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(71) Applicant: **ALKEM LABORATORIES LTD.** [IN/IN]; B64/1B, 3rd Stage, Peenya Industrial Area, Bangalore, 560058 (IN).

(72) Inventors: **NAGARAJ, Harish Kumar Mysore**; # I-1301, I-Block, 13th floor, NCC MEADOWS-2, DODDABALLAPUR ROAD, YELAHANKA, Bangalore 560064 (IN). **BANDODKAR, Balachandra S**; 68, 2nd Cross, SVK Layout, Basaveshwarnagar, Bangalore 560079 (IN). **YELLAPU, Sudhakar**; 4-838, Street behind Brilliant Vidya Mandir, Shivanagar, Dharmavaram, Anantapur(dist), Andhrapradesh, PIN-515671, Anantapur 515671 (IN). **SUGANDHAM, Srinivas Rao**; Door no 32-7, LIC Colony, P.R.Palem-Sujathangar, Andhra Pradesh, Visakhapatnam-530051 (IN). **M, Goutham**; D#204/1, 7th cross, III main, Maruthinagar, Yelahanka, Bangalore 560064 (IN). **MUKHERJEE, Kakoli**; Canopy Calyx Apartment, Flat#G007A, B-Block, MMR Road, Kempapura, Hebbal, Bangalore - 560024 Karnataka (IN). **THIMMAPPA, Kiran Hanchinamanay**; S/O Thimmappa.H rtd bank manager, Door no 25, Channagiri(T) Kakanur(Post) Dodderikatte village, Davanagere(Dist) Karnataka-577552, Davanagere 577552 (IN). **HANUMESH, Parimala B.**; Bellara post, C. N Hally Taluk, Tumkur District. Karnataka-572218, Tumkur 572218 (IN).

(74) Agent: **CHAKRAVARTHY, Kalyan**; BananaIP Counsels, No.40,2nd Floor, 3rd Main Road, JC Industrial Estate, Kanakapura Road, Bangalore-62., Bangalore 560062 (IN).

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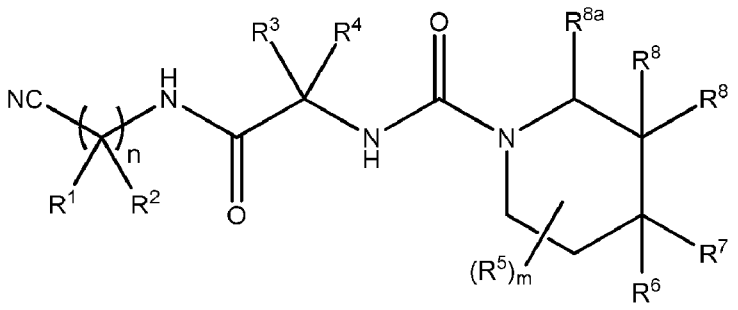

(57) Abstract: The present invention relates to substituted piperidine urea derivatives that are inhibitors of cathepsin K proteases and which are therefore useful in the treatment of certain disorders that can be prevented or treated by inhibition of these enzymes. In addition, the invention relates to the compounds, methods for their preparation, pharmaceutical compositions containing the compounds and the uses of these compounds in the treatment of certain disorders. It is expected that the compounds of the invention will find application in the treatment of bone diseases such as osteoporosis and osteoarthritis as well as other diseases and conditions. The compounds have the general formula: [Formula should be inserted here]

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PIPERIDINE UREAS AS CATHEPSIN CYSTEINE PROTEASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to substituted piperidine urea derivatives that are inhibitors of cathepsin K proteases and which are therefore useful in the treatment of certain disorders that can be prevented or treated by inhibition of these enzymes. In addition, the invention relates to the compounds, methods for their preparation, pharmaceutical compositions containing the compounds and the uses of these compounds in the treatment of certain disorders. It is expected that the compounds of the invention will find application in the treatment of bone diseases such as osteoporosis and osteoarthritis as well as other diseases and conditions.

BACKGROUND OF THE INVENTION

Cathepsins belong to the papain superfamily of cysteine proteases, which share a common papain-like structural fold and a conserved catalytic Cys-His-Asn triad. 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 remodelling. To date, a number of cathepsins have been identified and sequenced from a number of sources. These cathepsins are naturally found in a wide variety of tissues. There are currently 11 of these cathepsins known in human, that is, cathepsin (Cat) B, H, L, S, C, K, O, F, V, X and W. Cathepsin K (which is also known by the abbreviation cat K) is also known as cathepsin O and cathepsin O2. See PCT Application WO 96/13523, Khepri Pharmaceuticals, Inc., and published May 9, 1996, which is hereby incorporated by reference in its entirety. 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 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 tumours, suggesting a role in tumour invasion and metastasis. In addition, aberrant cathepsin B activity is implicated in such disease states as rheumatoid arthritis, osteoarthritis,

pneumocystosis carinii, acute pancreatitis, inflammatory airway disease and bone and joint disorders.

A variety of disorders in humans and other mammals involve 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, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma. One of the most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. 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, is generally a chronic condition, it is believed that appropriate therapy will typically require chronic treatment.

Osteoporosis is characterized by progressive loss of bone architecture and mineralization leading to the loss in bone strength and an increased fracture rate. The skeleton is constantly being remodelled by a balance between osteoblasts that lay down new bone and osteoclasts that breakdown, or resorb, bone. In some disease conditions and advancing age the balance between bone formation and resorption is disrupted; bone is removed at a faster rate. Such a prolonged imbalance of resorption over formation leads to weaker bone structure and a higher risk of fractures.

Bone resorption is primarily performed by osteoclasts, which are multinuclear giant cells. Osteoclasts resorb bone by forming an initial cellular attachment to bone tissue, followed by the formation of an extracellular compartment or lacunae. The lacunae are maintained at a low pH by a proton-ATP pump. Acid secretion subsequently dissolves the inorganic content of bone, mainly calcium phosphate. The exposed organic bone matrix composed primarily of type I collagen is then degraded by proteases. The osteoclast-specific localization and high expression level of Cat K suggest that this cysteine protease plays a critical role in bone matrix degradation. See Delaisse, J. M. et al, 1980, Biochem J 192:365-368; Delaisse, J. et al, 1984, Biochem

Biophys Res Commun:441-447; Delaisse, J. M. et al., 1987, Bone 8:305-313, which are hereby incorporated by reference in their entirety.Collagen constitutes 95 % of the organic matrix of bone. Therefore, proteases involved in collagen degradation are an essential component of bone turnover, and as a consequence, the development and progression of osteoporosis.

Cysteine protease inhibitors such as E-64 (trans-epoxysuccinyl-L- leucylamide-(4-guanidino) butane) are known to be effective in inhibiting bone resorption. See Delaisse, J. M. et al., 1987, Bone 8:305-313, which is hereby incorporated by reference in its entirety. Recently, cathepsin K was cloned and found specifically expressed in osteoclasts See Tezuka, K. et al., 1994, J Biol Chem 269:1106-1109; Shi, G. P. et al.,1995, EEES Lett 357: 129-134; Bromme, D. and Okamoto, K., 1995, Biol Chem Hoppe Seyler 376:379-384; Bromme, D. et al, 1996, J Biol Chem 271:2126-2132: Drake, F. H. et al, 1996, J Biol Chem 271:12511- 12516, which are hereby incorporated by reference in their entirety. Concurrent to the cloning, the autosomal recessive disorder, pycnodysostosis, characterized by an osteopetrotic phenotype with a decrease in bone resorption, was mapped to mutations present in the cathepsin K gene. To date, all mutations identified in the cathepsin K gene are known to result in inactive protein.See Gelb, B. D. et al., 1996, Science 273:1236-1238; Johnson, M. R. et al., 1996, Genome Res 6:1050-1055, which are hereby incorporated by reference in their entirety. Therefore, it appears that cathepsin K is involved in osteoclast mediated bone resorption.

Cathepsin K is synthesized as a 37 kDa pre-pro enzyme, which is localized to the lysosomal compartment and where it is presumably autoactivated to the mature 27 kDa enzyme at low pH. See McQueney, M. S. et al., 1997, J Biol Chem 272:13955-13960; Littlewood-Evans, A. et al, 1997, Bone 20:81-86, which are hereby incorporated by reference in their entirety. Cathepsin K is most closely related to cathepsin S having 56 % sequence identity at the amino acid level. The S_2P_2substrate specificity of cathepsin K is similar to that of cathepsin S with a preference in the P1 and P2 positions for a positively charged residue such as arginine, and a hydrophobic residue such as phenylalanine or leucine, respectively. See Bromme, D. et al., 1996, J Biol Chem 271: 2126-2132; Bossard, M. J. et al, 1996, J Biol Chem 271:12517-12524, which are hereby incorporated by reference in their entirety. Cathepsin K is active at a broad pH range with significant activity between pH 4-8, thus allowing for good catalytic activity in the resorption lacunae of osteoclasts where the pH is about 4-5.

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, 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 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.

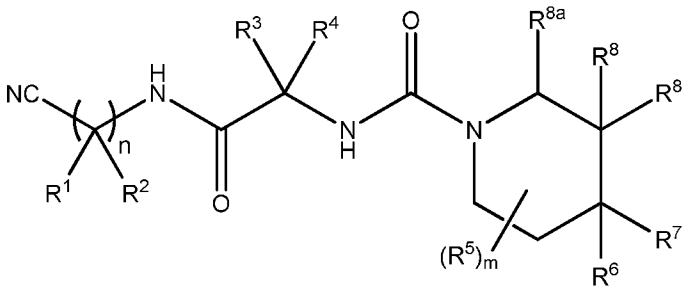
SUMMARY OF INVENTION

In oneaspect,the present invention provides compounds that are inhibitors of cathepsin K. These compounds would be expected to be useful in the treatment of conditions that can be treated by inhibition of these proteases.

In afurther aspect, the present invention provides a pharmaceutical composition containing a compound that is an inhibitor of cathepsin K and a pharmaceutically acceptable excipient, diluent or carrier.

In afurther aspect,the present invention provides a method of prevention or treatment of a condition that can be treated by inhibition of cathepsin K in a mammal.

The present invention provides a compound of formula (I)



(I)

wherein

each R^1 is independently selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6 haloalkyl,

each R^2 is independently selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6 haloalkyl, or

R^1 and R^2 when taken together with the carbon atoms to which they are attached form a C_3-C_8cycloalkyl group;

R^3 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl,

R^4 is selected from the group consisting of hydrogen andoptionally substituted C_1-C_6 alkyl, or

R^3 and R^4 when taken together with the carbon atoms to which they are attached form a C_3-C_8cycloalkyl group;

R^5 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl;

m is an integer selected from the group consisting of 0, 1, 2, 3, or 4;

n is an integer selected from the group consisting of 1, 2, or 3;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide;

R^7 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl,

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide,

$R^{8a}$is selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide; or

R^7 and one R^8 when taken together form a bond, or

one R^8 and R^{8a} when taken together form a bond, or

R^7 and one R^8 when taken together with the carbon atoms to which they are attached form an optionally substitutedaliphatic or aromatic cyclic moiety, wherein when the cyclic moiety is aromatic R^6 and the other R^8 group is absent, or

one R^8 and R^{8a} when taken together with the carbon atoms to which they are attached form an optionally substituted aliphatic or aromatic cyclic moiety, wherein when the cyclic moiety is aromatic the other R^8 group is absent;

or a pharmaceutically acceptable salt thereof.

In a further aspect the invention relates to a pharmaceutical composition containing a compound of the invention and a pharmaceutically acceptable diluent, excipient or carrier.

In yet an even further aspect the invention relates to a method of treating a cathepsin dependent condition in a patient which comprises administering to a patient in need thereof an effective amount of a compound of the invention. In one embodiment the condition is a condition that can be prevented or treated by the inhibition of cathepsin K.

In yet an even further aspect the invention relates to a method of selectively inhibiting cathepsin K activity in a patient which comprises administering to a patient in need thereof an effective amount of a compound of the invention.

In yet an even further aspect the invention relates to the use of a compound of the invention in the preparation of a medicament for the treatment of acathepsin dependent condition. In one embodiment the condition is a condition that can be prevented or treated by the inhibition of cathepsin K.

These and other teachings of the invention are set forth herein.

DETAILED DESCRIPTION OF THE INVENTION

In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined.

As used herein, the term “unsubstituted” means that there is no substituent or that the only substituents are hydrogen.

The term "optionally substituted" as used throughout the specification denotes that the group may or may not be further substituted or fused (so as to form a condensed polycyclic system), with one or more non-hydrogen substituent groups. In certain embodiments the substituent groups are one or more groups independently selected from the group consisting of halogen, =O, =S, -CN, -NO_2, -CF_3, -OCF_3, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkyloxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -C(=O)OH, -$C(=O)R^e$, -$C(=O)OR^e$, $C(=O)NR^eR^f$, $C(=NOH)R^e$, $C(=NR^e)NR^fR^g$, NR^eR^f, $NR^eC(=O)R^f$, $NR^eC(=O)OR^f$, $NR^eC(=O)NR^fR^g$, $NR^eC(=NR^f)NR^gR^h$, $NR^eSO_2R^f$, -SR^e, $SO_2NR^eR^f$, -OR^e, $OC(=O)NR^eR^f$, $OC(=O)R^e$ and acyl,

wherein R^e, R^f, R^g and R^h are each independently selected from the group consisting of H, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_1-C_{10} heteroalkyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_1-C_{12}heterocycloalkyl, C_1-C_{12}heterocycloalkenyl, C_6-C_{18}aryl, C_1-C_{18}heteroaryl, and acyl, or any two or more of R^a, R^b, R^c and R^d, when taken together with the atoms to which they are attached form a heterocyclic ring system with 3 to 12 ring atoms.

In some embodiments each optional substituent is independently selected from the group consisting of: halogen, =O, =S, -CN, -NO_2, -CF_3, -OCF_3, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, aminoalkyl, -COOH, -SH, and acyl.

Examples of particularly suitable optional substituents include F, Cl, Br, I, CH_3, CH_2CH_3, OH, OCH_3, CO_2H, CO_2CH_3, SO_2H, SO_2CH_3, CF_3, OCF_3, NO_2, NH_2, and CN.

In the definitions of a number of substituents below it is stated that "the group may be a terminal group or a bridging group". This is intended to signify that the use of the term is intended to encompass the situation where the group is a linker between two other portions of the molecule as well as where it is a terminal moiety. Using the term alkyl as an example, some publications would use the term "alkylene" for a bridging group and hence in these other publications there is a distinction between the terms "alkyl" (terminal group) and "alkylene" (bridging group). In the present application no such distinction is made and most groups may be either a bridging group or a terminal group.

"Acyl" means an R-C(=O)- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. Examples of acyl include acetyl and benzoyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Acylamino" means an R-C(=O)-NH- group in which the R group may be an alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Alkenyl" as a group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched preferably having 2-12 carbon atoms, more preferably 2-10 carbon atoms, most preferably 2-6 carbon atoms, in the normal chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently *E* or *Z*. The alkenyl group is preferably a 1-alkenyl group. Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and nonenyl. The group may be a terminal group or a bridging group.

"Alkenyloxy" refers to an alkenyl-O- group in which alkenyl is as defined herein. Preferred alkenyloxy groups are C_1-C_6 alkenyloxy groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, preferably a C_1–C_{12} alkyl, more preferably a C_1-C_{10} alkyl, most preferably C_1-C_6 unless otherwise noted. Examples of suitable straight and branched C_1-C_6 alkyl substituents include methyl, ethyl, *n*-propyl, 2-propyl, *n*-butyl, *sec*-butyl, *t*-butyl, hexyl, and the like. The group may be a terminal group or a bridging group.

"Alkylamino" includes both mono-alkylamino and dialkylamino, unless specified. "Mono-alkylamino" means an Alkyl-NH- group, in which alkyl is as defined herein. "Dialkylamino" means a $(alkyl)_2N$- group, in which each alkyl may be the same or different and are each as defined herein for alkyl. The alkyl group is preferably a C_1-C_6alkyl group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Alkylaminocarbonyl" refers to a group of the formula $(Alkyl)_x(H)_yNC(=O)$- in which alkyl is as defined herein, x is 1 or 2, and the sum of X+Y =2. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Alkyloxy" refers to an alkyl-O- group in which alkyl is as defined herein. Preferably the alkyloxy is a C_1-C_6alkyloxy. Examples include, but are not limited to, methoxy and ethoxy. The group may be a terminal group or a bridging group.

"Alkyloxyalkyl" refers to an alkyloxy-alkyl- group in which the alkyloxy and alkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Alkyloxyaryl" refers to an alkyloxy-aryl- group in which the alkyloxy and aryl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the aryl group.

"Alkyloxycarbonyl" refers to an alkyl-O-C(=O)- group in which alkyl is as defined herein. The alkyl group is preferably a C_1-C_6 alkyl group. Examples include, but are not limited to, methoxycarbonyl and ethoxycarbonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the carbonyl carbon.

"Alkyloxycycloalkyl" refers to an alkyloxy-cycloalkyl- group in which the alkyloxy and cycloalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the cycloalkyl group.

"Alkyloxyheteroaryl" refers to an alkyloxy-heteroaryl- group in which the alkyloxy and heteroaryl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroaryl group.

"Alkyloxyheterocycloalkyl" refers to an alkyloxy-heterocycloalkyl- group in which the alkyloxy and heterocycloalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heterocycloalkyl group.

"Alkylsulfinyl" means an alkyl-S-(=O)- group in which alkyl is as defined herein. The alkyl group is preferably a C_1-C_6 alkyl group. Exemplary alkylsulfinyl groups include, but not limited to, methylsulfinyl and ethylsulfinyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Alkylsulfonyl" refers to an alkyl-$S(=O)_2$- group in which alkyl is as defined above. The alkyl group is preferably a C_1-C_6alkyl group. Examples include, but not limited to methylsulfonyl and ethylsulfonyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Alkynyl" as a group or part of a group means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched preferably having from 2-12 carbon atoms, more preferably 2-10 carbon atoms, more preferably 2-6 carbon atoms in the normal chain. Exemplary structures include, but are not limited to, ethynyl and propynyl. The group may be a terminal group or a bridging group.

"Alkynyloxy" refers to an alkynyl-O- group in which alkynyl is as defined herein. Preferred alkynyloxy groups are C_1-C_6alkynyloxy groups. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Aminoalkyl" means an NH_2-alkyl- group in which the alkyl group is as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Aminosulfonyl" means an NH_2-S(=O)$_2$- group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Aryl" as a group or part of a group denotes (i) an optionally substituted monocyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) preferably having from 5 to 12 atoms per ring. Examples of aryl groups include phenyl, naphthyl, and the like; (ii) an optionally substituted partially saturated bicyclic aromatic carbocyclic moiety in which a phenyl and a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl group are fused together to form a cyclic structure, such as tetrahydronaphthyl, indenyl or indanyl. The group may be a terminal group or a bridging group. Typically an aryl group is a C_6-C_{18} aryl group.

"Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as defined herein. Exemplary arylalkenyl groups include phenylallyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as defined herein. Preferred arylalkyl groups contain a C_{1-5}alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl, 1-naphthalenemethyl and 2-naphthalenemethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Arylalkyloxy" refers to an aryl-alkyl-O- group in which the alkyl and aryl are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Arylamino" includes both mono-arylamino and di-arylamino unless specified. Mono-arylamino means a group of formula arylNH-, in which aryl is as defined herein. Di-arylamino means a group of formula (aryl)$_2$N- where each aryl may be the same or different and are each as defined herein for aryl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Arylheteroalkyl" means an aryl-heteroalkyl- group in which the aryl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

"Aryloxy" refers to an aryl–O- group in which the aryl is as defined herein. Preferably the aryloxy is a C_6-C_{18}aryloxy, more preferably a C_6-C_{10}aryloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Arylsulfonyl" means an aryl-$S(=O)_2$- group in which the aryl group is as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

A "bond" is a linkage between atoms in a compound or molecule. The bond may be a single bond, a double bond, or a triple bond.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. The cycloalkenyl group may be substituted by one or more substituent groups. A cycloalkenyl group typically is a C_3-C_{12} alkenyl group. The group may be a terminal group or a bridging group.

"Cycloalkyl" refers to a saturated monocyclic or fused or spiro polycyclic, carbocycle preferably containing from 3 to 9 carbons per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. It includes monocyclic systems such as cyclopropyl and cyclohexyl, bicyclic systems such as decalin, and polycyclic systems such as adamantane. A cycloalkyl group typically is a C_3-C_{12} alkyl group. The group may be a terminal group or a bridging group.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as defined herein. Exemplary monocycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Cycloalkylalkenyl" means a cycloalkyl-alkenyl- group in which the cycloalkyl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

"Cycloalkylheteroalkyl" means a cycloalkyl-heteroalkyl- group in which the cycloalkyl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

"Cycloalkyloxy" refers to a cycloalkyl-O- group in which cycloalkyl is as defined herein. Preferably the cycloalkyloxy is a C_1-C_6cycloalkyloxy. Examples include, but are not limited to, cyclopropanoxy and cyclobutanoxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Cycloalkenyloxy" refers to a cycloalkenyl-O- group in which the cycloalkenyl is as defined herein. Preferably the cycloalkenyloxy is a C_1-C_6cycloalkenyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Haloalkyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom selected from the group consisting of fluorine, chlorine, bromine and iodine. A haloalkyl group typically has the formula $C_nH_{(2n+1-m)}X_m$ whereineach X is independently selected from the group consisting of F, Cl, Br and I. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably 1 to

3. m is typically 1 to 6, more preferably 1 to 3. Examples of haloalkyl include fluoromethyl, difluoromethyl and trifluoromethyl.

"Haloalkenyl" refers to an alkenyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

"Haloalkynyl" refers to an alkynyl group as defined herein in which one or more of the hydrogen atoms has been replaced with a halogen atom independently selected from the group consisting of F, Cl, Br and I.

"Halogen" represents chlorine, fluorine, bromine or iodine.

"Heteroalkyl" refers to a straight- or branched-chain alkyl group preferably having from 2 to 12 carbons, more preferably 2 to 6 carbons in the chain, in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced by a heteroatomic group selected from S, O, P and NR' where R' is selected from the group consisting of H, optionally substituted C_1-C_{12} alkyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_6-C_{18} aryl, and optionally substituted C_1-C_{18} heteroaryl. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, amides, alkyl sulfides, and the like. Examples of heteroalkyl also include hydroxyC_1-C_6alkyl, C_1-C_6alkyloxyC_1-C_6alkyl, aminoC_1-C_6alkyl, C_1-C_6alkylaminoC_1-C_6alkyl, and di(C_1-C_6alkyl)aminoC_1-C_6alkyl. The group may be a terminal group or a bridging group.

"Heteroalkyloxy" refers to a heteroalkyl-O- group in which heteroalkyl is as defined herein. Preferably the heteroalkyloxy is a C_2-C_6heteroalkyloxy. The group may be a terminal group or a bridging group.

"Heteroaryl" either alone or part of a group refers to groups containing an aromatic ring (preferably a 5 or 6 membered aromatic ring) having one or more heteroatoms as ring atoms in the aromatic ring with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include nitrogen, oxygen and sulfur. The group may be a monocyclic or bicyclic heteroaryl group. Examples of heteroaryl include thiophene, benzothiophene, benzofuran, benzimidazole,

benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolizine, xantholene, phenoxatine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, tetrazole, indole, isoindole, 1H-indazole, purine, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, cinnoline, carbazole, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isooxazole, furazane, phenoxazine, 2-, 3- or 4- pyridyl, 2-, 3-, 4-, 5-, or 8- quinolyl, 1-, 3-, 4-, or 5- isoquinolinyl 1-, 2-, or 3- indolyl, and 2-, or 3-thienyl. A heteroaryl group is typically a C_1-C_{18} heteroaryl group. The group may be a terminal group or a bridging group.

"Heteroarylalkyl" means a heteroaryl-alkyl group in which the heteroaryl and alkyl moieties are as defined herein. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Heteroarylalkenyl" means a heteroaryl-alkenyl- group in which the heteroaryl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

"Heteroarylheteroalkyl" means a heteroaryl-heteroalkyl- group in which the heteroaryl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

"Heteroaryloxy" refers to a heteroaryl-O- group in which the heteroaryl is as defined herein. Preferably the heteroaryloxy is a C_1-C_{18}heteroaryloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Heterocyclic" refers to saturated, partially unsaturated or fully unsaturated monocyclic, bicyclic or polycyclic ring system containing at least one heteroatom selected from the group

consisting of nitrogen, sulfur and oxygen as a ring atom. Examples of heterocyclic moieties include heterocycloalkyl, heterocycloalkenyl and heteroaryl.

"Heterocycloalkenyl" refers to a heterocycloalkyl group as defined herein but containing at least one double bond. A heterocycloalkenyl group typically is a C_2-C_{12} heterocycloalkenyl group. The group may be a terminal group or a bridging group.

"Heterocycloalkyl" refers to a saturated monocyclic, bicyclic, or polycyclic ring containing at least one heteroatom selected from nitrogen, sulfur, oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, and 1,4-oxathiapane. A heterocycloalkyl group typically is a C_2-C_{12}heterocycloalkyl group. The group may be a terminal group or a bridging group.

"Heterocycloalkylalkyl" refers to a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as defined herein. Exemplary heterocycloalkylalkyl groups include (2-tetrahydrofuryl)methyl, (2-tetrahydrothiofuranyl) methyl. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkyl group.

"Heterocycloalkylalkenyl" refers to a heterocycloalkyl-alkenyl- group in which the heterocycloalkyl and alkenyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the alkenyl group.

"Heterocycloalkylheteroalkyl" means a heterocycloalkyl-heteroalkyl- group in which the heterocycloalkyl and heteroalkyl moieties are as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the heteroalkyl group.

"Heterocycloalkyloxy" refers to a heterocycloalkyl-O- group in which the heterocycloalkyl is as defined herein. Preferably the heterocycloalkyloxy is a C_1-C_6heterocycloalkyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Heterocycloalkenyloxy" refers to a heterocycloalkenyl-O- group in which heterocycloalkenyl is as defined herein. Preferably the Heterocycloalkenyloxy is a C_1-C_6 Heterocycloalkenyloxy. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the oxygen atom.

"Hydroxyalkyl" refers to an alkyl group as defined herein in which one or more of the hydrogen atoms has been replaced with an OH group. A hydroxyalkyl group typically has the formula $C_nH_{(2n+1-x)}(OH)_x$. In groups of this type n is typically from 1 to 10, more preferably from 1 to 6, most preferably 1 to 3. x is typically 1 to 6, more preferably 1 to 3.

"Sulfinyl" means an R-S(=O)- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Sulfinylamino" means an R-S(=O)-NH- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

"Sulfonyl" means an R-S(=O)$_2$- group in which the R group may be OH, alkyl, cycloalkyl, heterocycloalkyl; aryl or heteroaryl group as defined herein. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the sulfur atom.

"Sulfonylamino" means an R-S(=O)$_2$-NH- group. The group may be a terminal group or a bridging group. If the group is a terminal group it is bonded to the remainder of the molecule through the nitrogen atom.

It is understood that included in the family of compounds of Formula (I) are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in "*E*" or "*Z*" configurational isomer or a mixture of *E* and *Z* isomers. It is also understood that some isomeric forms such as diastereomers, enantiomers, and geometrical isomers can be separated by physical and/or chemical methods and by those skilled in the art. For those compounds where there is the possibility of geometric isomerism the applicant has drawn the isomer that the compound is thought to be although it will be appreciated that the other isomer may be the correct structural assignment.

Some of the compounds of the disclosed embodiments may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and /or diastereomers. All such single stereoisomers, racemates and mixtures thereof, are intended to be within the scope of the subject matter described and claimed.

Additionally, Formula (I) is intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

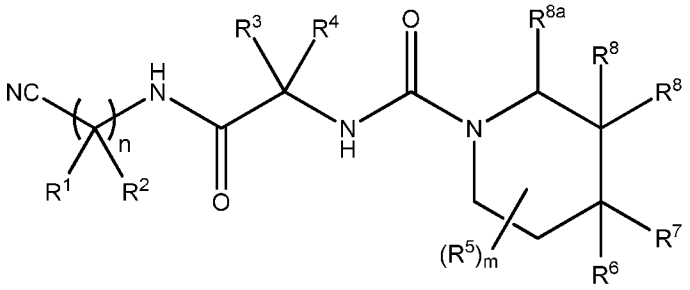
The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula (I) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propanoic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic, arylsulfonic. In a similar vein base addition salts may be prepared by ways well known in the art using organic or inorganic bases. Examples of suitable organic bases include simple amines such as methylamine, ethylamine, triethylamine and the like. Examples of suitable inorganic bases include NaOH, KOH, and the like. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by those

skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

The term "nitrogen protecting group" means a group that can prevent the nitrogen moiety reacting during further derivatisation of the protected compound and which can be readily removed when desired. In one embodiment the protecting group is removable in the physiological state by natural metabolic processes. Examples of suitable nitrogen protecting groups that may be used include formyl, trityl, phthalimido,acetyl, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl; urethane-type blocking groups such as benzyloxycarbonyl ('CBz'), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, t-butoxycarbonyl ('t-Boc'), 2-(4-xenyl)-isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(p-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxy-carbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfono)-ethoxycarbonyl, 2-(methylsulfono)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decycloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonlyl, and the like; benzoylmethylsulfono group, 2-nitrophenylsulfenyl, diphenylphosphine oxide, and the like. The actual nitrogen protecting group employed is not critical so long as the derivatised nitrogen group is stable to the condition of subsequent reaction(s) and can be selectively removed as required without substantially disrupting the remainder of the molecule including any other nitrogen protecting group(s). Further examples of these groups are found in: Greene, T. W. and Wuts, P. G. M., Protective Groups in Organic Synthesis, Second edition; Wiley-Interscience: 1991; Chapter 7; McOmie, J. F. W. (ed.), Protective Groups in Organic Chemistry, Plenum Press, 1973; and Kocienski, P. J., Protecting Groups, Second Edition, Thieme Medical Pub., 2000.

The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state.

As stated above the compounds of the invention have the formula (I):



(I)

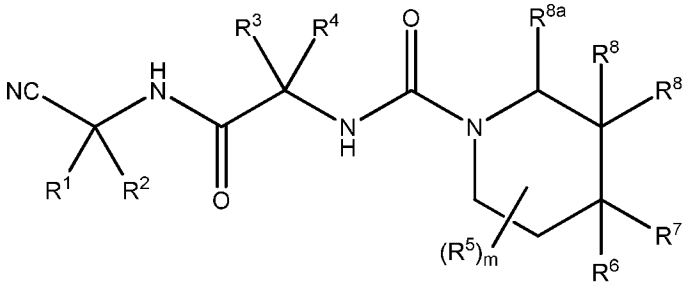
or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{8a}, n and m are as described above.

As with any group of structurally related compounds which possess a particular utility, certain embodiments of variables of the compounds of the Formula (I), are particularly useful in their end use application.

In the compounds of the invention n is an integer selected from the group consisting of 1 and 2. In some embodiments n is 1. In some embodiments n is 2.

In some embodiments n is 1 which provides compounds of formula (Ia):

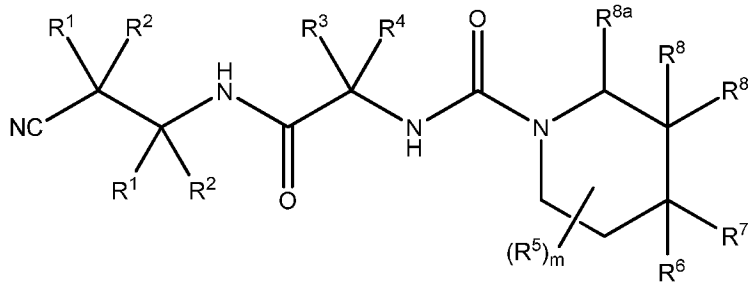


(Ia)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, $R^{8a}$and m are as described above.

In some embodiments n is 2 which provides compounds of formula (Ib):

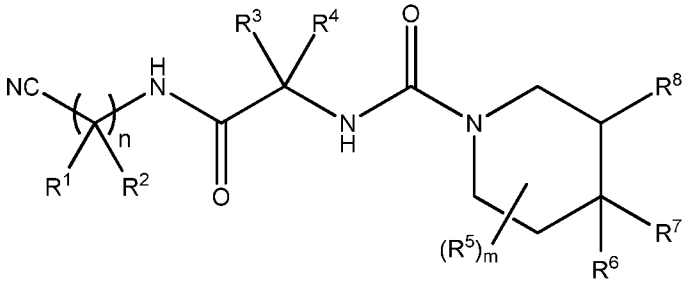


(Ib)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{8a} and m are as described above.

In some embodiments one R^8 and R^{8a} are both H which provides compounds of formula (2):

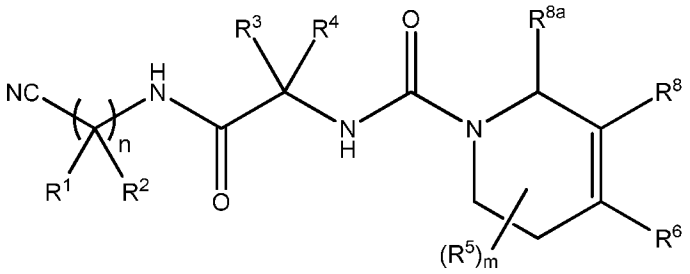


(2)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and m are as described above.

In some embodiments R^7 and one R^8 when taken together form a bond which provides compounds of formula (3):

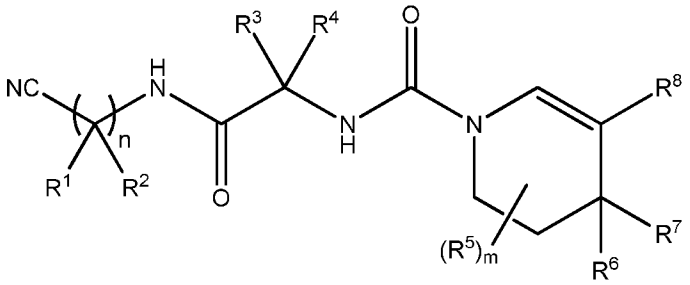


(3)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^{8a}, and m are as described above.

In some embodiments one R^8 and R^{8a} when taken together form a bond which provides compounds of formula (4):



(4)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, and m are as described above.

In the compounds of the invention, each R^1 and R^2 are independently selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl, or R^1 and R^2 when taken together with the carbon atom to which they are attached form a C_3-C_8cycloalkyl group;

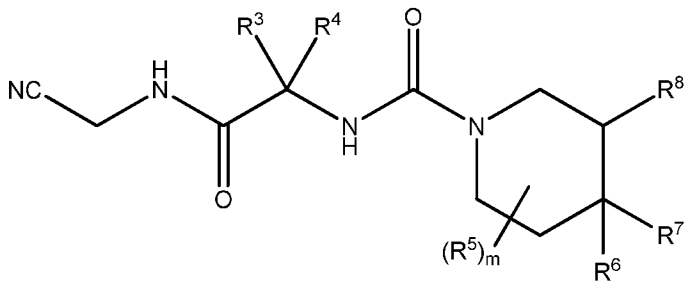
In certain embodiments R^1 is H. In certain embodiments R^1 is C_1-C_6alkyl. In certain embodiments R^1 is C_1-C_6haloalkyl.

In certain embodiments R^2 is H. In certain embodiments R^2 is C_1-C_6 alkyl. In certain embodiments R^2 is C_1-C_6 haloalkyl.

Examples of suitable values for R^1 and R^2 are H, methyl, fluoromethyl, difluoromethyl and trifluoromethyl.ethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl, pentyl, and hexyl. In some embodiments R^1 and R^2 are both H. In some embodiments R^1 and R^2 are both methyl.

In certain embodiments R^1 and R^2 when taken together with the carbon atom to which they are attached form a C_3-C_8cycloalkyl group. Examples of suitable C_3-C_8cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. In certain embodiments R^1 and R^2 when taken together with the carbon atom to which they are attached form a cyclopropyl group. In certain embodiments R^1 and R^2 when taken together with the carbon atom to which they are attached form a cyclobutyl group. In certain embodiments R^1 and R^2 when taken together with the carbon atom to which they are attached form a cyclopentyl group. In certain embodiments R^1 and R^2 when taken together with the carbon atom to which they are attached form a cyclohexyl group. In certain embodiments R^1 and R^2 when taken together with the carbon atom to which they are attached form a cycloheptyl group. In certain embodiments R^1 and R^2 when taken together with the carbon atom to which they are attached form a cyclooctyl group.

In some embodiments n is 1 and R^1 and R^2 are both H and one R^8 and R^{8a} are both H which provides compounds of formula (2a):

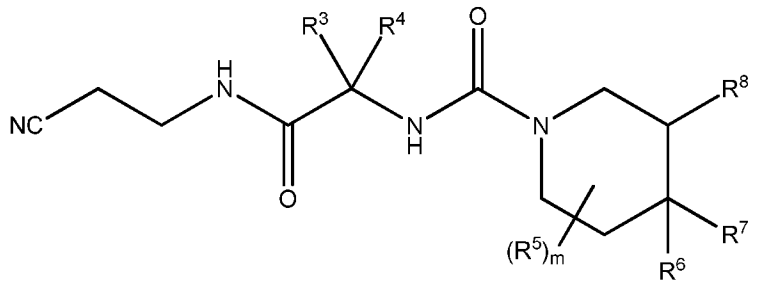


(2a)

or a pharmaceutically acceptable salt thereof;

wherein R^3, R^4, R^5, R^6, R^7, R^8, and m are as described above.

In some embodiments n is 2 and each R^1 and R^2 are H and one R^8 and R^{8a} are both H which provides compounds of formula (2b):

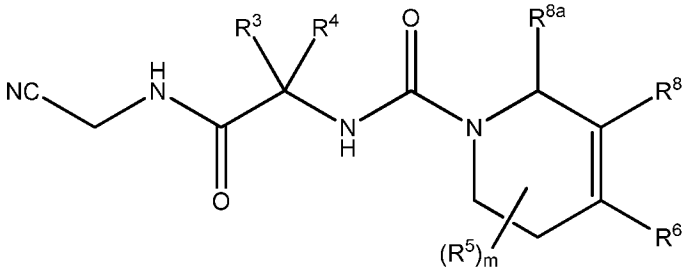


(2b)

or a pharmaceutically acceptable salt thereof;

wherein R^3, R^4, R^5, R^6, R^7, R^8, and m are as described above.

In some embodiments n is 1 and R^1 and R^2 are both H and R^7 and one R^8 when taken together form a bondwhich provides compounds of formula (3a):

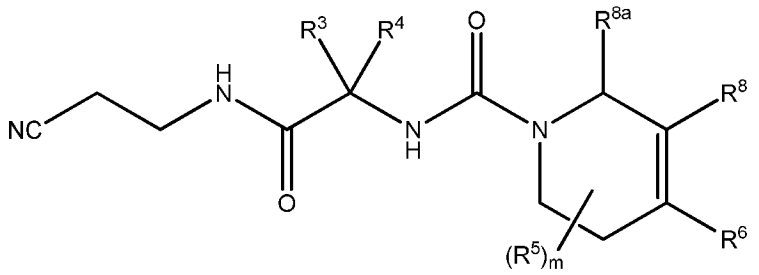


(3a)

or a pharmaceutically acceptable salt thereof;

wherein R^3, R^4, R^5, R^6, R^8, R^{8a}, and m are as described above.

In some embodiments n is 2 and each R^1 and R^2 are H and R^7 and one R^8 when taken together form a bondwhich provides compounds of formula (3b):

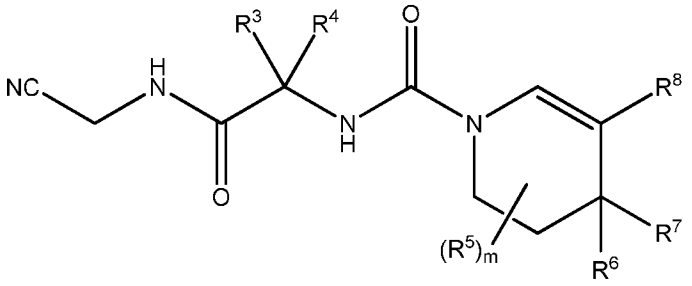


(3b)

or a pharmaceutically acceptable salt thereof;

wherein R^3, R^4, R^5, R^6, R^8, R^{8a}, and m are as described above.

In some embodiments n is 1 and R^1 and R^2 are both H and one R^8 and R^{8a} when taken together form a bondwhich provides compounds of formula (4a):

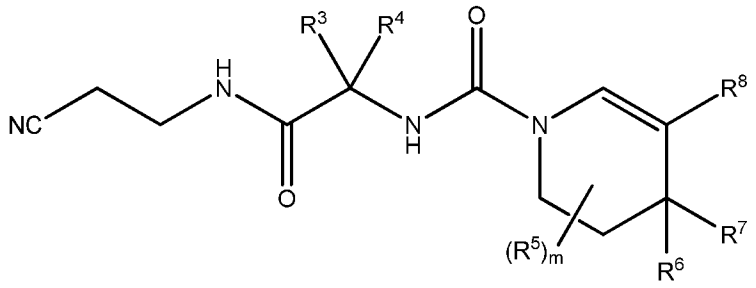


(4a)

or a pharmaceutically acceptable salt thereof;

wherein R^3, R^4, R^5, R^6, R^7, R^8, and m are as described above.

In some embodiments n is 2 and each R^1 and R^2 are H and one R^8 and R^{8a} when taken together form a bondwhich provides compounds of formula (4b):



(4b)

or a pharmaceutically acceptable salt thereof;

wherein R^3, R^4, R^5, R^6, R^7, R^8, and m are as described above.

In the compounds of the invention R^4 is selected from the group consisting of hydrogen and optionally substituted C_1-C_6alkyl. In certain embodiments R^4 is H. In certain embodiments R^4 is optionally substituted C_1-C_6alkyl

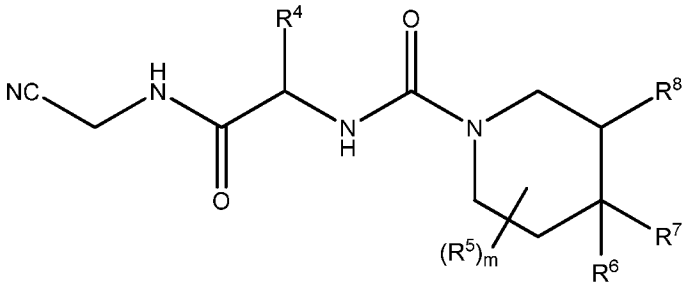
Examples of suitable values for R^3 and R^4 are H, methyl, fluoromethyl, difluoromethyl and trifluoromethyl.ethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl, pentyl, and hexyl.

