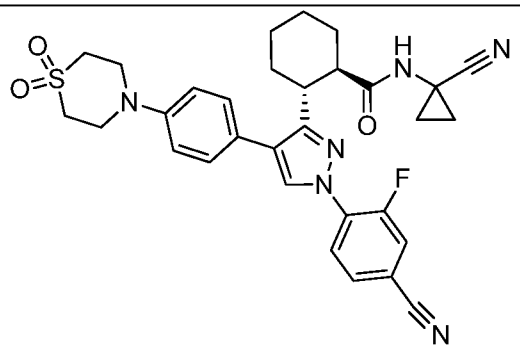
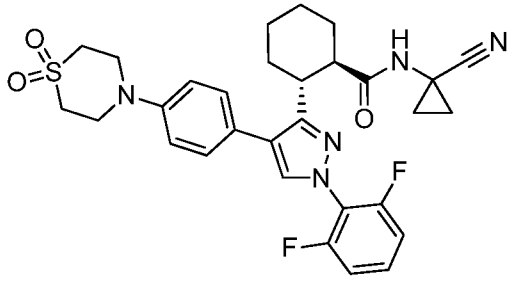
105		(1R,2R)-2-(1-(4-chloro-2-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	603.3	3.23	1,264
106		(1R,2R)-2-(1-(2-cyano-4-fluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	587.2	2.88	1,922
107		(1R,2R)-2-(1-(2-cyano-4-methylphenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	583.2	3.00	1,400
108		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide	598.1	2.32	1,012
109		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	710.2	2.67	267

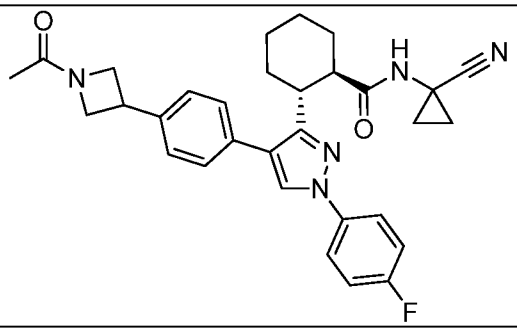
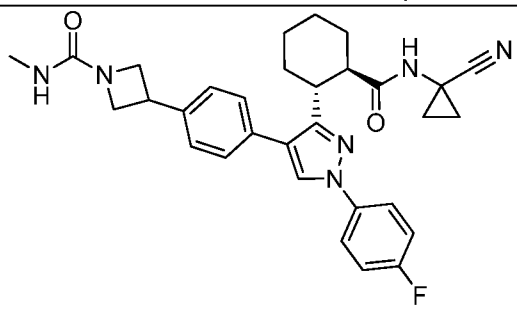
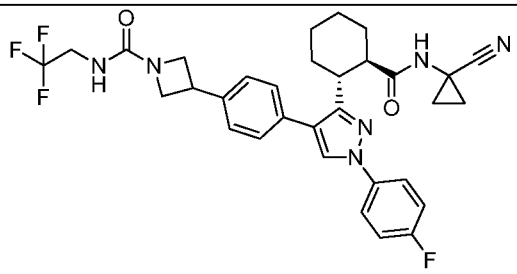
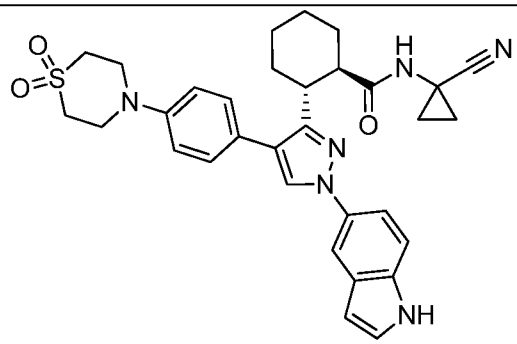
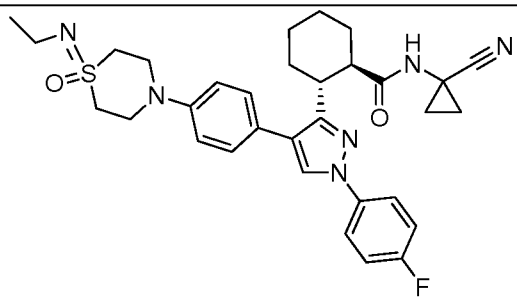
110		(1R,2R)-2-(1-(3-cyano-4-fluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	587.2	0.83	275
111		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-(difluoromethoxy)phenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	610.2	0.86	392
112		(1R,2R,5S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide	580.4	1.33	922
113		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-((S and R)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	642.4	0.88	360

