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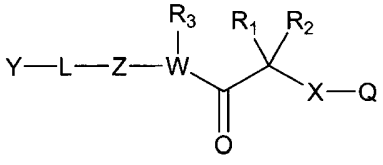
(54) Title: INHIBITORS OF HISTONE DEACETYLASE



(I)

(57) Abstract: This invention relates to compounds for the inhibition of histone deacetylase. More particularly, the invention provides for compounds of formula (I); wherein Y, L, Z, W, X, Q, R_1, R_2 and R_3 are as defined in the specification.

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INHIBITORS OF HISTONE DEACETYLASE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority from U.S. provisional application serial no. 60/667,708, filed April 1, 2005, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to compounds for the inhibition of histone deacetylase.

Description of Related Art

[0002] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0003] Csordas, *Biochem. J.*, 286: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the α,ε-amino groups of *N*-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton *et al.*, *Science,* 272: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton *et al.* further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0004] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Grozinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 96:4868-4873 (1999), teaches that HDACs may be divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hd1-like proteins. Grozinger *et al.* also teaches that the human HDAC-1, HDAC-2, and HDAC-3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC-4, HDAC-5, and HDAC-6, which are members of the second class of HDACs. Kao *et al.*, *Gene & Development* 14:55-66 (2000), discloses an additional member of this second class, called HDAC-7. More recently, Hu, E. *et al. J. Bio. Chem.* 275:15254-13264 (2000) disclosed another member of the first class of histone deacetylases, HDAC-8. Zhou *et al.*,

Proc. Natl. Acad. Sci. U.S.A., 98: 10572-10577 (2001) teaches the cloning and characterization of a new histone deacetylase, HDAC-9. Kao *et al., J. Biol. Chem.*, 277:187-93 (2002) teaches the isolation and characterization of mammalian HDAC10, a novel histone deacetylase. Gao *et al, J. Biol. Chem.* (In press) teaches the cloning and functional characterization of HDAC11, a novel member of the human histone deacetylase family. Shore, *Proc. Natl. Acad. Sci. U.S.A.* 97: 14030-2 (2000) discloses a third class of deacetylase activity, the Sir2 protein family. It has been unclear what roles these individual HDAC enzymes play.

[0005] Studies utilizing known HDAC inhibitors have established a link between acetylation and gene expression. Numerous studies have examined the relationship between HDAC and gene expression. Taunton *et al., Science* 272:408-411 (1996), discloses a human HDAC that is related to a yeast transcriptional regulator. Cress *et al., J. Cell. Phys.* 184:1-16 (2000), discloses that, in the context of human cancer, the role of HDAC is as a corepressor of transcription. Ng *et al., TIBS* 25: March (2000), discloses HDAC as a pervasive feature of transcriptional repressor systems. Magnaghi-Jaulin *et al., Prog. Cell Cycle Res.* 4:41-47 (2000), discloses HDAC as a transcriptional co-regulator important for cell cycle progression.

[0006] Richon *et al., Proc. Natl. Acad. Sci. USA*, **95**: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus*, which has been shown to inhibit histone deacetylase activity and arrest cell cycle progression in cells in the G1 and G2 phases (Yoshida *et al., J. Biol. Chem.* 265: 17174-17179, 1990; Yoshida *et al., Exp. Cell Res.* 177: 122-131, 1988), and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA). Yoshida and Beppu, *Exper. Cell Res.*, 177: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G_1 and G_2 phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin *et al., Nature,* 401: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki *et al.,* U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No. 10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC. Delorme *et al.*, WO 01/38322 and PCT/IB01/00683, disclose additional compounds that serve as HDAC inhibitors. Other inhibitors of histone deacetylase activity, including trapoxin, depudecin, FR901228 (Fujisawa Pharmaceuticals), and butyrate, have been found to similarly inhibit cell cycle progression in cells (Taunton *et al., Science* 272: 408-411, 1996; Kijima *et al., J. Biol. Chem.* 268(30):22429-22435, 1993; Kwon *et al., Proc. Natl. Acad. Sci. USA* 95(7):3356-61, 1998).

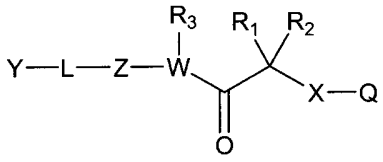
[0007] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great

therapeutic potential in the treatment of cell proliferative diseases or conditions. To date, few inhibitors of histone deacetylase are known in the art.It would be highly desirable to have inhibiters of histone deacetylase.

SUMMARY OF THE INVENTION

[0008] The present invention provides compounds for the inhibition of histone deacetylase.

[0009] In a first aspect, the present invention provides compounds that are useful as inhibitors of histone deacetylase that have the formula



(I)

[0010] wherein Y, L, Z, W, X, Q, R_1, R_2 and R_3 are as defined below.

[0011] In a second aspect, the invention provides a composition comprising a compound according to the first aspect and a pharmaceutically acceptable carrier.

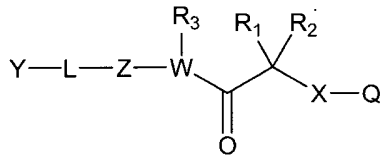
[0012] In a third aspect, the invention provides a method of inhibiting histone deacetylase, the method comprising contacting the histone deacetylase or a cell containing histone deacetylase, with an inhibiting effective amount of a compound according to the first aspect or a composition according to second aspect.

[0013] The foregoing merely summarizes the one aspect of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention provides compounds that are useful as inhibitors of histone deacetylase.

[0015] In one aspect, the invention provides compound of the formula

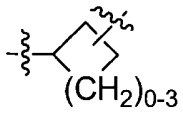


(I)

or pharmaceutically acceptable salts thereof, wherein

W is nitrogen or oxygen, wherein when W is oxygen, R_3 is absent;

X is a covalent bond, -S-, -SO-, -SO_2-, -O-, -NR_3-, -CH_2-, optionally substituted C_1-C_6 alkyl, or a structure of the formula



R_1 and R_2 are independently selected from the group consisting of -H, C_1-C_6 alkyl, halo, -N(H)-C(O)-O-C_1-C_6 alkyl, -N(H)-C(O)-O-benzyl, C_3-C_6 cycloalkyl, aryl, aryl-C_1-C_6 alkyl-, and heteroaryl-C_1-C_6 alkyl, wherein the alkyl, benzyl, cycloalkyl, aryl and heteroaryl moieties of said R_1 and R_2 are optionally substituted; or

R_1 and R_2 together with the carbon atom to which they are attached form a 3 to 9-membered heterocyclyl-aryl, C_3-C_6-cycloalkyl or 3 to 9-membered heterocyclyl group, wherein each of the cycloalkyl, heterocyclyl and heterocyclyl-aryl is optionally substituted with one or more groups selected from oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2, -N(R_3)(R_{3a}), halo, -SH, mono- to per-halogenated C_1-C_6 alkyl; or

when X-Q is absent, R_1 and R_2 together with the atom to which they are attached form an aryl, heterocyclyl, cycloalkyl or heteroaryl group, wherein said aryl, heterocyclyl, cycloalkyl and heteroaryl are optionally substituted, and wherein R^3 is optionally connected to the aryl, heterocyclyl, cycloalkyl or heteroaryl by a covalent bond;

X-Q, R_3 and R_{3a} are independently selected from the group consisting of -H, -OH, -C(O)H, heterocyclyl, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_3alkynyl, C_2-C_4 alkyl-OR_3, C_2-C_6 hydroxyalkyl, heteroaryl, C_1-C_6heteroalkyl-aryl, C_0-C_6alkylheteroaryl, C_0-C_6heteroalkylheteroaryl, C_1-C_3alkyl-C(O)NR_3-heteroaryl, C_1-C_3alkyl-C(O)NR_3-aryl, C_1-C_4alkyl-C(O)OR_3, -C_1-C_6 hydroxyalkyl-C(O)-OH, -C(O)-NH-aryl, -C(O)CF_3, -C(O)-NH_2, -CH(NH_2)-C(O)-OH, -NH_2, -CH(NH_2)-C(O)-O-C_1-C_6 alkyl, -C(O)-OH, -C(O)-O-C_1-C_6 alkyl, C_1-C_6 heteroalkyl-C_1-C_6 alkyl-, C_3-C_6 cycloalkyl, heterocyclyl-C_1-C_6 alkyl-, -C_1-C_6 alkylaryl, aryl, -C_0-C_6 alkyl-S(O)-C_1-C_6 alkylaryl, -C_0-C_6 alkyl-O-C_0-C_6 alkylaryl, -C_0-C_6 alkyl-S-C_0-C_6 alkylaryl, -C_0-C_6 alkyl-S-C_0-C_6 alkylheteroaryl, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-OH, -C_0-C_6 alkyl-S-C_1-C_6 hydroxyalkyl-C(O)-O-C_1-C_6 alkyl, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-CH(NH_2)-C(O)-OR_4, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-OH, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-O-C_1-C_6 alkyl, -C_0-C_6 alkyl-S(O)-C_1-C_6 alkyl-C(O)-OR_4, -C_0-C_6 alkyl-S(O)-C_1-C_6 alkyl-C(O)-N(R_4)-aryl, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-N(R_4)(R_{4a}), -C_0-C_6 alkyl-S-C_1-C_6 alkyl-N(R_4)(R_{4a}), -C_1-C_6 alkylheteroaryl and heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of the aforementioned X-Q, R^3 and R^{3a} is optionally substituted;

Q is selected from the group consisting of -H, -OH, -N(R_3)(R_{3a}), halo, -SH, -C(O)OR_3, -C(O)R_3, -C_0-C_3alkyl-diphenyl-R_4, -C_0-C_3alkyl-aryl-, -C_0-C_3alkyl-heteroaryl, -C_1-C_6 alkyl-N(R_3)-C(O)-C_1-C_6 alkyl-B-$(CH_2)_n$-R_3, -C_1-C_6-alkyl-N(R_3)-C(O)-C_1-C_6 alkyl-O-C_1-C_6 alkyl-R_3, -C_1-C_6-alkyl-C(O)-OR_3, -C_1-C_6-alkyl-N(R_3)(R_{3a}), -C_1-C_6-alkyl-CN, -C_1-C_6 alkyl-C(O)-N(R_3)-N(R_3)-aryl, -C_1-C_6 alkyl-N(R_3)-C_1-C_6 heteroalkyl, -C_1-C_6 alkyl-N(R_3)-C_3-C_6 cycloalkyl, -C_1-C_6 alkyl-N(R_3)-heterocyclyl, -C_1-C_6 alkyl-N(R_3)-aryl, -C_1-C_6 alkyl-N(R_3)-C_1-C_6-alkyl-aryl, -C_1-C_6 alkyl-N(R_3)-heteroaryl, -C_1-C_6 alkyl-N(R_3)-C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted with -OH, -C_1-C_6 alkyl-O-C_1-C_6 alkyl, -C_1-C_6 alkyl-O-C_3-C_6 cycloalkyl, -C_1-C_6-alkyl-O-C_1-C_6 alkyl-(C_1-C_6 heteroalkyl), -C_1-C_6-alkyl-O-C_1-C_6 alkyl-heterocyclyl, -C_1-C_6 alkyl-O-aryl, -C_1-C_6-alkyl-O-C_1-C_6 alkylaryl, -C_1-C_6 alkyl-O-heteroaryl, -C_1-C_6 alkylhydroxamate, C_1-C_6 alkyl, -C_1-C_6 alkyl-(C_1-C_6 heteroalkyl), C_3-C_6 cycloalkyl, -C_1-C_6 alkylheterocyclyl, -C_1-C_6 alkyl-C_2-C_6 alkenyl, -C_1-C_6 alkyl-C_2-C_6 alkynyl, aryl, -C_1-C_6 alkylaryl, heteroaryl, C_1-C_6 alkylheteroaryl, C_1-C_3 alkyl-CN, -C_1-C_6 alkyl-CH(OR_3)-C(O)-OR_3, -C_1-C_6 alkyl-CH(N(R_3)(R_{3a}))-C(O)-OR_3, -C_1-C_6 alkyl-C(O)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-N(R_3)-C(O)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-N(R_3)-C(O)-OR_3, -C_1-C_6 alkyl-N(R_3)-C(O)-R_3, -C_1-C_6 alkyl-N(R_3)-S$(O)_2$-R_3, -C_1-C_6 alkyl-S$(O)_2$-N(R_3)(R_{3a}), -C_1-C_6 alkyl-CH(N(R_3)(R_{3a}))-C_1-C_6 alkyl-OR_3, or -C_1-C_6 alkyl-O-C(O)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-(C=NR_3)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-X-C_1-C_6 alkyl-C(O)OR_3, -C_1-C_6 alkyl-X-C_1-C_6 alkyl-OR_3, and -C_1-C_6 alkyl-X-C_1-C_6 alkyl-N(R_3)(R_{3a}), C_1-C_4 alkyl-aryl- wherein the C_1-C_4 alkyl is optionally substituted with -C_1-C_4 alkylOR_3, C_1-C_4 alkylNR_3 R_{3a}, C_0-C_4 alkylC(O)N(R_3)(R_{3a}) or C_0-C_4 alkylC(O)OR_3, C_1-C_4 alkyl-heteroaryl- wherein the C_1-C_4 alkyl is optionally substituted with - C_1-C_4 alkylOR_3, C_1-C_4 alkylN(R_3)(R_{3a}), C_0-C_4 alkylC(O)N(R_3)(R_{3a}) or C_0-C_4 alkylC(O)OR_3, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_0-C_6 alkylC(O)NR_3-NR_3aryl and C_0-C_6 alkylC(O)NR_3-NR_3heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of the aforementioned Q is optionally substituted;

B is selected from the group consisting of -O-, -S(O)-, -S- and -S$(O)_2$-,

n is 0 or an interger from 1 to 3;

R_4 and R_{4a} are independently selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkyl-R_3, -C_0-C_6 alkyl-OR_3, -C_0-C_6 alkyl-C(O)-OR_3, -C_0-C_6 alkyl-C(O)NR_3 R_{3a}, -CH=CH-C(O)-OR_3, -CH=CH-C(O)-N(R_3)(R_{3a}), -N(R_3)-C(O)-CF_3, -N(R_3)-C_2-C_6 alkyl-N(R_3)(R_{3a}), -C_0-C_6 alkyl-N(R_3)(R_{3a}), -N(R_3)-C(O)-C_1-C_6 alkyl-R_3, -N(R_3)-S$(O)_2$-C_1-C_6 alkyl-R_3, - S$(O)_2$- N(R_3)R_{3a}, -O-C_2-C_6 alkyl-N(R_3)(R_{3a}), -S-R_3, -S(O)-C_1-C_6 alkyl-R_3, -S$(O)_2$-C_1-C_6 alkyl-R_3, C_3-C_6 cycloalkyl, heterocyclyl, C_4-C_7heterocyclyl-R_3, -O-C_2-C_4alkyl-heterocyclyl, -O-heterocyclyl-C(O)-OR_3, -NR_3-C_2-C_4alkyl-heterocyclyl, halo, -CF_3,-SO_3H, -CN, -C_1-C_6 alkylaryl, aryl, heteroaryl, -C_1-C_6 alkylheteroaryl, wherein each

alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moeity of the aformentioned R_4 and R_{4a} are optionally substituted;

Z is selected from the group consisting of C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_1-C_8 heteroalkyl, -C_0-C_3alkyl-alkenyl-C_0-C_3-alkyl, -C_0-C_3alkyl-alkynyl-C_0-C_3-alkyl, -C_0-C_3alkyl-heteroalkyl-C_0-C_3-alkyl, aryl, -C_1-C_6 alkylaryl-, -C_0-C_6 alkylaryl-C_0-C_6-alkyl-,-C_0-C_6 alkylaryl-C_2-C_6-heteroalkyl-,-C_2-C_6 heteroalkylaryl-C_0-C_6-alkyl-,-C_4-C_6 heterocyclylaryl-C_0-C_6-alkyl-, -C_0-C_6 alkylaryl-C_4-C_6-heterocyclyl-, -C_0-C_6 alkylheteroaryl-, -C_0-C_6-alkylheteroaryl-C_0-C_6-alkyl-, heteroaryl, -C_0-C_6 alkylheteroaryl-C_2-C_6-heteroalkyl-,-C_2-C_6 heteroalkyl-heteroaryl-C_0-C_6-alkyl-,-C_4-C_6 heterocyclyl-heteroaryl-C_0-C_6-alkyl-, -C_0-C_6 alkyl-heteroaryl-C_4-C_6-heterocyclyl-, -C_3-C_6 alkynyl-aryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-aryl-C_3-C_6-alkynyl, -C_3-C_6 alkynyl-heteroaryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-heteroaryl-C_3-C_6-alkynyl, -C_3-C_6 alkenyl-aryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-aryl-C_3-C_6-alkenyl, -C_3-C_6 alkenyl-heteroaryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-heteroaryl-C_3-C_6-alkenyl, -C_0-C_6 alkylaryl-aryl-, -C_0-C_6 alkylaryl-aryl-C_0-C_6-alkyl-, -C_0-C_6 alkylaryl-heteroaryl-, -C_0-C_6 alkylaryl-heteroaryl-C_0-C_6-alkyl-, -C_0-C_6 alkyl-C_3-C_6 cycloalkyl-, -C_0-C_6 alkyl-C_3-C_6 cycloalkyl-C_0-C_6-alkyl-, -C_1-C_6 alkyl-X-C_3-C_6 cycloalkyl-, -C_1-C_6 alkyl-X-C_3-C_6 cycloalkyl-C_0-C_6-alkyl-, -C_1-C_6 alkyl-N(R_3)-C_1-C_6 alkyl-C_3-C_6 cycloalkyl-, -C_1-C_6 alkyl-N(R_3)-C_1-C_6 alkyl-C_3-C_6 cycloalkyl-C_0-C_6-alkyl-, and -C_1-C_6 alkyl-S-S-C_1-C_6 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl moiety is optionally substituted;

L is selected from the group consisting of a covalent bond, -C_0-C_6alkyl-aryl-C_0-C_3alkyl-X-C_0-C_3alkyl, C_0-C_6alkyl-heteroaryl-C_0-C_3alkyl-X-C_0-C_3alkyl, C_0-C_3alkyl-X-C_0-C_3alkyl, C_0-C_6alkyl-N(R_3)-C(O)-N(R_3)-S(O)$_2$-C_0-C_3alkyl-aryl, -C_0-C_3alkyl-S(O)$_2$-N(R_3)-C_0-C_3alkyl-aryl-C_0-C_3alkyl-C(O)-N(R_3)-C_0-C_3alkyl, -C_0-C_3alkyl-N(R_3)-C(O)-O-heterocyclyl-C_0-C_3alkyl, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl-N(R_3)-C_0-C_3alkyl, -C_0-C_6 alkyl-N(R_3)C(O)heterocyclyl-C_0-C_3alkyl, -C_0-C_6 alkyl-S(O)$_2$heterocyclyl-C_0-C_3alkyl-, -C_0-C_6 alkyl-N(R_3)S(O)$_2$heterocyclyl-C_0-C_3alkyl, -C_0-C_6 alkyl-, -C_2-C_6 alkenyl-, -C_2-C_6 alkynyl-, -C_0-C_6 alkyl-N(R_3)C(O)-C_0-C_3 alkyl, -C_0-C_6 alkyl-N(R_3)C(S)-C_0-C_3 alkyl, -C_0-C_6 alkyl-C(O)N(R_3)C(O)-C_0-C_3 alkyl, -C_2-C_6 heteroalkyl-N(R_3)C(O)-C_0-C_3 alkyl, -C_0-C_6 alkyl-C(O)-N(R_3)-C_0-C_3 alkyl, -C_0-C_6 alkyl-C(S)-N(R_3)-C_0-C_3 alkyl, -C_0-C_6 alkyl-OC(O)-, -C_0-C_6 alkyl-C(O)-O-, -C_0-C_6 alkyl-C(O)-C_0-C_3 alkyl, -C_0-C_6 alkyl-SO_2-N(R_3)-C_0-C_3 alkyl, -C_0-C_6 alkyl-N(R_3)-SO_2-C_0-C_3 alkyl, -C_0-C_6 alkyl-C(O)-N(R_3)-SO_2-C_0-C_3 alkyl, -C_0-C_6 alkyl-C(O)-N(R_3)-SO_2-C_0-C_3 alkyl-aryl, -C_0-C_6 alkyl-C(O)-N(R_3)-SO_2-C_0-C_3 alkyl-heteroaryl, -C_0-C_6 alkyl-N(R_3)-C_0-C_3 alkyl, -C_0-C_6 alkyl-N(R_7)-C_0-C_3 alkyl, -C_0-C_6 alkyl-S-C_0-C_3 alkyl, -C_0-C_6 alkyl-O-C_0-C_3 alkyl -, -C_0-C_6 alkyl-S(O)-C_0-C_3 alkyl, -C_0-C_6 alkyl-S(O)$_2$-C_0-C_3 alkyl, -C_0-C_6 alkyl-(CR_3=CR_3)$_{1-2}$-C_1-C_6 alkyl-, -C_0-C_6 alkyl-(C≡C)$_{1-2}$-C_1-C_6 alkyl-, -C_0-C_6 alkyl-N(R_3)-C(O)-N(R_3)-C_0-C_3 alkyl, -C_0-C_6 alkyl-N(R_3)-C(O)-O-C_0-C_3 alkyl, -C_0-C_6 alkyl-O-C(O)-N(R_3)-C_0-C_3 alkyl, -C_0-C_3 alkyl N(R_3)C(O)

-C_0-C_3 alkyl-heterocyclyl-C(O)-C_0-C_6 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_2-C_4 alkenyl- C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl-O-C_0-C_3 alkyl, -C_0-C_3 alkyl-O-C_0-C_3 alkyl heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl-N(R_3)-C_0-C_3 alkyl, -C_0-C_3 alkyl-N(R_3)-C_0-C_3 alkyl heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl-S-, -C_0-C_3 alkyl $S(O)_2$N(R_3)-C_0-C_3 alkyl heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $S(O)_2$-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-C(O)N(R_3)-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-C(S)N(R_3)-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl C(O)-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl OC(O)N(R_3)-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-OC(S)N(R_3)-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-OC(O)-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl N(R_3)C(O)N(R_3)-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl N(R_3)C(S)N(R_3)-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl N(R_3)C(O)-heterocyclyl-C_0-C_3alkyl, -C_0-C_3 alkyl N(R_3)C(S)-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl N(R_3)$S(O)_2$N(R_3)-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-C=N-O-C_0-C_3 alkyl, -C_0-C_3 alkyl N(R_3)C(O)-C_1-C_3 alkyl-N(R_3)C(O)-C_0-C_3 alkyl, -C_0-C_3 alkyl N(R_3)C(S)-C_1-C_3 alkyl-N(R_3)C(S)-C_0-C_3 alkyl, -$S(O)_2$-N(R_3)-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-N(R_3)C(O)-C_1-C_3 alkyl-, -$S(O)_2$-N(R_3)-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-N(R_3)C(S)-C_1-C_3 alkyl-,-N(R_3)-$S(O)_2$-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-N(R_3)C(O)-C_1-C_3 alkyl-, -N(R_3)-$S(O)_2$-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-N(R_3)C(S)-C_1-C_3 alkyl-,-$S(O)_2$-N(R_3)-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-N(R_3)C(O)-C_1-C_3 alkyl-, -$S(O)_2$-N(R_3)-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-N(R_3)C(S)-C_1-C_3 alkyl-, -N(R_3)-$S(O)_2$-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-N(R_3)C(O)-C_1-C_3 alkyl- and -N(R_3)-$S(O)_2$-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-N(R_3)C(S)-C_1-C_3 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety of the aforementioned L are optionally substituted,

-(C_0-C_3alkyl)(R_3)N-$S(O)_2$-N(R_3)-C_2-C_4alkyl-O-C_0-C_3alkyl, when Y is absent,

-R_3R_{3a}N$S(O)_2$N(R_3)-C_2-C_4alkyl-O-C_0-C_6 alkyl-, when Y is absent, and

-R_3R_{3a}N$S(O)_2$N(R_3)-C_2-C_4alkyl, when Y is absent,

wherein the right end attaches to Z and the left end attaches to Y;

Y is selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocyclyl, alkylcycloalkyl, alkylheterocyclyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, aryl-heteroaryl, alkylaryl-heteroaryl, heteroaryl-alkylaryl, aryl-aryl, alkylaryl-aryl, aryl-alkylaryl, heteroaryl-heteroaryl, heteroaryl-aryl, alkylheteroaryl-aryl, aryl-alkylheteroaryl, heteroaryl-aryl-aryl, aryl-aryl-heteroaryl, alkylheteroaryl-aryl-aryl, aryl-aryl-alkylheteroaryl, heteroaryl-aryl-heteroaryl, alkylheteroaryl-aryl-heteroaryl, heteroaryl-aryl-alkylheteroaryl, alkylheteroaryl-heteroaryl, heteroaryl-alkylheteroaryl, heterocyclyl-heteroaryl, heteroaryl-heterocyclyl, heterocyclyl-aryl, aryl-heterocyclyl, heterocyclyl-alyl-aryl, aryl-alkyl-heterocyclyl, aryl-C_1-C_3alkyl-aryl, -(O)C-C_0-C_3alkyl-aryl, C_0-C_3alkyl-aryl, -

C_0-C_3alkyl-aryl-O-C_2-C_4alkyl-N(R_3)(R_{3a}), -C_0-C_3alkyl-heteroaryl-O-C_2-C_4alkyl-N(R_3)(R_{3a}), -C_0-C_3alkyl-aryl-C_0-C_3alkyl, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl and aryl-C_1-C_3alkyl-heteroaryl, each optionally substituted with one or more groups selected from R_3, R_4 or R_7; or

Y-L-Z- is selected from the group consisting of aryl-C_2-C_6 alkynyl-C_1-C_4alkyl, heteroaryl-C_2-C_6-alkynyl-C_1-C_4alkyl, R_3-heterocyclyl-C_0-C_3 alkyl-$NR_3C(O)NR_3$-heteroaryl-C_2-C_7alkyl; R_3-heterocyclyl-C_o-C_3 alkyl-$NR_3C(O)NR_3$-aryl-C_2-C_7alkyl; aryl-C_0-C_6 alkyl-, heteroaryl-C_1-C_6 alkyl-N(R_4)-C_1-C_6-alkyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_6-alkyl, heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_3-alkyl, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_3-alkyl, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-heteroaryl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-heteroaryl-C_0-C_3-alkyl, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_3-alkyl, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_7 alkyl-, heteroaryl-C(O)-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-, heteroaryl-C(O)-C_0-C_6 alkyl-aryl-C_0-C_7 alkyl-, heteroaryl-$S(O)_2$-C_0-C_6 alkyl-heteroaryl-, heteroaryl-C_0-C_6 alkyl-N(R_3)-C(O)-C_1-C_7 alkyl-, aryl-C_0-C_6 alkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, heteroaryl-C_0-C_6 alkyl- C(O)-N(R_3)-

C_1-C_7 alkyl-, C_1-C_6 alkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, heterocyclyl-C_0-C_6 alkyl- C(O)-N(R_3)-C_1-C_7 alkyl-, C_1-C_6 cycloalkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, (R_3)(R_{3a})N-C_0-C_6alkyl-C(O)-N(R_3)-C_1-C_7alkyl, aryl-C_0-C_6alkyl-O-C(O)-N(R_3)-C_1-C_7alkyl, aryl-C_1-C_3 alkyl-N(R_3)-C(O)-C_1-C_7 alkyl-, C_1-C_3 alkyl-N(R_3)- C(O)- C_1-C_7 alkyl-, heteroaryl-S(O)$_2$-C_0-C_6 alkyl-aryl-, aryl-C_0-C_6 alkyl-N(R_3)-C(O)-C_1-C_7 alkyl-, -R_3-O-C(O)NR_3-C_0-C_3alkyl-heteroaryl-C_1-C_7alkyl-, R_3-C(O)-C_0-C_3alkyl-heteroaryl-C_1-C_7alkyl-, R_3-C(O)-heterocyclyl-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl-, R_3-heterocyclyl-C_0-C_3alkyl-N(R_3)C(O)N(R_3)-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl-, R_3-heterocyclyl-C_0-C_3alkyl-N(R_3)C(O)-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl- and R_3-heterocyclyl-C_0-C_3alkyl-N(R_3)S(O)$_2$-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl-, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl moieties of the aforementioned Y-L-Z are optionally substituted,

Y-C_1-C_3 alkyl-N(R_3)- C(O)- C_1-C_7 alkyl- wherein the C_1-C_3 alkyl is optionally substituted with –C(O)NR_3-C_1-C_3 alkyl A_{1a} and C_1-C_7 alkyl is optionally substituted with -NR_3-C(O)O-C_1-C_3 alkyl -A_{1b}, -NR_3-C(O)-C_1-C_3 alkyl-A_{1b}, -NR_3-S(O)$_2$-C_1-C_3 alkyl-A_{1b}, -NR_3-C(O)-NR_3-C_1-C_3 alkyl-A_{1b} or -NR_3-S(O)$_2$-NR_3-C_1-C_3 alkyl-A_{1b}, aryl-C_1-C_3 alkyl-N(R_3)- C(O)- C_1-C_7 alkyl- wherein the C_1-C_3 alkyl is optionally substituted with –C(O)NR_3-C_1-C_3 alkyl-A_{1a} and C_1-C_7 alkyl is optionally substituted with –NR_3-C(O)O-C_1-C_3 alkyl-A_{1b}, -NR_3-C(O)-C_1-C_3 alkyl-A_{1b}, -NR_3-S(O)$_2$-C_1-C_3 alkyl-A_{1b}, -NR_3-C(O)-NR_3-C_1-C_3 alkyl A_{1b} or -NR_3-S(O)$_2$-NR_3-C_1-C_3 alkyl-A_{1b}, A_{2a}-arylene-C_0-C_3 alkyl-N(R_3)- C(O)- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –NR_3-C(O)-C_1-C_5 alkyl- C_2-C_4 alkenyl-C_1-C_3 alkyl-O-A_{2b}, or –N(R_3)-C(O)-C_1-C_7alkyl-O-A_{2b},

A_{2a}-heteroarylene-C_0-C_3 alkyl-N(R_3)-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –NR_3-C(O)-C_1-C_5 alkyl-C_2-C_4 alkenyl-C_1-C_3 alkyl-O-A_{2b},

A_{1a}-O-aryl-C_0-C_3alkyl-N(R_3)-C(O)-C_1-C_7alkyl, wherein the C_1-C_7 alkyl is optionally substituted with –N(R_3)-C(O)-C_1-C_7alkyl-A_{1b}, and

B_2-B_1-N(R_3)-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –NR_3-B_3 and the amine of B_3 is conected with the acid of B_2 to form a amidepeptide bond.

heteroaryl-S(O)$_2$-C_0-C_6 alkyl-aryl- or aryl-C_0-C_6 alkyl-N(R_3)-C(O)-C_1-C_7 alkyl-, wherein each of the aryl and heteroaryl groups is optionally substituted with one or more groups selected from oxo, -NO_2, C_1-C_6 alkoxy, halo, R_3, R_4 or R_6; whereinor

A_{1a} and A_{1b} are independently selected from the group consisting of alkyl, alkenyl and a, protecting group ; or

A_{1a} and A_{1b} together, they are attached to via a form a ring with –C_2-C_6alkylene, –C_2-C_6alkenylene or, –C_2-C_6alkynylene linker, form an optionally substituted ring; moieties.

A_{2a} and A_{2b} together are a covalent bond and, together with the aryl to which they are attached to form a ring;, and

B_1, B_2 and B_3 are attached to form peptide bond.

B_1, B_2 and B_3 are each independently D or L-Gly, D or L-Pro, D or L-Tyr, D or L-Tyr(OR_3), D or L-Phe, D or L-PheR_4, D or L-Aib, D or L-Ala, D or L-ProR_3, D or L-Ile, D or L-Leu. D or L-PheR_3, D or L-Pip, a natural or synthetic amino acid; or

L is a covalent bond and Z is C_0-C_6alkyl, heteroalkyl, -C_0-C_6 alkyl-heterocyclyl-C_0-C_6 alkyl-, -heterocyclyl-C(O)-C_2-C_6 alkenyl-C_1-C_3 alkyl-, - C_0-C_7 alkyl-N(R_3)-C(O)-heterocyclyl-C_0-C_7 alkyl-, -C_0-C_7 alkyl-N(R_3)-C(S)-heterocyclyl-C_0-C_7 alkyl-, -C_0-C_7 alkyl-,O-C(O)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_7 alkyl-O-C(S)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-C(O)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-C(S)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-$S(O)_2$-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-C(O)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-C(S)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-$S(O)_2$-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-N(R_3)C(O)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-O-C(O)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-N(R_3)C(S)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-O-C(S)-C_0-C_6 alkyl-, and -X-C_1-C_6 alkyl-C(R_3)=C(R_3)-C_1-C_6 alkyl-, wherein each alkyl, alkenyl and heterocyclyl of the aforementioned Z is optionally substituted;

R_6 is selected from the group consisting of -H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, heterocyclyl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-, C_3-C_6 cycloalkyl-C_0-C_6 alkyl-, N(R_3)(R_{3a})-C_1-C_6 alkyl- and N(R_3)(R_{3a})-C(O)-C_1-C_6 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteoralkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl moiety is optionally substituted; and

R_7 and R_{7a} are independently selected from the group consisting of -H, C_1-C_6 alkyl-, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, R_3-O-C_1-C_6 alkyl-, N(R_3)(R_{3a})-C_1-C_6 alkyl-, a protecting group, -C(O)-O-C_1-C_6 alkyl, -C(O)-O-benzyl and heterocyclyl-C_1-C_6 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, benzyl and heterocyclyl moiety is independently optionally substituted; or

R_7 is -OR_3 when attached to the N atom of an indolyl moiety;

wherein in a -N(R_3)(R_{3a}) group, optionally the R_3 and R_{3a} together with the nitrogen atom to which they are attached form a heterocyclyl group; or

wherein in a -N(R_4)(R_{4a}) group, optionally the R_4 and R_{4a} together with the nitrogen atom to which they are attached form a heterocyclyl group; and

provided that

when R_3, R_{3a}, R_4 and R_{4a} are present in -N(R_3)(R_{3a}), -N(R_4)(R_{4a}), -NR_3, -OR_3, -SR_3, -alkyl-R_3, -$NR_3S(O)_2R_3$, -S(O)CH_2R_3, -$NR_3S(O)_2CH_2R_3$, -$NR_3C(O)CH_2R_3$(C=NR_3)N(R_3)(R_{3a}), -

$C(O)R_3$, $-NR_4$ and $-CR_3=CR_3$, then R_3, R_{3a}, R_4 and R_{4a} are independently H, $-C_1$-C_6-alkyl, $-C_3$-C_6-cycloalkyl, heteroalkyl, aryl, alkyl-aryl, heteroaryl or alkyl-heteroary;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1 and R_2 are -H, and Q is $-C_1$-C_6-alkyl-$C(O)-OR_3$, then R_3 is not -H;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1 and R_2 are -H, and Q is $-C_1$-C_6-alkyl-$N(R_3)(R_{3a})$, and R_3 is -H, then R_{3a} is not -H;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1 and R_2 are -H, Q is $-C_1$-C_6 alkyl-$C(O)-N(R_3)(R_{3a})$, and R_3 is -H, then R_{3a} is not -H, -OH, or phenyl substituted with $-NH_2$ or -OH;

when Y-L-Z- is phenyl or phenyl-CH_2-, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1 and R_2 are -H, and Q is $-C_1$-C_6 alkyl-$N(H)-S(O)_2-R_3$, then R_3 is not $-CH_3$;

when Y-L-Z- is aryl-C_1-C_6 alkyl- or heteroaryl-C_1-C_6 alkyl-, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1 and R_2 are -H, Q is $-C_1$-C_6 alkyl-$C(O)-N(R_3)(R_{3a})$, and R_3 is -H, then R_{3a} is not -OH;

when Y-L-Z- is aryl-C_1-C_6 alkyl-, aryl, cycloalkyl, heterocyclyl, heteroaryl, or heteroaryl-C_1-C_6 alkyl-, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1, R_2 and R_3 are -H, Q is not $-C_1$-C_6 alkyl-$N(H)-C(O)-CH_2-SH$;

when Y-L-Z- is aryl-C_1-C_6 alkyl-, aryl, or heteroaryl, W is nitrogen, R_1, R_2 and R_3 are -H, -X-Q is not $-C_1$-C_6 alkyl-SH;

when Y-L-Z- is phenyl optionally para substituted with $-N(CH_3)_2$, naphthyl, indolyl, or benzofuranyl, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1, R_2 and R_3 are -H, then Q is not $-C_1$-C_6 alkyl-OH;

when Y-L-Z- is phenyl optionally para substituted with $-N(CH_3)_2$, quinolinyl, biphenyl or benzyl, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1, R_2 and R_3 are -H, then Q is not $-C_1$-C_6 alkyl-$N(H)-S(O)_2-CH_3$, $-C_1$-C_6 alkyl-$S(O)_2-N(H)$-OH, $-C_1$-C_6 alkyl-$N(H)-C(O)-NH_2$, $-C_1$-C_6 alkyl-$N(H)-C(O)-C_1$-C_2 alkyl-SH, $-C_1$-C_6 alkyl-$C(O)-N(H)$-OH, $-C_1$-C_6 alkyl-C(O)-OH, or $-C_1$-C_6 alkyl-$N(H)-C(O)-O$-t-butyl;

when Y-L-Z- is phenyl optionally para substituted with $-N(CH_3)_2$, biphenyl, substituted pyrrolyl, or substituted pyrrolidinyl, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1, R_2 and R_3 are -H, then Q is not $-C_1$-C_6 alkyl-$C(O)-N(H)$-OH;

when Y-L-Z- is phenyl, benzyl, or quinolinyl, W is nitrogen, X is a covalent bond or $-CH_2-$, R_1 is -H, R_2 is -N(H)-C(O)-O-t-butyl or -N(H)-C(O)-O-benzyl, then Q is not $-C_1$-C_6 alkyl-$C(O)-N(H)$-OH, $-C_1$-C_6 alkyl-imidazolyl, $-C_1$-C_6 alkyl-SO_2-NH_2, $-C_1$-C_6 alkyl-$C(O)-N(H)$-imidazolyl, $-C_1$-C_6 alkyl-$C(O)-N(H)$-thiazolyl, $-C_1$-C_6 alkyl-$C(O)-N(H)$-pyridinyl, $-C_1$-C_6 alkyl-$C(O)-N(H)$-anilinyl, $-C_1$-C_6 alkyl-NH_2, $-C_1$-C_6 alkyl-$N(H)-S(O)_2-CH_3$, or $-C_1$-C_6 alkyl-$C(O)-O-R_3$, wherein R_3 is $-CH_3$, -t-butyl, or -H;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1, R_2 and R_3 are -H, then Q is not C_1-C_6-alkyl-NH-S(O)$_2$-CH_3, C_1-C_6-alkyl-S(O)$_2$-NH-OH, C_1-C_6-alkyl-NH-C(O)-NH_2, -C_1-C_6-alkyl-NH_2, -C_1-C_6-alkyl-NH-C(O)-C_1-C_2-alkyl-halo, -C_1-C_6-alkyl-NH-C(O)-C_1-C_2-alkyl-NH_2 or -C_1-C_6-alkyl-NH-C(O)-CH_2-OH; or

when Y is phenyl optionally para substituted with -N(CH_3)$_2$, L is -C(O)-NH-CH_2-, Z is phenyl-CH_2, W is N, R_1, R_2 and R_3 are -H, and X is a covalent bond, Q is not –SH; and

further provided that Formula (I) excludes those compounds wherein

X is S;

Q is selected from the group consisting of H, methyl, ethyl, phenyl, benzyl and acetyl;. and

Y-L-Z is selected from the group consisting of R^a-(CH_2)$_{4-6}$ and R^b-Ar-(CH_2)$_{1-2}$-, wherein

R^a is selected from the group consisting of R^cNR^dC(O)-, R^cNHC(O)NH-, R^cNHC(S)NH-, R^cSO_2NH- and R^cC(O)NH-;

R^b is selected from the group consisting of R^cNR^dC(O)(CH_2)$_{1-2}$-, R^cNHC(O)NH(CH_2)$_{1-2}$-, R^cNHC(S)NH(CH_2)$_{1-2}$, R^cSO_2NH(CH_2)$_{1-2}$- and R^cC(O)NH(CH_2)$_{1-2}$-;

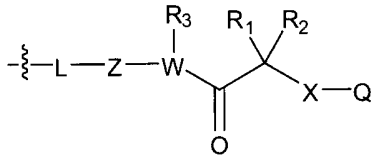
R^c is selected from the group consisting of C_{0-2}alkyl, aryl, heteroaryl, carbocyclyl, -heteroaryl-heteroaryl, -heteroaryl-C_{1-4}alkyl, -heteroaryl-OCH_3, -heteroaryl-aryl-halogen, -heteroaryl-aryl, aryl-aryl, -aryl-SCH_3, -aryl-OCH_3, -aryl-CF_3, -aryl-O-C_2alkyl-heterocyclyl, -C_{3-10}cycloalkyl-aryl, -C_{0-2}alkyl-heterocyclyl, -C_{0-2}alkyl-heteroaryl, -C_{0-2}alkyl-aryl, -C_{0-1}alkyl-heteroaryl, -aryl-OCH_2-aryl, -aryl-CH_2O-aryl, -aryl-carbonyl-aryl, -aryl-C(O)CH_3, -aryl-O-aryl, -aryl-O-heterocyclyl, -aryl-C_{1-4}alkyl, -aryl-O-C_{2-3}alkyl-N(CH_3)(CH_3), C_{0-1}alkyl-heterocyclyl-C_{0-1}allkyl, C_{0-1}alkyl-heteroaryl-C_{0-1}alkyl, -heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -aryl-heterocyclyl, -aryl-heteroaryl and –CH(aryl)(aryl), any of which is optionally substituted with one or more of R^e or R^f;

R^e or R^f are C_{0-4}alkyl, halogen, -OH, -CF_3, -SCH_3, -OCH_3, -NH_2, -O(CH_2)$_2$N(CH_3)(CH_3), -OCH_2-aryl, -O(CH_2)$_2$-heterocyclyl, -C(O)CH_3, -O-heterocyclyl, aryloxy-C_{0-1}alkyl-, aryl or heterocyclyl; and

R^d is C_{0-1}alkyl, or R^c and R^d taken together form a heterocyclic or carbocyclic ring, any of which is optionally substituted with one or more independent C_{0-4}alkyl, halogen, -OH, -SCH_3, OCH_3, -NH_2, aryl, or heterocyclyl substituents; and

Ar is aryl optionally substituted with one or more independent C_{1-4}alkyl, halogen, -OH, -SCH_3, -OCH_3, -NH_2, aryl or heterocyclyl substituents; and

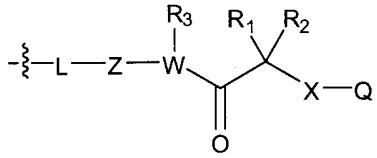
further provided that Formula (I) excludes those compounds wherein



is -$(CH_2)_{3-4}$-NH(CO)-CH_2-O-CH_2-phenyl or –$(CH_2)_{3-4}$-NHC(O)-CH_2-S-phenyl and

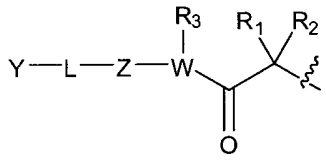
Y is selected from the group consisting of optionally substituted imidazopyridinyl or optionally substituted imidazonaphthyridine; and

further provided that Formula (I) excludes those compounds wherein

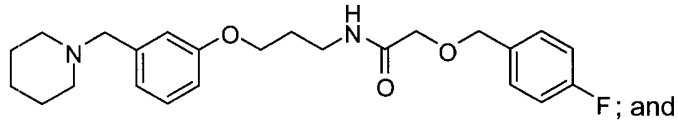


is -$(CH_2)_{2-3}$-NHC(O)-CH_2-O-CH_2-phenyl or -$(CH_2)_{2-3}$-NHC(O)-CH_2-S-phenyl, wherein the phenyl is optionally substituted with halogen, and Y is dimethyoxyphenyl; and

further provided that Formula (I) excludes those compounds wherein

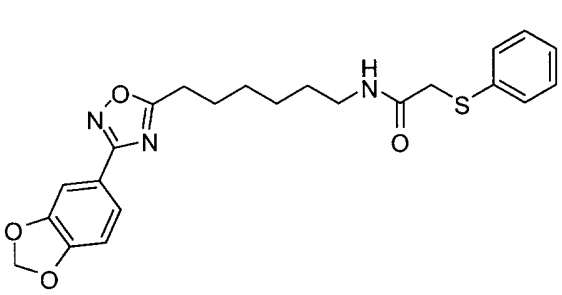


is 3-(R^t)(R^{tt})CH-phenyl-1-O-C_3-C_4alkyl-NHC(O)-, 3-(R^t)(R^{tt})CH-phenyl-1-O-C_3-C_4alkenyl-NHC(O)-, (R^t)(R^{tt})CH-thiophene-O-C_3-C_4alkyl-NHC(O)-, (R^t)(R^{tt})CH-thiophene-O-C_3-C_4alkenyl-NHC(O)-, (R^t)(R^{tt})CH-pyridine-O-C_3-C_4alkyl-NHC(O)- and (R^t)(R^{tt})CH-pyridinyl-O-C_3-C_4alkenyl-NHC(O)-, wherein R^t is selected from the group consisting of H, halogen, OH, Me, optionally substituted piperidino, dimethylamino, 1-pyrrolidinyl and 1-perhydroazepinyl, and R^{tt} is H or Me, or R^t is oxo and R^{tt} is absent, with the exception the this proviso does not include the compound



F; and

further provided that Formula (I) excludes indol-$(CH_2)_2$-NHC(O)-CH_2-O-CH_2-phenyl, indol-$(CH_2)_2$-NHC(O)-CH_2-$S(O)_2$-phenyl-Me, phenyl-$(CH_2)_2$-NHC(O)-CH_2-S(O)2-phenyl, phenyl-$(CH_2)_2$-NHC(O)-CH_2-$S(O)_2$-phenyl-Me, T-$(CH_2)_{2-5}$-NHC(O)-CH_2-S-phenyl (wherein T is pheny, fluro-phenyl, pyridine, methyl-pyrrolidine or methyl), NH_2-$S(O)_2$-phenyl-$(CH_2)_2$-NHC(O)-CH_2-S-phenyl, CH_3-$(CH_2)_2$-NHC(O)-CH_2-O-CH_2-phenyl, CH_3-$(CH_2)_2$-NHC(O)-CH_2-$S(O)_2$-phenyl, CH_3-$(CH_2)_2$-NHC(O)-CH_2-S-phenyl, N-[[[[(aryloxy- or –thio)alkyl]carbonyl]amino]alkyl]-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamide,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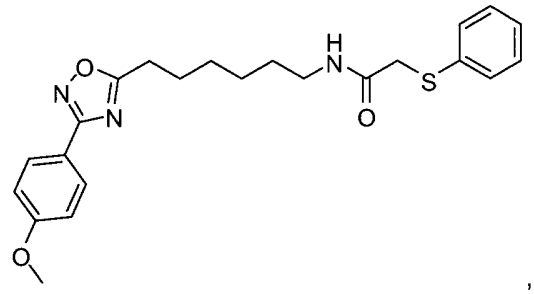
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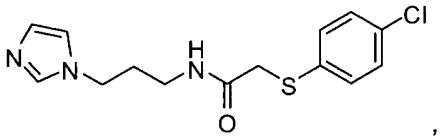
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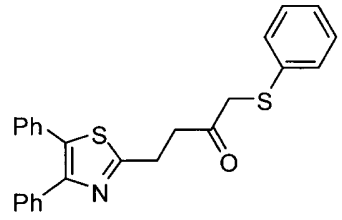
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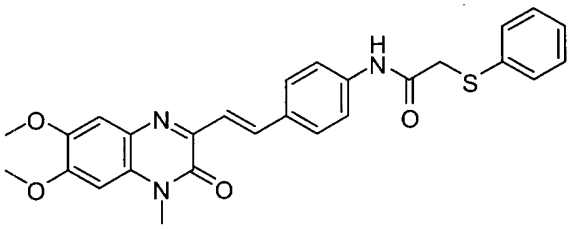
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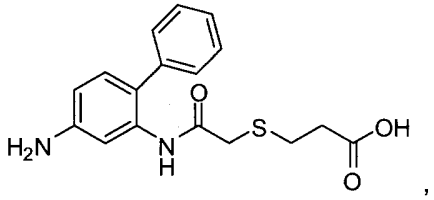
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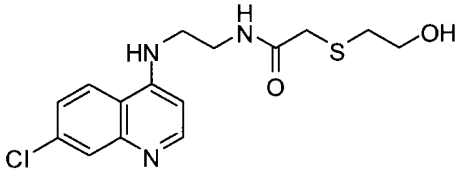
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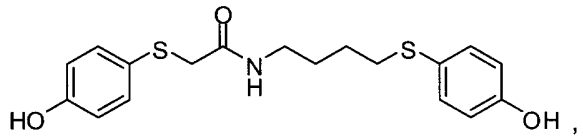
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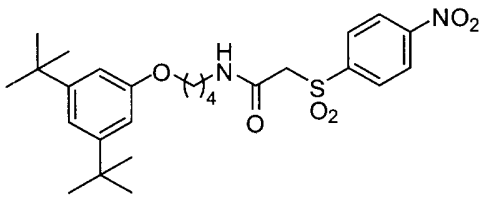
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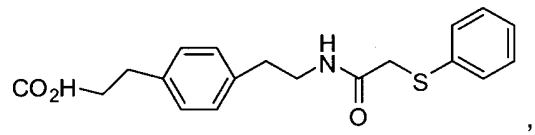
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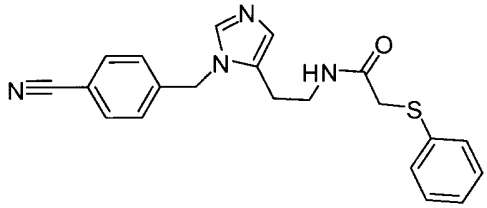
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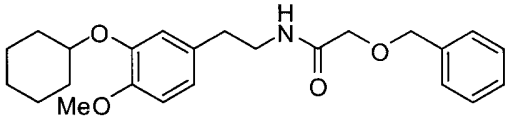

, and

further provided that Formula (I) excludes compounds of formula $(R^{v})(R^{vv})$pyrimidine-$NHS(O)_2$-phenyl-C_0-C_4alkyl-NHC(O)-A, wherein A is aryloxylalkyl or arylmercaptoalkyl, R^{v} is a lower alkyl, and R^{vv} is selected from the group consisting of H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl, alkoxy, alkoxyalkyl and alkoxyalkoxy, or wherein R^{v} and R^{vv} taken together form a ring of 3 to 5 methylene groups which can contain oxygen or sulfur atoms.

[0016] A preferred embodiment, Embodiment A, provides compounds according to formula (I), wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of X-Q, Q, L, Z, R^3 and R^{3a} is independently optionally substituted with one or more groups independently selected from R^4.

[0017] A preferred embodiment, Embodiment B, provides compounds according to formula (I), wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of X-Q, Q, R^3 and R^{3a} is independently optionally substituted with one or more groups independently selected from oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2, -$N(R_4)(R_{4a})$, halo, -SH, -S-C_1-C_6 alkyl, -S(O)-C_1-C_6 alkyl, -S-C(O)-C_1-C_6 alkyl and mono- to per-halogenated C_1-C_6 alkyl.

[0018] A preferred embodiment, Embodiment C, provides compounds according to formula (I), wherein C_1-C_6 alkyl of R_4 and R_{4a} is optionally substituted with -OH, -NO_2 or C_0-C_6 alkyl-C(O)-$N(R_3)(R_{3a})$.

[0019] A preferred embodiment, Embodiment D, provides compounds according to formula (I), wherein each alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl moiety of Z is independently optionally substituted with one or more groups independently selected from oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2, -$N(R_3)(R_{3a})$, halo, -SH and mono- to per-halogenated C_1-C_6 alkyl.

[0020] A preferred embodiment, Embodiment E, provides compounds according to formula (I), wherein L is selected from the group consisting of

-C_1-C_6 alkyl-$N(R_3)$-C_0-C_3 alkyl wherein the C_1-C_6 alkyl is optionally substituted with -C_1-C_4 alkyl-OR_3, or –C_0-C_4 alkyl-C(O)OR_3,

-C_0-C_6 alkyl-$N(R_3)$-C(O)-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-C(O)$O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-,

-C_0-C_6 alkyl-$N(R_3)$-C(S)-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-C(O)$O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-,

-C_0-C_6 alkyl-C(O)-$N(R_3)$-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-C(O)$O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-,

-C_0-C_6 alkyl-C(S)-$N(R_3)$-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-C(O)$O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-, and

-C_0-C_6 alkyl-$N(R_3)$-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-C(O)$O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-.

[0021] A preferred embodiment, Embodiment F, provides compounds according to formula (I), wherein each alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl moiety of Y-L-Z is independently optionally substituted with one or more groups independently selected from oxo, -NO_2, C_1-C_6 alkoxy, halo, R_3, R_4 and R_6.

[0022] A preferred embodiment, Embodiment G, provides compounds according to formula (I), wherein Y-L-Z- is selected from the group consisting of

heteroaryl-C_0-C_6 alkyl-N(R_3)-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with -N(R_7)(R_{7a}) or -N(R_3)-C(O)-C_1-C_6 alkyl-R_3,

aryl-C_0-C_6 alkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with -N(R_7)(R_{7a}), aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

heteroaryl-C_0-C_6 alkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with -N(R_7)(R_{7a}), aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

C_1-C_6 alkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with -N(R_7)(R_{7a}), aryl-aryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

heterocyclyl-C_0-C_6 alkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with -N(R_7)(R_{7a}), aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

C_1-C_6 cycloalkyl- C(O)-N(R_3)- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with -N(R_7)(R_{7a}), aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl, or heteroaryl,

C_1-C_3 alkyl-N(R_3)-C(O)- C_1-C_7 alkyl-, wherein the C_1-C_3 alkyl is optionally substituted with –C(O)NR_3-C_1-C_3 alkyl-A_{1a} and the C_1-C_7 alkyl is optionally substituted with -NR_3-C(O)O-C_1-C_3 alkyl-A_{1b}, -NR_3-C(O)-C_1-C_3 alkyl-A_{1b}, -NR_3-S(O)$_2$-C_1-C_3 alkyl-A_{1b}, -NR_3-C(O)-NR_3-C_1-C_3 alkyl-A_{1b} or -NR_3-S(O)$_2$-NR_3-C_1-C_3 alkyl-A_{1b}, and

aryl-C_1-C_3 alkyl-N(R_3)-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_3 alkyl is optionally substituted with –C(O)NR_3-C_1-C_3 alkyl-A_{1a} and the C_1-C_7 alkyl is optionally substituted with –N(R_3)-C(O)O-C_1-C_3 alkyl-A_{1b}, -N(R_3)-C(O)-C_1-C_3 alkyl-A_{1b}, -NR_3-S(O)$_2$-C_1-C_3 alkyl-A_{1b}, -NR_3-C(O)-NR_3-C_1-C_3 alkyl A_{1b} or -NR_3-S(O)$_2$-NR_3-C_1-C_3 alkyl-A_{1b}.

[0023] A preferred embodiment, Embodiment H, provides compounds according to formula (I), wherein B_1, B_2 and B_3 are independently selected from the group consisting of D-Gly, L-Gly, D-Pro, L-Pro, D-Tyr, L-Tyr, D-Tyr(OR_3), L-Tyr(OR_3), D-Phe, L-Phe, D-PheR_4, L-PheR_4, D-Aib, L-Aib, D-Ala, L-Ala, D-ProR_3, L-ProR_3, D-Ile, L-Ile, D-Leu, L-Leu D-PheR_3, L-PheR_3, D-Pip and L-Pip.

[0024] A preferred embodiment, Embodiment I, provides compounds according to formula (I), wherein each alkyl, alkenyl and heterocyclyl moiety of Y-Z is independently optionally substituted with one or more groups independently selected from R^4.

[0025] A preferred embodiment, Embodiment J, provides compounds according to formula (I), wherein each alkyl, alkenyl, alkynyl, heteoralkyl, cycloalkyl, aryl, heteroaryl, and

heterocyclyl moiety of R_6 is independently optionally substituted with one or more groups independently selected from R_3 and R_4.

[0026] A preferred embodiment, Embodiment K, provides compounds according to formula (I), wherein each alkyl, alkenyl, alkynyl, heteroalkyl, benzyl and heterocyclyl moiety of R_7 and R_{7a} is independently optionally substituted with one or more groups independently selected oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2, -$N(R_3)(R_{3a})$, halo, -SH and mono- to per-halogenated C_1-C_6 alkyl.

[0027] A preferred embodiment, Embodiment L, provides compounds according to formula (I), wherein Y is selected from the group consisting of aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, mixed aryl and non-aryl polyheterocycle, each of which is optionally substituted.

[0028] A preferred embodiment, Embodiment M, provides compounds according to formula (I), wherein Y is selected from the group consisting of -(O)C-C_0-C_3alkyl-aryl, -C_0-C_3alkyl-aryl, -C_0-C_3alkyl-aryl-O-C_2-C_4alkyl-$N(R_3)(R_{3a})$, -C_0-C_3alkyl-heteroaryl-O-C_2-C_4alkyl-$N(R_3)(R_{3a})$, -C_0-C_3alkyl-aryl-C_0-C_3alkyl, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl and aryl-C_1-C_3alkyl-aryl, each of which is optionally substituted.

[0029] A preferred embodiment, Embodiment N, provides compounds according to formula (I), wherein Y is aryl-C_1-C_3alkyl-aryl , wherein C_1-C_3 alkyl is optionally substituted with C_0-C_3alkyl.

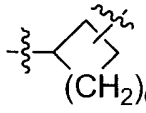
[0030] A preferred embodiment, Embodiment O, provides compounds according to formula (I), wherein L is a covalent bond and Z is selected from the group consisting of

-C_0-C_7 alkyl-$N(R_3)$-C(O)-heterocyclyl-C_0-C_6 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –C_0-C_3alkyl-C(O)OR_3 or –C_0-C_3alkyl-OR_3,

- C_0-C_7 alkyl-O-C(O)-heterocyclyl-C_0-C_6 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –C_0-C_3alkyl-C(O)OR_3 or –C_0-C_3alkyl-OR_3, and

-C_1-C_4alkyl-$N(R_3)$C(O)-heteorcyclyl-C_1-C_7alkyl, wherein the C_1-C_4alkyl is optionally substituted with C_0-C_3alkyl-C(O)OR_3 or C_0-C_3alkyl-OR_3.

[0031] A preferred embodiment, Embodiment P, provides compounds according to formula (I), wherein X is -S-, -SO-, -SO_2-, -O-, -NR_3-, -CH_2-, -CH(OH)-, or



[0032] Yet another preferred embodiment, Embodiment Q, provides compounds according to formula (I), wherein R_1 and R_2 are independently -H, C_1-C_3 alkyl, C_3-C_6 cycloalkyl, aryl, or aryl-C_1-C_3 alkyl-. Preferably, R_1 and R_2 are independently -CH_3, -CH_2CH_3, phenyl or benzyl.

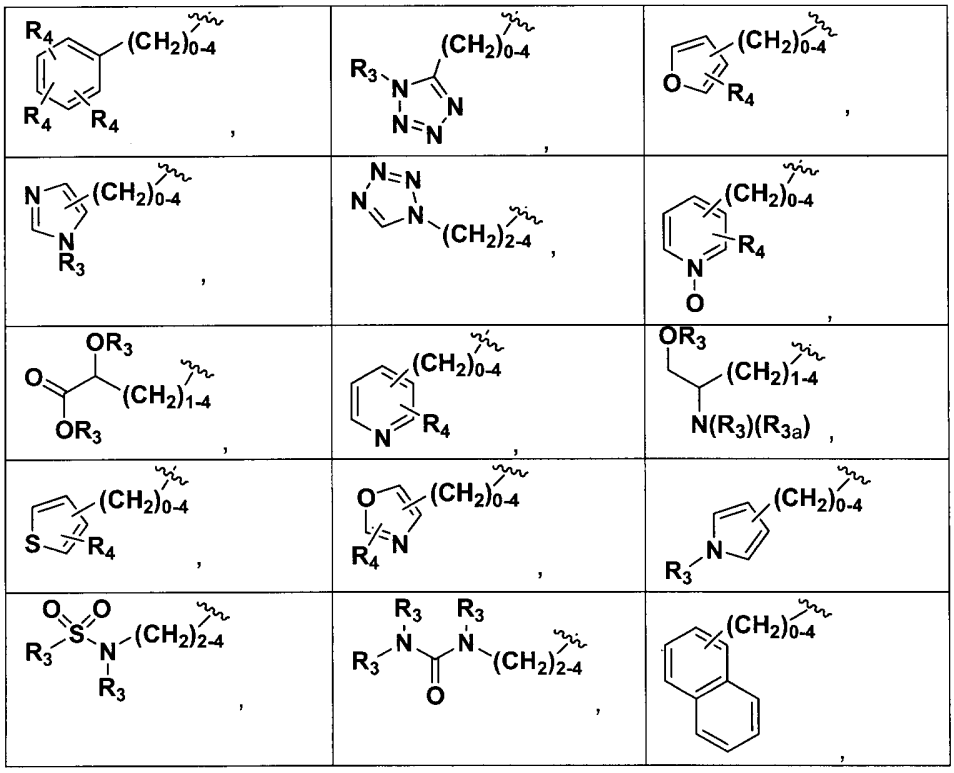
[0033] One other preferred embodiment, Embodiment R, provides compounds according to formula (I), wherein R_1 and R_2 together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or heterocyclyl group.

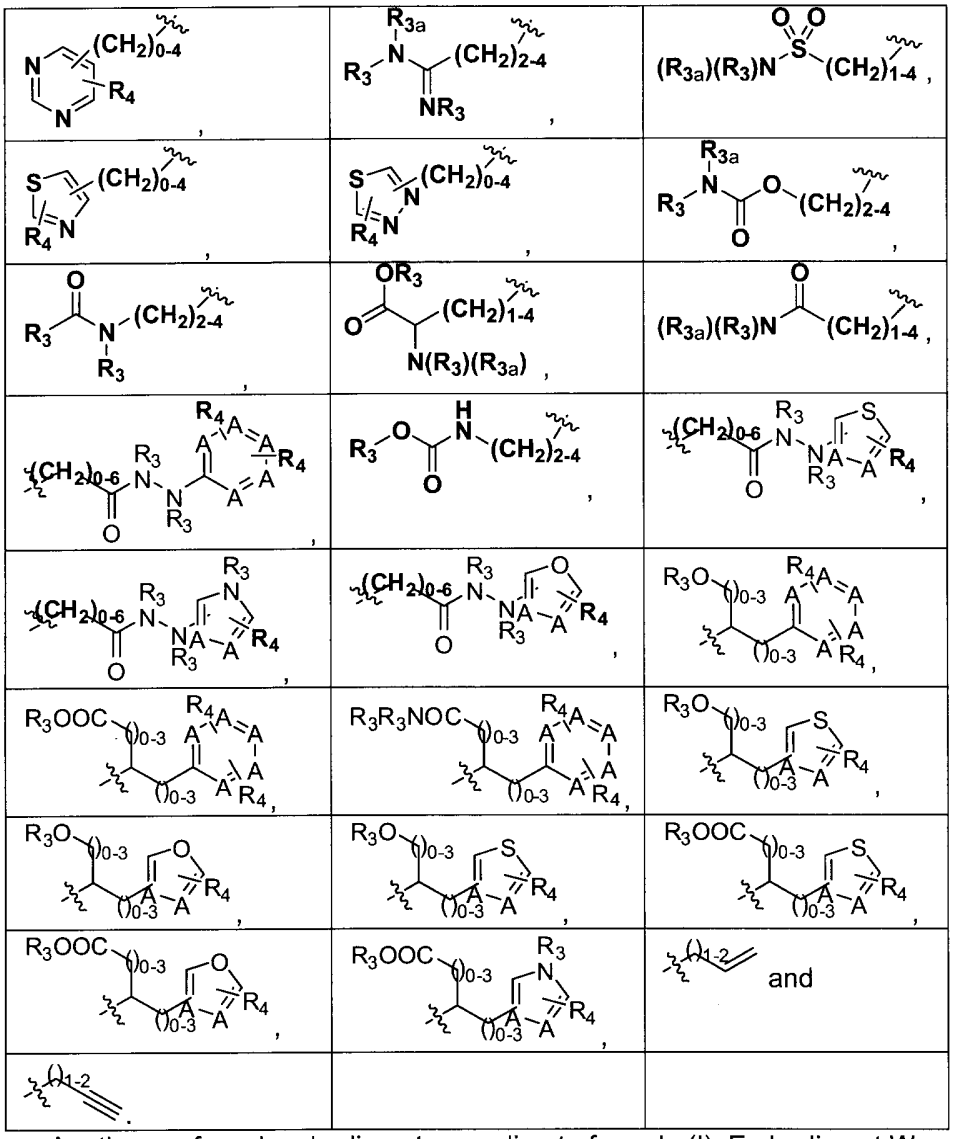
[0034] Another preferred embodiment, Embodiment S, provides compounds according to formula (I), wherein R_3 and R_{3a} are independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -C_1-C_6 alkylaryl, aryl or heteroaryl. Preferably, R_3 and R_{3a} are independently -C_1-C_6 alkylaryl, or aryl. More preferably, R_3 and R_{3a} are independently phenyl or benzyl. Also preferred are compounds wherein R_3 and R_{3a} are C_1-C_4 alkyl. Preferably, R_3 and R_{3a} are independently *t*-butyl or *i*-propyl.

[0035] Another preferred embodiment, Embodiment T, provides compounds wherein in a NR_3R_{3a} group or a NR_4R_{4a} group, optionally the R_3 together or the R_4 together with the nitrogen atom to which they are attached form a group selected from morpholinyl, piperazinyl, piperidinyl, pyrrolydinyl, and azetidinyl.

[0036] Another preferred embodiment, Embodiment U, provides compounds according to formula (I), wherein X-Q is -OH, -NH_2, -Cl, -F, -SH or -Br. Preferably, X-Q is absent and R_1 and R_2 together with the carbon atom to which they attached form a 5- to 6-membered aromatic or heteroaromatic ring.