In certain embodiments R^3 is H and R^4 is optionally substituted C_1-C_6alkyl.

In certain embodiments of the compounds of the invention R^3 and R^4 when taken together with the carbon atom to which they are attached form a C_3-C_8cycloalkyl group. Examples of suitable C_3-C_8cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. In certain embodiments R^3 and R^4 when taken together with the carbon atom to which they are attached form a cyclopropyl group. In certain embodiments R^3 and R^4 when taken together with the carbon atom to which they are attached form a cyclobutyl group. In certain embodiments R^3 and R^4 when taken together with the carbon atom to which they are attached form a cyclopentyl group. In certain embodiments R^3 and R^4 when taken together with the carbon atom to which they are attached form a cyclohexyl group. In certain embodiments R^3 and R^4 when taken together with the carbon atom to which they are

attached form a cycloheptyl group. In certain embodiments R^3 and R^4 when taken together with the carbon atom to which they are attached form a cyclooctyl group.

In some embodiments n is 1 and R^1, R^2 and R^3 are H and one R^8 and R^{8a} are both H which provides compounds of formula (2c):

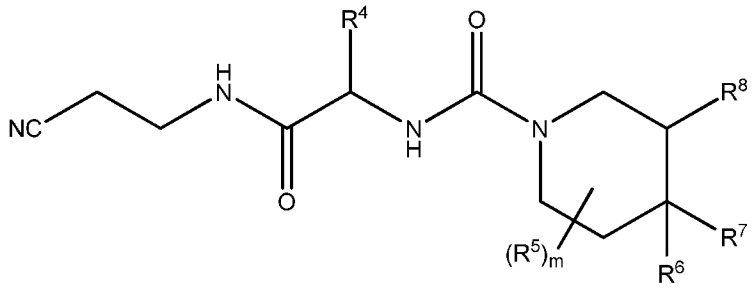


(2c)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^5, R^6, R^7, R^8, and m are as described above.

In some embodiments n is 2 and R^1, $R^{2,}$ and R^3 are H and one R^8 and R^{8a} are both H which provides compounds of formula (2d):

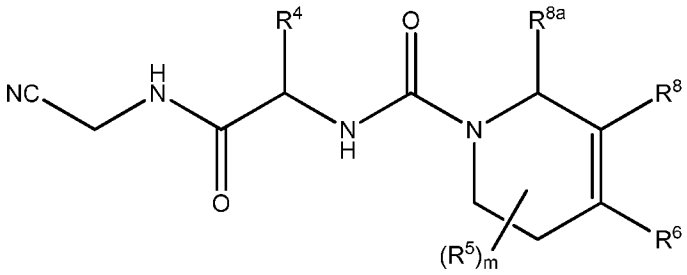


(2d)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^5, R^6, R^7, R^8, and m are as described above.

In some embodiments n is 1 and R^1, R^2 and R^3 are H and R^7 and one R^8 when taken together form a bondwhich provides compounds of formula (3c):

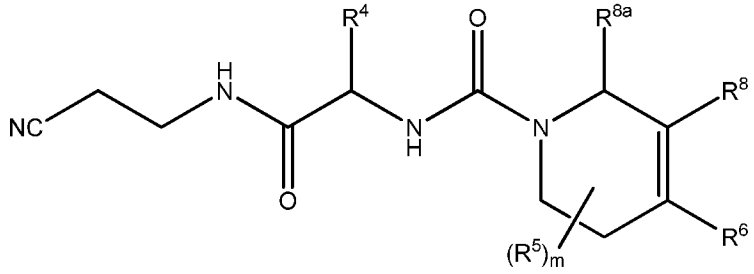


(3c)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^5, R^6, R^8, R^{8a}, and m are as described above.

In some embodiments n is 2 and R^1, $R^{2,}$ and R^3 are H and R^7 and one R^8 when taken together form a bondwhich provides compounds of formula (3d):

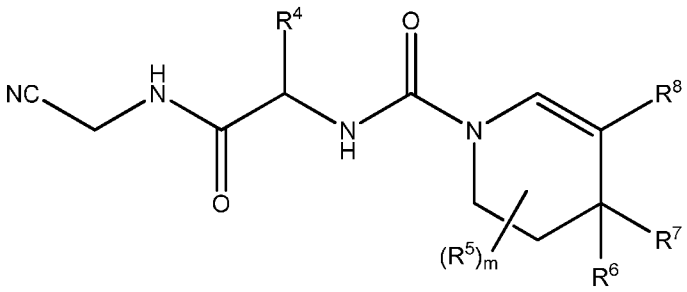


(3d)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^5, R^6, R^8, R^{8a}, and m are as described above.

In some embodiments n is 1 and R^1, R^2 and R^3 are H and one R^8 and R^{8a} when taken together form a bondwhich provides compounds of formula (4c):

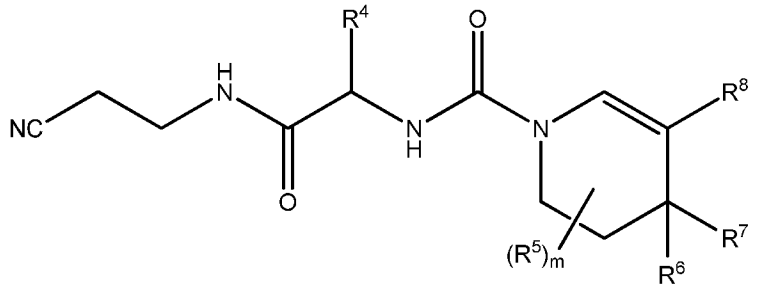


(4c)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^5, R^6, R^7, R^8, and m are as described above.

In some embodiments n is 2 and R^1, $R^{2,}$ and R^3 are H and one R^8 and R^{8a} when taken together form a bondwhich provides compounds of formula (4d):



(4d)

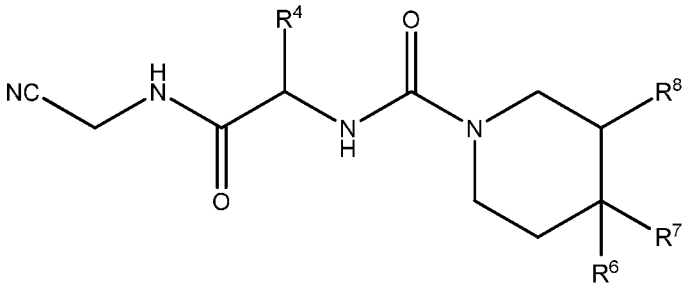
or a pharmaceutically acceptable salt thereof;

wherein R^4, R^5, R^6, R^7, R^8, and m are as described above.

In the compounds of the invention R^5 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl. In certain embodiments R^5 is H. In certain embodiments R^5 is optionally substituted C_1-C_6alkyl. In certain embodiments R^5 is C_1-C_6haloalkyl. Suitable examples of R^5 include H, methyl, fluoromethyl, difluoromethyl, trifluoromethyl. ethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl, pentyl, and hexyl.

In the compounds of the invention m is an integer selected from the group consisting of 0, 1, 2, 3, and 4. In certain embodiments m is 0. In certain embodiments m is 1. In certain embodiments m is 2. In certain embodiments m is 3. In certain embodiments m is 4.

In some embodiments n is 1, R^1, R^2, and R^3 are H,and one R^8 and R^{8a} are both H and m is 0 which provides compounds of formula (2e):

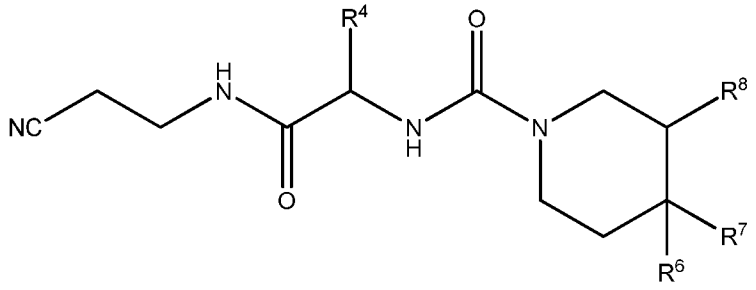


(2e)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^6, R^7, and R^8, are as described above.

In some embodiments n is 2, R^1, R^2, and R^3 are H, and one R^8 and R^{8a} are both H and m is 0 which provides compounds of formula (2f):

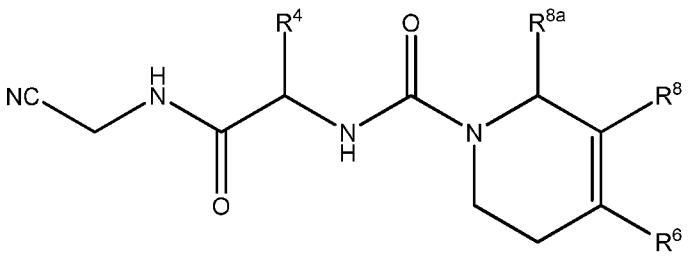


(2f)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^6, R^7, and R^8, are as described above.

In some embodiments n is 1, R^1, R^2, and R^3 are H,and R^7 and one R^8 when taken together form a bondand m is 0 which provides compounds of formula (3e):

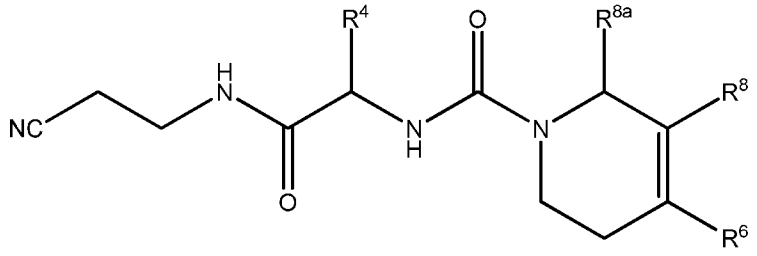


(3e)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^6, R^8, $R^{8a}$are as described above.

In some embodiments n is 2, R^1, R^2, and R^3 are H, and R^7 and one R^8 when taken together form a bondand m is 0 which provides compounds of formula (3f):

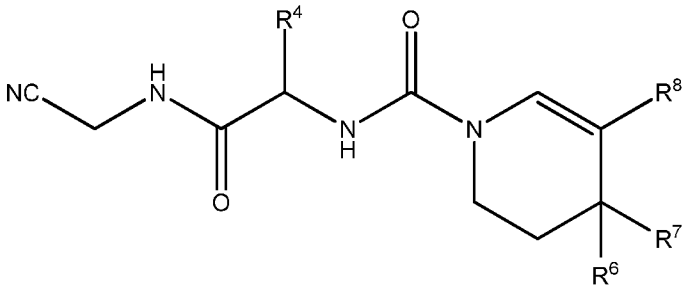


(3f)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^6, R^8, $R^{8a}$are as described above.

In some embodiments n is 1, R^1, R^2, and R^3 are H,and one R^8 and R^{8a} when taken together form a bondand m is 0 which provides compounds of formula (4e):

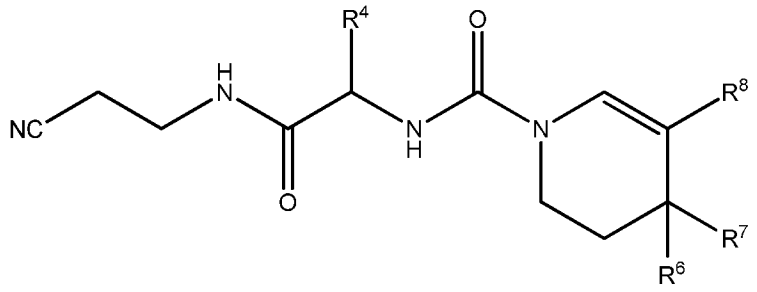


(4e)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^6, R^7, $R^8$are as described above.

In some embodiments n is 2, R^1, R^2, and R^3 are H, and one R^8 and R^{8a} when taken together form a bondand m is 0 which provides compounds of formula (4f):



(4f)

or a pharmaceutically acceptable salt thereof;

wherein R^4, R^6, R^7, $R^8$are as described above.

In certain embodiments of the compounds of the invention R^6 is selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide.

In certain embodiments R^6 is hydrogen. In certain embodiments R^6 is optionally substituted C_6-C_{18}aryl. In certain embodiments R^6 is optionally substituted C_1-C_{18}heteroaryl. In certain embodiments R^6 is optionally substituted carboxamide.

In certain embodiments of the compounds of the invention R^7 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl.

In certain embodiments R^7 is hydrogen. In certain embodiments R^7 is C_1-C_6alkyl. In certain embodiments R^7 is C_1-C_6haloalkyl.

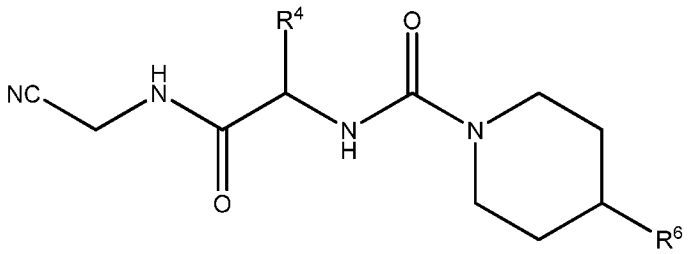
In certain embodiments of the compounds of the invention each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide.

In certain embodiments R^8 is hydrogen. In certain embodiments R^8 is optionally substituted C_6-C_{18}aryl. In certain embodiments R^8 is optionally substituted C_1-C_{18}heteroaryl. In certain embodiments R^8 is optionally substituted carboxamide.

In certain embodiments of the compounds of the invention each R^{8a} is independently selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide.

In certain embodiments R^{8a} is hydrogen. In certain embodiments R^{8a} is optionally substituted C_6-C_{18}aryl. In certain embodiments R^{8a} is optionally substituted C_1-C_{18}heteroaryl. In certain embodiments R^{8a} is optionally substituted carboxamide.

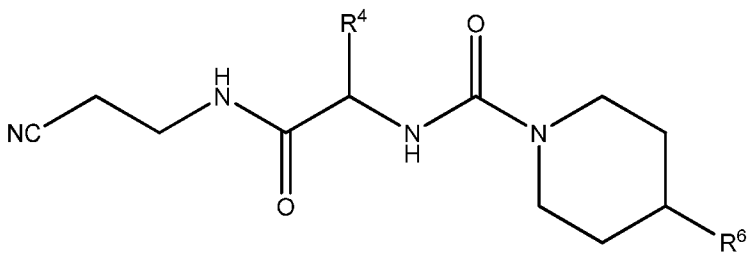
In some embodiments n is 1, R^1, R^2, R^3, R^7 and $R^8$are H, and m is 0, which provides compounds of formula (5a).



(5a)

wherein R^4 and R^6 are as described above.

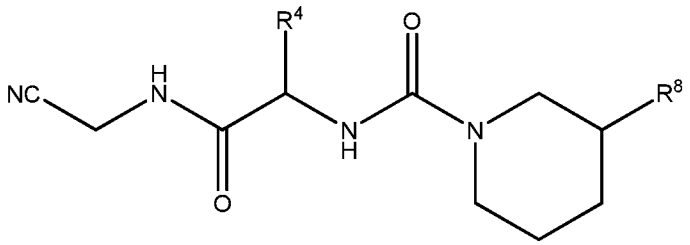
In some embodiments n is 2, R^1, R^2, R^3, R^7 and $R^8$are H, and m is 0, which provides compounds of formula (5b).



(5b)

wherein R^4 and R^6 are as described above.

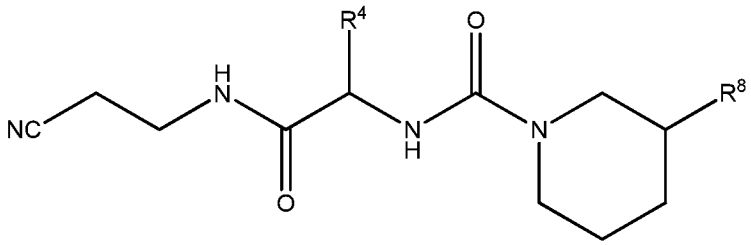
In some embodiments n is 1, R^1, R^2, R^3, R^6 and $R^7$are H, and m is 0, which provides compounds of formula (6a).



(6a)

wherein R^4 and R^8 are as described above.

In some embodiments n is 2, R^1, R^2, R^3, R^6 and $R^7$are H, and m is 0, which provides compounds of formula (6b).

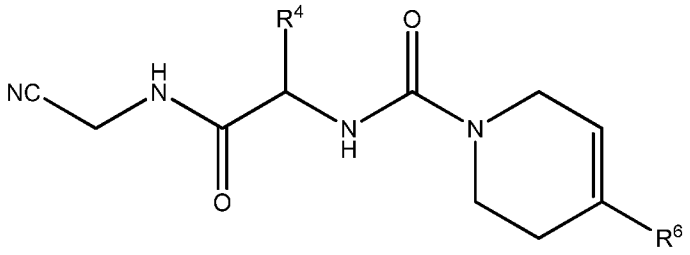


(6b)

wherein R^4 and R^8 are as described above.

In certain embodiments of the compounds of the invention R^7 and R^8 when taken together form a bond.

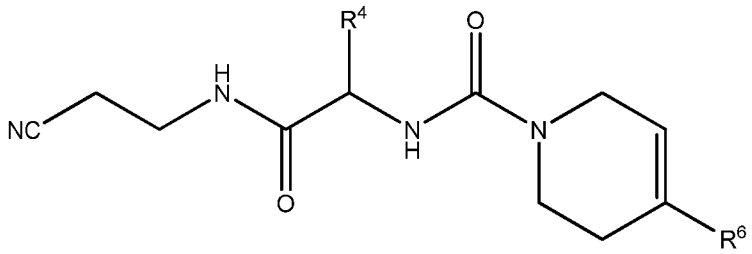
In some embodiments n is 1, R^1, R^2, and R^3 are H, m is 0, and R^7 and R^8 when taken together form a bond, which provides compounds of formula (7a).



(7a)

wherein R^4 and R^6 are as described above.

In some embodiments n is 2, R^1, R^2, and R^3 are H, m is 0, and R^7 and R^8 when taken together form a bond, which provides compounds of formula (7b).



(7b)

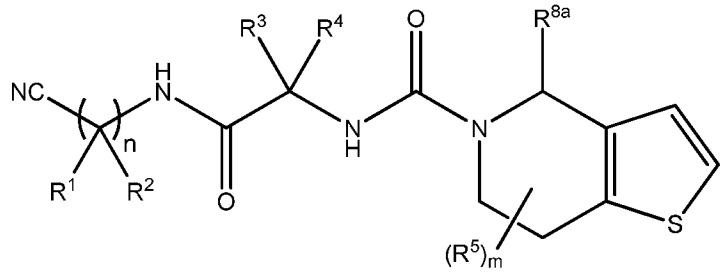
wherein R^4 and R^6 are as described above.

In some embodiments, R^7 and one R^8 when taken together with the carbon atoms to which they are attached form an optionally substitutedaliphatic cyclic moiety. In some embodiments, R^7 and one R^8 when taken together with the carbon atoms to which they are attached form an optionally substitutedaromatic cyclic moiety, wherein R^6 and the other R^8 group are absent.

In some embodiments, one R^8 and R^{8a} when taken together with the carbon atoms to which they are attached form an optionally substituted aliphatic cyclic moiety. In some embodiments, one R^8 and R^{8a} when taken together with the carbon atoms to which they are

attached form an optionally substituted aromatic cyclic moiety, wherein the other R^8 group is absent.

In some embodiments, R^7 and one R^8 when taken together with the carbon atoms to which they are attached form a thiophenyl moiety which provide compounds of formula(8)

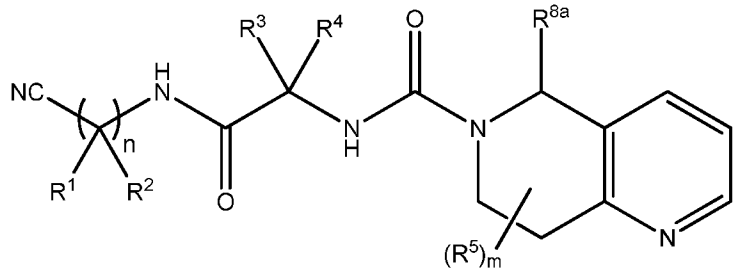


(8)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^{8a}, n and m are as described above.

In some embodiments, R^7 and one R^8 when taken together with the carbon atoms to which they are attached form a pyridinyl moiety which provide compounds of formula (9)

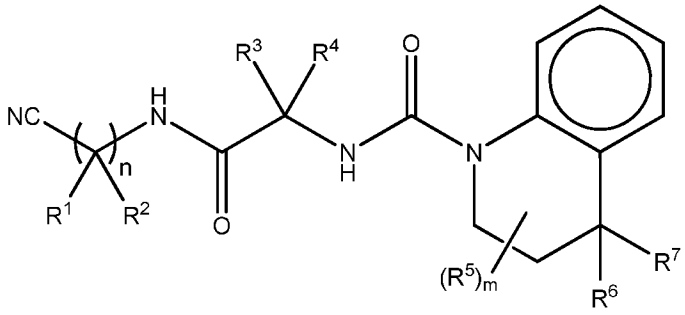


(9)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^{8a}, n and m are as described above,

In some embodiments, one $R^8$and $R^{8a}$when taken together with the carbon atoms to which they are attached form a benzyl moiety which provide compounds of formula (10)



(10)

or a pharmaceutically acceptable salt thereof;

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, n and m are as described above.

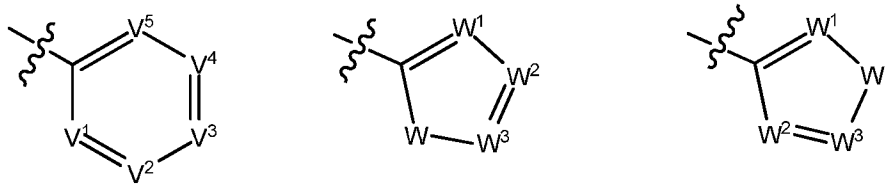
In some embodiments R^6,$R^8$and $R^{8a}$are independently selected from the group consisting of optionally substituted C_6-C_{18}aryl and optionally substituted C_1-C_{18}heteroaryl and may be a monocyclic, bicyclic or polycyclic moiety.

In certain embodiments R^6 is a monocyclic or bicyclic moiety. In certain embodiments R^6 is a monocyclic moiety.

In certain embodiments R^8 is a monocyclic or bicyclic moiety. In certain embodiments R^8 is a monocyclic moiety.

In certain embodiments $R^{8a}$is a monocyclic or bicyclic moiety. In certain embodiments R^{8a} is a monocyclic moiety.

In certain embodiments R^6, $R^8$and $R^{8a}$are independently selected from the group consisting of:



wherein V^1, V^2, V^3, V^4 and V^5 are each independently selected from the group consisting of N, and $C(R^9)$;

W is selected from the group consisting of O, S and NR^9;

W^1, W^2 and W^3 are each independently selected from the group consisting of N and CR^9;

wherein each R^9 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^{10}, SO_3H, $SO_2NR^{10}R^{10}$, SO_2R^{10}, $SONR^{10}R^{10}$, SOR^{10}, COR^{10}, COOH, $COOR^{10}$, $CONR^{10}R^{10}$, $NR^{10}COR^{10}$, $NR^{10}COOR^{10}$, $NR^{10}SO_2R^{10}$, $NR^{10}CONR^{10}R^{10}$, $NR^{10}R^{10}$, and acyl;

wherein each R^{10} is independently selected from H, C_1-C_6alkyl, or optionally substituted C_6-C_{18}aryl.

R^9 may be selected from a wide range of possible substituents as discussed above. In some embodiments each R^9 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_1-C_{12}alkoxyl, and C_1-C_{12}haloalkoxyl. Exemplary R^9 substituents include F, Cl, Br, I, CH_3, CH_2CH_3, OH, OCH_3, CF_3, OCF_3, NO_2, NH_2, SO_2CH_3, and CN.

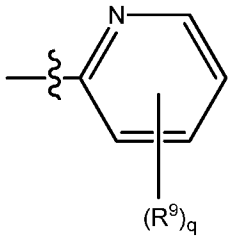
In some embodiments R^6, $R^8$and $R^{8a}$are independently selected from the group consisting of–CONHPh, a pyrimidin-2-yl group, a pyridin-2-yl group, a pyrazin-2-yl group, a pyridyl group, a pyrazolyl group, a phenyl group, and a substituted phenyl group.

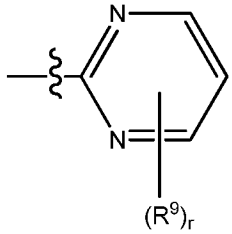
In some embodiments R^6 is an optionally substituted phenyl group. The group may be unsubstituted or may be substituted with one or more optional substituents. A wide variety of optional substituents may be used as defined above. Examples of particularly suitable optional substituents include but are not limited to OH, F, Br, Cl, methyl, CN, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, pent-4-enyl, hexyl, heptyl, octyl, phenyl, NH_2, phenoxy, methoxy, ethoxy, pyrrol-1-yl, methanesulfonyl, and 3,5-dimethyl-pyrazol-1-yl.

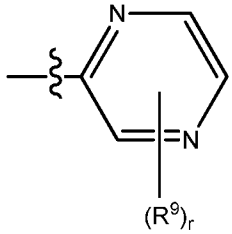
In some embodiments R^8 is an optionally substituted phenyl group. The group may be unsubstituted or may be substituted with one or more optional substituents. A wide variety of optional substituents may be used as defined above. Examples of particularly suitable optional substituents include but are not limited to OH, F, Br, Cl, methyl, CN, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, *iso*propyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, *iso*butyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, pent-4-enyl, hexyl, heptyl, octyl, phenyl, NH_2, phenoxy, methoxy, ethoxy, pyrrol-1-yl, methanesulfonyl, and 3,5-dimethyl-pyrazol-1-yl.

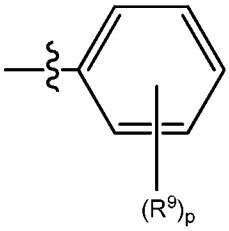
In some embodiments R^{8a} is an optionally substituted phenyl group. The group may be unsubstituted or may be substituted with one or more optional substituents. A wide variety of optional substituents may be used as defined above. Examples of particularly suitable optional substituents include but are not limited to OH, F, Br, Cl, methyl, CN, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, *iso*propyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, *iso*butyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, pent-4-enyl, hexyl, heptyl, octyl, phenyl, NH_2, phenoxy, methoxy, ethoxy, pyrrol-1-yl, methanesulfonyl, and 3,5-dimethyl-pyrazol-1-yl.

In some embodiments R^6, $R^8$and $R^{8a}$are independently selected from the group consisting of









wherein R^9 is as defined above,

p is an integer selected from the group consisting of 0, 1, 2, 3, 4 and 5;

q is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

r is an integer selected from the group consisting of 0, 1, 2, and 3.

In the compounds of the invention containing p, p is an integer selected from the group consisting of 0, 1, 2, 3, 4 and 5. In some embodiments p is 0. In some embodiments p is 1. In some embodiments p is 2. In some embodiments p is 3. In some embodiments p is 4. In some embodiments p is 5.

In the compounds of the invention containing q, q is an integer selected from the group consisting of 0, 1, 2, 3, and 4. In some embodiments q is 0. In some embodiments q is 1. In some embodiments q is 2. In some embodiments q is 3. In some embodiments q is 4.

In the compounds of the invention containing r, r is an integer selected from the group consisting of 0, 1, 2, and 3. In some embodiments r is 0. In some embodiments r is 1. In some embodiments r is 2. In some embodiments r is 3.

Many if not all of the variables discussed above may be optionally substituted. If the variable is optionally substituted then in some embodiments each optional substituent is independently selected from the group consisting of halogen, =O, =S, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkyloxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -C(=O)OH, $-C(=O)R^e$, $-C(=O)OR^e$, $C(=O)NR^eR^f$, $C(=NOH)R^e$, $C(=NR^e)NR^fR^g$, NR^eR^f, $NR^eC(=O)R^f$, $NR^eC(=O)OR^f$, $NR^eC(=O)NR^fR^g$, $NR^eC(=NR^f)NR^gR^h$, $NR^eSO_2R^f$, $-SR^e$, $SO_2NR^eR^f$, $-OR^e$, $OC(=O)NR^eR^f$, $OC(=O)R^e$ and acyl,

wherein R^e, R^f, R^g and R^h are each independently selected from the group consisting of H, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_1-C_{10} heteroalkyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_1-C_{12}heterocycloalkyl, C_1-C_{12} heterocycloalkenyl, C_6-C_{18}aryl, C_1-C_{18}heteroaryl, and acyl, or any two or more of R^a, R^b, R^c and R^d, when taken together with the atoms to which they are attached form a heterocyclic ring system with 3 to 12 ring atoms.

In some embodiments each optional substituent is independently selected from the group consisting of: F, Cl, Br, =O, =S, -CN, $-NO_2$, alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, hydroxy, hydroxyalkyl, alkoxy, alkylamino, aminoalkyl, acylamino, phenoxy, alkoxyalkyl, benzyloxy, alkylsulfonyl, arylsulfonyl, aminosulfonyl, $-C(O)OR^a$, COOH, SH, and acyl.

In some embodiments each optional substituent is independently selected from the group consisting of: F, Br, Cl, =O, =S, -CN, methyl, trifluoro-methyl, methanesulfonyl, ethyl, 2,2,2-trifluoroethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-

dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, pent-4-enyl, hexyl, heptyl, octyl, phenyl, NH_2, $-NO_2$, phenoxy, hydroxy, methoxy, trifluoro-methoxy, ethoxy, and methylenedioxy.

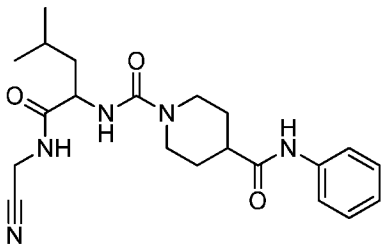
In some embodiments each optional substituent is independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, Cl, Br, F, I, OH, NO_2, NH_2, CN, OCH_3, $OCH_2CH_2CH_3$, CF_3, and OCF_3.

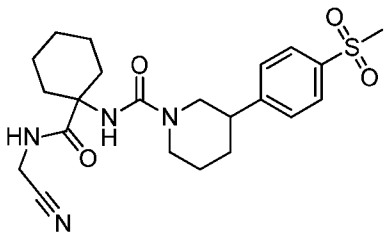
Alternatively, two optional substituents on the same moiety when taken together may be joined to form a fused cyclic substituent attached to the moiety that is optionally substituted. Accordingly the term optionally substituted includes a fused ring such as a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring or a heteroaryl ring.

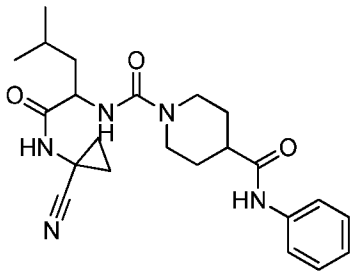
In addition to compounds of formula (I), the embodiments disclosed are also directed to pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites.

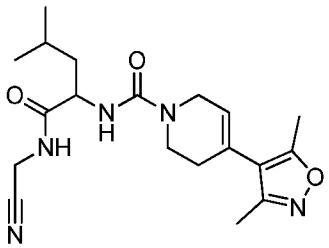
The invention also relates to pharmaceutical compositions including a compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient.

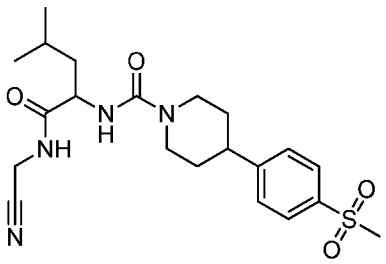
Specific compounds of the invention include the following:

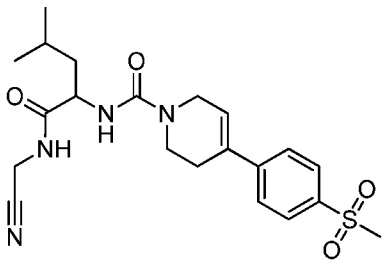


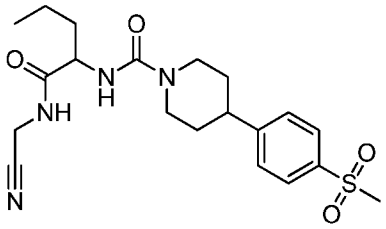


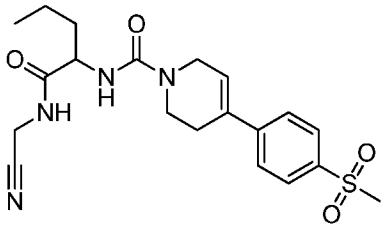


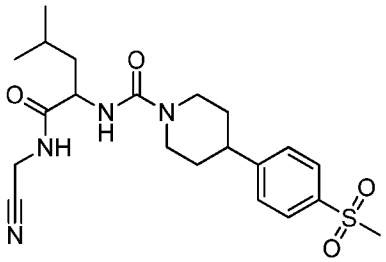


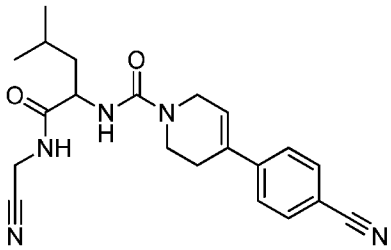


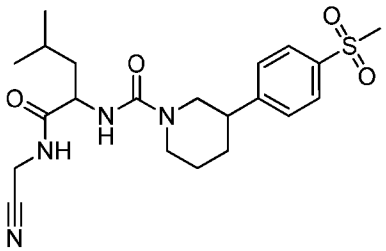


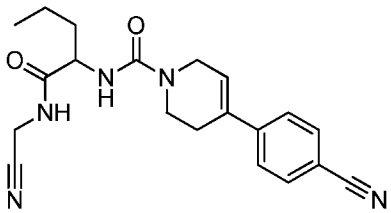


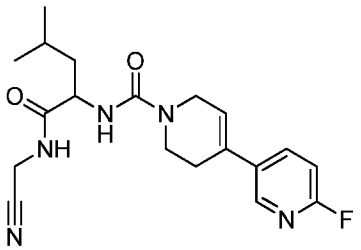


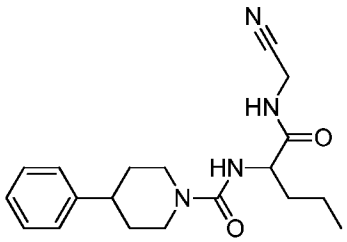


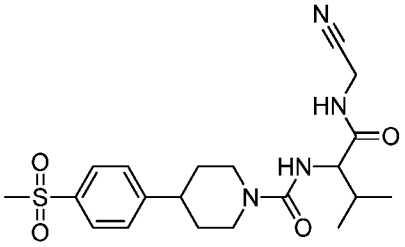


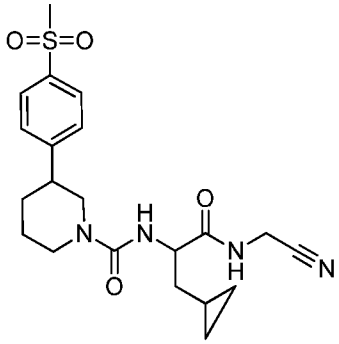


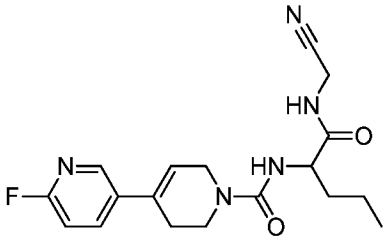


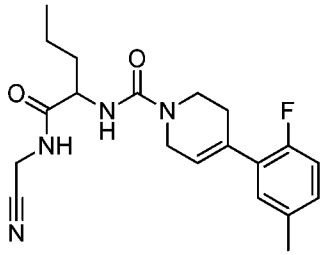


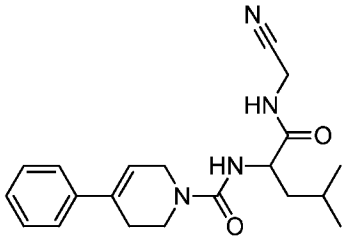


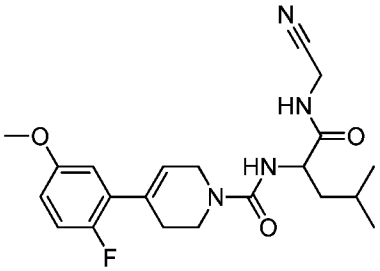


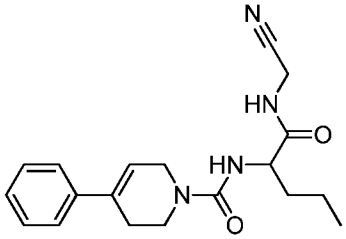


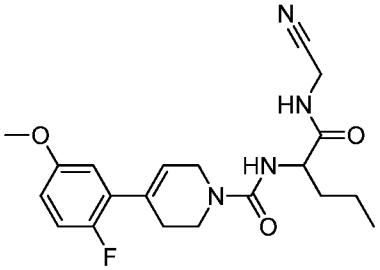


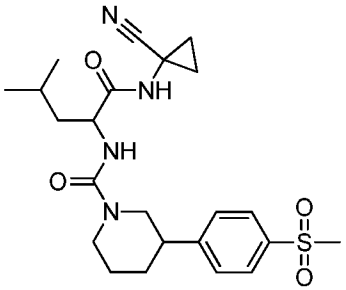


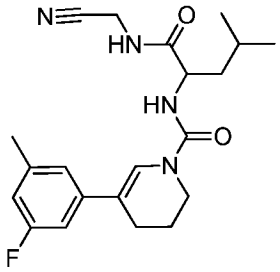


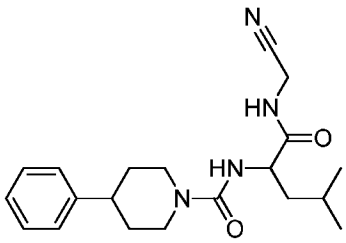


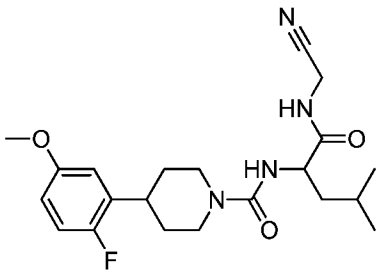


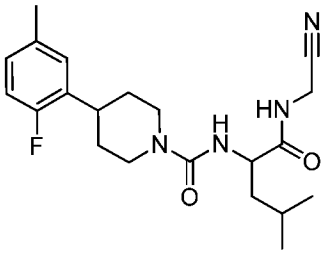


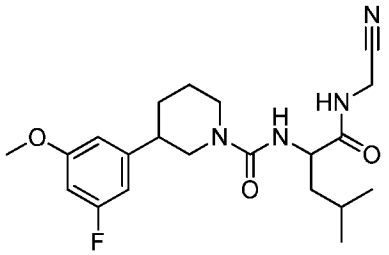


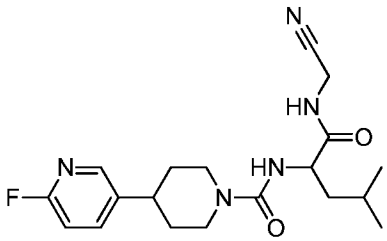


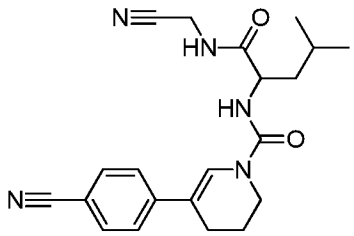


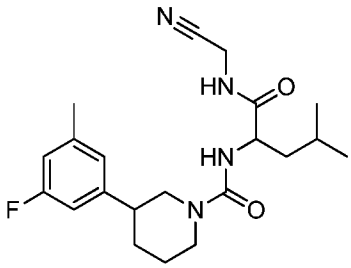


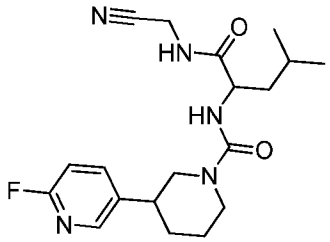


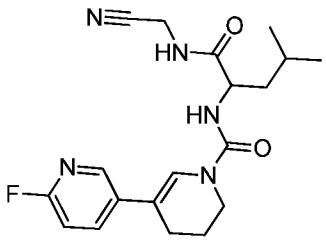


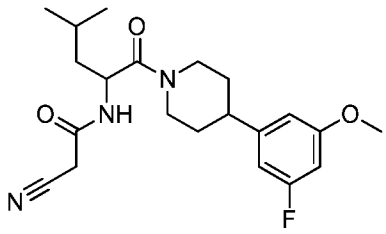


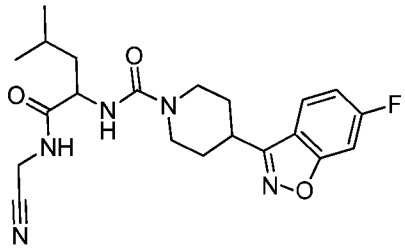


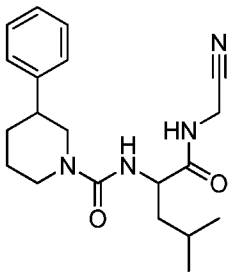


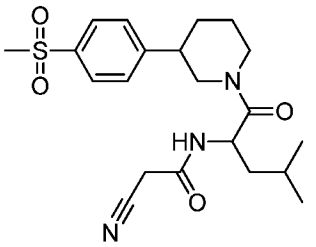


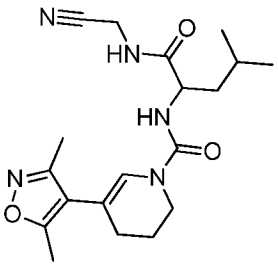


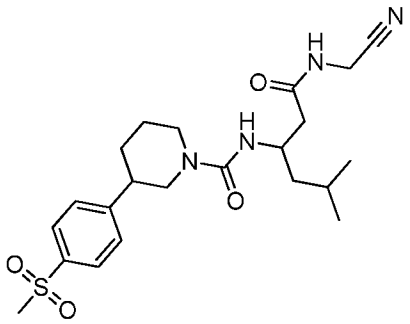


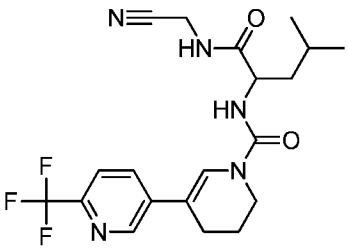


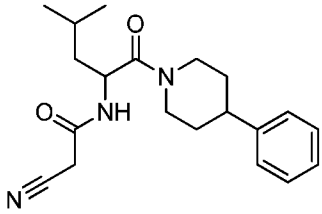


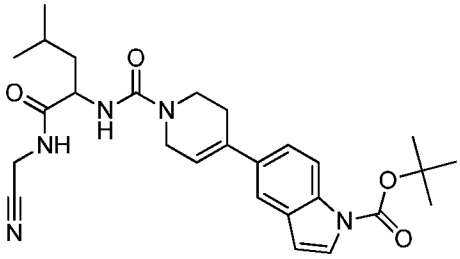


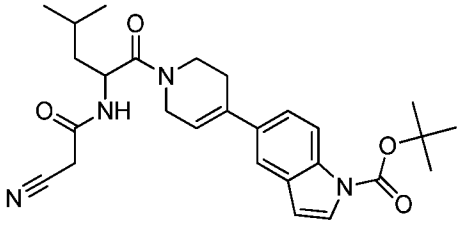


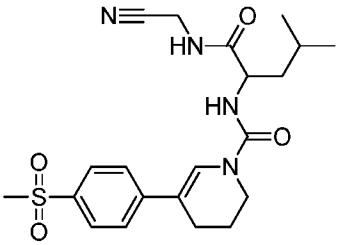


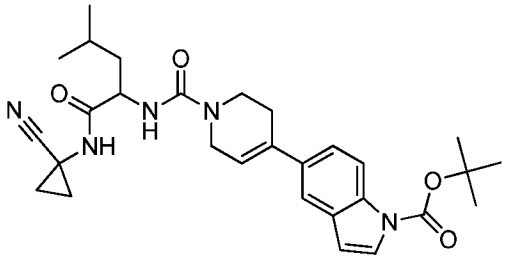


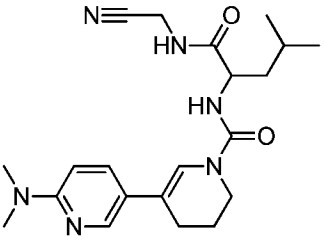


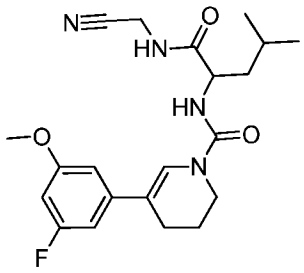


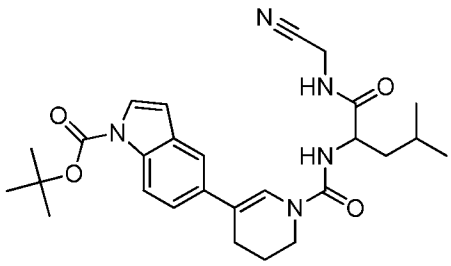


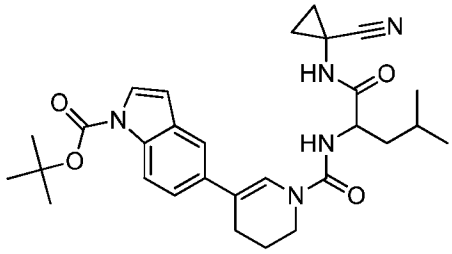


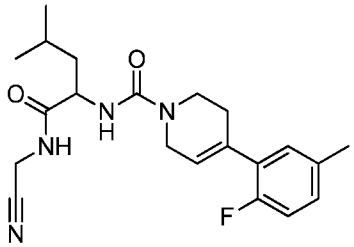


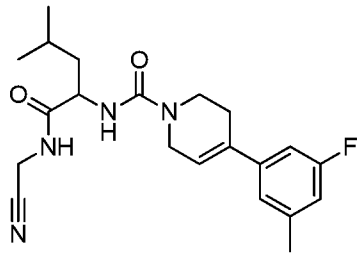


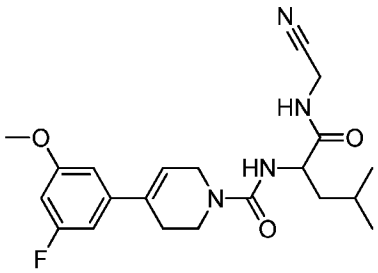


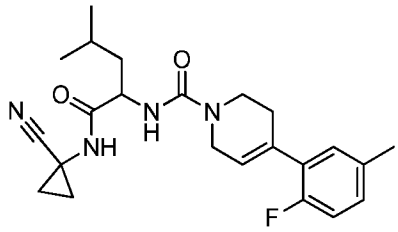


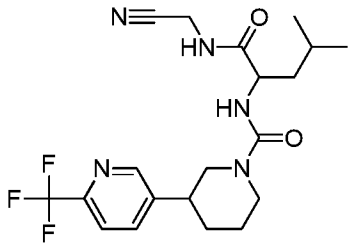


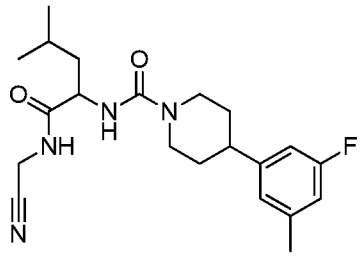


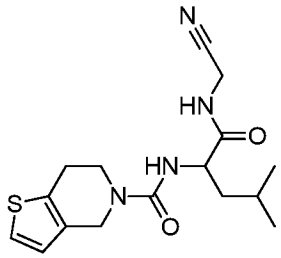


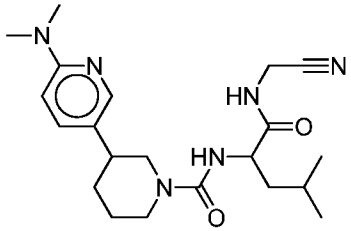


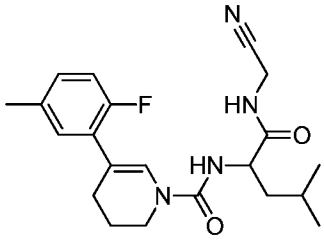


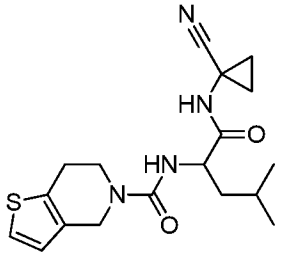


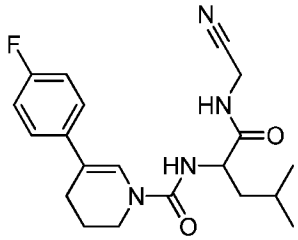


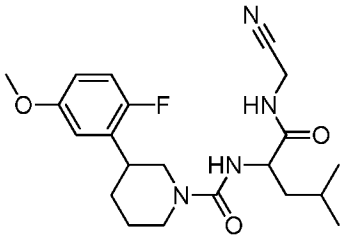


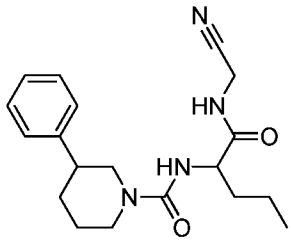


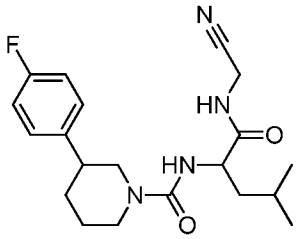


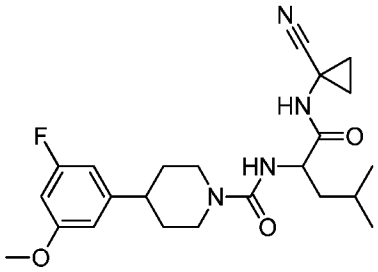


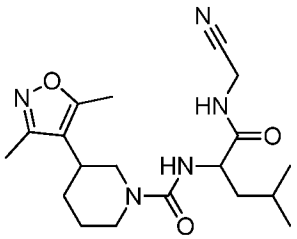


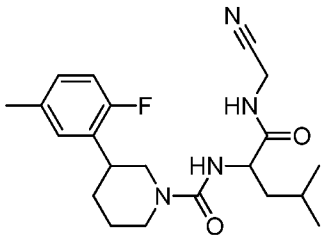


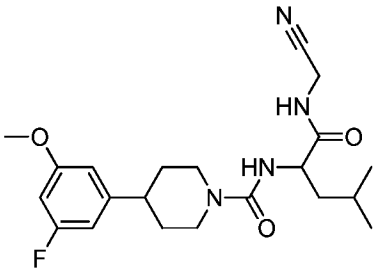


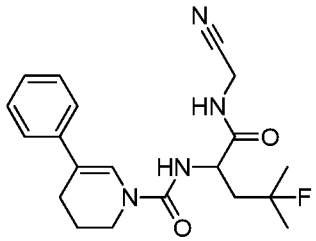


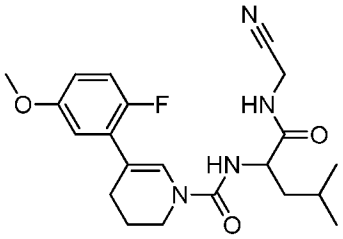


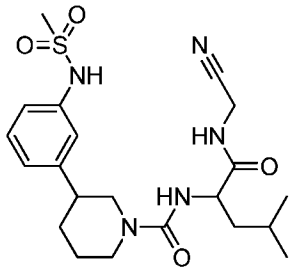


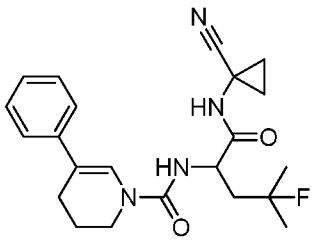


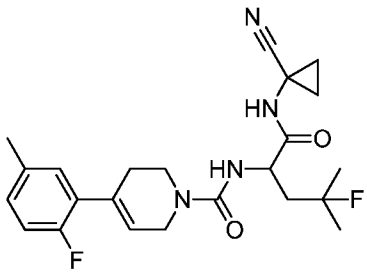


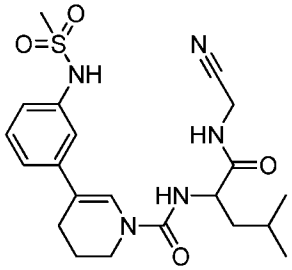


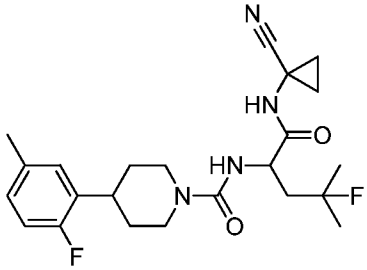


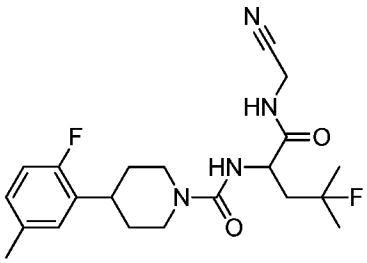


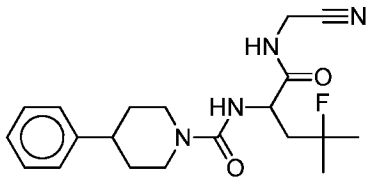


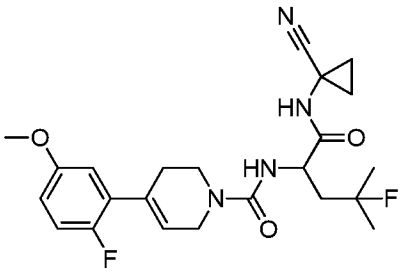


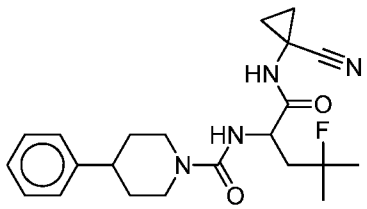


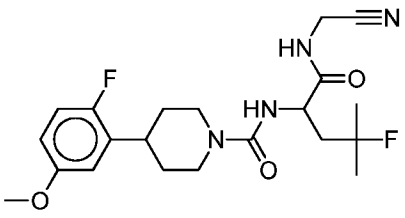


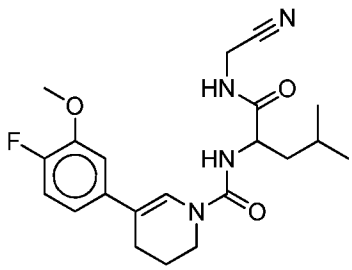


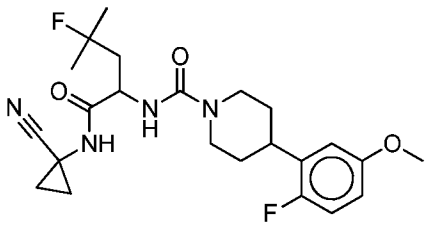


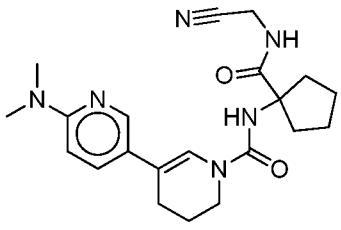


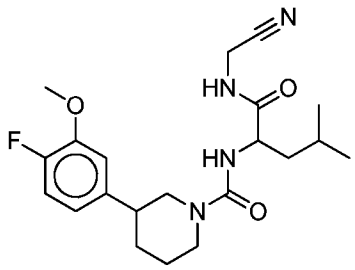


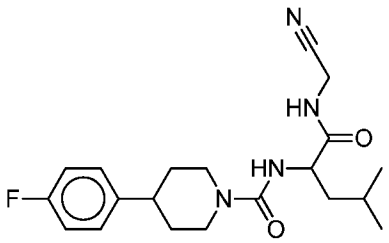


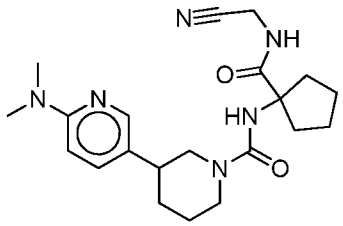


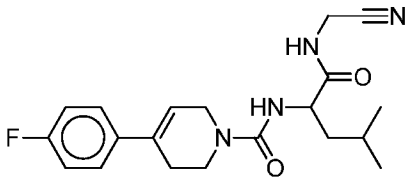


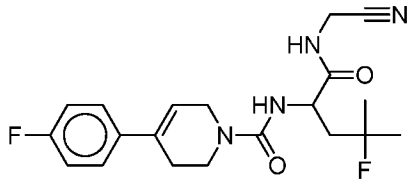


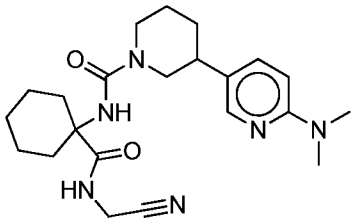


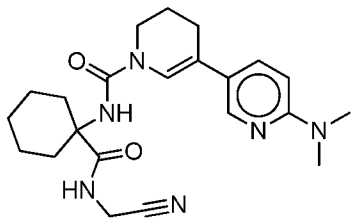


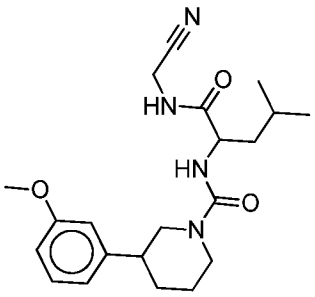


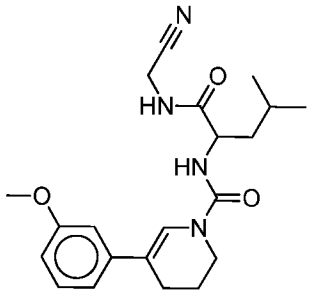


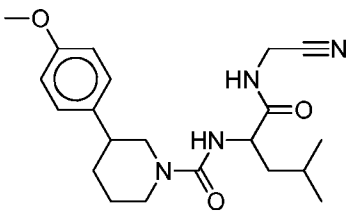


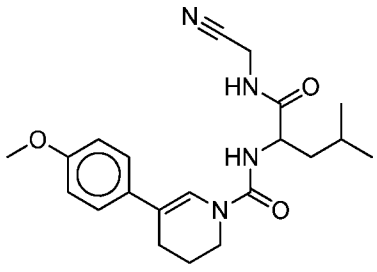


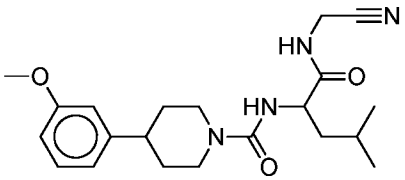


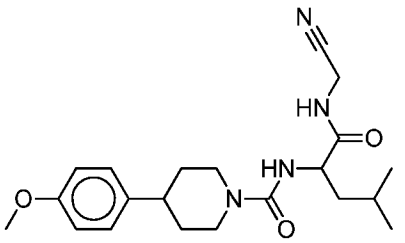


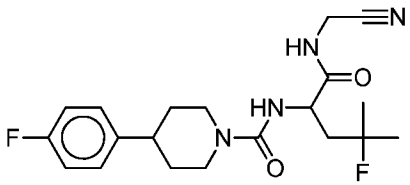


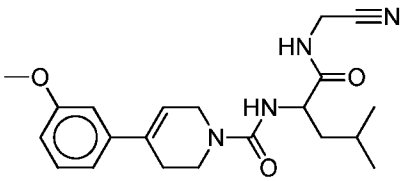


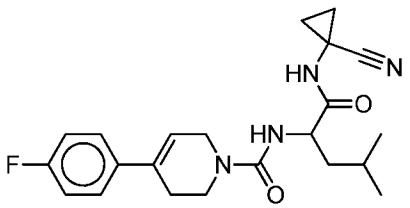


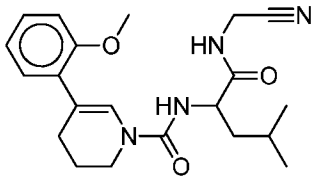


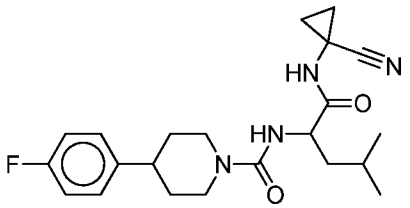


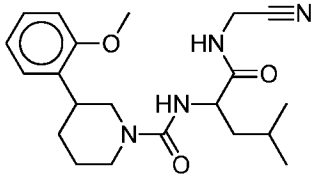


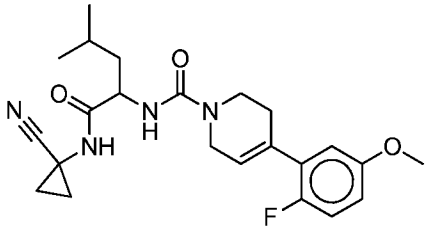


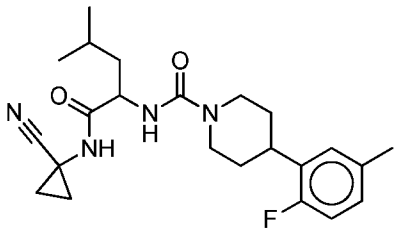


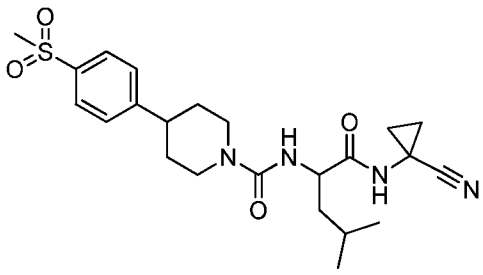


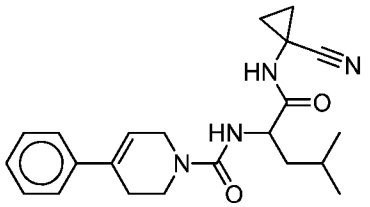


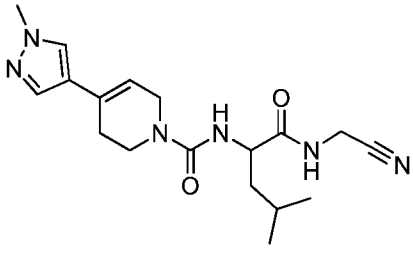


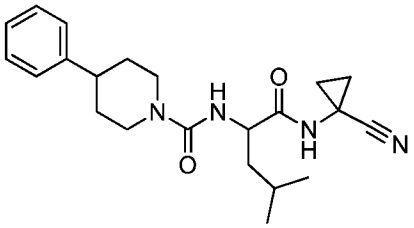


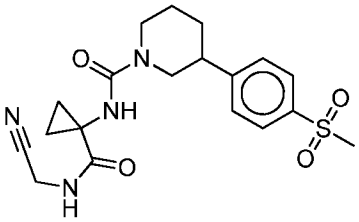


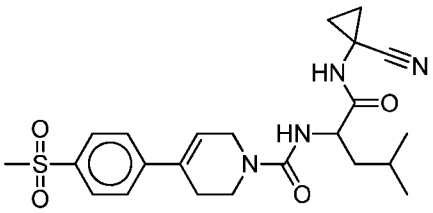


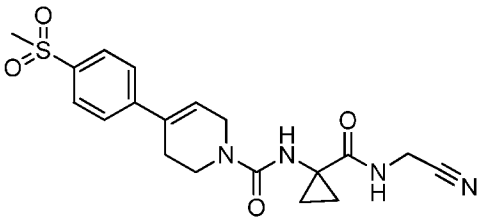


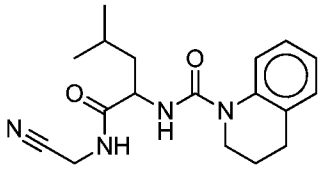


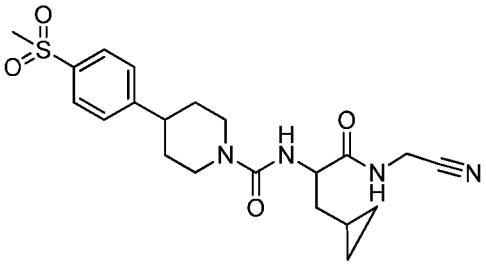


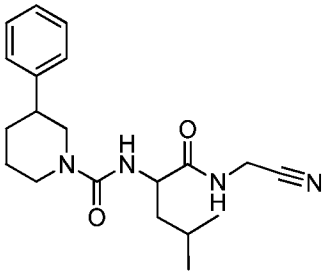


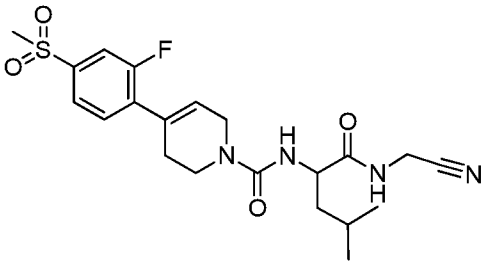


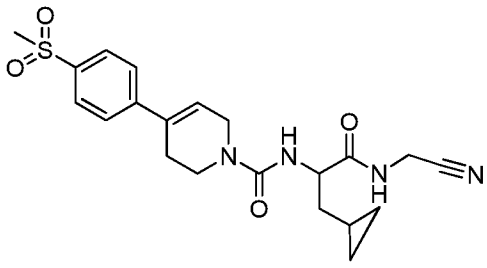


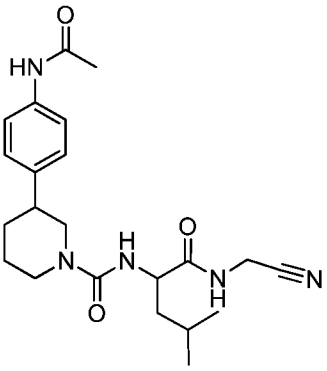


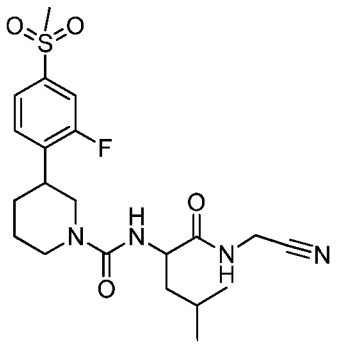


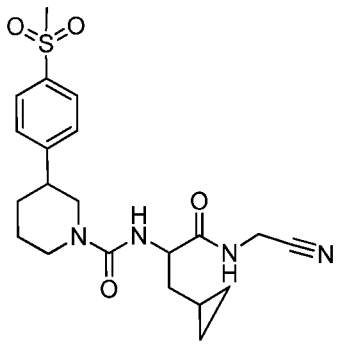


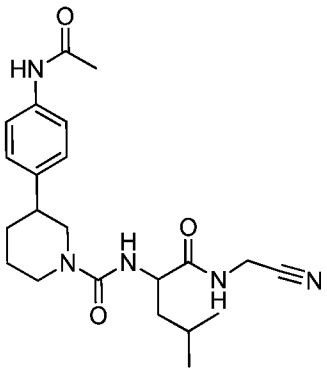


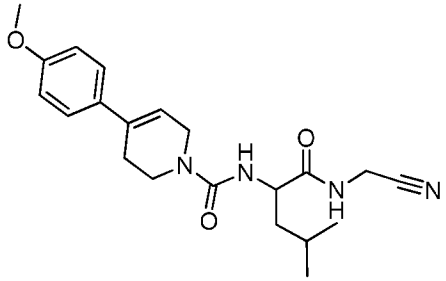


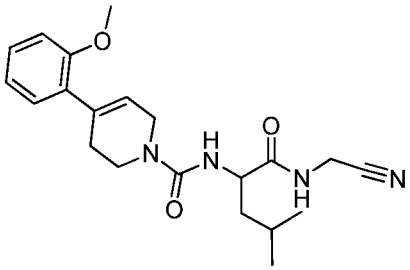


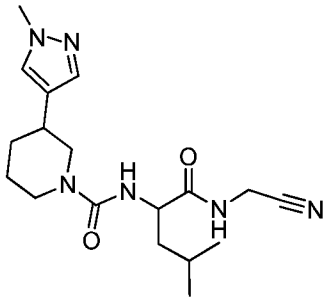


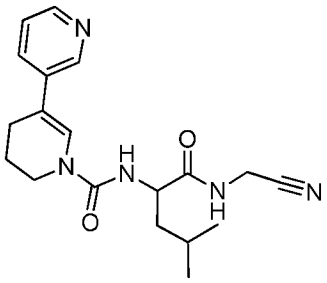


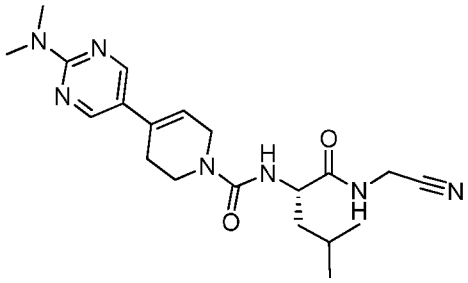


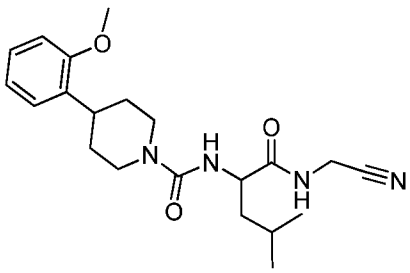


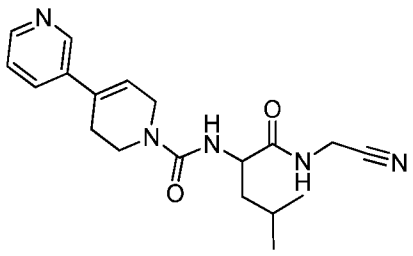


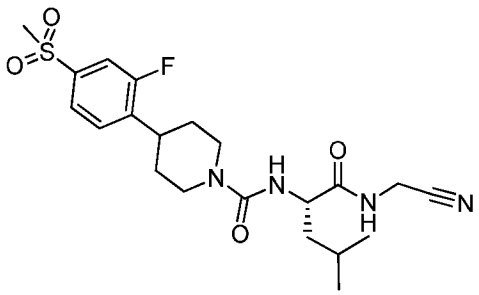


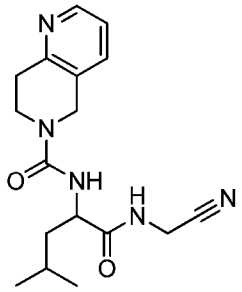


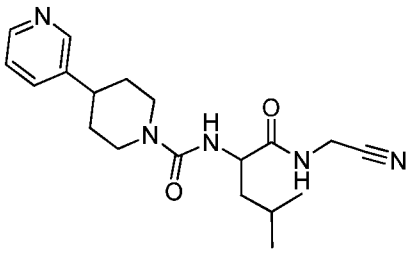


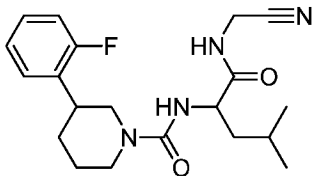


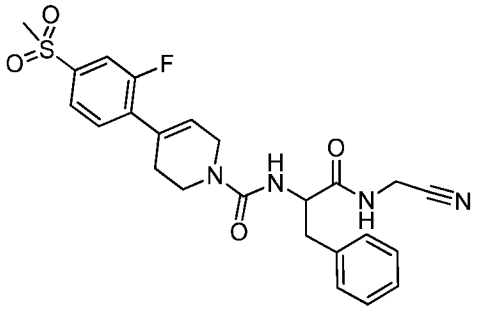


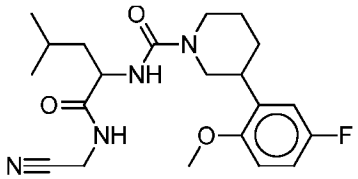


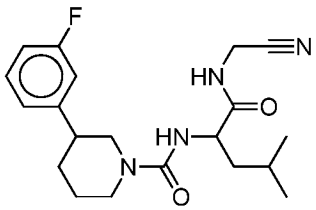


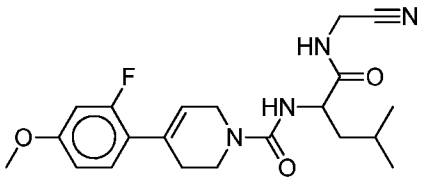


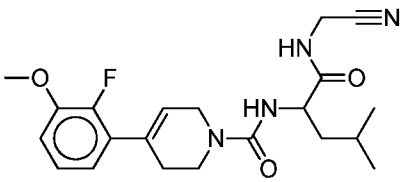


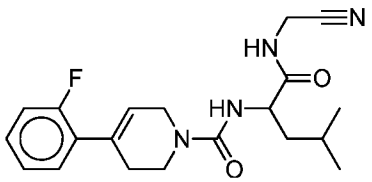


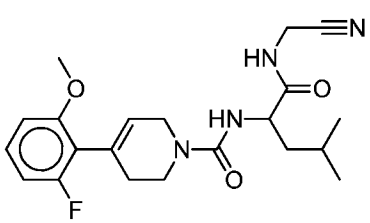


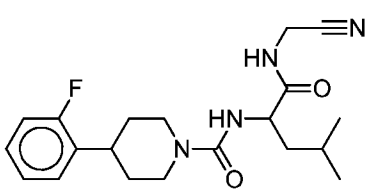


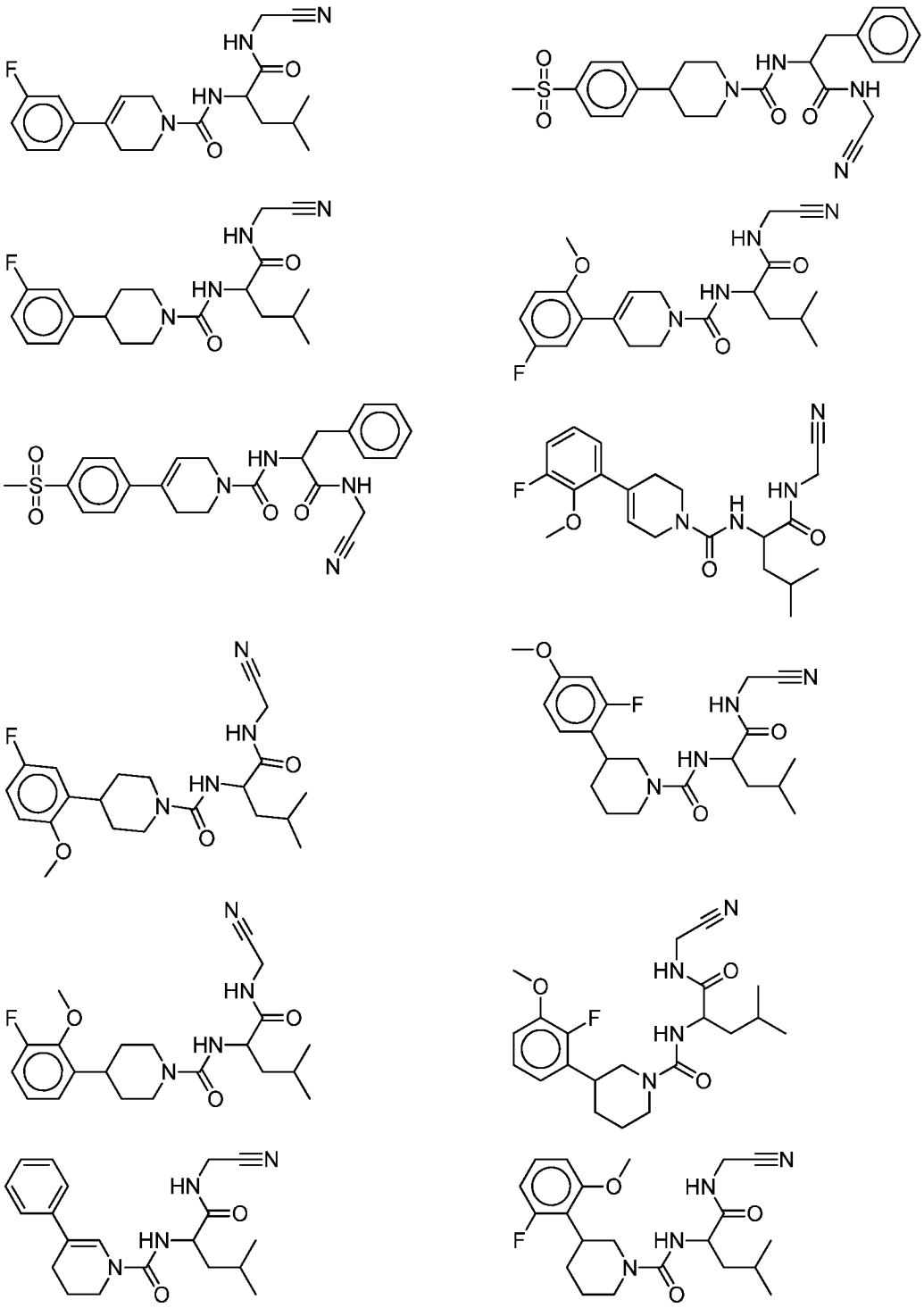












or a pharmaceutically acceptable salt thereof.

The compounds of the invention are inhibitors of cathepsin K and therefore have the ability to inhibit these enzymes. The ability to inhibit the enzymes may be a result of the compounds acting directly and solely on the enzyme to modulate/potentiate biological activity. However, it is understood that the compounds may also act at least partially on other factors associated with the activity of the enzyme.

The inhibition of cathepsin K may be carried out in any of a number of ways known in the art. For example if inhibition *in vitro* is desired an appropriate amount of the compound may be added to a solution containing the cathepsin K. In circumstances where it is desired to inhibit cathepsin K in a mammal, the inhibition of the cathepsin K typically involves administering the compound to a mammal containing the cathepsin K.

In a further aspect the present invention provides a method of prevention or treatment of a condition in a mammal, the method comprising administering an effective amount of a compound of the invention. In one embodiment the condition is a condition that can be treated by inhibition of cathepsin K.

In yet an even further aspect the invention provides the use of a compound of the invention in the preparation of a medicament for the treatment of a condition in a mammal. In one embodiment the condition is a condition that can be treated by inhibition of cathepsin K.

In yet an even further aspect the invention provides the use of a compound of the invention in the treatment of a condition in a mammal. In one embodiment the condition is a condition that can be treated by inhibition of cathepsin K.

In some embodiments the condition is selected from the group consisting 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, metastatic bone disease, hypercalcemia of malignancy, and multiple myeloma.

In some embodiments the condition is bone disease. In some embodiments the condition is osteoporosis.

Administration of compounds within Formula (I) to humans can be by any of the accepted modes for enteral administration such as oral or rectal, or by parenteral administration such as subcutaneous, intramuscular, intravenous and intradermal routes. Injection can be bolus or via constant or intermittent infusion. The active compound is typically included in a pharmaceutically acceptable carrier or diluent and in an amount sufficient to deliver to the patient a therapeutically effective dose.

In using the compounds of the invention they can be administered in any form or mode which makes the compound bioavailable. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the condition to be treated, the stage of the condition to be treated and other relevant circumstances. We refer the reader to Remingtons Pharmaceutical Sciences, 19th edition, Mack Publishing Co. (1995) for further information.

The compounds of the present invention can be administered alone or in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier, diluent or excipient. The compounds of the invention, while effective themselves, are typically formulated and administered in the form of their pharmaceutically acceptable salts as these forms are typically more stable, more easily crystallised and have increased solubility.

The compounds are, however, typically used in the form of pharmaceutical compositions which are formulated depending on the desired mode of administration. As such in some embodiments the present invention provides a pharmaceutical composition including a compound of Formula (I) and a pharmaceutically acceptable carrier, diluent or excipient. The compositions are prepared in manners well known in the art.

The invention in other embodiments provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. In such a pack or kit can be found a container having a unit dosage of the agent(s). The kits can include a composition comprising an effective agent either as concentrates (including lyophilized compositions), which can be diluted further prior to use or they can be provided at the concentration of use, where the vials may include one or more

dosages. Conveniently, in the kits, single dosages can be provided in sterile vials so that the physician can employ the vials directly, where the vials will have the desired amount and concentration of agent(s). Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The compounds of the invention may be used or administered in combination with one or more additional drug(s) for the treatment of the disorder/diseases mentioned. The components can be administered in the same formulation or in separate formulations. If administered in separate formulations the compounds of the invention may be administered sequentially or simultaneously with the other drug(s).

In addition to being able to be administered in combination with one or more additional drugs, the compounds of the invention may be used in a combination therapy. When this is done the compounds are typically administered in combination with each other. Thus one or more of the compounds of the invention may be administered either simultaneously (as a combined preparation) or sequentially in order to achieve a desired effect. This is especially desirable where the therapeutic profile of each compound is different such that the combined effect of the two drugs provides an improved therapeutic result.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of micro-organisms may be

ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminium monostearate and gelatin.

If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Dosage forms for topical administration of a compound of this invention include powders, patches, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required.

The amount of compound administered will preferably treat and reduce or alleviate the condition. A therapeutically effective amount can be readily determined by an attending diagnostician by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount a number of factors are to be considered including but not limited to, the species of animal, its size, age and general health, the specific condition involved, the severity of the condition, the response of the patient to treatment, the particular compound administered, the mode of administration, the bioavailability of the preparation administered, the dose regime selected, the use of other medications and other relevant circumstances.

A preferred dosage will be a range from about 0.01 to 300 mg per kilogram of body weight per day. A more preferred dosage will be in the range from 0.1 to 100 mg per kilogram of body weight per day, more preferably from 0.2 to 80 mg per kilogram of body weight per day, even more preferably 0.2 to 50 mg per kilogram of body weight per day. A suitable dose can be administered in multiple sub-doses per day.

SYNTHESIS OF COMPOUNDS OF THE INVENTION

The agents of the various embodiments may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available. The preparation of particular compounds of the embodiments is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other agents of the various embodiments. For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g. by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. A list of suitable protecting groups in organic synthesis can be found in T.W. Greene's Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, 1991. Alternatively, other reactions disclosed herein or known in

the art will be recognized as having applicability for preparing other compounds of the various embodiments.

Reagents useful for synthesizing compounds may be obtained or prepared according to techniques known in the art.

The symbols, abbreviations and conventions in the processes, schemes, and examples are consistent with those used in the contemporary scientific literature. Specifically but not meant as limiting, the following abbreviations may be used in the examples and throughout the specification.

- g (grams)
- L (litres)
- Hz (Hertz)
- mol (moles)
- RT (room temperature)
- min (minutes)
- MeOH (methanol)
- $CHCl_3$ (chloroform)
- DCM (dichloromethane)
- DMSO (dimethylsulfoxide)
- EtOAc (ethyl acetate)
- mg (milligrams)
- mL (millilitres)
- psi (pounds per square inch)
- mM (millimolar)
- MHz (megahertz)
- h (hours)
- TLC (thin layer chromatography)
- EtOH (ethanol)
- $CDCl_3$ (deuterated chloroform)
- HCl (hydrochloric acid)

- DMF (N, N-dimethylformamide)
- THF (tetrahydro furan)
- K_2CO_3 (potassium carbonate)
- Na_2SO_4 (sodium sulfate)
- RM (Reaction Mixture)
- HATU (O-(7-Aza-1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate)
- DMF (dimethylformamide)
- DIPEA (diisopropyl ethyl amine)
- PyBOP (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate)
- TEA (triethylamine)

Unless otherwise indicated, all temperatures are expressed in °C (degree centigrade). All reactions conducted at room temperature unless otherwise mentioned.

All the solvents and reagents used are commercially available and purchased from Sigma Aldrich, Fluka, Acros, Spectrochem, Alfa Aesar, Avra, Qualigens, Merck, Rankem and Leonid Chemicals.