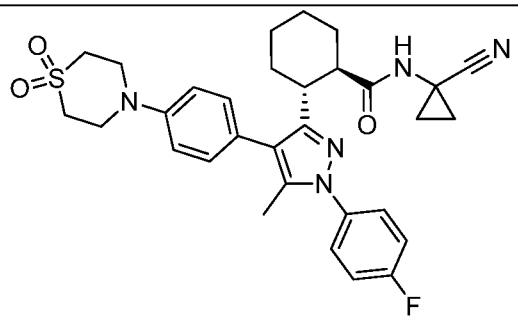
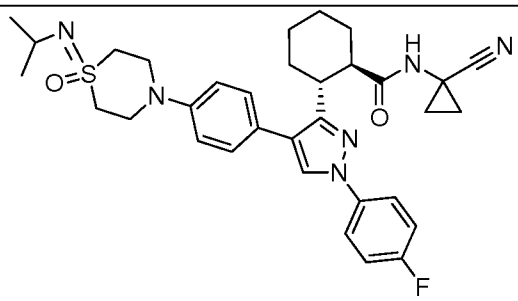
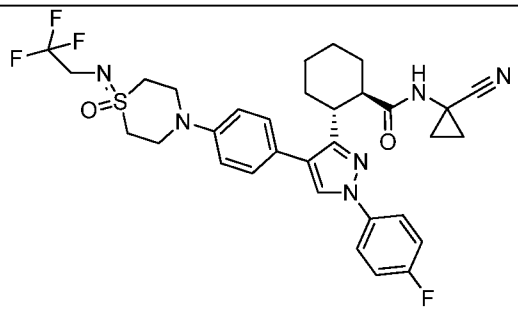
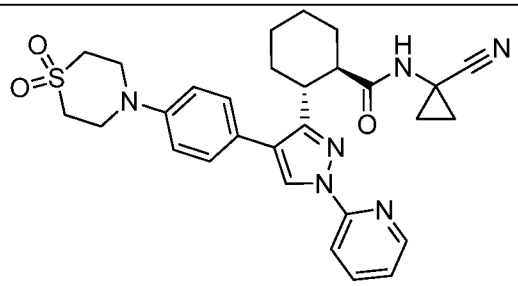
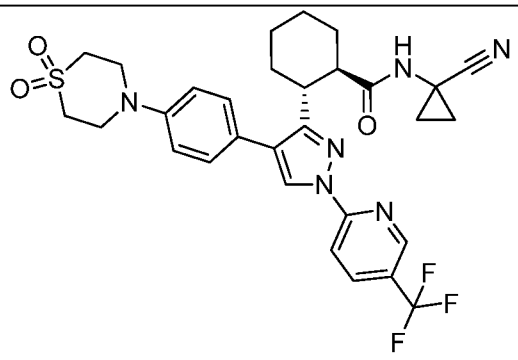
114		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,5-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.2	1.06	633
115		(1R,2R)-2-(4-(4-(4-cyano-4-fluoropiperidin-1-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	555.3	6.62	804
116		(1R,2R or 1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-4,4-dimethylcyclohexanecarboxamide	590.4	328.50	1,199
117		(1S,2S, or 1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-4,4-dimethylcyclohexanecarboxamide	590.4	13.88	1,568
118		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3,5-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.2	0.54	273

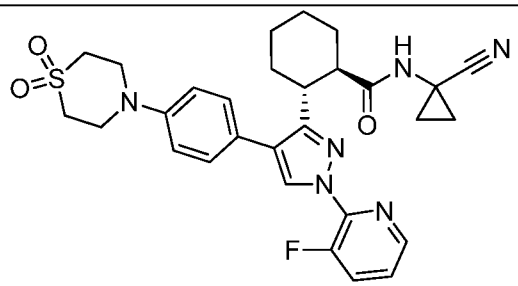
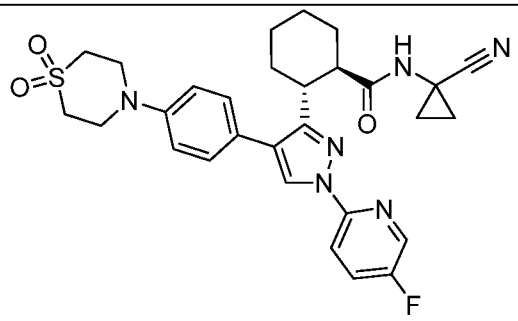
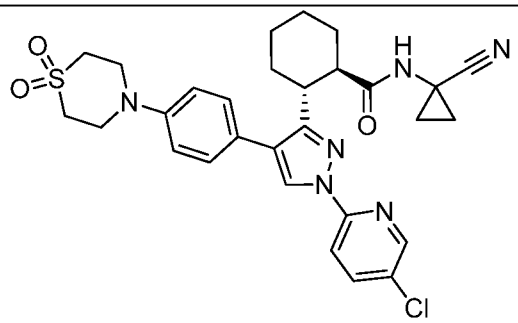
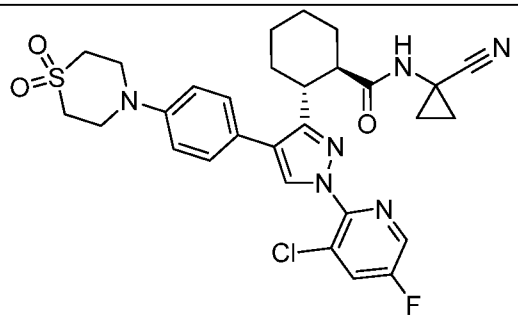
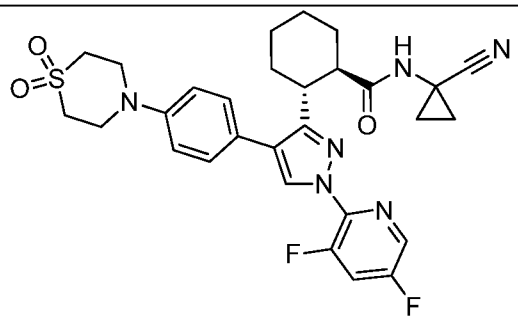
119		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	628.2	1.80	562
120		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide Molecular Weight: 611.68	612.3	6.72	3,116
121		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	612.2	3.08	649
122		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide Molecular Weight: 627.68	628.2	0.78	466
123		(1R,2R)-2-(1-(4-(1H-pyrazol-1-yl)phenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	610.0	0.96	593