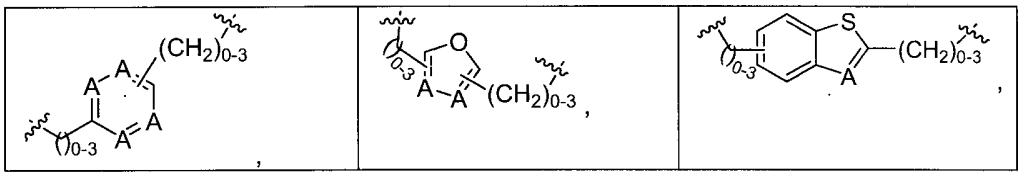
[0037] Embodiment V is another preferred embodiment according to formula (I), wherein Q is preferably one of the following groups:

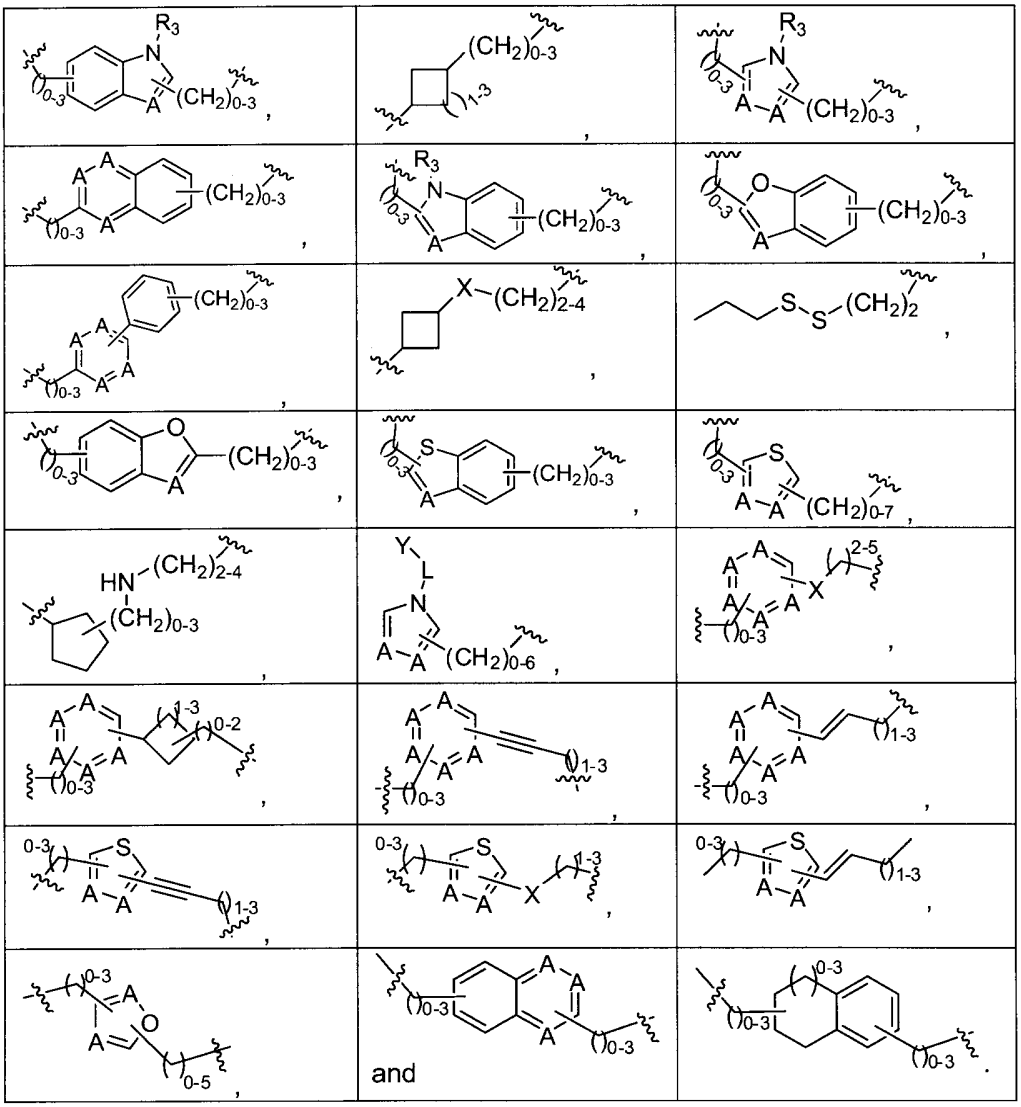




[0038] Another preferred embodiment according to formula (I), Embodiment W, provides compounds wherein R_4 is -H, $-CH_3$, $-(CH_2)_{0-4}OR_3$, $-(CH_2)_{0-4}N(R_3)(R_{3a})$, -F, -Cl, -Br, $-CF_3$, -CN, $-CH_2OH$, $-NO_2$, $-N(R_3)C(O)CH_2R_3$, $-N(R_3)SO_2CH_2R_3$, $-O(CH_2)_{2-4}N(R_3)(R_{3a})$, $-SR_3$, $-S(O)CH_2R_3$, $-SO_2CH_2R_3$, $-(CH_2)_{0-4}C(O)OR_3$, $-CH=CHC(O)OR_3$, $-CH=CHC(O)N(R_3)(R_{3a})$, $-N(R_3)C(O)CF_3$ or $-N(R_3)(CH_2)_2N(R_3)(R_{3a})$.

[0039] Embodiment X is another preferred embodiment according to formula (I), wherein Z is preferably one of the following groups:



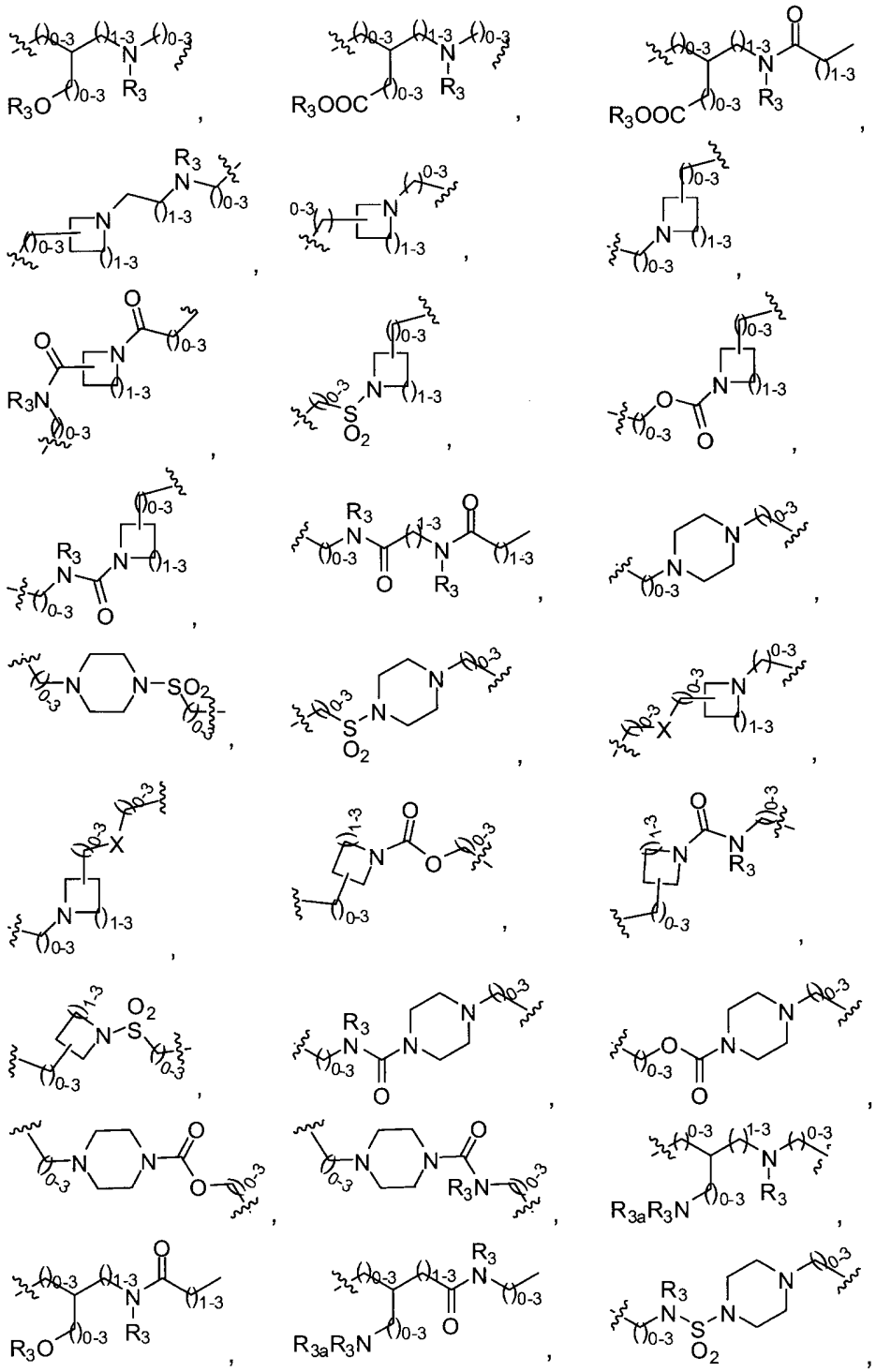


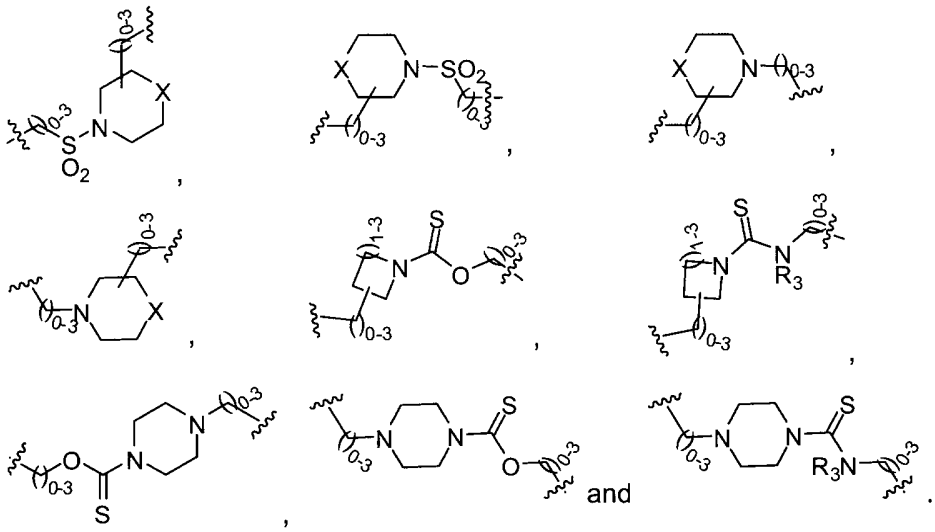
and

wherein A is -CH= or -N=.

[0040] In a preferred Embodiment Y according to formula (I), the compounds are compounds wherein L is selected from the group consisting of a covalent bond, $-(CH_2)_{0-3}N(R_3)C(O)-$, $-(CH_2)_{0-3}C(O)N(R_3)-$, $-(CH_2)_{0-3}OC(O)-$, $-(CH_2)_{0-3}C(O)O-$, $-C_0-C_6$ alkyl-$N(R_3)C(O)$heterocyclyl-C_0-C_3alkyl, $-C_0-C_6$ alkyl-$S(O)_2$heterocyclyl-C_0-C_3alkyl,-, $-(CH_2)_{0-3}C(O)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}SO_2N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}NR_3S(O)_2-(CH_2)_{0-3}$, $-(CH_2)_{0-3}N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}N(R_7)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}S-(CH_2)_{0-3}$, $-(CH_2)_{0-3}O-(CH_2)_{0-3}$, $-(CH_2)_{0-3}S(O)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}S(O)_2-(CH_2)_{0-3}$, $-(CH_2)_{0-3}CH=CH-(CH_2)_{2-3}-$, $-(CH_2)_{0-3}N(R_3)C(O)N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}N(R_3)C(O)O-(CH_2)_{0-3}$ and $-(CH_2)_{0-3}OC(O)N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}NR_3C(O)NR_3S(O)_2-(CH_2)_{0-3}$, $-(CH_2)_{0-3}NR_3C(O)NR_3C(O)-(CH_2)_{0-3}$, and $-(CH_2)_{0-3}-C(O)-N(R_3)-C(O)N(R_3)-(CH_2)_{0-3}$ and $-(C_0-C_3alkyl)(R_3)N-S(O)_2-N(R_3)-C_2-C_4alkyl-O-C_0-C_3alkyl$, -and $R_3R_{3a}NS(O)_2NR_3-C_2-C_4alkyl-O-C_0-C_6$ alkyl- , when Y is absent, and $-R_3R_{3a}NS(O)_2NR_3-C_2-C_4alkyl$, when Y is absent.

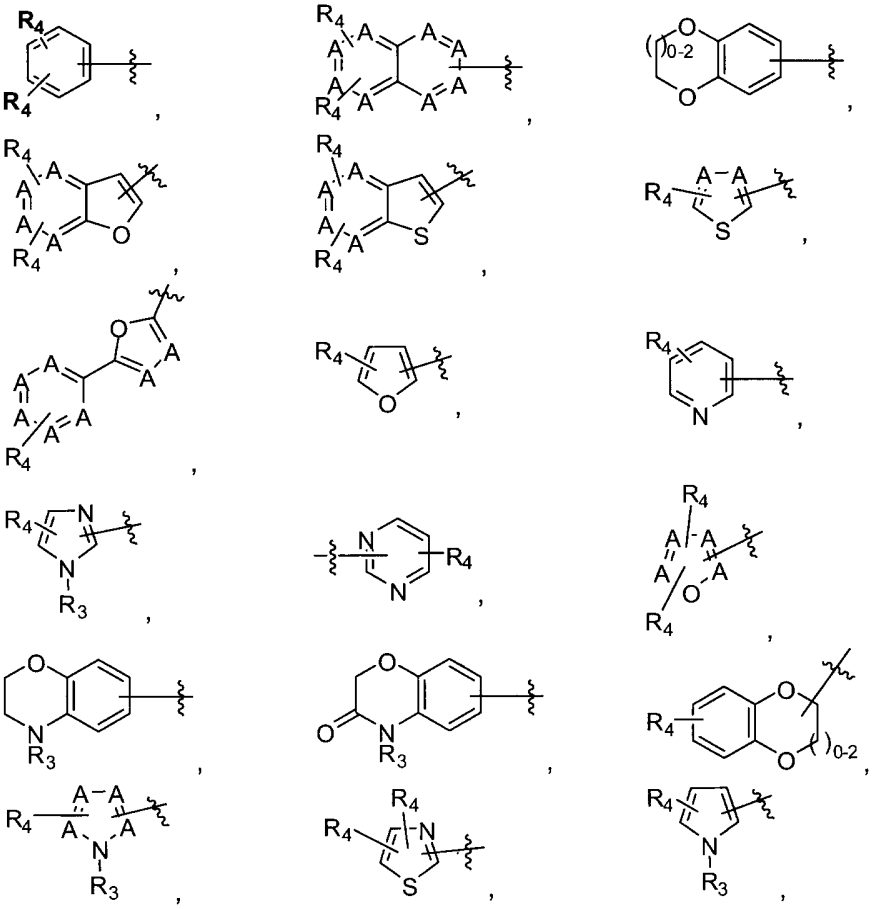
[0041] Embodiment Z is another preferred embodiment according to formula (I), wherein L is preferably one of the following groups:

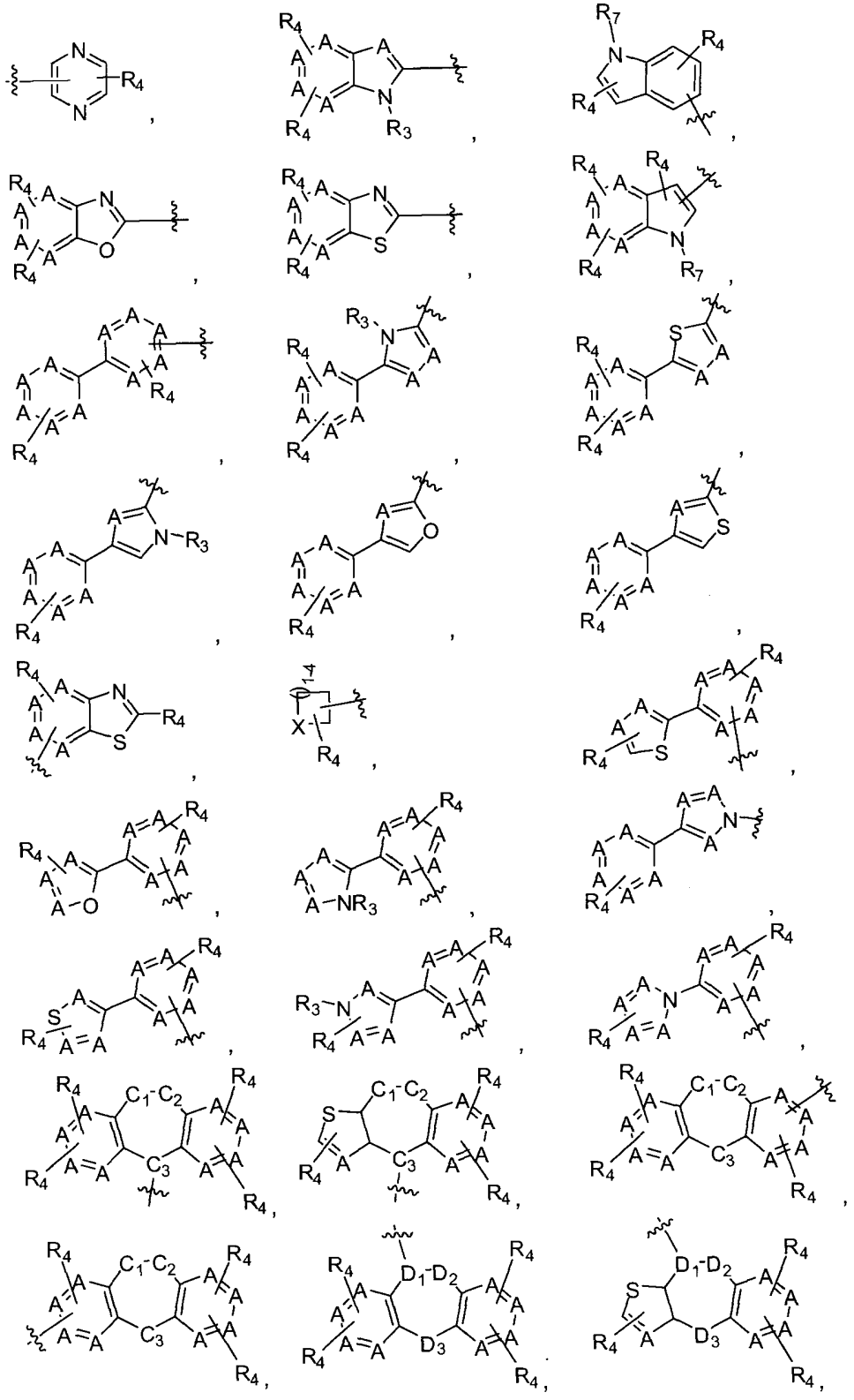


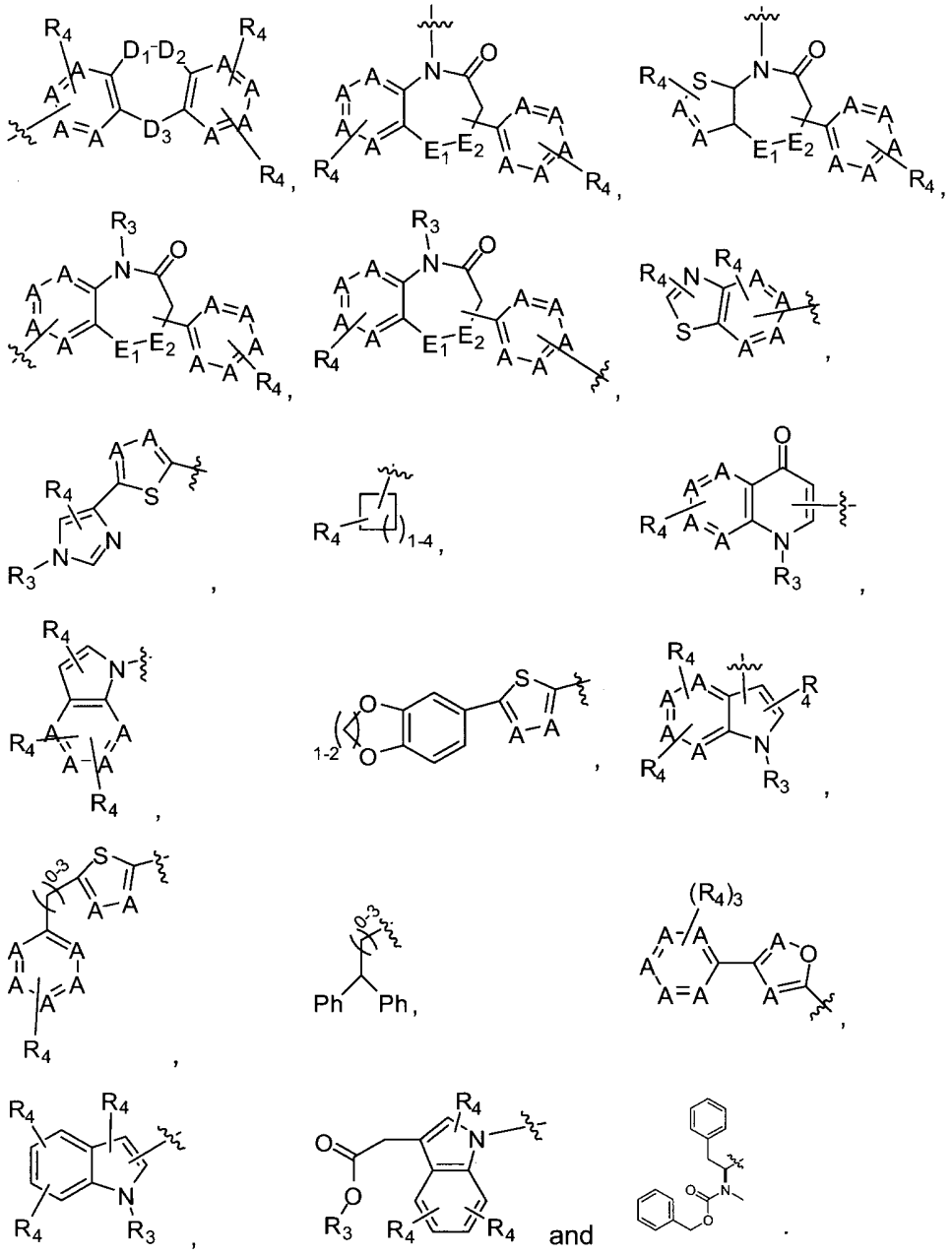


wherein A is -CH= or -N=.

[0042] Embodiment AA is another preferred embodiment according to formula (I), wherein Y is selected from the group consisting of







wherein A is -CH= or -N=;

C_1 is selected from the group consisting of absent, a covalent bond, CH, CH_2, S, O, SO_2, C(O) and CR_3R_3;

C_2 is selected from the group consisting of absent, a covalent bond, CH, CH_2 and NR_3;

C_3 is selected from the group consisting of CH, N and NR_3;

D_1 is selected from the group consisting of N, CO and CH_2;

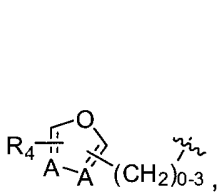
D_2 is selected from the group consisting of C, N and CH;

D_3 is selected from the group consisting of O, NR_3, SO and S;

E_1 is selected from the group consistingof S, C and N; and

E_2 is selected from the group consisting of CH, N and C(O).

[0043] Embodiment BB is another preferred embodiment according to formula (I), wherein Y-L-Z- is preferably one of the following groups: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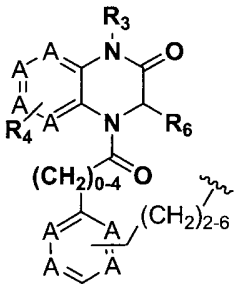
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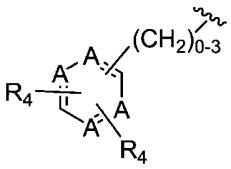
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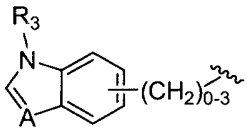
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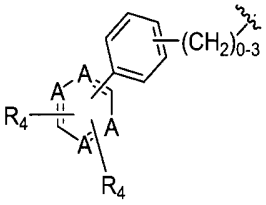
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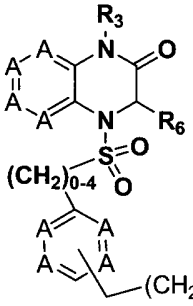
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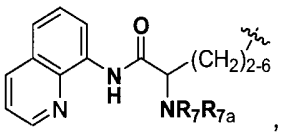
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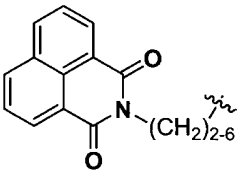
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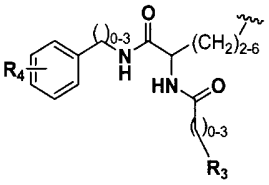
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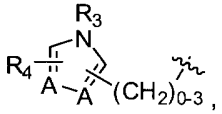
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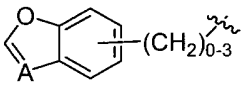
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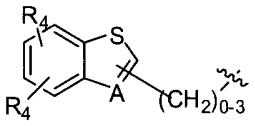
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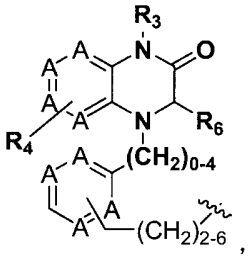
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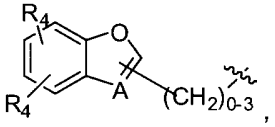
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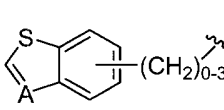
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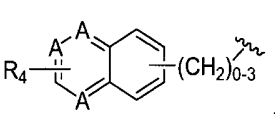
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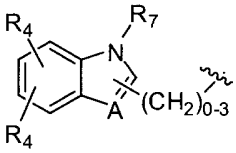
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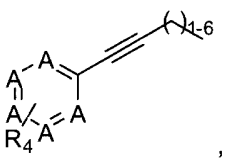

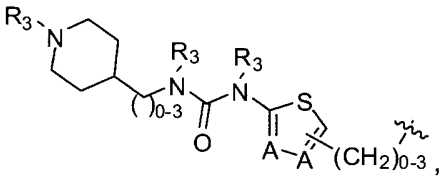

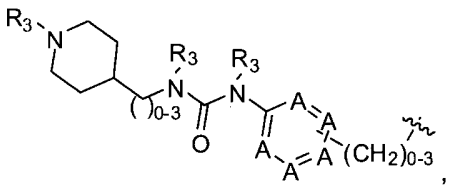

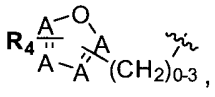

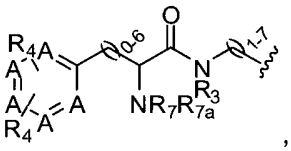

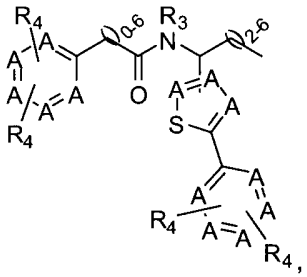

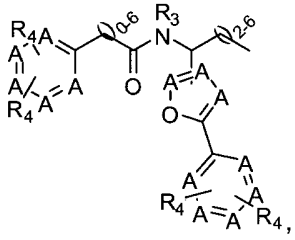

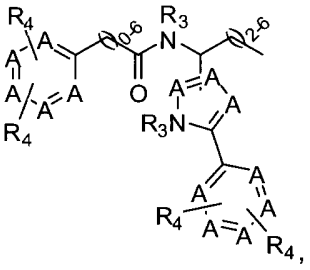

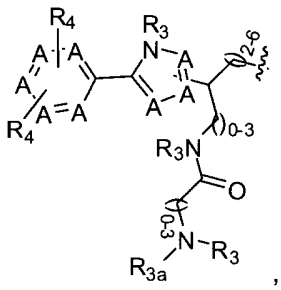

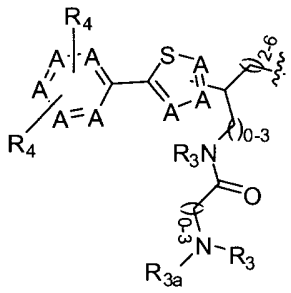

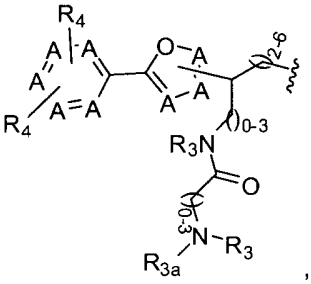

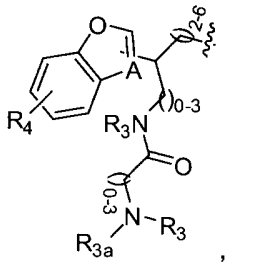

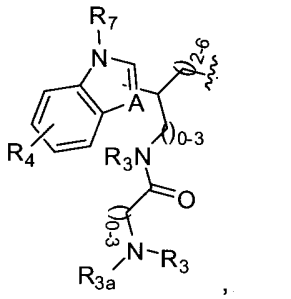

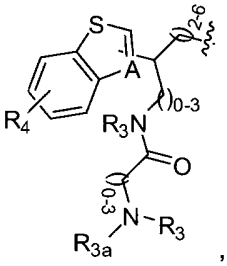

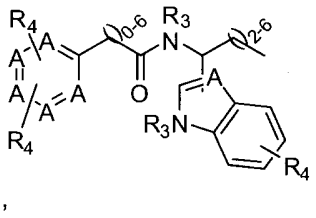

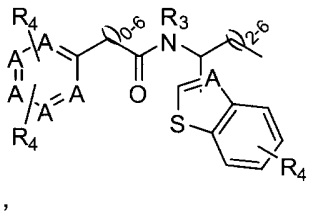

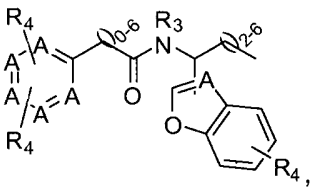
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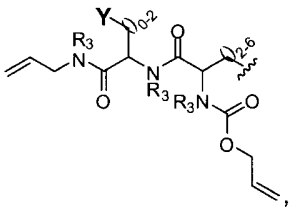
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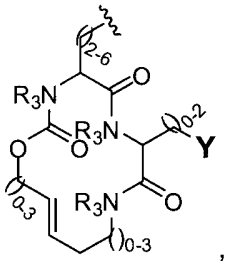
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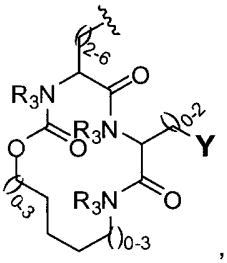
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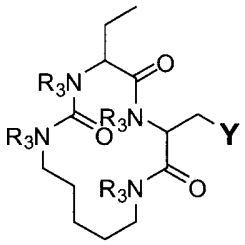
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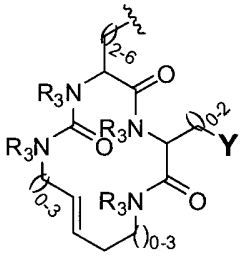
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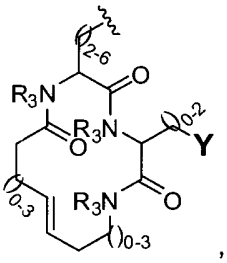
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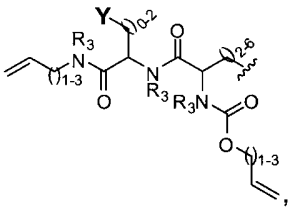
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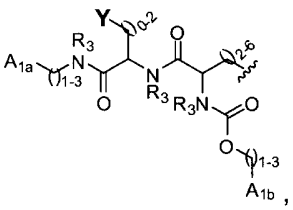
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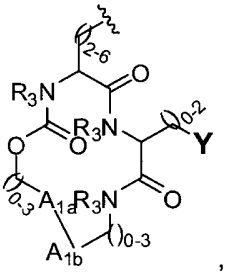
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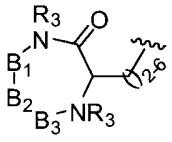
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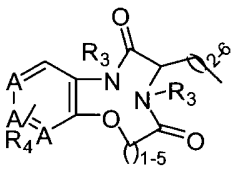
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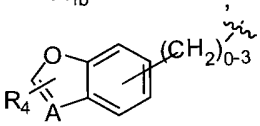
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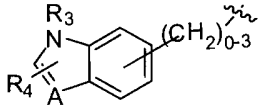
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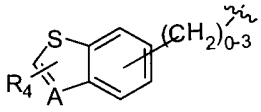
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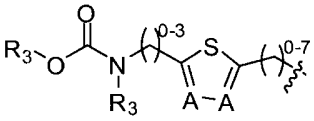
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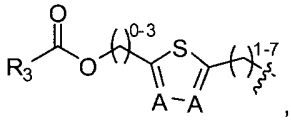
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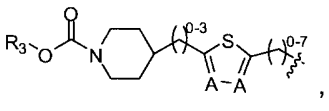
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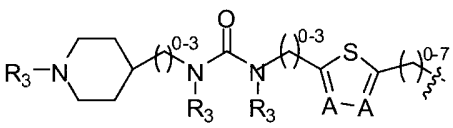
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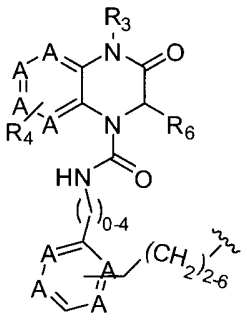
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wherein A is -CH= or -N=;

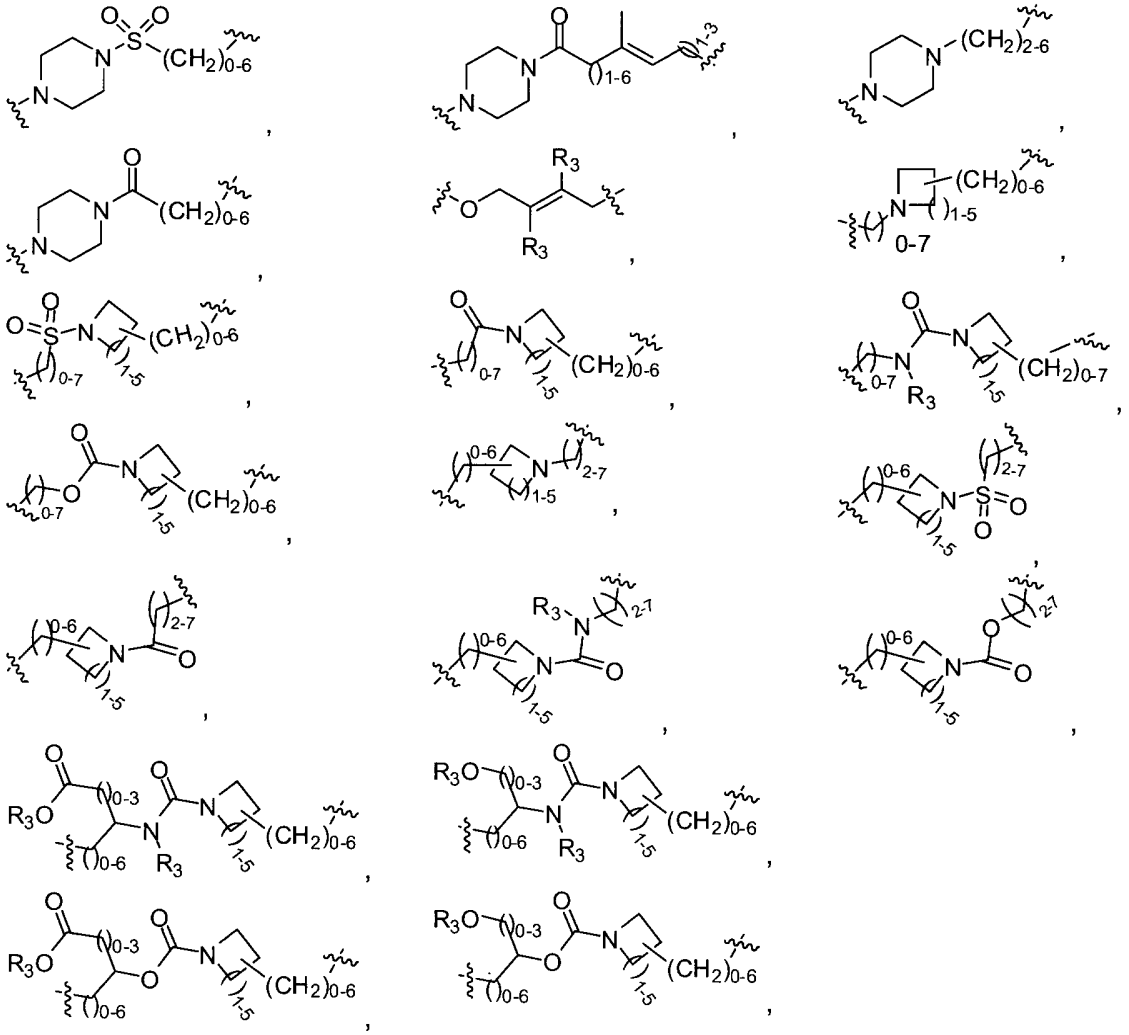
A_{1a} and A_{1b} are independently selected from the group consisting of alkyl, alkenyl and protecting group; or

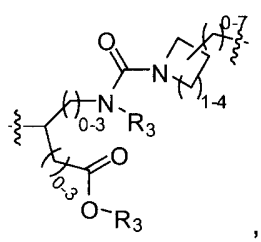
A_{1a} and A_{1b} together via a $-C_2$-C_6alkylene, $-C_2$-C_6alkenylene or $-C_2$-C_6alkynylene linker, form an optionally substituted ring; and

B_1, B_2 and B_3 are each independently a natural or synthetic amino acid.

[0044] Another preferred embodiment according to formula (I), EmbodimentCC, provides compounds wherein B_1, B_2 and B_3 are independently selected from the group consisting of D-Gly, L-Gly, D-Pro, L-Pro, D-Tyr, L-Tyr, D-Tyr(OR_3), L-Tyr(OR_3), D-Phe, L-Phe, D-PheR_4, L-PheR_4, D-Aib, L-Aib, D-Ala, L-Ala, D-ProR_3, L-ProR_3, D-Ile, L-Ile, D-Leu, L-Leu D-PheR_3, L-PheR_3, D-Pip and L-Pip.

[0045] Embodiment DD is another preferred embodiment according to formula (I), wherein L is preferably a covalent bond and Z- is preferably one of the following groups:

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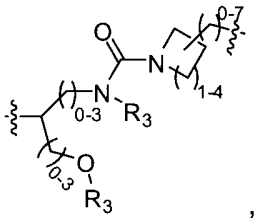
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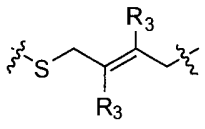
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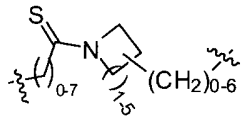
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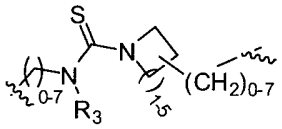
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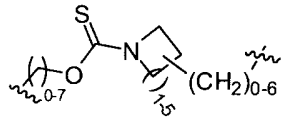
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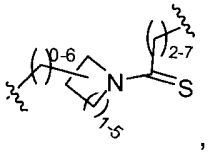
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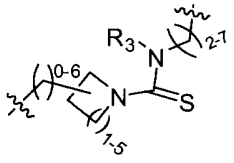
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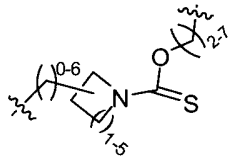
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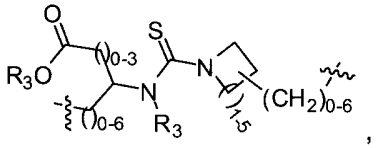
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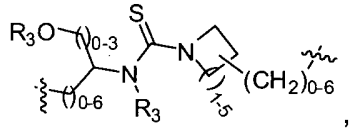
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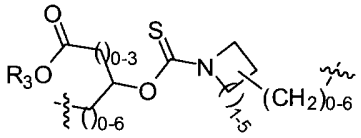
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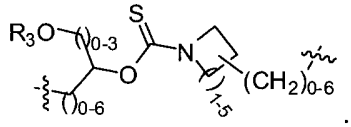
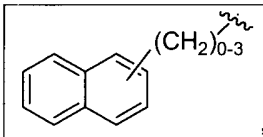
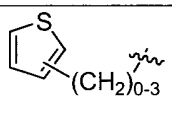
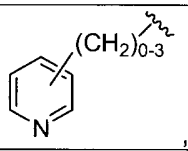
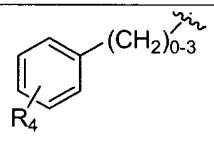
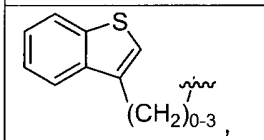
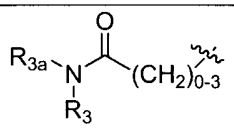
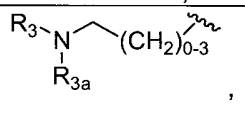
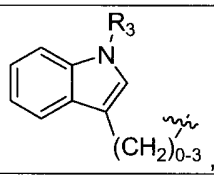
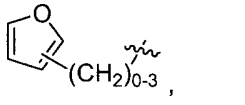
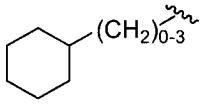
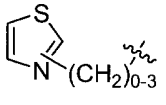

.

[0046] Embodiment EE is another preferred embodiment according to formula (I), wherein R_6 is preferably one of the following groups:

 ,	 ,	 ,	 ,
 ,	 ,	 ,	 ,
 ,	 or	 .	

[0047] In another preferred embodiment, Embodiment FF, the invention provides compounds according to formula (I), wherein R_7 is -H, optionally substituted C_1-C_6 alkyl, -$(CH_2)_{2-4}OR_3$, -$(CH_2)_{2-4}N(R_3)(R_{3a})$, -C(O)Ot-butyl, -C(O)O-benzyl, -$(CH_2)_2$-morpholinyl or -$(CH_2)_2$-piperazynyl.

[0048] In yet another preferred embodiment, Embodiment GG, the invention provides compounds according to formula (I), wherein then Q is $-C(O)-OR_3$ and X is $-N(R_3)-$, $-C(H)_2-$ or $-CH(OH)-$. Preferably, Q is $-C(O)R_3$ and X is -S-, -O- or $-N(R_3)-$. Also preferred are compounds wherein X is $-CH_2-$ and Q is $-(CH_2)_{0-3}-X-(CH2)_{1-3}-C(O)OR_3$, $-(CH_2)_{0-3}-X-(CH_2)_{2-3}-OR_3$, or $-(CH_2)_{0-3}-X-(CH_2)_{2-3}-N(R_3)(R_{3a})$.

[0049] In another preferred embodiment, Embodiment HH according to formula (I), the compounds are compounds wherein Y, L, Z, X, Q, R_1, R_2, R_3, R_{3a}, R_4, R_{4a}, R_6, R_7, and R_{7a} are as defined in Embodiments A to GG.

[0050] Another preferred embodiment, Embodiment II provides compounds according to formula (I), wherein

W is nitrogen;

X is a covalent bond or $-CH_2-$;

R_1 and R_2 are -H

R_3 is -H, -OH, -C(O)-NH-aryl, $-C(O)-NH_2$, $-C(NH_2)-C(O)-OH$, NH_2, $-C(NH_2)-C(O)-O-C_1-C_6$ alkyl, -C(O)-OH, $-C(O)-O-C_1-C_6$ alkyl, aryl, heteroaryl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from -OH, -CN, C_1-C_6 alkyl, $-N(R_4)(R_{4a})$, halo;

Q is $-C_1-C_6$ alkyl-$N(R_3)-C(O)-C_1-C_6$ alkyl-$B-(CH_2)_n-R_3$;

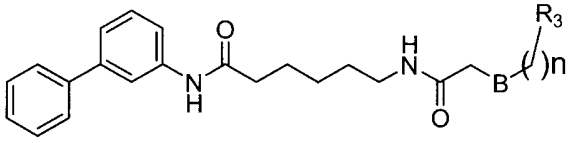
B is -O-, -S(O)-, or -S-;

n is 0 or an interger from 1 to 3;

R_4 and R_{4a} are -H; and

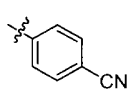
Y-L-Z- is aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkynyl-.

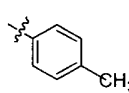
[0051] Another preferred embodiment, Embodiment JJ provides compounds according to Embodiment II of the formula

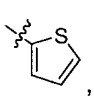


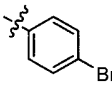
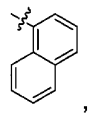
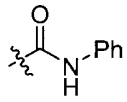
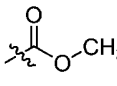
(II)

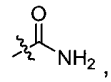
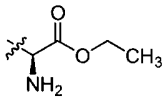
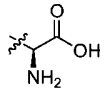
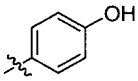
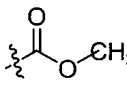
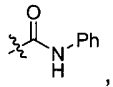
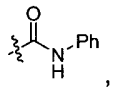
or a pharmaceutically acceptable salt thereof, wherein B, n and R_3 are any one of the following combination:

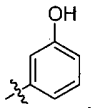
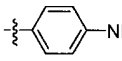
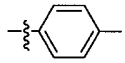
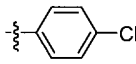
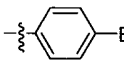
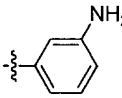
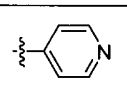
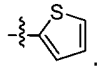
n	B	R_3
1	O	

n	B	R_3
1	O	

n	B	R_3
1	O	

n	B	R_3
1	O	
1	O	
1	O	
1	O	
1	S O	
2	S	
2	S O	
3	S	-OH,
2	S	-OH,

n	B	R_3
1	S	
1	S	
1	S	
2	S	-NH2
0	S	
1	S O	
2	S	
2	S O	

n	B	R_3
0	S	
0	S	
0	S	
0	S	
0	S	
0	S	
0	S	
0	S	 or
0	S	

[0052] Another preferred embodiment, Embodiment KK provides compounds according to formula (I), wherein

W is nitrogen;

X is a covalent bond or $-CH_2-$;

R_1 and R_2 are -H;

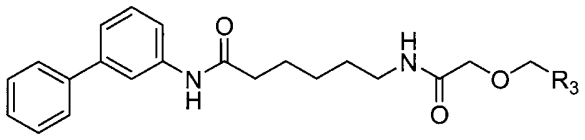
R_3 is H, aryl or heteroaryl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from -CN, -S(O)- C_1-C_6 alkyl, C_1-C_6 alkyl, or halo;

Q is -C_1-C_6 alkyl-N(R_3)-C(O)-C_1-C_6 alkyl-B-C_1-C_6 alkyl-R_3;

B is -S-, -S(O)- or -O-; and

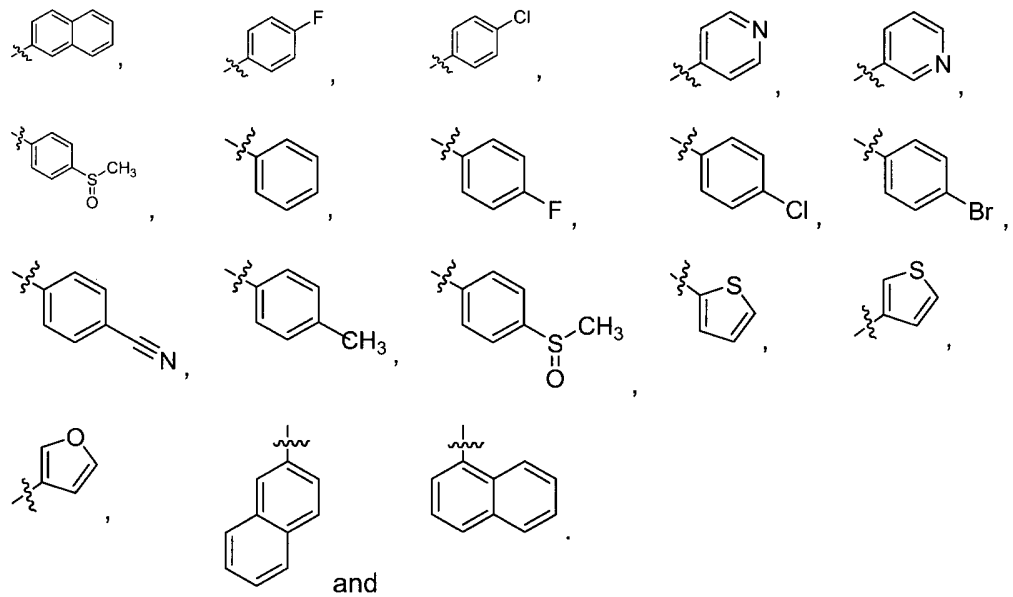
Y-L-Z- is aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-.

[0053] Another preferred embodiment, Embodiment LL provides compounds according to Embodiment KK of the formula



(III)

or a pharmaceutically acceptable salt thereof, wherein R_3 is selected from the group consisting of



and

[0054] Another preferred embodiment, Embodiment MM provides compounds according to formula (I), wherein

W is nitrogen;

X is a covalent bond or $-CH_2-$;

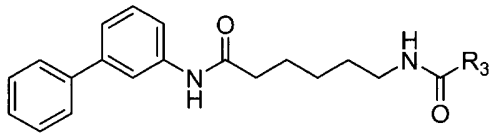
R_1 and R_2 are -H;

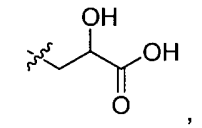
R_3 is -H, $-C_1-C_6$ hydroxyalkyl-C(O)-OH, $-C_1-C_6$ alkyl-S-C_1-C_6 alkyl-$C(NH_2)$-C(O)-OR_4, $-C_1-C_6$ alkyl-S(O)-C_1-C_6 alkylaryl, $-C_1-C_6$ alkyl-S-C_0-C_6 alkylaryl, $-C_1-C_6$ alkyl-S-C_0-C_6 alkylheteroaryl, $-C_1-C_6$ alkyl-S-C_1-C_6 alkyl-OH, $-C_1-C_6$ alkyl-S-C_1-C_6 alkyl-C(O)-OH, $-C_1-C_6$ alkyl-S-C_1-C_6 hydroxyalkyl-C(O)-O-C_1-C_6 alkyl, $-C_1-C_6$ alkyl-S-C_1-C_6 alkyl-C(O)-O-C_1-C_6 alkyl, $-C_1-C_6$ alkyl-S(O)-C_1-C_6 alkyl-C(O)-OR_4, $-C_1-C_6$ alkyl-S-C_1-C_6 alkyl-C(O)-$N(R_4)(R_{4a})$, $-C_1-C_6$ alkyl-S(O)-C_1-C_6 alkyl-C(O)-$N(R_4)$-aryl, $-C_1-C_6$ alkyl-S-C_1-C_6 alkyl-$N(R_4)(R_{4a})$, and $-C_1-C_6$-alkylheteroaryl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from oxo, -OH, $-N(R_4)(R_{4a})$, halo, -S-C_1-C_6 alkyl, or -S(O)-C_1-C_6 alkyl;

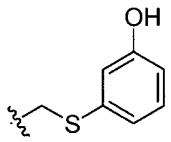
Q is $-C_1-C_6$ alkyl-$N(R_3)$-C(O)-R_3;

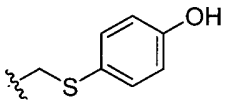
R_4 and R_{4a} are independently -H, C_1-C_6 alkyl, or aryl; and

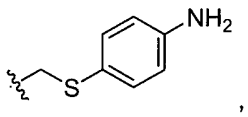
Y-L-Z- is aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-.

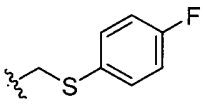


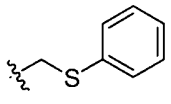


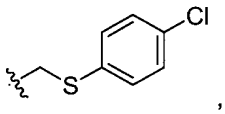


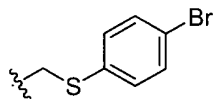


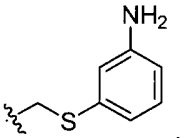


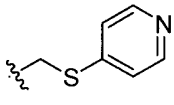


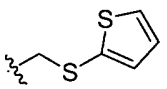


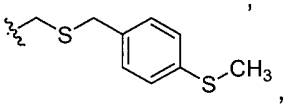


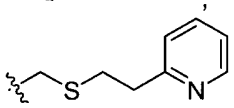


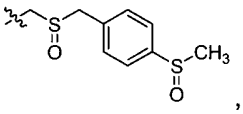


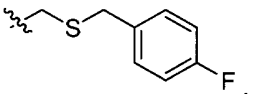


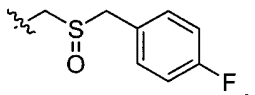


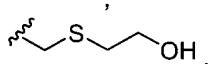


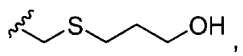


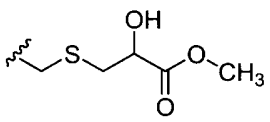


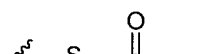


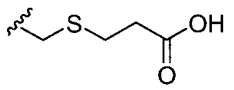


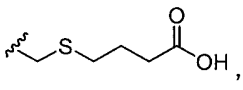


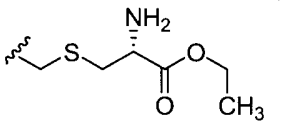


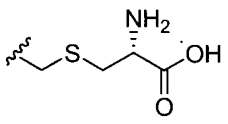


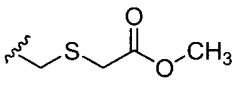


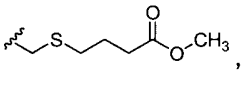


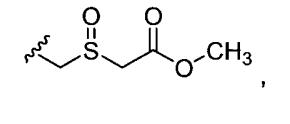


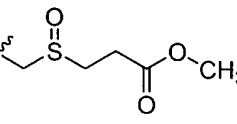


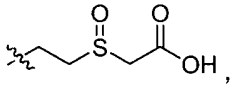


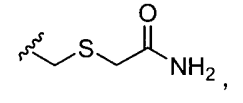


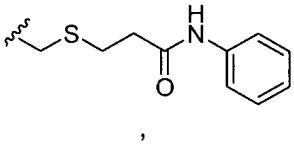


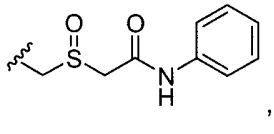


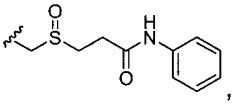


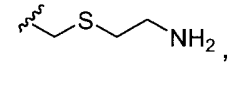


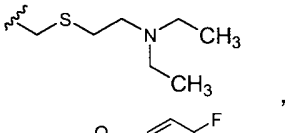


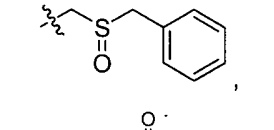


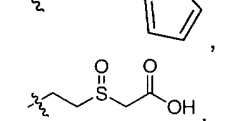


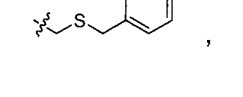


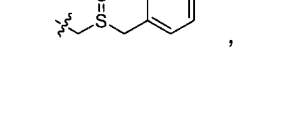












[0055] Another preferred embodiment, Embodiment NN provides compounds according to Embodiment MM of the formula

(IV)

or a pharmaceutically acceptable salt thereof, wherein R_3 is selected from the group consisting of

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and

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[0056] Another preferred embodiment, Embodiment OO provides compounds according to formula (I), wherein

W is nitrogen;

X is -S-;

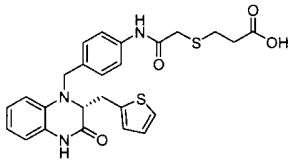
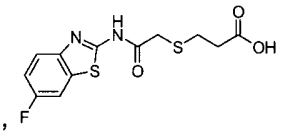
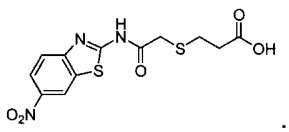
R_1 and R_2 are -H;

R_3 is -H;

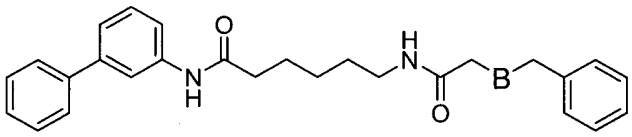
Q is -C_1-C_6-alkyl-C(O)-OR_3; and

Y-L-Z- is heteroaryl-C_0-C_6 alkyl- or heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_6-alkyl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from oxo or halo.

[0057] Another preferred embodiment, Embodiment PP provides compounds according to Embodiment OO that is one of the following structures:



or 

[0058] Embodiment QQ provides compounds according to formula (I) having the formula


(VI)

wherein B is -S- or -S(O)-.

[0059] Another preferred embodiment, Embodiment RR, provides compounds according to formula (I), wherein

W is nitrogen;

X is -S-;

R_1 and R_2 are -H;

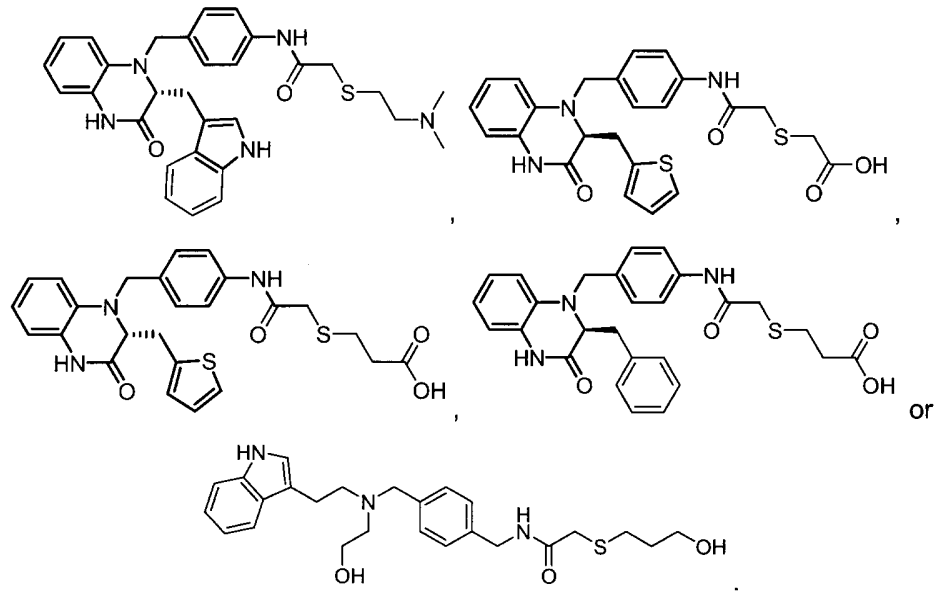
R_3 is -H or C_1-C_6 alky;

R_4 is C_1-C_6 alkyl-OR_3;

Q is -C_1-C_6-alkyl-C(O)-OR_3, -C_1-C_6-alkyl-N(R_3)(R_{3a}), C_1-C_6 alkyl substituted with -OH; and

Y-L-Z- is heteroaryl-C_1-C_6 alkyl-N(R_4)-C_1-C_6-alkyl-aryl-C_0-C_6 alkyl- or heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_6-alkyl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from oxo.

[0060] Another preferred embodiment, Embodiment SS, provides compounds according to Embodiment RR that is one of the following structures:



[0061] Another preferred embodiment, Embodiment TT, provides compounds according to formula (I), wherein

W is nitrogen;

X is a covalent bond or $-CH_2-$;

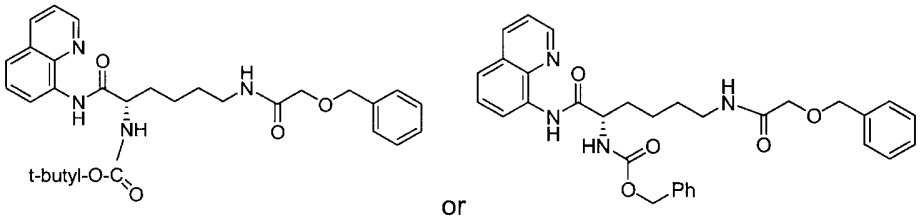
R_1 and R_2 are independently -H, $-N(H)-C(O)-O-C_1-C_6$ alkyl or -N(H)-C(O)-O-benzyl;

R_3 is -H or $-C_1-C_6$ alkyl-$O-C_0-C_6$ alkylaryl;

Q is $-C_1-C_6$ alkyl-$N(R_3)-C(O)-R_3$; and

Y-L-Z- is heteroaryl-C_0-C_6 alkyl-.

[0062] Another preferred embodiment, Embodiment UU, provides compounds according to Embodiment TT that is one of the following structures:



[0063] Another preferrec embodiment, Embodiment VV, provides compounds according to formula (I), wherein

W is nitrogen;

X is -S-;

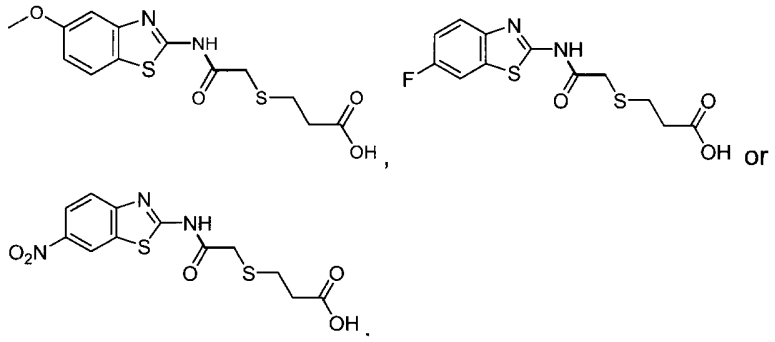
R_1 and R_2 are -H;

R_3 is -H;

Q is $-C_1-C_6$-alkyl-$C(O)-OR_3$; and

Y-L-Z- is heteroaryl-C_0-C_6 alkyl-, wherein the heteroaryl is optionally substituted with one or more groups selected from C_1-C_6 alkoxy, halo or $-NO_2$.

[0064] Another preferred embodiment, Embodiment WW, provides compounds according to Embodiment VV that is one of the following structures:



[0065] Another preferred embodiment, Embodiment XX, provides compounds according to Formula (I) wherein

W is nitrogen;

X is selected from the group consisting of S, O, SO and SO_2;

R_1 and R_2 are H or halogen;

Q is selected from the group consisting of aryl-NH_2, C_1-C_6alkyl-aryl, C_1-C_6alkyl-heteroaryl, C_1-C_6alkyl-CN, wherein the alkyl, aryl and heteroaryl are each independently optionally substituted;

Z is selected from the group consisting of -C_1-C_6alkyl-, -C_1-C_8heteroalkyl-, -C_0-C_6alkyl-aryl-C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-heteroaryl-C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-heteroaryl-C_2-C_6heteroalkyl-, -C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-aryl-C_3-C_6alkynyl- and -C_0-C_6alkyl-aryl-C_3-C_6alkenyl-, wherein the alkyl, heteroalkyl, aryl, heteroaryl and alkenyl are each independently optionally substituted;

L is selected from the group consisting of -C_0-C_6alkyl-$S(O)_2$-$N(R_3)$-C_0-C_6alkyl-, -C_0-C_6alkyl-O-C(O)-$N(R_3)$-C_0-C_3alkyl-, -C_0-C_6alkyl-$N(R_3)$-$S(O)_2$-C_0-C_3alkyl-, -heterocyclyl-C(O)-C_0-C_3alkyl-, -C_0-C_6alkyl-$N(R_3)$-C(O)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-$N(R_3)$-C_0-C_3alkyl-, covalent bond, -C_0-C_6alkyl-$N(R_3)$-C_0-C_3alkyl-, -C_0-C_6alkyl-, -$S(O)_2$-$N(R_3)$-C_0-C_3alkyl-aryl-C_0-C_3alkyl-C(O)-$N(R_3)$-C_1-C_3alkyl-, -C_0-C_6alkyl-$S(O)_2$-C_0-C_3alkyl-, -C_0-C_3alkyl-$S(O)_2$-$N(R_3)$-C_0-C_3alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-O-C(O)-$N(R_3)$-C_0-C_3alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-C(O)-$N(R_3)$-C_0-C_3alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-$N(R_3)$-C(O)-O-heterocyclyl-C_0-C_3alky- and -C_0-C_6alkyl-C(O)-$N(R_3)$-C(O)-C_0-C_3alkyl-, wherein the alkyl, heterocyclyl and aryl are each independently optionally substituted; and

Y is selected from the group consisting of aryl-aryl, aryl, heterocyclyl-aryl, heteroaryl, heteroaryl-aryl, heterocyclyl, alkylaryl, alkylheterocyclyl, aryl-alkylheterocyclyl, heterocyclyl-alkyl-aryl, alkyl, heteroaryl-heteroaryl and heterocyclyl-heteroaryl, wherein each said Y is independently optionally substituted.

[0066] Another preferred embodiment, Embodiment YY, provides compounds according to Embodiment XX wherein Q is C_1-C_6alkyl-heteroaryl, wherein said C_1-C_6alkyl is optionally substituted with $-CH_2$-C(O)-O-C_1-C_6alkyl.

[0067] Another preferred embodiment, Embodiment ZZ, provides compounds according to Formula (I) wherein

W is nitrogen;

X is –O- or –S-;

R_1, R_2 are H;

Q is selected from the group consisting of C_0-C_6alkyl-aryl and heteroaryl, wherein said alkyl, aryl and heteroaryl are independently optionally substituted;

Y-L-Z is selected from the group consisting of aryl-C_0-C_6alkyl-C(O)-N(R_3)-C_1-C_7alkyl-, (R_3)(R_{3a})N-C_0-C_6alkyl-C(O)-N(R_3)-C_1-C_7alkyl-, aryl-C_0-C_6alkyl-O-C(O)-N(R_3)-C_1-C_7alkyl-, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl-N(R_3)-C(O)-C_1-C_7alkyl-, C_1-C_7alkyl-N(R_3)-C(O)-C_0-C_6alkyl-, heteroaryl-C_0-C_6alkyl-C(O)-N(R_3)-C_1-C_7alkyl-, wherein each of said aryl, alkyl and heteroaryl are independently optionally substituted.

[0068] Another preferred embodiment, Embodiment AAA, provides compounds according to Embodiment ZZ, wherein said C_1-C_7alkyl is optionally substituted with a substituent selected from the group consisting of heteroaryl-aryl, -C(O)-N(R_3)-heteroaryl, -N(R_3)-C(O)-O-alkenyl, heteroaryl and –N(R_3)-C(O)-O-C_0-C_3alkyl-aryl, and said C_0-C_3alkyl is optionally substituted with –C(O)-N(R_3)alkenyl.

[0069] Another preferred embodiment, Embodiment BBB, provides compounds according to Formula (I) wherein

W is nitrogen;

X is -O- or -S-;

R_1 and R_2 are H;

Q is alkyl-aryl; and

Y-L-Z is selected from the group consisting of aryl-C_0-C_3alkyl-N(R_3)-C(O)-C_1-C_7alkyl-, A_{2a}-aryl-C_0-C_3alkyl-N(R_3)-C(O)-C_1-C_7alkyl- and heteroaryl-C_0-C_3alkyl-N(R_3)-C(O)-C_1-C_7alkyl-, wherein said aryl and heteroaryl are each independently optionally substituted, and wherein

said C_0-C_3alkyl is optionally substituted with –C(O)-N(R_3)-C_1-C_6alkyl-A_{1a} or –C(O)-N(R_3)-C_0-C_6alkyl-C(O)-A_{2a}; and

said C_1-C_7alkyl is optionally substituted with a substituent selected from the group consisting of –N(R_3)-C(O)-O-C_1-C_3alkyl-A_{1b}, -N(R_3)-C(O)-C_1-C_7alkyl-O-A_{2b}, -N(R_3)-C(O)-heteorcyclyl-A_{2b} and –N(R_3)-C(O)-C_2-C_7alkenyl-O-A_{2b}, wherein

A_{1a} and A_{1b} optionally together via a C_2-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene linker, form an optionally substituted ring system; and

A_{2a} and A_{2b} together are a covalent bond and are attached to form a ring, or

Y-L-Z is B_2-B_1-N(R_3)-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –NR_3-B_3 and the amine of B_3 is conected with the acid of B_2 to form a peptide bond; wherein

B_1, B_2 and B_3 are each independently a natural or synthetic amino acid.

[0070] Another preferred embodiment, Embodiment CCC, provides compounds according to Formula (I) wherein

W is nitrogen;

X is –O-;

R_1 and R_2 are H;

Q is optionally substituted alkyl-aryl;

Z is optionally substituted C_1-C_8alkyl;

L is selected from the group consisting of –C_0-C_3alkyl-N(R_3)-C(O)-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-N(R_3)-C(S)-heterocyclyl-C_0-C_3alkyl-, -C_0-C_7alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-O-C(O)-heterocyclyl-C_0-C_3alkyl-, C_0-C_3alkyl-$S(O)_2$-heterocyclyl-C_0-C_3alkyl- and -C_0-C_3alkyl-C(O)-heterocyclyl-C_0-C_3alkyl, wherein said alkyl and heterocyclyl are independently optionally subsituted; and

Y is selected from the group consisting of heteroaryl, aryl, cycloalkyl and heteroaryl-aryl, each of which is optionally substituted.

[0071] Another preferred embodiment, Embodiment DDD, provides compounds according to Formula (I) wherein

W is nitrogen;

X is -O-;

R_1 and R_2 are H;

Q is optionally substituted alkyl-aryl;

Z is optionally substituted –C_0-C_6alkyl-heteroaryl-C_0-C_6alkyl and optionally substituted C_1-C_8alkyl;

L is selected from the group consisting of –C_0-C_6alkyl-$S(O)_2$-heterocyclyl-C_0-C_3alkyl, covalent bond, -C_0-C_6alkyl- , -C_0-C_6alkyl-O-C(O)-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-O-, -C_0-C_6alkyl-N(R_3)-C(O)-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-N(R_3)-C(O)-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-$S(O)_2$-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-N(R_3)-C(O)-N(R_3)-C_0-C_6alkyl- and -C_0-C_6alkyl-$S(O)_2$-C_0-C_3alkyl, wherein the alkyl, heterocyclyl, heteroaryl are independently optionally substituted; and

Y is selected from the group consisting of aryl, alkylaryl, heteroaryl, aryl-heterocyclyl, aryl-heteroaryl, alkyl and heterocyclyl, each of which is independently optionally substituted.