^1H NMR spectra were recorded on a Bruker AV 300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

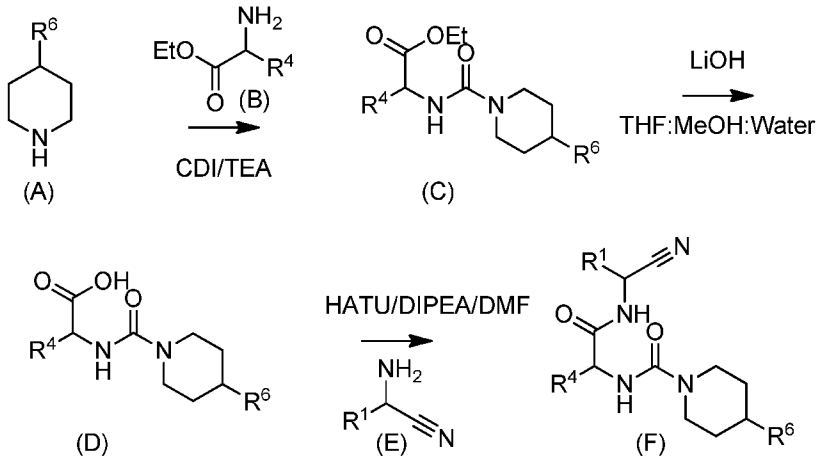
Mass spectra were obtained on single quadruple 6120 LCMS from Agilent technologies, using either atmospheric chemical ionization (APCI) or Electrospray ionization (ESI) or in the combination of these two sources.

All samples were run on SHIMADZU system with an LC-20 AD pump, SPD-M20A diode array detector, SIL-20A auto sampler.

SYNTHETIC SCHEMES

As stated above there are a number of ways in which the compounds of the invention can be synthesized as would be appreciated by a person skilled in the art. Nevertheless we provide a reaction scheme for making the certain compounds of the invention in Scheme 1.

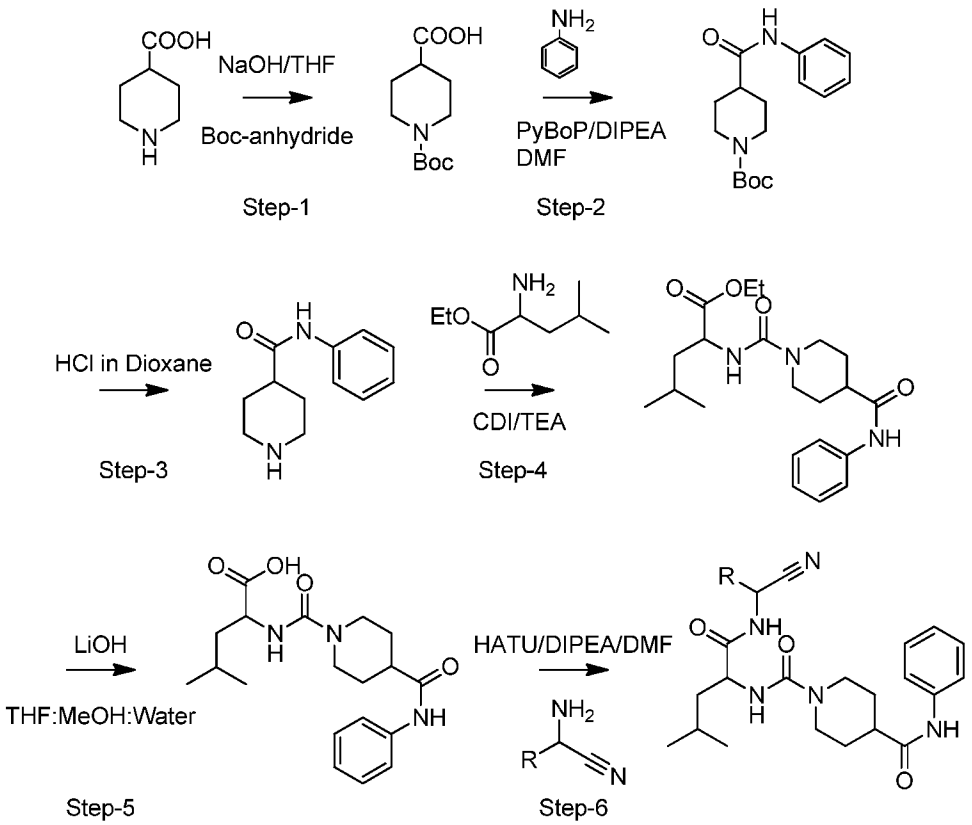
Scheme1



In general, the scheme progresses via reaction of an appropriately substituted piperidine (A) with an appropriately substituted leucine ester (B) in a coupling reaction to provide intermediate (C). The ester protecting group is removed to produce intermediate (D) which is then reacted with an appropriately substituted amino nitrile (E) to form the desired compound (F). A skilled worker would readily appreciate that minor modifications to the starting materials or the amino nitrile would result in the formation of compounds of the invention with different substitution patterns. Accordingly a skilled worker would be able to make minor modifications to this disclosed experimental route to arrive at the compounds of the invention disclosed herein.

By way of exemplification we provide actual reaction conditions for one such transformation.

Scheme 2



Step 1: To a 250 mL single neck round-bottomed flask isonepicotic acid (2.0 g, 15.48 mmol), THF (40 mL), 1N NaOH (40 mL) were stirred under nitrogen. To the turbid solution was added Boc anhydride (4.05 g, 18.58 mmol). Stirring was continued for 20 hours. The completion of the reaction was confirmed by TLC. The reaction mixture was cooled to 0-5 °C and pH of the reaction mixture adjusted to 5.5-6 using 1N HCl. Organics were distilled off from the reaction mixture to get a white precipitate, which was filtered and washed well with water. The white solid was dried under vacuum to get 1.5 g (43%) of the required material which was taken without further purification.

Step 2: To a 50 mL single neck round-bottomed flask N-Boc isonepocotic acid (1 g, 4.36 mmol), aniline(0.52 mL, 5.67 mmol), PyBOP (3.17 g, 6.11 mmol) and DMF (150 mL) were added and stirred well. After the formation of a clear solution, DIPEA (1.52 mL, 8.72 mmol) was added and the reaction was stirred at 20 to 30 °C for 20 h. The progress of the reaction and completion was confirmed by TLC. Quenched the reaction mixture with 50 mL of cold water (slow addition), under stirring. The aqueous layer was extracted with EtOAc (3x 30 mL) and washed

the EtOAc layer with water (1x 50 mL). Organic layer was separated, dried over anhydrous sodium sulfate and concentrated the organic layer to get 2.8 g of crude product as dense light brown semi solid.

The crude material was adsorbed on silica and purified using flash chromatography, to get 1.05 g (79%) of the desired product.

Step 3: To a 50 mL single neck round-bottomed flask containing (1 g, 3.286 mmol) the material from step 2) at 5-10 ^{0}C, was added 1,4-dioxane (25 mL), under nitrogen and started stirring. Hydrochloric acid in dioxane (3.0 g, 16.43 mmol) was added drop wise so that the temperature does not raise above 5-10 °C. After complete addition, the contents were stirred and allowed to attain room temperature slowly, during which time solid formation was observed. The reaction was checked for its progress by LCMS and found to be complete. The organics were distilled off and the residual material was taken in dichloromethane and stirred well, during which time some solid started to separate out. This was filtered off and the dichloromethane layer was dried and evaporated under vacuum to get 0.402 g (96%) of **N-phenylpiperidine-4-carboxamide** as off-white solid, which was confirmed by ^{1}H NMR.

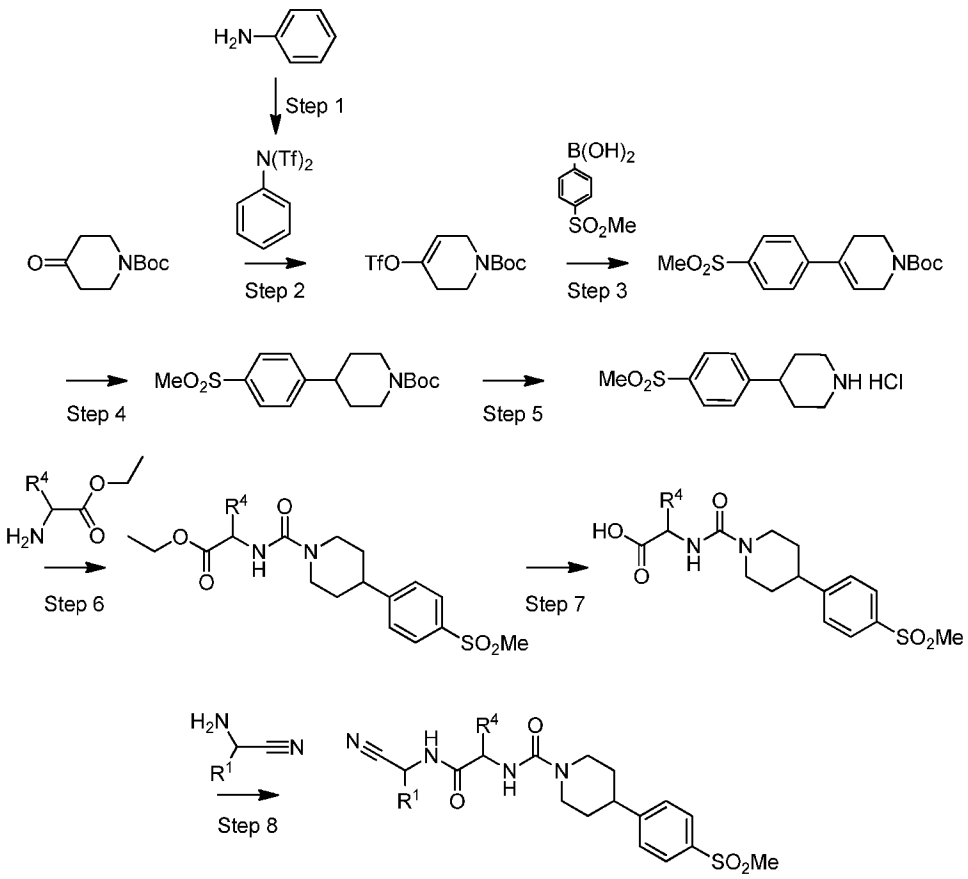
Step 4: To a 25 mL single necked round-bottomed flask containing carbonyldiimidazole (81 mg, 0.49 mmol) in 10 mL of anhydrous THF, under nitrogen was added L- Luecine-ethyl ester HCl (106 mg, 0.54 mmol), 0.12 mL of TEA. The mixture was stir at 20-30 °C for 3 hours. A solution of 100 mg of N-phenylpiperidine-4-carboxamide in 0.1 mL of TEA added and the contents were stirred for 15 hours. The reaction was complete as evident by TLC and LCMS. The reaction mixture was quenched with 10 mL of water and stirred for 30 mins. The aqueous layer was separated and extracted once with EtOAc. The organic layer was washed once with water and the organics were combined, dried over anhydrous Na_2SO_4. The volatiles were removed under vacuum and the crude material was checked for ^{1}H NMR, which confirmed the product. This material [0.150 g, 93% of **ethyl 4-methyl-2-(4-(phenylcarbamoyl)piperidine-1-carboxamido)pentanoate]** was taken directly without further purification.

Step 5: To a 50 mL round-bottomed flask containing ethyl 4-methyl-2-(4-(phenylcarbamoyl)piperidine-1-carboxamido)pentanoate(0.150g), in 5 mL THF, 5 mL Methanol and 2.5 mL of water at room temperature was added LiOH (27.7 mg, 1.15 mmol). The contents

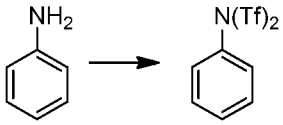
were stirred at this temperature for 6 h. The reaction was complete which was confirmed by LCMS and TLC. The contents were concentrated to dryness and the residual material was taken in 20 mL of water. The pH of the residual material was adjusted to 3 using 1N HCl. The aqueous layer was transferred into the separating funnel and extracted with DCM (20 mL x 2). The organic layer was separated washed once with water, dried over anhydrous Na_2SO_4, evaporation of the solvents afforded 0.130 g (93%) of **4-methyl-2-(4-(phenylcarbamoyl)piperidine-1-carboxamido)pentanoic acid**, which was directly used up without further purification.

Step 6: To a 8 mL reaction vial with a septum, containing 4-methyl-2-(4-(phenylcarbamoyl)piperidine-1-carboxamido)pentanoic acid (0.065 g, 0.23 mmol), was added corresponding aminoacetonitrile HCl (32 mg, 0.34 mmol), HATU (96 mg, 0.25 mmol) and DMF (1.5 mL). The contents were stirred were stirred for 5 mins. After clear solution was observed, DIPEA (0.08 mL, 0.46 mmol) was added. The reaction was stirred for 20 h at 20-30 °C. The reaction was complete, as observed by LCMS/TLC analysis. To the reaction mixture was added 5 mL of cold water and stirred the reaction mix for 20 mins. The aqueous layer was extracted with EtOAc (2x 20 mL) and the EtOAc layer separated, washed once with water (10 mL). EtOAc layer was dried over anhydrous Na_2SO_4, volatiles were distilled off to get 75 mg of crude material as dense light brown liquid. This crude material was purified by RP HPLC to get 0.04 g (56%) of **N^1-(1-(cyanomethylamino)-4-methyl-1-oxopentan-2-yl)-N4-phenylpiperidine-1,4-dicarboxamide** as white solid with 99% pure by HPLC.

Scheme 3



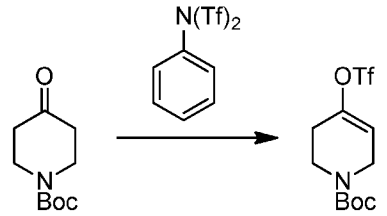
Scheme 3a



Step 1: To a solution of aniline (1.0 g,1.0 eq) and triethylamine (2.99 mL, 2.0 eq) in methylene chloride (100 mL) at -80 ^{0}C, under N_2 was added trifluoromethane sulfonic anhydride (3.61 mL, 2.0 eq) in 25 mL of methylene chloride drop wise using a pressure equalising dropping funnel over 15 mins. The contents were stirred at this temperature 15 mins, and then slowly allowed to attain room temperature, stirred for 2 h at RT. TLC showed the complete consumption of starting material. The reaction mixture was diluted with ice water (200 mL). After 10 min organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 25 mL). The pooled organic layers were washed with saturated sodium bicarbonate solution and once with water. Finally dried and concentrated to give 4 g of pale pinkish brown crystalline solid as crude. The crude was dissolved in methanol (40 mL), added water (120 mL) slowly

with stirring. The formed precipitate was filtered and washed with water, dried under vacuum to get 2.7 g (yield: 64.55%) of **1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide** as pale pink solid.

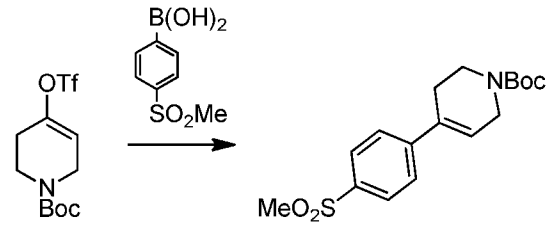
Scheme 3b



Step 2: Lithium diisopropylamide solution was prepared by adding n-butyllithium (1.1 eq) to the -70 ºC cold solution of diisopropylamine (1.3 eq) dissolved in THF (15 mL) under nitrogen atmosphere and by stirring the resultant pale yellow solution at -20 °C for one hour.

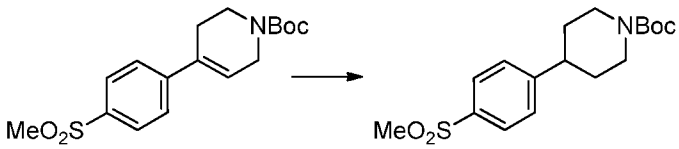
To a solution of lithium diisopropylamide at -70 ºC, tert-butyl 4-hydroxypiperidine-1-carboxylate(1.5 g, 1.0 eq) dissolved in THF (10 mL) was added drop wise over 10minutes. The resultant yellow solution was stirred for one hour at the same temperature. 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl) methanesulfonamide (2.82 g, 1.05 eq) dissolved in THF (10 mL) was added drop wise over 5 minutes. Finally the resultant brown solution was allowed to stir for 18 hours. TLC showed the complete consumption of starting material. The reaction mixture was cooled to -20 °C and then added saturated ammonium chloride solution drop wise. The resultant biphasic layer was allowed to stir at room temperature for 10 minutes then the organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 20 mL). The pooled organic layers were washed with brine, dried and concentrated to get 2.5 g of pale yellow oil. The crude material was purified on basic alumina column, using ethyl acetate and petroleum ether as eluents. Pure desired fractions were collected and concentrated to get 1.6 g (yield: 63.74%) of **tert-butyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate** as pale yellow oil.

Scheme 3c



Step 3: To a pale yellow solution of 4-(methylsulfonyl)phenylboronic acid (0.8 g,1.0 eq) and *tert*-butyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (1.58 g, 1.2 eq) in DMF (15 mL) was added caesium carbonate (2.606 g, 1.5 eq). The resultant pale yellow suspension was degassed and stirred under nitrogen atmosphere for 10 minutes. To this mixture was added [1,1'-bis[(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane] (0.163 g,0.05 eq). The resultant red colour suspension was left for stirring for 6 h under nitrogen gas atmosphere at room temperature, during which time the contents became dark coloured. TLC had shown that complete consumption of starting materials and formation of new spot. The reaction mixture was diluted with ethyl acetate filtered on celite and the celite bed was washed twice with ethyl acetate. The filtrate was concentrated to dryness to get 1.7 g of black oil. This crude material was purified on a silica column hexane and ethyl acetate as eluents. The pure desired fractions were collected and concentrated under reduced pressure to get 1.1 g (yield: 81.6%) of **tert-butyl 4-(4-(methylsulfonyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate** as pale yellow solid.

Scheme 3d



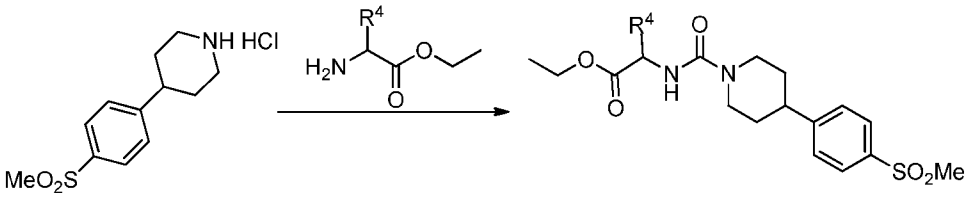
Step 4: To a solution of tert-butyl 4-(4-(methylsulfonyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (1.1 g,1.0 eq) in a mixture of methanol and ethyl acetate (25 mL, 3:1) was added 10% palladium on carbon (0.224 g, 0.65 eq) under nitrogen atmosphere. The resultant heterogeneous solution was stirred with bubbling hydrogen gas through the mixture using a H_2 balloon, for 1h at room temperature. TLC showed that complete consumption of starting material. The reaction mixture was filtered over a celite bed; the bed was washed with methanol (2 x 10 mL). The filtrate was concentrated to dryness to get 0.92 g (yield: 83.25%) of **tert-butyl**

4-(4-(methylsulfonyl)phenyl)piperidine-1-carboxylate as off white solid. This material was not further purified.

Scheme 3e

Step 5: To an ice cold solution of tert-butyl 4-(4-(methylsulfonyl)phenyl)piperidine-1-carboxylate (0.9 g, 1.0 eq) in 1,4-dioxane (3 mL) was added a solution of HCl in dioxane (4M)(6.64 mL, 10 eq) drop wise under nitrogen gas atmosphere. The resultant pale yellow solution was allowed to stir at room temperature for 2 hours. TLC showed that complete consumption of starting material. The volatiles were removed from the reaction mass and the yellow solid obtained was washed with methylene chloride (3 x 5 mL) to get 0.7 g (yield 95.60%) of **4-(4-(methylsulfonyl)phenyl)piperidine hydrochloride** as off white solid.

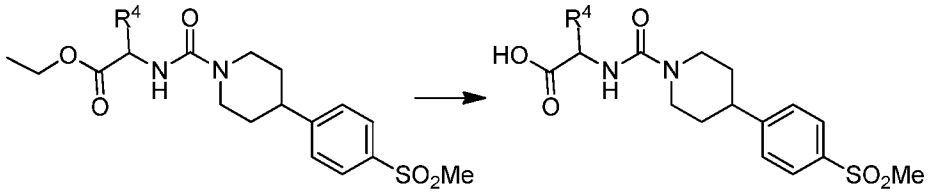
Scheme 3f



Step 6: To a 0 °C cold solution of triphosgene (1.1 eq) in methylene chloride was added a mixture of 4-[4-(methylsulfonyl)phenyl)]piperidine hydrochloride (1.0 eq) and triethylamine (1.5 eq) dissolved in methylene chloride (5 mL), drop wise under nitrogen atmosphere. The resultant pale yellow solution was stirred for one hour at 0 °C to 5 °C. Finally a mixture of amino acid ester hydrochloride (1.2 eq) and triethylamine (1.5 eq) dissolved in methylene chloride (5 mL) was added drop wise. The resultant pale yellow turbid reaction mixture was allowed to stir at room temperature for 2 hours. TLC showed the complete consumption of starting material. The reaction mixture was quenched with water and the organic layer was separated. The aqueous layer was extracted with methylene chloride. The combined organic layers were washed with saturated bicarbonate solution, water and then dried and concentrated to get crude material,

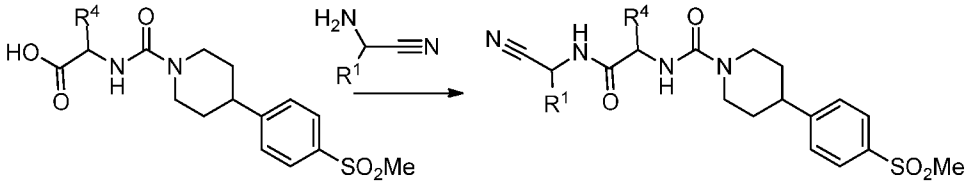
which was flash chromatographed to get the desired product in 85-93% yields based on the amino acid used.

Scheme 3g



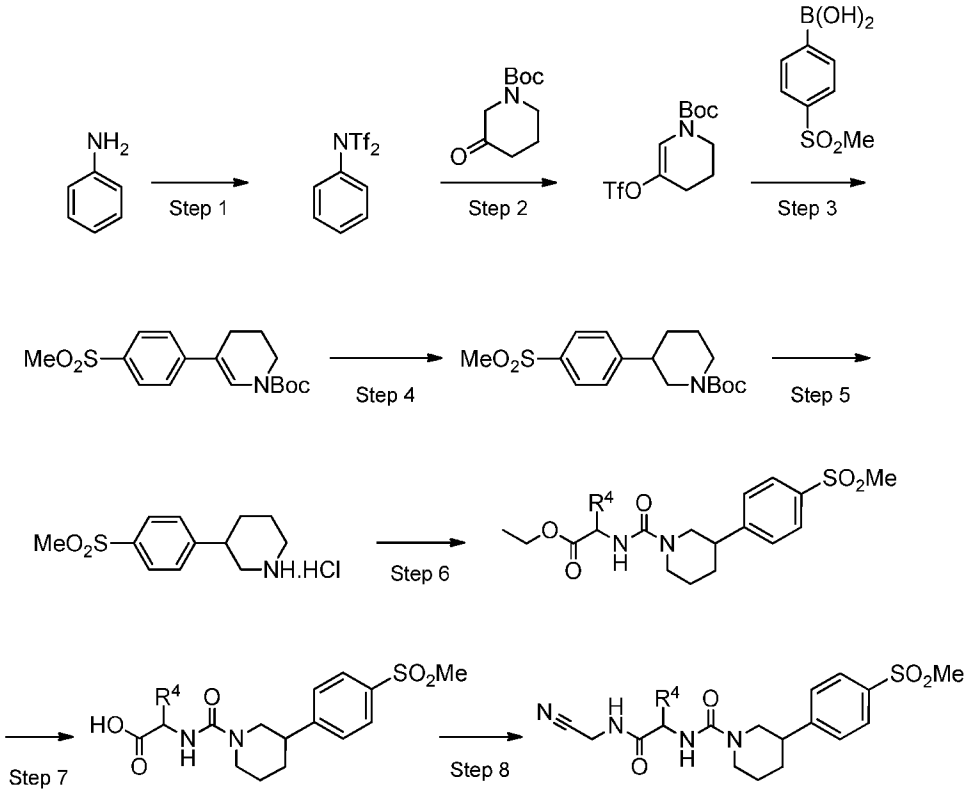
Step 7: To a pale yellow solution of ester (1 eq) in a mixture of THF (2.5 mL) and methanol (2.5 mL) was added aqueous lithium hydroxide monohydrate (2 M, 4 eq). The resultant yellow solution was stirred for 30 min at room temperature. TLC showed the complete consumption of starting material. The volatiles were removed from the reaction mixture and then diluted with water and washed with ethyl acetate and these washings are discarded. The aqueous layer was acidified with 1N HCl and the aqueous layer was extracted with methylene chloride. The pooled organic layers were washed with water and brine, dried and filtered to get the desired acid in 75-90% yields based on the side chain(R).

Scheme 3h



Step 8: To a pale brown solution of the acid (1.0 eq), aminoacetonitrile hydrochloride (1.5 eq) and PyBOP (1.1 eq) in DMF was added DIPEA (1.5 eq).The resultant pale yellow solution was stirred under nitrogen atmosphere at room temperature for 16 hours. TLC showed the complete consumption of starting material carboxylic acid. The reaction mixture was diluted with cold water (10 mL) and then ethyl acetate (5 mL) was added. The biphasic layer was stirred for 10 minutes and the ethyl acetate layer was separated. The aqueous phase was extracted with ethyl acetate (3 x 8 mL) and the pooled organic layers was washed with cold water (2 x 15 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to get yellow solid. The crude material was purified using reverse phase preparative HPLC to get desired products in 30-55% isolated yield.

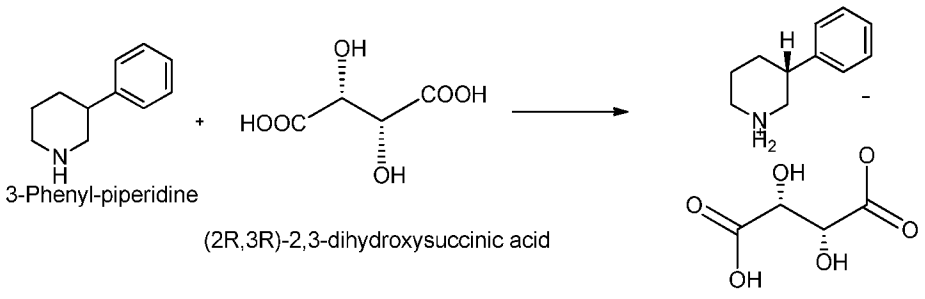
Scheme 4: Synthesis of Piperidine Ureas



The synthetic procedures for Steps 1 - 8 in Scheme 4 were identical with those described for Scheme 3, however the yields varied, and the over yield was lower than the yields in Scheme 3.

Chemical resolution of 3-Phenylpiperidine:

Synthesis of (R)-3-phenylpiperidine tartarate salt:



In a 100 mL two neck RB flask ethanol (30 mL), racemic 3-Phenyl piperidine (0.8 g, 4.965 mmol) heating to 70-75 °C. L-(+)-Tartaric acid (4.965 mmol) in 1 mL of water and 1 mL of

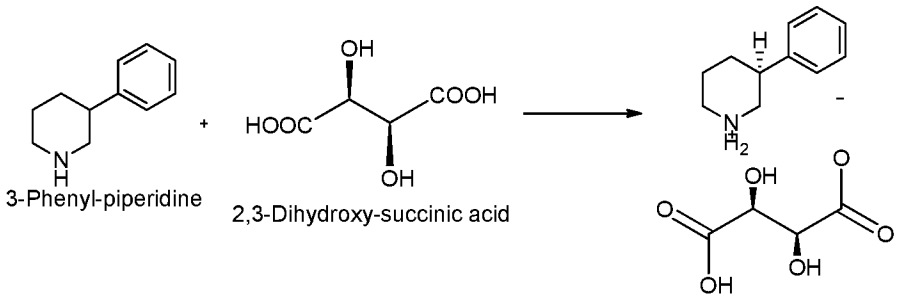
ethanol added to reaction mixture, and stirred for 10 mins. Heating was stopped and allowed the reaction mixture to cool to 20-30 °C. During this time, the material started to precipitated at around 45-50 °C. Stirring was continued for additional 2 h at 20-30 °C. The precipate was filtered off, washed with ethanol. The solid was dried for 2 h under vacuum at 50 °C, upon complete drying 0.6 g of pure material was obtained.

Sp Rotation: +306°; Chiral purity: 87.12% by chiral HPLC analysis on Chiracel OC column.

Melting Point: 142-147 °C

The Mother liquors (MLR) containing major of S-Isomer, from the above experiment was used to recover the pure isomer. The volatiles were evaporated from the MLR completely and the residual material was diluted with 10 mL of water. Basified with 1N NaOH (3 mL) and extracted the free base with ethyl acetate (25 mL). The organics were separated and concentrated under vacuum, dried for 1h, to recover 0.3 g of oil. This was used to make the tartarate salt of the S-Isomer, suing D-(-)-tartaric acid in the same procedure.

Synthesis of (S)-3-phenylpiperidine tartarate salt:



3-Carboxy-2,3-dihydroxy-propionate3-phenyl-piperidinium

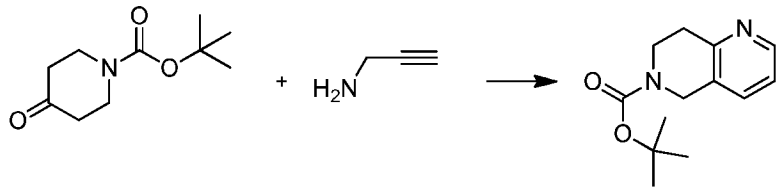
In a 100 mL two neck RB flask ethanol (20 mL), 3-Phenyl piperidine (0.3 g, 1.86 mmol), recovered from the above reaction, heating to 70-75 °C. D-(-)-Tartaric acid (1.86 mmol) in 1 mL of water and 1 mL of ethanol added to reaction mixture, and stirred for 10 mins. Heating was stopped and allowed the reaction mixture to cool to 20-30 °C. During this time, the material started to precipitated at around 45-50 °C. Stirring was continued for additional 2 h at 20-30 °C. The precipitate was filtered off, washed with ethanol. The solid was dried for 2 h under vacuum at 50 °C, upon complete drying 0.35 g of pure material was obtained.

Sp Rotation: -512°; Chiral purity: 81% by chiral HPLC analysis on Chiracel OC column.

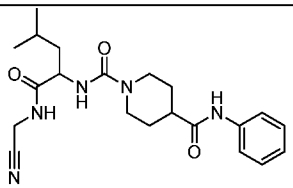
Melting Point: 150-153 °C

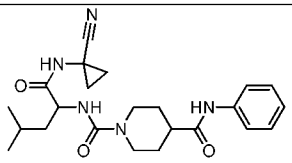
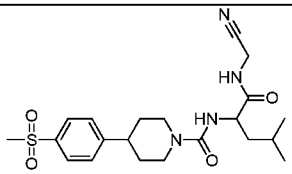
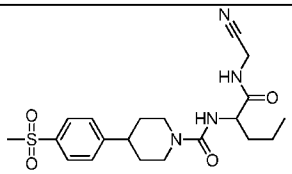
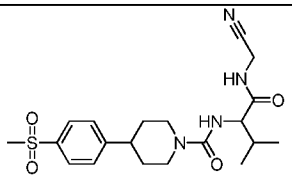
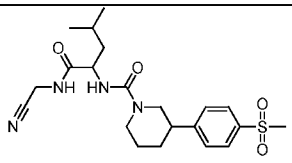
The above schemes were used to synthesis Compounds 112,113, 119 and 120.

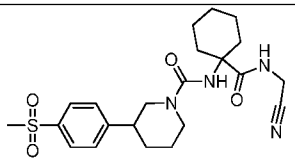
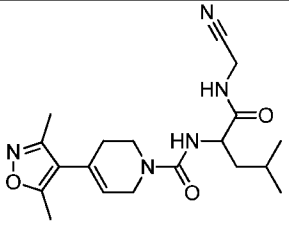
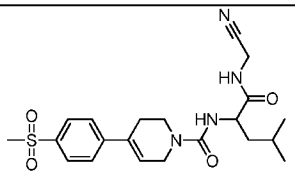
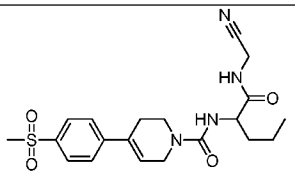
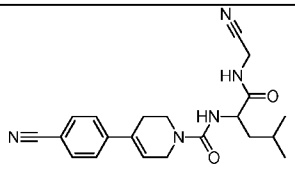
Synthesis of 7,8-Dihydro-5H-[1,6]naphthyridine-6-carboxylic acid tert-butyl ester

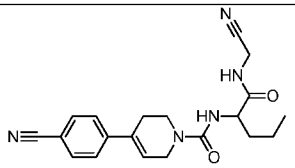
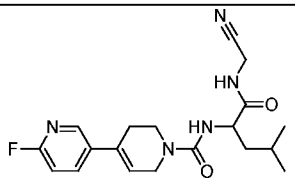
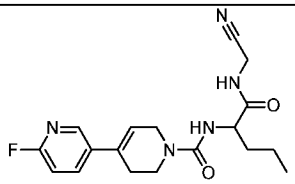
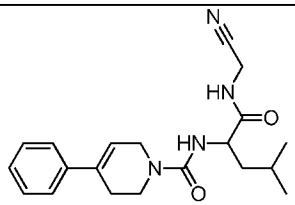
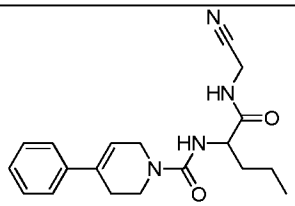


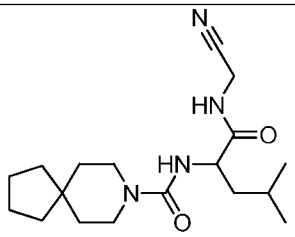
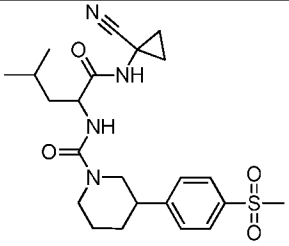
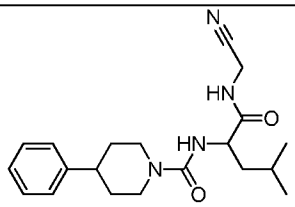
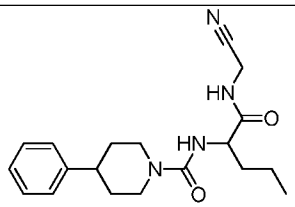
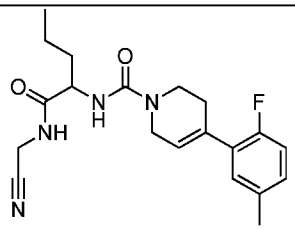
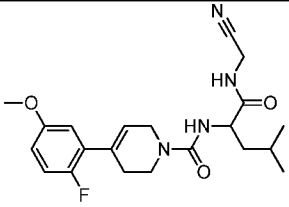
To a solution of 4-Oxo-piperidine-1-carboxylic acid tert-butyl ester(0.5g, 1.0eq) and Propargylamine(0.32mL, 2.05eq) in Ethanol(5mL) was added Sodium tetrachloroaurate(III) dihydrate(0.03g, 0.03eq). The resultant yellowish brown heterogeneous reaction mass was irradiated in Microwave at 100 °C for 1hr. The reaction mass was filtered on Celite and twice washed with Ethanol. The filtrate was concentrated to get brown oil as crude which on purification by flash chromatography gave 0.257g of **tert-butyl 7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate** as pale yellow oil. This material was used to synthesis of N-(cyanomethyl)-4-methyl-2-[(5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)amino]pentanamide after deprotection.

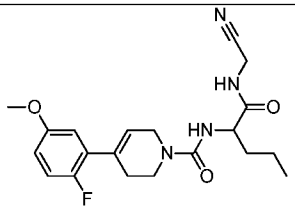
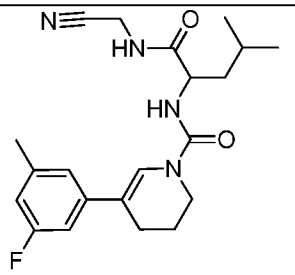
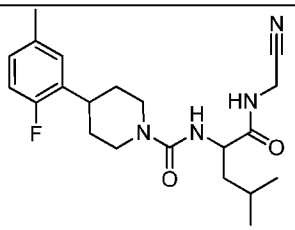
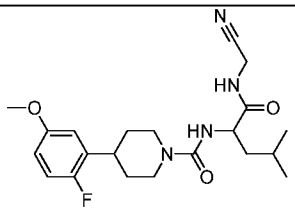
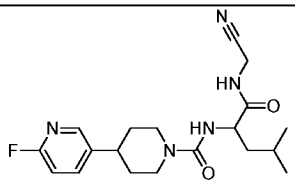
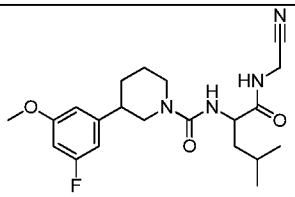
Sl No.	Name	1H NMR(300MHz, DMSO-d6, δ ppm)	Mass(ESI)m/z
1		0.87 (dd, J=13.53, 6.37 Hz, 6H), 1.31 - 1.66 (m, 5H), 1.75 (d, J=10.55 Hz, 2H), 2.61 - 2.83 (m, 2H), 3.98 -4.25 (m, 5H), 6.54 (d, J=8.07 Hz, 1H), 6.98 - 7.11 (m, 1H), 7.29 (t, J=7.84 Hz, 2H), 7.60 (d, J=7.98 Hz, 2H), 8.54 (t, J=5.69 Hz, 1H), 9.81 - 9.97(m, 1H).	400.35

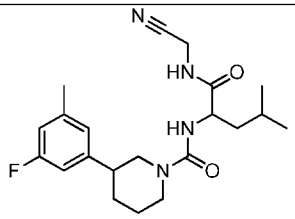
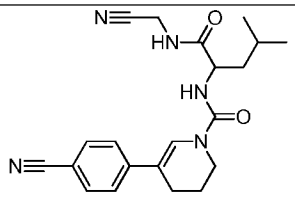
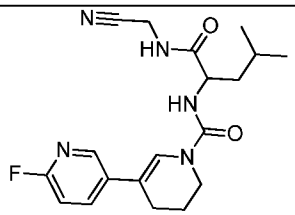
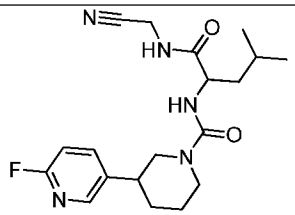
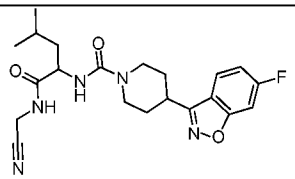
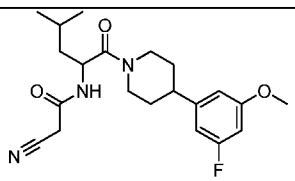
2		0.86 (dd, J=12.29, 6.51 Hz, 6H) 1.04 - 1.12 (m, 1H) 1.27 - 1.66 (m, 7H) 1.74 (d,J=11.92 Hz, 2H) 2.55 (br. s., 1H) 2.61 - 2.81 (m, 2H) 3.94 - 4.16 (m, 3H) 6.42 - 6.54 (m, 1 H) 6.96 - 7.09 (m, 1H) 7.29 (t, J=7.89 Hz, 2H) 7.60(d, J=7.70 Hz, 2H) 8.72 - 8.87 (m, 1H) 9.91 (s, 1H)	426.35
3		0.88 (dd, J=12.10,6.42 Hz, 6 H) 1.35 - 1.68 (m, 5H) 1.77 (d, J=11.92 Hz, 2H) 2.69 - 2.90 (3m, 3H) 3.20 (s, 3H) 4.10 - 4.23 (m, 5H) 6.57 (d, J=7.98 Hz, 1H) 7.53 (d, J=8.34 Hz, 2H) 7.86 (d, J=8.25 Hz, 2H) 8.55 (t, J=5.59 Hz, 1H)	435.25
4		0.87 (3 H, t, J=7.29 Hz, 3H) 1.17 - 1.42 (m, 2H) 1.46 - 1.65 (m,4H) 1.69 - 1.83 (m, 2H) 2.68 - 2.89 (m,3H) 3.20 (s,3H) 4.04 - 4.22 (m,5H) 6.55 (d, J=7.79 Hz,1H) 7.53 (d, J=8.34 Hz,2H) 7.86 (d, J=8.25 Hz,2H) 8.54 (t, J=5.59 Hz,1H)	421.25
5		0.87 (dd, J=9.58,6.74 Hz,6H) 1.41 - 1.60 (m,2H) 1.77 (d, J=11.37 Hz,2H) 1.92 - 2.08 (m,1H) 2.69 - 2.90 (m,3H) 3.20 (s,3H) 3.92 (t, J=8.25 Hz,1H) 4.10 - 4.24(m,4H) 6.41 (d, J=8.34 Hz,1H) 7.53 (d, J=8.34 Hz,2H) 7.85 (d, J=8.34 Hz,2H) 8.65 (t, J=5.59 Hz,1H)	421.25
6		0.78-0.94 (m, 7H) 1.29-1.75 (m, 7H), 1.91 (d, J=11.46 Hz, 1H), 2.59-2.89 (m, 4H), 3.20 (s, 3H), 3.98-4.24 (m, 5H), 6.60 (d, J=7.98 Hz, 1H), 7.57 (dd, J=3.99, 2H), 7.88 (d, J=8.25 Hz, 2H), 8.52 (q, J=5.32 Hz, 1H)	435.25