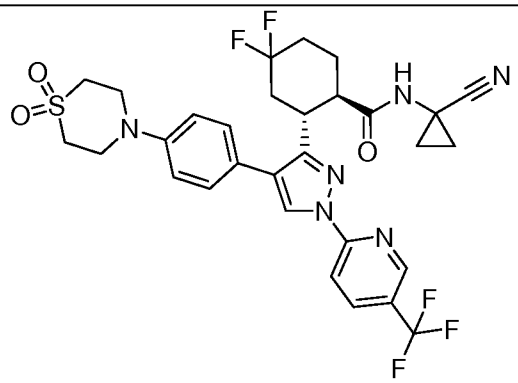
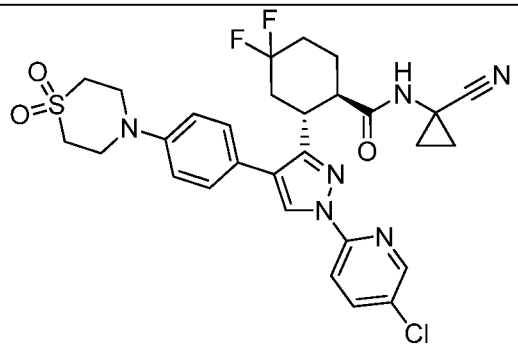
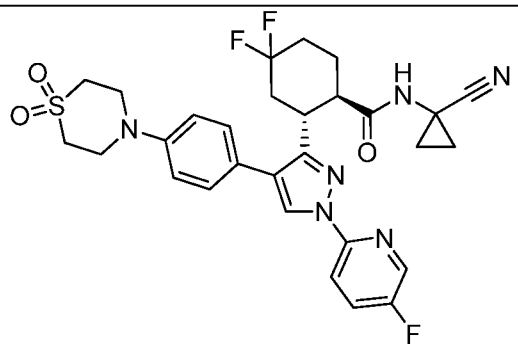
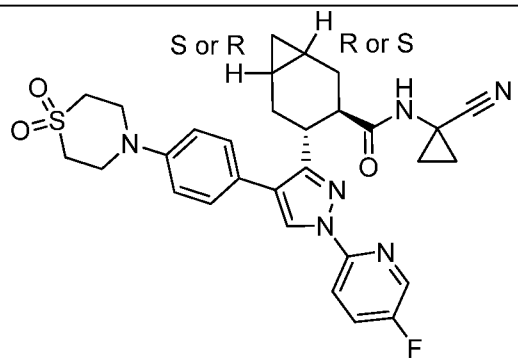
124		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	612.0	1.58	588
125		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	628.2	2.18	836
126		(1R,2R) or (1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-dimethylcyclohexanecarboxamide	590.3	115.50	1,000
127		(1S,2S) or (1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-dimethylcyclohexanecarboxamide	590.3	1.50	632
128		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3,4,5-trifluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	598.2	0.79	319