[0072] Another preferred embodiment, Embodiment EEE, provides compounds according to Formula (I) wherein

W is nitrogen;

X is -O-;

R_1 and R_2 are H;

Q is optionally substituted alkyl-aryl;

Z is selected from the group consisting of -C_0-C_6alkyl-aryl-C_0-C_6alkyl-, -C_0-C_6alkyl-aryl-C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-aryl-C_3-C_6alkenyl-C_0-C_3alkyl and –C_0-C_6alkyl-aryl-C_3-C_6alkynyl-C_0-C_3alkyl, wherein the alkyl, aryl and alkynyl are each independently optionally substituted;

L is selected from the group consisting of -C_0-C_3alkyl-N(R_3)-C_0-C_3alkyl, –C_0-C_3alkyl-heterocyclyl-C_0-C_3alkyl-O-C_0-C_3alkyl-, -C_0-C_6alkyl-S(O)$_2$-N(R_3)-C_0-C_6alkyl-, -C_0-C_6alkyl-O-C(O)-, -C_0-C_6alkyl-C(O)-N(R_3)-S(O)$_2$-C_0-C_3alkyl- and –C_0-C_6alkyl-N(R_3)-S(O)$_2$-C_0-C_3alkyl, wherein said alkyl and heterocyclyl are each independently optionally substituted; and

Y is selected from the group consisting of heteroaryl, aryl, heteroaryl-hetercyclyl, alkyl, aryl-heterocyclyl and cycloalky, each of which is independently optionally substituted.

[0073] Another preferred embodiment, Embodiment FFF, provides compounds according to Formula (I) wherein

W is nitrogen;

X is -O-;

R_1 and R_2 are H;

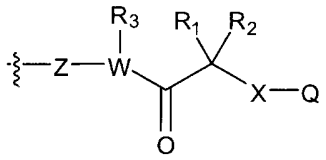
Q is optionally substituted alkyl-aryl;

Z is optionally substituted C_1-C_6alkyl;

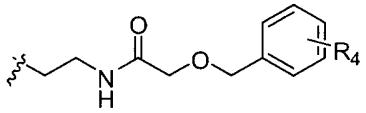
L is –C_0-C_3alkyl-N(R_3)-C(O)-C_0-C_3alkyl-heterocyclyl-C(O)-C_0-C_3alkyl, wherein the alkyl and heterocyclyl are independently optionally substituted; and

Y is selected from the group consisting of aryl-aryl, alkyl-heteroaryl, aryl and heteroaryl, each of which is independently optionally substituted.

[0074] Another preferred embodiment, Embodiment GGG, provides compounds according to Formula (I) wherein



is the structure



[0075] In the second aspect, the invention provides a composition comprising a compound according to the first aspect and Embodiments A to GGG and a pharmaceutically acceptable carrier.

[0076] In the third aspect, the invention provides a method of inhibiting histone deacetylase. In one embodiment, the method comprising contacting the histone deacetylase with an inhibiting effective amount of a compound according to the first aspect and Embodiments A to GGG. In a further embodiment of the third aspect, the method comprises contacting the histone deacetylase with an inhibiting effective amount of a composition according to the second aspect. In yet another embodiment, the method of inhibiting histone deacetylase in a cell comprises contacting the cell with an inhibiting effective amount of compound according to the first aspect and Embodiments A to GGG. In still another embodiment, the method of inhibiting histone deacetylase in a cell comprising contacting the cell with an inhibiting effective amount of a composition according to the second aspect.

[0077] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise).

[0078] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ω-amino groups of lysine residues at the *N*-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Other preferred histone deacetylases include class III enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10, HDAC-11, SirT1, SirT2, SirT3, SirT4, SirT5, SirT6 and SirT7. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

[0079] The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are intended to mean a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity.

[0080] The term "inhibiting histone deacetylase enzymatic activity" is intended to mean reducing the ability of a histone deacetylase to remove an acetyl group from a histone. The concentration of inhibitor which reduces the activity of a histone deacetylase to 50% of that of the uninhibited enzyme is determined as the IC_{50} value.

[0081] Preferably, such inhibition is specific, *i.e.*, the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for

histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

[0082] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (*e.g.* CH_3-CH_2-), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene). All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-.

[0083] For simplicity, reference to a "C_n-C_m" heterocyclyl or "C_n-C_m" heteroaryl means a heterocyclyl or heteroaryl having from "n" to "m" annular atoms, where "n" and "m" are integers. Thus, for example, a C_5-C_6-heterocyclyl is a 5- or 6- membered ring having at least one heteroatom, and includes pyrrolidinyl (C_5) and piperidinyl (C_6); C_6-hetoaryl includes, for example, pyridyl and pyrimidyl.

[0084] The term "hydrocarbyl" refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A "C_0" hydrocarbyl is used to refer to a covalent bond. Thus, "C_0-C_3-hydrocarbyl" includes a covalent bond, methyl, ethyl, ethenyl, ethynyl, propyl, propenyl, propynyl, and cyclopropyl.

[0085] The term "alkyl" is intended to a mean straight and branched chain aliphatic group having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Other preferred alkyl groups have from 2 to 12 carbon atoms, preferably 2-8 carbon atoms and more preferably 2-6 carbon atoms. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A "C_0" alkyl (as in "C_0-C_3-alkyl") is a covalent bond.

[0086] The term "alkenyl" is intended to mean an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0087] The term "alkynyl" is intended to mean an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0088] The terms "alkylene," "alkenylene," or "alkynylene" as used herein are intended to mean an alkyl, alkenyl, or alkynyl group, respectively, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0089] The term "cycloalkyl" is intended to mean a saturated or unsaturated mono-, bi, tri- or poly-cyclic hydrocarbon group having about 3 to 15 carbons, preferably having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0090] The term "heteroalkyl" is intended to mean a saturated or unsaturated, straight or branched chain aliphatic group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

[0091] The term "aryl" is intended to mean a mono-, bi-, tri- or polycyclic C_6-C_{14} aromatic moiety, preferably comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C_6-C_{10} aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl.

[0092] The terms "aralkyl" or "arylalkyl" is intended to mean a group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C_1-C_6)alk(C_6-C_{10})aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl. For simplicity, when written as "arylalkyl" this term, and terms related thereto, is intended to indicate the order of groups in a compound as "aryl – alkyl". Similarly, "alkyl-aryl" is intended to indicate the order of the groups in a compound as "alkyl-aryl".

[0093] The term "heterocyclyl" is intended to mean a group which is an optionally substituted mono-, bi-, tri- or polycyclic structure having from about 3 to 17, preferably about 3 to about 14 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. One ring of a bicyclic heterocycle or two rings of a tricyclic heterocycle may be aromatic, as in indan and 9,10-dihydro anthracene. The heterocyclic group is optionally

substituted on carbon with oxo or another substituent. The heterocyclic group may also independently be substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds where an annular O or S atom is adjacent to another O or S atom.

[0094] In certain preferred embodiments, the heterocyclic group is a heteroaryl group. As used herein, the term "heteroaryl" is intended to mean an optionally substituted mono-, bi-, tri- or polycyclic group having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 pi electrons shared in a cyclic array; and having, in addition to carbon atoms, between one or more heteroatoms selected from the group consisting of N, O, and S. For example, a heteroaryl group may be pyrimidinyl, pyridinyl, benzimidazolyl, thienyl, benzothiazolyl, benzofuranyl and indolinyl. Preferred heteroaryl groups include, without limitation, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl.

[0095] The terms "arylene," "heteroarylene," or "heterocyclylene" are intended to mean an aryl, heteroaryl, or heterocyclyl group, respectively, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0096] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-

pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0097] Aromatic polycycles include, but are not limited to, naphthyl, and naphthyl substituted by one or more suitable substituents, including C_1-C_6alkyl, cycloalkylalkyl (e.g. cyclopropylmethyl), oxyalkyl, halo, nitro, amino, alkylamino, aminoalkyl, alkyl ketones, nitrile, carboxyalkyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl and OR_{aa}, such as alkoxy, wherein R_{aa} is selected from the group consisting of H, C_1-C_6alkyl, C_4-C_9cycloalkyl, C_4-C_9heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and $(CH_2)_{0-6}Z_aR_{bb}$, wherein Z_a is selected from the group consisting of O, NR_{cc}, S and S(O), and R_{bb} is selected from the group consisting of H, C_1-C_6alkyl, C_4-C_9cycloalkyl, C_4-C_9heterocycloalkyl, C_4-C_9heterocycloalkylalkyl, aryl, mixed aryl and non-aryl polycycle, heteroaryl, arylalkyl, (e.g. benzyl), and heteroarylalkyl (e.g. pyridylmethyl); and R_{cc} is selected from the group consisting of H, C_1-C_6alkyl, C_4-C_9cycloalkyl, C_4-C_9heterocycloalkyl, aryl, heteroaryl, arylalkyl (e.g. benzyl), heteroarylalkyl (e.g. pyridylmethyl) and amino acyl.

[0098] Non-aromatic polycycle substituents include, but are not limited to, bicyclic and tricyclic fused ring systems where each ring can be 4-9 membered and each ring can conatin zero, 1 or more double and/or triple bonds. Suitable examples of non-aromatic polycycles include, but are not limited to, decalin, octahydroindene, perhydrobenzocycloheptene and perhydrobenzo-[*f*]-azulene. Such substituents are themselves optionally substituted with for example, but not limited to, C_3-C_9cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. Unless otherwise noted, non-aromatic polycycle substituents include both unsubstituted cycloalkyl groups and cycloalkyl groups that are substituted by one or more suitable substituents, including but not limited to, C_1-C_6alkyl, halo, hydroxy, aminoalkyl, oxyalkyl, alkylamino and OR_{aa}, such as alkoxy. Preferred substituents for such cycloalkyl groups include halo, hydroxy, alkoxy, oxyalkyl, alkylamino and aminoalkyl.

[0099] Mixed aryl and non-aryl polycycle substituents include bicyclic and tricylic fused ring systems where each ring can be 4-9 membered and at least one ring is aromatic. Suitable examples of mixed aryl and non-aryl polycycles include methylenedioxyphenyl, *bis*-methylenedioxyphenyl, 1,2,3,4-tetrahydronaphthalene, dibenzosuberane dihydroanthracene and 9H-fluorene. Such substituents are unsubstituted or substituted by nitro or as described above for non-aromatic polycycle substituents.

[0100] Polyheteroaryl substituents include bicyclic and tricyclic fused rings systems where each ring can independently be 5 or 6 membered and contain one or more

heteroatom, for example, 1, 2, 3 or 4 heteroatoms, chosen from O, N or S such that the fused ring system is aromatic. Suitable examples or polyheteroaryl ring systems include quinoline, isoquinoline, pyridopyrazine, pyrrolopyridine, furopyridine, indole, benzofuran, benzothiofuran, benzindole, benzoxazole, pyrroloquinoline, and the like. Unless otherwise noted, polyheteroaryl substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents, including but not limited to, straight and branched optionally substituted C_1-C_6alkyl, unsaturation (i.e., there are one or more double or triple C-C bonds), acyl, cycloalky, halo, oxyalkyl, alkylamino, aminoalkyl, acylamino and ORaa, for example alkoxy, and a substituent of the formula $-O-(CH_2CH=CH(CH_3)(CH_2))_{1-3}H$. Examples of suitable straight and branched C_1-C_6alkyl substituents include but are not limited to methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl and the like. Preferred substituents include halo, hydroxy, alkoxy, oxyalkyl, alkylamino and aminoalkyl. Nitrogen atoms are unsubstituted or substituted, for example by R_{cc}. Preferred substituents on such nitrogen atoms include H, C_1-C_4alkyl, acyl, aminoacyl and sulfonyl.

[0101] Non-aromatic polyheterocyclic substituents include but are not limited to bicyclic and tricyclic ring systems where each ring can be 4-9 membered, contain one or more heteratom, for example 1, 2, 3 or 4 heteratoms, chosen from O, N or S and contain zero, or one or more C-C double or triple bonds. Suitable examples of non-aromatic polyheterocycles include but are not limited to, hexitol, cis-perhydro-cyclohepta[b]pyridinyl, decahydro-benzo[f][1,4]oxazepinyl, 2,8-dioxabicyclo[3.3.0]octane, hexahydro-thieno[3,2-b]thiophene, perhydropyrrolo[3,2-b]pyrrole, perhydronaphthyridine, perhydrop-1H-dicyclopenta[b,e]pyran. Unless otherwise noted, non-aromatic polyheterocyclic substituents are unsubstituted or substituted on a carbon atom by one or more substituents, including but not limited to straight and branched optionally substituted C_1-C_6alkyl, unsaturation (i.e., there are one or more double or triple C-C bonds), acyl, cycloalky, halo, oxyalkyl, alkylamino, aminoalkyl, acylamino and OR_{aa}, for example alkoxy. Examples of suitable straight and branched C_1-C_6alkyl substituents include but are not limited to methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl and the like. Preferred substituents include halo, hydroxy, alkoxy, oxyalkyl, alkylamino and aminoalkyl. Nitrogen atoms are unsubstituted are substituted, for example, by R_{cc}. Preferred N substituents include H, C_1-C_4 alkyl, acyl, aminoacyl and sulfonyl.

[0102] Mixed aryl and non-aryl polyheterocycles substituents include but are not limited to bicyclic and tricyclic fused ring systems where each ring can be 4-9 membered, contain one or more heteroatom chosen from O, N or S and at least one of the rings must be aromatic. Suitable examples of mixed aryl and non-aryl polyheteorcycles include 2,3-dihydroindole, 1,2,3,4-tetrahydroquinoline, 5,11-dihydro-10H-dibenz[b,e][1,4]diazepine, 5H-dibenzo[b,e][1,4]diazepine, 1,2-dihydropyrrolo[3,4-b][1,5]benzodiazepine, 1,5-

dihydropyrido[2,3-b][1,4]diazepin-4-one, 1,2,3,4,6,11-hexhydro-benzo[b]pyrido[2,3-e][1,4]diazepine-5-one. Unless otherwise noted, mixed aryl and non-aryl polyheterocyclic substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents including but not limited to –N-OH, =N-OH, optionally substituted alkyl unsaturation (i.e., there are one or more double or triple C-C bonds), acyl, cycloalky, halo, oxyalkyl, alkylamino, aminoalkyl, acylamino and OR_{aa}, for example alkoxy. Nitrogen atoms are unsubstituted or substituted, for example, by R_{cc}. Preferred N substituents include H, C_1-$_4$alkyl, acyl aminoacyl and sulfonyl.

[0103] As employed herein, when a moiety (*e.g.*, alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (*e.g.*, an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

(a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,

(b) C_1-C_5 alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, C_1-C_8 alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 *N*-alkyl carbamoyl, C_2-C_{15} *N,N*-dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, C_5-C_{15} heteroaryl or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and

(c) $-(CH_2)_n-NR_{30}R_{31}$, wherein n is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R_{30} and R_{31} are each independently hydrogen, cyano, oxo, carboxamido, amidino, C_1-C_8 hydroxyalkyl, C_1-C_3 alkylaryl, aryl-C_1-C_3 alkyl, C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, aryl-C_1-C_3 alkoxycarbonyl, C_2-C_8 acyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

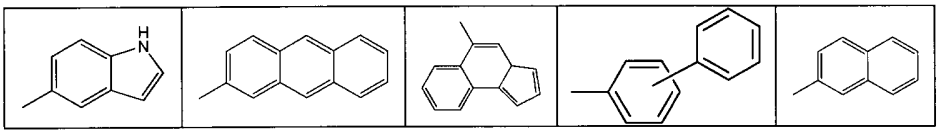
[0104] The term "halogen" or "halo" is intended to mean chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (*i.e.*, R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (*i.e.*, NH_2-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH_2, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0105] The term "radical" is intended to mean a chemical moiety comprising one or more unpaired electrons.

[0106] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluoro-3-propylphenyl. As another non-limiting example, substituted *N*-octyls include 2,4-dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH_2-) substituted with oxygen to form carbonyl -CO-).

[0107] Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

[0108] In addition, substituents on cyclic moieties (i.e., cycloalkyl, heterocyclyl, aryl, heteroaryl) include 5-6 membered mono- and 9-14 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. Substituents on cyclic moieties also include 5-6 membered mono- and 9-14 membered bi-cyclic moieties attached to the parent cyclic moiety by a covalent bond to form a bi- or tri-cyclic bi-ring system. For example, an optionally substituted phenyl includes, but is not limited to, the following:



[0109] An "unsubstituted" moiety as defined above (*e.g.*, unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0110] The term "protecting group" is intended to mean a group used in synthesis to temporarily mask the characteristic chemistry of a functional group because it interferes with

another reaction. A good protecting group should be easy to put on, easy to remove and in high yielding reactions, and inert to the conditions of the reaction required. A protecting group or protective group is introduced into a molecule by chemical modification of a functional group in order to obtain chemoselectivity in a subsequent chemical reaction. One skilled in the art will recognize that during any of the processes for preparation of the compounds in the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as but not limited to Bn- (or $-CH_2Ph$), $-CHPh_2$, alloc (or $CH_2=CH-CH_2-O-C(O)-$), BOC-, -Cbz (or Z-), -F-moc, $-C(O)-CF_3$, N-Phthalimide,1-Adoc-, TBDMS-, TBDPS-, TMS-, TIPS-, IPDMS-, $-SiR_3$, SEM-, t-Bu-, Tr-, THP- and Allyl-. These protecting groups may be removed at a convenient stage using methods known from the art.

[0111] Some compounds of the invention may have chiral centers and/or geometric isomeric centers (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers. The invention also comprises all tautomeric forms of the compounds disclosed herein.

[0112] The compounds of the invention may be administered as is or in the form of an *in vivo* hydrolyzable ester or *in vivo* hydrolyzable amide. An *in vivo* hydrolyzable ester of a compound of the invention containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolyzed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}-alkoxymethyl esters (*e.g.*, methoxymethyl), C_{1-6}-alkanoyloxymethyl esters (*e.g.*, for example pivaloyloxymethyl), phthalidyl esters, C_{3-8}-cycloalkoxycarbonyloxyC_{1-6}-alkyl esters (*e.g.*, 1-cyclohexylcarbonyloxyethyl); 1,3-dioxolen-2-onylmethyl esters (*e.g.*, 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}-alkoxycarbonyloxyethyl esters (*e.g.*, 1-methoxycarbonyloxyethyl) and may be formed at any carboxy group in the compounds of this invention.

[0113] An *in vivo* hydrolyzable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters and a-acyloxyalkyl ethers and related compounds which as a result of the in vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolyzable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(*N,N*-dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), *N,N*-dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl

ring. A suitable value for an *in vivo* hydrolyzable amide of a compound of the invention containing a carboxy group is, for example, a *N*-C_{1-6}-alkyl or N,N-di-C_{1-6}-alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

[0114] The foregoing merely summarizes the one aspect and embodiments of the invention and is not intended to be limiting in nature. These aspects and embodiments are described more fully below.

Compounds

[0115] Some examples of the compounds according to the one aspect of the invention and Embodiments A to FFF are listed in the table below. These examples merely serve to exemplify some of the compounds of the one aspect of the invention and do not limit the scope of the invention.

Table 1a

2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)acetic acid
N-(biphenyl-3-yl)-6-(2-(4-(methylthio)benzylthio)acetamido)hexanamide
methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-hydroxypropanoate
methyl 4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)butanoate
methyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)acetate
(*S*)-tert-butyl 6-(2-(benzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate
N-(biphenyl-3-yl)-6-(2-(2-oxo-2-(phenylamino)ethylthio)acetamido)hexanamide
2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)acetic acid
Methyl 2-(2-(2-(biphenyl-3-ylamino)-2-oxoethylamino)-2-oxoethylsulfonyl)acetate
6-(2-(2-aminoethoxy)acetamido)-N-(biphenyl-3-yl)hexanamide
N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)ethanethioamido)hexanamide
4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)benzoic acid
N-(biphenyl-3-yl)-6-(2-(4-(hydroxymethyl)benzyloxy)acetamido)hexanamide
N-(biphenyl-3-yl)-6-(2-(4-cyanobenzyloxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-methylbenzyloxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(thiophen-2-ylmethoxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(thiophen-3-ylmethoxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(furan-3-ylmethoxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-bromobenzyloxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(naphthalen-1-ylmethoxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(2-oxo-2-(phenylamino)-ethylsulfinyl)-acetamido)-hexanamide
3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoic acid
methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-propanoate
N-(biphenyl-3-yl)-6-(2-(3-hydroxypropylthio)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(2-hydroxyethylthio)-acetamido)-hexanamide
6-(2-(2-amino-2-oxoethylthio)-acetamido)-*N*-(biphenyl-3-yl)hexanamide
(*R*)-ethyl 2-amino-3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoate
(*R*)-2-amino-3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoic acid
6-(2-(2-aminoethylthio)-acetamido)-*N*-(biphenyl-3-yl)hexanamide
N-(biphenyl-3-yl)-6-(2-(4-hydroxyphenylthio)-acetamido)-hexanamide
methyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-acetate

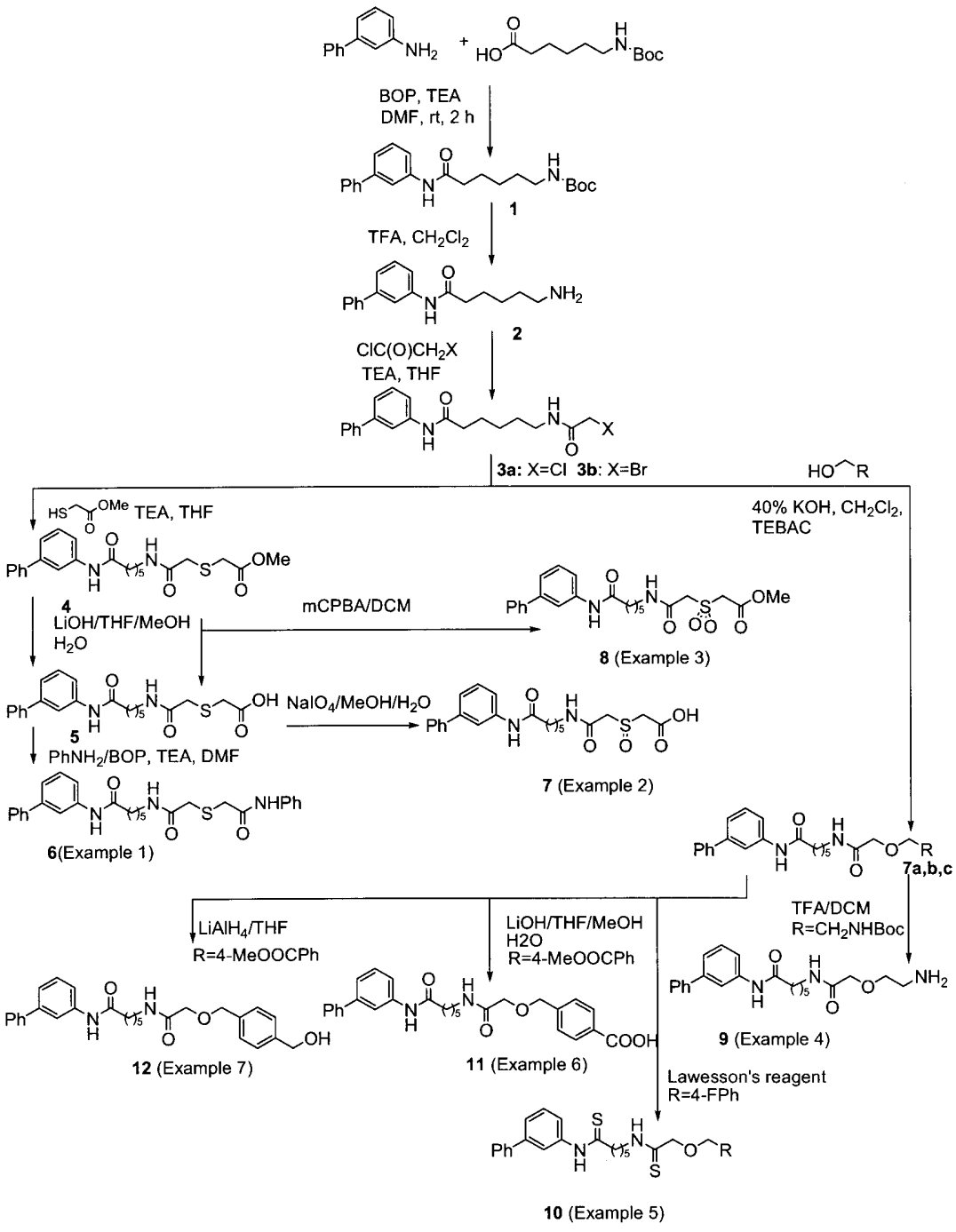
N-(biphenyl-3-yl)-6-(2-(3-oxo-3-(phenylamino)-propylthio)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(3-oxo-3-(phenylamino)-propylsulfinyl)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(3-hydroxyphenylthio)-acetamido)-hexanamide
6-(2-(4-aminophenylthio)-acetamido)-*N*-(biphenyl-3-yl)hexanamide
N-(biphenyl-3-yl)-6-(2-(4-fluorophenylthio)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(phenylthio)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-chlorophenylthio)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-bromophenylthio)-acetamido)-hexanamide
6-(2-(3-aminophenylthio)-acetamido)-N-(biphenyl-3-yl)hexanamide
N-(biphenyl-3-yl)-6-(2-(pyridin-4-ylthio)acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(thiophen-2-ylthio)acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-(methylthio)benzyloxy)acetamido)hexanamide)
N-(biphenyl-3-yl)-6-(2-(naphthalen-2-ylmethoxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-chlorobenzyloxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(pyridin-4-ylmethoxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(pyridin-3-ylmethoxy)-acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-(methylsulfinyl)-benzyloxy)-acetamido)-hexanamide
6-(2-(benzylthio)acetamido)-*N*-(biphenyl-3-yl)hexanamide
6-(2-(benzylsulfinyl)acetamido)-*N*-(biphenyl-3-yl)hexanamide
N-(biphenyl-3-yl)-6-(4-(thiophen-2-yl)butanamido)-hexanamide
N-(biphenyl-3-yl)-6-(3-(4-fluorobenzylthio)propanamido)hexanamide
N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyl-thio)acetamido)-hexanamide
N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyl-sulfinyl)-acetamido)-hexanamide
2-(3-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-3-oxopropylthio)-acetic acid
2-(3-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-3-oxopropyl-sulfinyl)acetic acid
6-(2-(benzyloxy)acetamido)-N-(biphenyl-3-yl)hexanamide
(*S*)-2-amino-6-(2-(benzyloxy)acetamido)hexanoic acid
(*S*)-benzyl 6-(2-(benzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate
(*S*)-2-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)ethylthio)acetic acid
N-(biphenyl-3-yl)-6-(2-(2-(pyridin-2-yl)ethylthio)acetamido)hexanamide,
N-(biphenyl-3-yl)-6-(2-(2-(diethylamino)ethylthio)acetamido)hexanamide
4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)butanoic acid
N-(biphenyl-3-yl)-6-(2-(4-(methylsulfinyl)benzylthio)acetamido)hexanamide
N-(biphenyl-3-yl)-6-(2-(2-(dimethylamino)ethylthio)-acetamido)-hexanamide
(*S*)-3-(2-(4-((2-benzyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)-2-oxoethylthio)propanoic acid
(*R*)-3-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)-phenylamino-)ethylthio)-propanoic acid
3-(2-(6-methoxybenzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid
4-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-hydroxy-4-oxobutanoic acid
3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-hydroxypropanoic acid
N-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)benzyl)-2-(3-hydroxypropylthio)acetamide
(*R*)-*N*-(4-((2-((1H-indol-3-yl)methyl)-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenyl)-2-(2-(dimethylamino)ethylthio)acetamide
3-(2-(benzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid
3-(2-(6-fluorobenzo[d]-thiazol-2-ylamino)-2-oxoethylthio)-propanoic acid
3-({2-[(6-nitro-1,3-benzothiazol-2-yl)amino]-2-oxoethyl}thio)propanoic acid
3-(2-(6-nitrobenzo[d]-thiazol-2-ylamino)-2-oxoethylthio)-propanoic acid
3-(2-oxo-2-(6-oxo-6-(3-(pyridin-3-yl)phenylamino)hexylamino)ethylthio)-propanoic acid

N-biphenyl-3-yl-6-({[(4-fluorobenzyl)oxy]acetyl}amino)hexanamide

Synthetic Schemes and Experimental Procedures

[0116] The compounds of the invention can be prepared according to the reaction schemes for the examples illustrated below utilizing methods known to one of ordinary skill in the art. These schemes serve to exemplify some procedures that can be used to make the compounds of the invention. One skilled in the art will recognize that other general synthetic procedures may be used. The compounds of the invention can be prepared from starting components that are commercially available. Any kind of substitutions can be made to the starting components to obtain the compounds of the invention according to procedures that are well known to those skilled in the art.

Scheme 1



Example 1

N-(biphenyl-3-yl)-6-(2-(2-oxo-2-(phenylamino)ethylthio)acetamido)hexanamide (6)

Step 1: tert-butyl 6-(biphenyl-3-ylamino)-6-oxohexylcarbamate (**1**)

[0117] *N*-Boc-caproic acid (1.1g, 4.77 mmol), 3-phenyl aniline (806 mg, 4.77 mmol) and BOP (2.11g, 4.77 mmol) were dissolved in DMF (10 mL). Triethylamine (11.92 mmol, 1.66 mL) was added and the reaction was stirred for 3 hours at room temperature. The reaction

was then quenched with water and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **1** (1.65 g, 91%) as a beige solid . LRMS (ESI): (calc.) 382.2; (found) 383.3 $(MH)^+$.

Step 2: 6-amino-*N*-(biphenyl-3-yl)hexanamide (**2**)

[0118] To a solution of **1** (1.23 g, 3.22 mmol) in DCM (40 mL) was added TFA (6 mL). The mixture was stirred for 2 hours. The reaction was basified with $NaHCO_3$ (ss) and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, and evaporated to afford **2** (0.90 g, 98%) as viscous colorless oil. LRMS (ESI): (calc.) 282.5; (found) 283.0 $(MH)^+$.

Step 3: *N*-(biphenyl-3-yl)-6-(2-chloroacetamido)hexanamide (**3a**), *N*-(biphenyl-3-yl)-6-(2-bromoacetamido)hexanamide (**3b**)

[0119] Compound **3a**: To a solution of **2** (1.41g, 5.00 mmol) in DCM (10 mL) was added triethylamine (1.00 mL, 7.17 mmol) and chloroacetyl chloride (0.40 mL, 5.00 mmol). The resulting mixture was stirred for 5 min at room temperature, and then concentrated under reduced pressure. The crude material was dissolved in EtOAc, washed with $NaHCO_3$ (ss), water and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give a brown oil which was purified by silica gel column chromatography with EtOAc/Hexanes/MeOH (10 : 9 : 1) to afford **3a** (1.06 g, 59% after 3 steps) as a white solid. ^1H NMR: (MeOH-*d*4) δ (ppm): 7.84-7.83 (m, 1H), 7.60-7.58 (m, 2H), 7.53-7.50 (m, 1H), 7.43-7.31 (m, 5H), 4.00 (s, 2H), 3.25 (t, J = 7.2Hz, 2H), 2.42 (t, J = 7.2Hz, 2H), 1.80-1.72 (m, 2H), 1.64-1.57 (m, 2H), 1.48-1.42 (m, 2H); LRMS (ESI) : (found) 359.1: 361.1 (*r*: 3:1) $(MH)^+$.

[0120] Compound **3b**: To a solution of **2** (4.83 g, 17.1 mmol) in THF (50 mL) was added bromoacetyl chloride (1.43 mL, 17.1 mmol) and triethylamine (7.15 mL, 51.3 mmol). The mixture was stirred for 10 min prior to extraction from brine with EtOAc, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **3b** (2.16 g, 31%) as a light pink solid.. ^1H NMR: (DMSO-d_6) δ (ppm): 10.00 (s,1H), 8.29 (m,1H), 7.94 (s,1H), 7.61 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.40 (t, J = 7.8 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 3.38 (s,2H), 3.10 (q, J = 13.2,6.6 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.70-1.60 (m,2H), 1.54-1.44 (m,2H), 1.40-1.30 (m,2H). LRMS (ESI): (found) 403.2: 405.1 (*r*: 1:1) $(MH)^+$.

Step 4: methyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)acetate (**4**)

[0121] To a solution of **3b** (270 mg, 0.67 mmol) in THF (10 mL) was added methyl thioglycolate (0.67 mmol, 0.061 mL), and triethylamine (1.68 mmol, 0.24 mL). The reaction was stirred for 15 hours at room temperature (some related examples heat at reflux) then quenched with water and extracted with ethyl acetate. The organic extract was dried

(Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-50%) in Hexane to afford **4** (230 mg, 81%) as a white solid . ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.94 (s, 1H), 7.98 (t, J=5.7 Hz, 1H), 7.90 (s, 1H), 7.59 - 7.54 (m, 3H), 7.45 (t, J=7.2 Hz, 2H), 7.35 (t, J=6.5 Hz, 2H), 7.30 - 7.27 (m, 1H), 3.62 (s, 3H), 3.43 (s, 2H), 3.18 (s, 2H), 3.05 (q, J=6.8 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 1.62 - 1.58 (m, 2H), 1.45 - 1.39 (m, 2H), 1.34 - 1.28 (m, 2H). LRMS (ESI): (calc.) 428.2; (found) 429.2 $(MH)^+$.

Step 5: 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)acetic acid (**5**)

[0122] To a solution of methyl ester **4** (210 mg, 0.49 mmol) in THF: methanol: water solvent mixture (5:1:1), was added lithium hydroxide monohydrate (103 mg, 2.45 mmol) and heated at 60°C for 1 hour. The reaction was acidified with 1M HCl solution and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated to afford **5** (130 mg, 65%) as a white solid. ^{1}H NMR: (DMSO-d_6) δ (ppm): 9.95 (s, 1H), 8.01 (t, J=5.3 Hz, 1H), 7.90 (s, 1H), 7.59 - 7.54 (m, 3H), 7.45 (t, J=7.6 Hz, 2H), 7.35 (t, J=7.8 Hz, 2H), 7.30 - 7.27 (m, 1H), 3.33 (s, 2H), 3.18 (s, 2H), 3.05 (q, J=6.7 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 1.64 - 1.57 (m, 2H), 1.47 - 1.40 (m, 2H), 1.35 - 1.28 (m, 2H). LRMS (ESI): (calc) 414.2; (found) 415.4$(MH)^+$.

Step 6: *N*-(biphenyl-3-yl)-6-(2-(2-oxo-2-(phenylamino)ethylthio)acetamido)hexanamide (**6**)

[0123] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting acid **5** for *N*-Boc-caproic acid and aniline for 3-phenyl aniline to afford **6** (70 mg, 84%) as a white solid. ^{1}H NMR: (DMSO-d_6) δ (ppm): 10.11 (s, 1H), 9.94 (s, 1H), 8.04 (t, J=5.4 Hz, 1H), 7.90 (s, 1H), 7.58 - 7.54 (m, 5H), 7.45 (t, J=7.2 Hz, 2H), 7.35 (t, J=7.8 Hz, 2H), 7.30 - 7.25 (m, 3H), 7.28 (t, J=7.4 Hz, 2H), 3.42 (s, 2H), 3.27 (s, 2H), 3.06 (q, J=6.6 Hz, 2H), 2.31 (t, J=7.2 Hz, 2H), 1.63 - 1.56 (m, 2H), 1.47 - 1.40 (m, 2H), 1.34 - 1.27 (m, 2H). LRMS (ESI): (calc) 505.2; (found) 506.5 $(MH)^+$.

Example 2

2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)acetic acid (7)

Step 6: 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)acetic acid (**7**)

[0124] To a stirred solution of **5** (30 mg, 0.061 mmol) (see step 1-5 example 1, scheme 1 for preparation) in methanol: water solution (2:1) was added sodium periodate (100 mg, 0.42 mmol). The mixture was stirred at room temperature for a week. After water was added to the reaction and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by trituration with EtOAc: MeOH (10:1) to afford **7** (24 mg, 78%) as a beige solid . ^{1}H NMR: (DMSO-d_6) δ (ppm): 10.33 (s, 1H), 9.94 (s, 1H), 8.31 - 8.29 (m, 1H), 7.90 (s, 1H), 7.59 - 7.53 (m, 5H), 7.45 (t, J=7.5 Hz, 2H), 7.37 - 7.28 (m, 5H), 7.06 (t, J=7.5 Hz, 1H), 3.83 (dd, J=32.7, 13.3 Hz, 1H), 3.84 (d, J=12.5 Hz, 2H), 3.12

(q, J=6.3 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 1.63 - 1.59 (m, 2H), 1.48 - 1.44 (m, 2H), 1.34 - 1.32 (m, 2H). LRMS (ESI): (calc) 430.1; (found) 431.0 $(MH)^+$.

Example 3

Methyl 2-(2-(2-(biphenyl-3-ylamino)-2-oxoethylamino)-2-oxoethylsulfonyl)acetate (8)

Step 5: Methyl 2-(2-(2-(biphenyl-3-ylamino)-2-oxoethylamino)-2-oxoethylsulfonyl)-acetate (**8**)

[0125] To a solution of **4** (as described in example 1, scheme 1, steps 1-4 for preparation) in DCM (6 mL) was added *m*CPBA (0.034 g, 0.196 mmol). The resulting solution was stirred at room temperature for 2 h and then evaporated. The residue was purified by silica gel column chromatography with gradient of MeOH (0-20%) in EtOAc to afford **8** (20 mg, 44%) as a white crystalline solid. (DMSO-*d*6) δ (ppm) ^{1}H: 10.00 (s,1H), 8.44 (s,1H), 7.96 (s,1H), 7.65-7.57 (m,3H), 7.49 (t, J = 7.6 Hz, 2H), 7.43-7.36 (m,2H), 7.35-7.31 (m,1H), 4.59 (s,2H), 4.23 (s,2H), 3.74 (s,3H), 3.20-3.11 (m,2H), 2.37 (t, J = 7.2 Hz, 2H), 1.71-1.60 (m,2H), 1.55-1.45 (m,2H), 1.43-1.32 (m,2H) LRMS (ESI): (calc.) 460.5; (found) 461.3 $(MH)^+$.

Example 4

6-(2-(2-aminoethoxy)acetamido)-N-(biphenyl-3-yl)hexanamide (9)

Step 4: tert-butyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)ethylcarbamate (**7a**)

[0126] To a solution of **3b** (as described in example 1, scheme 1, steps 1-3 for preparation) (0.150 g, 0.372 mmol) in DCM (3mL) was added tert-butyl-2-hydroxyethylcarbamate (0.575 mL, 3.72 mmol), benzyltriethylammonium chloride (0.169 g, 0.744 mmol), and 40% (w/v) aqueous KOH (3 mL). The resulting solution was stirred at room temperature for 2 h prior to extraction from brine with EtOAc. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in hexane to afford **7a** (110 mg, 61%) as a light yellow foam. LRMS (ESI): (calc.) 483.6; (found) 484.3 $(MH)^+$.

Step 5: 6-(2-(2-aminoethoxy)acetamido)-N-(biphenyl-3-yl)hexanamide (**9**)

[0127] To a solution of **7a** (0.100 g, 0.207 mmol) in DCM (5 mL) was added TFA (0.5 mL). The mixture was stirred for 2 h at room temperature. The reaction was basified with aqueous NaOH and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated to afford **9** (75 mg, 95%) as a white foam. LRMS (ESI): (calc.) 383.5; (found.) 384.2 $(MH)^+$.

Example 5

N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)ethanethioamido)hexanamide (10)

Step 4: *N*-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)acetamido)hexanamide (**7b**)

[0128] Following the same procedure as described for compound **7a** (scheme 1, example 4) but substituting (4-fluorophenyl) methanol for tert-butyl-2-hydroxyethylcarbamate to afford **7b** (160 mg, 91%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.95 (s, 1H), 7.90 (s,

1H), 7.80 (t, J=5.5 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.47 - 7.28 (m, 7H), 7.18 - 7.13 (m, 2H), 4.49 (s, 2H), 3.86 (s, 2H), 3.10 (q, J=6.7 Hz, 2H), 2.33 (t, J=7.4 Hz, 2H), 1.65 - 1.57 (m, 2H), 1.48 - 1.43 (m, 2H), 1.33 - 1.27 (m, 2H). MS: 448.2 (calc) 449.2 (found). LRMS (ESI): (calc) 448.2; (found) 449.2 $(MH)^+$.

Step 5: *N*-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)ethanethioamido)hexanamide (**10**)

[0129] To a solution of **7b** (0.026 g, 0.058 mmol) in THF (3 mL) was added Lawesson's reagent (0.059 g, 0.145 mmol). The mixture was heated to 80 °C for 10 min prior to extraction from brine with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **10** (21 mg, 75%) as a light yellow oil. (DMSO-*d*6) δ (ppm) ^1H: 9.58 (m,1H), 8.21 (s,1H), 7.78-7.68 (m,3H), 7.65 (d, J = 7.0 Hz, 2H), 7.56-7.38 (m,7H), 7.20 (t, J = 9.0 Hz, 2H), 4.56 (s,2H), 4.28 (s,2H), 3.65 (q, J = 13.3,6.7 Hz, 2H), 2.81 (t, J = 7.4 Hz, 2H), 1.90-1.80 (m,2H), 1.74-1.63 (m,2H), 1.46-1.36 (m,2H). LRMS (ESI): (calc.) 480.7; (found) 481.4 $(MH)^+$.

Example 6

4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)benzoic acid (11)

Step 4: methyl 4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)benzoate (**7c**)

[0130] Following the same procedure as described for compound **7a** (scheme 1, example 4) but substituting methyl 4-(hydroxymethyl)benzoate for tert-butyl-2-hydroxyethylcarbamate to **7c** (43 mg, 18%) as a white solid (DMSO-*d*6) δ (ppm) ^1H: 9.98 (s,1H), 7.95 (m,3H), 7.89 (t, J = 5.6 Hz, 1H), 7.60 (m,3H), 7.53 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 4.64 (s,2H), 3.95 (s,2H), 3.88 (s,3H), 3.14 (q, J = 13.0,6.5 Hz, 2H), 2.36 (t, J = 7.0 Hz, 2H), 1.70-1.60 (m,2H), 1.56-1.46 (m,2H), 1.40-1.30 (m,2H). LRMS (ESI): (calc) 488.6; (found) 489.1 $(MH)^+$.

Step 5: 4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)benzoic acid (**11**)

[0131] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting **7c** for **4** to afford **11** (43 mg, 18%) as a white solid. (DMSO-*d*6) δ (ppm) ^1H: 10.18 (s,1H), 7.97 (s,1H), 7.94 (d, J = 7.8 Hz, 2H), 7.82 (t, J = 5.7 Hz, 1H), 7.61 (m,3H), 7.48 (t, J = 7.8 Hz, 2H), 7.44-7.34 (m,4H), 7.32 (d, J = 7.6 Hz, 1H), 4.58 (s,2H), 3.91 (s,2H), 3.13 (q, J = 13.2,6.6 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.68-1.58 (m,2H), 1.52-1.42 (m,2H), 1.36-1.24 (m,2H). LRMS (ESI): (calc.) 474.5; (found) 475.3 $(MH)^+$.

Example 7

N-(biphenyl-3-yl)-6-(2-(4-(hydroxymethyl)benzyloxy)acetamido)hexanamide (12)

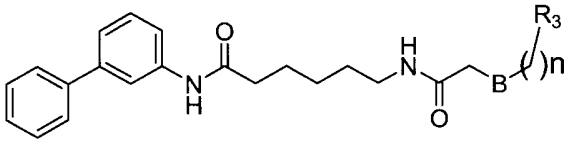
Step 5: *N*-(biphenyl-3-yl)-6-(2-(4-(hydroxymethyl)benzyloxy)acetamido)hexanamide (**12**)

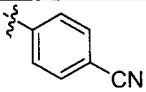
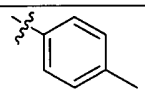
[0131] To a solution of **7c** (as described in example 6, scheme 1, steps 1-4 for preparation) (0.040 g, 0.082 mmol) in THF (2 mL) was added $LiAlH_4$ (0.006 g, 0.164 mmol). The resulting solution was stirred at room temperature for 5 min prior to extraction with EtOAc. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by trituration with EtOAc in hexanes to afford **12** (20 mg, 54%) as a light yellow solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.98 (s,1H), 7.94 (s,1H), 7.81 (t, J = 5.7 Hz, 1H), 7.64-7.57 (m,3H), 7.48 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.35-7.30 (m,5H), 4.52 (s,2H), 4.51 (s,2H), 3.87 (s,2H), 3.14 (q, J = 13.3,6.6 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.70-1.60 (m,2H), 1.54-1.45 (m,2H), 1.38-1.26 (m,2H). LRMS (ESI): (calc.) 460.6; (found) 461.2 $(MH)^+$.

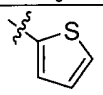
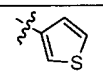
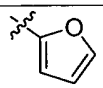
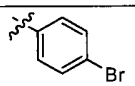
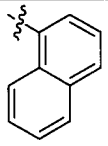
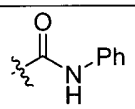
Examples 8-25

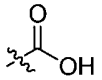
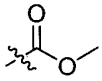
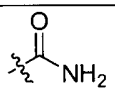
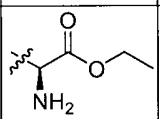
[0132] Example 8-25 describe the preparation of compound **13-30** using the same procedures as described Example 1-6. Characterization data are presented in a Table 1.

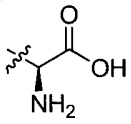
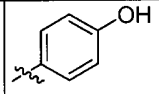
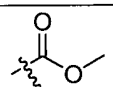
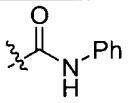
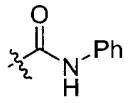
Table 1

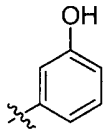
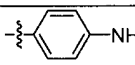
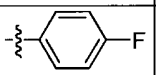
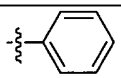
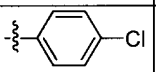
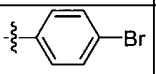


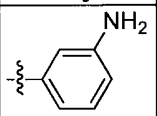
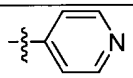
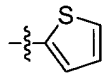
Ex	Cpd	n	B	R_3	Name	Characterization	Scheme
8	13	1	O		*N*-(biphenyl-3-yl)-6-(2-(4-cyanobenzyloxy)-acetamido)-hexanamide	(DMSO-*d*6) δ(ppm) ^{1}H: 9.94 (s, 1H), 7.90 - 7.85 (m, 2H), 7.79 (d, J=8.2 Hz, 2H), 7.58 - 7.53 (m, 5H), 7.44 (t, J=7.2 Hz, 2H), 7.34 (t, J=7.6 Hz, 2H), 7.29 - 7.27 (m, 1H), 4.60 (s, 2H), 3.91 (s, 2H), 3.10 (q, J=6.7 Hz, 2H), 2.32 (t, J=7.4 Hz, 2H), 1.62 - 1.56 (m, 2H), 1.48 - 1.42 (m, 2H), 1.33 - 1.27 (m, 2H). LRMS (ESI): (calc) 455.2; (found) 456.3 $(MH)^+$.	1 Step 1-4 Cpd 7c Ex 5
9	14	1	O		*N*-(biphenyl-3-yl)-6-(2-(4-methylbenzyloxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.95 (s, 1H), 7.90 (s, 1H), 7.75 (t, J=6.2 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.45 (t, J=7.2 Hz, 2H), 7.35 (t, J=7.8 Hz, 2H), 7.30 - 7.27 (m, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.13 (d, J=7.8 Hz, 2H), 4.45 (s, 2H), 3.82 (s, 2H), 3.09 (q, J=6.6 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 2.28 (s, 3H), 1.62 - 1.57 (m, 2H), 1.47 - 1.42 (m, 2H), 1.33 - 1.27 (m, 2H). LRMS (ESI): (calc) 444.3; (found) 445.3 $(MH)^+$.	1 Step 1-4 Cpd 7c Ex 5

Ex	Cpd	n	B	R_3	Name	Characterization	Scheme
10	15	1	O		*N*-(biphenyl-3-yl)-6-(2-(thiophen-2-ylmethoxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.98 (br s,1H), 7.94 (br s,1H), 7.79 (br t,1H), 7.64-7.57 (m,3H), 7.54 (d, J = 4.9 Hz, 1H), 7.49 (t, J = 7.6 Hz,2H), 7.39 (t, J = 7.8 Hz, 2H), 7.34 (d, J = 7.4 Hz, 1H), 7.11 (m,1H), 7.03 (m,1H), 4.72 (s,2H), 3.88 (s,2H), 3.12 (q, J = 13.0,6.3 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.70-1.60 (m,2H), 1.54-1.44 (m,2H), 1.38-1.28 (m,2H). LRMS (ESI): (calc) 436.6; (found) 437.2 $(MH)^+$.	1 Step 1-4 Cpd 7c Ex 5
11	16	1	O		*N*-(biphenyl-3-yl)-6-(2-(thiophen-3-ylmethoxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.98 (s,1H), 7.94 (s,1H), 7.79 (t, J = 5.7 Hz, 1H), 7.64-7.55 (m,3H), 7.53 (m,1H), 7.49 (m,3H), 7.39 (t, J = 7.8 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.13 (d, J = 4.8 Hz, 1H), 4.54 (s,2H), 3.87 (s,2H), 3.13 (q, J = 13.0,6.6 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.70-1.59 (m,2H), 1.54-1.44 (m,2H), 1.38-1.26 (m,2H). LRMS (ESI): (calc) 436.6; (found) 437.2 $(MH)^+$.	1 Step 1-4 Cpd 7c Ex 5
12	17	1	O		*N*-(biphenyl-3-yl)-6-(2-(furan-3-ylmethoxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.98 (br s,1H), 7.94 (br s,1H), 7.76 (t, J = 5.7 Hz, 1H), 7.71 (s,1H), 7.65 (t, J = 1.6 Hz, 1H), 7.64-7.56 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.35 (d, J = 7.6 Hz, 1H), 6.54 (s,1H), 4.41 (s,2H), 3.85 (s,2H), 3.13 (q, J = 13.3,6.8 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.70-1.60 (m,2H), 1.54-1.44 (m,2H), 1.38-1.28 (m,2H). LRMS (ESI): (calc) 420.5; (found) 421.3 $(MH)^+$.	1 Step 1-4 Cpd 7c Ex5
13	18	1	O		*N*-(biphenyl-3-yl)-6-(2-(4-bromobenzyloxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.99 (br s,1H), 7.94 (br s,1H), 7.85 (t, J = 5.7 Hz, 1H), 7.64-7.58 (m,2H), 7.58-7.54 (m,2H), 7.49 (t, J = 7.8 Hz, 2H), 7.42-7.30 (m,5H), 4.52 (s,2H), 3.38 (s,2H), 3.14 (q, J = 13.1,6.5 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.70-1.60 (m,2H), 1.54-1.44 (m,2H), 1.38-1.28 (m,2H). LRMS (ESI): (calc) 509.4; (found) 511.2 $(MH)^+$.	1 Step 1-4 Cpd 7c Ex5
14	19	1	O		*N*-(biphenyl-3-yl)-6-(2-(naphthalen-1-ylmethoxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 10.00 (s,1H), 8.17 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 5.7 Hz, 1H), 7.65-7.55 (m,5H), 7.54-7.45 (m,3H), 7.42-7.35 (m,2H), 7.32 (d, J = 7.6 Hz, 1H), 5.01 (s,2H), 4.00 (s,2H), 3.15 (q, J = 12.5,6.3 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 1.71-1.60 (m,2H), 1.55-1.44 (m,2H), 1.38-1.28 (m,2H). LRMS (ESI): (calc) 480.6; (found) 481.3 $(MH)^+$.	1 Step 1-4 Cpd 7c Ex5
15	20	1	SO		*N*-(biphenyl-3-yl)-6-(2-(2-oxo-2-(phenylamino)-ethylsulfinyl)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 10.33 (s, 1H), 9.94 (s, 1H), 8.31 - 8.29 (m, 1H), 7.90 (s, 1H), 7.59 - 7.53 (m, 5H), 7.45 (t, J=7.5 Hz, 2H), 7.37 - 7.28 (m, 5H), 7.06 (t, J=7.5 Hz, 1H), 3.83 (dd, J=32.7, 13.3 Hz, 1H), 3.84 (d, J=12.5 Hz, 2H), 3.12 (q, J=6.3 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 1.63 - 1.59 (m, 2H), 1.48 - 1.44 (m, 2H), 1.34 - 1.32 (m, 2H). LRMS (ESI): (calc) 505.2; (found) 506.5 $(MH)^+$.	1 Step 1-6 Ex 1 Step 6 Ex 2

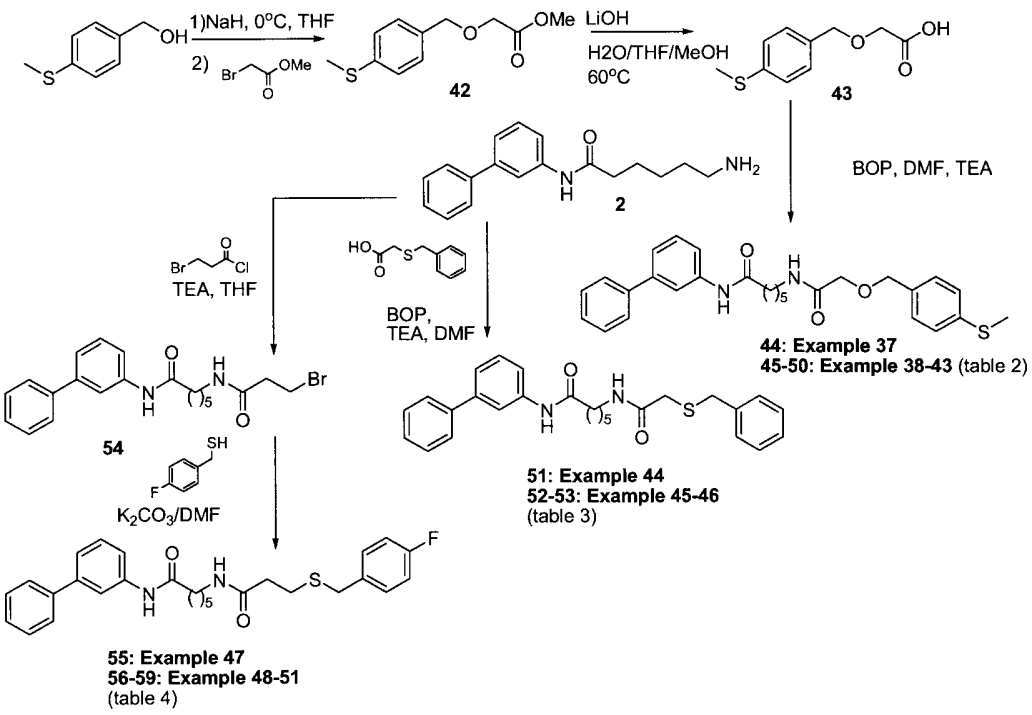
Ex	Cpd	n	B	R_3	Name	Characterization	Scheme
16	21	2	S		3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoic acid	(DMSO-*d*6) δ (ppm) ^{1}H: 12.28 (br s,1H), 9.99 (s,1H), 8.01 (m,1H), 7.94 (s,1H), 7.57-7.65 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.36-7.43 (m,2H), 7.31-7.36 (m,1H), 3.12 (s,2H), 3.14-3.06 (m,2H), 2.75 (t, J = 7.0 Hz, 2H), 2.52-2.58 (m,2H), 2.36 (t, J = 7.6 Hz, 2H), 1.60-1.70 (m,2H), 1.42-1.53 (m,2H), 1.31-1.40 (m,2H) LRMS (ESI): (calc) 428.5; (found) 429.5 $(MH)^+$.	1 Step 1-5 Ex 1
17	22	2	SO		methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-propanoate	(DMSO-*d*6) δ (ppm) ^{1}H: 9.99 (s,1H), 8.26 (m,1H), 7.94 (s,1H), 7.56-7.64 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.36-7.43 (m,2H), 7.32 (m,1H), 3.73 (d, J = 12.9 Hz, 1H), 3.66 (s,3H), 3.58 (d, J = 12.9 Hz, 1H), 3.09-3.20 (m,3H), 2.95-3.03 (m,1H), 2.77 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.60-1.70 (m,2H), 1.43-1.54 (m,2H), 1.31-1.42 (m,2H) LRMS (ESI): (calc) 458.6; (found) 458.9 $(MH)^+$.	1 Step 1-4 Ex 1 Step 5 Ex 2
18	23	3	S	-OH	*N*-(biphenyl-3-yl)-6-(2-(3-hydroxypropylthio)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 10.00 (s,1H), 7.97 (m,2H), 7.56-7.66 (m,3H), 7.45-7.53 (m,2H), 7.30-7.44 (m,3H), 4.54 (m,1H), 3.53-3.44 (m,2H), 3.19-3.02 (m,4H), 2.58-2.68 (m,2H), 2.30-2.44 (m,2H), 1.56-1.78 (m,4H), 1.42-1.56 (m,2H), 1.30-1.40 (m,2H) LRMS (ESI): (calc) 414.6; (found) 415.2 $(MH)^+$.	1 Step 1-4 Ex 1 Step 5 Ex 2 Step 5 Ex 6
19	24	2	S	-OH	*N*-(biphenyl-3-yl)-6-(2-(2-hydroxyethylthio)-acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.84 - 7.83 (m, 1H), 7.60 - 7.57 (m, 2H), 7.53 - 7.50 (m, 1H), 7.44 - 7.30 (m, 5H), 3.69 (t, J=6.5 Hz, 2H), 3.23 (t, J=6.9 Hz, 2H), 3.19 (s, 2H), 2.71 (t, J=6.2 Hz, 2H), 2.42 (t, J=7.2 Hz, 2H), 1.92 - 1.91 (m, 1H), 1.79 - 1.72 (m, 2H), 1.63 - 1.56 (m, 2H), 1.49 - 1.41 (m, 2H). LRMS (ESI): (calc)400.2; (found) 401.2 $(MH)^+$.	1 Step 1-5 Ex 1 Step 5 Ex 6
20	25	1	S		6-(2-(2-amino-2-oxoethylthio)-acetamido)-*N*-(biphenyl-3-yl)hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.94 (s, 1H), 8.03 (t, J=7.1 Hz, 1H), 7.90 (s, 1H), 7.59 - 7.54 (m, 3H), 7.47 - 7.43 (m, 3H), 7.37 - 7.33 (m, 2H), 7.30 - 7.28 (m, 1H), 7.06 (br s, 1H), 3.19 (s, 2H), 3.17 (s, 2H), 3.05 (q, J=6.6 Hz, 2H), 2.32 (t, J=7.4 Hz, 2H), 1.64 - 1.59 (m, 2H), 1.48 - 1.41 (m, 2H), 1.35 - 1.29 (m, 2H). LRMS (ESI): (calc) 413.2; (found) 414.2 $(MH)^+$.	1 Step 1-4 Ex 1
21	26	1	S		(*R*)-ethyl 2-amino-3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoate	(DMSO-*d*6) δ (ppm) ^{1}H: 9.95 (s, 1H), 8.00 (t, J=.5 Hz, 1H), 7.90 (s, 1H), 7.59 - 7.56 (m, 3H), 7.45 (t, J=7.5 Hz, 2H), 7.37 - 7.33 (m, 2H), 7.30 - 7.28 (m, 1H), 4.07 (q, J=7.2 Hz, 2H), 3.10 (s, 2H), 3.05 (q, J=6.3 Hz, 2H), 2.80 - 2.67 (m, 2H), 2.32 (t, J=7.4 Hz, 2H), 1.62 - 1.58 (m, 2H), 1.45 - 1.41 (m, 2H), 1.34 - 1.30 (m, 2H), 1.19 (t, J=7.0 Hz, 3H). LRMS (ESI): (calc) 471.3; (found) 472.9 $(MH)^+$.	1 Step 1-5 Ex 1

Ex	Cpd	n	B	R_3	Name	Characterization	Scheme
22	27	1	S		(*R*)-2-amino-3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoic acid	(DMSO-*d6*) δ (ppm) ^{1}H: 10.39 (s, 1H), 8.27 (t, J=6.7 Hz, 1H), 7.98 (s, 1H), 7.64 - 7.58 (m, 5H), 7.44 (t, J=7.6 Hz, 2H), 7.36 - 7.32 (m, 2H), 7.30 - 7.26 (m, 1H), 3.41 - 3.38 (m, 2H), 3.16 (dd, J=14.5, 10.0 Hz, 2H), 3.09 - 3.05 (m, 2H), 2.88 - 2.82 (m, 2H), 2.33 (t, J=7.0 Hz, 2H), 1.63 - 1.56 (m, 2H), 1.48 - 1.42 (m, 2H), 1.36 - 1.31 (m, 2H). LRMS (ESI): (calc) 443.2; (found) 444.2 $(MH)^+$.	1 Step 1-6 Ex 1
23	28	2	S	$-NH_2$	6-(2-(2-aminoethylthio)-acetamido)-*N*-(biphenyl-3-yl)hexanamide	(DMSO-*d6*) δ (ppm) ^{1}H: 9.95 (s, 1H), 8.02 (s, 1H), 7.90 (s, 1H), 7.59 - 7.53 (m, 3H), 7.45 (t, J=7.3 Hz, 2H), 7.35 (t, J=6.5 Hz, 2H), 7.30 - 7.28 (m, 1H), 3.10 - 3.01 (m, 4H), 2.74 (t, J=6.8 Hz, 2H), 2.32 (t, J=6.9 Hz, 2H), 1.91 (s, 2H), 1.79 (s, 2H), 1.62 - 1.58 (m, 2H), 1.46 - 1.42 (m, 2H), 1.36 - 1.29 (m, 2H). LRMS (ESI): (calc) 399.2; (found) 400.7 $(MH)^+$.	
24	29	--	S		*N*-(biphenyl-3-yl)-6-(2-(4-hydroxyphenylthio)-acetamido)-hexanamide	(DMSO-*d6*) δ (ppm) ^{1}H: 9.94 (s, 1H), 9.56 (s, 1H), 7.94 - 7.90 (m, 2H), 7.59 - 7.54 (m, 3H), 7.45 (t, J=7.6 Hz, 2H), 7.37 - 7.33 (m, 2H), 7.30 - 7.28 (m, 1H), 7.20 (d, J=8.8 Hz, 2H), 6.69 (d, J=8.7 Hz, 2H), 3.41 (s, 2H), 3.02 (q, J=6.5 Hz, 2H), 2.31 (t, J=7.2 Hz, 2H), 1.62 - 1.54 (m, 2H), 1.41 - 1.34 (m, 2H), 1.29 - 1.24 (m, 2H). LRMS (ESI): (calc) 448.2; (found) 449.4 $(MH)^+$.	1 Step 1-4 Ex 1
25	30	1	SO		methyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-acetate	(DMSO-*d6*) δ (ppm) ^{1}H: 9.96 (s, 1H), 8.28 - 8.29 (m, 1H), 7.90 (s, 1H), 7.59 - 7.54 (m, 3H), 7.45 (t, J=7.4 Hz, 2H), 7.36 (t, J=7.4 Hz, 2H), 7.30 - 7.28 (m, 1H), 4.08 (d, J=14.3 Hz, 1H), 3.91 - 3.80 (m, 2H), 3.69 (s, 3H), 3.68 - 3.66 (m, 2H), 3.10 - 3.08 (m, 2H), 2.32 (t, J=7.0 Hz, 2H), 1.62 - 1.58 (m, 2H), 1.46 - 1.43 (m, 2H), 1.34 - 1.31 (m, 2H). LRMS (ESI): (calc) 444.2; (found) 445.5 $(MH)^+$.	1 Step 1-4 Ex 1 Step 6 Ex 2
26	31	2	S		*N*-(biphenyl-3-yl)-6-(2-(3-oxo-3-(phenylamino)-propylthio)-acetamido)-hexanamide	(DMSO-*d6*) δ (ppm) ^{1}H: 9.93 (s, 2H), 7.98 (t, J=5.5Hz, 1H), 7.90 (s, 1H), 7.58 - 7.54 (m, 5H), 7.44 (t, J=7.2 Hz, 2H), 7.37 - 7.32 (m, 2H), 7.29 - 7.23 (m, 3H), 6.99 (td, J=7.3, 1.0 Hz, 1H), 3.11 (s, 2H), 3.06 (q, J=6.0 Hz, 2H), 2.82 (t, J=7.2 Hz, 2H), 2.61 (t, J=7.0 Hz, 2H), 2.31 (t, J=7.2 Hz, 2H), 1.64 - 1.56 (m, 2H), 1.46 - 1.40 (m, 2H), 1.34 - 1.30 (m, 2H). MS: 503.3 (calc) 504.4 (found) LRMS (ESI): (calc) 503.3; (found) 504.4 $(MH)^+$.	1 Step 1-6 Ex 1
27	32	2	SO		*N*-(biphenyl-3-yl)-6-(2-(3-oxo-3-(phenylamino)-propylsulfinyl)-acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.83 (s, 1H), 7.60 - 7.57 (m, 2H), 7.54 - 7.51 (m, 3H), 7.43 - 7.26 (m, 7H), 7.07 (t, J=7.4 Hz, 1H), 3.81 - 3.65 (m, 2H), 3.27 (t, J=6.7 Hz, 2H), 3.33 - 2.92 (m, 2H), 2.88 (t, J=6.8 Hz, 2H), 2.42 (t, J=7.4 Hz, 2H), 1.75 (quintet, J=7.8 Hz, 2H), 1.61 (quintet, J=7.3 Hz, 2H), 1.50 - 1.54 (m, 2H). LRMS (ESI): (calc) 519.2; (found) 520.3 $(MH)^+$.	1 Step 1-6 Ex 1 Step 6 Ex 2

Ex	Cpd	n	B	R_3	Name	Characterization	Scheme
28	33	--	S		*N*-(biphenyl-3-yl)-6-(2-(3-hydroxyphenylthio)-acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.83 (s, 1H), 7.60 - 7.58 (m, 2H), 7.52 (dt, J=7.6, 1.9 Hz, 1H), 7.44 - 7.30 (m, 5H), 7.09 (t, J=7.7 Hz, 1H), 6.82 - 6.78 (m, 2H), 6.65 - 6.61 (m, 1H), 3.57 (s, 2H), 3.19 (t, J=6.8 Hz, 2H), 2.37 (t, J=7.4 Hz, 2H), 1.70 - 1.66 (m, 2H), 1.51 - 1.46 (m, 2H), 1.35 - 1.28 (m, 2H). LRMS (ESI): (calc) 448.2 (found) 449.2 $(MH)^+$.	1 Step 1-4 Ex 1
29	34	--	S		6-(2-(4-aminophenylthio)-acetamido)-*N*-(biphenyl-3-yl)hexanamide	(DMSO-*d6*) δ (ppm) ^{1}H: 9.94 (s, 1H), 7.90 (s, 1H), 7.87 (t, J=5.7 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.45 (t, J=7.6 Hz, 2H), 7.37 - 7.33 (m, 2H), 7.30 - 7.26 (m, 1H), 7.07 (d, J=8.6 Hz, 2H), 6.47 (d, J=8.4 Hz, 2H), 5.24 (s, 2H), 3.31 (s, 2H), 3.01 (q, J=6.5 Hz, 2H), 2.31 (t, J=7.4 Hz, 2H), 1.60 - 1.54 (m, 2H), 1.40 - 1.34 (m, 2H), 1.30 - 1.25 (m, 2H). LRMS (ESI): (calc) 447.2; (found) 448.3 $(MH)^+$.	1 Step 1-4 Ex 1
30	35	--	S		*N*-(biphenyl-3-yl)-6-(2-(4-fluorophenylthio)-acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.84 (t, J=2.4 Hz, 1H), 7.60 - 7.57 (m, 2H), 7.52 (dt, J=7.5, 1.6 Hz, 1H), 7.44 - 7.30 (m, 7H), 7.07 - 7.02 (m, 2H), 3.52 (s, 2H), 3.17 (t, J=6.8 Hz, 2H), 2.38 (t, J=7.2 Hz, 2H), 1.72 - 1.67 (m, 2H), 1.50 - 1.44 (m, 2H), 1.36 - 1.30 (m, 2H). LRMS (ESI): (calc) 450.2; (found) 451.3 $(MH)^+$. LRMS (ESI): (calc); (found) $(MH)^+$.	1 Step 1-4 Ex 1
31	36	--	S		*N*-(biphenyl-3-yl)-6-(2-(phenylthio)-acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H 7.84 (s, 1H), 7.60 - 7.58 (m, 2H), 7.53 - 7.50 (m, 1H), 7.44 - 7.26 (m, 9H), 7.21 - 7.17 (m, 1H), 3.58 (s, 2H), 3.18 (t, J=6.9 Hz, 2H), 2.37 (t, J=7.2 Hz, 2H), 1.68 (quintet, J=7.8 Hz, 2H), 1.46 (quintet, J=7.8 Hz, 2H), 1.34 - 1.28 (m, 2H). LRMS (ESI): (calc) 432.2; (found) 433.3 $(MH)^+$.	1 Step 1-4 Ex 1
32	37	--	S		*N*-(biphenyl-3-yl)-6-(2-(4-chlorophenylthio)-acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H 7.84 (t, J=1.7 Hz, 1H), 7.60 - 7.57 (m, 2H), 7.52 (dt, J=7.6, 1.7 Hz, 1H), 7.44 - 7.27 (m, 9H), 3.58 (s, 2H), 3.18 (t, J=6.8 Hz, 2H), 2.38 (t, J=7.4 Hz, 2H), 1.69 (quintet, J=7.6 Hz, 2H), 1.48 (quintet, J=7.4 Hz, 2H), 1.36 - 1.30 (m, 2H). LRMS (ESI): (calc) 466.2; (found) 467.2 $(MH)^+$.	1 Step 1-4 Ex 1
33	38	--	S		*N*-(biphenyl-3-yl)-6-(2-(4-bromophenylthio)-acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H 7.84 (s, 1H), 7.60 - 7.57 (m, 2H), 7.53 - 7.50 (m, 1H), 7.44 - 7.26 (m, 9H), 3.58 (s, 2H), 3.18 (t, J=6.7 Hz, 2H), 2.38 (t, J=7.4 Hz, 2H), 1.69 (quintet, J=7.6 Hz, 2H), 1.48 (quintet, J=7.3 Hz, 2H), 1.35 - 1.27 (m, 2H). LRMS (ESI): (calc) 511.1; 512.2 (found) $(MH)^+$.	1 Step 1-4 Ex 1

Ex	Cpd	n	B	R_3	Name	Characterization	Scheme
34	39	--	S		6-(2-(3-aminophenylthio)-acetamido)-N-(biphenyl-3-yl)hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H 7.84 (s, 1H), 7.61 - 7.58 (m, 2H), 7.53 - 7.50 (m, 1H), 7.44 - 7.31 (m, 5H), 7.00 (t, J=7.8 Hz, 1H), 6.71 (t, J=1.8 Hz, 1H), 6.67 - 6.63 (m, 1H), 6.56 - 6.53 (m, 1H), 3.55 (s, 2H), 3.19 (t, J=6.8 Hz, 2H), 2.37 (t, J=7.4 Hz, 2H), 1.68 (quintet, J=7.3 Hz, 2H), 1.51 - 1.45 (m, 2H), 1.34 - 1.28 (m, 2H). LRMS (ESI): (calc) 447.2 ; 447.7 (found) $(MH)^+$.	1 Step 1-4 Ex 1
35	40	--	S		N-(biphenyl-3-yl)-6-(2-(pyridin-4-ylthio)acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H: 8.34-8.30 (m,2H), 7.87 (t, J = 1.6 Hz, 1H), 7.64-7.58 (m,2H), 7.57-7.53 (m,1H), 7.47-7.30 (m,7H), 3.80 (s,2H), 3.25 (t, J = 6.8 Hz, 2H), 2.40 (t, J = 7.4 Hz, 2H), 1.78-1.68 (m,2H), 1.62-1.52 (m,2H), 1.44-1.35 (m,2H). LRMS (ESI): (calc) 433.6 ; 434.4 (found) $(MH)^+$.	1 Step 1-4 Ex 1
36	41	--	S		*N*-(biphenyl-3-yl)-6-(2-(thiophen-2-ylthio)acetamido)-hexanamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.87 (t, J = 1.8 Hz, 1H), 7.64-7.59 (m,2H), 7.57-7.53 (m,1H), 7.50-7.32 (m,6H), 7.22-7.19 (m,1H), 7.03-6.99 (m,1H), 3.43 (s,2H), 3.38 (s,[?]), 3.20 (t, J = 6.8 Hz,2H), 2.43 (t, J = 7.2 Hz, 2H), 1.80-1.70 (m,2H), 1.58-1.49 (m,2H), 1.43-1.33 (m,2H) LRMS (ESI): (calc) 438.6; (found) 438.8 $(MH)^+$.	1 Step 1-4 Ex 1

Scheme 2



Example 37

N-(biphenyl-3-yl)-6-(2-(4-(methylthio)benzyloxy)acetamido)hexanamide) (44)

Step 1: methyl 2-(4-(methylthio)benzyloxy)acetate (**42**)

[0133] To a stirred solution of (4-(methylthio)phenyl)methanol (500 mg, 3.24 mmol) in THF (10 mL) at 0 °C was added sodium hydride (143 mg, 3.56 mmol). Bromomethyl acetate (3.24 mmol, 0.31 mL) was then added *via* a syringe and the reaction was allowed to warm to room temperature with stirring over 15 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (20-25%) in hexane to afford **42** (240 mg, 33%) as a clear oil.