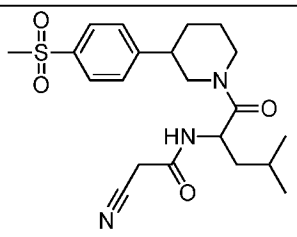
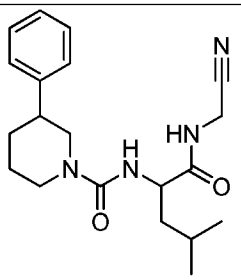
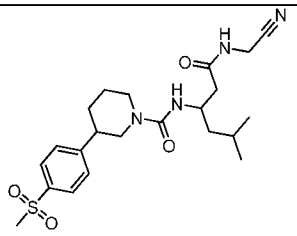
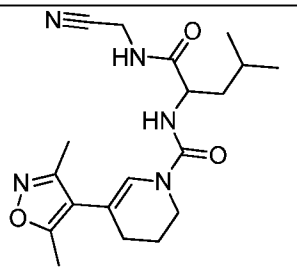
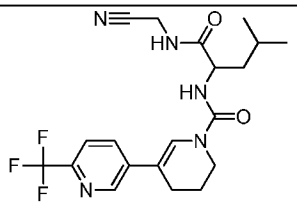
7		1.24 (br. s., 12H) 1.30-1.77 (m, 10H), 1.85-2.05 (m, 3H), 2.66-2.92 (m, 4H), 3.21 (s, 3H), 4.05 (d, J=5.69 Hz, 4H), 6.21 (s, 1H), 7.58 (d, J=8.07 Hz, 2H), 7.89 (d, J=8.16 Hz, 2H), 8.09 (t, J=5.46 Hz, 1H)	447.20
8		0.87 (dd, J=13.34, 6.37 Hz, 7 H) 1.37 - 1.49 (m, 1 H) 1.51 - 1.68 (m, 3 H) 2.18 (s, 3 H) 2.27 (br. s., 2 H)2.35 (s, 3 H) 3.47 - 3.58 (m, 2 H) 3.92 - 4.03 (m, 2 H) 4.11 (d, J=5.59 Hz, 2 H) 4.14 - 4.26 (m, 1 H) 5.74 (br. s., 1 H) 6.57 (d, J=7.70 Hz, 1 H) 8.57(t, J=5.46 Hz, 1 H).	374.15
9		0.87 (dd, J=14.03, 6.33 Hz, 6 H) 1.33 -1.52 (m, 1 H) 1.48 - 1.74 (m, 2 H) 3.22 (s, 3 H) 3.51 - 3.64 (m, 2 H) 3.97 - 4.28 (m, 5 H) 6.34 - 6.45 (m, 1 H) 6.51 - 6.67 (m, 1 H) 7.65 - 7.77 (m,2 H) 7.83 - 7.96 (m, 2 H) 8.50 - 8.64 (m, 1 H).	433.15
10		0.87 (t, J=7.29 Hz, 3 H) 1.18 - 1.43 (m,2 H) 1.47 - 1.72 (m, 2 H) 3.22 (s, 3 H) 3.50 - 3.64 (m, 2 H) 4.11 (s, 5 H) 6.33 - 6.48 (m, 1 H) 6.54 - 6.68 (m, 1 H) 7.65 - 7.78 (m, 2 H) 7.85 - 7.99(m, 2 H) 8.48 - 8.60 (m, 1 H).	419
11		0.87 (dd, J=14.35, 6.37 Hz, 7 H) 1.28 - 1.75 (m, 3 H) 1.36- 1.73 (m, 3 H) 3.50 - 3.65 (m, 2 H) 3.95 - 4.26(m, 5 H) 3.95 - 4.26 (m, 5 H) 5.66 - 5.73 (m, 1 H) 6.44 (br. s., 1 H) 6.55 - 6.72 (m, 1 H) 7.66 (d, J=8.44 Hz, 2 H) 7.75 - 7.93 (m, 2 H) 8.57 (t, J=5.55 Hz, 1 H)	379

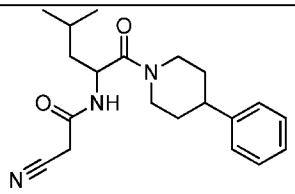
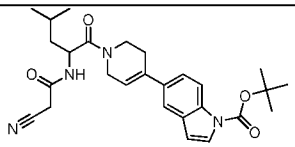
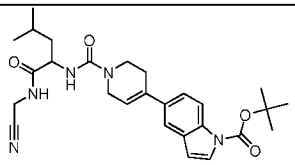
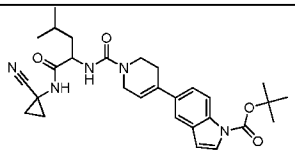
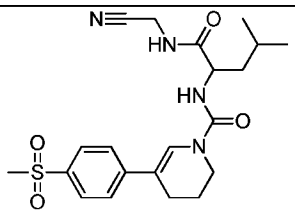
12		0.87 (dd, J=14.35, 6.37 Hz, 7 H) 1.28 - 1.75 (m, 3 H) 1.36- 1.73 (m, 3 H) 3.50 - 3.65 (m, 2 H) 3.95 - 4.26 (m, 5 H) 3.95 - 4.26 (m, 5 H) 5.66 - 5.73 (m, 1 H) 6.44 (br. s., 1 H) 6.55 - 6.72 (m, 1 H) 7.66 (d, J=8.44 Hz, 2 H) 7.75 - 7.93 (m, 2 H) 8.57 (t, J=5.55 Hz, 1 H).	365
13		0.74 - 1.00 (m, 1 H) 1.26 - 1.77 (m, 3 H) 3.43 - 3.71 (m, 2H) 3.88 - 4.31 (m, 4 H) 3.88 - 4.28 (m, 4 H) 6.30(br. s., 1 H) 6.53 - 6.74 (m, 1 H) 7.09 - 7.31 (m, 1 H) 8.09 (td, J=8.21, 2.57 Hz, 1 H) 8.27 - 8.42(m, 1 H) 8.57 (t, J=5.69 Hz, 1 H)	370
14		2.50 (t, J=7.24 Hz, 3 H) 2.81 - 3.04 (m,2 H) 3.25 (d, J=7.70 Hz, 2 H) 5.20 (d, J=4.95 Hz, 3 H) 5.58 - 5.82 (m, 5 H)7.93 (br. s., 1 H) 8.27 (d, J=7.89 Hz, 1 H) 8.81 (dd, J=8.44, 2.38 Hz, 1 H) 9.72(d, J=2.02 Hz, 1 H) 9.95 (br. s., 1 H) 10.19 - 10.31 (m,1H).	382.1(M+ Na)
15		2.43 - 2.55 (m, 6 H) 2.72 - 2.91 (m, 1 H) 3.04 - 3.24 (m, 1 H) 3.48 (d, J=4.49 Hz, 1 H) 5.02 (br. s., 4 H) 5.16 - 5.30 (m,2 H) 5.57 - 5.86 (m, 5 H) 7.84 (br. s., 1 H) 8.09 (d, J=8.25 Hz, 1 H) 8.87 - 9.17 (m, 5 H).	377.15(M +Na)
16		0.87 (t, J=7.29 Hz, 3 H) 1.18 - 1.44 (m,2 H) 1.54 - 1.70 (m, 2 H) 3.50 - 3.62 (m, 2 H) 3.89 - 4.22 (m, 5 H) 6.14 - 6.24(m, 1 H) 6.51 - 6.64 (m, 1 H) 7.18 - 7.54 (m, 5 H) 8.50 - 8.62 (m, 1 H)	363.25(M +Na)

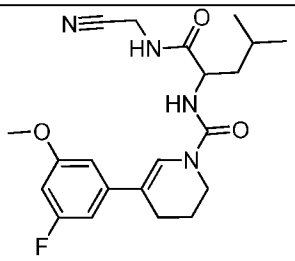
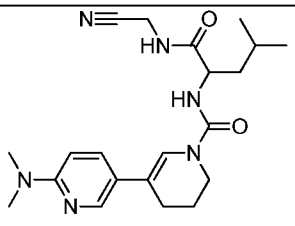
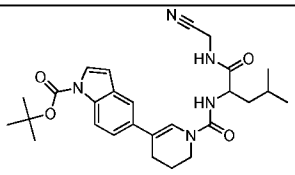
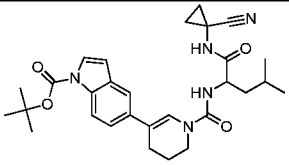
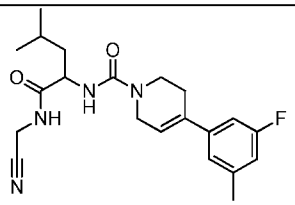
17		0.86 (dd, J=6.33, 14.03 Hz, 6H), 1.22-1.34 (m, 4H), 1.34-1.47 (m, 5H), 1.49-1.70 (m, 6H), 3.24-3.3 2 (m, 4H), 4.05-4.20 (m, 3H), 6.43 (d, J=7.98 Hz, 1H), 8.48 (t, J=5.50 Hz, 1H)	357.20(M +Na)
18		0.79 - 0.93 (m, 6 H), 0.99 - 1.13 (m, 2 H), 1.41 - 1.79 (m, 6 H), 1.91 (d, J = 10.27 Hz, 1 H), 2.55 (s, 1 H), 2.64 - 2.88 (m, 4 H), 3.21 (s, 3 H), 4.08 (d, J = 9.35 Hz, 3 H), 6.56 (d, J = 7.52 Hz, 1 H), 7.58 (dd, J = 8.12, 4.17 Hz, 2 H), 7.88 (d, J = 8.25 Hz, 2 H), 8.80 (br. s., 1 H)	483.25(M +Na)
19		0.88 (dd, J=13.34, 6.37 Hz, 6 H) 1.36 -1.80 (m, 7 H) 2.61 - 2.83 (m, 3 H) 4.00 - 4.23 (m, 4 H) 6.48 - 6.60 (m, 1 H)7.14 - 7.36 (m, 5 H) 8.47 - 8.58 (m, 1 H)	379.15(M +Na)
20		0.87 (t, J=7.29 Hz, 3 H) 0.76 - 0.94 (m,1 H) 1.17 - 1.79 (m, 8 H) 2.60 - 2.84 (m, 3 H) 3.88 - 4.23 (m, 4 H) 6.46 - 6.58(m, 1 H) 7.13 -7.37 (m, 5 H) 8.48 - 8.60 (m, 1 H).	365.15(M +Na)
21		0.87 (t, J=7.24 Hz, 3 H) 1.19 - 1.43 (m,2 H) 1.65 (d, J=7.15 Hz, 2 H) 2.28 (s, 3 H) 2.41 (br. s., 2 H) 3.49 - 3.61 (m, H) 3.90 - 4.18(m, 4 H) 5.92 - 6.03 (m, 1 H) 6.50 - 6.60 (m, 1 H) 6.90 - 7.23 (m, 3 H) 8.51 - 8.61 (m, 1 H).	395.15
22		0.87 (dd, J=13.20, 6.33 Hz, 6 H) 1.35 -1.70 (m, 3 H) 2.37 - 2.47 (m, 2 H) 3.55 (s, 2 H) 3.75 (s, 3 H) 4.11 (d, J=5.59 Hz, 5 H) 5.94 - 6.10 (m, 1 H) 6.53 - 6.64 (m, 1 H) 6.87 (s, 2 H) 7.02 - 7.20 (m, 1 H) 8.50 - 8.67 (m, 1 H).	425.15 (M+Na)

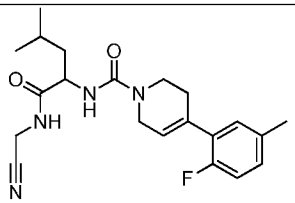
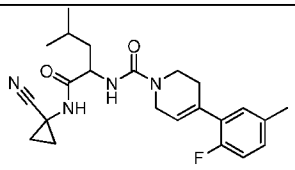
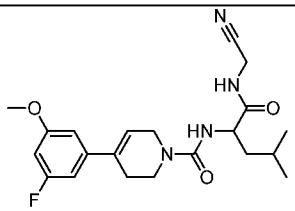
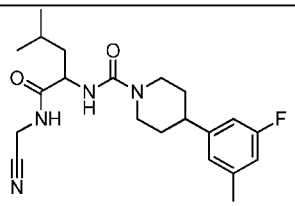
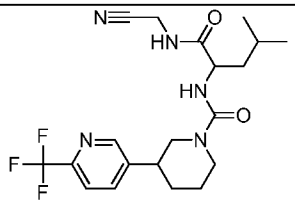
23		0.80 - 0.92 (m, 3 H) 1.17 - 1.42 (m, 2H) 1.51 - 1.71 (m, 2 H) 2.27 - 2.46 (m, 2 H) 3.55 (t, J=5.41 Hz, 2 H) 3.75 (s, 3H) 3.91 - 4.20 (m, 5 H) 6.02 (br. s., 1 H) 6.57 (d, J=7.70 Hz, 1 H) 6.78 - 6.91(m, 2 H) 7.04 - 7.20 (m, 1 H) 8.58 (s, 1 H)	411.13(M +Na)
24		0.86 (dd, J=5.96, 14.40 Hz, 6H), 1.36-1.70 (m, 3H), 2.24 (br. s., 2H), 2.33 (s, 3H), 3.47 (br. s., 2H), 4.07-4.18 (m, 3H), 4.21 (br. s., 2H), 6.38 (br. s., 1H), 6.69 (d, J=7.70 Hz, 1H), 6.95 (d, J=9.35 Hz, 1H), 7.07-7.20 (m, 2H), 8.58 (br. s., 1H).	409.2(M+ Na)
25		0.88 (d, J=5.04 Hz, 6 H) 1.34 - 1.83 (m,7 H) 2.26 (br. s., 3 H) 2.67 - 3.03 (m, 3 H) 3.48 - 3.75 (m, 1 H) 3.96 - 4.28 (m,4 H) 6.56 (d, J=6.14 Hz, 1 H) 7.03 (br. s., 3 H) 8.48 - 8.64 (m, 1 H).	411.2(M+ Na)
26		0.88 (dd, J=11.19, 5.96 Hz, 6 H) 1.33 -1.78 (m, 7 H) 2.70 - 3.02 (m, 3 H) 3.46 - 3.56 (m, 1 H) 3.73 (s, 3 H) 4.08 - 4.27(m, 4 H) 6.47 - 6.62 (m, 1 H) 6.73 - 6.87 (m, 2 H) 7.00 - 7.16 (m, 1 H) 8.46 -8.61 (m, 1 H)	427.2(M+ Na)
27		0.78 - 0.94 (m, 7 H) 1.38 - 1.83 (m, 8H) 2.67 - 2.85 (m, 3 H) 4.02 - 4.24 (m, 5 H) 6.57 (d, J=7.61 Hz, 1 H) 7.06 - 7.18(m, 1 H) 7.84 - 7.95 (m, 1 H) 8.07 - 8.19 (m, 1 H) 8.51 - 8.63 (m, 1 H)	398.2(M+ Na)
28		0.78-0.93 (m, 6H), 1.29-1.72 (m, 6H), 1.87 (d, J=11.46 Hz, 1H), 2.53-2.83 (m, 3H), 3.75 (s, 3H), 3.97-4.21 (m, 5H), 6.58 (d, J=7.98 Hz, 1H), 6.63-6.74 (m, 3H), 8.51 (q, J=5.38 Hz, 1H).	409.2

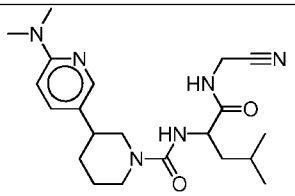
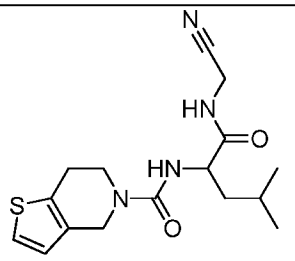
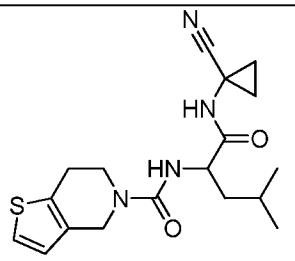
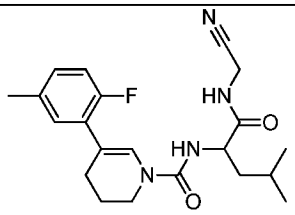
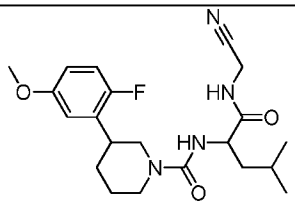
29		0.76-0.97 (m, 6H), 1.29-1.71 (m, 6H), 1.87 (d, J=11.37 Hz, 1H), 2.31 (s, 3H), 2.54-2.83 (m, 3H), 3.90-4.30 (m, 5H), 6.58 (d, J=6.79 Hz, 1H), 6.82-6.96 (m, 3H), 8.52 (q, J=5.44 Hz, 1H).	389.2
30		0.87 (dd, J=6.24, 14.76 H z, 6H), 1.37-1.72 (m, 3H), 2.29 (br. s., 2H), 3.50 (br. s., 2H), 4.07-4.37 (m, 5H), 6.58 (br. s., 1H), 6.74 (d, J=7.9 8 Hz, 1H), 7.70 (d, J=8.34 Hz, 2H), 7.85 (d, J=8.44 Hz, 2H), 8.60 (t, J=5.46 Hz, 1H).	402.2(M+ Na)
31		0.86 (dd, J=6.33, 14.67 Hz, 6H), 1.36-1.68 (m, 3H), 2.25 (br. s., 2H), 3.48 (t, J=5.50 Hz, 2H), 4.02-4.33 (m, 5H), 6.42 (br. s., 1H), 6.71 (d, J=7.98 Hz, 1H), 7.21 (d d, J=2.93, 8.62 Hz, 1H), 8.11 (dt, J=2.66, 8.25 Hz, 1H), 8.36 (d, J=2.11 Hz, 1H), 8.62 (t, J=5.50 Hz, 1H).	396.2(M+ Na)
32		0.82-0.92 (m, 6H), 1.37-1.73 (m, 6H), 1.89 (d, J=11.46 Hz, 1H), 2.63-2.85 (m, 3H), 4.00-4.20 (m, 5H), 6.60 (d, J=8.07 Hz, 1H), 7.16 (d d, J=1.88, 8.57 Hz, 1H), 7.94 (tt, J=2.37, 8.26 Hz, 1H), 8.17 (d, J=3.21 Hz, 1H), 8.54 (d, J=2.48 Hz, 1H).	398.2(M+ Na)
33		0.88 (dd, J=11.74, 6.33 Hz, 6 H) 1.34 -1.82 (m, 5 H) 1.93 - 2.09 (m, 2 H) 2.82 - 3.02 (m, 2 H) 4.13 (d, J=5.59 Hz, 5H) 6.53 - 6.68 (m, 1 H) 7.23 - 7.37 (m, 1 H) 7.64 - 7.77 (m, 1 H) 7.97 - 8.09(m, 1 H) 8.51 - 8.65 (m, 1 H).	415.46(M +1)
34		0.90 (br. s., 6 H) 1.30 - 1.69 (m, 6 H)1.81 (br. s., 2 H) 1.97 - 1.98 (m, 1 H) 2.65 - 2.88 (m, 1 H) 2.87 - 2.89 (m, 1 H)3.18 (d,	390.20(M +1)

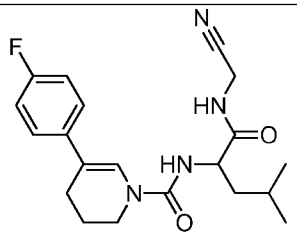
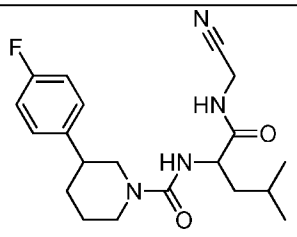
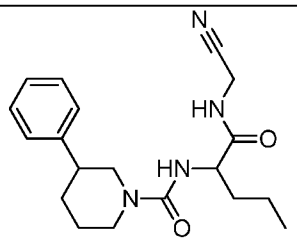
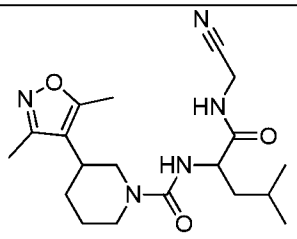
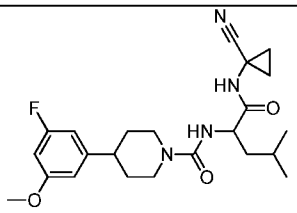
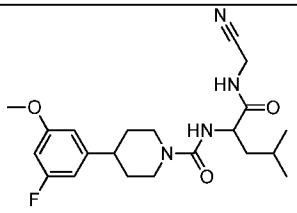
		J=11.83 Hz, 1 H) 3.58 - 3.84 (m, 5 H) 3.88 - 4.07 (m, 1 H) 4.42 - 4.59(m, 1 H) 4.72 - 4.91 (m, 1 H) 6.67 (br. s., 3 H) 8.52 - 8.70 (m, 1 H)	
35		0.71-0.99 (m, 6H) 1.29-1.67 (m, 4H), 1.68-2.02 (m, 3H), 2.59-2.90 (m, 2H), 3.12-3.27 (m, 4H), 3.60-3.80 (m, 2H), 3.94 (d, 1H), 4.42 (t, 1H), 4.64-4.92 (m, 1H), 7.48-7.68 (m, 2H), 7.75-7.97 (m, 2H), 8.52-8.75 (m, 1H)	420.2
36		0.75-0.95 (m, 6H) 1.28-1.76 (m, 6H), 1.89 (d, J=11.28 Hz, 1H), 2.58-2.83 (m, 3H), 4.05 (br. s., 5H), 6.59 (d, J=6.24 Hz, 1H), 7.16-7.40 (m, 5H), 8.51 (q, J=5.84 Hz, 1H)	357.2
37		0.72-0.94 (m, 6H) 1.03-1.27 (m, 1H), 1.34-1.75 (m, 5H), 1.90 (d, J=9.72 Hz, 1H), 2.11-2.39 (m, 2H), 2.62-2.86 (m, 3H), 3.21 (s, 3H), 3.85-4.18 (m, 5H), 6.28 (d, J=8.34 Hz, 1H), 7.57 (t, J=7.79 Hz, 2H), 7.88 (d, J=8.44 Hz, 2H), 8.56 (d, J=3.67 Hz, 1H)	449.2
38		0.86 (dd, J=6.28, 12.70 Hz, 6H), 0.80-0.90 (m, 6H), 1.38-1.65 (m, 3H), 2.18 (s, 5H), 2.35 (s, 3H), 3.44-3.59 (m, 2H), 3.86-4. 01 (m, 2H), 4.07-4.25 (m, 3H), 5.82 (br. s., 1H), 6.61 (d, J=8.07 Hz, 1H), 8.51-8.62 (m, 1H).	374.15
39		0. 87 (dd, J=6.33, 14.31 Hz, 6H), 1.41-1.71 (m, 3H), 2.27-2.34 (m, 2H), 3.52 (t, J=5.41 Hz, 2H), 4.12 (d, J=5.50 Hz, 2H), 4.16-4.42 (m, 3H), 6.58-6.78 (m, 2H), 7.93 (d, J=8.25 Hz, 1H), 8.16 (d, J=7.15 Hz, 1H), 8.61 (t,	424.2(M+ Na)

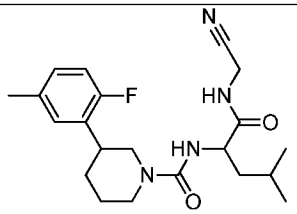
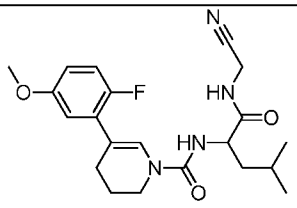
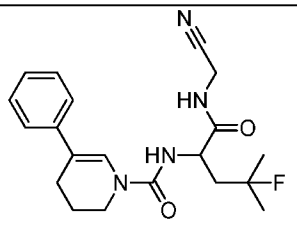
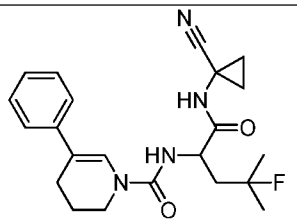
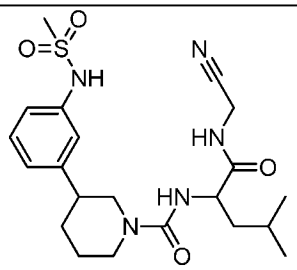
		J=5.50 Hz, 1H), 8.93 (s, 1H).	
40		2.50 (br. s., 6 H) 2.93 - 3.30 (m, 5 H)3.32 - 3.56 (m, 2 H) 4.17 - 4.50 (m, 2 H) 4.79 (t, J=12.20 Hz, 1 H) 5.30 (br. s., 2H) 5.59 (d, J=12.93 Hz, 1 H) 6.12 (d, J=11.74 Hz, 1 H) 6.42 (br. s., 1 H) 8.75 -8.99 (m, 5 H) 10.14 - 10.30 (m, 1 H).	342.20(M +H)
41		0.91 (m, J=18.25 Hz, 7 H) 1.26 - 1.50(m, 2 H) 1.63 (s, 11 H) 2.64 (br. s., 1 H) 3.44 (br. s., 1 H) 3.64 - 3.83 (m, 4 H)4.01 - 4.34 (m, 2 H) 4.74 - 4.97 (m, 1 H) 6.21 (br. s., 1 H) 6.71 (d, J=3.67 Hz,1 H) 6.96 - 6.97 (m, 1 H) 7.48 (d, J=8.71 Hz, 1 H) 7.67 (d, J=3.94 Hz, 2 H) 7.94- 8.07 (m, 1 H) 8.59 - 8.73 (m, 1 H).	479.25(M +H)
42		0.84 - 0.95 (m, 6 H) 1.30 - 1.37 (m, 1H) 1.35 - 1.53 (m, 2 H) 1.64 (br. s., 12 H) 3.59 (br. s., 2 H) 3.99 - 4.28 (m, 6 H)6.21 (br. s., 1 H) 6.58 (d, J=6.79 Hz, 1 H) 6.71 (br. s., 1 H) 7.48 (d,J=8.16Hz, 1 H) 7.67 (br. s., 2 H) 8.00 (d, J=8.25 Hz, 1 H) 8.56 (br. s., 1 H)	494.30(M +H)
43		0.86 (br. s., 6 H) 1.09 (br. s., 2 H) 1.24(br. s., 1 H) 1.47 (br. s., 5 H) 3.58 (br. s., 3 H) 3.92 - 4.20 (m, 3 H) 6.20 (br. s.,1 H) 6.51 (br. s., 1 H) 6.71 (br. s., 1 H) 7.47 (d, J=6.33 Hz, 1 H) 7.67 (br. s., 2H) 8.00 (d, J=7.43 Hz, 1 H) 8.82 (br. s., 1 H).	520.35(M +H)
44		0.87 (dd, J=14.26, 6.37 Hz, 6 H), 1.29 - 1.76 (m, 3 H) ,2.28 (br. s., 2 H), 3.23 (s, 3 H), 3.46 - 3.56 (m, 2 H), 3.99 - 4.43 (m, 5 H), 6.55 (br. s., 1 H), 6.74 (d, J=8.07 Hz, 1 H), 7.75 (d, J=8.34 Hz, 2 H) ,7.91 (d, J=8.44 Hz,	433.2

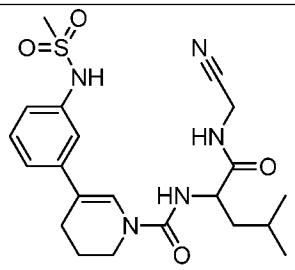
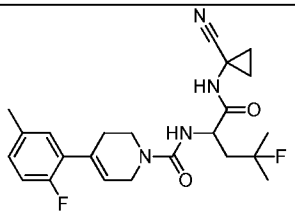
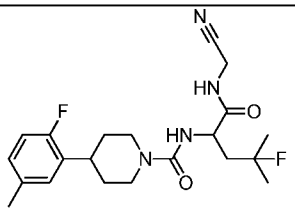
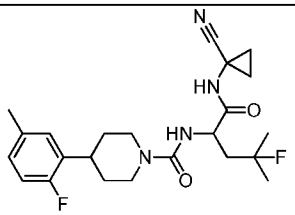
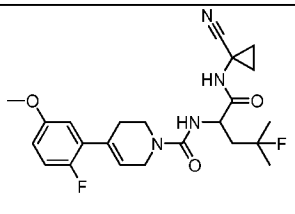
		2 H), 8.60 (t, J=5.78 Hz, 1 H)	
45		0.87 (dd, J=14.95, 6.24 Hz, 6 H), 1.40 - 1.73 (m, 3 H), 2.24 (br. s., 2 H), 3.47 (t, J=5 .27 Hz, 2 H), 3.80 (s, 3 H), 4.01 - 4.31 (m, 5 H), 6.44 (br. s., 1 H), 6.66 - 6.83 (m, 2 H), 6.85 - 6.98 (m, 2 H), 8.59 (t, J=5.59 Hz, 1 H)	403.2
46		0.87 (dd, J=14.76, 5.78 Hz, 6 H) 1.39 - 1.71 (m, 3 H) 2.22 (br. s., 2 H) 3.03 (s, 6 H) 3.47 (br. s., 2 H) 3.99 - 4.35 (m, 5 H) 6.16 (br. s., 1 H) 6.56 - 6.77 (m, 2 H) 7.65 (d, J=8.80 Hz, 1 H) 8.24 (br. s., 1 H) 8.57 (br. s., 1 H)	399.2
47		0.74-1.00 (m, 9H) 1.24 (br. s., 1H), 1.40-1.75 (m, 8H), 2.27 (br. s., 2H), 3.51 (br. s., 2H), 4.12 (br. s., 2H), 4.18-4.43 (m, 3H), 6.34 (br. s., 1H), 6.73 (br. s., 2H), 7.50 (d, J=8.34 Hz, 1H), 7.70 (d, J=9.81 Hz, 2H), 8.02 (d, J=8.71 Hz, 1H), 8.58 (br. s., 1H	494.2
48		0.86 (br. s., 9H) 1.09 (br. s., 2H), 1.03-1.14 (m, 1H), 1.25 (br. s., 4H), 1.32-1.51 (m, 4H), 2.27 (br. s., 3H), 3.50 (br. s., 3H), 4.08-4.42 (m, 3H), 6.33 (br. s., 1H), 6.57-6.84 (m, 2H), 7.49 (d, J=8.62 Hz, 1H), 7.70 (d, J=9.63 Hz, 2H), 8.01 (d, J=7.61 Hz, 1H), 8.84 (br. s., 1H	520.3
49		0.75 - 1.00 (m, 6 H) 1.44 (d,J=5.50 Hz, 1 H) 1.61 (d,J=9.35 Hz, 2 H) 2.25 - 2.38 (m, 4 H) 2.44 (br. s., 3 H) 3.55 (br. s., 2 H) 3.95 - 4.31 (m, 5 H) 6.26 (br. s., 1 H) 6.59 (d, J=7.34 Hz, 1 H) 6.93 (d,J=9.54 Hz, 1 H) 7.03 - 7.18 (m, 2 H) 8.57 (br. s., 1 H)	387.2

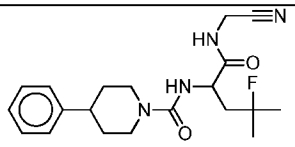
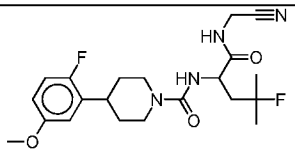
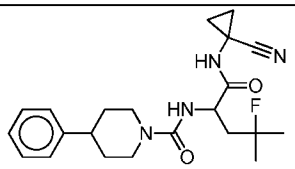
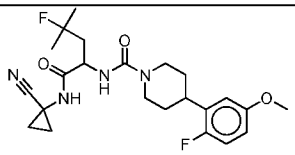
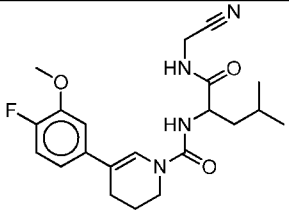
50		0.91 (dd,J=12.84, 6.33 Hz, 6 H) 1.02 (d,J=6.69 Hz, 6 H) 1.47 - 1.61 (m, 1 H) 1.62 - 1.86 (m, 2 H) 2.02 - 2.21 (m, 1H) 4.15 (d,J=5.59 Hz, 2 H) 4.23 (d,J=6.51 Hz, 2 H) 4.46 - 4.62 (m, 1 H) 6.88 (d,J=3.67 Hz, 1 H) 7.82 (d,J=3.76 Hz, 1 H) 7.93 (dd,J=8.76, 1.42 Hz, 1 H) 8.14 (d,J=8.71 Hz, 1 H) 8.26 (d,J=0.92 Hz, 1 H) 8.62 (d,J=7.89 Hz, 1 H) 8.74 (t,J=5.55 Hz, 1 H)	413.2
51		0.76 - 0.94 (m, 6 H) 1.02 - 1.17 (m, 2 H) 1.28 - 1.72 (m, 5 H) 2.28 (br. s., 3 H) 2.41 (br. s., 2 H) 3.53 (br. s., 2 H) 3.89 4.21 (m, 3 H) 5.97 (br. s., 1 H) 6.52 (d,J=7.24 Hz, 1 H) 6.97 - 7.23 (m, 3 H) 8.83 (br. s., 1 H)	413.25
52		0.87 (dd,J=13.75, 4.31 Hz, 6 H) 1.44 (d,J=6.51 Hz, 1 H) 1.61 (d,J=10.09 Hz, 2 H) 2.44 (br. s., 2 H) 3.55 (br. s., 2 H)3.79 (br. s., 3 H) 3.92 - 4.31 (m, 5 H) 6.29 (br. s., 1 H) 6.60 (d, J=7.52 Hz, 1 H) 6.74 (d,J=10.82 Hz, 1 H) 6.81 - 6.96 (m, 2 H) 8.56 (br. s., 1 H)	403.2
53		0.87 (dd,J=11.55, 5.78 Hz, 6 H) 1.33 - 1.82 (m, 7 H) 2.29 (br. s., 3 H) 2.59 - 2.84 (m, 3 H) 4.04 - 4.24 (m, 5 H) 6.55(d,J=7.52 Hz, 1 H) 6.79 - 6.96 (m, 3 H) 8.54 (br. s., 1 H)	389.2
54		0.78 - 0.91 (m, 6 H) 1.35 - 1.75 (m, 6 H) 1.93 (d, J=9.90 Hz, 1 H) 2.68 - 2.97 (m, 3 H) 3.98 - 4.20 (m, 5 H) 6.60 (d, J=7.89 Hz, 1 H) 7.87 (d, J=8.16 Hz, 1 H) 8.02 (d, J=8.25 Hz, 1 H) 8.53 (br. s., 1 H) 8.73 (d, J= 5.69 Hz, 1 H)	426.2

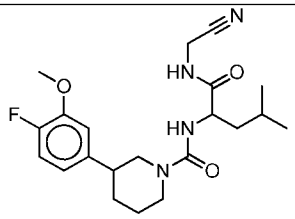
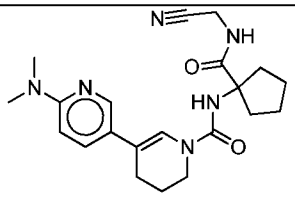
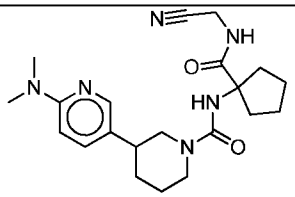
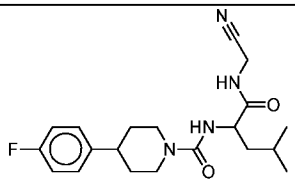
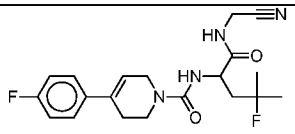
55		0.82 - 0.91 (m, 6 H) 1.29 - 1.72 (m, 7 H) 1.83 (d, J=13.94 Hz, 1H) 2.61 - 2.74 (m, 2 H) 2.99 (s, 6 H) 3.96 - 4.18 (m, 5 H) 6.60(dd, J=18.84, 8.30 Hz, 2 H) 7.46 (d, J=8.53 Hz, 1 H) 7.99 (dd,J=6.60, 2.02 Hz, 1 H) 8.51 (q, J=5.41 Hz, 1 H)	401.25
56		0.86 (dd, *J* =15.59, 4.03 Hz, 6 H) 1.43 (d, *J* =5.69 Hz, 1 H) 1.61 (d, *J* =9.63 Hz, 2 H) 2.78 (br. s., 2 H) 3.67 (br. s., 2 H)4.11 (br. s., 2 H) 4.19 (br. s., 1 H) 4.33 - 4.59 (m, 2 H) 6.68 (d, *J* =7.24 Hz, 1 H) 6.87 (br. s., 1 H) 7.34 (br. s., 1 H) 8.57 (br. s., 1 H)	334.44
57		0.85 (dd, *J* =14.31, 5.96 Hz, 6 H) 1.07 (br. s., 2 H) 1.36 (br. s., 1H) 1.46 (br. s., 2 H) 1.57 (d, *J* =11.00 Hz, 2 H) 2.77(br. s., 2 H) 3.66 (br. s., 2 H) 4.09 (br. s., 1 H) 4.32 - 4.56 (m, 2 H) 6.61 (d,*J* =8.53 Hz, 1 H) 6.86 (d, *J* =4.95 Hz, 1 H) 7.33 (d, *J* =4.58 Hz, 1H) 8.81 (s, 1 H)	360.47
58		0.86 (dd, J=6.37, 12.52 Hz, 6H) 1.30-1.71 (m, 3H), 2.11-2.37 (m, 5H), 3.39-3.63 (m, 2H), 4.01-4.27 (m, 5H), 6.05 (br. s., 1H), 6.63 (d, J=8.07 Hz, 1H), 7.03-7.28 (m, 3H), 8.56 (t, J=5.64 Hz, 1H)	387.2
59		0.79 - 0.93 (m, 6 H) 1.35 - 1.77 (m, 6 H) 1.78 - 1.89 (m, 1 H), 2.64 - 2.92 (m, 3 H) 3.74 (s, 3 H) 3.97 - 4.22 (m, 5 H) 6.60 (d, J=7.98 Hz, 1 H) 6.81 (dt, J=8.78, 3.54 Hz, 1 H) 6.89 (dd, J=5.78, 3.03 Hz, 1 H) 7.10 (t, J=9.40 Hz, 1 H) 8.50 - 8.61 (m, 1 H)	427.2(M+ Na)

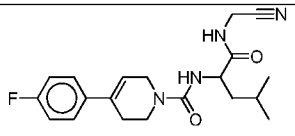
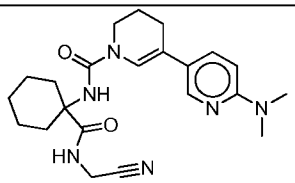
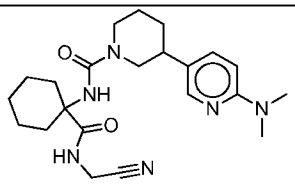
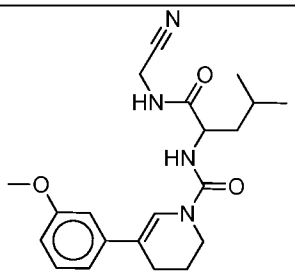
60		0.87 (dd, *J* =14.35, 6.37 Hz, 6 H) 1.39 - 1.69 (m, 3 H) 2.24 (br.s., 2 H) 3.48 (t, *J* =5.59 Hz, 2 H) 4.11 (d, *J* =5.59 Hz, 2 H) 4.16 - 4.32 (m, 3 H) 6.29 (br. s., 1 H) 6.70 (d, *J* =7.89 Hz, 1 H) 7.21 (t,*J* =8.89 Hz, 2 H) 7.48 - 7.58 (m, 2 H) 8.58 (t, *J* =5.64 Hz, 1 H)	395.15(M +Na)
61		0.79 - 0.92 (m, 6 H) 1.34 - 1.73 (m, 6 H) 1.87 (d, J=11.55 Hz, 1H) 2.57 - 2.81 (m, 3 H) 3.98 - 4.23 (m, 5 H) 6.58 (d, J=6.88 Hz, 1H) 7.10 - 7.20 (m, 2 H) 7.27 - 7.38 (m, 2 H) 8.51 (q, J=5.53 Hz, 1 H)	397.15(M +Na)
62		0.87 (td, J=7.29, 2.93 Hz, 3 H) 1.22 - 1.74 (m, 8 H) 1.90 (d,J=11.19 Hz, 1 H) 2.66 - 2.78 (m, 2 H) 4.01 - 4.18 (m, 5 H) 6.53(d, J=7.79 Hz, 1 H) 7.16 - 7.40 (m, 5 H) 8.42 - 8.54 (m, 1 H)	365.15(M +Na)
63		0.81 - 0.93 (m, 6 H) 1.36 - 1.85 (m, 8 H) 2.21 (d, J=3.30 Hz, 3 H) 2.37 (d, J=1.74 Hz, 3 H) 2.65 - 2.87 (m, 2 H) 3.91 - 4.25 (m, 5 H) 6.46 - 6.60 (m, 1 H) 8.50 (q, J=5.65 Hz, 1 H)	398.2(M+ Na)
64		0.87 (dd,J=10.87, 6.46 Hz, 6 H) 1.04 - 1.13 (m, 2 H) 1.27 - 1.68 (m, 7 H) 1.73 (d, J=12.29 Hz, 2 H) 2.61 - 2.80 (m, 3H) 3.76 (s, 3 H) 4.00 - 4.20 (m, 3 H) 6.45 (d, J=7.98 Hz, 1 H) 6.64 (d,J=1.00 Hz, 3 H) 8.76 (s, 1H)	453.25
65		0.88 (dd,J=12.01, 6.42 Hz, 6 H) 1.34 - 1.67 (m, 5H) 1.74 (d,J=11.55 Hz, 2 H) 2.61 - 2.82 (m, 3 H) 3.76 (s, 3 H) 4.07- 4.24 (m, 5 H) 6.51 (d,J=7.98 Hz, 1 H) 6.64 (d,J=1.00 Hz, 3 H) 8.50(t,J=5.59 Hz, 1 H)	427.15(M +Na)