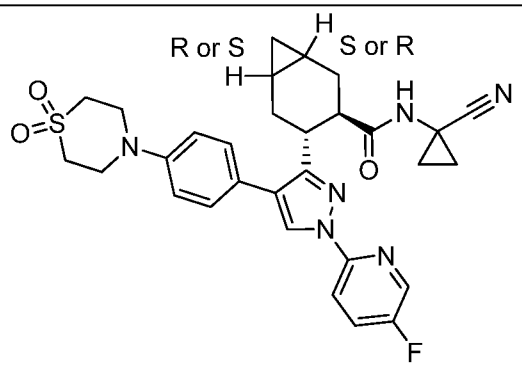
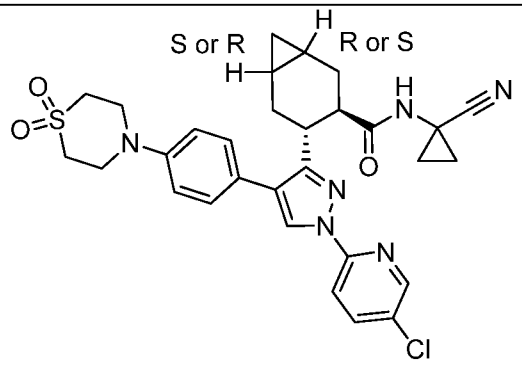
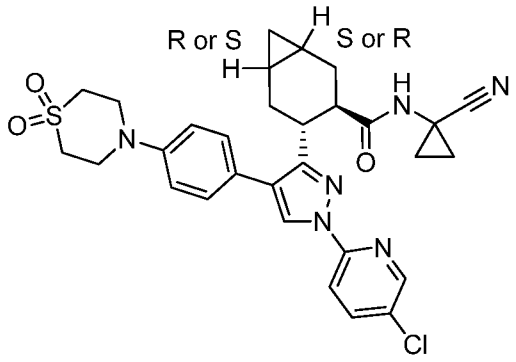
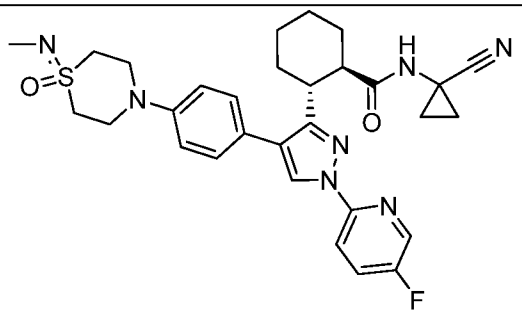
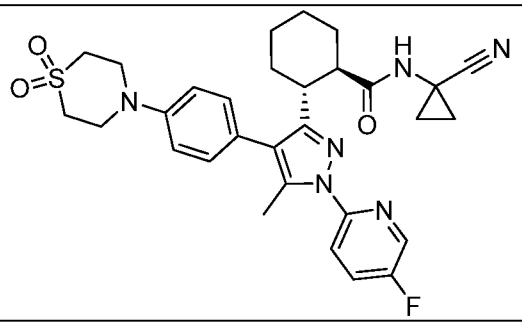
129		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	561.0	1.84	932
130		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	575.0	1.92	854
131		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,4-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.6	2.49	1,542
132		(1R,2R)-2-(1-(4-cyano-2-fluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	587.2	2.51	733
133		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,6-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.2	3.56	2,343

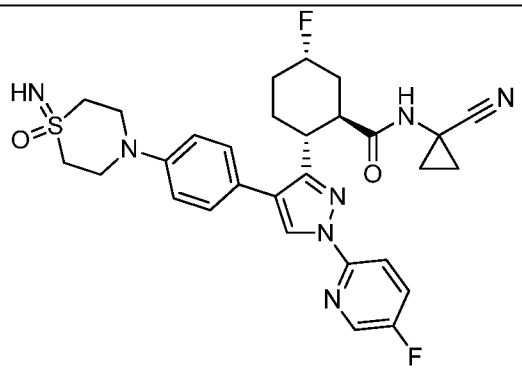
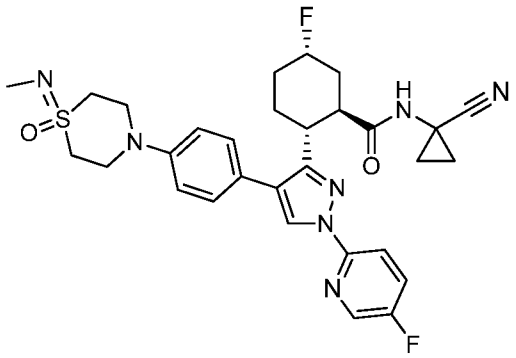
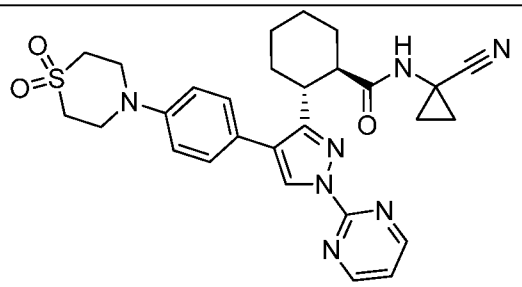
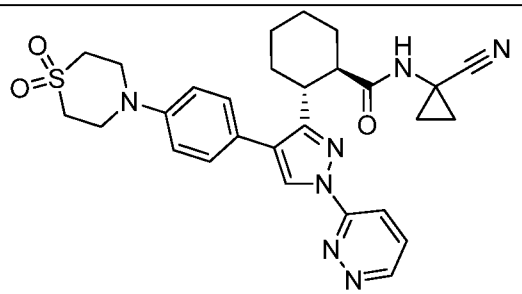
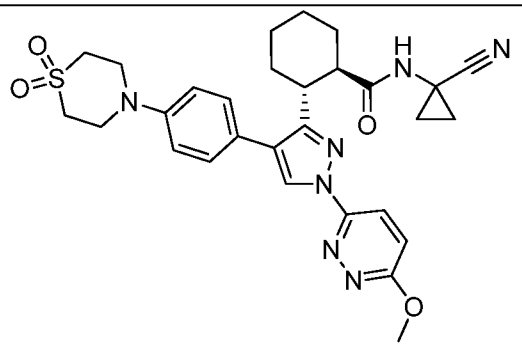
134		(1R,2R)-2-(4-(4-(1-acetylazetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	526.2	1.57	210
135		3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)-N-methylazetidine-1-carboxamide	541.2	0.71	64
136		3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)-N-(2,2,2-trifluoroethyl)azetidine-1-carboxamide	609.3	0.97	83
137		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(1H-indol-5-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	583.1	8.43	2,825
138		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1-(ethylimino)-1-oxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	589.4	1.62	725