^{1}H NMR: ($CDCl_3$) δ (ppm): 7.21 (d, J=8.6 Hz, 2H), 7.16 (d, J=8.4 Hz, 2H), 4.51 (s, 2H), 4.03 (s, 2H), 3.69 (s, 3H), 2.41 (s, 3H).

Step 2: 2-(4-(methylthio)benzyloxy)acetic acid (**43**)

[0134] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting **42** for methyl ester **4**, to afford **43** (160 mg, 60 %) as a white solid. ^{1}H NMR: ($CDCl_3$) δ (ppm): 9.84 (br s, 1H), 7.45 – 7.32 (m, 4H), 4.73 (s, 2H), 4.27 (s, 2H), 2.63 (s, 3H).

Step 3: *N*-(biphenyl-3-yl)-6-(2-(4-(methylthio)benzyloxy)acetamido)hexanamide) (**44**)

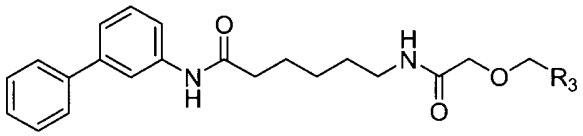
[0135] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting acid **43** for *N*-Boc-caproic acid, to afford **44** (160 mg, 15% from step 1-3)

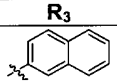
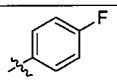
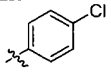
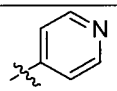
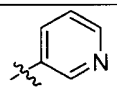
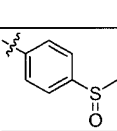
as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.95 (s, 1H), 7.90 (t, J=1.8 Hz, 1H), 7.78 (t, J=5.8 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.47 - 7.43 (m, 2H), 7.37 - 7.33 (m, 2H), 7.30 - 7.27 (m, 3H), 7.23 - 7.20 (m, 2H), 4.46 (s, 2H), 3.83 (s, 2H), 3.10 (q, J=7.0 Hz, 2H), 2.46 (s, 3H), 2.33 (t, J=7.5 Hz, 2H), 1.63 - 1.59 (m, 2H), 1.48 - 1.42 (m, 2H), 1.33 - 1.27 (m, 2H). LRMS (ESI): (calc) 476.3; (found) 477.3 $(MH)^+$.

Example 38-43

[0136] Example 38-43 describe the preparation of compound **45-50** using the same procedures as described for compound **44** in Example 37, scheme 2. Characterization data are presented in a Table 2.

Table 2



Ex	Cpd	R_3	Name	Characterization	Scheme
38	45		*N*-(biphenyl-3-yl)-6-(2-(naphthalen-2-ylmethoxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.96 (s, 1H), 7.92 - 7.84 (m, 6H), 7.60 - 7.55 (m, 3H), 7.52 - 7.49 (m, 3H), 7.48 - 7.43 (m, 2H), 7.38 - 7.34 (m, 2H), 7.31 - 7.28 (m, 1H), 4.69 (s, 2H), 3.93 (s, 2H), 3.13 (q, J=6.7 Hz, 2H), 2.34 (t, J=7.4 Hz, 2H), 1.64 - 1.60 (m, 2H), 1.50 - 1.46 (m, 2H), 1.33 - 1.29 (m, 2H). LRMS (ESI): (calc) 480.3; (found) 481.3 $(MH)^+$.	2 Step 1-3 Ex 26
39	46		*N*-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.95 (s, 1H), 7.90 (s, 1H), 7.80 (t, J=5.5 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.47 - 7.28 (m, 7H), 7.18 - 7.13 (m, 2H), 4.49 (s, 2H), 3.86 (s, 2H), 3.10 (q, J=6.7 Hz, 2H), 2.33 (t, J=7.4 Hz, 2H), 1.65 - 1.57 (m, 2H), 1.48 - 1.43 (m, 2H), 1.33 - 1.27 (m, 2H). LRMS (ESI): (calc) 448.2; (found) 449.2 $(MH)^+$.	2 Step 1-3 Ex 26
40	47		*N*-(biphenyl-3-yl)-6-(2-(4-chlorobenzyloxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.94 (s, 1H), 7.89 (s, 1H), 7.80 (t, J=5.9 Hz, 1H), 7.58 - 7.53 (m, 3H), 7.46 - 7.42 (m, 2H), 7.40 - 7.32 (m, 6H), 7.30 - 7.27 (m, 1H), 4.49 (s, 2H), 3.86 (s, 2H), 3.09 (q, J=6.8 Hz, 2H), 2.32 (t, J=7.0 Hz, 2H), 1.64 - 1.56 (m, 2H), 1.47 - 1.42 (m, 2H), 1.33 - 1.25 (m, 2H) . LRMS (ESI): (calc) 464.2; (found) 465.3 $(MH)^+$.	2 Step 1-3 Ex 26
41	48		*N*-(biphenyl-3-yl)-6-(2-(pyridin-4-ylmethoxy)-acetamido)-hexanamide	($CDCl_3$-*d*6) δ (ppm) ^{1}H: 8.57 (d, J=5.9 Hz, 2H), 7.81 (s, 1H), 7.72 (s, 1H), 7.58 - 7.50 (m, 3H), 7.42 - 7.30 (m, 5H), 7.24 (d, J=6.1 Hz, 2H), 6.61 (br s, 1H), 4.56 (s, 2H), 3.99 (s, 2H), 3.33 (q, J=6.8 Hz, 2H), 2.40 (t, J=7.2 Hz, 2H), 1.82 - 1.74 (m, 2H), 1.61 - 1.55 (m, 2H), 1.46 - 1.40 (m, 2H) LRMS (ESI): (calc) 431.3; (found) 432.3 $(MH)^+$.	2 Step 1-3 Ex 26
42	49		*N*-(biphenyl-3-yl)-6-(2-(pyridin-3-ylmethoxy)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 9.95 (s, 1H), 8.56 (s, 1H), 8.48 (d, J=3.1 Hz, 1H), 7.90 (s, 1H), 7.82 (t, J=5.6 Hz, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.58 - 7.53 (m, 3H), 7.45 (t, J=7.3 Hz, 2H), 7.38 - 7.33 (m, 3H), 7.29 - 7.27 (m, 1H), 4.54 (s, 2H), 3.90 (s, 2H), 3.10 (q, J=6.5 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 1.61 - 1.59 (m, 2H), 1.47 - 1.42 (m, 2H), 1.33 - 1.27 (m, 2H) LRMS (ESI): (calc) 431.3; (found) 432.3 $(MH)^+$.	2 Step 1-3 Ex 26
43	50		*N*-(biphenyl-3-yl)-6-(2-(4-(methylsulfinyl)-benzyloxy)-	(DMSO-*d*6) δ (ppm) ^{1}H: 10.03 (s,1H), 7.95 (s,1H), 7.89 (t, J = 5.6 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.56-7.63 (m,5H), 7.48 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.32 (d, 7.8 Hz, 1H), 4.62 (s,2H),	2 Step 1-3 Ex 26 1

			acetamido)-hexanamide	3.94 (s,2H), 3.14 (q, J = 12.9,6.5 Hz, 2H), 2.76 (s,3H), 2.37 (t, J = 7.3 Hz, 2H), 1.60-1.70 (m,2H), 1.45-1.55 (m,2H), 1.28-1.39 (m,2H). LRMS (ESI): (calc) 492.6; (found) 493.0 $(MH)^+$.	Step 6 Ex 2

Example 44

6-(2-(benzylthio)acetamido)-*N*-(biphenyl-3-yl)hexanamide (51)

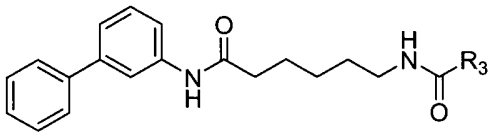
Step 1: 6-(2-(benzylthio)acetamido)-*N*-(biphenyl-3-yl)hexanamide (**51**)

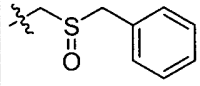
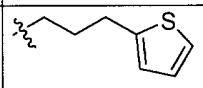
[0137] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 2-(benzylthio)acetic acid for *N*-Boc-caproic acid to afford **51** (142 mg, 64%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 10.00 (br s,1H), 7.99 (t, J = 5.5 Hz, 1H), 7.94 (br t, 1H), 7.60 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.36-7.30 (m,4H), 7.28-7.22 (m,1H), 3.81 (s,2H), 3.09 (q, J = 12.5, 6.7 Hz, 2H), 3.03 (s,2H), 2.37 (t, J = 7.4 Hz, 2H), 1.70-1.60 (m,2H), 1.52-1.40 (m,2H), 1.40-1.30 (m,2H). LRMS (ESI): (calc) 446.6; (found) 447.2 $(MH)^+$.

Example 45-46

[0138] Example 45-46 describe the preparation of compound **52-53** using the same procedures as described for compound **51** in Example 44. Characterization data are presented in a table 3.

Table 3



Ex	Cpd	R_3	Name	Characterization	Scheme
45	52		6-(2-(benzylsulfinyl)acetamido)-*N*-(biphenyl-3-yl)hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 10.01 (s,1H), 8.30 (t, J = 5.5 Hz, 1H), 7.95 (s,1H), 7.64-7.57 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.42-7.36 (m,4H), 7.35-7.31 (m,3H), 4.26 (d, J = 12.7 Hz, 1H), 4.02 (d, J = 12.9 Hz, 1H), 3.68 (d, J = 13.1 Hz, 1H), 3.46 (d, J = 13.1 Hz, 1H), 3.14 (m,2H), 2.36 (t, J = 7.3 Hz, 2H), 1.70-1.60 (m,2H), 1.54-1.43 (m,2H), 1.40-1.30 (m,2H) LRMS (ESI): (calc) 462.6; (found) 463.2 $(MH)^+$.	2 Step 1 Ex 33 1 Step 6 Ex 2
46	53		*N*-(biphenyl-3-yl)-6-(4-(thiophen-2-yl)butanamido)-hexanamide	(DMSO-*d*6) δ (ppm) 1H: 9.94 (s, 1H), 7.90 (t, J=1.8 Hz, 1H), 7.78 (t, J=5.7 Hz, 1H), 7.59 - 7.54 (m, 3H), 7.47 - 7.43 (m, 2H), 7.37 - 7.30 (m, 2H), 7.30 - 7.27 (m, 2H), 6.90 (dd, J=5.1, 3.3 Hz, 1H), 6.81 - 6.80 (m, 1H), 3.04 (q, J=6.7 Hz, 2H), 2.75 (t, J=7.4 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 2.10 (t, J=7.4 Hz, 2H), 1.85 - 1.77 (m, 2H), 1.63 - 1.57 (m, 2H), 1.45 - 1.39 (m, 2H), 1.34 - 1.28 (m, 2H) LRMS (ESI): (calc) 434.3; (found) 435.3 $(MH)^+$.	2 Step 1 Ex 33

Example 47

N-(biphenyl-3-yl)-6-(3-(4-fluorobenzylthio)propanamido)hexanamide (55)

Step 1: *N*-(biphenyl-3-yl)-6-(3-bromopropanamido)hexanamide (**54**)

[0139] To a solution of **2** (2.04 g, 7.22 mmol) in THF (20 mL) was added 3-bromo-propionyl chloride (0.73 mL, 7.22 mmol) and triethylamine (3.02 mL, 21.7 mmol). After stirring at room temperature for 30 min, the solution was diluted with brine, extracted with EtOAc.

[0140] The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **54** (270 mg, 9%) as a white solid. LRMS (ESI): (calc.) 417.5; (found) 418.2 $(MH)^+$.

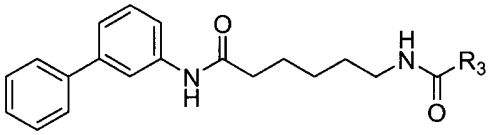
Step 2: *N*-(biphenyl-3-yl)-6-(3-(4-fluorobenzylthio)propanamido)hexanamide (**55**)

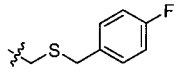
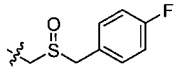
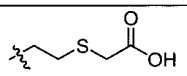
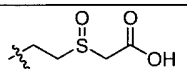
[0141] To a solution of **54** (132 mg, 0.32 mmol) in DMF (5 mL) was added (4-fluorophenyl)-methanethiol (0.04 mL, 0.32 mmol) and K_2CO_3 (131 mg, 0.95 mmol). The resulting solution was stirred for 16 h at 60 °C prior to removal of the solvent. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **55** (109 mg, 71%) as a light brown solid. (DMSO-*d*6) δ (ppm) ^1H: 9.99 (s,1H), 7.96 (s,1H), 7.91 (m,1H), 7.65-7.57 (m,3H), 7.48 (t, J = 7.8 Hz, 2H), 7.42-7.30 (m,5H), 7.14 (t, J = 8.6 Hz, 2H), 3.74 (s,2H), 3.09 (m,2H), 2.59 (t, J = 7.0 Hz, 2H), 2.37 (t, J = 7.0 Hz, 4H), 1.70-1.59 (m,2H), 1.53-1.42 (m,2H), 1.40-1.30 (m,2H). LRMS (ESI): (calc.) 478.6; (found) 479.6 $(MH)^+$.

Example 48-51

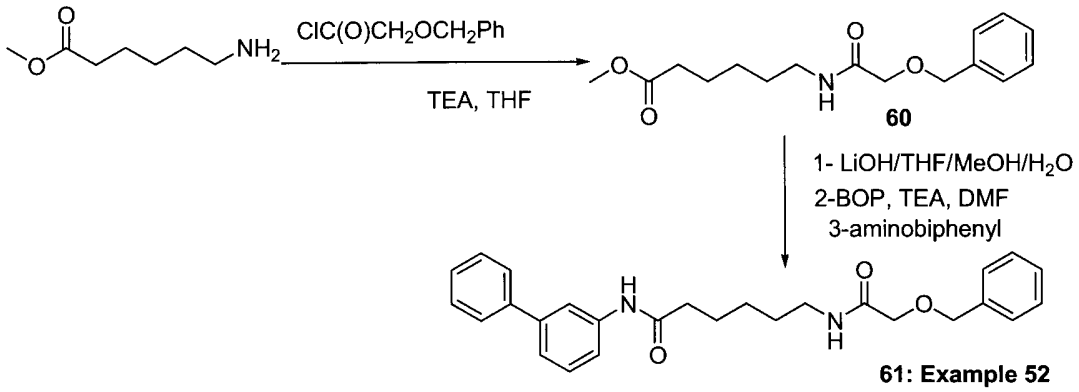
[0142] Example 48-51 describe the preparation of compound **54-59** using the same procedures as described for compound **55** in Example 47. Characterization data are presented in a Table 4.

Table 4



Ex	Cpd	R_3	Name	Characterization	Scheme
48	56		*N*-(biphenyl-3-yl)-6-(2-(4-fluorobenzyl-thio)acetamido)-hexanamide	(DMSO-*d*6) δ(ppm) ^{1}H: 10.06 (s,1H), 8.08 (m,1H), 7.96 (s,1H), 7.64-7.58 (m,3H), 7.49 (t, J = 7.6 Hz, 2H), 7.42-7.30 (m,5H), 7.22 (t, J = 8.8 Hz, 2H), 4.17 (d, J = 12.7 Hz, 1H), 3.97 (d, J = 12.9 Hz, 1H), 3.08 (q, J = 12.5,6.4 Hz, 2H), 3.04-2.94 (m,1H), 2.80-2.70 (m,1H), 2.52 (m,2H), 2.36 (t, J = 7.2 Hz, 2H), 1.70-1.58 (m,2H), 1.52-1.41 (m,2H), 1.40-1.29 (m,2H) LRMS (ESI): (calc.) 494.6; (found) 495.3 $(MH)^+$.	2 Step 1-2 Ex 36
49	57		*N*-(biphenyl-3-yl)-6-(2-(4-fluorobenzyl-sulfinyl)-acetamido)-hexanamide	(DMSO-*d*6) δ (ppm) ^{1}H: 10.12 (s,1H), 8.35 (br t,1H), 7.96 (s,1H), 7.65-7.59 (m,3H), 7.49 (t, J = 7.6 Hz, 2H), 7.42-7.30 (m,5H), 7.23 (t, J = 8.8 Hz, 2H), 4.26 (d, J = 13.1 Hz, 1H), 4.02 (d, J = 12.9 Hz, 1H), 3.68 (d, J = 13.1 Hz, 1H), 3.43 (d, J = 13.3 Hz, 1H), 3.16-3.08 (m,2H), 2.37 (t, J = 7.2 Hz, 2H), 1.69-1.57 (m,2H), 1.52-1.42 (m,2H), 1.40-1.30 (m,2H) LRMS (ESI): (calc.) 480.6; (found) 481.2 $(MH)^+$.	2 Step 1-2 Ex 36 1 Step 6 Ex 2
50	58		2-(3-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-3-oxopropylthio)-acetic acid	(DMSO-*d*6) δ (ppm) ^{1}H: 9.95 (s,1H), 7.90 (s,1H), 7.87 (t, J = 5.5 Hz, 1H), 7.60-7.53 (m,3H), 7.45 (t, J = 7.8 Hz, 2H), 7.37-7.32 (m,2H), 7.28 (d, J = 7.6 Hz, 1H), 3.23 (s,2H), 3.03 (q, J = 12.5,6.7Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 2.32 (m,4H), 1.65-1.54 (m,2H), 1.48-1.37 (m,2H), 1.36-1.24 (m,2H) LRMS (ESI): (calc.) 428.5; (found) 429.5 $(MH)^+$.	2 Step 1-2 Ex 36 1 Step 5 Ex 1
51	59		2-(3-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-3-oxopropyl-sulfinyl)acetic acid	(DMSO-*d*6) δ (ppm) ^{1}H: 10.00 (s,1H), 8.05 (m,1H), 7.94 (s,1H), 7.65-7.57 (m,3H), 7.49 (t, J = 7.4 Hz, 2H), 7.43-7.36 (m,2H), 7.32 (d, J = 7.8 Hz, 1H), 3.91 (d, J = 14.3 Hz, 1H), 3.64 (d, J = 14.3 Hz, 1H), 3.15-3.04 (m,4H), 3.00-2.92 (m,2H), 2.36 (t, J = 7.2 Hz, 2H), 1.69-1.58 (m,2H), 1.52-1.42 (m,2H), 1.40-1.30 (m,2H) LRMS (ESI): (calc.) 444.5; (found) 445.4 $(MH)^+$.	2 Step 1-2 Ex 36 1 Step 5 Ex 1 1 Step 6 Ex 2

Scheme 3



Example 52

6-(2-(benzyloxy)acetamido)-N-(biphenyl-3-yl)hexanamide (61)

Step 1: methyl 6-(2-(benzyloxy)acetamido)hexanoate (**60**)

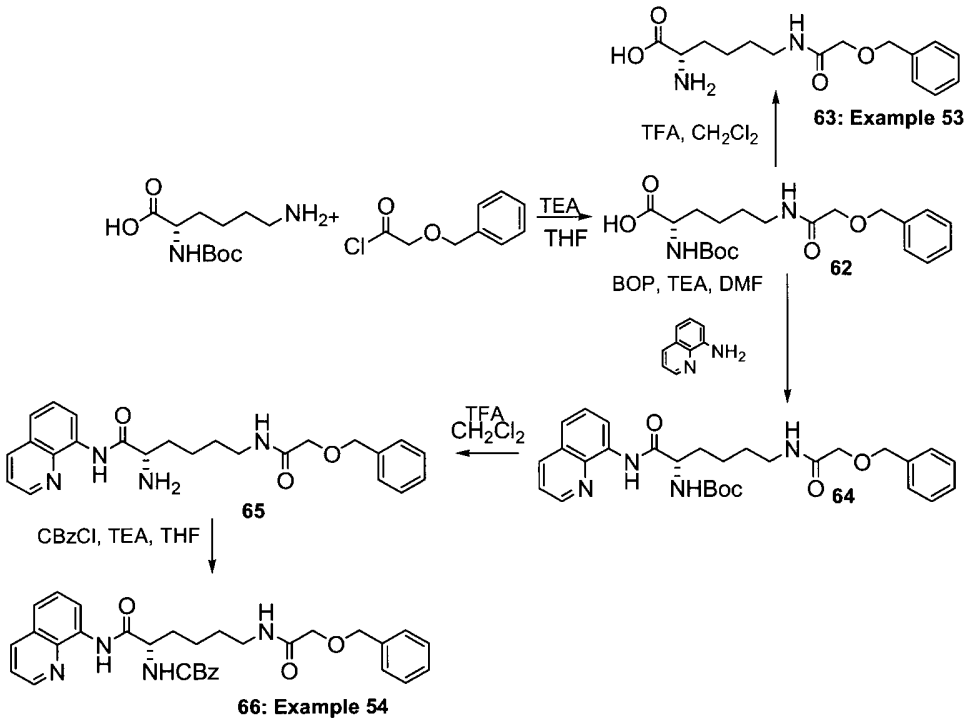
[0143] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting amine 5-Aminohexanoic for acid **2** and to afford **60** (1.60 g, 99%) as a yellow oil. LRMS (ESI): (calc.) 293.4; (found) 294.1 $(MH)^+$.

Step 2-3: 6-(2-(benzyloxy)acetamido)-N-(biphenyl-3-yl)hexanamide (**61**)

[0144] Following the same procedure as described for compound **5** (step5, scheme 1, example 1) but substituting ester **60** for 4 to afford 6-(2-(benzyloxy)acetamido)hexanoic acid (1.2 g, 62%) as an off white solid.

[0145] Following the same procedure as described for compound **1** (step1, scheme 1, example 1) but substituting acid **60** for *N*-Boc-caproic acid to afford **61** (1.14 g, 62%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.96 (s, 1H), 7.93 (s, 1H), 7.79 (s, 1H), 7.60 - 7.56 (m, 3H), 7.47 (t, J=7.5 Hz, 2H), 7.35 - 7.30 (m, 7H), 4.52 (s, 2H), 3.87 (s, 2H), 3.11 - 3.10 (m, 2H), 2.33 (t, J=7.5 Hz, 2H), 1.61 (t, J=6.5 Hz, 2H), 1.47 (t, J=7.0 Hz, 2H), 1.32 - 1.29 (m, 2H). LRMS (ESI): (calc.) 430.5; (found) 431.3 $(MH)^+$.

Scheme 4



Example 53

(*S*)-2-amino-6-(2-(benzyloxy)acetamido)hexanoic acid (63)

Step 1: (*S*)-6-(2-(benzyloxy)acetamido)-2-(tert-butoxycarbonylamino)hexanoic acid (**62**)

[0146] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting (S)-6-Amino-2-(tert-butoxycarbonylamino)hexanoic acid for amine **2** and using 2 eq of 2-(benzyloxy)acetyl chloride to afford **62** (311 mg, 66%) as a white foam. LRMS (ESI): (calc.) 394.5; (found) 395.2 $(MH)^+$.

Step 2: (*S*)-2-amino-6-(2-(benzyloxy)acetamido)hexanoic acid (**63**)

[0147] Following the same procedure as described for compound **9** (step 5, scheme 1, example 4) but substituting **62** for **7a** to afford **63** (35 mg, 29%) as a white solid. (DMSO-*d*6) δ (ppm) ^1H: 7.85 (m,1H), 7.40 (m,3H), 7.37-7.30 (m,2H), 4.56 (s,2H), 3.90 (s,2H), 3.14-3.08 (m,4H), 1.80-1.70 (m,1H), 1.66-1.55 (m,1H), 1.48-1.38 (m,2H), 1.38-1.26 (m,2H). LRMS (ESI): (calc.) 294.3; (found) 295.2 $(MH)^+$.

Example 54

(*S*)-benzyl 6-(2-(benzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate (66)

Step 2: (*S*)-tert-butyl 6-(2-(benzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate (**64**)

[0148] Following the same procedure as described for compound **1** (step1, scheme 1, example 1) but substituting **62** for *N*-Boc-caproic acid to afford **64** (127 mg, 69%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 10.51 (br s,1H), 8.90 (dd, J = 4.1,1.4 Hz, 1H), 8.66 (d, J = 7.6 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 7.86 (t, J = 5.1 Hz, 1H), 7.74-7.64 (m,3H), 7.61 (t, J = 8.0 Hz, 1H), 7.39 (m,4H), 7.36-7.28 (m,1H), 4.56 (s,2H), 4.10 (m,1H), 3.89 (s,2H), 3.14 (m,2H), 1.94-1.84 (m,1H), 1.76-1.68 (m,1H), 1.50-1.40 (br s,11H), 1.32-1.26 (m,2H). LRMS (ESI): (calc.) 520.6; (found) 521.2 $(MH)^+$.

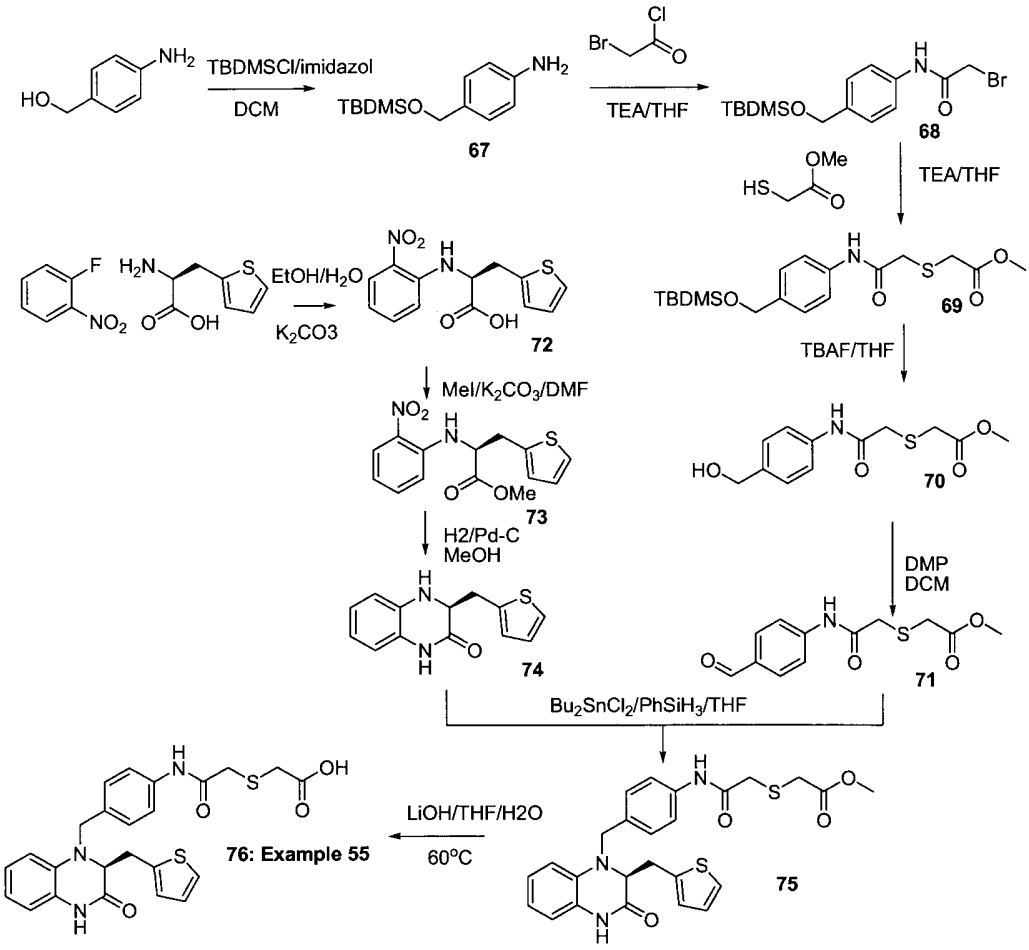
Step 3: (*S*)-2-amino-6-(2-(benzyloxy)acetamido)-N-(quinolin-8-yl)hexanamide (**65**)

[0149] Following the same procedure as described for compound **9** (step 5, scheme 1, example 4) but substituting **64** for **7a** to afford **65** (75 mg, 92%) as a light green solid. (DMSO-*d*6) δ (ppm) ^{1}H: 11.30 (br s,1H), 8.96 (d, J = 4.1 Hz, 1H), 8.67 (d, J = 7.6 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 7.84 (t, J = 5.4 Hz, 1H), 7.72 (d, J = 8.61 Hz, 1H), 7.66 (m,1H), 7.61 (t, J = 7.6 Hz, 1H), 7.35 (m,4H), 7.33-7.28 (m,1H), 4.51 (s,2H), 3.86 (s,2H), 3.13 (m,2H), 1.94-1.84 (m,1H), 1.82-1.72 (m,1H), 1.56-1.40 (m,4H), 1.30-1.26 (m,1H). LRMS (ESI): (calc.) 420.5; (found) 421.3 $(MH)^+$.

Step 4: (*S*)-benzyl 6-(2-(benzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate (**66**)

[0150] To a solution of **65** (81 mg, 0.192 mmol) in THF (5 mL) was added benzyl chloroformate (0.03 mL, 0.192 mmol) and triethylamine (0.15 mL, 1.08 mmol). The resulting solution was stirred at room temperature for 5 min prior to dilution with brine. The aqueous layer was then extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **66** (44 mg, 42%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 10.50 (br s,1H), 8.87 (d, J = 2.9 Hz, 1H), 8.66 (d, J = 7.4 Hz, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 6.8 Hz, 1H), 7.86 (m,1H), 7.73-7.64 (m,2H), 7.61 (t, J = 8.0 Hz, 1H), 7.38 (m,5H), 7.32 (m,3H), 5.17 (d, J = 12.7 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 4.55 (s,2H), 4.27 (m,1H), 3.90 (s,2H), 3.14 (m,2H), 1.98-1.83 (m,1H), 1.80-1.70 (m,1H), 1.40-1.38 (m,4H). LRMS (ESI): (calc.) 554.6; (found) 555.9 $(MH)^+$.

Scheme 5



Example 55

(*S*)-2-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)ethylthio)acetic acid (76)

Step 1: 4-((tert-butyldimethylsilyloxy)methyl)benzenamine (**67**)

[0151] To a solution of (4-Aminophenyl)methanol (1.50 g, 12.18 mmol) in CH_2Cl_2 (20 mL) was added TBDMSCl (1.84 g, 12.18 mmol) and imidazole (0.91 g, 13.40 mmol). After stirring for 1 h at room temperature, the solution was diluted with brine, and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **67** (2.76 g, 96%) as a light yellow oil. LRMS (ESI): (calc.) 237.4; (found) 238.2 $(MH)^+$.

Step 2: 2-bromo-*N*-(4-((tert-butyldimethylsilyloxy)methyl)phenyl)acetamide (**68**)

[0152] Following the same procedure as described for compound **3b** (step 3, scheme 1, example 1) but substituting amine **67** for amine **2** to afford **68** (1.72 g, 41%) as a white solid. LRMS (ESI): (calc.) 358.4; (found) 359.2 $(MH)^+$.

Step 3: methyl 2-(2-(4-((tert-butyldimethylsilyloxy)methyl)phenylamino)-2-oxoethylthio)acetate (**69**)

[0153] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting compound **68** for compound **3b** to afford **69** (960 mg, 99%) as a light yellow oil. LRMS (ESI): (calc.) 383.5; (found) 384.2 $(MH)^+$.

Step 4: methyl 2-(2-(4-(hydroxymethyl)phenylamino)-2-oxoethylthio)acetate (**70**)

[0154] To a solution of **69** (0.963 g, 2.51 mmol) in THF (20 mL) was added TBAF (2.76 mL, 2.76 mmol). The resulting solution was stirred at room temperature for 2 h prior to dilution with brine, and extraction with EtOAc. The organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **70** (170 mg, 25%) as a light yellow oil. (DMSO-*d*6) δ (ppm) ^1H: 10.08 (s,1H), 7.53 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 5.14 (t, J = 3.9 Hz, 1H), 4.46 (d, J = 5.7 Hz, 2H), 3.66 (s,3H), 3.56 (s,2H), 3.45 (s,2H). LRMS (ESI): (calc.) 269.3; (found) 270.1 $(MH)^+$.

Step 5: methyl 2-(2-(4-formylphenylamino)-2-oxoethylthio)acetate (**71**)

[0155] To a solution of **70** (170 mg, 0.63 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (290 mg, 0.69 mmol). The resulting solution was stirred at room temperature for 30 min prior to dilution with brine, and extraction with EtOAc. The organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **71** (112 mg, 67%) as a light yellow oil. LRMS (ESI): (calc.) 267.3; (found) 268.2 $(MH)^+$.

Synthesis of (*S*)-3-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-2(1H)-one (74). Step 1-3:

Step 1: (*S*)-2-(2-nitrophenylamino)-3-(thiophen-2-yl)propanoic acid (**72**)

[0156] To a solution of (L)-2-amino-3-thiophen-2-yl-propionic acid (965 mg, 5.64 mmol) and 1-fluoro-2-nitrobenzene (0.59 mL, 5.64 mmol) in $EtOH/H_2O$ (5:1, 12 mL) at room temperature was added potassium carbonate (1.56 g, 11.28 mmol). The resulting solution was heated at 100 °C for 16 h. After cooling, the solution was filtered, and evaporated to give **72** in quantitative yield. The crude was used in the subsequent reaction without further purification. LRMS (ESI): (calc.) 292.3; (found) 293.1 $(MH)^+$.

Step 2: (*S*)-methyl 2-(2-nitrophenylamino)-3-(thiophen-2-yl)propanoate (**73**)

[0157] To a solution of **72** (1.65 g, 5.64 mmol) in DMF (10 mL) was added potassium carbonate (3.12 g, 22.56 mmol) and methyl iodide (1.06 mL, 16.92 mmol). The resulting solution stirred at room temperature for 16 h. Following extraction from brine with EtOAc, the

organic extracts were evaporated to give residue **73** in near quantitative yield. This material was used in the subsequent reaction without further purification. LRMS (ESI): (calc.) 306.3; (found) 307.2 $(MH)^+$.

Step 3: ((*S*)-3-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-2(1H)-one (**74**)

[0158] To a solution of **73** (1.73 g, 5.64 mmol) in MeOH/EtOAc (2:1, 15 mL) was added 10% Pd/C (620 mg, 0.564 mmol). The resulting mixture was stirred under hydrogen atmosphere for 16 h, filtered through a pad of celite, and concentrated. The residue was purified by trituration with EtOAc: Hexane to afford **74** (1.31 g, 95%) as a light orange crystalline solid. LRMS (ESI): (calc.) 244.3; (found) 245.1 $(MH)^+$.

Step 6: (*S*)-methyl 2-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)ethylthio)acetate (**75**)

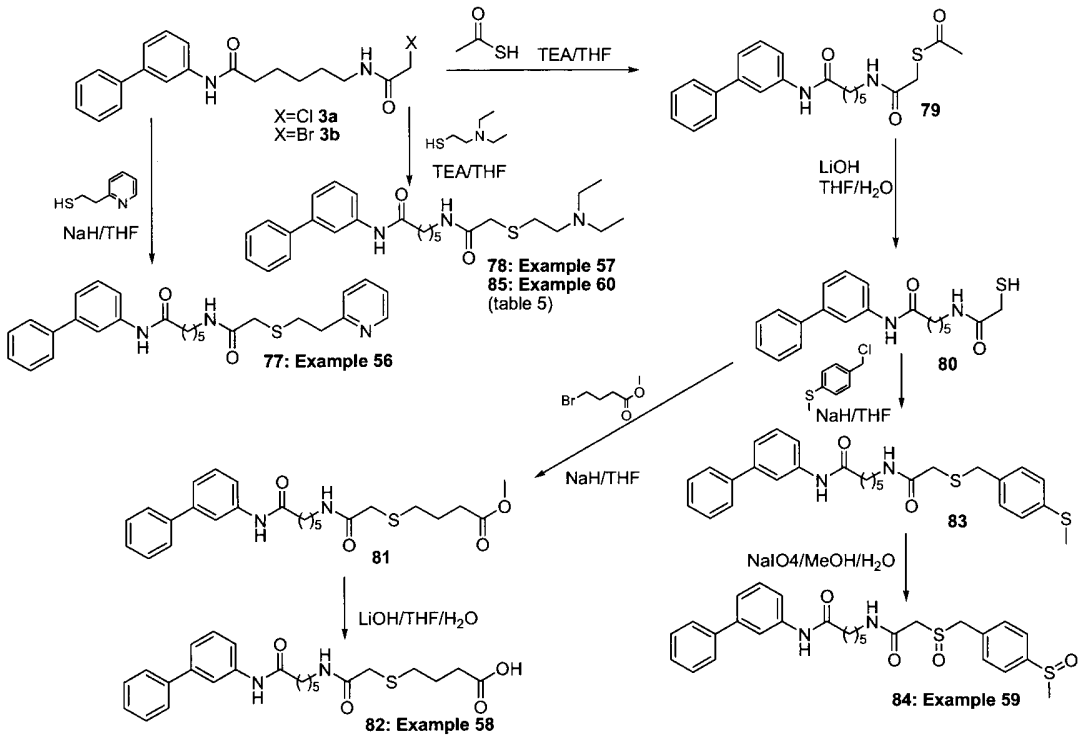
[0159] To a solution of **74** (102 mg, 0.419 mmol) in THF (1.5 mL) was added aldehyde **710** (112 mg, 0.419 mmol), dibutyltin dichloride (13 mg, 0.0419 mmol) and triphenyl silane (0.06 mL, 0.461 mmol). The resulting solution was stirred at room temperature for 16 h and then evaporated The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **75** (113 mg, 54%) as a white foam. ^1H (DMSO-*d*6) δ (ppm) ^1H: 10.48 (s,1H), 10.10 (s,1H), 7.50 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.91 (m,1H), 6.75-6.86 (m,3H), 6.64-6.74 (m,2H), 4.54 (d, J = 15.1 Hz, 1H), 4.14 (d, J = 15.1 Hz, 1H), 4.07 (t, J = 6.1 Hz, 1H), 3.64 (s,3H), 3.54 (s,2H), 3.43 (s,2H), 2.98-3.10 (m,2H). MS: (calc.) 495.6; (obt.) 496.2 $(MH)^+$.

LRMS (ESI): (calc.) 495.6; (found) 496.2 $(MH)^+$.

Step 7: (*S*)-2-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)ethylthio)acetic acid (**76**)

[0160] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **75** for compound **4** to afford **76** (34 mg, 35%) as a light orange foam. (DMSO-*d*6) δ (ppm) ^1H: 12.65 (br s,1H), 10.48 (s,1H), 10.12 (s,1H), 7.51 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 6.92 (m,1H), 6.75-6.86 (m,3H), 6.64-6.74 (m,2H), 4.54 (d, J = 15.1 Hz, 1H), 4.14 (d, J = 15.1 Hz, 1H), 4.08 (t, J = 6.3 Hz, 1H), 3.45 (s,2H), 3.43 (s,2H), 2.98-3.10 (m,2H). LRMS (ESI): (calc.) 481.6; (found) 482.4 $(MH)^+$.

Scheme 6



Example 56

N-(biphenyl-3-yl)-6-(2-(2-(pyridin-2-yl)ethylthio)acetamido)hexanamide (77)

Step 1: *N*-(biphenyl-3-yl)-6-(2-(2-(pyridin-2-yl)ethylthio)acetamido)hexanamide (**77**)

[0161] To a solution of **3a** (108 mg, 0.302 mmol) in THF (3 mL) was added 2-(pyridin-2-yl)ethanethiol (50 mg, 0.333 mmol) and NaH (0.048 g, 1.21 mmol, 60% dispersion in oil). The resulting solution was stirred at room temperature for 2 h before being diluted with brine, basified to pH = 10 with NaOH solution, and extracted with EtOAc. The organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of MeOH (0-25%) in AcOEt to afford **77** (44 mg, 32%) as a light yellow oil. (DMSO-*d*6) δ (ppm) ^{1}H: 10.18 (s,1H), 8.68 (s,1H), 8.22 (s,1H), 8.14 (s,1H), 7.94-7.84 (m,1H), 7.84-7.74 (m,3H), 7.72-7.63 (m,2H), 7.62-7.53 (m,2H), 7.54-7.43 (m,2H), 7.43-7.36 (m,1H), 3.60 (s,2H), 3.28 (m,2H), 3.24-3.10 (m,4H), 2.60-2.50 (m,2H), 1.90-1.76 (m,2H), 1.72-1.60 (m,2H), 1.60-1.48 (m,2H). LRMS (ESI): (calc.) 461.6; (found) 462.4 $(MH)^+$.

Example 57

N-(biphenyl-3-yl)-6-(2-(2-(diethylamino)ethylthio)acetamido)hexanamide (78)

Step 1: *N*-(biphenyl-3-yl)-6-(2-(2-(diethylamino)ethylthio)acetamido)hexanamide (**78**)

[0162] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting 2-(diethylamino)ethanethiol for methyl 2-mercaptoacetate to afford **78** (48 mg, 35%) as a light yellow solid. ^{1}H NMR: ($CDCl_3$) δ (ppm): 7.92 (br s,1H), 7.82

(s,1H), 7.60-7.50 (m,3H), 7.44-7.28 (m,6H), 3.29 (q, J = 13.1,6.7 Hz, 2H), 3.23 (s,2H), 2.73-2.63 (m,4H), 2.58 (q, J = 14.1,7.0 Hz, 4H), 2.41 (t, J = 7.2 Hz, 2H), 1.83-1.73 (m,2H), 1.64-1.54 (m,2H), 1.80-1.40 (m,2H), 1.04 (t, J = 7.1 Hz, 6H). LRMS (ESI): (calc.) 455.7; (found) 456.3 $(MH)^+$.

Example 58

4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)butanoic acid (82)

Step 1: *S*-2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethyl ethanethioate (**79**).

[0163] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting methyl 2-mercaptoacetate for thioacetic acid to afford **79** (383 mg, 96%) as a light grey solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.99 (s,1H), 8.12 (m,1H), 7.94 (s,1H), 7.65-7.57 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.42-7.36 (m,2H), 7.35-7.31 (m,1H), 3.59 (s,2H), 3.37 (s,3H), 3.08 (q, J = 12.7,6.7 Hz, 2H), 2.36 (m,2H), 1.69-1.59 (m,2H), 1.51-1.42 (m,2H), 1.40-1.30 (m,2H). LRMS (ESI): (calc.) 398.5; (found) 399.0 $(MH)^+$.

Step 2: *N*-(biphenyl-3-yl)-6-(2-mercaptoacetamido)hexanamide (**80**)

[0164] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **79** for methyl ester **4** to afford **80** (323 mg, 94%) as a orange solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.99 (s,1H), 8.01 (m,1H), 7.94 (s,1H), 7.65-7.56 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.43-7.36 (m,2H), 7.35-7.31 (m,1H), 3.14-3.08 (m,4H), 2.75 (t, J = 7.8 Hz, 1H), 2.36 (t, J = 7.4 Hz, 2H), 1.70-1.59 (m,2H), 1.53-1.42 (m,2H), 1.40-1.31 (m,2H). LRMS (ESI): (calc.) 356.5; (found) 357.2 $(MH)^+$.

Step 3: methyl 4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)butanoate (**81**)

[0165] Following the same procedure as described for compound **77** (step 1, scheme 6, example 66) but substituting methyl 4-bromobutanoate for compound **3a** and compound **80** for 2-(pyridin-2-yl)ethanethiol to afford **81** (40 mg, 22%) as a light yellow solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.98 (s,1H), 7.99 (m,1H), 7.94 (s,1H), 7.64-7.56 (m,3H), 7.49 (t, J = 7.8 Hz, 2H), 7.40 (t, J = 7.8 Hz, 2H), 7.35-7.31 (m,1H), 3.61 (s,3H), 3.11-3.07 (m,4H), 2.58 (t, J = 7.2 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.24 Hz, 2H), 1.78-1.85 (m,2H), 1.70-1.60 (m,2H), 1.52-1.43 (m,2H), 1.40-1.30 (m,2H). LRMS (ESI): (calc.) 456.6; (found) 457.0 $(MH)^+$.

Step 4: 4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)butanoic acid (**82**)

[0166] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **81** for methyl ester **4** to afford **82** (15 mg, 61%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 12.11 (br s,1H), 9.99 (s,1H), 8.00 (t, J = 5.5 Hz, 1H), 7.95 (s,1H), 7.65-7.57 (m,3H), 7.49 (t, J = 7.5 Hz, 2H), 7.43-7.36 (m,2H), 7.35-7.31 (m,1H), 3.14-3.06 (m,4H), 2.59 (t, J = 7.2 Hz, 2H), 2.40-2.30 (m,4H), 1.84-1.73 (m,2H), 1.70-1.60 (m,2H), 1.54-1.42 (m,2H), 1.40-1.31 (m,2H). LRMS (ESI): (calc.) 442.6; (found) 443.4 $(MH)^+$.

Example 59

N-(biphenyl-3-yl)-6-(2-(4-(methylsulfinyl)benzylthio)acetamido)hexanamide (84)

Step 3: N-(biphenyl-3-yl)-6-(2-(4-(methylthio)benzylthio)acetamido)hexanamide (**83**)

[0167] Following the same procedure as described for compound **77** (step 1, scheme 6, example 56) but substituting (4-thiomethyl)-benzyl chloride for compound **3a** and compound **80** for 2-(pyridin-2-yl)ethanethiol to afford **83** (75 mg, 30%) as a light yellow solid. (DMSO-*d*6) δ (ppm) ^{1}H: 9.99 (s,1H), 7.98 (t, J = 5.5 Hz, 1H), 7.94 (s,1H), 7.64-7.57 (m,3H), 7.52-7.46 (m,2H), 7.43-7.36 (m,2H), 7.35-7.31 (m,1H), 7.29-7.24 (m,2H), 7.24-7.19 (m,2H), 3.77 (s,2H), 3.09 (q, J = 12.5,6.5 Hz, 2H), 3.01 (s,2H), 2.48 (s,3H), 2.37 (t, J = 7.4 Hz, 2H), 1.70-1.60 (m,2H), 1.51-1.43 (m,2H), 1.41-1.30 (m,2H). LRMS (ESI): (calc.) 492.7; (found) 493.2 $(MH)^+$.

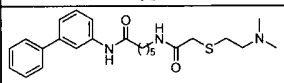
Step 4: *N*-(biphenyl-3-yl)-6-(2-(4-(methylsulfinyl)benzylthio)acetamido)hexanamide (**84**)

[0168] Following the same procedure as described for compound **7** (step 6, scheme 1, example 2) but substituting compound **83** for compound **5** to afford **84** (24 mg, 32%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 10.32 (s,1H), 8.50 (m,1H), 8.00 (s,1H), 7.70 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.4 Hz, 2H), 7.56-7.44 (m,4H), 7.41-7.35 (m,2H), 7.29-7.34 (m,1H), 4.36 (d, J = 12.7 Hz, 1H), 4.27-4.20 (m,1H), 4.10 (d, J = 12.9 Hz, 1H), 3.77 (d, J = 13.3 Hz, 1H), 3.48 (d, J = 11.4 Hz, 1H), 3.18 (d, J = 5.3 Hz, 2H), 3.16-3.08 (m,2H), 2.79 (s,3H), 2.39 (t, J = 7.0 Hz, 2H), 1.70-1.57 (m,2H), 1.54-1.42 (m,2H), 1.40-1.30 (m,2H). LRMS (ESI): (calc.) 524.7; (found) 525.1 $(MH)^+$.

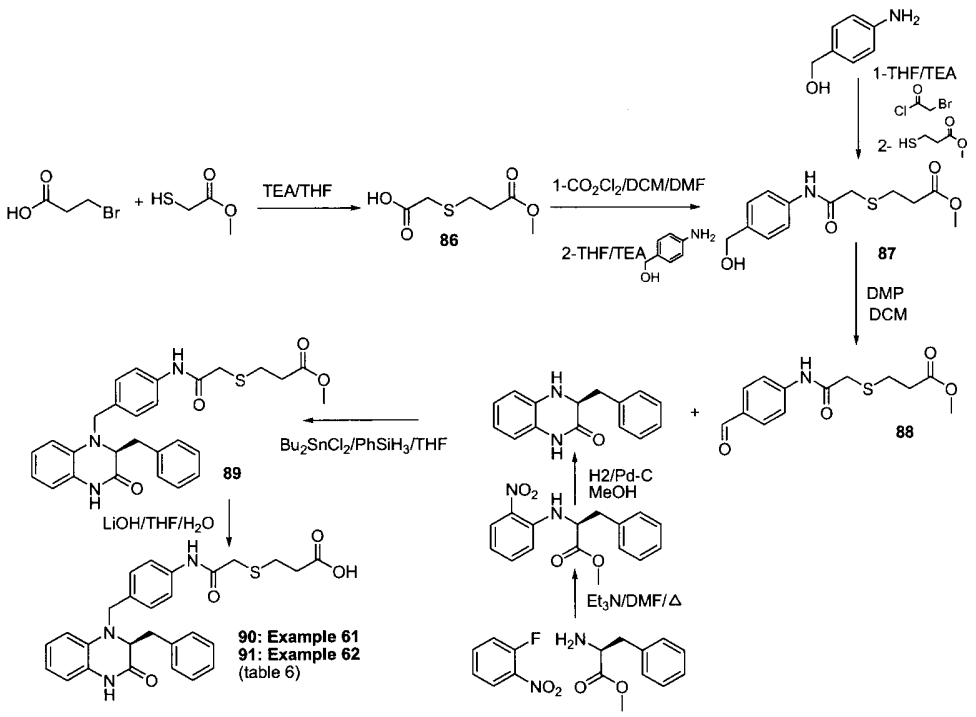
Example 60

[0169] Example 60 describes the preparation of compound **85** using the same procedures as described Example 57. Characterization data are presented in a Table 5.

Table 5

Ex	Cpd	R	Name	Characterization	Scheme
60	85		*N*-(biphenyl-3-yl)-6-(2-(2-(dimethylamino)ethylthio)-acetamido)-hexanamide	^{1}H NMR: (MeOD) δ (ppm): 7.87 (m,1H), 7.64-7.60 (m,2H), 7.57-7.53 (m,1H), 7.48-7.43 (m,2H), 7.42-7.32 (m,3H), 3.26 (t, J = 6.8 Hz, 2H), 3.21 (s,2H), 2.79-2.73 (m,2H), 2.69-2.63 (m,2H), 2.45 (t, J = 7.4 Hz, 2H), 2.35 (s,6H), 1.84-1.74 (m,2H), 1.67-1.57 (m,2H), 1.53-1.43 (m,2H) LRMS (ESI): (calc.) 427.6; (found) 428.4 $(MH)^+$.	6 Step 1 Ex57

Scheme 7



Example 61

(*S*)-3-(2-(4-((2-benzyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)-2-oxoethylthio)propanoic acid (90)

Procedure 1: methyl 3-(2-(4-(hydroxymethyl)phenylamino)-2-oxoethylthio)propanoate (**87**)

Step 1: 2-(3-methoxy-3-oxopropylthio)acetic acid (**86**)

[0170] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting 3-bromopropanoic acid for compound **3b** to afford **86** (942 mg, 88%) as a light yellow oil. LRMS (ESI): (calc.) 178.2; (found) 179.2 $(MH)^+$.

Step 2: methyl 3-(2-(4-(hydroxymethyl)phenylamino)-2-oxoethylthio)propanoate (**87**)

[0171] To a solution of **86** (665 mg, 3.73 mmol) in CH_2Cl_2 (4 mL) was added oxalyl chloride (2.24 mL, 4.48 mmol) and DMF (3 drops). The reaction was stirred for 30 min at room temperature. To this mixture was added drop wise a solution of 4-amino-benzyl alcohol (3.73 mmol) in THF (10 mL) and triethylamine (12 mmol). The mixture was stirred at room temperature for another 15 min prior to dilution with brine, and extraction with EtOAc. The organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (25-100%) in Hexane to afford **87** (264 mg, 25%) as a light yellow foam. LRMS (ESI): (calc.) 283.2; (found) 284.2 $(MH)^+$.

Procedure 2: methyl 3-(2-(4-(hydroxymethyl)phenylamino)-2-oxoethylthio)propanoate (**87**)

Step 1: methyl 3-(2-(4-(hydroxymethyl)phenylamino)-2-oxoethylthio)propanoate (**87**)

[0172] Following the same procedure as described for compound **69** (step 2-3, scheme 5, example 55) but substituting (4-aminophenyl)methanol for compound **67** to afford **87** (1.15 g, 45%) as a yellow oil. (DMSO-*d*6) δ (ppm) ^{1}H: 10.01 (s, 1H), 7.49 (d, J=8.6 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 5.10 (t, J=5.7 Hz, 1H), 4.42 (d, J=5.7 Hz, 2H), 3.59 (s, 3H), 3.30 (s, 2H), 2.83 (t, J=7.2 Hz, 2H), 2.67 (t, J=7.0 Hz, 2H). LRMS (ESI): (calc.) 283.2; (found) 284.2 $(MH)^+$.

Step 3: methyl 3-(2-(4-formylphenylamino)-2-oxoethylthio)propanoate (**88**)

[0173] Following the same procedure as described for compound **71** (step 5, scheme 5, example 55) but substituting compound **87** for compound **70** to afford **88** (320 mg, 67%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 10.49 (s, 1H), 9.85 (s, 1H), 7.85 (d, J=8.6 Hz, 2H), 7.77 (d, J=8.6 Hz, 2H), 3.58 (s, 3H), 3.37 (s, 2H), 2.84 (t, J=6.6 Hz, 2H), 2.67 (t, J=6.8 Hz, 2H).

Synthesis of (*S*)-3-benzyl-3,4-dihydroquinoxalin-2(1H)-one. Step 1 and 2:

Step 1: (S)-methyl 2-(2-nitrophenylamino)-3-phenylpropanoate

[0174] To a solution of (*S*)-methyl 2-amino-3-phenylpropanoate (3.26 g, 23.2 mmol) and 1-fluoro-3-nitrobenzene (5 g, 23.2 mmol) in DMF (40 mL) were added triethyl amine (8.08 mL, 58.0 mmol). The reaction was heated at 100°C for 16 hours and then the solvent was evaporated. EtOAc was added (30 mL), and the organic layer was washed with water. The organic extracts were dried (Na_2SO_4), filtered, and evaporated to afford the crude methyl ester as an orange gum. The crude was used in the next step without further purification.

Step 2: (*S*)-3-benzyl-3,4-dihydroquinoxalin-2(1H)-one

[0175] Following the same procedure as described for compound **74** (step 3, scheme 5, example 55) but substituting (*S*)-methyl 2-(2-nitrophenylamino)-3-phenylpropanoate for **73** to afford (S)-3-benzyl-3,4-dihydroquinoxalin-2(1H)-one (130 mg, 12% after two steps) as a colourless oil. (DMSO-*d*6) δ (ppm) ^{1}H: 10.20 (s, 1H), 7.30 – 7.22 (m, 2H), 7.18 – 7.16 (m, 3H), 6.74 – 6.70 (m, 1H), 6.65 (d, J=7.7 Hz, 2H), 6.56 – 6.51 (m, 1H), 5.84 (s, 1H), 4.01 – 3.97 (m, 1H), 2.94 – 2.81 (m, 2H).

Step 4: (*S*)-methyl 3-(2-(4-((2-benzyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)-2-oxoethylthio)propanoate (**89**)

[0176] Following the same procedure as described for compound **75** (step 6, scheme 5, example 55) but substituting (S)-3-benzyl-3,4-dihydroquinoxalin-2(1H)-one for compound **73** and compound **88** for **71** to afford **89** (90 mg, 36%) as a light yellow solid. (DMSO-*d*6) δ (ppm) ^{1}H: 10.41 (s, 1H), 10.04 (s, 1H), 7.47 (d, J=8.6 Hz, 2H), 7.22 - 7.13 (m, 3H), 7.09 (d, J=8.4 Hz, 2H), 7.05 - 7.03 (m, 2H), 6.82 - 6.74 (m, 2H), 6.67 - 6.63 (m, 2H), 4.40 (d, J=14.7 Hz, 1H), 4.01 - 3.97 (m, 2H), 3.57 (s, 3H), 3.28 (s, 2H), 2.83 - 2.75 (m, 3H), 2.70 - 2.64 (m, 3H). MS: 503.2 (calc) 504.2 (found)

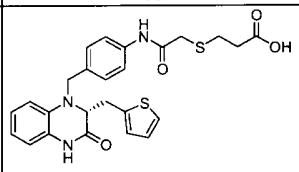
Step 5: (S)-3-(2-(4-((2-benzyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)-2-oxoethylthio)propanoic acid (**90**)

[0177] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **89** for compound **4** to afford **90** (50 mg, 64%) as a yellow solid. (DMSO-*d*6) δ (ppm) ^{1}H: 12.22 (br s, 1H), 10.41 (s, 1H), 10.04 (s, 1H), 7.47 (d, J=8.4 Hz, 2H), 7.22 - 7.13 (m, 3H), 7.09 (d, J=8.0 Hz, 2H), 7.04 (d, J=7.0 Hz, 2H), 6.82 - 6.74 (m, 2H), 6.67 - 6.63 (m, 2H), 4.39 (d, J=14.7 Hz, 1H), 4.01 - 3.97 (m, 2H), 3.28 (s, 2H), 3.11 - 3.06 (m, 1H), 2.78 (t, J=7.2 Hz, 2H), 2.70 - 2.66 (m, 1H), 2.55 (t, J=6.9 Hz, 2H). LRMS (ESI): (calc.) 489.2; (found) 490.4 $(MH)^+$.

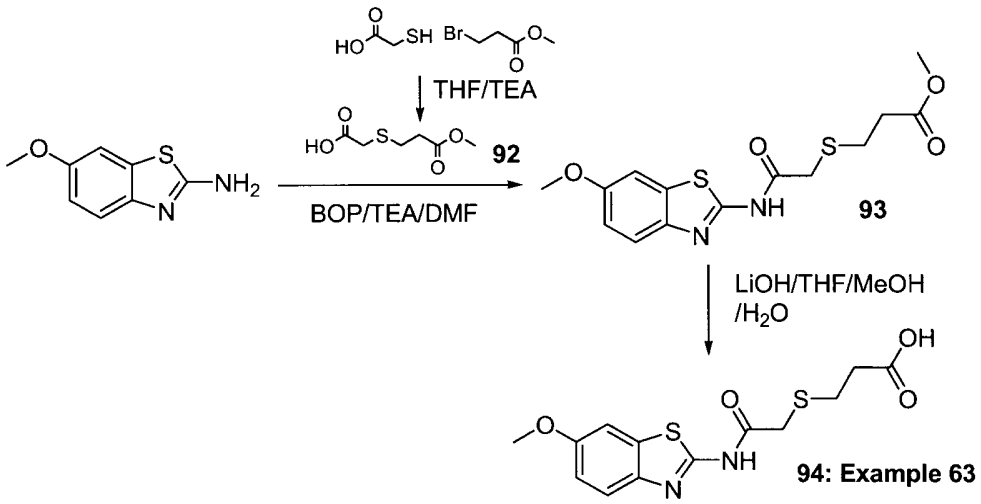
Example 62

[0178] Example 62 describe the preparation of compound **91** using the same procedures as described for compound **90** in Example 61. Characterization data are presented in a Table 6.

Table 6

Ex	Cpd	R	Name	Characterization	Scheme
62	91		(*R*)-3-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)-phenylamino-)ethylthio)-propanoic acid	(DMSO-*d*6) δ (ppm) ^{1}H: 10.24 (s,1H), 10.09 (s,1H), 7.20-7.40 (m,2H), 6.80-7.10 (m,3H), 6.25-6.70 (m,6H), 4.26 (m,1H), 3.84 (m,2H), 3.05 (m,2H), 2.78 (m,2H), 2.16-2.34 (m,2H), 1.76-1.86 (m,2H) LRMS (ESI): (calc.) 495.6; (found) 496.2$(MH)^+$.	7

Scheme 8



Example 63

3-(2-(6-methoxybenzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid (94)

Step 1: 2-(3-methoxy-3-oxopropylthio)acetic acid (**92**)

[0179] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting methyl 3-bromopropanoate for compound **3b** and 2-mercaptoacetic acid for methyl 2-mercaptoacetate to afford **92** (10.1 mg, 95%) of the title compound as colorless oil.

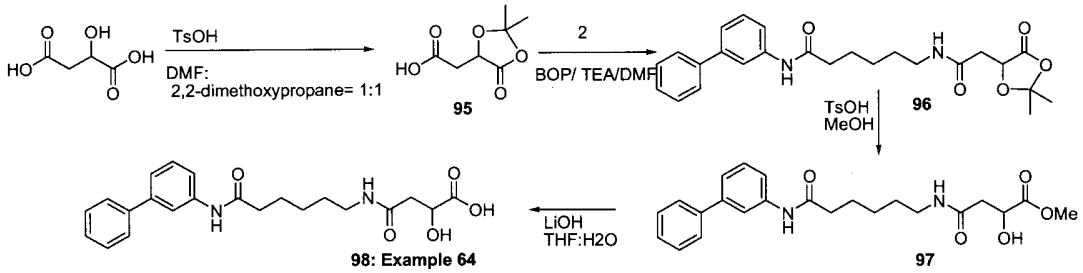
Step 1: methyl 3-(2-(6-methoxybenzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoate (**93**)

[0180] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting 6-methoxybenzo[d]thiazol-2-amine for biphenyl-3-amine and using acid **92** to afford **93** (250 mg, 51%) as white solid.

Step 2: 3-(2-(6-methoxybenzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid (**94**)

[0181] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **93** for compound **4** to afford **94** (30 mg, 13%) as a white solid. (DMSO-*d*6) δ (ppm) ^{1}H: 12.31 (br s, 1H), 7.62 (d, J=8.7 Hz, 1H), 7.56 (d, J=2.3 Hz, 1H), 7.01 (dd, J=8.8, 2.5 Hz, 1H), 3.80 (s, 3H), 3.46 (s, 2H), 2.80 (t, J=7.2 Hz, 2H), 2.57 (t, J=6.9 Hz, 2H).

Scheme 9



Example 64

4-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-hydroxy-4-oxobutanoic acid (98)

Step 1: 2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (**95**)

[0182] To a solution of DL-malic acid (4 g, 29.8 mmol) in DMF:2,2'-dimethoxypropane(1:1, 35 ml) was added *p*-TsOH (285 mg,1.5mmol). The reaction was stirred for 4h at room temperature. EtOAc was added, and the organic layer was washed with 2M aqueous HCl (pH=2). The organic extracts were dried (Na_2SO_4), filtered, and evaporated to afford **95** (5.2 g, 99%) as a white solid. LRMS (ESI): (calc.) 174.05; (found) 197.00 $(MNa)^+$.

Step 2: *N*-(biphenyl-3-yl)-6-(2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetamido)hexanamide (**96**)

[0183] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting compound **2** for biphenyl-3-amine and using acid **95** to afford **96** (87 mg, 63 %) as a clear translucent oil. LRMS (ESI): (calc.) 438.22; (found) 461.51 $(MNa)^+$.