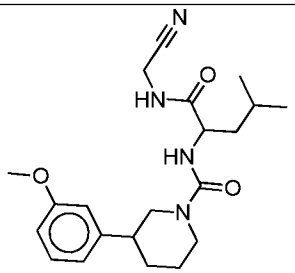
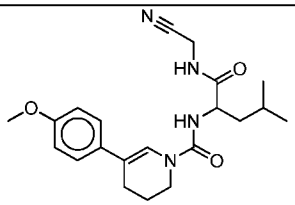
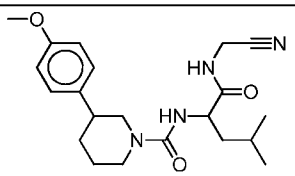
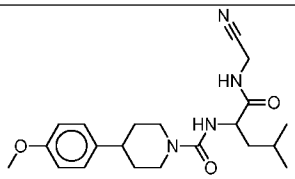
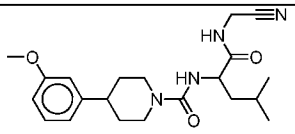
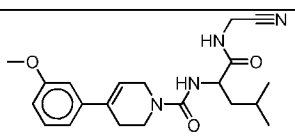
66		0.68 - 0.96 (m, 6 H), 1.32 - 1.74 (m, 6 H), 1.84 (d, J = 10.45 Hz,1 H), 2.28 (s, 3 H), 2.58 - 2.93 (m, 3 H), 3.96 - 4.25 (m, 5 H), 6.57 (d, J = 7.79 Hz, 1 H), 7.00 - 7.11 (m, 2 H), 7.17 (d, J = 7.15 Hz, 1 H), 8.44 - 8.59 (m, 1 H)	411.20(M +Na)
67		0.86 (dd, 6H, J=12.6, 6.4 Hz,), 1.35 - 1.68 (m, 3H,), 2.25 (br. s.,2H,), 3.50 (q, 2H, J=5.9 Hz,), 3.76 (s, 3H,), 4.03 - 4.25 (m, 5H,), 6.11 (br. s., 1H,), 6.65 (d, 1H, J=7.9 Hz,), 6.82 - 6.93 (m, 2H,), 7.10 - 7.21 (m, 1H,), 8.56 (t, 1H, J=5.5 Hz,)	425.15
68		1.28 - 1.38 (m, 6 H) 1.99 - 2.13 (m, 2 H) 2.28 (s, 1 H) 2.73 (s, 1 H) 3.57 (t, J=5.59 Hz, 2 H) 3.96 - 4.15 (m, 4 H) 4.30 4.40(m,1H)6.20(br.s.,1H)6.70 (d,J=8.07 Hz, 1 H) 7.23 - 7.49 (m, 5 H) 8.57 (t, J=5.59 Hz, 1 H).	395.15 (M+Na)
69		1.07 - 1.13 (m, 2 H) 1.25 - 1.38 (m,6 H) 1.42 - 1.50 (m, 2 H) 1.92 - 2.08 (m, 2 H) 2.34 - 2.46 (m, 2 H) 3.56 (t,*J* =5.59Hz, 2 H) 3.89 - 4.13 (m, 2 H) 4.18 - 4.33 (m, 1 H) 6.19 (br. s., 1 H) 6.63 (d, *J* =8.16 Hz, 1 H) 7.22 - 7.50 (m, 5 H) 8.85 (s, 1 H).	421.20 (M+Na)
70		0.78 - 0.93 (m, 6H,), 1.31 - 1.74 (m, 7H,), 1.87 (d, 1H, J=12.3Hz,), 2.60 - 2.81 (m, 2H,), 2.96 (s, 3H,), 3.97 - 4.26 (m, 5H,), 6.57 (d, 1H, J=7.8 Hz,), 7.08 - 7.19 (m, 2H,), 7.20 - 7.33 (m,2H,), 8.51 (d, 1H, J=5.7 Hz,), 9.65 (s, 1H,)	450.25

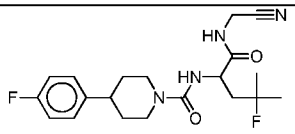
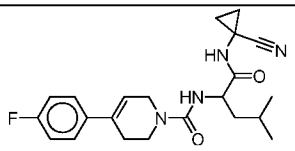
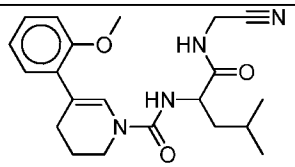
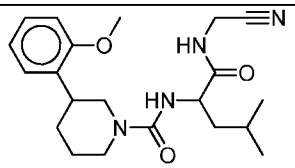
71		0.87 (dd, 6H, J=14.6, 6.3 Hz,), 1.37 - 1.70 (m, 3H,), 2.26 (d, 2H,J=12.3 Hz,), 2.99 (s, 3H,), 3.48 (br. s., 2H,), 4.07 - 4.30 (m, 5H,), 6.27 (br. s., 1H,), 6.69 (d, 1H, J=7.8 Hz,), 7.20 (d, 2H, J=8.6 Hz,), 7.46 (d, 2H, J=8.5Hz,)8.58 (t, 1H, J=5.3 Hz,), 9.79 (s,1H)	448.2
72		1.03 - 1.15 (m, 2 H) 1.29 (d,J=4.77 Hz, 3 H) 1.36 (d,J=4.58 Hz, 3H) 1.42 - 1.52 (m, 2 H) 1.91 - 2.06 (m, 2 H) 2.28(s, 3 H) 2.41 (br.s., 2 H) 3.53 (t,J=5.46 Hz, 2 H) 3.86 - 4.12 (m, 2 H) 4.19 - 4.31(m, 1 H) 5.98 (br. s., 1 H) 6.63 (d, J=7.89 Hz, 1 H) 7.01 - 7.21(m, 3 H) 8.86(s, 1 H)	431.2
73		1.30 (d,J=3.03 Hz, 3 H) 1.38 (d,J=2.84 Hz, 3 H) 1.44 - 1.60 (m, 2H) 1.69 (d,J=1.00 Hz, 2 H) 1.96 - 2.11 (m, 2 H)2.26 (s, 3 H) 2.69 - 3.02 (m, 3 H) 4.02 - 4.23 (m, 4 H) 4.27 - 4.41 (m, 1 H) 6.68 (d,J=7.98 Hz, 1 H) 6.97 - 7.13 (m, 3 H) 8.55 (t, J=5.55 Hz, 1 H)	407.2
74		1.10 (br. s., 2 H) 1.29 (d,J=5.32 Hz, 3 H) 1.37 (d,J=5.23 Hz, 3 H) 1.47 (br. s., 2 H) 1.50 - 1.76 (m, 4 H) 1.88 - 2.07(m, 2 H) 2.26 (s, 3 H) 2.65 - 2.85 (m, 2 H) 2.94 (t, J=11.46 Hz, 1 H) 3.99 - 4.31 (m, 3 H) 6.61 (d,J=8.16 Hz, 1 H) 6.94 - 7.15 (m, 3 H) 8.83 (s, 1H)	433.25
75		1.08 - 1.14 (m, 2 H) 1.24 - 1.39 (m, 6 H) 1.44 - 1.51 (m, 2 H) 2.42 (br. s., 2 H) 3.54 (t,J=5.50 Hz, 2 H) 3.75 (s, 3 H) 4.01 (d, J=19.53 Hz, 2 H) 4.25 (d, J=5.59 Hz, 1 H) 6.02 (br. s., 1 H) 6.65 (d, J=7.79 Hz, 1 H) 6.80 -6.90 (m, 2 H) 7.06 - 7.18 (m, 1 H) 8.88	447.25 (M+H)

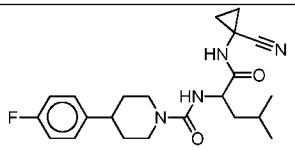
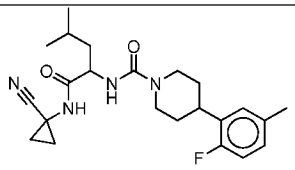
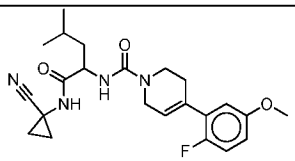
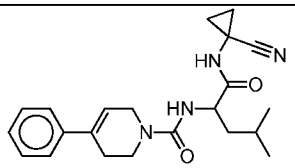
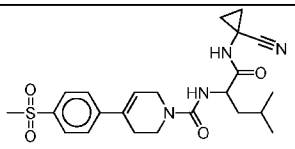
		(s, 1 H).	
76		1.29 - 1.53 (m, 6 H) 1.74 (d, J=11.19 Hz, 2 H) 1.96 - 2.10 (m, 2 H) 2.63 - 2.86 (m, 2 H) 4.12 (d, J=5.59 Hz, 4 H) 4.30 - 4.39 (m, 1 H) 6.67 (d, J=8.25 Hz, 1 H) 7.16 - 7.35 (m, 5 H) 8.55 (t, J=5.55 Hz, 1 H).	375.20(M +H)
77		1.28 - 1.40 (m, 6 H) 1.48 - 1.74 (m, 5 H) 2.05 (d, J=19.90 Hz, 2 H) 2.71 - 3.00 (m, 4 H) 3.73 (s, 3 H) 4.02 - 4.21 (m, 4 H) 4.33 (br. s., 1 H) 6.63 - 6.84(m, 3 H) 6.99 - 7.15 (m, 1 H) 8.54 (br. s., 1 H).	423.25(M +H)
78		1.10 (br. s., 2 H) 1.25 - 1.38 (m, 6 H) 1.47 (m, 3 H) 1.69 - 1.78 (m, 2 H) 1.92 - 2.04 (m,2 H) 2.74 (m, 4 H) 4.07 - 4.29 (m, 3 H) 6.56 - 6.64 (m, 1 H) 7.18 -7.34 (m, 5 H) 8.84 (s, 1 H).	401.28(M +H)
79		1.10 (d, J=2.75 Hz, 2 H) 1.28 - 1.39 (m, 6 H) 1.47 (d, J=2.66 Hz, 4 H) 1.63 - 1.72 (m, 2 H), 1.93 - 2.04 (m, 2 H) 2.72 - 2.85 (m, 2 H) 2.90 - 3.00 (m, 1 H) 3.73 (s, 3 H) 4.07 - 4.27 (m, 3 H) 6.57 - 6.61 (m, 1 H) 6.79 (d,J=6.24 Hz, 2 H) 7.03 - 7.11 (m, 1 H) 8.82 (s, 1 H).	449.21(M +H)
80		0.87 (dd, J = 13.94, 6.05 Hz, 6 H), 1.35 - 1.74 (m, 3 H), 2.24 (br.s., 2 H), 3.48 (br. s., 2 H), 3.88 (s, 3 H), 4.05 - 4.36 (m, 5 H), 6.32 (br. s., 1 H), 6.70 (d, J = 7.61 Hz, 1 H), 7.03 (br. s., 1 H), 7.13 - 7.32 (m, 2 H), 8.59 (br. s., 1 H)	403.2

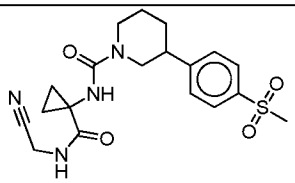
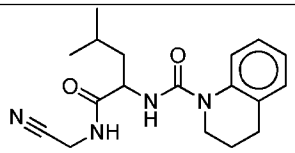
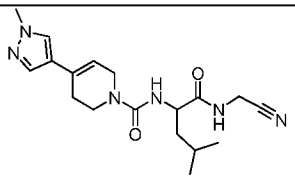
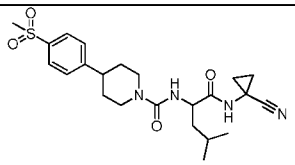
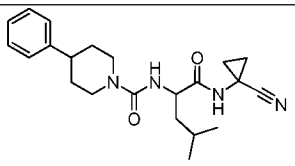
81		0.79 - 0.93 (m, 6 H), 1.30 - 1.75 (m, 6 H), 1.88 (d, J = 11.00 Hz, 1 H), 2.54 - 2.85 (m, 3 H), 3.84 (s, 3 H), 3.93 - 4.25 (m, 5 H), 6.58 (dd, J = 7.79, 4.31 Hz, 1 H), 6.83 (td, J = 4.10, 1.97 Hz, 1H), 7.00 - 7.21 (m, 2 H), 8.46 - 8.59 (m, 1 H)	405.25
82		1.63 (d, J=5.14 Hz, 4 H) 1.83 - 1.95 (m, 2 H) 1.97 - 2.11 (m, 2 H) 2.22 (br. s., 2 H) 3.03 (s, 6 H) 3.43 (t, J=5.59 Hz, 2 H) 4.04 (d, J=5.59 Hz, 2 H) 4.16 (br. s., 2 H) 6.16 (br. s., 1 H) 6.51 (s, 1 H), 6.64 (d, J=8.89 Hz, 1 H) 7.65 (dd, J=8.94, 2.52 Hz, 1 H) 8.14 (t, J=5.64 Hz, 1 H) 8.24 (d, J=2.29 Hz, 1 H)	397.2
83		1.45 - 1.72 (m, 7 H) 1.77 - 1.93 (m, 4 H) 1.93 - 2.07 (m, 2 H), 2.60 - 2.76 (m, 2 H) 2.98 (s, 6 H) 3.92 - 4.10 (m, 4 H) 6.46 (s, 1 H) 6.61 (d, J=8.71 Hz, 1 H) 7.43 (dd, J=8.76, 2.43 Hz, 1 H) 8.00 (d, J=2.20 Hz, 1 H) 8.07 (t, J=5.69 Hz, 1 H)	399.25
84		0.87 (dd,J=12.20, 6.33 Hz, 6 H) 1.28 - 1.80 (m, 7 H) 2.60 - 2.86(m, 3 H) 3.99 - 4.26 (m, 5 H) 6.54 (d, J=7.79 Hz, 1H) 7.00 - 7.20 (m, 2 H) 7.19 - 7.38 (m, 2 H) 8.53 (t, J=5.55 Hz, 1 H)	375.2
85		1.26 - 1.42 (m, 16 H) 1.96 - 2. 14 (m, 5H) 3.56 (s, 5 H) 3.88 - 4.15 (m, 11 H) 4.26 - 4.42 (m, 3 H) 6.17 (br. s., 2 H)6.12 - 6.20 (m, 2 H) 6.70 (d,J=7.98 Hz, 2 H)6.64 - 6.77 (m, 2 H) 7.10 - 7.25(m, 5 H) 7.18 (t, J=8.89 Hz, 5 H) 7.42 - 7.56 (m, 5 H) 7.50	391.15(M +H)

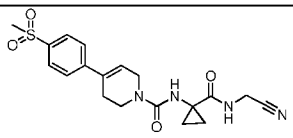
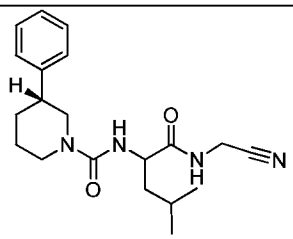
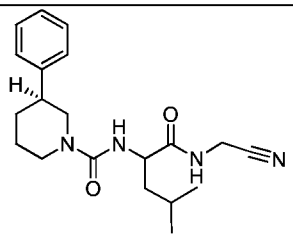
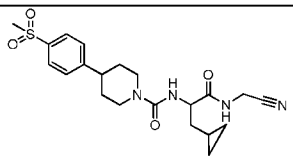
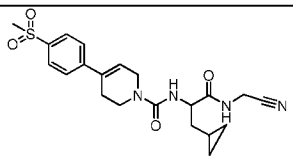
86		0.87 (dd,J=14.12, 6.33 Hz, 6 H) 1.33 - 1.50 (m, 1 H) 1.50 - 1.70 (m, 2 H) 2.45 (br. s., 2 H) 3.56 (t, J=4.95 Hz, 2 H)4.02 (d,J=10.64 Hz, 2 H) 4.11 (d,J=3.03 Hz, 2 H) 4.14 - 4.26 (m, 1 H) 6.16 (br. s.,1 H) 6.61 (d, J=7.89 Hz, 1 H) 7.18 (t,J=8.85 Hz, 2 H) 7.50(dd,J=8.76,5.55 Hz, 2 H) 8.59 (br. s., 1 H)	373.15
87		1.11 - 1.30 (m, 1 H) 1.33 - 1.57 (m, 5 H) 1.66 (td, J=11.53, 2.98 Hz, 2 H) 2.01 (d, J=13.11 Hz, 2 H) 2.24 (br. s., 2 H) 3.03 (s, 6 H) 3.46 (t, J=5.46 Hz, 2 H) 4.05 (d, J=5.59 Hz, 2 H) 4.19 (br. s., 2 H) 6.16 (br. s., 1 H) 6.22 (s, 1 H) 6.65 (d, J=8.99 Hz, 1 H) 7.57 - 7.71 (m, 1 H) 7.65 (dd, J=8.94, 2.52 Hz, 1 H) 8.15 (t, J=5.64 Hz, 1 H) 8.23 (d, J=2.29 Hz, 1 H)	411.25
88		1.23 (d, J=2.75 Hz, 1 H) 1.31 - 1.73 (m, 11 H) 1.84 (d, J=12.47 Hz, 1 H) 1.99 (br. s., 2 H) 2.69 (t, J=12.10 Hz, 2 H) 2.98 (s, 6 H) 3.89 - 4.14 (m, 4 H) 6.17 (s, 1 H) 6.61 (d, J=8.71 Hz, 1 H) 7.43 (dd, J=8.76, 2.43 Hz, 1 H) 7.99 (d, J=2.20 Hz, 1 H) 8.11 (t, J=5.59 Hz, 1 H)	413.25
89		0.87 (dd, J = 14.49, 6.33 Hz, 6 H), 1.39 - 1.51 (m, 1 H), 1.53 - 1.71 (m, 2 H), 2.24 (br. s., 1 H), 3.48 (t, J = 5.59 Hz, 2 H), 3.78 (s, 3 H), 4.11 (d, J = 5.59 Hz, 2 H), 4.16 - 4.34 (m, 3 H), 6.33 (br. s., 1 H), 6.72 (d, J = 7.79 Hz, 1 H), 6.88 (dd, J = 8.12, 2.15 Hz, 1 H), 6.94 - 7.10 (m, 2 H), 7.19 - 7.34 (m, 1 H), 8.58 (t, J = 5.55 Hz, 1 H)	385.2

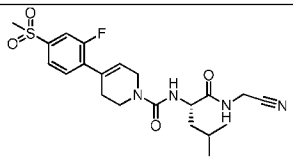
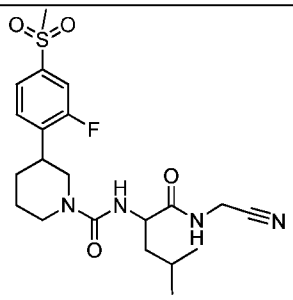
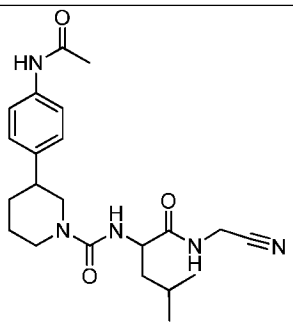
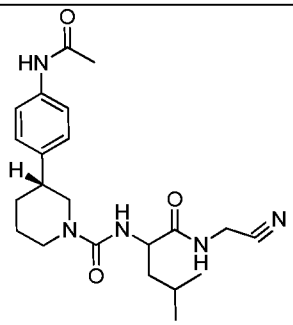
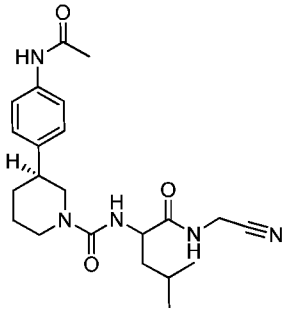
90		0.76 - 0.96 (m, 6 H), 1.28 - 1.75 (m, 6 H), 1.88 (d, J = 11.00 Hz, 1 H), 2.54 - 2.85 (m,2H), 3.75 (s, 3 H), 3.97 - 4.22 (m, 5 H), 6.58 (dd, J = 7.93, 3.71 Hz, 1 H), 6.74 - 6.93 (m, 3 H), 7.23 (t, J = 7.79 Hz, 1 H), 8.51 (q, J = 5.78 Hz, 1 H)	387.25
91		0.87 (dd, J = 14.67, 6.24 Hz, 6 H), 1.35 - 1.70 (m, 3 H), 2.22 (br. s., 2 H), 3.47 (t, J = 5.46 Hz, 2 H), 3.76 (s, 3 H), 4.06 - 4.32 (m, 5 H), 6.20 (br. s., 1 H), 6.70 (d, J = 8.07 Hz, 1 H), 6.93 (d, J = 8.80 Hz, 2 H), 7.42 (d, J = 8.71 Hz, 2 H), 8.58 (t, J = 5.64 Hz, 1 H)	385.25
92		0.75 - 0.96 (m, 6 H), 1.30 - 1.74 (m, 6 H), 1.85 (d, J = 11.83 Hz, 1 H), 2.57 - 2.75 (m, 3 H), 3.73 (s, 3 H), 3.94 - 4.22 (m, 5 H), 6.58 (d, J = 7.98 Hz, 1 H), 6.88 (d, J = 8.44 Hz, 2 H), 7.12 - 7.27 (m, 2 H), 8.51 (q, J = 5.78 Hz, 1 H)	387.25
93		0.82 - 0.92 (m, 6 H) 1.37 - 1.74 (m, 7 H) 2.61 - 2.79 (m, 3 H) 3.79(s, 3 H) 6.54 (d, J=7.70 Hz, 1 H) 6.86 (d, J=7.34 Hz, 2 H) 7.14 (d, J=7.43 Hz, 2 H) 8.54 (t, J=5.23 Hz, 1 H)	387.25(M +H)
94		0.87 (dd,J=12.20, 6.42 Hz, 6 H) 1.30 - 1.67 (m, 5 H) 1.73 (d, J=12.38 Hz, 2 H) 2.58 - 2.84 (m, 3 H) 3.74 (s, 3 H) 4.02- 4.26 (m, 5 H) 6.55 (d,J=7.89 Hz, 1 H) 6.69 - 6.90 (m, 3 H) 7.13 - 7.32 (m, 1 H) 8.54 (t, J=5.64 Hz, 1 H)	387.25
95		0.87 (dd,J=14.12, 6.33 Hz, 6 H) 1.35 - 1.51 (m, 1 H) 1.51 - 1.72 (m, 2 H) 2.45 (br. s., 2 H) 3.56 (t, J=5.14 Hz, 2 H)3.77 (s, 3 H) 4.02	385.2

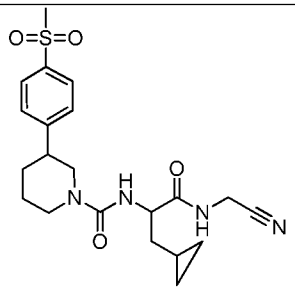
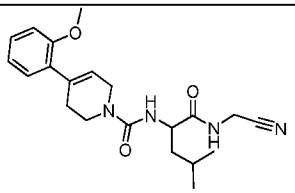
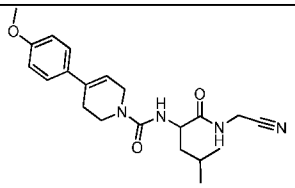
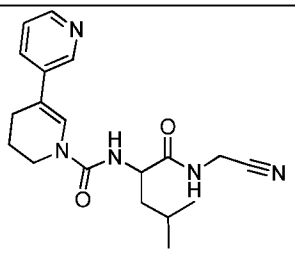
		(dd,J=10.96, 2.15 Hz, 2 H) 4.11 (d,J=5.59 Hz, 2 H) 4.15 - 4.26 (m, 1 H) 6.20 (br. s., 1 H) 6.59 (d, J=7.89 Hz, 1 H) 6.84 (dd,J=8.07, 2.11Hz, 1 H) 6.97 (s, 1 H) 7.03 (d,J=7.89 Hz, 1 H) 7.27 (t,J=1.00 Hz, 1 H) 8.57 (t,J=5.59 Hz, 1 H)	
96		1.28 - 1.40 (m, 6 H) 1.73 (d, J=12.38 Hz, 2 H) 1.99 - 2.10 (m, 2 H) 2.66 - 2.84 (m, 4 H) 4.28 - 4.37 (m, 3 H) 4.34 - 4.36 (m, 1 H) 6.66 (d, J=8.07 Hz, 1 H) 7.08 - 7.16 (m, 2 H) 7.22 - 7.30 (m, 2 H) 8.54 (t, J=5.64 Hz, 1 H).	415.20 (M+Na)
97		0.86 (dd,J=12.88, 6.37 Hz, 6 H) 1.02 - 1.15 (m, 2 H) 1.29 - 1.41 (m, 1 H) 1.42 - 1.50 (m, 2 H) 1.51 - 1.65 (m, 2 H)2.45 (br. s., 2 H) 3.50 - 3.61 (m, 2 H) 4.01 (d, J=6.05 Hz, 2 H) 4.06 - 4.15 (m, 1 H) 6.16 (br. s., 1H) 6.52 (d, J=7.70 Hz, 1H) 7.18 (t,J=8.85 Hz, 2H) 7.50(dd,J=8.71, 5.59 Hz, 2 H) 8.82 (s, 1H)	421.20(M +Na)
98		0.86 (dd, J = 11.10, 6.42 Hz, 6 H), 1.34 - 1.48 (m, 1 H), 1.49 - 1.69 (m, 2 H), 2.22 (br. s., 2 H), 3.37 - 3.61 (m, 2 H), 3.77 (s, 3 H), 4.05 - 4.25 (m, 5 H), 5.83 (br. s., 1 H), 6.52 (d, J = 7.79 Hz, 1 H), 6.90 - 7.05 (m, 2 H), 7.15 (dd, J = 7.47, 1.70 Hz, 1 H), 7.24 - 7.33 (m, 1 H), 8.53 (t, J = 5.69 Hz, 1 H)	407.20(M +Na)
99		0.78 - 0.95 (m, 6 H), 1.32 - 1.72 (m, 6 H), 1.81 (d, J = 9.81 Hz, 1 H), 2.61 - 2.82 (m, 2 H), 2.97 (br. s., 1 H), 3.79 (d, J = 3.58 Hz, 3 H), 3.92 - 4.25 (m, 5 H), 6.46 (d, J = 7.98 Hz, 1 H), 6.86 - 7.02 (m, 2 H), 7.12 - 7.29 (m, 2 H), 8.44 - 8.59 (m, 1 H)	409.20(M +Na)

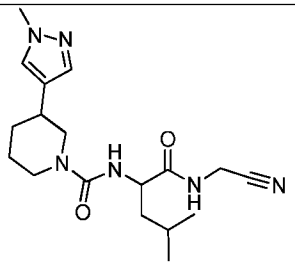
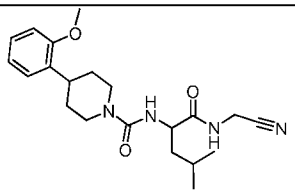
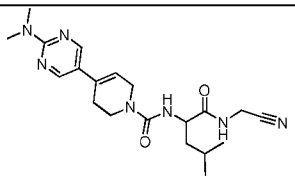
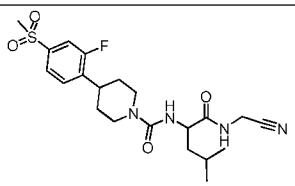
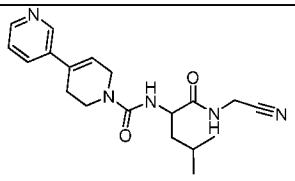
100		0.83 - 0.90 (m, 6 H) 1.31 - 1.63 (m, 7 H) 1.33 - 1.63 (m, 2 H) 2.65 - 2.80 (m, 3 H) 4.17 (br. s., 1 H) 4.11 (d, J=11.65 Hz, 3 H) 6.45 - 6.51 (m, 1 H) 7.08 - 7.16 (m, 2 H) 7.24 - 7.32 (m, 2 H) 8.77 (s, 1 H).	423.20(M +Na)
101		0.87 (dd, J=10.64, 6.42 Hz, 6 H) 1.09 (d, J=2.66 Hz, 2 H) 1.32 - 1.41 (m, 1 H) 1.45 - 1.70 (m, 8 H) 2.26 (s, 3 H) 2.71 - 2.82 (m, 2 H) 2.89 - 2.99 (m, 1 H) 4.10 (m, 3 H) 6.47 - 6.53 (m, 1 H) 7.00 - 7.13 (m, 3 H) 8.80 (s, 1 H).	437.25(M +Na)
102		0.86 (dd,J=12.10, 6.42 Hz, 6 H) 1.03 - 1.14 (m, 2 H) 1.31 - 1.42 (m, 1 H) 1.44 - 1.52 (m, 2 H) 1.53 - 1.67 (m, 2 H)2.42 (br. s., 2 H) 3.47 - 3.58 (m, 2 H) 3.75 (s, 3 H) 4.01 (dd, J=8.44, 2.84 Hz, 2 H) 4.06 - 4.17 (m, 1 H) 6.02 (br. s., 1 H) 6.53 (d, J=7.98 Hz, 1 H) 6.80 - 6.90(m, 2 H) 7.05 - 7.18 (m, 1 H) 8.83 (s, 1 H)	429.2
103		0.86 (dd,J=12.88, 6.37 Hz, 6 H) 1.04 - 1.13 (m, 2 H) 1.32 - 1.42 (m, 1 H) 1.43 - 1.50 (m, 2 H) 1.51 - 1.67 (m, 2 H)2.45 (s, 2 H) 3.50 - 3.61 (m, 2 H) 3.96 - 4.18 (m, 3 H) 6.19 (br. s., 1 H) 6.53 (d, J=8.07 Hz, 1 H) 7.28 (d,J=7.06 Hz, 1H) 7.36 (t,J=7.47 Hz, 2H) 7.41 - 7.50(m, 2H) 8.83 (s, 1H)	381.2
104		0.86 (dd,J=13.07, 6.37 Hz, 6 H) 1.03 - 1.13 (m, 2 H) 1.14 - 1.42 (m, 2 H) 1.44 - 1.52 (m, 2 H) 1.52 - 1.70 (m, 2 H)2.37 - 2.45 (m, 1 H) 3.22 (s, 3 H) 3.49 - 3.64 (m, 2 H) 3.99 - 4.16 (m, 3 H) 6.42 (br. s., 1 H) 6.58 (d, J=8.07 Hz, 1 H) 7.72 (d,J=8.53 Hz, 2 H)	459.2

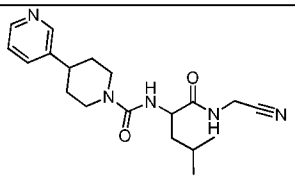
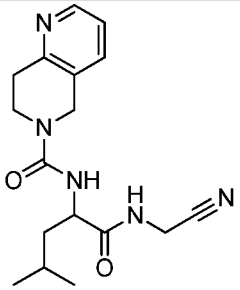
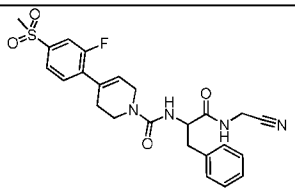
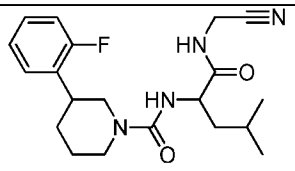
		7.89 (d,J=8.53Hz, 2 H) 8.84 (s, 1 H)	
105		0.84 - 0.99 (m, 2 H) 1.17 - 1.35 (m, 2 H) 1.44 - 1.58 (m, 1 H) 1.59 - 1.76 (m, 2 H) 1.85 - 1.98 (m, 1 H) 2.67 - 2.86 (m, 3 H) 3.21 (s, 3 H) 3.97 - 4.06 (m, 2 H) 4.09 (d, J=5.78 Hz, 2 H) 7.18 (d, J=0.28 Hz, 1 H) 7.51 - 7.64 (m, 2 H) 7.81 - 7.94 (m, 2 H) 8.20 - 8.32 (m, 1 H)	405.15
106		0.89 (t, J = 6.74 Hz, 6 H), 1.38 - 1.52 (m, 1 H), 1.55 - 1.71 (m, 2 H), 1.83 (quin, J = 6.26 Hz, 2 H), 2.69 (t, J = 6.46 Hz, 2 H), 3.62 (t, J = 6.01 Hz, 2 H), 4.15 (d, J = 5.59 Hz, 2 H), 4.25 (dd, J = 7.98, 4.95 Hz, 1 H), 6.70 (d, J = 7.89 Hz, 1 H), 6.89 - 6.97 (m, 1 H), 7.05 - 7.14 (m, 2 H), 7.46 (d, J = 7.89 Hz, 1 H), 8.67 (t, J = 5.59 Hz, 1 H)	329.15
107		0.86 (dd, J = 14.49, 6.33 Hz, 6 H), 1.35 - 1.50 (m, 1 H), 1.51 - 1.69 (m, 2 H), 2.28 (d, J = 1.83 Hz, 2 H), 3.52 (t, J = 5.91 Hz, 2 H), 3.80 (s, 3 H), 3.95 (d, J = 15.86 Hz, 2 H), 4.06 - 4.25 (m, 3 H), 5.93 (br. s., 1 H), 6.52 (d, J = 7.70 Hz, 1 H), 7.58 (s, 1 H), 7.76 (s, 1 H), 8.53 (t, J = 5.69 Hz, 1 H)	359.2
108		0.87 (dd, J=10.77, 6.46 Hz, 6 H) 1.06 - 1.12 (m, 2 H) 1.35 (m, 1 H) 1.44 - 1.62 (m, 6 H) 1.76 (d, J=12.29 Hz, 2 H) 2.71 - 2.88 (m, 3 H) 3.20 (s, 3 H) 4.14 (d, J=10.82 Hz, 3 H) 6.51 (d, J=7.89 Hz, 1 H) 7.53 (d, J=8.25 Hz, 2 H) 7.86 (d, J=8.34 Hz, 2 H) 8.80 (s, 1 H)	461.30(M +H)
109		0.87 (dd, J=10.82, 6.51 Hz, 6 H) 1.05 - 1.12 (m, 2 H) 1.35 (m, 1 H) 1.44 - 1.64 (m, 6 H) 1.73 (d, J=12.20 Hz, 2 H) 2.65 - 2.82 (m, 3	383.30(M +H)

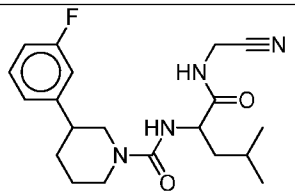
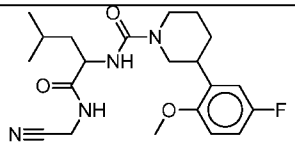
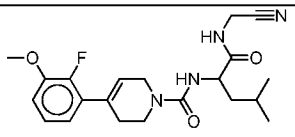
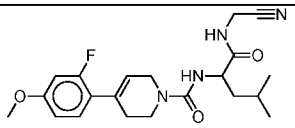
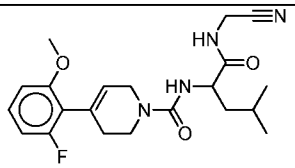
		H) 4.12 (d, J=11.37 Hz, 3 H) 6.49 (d, J=7.79 Hz, 1 H) 7.18 - 7.33 (m, 5 H) 8.79 (s, 1 H).	
110		0.82 - 0.93 (m, 2 H) 1.14 - 1.28 (m, 2 H) 3.14 (s, 3 H) 3.49 (t, J=5.32 Hz, 2 H) 3.97 (br. s., 2 H) 4.02 (d, J=5.69 Hz, 2 H) 6.34 (br. s., 1 H) 7.15 (s, 1 H) 7.65 (d, J=8.44 Hz, 2 H) 7.82 (d, J=8.44 Hz, 2 H) 8.34 (t, J=5.59 Hz, 1 H)	403.15
111		0.77 - 0.97 (m, 6 H) 1.34 - 1.78 (m, 6 H) 1.90 (d, J=11.19 Hz, 1 H) 2.63 - 2.86 (m, 2 H) 3.97 - 4.26 (m, 5 H) 6.56 (d, J=7.89 Hz, 1 H) 7.16 - 7.39 (m, 5 H) 8.46 (t, J=5.59 Hz, 1 H)	357.2
112		0.70 - 0.95 (m, 6 H) 1.30 - 1.76 (m, 6 H) 1.89 (d, J=11.00 Hz, 1 H) 2.57 - 2.84 (m, 3 H) 3.95 - 4.25 (m, 5 H) 6.58 (d, J=8.07 Hz, 1 H) 7.17 - 7.38 (m, 5 H) 8.44 - 8.58 (m, 1 H)	357.2
113		0.07 (m, 2 H), 0.27 (dd, J = 7.61, 3.21 Hz, 2 H), 0.55 - 0.70 (m, 1 H), 1.21 - 1.72 (m, 5 H), 2.58 - 2.79 (m, 4 H), 3.08 (s, 3 H), 3.G6396 - 4.16 (m, 5 H), 6.46 (d, J = 7.70 Hz, 1 H), 7.41 (d, J = 8.34 Hz, 2 H), 7.74 (d, J = 8.34 Hz, 2 H), 8.43 (t, J = 5.59 Hz, 1 H)	433.2
114		0.20 - 0.09 (m, 2 H) 0.16 - 0.38 (m, 2 H) 0.52 - 0.75 (m, 1 H) 1.27 (ddd, J=13.71, 7.79, 5.64 Hz, 1 H) 1.47 - 1.71 (m, 1 H) 3.09 (s, 3 H) 3.47 (t, J=5.41 Hz, 2 H) 3.91 - 4.15 (m, 5 H) 6.30 (br. s., 1 H) 6.53 (d, J=7.70 Hz, 1 H) 7.60 (d, J=8.53 Hz, 2 H) 7.77 (d, J=8.53 Hz, 2 H) 8.46 (t, J=5.69 Hz, 1 H)	431.2

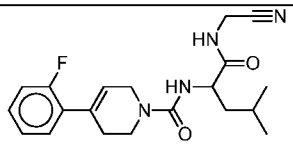
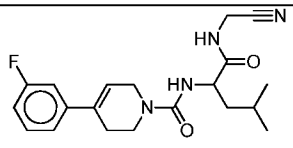
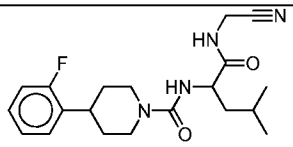
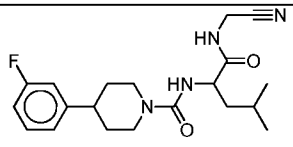
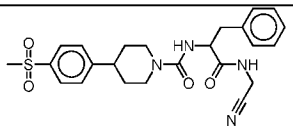
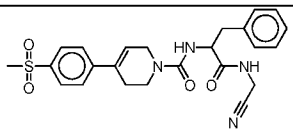
115		0.88 (dd, J=13.16, 6.37 Hz, 6 H) 1.36 - 1.70 (m, 3 H) 2.41 - 2.48 (m, 2 H) 3.36 (s, 3 H) 3.57 (t, J=5.50 Hz, 2 H) 3.96 - 4.26 (m, 5 H) 6.18 (br. s., 1 H) 6.61 (d, J=7.89 Hz, 1 H) 7.63 - 7.71 (m, 1 H) 7.72 - 7.83 (m, 2 H) 8.57 (t, J=5.59 Hz, 1 H)	451.2
116		0.78 - 0.96 (m, 6 H) 1.29 - 1.78 (m, 6 H) 1.90 (d, J=10.45 Hz, 1 H) 2.61 - 3.07 (m, 3 H) 3.27 (s, 3 H) 3.94 - 4.26 (m, 5 H) 6.59 (d, J=7.79 Hz, 1 H) 7.59 - 7.82 (m, 3 H) 8.53 (q, J=5.72 Hz, 1 H)	453.15
117		0.73 - 0.98 (m, 6 H) 1.30 - 1.73 (m, 6 H) 1.86 (d, J=11.83 Hz, 1 H) 2.02 (s, 3 H) 2.60 - 2.81 (m, 2 H) 3.89 - 4.26 (m, 5 H) 6.57 (d, J=7.24 Hz, 1 H) 7.19 (dd, J=8.44, 3.94 Hz, 2 H) 7.51 (d, J=8.44 Hz, 2 H) 8.50 (q, J=5.75 Hz, 1 H) 9.88 (s, 1 H)	414.25
118		0.76 - 0.97 (m, 6 H) 1.32 - 1.75 (m, 6 H) 1.87 (d, J=12.93 Hz, 1 H) 2.02 (s, 3 H) 2.60 - 2.82 (m, 2 H) 3.94 - 4.24 (m, 5 H) 6.57 (d, J=7.89 Hz, 1 H) 7.11 - 7.27 (m, 2 H) 7.51 (d, J=8.53 Hz, 2 H) 8.40 - 8.60 (m, 1 H) 9.89 (s, 1 H)	414.25
119		0.86 (dd, J=10.91, 6.33 Hz, 6 H) 1.28 - 1.72 (m, 6 H) 1.78 - 1.94 (m, 1 H) 2.02 (s, 3 H) 2.59 - 2.84 (m, 2 H) 3.90 - 4.27 (m, 5 H) 6.58 (d, J=7.98 Hz, 1 H) 7.20 (d, J=7.98 Hz, 2 H) 7.51 (d, J=7.98 Hz, 2 H) 8.42 - 8.58 (m, 1 H) 9.90 (s, 1 H)	414.25