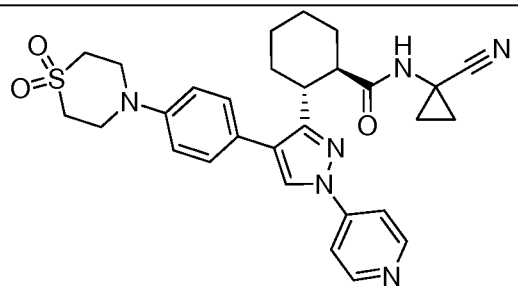
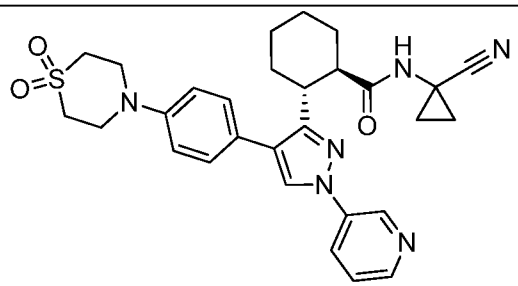
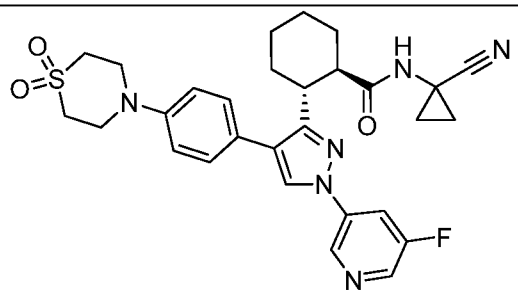
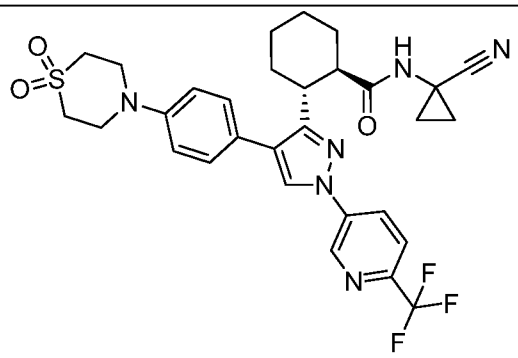
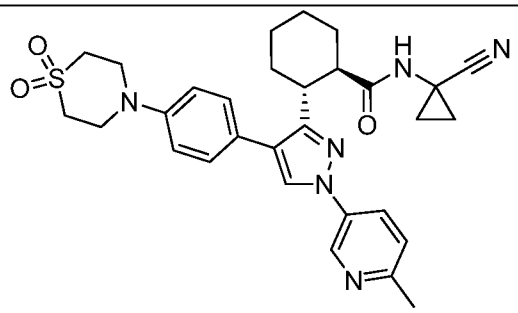
139		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	576.1	7.48	649
140		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-(isopropylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	603.4	1.29	782
141		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-oxido-1-((2,2,2-trifluoroethyl)imino)thiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	643.4	2.10	816
142		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	545.2	0.52	232
143		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	613.0	1.17	395

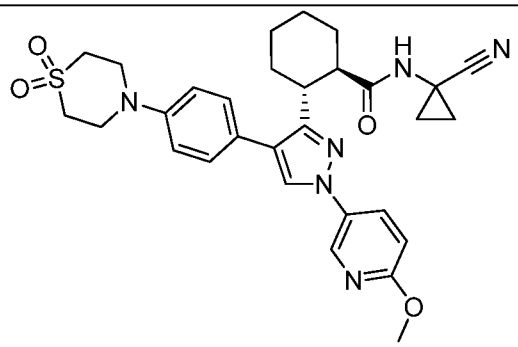
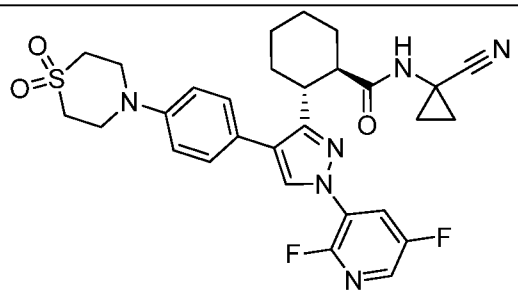
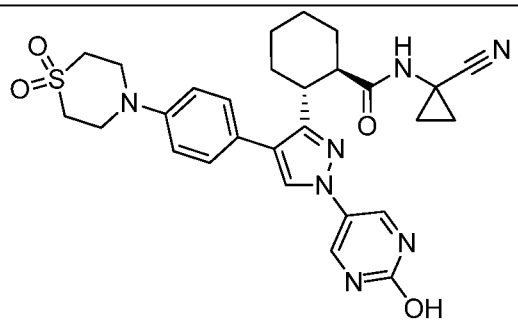
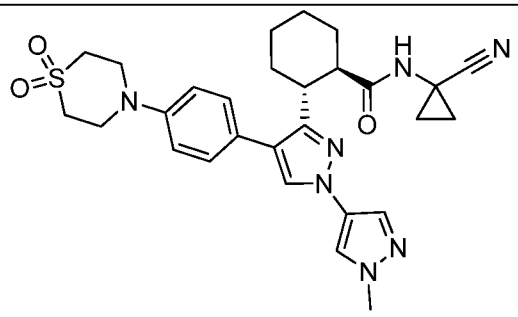
144		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	563.2	5.59	3,062
145		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	563.2	1.24	481
146		(1R,2R)-2-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	579.1	1.15	272
147		(1R,2R)-2-(1-(3-chloro-5-fluoropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide	597.2	3.26	1,194
148		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3,5-difluoropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide Molecular Weight: 580.65	581.2	1.01	502