Step 3: methyl 4-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-hydroxy-4-oxobutanoate (**97**)

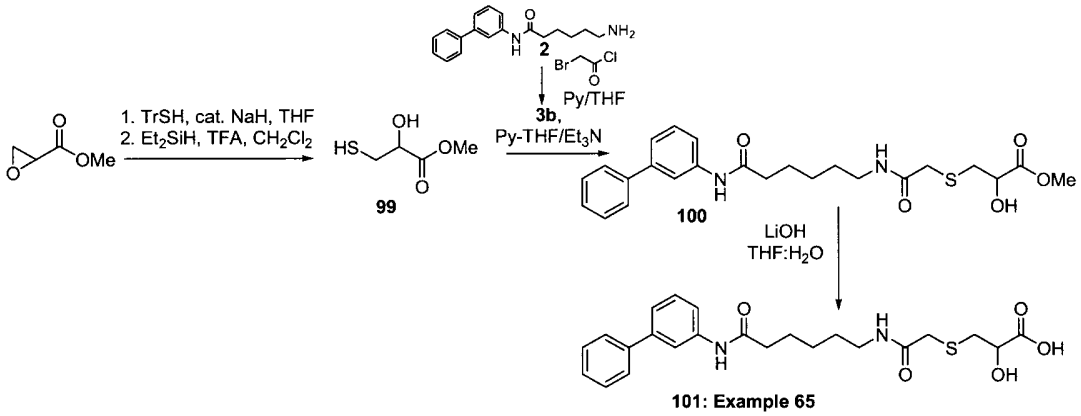
[0184] To a solution of **96** (87 mg) in methanol was added p-TsOH (86 mg, 0.2 mmol). The reaction was stirred 3h at room temperature and the concentrated in vacuo. The residue was purified by silica gel column chromatography with gradient of MeOH (50-90%) in AcOEt and then MeOH (10%) in EtOAc to afford **97** (28 mg, 35%) as a clear translucent oil. ($CDCl_3$)

δ (ppm) ^{1}H: 8.08-8.01(m,1H), 7.81(s,1H), 7.56-7.50(m,3H), 7.41-7.29(m,5H), 6.51(s,1H), 4.49(s,1H), 3.73(s,3H), 3.67(s,1H), 3.23(m,2H), 2.74-2.61(m,2H), 2.38(t,2H,J=7Hz), 1.72(2,H), 1.52(s,2H), 1.37(m,2H). LRMS (ESI): (calc.) 412.2; (found) 413.3 $(MH)^+$.

Step 4: 4-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-hydroxy-4-oxobutanoic acid (**98**)

[0185] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **97** for compound **4** to afford **98** (25 mg, 99 %) as a white solid. (acetone-*d*6) δ (ppm) ^{1}H: 9.05(s,1H), 7.86(s,1H), 7.50- Hz), 2.73(s,1H), 2.49(m,2H), 2.26(t,2H,J=7Hz), 1.59(m,2H), 1.42(m,2H), 1.27(m,2H). LRMS (ESI): (calc.) 398.18; (found) 399.2 $(MH)^+$.

Scheme 10



Example 65

3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-hydroxypropanoic acid (101)

Step 1: methyl 2-hydroxy-3-mercaptopropanoate (**99**)

[0186] To a suspension of triphenylmethane thiol (1.35 g, 4.9 mmol) and NaH (20 mg, 0.49 mmol) in THF (20 ml) was slowly added methyl glycidyl ester (500 mg, 4.9 mmol). The reaction was stirred at 0°C and then warmed to 23°C over 20 minutes. The reaction mixture was quenched with sat. aqueous NH_4Cl (20 ml) and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (10-20%) in hexane to afford the desired compound (950 mg, 51%) as a clear translucent oil. LRMS (ESI): (calc.) 378.13; (found) 401.29 $(MH)^+$.

[0187] To a solution of ester (950 mg, 2.5 mmol) and Et_3SiH (441 µl, 2.76 mmol) in CH_2Cl_2 (12 ml) was added TFA (970 µl, 5 equiv, 12.6 mmol). The reaction was stirred for 30 minutes at room temperature. The reaction mixture was quenched with $NaHCO_3$ (ss) (10 ml) and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (10-

50%) in hexane to afford **99** (299 mg, 87%) as a clear translucent oil. LRMS (ESI): (calc.) 136.2; (found) $(MH)^+$.

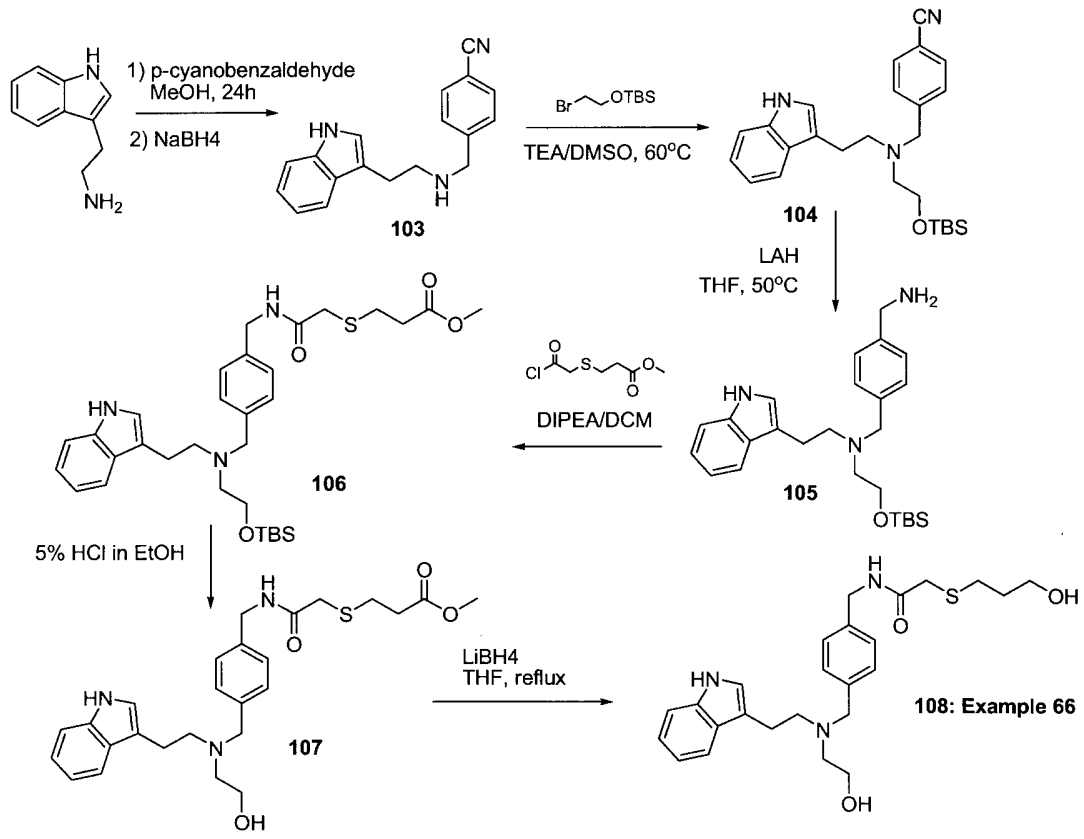
Step 2: methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-hydroxypropanoate (**100**)

[0188] To a solution of **2** (100 mg, 0.35 mmol) in pyridine (71 mL):THF (1ml) was added bromoacetyl chloride (29 ml, 0.35 mmol). The reaction was stirred at 0°C and then warmed to 23°C over 15 minutes. After the mixture was cooled back to 0°C followed by the sequential addition of methyl 3-mercapto-2-hydroxy propionate (48 mg, 0.35 mmol) and Et_3N (123 ml, 0.89 mmol). The reaction was stirred for another 20 minutes at room temperature and extracted from brine with EtOAc. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (50-100%) in hexane to afford **100** (36 mg, 22%) as a clear translucent oil. (acetone-*d6*) δ (ppm) ^1H: 9.20(s,1H), 8.01(s,1H), 7.63-7.61(m,3H), 7.47-7.43(m,3H), 7.37-7.33(m,3H), 4.41(dd,1H,J=4,6Hz), 3.70(s,3H), 3.28-3.22(m,2H), 3.03(dd,1H,J=6,14Hz), 2.93(dd,1H,J=6,14Hz), 2.87(d,1H,J=12Hz), 2.42(t,2H,J=7Hz), 1.73(m,2H), 1.57(m,2H), 1.43(m,2H). LRMS (ESI): Ccalc.) 458.1; (found) 459.5 (MH^+).

Step 3: 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-hydroxypropanoic acid (101)

[0189] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **100** for compound **4** to afford **101** (34 mg, 98 %) as a solid. (MeOD-*d4*) δ (ppm) ^1H: 7.85(s,1H), 7.58-7.52(m,3H), 7.42-7.34(m,5H), 4.29(m, 1H), 3.31-3.24(m,5H), 3.03-2.99(dd,1H,J=5,14Hz), 2.87-2.83(dd,1H,J=5,14Hz), 2.43(m,2H), 1.88(m,2H), 1.61(m,2H), 1.46-1.41(m,2H). LRMS (ESI): (calc.) 444.1; (found) 451.5 (MLi^+).

Scheme 11



Example 66

N-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)benzyl)-2-(3-hydroxypropylthio)acetamide (108)

Step 1: 4-((2-(1H-indol-3-yl)ethylamino)methyl)benzonitrile (**103**)

[0190] To a solution of tryptamine (1.02g, 6.28 mmol) in 25 mL of MeOH was added p-cyanobenzaldehyde (841mg, 6.41 mmol). The mixture was stirred at room temperature for 60h. Sodium borohydride (238mg, 6.28 mmol) was added and then the solution was stirred for another 1h at room temperature. The reaction mixture was quenched with aqueous NH_4Cl (ss) (20 ml) and extracted with ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4), filtered, and evaporated to give **103** in quantitative yield as a brown oil which was used for the next step without further purification. LRMS (ESI): (calc) 275.1 (found) 276.2 (MH^+).

Step 2:4-((2-(1H-indol-3-yl)ethyl)(2-(tert-butyldimethylsilyloxy)ethyl)amino)methyl)benzonitrile (**104**)

[0191] To a crude mixture of **103** (1.73 g, 6.28 mmol) in DMSO (10 mL) was added DIPEA (1.40 mL, 8.00 mmol) and (2-bromoethoxy)-*tert*-butyldimethylsilane (1.67g, 7.00 mmol). The reaction was stirred at 55°C during 48h. The mixture was quenched with water and extracted with DCM. The organic extracts were washed with water, dried (Na_2SO_4),

filtered, and evaporated. The residue was purified by silica gel column chromatography with EtOAc (40%) in hexane to afford **104** (2.09g, 77% after two steps) as a solid. LRMS (ESI): (calc.) 433.3; (found) 434.4$(MH)^+$.

Step 3:N-(2-(1H-indol-3-yl)ethyl)-N-(4-(aminomethyl)benzyl)-2-(tert-butyldimethylsilyloxy)ethanamine (**105**)

[0192] To a solution of **104** (690 mg, 1.59 mmol) in THF (15 mL) was added LAH (0.121 g, 3.19 mmol). The mixture was stirred for 1h at 50°C. The mixture was quenched with aqueous solution of sodium sulfate (ss), filtered through a pad of celite and extracted with DCM. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with MeOH (15%) in DCM with 1% of ammonium hydroxide to afford **105** (340 mg, 49%) as a yellow oil. LRMS (ESI): (calc.) 437.29; (found) 438.4 $(MH)^+$.

Step 4: methyl3-(2-(4-(((2-(1H-indol-3-yl)ethyl)(2-(tert-butyldimethylsilyloxy)ethyl)amino)methyl)benzylamino)-2-oxoethylthio)propanoate (**106**)

[0193] To a solution of **105** (340 mg, 0.778 mmol) in DCM (5 mL) was added DIPEA (0.23 mL, 1.3 mmol) and 3-chlorocarbonylmethylsulfanyl-propionic acid methyl ester (0.196 g, 1.0 mmol) in DCM (2 mL). The reaction mixture was stirred at room temperature for 5 minutes, then poured into a $Na(HCO_3)$ (ss) and extracted with DCM. The organic extracts were washed with water, dried (Na_2SO_4), filtered, and evaporated to afford **106** (471 mg, 100%) which was used for the next step without purification. LRMS (ESI): (calc.) 597.3; (found) 598.5 $(MH)^+$.

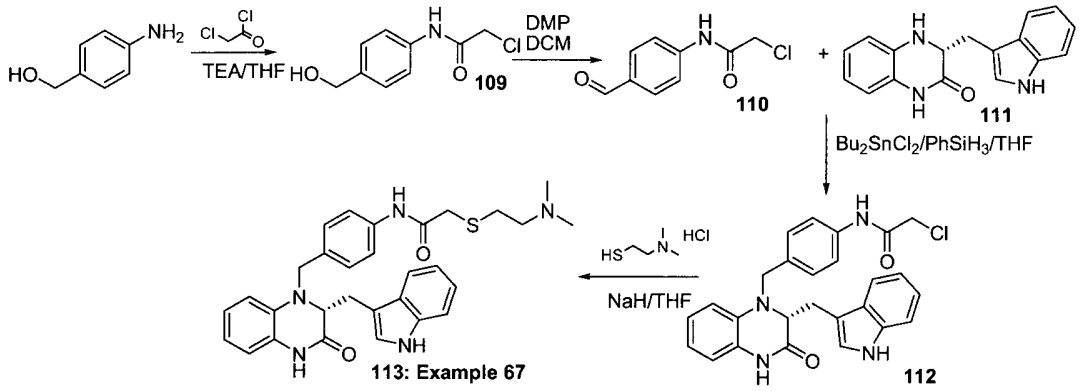
Step 5: methyl3-(2-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)benzylamino)-2-oxoethylthio)propanoate (**107**)

[0194] To a solution of **106** (465 mg, 0.778 mmol) in ethanol (5 mL) was added HCl (1 mL, 5%). The mixture was stirred 1 hour a room temperature. The reaction mixture was diluted in EtOAc and washed with $Na(HCO_3)$ (ss), water and brine. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with MeOH (15%) in DCM to afford **107** (0.252 g, 67%). LRMS (ESI): (calc.) 483.2; (found) 484.4 $(MH)^+$.

Step 6: *N*-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)benzyl)-2-(3-hydroxypropylthio)acetamide (**108**)

[0195] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **107** for compound **4** to afford **108** (39 mg, 11%) as a solid. (MeOD-*d4*) δ (ppm) ^1H: 7.42-7.38 (m, 3H), 7.34-7.32 (m, 3H), 7.11-7.08 (m, 2H), 7.00-6.96 (m, 1H), 4.40 (s, 2H), 4.29 (s, 2H), 3.87-3.84 (m, 2H), 3.60 (t, J = 5.6Hz, 2H), 3.36-3.30 (m, 2H, overlap with MeOH), 3.28-3.15 (m, 6H), 2.66 (t, J = 7.2Hz, 2H), 1.82-1.75 (m, 2H). LRMS (ESI): (calc.) 455.2; (found) 456.4 $(MH)^+$.

Scheme 12



Example 67

(*R*)-*N*-(4-((2-((1H-indol-3-yl)methyl)-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenyl)-2-(2-(dimethylamino)ethylthio)acetamide (113)

Step 1: 2-chloro-*N*-(4-(hydroxymethyl)phenyl)acetamide (**109**)

[0196] Following the same procedure as described for compound **68** (step 2, scheme 5, example 55) but substituting (4-aminophenyl)methanol for compound **67** and 2-chloroacetyl chloride for 2-bromoacetyl chloride to afford **109** (850 mg, 66 %) as a yellow solid. (DMSO-*d6*) δ (ppm) ^{1}H: 10.23 (s, 1H), 7.51 (d, J=8.4 Hz, 2H), 7.25 (d, J=8.1 Hz, 2H), 5.11 (t, J=5.5 Hz, 1H), 4.43 (d, J=4.9 Hz, 2H), 4.23 (s, 2H).

Step 2: 2-chloro-*N*-(4-formylphenyl)acetamide (**110**)

[0197] Following the same procedure as described for compound **65** (step 5, scheme 5, example 44) but substituting compound **109** for **70** to afford **110** (380 mg, 86 %) as a yellow solid. (DMSO-*d6*) δ (ppm): 10.68 (s, 1H), 9.87 (s, 1H), 7.87 (d, J=8.6 Hz, 2H), 7.78 (d, J=8.5 Hz, 2H), 4.31 (s, 2H).

Synthesis (*R*)-3-((1H-indol-3-yl)methyl)-3,4-dihydroquinoxalin-2(1H)-one (111)

[0198] Following the same procedure as described for (S)-3-benzyl-3,4-dihydroquinoxalin-2(1H)-one (step 1 and 2, scheme 7, example 61) but substituting (*R*)-methyl 2-amino-3-(1H-indol-3-yl)propanoate for (*S*)-methyl 2-amino-3-phenylpropanoate to afford **111** (550 mg, 51 %) as a clear oil. (DMSO-*d6*) δ (ppm): 10.84 (s, 1H), 10.19 (s, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.10 (s, 1H), 7.04 (td, J=7.0, 1.0 Hz, 1H), 6.94 (td, J=7.0, 1.0 Hz, 1H), 6.73 – 6.63 (m, 3H), 6.56 – 6.51 (m, 1H), 5.74 (s,1H), 4.01 – 3.99 (m, 1H), 3.10 – 2.89 (m, 2H).

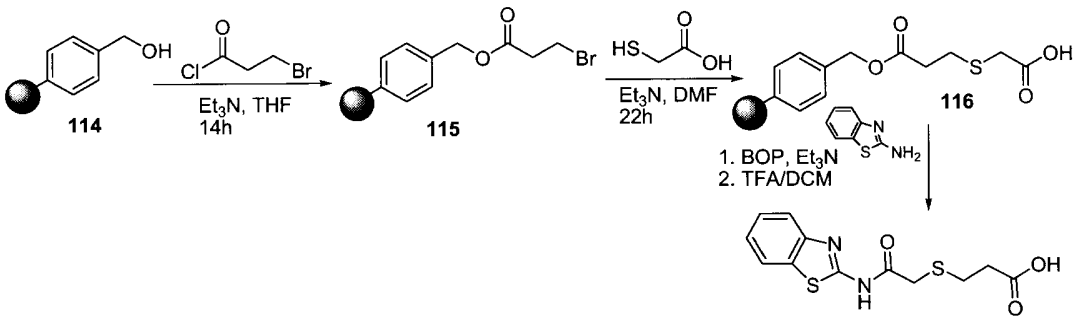
Step 3: (*R*)-*N*-(4-((2-((1H-indol-3-yl)methyl)-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenyl)-2-chloroacetamide (**112**)

[0199] Following the same procedure as described for compound **75** (step 6, scheme 5, example 55) but substituting compound **110** for **71** and aniline **111** for **74** to afford **112** (230 mg, 40%) as a colourless oil. LRMS (ESI): (calc.) 458.2; (found) 459.2 $(MH)^+$.

Step 4: (*R*)-*N*-(4-((2-((1H-indol-3-yl)methyl)-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenyl)-2-(2-(dimethylamino)ethylthio)acetamide (**113**)

[0200] Following the same procedure as described for compound **77** (step 1, scheme 6, example 56) but substituting compound **112** for compound **3a** and 2-(dimethylamino)ethanethiol hydrochloride for 2-(pyridin-2-yl)ethanethiol to afford **113** (20 mg, 16 %) as a white solid. (MeOD-*d4*) δ(ppm) ^{1}H: 7.38 - 7.32 (m, 4H), 7.09 (t, J=7.1 Hz, 1H), 6.99 - 6.80 (m, 6H), 6.76 - 6.71 (m, 2H), 4.36 (d, J=14.7 Hz, 1H), 4.11 - 4.07 (m, 1H), 3.72 (d, J=14.8 Hz, 1H), 3.36 (s, 2H), 2.98 - 2.93 (m, 2H), 2.87 - 2.81 (m, 4H), 2.45 (s, 6H). . LRMS (ESI): (calc.) 527.2; (found) 528.3 $(MH)^+$.

Scheme 13



117: Example 68
118-119: Example 69-70
(table 7)

Example 68

3-(2-(benzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid (117)

Step 1: polymer supported 3-bromopropionate (**115**)

[0201] Wang resin **114** (3g, 5.1 mmol, loading 1.7 mmol/g) was washed with dry THF, and then added 3-bromopropanoyl chloride (2.57 mL, 25.5 mmol), and triethylamine (3.55 mL, 25.5 mmol) in THF. The reaction was mechanically stirred gently for 14h at room temp. The mixture was filtered and washed with DMF(x2), MeOH, DMF (x2), MeOH, DMF, THF, MeOH. The resin was dried under N_2 then under vacuum overnight to afford **115** (3.87g, 80%).

Step 2: polymer supported 2-(3-(benzyloxy)-3-oxopropylthio)acetic acid (**116**)

[0202] The resin **115** (3.87g, 20.4 mmol) was swollen in DMF (100 ml), and then added 2-mercaptoacetic acid (7.1 ml, 102 mmol) and triethylamine (28.4 ml, 204 mmol). The misture was stirred gently at room temp for 22h. The resin was filtered and washed with DMF (x5), 5% AcOH in DCM (x5), MeOH, DMF (x5), DCM (x5), and diethyl ether (x2) and dried under vacuum to afford **116** in quantitative yield.

Step 3: 3-(2-(benzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid (**117**)

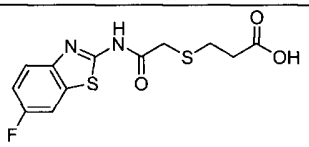
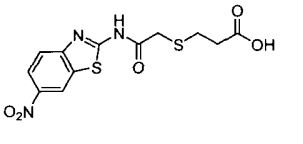
[0203] To resin **116** (500 mg, 0.3 mmol) in DMF (5 ml) was added BOP (402 mg, 0.9 mmol), triethylamine (169 uL, 1.2 mmol). The mixture was stirred for 35 minutes, and then

added 2-aminobenzothiazole (273 mg, 1.8 mmol). The reaction was stirred for another 16h. The resin was filtered and washed exhaustively with DMF, 5% AcOH/DCM, MeOH, DMF, DCM, MeOH, then with DCM. The resin was then treated with 1:1 mixture of trifluoroacetic acid and dichloromethane for 3h, and the filtrate was concentrated to afford **117** (5 mg, 5.5%) as beige solid after trituration from MeOH/H_2O and then from ether. (DMSO-*d6*) δ (ppm) ^{1}H: 7.96 (d, J=7.6 Hz, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.42 (t, J=7.0 Hz, 1H), 7.30 (t, J=7.2 Hz, 1H), 3.49 (s, 2H), 2.81 (t, J=7.2 Hz, 2H), 2.57 (t, J=7.2 Hz, 2H). LRMS (ESI): (calc.) 296.03; (found) 297.1 $(MH)^+$.

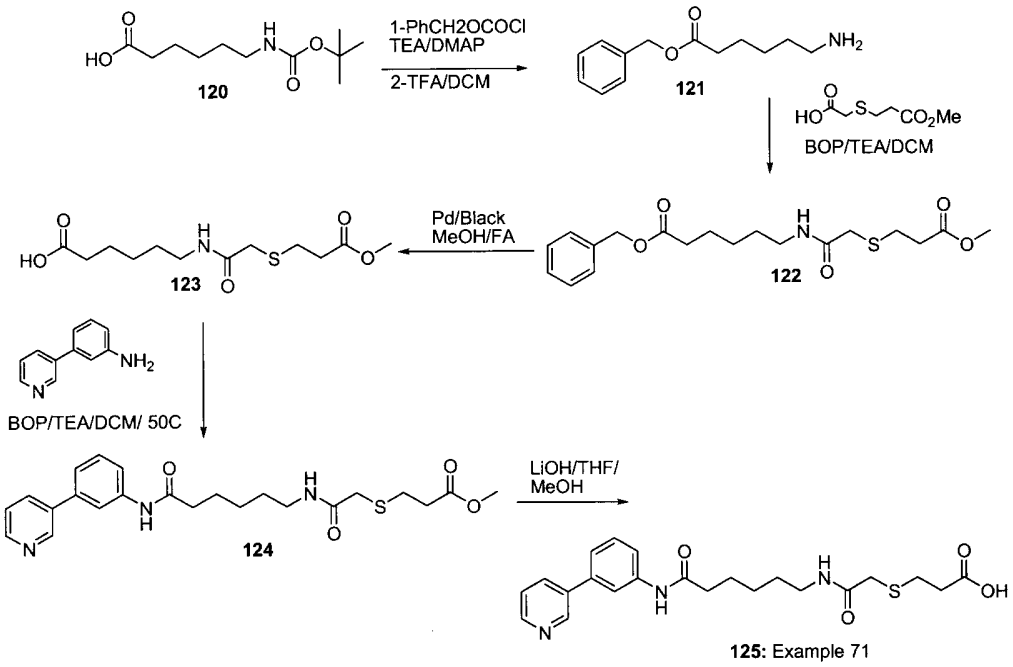
Example 69-70

[0204] Example 69-70 describe the preparation of compound **118-119** using the same procedures as described for compound **117** in Example 68. Characterization data are presented in a Table 7.

Table 7

Ex	Cpd	Structure	Name	Characterization	Scheme
69	118		3-(2-(6-fluorobenzo[d]-thiazol-2-ylamino)-2-oxoethylthio)-propanoic acid	(DMSO-*d6*) δ (ppm) ^{1}H: 12.45 (bs, 1H), 12.28 (bs, 1H), 7.88 (dd, J1=8.8 Hz, J2=2.4 Hz, 1H), 7.74 (q, J=4.5 Hz, 1H), 7.28 (td, J1=8.8 Hz, J2=2.4 Hz, 1H), 3.48 (s, 2H), 2.80 (t, J= 7.2 Hz, 2H), 2.57 (t, J= 7.2 Hz, 2H). LRMS (ESI): (calc.) 314.02; (found) 315.1 $(MH)^+$.	13 Step 1-3
70	119		3-(2-(6-nitrobenzo[d]-thiazol-2-ylamino)-2-oxoethylthio)-propanoic acid	(DMSO-*d6*) δ (ppm) ^{1}H: 12.88 (s, 1H), 12.28 (bs, 1H), 9.05 (d, J=2.4 Hz, 1H), 8.27 (dd, J1=9.0 Hz, J2=2.6 Hz, 1H), 7.89 (d, J=9.2 Hz, 1H), 3.53 (s, 2H), 2.81 (t, J=7.2 Hz, 2H), 2.57 (t, J=7.0 Hz, 2H). LRMS (ESI): (calc.) 341.0; (found) 342.0 $(MH)^+$.	13 Step 1-3

Scheme 14



Example 71

3-(2-oxo-2-(6-oxo-6-(3-(pyridin-3-yl)phenylamino)hexylamino)ethylthio)-propanoic acid (125)

Step 1: benzyl 6-aminohexanoate (**121**)

[0205] To a solution of **120** (5.0 g, 22 mmol) in DCM was added benzyl chloroformate (3.7 g, 3.34 mL, 22 mmol) at 0°C followed by triethylamine (9 ml, 65 mmol) and DMAP (cat. amount). The mixture was stirred at room temperature for 4 hour and then the solvent was evaporated. EtOAc was added, and the organic layer was washed with $NaHCO_3$ (ss) and brine. The organic extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of EtOAc (20-50%) in hexanes to afford the desired compound (3.2 g, 50%) as colorless oil.

[0206] The Boc analog (3.2 g, 11 mmol) was treated with excess TFA. The reaction was stirred for 18 h at room temp and **121** was obtained in quantitative yield LRMS (ESI): (calc.) 221.3; (found) 222 $(MH)^+$.

Step 2: benzyl 6-(2-(3-methoxy-3-oxopropylthio)acetamido)hexanoate (**122**)

[0207] To a solution of 2-(3-methoxy-3-oxopropylthio)acetic acid (0.322 g, 2 mmol) in DCM was added triethylamine (1.0 mL , 4 mmol) and BOP (0.8 g, 2 mmol). The mixture was stirred for 15 minutes at room temperature, and then **121** was added (0.4 g, 2 mmol) and triethylamine (1.0 mL, 4 mmol). The mixture was heated at 50° C for 16 h, and then the solvent was evaporated. EtOAc was added, and the organic layer was washed with water, $NaHCO_3$ (ss) and brine. The organic extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography to afford **122** (0.17 g, 25%) as an oil. LRMS (ESI): (calc.) 381.5; (found) 382.3 $(MH)^+$.

Step3: 6-(2-(3-methoxy-3-oxopropylthio)acetamido)hexanoic acid (**123**)

[0208] To a solution of **122** (0.17 g, 0.45 mmol) in MeOH: formic acid (1:1) (10 mL each) was added palladium black (0.17 g, 1 equivalent). The mixture was stirred for 16h and then filtered over Celite to afford 118 (0.11 g, 84 %).

Step 4: methyl 3-(2-oxo-2-(6-oxo-6-(3-(pyridin-3-yl)phenylamino)hexylamino)-ethylthio)propanoate (**124**)

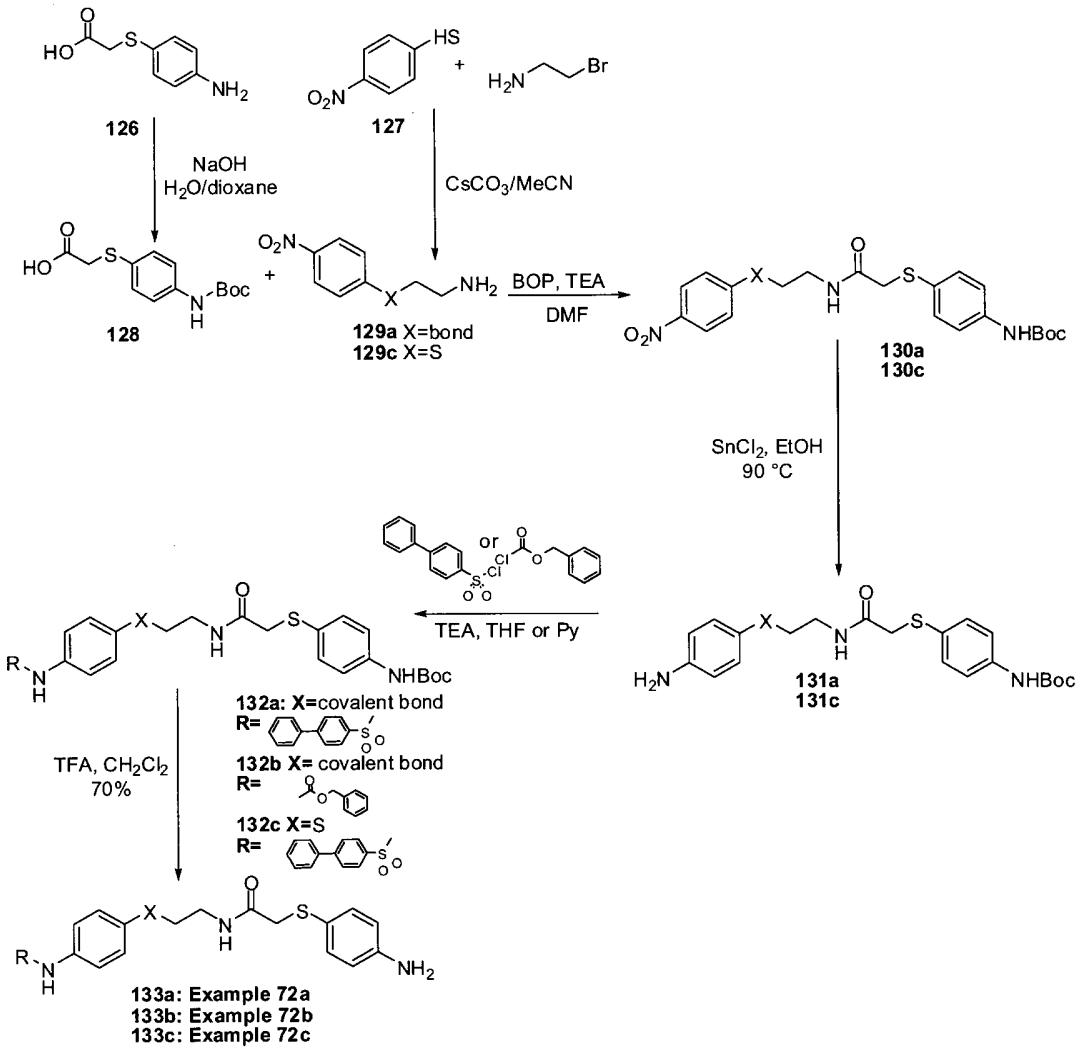
[0209] Following the same procedure as described for compound **122** (step 2, scheme 14, example 71) but substituting 3-(pyridin-3-yl)benzenamine for compound **121** and **123** for 2-(3-methoxy-3-oxopropylthio)acetic acid to afford **124** (20 mg, 41 %) as a colorless oil. LRMS (ESI): (calc.) 443.6; (found) 444 $(MH)^+$.

Step 5: 3-(2-oxo-2-(6-oxo-6-(3-(pyridin-3-yl)phenylamino)hexylamino)ethylthio)-propanoic acid (**125**)

[0210] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting compound **124** for compound **4** to obtain the crude acid. The residue was purified by preparative HPLC (Aquasil C-18, 100X4.6, 5uM) with MeOH in H_2O to afford **125** (1.5 mg, 3%) as a colorless oil.

(actone-*d6*) δ (ppm) ^1H: 8.8(s, 1H); 8.6(m, 1H); 8-8.2(m, 2H); 7.8(m, 1H); 7.6(m, 1H); 7.4(m, 2H); 3.3(m, 2H); 3.2(s, 2H); 2.6(dd, J = 6Hz,2H); 2.4(dd, J= 6Hz, 2H); 1.7(m, 2H); 1.6(m, 2H); 1.4(m, 2H). LRMS (ESI): (calc.) 429.5; (found) 430.2 $(MH)^+$.

Scheme 15



Example 72a

2-(4-aminophenylthio)-*N*-(4-(biphenyl-4-ylsulfonamido)phenethyl)acetamide (**133a**)

Step 1: 2-(4-(*tert*-butoxycarbonylamino)phenylthio)acetic acid (**128**)

[0211] To a stirred solution of 2-(4-aminophenylthio)acetic acid **126** (678 mg, 3.70 mmol) in dioxane/water (2:1, 15 ml) was added di-*tert*-butyl dicarbonate (848 mg, 3.90 mmol) and NaOH (326 mg, 8.10 mmol). After stirring at room temperature for 4 hours, a precipitate formed, to which ethyl acetate (35 mL) and 3N HCl (8 mL) were added. Following extraction with ethyl acetate, the organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue of **128** (608 mg, 58%) was isolated as a white solid, and used in the subsequent reaction without further purification. LRMS (ESI): (calc) 283.3; (found) 284.2 $(MH)^+$.

Intermediate: 2-(4-nitrophenylthio)ethanamine (**129c**) (to make **130c**)

[0212] To a stirred solution of 4-nitrobenzenethiol **127** (500 mg, 3.22 mmol) in acetonitrile (10 mL) at room temperature was added 2-bromoethaneamine hydrobromide (792 mg, 3.87 mmol) and Cs_2CO_3 (5.25 g, 16.1 mmol). The resulting mixture was then heated to 100 °C for 2 hours, cooled, diluted with brine, basified to pH = 12 with NaOH, and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with a gradient of MeOH (0-10%) in EtOAc to afford **129c** (475 mg, 74%) as a light orange solid. LRMS (ESI): (calc) 198.2; (found) 199.4 $(MH)^+$.

Step 2: *tert*-butyl 4-(2-(4-nitrophenethylamino)-2-oxoethylthio)phenylcarbamate (**130a**)

[0213] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting acid **128** for *N*-Boc-caproic acid and amine **129a** for 3-phenyl aniline to afford **130a** (289 mg, 94%) as a white solid. LRMS (ESI): (calc) 431.5; (found) 432.2 $(MH)^+$.

Step 3: *tert*-butyl 4-(2-(4-aminophenethylamino)-2-oxoethylthio)phenylcarbamate (**131a**)

[0214] To a stirred solution of *tert*-butyl 4-(2-(4-nitrophenethylamino)-2-oxoethylthio)phenyl-carbamate **130a** (289 mg, 0.670 mmol) in ethanol (10 mL) was added tin(II) chloride dihydrate (604 mg, 2.68 mmol) at room temperature. The resulting mixture was then heated to 90 °C for 30 minutes prior to cooling, dilution with brine, and extraction with ethyl acetate. The residue was purified by silica gel column chromatography with a gradient of EtOAc (90-100%) in hexanes to afford **131a** (164 mg, 61%) as a light yellow foam. LRMS (ESI): (calc) 401.5; (found) 402.4 $(MH)^+$.

Step 4: *tert*-butyl 4-(2-(4-(biphenyl-4-ylsulfonamido)phenethylamino)-2-oxoethylthio)phenylcarbamate (**132a**)

[0215] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting amine **131a** for amine **2** and biphenyl-4-sulfonyl chloride for 3-bromo-propionyl chloride to afford **132a** (103 mg, 46%) as white solid. LRMS (ESI): (calc.) 617.8; (found) 640.6 $(M+Na)^+$.

Step 5: 2-(4-aminophenylthio)-*N*-(4-(biphenyl-4-ylsulfonamido)phenethyl)acetamide (**133a**)

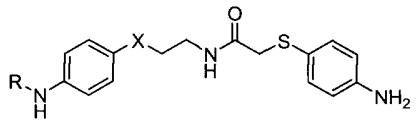
[0216] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **132a** for **1** to afford **133a** (15 mg, 17%) as a light yellow solid. (MeOD-*d4*) δ (ppm) ^1H: 8.00-7.92 (m,1H), 7.86-7.80 (m,2H), 7.76-7.70 (m,2H), 7.66-7.61

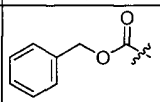
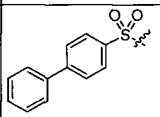
(m,2H), 7.51-7.38 (m,3H), 7.18-7.13 (m,2H), 7.10-7.03 (m,4H), 6.69-6.64 (m,2H), 3.37-3.31 (m,4H), 2.65 (t, J = 7.0 Hz, 2H). LRMS (ESI): (calc) 517.7; (found) 518.7 $(MH)^+$.

Example 72b and 72c

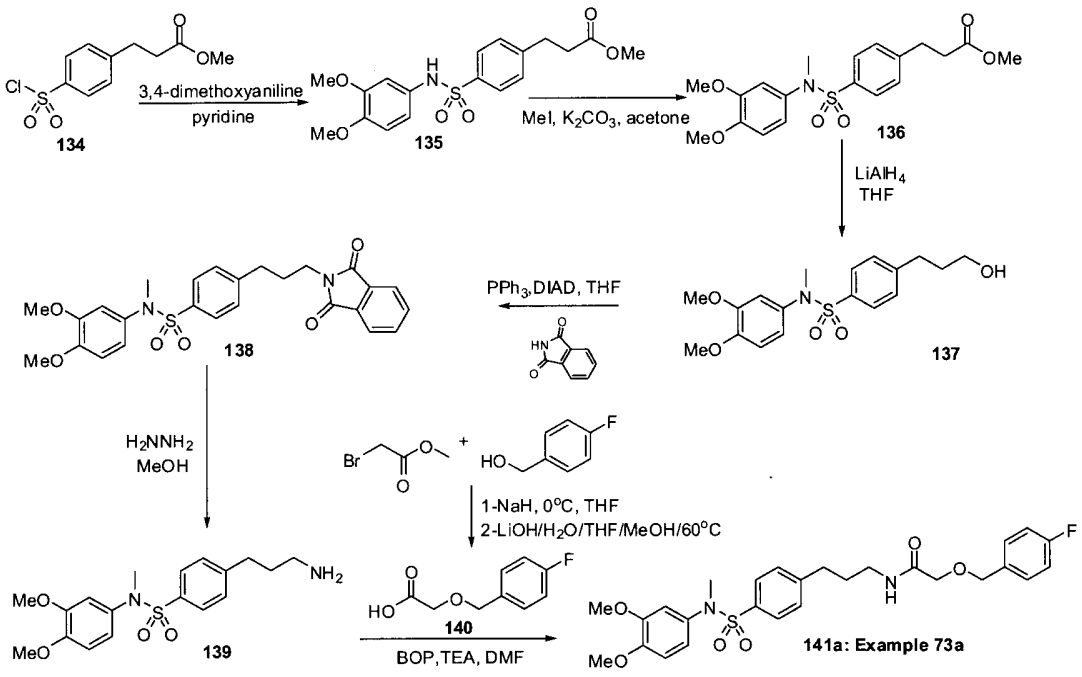
[0217] Example 72b, c describe the preparation of compound **133b** and **133c** using the same procedures as described for compound **133a** in Example 72a. Characterization data are presented in a Table 8.

Table 8



Ex	Cpd	R	X	Name	Characterization	Scheme
72b	133b		Covalent bond	benzyl 4-(2-(2-(4-aminophenylthio)acetamido)ethyl)phenylcarbamate	(MeOD-*d4*) δ(ppm) ^{1}H: 7.46-7.31 (m,7H), 7.19 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 5.20 (s,2H), 3.38-3.35 (m,4H), 2.68 (t, J = 7.2 Hz, 2H) LRMS (ESI): (calc) 435.5; (found) 436.7 $(MH)^+$.	15
72c	133c		S	2-(4-aminophenylthio)-*N*-(2-(4-(biphenyl-4-ylsulfonamido)phenylthio)ethyl)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 8.18-8.13 (m,1H), 7.87-7.82 (m,2H), 7.76-7.71 (m,2H), 7.65-7.60 (m,2H), 7.52-7.37 (m,3H), 7.30-7.24 (m,2H), 7.23-7.18 (m,2H), 7.14-7.09 (m,2H), 6.66-6.00 (m,2H), [3.44-3.40 (t)], [3.40 (s)], 3.29 (s,2H), 3.26 (t, J = 7.2 Hz, 2H), [3.12-3.07 (t)], 2.86 (t, J = 6.7 Hz, 2H) LRMS (ESI): (calc) 549.7; (found) 550.7 $(MH)^+$.	15

Scheme 16



Example 73a

N-(3-(4-(N-(3,4-dimethoxyphenyl)-*N*-methylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**141a**)

Step 1: methyl 3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propanoate (**135**)

[0218] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting amine 3,4-dimetoxyaniline for amine **2**, and **134** for 3-bromo-propionyl chloride and using pyridine (some examples DMAP was used) as a solvent and base to afford **135** (1.90 g, 89%) as light purple solid. LRMS (ESI): (calc.) 379.4; (found) 402.1 $(M+Na)^+$.

Step 2: methyl 3-(4-(*N*-(3,4-dimethoxyphenyl)-*N*-methylsulfamoyl)phenyl)propanoate (**136**)

[0219] Following the same procedure as described for compound **73** (scheme 5, example 55) but substituting **135** for **72** and using acetone as a solvent to afford **136** (740 mg, 95%) as a light brown foam. LRMS (ESI): (calc.) 393.5; (found) 432.2 $(M+K)^+$.

Step 3: *N*-(3,4-dimethoxyphenyl)-4-(3-hydroxypropyl)-*N*-methylbenzenesulfonamide (**137**)

[0220] To a stirred solution of methyl 3-(4-(*N*-(3,4-dimethoxyphenyl)-*N*-methylsulfamoyl)phenyl)propanoate **136** (740 mg, 1.88 mmol) in tetrahydrofuran (10 mL) at 0 °C was added lithium aluminum hydride (178 mg, 4.70 mmol). The resulting solution was

stirred for 30 minutes prior to quench with water, acidification to pH = 1 with HCl, and extraction with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue comprised of **137** (560 mg, 81%) as a light brown foam was used in the subsequent reaction without further purification. LRMS (ESI): (calc) 365.4; (found) 366.2 $(MH)^+$.

Step 4: *N*-(3,4-dimethoxyphenyl)-4-(3-(1,3-dioxoisoindolin-2-yl)propyl)-*N*-methylbenzenesulfonamide (**138**)

[0221] To a stirred solution of *N*-(3,4-dimethoxyphenyl)-4-(3-hydroxypropyl)-*N*-methylbenzenesulfonamide **137** (560 mg, 1.53 mmol) in tetrahydrofuran (5 mL) at 0 °C was added phthalimide (306 mg, 2.08 mmol) and triphenylphosphine (532 mg, 2.03 mmol). After stirring for 5 minutes, DIAD (di-isopropylazodicarboxylate) (0.39 mL, 1.99 mmol) was added dropwise, and the reaction warmed to room temperature. After stirring for 1 hour, the solution was diluted with brine, acidified to pH = 2 with HCl, and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography using EtOAc (0-100%) in hexanes to afford **138** (546 mg, 72%) as a white foam. LRMS (ESI): (calc) 494.5; (found) 495.2 $(MH)^+$.

Step 5 : 4-(3-aminopropyl)-*N*-(3,4-dimethoxyphenyl)-*N*-methylbenzenesulfonamide (**139**)

[0222] To a stirred solution of *N*-(3,4-dimethoxyphenyl)-4-(3-(1,3-dioxoisoindolin-2-yl)propyl)-*N*-methylbenzenesulfonamide **138** (546 mg, 1.10 mmol) in methanol (4 mL) at room temperature was added hydrazine hydrate (0.11 mL, 2.20 mmol), and the resulting solution was stirred for 16 hours. After filtering the solution through a pad of celite, the filtrate was evaporated to afford **139** (398 mg, 99%) as a light yellow foam. LRMS (ESI): (calc) 364.4; (found) 365.2 $(MH)^+$.

Intermediate: 2-(4-fluorobenzyloxy)acetic acid (**140**)

[0223] Following the same procedure as described for compound **43** (scheme 2, example 37) but substituting (4-fluorophenyl)methanol for (4-(methylthio)phenyl)methanol to afford **140** (13.0 g, 71 %) as a white solid. (DMSO-*d*6) δ (ppm) ^1H: 12.62 (br s,1H), 7.37 (dd, J = 8.2, 5.5 Hz, 2H), 7.50 (t, J = 8.8 Hz, 2H), 4.49 (s, 2H), 4.04 (s, 2H). LRMS (ESI): (calc.) 184.2; (found) 207.2 $(M+Na)^+$.

Step 6: *N*-(3-(4-(*N*-(3,4-dimethoxyphenyl)-*N*-methylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**141a**)

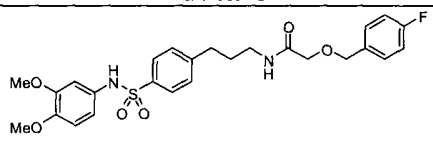
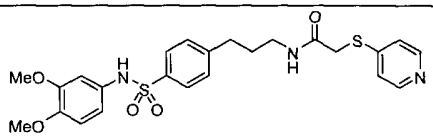
[0224] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting acid **140** for *N*-Boc-caproic acid and amine **139** for 3-phenyl aniline to afford **141a** (44 mg, 1%) as a light pink oil. (MeOD-*d4*) δ (ppm) ^1H: 7.51-7.36 (m,6H), 7.14-7.07 (m,2H), 6.85 (d, J = 8.6 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.58 (dd, J = 8.6,2.5 Hz, 1H),

4.59 (s,2H), 3.95 (s,2H), 3.82 (s,3H), 3.69 (s,3H), 3.29 (t, J = 7.0 Hz, 2H), 3.15 (s,3H), 2.73 (t, J = 8.0 Hz, 2H), 1.92-1.83 (m,2H). LRMS (ESI): (calc) 530.6; (found) 531.3 $(MH)^+$.

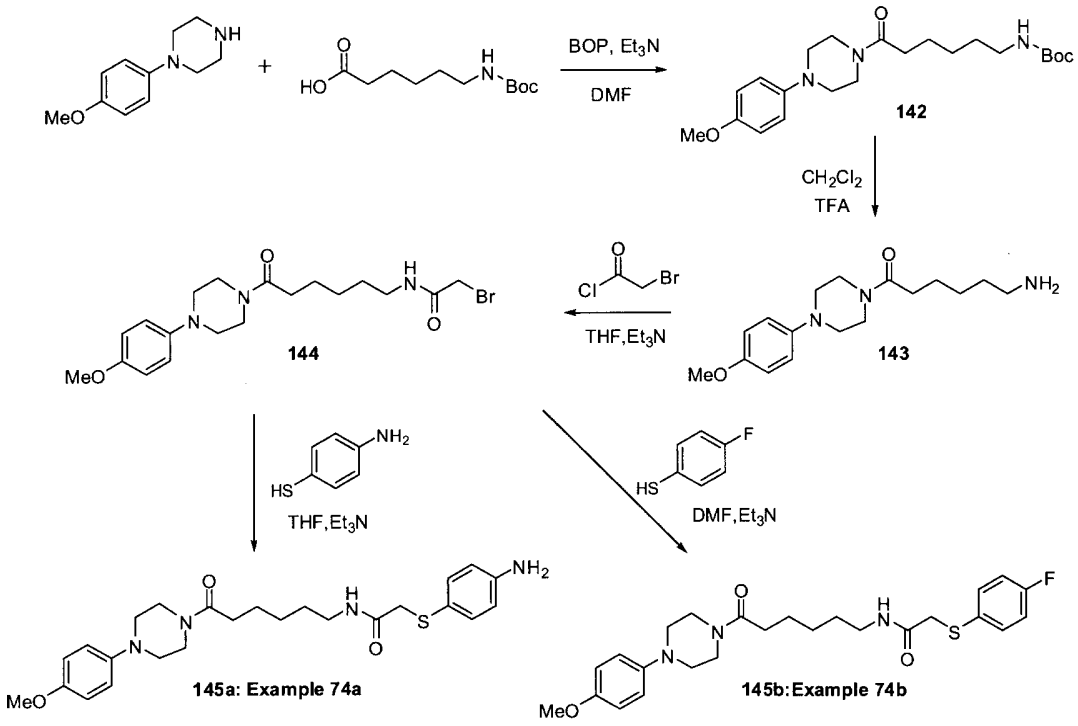
Example 73b

[0225] Example 73b describe the preparation of compound **141b** using the same procedures as described for compound **141a** in Example 73a. Characterization data are presented in a Table 9.

Table 9

Ex	Cpd	structure	Name	Characterization	Scheme
73b	141b		*N*-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.67-7.62 (m,2H), 7.46-7.40 (m,2H), 7.37-7.32 (m,2H), 7.15-7.07 (m,2H), 6.80 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.62-6.56 (m,1H), 4.58 (s,2H), 3.93 (s,2H), 3.77 (s,3H), 3.72 (s,3H), 3.26 (t, J = 7.0 Hz, 2H), 2.70 (t, J = 8.0 Hz, 2H), 1.90-1.80 (m,2H) LRMS (ESI): (calc) 516.6; (found) 517.2 $(MH)^+$.	16 (steps 1, 3-6)
73c	141c		*N*-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(pyridin-4-ylthio)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 8.34 (dd, J = 4.7,1.6 Hz, 2H), 7.64-7.59 (m,2H), 7.36 (dd, J = 4.7,1.6 Hz, 2H), 7.28-7.23 (m,2H), 6.78 (d, J = 8.6 Hz, 1H), 6.68 (d, J = 2.3 Hz, 1H), 6.58 (dd, J = 8.6,2.5 Hz, 1H), 3.81 (s,2H), 3.76 (s,3H), 3.71 (s,3H), 3.22 (t, J = 6.8 Hz, 2H), 2.62 (t, J = 8.0 Hz, 2H), 1.83-1.74 (m,2H) LRMS (ESI): (calc) 501.6; (found) 502.6 $(MH)^+$.	16 (steps 1, 3-6)

Scheme 17



Example 74a

2-(4-aminophenylthio)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide (**145a**)

Step 1: *tert*-butyl 6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexylcarbamate (**142**)

[0226] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 1-(4-methoxyphenyl)piperazine for 3-phenyl aniline to afford **142** (5.22 g, 99%) as a yellow oil. LRMS (ESI): (calc) 405.5; (found) 406.2 $(MH)^+$.

Step 2: 6-amino-1-(4-(4-methoxyphenyl)piperazin-1-yl)hexan-1-one (**143**)

[0227] Following the same procedure as described for compound **2** (step 2, scheme 1, example 1) but substituting **142** for **1** to afford **143** (2.08 g, 53%) as an orange oil. LRMS (ESI): (calc) 305.4; (found) 306.4 $(MH)^+$.

Step 3: 2-bromo-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide (**144**)

[0228] Following the same procedure as described for compound **3b** (step 3, scheme 1, example 1) but substituting **143** for **2** to afford **144** (934 mg, 67%) as a yellow oil. LRMS (ESI): (calc) 426.4; (found) 427.5 $(MH)^+$.

Step 4: 2-(4-aminophenylthio)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6 -oxohexyl)acetamide (**145a**)

[0229] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting **144** for **3b** and 4-aminobenzenethiol for methyl 2-mercaptoacetate to afford **145a** (165 mg, 75%) as a yellow oil. (MeOD-*d4*) δ (ppm) ^{1}H: 7.23 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 9.2 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 3.77 (s,3H), 3.76-3.72 (m,2H), 3.71-3.67 (m,2H), 3.38 (m,2H), 3.17 (t, J = 6.8 Hz, 2H), 3.07 (t, J = 5.1 Hz, 2H), 3.02 (t, J = 5.1 Hz, 2H), 2.40 (t, J = 7.8 Hz, 2H), 1.65-1.58 (m,2H), 1.51-1.42 (m,2H), 1.34-1.26 (m,2H). LRMS (ESI): (calc) 470.2; (found) 471.6 $(MH)^+$.

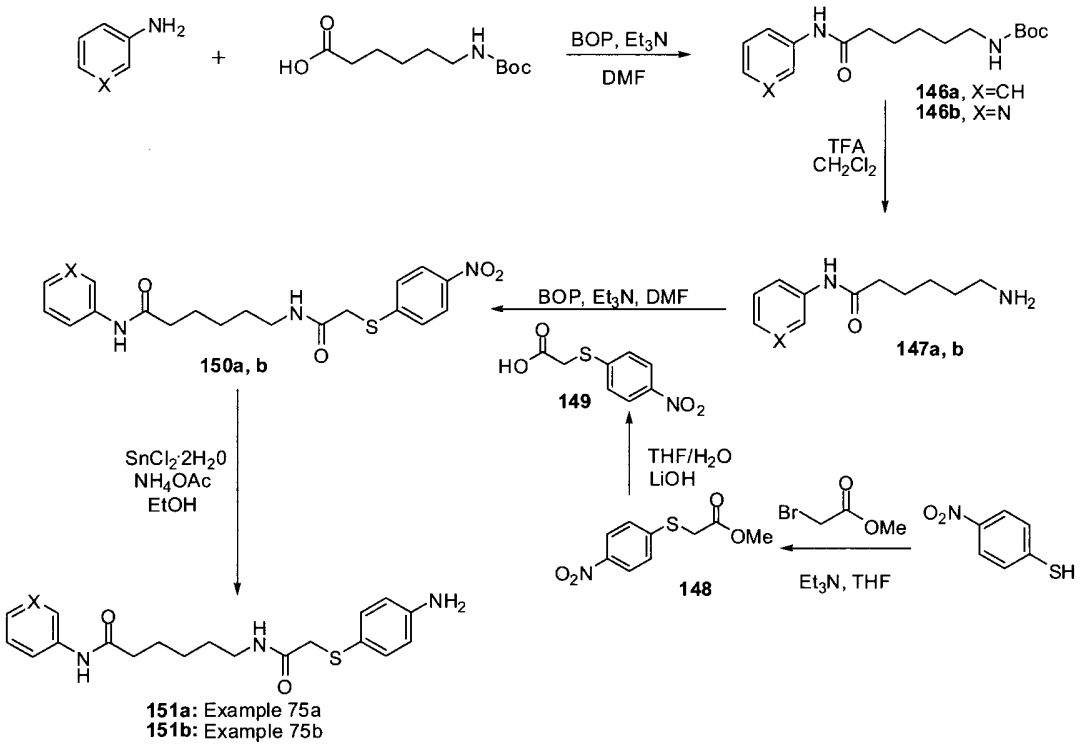
Example 74b

2-(4-fluorophenylthio)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide (**145b**)

Step 1- 4: 2-(4-fluorophenylthio)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide(**145b**)

[0230] Following the same procedure as described for compound **145a** (step 1-4, scheme 17, example 74a) but substituting 4-fluorobenzenethiol for 4-aminobenzenethiol to afford **145b** (445 mg, 85%) as a white solid. (MeOD-*d4*) δ (ppm) ^{1}H: 7.47 (t, J = 6.8 Hz, 2H), 7.09 (t, J = 8.6 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.77 (s,3H), 3.76-3.73 (m,2H), 3.72-3.68 (m,2H), 3.57 (s,2H), 3.18 (t, J = 6.7 Hz, 2H), 3.09-3.07 (m,2H), 3.04-3.02 (m,2H), 2.42 (t, J = 7.4 Hz, 2H), 1.63-1.56 (m,2H), 1.51-1,44 (m,2H), 1.33-1.26 (m,2H). LRMS (ESI): (calc) 473.6; (found) 474.5 $(MH)^+$.

Scheme 18



Example 75a

6-(2-(4-aminophenylthio)acetamido)-*N*-phenylhexanamid (**151a**)

Step 1: *tert*-butyl 6-oxo-6-(phenylamino)hexylcarbamate (**146a**)

[0231] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting aniline for 3-phenyl aniline to afford **146a** (2.90 g, 32%) as a light yellow solid. LRMS (ESI): (calc) 306.2; (found) 307.4 $(MH)^+$.

Step 2: 6-amino-*N*-phenylhexanamide (**147a**)

[0232] Following the same procedure as described for compound **2** (step 2, scheme 1, example 1) but substituting **146a** for **1** to afford **147a** (631 mg, 69%) as a light yellow oil. LRMS (ESI): (calc) 206.3; (found) 207.2 $(MH)^+$.

Intermediate: 2-(4-nitrophenylthio)acetic acid (**149**)

Step A: methyl 2-(4-nitrophenylthio)acetate (**148**)

[0233] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting methyl 2-bromoacetate for **3b** and 4-nitrobenzenethiol for methyl 2-mercaptoacetate to afford **148** (1.33 g, 90%) as an orange solid. LRMS (ESI): (calc) 227.2; (found) 228.2 $(MH)^+$.

Step B: 2-(4-nitrophenylthio)acetic acid (**149**)

[0234] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting **148** for **4** to afford **149** (1.12 g, 94%) as a yellow solid. LRMS (ESI): (calc) 213.0; (found) 211.9 ($M-H^+$).

Step 3: 6-(2-(4-nitrophenylthio)acetamido)-*N*-phenylhexanamide (**150a**)

[0235] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting acid **149** for *N*-Boc-caproic acid and amine **147a** for 3-phenyl aniline to afford **150a** (361 mg, 57%) as a light yellow solid. LRMS (ESI): (calc) 401.5; (found) 402.7 $(MH)^+$.

Step 4: 6-(2-(4-aminophenylthio)acetamido)-*N*-phenylhexanamide (**151a**)

[0236] To a stirred solution of 6-(2-(4-nitrophenylthio)acetamido)-*N*-phenylhexanamide **150a** (204 mg, 0.51 mmol) in ethanol (10 mL) was added tin(II) chloride dihydrate (460 mg, 204 mmol) and NH_4OAc (393 mg, 5.10 mmol) at room temperature. After heating to 100 °C for 20 minutes, the solution was cooled, diluted with water, basified to pH = 9 with NaOH, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography using EtOAc (0-100%) in hexanes to afford **151a** (155 mg, 82%) as a colorless oil. (MeOD-*d4*) δ (ppm) ^1H: 8.57-8.49 (m,1H), 7.57- 7.50 (m,2H), 7.33-7.24 (m,2H), 7.23-7.17 (m,2H), 7.11-7.02 (m,1H), 6.68-6.60 (m,2H), 3.39-3.34 (m,2H), 3.18-3.10 (m,2H), 2.40-2.31 (m,2H), 1.74-1.62 (m,2H), 1.51-1.41 (m,2H), 1.35-1.23(m,2H). LRMS (ESI): (calc) 371.5; (found) 394.0 $(M+Na)^+$.

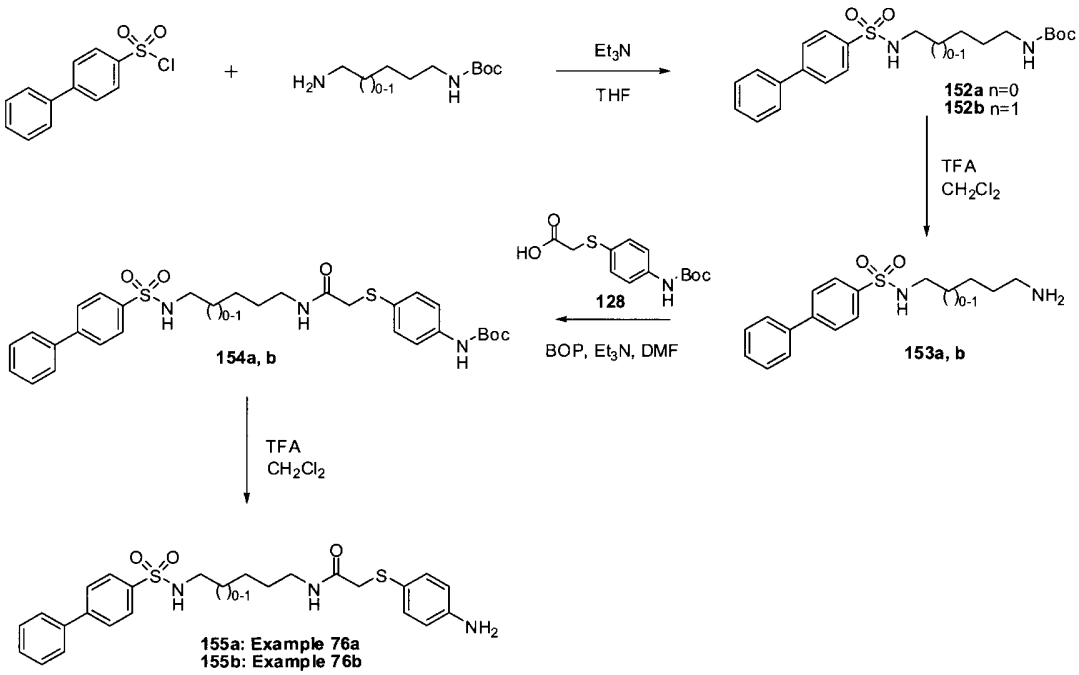
Example 75b

6-(2-(4-aminophenylthio)acetamido)-*N*-(pyridin-3-yl)hexanamide (**151b**)

Step 1- 4: 6-(2-(4-aminophenylthio)acetamido)-*N*-(pyridin-3-yl)hexanamide (**151b**)

[0237] Following the same procedure as described for compound **151a** (step 1-4, scheme 18, example 75a) but substituting pyridin-3-amine for aniline to afford **151b** (252 mg, 79%) as an orange oil. (MeOD-*d4*) δ (ppm) ^1H: 8.77-8.73 (m,1H), 8.27-8.24 (m,1H), 8.15-8.11 (m,1H), 8.00-7.95 (m,1H), 7.43-7.38 (m,1H), 7.24 (s,1H), 7.21 (s,1H), 6.67 (s,1H), 6.65 (s,1H), 3.39-3.38 (m,2H), 3.21-3.14 (m,2H), 2.42 (t, J = 7.4 Hz, 2H), 1.75-1.66 (m,2H), 1.53-1.43 (m,2H), 1.36-1.27 (m,2H). LRMS (ESI): (calc) 372.5; (found) 373.2 $(MH)^+$.

Scheme 19



Example 76a

2-(4-aminophenylthio)-*N*-(4-(biphenyl-4-ylsulfonamido)butyl)acetamide (**155a**)

Step 1: *tert*-butyl 4-(biphenyl-4-ylsulfonamido)butylcarbamate (**152a**)

[0238] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting *tert*-butyl 4-aminobutylcarbamate for amine **2** and biphenyl-4-sulfonyl chloride for 3-bromo-propionyl chloride to afford **152a** (534 mg, quantitative) as a yellow solid. LRMS (ESI): (calc.) 404.2; (found) 405.3 $(MH)^+$.

Step 2: *N*-(4-aminobutyl)biphenyl-4-sulfonamide (**153a**)

[0239] Following the same procedure as described for compound **2** (step 2, scheme 1, example 1) but substituting **152a** for **1** to afford **153a** (374 mg, 87%) as a yellow solid. LRMS (ESI): (calc) 304.1; (found) 305.0 $(MH)^+$.

Step 3: *tert*-butyl 4-(2-(4-(biphenyl-4-ylsulfonamido)butylamino)-2-oxoethylthio)phenylcarbamate (**154a**)

[0240] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting acid **128** for *N*-Boc-caproic acid and amine **153a** for 3-phenyl aniline to afford **154a** (284 mg, 70%) as a white solid. LRMS (ESI): (calc) 569.2; (found) 570.2 $(MH)^+$.

Step 4: 2-(4-aminophenylthio)-*N*-(4-(biphenyl-4-ylsulfonamido)butyl)acetamide (**155a**)

[0241] Following the same procedure as described for compound **2** (step 2, scheme 1, example 1) but substituting **154a** for **1** to afford **155a** (235 mg, 74%) as a white solid.

(DMSO-*d*6) δ (ppm) ^{1}H: 7.95-7.87 (m,5H), 7.80-7.76 (m,2H), 7.68 (t, J = 8.0 Hz, 1H), 7.56-7.53 (m,2H), 7.50-7.46 (m,1H), 7.12 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 5.69 (s,2H), 3.32 (s,2H), 3.02-2.99 (m,2H), 2.81-2.74 (m,2H), 1.40-1.34 (m,4H). LRMS (ESI): (calc) 469.6; (found) 470.0 $(MH)^+$.

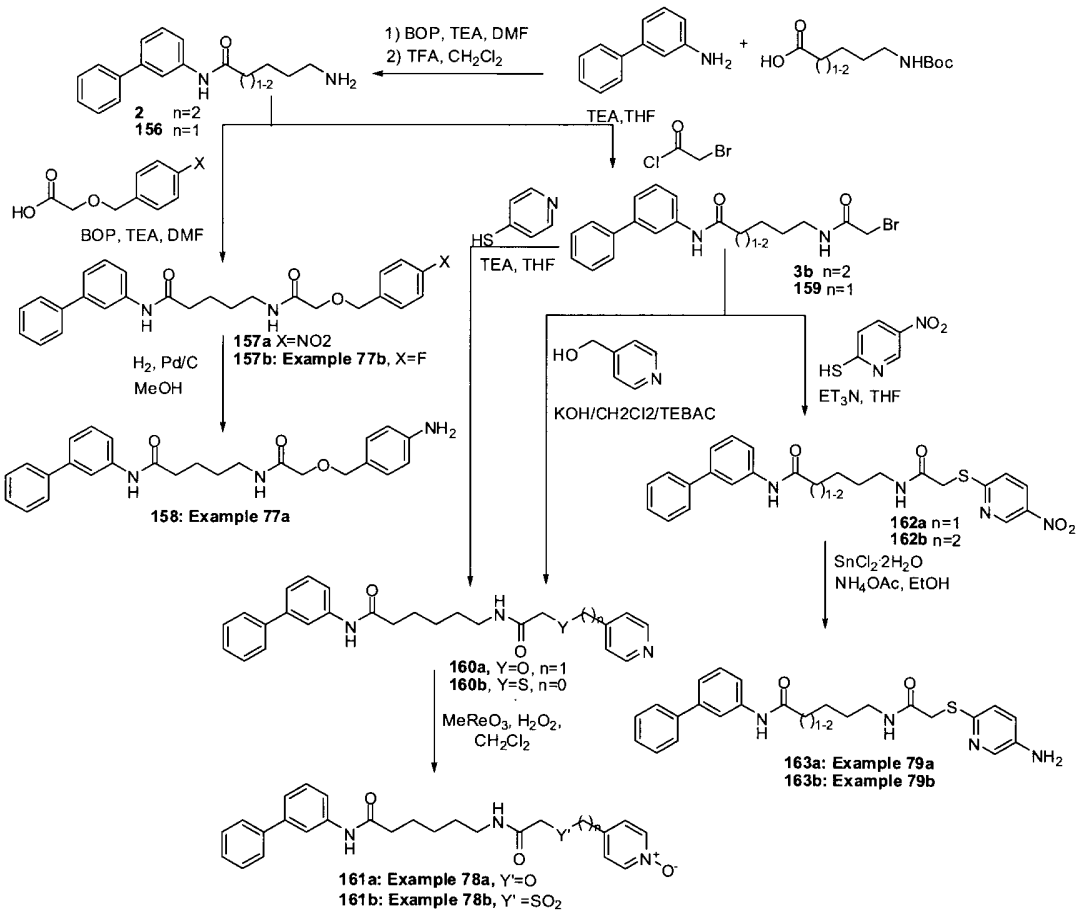
Example 76b

2-(4-aminophenylthio)-*N*-(5-(biphenyl-4-ylsulfonamido)pentyl)acetamide (**155b**)

Step 1- 4: 2-(4-aminophenylthio)-*N*-(5-(biphenyl-4-ylsulfonamido)pentyl)acetamide (**155b**)

[0242] Following the same procedure as described for compound **155a** (step 1-4, scheme 19, example 76a) but substituting *tert*-butyl 5-aminopentylcarbamate for *tert*-butyl 4-aminobutylcarbamate to afford **155b** (42 mg, 73%) as a white solid. (MeOD-*d4*) δ (ppm) ^{1}H: 7.97-7.93 (m,2H), 7.87-7.84 (m,2H), 7.74-7.70 (m,2H), 7.54-7.49 (m,2H), 7.47-7.42 (m,1H), 7.24-7.20 (m,2H), 6.68-6.63 (m,2H), 3.36 (s,2H), 3.09 (t, J = 6.9 Hz, 2H), 2.88 (t, J = 7.0 Hz, 2H), 1.49-1.41 (m,2H), 1.40-1.31 (m,2H), 1.25-1.15 (m,2H). LRMS (ESI): (calc) 483.6; (found) 484.7 $(MH)^+$.