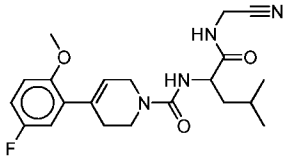
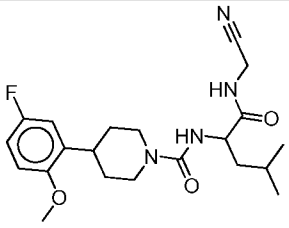
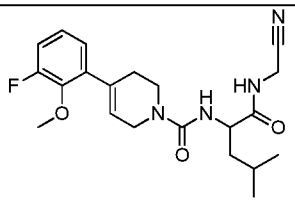
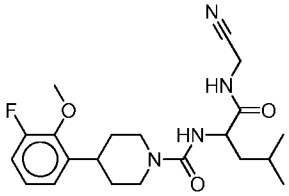
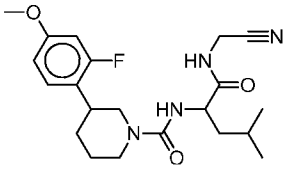
120		0.08 - 0.14 (m, 2 H) 0.24 - 0.44 (m, 2 H) 0.68 (br. s., 1 H) 1.25 - 1.50 (m, 2 H) 1.53 - 1.74 (m, 3H) 1.88 (d, J=10.36 Hz, 1 H) 2.59 - 2.86 (m, 3 H) 3.16 (s, 3 H) 3.94 - 4.21 (m, 5 H) 6.51 - 6.63 (m, 1 H) 7.53 (dd, J=8.39, 1.97 Hz, 2 H) 7.84 (d, J=8.34 Hz, 2 H) 8.41 - 8.53 (m, 1 H)	433.2
121		0.88 (dd, J = 12.24, 6.28 Hz, 6 H), 1.36 - 1.50 (m, 1 H), 1.51 - 1.73 (m, 2 H), 2.41 (br. s., 2 H), 3.51 (t, J = 5.32 Hz, 2 H), 3.77 (s, 3 H), 3.87 - 4.03 (m, 2 H), 4.04 - 4.14 (m, 2 H), 4.16 - 4.25 (m, 1 H), 5.77 (br. s., 1 H), 6.50 (d, J = 7.98 Hz, 1 H), 6.88 - 6.95 (m, 1 H), 6.99 (d, J = 8.07 Hz, 1 H), 7.14 (d, J = 6.79 Hz, 1 H), 7.20 - 7.30 (m, 1 H), 8.54 (t, J = 5.46 Hz, 1 H)	385.2
122		0.87 (dd, J = 13.85, 6.33 Hz, 6 H), 1.38 - 1.49 (m, 1 H), 1.52 - 1.69 (m, 2 H), 2.44 (br. s., 2 H), 3.56 (t, J = 5.64 Hz, 2 H), 3.76 (s, 3 H), 4.01 (d, J = 10.45 Hz, 2 H), 4.11 (d, J = 5.59 Hz, 2 H), 4.20 (br. s., 1 H), 6.07 (br. s., 1 H), 6.53 (d, J = 8.07 Hz, 1 H), 6.91 (d, J = 8.80 Hz, 2 H), 7.38 (s, 2 H), 8.53 (t, J = 5.87 Hz, 1 H)	385.25
123		0.87 (d, J=14.40 Hz, 6 H) 1.13 (br. s., 1 H) 1.41 - 1.69 (m, 2 H) 2.27 (br. s., 2 H) 3.50 (br. s., 2 H) 4.11 (br. s., 2 H) 4.25 (d, J=14.21 Hz, 3 H) 6.44 (br. s., 1 H) 6.70 (d, J=6.97 Hz, 1 H) 7.41 (d, J=4.13 Hz, 1 H) 7.89 (d, J=7.15 Hz, 1 H) 8.45 - 8.62 (m, 2 H) 8.73 (br. s., 1 H)	356.2

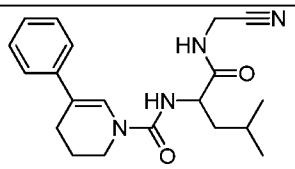
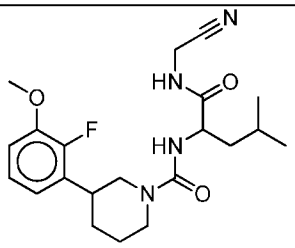
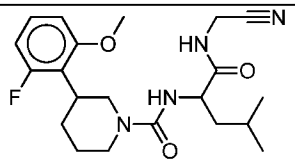
124		0.77 - 0.95 (m, 6 H) 1.23 (br. s., 1 H) 1.30 - 1.47 (m, 3 H) 1.61 (br. s., 3 H) 1.94 (br. s., 1 H) 2.61 - 2.81 (m, 2 H) 3.78 (br. s., 3 H) 3.91 - 4.24 (m, 5 H) 6.52 (br. s., 1 H) 7.31 (d, J=2.29 Hz, 1 H) 7.51 (d, J=3.03 Hz, 1 H) 8.48 (br. s., 1 H)	361.2
125		0.88 (dd, J = 11.92, 6.42 Hz, 6 H), 1.32 - 1.72 (m, 7 H), 2.65 - 2.84 (m, 2 H), 3.05 (t, J = 12.01 Hz, 1 H), 3.79 (s, 3 H), 4.04 - 4.26 (m, 5 H), 6.53 (d, J = 7.79 Hz, 1 H), 6.83 - 7.02 (m, 2 H), 7.10 - 7.24 (m, 2 H), 8.53 (t, J = 5.46 Hz, 1 H)	387.2
126		0.87 (dd, J=14.31, 6.33 Hz, 6 H) 1.34 - 1.69 (m, 3 H) 2.41 (br. s., 2 H) 3.13 (s, 6 H) 3.55 (br. s., 2 H) 4.01 (br. s., 2 H) 4.11 (d, J=5.50 Hz, 2 H) 4.14 - 4.24 (m, 1 H) 6.10 (br. s., 1 H) 6.56 (d, J=7.98 Hz, 1 H) 8.47 (s, 2 H) 8.54 (t, J=5.73 Hz, 1 H)	400.25
127		0.88 (dd, J=11.88, 6.37 Hz, 6 H) 1.35 - 1.48 (m, 1 H) 1.48 - 1.68 (m, 4 H) 1.68 - 1.81 (m, 2 H) 2.71 - 2.90 (m, 2 H) 3.09 (t, J=11.92 Hz, 1 H) 3.27 (s, 3 H) 4.08 - 4.26 (m, 5 H) 6.58 (d, J=7.89 Hz, 1 H) 7.56 - 7.68 (m, 1 H) 7.70 - 7.79 (m, 2 H) 8.55 (t, J=5.64 Hz, 1 H)	453.2
128		0.87 (dd, J = 13.94, 6.33 Hz, 6 H), 1.37 - 1.51 (m, 1 H), 1.52 - 1.71 (m, 2 H), 3.17 (d, J = 5.23 Hz, 2 H), 3.59 (br. s., 2 H), 4.00 - 4.14 (m, 4 H), 4.15 - 4.26 (m, 1 H), 6.32 (br. s., 1 H), 6.60 (d, J = 7.61 Hz, 1 H), 7.38 (dd, J = 7.93, 4.63 Hz, 1 H), 7.85 (d, J = 8.25 Hz, 1 H), 8.47 (d, J = 3.67 Hz, 1 H), 8.56 (t, J =	356.2

		5.41 Hz, 1 H), 8.69 (d, J = 1.74 Hz, 1 H)	
129		0.88 (dd, J = 11.97, 6.37 Hz, 6 H), 1.33 - 1.68 (m, 5 H), 1.76 (d, J = 11.65 Hz, 2 H), 2.67 - 2.86 (m, 3 H), 4.07 - 4.24 (m, 5 H), 6.56 (d, J = 7.89 Hz, 1 H), 7.33 (dd, J = 7.66, 4.81 Hz, 1 H), 7.66 (d, J = 7.79 Hz, 1 H), 8.42 (d, J = 3.39 Hz, 1 H), 8.46 - 8.57 (m, 2 H)	358.15
130		0.86 (dd, J=16.51, 6.33 Hz, 6 H) 1.37 - 1.51 (m, 1 H) 1.52 - 1.70 (m, 2 H) 2.87 (q, J=5.75 Hz, 2 H) 3.71 (t, J=5.87 Hz, 2 H) 4.10 (d, J=5.59 Hz, 2 H) 4.15 - 4.25 (m, 1 H) 4.49 - 4.63 (m, 2 H) 6.71 (d, J=7.89 Hz, 1 H) 7.22 (dd, J=7.66, 4.81 Hz, 1 H) 7.55 (d, J=7.43 Hz, 1 H) 8.37 (d, J=3.39 Hz, 1 H) 8.56 (t, J=5.46 Hz, 1 H)	330.15
131		2.39 (br. s., 2 H), 2.82 - 3.06 (m, 3 H), 3.28 (s, 3 H), 3.49 (br. s., 2 H), 3.85 - 3.97 (m, 1 H), 4.06 - 4.18 (m, 2 H), 4.34 (br. s., 1 H), 6.14 (br. s., 1 H), 6.79 (d, J = 8.07 Hz, 1 H), 7.19 (d, J = 6.79 Hz, 1 H), 7.22 - 7.34 (m, 4 H), 7.57 - 7.68 (m, 1 H), 7.70 - 7.82 (m, 2 H), 8.69 (t, J = 5.69 Hz, 1 H)	485.2
132		0.76 - 0.98 (m, 6 H) 1.31 - 1.47 (m, 2 H) 1.49 - 1.76 (m, 4 H) 1.86 (d, J=11.65 Hz, 1 H) 2.72 (d, J=11.65 Hz, 1 H) 2.77 - 2.96 (m, 2 H) 3.97 - 4.23 (m, 5 H) 6.58 (d, J=7.89 Hz, 1 H) 7.10 - 7.23 (m, 2 H) 7.24 - 7.33 (m, 1 H) 7.38 (t, J=7.61 Hz, 1 H) 8.44 - 8.58 (m, 1 H)	397.15[M+Na]

133		0.76 - 0.96 (m, 6 H) 1.42 (dd, J=8.71, 3.94 Hz, 2 H) 1.47 - 1.75 (m, 4 H) 1.90 (d, J=12.01 Hz, 1 H) 2.57 - 2.85 (m, 3 H) 3.99 - 4.24 (m, 5 H) 6.60 (d, J=7.34 Hz, 1 H) 7.06 (t, J=8.30 Hz, 1 H) 7.10 - 7.21 (m, 2 H) 7.30 - 7.43 (m, 1 H) 8.53 (d, J=5.32 Hz, 1 H)	397.15 [M+Na]
134		0.80 - 0.95 (m, 6 H) 1.41 (d, J=8.62 Hz, 2 H) 1.46 - 1.69 (m, 4 H) 1.80 (d, J=8.99 Hz, 1 H) 2.61 - 2.82 (m, 2 H) 2.95 (br. s., 1 H) 3.78 (d, J=3.76 Hz, 3 H) 3.90 - 4.24 (m, 5 H) 6.48 (d, J=7.98 Hz, 1 H) 6.91 - 7.15 (m, 3 H) 8.47 - 8.60 (m, 1 H)	427.15 [M+Na]
135		0.87 (dd, J = 13.30, 6.33 Hz, 6 H), 1.33 - 1.49 (m, 1 H), 1.51 - 1.74 (m, 2 H), 2.42 (br. s., 2 H), 3.54 (t, J = 5.27 Hz, 2 H), 3.83 (s, 3 H), 3.91 - 4.26 (m, 5 H), 5.98 (br. s., 1 H), 6.58 (d, J = 7.79 Hz, 1 H), 6.85 - 6.95 (m, 1 H), 7.03 - 7.16 (m, 2 H), 8.57 (t, J = 5.36 Hz, 1 H)	425.15(M +Na)
136		0.87 (dd, J = 13.34, 6.28 Hz, 6 H), 1.44 (d, J = 8.80 Hz, 1 H), 1.51 - 1.71 (m, 2 H), 2.40 (br. s., 2 H), 3.54 (br. s., 2 H), 3.77 (s, 3 H), 3.92 - 4.26 (m, 5 H), 5.93 (br. s., 1 H), 6.57 (d, J = 8.07 Hz, 1 H), 6.74 - 6.88 (m, 2 H), 7.28 (t, J = 8.71 Hz, 1 H), 8.53 - 8.61 (m, 1 H)	425.15(M +Na)
137		0.88 (dd, J = 12.01, 6.33 Hz, 6 H), 1.33 - 1.50 (m, 1 H), 1.51 - 1.72 (m, 2 H), 2.26 (br. s., 2 H), 3.53 (t, J = 5.32 Hz, 2 H), 3.78 (s, 3 H), 3.85 - 4.27 (m, 5 H), 5.65 (br. s., 1 H), 6.56 (d, J = 8.07 Hz, 1 H), 6.75 - 6.89 (m, 2 H), 7.22 - 7.34 (m, 1 H), 8.59 (t, J = 5.41	425.15

		Hz, 1 H)	
138		0.88 (dd, J=13.02, 6.33 Hz, 6 H) 1.35 - 1.51 (m, 1 H) 1.52 - 1.74 (m, 2 H) 2.44 (br. s., 2 H) 3.56 (t, J=5.23 Hz, 2 H) 3.97 - 4.27 (m, 5 H) 6.01 (br. s., 1 H) 6.58 (d, J=7.89 Hz, 1 H) 7.13 - 7.24 (m, 2 H) 7.26 - 7.45 (m, 2 H) 8.57 (t, J=5.41 Hz, 1 H)	395.15
139		0.87 (dd, J=14.08, 6.28 Hz, 6 H) 1.36 - 1.51 (m, 1 H) 1.52 - 1.71 (m, 2 H) 2.46 (br. s., 2 H) 3.50 - 3.65 (m, 2 H) 3.99 -4.26 (m, 5 H) 6.30 (br. s., 1 H) 6.60 (d, J=7.79 Hz, 1 H) 7.10 (t, J=8.25 Hz, 1 H) 7.23 - 7.34 (m, 2 H) 7.35 - 7.46 (m, 1 H) 8.56 (t, J=5.46 Hz, 1 H)	395.15
140		0.88 (dd, J=11.97, 6.37 Hz, 6 H) 1.37 - 1.77 (m, 7 H) 2.69 - 2.87 (m, 2 H) 2.99 (t, J=11.83 Hz, 1 H) 4.04 - 4.26 (m, 5H) 6.57 (d, J=7.98 Hz, 1 H) 7.09 - 7.20 (m, 2 H) 7.22 - 7.37 (m, 2 H) 8.54 (t, J=5.46 Hz, 1 H)	397.15
141		0.87 (dd, J=12.24, 6.28 Hz, 6 H) 1.29 - 1.65 (m, 5 H) 1.75 (d, J=11.92 Hz, 2 H) 2.75 (q, J=11.31 Hz, 3 H) 3.98 - 4.25(m, 5 H) 6.55 (d, J=7.79 Hz, 1 H) 6.91 - 7.14 (m, 3 H) 7.25 - 7.43 (m, 1 H) 8.54 (t, J=5.41 Hz, 1 H)	397.2
142		1.22 - 1.48 (m, 2 H), 1.60 - 1.76 (m, 2 H), 2.61 - 3.06 (m, 5 H), 3.20 (s, 3 H), 3.99 - 4.21 (m, 4 H), 4.36 (br. s., 1 H), 6.74 (d, J = 8.25 Hz, 1 H), 7.16 - 7.34 (m, 5 H), 7.45 (d, J = 8.25 Hz, 2 H), 7.86 (d, J = 8.16 Hz, 2 H), 8.66 (t, J = 5.36 Hz, 1 H)	491.5(M+ Na)
143		2.42 (br. s., 2 H), 2.83 - 2.93 (m, 1 H), 2.95 - 3.07 (m, 2 H), 3.22 (s, 3 H), 3.51 (br. s., 2 H), 4.00 - 4.19 (m, 3 H), 4.28 - 4.41 (m, 1	489.15(M +Na)

		H), 6.38 (br. s., 1 H), 6.80 (d, J = 7.79 Hz, 1 H), 7.18 (d, J = 6.14 Hz, 1 H), 7.21 - 7.35 (m, 4 H), 7.68 (d, J = 8.25 Hz, 2 H), 7.89 (d, J = 8.44 Hz, 2 H), 8.69 (br. s., 1 H)	
144		0.88 (dd, J=11.83, 6.42 Hz, 6 H) 1.34 - 1.74 (m, 7 H) 2.75 (q, J=10.88 Hz, 2 H) 2.97 - 3.11 (m, 1 H) 3.78 (s, 3 H) 4.05 - 4.23 (m, 5 H) 6.54 (d, J=7.89 Hz, 1 H) 6.97 (dd, J=5.04, 2.84 Hz, 3 H) 8.54 (t, J=5.46 Hz, 1 H)	425.15
145		0.88 (dd, J=11.83, 6.42 Hz, 6 H) 1.34 - 1.74 (m, 7 H) 2.75 (q, J=10.88 Hz, 2 H) 2.97 - 3.11 (m, 1 H) 3.78 (s, 3 H) 4.05 - 4.23 (m, 5 H) 6.54 (d, J=7.89 Hz, 1 H) 6.97 (dd, J=5.04, 2.84 Hz, 3 H) 8.54 (t, J=5.46 Hz, 1 H)	427.2
146		0.88 (dd, J=12.93, 6.33 Hz, 6 H) 1.37 - 1.50 (m, 1 H) 1.53 - 1.73 (m, 2 H) 2.42 (br. s., 2 H) 3.54 (t, J=5.32 Hz, 2 H) 3.78 (s, 3 H) 4.01 (d, J=16.78 Hz, 2 H) 4.12 (d, J=5.50 Hz, 2 H) 4.15 - 4.26 (m, 1 H) 5.89 (br. s., 1 H) 6.57 (d, J=7.98 Hz, 1 H) 6.98 - 7.12 (m, 2 H) 7.13 - 7.25 (m, 1 H) 8.57 (t, J=5.32 Hz, 1 H)	425.15
147		0.88 (dd, J=11.51, 6.37 Hz, 6 H) 1.35 - 1.75 (m, 7 H) 2.66 - 2.88 (m, 2 H) 3.01 - 3.15 (m, 1 H) 3.84 (s, 3 H) 4.17 (d, J=8.34 Hz, 5 H) 6.54 (d, J=7.79 Hz, 1 H) 6.96 - 7.19 (m, 3 H) 8.55 (br. s., 1 H)	427.2
148		0.73 - 0.98 (m, 6 H) 1.31 - 1.90 (m, 7 H) 2.62 - 2.90 (m, 3 H) 3.75 (s, 3H) 3.91 - 4.28 (m, 5 H) 6.56 (br. s., 1 H) 6.67 - 6.92 (m, 2	427.2

		H) 7.16 - 7.36 (m, 1 H) 8.53 (d, J=5.87 Hz, 1 H)	
149		0.87 (dd, J = 1.00 Hz, 6 H), 1.37 - 1.50 (m, 1 H), 1.52 - 1.74 (m, 2 H), 2.25 (br. s., 2 H), 3.49 (br. s., 2 H), 4.11 (d, J = 3.03 Hz, 2 H), 4.18 - 4.34 (m, 3 H), 6.32 (br. s., 1 H), 6.71 (d, J = 7.70 Hz, 1 H), 7.30 (d, J = 6.60 Hz, 1 H), 7.37 (t, J = 7.20 Hz, 2 H), 7.49 (d, J = 7.15 Hz, 2 H), 8.58 (br. s., 1 H)	377.15(M +Na)
150		0.77 - 0.98 (m, 6 H) 1.30 - 1.93 (m, 7 H) 2.60 - 2.98 (m, 3 H) 3.85 (s, 3H) 3.97 - 4.25 (m, 5 H) 6.59 (br. s., 1 H) 6.91 (t, J=6.51 Hz, 1 H) 6.97 - 7.19 (m, 2 H) 8.40 - 8.65 (m, 1 H)	427.2
151		0.87 (dd, J=8.85, 6.74 Hz, 6 H) 1.29 - 1.91 (m, 7 H) 2.60 - 3.08 (m, 3 H) 3.83 (br. s., 3 H) 3.91 - 4.29 (m, 5 H) 6.54 (d, J=7.79 Hz, 1 H) 6.97 - 7.22 (m, 3 H) 8.46 - 8.68 (m, 1 H)	427.2

BIOLOGICAL ACTIVITY

The pharmacological activities of the compound of this present invention were confirmed by the following experiments.

(a) Measurement of Human Cathepsin K, L, V and S Inhibitory Activity:

All assays for cathepsin K was carried out with human recombinant enzyme (purchased from Enzo Lifesciences). Assays for cathepsins L, S and V were carried out with human recombinant enzyme (purchased from RnD Systems). Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically (5*S*,8*S*)-13-amino-5-benzyl-13-imino-3-methylene-N-(4-methyl-2-oxo-2H-chromen-7-yl)-6-oxo-1-phenyl-2-oxa-4,7,12-triazatridecane-8-carboxamide (Cbz-Phe-Arg-AMC) for Cat K and were determined in 50 mM sodium acetate at pH 5.5 containing 1 mM dithiothreitol, 2.5 mM EDTA and 0.01% TritinX-100. For Cat L, S And V, the substrate used was benzyl N-[1-[[5-

(diaminomethylideneamino)-1-[(4-methyl-2-oxochromen-7-yl)amino]-1-oxopentan-2-yl]amino]-4-methyl-1-oxopentan-2-yl]carbamate (Cbz-Leu-Arg-AMC). A stock substrate solution of Cbz-Phe-Arg-AMC or Cbz-Leu-Arg-AMC was prepared at a concentration of 50 mM in dimethyl sulfoxide. This substrate was diluted into the assay for a final substrate concentration of 10 μM in all the assays. The K*m* value for Cbz-Phe-Arg-AMC on human Cat K is 12 μM. The Km value for Cbz-Leu-Arg-AMC on human Cat S is 32 μM, on human Cat L is 4 μM and on human cathepsin V is 7 μM. The total reaction time was 60 min for human Cat K, L and V (final protein concentrations were 0.3 nM, 0.1 nM and 5 nM respectively); for human Cat S it was 30 min (final protein concentration was 1.25 nM).

Prior to the addition of substrate, different concentrations of the inhibitor ranging from 100 μM to 0.2 nM were pre-incubated for 15 min with each enzyme to allow the establishment of the enzyme-inhibitor complex. Substrate was then added and the enzyme activity measured from the increase of fluorescence measured (λ_{ex} (excitation wavelength) =355 nm, λ_{em} (fluorescence wavelength) =460 nm). The final volume of the reaction was 100 μL. Assays were performed in 96-well plate format and the plate read using an Envision (PerkinElmer) plate reader. The percent inhibition of the reaction was calculated from a control reaction containing only vehicle. IC_{50} curves were generated by fitting percent inhibition values to a four parameter logistic model (PRISM).

(ii) Measurement of Rat Cathepsin K Inhibitory Activity

All assays for rat cathepsin K was carried out with rat recombinant enzyme (purchased from Biovision Inc.). Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically (5*S*,8*S*)-13-amino-5-benzyl-13-imino-3-methylene-N-(4-methyl-2-oxo-2H-chromen-7-yl)-6-oxo-1-phenyl-2-oxa-4,7,12-triazatridecane-8-carboxamide (Cbz-Phe-Arg-AMC) and were determined in 100 mM sodium acetate at pH 5.5 containing 10 mM dithiothreitol and 120 mM sodium chloride. A stock substrate solution of Cbz-Phe-Arg-AMC was prepared at a concentration of 50 mM in dimethyl sulfoxide. This substrate was diluted into the assay for a final substrate concentration of 30 μM in the rat cathepsin K assay. The Km value for Cbz-Phe-Arg-AMC on rat cathepsin K is 27 μM. The total reaction time was 120 min for rat Cat K (final protein concentrations was 50 nM).

Prior to the addition of substrate, different concentrations of the inhibitor ranging from 100 μM to 0.2 nM were pre-incubated for 15 min with each enzyme to allow the establishment of the enzyme-inhibitor complex. Substrate was then added and the enzyme activity measured from the increase of fluorescence measured (λ_{ex} (excitation wavelength) =355 nm, λ_{em} (fluorescence wavelength) =460 nm). The final volume of the reaction was 100 μL. Assays were performed in 96-well plate format and the plate read using an Envision (PerkinElmer) plate reader. The percent inhibition of the reaction was calculated from a control reaction containing only vehicle. IC_{50} curves were generated by fitting percent inhibition values to a four parameter logistic model (PRISM).

Results of *in-vitro* inhibition: Cathepsin K, S, L and V enzymes. The IC_{50}s on isolated enzymes and aqueous solubility of compounds were categorised as follows:

IC_{50} range for Cat K,S,L and V	Aqueous solubility range
IC_{50}=1000-100nm: +	≤100μM = +
IC_{50}=100-10: ++	100-300μM = ++
$IC_{50} \leq$ 10nm: +++	≥300μM = +++
Rat Cat K $IC_{50}\leq$: 500nm: +++	
Rat Cat K $IC_{50}\geq$: 500nm: +	

Sl No.	**IC50-catK_nM**	**IC50-catS_nM**	**Aq.sol_uM**	**Rat IC50-catK_nM**
1	++	++	+++	+++
2	+++	++	+++	+++
3	+++	++	+++	+++
4	++	+	+++	+++
5	+	+	++	NA
6	++	++	+++	+++
7	+	+	+++	+
8	++	+	+++	+++

9	+++	++	+++	+++
10	+++	++	+++	+++
11	+++	++	+++	+++
12	++	++	+++	+++
13	++	++	+++	+++
14	++	++	+++	+
15	++	+	+++	+++
16	++	+	+++	+
17	+++	++	++	+++
18	++	++	+++	+++
19	++	+	+++	+++
20	++	+	+++	+
21	++	+	+++	+++
22	+++	+	++	+++
23	+++	+	+++	+++
24	++	++	+	+++
25	++	++	+++	+++
26	+++	++	+++	+++
27	++	++	+++	+++
28	++	+++	+	+++
29	++	+++	++	+++
30	++	+++	+++	+++
31	++	+++	++	+++
32	++	+++	+++	+++
33	+++	++	+++	+++

34	+	+	++	+
35	+	+	+++	NA
36	++	+++	+	NA
37	+	+	+	NA
38	+	+	++	NA
39	++	++	+	NA
40	+	+	++	NA
41	+	+	+	NA
42	++	++	+	NA
43	++	++	+	NA
44	++	++	+++	NA
45	++	++	++	NA
46	++	++	+++	NA
47	+	++	+	NA
48	+	++	+	NA
49	++	++	+	NA
50	+++	++	+	+++
51	+++	++	+	+++
52	++	++	+	NA
53	++	++	++	NA
54	++	++	+++	NA
55	++	++	+++	NA
56	+++	++	++	+++
57	+++	++	+++	+++
58	++	++	+	NA

59	++	++	++	NA
60	++	+++	++	NA
61	++	+++	++	NA
62	+	++	++	NA
63	++	++	++	NA
64	+++	++	++	+++
65	++	++	++	NA
66	++	++	++	NA
67	++	++	++	NA
68	++	+	+	NA
69	++	+	+	NA
70	++	++	+++	NA
71	++	++	+++	NA
72	++	+	+	+++
73	+	+	++	NA
74	+	+	+	NA
75	++	+	+	+++
76	+	+	++	NA
77	+	+	++	NA
78	+	+	++	NA
79	+	+	+	NA
80	+	++	++	NA
81	++	++	+++	NA
82	+	+	+++	NA
83	+	+	+++	NA

84	++	++	++	+++
85	+	++	+	NA
86	++	+	+	+++
87	+	+	+++	+++
88	+	+	+++	+
89	++	++	++	NA
90	++	++	++	NA
91	+	++	++	NA
92	++	++	+++	NA
93	++	++	+++	+++
94	++	++	+++	+++
95	+++	++	++	+++
96	+	+	++	NA
97	++	++	+	+++
98	+	++	+	NA
99	+	++	+++	NA
100	+	+	++	NA
101	+	+	++	NA
102	+++	++	+	+++
103	+++	++	+	+++
104	+++	++	+++	+++
105	+	+	++	NA
106	+	++	+++	NA
107	++	++	+++	NA
108	++	++	++	+++

109	++	++	++	+++
110	+	+	++	NA
111	++	++	++	NA
112	++	++	++	NA
113	+	+	++	NA
114	++	+	+++	NA
115	+++	++	+++	+++
116	++	++	++	NA
117	++	++	+++	NA
118	++	++	+++	NA
119	++	++	+++	NA
120	+	++	+++	NA
121	++	+	+++	+++
122	+++	++	++	+++
123	++	++	+++	NA
124	++	++	++	NA
125	++	++	++	NA
126	+++	++	+++	NA
127	+++	++	+++	NA
128	+++	++	+++	NA
129	+++	+	+++	+
130	+++	++	+++	+
131	++	++	++	NA
132	++	+++	+++	NA
133	++	+++	++	NA

134	+	++	++	NA
135	++	+	++	NA
136	+++	++	++	NA
137	+++	+	++	NA
138	+++	++	++	NA
139	+++	++	++	NA
140	++	++	++	NA
141	+++	++	++	NA
142	+	+	+++	NA
143	++	+	+++	NA
144	+++	++	++	NA
145	++	++	++	NA
146	+++	++	+	NA
147	++	++	++	NA
148	+++	+++	++	NA
149	+++	++	+	NA
150	++	++	++	NA
151	++	++	+++	NA

NA=Not available/Not determined

As can be seen from the table the compounds of the invention demonstrated good solubility coupled with cathepsin K activity.

Efficacy study of a test compound in Ovariectomized rat osteoporosis model:

Abbreviations

- OVX -Ovariectomy
- µg - microgram

- g -Gram
- µL - microliter
- mg - milligram
- mL - milliliter
- SC - subcutaneous
- Kg -Kilogram
- ODN - Odanacatib
- ALN -Alendronate
- ESD -17-a-ethinyl oestradiol
- OD -Once in a day
- BID -Twice in a day
- PO - Per Oral
- MC -Methyl cellulose
- q.s. -Quantity sufficient
- DMSO -Dimethyl sulphoxide
- EDTA - Ethylenediaminetetraacetic acid
- CPCSEA - Committee for the Purpose of Control and Supervision on Experiments on Animals
- IAEC - Institutional Animal Ethic Committee
- Test Compound: Compound#1

Efficacy study: Biomarkers & parameters followed:

CTx-1: C-terminal telopeptide (or more formally, carboxy-terminal collagen crosslinks), is a telopeptide generated from Collagen type 1 by the action of CatK, used as a biomarker in the serum to measure the rate of bone turnover/CatK activity.

Osteocalcin: Osteocalcin is secreted solely by osteoblasts & is often used as a marker for the bone formation process.

P1NP: amino-terminal propeptide (PINP), sensitive marker of bone formation.

Body weight gain: Ovariectomy is manifested by increase in body weight.

Toxicity evaluation: Necropsy after treatment & visual observation during treatment.

Study Design: Species: Rat

Strain : Sprague Dawley

Sex: Female

Age, Weight : 12-13 weeks of age at study, 220-260g

No of animals per group : 10

Animals were dosed for a period of 3 weeks with test compound#1, as PO at 3 and 10mg/kg BID. Reference drugs ODN and ALN were dosed as PO at 10 and 3mg/kg OD. ESD was dosed at 0.03mg/kg(SC dosing) OD.

Results:

1. There was no toxicityseen due to compound administration over 3 weeks. No gross pathological observation of abnormality for all organs after necropsy in all treated animals.

2. Compound#6 showed dose dependant reduction in CTx-1 levels after 3 weeks when compared to untreated OVX animals.

3. Compound#6 at 10mpk showed significant reduction in relative change (%) in body weight from day 15 onwards.

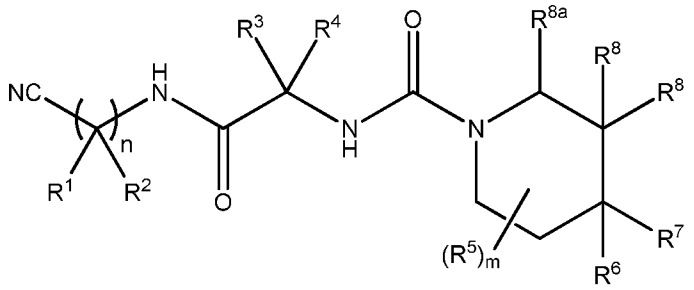
4. Compound#6 pharmacokinetics did not show any apparent accumulation or decrease in steady state concentration on repeated dosing for 3 weeks.

5. Reference drugs Estradiol (ESD) and Alendronate (ALN) showed significant CTx-1 reduction.

The details of specific embodiments described in this invention are not to be construed as limitations. Various equivalents and modifications may be made without departing from the essence and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

THE CLAIMS DEFINING THIS INVENTION ARE AS FOLLOWS:

1. A compound of formula (I)



(I)

wherein

each R^1 is independently selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6 haloalkyl,

each R^2 is independently selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6 haloalkyl, or

R^1 and R^2 when taken together with the carbon atoms to which they are attached form a C_3-C_8cycloalkyl group;

R^3 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl,

R^4 is selected from the group consisting of hydrogen andoptionally substituted C_1-C_6 alkyl, or

R^3 and R^4 when taken together with the carbon atoms to which they are attached form a C_3-C_8cycloalkyl group;

R^5 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl;

m is an integer selected from the group consisting of 0, 1, 2, 3, or 4;

n is an integer selected from the group consisting of 1, 2, or 3;

R^6 is selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide;

R^7 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl,

each R^8 is independently selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide,

$R^{8a}$is selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide; or

R^7 and one R^8 when taken together form a bond, or

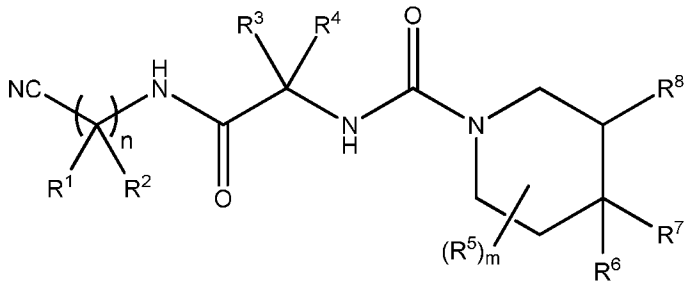
one R^8 and R^{8a} when taken together form a bond, or

R^7 and one R^8 when taken together with the carbon atoms to which they are attached form an optionally substitutedaliphatic or aromatic cyclic moiety, wherein when the cyclic moiety is aromatic R^6 and the other R^8 group is absent, or

one R^8 and R^{8a} when taken together with the carbon atoms to which they are attached form an optionally substituted aliphatic or aromatic cyclic moiety, wherein when the cyclic moiety is aromatic the other R^8 group is absent;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the compound has the formula



wherein

each R^1 is independently selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6 haloalkyl,

each R^2 is independently selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6 haloalkyl, or

R^1 and R^2 when taken together with the carbon atoms to which they are attached form a C_3-C_8cycloalkyl group;

R^3 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl,

R^4 is selected from the group consisting of hydrogen andoptionally substituted C_1-C_6 alkyl, or

R^3 and R^4 when taken together with the carbon atoms to which they are attached form a C_3-C_8cycloalkyl group;

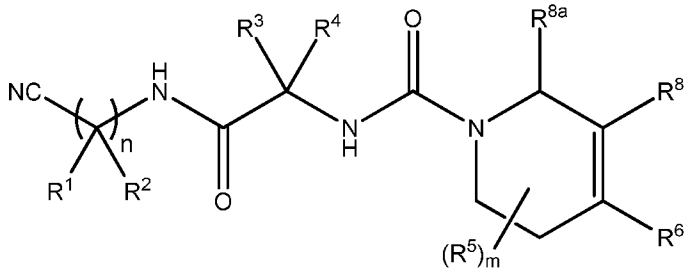
R^5 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl;

m is an integer selected from the group consisting of 0, 1, 2, 3, or 4;

n is an integer selected from the group consisting of 1, 2, or 3;

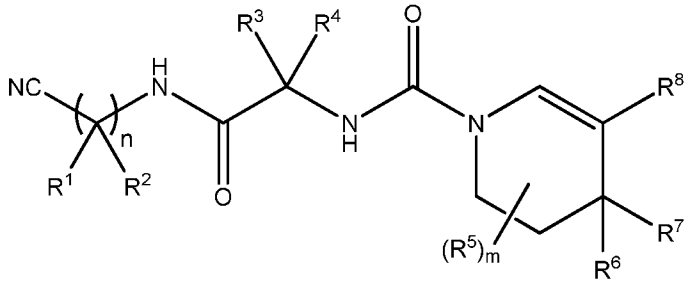
R^6 is selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide;
R^7 is selected from the group consisting of hydrogen, C_1-C_6alkyl and C_1-C_6haloalkyl,
R^8 is selected from the group consisting of hydrogen, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl and optionally substituted carboxamide, or
R^7 and R^8 when taken together form a bond, or
or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1, wherein the compound has theformula



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^{8a}, n and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1, wherein the compound has theformula



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, n and m are as defined in claim 1,
or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4, wherein R^1 is hydrogen.

6. A compound according to claim any one of claims 1 to 5, wherein R^2 is hydrogen.

7. A compound according to any one of claims 1 to 4, wherein R^1 and R^2 when taken together with the carbon atoms to which they are attached form a cyclopropyl group.

8. A compound according to any one of claims 1 to 7, wherein R^3 is hydrogen.

9. A compound according to any one of claims 1 to 8, wherein R^4 is C_{1-6} alkyl optionally substituted with methanesulfonyl-, halo- or alkoxy- groups.

10. A compound according to any one of claims 1 to 7, wherein R^3 and R^4 when taken together with the carbon atoms to which they are attached form a cyclohexyl group

11. A compound according to any one of claims 1 to 10, wherein R^5 is hydrogen.

12. A compound according to any one of claims 1 to 11, wherein R^6 is selected from the group consisting of a *N*-phenylamido group, a substituted phenyl group, a substituted pyridyl group, a substituted pyrazolyl group, a substituted pyrimidinyl group,a substituted indolyl group and a substituted isoxazole.

13. A compound according to any one of claims 1 to 12, wherein R^7 is hydrogen.

14. A compound according to any one of claims 1 to 13, wherein R^8 is selected from the group consisting of a *N*-phenylamido group, a substituted phenyl group, a substituted pyridyl group, a substituted pyrazolyl group, a substituted pyrimidinyl group,a substituted indolyl group and a substituted isoxazole.

15. A compound according to any one of claims 1 to 14, wherein R^{8a} is hydrogen.

16. A compound according to claim 1 or claim 2, wherein
R^1 is hydrogen;
R^2 is hydrogen;
R^3 is hydrogen;
R^4 is C_{1-6}alkyl;

R^5 is hydrogen;

R^6 is hydrogen;

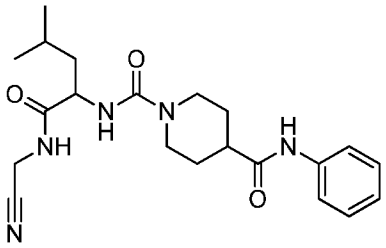
R^7 is hydrogen;

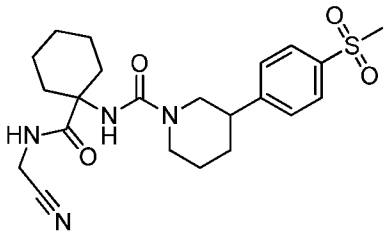
R^8 is a *N*-phenylamido group;

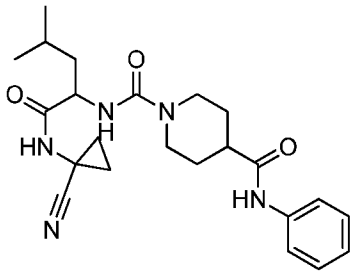
R^{8a} is hydrogen;

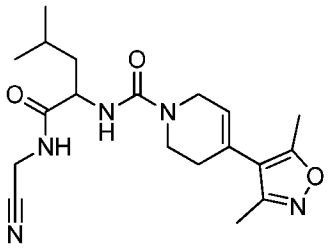
or a pharmaceutically acceptable salt thereof.

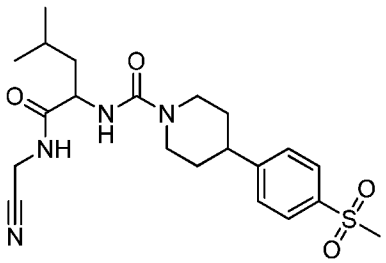
17. A compound according to claim 1, selected from the following:

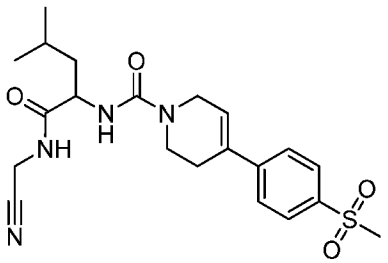


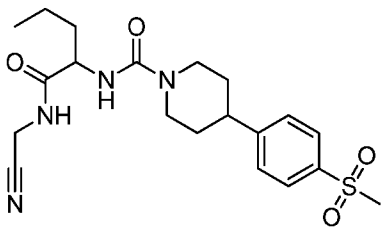


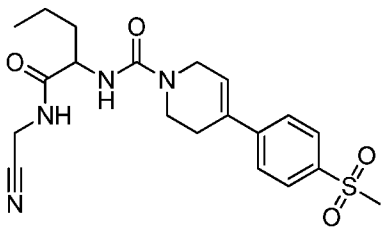


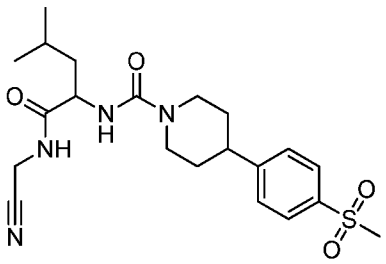
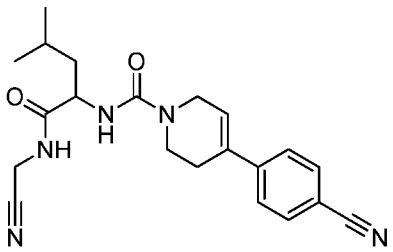
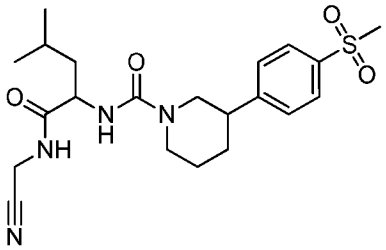
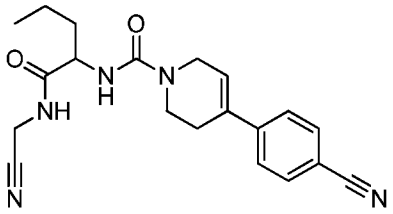
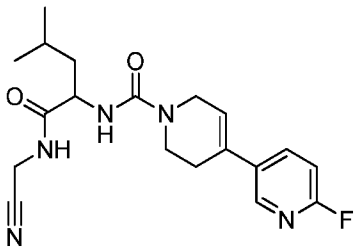






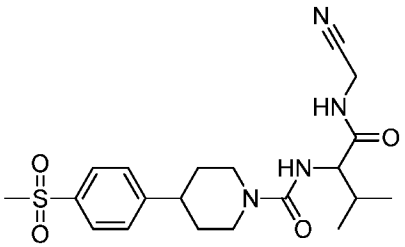
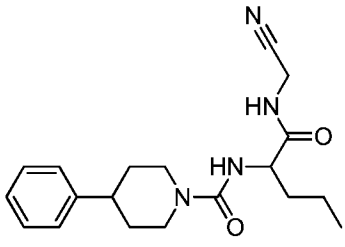
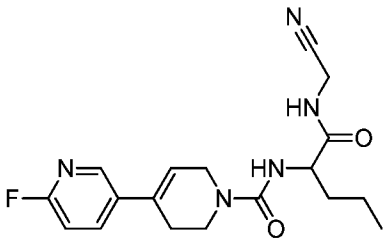
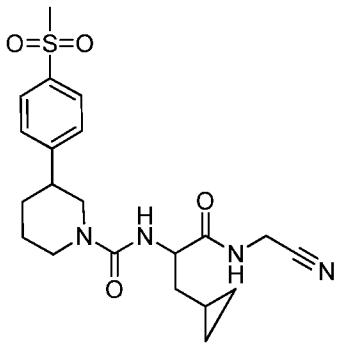


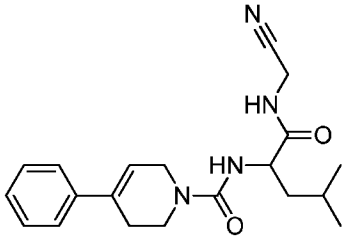


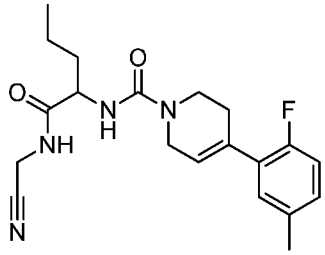






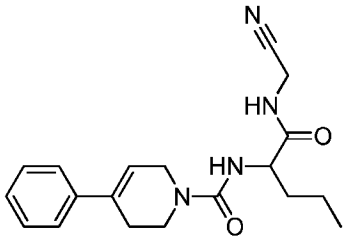
or a pharmaceutically acceptable salt thereof.