149		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide	649.6	2.58	10,000
150		(1R,2R)-2-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)-4,4-difluorocyclohexanecarboxamide	615.1	1.43	1,000
151		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide Molecular Weight: 598.64	599.5	2.44	1,000
152		(1S,3R,4R,6R) or (1R,3R,4R,6S)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide	575.0	1.06	338

153		(1R,3R,4R,6S) or (1S,3R,4R,6R)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide	575.0	0.66	265
154		(1R,3R,4R,6S) or (1S,3R,4R,6R)-4-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)bicyclo[4.1.0]heptane-3-carboxamide	591.2	0.74	279
155		(1S,3R,4R,6R)or (1R,3R,4R,6S)-4-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)bicyclo[4.1.0]heptane-3-carboxamide	591.2	0.56	197
156		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	576.3	1.47	945
157		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide	577.3	4.26	2,982

158		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	580.2	2.00	2,018
159		(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	594.1	3.22	1,407
160		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyrimidin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	546.1	34.66	1,000
161		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	546.3	1.61	751
162		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	575.9	0.84	654

163		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridin-4-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	545.2	0.32	237
164		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	545.2	0.48	697
165		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	563.0	0.90	319
166		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-(trifluoromethyl)pyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	613.2	1.31	428
167		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	559.0	0.66	602

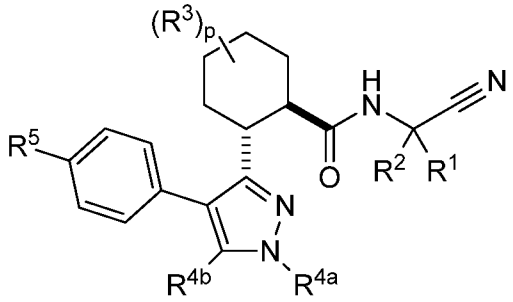
168		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methoxypyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	575.2	2.40	763
169		(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,5-difluoropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	581.2	3.94	5,669
170		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-hydroxypyrimidin-5-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide	562.0	1.88	2,531
171		(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1'-methyl-1'H-[1,4'-bipyrazol]-3-yl)cyclohexanecarboxamide	548.1	3.38	2,760

Pharmaceutical Composition

As a specific embodiment of this invention, 100 mg of a compound of Example 1, is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0, hard-gelatin capsule.

CLAIMS

1. A compound of the formula:



wherein

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl or heterocyclyl, wherein said alkyl and alkenyl groups are optionally substituted with one to six substituents independently selected from the group consisting of hydroxy, C_{3-6} cycloalkyl, halo andR^8; and wherein said cycloalkyl and heterocyclyl groups are optionally substituted with one or two substituents independently selected from the group consisting of C_{1-6} alkyl, halo, OR^6 and keto;

R^2 is hydrogen, C_{1-6} alkyl or C_{2-6} alkenyl wherein said alkyl and alkenyl groups are optionally substituted with one to six substituents independently selected from the group consisting of hydroxy, C_{3-6} cycloalkyl, halo and R^8;

or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-6}cycloalkyl or heterocyclyl ring wherein said cycloalkyl and heterocyclyl rings are optionally substituted with one to two substituents independently selected from the group consisting of R^6, C_{1-6} haloalkyl and halo;

each R^3 is independently selected from the group consisting of halo, and C_{1-2} alkyl, wherein said alkyl group is optionally substituted with one to three halo; or

two R^3 groups on adjacent carbons can be taken together with the carbon atoms to which they are attached to form a C_{3-4} cycloalkyl ring, wherein said ring is optionally substituted with one to three halo;

R^{4a} is aryl or heteroaryl, wherein said aryl and heteroaryl groups are optionally substituted with one to foursubstituents independently selected from the group consisting of halo, hydroxy, cyano, R^6, OR^6 and R^8;

R^{4b} is hydrogen or C_{1-6} alkyl which is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and O(C_{1-6} alkyl);

or R^{4a} and R^{4b} can be taken together with the atoms to which they are attached to form a 4 to 7 membered saturated or unsaturated ring wherein said ring is optionally substituted with one to two substituents independently selected from the group consisting of R^6, C_{1-6} haloalkyl and halo;

R^5 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} haloalkyl, aryl, heteroaryl, C_{3-8} cycloalkyl, heterocycyl, $C(O)NR^6R^8$, $C(O)R^8$, $NR^6C(O)OR^7$ or SO_mR^6, wherein said aryl, heteroaryl, cycloalkyl and heterocycyl groups are optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6} alkyl, halo, oxo, cyano, C_{1-6} haloalkyl, OR^6,$C(O)NR^6R^7$, $C(O)OR^6$, $C(O)R^6$, $=NR^6$, =NCNand SO_mR^6;