Scheme 20



Example 77a

5-(2-(4-aminobenzyloxy)acetamido)-*N*-(biphenyl-3-yl)pentanamide (**158**)

Step 1: 5-amino-*N*-(biphenyl-3-yl)pentanamide (**156**)

[0243] Following the same procedure as described for compound **2** (step 1 and 2, scheme 1, example 1) but substituting 5-(*tert*-butoxycarbonylamino)pentanoic acid for 6-(*tert*-butoxycarbonylamino)hexanoic acid to afford **156** (4.10 g, 95%) as light orange oil. LRMS (ESI): (calc) 368.5; (found) 369.2 $(MH)^+$.

Intermediate: 2-(4-nitrobenzyloxy)acetic acid

[0244] Following the same procedure as described for compound **43** (step 1 and 2, scheme 2, example 37) but substituting (4-nitrophenyl)methanol for (4-(methylthio)phenyl)methanol to afford 2-(4-nitrobenzyloxy)acetic acid (1.56 g, 77%) as light orange solid. LRMS (ESI): (calc) 211.2; (found) 210.0 $(M-H^+)$.

Step 2: *N*-(biphenyl-3-yl)-5-(2-(4-nitrobenzyloxy)acetamido)pentanamide (**157a**)

[0245] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting 2-(4-nitrobenzyloxy)acetic acid for *N*-Boc-caproic acid and amine

156 for 3-phenyl aniline to afford **157a** (253 mg, 44%) as an orange oil. LRMS (ESI): (calc) 461.5; (found) 462.3 $(MH)^+$.

Step 3: 5-(2-(4-aminobenzyloxy)acetamido)-*N*-(biphenyl-3-yl)pentanamide (**158**)

[0246] Following the same procedure as described for compound **74** (step 3, scheme 5, example 55) but substituting **157a** for **73** to afford **158** (7 mg, 3%) as a white foam. (MeOD-*d4*) δ (ppm) ^1H: 7.87 (t, J = 1.6 Hz, 1H), 7.64-7.58 (m,2H), 7.57-7.52 (m,1H), 7.47-7.31 (m,5H), 7.12 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 4.45 (s,2H), 3.89 (s,2H), 3.29 (t, J = 6.8 Hz, 2H), 2.46 (t, J = 5.1 Hz, 2H), 1.80-1.70 (m,2H), 1.67-1.56 (m,2H). LRMS (ESI): (calc) 431.5; (found) 432.2 $(MH)^+$.

Example 77b

N-(biphenyl-3-yl)-5-(2-(4-fluorobenzyloxy)acetamido)pentanamide (**157b**)

Step 1-2: *N*-(biphenyl-3-yl)-5-(2-(4-fluorobenzyloxy)acetamido)pentanamide (**157b**)

[0247] Following the same procedure as described for compound **157a** (scheme 20, example 77a) but substituting 2-(4-fluorobenzyloxy)acetic acid (**140**) for 2-(4-nitrobenzyloxy)acetic acid to afford **157b** (75 mg, 86%) as light yellow solid. (MeOD-*d4*) δ (ppm) ^1H: 7.89 (t, J = 1.8 Hz, 1H), 7.63-7.58 (m,2H), 7.55 (dt, J = 7.6,1.6 Hz, 1H), 7.46-7.31 (m,7H), 7.10-7.04 (m,2H), 4.56 (s,2H), 3.95 (s,2H), 3.30 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 1.80-1.70 (m,2H), 1.67-1.57 (m,2H). LRMS (ESI): (calc) 434.5; (found) 435.2 $(MH)^+$.

Example 78a

4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)pyridine 1-oxide (**161a**)

Step 1: *N*-(biphenyl-3-yl)-6-(2-(pyridin-4-ylmethoxy)acetamido)hexanamide (**160a**)

[0248] Following the same procedure as described for compound **7a** (step 4, scheme 1, example 4) but substituting 2 pyridin-4-ylmethanol for tert-butyl-2-hydroxyethylcarbamate to afford **160a** (83 mg, 52%) as a yellow oil. LRMS (ESI): (calc) 431.7; (found) 432.2 $(MH)^+$.

Step 2: 4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)pyridine 1-oxide (**161a**)

[0249] To a stirred solution of **160a** (83 mg, 0.192 mmol) in dichloromethane (3.5 mL) was added methyl trioxorhenium (3 mg, 0.013 mmol) and hydrogen peroxide (35% by wt in water, 0.02 mL, 0.231 mmol). The resulting solution was stirred for 2 hours prior to evaporation of solvents, and direct purification of the residue by silica gel column chromatography with a gradient of MeOH (0-40%) in EtOAc to afford **161a** (73 mg, 85%) as a light yellow oil. (MeOD-*d4*) δ (ppm) ^1H: 8.32-8.23 (m,3H), 7.87 (t, J = 1.8 Hz, 1H), 7.61-

7.56 (m,2H), 7.55-7.50 (m,3H), 7.45-7.31 (m,4H), 4.68 (s,1H), 4.59 (s,2H), 4.03 (s,2H), 3.30 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 1.82-1.72 (m,2H), 1.66-1.56 (m,2H), 1.50-1.40 (m,2H). LRMS (ESI): (calc) 447.5; (found) 448.5 $(MH)^+$.

Example 78b

4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfonyl)pyridine 1-oxide (**161b**)

Step 1: *N*-(biphenyl-3-yl)-6-(2-(pyridin-4-ylthio)acetamido)hexanamide (**160b**)

[0250] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting pyridine-4-thiol for 4-aminobenzenethiol to afford **160b** (75 mg, 66%) as a light yellow solid. (MeOD-*d4*) δ (ppm) ^{1}H: 8.34-8.30 (m,2H), 7.87 (t, J = 1.6 Hz, 1H), 7.64-7.58 (m,2H), 7.57-7.53 (m,1H), 7.47-7.30 (m,7H), 3.80 (s,2H), 3.25 (t, J = 6.8 Hz, 2H), 2.40 (t, J = 7.4 Hz, 2H), 1.78-1.68 (m,2H), 1.62-1.52 (m,2H), 1.44-1.35 (m,2H). LRMS (ESI): (calc) 433.6; (found) 434.4 $(MH)^+$.

Step 2: 4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfonyl)pyridine 1-oxide (**161b**)

[0251] Following the same procedure as described for compound **161a** (step 2, scheme 20, example 78a) but substituting **160b** for **160a** to afford **161b** (9 mg, 6%) as light yellow solid. (MeOD-*d4*) δ (ppm) ^{1}H: 8.49-8.45 (m,2H), 7.95-7.92 (m,2H), 7.89-7.87 (m,1H), 7.64-7.60 (m,2H), 7.58-7.54 (m,1H), 7.48-7.34 (m,5H), 3.38 (s,4H), 3.22 (t, J = 6.9 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 1.80-1.72 (m,2H), 1.61-1.52 (m,2H), 1.48-1.40 (m,2H). LRMS (ESI): (calc) 481.6; (found) 482.5 $(MH)^+$.

Example 79a

5-(2-(5-aminopyridin-2-ylthio)acetamido)-*N*-(biphenyl-3-yl)pentanamide (**163a**)

Step 1: *N*-(biphenyl-3-yl)-5-(2-bromoacetamido)pentanamide (**159**)

[0252] Following the same procedure as described for compound **3b** (step 3, scheme 1, example 1) but substituting **156** for **2** to afford **159** (683 mg, 34%) as a light orange solid. LRMS (ESI): (calc) 389.4; (found) 390.1 $(MH)^+$.

Step 2: *N*-(biphenyl-3-yl)-5-(2-(5-nitropyridin-2-ylthio)acetamido)pentanamide (**162a**)

[0253] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting **159** for **3b** and 5-nitropyridine-2-thiol for methyl thioglycolate to afford **162a** (218 mg, 90%) as an orange oil. LRMS (ESI): (calc) 464.2; (found) 465.2 $(MH)^+$.

Step 3: 5-(2-(5-aminopyridin-2-ylthio)acetamido)-*N*-(biphenyl-3-yl)pentanamide (**163a**)

[0254] Following the same procedure as described for compound **151a** (step 4, scheme 18, example 75a) but substituting **162a** for **150a** to afford **163a** (195 mg, 84%) as a white solid. (MeOD-*d4*) δ (ppm) ^{1}H: 7.96-7.94 (m,1H), 7.88-7.87 (m,1H), 7.65-7.61 (m,2H), 7.58-7.54 (m,1H), 7.49-7.34 (m,5H), 7.16-7.12 (m,1H), 7.01-6.96 (m,1H), 3.69 (s,2H), 3.25 (t, J = 8.0 Hz, 2H), 2.40 (t, J = 8.2 Hz, 2H), 1.73-1.64 (m,2H), 1.60-1.52 (m,2H). LRMS (ESI): (calc) 434.6; (found) 435.1 $(MH)^+$.

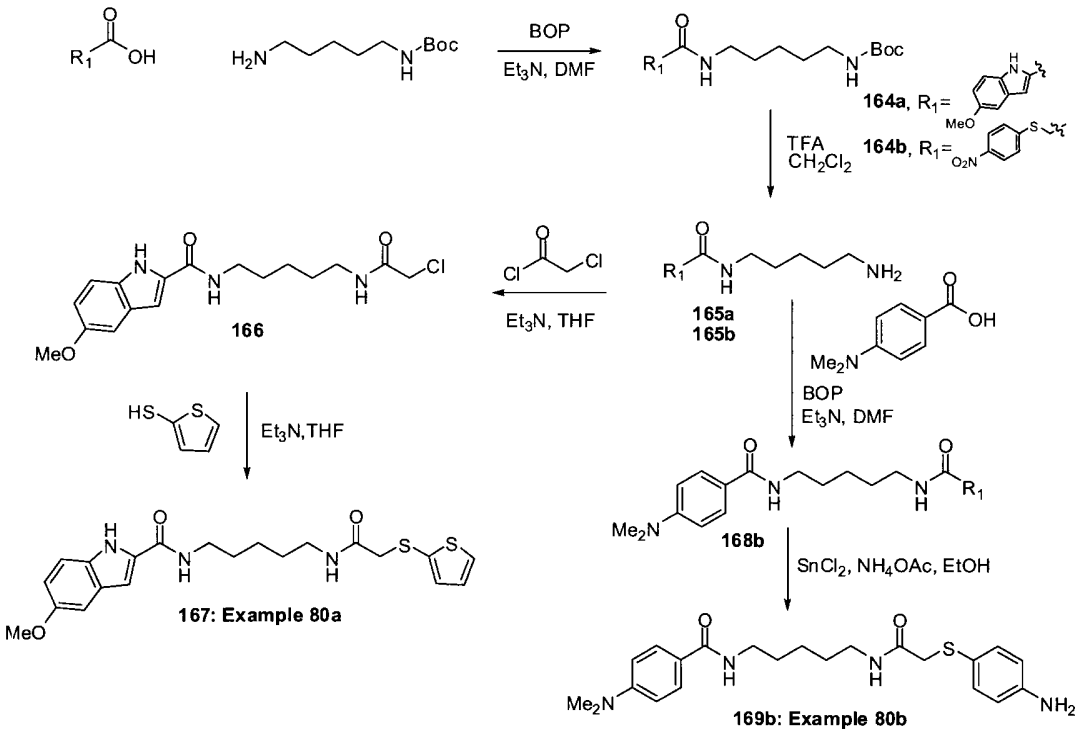
Example 79b

6-(2-(5-aminopyridin-2-ylthio)acetamido)-*N*-(biphenyl-3-yl)hexanamide (**163b**)

Step 1: 6-(2-(5-aminopyridin-2-ylthio)acetamido)-*N*-(biphenyl-3-yl)hexanamide (**163b**)

[0255] Following the same procedure as described for compound **163a** (scheme 20, example 79a) but substituting **3b** for **159** in Step 2 to afford **162b**, which was then immediately reacted according to the same procedure as described for compound **151a** (step 4, scheme 18, example 75a) but substituting the crude material for **150a** to afford **163b** (19 mg, 20%) as a yellow oily solid. (MeOD-*d4*) δ (ppm) ^{1}H: 7.94 (dd, J = 2.7,0.8 Hz, 1H), 7.88-7.85 (m,1H), 7.63-7.58 (m,2H), 7.56-7.52 (m,1H), 7.46-7.32 (m,5H), 7.12 (dd, J = 8.4,0.8 Hz, 1H), 7.00 (dd, J = 5.7,2.7 Hz, 1H), 3.66 (s,2H), 3.21 (t, J = 6.8 Hz, 2H), 2.38 (t, J = 7.8 Hz, 2H), 1.76-1.65 (m,2H), 1.56-1.46 (m,2H), 1.39-1.29 (m,2H). LRMS (ESI): (calc) 448.6; (found) 449.3 $(MH)^+$.

Scheme 21



Example 80a

5-methoxy-*N*-(5-(2-(thiophen-2-ylthio)acetamido)pentyl)-1*H*-indole-2-carboxamide (**167**)

Step 1: *tert*-butyl 5-(5-methoxy-1*H*-indole-2-carboxamido)pentylcarbamate (**164a**)

[0256] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 5-methoxy-1*H*-indole-2-carboxylic acid for *N*-Boc-caproic acid and amine *tert*-butyl 5-aminopentylcarbamate for 3-phenyl aniline to afford **164a** (784 mg, 99%) as a yellow oil. LRMS (ESI): (calc) 375.2; (found) 376.2 $(MH)^+$.

Step 2: *N*-(5-aminopentyl)-5-methoxy-1*H*-indole-2-carboxamide (**165a**)

[0257] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **164a** for **1** to afford **165a** (402 mg, 52%) as a yellow oil. LRMS (ESI): (calc) 275.2; (found) 276.3 $(MH)^+$.

Step 3: *N*-(5-(2-chloroacetamido)pentyl)-5-methoxy-1*H*-indole-2-carboxamide (**166**)

[0258] Following the same procedure as described for compound **3a** (step 3, scheme 1, example 1) but substituting **165a** for **2** to afford **166** (436 mg, 85%) as a yellow solid. LRMS (ESI): (calc) 351.8; (found) 352.5 $(MH)^+$.

Step 4: 5-methoxy-*N*-(5-(2-(thiophen-2-ylthio)acetamido)pentyl)-1*H*-indole-2-carboxamide (**167**)

[0259] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting **166** for **3b** and thiophene-2-thiol for methyl 2-mercaptoacetate to afford **167** (156 mg, 98%) as a light yellow solid. (DMSO-*d6*) δ (ppm) ^{1}H: 11.42 (s,1H), 8.43 (t, J = 5.9 HZ, 1H), 8.04 (t, J = 5.5 Hz, 1H), 7.66-7.64 (m,1H), 7.34 (d, J = 8.8 Hz, 1H), 7.22-7.20 (m,1H), 7.11-7.03 (m,3H), 6.87-6.83 (m,1H), 3.79 (s,3H), 3.50 (s,2H), 3.32-3.25 (m,2H), 3.08 (q, J = 5.9,2.7 Hz, 2H), 1.60-1.50 (m,2H), 1.48-1.39 (m,2H), 1.34-1.25 (m,2H). LRMS (ESI): (calc) 431.6; (found) 432.4 $(MH)^+$.

Example 80b

N-(5-(2-(4-aminophenylthio)acetamido)pentyl)-4-(dimethylamino)benzamide (**169b**)

Step 1: *tert*-butyl 5-(2-(4-nitrophenylthio)acetamido)pentylcarbamate (**164b**)

[0260] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 2-(4-nitrophenylthio)acetic acid for *N*-Boc-caproic acid and amine *tert*-butyl 5-aminopentylcarbamate for 3-phenyl aniline to afford **164b** (668 mg, 99%) as a light yellow oil. LRMS (ESI): (calc) 397.4; (found) 398.2 $(MH)^+$.

Step 2: *N*-(5-aminopentyl)-2-(4-nitrophenylthio)acetamide (**165b**)

[0261] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **164b** for **1** to afford **165b** (500 mg, 99%) as a viscous yellow oil. LRMS (ESI): (calc) 297.4; (found) 298.2 $(MH)^+$.

Step 3: 4-(dimethylamino)-*N*-(5-(2-(4-nitrophenylthio)acetamido)pentyl)benzamide (**168b**)

[0262] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 4-(dimethylamino)benzoic acid for *N*-Boc-caproic acid and amine **165b** for 3-phenyl aniline to afford **168b** (98 mg, 26%) as a yellow solid. LRMS (ESI): (calc) 444.6; (found) 445.2 $(MH)^+$.

Step 4: *N*-(5-(2-(4-aminophenylthio)acetamido)pentyl)-4-(dimethylamino)benzamide (**169b**)

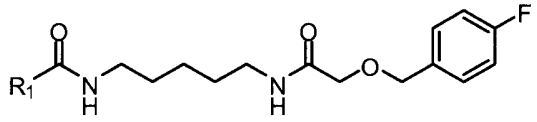
[0263] Following the same procedure as described for compound **163a** (scheme 20, example 79a) but substituting **168b** for **162a** to afford **169b** (11 mg, 12%) as a light yellow solid.

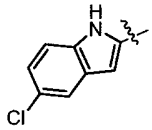
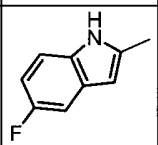
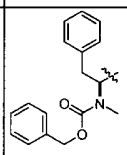
(MeOD-*d4*) δ (ppm) ^{1}H: 7.75-7.70 (m,2H), 7.24-7.20 (m,2H), 6.77-6.72 (m,2H), 6.69-6.63 (m,2H), 3.40-3.32 (m,4H), 3.16 (t, J = 6.7 Hz, 2H), 3.04 (s,6H), 1.66-1.54 (m,2H), 1.52-1.42 (m,2H), 1.34-1.24 (m,2H). LRMS (ESI): (calc) 414.6; (found) 415.5 $(MH)^+$.

Example 80c,d,e

[0264] Example 80c,d,e describe the preparation of compound **168c,d,e** using the same procedures as described for compound **168b** (steps 1 to 3) in Example 80b. Characterization data are presented in a Table 10.

Table 10

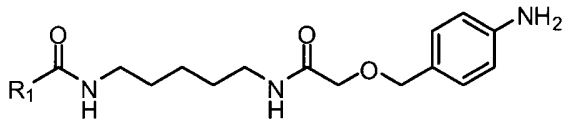


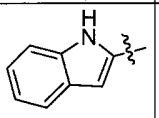
Ex	Cpd	R_1	Name	Characterization	Scheme
80c	168c		5-chloro-*N*-(5-(2-(4-fluorobenzyloxy) acetamido)pentyl)-1*H*-indole-2-carboxamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.60 (dd, J = 2.0,0.6 Hz, 1H), 7.45-7.35 (m,3H), 7.20 (dd, J = 8.8,2.0 Hz, 1H), 7.12-7.03 (m,3H), 4.54 (s,2H), 3.94 (s,2H), 3.43 (t, J = 7.0 Hz, 2H), 3.29 (t, J = 7.0 Hz, 2H), 1.75-1.56 (m,4H), 1.50-1.40 (m,2H) LRMS (ESI): (calc) 445.9; (found) 446.2 $(MH)^+$.	21 (steps 1-3)
80d	168d		5-fluoro-*N*-(5-(2-(4-fluorobenzyloxy) acetamido)pentyl)-1*H*-indole-2-carboxamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.45-7.41 (m,1H), 7.39-7.34 (m,2H), 7.29-7.25 (m,1H), 7.10-6.98 (m,4H), 4.53 (s,2H), 3.93 (s,2H), 3.42 (t, J = 7.0 Hz, 2H), 3.28 (t, J = 7.0 Hz, 2H), 1.73-1.55 (m,4H), 1.47-1.39 (m,2H) LRMS (ESI): (calc) 429.5; (found) 430.2 $(MH)^+$.	21 (steps 1-3)
80e	168e		(*S*)-benzyl 1-(5-(2-(4-fluorobenzyloxy) acetamido)pentyl amino)-1-oxo-3-phenylpropan-2-yl(methyl)carbamate	(MeOD-*d4*) δ (ppm) ^{1}H: 7.46-7.40 (m,2H), 7.39-7.15 (m,10H), 7.15-7.07 (m,2H), 5.15-4.80 (m,3H), 4.59 (s,2H), 3.96 (s,2H), 3.30-3.14 (m,5H), 3.05-2.95 (m,1H), 2.88 (s,3H), 1.57-1.45 (m,4H), 1.35-1.25 (m,2H) LRMS (ESI): (calc) 563.7; (found) 564.4 $(MH)^+$.	21 (steps 1-3)

Example 80f

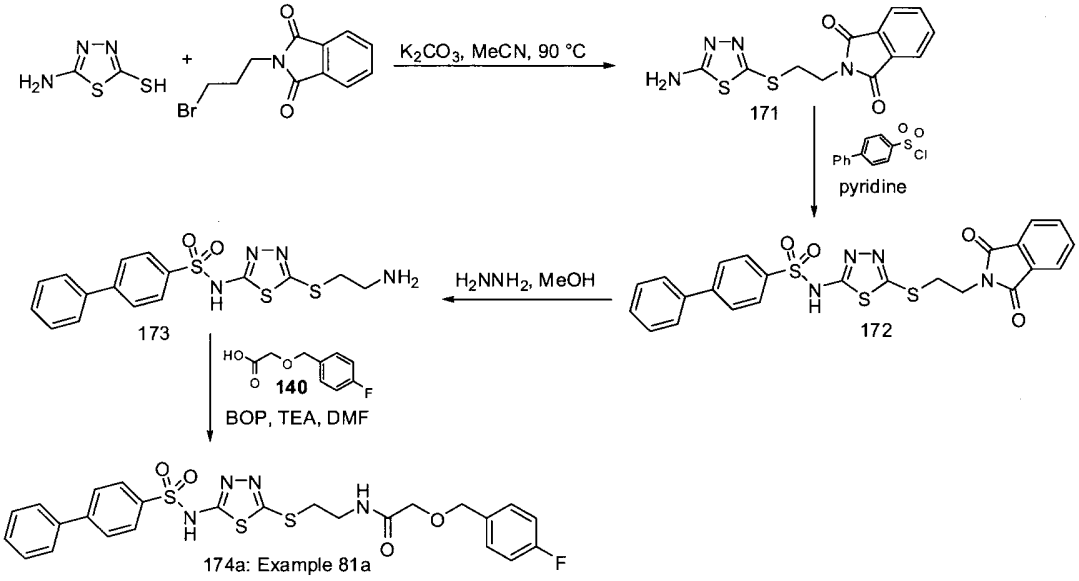
[0265] Example 80f describe the preparation of compound **169c** using the same procedures as described for compound **169b** in Example 80b. Characterization data are presented in a Table 11.

Table 11



Ex	Cpd	R_1	Name	Characterization	Scheme
81f	169c		*N*-(5-(2-(4-aminophenylthio) acetamido)pentyl)-1*H*-indole-2-carboxamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.60 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.27-7.19 (m,3H), 7.10-7.04 (m,2H), 6.68-6.63 (m,2H), 3.42-3.36 (m,4H), 3.17 (t, J = 6.7 Hz, 2H), 1.69-1.59 (m,2H), 1.54-1.43 (m,2H), 1.36-1.26 (m,2H) LRMS (ESI): (calc) 409.5; (found) 411.1 $(MH)^+$.	21 (steps 1-4 (ex 80b))

Scheme 22



Example 81a

N-(2-(5-(biphenyl-4-ylsulfonamido)-1,3,4-thiadiazol-2-ylthio)ethyl)-2-(4-fluorobenzyloxy)acetamide (**174a**)

Step 1: 2-(2-(5-amino-1,3,4-thiadiazol-2-ylthio)ethyl)isoindoline-1,3-dione (**171**)

[0266] To a stirred solution of 5-amino-1,3,4-thiadiazole-2-thiol (600 mg, 4.50 mmol) in solvent (acetonitrile, dimethylformamide or acetone) (15 mL) at room temperature was added 2-(3-bromopropyl)isoindoline-1,3-dione (1.26 g, 4.95 mmol) and K_2CO_3 (3.11 g, 22.5 mmol). The resulting solution was heated to 90 °C for 30 minutes prior to cooling, dilution with brine, adjustment to pH = 13 with NaOH, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was

triturated from 20% MeOH in EtOAc with hexanes to afford **171** (350 mg, 25%) as a light yellow solid. LRMS (ESI): (calc) 306.4; (found) 307.2 $(MH)^+$.

Step 2: *N*-(5-(2-(1,3-dioxoisoindolin-2-yl)ethylthio)-1,3,4-thiadiazol-2-yl)biphenyl-4-sulfonamide (**172**)

[0267] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting amine **171** for amine **2** and biphenyl-4-sulfonyl chloride for 3-bromo-propionyl chloride to afford **172** (226 mg, 38%) as a light yellow solid. LRMS (ESI): (calc.) 522.6; (found) 523.5 $(MH)^+$.

Step 3: *N*-(5-(2-aminoethylthio)-1,3,4-thiadiazol-2-yl)biphenyl-4-sulfonamide (**173**)

[0268] To a stirred solution of *N*-(5-(2-(1,3-dioxoisoindolin-2-yl)ethylthio)-1,3,4-thiadiazol-2-yl)biphenyl-4-sulfonamide **172** (226 mg, 0.432 mmol) in methanol (4 mL) was added hydrazine hydrate (0.042 mL, 0.865 mmol) at room temperature. The resulting solution was stirred for 16 hours prior to removal of the white precipitate by filtration, and evaporation of the filtrate to afford **173** (170 mg, 99%) as a white solid which was used in the subsequent step without further purification. LRMS (ESI): (calc.) 392.5; (found) 393.1 $(MH)^+$.

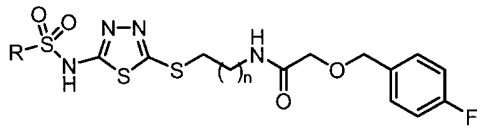
Step 4: *N*-(2-(5-(biphenyl-4-ylsulfonamido)-1,3,4-thiadiazol-2-ylthio)ethyl)-2-(4-fluorobenzyloxy)acetamide (**174a**)

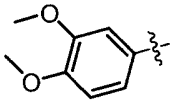
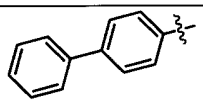
[0269] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 2-(4-fluorobenzyloxy)acetic acid **140** for *N*-Boc-caproic acid and amine **173** for 3-phenyl aniline to afford **174a** (42 mg, 17%) as a white solid. (MeOD-*d4*) δ (ppm) ^1H: 8.20-7.86 (m,3H), 7.68-7.63 (m,2H), 7.60-7.55 (m,2H), 7.46-7.38 (m,2H), 7.38-7.30 (m,3H), 7.06-6.99 (m,2H), 4.47 (s,2H), 3.85 (s,2H), 3.51 (t, J = 6.5 Hz, 2H), 3.21 (t, J = 6.5 Hz, 2H). LRMS (ESI): (calc) 558.7; (found) 559.2 $(MH)^+$.

Example 81b,c

[0270] Example 81b,c describe the preparation of compound **174b,c** using the same procedures as described for compound **174a** in Example 81a. Characterization data are presented in a Table 12.

Table 12



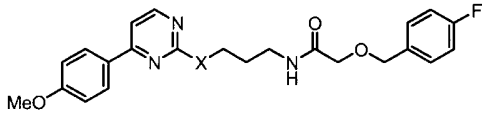
Ex	Cpd	n	R	Name	Characterization	Scheme
81b	174b	2		*N*-(3-(5-(3,4-dimethoxyphenylsulfonamido)-1,3,4-thiadiazol-2-ylthio)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.48 (dd, J = 8.4,2.2 Hz, 1H), 7.46-7.40 (m,3H), 7.14-7.07 (m,2H), 7.02 (d, J = 8.4 Hz, 1H), 4.59 (s,2H), 3.96 (s,2H), 3.88 (s,3H), 3.87 (s,3H), 3.40-3.35 (m,2H), 3.11 (t, J = 7.2 Hz, 2H), 1.96-1.88 (m,2H) LRMS (ESI): (calc) 556.7; (found) 557.4 $(MH)^+$.	22
81c	174c	3		*N*-(4-(5-(biphenyl-4-ylsulfonamido)-1,3,4-thiadiazol-2-ylthio)butyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 8.22-7.86 (m,3H), 7.71-7.58 (m,4H), 7.46-7.32 (m,5H), 7.10-7.02 (m,3H), 4.52 (s,2H), 3.89 (s,2H), 3.21 (t, J = 6.3 Hz, 2H), 3.06 (t, J = 7.0 Hz, 2H), 1.70-1.56 (m,4H) LRMS (ESI): (calc) 586.7; (found) 587.0 $(MH)^+$.	22

Example 81e,f

[0271] Example 81e describe the preparation of compound **174e** using the same procedures as described for compound **174a** in Example 81a. Characterization data is presented in a Table 13.

[0272] Example 81f describe the preparation of compound **174f** using the same procedures as described for compound **7** in Example 2. Characterization data is presented in a Table 13.

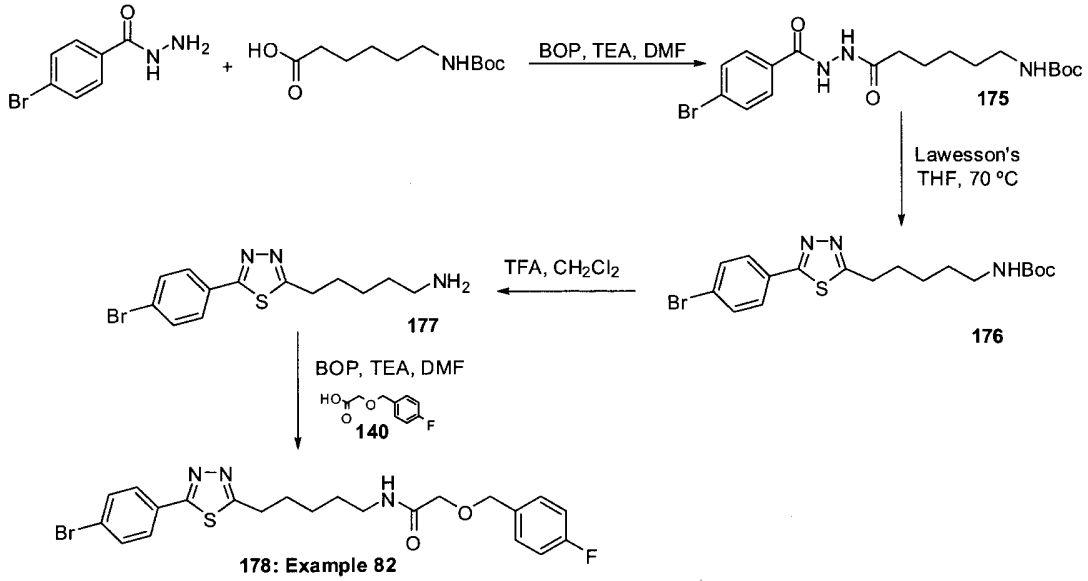
Table 13



Ex	Cpd	X	Name	Characterization	Scheme
81e	174e	S	2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methoxyphenyl)pyrimidin-2-ylthio)propyl)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 8.57 (d, J = 6.1 Hz, 1H), 8.32-8.26 (m,2H), 7.83 (d, J = 6.1 Hz, 1H), 7.44-7.38 (m,2H), 7.18-7.14 (m,2H), 7.11-7.05 (m,2H), 4.59 (s,2H), 3.97 (s,2H), 3.93 (s,3H), 3.48 (t, J = 6.7 Hz, 2H), 3.44 (t, J = 7.4 Hz, 2H), 2.13-2.05 (m,2H) LRMS (ESI): (calc) 441.5; (found) 442.5 $(MH)^+$.	22 (steps 1,3,4)

Ex	Cpd	X	Name	Characterization	Scheme
81f	174f	S=O	2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methoxyphenyl)pyrimidin-2-ylsulfinyl)propyl)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 8.86 (d, J = 5.5 Hz, 1H), 8.32-8.24 (m,2H), 8.01 (d, J = 5.5 Hz, 1H), 7.44-7.35 (m,2H), 7.15-7.04 (m,4H), 4.54 (s,2H), 3.91 (s,5H), 3.42-3.35 (m,3H), 3.25-3.17 (m,1H), 2.20-2.05 (m,1H), 1.90-1.77 (m,1H) LRMS (ESI): (calc) 457.5; (found) 458.3 $(MH)^+$.	22 (steps 1,3,4) 1 (step 6 (ex 2))

Scheme 23



Example 82

N-(5-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**178**)

Step 1: *tert*-butyl 6-(2-(4-bromobenzoyl)hydrazinyl)-6-oxohexylcarbamate (**175**)

[0273] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 4-bromobenzohydrazide for 3-phenyl aniline to afford **175** (1.03 mg, 74%) as a white solid. LRMS (ESI): (calc) 428.4; (found) 429.2 $(MH)^+$.

Step 2: *tert*-butyl 5-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)pentylcarbamate (**176**)

[0274] To a stirred solution of *tert*-butyl 6-(2-(4-bromobenzoyl)hydrazinyl)-6-oxohexylcarbamate **175** (1.03 g, 2.40 mmol) in tetrahydrofuran (20 mL) at room temperature was added Lawesson's reagent (1.07 g, 2.64 mmol). The resulting solution was heated to 70 °C for 2 hours prior to cooling, removal of the solvent, and direct purification of the residue by silica gel column chromatography using EtOAc (0-100%) in hexanes to afford **176** (378 mg, 37%) as a yellow solid. LRMS (ESI): (calc) 426.4; (found) 427.6 $(MH)^+$.

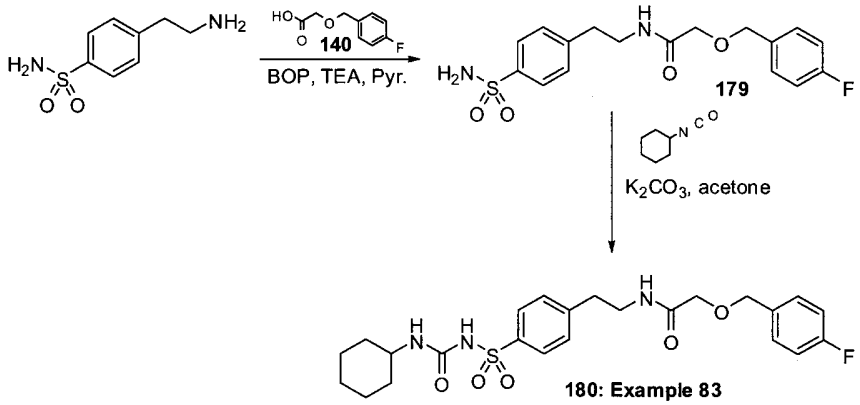
Step 3: 5-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)pentan-1-amine (**177**)

[0275] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **176** for **1** to afford **177** (275 mg, 95%) as light yellow solid. LRMS (ESI): (calc) 326.4; (found) 327.2 $(MH)^+$.

Step 4: *N*-(5-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**178**)

[0276] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 2-(4-fluorobenzyloxy)acetic acid **140** for *N*-Boc-caproic acid and amine **177** for 3-phenyl aniline to afford **178** (21 mg, 5%) as a light yellow solid. (MeOD-*d4*) δ (ppm) ^1H: 7.92-7.87 (m,2H), 7.75-7.70 (m,2H), 7.44-7.38 (m,2H), 7.13-7.07 (m,2H), 4.57 (s,2H), 3.95 (s,2H), 3.28 (t, J = 7.0 Hz, 2H), 3.20 (t, J = 7.6 Hz, 2H), 1.96-1.86 (m,2H), 1.67-1.58 (m,2H), 1.53-1.43 (m,2H). LRMS (ESI): (calc) 492.4; (found) 493.4 $(MH)^+$.

Scheme 24



Example 83

N-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**180**)

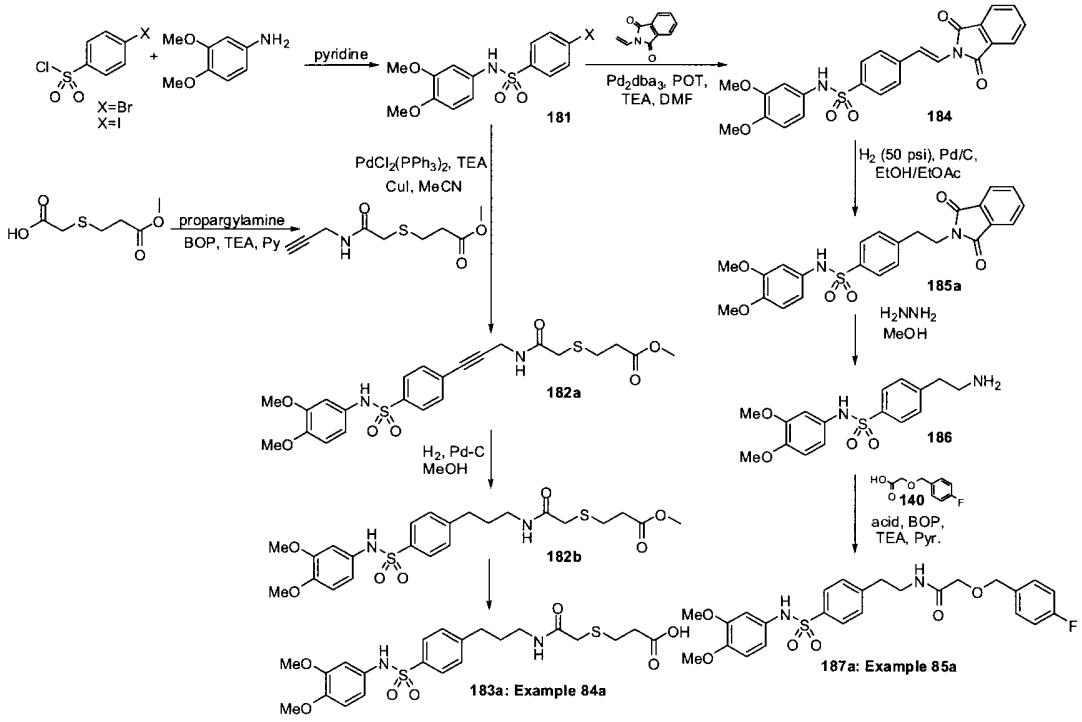
Step 1: 2-(4-fluorobenzyloxy)-*N*-(4-sulfamoylphenethyl)acetamide (**179**)

[0277] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 2-(4-fluorobenzyloxy)acetic acid **140** for *N*-Boc-caproic acid and 4-(2-aminoethyl)benzenesulfonamide for 3-phenyl aniline to afford **179** (275 mg, 55%) as a white solid. (MeOD-*d4*) δ (ppm) ^1H: 7.88-7.83 (m,2H), 7.46-7.36 (m,4H), 7.16-7.10 (m,2H), 4.45 (s,2H), 3.93 (s,2H), 3.54 (t, J = 7.6 Hz, 2H), 2.94 (t, J = 7.0 Hz, 2H). LRMS (ESI): (calc) 366.4; (found) 367.1 $(MH)^+$.

Step 2: *N*-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**180**)

[0278] To a stirred solution of 2-(4-fluorobenzyloxy)-*N*-(4-sulfamoylphenethyl)acetamide **179** (100 mg, 0.273 mmol) in acetone (2 mL) at room temperature was added K_2CO_3 (75 mg, 0.546 mmol), and the resulting solution stirred for 5 minutes prior to the addition of cyclohexylisocyanate (0.05 mL, 0.409 mmol). The resulting solution was heated to reflux for 16 hours prior to cooling, dilution with brine, acidification to pH = 1 with HCl, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was then purified by acid-base extraction to afford **180** (7 mg, 5%) as a white solid. (MeOD-*d*4) δ (ppm) ^{1}H: 7.95-7.90 (m,2H), 7.50-7.46 (m,2H), 7.41-7.35 (m,2H), 7.16-7.09 (m,2H), 4.54 (s,2H), 3.93 (s,2H), 3.55 (t, J = 7.2 Hz, 2H), 3.50-3.38 (m,1H), 2.96 (t, J = 6.8 Hz, 2H), 1.82-1.55 (m,6H), 1.39-1.14 (m,4H). LRMS (ESI): (calc) 491.6; (found) 492.3 $(MH)^+$.

Scheme 25



Example 84a

3-(2-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propylamino)-2-oxoethylthio)propanoic (**183a**)

Step 1: *N*-(3,4-dimethoxyphenyl)-4-iodobenzenesulfonamide (**181**)

[0279] To a stirred solution of 4-iodobenzene-1-sulfonyl chloride (1.00 g, 3.31 mmol) in pyridine (8 mL) at room temperature was added 3,4-dimethoxyaniline (507 mg, 3.31 mmol).

The resulting solution was stirred for 2 hours prior to removal of the solvent, and direct purification of the residue by silica gel column chromatography using MeOH (10%) in EtOAc to afford **181** (769 mg, 55%) as a light pink solid. LRMS (ESI): (calc) 419.2; (found) 420.2 $(MH)^+$.

Intermediate: methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate

[0280] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 2-(3-methoxy-3-oxopropylthio)acetic acid for *N*-Boc-caproic acid and propargylamine for 3-phenyl aniline to afford methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate (633 mg, 69%) as a white solid. LRMS (ESI): (calc) 215.3; (found) 216.2 $(MH)^+$.

Step 2: methyl 3-(2-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)prop-2-ynylamino)-2-oxoethylthio)propanoate (**182a**)

[0281] To a stirred solution of *N*-(3,4-dimethoxyphenyl)-4-iodobenzenesulfonamide **181** (560 mg, 1.34 mmol) in acetonitrile (7 mL) at room temperature was added methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate (316 mg, 1.47 mmol), $PdCl_2(PPh_3)_2$ (47 mg, 0.067 mmol), copper(I) iodide (26 mg, 0.134 mmol), and triethylamine (0.28 mL, 2.01 mmol). The resulting solution was stirred for 2 hours prior to dilution with brine, adjustment to pH = 1 with HCl, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography using EtOAc (0-75%) in hexanes to afford **182a** (336 mg, 49%) as an orange oil. LRMS (ESI): (calc) 506.6; (found) 507.2 $(MH)^+$.

Step 3: methyl 3-(2-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propylamino)-2-oxoethylthio)propanoate (**182b**)

[0282] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **182a** for **73** to afford **182b** (120 mg, 56%) as a yellow oil. (MeOD-*d4*) δ (ppm) ^1H: 7.67-7.62 (m,2H), 7.35-7.31 (m,2H), 6.77 (d, J = 8.6 Hz, 1H), 6.70 (d, J = 2.3 Hz, 1H), 6.60 (dd, J = 8.6,2.3 Hz, 1H), 3.75 (s,3H), 3.71 (s,3H), 3.65 (s,3H), 3.26-3.19 (m,4H), 2.85 (t, J = 6.8 Hz, 2H), 2.72-2.65 (m,4H), 1.87-1.77 (m,2H). LRMS (ESI): (calc) 510.6; (found) 511.3 $(MH)^+$.

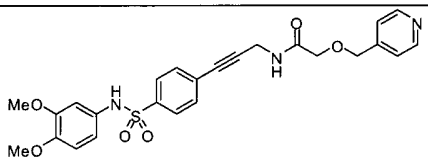
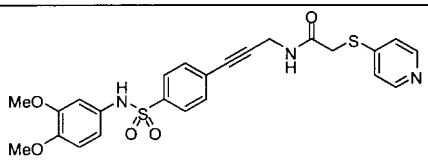
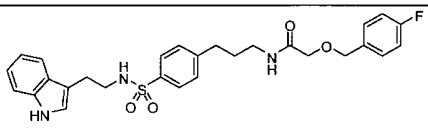
Step 4: 3-(2-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propylamino)-2-oxoethylthio)propanoic (**183a**)

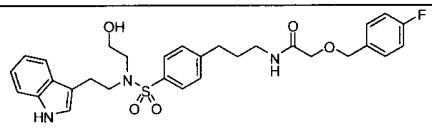
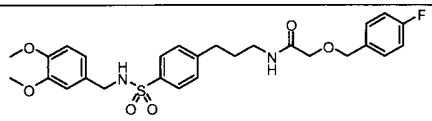
[0283] Following the same procedure as described for compound **5** (scheme 1, example 1) but substituting **182b** for **4** to afford **183a** (79mg, 80%) as a yellow oil. (MeOD-*d4*) δ (ppm) ^1H: 7.67-7.61 (m,2H), 7.37-7.31 (m,2H), 6.78 (d, J = 8.8 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.59 (dd, J = 8.4,2.3 Hz, 1H), 3.76 (s,3H), 3.72 (s,3H), 3.60-3.20 (m,4H), 2.84 (t, J = 6.8 Hz, 2H), 2.74-2.62 (m,4H), 1.88-1.80 (m,2H). LRMS (ESI): (calc) 496.6; (found) 497.2 $(MH)^+$.

Example 84b,c,d,e,f

[0284] Example 84b,c,d,e,f describe the preparation of compound **182b,c,d,e,f** using the same procedures as described for compound **182a** in Example 84a or mention in the table 14. Characterization data are presented in a Table 14.

Table 14

Ex	Cpd	structure	Name	Characterization	Scheme (step)
84b	182b		*N*-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)-2-(pyridin-4-ylmethoxy)acetamide	(DMSO-*d6*) δ (ppm) ^{1}H: 10.01 (s,1H), 8.53 (t, J = 5.7 Hz, 1H), 7.69 (d, J = 8.2 Hz, 3H), 7.59 (d, J = 8.2 Hz, 3H), 6.82 (d, J = 8.4 Hz, 1H), 6.69 (s,1H), 6.58-6.50 (m,1H), 4.61 (br s,2H), 4.21 (d, J = 5.7 Hz, 2H), 4.07 (s,2H), 3.69 (s,3H), 3.66 (s,3H) LRMS (ESI): (calc) 495.6; (found) 496.4 $(MH)^+$.	25 (1-2 (ex 84a))
84c	182c		*N*-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)-2-(pyridin-4-ylthio)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 8.33 (br s,2H), 7.69-7.64 (m,2H), 7.48-7.43 (m,2H), 7.36 (d, J = 5.5 Hz, 2H), 6.80 (d, J = 8.6 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 6.57 (dd, J = 8.6,2.3 Hz, 1H), 4.24 (s,2H), 3.88 (s,2H), 3.78 (s,3H), 3.74 (s,3H) LRMS (ESI): (calc) 497.6; (found) 498.2 $(MH)^+$.	25 (1-2 (ex 84a))
84d	182d		*N*-(3-(4-(*N*-(2-(1*H*-indol-3-yl)ethyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.74-7.70 (m,2H), 7.45-7.30 (m,6H), 7.13-7.05 (m,3H), 7.02-6.95 (m,2H), 4.57 (s,2H), 3.93 (s,2H), 3.29 (t, J = 7.0 Hz, 2H), 3.16 (t, J = 7.8 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 8.2 Hz, 2H), 1.92-1.82 (m,2H) LRMS (ESI): (calc) 523.6; (found) 524.1 $(MH)^+$.	25 (1-3 (ex 84a))

Ex	Cpd	structure	Name	Characterization	Scheme (step)
84e	182e		*N*-(3-(4-(*N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-(2-hydroxyethyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 10.21 (br s,1H), 7.90 (t, J = 5.7 Hz, 1H), 7.73-7.69 (m,2H), 7.55-7.51 (m,1H), 7.40-7.30 (m,5H), 7.12-6.95 (m,5H), 4.53 (s,2H), 3.91 (s,2H), 3.68 (t, J = 6.3 Hz, 2H), 3.48-3.41 (m,2H), 3.30-3.22 (m,4H), 3.06-2.98 (m,2H), 2.70-2.62 (m,2H), 1.87-1.77 (m,2H) LRMS (ESI): (calc) 567.7; (found) 568.4 $(MH)^+$.	25 (1 (ex 84a)) 22 (1 (ex 81a)) 25 (2-3 (ex 84a))
84f	182f		*N*-(3-(4-(*N*-(3,4-dimethoxybenzyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.72-7.68 (m,2H), 7.47-7.41 (m,2H), 7.35-7.30 (m,2H), 7.14-7.07 (m,2H), 6.82-6.77 (m,1H), 6.76-6.71 (m,2H), 4.59 (s,2H), 4.04 (s,2H), 3.96 (s,2H), 3.77 (s,3H), 3.71 (s,3H), 3.28 (t, J = 7.0 Hz, 2H), 2.69 (t, J = 7.8 Hz, 2H), 1.90-1.80 (m,2H) LRMS (ESI): (calc) 530.6; (found) 531.0 $(MH)^+$.	25 (1-3 (ex 84a))

Example 85a

N-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**187a**)

Step 1: 4-bromo-*N*-(3,4-dimethoxyphenyl)benzenesulfonamide(**181**)

[0285] Following the same procedure as described for compound **181** (X = I) (scheme 25, example 84a) but substituting 4-bromobenzene-1-sulfonyl chloride for 4-iodobenzene-1-sulfonyl chloride to afford **181** (X = Br) (887 mg, 90%) as a light pink solid. LRMS (ESI): (calc) 372.2; (found) 373.5 $(MH)^+$.

Step 2: (*E*)-*N*-(3,4-dimethoxyphenyl)-4-(2-(1,3-dioxoisoindolin-2 yl)vinyl)benzenesulfonamide (**184**)

[0286] To a stirred solution of 4-bromo-*N*-(3,4-dimethoxyphenyl)benzenesulfonamide **181** (887 mg, 2.39 mmol) in dimethylformamide (20 mL) at room temperature was added vinyl phthalamide (414 mg, 2.39 mmol), Pd_2dba_3 (131 mg, 0.143 mmol), tri-*o*-tolylphosphine (87 mg, 0.287 mmol), and triethylamine (0.83 mL, 5.98 mmol). The resulting solution was heated to 100 °C for 16 hours prior to cooling, dilution with brine, adjustment to pH = 2 with

HCl, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography using EtOAc (0-100%) in hexanes to afford **184** (285 mg, 26%) as a light yellow solid. LRMS (ESI): (calc) 464.5; (found) 465.2 $(MH)^+$.

Step 3: *N*-(3,4-dimethoxyphenyl)-4-(2-(1,3-dioxoisoindolin-2-yl)ethyl)benzenesulfonamide (**185a**)

[0287] To a solution of (*E*)-*N*-(3,4-dimethoxyphenyl)-4-(2-(1,3-dioxoisoindolin-2-yl)vinyl)benzenesulfonamide **184** (285 mg, 0.614 mmol) in ethanol/ethyl acetate (1:1, 20 mL) was added 10% Pd/C (83 mg). This solution was then placed under 50 p.s.i. of hydrogen in a Parr shaker for 7 hours. Subsequently, the solution was filtered through a pad of celite to remove the catalyst, and the filtrate evaporated to afford **185a** (190 mg, 67%) as a light yellow solid which was used in the subsequent reaction without further purification. LRMS (ESI): (calc) 466.5; (found) 467.2 $(MH)^+$.

Step 4: 4-(2-aminoethyl)-*N*-(3,4-dimethoxyphenyl)benzenesulfonamide (**186**)

[0288] Following the same procedure as described for compound **173** (scheme 22, example 81a) but substituting **185a** for **172** to afford **186** (100 mg, 73%) as a light yellow foam. LRMS (ESI): (calc) 336.4; (found) 337.4 $(MH)^+$.

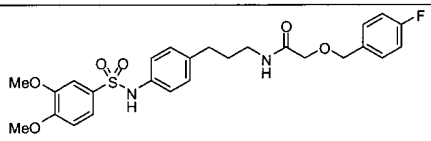
Step 5: *N*-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**187a**)

[0289] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting 2-(4-fluorobenzyloxy)acetic acid **140** for *N*-Boc-caproic acid and **186** for 3-phenyl aniline to afford **187a** (30 mg, 2%) as a white solid. (MeOD-*d4*) δ (ppm) ^1H: 7.69-7.64 (m,2H), 7.40-7.32 (m,4H), 7.15-7.07 (m,2H), 6.77 (d, J = 8.6 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.58 (dd, J = 8.4,2.3 Hz, 1H), 4.50 (s,2H), 3.88 (s,2H), 3.75 (s,3H), 3.73 (s,3H), 3.50 (t, J = 7.0 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H). LRMS (ESI): (calc) 502.6; (found) 503.2 $(MH)^+$.

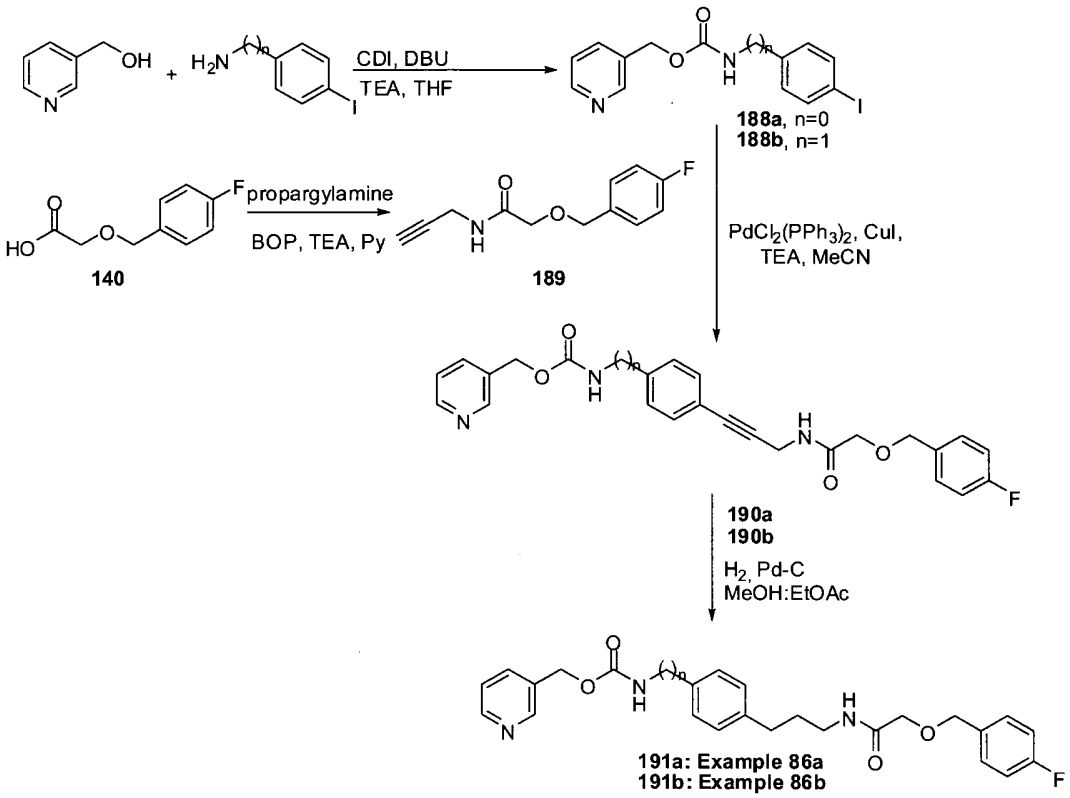
Example 85b

[0290] Example 85b describe the preparation of compound **185b** using the same procedures as described for compound **185a** in Example 85a. Characterization data are presented in a Table 15.

Table 15

Ex	Cpd	structure	Name	Characterization	Scheme
85b	185 b		*N*-(3-(4-(3,4-dimethoxyphenylsulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.46-7.41 (m,2H), 7.34 (dd, J = 8.4,2.2 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 7.15-7.07 (m,4H), 7.04-6.98 (m,3H), 4.58 (s,2H), 3.93 (s,2H), 3.87 (s,3H), 3.77 (s,3H), 3.24 (t, J = 7.0 Hz, 2H), 2.58 (t, J = 7.8 Hz, 2H), 1.84-1.74 (m,2H) LRMS (ESI): (calc) 516.6; (found) 517.0 $(MH)^+$.	25 (steps 1-3 (ex 85a))

Scheme 26



Example 86a

pyridin-3-ylmethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylcarbamate (**191a**)

Step 1: pyridin-3-ylmethyl 4-iodophenylcarbamate (**188a**)

[0291] To a stirred solution of carbonyl diimidazole (CDI) (2.69 g, 16.55 mmol) in tetrahydrofuran (12 mL) at 0 °C was added a solution of pyridin-3-ylmethanol (1.61 mL, 16.55 mmol) in tetrahydrofuran (5 mL). The resulting solution was stirred for 1 hour at room temperature prior to the addition of 4-iodoaniline (3.62 g, 16.55 mmol), DBU (2.48 mL, 16.55 mmol) and triethylamine (2.31 mL, 16.55 mmol) dissolved in tetrahydrofuran (10 mL). The resulting solution was then stirred at room temperature for 16 hours prior to dilution with brine, adjustment to pH = 13 with NaOH, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was the taken up in ethyl acetate, and triturated with hexanes to afford **188a** (1.27 g, 17%) as a light grey solid. LRMS (ESI): (calc) 354.2; (found) 355.2 $(MH)^+$.

Step 2: 2-(4-fluorobenzyloxy)-*N*-(prop-2-ynyl)acetamide (**189**)

[0292] Following the same procedure as described for methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate (scheme 25, example 84a) but substituting 2-(4-fluorobenzyloxy)acetic acid **140** for 2-(3-methoxy-3-oxopropylthio)acetic acid to afford **189** (1.52 g, 62%) as a light yellow oil. LRMS (ESI): (calc) 221.2; (found) 222.6 $(MH)^+$.

Step 3: pyridin-3-ylmethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)prop-1-ynyl)phenylcarbamate (**190a**)

[0293] Following the same procedure as described for compound **182a** (scheme 25, example 84a) but substituting **188a** for **181** and **189** for methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate to afford **190a** (270 mg, 62%) as a light grey solid. (MeOD-*d4*) δ (ppm) ^1H: 8.66 (s,1H), 8.58-8.50 (m,1H), 7.98-7.93 (m,1H), 7.53-7.33 (m,7H), 7.14-7.08 (m,2H), 5.28 (s,2H), 4.62 (s,2H), 4.25 (s,2H), 4.02 (s,2H). LRMS (ESI): (calc) 447.5; (found) 448.2 $(MH)^+$.

Step 4: pyridin-3-ylmethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylcarbamate (**191a**)

[0294] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **190a** for **73** to afford **191a** (40 mg, 50%) as a white solid. (MeOD-*d4*) δ (ppm) ^1H: 8.70-8.62 (m,1H), 8.57-8.50 (m,1H), 7.98-7.93 (m,1H), 7.53-7.34 (m,5H), 7.17-7.08 (m,4H), 5.26 (s,2H), 4.58 (s,2H), 3.94 (s,2H), 3.28 (t, J = 7.0 Hz, 2H), 2.61 (t, J = 7.4 Hz, 2H), 1.88-1.79 (m,2H). LRMS (ESI): (calc) 451.5; (found) 452.2 $(MH)^+$.

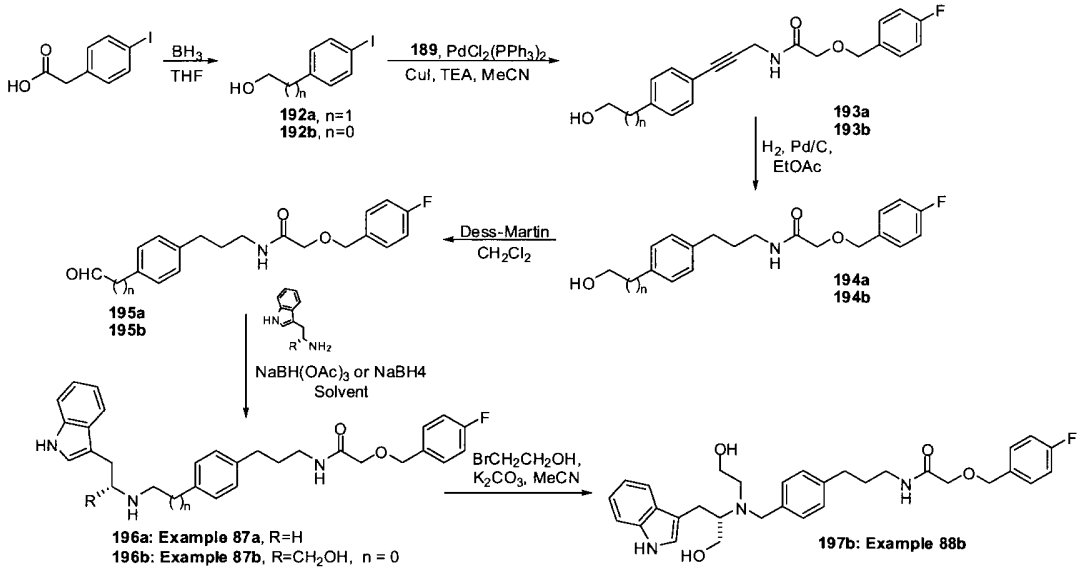
Example 86b

pyridin-3-ylmethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylcarbamate (**191b**)

Step 1-4: pyridin-3-ylmethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylcarbamate (**191b**)

[0295] Following the same procedure as described for compound **191a** (scheme 26, example 88a) but substituting (4-iodophenyl)methanamine for 4-iodoaniline to afford **191b** (25 mg, 23%) as a light yellow oil. (MeOD-*d4*) δ (ppm) ^{1}H: 8.59 (s,1H), 8.50 (d, J = 3.9 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.47-7.40 (m,3H), 7.24-7.07 (m,6H), 5.18 (s,2H), 4.59 (s,2H), 4.28 (s,2H), 3.94 (s,2H), 3.27 (t, J = 7.0 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 1.88-1.78 (m,2H). LRMS (ESI): (calc) 465.5; (found) 466.3 $(MH)^+$.

Scheme 27



Example 87a

N-(3-(4-(2-(2-(1*H*-indol-3-yl)ethylamino)ethyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**196a**)

Step 1: 2-(4-iodophenyl)ethanol (**192a**)

[0296] To a stirred solution of 2-(4-iodophenyl)acetic acid (2.00 g, 7.63 mmol) in tetrahydrofuran (150 mL) at room temperature was added borane-tetrahydrofuran complex (1.0 M in tetrahydrofuran, 7.63 mL, 7.63 mmol). The resulting solution was stirred for 6 hours prior to dilution with brine, adjustment to pH = 13 with NaOH, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford **192a** (620 mg, 33%) as a light orange solid which was used in the subsequent reaction without further purification. LRMS (ESI): (calc) 248.1; (found) 271.1 $(M+Na)^+$.

Step 2: 2-(4-fluorobenzyloxy)-*N*-(3-(4-(2-hydroxyethyl)phenyl)prop-2-ynyl)acetamide (**193a**)

[0297] Following the same procedure as described for compound **182a** (scheme 25, example 84a) but substituting **192a** for **181** and **189** for methyl 3-(2-oxo-2-(prop-2-

ynylamino)ethylthio)propanoate to afford **193a** (578 mg, 70%) as a light orange oil. LRMS (ESI): (calc) 341.4; (found) 342.2 $(MH)^+$.

Step 3: 2-(4-fluorobenzyloxy)-*N*-(3-(4-(2-hydroxyethyl)phenyl)propyl)acetamide (**194a**)

[0298] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **193a** for **73** to afford **194a** (500 mg, 86%) as a light orange oil. LRMS (ESI): (calc) 345.4; (found) 346.2 $(MH)^+$.

Step 4: 2-(4-fluorobenzyloxy)-*N*-(3-(4-(2-oxoethyl)phenyl)propyl)acetamide (**195a**)

[0299] To a stirred solution of 2-(4-fluorobenzyloxy)-*N*-(3-(4-(2-hydroxyethyl)phenyl)propyl)acetamide **194a** (500 mg, 1.45 mmol) in dichloromethane (5 mL) at room temperature was added Dess-Martin reagent (737 mg, 1.74 mmol). The resulting solution was stirred for 2 hours prior to dilution with brine, adjustment to pH = 13 with NaOH, and extraction with ethy lacetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to afford **195a** (392 mg, 79%) as a light yellow oil which was used in the subsequent reaction without further purification. LRMS (ESI): (calc) 343.4; (found) 344.2 $(MH)^+$.

Step 5: *N*-(3-(4-(2-(2-(1*H*-indol-3-yl)ethylamino)ethyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**196a**)

[0300] To a stirred solution of 2-(4-fluorobenzyloxy)-*N*-(3-(4-(2-oxoethyl)phenyl)propyl)acetamide **195a** (196 mg, 0.571 mmol) in solvent (tetrahydrofuran or methanol) (4 mL) at room temperature was added tryptamine (101 mg, 0.628 mmol), and the resulting solution stirred for 16 hours. Reductant ($NaBH(OAc)_3$ or $NaBH_4$) (0.742 mmol) was then added, and the solution stirred for a further 16 hours prior to dilution with brine, adjustment to pH = 13 with NaOH, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography using MeOH (0-30%) in EtOAc to afford **196a** (12 mg, 4%) as a light yellow oil. (MeOD-*d4*) δ (ppm) ^1H: 7.58-7.53 (m,1H), 7.46-7.40 (m,2H), 7.37-7.33 (m,1H), 7.14-6.95 (m,9H), 4.59 (s,2H), 3.96 (s,2H), 3.26 (t, J = 7.0 Hz, 2H), 3.00-2.92 (m,4H), 2.85 (t, J = 7.0 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.58 (t, J = 8.0 Hz, 2H), 1.86-1.76 (m,2H). LRMS (ESI): (calc) 487.6; (found) 488.6 $(MH)^+$.

Example 87b

(*S*)-2-(4-fluorobenzyloxy)-*N*-(3-(4-((1-hydroxy-3-(1*H*-indol-3-yl)propan-2-ylamino)methyl)phenyl)propyl)acetamide (**196b**)

Step 1: (*S*)-2-(4-fluorobenzyloxy)-*N*-(3-(4-((1-hydroxy-3-(1*H*-indol-3-yl)propan-2-ylamino)methyl)phenyl)propyl)acetamide (**196b**)

[0301] Following the same procedure as described for compound **196a** (scheme 27, steps 2-5, example 87a), but substituting (4-iodophenyl)methanol for **192a** in Step 1, and (*S*)-2-amino-3-(1*H*-indol-3-yl)propan-1-ol for tryptamine in Step 5 to afford **196b** (231 mg, 50%) as a light yellow oil. (MeOD-*d4*) δ (ppm) ^{1}H: 7.49-7.45 (m,1H), 7.40-7.34 (m,3H), 7.14-7.03 (m,8H), 7.20-6.96 (m,1H), 4.51 (s,2H), 3.92 (s,2H), 3.78 (d, J = 1.8 Hz, 2H), 3.64-3.52 (m,2H), 3.24 (t, J = 7.2 Hz, 2H), 3.10-3.00 (m,1H), 2.91 (d, J = 7.0 Hz, 2H), 2.57 (t, J = 7.8 Hz, 2H), 1.84-1.74 (m,2H). LRMS (ESI): (calc) 503.6; (found) 504.9 $(MH)^+$.