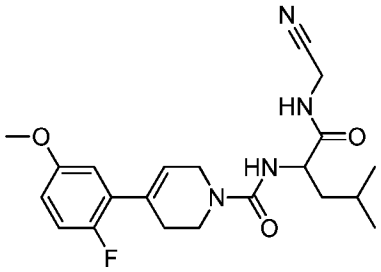
18. A compound according to claim 1, selected from the following:

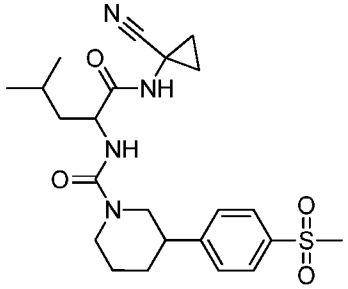





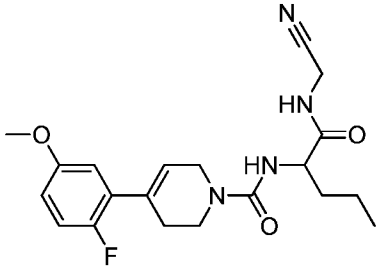


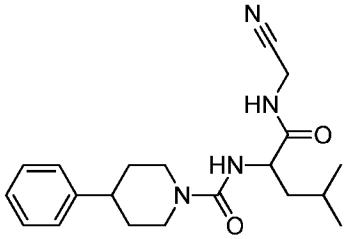


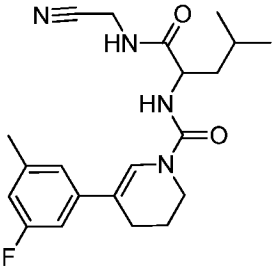


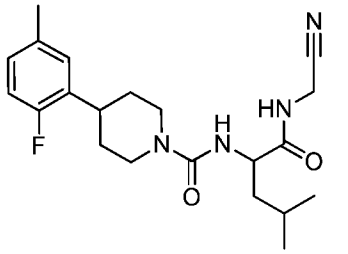


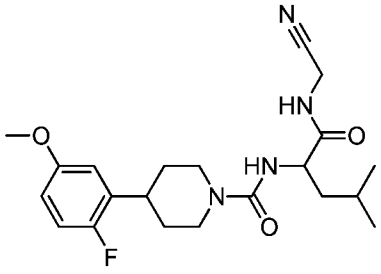


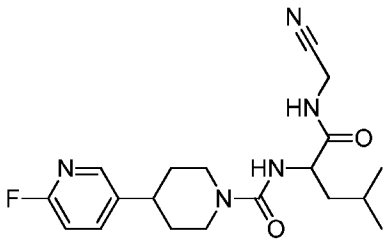


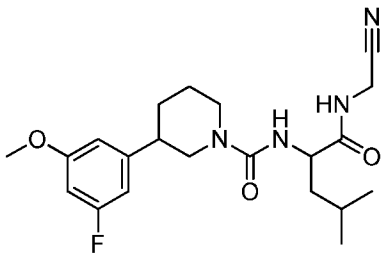


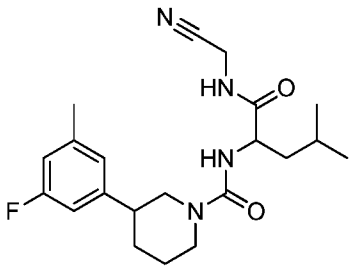


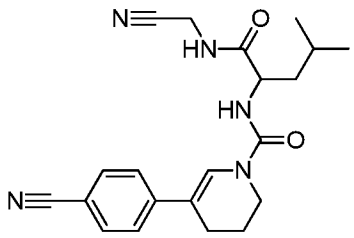


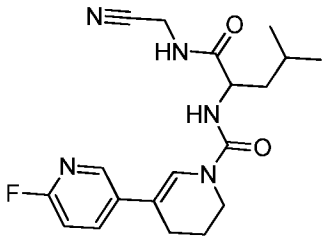


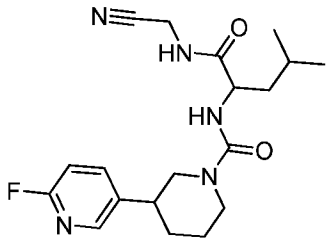


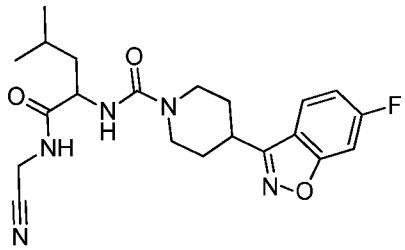


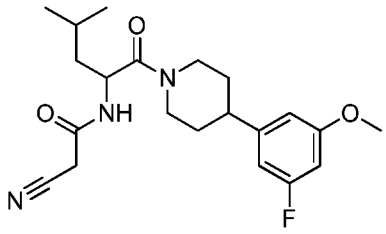


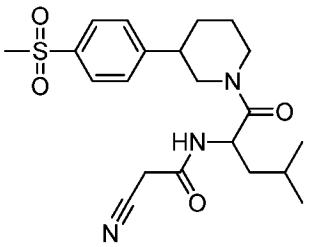


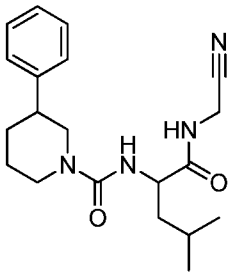


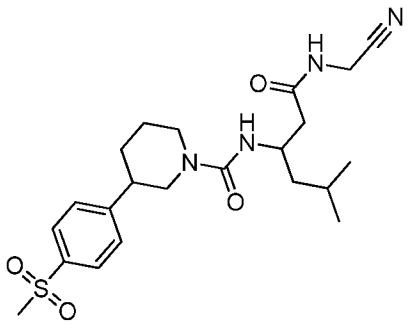


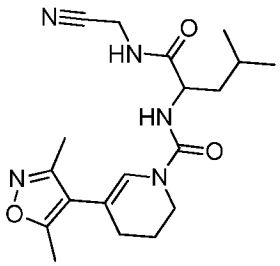


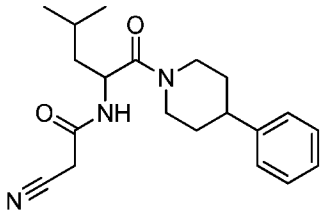


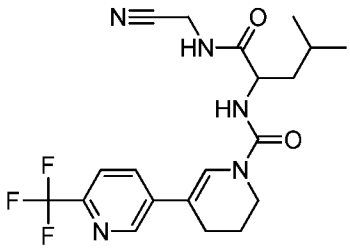


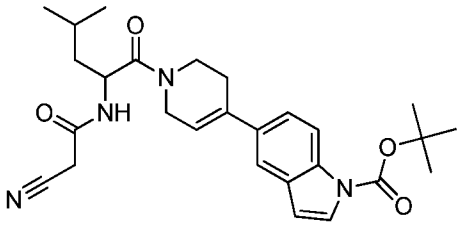


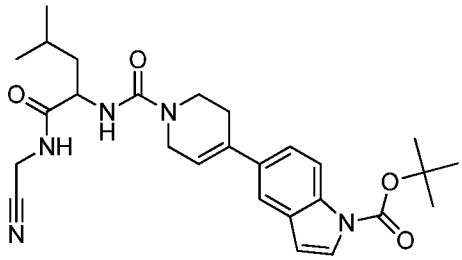


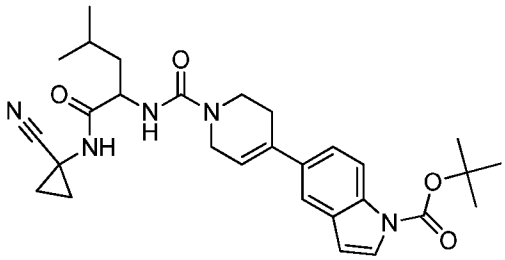


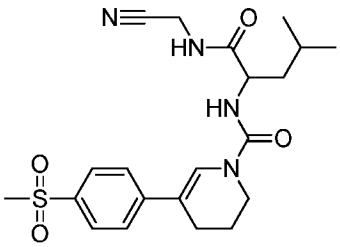


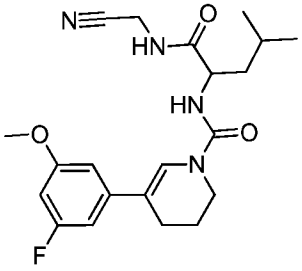


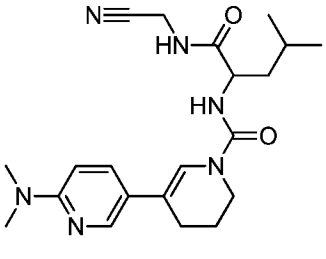


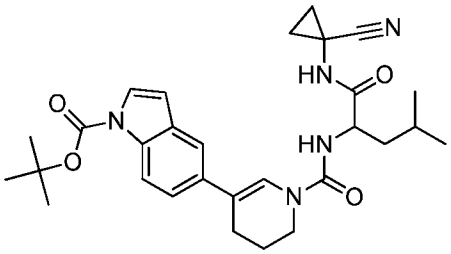


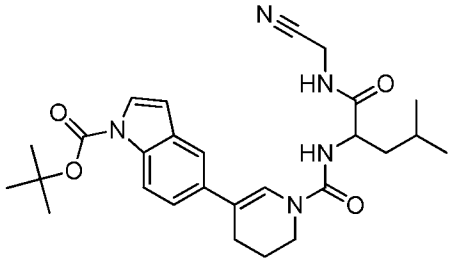


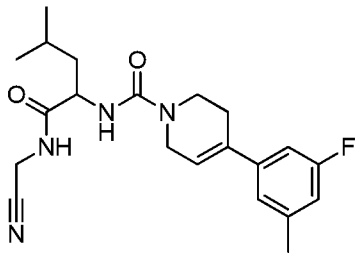


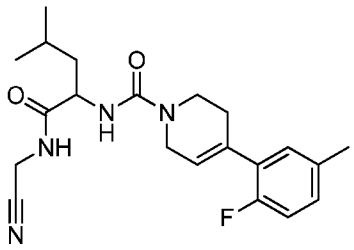


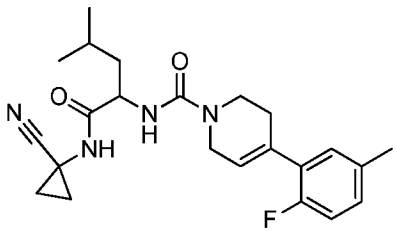


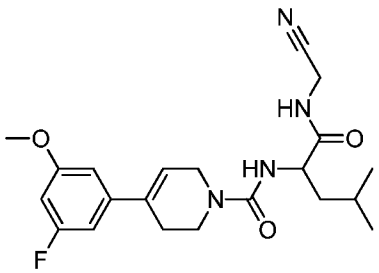


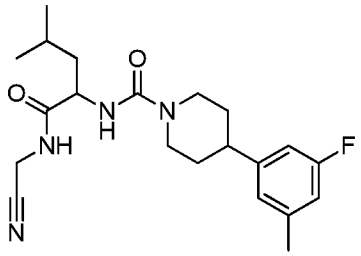


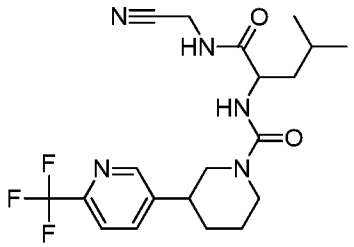


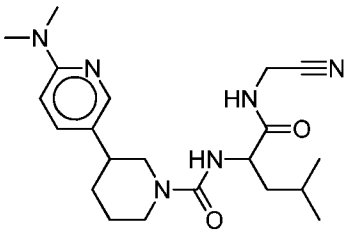


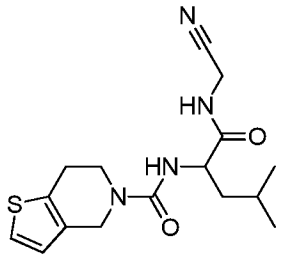


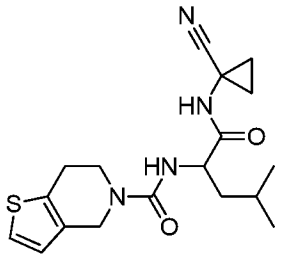


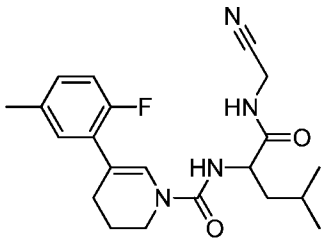


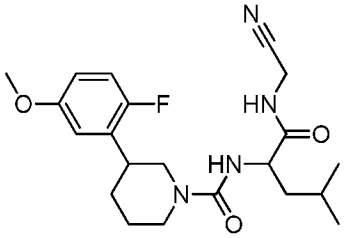


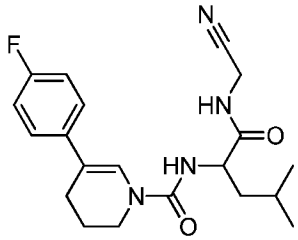


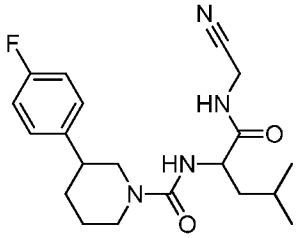


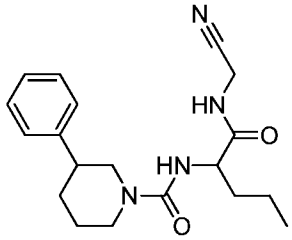


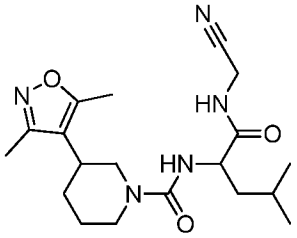


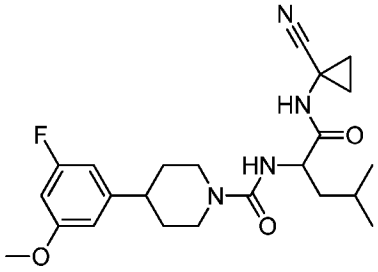


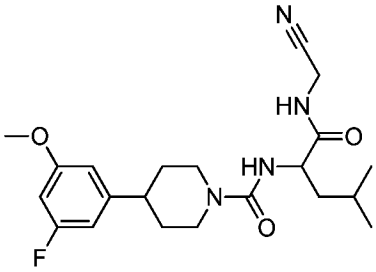


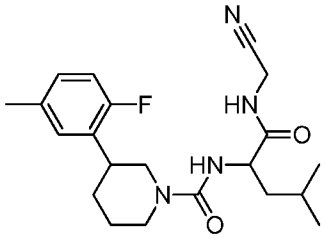


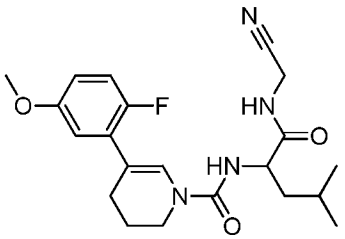


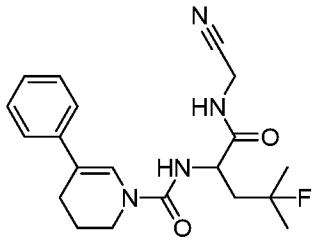


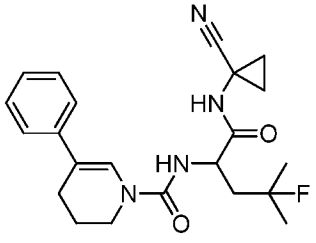


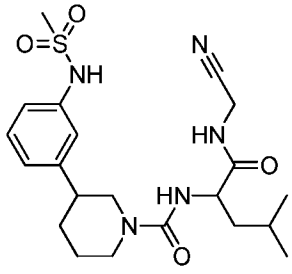


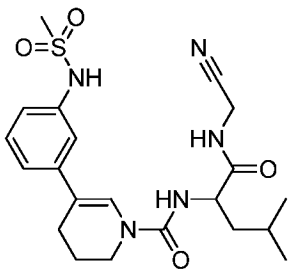


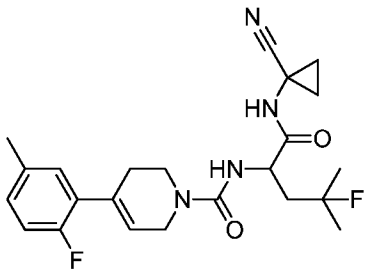


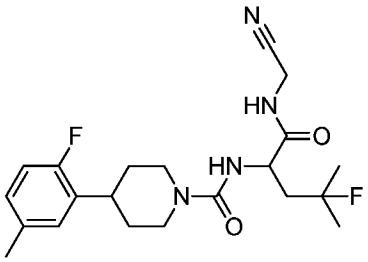


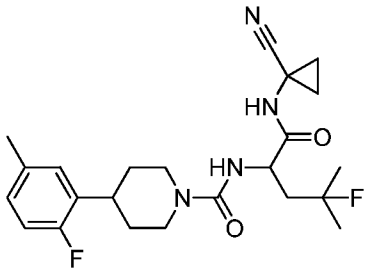


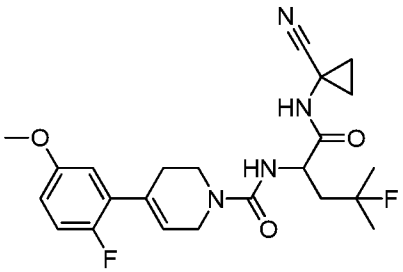


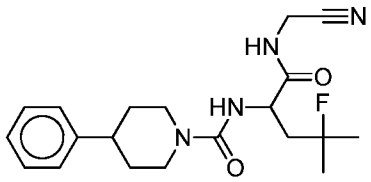


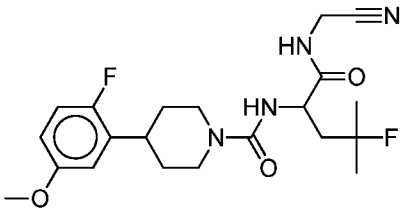


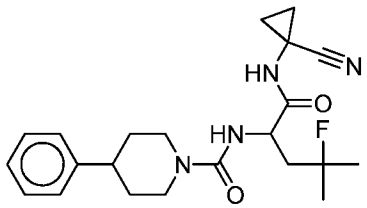


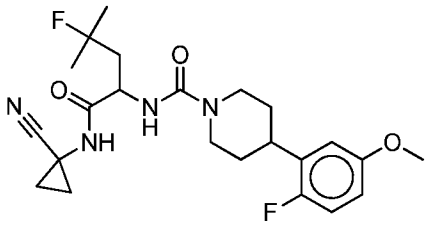


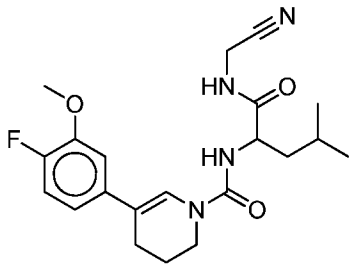


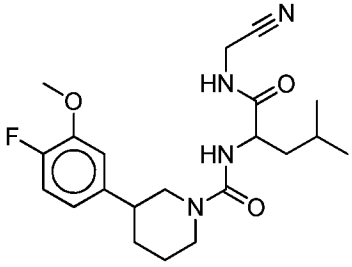


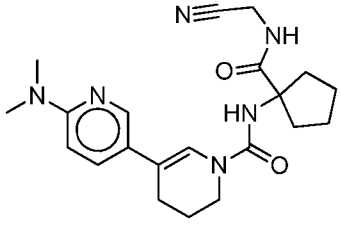


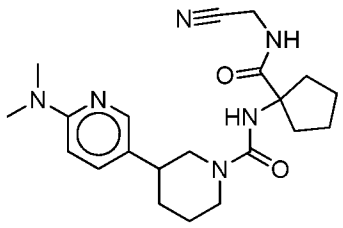


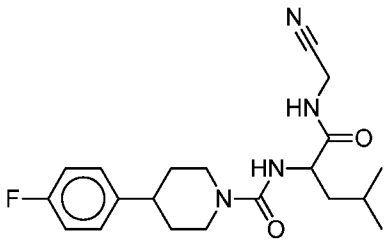


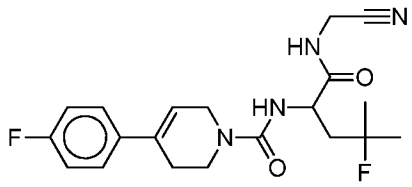


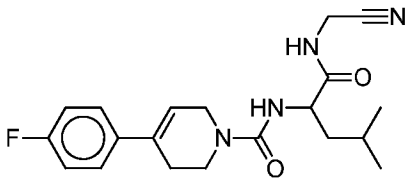


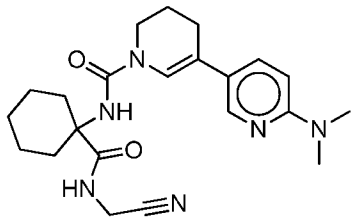


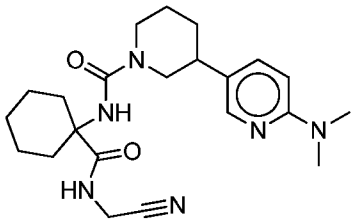


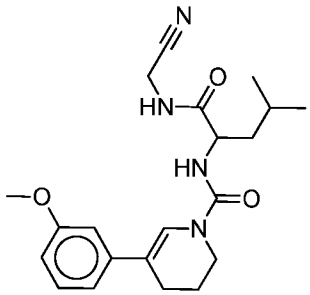


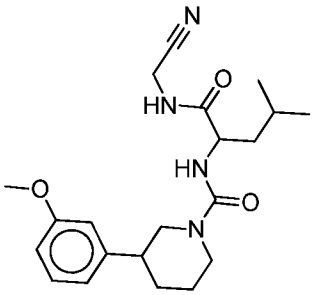


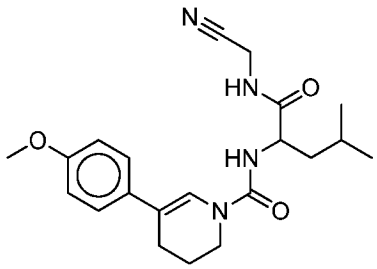


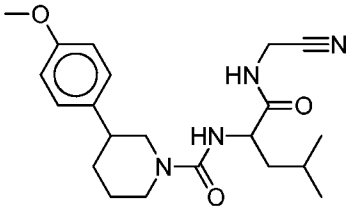


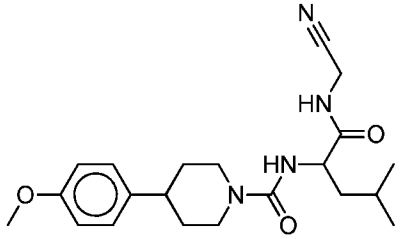


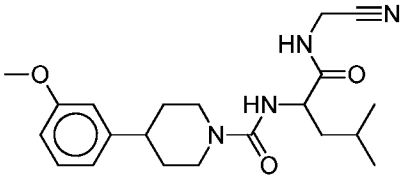


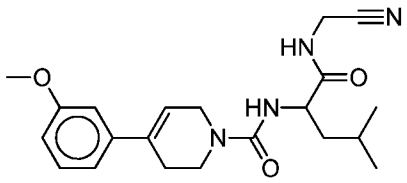


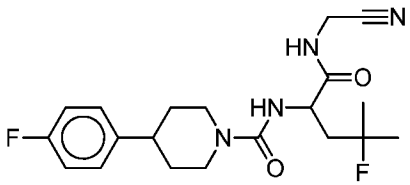


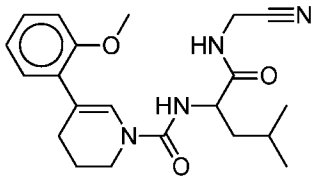


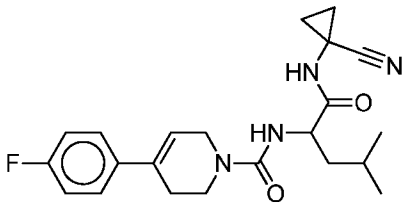


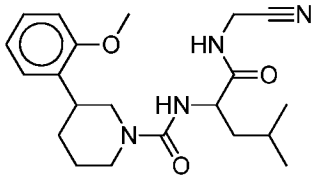


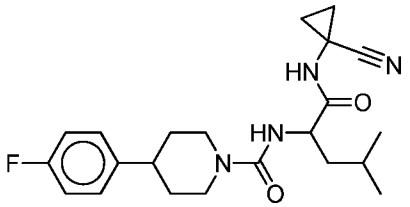


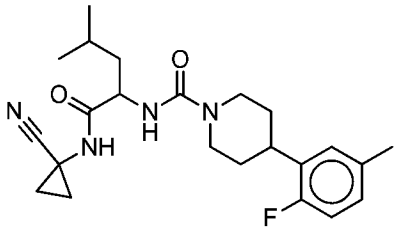


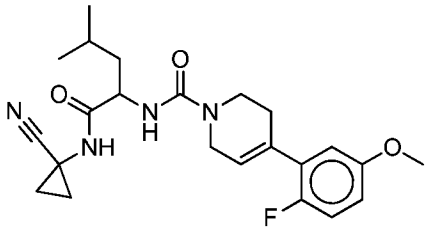


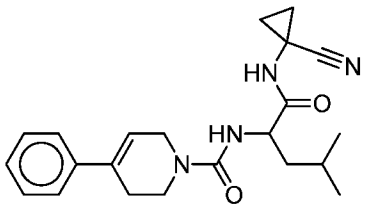


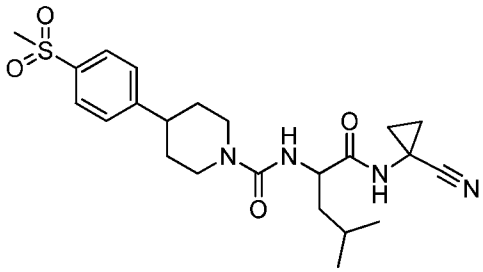


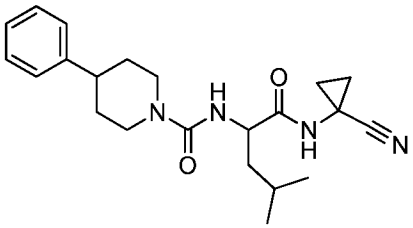


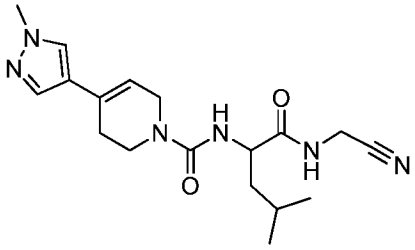


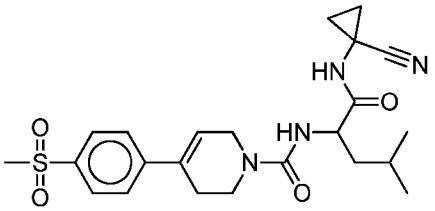


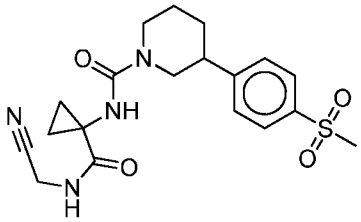


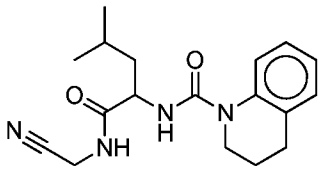


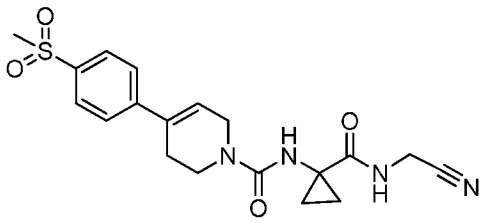


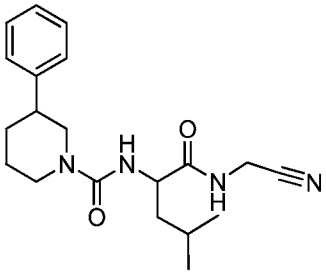


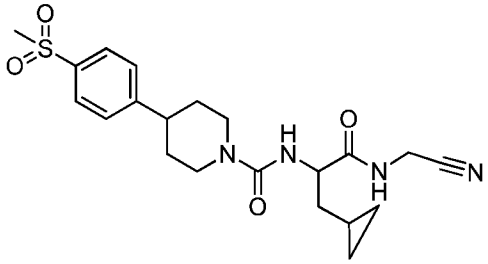


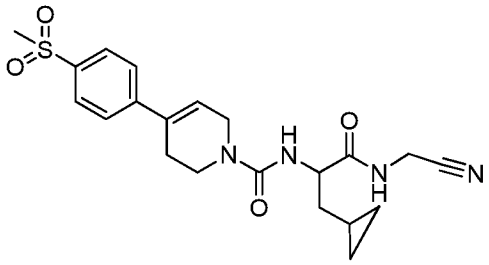


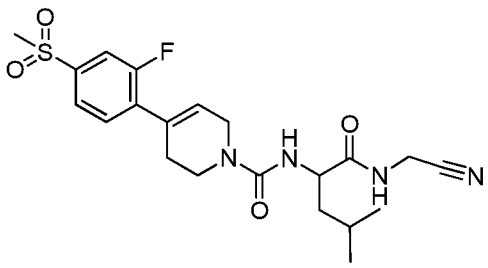


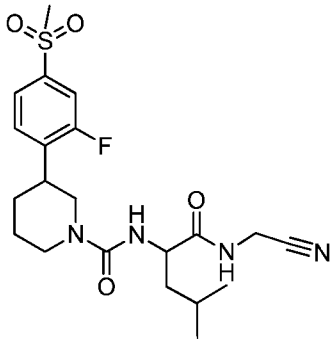


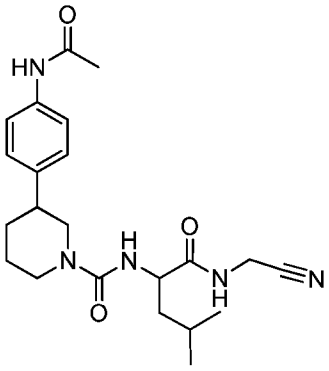


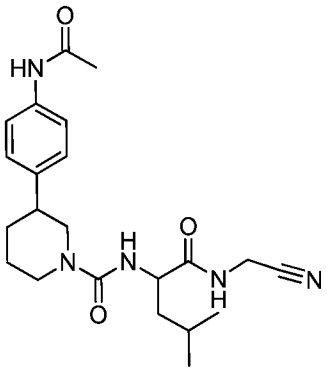


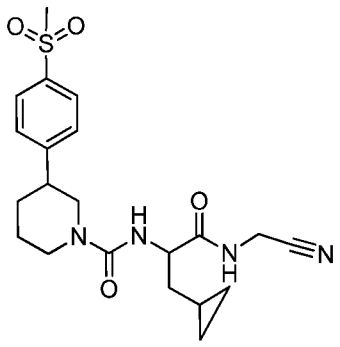


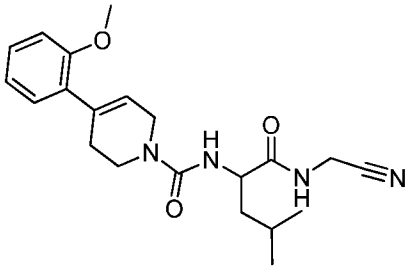


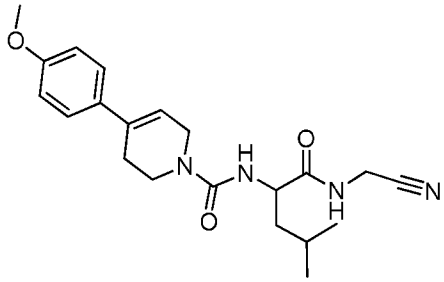


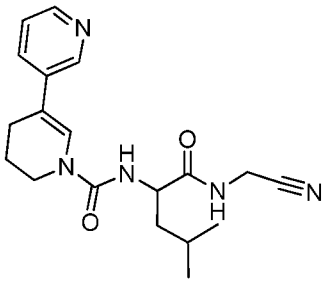


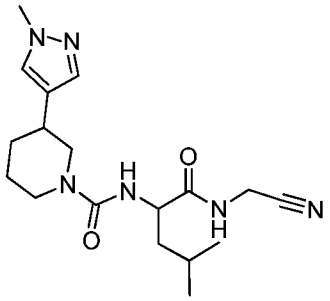


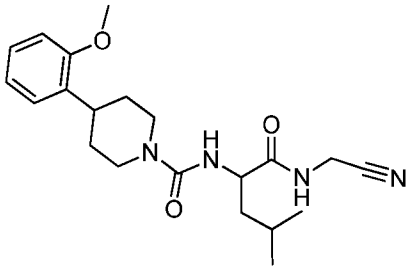


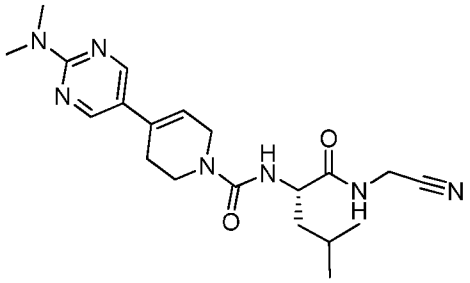


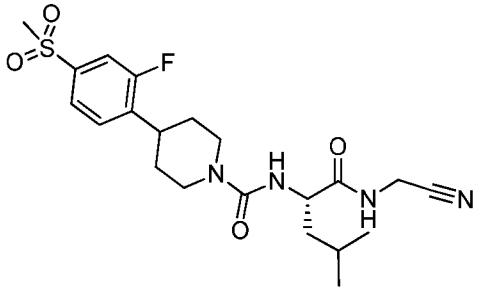


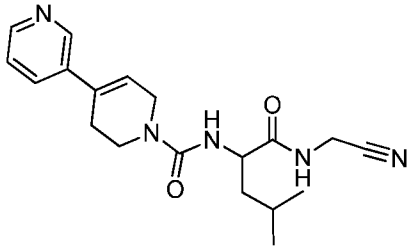


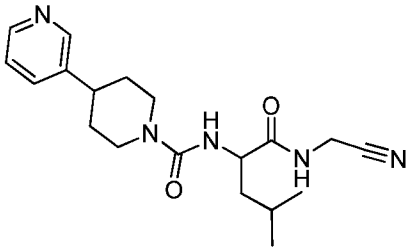


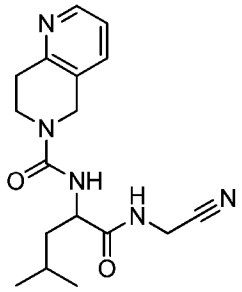


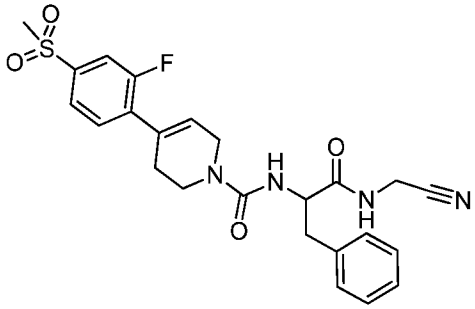


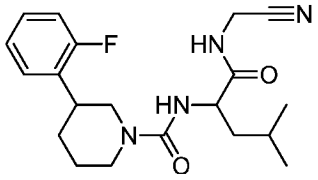


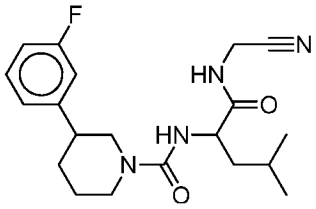


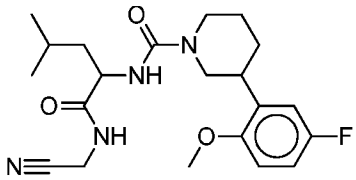


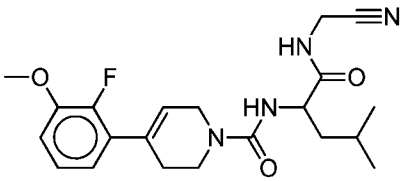


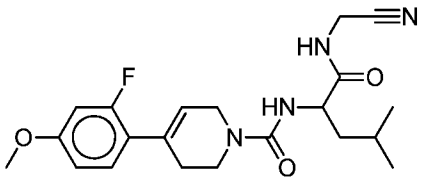


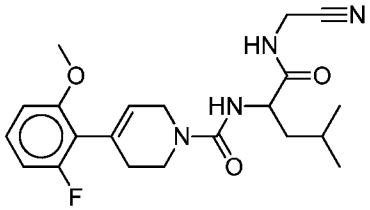


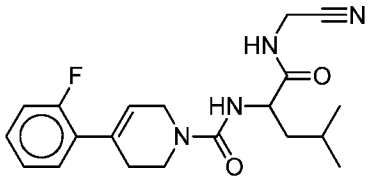


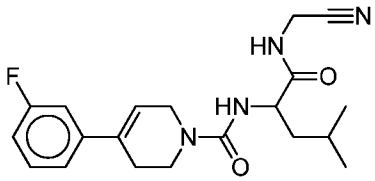


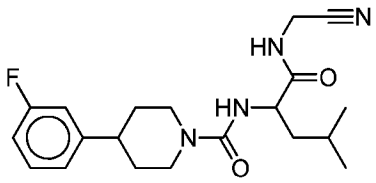


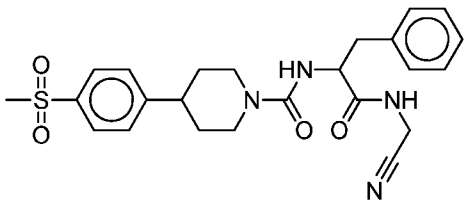


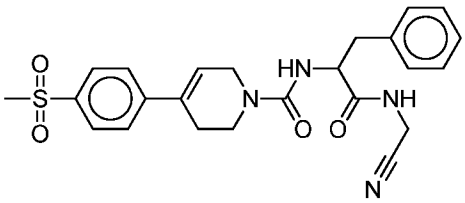


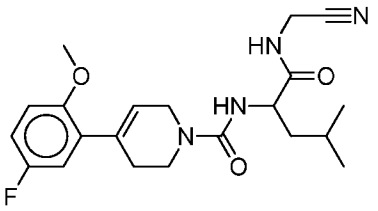


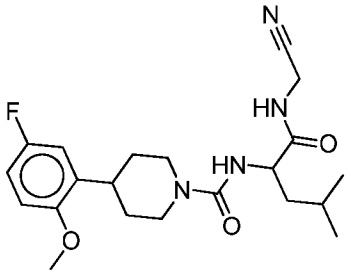


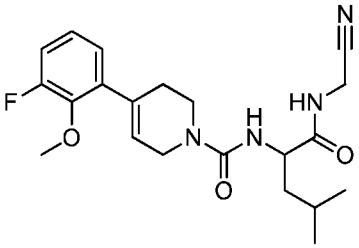


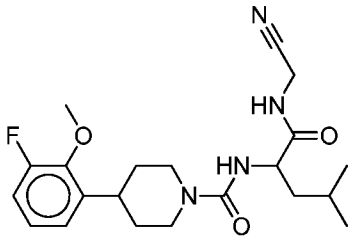


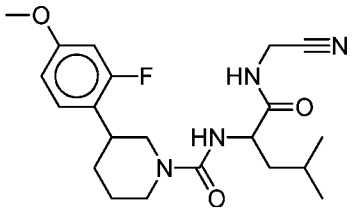


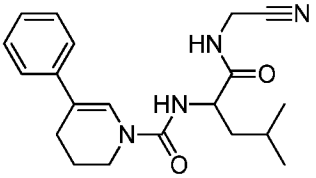


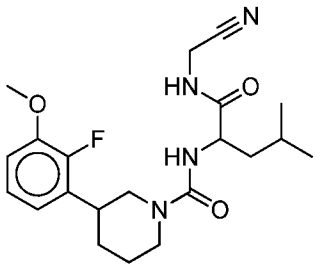


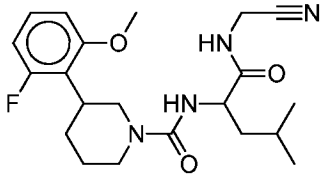












or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound according to any one of claims 1 to 18 and a pharmaceutically acceptable carrier, diluent or excipient.

20. A method of treating a cathepsin dependent condition in a patient which comprises administering to a patient in need thereof an effective amount of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof.

21. A method according to claim 20 wherein the condition is selected from the group consisting of inflammation, osteoporosis, rheumatoid arthritis and osteoarthritis.

22. A method of selectively inhibiting cathepsin K activity in a patient which comprises administering to a patient in need thereof an effective amount of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof.

23. Use of a compound according to any one of claims 1 to 18 in the manufacture of a medicament for the treatment of cathepsin dependent conditions.