R^6 is hydrogen or C_{1-6} alkyl, which is optionally substituted with one to four substituents independently selected from the group consisting of halo, hydroxy, cyano, C_{1-3}haloalkyl, and $O(C_{1-6}$ alkyl);

R^7 is hydrogen or C_{1-6} alkyl. which is optionally substituted with one to three substituents independently selected from the group consisting of halo, hydroxy, cyano and $O(C_{1-6}$ alkyl);

R^8 is C_{3-8} cycloalkyl, aryl, heteroaryl or heterocyclyl, wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups are optionally substituted with one to four substituents independently selected from the group consisting of halo, cyano, oxo, R^6, OR^6, NR^6R^7, C_{3-6} cycloalkyl, aryl, heteroaryl, heterocyclyl, SO_mR^6 and SF_5 ;

m is an integer from zero to two;

p is an integer from zero to two;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 where in$R^1$is hydrogen or C_{1-3} alkyl, wherein said alkyl group is optionally substituted with one to six halo;$R^2$is hydrogen or C_{1-3} alkyl, wherein said alkyl group is optionally substituted with one to six halo; or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1 wherein or R^1 and R^2 can be taken together with the carbon atom to which they are attached to form a C_{3-4}cycloalkyl ring; or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 1 wherein each $R^3$is independently selected from the group consisting of hydrogen, halo or methyl, or two R^3 groups on adjacent carbons can be taken together with the carbon atoms to which they are attached to form a C_{3-4} cycloalkyl ring, wherein said ring is optionally substituted with one to three halo; or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 1 wherein R^{4a} isaryl, wherein said aryl group is optionally substituted with one to four substituents independently selected from the group consisting of halo, hydroxy, cyano, R^6, OR^6 and heteroaryl; or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 5 wherein $R^{4a}$is heteroaryl, wherein said heteroaryl group is optionally substituted with one to two substituents independently selected from the group consisting of halo, hydroxy, cyano and methyl; or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 5 wherein R^5 is heterocyclyl, $C(O)R^8$or SO_mR^6, wherein said heterocycyl group is optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6} alkyl, halo, oxo, cyano, C_{1-6} haloalkyl, OR^6, $C(O)NR^6R^7$, $C(O)OR^6$, $C(O)R^6$, $=NR^6$, =NCN and SO_mR^6; or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 1 which is:

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(4-cyanopiperidin-1-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1S,3R,4R,6R) or (1R,3R,4R,6S)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide;

(1R,3R,4R,6S) or (1S,3R,4R,6R) -N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

isopropyl 3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)azetidine-1-carboxylate;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(5-chloropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-5,5-difluoro-2-(3-(4-(morpholine-4-carbonyl)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(4-fluorophenyl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(4-fluorophenyl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(4-(4-(1-(tert-butylimino)-1-oxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1-(cyanoimino)-1-oxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)cyclohexanecarboxamide;

(1R,2R)-N-((R or S)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S or R)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((R or S)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S or R)-1-cyanoethyl)-4,4-difluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3-fluoropyridin-2-yl)-5-methyl-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-4,4-difluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(1-(3-fluoropyridin-2-yl)-5-methyl-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(1-(3-fluoropyridin-2-yl)-5-methyl-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyano-2-methylpropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyano-2-methylpropyl)-5-fluoro-2-(1-(3-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-((S)-1-cyanoethyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-5-(fluoromethyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-(hydroxymethyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(5-(difluoromethyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyanoethyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S)-1-cyano-2-methylpropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((S or R)-1-cyano-3,3,3-trifluoropropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-((R or S)-1-cyano-3,3,3-trifluoropropyl)-2-(3-(4-(1,1-dioxidothiomorpholino)phenyl)pyrazolo[1,5-a]pyridin-2-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R and 1S,2S)-N-(cyanomethyl)-5,5-difluoro-2-(4-(4-(methylsulfonyl)phenyl)-1-phenyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R and 1S,2S)-N-(cyanomethyl)-5,5-difluoro-2-(1-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R and 1S,2S)-N-(cyanomethyl)-5,5-difluoro-2-(4-(4-(methylsulfonyl)phenyl)-1-(naphthalen-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R and 1S,2S)-N-(cyanomethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R and 1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(cyanomethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1S,2S)-N-(cyanomethyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(morpholine-4-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(3-oxopiperazine-1-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(4-hydroxypiperidine-1-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-methoxyphenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(4-(methylsulfonyl)piperazine-1-carbonyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(3-(methylsulfonyl)azetidin-1-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(4-chlorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-(2-hydroxypropan-2-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(2-hydroxypropan-2-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(3-chlorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(2-chlorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(4-cyano-2-methylphenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(2-chloro-4-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(4-chloro-2-cyanophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(2-cyano-4-fluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(2-cyano-4-methylphenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(3-cyano-4-fluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-(difluoromethoxy)phenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5-fluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-((S and R)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,5-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(4-(4-(4-cyano-4-fluoropiperidin-1-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R or 1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-4,4-dimethylcyclohexanecarboxamide;

(1S,2S, or 1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-4,4-dimethylcyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3,5-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(4-(1H-pyrazol-1-yl)phenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-(trifluoromethoxy)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R) or (1S,2S)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-dimethylcyclohexanecarboxamide;