Example 88b

(*S*)-2-(4-fluorobenzyloxy)-*N*-(3-(4-(((1-hydroxy-3-(1*H*-indol-3-yl)propan-2-yl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)acetamide (**197b**)

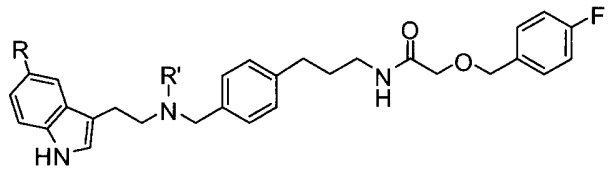
Step 1: (*S*)-2-(4-fluorobenzyloxy)-*N*-(3-(4-(((1-hydroxy-3-(1*H*-indol-3-yl)propan-2-yl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)acetamide (**197b**)

[0302] To a stirred solution of (*S*)-2-(4-fluorobenzyloxy)-*N*-(3-(4-((1-hydroxy-3-(1*H*-indol-3-yl)propan-2-ylamino)methyl)phenyl)propyl)acetamide **196b** (170 mg, 0.338 mmol) in acetonitrile (4 mL) at room temperature was added 2-bromoethanol (0.24 mL, 3.38 mmol) and K_2CO_3 (140 mg, 1.01 mmol). The resulting solution was heated to 60 °C for 16 hours prior to cooling, dilution with brine, adjustment to pH = 10 with NaOH, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography using MeOH (0-30%) in EtOAc to afford **197b** (67 mg, 36%) as a colorless oil. (MeOD-*d4*) δ (ppm) ^{1}H: 7.46-7.32 (m,4H), 7.27-7.21 (m,2H), 7.14-7.06 (m,5H), 7.02-6.94 (m,2H), 4.55 (s,2H), 3.94 (s,2H), 3.88 (d, J = 13.7 Hz, 1H), 3.73 (d, J = 13.7 Hz, 1H), 3.63-3.41 (m,4H), 3.26 (t, J = 7.2 Hz, 2H), 3.25-3.16 (m,1H), 3.06 (dd, J = 14.3,5.3 Hz, 1H), 2.99-2.90 (m,1H), 2.78-2.63 (m,2H), 2.61 (t, J = 7.8 Hz, 2H), 1.87-1.77 (m,2H). LRMS (ESI): (calc) 547.7; (found) 548.2 $(MH)^+$.

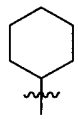
Example 87c-l and 88c-o

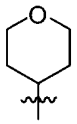
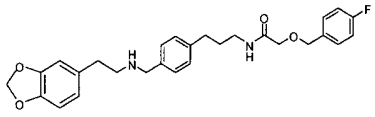
[0303] Example 87c-l and 88c-o describe the preparation of compound **196c-l** and **197c-o** using the same procedures as described for compound **196a,b and 197b** in Example 87a,b and 88b. Characterization data are presented in a Table 16.

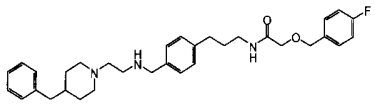
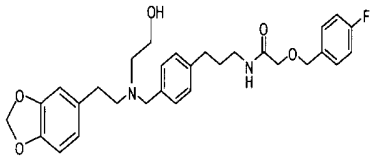
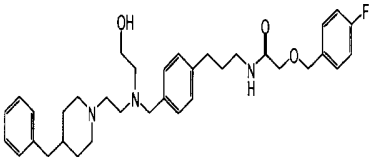
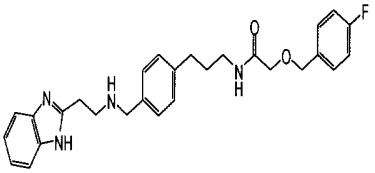
Table 16

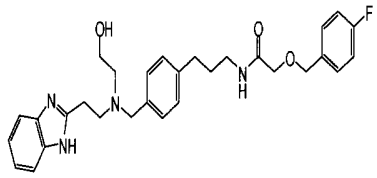
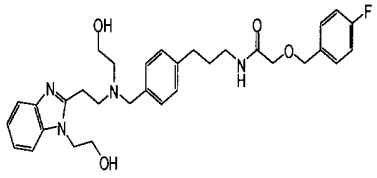
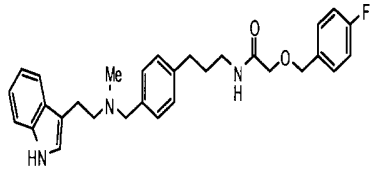
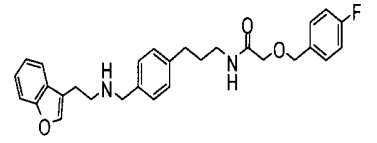


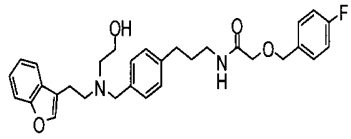
Ex	Cpd	R or structure	R' or structure	Name	Characterization	Scheme (steps)
87c	196c	OMe	H	2-(4-fluorobenzyloxy)-*N*-(3-(4-((2-(5-methoxy-1H-indol-3-yl)ethylamino) methyl)phenyl) propyl)acetamide	(MeOD-*d*4) (ppm): 7.35 (dd, J=8.6, 5.5 Hz, 2H), 7.20 (d, J=8.8 Hz, 1H), 7.12 - 6.95 (m, 8H), 6.73 (dd, J=8.6, 2.4 Hz, 1H), 4.49 (s, 2H), 3.89 (s, 2H), 3.74 (s, 3H), 3.67 (s, 2H), 3.21 (t, J=7.0 Hz, 2H), 2.92 - 2.81 (m, 4H), 2.55 (t, J=7.6 Hz, 2H), 1.78 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 503.2; (found) 504.3 $(MH)^+$.	27(2-5)
87d	196d	OBn	H	*N*-(3-(4-((2-(5-(benzyloxy)-1H-indol-3-yl)ethylamino) methyl)phenyl) propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) (ppm): 7.43 - 7.40 (m, 2H), 7.37 - 7.20 (m, 6H), 7.13 - 6.99 (m, 8H), 6.82 (dd, J=8.6, 2.3 Hz, 1H), 5.00 (s, 2H), 4.50 (s, 2H), 3.88 (s, 2H), 3.68 (s, 2H), 3.18 (t, J=7.2 Hz, 2H), 2.92 - 2.81 (m, 4H), 2.53 (t, J=7.4 Hz, 2H), 1.74 (quintet, J=7.2 Hz, 2H). LRMS (ESI): (calc) 579.3; (found) 580.6 $(MH)^+$.	27(2-5)
87e	196e	F	H	*N*-(3-(4-((2-(5-fluoro-1H-indol-3-yl)ethylamino) methyl)phenyl) propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) (ppm): 7.40 (dd, J=8.6, 5.5 Hz, 2H), 7.28 (dd, J=8.8, 4.5 Hz, 1H), 7.20 - 7.04 (m, 8H), 6.84 (td, J=9.0, 2.6 Hz, 1H), 4.55 (s, 2H), 3.92 (s, 2H), 3.77 (s, 2H), 3.24 (t, J=7.2 Hz, 2H), 2.96 - 2.87 (m, 4H), 2.61 (t, J=7.4 Hz, 2H), 1.81 (quintet, J=7.2 Hz, 2H). LRMS (ESI): (calc) 491.3; (found) 492.7 $(MH)^+$.	27(2-5)
87f	196f	H	H	*N*-(3-(4-((2-(1H-indol-3-yl)ethylamino) methyl)phenyl) propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) (ppm): 7.49 (dt, J=7.8, 1.0 Hz, 1H), 7.40 (dd, J=8.8, 5.3 Hz, 2H), 7.32 (dt, J=8.0, 0.8 Hz, 1H), 7.17 - 7.02 (m, 8H), 6.98 - 6.94 (m, 1H), 4.54 (s, 2H), 3.91 (s, 2H), 3.72 (s, 2H), 3.23 (t, J=7.0 Hz, 2H), 2.99 - 2.87 (m, 4H), 2.60 (t, J=7.4 Hz, 2H), 1.80 (quintet, J=7.2 Hz, 2H). LRMS (ESI): (calc) 473.3; (found) 474.3 $(MH)^+$.	27(2-5)

Ex	Cpd	R or structure	R' or structure	Name	Characterization	Scheme (steps)
88c	197c	OMe	-CH2CH2OH	2-(4-fluorobenzyloxy)-*N*-(3-(4-(((2-hydroxyethyl)(2-(5-methoxy-1H-indol-3-yl)ethyl)amino)methyl)phenyl)propyl)acetamide	(MeOD-*d*4) □(ppm): 7.38 (dd, J=8.8, 5.5 Hz, 2H), 7.24 (d, J=8.2 Hz, 2H), 7.18 (d, J=8.6 Hz, 2H), 7.12 - 7.04 (m, 4H), 6.95 (s, 1H), 6.84 (d, J=2.4 Hz, 1H), 6.70 (dd, J=8.8, 2.3 Hz, 1H), 4.53 (s, 2H), 3.91 (s, 2H), 3.76 - 3.62 (m, 7H), 3.24 (t, J=7.2 Hz, 2H), 2.91 - 2.72 (m, 6H), 2.59 (t, J=7.4 Hz, 2H), 1.80 (quintet, J=7.2 Hz, 2H). LRMS (ESI): (calc) 547.3; (found) 548.5 $(MH)^+$.	27 (2-6)
88d	197d	OBn	-CH2CH2OH	*N*-(3-(4-(((2-(5-(benzyloxy)-1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.43 - 7.18 (m, 10H), 7.09 - 7.02 (m, 4H), 6.95 - 6.92 (m, 2H), 6.78 (dd, J=8.8, 2.3 Hz, 1H), 4.96 (s, 2H), 4.50 (s, 2H), 3.87 (s, 2H), 3.66 - 3.60 (m, 4H), 3.17 (t, J=7.0 Hz, 2H), 2.88 - 2.84 (m, 2H), 2.76 - 2.68 (m, 4H), 2.51 (t, J=7.4 Hz, 2H), 1.73 (quintet, J=7.6 Hz, 2H). LRMS (ESI): (calc) 523.3; (found) 524.3 $(MH)^+$.	27 (2-6)
88e	197e	F	-CH2CH2OH	*N*-(3-(4-(((2-(5-fluoro-1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.39 (dd, J=8.8, 5.5 Hz, 2H), 7.25 - 7.21 (m, 3H), 7.15 - 7.03 (m, 5H), 6.97 (dd, J=10.0, 2.3 Hz, 1H), 6.79 (td, J=9.0, 2.3 Hz, 1H), 4.54 (s, 2H), 3.91 (s, 2H), 3.69 (s, 2H), 3.63 (t, J=6.5 Hz, 2H), 3.25 (t, J=7.0 Hz, 2H), 2.88 - 2.71 (m, 8H), 2.61 (t, J=7.7 Hz, 2H), 1.82 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 535.3; (found) 536.6 $(MH)^+$.	27 (2-6)
88g	197g	H		*N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(cyclohexyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 8.55 (s, 1H), 7.41 - 7.37 (m, 4H), 7.33 - 7.26 (m, 3H), 7.10 - 7.03 (m, 4H), 6.96 (t, J=7.8 Hz, 1H), 4.55 (s, 2H), 4.24 (s, 2H), 3.93 (s, 2H), 3.28 - 3.24 (m, 5H), 2.99 (t, J=7.4 Hz, 2H), 2.67 (t, J=7.6 Hz, 2H), 2.08 (d, J=10.7 Hz, 2H), 1.92 - 1.80 (m, 4H), 1.70 - 1.53 (m, 3H), 1.37 - 1.16 (m, 3H). LRMS (ESI): (calc) 555.3; (found) 556.3 $(MH)^+$.	27 (2-6)

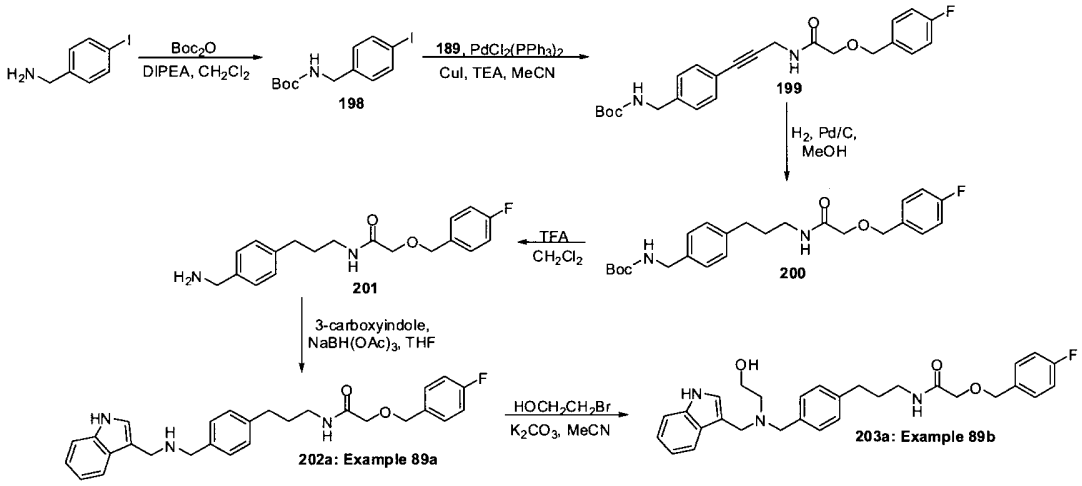
Ex	Cpd	R or structure	R' or structure	Name	Characterization	Scheme (steps)
88h	197h	H		*N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(tetrahydro-2H-pyran-4-yl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.40 - 7.21 (m, 8H), 7.08 - 6.99 (m, 4H), 6.94 - 6.90 (m, 1H), 4.54 (s, 2H), 4.02 - 3.92 (m, 6H), 3.37 (t, J=10.4 Hz, 2H), 3.26 (t, J=7.2 Hz, 2H), 3.18 - 3.17 (m, 1H), 3.03 - 2.96 (m, 2H), 2.91 - 2.87 (m, 2H), 2.65 (t, J=7.2 Hz, 2H), 1.88 - 1.69 (m, 6H). LRMS (ESI): (calc) 557.3; (found) 558.3 $(MH)^+$.	27 (2-6)
88k	197k	H	$-CH_2CH_2CH_2OH$	*N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(3-hydroxypropyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.39 - 7.32 (m, 3H), 7.29 (d, J=8.0 Hz, 1H), 7.21 (d, J=8.0 Hz, 2H), 7.13 (d, J=7.8 Hz, 2H), 7.08 - 7.01 (m, 3H), 6.96 (s, 1H), 6.92 (t, J=7.6 Hz, 1H), 4.52 (s, 2H), 3.90 (s, 2H), 3.64 - 3.60 (m, 4H), 3.24 (t, J=7.2 Hz, 2H), 2.93 - 2.89 (m, 2H), 2.76 - 2.68 (m, 4H), 2.60 (t, J=7.4 Hz, 2H), 1.85 - 1.79 (m, 4H). LRMS (ESI): (calc) 531.3; (found) 532.4 $(MH)^+$.	27 (2-6)
88l	197l	H	$-CH_2CH_2(OH)CH_2OH$	*N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2,3-dihydroxypropyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.39 - 7.32 (m, 3H), 7.29 (d, J=8.2 Hz, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.12 - 7.01 (m, 5H), 6.95 (s, 1H), 6.91 (t, J=7.0 Hz, 1H), 4.52 (s, 2H), 3.92 (s, 2H), 3.80 - 3.65 (m, 3H), 3.60 - 3.54 (m, 1H), 3.48 - 3.43 (m, 1H), 3.24 (t, J=7.0 Hz, 2H), 2.94 - 2.89 (m, 2H), 2.81 - 2.77 (m, 2H), 2.70 - 2.57 (m, 4H), 1.81 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 547.3; (found) 548.3 $(MH)^+$.	27 (2-6)
87g	196g			*N*-(3-(4-((2-(benzo[d][1,3]dioxol-5-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4)) □(ppm): 7.40 (dd, J=8.4, 5.9 Hz, 2H), 7.19 - 7.13 (m, 4H), 7.07 (t, J=8.8 Hz, 2H), 6.71 - 6.60 (m, 3H), 5.86 (s, 2H), 4.54 (s, 2H), 3.91 (s, 2H), 3.69 (s, 2H), 3.23 (t, J=7.0 Hz, 2H), 2.77 - 2.68 (m, 4H), 2.59 (t, J=7.4 Hz, 2H), 1.80 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 478.2; (found) 479.6 $(MH)^+$.	27(2-5)

Ex	Cpd	R or structure	R' or structure	Name	Characterization	Scheme (steps)
87h	196h			*N*-(3-(4-((2-(4-benzylpiperidin-1-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.41 (dd, J=8.2, 5.5 Hz, 2H), 7.26 - 7.22 (m, 4H), 7.18 - 7.06 (m, 7H), 4.57 (s, 2H), 3.92 (s, 2H), 3.72 (s, 2H), 3.24 (t, J=7.0 Hz, 2H), 2.84 (d, J=11.8 Hz, 2H), 2.69 (t, J=6.6 Hz, 2H), 2.61 (t, J=7.4 Hz, 2H), 2.53 - 2.45 (m, 4H), 1.96 - 1.90 (m, 2H), 1.81 (quintet, J=7.2 Hz, 2H), 1.62 - 1.51 (m, 3H), 1.31 - 1.21 (m, 2H). LRMS (ESI): (calc) 531.3; (found) 532.5 $(MH)^+$.	27(2-5)
88i	197i			*N*-(3-(4-(((2-(benzo[d][1,3]dioxol-5-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.39 (dd, J=8.8, 5.5 Hz, 2H), 7.20 (d, J=8.0 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 7.07 (t, J=8.8 Hz, 2H), 6.67 (d, J=7.9 Hz, 1H), 6.60 - 6.55 (m, 2H), 5.85 (s, 2H), 4.55 (s, 2H), 3.92 (s, 2H), 3.64 (s, 2H), 3.24 (t, J=7.0 Hz, 2H), 2.67 - 2.58 (m, 8H), 1.81 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 522.3; (found) 523.3 $(MH)^+$.	27 (2-6)
88j	197j			*N*-(3-(4-(((2-(4-benzylpiperidin-1-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.40 (dd, J=8.5, 5.5 Hz, 2H), 7.26 - 7.22 (m, 4H), 7.16 - 7.05 (m, 7H), 4.55 (s, 2H), 3.92 (s, 2H), 3.60 - 3.56 (m, 4H), 3.22 (t, J=7.0 Hz, 2H), 2.77 (d, J=11.7 Hz, 2H), 2.66 - 2.57 (m, 6H), 2.53 - 2.42 (m, 4H), 1.96 - 1.89 (m, 2H), 1.78 (quintet, J=7.2 Hz, 2H), 1.60 - 1.48 (m, 3H), 1.29 - 1.20 (m, 2H). LRMS (ESI): (calc) 575.4; (found) 576.6 $(MH)^+$.	27 (2-6)
87i	196i			*N*-(3-(4-((2-(1H-benzo[d]imidazol-2-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.50 - 7.47 (m, 2H), 7.38 (dd, J=8.4, 5.5 Hz, 2H), 7.24 (d, J=7.8 Hz, 2H), 7.20 - 7.17 (m, 2H), 7.14 (d, J=8.0 Hz, 2H), 7.06 (t, J=8.8 Hz, 2H), 4.54 (s, 2H), 3.91 (s, 2H), 3.80 (s, 2H), 3.23 (t, J=7.0 Hz, 2H), 3.09 (s, 4H), 2.59 (t, J=7.4 Hz, 2H), 1.79 (quintet,J=7.4 Hz, 2H). LRMS (ESI): (calc) 474.2; (found) 475.3 $(MH)^+$.	27 (2-5)

Ex	Cpd	R or structure	R' or structure	Name	Characterization	Scheme (steps)
88m	197m			*N*-(3-(4-(((2-(1H-benzo[d]imidazol-2-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.47 - 7.45 (m, 2H), 7.40 (dd, J=8.8, 5.7 Hz, 2H), 7.20 - 7.15 (m, 2H), 7.09 - 7.02 (m, 4H), 6.90 (d, J=8.2 Hz, 2H), 4.55 (s, 2H), 3.92 (s, 2H), 3.67 (t, J=5.6 Hz, 2H), 3.62 (s, 2H), 3.19 (t, J=7.2 Hz, 2H), 3.01 (t, J=6.8 Hz, 2H), 2.90 (t, J=6.1 Hz, 2H), 2.72 (t, J=6.7 Hz, 2H), 2.50 (t, J=7.4 Hz, 2H), 1.72 (quintet, J=7.2 Hz, 2H). LRMS (ESI): (calc) 518.3; (found) 519.4 $(MH)^+$.	27 (2-6)
88n	197n			2-(4-fluorobenzyloxy)-*N*-(3-(4-(((2-hydroxyethyl)(2-(1-(2-hydroxyethyl)-1H-benzo[d]imidazol-2-yl)ethyl)amino)methyl)phenyl)propyl)acetamide	(MeOD-*d*4) □(ppm): 7.56 - 7.54 (m, 1H), 7.44 - 7.38 (m, 3H), 7.25 - 7.18 (m, 2H), 7.10 - 7.05 (m, 4H), 6.95 (d, J=8.0 Hz, 2H), 4.56 (s, 2H), 4.17 (t, J=5.5 Hz, 2H), 3.92 (s, 2H), 3.77 (t, J=5.3 Hz, 2H), 3.68 - 3.62 (m, 4H), 3.23 (t, J=7.2 Hz, 2H), 3.12 (t, J=7.0 Hz, 2H), 2.98 (t, J=7.2 Hz, 2H), 2.75 (t, J=5.7 Hz, 2H), 2.54 (t, J=7.6 Hz, 2H), 1.77 (quintet, J=7.6 Hz, 2H). LRMS (ESI): (calc) 562.3; (found) 563.4 $(MH)^+$.	27 (2-6)
87k	196k			*N*-(3-(4-(((2-(1*H*-indol-3-yl)ethyl)(methyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm) ^{1}H: 7.46-7.38 (m,3H), 7.35-7.32 (m,1H), 7.29-7.25 (m,2H), 7.22-7.17 (m,2H), 7.13-7.06 (m,3H), 7.03 (s,1H), 7.01-6.95 (m,1H), 4.57 (s,2H), 3.94 (s,2H), 3.61 (s,2H), 3.28 (t, J = 7.2 Hz, 2H), 3.03-2.96 (m,2H), 2.77-2.70 (m,2H), 2.65 (t, J = 8.0 Hz, 2H), 2.35 (s,3H), 1.90-1.80 (m,2H) LRMS (ESI): (calc) 487.6 (found) 488.3 $(MH)^+$.	27 (2-5)
87l	196l			*N*-(3-(4-((2-(benzofuran-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) d(ppm): 7.54 - 7.51 (m, 2H), 7.43 - 7.37 (m, 3H), 7.28 - 7.04 (m, 8H), 4.55 (s, 2H), 3.91 (s, 2H), 3.74 (s, 2H), 3.24 (t, J=7.0 Hz, 2H), 2.89 (s, 4H), 2.60 (t, J=7.4 Hz, 2H), 1.80 (quintet, J=7.2 Hz, 2H). LRMS (ESI): (calc) 474.2; (found) 475.5 $(MH)^+$.	27 (2-5)

Ex	Cpd	R or structure	R' or structure	Name	Characterization	Scheme (steps)
88o	197o			*N*-(3-(4-(((2-(benzofuran-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) d(ppm): 7.49 (s, 1H), 7.41 - 7.36 (m, 4H), 7.24 - 7.19 (m, 3H), 7.15 - 7.04 (m, 5H), 4.55 (s, 2H), 3.92 (s, 2H), 3.68 (s, 2H), 3.62 (t, J=6.5 Hz, 2H), 3.24 (t, J=7.2 Hz, 2H), 2.86 - 2.78 (m, 4H), 2.72 (t, J=6.3 Hz, 2H), 2.60 (t, J=7.4 Hz, 2H), 1.81 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 518.3; (found) 519.4 $(MH)^+$.	27 (2-6)

Scheme 28



Example 89a

N-(3-(4-(((1*H*-indol-3-yl)methylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**202a**)

Step 1: *tert*-butyl 4-iodobenzylcarbamate (**198**)

[0304] To a stirred solution of (4-iodophenyl)methanamine hydrochloride (941 mg, 3.49 mmol) in dichloromethane (10 mL) at room temperature was added diisopropylethylamine (0.73 mL, 4.19 mmol) and di-*tert*-butyl dicarbonate (914 mg, 4.19 mmol). The resulting solution was stirred for 2 hours prior to dilution with brine, adjustment to pH = 1 with HCl, and extraction with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was the taken up in ethyl acetate, and triturated with hexanes to afford **198** (600 mg, 52%) as a white solid. LRMS (ESI): (calc) 333.2; (found) 334.2 $(MH)^+$.

Step 2: *tert*-butyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)prop-1-ynyl)benzylcarbamate (**199**)

[0305] Following the same procedure as described for compound **182a** (scheme 25, example 84a) but substituting **198** for **181** and **189** for methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate to afford **199** (553 mg, 82%) as a light yellow solid. LRMS (ESI): (calc) 426.5; (found) 427.2 $(MH)^+$.

Step 3: *tert*-butyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylcarbamate (**200**)

[0306] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **199** for **73** to afford **200** (505 mg, 90%) as a white solid. LRMS (ESI): (calc) 430.5; (found) 431.0 $(MH)^+$.

Step 4: *N*-(3-(4-(aminomethyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**201**)

[0307] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **200** for **1** to afford **201** (378 mg, 97%) as light white solid. LRMS (ESI): (calc) 330.4; (found) 331.2 $(MH)^+$.

Step 5: *N*-(3-(4-(((1*H*-indol-3-yl)methylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**202a**)

[0308] Following the same procedure as described for compound **196a** (step 5, scheme 27, example 87a) but substituting 1*H*-indole-3-carbaldehyde for **195a** and **201** for tryptamine to afford **202a** (42 mg, 8%) as white solid. (MeOD-*d4*) δ (ppm) ^{1}H: 7.55 (dt, J = 7.8,1.0 Hz, 1H), 7.44-7.36 (m,3H), 7.29-7.17 (m,5H), 7.15-7.01 (m,4H), 4.56 (s,2H), 3.95 (s,2H), 3.94 (s,2H), 3.78 (s,2H), 3.28 (t, J = 7.3 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H), 1.90-1.80 (m,2H). LRMS (ESI): (calc) 459.6; (found) 460.3 $(MH)^+$.

Example 89b

N-(3-(4-((((1*H*-indol-3-yl)methyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**203a**)

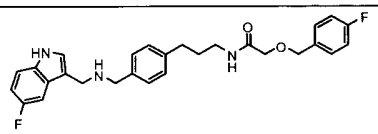
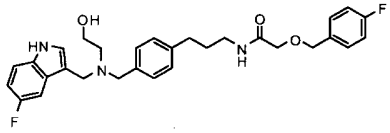
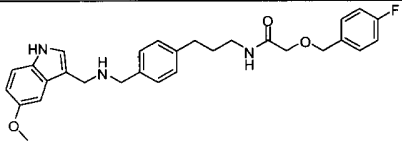
Step 1: *N*-(3-(4-((((1*H*-indol-3-yl)methyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**203a**)

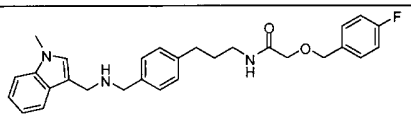
[0309] Following the same procedure as described for compound **197b** (step 1, scheme 27, example 88b) but substituting **202a** for **196b** to afford 203a (5 mg, 14%) as a light yellow oil. (MeOD-*d4*) δ (ppm) ^{1}H: 7.63-7.59 (m,1H), 7.44-7.35 (m,3H), 7.32-7.27 (m,2H), 7.24-7.16 (m,3H), 7.14-7.07 (m,3H), 7.05-7.00 (m,1H), 4.56 (s,2H), 3.93 (s,2H), 3.87 (s,2H), 3.69-3.62 (m,4H), 3.28 (t, J = 7.0 Hz, 2H), 2.69 (t, J = 6.7 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H), 1.90-1.80 (m,2H). LRMS (ESI): (calc) 503.6; (found) 504.2 $(MH)^+$.

Example 89c-f

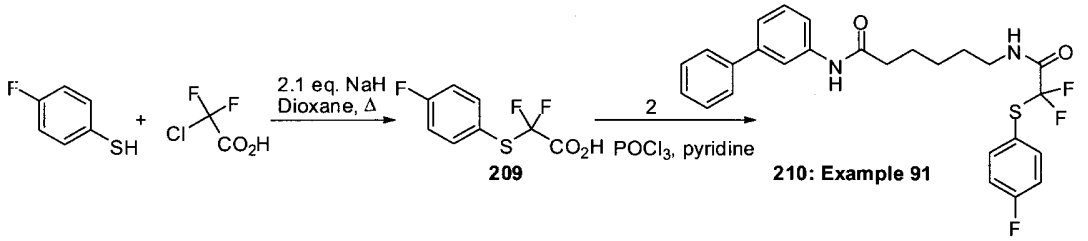
[0310] Example 89c-f describe the preparation of compound **202-f** using the same procedures as described for compound **202a** and **203a** in Example 89a and 89b. Characterization data are presented in a Table 17.

Table 17

Ex	Cpd	structure	Name	Characterization	Scheme (steps)
89c	202c		*N*-(3-(4-(((5-fluoro-1*H*-indol-3-yl)methylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) δ(ppm) ^{1}H: 7.44-7.23 (m,9H), 7.13-7.06 (m,2H), 6.98-6.91 (m,1H), 4.57 (s,2H), 4.17 (s,2H), 4.00 (s,2H), 3.94 (s,2H), 3.27 (t, J = 7.0 Hz, 2H), 2.66 (t, J = 7.8 Hz, 2H), 1.90-1.80 (m,2H) LRMS (ESI): (calc) 477.5 (found) 478.4 $(MH)^+$.	28 (1-5)
89d	203d		*N*-(3-(4-((((5-fluoro-1*H*-indol-3-yl)methyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) δ(ppm) ^{1}H: 7.44-7.38 (m,2H), 7.33-7.22 (m,5H), 7.21-7.16 (m,2H), 7.13-7.07 (m,2H), 6.91-6.84 (m,1H), 4.56 (s,2H), 3.93 (s,2H), 3.79 (s,2H), 3.67-3.62 (m,4H), 3.28 (t, J = 7.2 Hz, 2H), 2.70-2.61 (m,4H), 1.90-1.80 (m,2H) LRMS (ESI): (calc) 521.6 (found) 544.2 $(M+Na)^+$.	28 (1-6)
89e	203d		2-(4-fluorobenzyloxy)-*N*-(3-(4-(((5-methoxy-1H-indol-3-yl)methylamino)methyl)phenyl)propyl) acetamide	(MeOD-*d*4) δ(ppm) ^{1}H: 7.46-7.41 (m,2H), 7.40-7.35 (m,3H), 7.34-7.27 (m,3H), 7.14-7.07 (m,3H), 6.84 (dd, J = 8.8,2.3 Hz, 1H), 4.59 (s,2H), 4.26 (s,2H), 4.09 (s,2H), 3.96 (s,2H), 3.85 (s,3H), 3.28 (t, J = 7.0 Hz, 2H), 2.68 (t, J = 8.0 Hz, 2H), 1.90-1.80 (m,2H) LRMS (ESI): (calc) 489.6 (found) 512.3 (M+Na)+	28 (1-5)

Ex	Cpd	structure	Name	Characterization	Scheme (steps)
89f	203f		2-(4-fluorobenzyloxy)-*N*-(3-(4-(((1-methyl-1*H*-indol-3-yl)methylamino)methyl)phenyl)propyl) acetamide	(MeOD-*d*4) □(ppm) ^{1}H: 7.59 (dt, J = 8.0,0.8 Hz, 1H), 7.44-7.37 (m,3H), 7.33-7.28 (m,2H), 7.26-7.20 (m,4H), 7.14-7.06 (m,3H), 4.55 (s,2H), 4.11 (s,2H), 3.93 (s,4H), 3.79 (s,3H), 3.26 (t, J = 7.0 Hz, 2H), 2.64 (t, J = 8.0 Hz, 2H), 1.88-1.79 (m,2H) LRMS (ESI): (calc) 473.6 (found) 474.3 (MH)+	28 (1-5)

Scheme 30



Example 91

N-(biphenyl-3-yl)-6-(2,2-difluoro-2-(4-fluorophenylthio)acetamido)hexanamide (**210**)

Step 1: 2,2-difluoro-2-(4-fluorophenylthio)acetic acid (**209**).

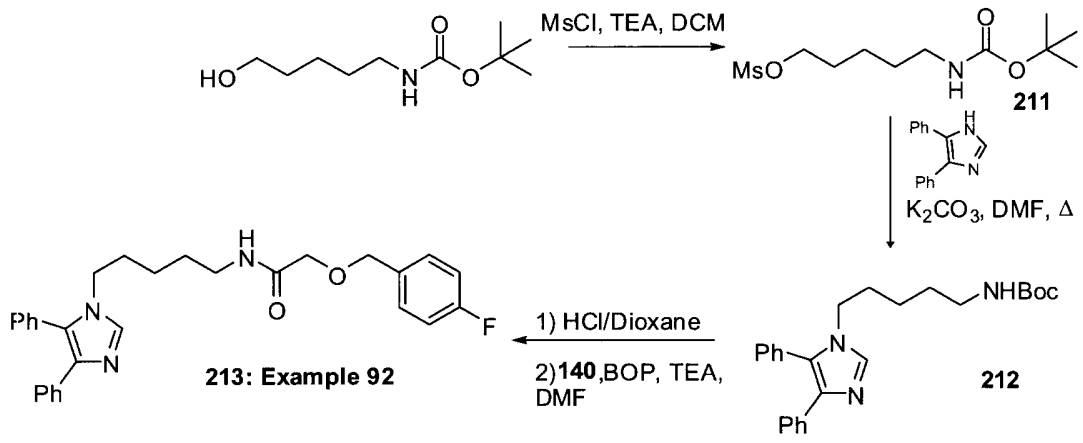
[0311] 4-Fluorothiophenol (1.64 mL, 15.3 mmol) and 2-chloro-2,2-difluoroacetic acid (1.47 mL, 15.3 mmol) were dissolved in dioxane, cooled to 0°C, and sodium hydride (60%, 1.28g, 32.1 mmol) was added. The mixture was then raised to room temperature and, when bubbling had ceased, was heated at 100 °C for 3 hours. The mixture was then cooled to room temperature, 5 mL of ethanol was added, and the suspension poured into a mixture of ice in 1N HCl. The mixture was then extracted with ethyl acetate and the organic layer washed with water, then brine and dried ($MgSO_4$). The residue was triturated with hexanes; the solvent was removed to afford **209** as a beige solid (3.05g, 90%). LRMS (ESI): (calc) 222.0; (found) 220.9 $(M)^-$.

Step 2 : *N*-(biphenyl-3-yl)-6-(2,2-difluoro-2-(4-fluorophenylthio)acetamido)-hexanamide (**210**).

[0312] Amide **2** (50 mg, 0.177 mmol) and acid **209** (39 mg, 0.177 mmol) were dissolved in pyridine (2 mL) and cooled to 0 °C. Phosphoryl trichoride (19 µL, 0.212 mmol) was then added dropwise and the mixture left to return to room temperature overnight. The solution

was then poured into ice water, extracted with ethyl acetate, and the combined organic layers were washed with water, brine and dried ($MgSO_4$). The residue was purified by column chromatography (25% to 75% ethyl acetate in hexanes) to obtain compound **210** (67 mg, 78%) as a colorless oil. (CD_3OD) δ (ppm) ^1H: 7.85 (s, 1H), 7.60 (m, 4H), 7.51 (d, J = 7.6 Hz, 1H), 7.32-7.42 (m, 5H), 7.16 (t, J = 8.4 Hz, 2H), 3.18 (t, J = 6.8 Hz, 2H), 2.4 (t, J = 7.2 Hz, 2H), 1.71 (quin, J = 8.0 Hz, 2H), 1.50 (quin, J = 7.2 Hz, 2H), 1.34 (m, 2H). LRMS (ESI): (calc) 486.1; (found), 509.1 $(M+Na)^+$.

Scheme 31



Example 92

N-(5-(4,5-diphenyl-1H-imidazol-1-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**213**)

Step 1: 5-(*tert*-butoxycarbonylamino)pentyl methanesulfonate (**211**).

[0313] *tert*-Butyl 5-hydroxypentylcarbamate (2g, 9.8 mmol) was dissolved in anhydrous dichloromethane (20 mL) and cooled to 0°C. Triethylamine (2.46 mL, 17.7 mmol) was added dropwise followed by slow addition of methanesulfonyl chloride (1.13 mL, 14.7 mmol). The mixture was stirred at room temperature overnight and quenched with saturated sodium bicarbonate solution. The reaction mixture was extracted with dichloromethane and the combined organic layers washed with water and brine. The organic extract was dried ($MgSO_4$) filtered, and concentrated to afford **211** as a yellow solid in quantitative yield. LRMS (ESI): (calc) 281.1; (found), 304.1 $(M+Na)^+$.

Step 2: *tert*-butyl 5-(4,5-diphenyl-1*H*-imidazol-1-yl)pentylcarbamate (**212**).

[0314] 4,5-diphenyl-1*H*-imidazole (200 mg, 0.907 mmol) and mesylate **211** (280 mg, 1mmol) were dissolved in DMF. Potassium carbonate (248 mg, 1.8 mmol) was then added and the mixture heated at 90 °C for 14 hours. The mixture was cooled and partitioned between water and ethyl acetate and the organic layer was washed with water, then once

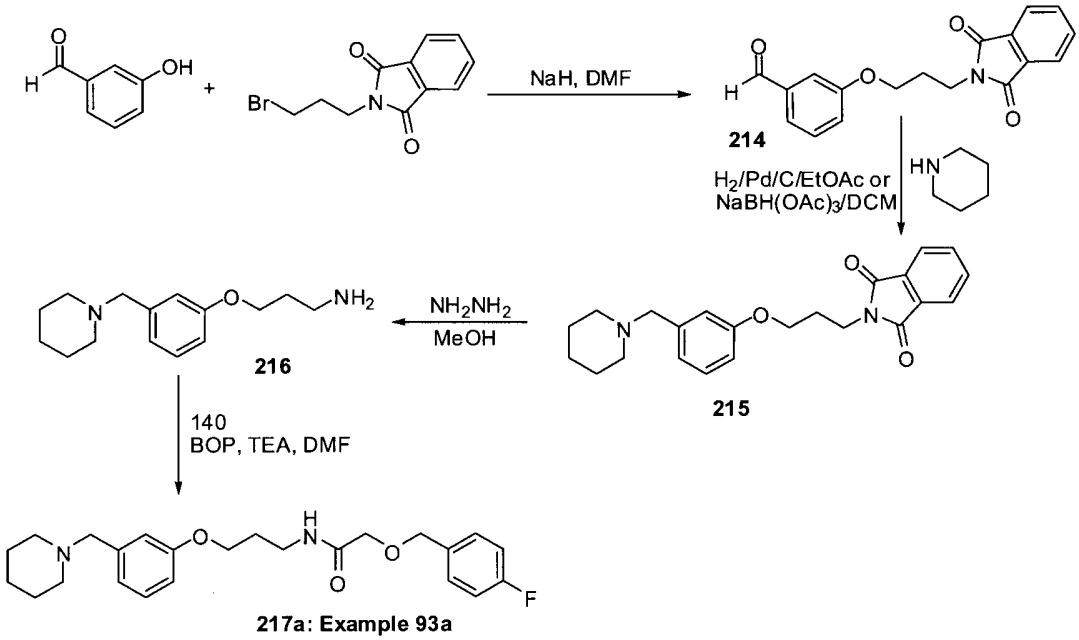
with brine and dried ($MgSO_4$). The solvent was removed and the residue purified by column chromatography (50% to 80% ethyl acetate in hexanes) to obtain compound **212** (294 mg, 81%). LRMS (ESI): (calc) 405.24; (found) 406.31 $(MH)^+$.

Step 3: *N*-(5-(4,5-diphenyl-1*H*-imidazol-1-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**213**).

[0315] Compound **212** (150 mg, 0.369 mmol) was dissolved in 4 M HCl in dioxane (922 uL, 3.69 mmol) and stirred at room temperature for 1 hour. The residue was used in the next step without further purification.

[0316] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting **140** for *N*-Boc-caproic acid and residue amine for 3-phenyl aniline to afford **213** (144mg, 83%) as a colorless oil. (CD_3OD) δ (ppm) ^1H: 7.80 (s, 1H), 7.45 (m, 3H), 7.31-7.35 (m, 6H), 7.13-7.16 (m, 3H), 7.05 (m, 2H), 4.51 (s, 2H), 3.88 (m, 4H), 3.11 (t, 2H, J = 7.2 Hz), 1.54 (quin, 2H, J = 7.2 Hz), 1.36 (quin, 2H, J = 7.2 Hz), 1.14 (m, 2H). LRMS (ESI): (calc) 471.2; (found), 472.4 $(MH)^+$.

Scheme 32



217a: Example 93a

Example 93a

2-(4-fluorobenzyloxy)-*N*-(3-(3-(piperidin-1-ylmethyl)phenoxy)propyl)acetamide (**217a**)

Step 1: 3-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzaldehyde (**214**)

[0317] Following the same procedure as described for compound **42** (scheme 2, step 1) but substituting 3-hydroxybenzaldehyde for (4-(methylthio)phenyl)methanol, bromopropyl phtalamide for bromomethyl acetate and DMF for THF to afford **214** (3.55 g, 70%) as a white solid.

(DMSO-*d6*) δ(ppm): 9.90 (s, 1H), 7.84 – 7.79 (m, 4H), 7.47 – 7.42 (m, 2H), 7.26 (d, J=2.2 Hz, 1H), 7.12 – 7.08 (m, 1H), 4.07 (t, J=5.9 Hz, 2H), 3.76 (t, J=6.7 Hz, 2H), 2.06 (quintet, J=6.3 Hz, 2H).

Step 2 : 2-(3-(3-(piperidin-1-ylmethyl)phenoxy)propyl)isoindoline-1,3-dione (**215**)

[0318] To a solution of **214** (3.55 g, 11.49 mmol) in ethyl acetate (50 mL) were added piperdine (1.14 mL) and Pd/C (500 mg). The reaction was stirred at room temperature under a H_2 atmosphere for 16 hours. The Pd/C was filtered off and the reaction mixture was concentrated. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate (75-100%) in hexanes to afford **215** (2.75 g, 64%) as a light yellow oil.

(DMSO-*d6*) δ(ppm): 7.86 – 7.80 (m, 4H), 7.13 (t, J=7.8 Hz, 1H), 6.79 (d, J=7.8 Hz, 1H), 6.65 – 6.62 (m, 2H), 3.97 (t, J=5.9 Hz, 2H), 3.74 (t, J=6.8 Hz, 2H), 3.29 (s, 2H), 2.24 (br s, 4H), 2.03 (quintet, J=6.3 Hz, 2H), 1.46 – 1.41 (m, 4H), 1.35 – 1.33 (m, 2H).

Step 3 : 3-(3-(piperidin-1-ylmethyl)phenoxy)propan-1-amine (**216**)

[0319] Following the same procedure as described for compound **139** (scheme 16, step 5) but substituting phtalamide **138** for **215** to afford **216** (1.60 g, 91%) as a yellow oil.

(DMSO-*d6*) δ(ppm): 7.17 (t, J=7.8 Hz, 1H), 6.81 – 6.74 (m, 3H), 3.97 (t, J=6.4 Hz, 2H), 3.34 (s, 2H), 2.66 (t, J=6.7 Hz, 2H), 2.27 (br s, 4H), 1.78 – 1.73 (m, 2H), 1.47 – 1.43 (m, 4H), 1.36 – 1.34 (m, 2H).

Step 4 : 2-(4-fluorobenzyloxy)-*N*-(3-(3-(piperidin-1-ylmethyl)phenoxy)propyl)acetamide (**217a**)

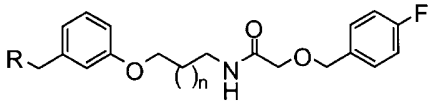
[0320] Following the same procedure as described for compound **1** (scheme 1, step 1) but substituting **140** for *N*-Boc-caproic acid and **216** for 3-phenyl aniline to afford **217a** (170 mg, 33%) as a white oily solid.

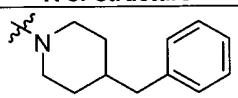
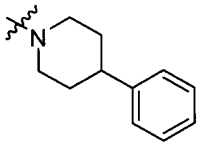
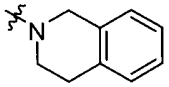
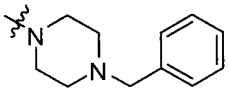
(MeOD-*d4*) δ(ppm): 7.38 (dd, J=8.6, 5.3 Hz, 2H), 7.19 (t, J=7.8 Hz, 1H), 7.05 (t, J=8.8 Hz, 2H), 6.90 - 6.87 (m, 2H), 6.81 - 6.77 (m, 1H), 4.57 (s, 2H), 4.02 (t, J=6.1 Hz, 2H), 3.94 (s, 2H), 3.46 - 3.42 (m, 4H), 2.39 (br s, 4H), 1.99 (quintet, J=6.3 Hz, 2H), 1.57 (quintet, J=5.5 Hz, 4H), 1.45 - 1.44 (m, 2H).

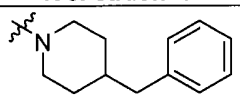
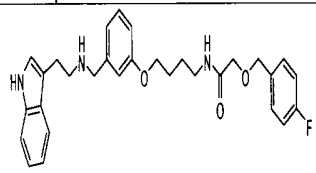
Example 93b-g

[0321] Example 93b-g describe the preparation of compound **217b-g** using the same procedures as described for compound **217a** in Example 93a. Characterization data are presented in a Table 18.

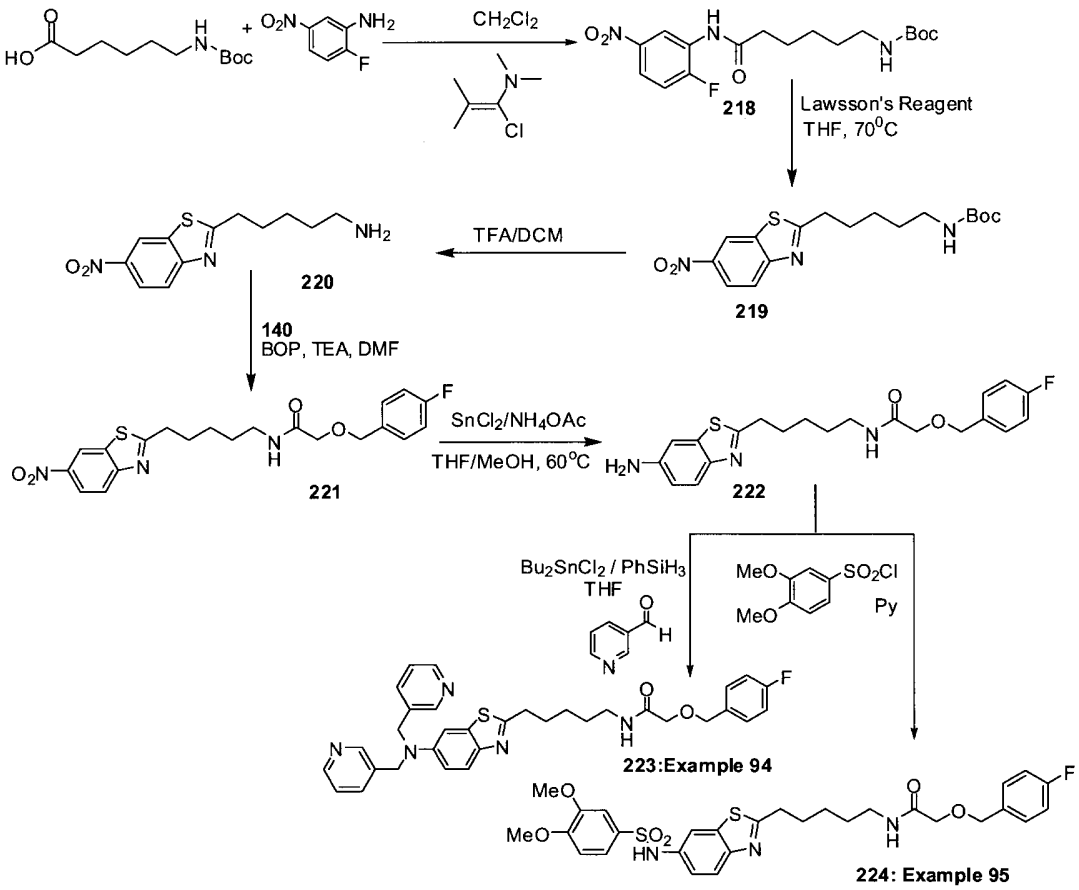
Table 18



Ex	Cpd	n	R or structure	Name	Characterization	Scheme
93b	217b	0		*N*-(3-(3-((4-benzylpiperidin-1-yl)methyl)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.39 - 7.36 (m, 2H), 7.25 - 7.02 (m, 6H), 6.91 - 6.87 (m, 2H), 6.82 (dd, J=8.2, 1.8 Hz, 1H), 4.56 (s, 2H), 4.02 (t, J=8.1 Hz, 2H), 3.93 (s, 2H), 3.55 (s, 2H), 3.43 (t, J=6.8 Hz, 2H), 2.93 (d, J=11.9 Hz, 2H), 2.52 (d, J=6.7 Hz, 2H), 2.08 (t, J=11.8 Hz, 2H), 1.99 (quintet, J=6.3 Hz, 2H), 1.64 - 1.52 (m, 3H), 1.35 - 1.24 (m, 2H). LRMS (ESI): (calc) 504.3; (found) 505.5 $(MH)^+$.	32
93c	217c	0		2-(4-fluorobenzyloxy)-*N*-(3-(3-((4-phenylpiperidin-1-yl)methyl)phenoxy)propyl)acetamide	(MeOD-*d*4)□(ppm): 7.39 - 7.36 (m, 2H), 7.27 - 7.19 (m, 5H), 7.17 - 7.13 (m, 1H), 7.05 (t, J=11.2 Hz, 2H), 6.95 - 6.90 (m, 2H), 6.83 - 6.80 (m, 1H), 4.57 (s, 2H), 4.04 (t, J=6.9 Hz, 2H), 3.94 (s, 2H), 3.52 (s, 2H), 3.45 (t, J=6.7 Hz, 2H), 3.00 (d, J=12.1 Hz, 2H), 2.55 - 2.49 (m, 1H), 2.16 - 2.09 (m, 2H), 2.00 (quintet, J=6.3 Hz, 2H), 1.80 - 1.71 (m, 4H). LRMS (ESI): (calc) 490.3; (found) 491.3 $(MH)^+$.	32
93d	217d	0		*N*-(3-(3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.36 (dd, J=8.8, 5.5 Hz, 2H), 7.22 (t, J=7.8 Hz, 1H), 7.10 - 6.94 (m, 8H), 6.82 (dd, J=8.2, 1.8 Hz, 1H), 4.55 (s, 2H), 4.04 (t, J=6.1 Hz, 2H), 3.93 (s, 2H), 3.65 (s, 2H), 3.60 (s, 2H), 3.44 (t, J=6.6 Hz, 2H), 2.88 (t, J=6.0 Hz, 2H), 2.74 (t, J=5.8 Hz, 2H), 1.99 (quintet, J=6.3 Hz, 2H). LRMS (ESI): (calc) 462.2; (found) 463.2 $(MH)^+$.	32
93e	217e	0		*N*-(3-(3-((4-benzylpiperazin-1-yl)methyl)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.40-7.34 (m, 7H), 7.26 (t, J=7.8Hz, 1H), 7.06 (t, J=8.8Hz, 2H), 6.95-6.93 (m, 2H), 6.89-6.87 (m, 1H), 4.56 (s, 2H), 4.02 (t, J=5.9Hz, 2H), 3.93 (s, 2H), 3.88 (s, 2H), 3.81 (s, 2H), 3.43 (t, J=6.8Hz, 2H), 2.88 (s, 8H), 2.01-1.96 (m, 2H). LRMS (ESI): (calc) 505.3; (found) 506.3 $(MH)^+$.	32

Ex	Cpd	n	R or structure	Name	Characterization	Scheme
93f	217f	1		*N*-(4-(3-((4-benzylpiperidin-1-yl)methyl)phenoxy)butyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm): 7.39 (dd, J=8.6, 5.5 Hz, 2H), 7.24 - 7.03 (m, 8H), 6.88 - 6.78 (m, 3H), 4.54 (s, 2H), 3.97 (t, J=5.8 Hz, 2H), 3.92 (s, 2H), 3.42 (s, 2H), 3.30 (t, J=6.5 Hz, 2H), 2.86 - 2.82 (m, 2H), 2.50 (d, J=6.9 Hz, 2H), 1.92 (t, J=9.8 Hz, 2H), 1.79 - 1.66 (m, 4H), 1.60 - 1.49 (m, 3H), 1.32 - 1.25 (m, 2H). LRMS (ESI): (calc) 518.3; (found) 519.3 $(MH)^+$.	32
93g	217g			*N*-(4-(3-((2-(1*H*-indol-3-yl)ethylamino)methyl)phenoxy)butyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) □(ppm) ^{1}H: 7.52 (d, J = 7.8Hz, 1H), 7.42-7.29 (m, 4H), 7.14-6.94 (m, 8H), 4.56 (s, 2H), 4.08 (s, 2H), 3.98 (t, J = 6.1Hz, 2H), 3.93 (s, 2H), 3.30-3.29 (m, 2H), 3.26-3.22 (m, 2H), 3.15-3.11 (m, 2H), 1.82-1.75 (m, 2H), 1.72-1.65 (m, 2H) LRMS (ESI): (calc) 503.3 (found) 504.6 $(MH)^+$.	32

Scheme 33



Example 94

N-(5-(6-(bis(pyridin-3-ylmethyl)amino)benzo[d]thiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**223**)

Step 1: *tert*-butyl 6-(2-fluoro-5-nitrophenylamino)-6-oxohexylcarbamate (**218**)

[0322] To a solution of 6-(*tert*-butoxycarbonylamino)hexanoic acid (4.95g, 21.40 mmol) in CH_2Cl_2 at room temperature was added 1-chloro-*N,N*,2-trimethylprop-1-en-1-amine (3.40ml, 25.68 mmol) and he reaction mixture was stirred for 1 hour. Then 2-fluoro-5-nitrobenzenamine (3.34g, 21.40 mmol) was added. The reaction was stirred for 20 minutes and quenched with water. Aqueous extraction was performed with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated to afford **218** (3.08 g, 39%) as a white solid. (MeOD-*d*4) □(ppm): 9.05 (dd,J=2.7, 6.7 Hz, 1H), 8.06 - 8.02 (m, 1H), 7.39 (t, J=9.2 Hz, 1H), 3.04 (t, J=6.8 Hz, 2H), 2.49 (t, J=7.4 Hz, 2H), 1.74 - 1.69 (m, 2H), 1.54 - 1.48 (m, 2H), 1.41 (s, 11H).

Step 2: *tert*-butyl 5-(6-nitrobenzo[d]thiazol-2-yl)pentylcarbamate (**219**)

[0323] Following the same procedure as described for compound **10** (scheme 1, step 5) but substituting **218** for **7b** to afford **219** (1.97 g, 65%) as a yellow solid.
(DMSO-*d6*) □(ppm):8.70 (d, J= 2.2 Hz, 1H), 8.35 - 8.33 (m, 1H), 8.25 - 8.22 (m, 1H), 6.78 (t, J=5.5 Hz, 1H), 3.15 (t, J=7.4 Hz, 2H), 2.88 (dd, J=6.3, 12.5 Hz, 2H), 1.82 - 1.78 (m, 2H), 1.42 - 1.37 (m, 2H), 1.32 (s, 9H).
Step 3: 5-(6-nitrobenzo[d]thiazol-2-yl)pentan-1-amine (**220**)
[0324] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **219** for **1** to afford **220** (1.32 g, 92%) as a red oil.
(MeOD-*d4*) □(ppm): 8.74 (d, J= 2.3 Hz, 1H), 8.30 - 8.26 (m, 1H), 8.20 - 8.17 (m, 1H), 3.22 (t, J=7.6 Hz, 2H), 2.70 (t, J=7.0 Hz, 2H), 1.98 - 1.91 (m, 2H), 1.61 - 1.48 (m, 4H).
Step 4: 2-(4-fluorobenzyloxy)-*N*-(5-(6-nitrobenzo[d]thiazol-2-yl)pentyl)acetamide (**221**)
[0325] Following the same procedure as described for compound **1** (scheme 1, step 1) but substituting **140** for *N*-Boc-caproic acid and **220** for 3-phenyl aniline to afford **221** (1.01g, 47%) as an orange oil.
(MeOD-*d4*) □(ppm): 8.71 (d, J=2.2 Hz, 1H), 8.27 - 8.24 (m, 1H), 8.17 - 8.14 (m, 1H), 7.39 - 7.34 (m, 2H), 7.06 (t, J=8.8 Hz, 2H), 4.52 (s, 2H), 3.91 (s, 2H), 3.25 (t, J=6.8 Hz, 2H), 3.20 (t, J=7.4 Hz), 1.94 (m, 2H), 1.62 - 1.56 (m, 2H), 1.50 - 1.44 (m, 2H).
Step 5: *N*-(5-(6-aminobenzo[d]thiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**222**)
[0326] Following the same procedure as described for compound **163a** (scheme 20, example 79a) but substituting **221** for **162a** and employing 3:1 methanol:THF as solvent to afford **222** (753 mg, 80%) as an orange oil.
(DMSO-*d6*) □(ppm): 8.69 (d, J= 2.2 Hz, 1H), 8.34 - 8.32 (m, 1H), 8.24 - 8.21 (m, 1H), 7.80 (t, J=5.7 Hz, 1H), 7.40 - 7.36 (m, 2H), 7.17 - 7.13 (m, 2H), 4.46 (s, 2H), 3.84 (s, 2H), 3.16 (t, J=7.4 Hz, 2H), 3.08 (dd, J=6.7, 13.1 Hz, 2H), 1.84 - 1.80 (m, 2H), 1.49 - 1.45 (m, 2H), 1.37 - 1.32 (m, 2H).
Step 6: *N*-(5-(6-(bis(pyridin-3-ylmethyl)amino)benzo[d]thiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**223**)
[0327] Following the same procedure as described for compound **75** (step 6, scheme 5, example 55) but substituting **222** for compound **74** and 2 equivalents of nicotinaldehyde for **71** to afford **223** (92mg, 25%) as a colourless oil.
(MeOD-*d4*) □(ppm): 8.49 - 8.48 (m, 2H), 8.41 (d, J=4.9 Hz, 2H), 7.88 (s, 1H), 7.77 (d, J=8.0 Hz, 2H), 7.66 (d, J=8.8 Hz, 1H), 7.40 - 7.34 (m, 4H), 7.18 (d, J=2.5 Hz, 1H), 7.08 - 7.00 (m, 3H), 4.84 (s, 4H), 4.50 (s, 2H), 3.89 (s, 2H), 3.21 (dd, J=6.8, 13.3 Hz, 2H), 3.03 (t, J=7.4 Hz, 2H), 1.85 - 1.81 (m, 2H), 1.57 - 1.52 (m, 2H), 1.43 - 1.37 (m, 2H).

Example 95

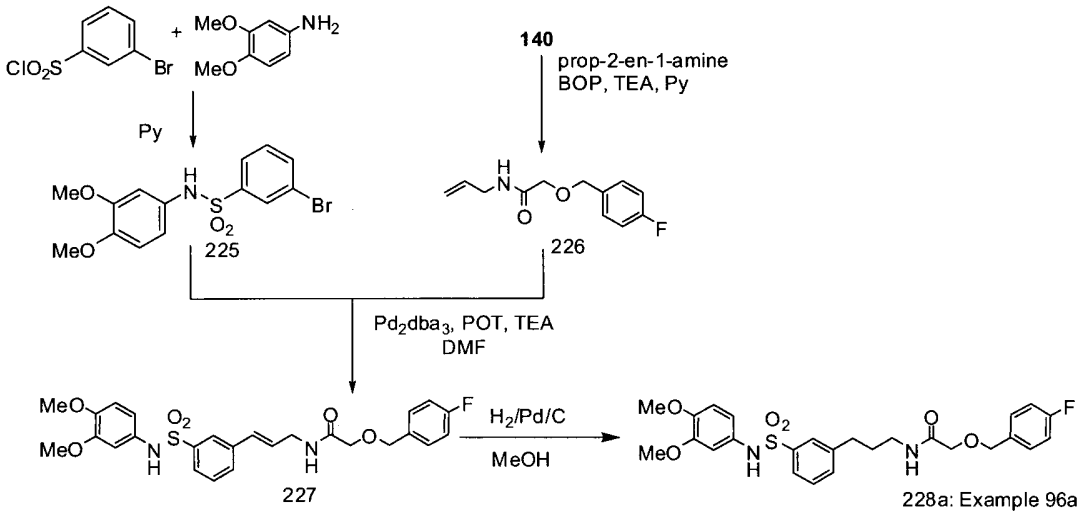
N-(5-(6-(3,4-dimethoxyphenylsulfonamido)benzo[d]thiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**224**)

Step 6: *N*-(5-(6-(3,4-dimethoxyphenylsulfonamido)benzo[d]thiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**224**)

[0328] To a solution of **222** (251 mg, 0.63 mmol) and DMAP (8 mg, 0.063 mmol) in pyridine was added 3,4-dimethoxybenzene-1-sulfonyl chloride (149 mg, 0.63 mmol). The reaction was stirred at room temperature for 2 hours and quenched with water. Aqueous extraction was performed with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on prep HPLC (with gradient of ethyl acetate 50-100% in hexanes in silicagel column) to afford **224** (110mg, 30%) as a white solid.

(MeOD-*d*4) □(ppm): 7.75 (d, J=8.6 Hz, 1H), 7.63 (d, J=1.8 Hz, 1H), 7.37 - 7.33 (m, 3H), 7.24 (d, J=2.2 Hz, 1H), 7.16 (dd, J=8.6, 2.2 Hz, 1H), 7.08 - 7.03 (t, J=9.0 Hz, 2H), 6.94 (d, J=8.6 Hz, 1H), 4.50 (s, 2H), 3.89 (s, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.23 (t, J=6.8 Hz, 2H), 3.08 (t, J=7.4 Hz, 2H), 1.90 - 1.82 (m, 2H), 1.58 - 1.53 (m, 2H), 1.45 - 1.39 (m, 2H).

Scheme 34



Example 96a

N-(3-(3-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**228a**)

Step 1: 3-bromo-*N*-(3,4-dimethoxyphenyl)benzenesulfonamide (**225**)

[0329] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting 3,4-dimethoxyaniline for amine **2** and 3-bromobenzene-1-sulfonyl chloride for 2-(benzyloxy)acetyl chloride along with catalytic DMAP to afford **225** (900 mg, 80%) as a white solid. (DMSO-*d6*) □(ppm): 10.00 (s, 1H), 7.83 – 7.79 (m, 2H), 7.66 – 7.63 (m, 1H), 7.51 – 7.46 (m, 1H), 6.80 (d, J=8.8 Hz, 1H), 6.65 (d, J=2.3 Hz, 1H), 6.53 (dd, J=8.4, 2.4 Hz, 1H), 3.65 (s, 3H), 3.62 (s, 3H).

Step 2: *N*-allyl-2-(4-fluorobenzyloxy)acetamide (**226**)

[0330] Following the same procedure as described for compound **1** (scheme 1, step 1) but substituting **140** for *N*-Boc-caproic acid and allyl amine for 3-phenyl aniline to afford **226** (750 mg, 62%) as a colourless oil. (DMSO-*d6*) □(ppm): 7.97 (s, 1H), 7.42 (dd, J=8.6, 5.8 Hz, 2H), 7.17 (t, J=8.8 Hz, 2H), 5.83 – 5.73 (m, 1H), 5.11 – 5.00 (m, 2H), 4.50 (s, 2H), 3.90 (s, 2H), 3.73 – 3.69 (m, 2H).

Step 3: (*E*)-*N*-(3-(3-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)allyl)-2-(4-fluorobenzyloxy)acetamide (**227**)

[0331] Following the same procedure as described for compound **184** (scheme 25, step 2, example 85a) but substituting **225** for compound **181** and **226** for vinyl phthalamide to afford **227** (250 mg, 28%) as a colourless oily solid. (MeOD-*d4*) □(ppm): 7.67 (t, J=1.8 Hz, 1H), 7.58 - 7.53 (m, 2H), 7.44 - 7.39 (m, 3H), 7.08 (t, J=9.0 Hz, 2H), 6.76 (d, J=8.6 Hz, 1H), 6.65 (d, J=2.4 Hz, 1H), 6.57 - 6.49 (m, 2H), 6.27 - 6.20 (m, 1H), 4.60 (s, 2H), 4.00 - 3.98 (m, 4H), 3.73 (s, 3H), 3.68 (s, 3H).

Step 4: *N*-(3-(3-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**228a**)

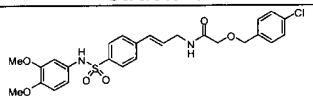
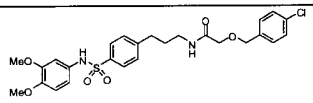
[0332] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **227** for **73** to afford **228** (160 mg, 80%) as a white solid.

[0333] (MeOD-*d4*) □(ppm): 7.53 (dt, J=6.9, 2.0 Hz, 1H), 7.48 (s, 1H), 7.42 - 7.34 (m, 4H), 7.08 (t, J=11.2 Hz, 2H), 6.74 (d, J=8.6 Hz, 1H), 6.63 (d, J=2.3 Hz, 1H), 6.56 (dd, J=8.4, 2.4 Hz, 1H), 4.56 (s, 2H), 3.93 (s, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.15 (t, J=7.0 Hz, 2H), 2.61 (t, J=7.6 Hz, 2H), 1.72 (quintet, J=7.2 Hz, 2H).

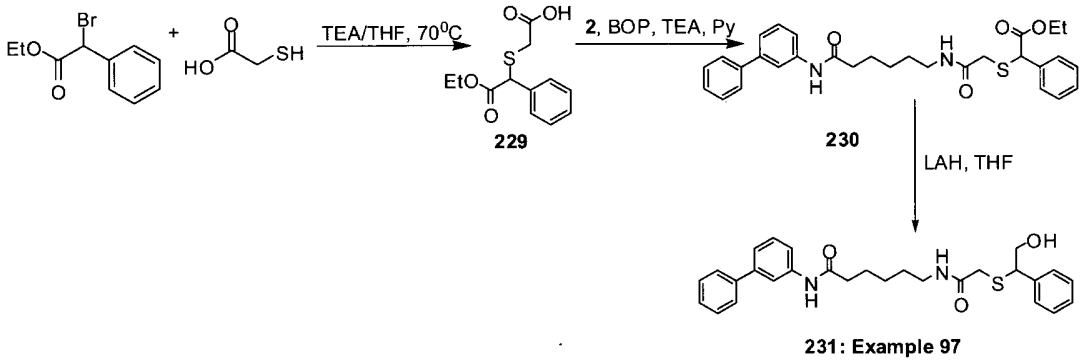
Example 96b,c

[0334] Example 96b,c describe the preparation of compound **228b,c** using the same procedures as described for compound **228a** in Example 96a. Characterization data are presented in a Table 19.