(1S,2S) or (1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-5,5-dimethylcyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3,4,5-trifluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,4-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(4-cyano-2-fluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,6-difluorophenyl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(4-(4-(1-acetylazetidin-3-yl)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)-N-methylazetidine-1-carboxamide;

3-(4-(3-((1R,2R)-2-((1-cyanocyclopropyl)carbamoyl)cyclohexyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)phenyl)-N-(2,2,2-trifluoroethyl)azetidine-1-carboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(1H-indol-5-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1-(ethylimino)-1-oxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(4-fluorophenyl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-(isopropylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(4-fluorophenyl)-4-(4-(1-oxido-1-((2,2,2-trifluoroethyl)imino)thiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(3-fluoropyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-2-(1-(3-chloro-5-fluoropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(3,5-difluoropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-(trifluoromethyl)pyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide;

(1R,2R)-2-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)-4,4-difluorocyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)-4,4-difluorocyclohexanecarboxamide;

(1S,3R,4R,6R) or (1R,3R,4R,6S)-N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide;

(1R,3R,4R,6S) or (1S,3R,4R,6R)- N-(1-cyanocyclopropyl)-4-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-1H-pyrazol-3-yl)bicyclo[4.1.0]heptane-3-carboxamide;

(1R,3R,4R,6S) or (1S,3R,4R,6R)-4-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)bicyclo[4.1.0]heptane-3-carboxamide;

(1S,3R,4R,6R)or (1R,3R,4R,6S)-4-(1-(5-chloropyridin-2-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)-N-(1-cyanocyclopropyl)bicyclo[4.1.0]heptane-3-carboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-2-yl)-5-methyl-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-imino-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R,5S)-N-(1-cyanocyclopropyl)-5-fluoro-2-(1-(5-fluoropyridin-2-yl)-4-(4-(1-(methylimino)-1-oxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyrimidin-2-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methoxypyridazin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridin-4-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(pyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(5-fluoropyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-(trifluoromethyl)pyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methylpyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(6-methoxypyridin-3-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(1-(2,5-difluoropyridin-3-yl)-4-(4-(1,1-dioxidothiomorpholino)phenyl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1-(2-hydroxypyrimidin-5-yl)-1H-pyrazol-3-yl)cyclohexanecarboxamide;

(1R,2R)-N-(1-cyanocyclopropyl)-2-(4-(4-(1,1-dioxidothiomorpholino)phenyl)-1'-methyl-1'H-[1,4'-bipyrazol]-3-yl)cyclohexanecarboxamide;

or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

10. The use of a compound of Claim 1 in the preparation of a medicament useful for the treatment of: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof.

11. A pharmaceutical composition comprising a compound of Claim 1 and another agent selected from the group consisting of: an organic bisphosphonate, a selective estrogen receptor modulator, an estrogen receptor beta modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, or an osteoblast anabolic agent, vitamin D, a synthetic Vitamin D analogue, a Nonsteroidal anti-inflammatory drug, a selective cyclooxygenase-2 inhibitor, an inhibitor of interleukin-1 beta, a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof.

12. The use of a compound of Claim 1 and another agent selected from the group consisting of: an organic bisphosphonate, a selective estrogen receptor modulator, an androgen receptor modulator, an inhibitor of osteoclast proton ATPase, an inhibitor of HMG-CoA reductase, an integrin receptor antagonist, an osteoblast anabolic agent, vitamin D, a synthetic Vitamin D analogue, a Nonsteroidal anti-inflammatory drug, a selective cyclooxygenase-2 inhibitor, an inhibitor of interleukin-1 beta, a LOX/COX inhibitor and the pharmaceutically acceptable salts and mixtures thereof, in the preparation of a medicament useful for the treatment of: osteoporosis, glucocorticoid induced osteoporosis, Paget's disease, abnormally increased bone turnover, periodontal disease, tooth loss, bone fractures, rheumatoid arthritis, osteoarthritis, periprosthetic osteolysis, osteogenesis imperfecta, atherosclerosis, obesity, glaucoma, chronic obstructive pulmonary disease, metastatic bone disease, hypercalcemia of malignancy or multiple myeloma in a mammal in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/071982

A. CLASSIFICATION OF SUBJECT MATTER

C07D 231/12(2006.01)i; A61K 31/415(2006.01)i; A61P 19/08(2006.01)i; A61P 19/10(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D231/-; A61K 31/-; A61P 19/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, CNKI, WPI, EPODOC, ISI Web of Knowledge, STN: MERCK, FROSST, cathepsin, cysteine protease, bone resorption, +pyrazol+, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007003056 A1 (MERCK FROSST CANADA LTD. ET AL.) 11 January 2007 (2007-01-11) see claims 1-11, examples 1-5	1-12
X	WO 2005000800 A1 (MERCK FROSST CANADA & CO. ET AL.) 06 January 2005 (2005-01-06) see claims 1-11, example 4	1-12

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2014	**19 November 2014**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN)** **6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088 China** Facsimile No. **(86-10)62019451**	Authorized officer **FENG,Shuwen** Telephone No. **(86-10)82246763**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2014/071982

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