Table 19

Ex	Cpd	structure	Name	Characterization	Scheme
96b	228b		(*E*)-2-(4-chlorobenzyloxy)-*N*-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)allyl)acetamide	(MeOD-*d4*) d(ppm): d(ppm): 7.62 (d, J=8.6Hz, 2H), 7.47 (d, J=8.6Hz, 2H), 7.40-7.34 (m, 4H), 6.76 (d, J=8.6Hz, 1H), 6.67 (d, J=2.5Hz, 1H), 6.55 (dd, J=8.6and2.3Hz, 1H), 6.53 (bd, J=16Hz, 1H), 6.36 (dt, J=16, 5.7Hz, 1H), 4.60 (s, 2H), 4.02 (m, 2H), 4.00 (s, 2H), 3.74 (s, 3H), 3.69 (s, 3H). LRMS (ESI): 530.1 (calc) 529.0 (M-) (found).	34 (step 1-3)
96c	228c		2-(4-chlorobenzyloxy)-*N*-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)acetamide	(DMSO-*d6*) d(ppm): 9.84 (s, 1H), 7.87 (t, J=6.5Hz, 1H), 7.59 (d, J=8.4Hz, 2H), 7.42-7.33 (m, 6H), 6.76 (d, J=8.6Hz, 1H), 6.62 (d, J=2.5Hz, 1H), 6.52 (dd, J=8.6, 2.5Hz, 1H), 4.50 (s, 2H), 3.86 (s, 2H), 3.63 (s, 3H), 3.59 (s, 3H), 3.07 (q, J=6.1Hz, 2H), 2.58 (t, J=7.8Hz, 2H), 1.67 (qi, J=7.2Hz, 2H). LRMS (ESI): 532.1 (calc) 531.0 (M-) (found).	34 (step 4)

Scheme 35



Example 97

N-(biphenyl-3-yl)-6-(2-(2-hydroxy-1-phenylethylthio)acetamido)hexanamide (**231**)

Step 1: 2-(2-ethoxy-2-oxo-1-phenylethylthio)acetic acid (**229**)

[0335] Following the same procedure as described for compound **4** (step 4, scheme 1, example 1) but substituting 2-mercaptoacetic acid for methyl 2-mercaptoacetate and ethyl 2-bromo-2-phenylacetate for **3b** and heating to 80 °C to afford **229** (1.05 g, 99%) as a colourless oil. (DMSO-*d6*) δ (ppm): 12.71 (br s, 1H), 7.39 – 7.29 (m, 5H), 4.87 (s, 1H), 4.15 – 4.04 (m, 2H), 3.28 (d, J=15.3 Hz, 1H), 3.18 (d, J=15.4 Hz, 1H), 1.17 – 1.11 (m, 3H).

Step 2: ethyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-phenylacetate (**230**)

[0336] Following the same procedure as described for compound **1** (scheme 1, step 1) but substituting **229** for *N*-Boc-caproic acid and **2** for 3-phenyl aniline to afford **230** (520 mg, 78%) as a colourless oil.

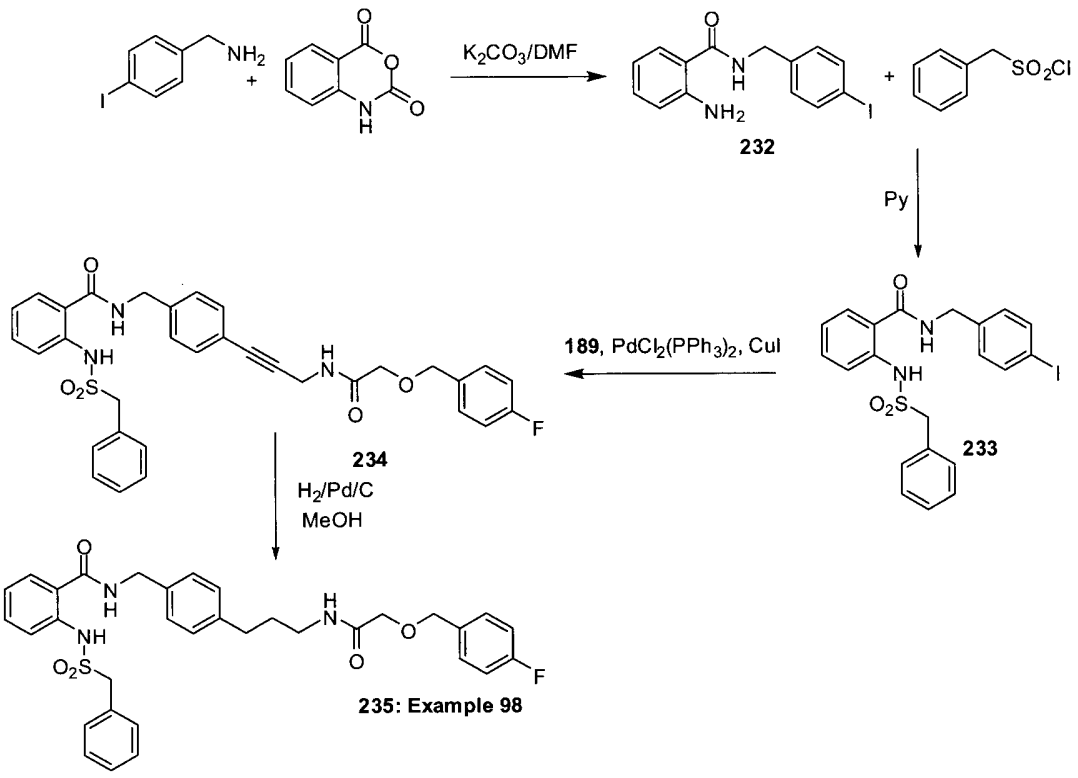
(MeOD-*d4*) δ(ppm): 7.85 (s, 1H), 7.61 - 7.58 (m, 2H), 7.53 (dt, J=7.3, 1.7 Hz, 1H), 7.44 - 7.26 (m, 10H), 4.82 (s, 1H), 4.18 - 4.10 (m, 2H), 3.22 - 3.04 (m, 4H), 2.41 (t, J=7.4 Hz, 2H), 1.73 (quintet, J=7.2 Hz, 2H), 1.56 - 1.50 (m, 2H), 1.43 - 1.41 (m, 2H), 1.19 (t, J=7.2 Hz, 3H).

Step 3: *N*-(biphenyl-3-yl)-6-(2-(2-hydroxy-1-phenylethylthio)acetamido)hexanamide (**231**)

[0337] Following the same procedure as described for compound **12** (scheme 1, step 5, example) but substituting **230** for **7c** and employing 2 equivalents of $LiAlH_4$ with 1h stir time to afford **231** (25 mg, 16%) as a colourless oil.

(MeOD-*d4*) δ(ppm): 7.85 (t, J=1.6 Hz, 1H), 7.60 - 7.57 (m, 2H), 7.53 (dt, J=7.5, 2.0 Hz, 1H), 7.44 - 7.21 (m, 10H), 4.02 (t, J=7.0 Hz, 1H), 3.85 - 3.83 (m, 1H), 3.16 - 3.12 (m, 3H), 2.98 (d, J=15.1 Hz, 1H), 2.40 (t, J=7.4 Hz, 2H), 1.73 (quintet, J=7.6 Hz, 2H), 1.55 - 1.49 (m, 2H), 1.44 - 1.40 (m, 2H).

Scheme 36



Example 98

N-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzyl)-2-(phenylmethylsulfonamido)benzamide (**235**)

Step 1: 2-amino-*N*-(4-iodobenzyl)benzamide (**232**)

[0338] 4-iodobenzylamine hydrochloride (1.07 g, 3.98 mmol) was dissolved in DMF (15 mL) with 1H-benzo[d][1,3]oxazine-2,4-dione (650 mg, 3.98 mmol). K_2CO_3 (1.38 g, 9.95 mmol) was added and the reaction stirred at 50°C for 1h. Aqueous extraction was performed with ethyl acetate and water and the organic layer was separated, dried with $MgSO_4$ and the concentrated. The residue was triturated with a 50% hexanes : ethyl acetate solvent mixture to afford **233** (820 mg, 50%) as a beige solid.

(DMSO-*d6*) δ(ppm): 8.78 (t, J=5.9 Hz, 1H), 7.77 – 7.63 (m, 2H), 7.53 – 7.50 (m, 1H), 7.25 – 7.22 (m, 3H), 7.14 – 7.09 (m, 1H), 6.68 – 6.47 (m, 1H), 6.42 (br s, 2H), 4.34 (d, J=6.0 Hz, 2H).

Step 2: *N*-(4-iodobenzyl)-2-(phenylmethylsulfonamido)benzamide (**233**)

[0339] Following the same procedure as described for compound **54** (scheme 2, example 47) but substituting **232** for amine **2** and phenylmethanesulfonyl chloride for 2-(benzyloxy)acetyl chloride to afford **233** (640 mg, 56%) as a white solid.

(DMSO-*d6*) δ(ppm): 11.16 (s, 1H), 9.42 (t, J=5.3 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.68 (d, J=8.2 Hz, 2H), 7.53 – 7.47 (m, 2H), 7.31 – 7.09 (m, 8H), 4.58 (s, 2H), 4.33 (d, J=5.9 Hz, 2H).

Step 3: *N*-(4-(3-(2-(4-fluorobenzyloxy)acetamido)prop-1-ynyl)benzyl)-2-(phenylmethylsulfonamido)benzamide (**234**)

[0340] Following the same procedure as described for compound **182a** (scheme 25, example 84a) but substituting **233** for **181** and **189** for methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate to afford **234** which was used in the next step without further purification.

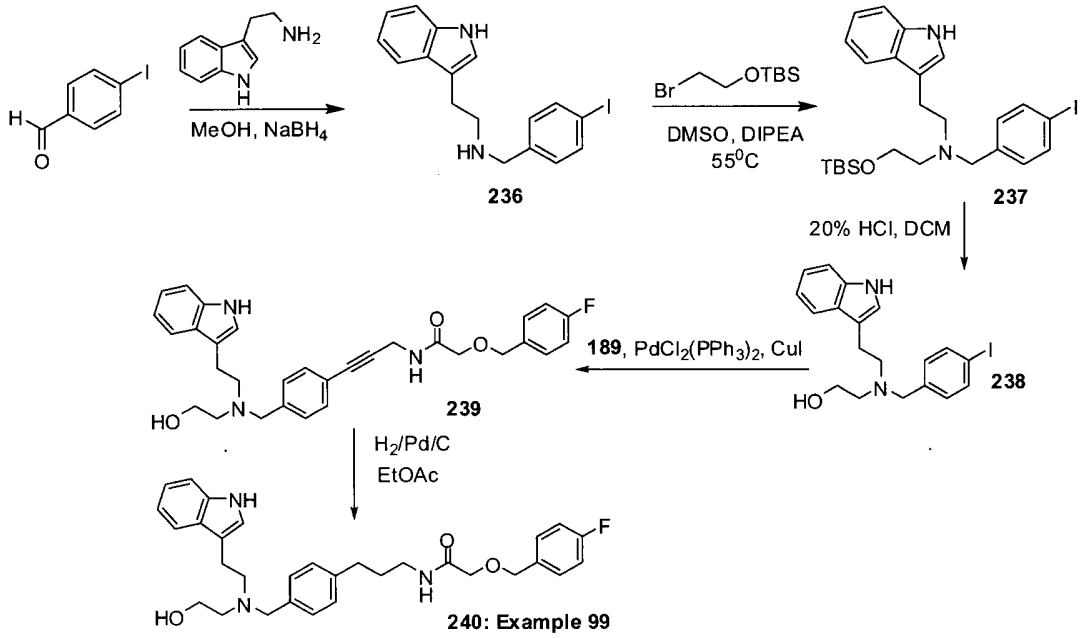
(MeOD-*d4*) δ(ppm): 7.73 (dd, J=7.8, 1.4 Hz, 1H), 7.66 (dd, J=8.4, 1.2 Hz, 1H), 7.49 - 7.44 (m, 1H), 7.43 - 7.36 (m, 4H), 7.30 - 7.12 (m, 8H), 7.07 (t, J=8.8 Hz, 2H), 4.58 (s, 2H), 4.43 (s, 2H), 4.40 (s, 2H), 4.23 (s, 2H), 3.98 (s, 2H).

Step 4: *N*-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzyl)-2-(phenylmethylsulfonamido)benzamide (**235**)

[0341] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **234** for **73** to afford **235** (90 mg, 13% (2 steps)) as a white foam.

(MeOD-*d4*) δ(ppm): 7.71 (dd, J=8.0, 1.6 Hz, 1H), 7.64 (dd, J=8.4, 1.0 Hz, 1H), 7.46 - 7.42 (m, 1H), 7.38 (dd, J=8.6, 5.5 Hz, 2H), 7.28 - 7.10 (m, 10H), 7.06 (t, J=8.8 Hz, 2H), 4.53 (s, 2H), 4.39 (s, 2H), 4.38 (s, 2H), 3.89 (s, 2H), 3.22 (t, J=7.0 Hz, 2H), 2.59 (t, J=7.4 Hz, 2H), 1.78 (quintet, J=7.2 Hz, 2H).

Scheme 37



Example 99

N-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**240**)

Step 1: 2-(1H-indol-3-yl)-*N*-(4-iodobenzyl)ethanamine (**236**)

[0342] Following the same procedure as described for compound **196a** (step 5, scheme 27, example 87a) but substituting 4-iodobenzaldehyde for **195a** to afford **236** (950 mg, 62%) as an off-white solid.

(DMSO-*d6*) δ(ppm): 10.75 (s, 1H), 7.64 – 7.60 (m, 2H), 7.45 (d, J=7.8 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.13 – 7.08 (m, 3H), 7.02 (td, J=7.0, 1.0 Hz, 1H), 6.95 – 6.90 (m, 1H), 3.66 (s, 2H), 2.82 – 2.70 (m, 4H).

Step 2: *N*-(2-(1H-indol-3-yl)ethyl)-2-(*tert*-butyldimethylsilyloxy)-*N*-(4-iodobenzyl)ethanamine (**237**)

[0343] To a solution of **236** (925 mg, 2.46 mmol) in DMSO (10 mL) was added (2-Bromoethoxy)(*tert*-butyl)dimethylsilane (577 μL, 2.71 mmol) and DIPEA (556 μL, 3.20 mmol). The reaction heated to 55°C and allowed to stir for 16h. Aqueous extraction was performed with ethyl acetate and water and the organic layer was separated, dried with $MgSO_4$ and concentrated. The residue was purified was in prep HPLC (gradient ethyl acetate (0-50%) in: hexanes) to afford **237** (520 mg, 40%) as a clear oil.

(DMSO-*d6*) δ(ppm): 10.75 (s, 1H), 7.65 – 7.62 (m, 2H), 7.35 – 7.29 (m, 2H), 7.15 (d, J=8.2 Hz, 2H), 7.09 (d, J=2.4 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.93 – 6.89 (m, 1H), 3.67 (s, 2H), 3.64 (t, J=6.5 Hz, 2H), 2.84 – 2.71 (m, 4H), 2.63 (t, J=6.5 Hz, 2H), 0.83 (s, 9H), 0.00 (s, 6H).

Step 3: *N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2-(*tert*-butyldimethylsilyloxy)ethyl)amino)methyl)phenyl)prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide (**238**)

[0344] Following the same procedure as described for compound **182a** (scheme 25, example 84a) but substituting **237** for **181** and **189** for methyl 3-(2-oxo-2-(prop-2-ynylamino)ethylthio)propanoate to afford **238** (150 mg, 25%) as a yellow oil.

[0345] (DMSOD6) δ(ppm): 10.75 (s, 1H), 8.41 – 8.39 (m, 1H), 7.45 (dd, J=8.6, 5.5 Hz, 2H), 7.37 – 7.29 (m, 6H), 7.19 (t, J=9.0 Hz, 2H), 7.09 (d, J=2.3 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.94 – 6.89 (m, 1H), 4.54 (s, 2H), 4.15 (d, J=5.8 Hz, 2H), 3.96 (s, 2H), 3.73 (s, 2H), 3.65 (t, J=6.4 Hz, 2H), 2.86 – 2.74 (m, 4H), 2.64 (t, J=6.3 Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H).

Step 4: *N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide (**239**)

[0346] **238** (130 mg, 0.207 mmol) was dissolved in 20% HCL in ethanol (20 mL). The reaction was stirred at room temperature for 1h and quenched with saturated $NaHCO_3$ solution Aqueous extraction was performed with ethyl acetate and water and the organic layer was separated, dried with $MgSO_4$ and concentrated. The residue was purified in silica gel column chromatography with ethyl acetate (5 %) in methanol to afford **239** (55 mg, 52%) as a yellow oil.

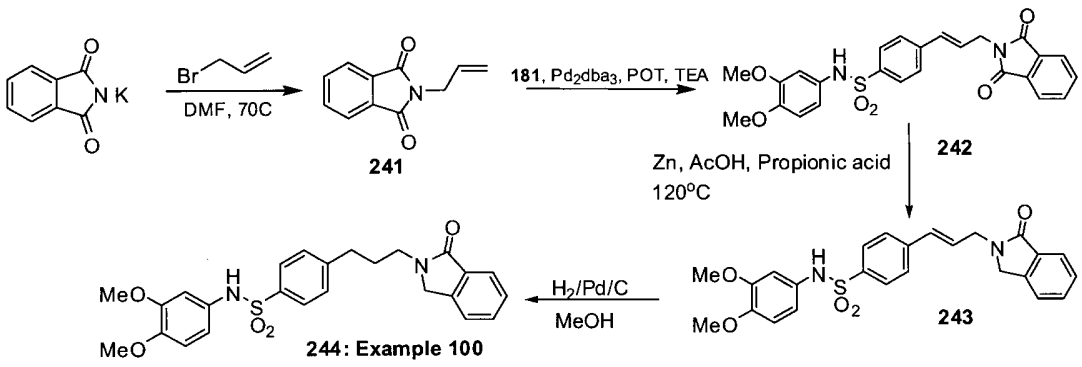
(MeOD-*d*4) δ(ppm): 7.40 (dd, J=8.8, 5.5 Hz, 2H), 7.37 - 7.27 (m, 6H), 7.09 - 7.01 (m, 3H), 6.97 (s, 1H), 6.95 - 6.90 (m, 1H), 4.57 (s, 2H), 4.23 (s, 2H), 3.98 (s, 2H), 3.72 (s, 2H), 3.62 (t, J=6.3 Hz, 2H), 2.94 - 2.89 (m, 2H), 2.82 - 2.77 (m, 2H), 2.72 (t, J=6.2 Hz, 2H).

Step 5: *N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**240**)

[0347] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **234** for **73** and ethyl acetate for methanol to afford **240** (4 mg, 20%) as a clear oil.

(MeOD-*d*4) δ(ppm): 7.42 - 7.37 (m, 3H), 7.34 - 7.30 (m, 3H), 7.22 (d, J=7.8 Hz, 2H), 7.11 - 7.04 (m, 4H), 6.97 - 6.93 (m, 1H), 4.56 (s, 2H), 4.20 (s, 2H), 3.93 (s, 2H), 3.82 (t, J=5.5 Hz, 2H), 3.27 - 3.11 (m, 8H), 2.64 (t, J=7.4 Hz, 2H), 1.83 (quintet, J=7.2 Hz, 2H).

Scheme 38



Example 100

N-(3,4-dimethoxyphenyl)-4-(3-(1-oxoisoindolin-2-yl)propyl)benzenesulfonamide (**244**)

Step 1: 2-allylisoindoline-1,3-dione (**241**)

[0348] To a solution of phtalamide potassium salt (6 g, 32.4 mmol) in DMF (40 mL), was added allyl bromide (2.78 mL, 32.4 mmol). The solution was heated to 70°C and stirred for 16h. The DMF was removed by rotary evaporation and aqueous extraction was performed with ethyl acetate and water and the organic layer was separated, dried with $NaSO_4$ and

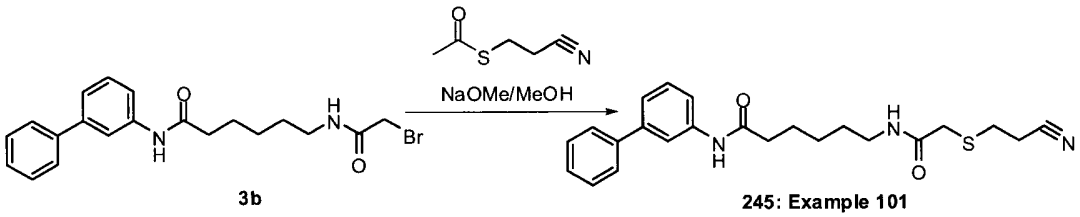
concentrated. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate (20-80%) in hexanes to afford **241** (3.4 g, 57%) as a white solid.
(DMSO-*d6*) δ(ppm): 7.89 – 7.80 (m, 4H), 5.90 – 5.80 (m, 1H), 5.12 (t, J=1.6 Hz, 1H), 5.10 – 5.06 (m, 1H), 4.16 (dt, J=5.1, 1.8 Hz, 2H).
Step 2: (E)-*N*-(3,4-dimethoxyphenyl)-4-(3-(1,3-dioxoisoindolin-2-yl)prop-1-enyl)benzenesulfonamide (**242**)

[0349] Following the same procedure as described for compound **184** (scheme 25, step 2, example 85a) but substituting **241** for vinyl phthalamide to afford **242** (1.0 g, 18%) as a white solid.
(DMSO-*d6*) δ(ppm): 9.84 (s, 1H), 7.90 – 7.81 (m, 4H), 7.68 – 7.53 (m, 4H), 6.74 (d, J=8.8 Hz, 1H), 6.64 (d, J=2.5 Hz, 1H), 6.59 – 6.42 (m, 3H), 4.35 – 4.33 (m, 2H), 3.62 (s, 3H), 3.59 (s, 3H).
Step 3: (E)-*N*-(3,4-dimethoxyphenyl)-4-(3-(1-oxoisoindolin-2-yl)prop-1-enyl)benzenesulfonamide (**243**)

[0350] To a solution of **242** (235 mg, 0.492 mmol) in acetic acid (25 mL), was added zinc dust (1.8 g, 27.6 mmol) and propionic acid (2.5 mL). The suspension was heated to 120°C and stirred for 3h. The zinc dust was filtered off through Celite and the acetic acid removed via rotary evaporation. Aqueous extraction was performed with ethyl acetate and water. The organic layer was separated, dried with $NaSO_4$ and concentrated. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate (33-100%) in hexanes to afford **243** (140 mg, 62%) as a colourless oil.
(MeOD-*d4*) δ(ppm): 7.78 (d, J=7.6 Hz, 1H), 7.63 - 7.48 (m, 7H), 6.75 (d, J=8.6 Hz, 1H), 6.68 (d, J=2.6 Hz, 1H), 6.64 - 6.61 (m, 1H), 6.54 (dd, J=8.6, 2.5 Hz, 1H), 6.50 - 6.42 (m, 1H), 4.52 (s, 2H), 4.42 - 4.40 (m, 2H), 3.73 (s, 3H), 3.69 (s, 3H).
Step 4: *N*-(3,4-dimethoxyphenyl)-4-(3-(1-oxoisoindolin-2-yl)propyl)benzenesulfonamide (**244**)

[0351] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **243** for **73** to afford **244** (65 mg, 59%) as a light yellow oily solid.
(MeOD-*d4*) δ(ppm): 7.75 - 7.72 (m, 1H), 7.60 - 7.45 (m, 5H), 7.32 (d, J=8.4 Hz, 2H), 6.74 (d, J=8.6 Hz, 1H), 6.65 (d, J=2.3 Hz, 1H), 6.55 (dd, J=8.6, 2.5 Hz, 1H), 4.46 (s, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.62 (t, J=7.0 Hz, 2H), 2.69 (t, J=7.4 Hz, 2H), 1.98 (quintet, J=5.5 Hz, 2H).

Scheme 39



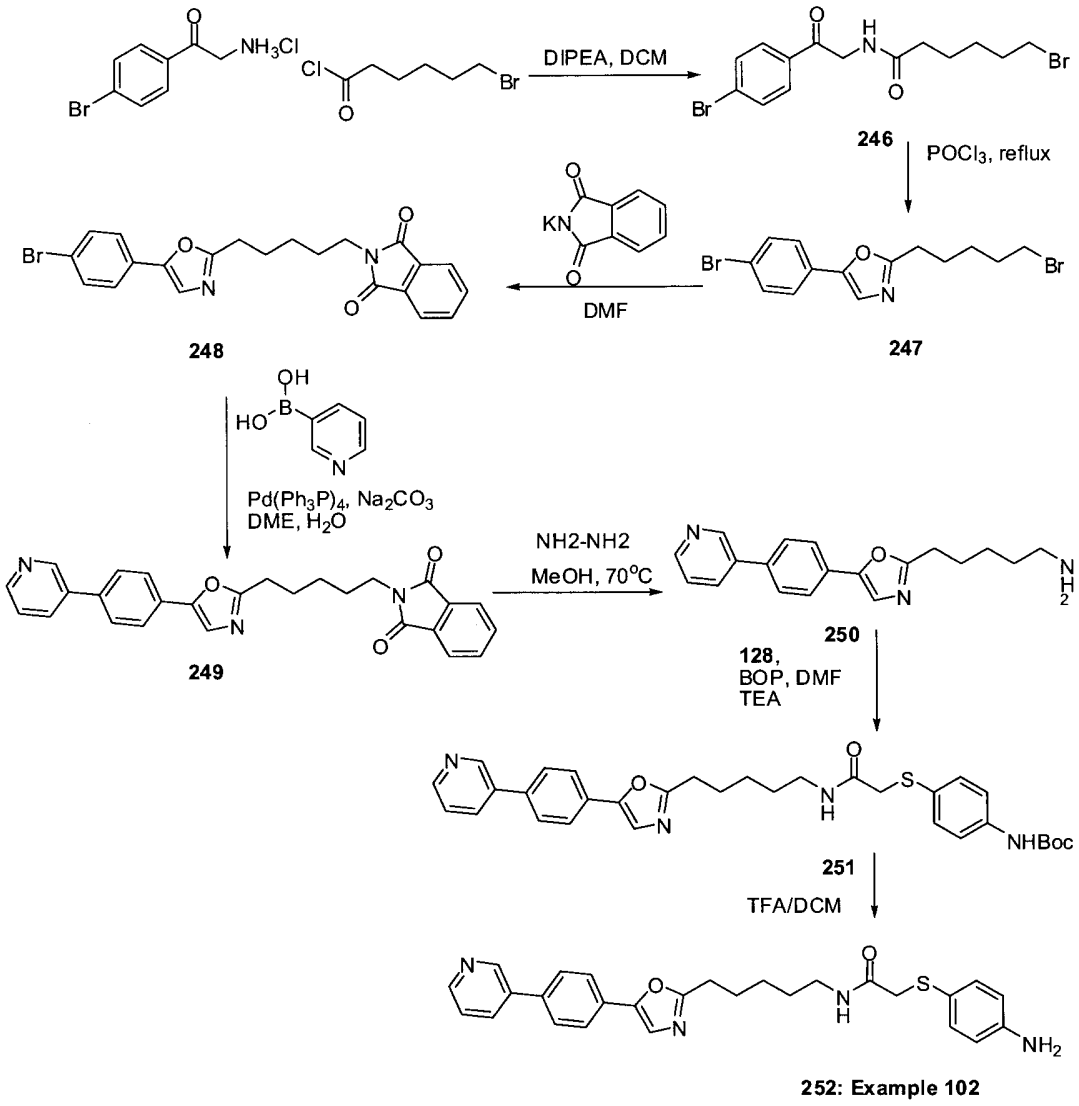
Example 101

N-(biphenyl-3-yl)-6-(2-(2-cyanoethylthio)acetamido)hexanamide (**245**)

Step 1: *N*-(biphenyl-3-yl)-6-(2-(2-cyanoethylthio)acetamido)hexanamide (**245**)

[0352] To a solution of **3b** (0.250 mg, 0.622 mmol) in methanol (5.0 mL) with 3-(acetylthio)propionitrile) (0.088 mg, 0.684 mmol) was added 25% sodium methoxide in methanol (40 μl, 0.684 mmol). After stirring 30 minutes at room temperature, the solution was diluted in ethyl acetate and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography with ethyl acetate to afford **245** (143 mg, 56%) as an off-white solid. (MeOD-*d4*) δ(ppm) ^{1}H: 7.84 (m, 1H), 7.61-7.58 (m, 2H), 7.53-7.51 (m, 1H), 7.44-7.31 (m, 5H), 3.25-3.21 (m, 4H), 2.86-2.83 (m, 2H), 2.78-2.75 (m, 2H), 2.43 (t, J = 7.6Hz, 2H), 1.80-1.72 (m, 2H), 1.63-1.56 (m, 2H), 1.49-1.43 (m, 2H). LRMS (ESI): (calc) 409.2 (found) 410.3 $(MH)^+$.

Scheme 40



Example 102

2-(4-aminophenylthio)-*N*-(5-(5-(4-(pyridin-3-yl)phenyl)oxazol-2-yl)pentyl)acetamide (**252**)

Step 1: 6-bromo-*N*-(2-(4-bromophenyl)-2-oxoethyl)hexanamide (**246**)

[0353] Following the same procedure as described for compound **106** (step 4, scheme 11, example 66) but substituting 6-bromohexanoyl chloride for 3-chlorocarbonylmethylsulfanyl-propionic acid methyl ester and 4-bromophenacylamine hydrochloride for amine **105** to afford **246** as a pink solid. LRMS (ESI): (calc) 389.0 (found) 390.1 $(MH)^+$.

Step 2: 2-(5-bromopentyl)-5-(4-bromophenyl)oxazole (**247**)

[0354] The crude compound **246** was dissolved in 20 mL of $POCl_3$ and stirred at 100°C for 45 minutes. The mixture was then concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The organic solution was washed with a $NaHCO_3$ (ss), water and brine. The organic phase was dried (Na_2SO_4), filtered and evaporated to afford **247** (530 mg, 33% for 2 steps) as a beige solid. LRMS (ESI): (calc) 371.0 (found) 372.0 $(MH)^+$.

Step 3: 2-(5-(5-(4-bromophenyl)oxazol-2-yl)pentyl)isoindoline-1,3-dione (**248**)

[0355] The crude compound **247** (530 mg, 1.43 mmol) was dissolved in DMF (10 mL) and potassium phthalamide (344 mg, 1.86 mmol) was added. The solution was stirred at 70°C for 3h then cooled at room temperature and poured into water. The product was extracted with ethyl acetate/hexanes 1:1. The combined organic phases were washed with water, 5% aqueous sodium hydroxide solution and brine. The organic phase was dried (Na_2SO_4), filtered and evaporated to afford **248** (204 mg, 33%) as white solid. LRMS (ESI): (calc) 438.1 (found) 439.2 $(MH)^+$.

Step 4: 2-(5-(5-(4-(pyridin-3-yl)phenyl)oxazol-2-yl)pentyl)isoindoline-1,3-dione (**249**)

[0356] Compound **248** (204 mg, 0.466 mmol) and 3-pyridineboronic acid (63 mg, 0.512 mmol) were dissolved in 10 mL of DME/water 4:1. $Pd(Ph_3P)_4$ (54 mg, 0.047 mmol) and sodium carbonate (100 mg, 0.932 mmol) were added and the solution was stirred at 90°C for 1 hour. The reaction mixture was cooled at room temperature and poured into ether. The organic phase was washed with water, brine and dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography with 100% ethylacetate to afford **249** (122 mg, 60%) as a white solid. LRMS (ESI): (calc) 437.2 (found) 438.3 $(MH)^+$.

Step 5: 5-(5-(4-(pyridin-3-yl)phenyl)oxazol-2-yl)pentan-1-amine (**250**)

[0357] Following the same procedure as described for compound **139** (step 5, scheme 16, example 73a) but substituting **249** for **138** and stirring at 70°C for 3h to afford **250** (55 mg, 64%) as a white solid. LRMS (ESI): (calc) 307.2 (found) 308.4 $(MH)^+$.

Step 6: *tert*-butyl 4-(2-oxo-2-(5-(5-(4-(pyridin-3-yl)phenyl)oxazol-2-yl)pentylamino)ethylthio)phenylcarbamate (**251**)

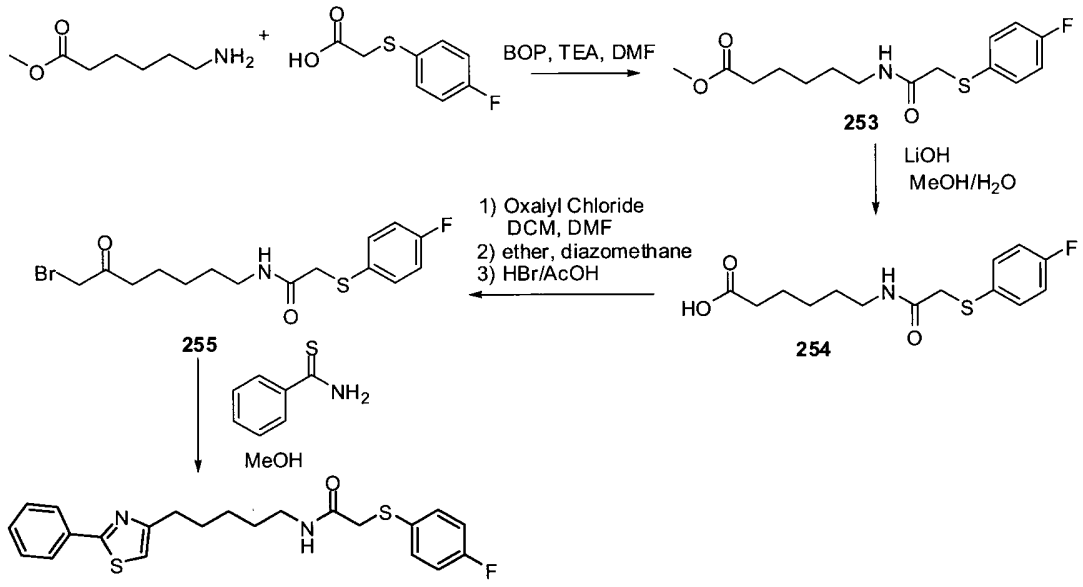
[0358] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting 2-(4-(*tert*-butoxycarbonylamino)phenylthio)acetic acid for *N*-Boc-caproic acid and amine **250** for 3-phenyl aniline to afford **251** (19 mg, 19%) as a colorless oil. LRMS (ESI): (calc) 572.3 (found) 573.5 $(MH)^+$.

Step7: 2-(4-aminophenylthio)-*N*-(5-(5-(4-(pyridin-3-yl)phenyl)oxazol-2-yl)pentyl)acetamide (**252**)

[0359] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **251** for **1** to afford **252** (10 mg, 63%) as a white solid. (MeOD-*d4*) δ(ppm) ^1H: 8.85 (dd, J = 2.4, 0.8 Hz, 1H), 8.53 (dd, J = 5.0, 1.6 Hz, 1H),

8.14 (ddd, J = 8.0, 2.4, 1.6 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.54 (ddd, J = 8.0, 5.0, 0.8 Hz, 1H), 7.47 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4Hz, 2H), 3.34 (s, 2H), 3.14 (t, J = 6.8Hz, 2H), 2.85 (t, J = 7.6Hz, 2H), 1.84-1.76 (m, 2H), 1.50-1.43 (m, 2H), 1.35-1.27 (m, 2H). LRMS (ESI): (calc) 472.2 (found) 473.6 $(MH)^+$.

Scheme 41



256a: Example 103a

Example 103a

2-(4-fluorophenylthio)-*N*-(5-(2-phenylthiazol-4-yl)pentyl)acetamide (**256a**)

Step 1: methyl 6-(2-(4-fluorophenylthio)acetamido)hexanoate (**253**)

[0360] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting 2-(4-fluorophenylthio)acetic acid for *N*-Boc-caproic acid and methyl 6-aminohexanoate hydrochloride for 3-phenyl aniline to afford **253** (1.24 g, quantitative yield) as a colorless oil. LRMS (ESI): (calc) 313.1 (found) 314.3 $(MH)^+$.

Step 2: 6-(2-(4-fluorophenylthio)acetamido)hexanoic acid (**254**)

[0361] Following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting **253** for methyl ester **4** and using MeOH/water 3:1 as solvent to afford **254** (1.20 g, quantitative yield) as a white solid. LRMS (ESI): (calc) 299.1 (found) 300.1 $(MH)^+$.

Step 3: *N*-(7-bromo-6-oxoheptyl)-2-(4-fluorophenylthio)acetamide (**255**)

[0362] To a solution of **254** (1.20 g, 4.0 mmol) in dichloromethane (20 mL) was added oxalyl chloride (0.45 mL, 1.3 eq) and DMF (3 drops). The reaction was stirred for 30 minutes

at room temperature and then concentrated under reduced pressure. The residue was dissolved in DCM (75 mL) and an excess of diazomethane (prepared from *N*-nitroso-*N*-methylurea) was added at room temperature. After stirring 16 hours at room temperature, the solution was cooled at 0°C and a solution of 33 wt. % of HBr in acetic acid (3.0 mL, 16.6 mmol) was added dropwise. The reaction mixture was stirred 1h and then washed with $NaHCO_3$ (ss). The organic phase was dried (Na_2SO_4), filtered and evaporated. The brown oil was purified by silica gel column chromatography with ethyl acetate (50%) in hexanes to afford **255** (0.721 g, 48%) as a brown oil. LRMS (ESI): (calc) 375.0 (found) 376.0 $(MH)^+$.

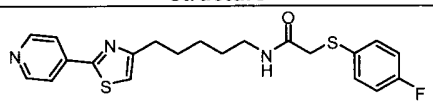
Step 4: 2-(4-fluorophenylthio)-*N*-(5-(2-phenylthiazol-4-yl)pentyl)acetamide (**256a**)

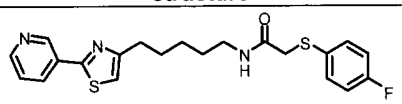
[0363] To a solution of **255** (113 mg, 0.301 mmol) in MeOH (3.0 mL) was added benzothioamide (45 mg, 0.331 mmol). After stirring 1 hour at room temperature, the solution was concentrated under reduced pressure. The residue was purified by preparative HPLC with a gradient of methanol (30-90%) in water in aquasil-C_{18} column to afford **256a** (58 mg, 12%). (MeOD-*d4*) δ(ppm) ^{1}H: 7.92-7.89 (m, 2H), 7.48-7.42 (m, 5H), 7.13 (t, J = 0.8Hz, 1H), 7.08-7.04 (m, 2H), 3.52 (s, 2H), 3.15 (t, J = 6.8Hz, 2H), 2.77 (t, J = 7.2Hz, 2H), 1.76-1.68 (m, 2H), 1.50-1.43 (m, 2H), 1.33-1.26 (m, 2H). LRMS (ESI): (calc) 414.12 (found) 415.30 $(MH)^+$.

Example 103b,c

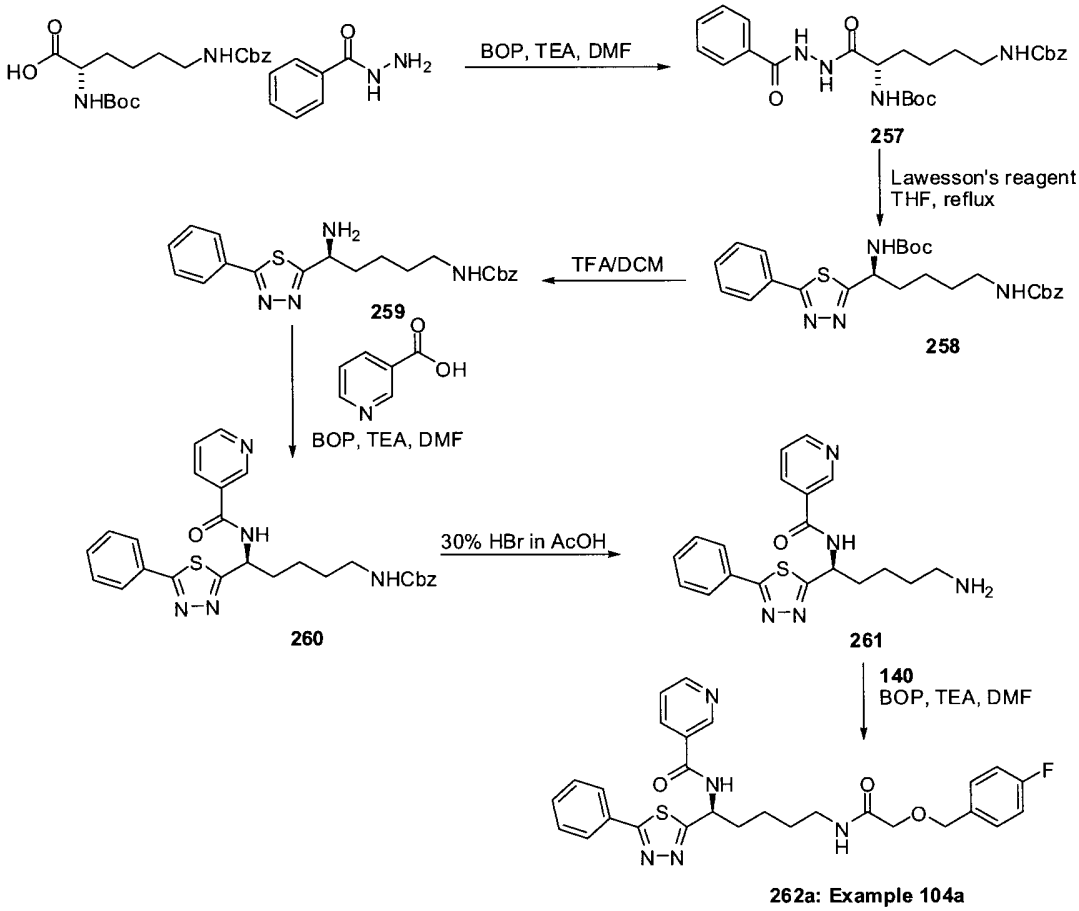
[0364] Example 103b,c describe the preparation of compound **256b,c** using the same procedures as described for compound **256a** in Example 103a. Characterization data are presented in a Table 20.

Table 20

Ex	Cpd	structure	Name	Characterization	Scheme
103 b	256b		2-(4-fluorophenylthio)-*N*-(5-(2-(pyridin-4-yl)thiazol-4-yl)pentyl)acetamide	(MeOD-*d4*) δ(ppm) ^{1}H: 8.64 (d, J = 1.6Hz, 1H), 8.63 (d, J = 1.6Hz, 1H), 7.94 (d, J = 1.6Hz, 1H), 7.93 (d, J = 1.6Hz, 1H), 7.44 (dd, J = 8.8Hz, 5.6Hz, 2H), 7.34 (s, 1H), 7.06 (t, J = 8.8Hz, 2H), 3.52 (s, 2H), 3.15 (t, J = 6.8Hz, 2H), 2.81 (t, J = 7.6Hz, 2H), 1.77-1.70 (m, 2H), 1.50-1.43 (m, 2H), 1.33-1.25 (m, 2H) LRMS (ESI): (calc) 415.12 (found) 416.19 $(MH)^+$	41 (Steps 1-4) Ex 103a

Ex	Cpd	structure	Name	Characterization	Scheme
103c	256c		2-(4-fluorophenylthio)-*N*-(5-(2-(pyridin-3-yl)thiazol-4-yl)pentyl)acetamide	(MeOD-*d4*) δ(ppm) ^{1}H: 9.90 (d, J = 2.4Hz, 1H), 8.60 (dd, J = 4.8, 1.6Hz, 1H), 8.35-8.32 (m, 1H), 7.54 (ddd, J = 8.0, 4.8, 0.4Hz, 1H), 7.46-7.42 (m, 2H), 7.26 (s, 1H), 7.08-7.04 (m, 2H), 3.52 (s, 2H), 3.15 (t, J = 6.8Hz, 2H), 2.80 (t, J = 7.2Hz, 2H), 1.77-1.70 (m, 2H), 1.50-1.42 (m, 2H), 1.33-1.26 (m, 2H) LRMS (ESI): (calc) 415.12 (found) 416.16 $(MH)^+$	41 (Steps 1-4) Ex 103a

Scheme 42



Example 104a

(S)-*N*-(5-(2-(4-fluorobenzyloxy)acetamido)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)nicotinamide (**262a**)

Step 1: (S)-benzyl 5-(*t*-butylcarbamate)-6-(2-benzoylhydrazinyl)-6-oxohexylcarbamate (**257**)

[0365] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting BOC-LYS(Z)-OH for *N*-Boc-caproic acid and benzhydrazide for 3-phenyl aniline to afford **257** (7.4 g, 80%) as a white solid. LRMS (ESI): (calc) 498.2 (found) 499.4 $(MH)^+$.

Step 2: (S)-benzyl 5-(*t*-butylcarbamate)-5-(5-phenyl-1,3,4-thiadiazol-2-yl)pentylcarbamate (**258**)

[0366] Following the same procedure as described for compound **176** (step 2, scheme 23, example 82) but substituting **257** for **175** to afford **258** (2.39 g, 46%) as a white solid. LRMS (ESI): (calc) 496.2 (found) 497.3 $(MH)^+$.

Step 3: (S)-benzyl 5-amino-5-(5-phenyl-1,3,4-thiadiazol-2-yl)pentylcarbamate (**259**)

[0367] Following the same procedure as described for compound **2** (step2, scheme 1, example 1) but substituting **258** for **1** to afford **259** (2.39 g, 46%) as a white solid. LRMS (ESI): (calc) 496.2 (found) 497.3 $(MH)^+$.

Step 4: (S)-benzyl 5-(nicotinamido)-5-(5-phenyl-1,3,4-thiadiazol-2-yl)pentylcarbamate (**260**)

[0368] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting nicotinic acid for *N*-Boc-caproic acid and **259** for 3-phenyl aniline to afford **260** (256 mg, 92%) as a white foam. LRMS (ESI): (calc) 501.2 (found) 502.3 $(MH)^+$.

Step 5: (S)-*N*-(5-amino-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)nicotinamide (**261**)

[0369] Compound **260** (256 mg, 0.511 mmol) was dissolved in 33% wt. HBr in acetic acid (3.0 mL) and stirred 1 hour. Then the reaction mixture was concentrated and the orange solid obtained was washed with 30% ethyl acetate in hexanes. The solid was dissolved in water. A solution of 5% aqueous sodium hydroxide solution was added until PH=12. The product was extracted with DCM. The combined organic phases were dried (Na_2SO_4), filtered and evaporated to afford **260** (251 mg, quantitative) as a beige solid. LRMS (ESI): (calc) 367.1 (found) 368.3 $(MH)^+$.

Step 6: (S)-*N*-(5-(2-(4-fluorobenzyloxy)acetamido)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)nicotinamide (**262a**)

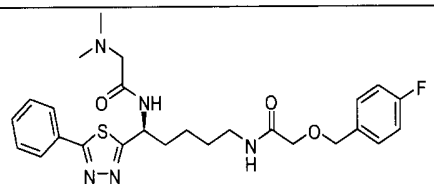
[0370] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting 2-(4-fluorobenzyloxy)acetic acid for *N*-Boc-caproic acid and **261** for 3-phenyl aniline to afford **262a** (78 mg, 27%) as a colorless oil. (MeOD-*d4*) δ(ppm) ^1H: 9.04 (s, 1H), 8.71 (s, 1H), 8.31 (d, J = 3.6Hz, 1H), 7.94 (s, 2H), 7.53-7.51 (m, 4H), 7.35 (d, J = 5.3Hz, 2H), 7.08-7.04 (m, 2H), 5.60 (t, J = 6.1Hz, 1H), 4.52 (s, 2H), 3.90 (s, 2H), 3.30-3.27 (m, 2H), 2.28-2.18 (m, 2H), 1.65-1.55 (m, 4H)

LRMS (ESI): (calc) 533.19 (found) 534.57 $(MH)^+$.

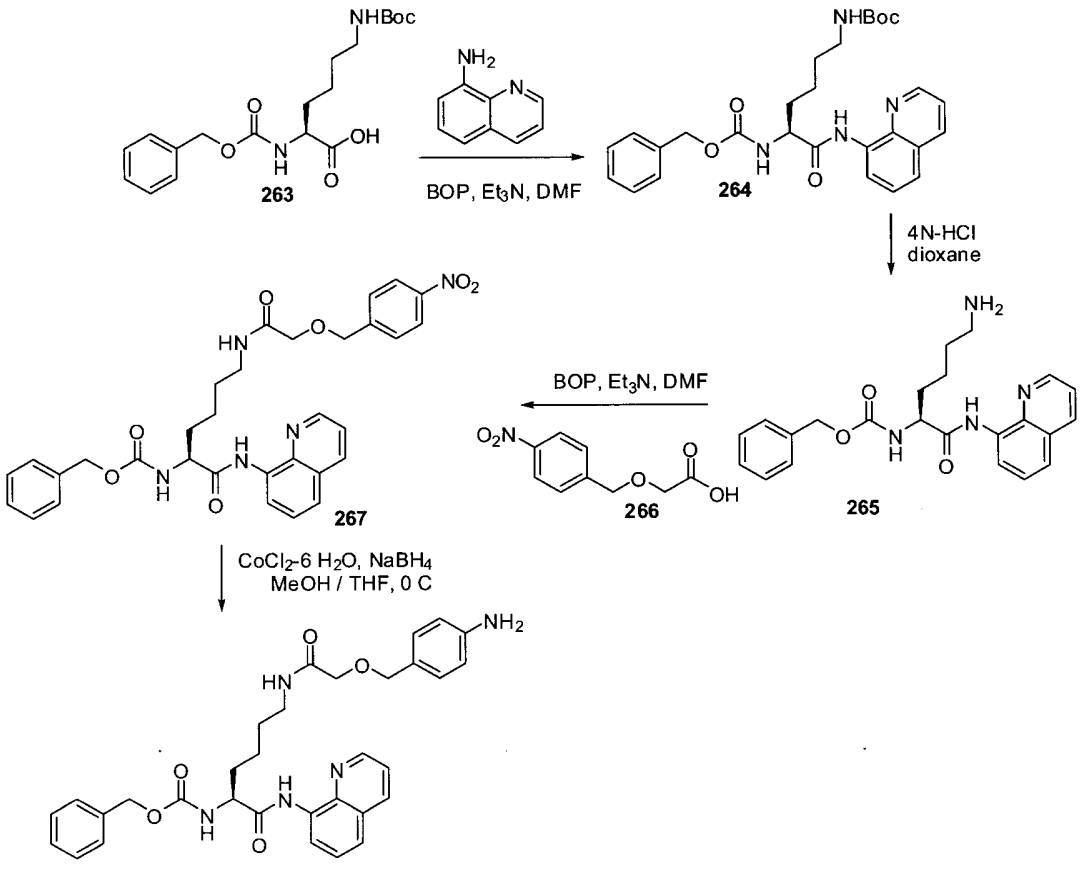
Example 104b

[0371] Example 104b describe the preparation of compound **262b** using the same procedures as described for compound **262a** in Example 104a. Characterization data are presented in Table 21.

Table 21

Ex	Cpd	structure	Name	Characterization	Scheme (steps)
104b	262b		(*S*)-2-(dimethylamino)-*N*-(5-(2-(4-fluorobenzyloxy)acetamido)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)acetamide	(MeOD-*d4*) δ(ppm) ^{1}H: 7.93 (d, J = 7.4Hz, 2H), 7.57-7.52 (m, 3H), 7.41-7.37 (m, 2H), 7.08 (t, J = 8.6Hz, 2H), 5.40 (dd, J = 8.8, 5.9Hz, 1H), 4.55 (s, 2H), 3.92 (s, 2H), 3.27 (t, J = 6.8Hz, 2H), 3.06 (s, 2H), 2.31 (s, 6H), 2.12-2.02 (m, 2H), 1.65-1.42 (m, 4H) LRMS (ESI): (calc) 513.22 (found) 514.87 $(MH)^+$	42 (1-6 (ex 104a))

Scheme 43



268a: Example 105a

Example 105a

(*S*)-benzyl 6-(2-(4-aminobenzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate (**268a**)

Step 1: (*S*)-benzyl 6-amino-(tert-butoxycarbonylamino)-1-oxo-1-(quinoline-8-ylamino)hexan-2-ylcarbamate (**264**)

[0372] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting Z-L-Lys(Boc)-OH for *N*-Boc-caproic acid and 8-aminoquinoline for 3-phenyl aniline to afford **264** (0.92 g, 70%) as an oil. LRMS (ESI): (calc) 506.3; (found) 507.4 $(MH)^+$.

Step 2: (*S*)-benzyl 6-amino-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate bis hydrochloride (**265**)

[0373] Compound **264** (0.3g, 0.59 mmol) was treated with 4N-HCl in dioxane (10 mL) for 2 hours at room temperature. The mixture was then concentrated to afford **265** (0.38g, quantitative yield) as a solid. LRMS (ESI): (calc) 406.2; (found) 406.5 $(MH)^+$.

Intermediate : 2-(4-nitrobenzyloxy)acetic acid (**266**)

[0374] Following the same procedure as described for compound **42** (scheme 2, example 37 step 1) but substituting (4-nitrophenyl)methanol for (4-(methylthio)phenyl)methanol and then following the same procedure as described for compound **5** (step 5, scheme 1, example 1) but substituting ethyl 2-(4-nitrobenzyloxy)acetate for methyl ester **4**, to afford **266** (0.96g, 94%). LRMS (ESI): (calc) 211.1; (found) 210.2 $(MH)^+$.

Step 3: (*S*)-benzyl 6-(2-(4-nitrobenzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate (**267**)

[0375] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting acid 2-(4-nitrobenzyloxy)acetic acid for *N*-Boc-caproic acid and compound **265** for 3-phenyl aniline to afford **267** (40 mg, 22%). LRMS (ESI): (calc) 599.2; (found) 600.3 $(MH)^+$.

Step 4: (*S*)-benzyl 6-(2-(4-aminobenzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate (**268**)

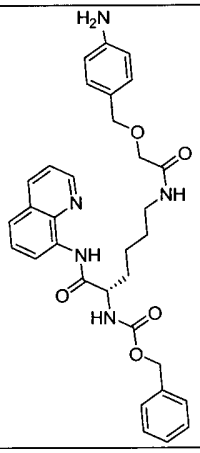
[0376] To solution of compound **267** (18 mg, 30 umol) and cobalt chloride hexahydrate (71 mg, 0.3 mmol) in a 1:1 mixture of THF and MeOH (1 mL) at 0 °C was added sodium borohydride (11 mg, 0.3 mmol). After stirring for 35 minutes, the mixture was acidified with 3N HCl, and then basified with concentrated ammonium hydroxide. Extraction with DCM, the organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel column chromatography with a 5% MeOH in DCM to afford **268** (7 mg, 41%).

(MeOD-*d*4) δ(ppm) ^{1}H: 8.75 (dd, J=4.3, 1.3Hz, 1H), 8.64 (d, J=7.4Hz, 1H), 8.29 (dd, J=8.1, 1.3Hz, 1H), 7.62 (d, J=8.4Hz, 1H), 7.56-7.50 (m, 2H), 7.40-7.20 (m, 5H), 7.07 (d, J=8.4Hz, 2H), 6.68 (d, J=8.2Hz, 2H), 5.21 and 5.10 (AB doublet, J=12.4Hz, 2H), 4.40 (s, 2H), 4.36-4.32 (m, 1H), 3.84 (s, 2H), 3.23 (t, J=6.6Hz, 2H), 2.12-1.98, (m, 1H), 1.90-1.77 (m, 1H), 1.70-1.43 (m, 4H); LRMS (ESI): (calc) 569.3 (found) 570.4 $(MH)^+$.

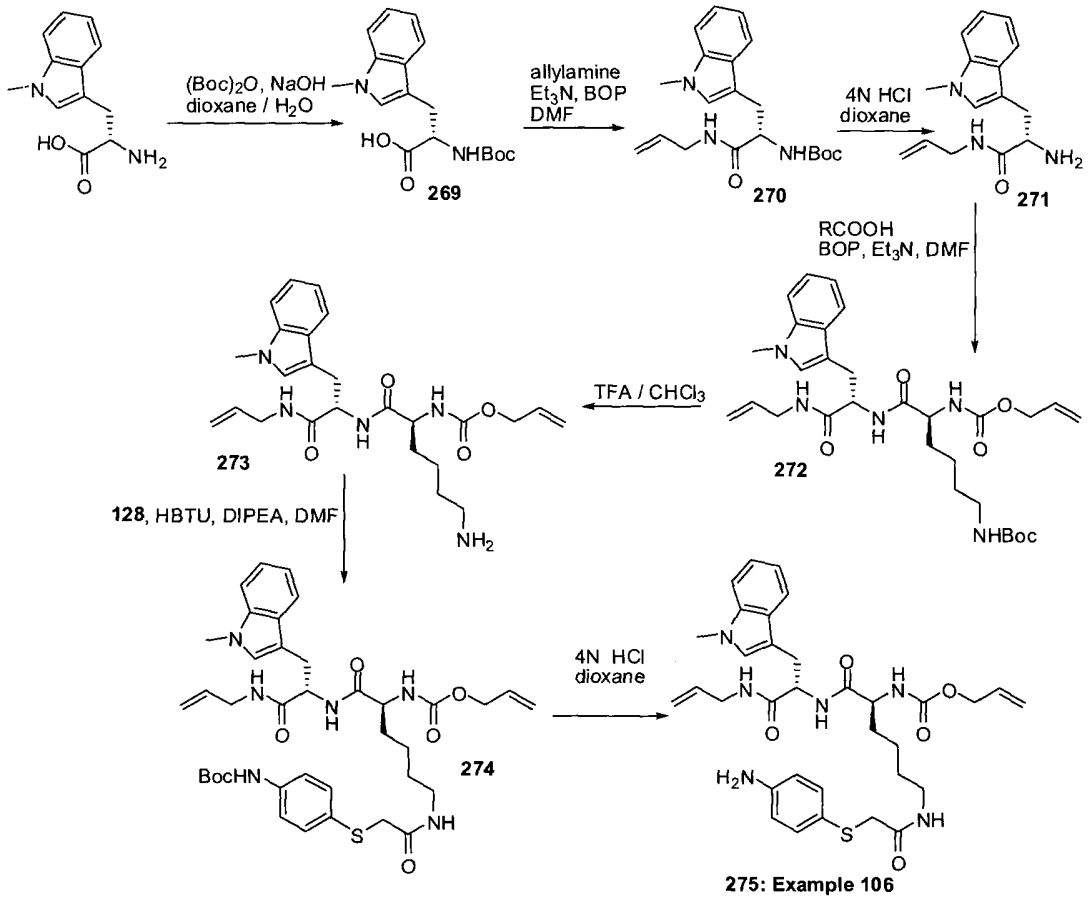
Example 105b

[0377] Example 105b describe the preparation of compound **268b** using the same procedures as described for compound **268a** in Example 105a. Characterization data are presented in Table 22.

Table 22

Ex	Cpd	structure	Name	Characterization	Scheme (steps)
105b	268b		(R)-benzyl 6-(2-(4-aminobenzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate	(MeOD-*d*4) δ(ppm) ^{1}H: 8.76-8.74 (m, 1H), 8.63 (d, J=7.6Hz, 1H), 8.30-8.27 (m, 1H), 7.61 (d, J=8.3Hz, 1H), 7.55-7.50 (m, 2H), 7.40-7.20 (m, 5H), 7.07 (d, J=8.2Hz, 2H), 6.68 (d, J=8.2Hz, 2H), 5.21 and 5.10 (AB doublet, J=12.5Hz, 2H), 4.40 (s, 2H), 4.36-4.32 (m, 1H), 3.84 (s, 2H), 3.23 (t, J=6.3Hz, 2H), 2.12-1.95, (m, 1H), 1.90-1.77 (m, 1H), 1.65-1.43 (m, 4H). LRMS (ESI): (calc) 569.3 (found) 570.97 $(MH)^+$.	43

Scheme 44



Example 106

allyl (*S*)-1-((S)-1-(allylamino)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-ylamino)-6-(2-(4-aminophenylthio)acetamido)-1-oxohexan-2-ylcarbamate (**275**)

Step 1: (*S*)-2-(tert-butoxycarbonylamino)-3-(1-methyl-1H-indol-3-yl)propanoic acid (**269**)

[0378] To a solution of 1-methyl-L-trp-OH (1g, 4.6 mmol) and di-tert-butyl dicarbonate (1.5g, 6.9 mmol) in a 1:1 mixture of water / dioxane (40 mL) at 0 °C was added sodium hydroxide (0.4g, 10 mmol). The resulting mixture was stirred at 0 °C for 2 hours, then diluted with ethyl ether, acidified with 3N HCl and extracted with ethyl acetate. The organic layer was extracted from brine and dried (Na_2SO_4), filtered and concentrated to afford **275** (1.4g, 96%). LRMS (ESI): (calc) 318.2 (found) 317.3 $(MH)^+$.

Step 2: (S)-tert-butyl 1-(allylamino)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-ylcarbamate (**270**)

[0379] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting compound **269** for *N*-Boc-caproic acid and allylamine for 3-phenyl aniline to afford **270** (1.6 g, quantitavive). LRMS (ESI): (calc) 357.2; (found) 357.3 $(MH)^+$.

Step 3: (S)-N-allyl-2-amino-3-(1-methyl-1H-indol-3-yl)propanamide (**271**)

[0380] Following the same procedure as described for compound **265** (scheme **43**, example 105a, step 2) but substituting **270** for **264** to afford **271** (1.3 g, quant.). LRMS (ESI): (calc) 257.2; (found) 257.3 $(MH)^+$.

Step 4: allyl (S)-1-((S)-1-(allylamino)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-ylamino)-6-(tert-butoxycarbonylamino)-1-oxohexan-2-ylcarbamate (S)-2-amino-3-(1-methyl-1H-indol-3-yl)propanoate (**272**)

[0381] Following the same procedure as described for compound **1** (scheme 1, example 1) but substituting Aloc-L-Lys(Boc)-OH-DCHA for *N*-Boc-caproic acid and compound **271** for 3-phenyl aniline to afford **272** (1.6 g, quantitative yield). LRMS (ESI): (calc) 569.3; (found) 570.3 $(MH)^+$.

Step 5: allyl (S)-1-((S)-1-(allylamino)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-ylamino)-6-amino-1-oxohexan-2-ylcarbamate (S)-2-amino-3-(1-methyl-1H-indol-3-yl)propanoate (**273**)

[0382] Following the same procedure as described for compound **9** (scheme 1, example 4, step 5) but substituting compound **272** for compound **7a** and using chloroform as a solvent to afford **273** (45 mg, 74 %). LRMS (ESI): (calc) 469.3; (found) 470.4 $(MH)^+$.

Step 6: allyl (S)-1-((S)-1-(allylamino)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-ylamino)-6-(2-(4-tert-butyl thiophenylcarbamate)acetamido)-1-oxohexan-2-ylcarbamate (**274**)

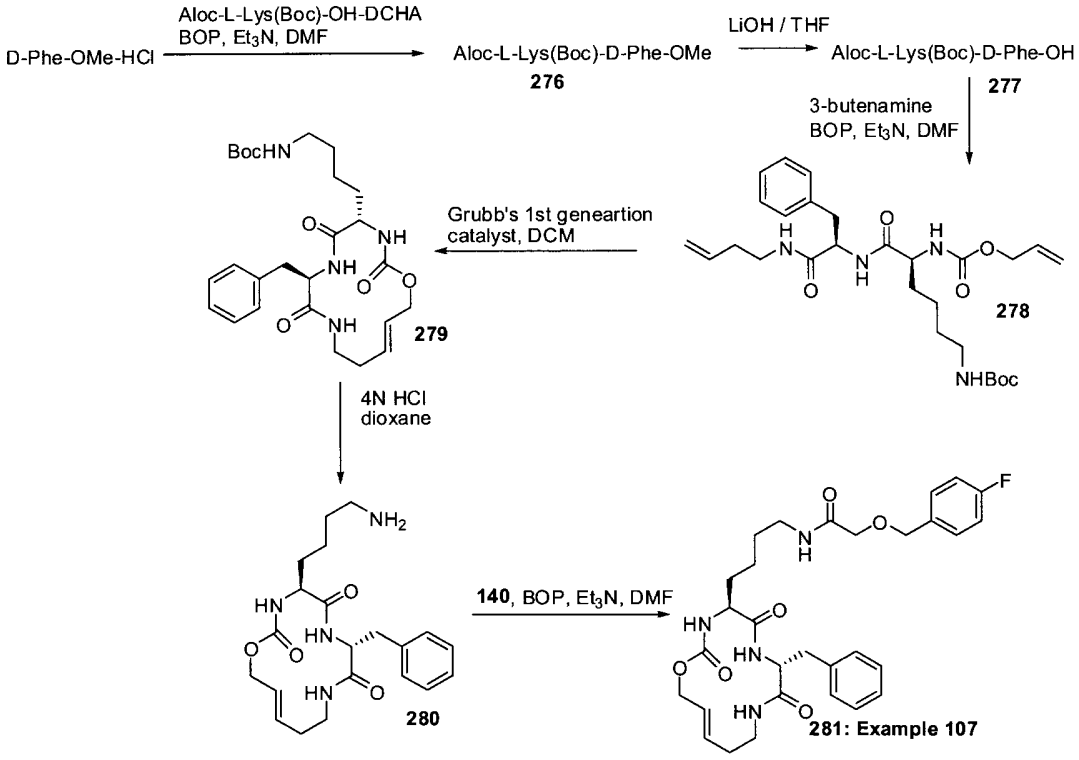
[0383] To a stirred solution of **128** (33 mg, 0.12 mmol) and DIPEA (37 mg, 0.29 mmol) in DMF (1 mL) was added HBTU (40 mg, 0.11 mmol). After 15 minutes **273** (45 mg, 0.1 mmol) was added at room temperature for 3h. The mixture was diluted with ethyl acetate, extracted from brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography with gradient of MeOH (0-5%) in DCM to afford **274** (25 mg, 35%). LRMS (ESI): (calc) 734.4; (found) 735.4 $(MH)^+$.

Step 7: allyl (S)-1-((S)-1-(allylamino)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-ylamino)-6-(2-(4-aminophenylthio)acetamido)-1-oxohexan-2-ylcarbamate (**275**)

[0384] Following the same procedure as described for compound **265** (scheme **43**, example 105a, step 2) but substituting compound **274** for compound **264** to afford **275** (5 mg, 26%). (MeOD-*d*4) δ(ppm) ^1H: 7.57 (d, J=7.9Hz, 1H), 7.30 (d, J=7.8Hz, 1H), 7.20 (dd, J=6.6, 1.5Hz, 2H), 7.15 (t, J=7.0Hz, 1H), 7.04 (t, J=7.4Hz, 1H), 7.01 (s, 1H), 6.62 (dd, J=6.5, 1.8Hz, 2H), 5.98-5.82 (m, 1H), 5.73-5.60 (m, 1H), 5.28 (d, J=17.0Hz, 1H), 5.16 (d, 10.4Hz, 1H), 5.03-4.95 (m, 2H), 4.62 (t, J=6.9Hz, 1H), 4.58-4.40 (m, 2H), 4.0-3.90 (m, 1H), 3.74 (s, 3H), 3.73-3.60 (m, 2H), 3.34 (s, 2H), 3.25 and 3.16 (AB doublet, J=14.6, 6.9Hz, 2H), 3.10-2.97 (m, 2H), 1.60-1.40 (m, 2H), 1.40-1.20 (m, 2H), 1.22-1.0 (m, 2H).

LRMS (ESI): (calc) 634.3 (found) 636.1 $(MH)^+$.

Scheme 45



Example 107

N-(4-((4*S*,7*R*,*E*)-7-benzyl-2,5,8-trioxo-1-oxa-3,6,9-triazacyclotetradec-12-en-4-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**281**)

Step 1: Aloc-L-Lys(Boc)-D-Phe-OMe (**276**)

[0385] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting Aloc-L-Lys(Boc)-OH-DHCA for *N*-Boc-caproic acid and D-Phe-OMe-HCl for 3-phenyl aniline to afford **276** (0.12 g, 51%). LRMS (ESI): (calc) 491.3; (found) 492.6 $(MH)^+$.

Step 2: Aloc-L-Lys(Boc)-D-Phe-OH (**277**)

[0386] Following the same procedure as described for compound **5** (scheme1, example 1, step 5) but substituting **276** for methyl ester **4**, to afford **277** (0.21g, 88%). LRMS (ESI): (calc) 477.3; (found) 476.6 $(MH)^+$.

Step 3: allyl (S)-6-tert-butoxycarbonylamino-1-((R)-1-(but-3-enylamino)-1-oxo-3-phenylpropan-2-ylamino)-1-oxohexan-2-ylcarbamate (**278**)

[0387] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting compound **277** for *N*-Boc-caproic acid and 3-butenamine for 3-phenyl aniline to afford **278** (0.16 g, 70%). LRMS (ESI): (calc) 530.3; (found) 531.3 $(MH)^+$.

Step 4: (4S,7R,E)-4-(4-(tert-butoxycarbonylamino)-butyl)-7-benzyl-1-oxa-3,6,9-triazacyclotetradec-12-ene-2,5,8-trione (**279**)

[0388] To a stirred solution of compound **278** (47 mg, 0.09 mmol) in DCM was added Grubb's 1st generation catalyst (11 mg, 0.01 mmol). The mixture was stirred over night, diluted with methanol and treated with activated charcoal for 1h then silica gel was added and the suspension was concentrated. The residue was purified by silica gel column chromatography with a gradient of ethyl acetate (25-100%) in hexanes to afford **279** (15 mg, 33%). LRMS (ESI): (calc) 502.3; (found) 503.1 $(MH)^+$.

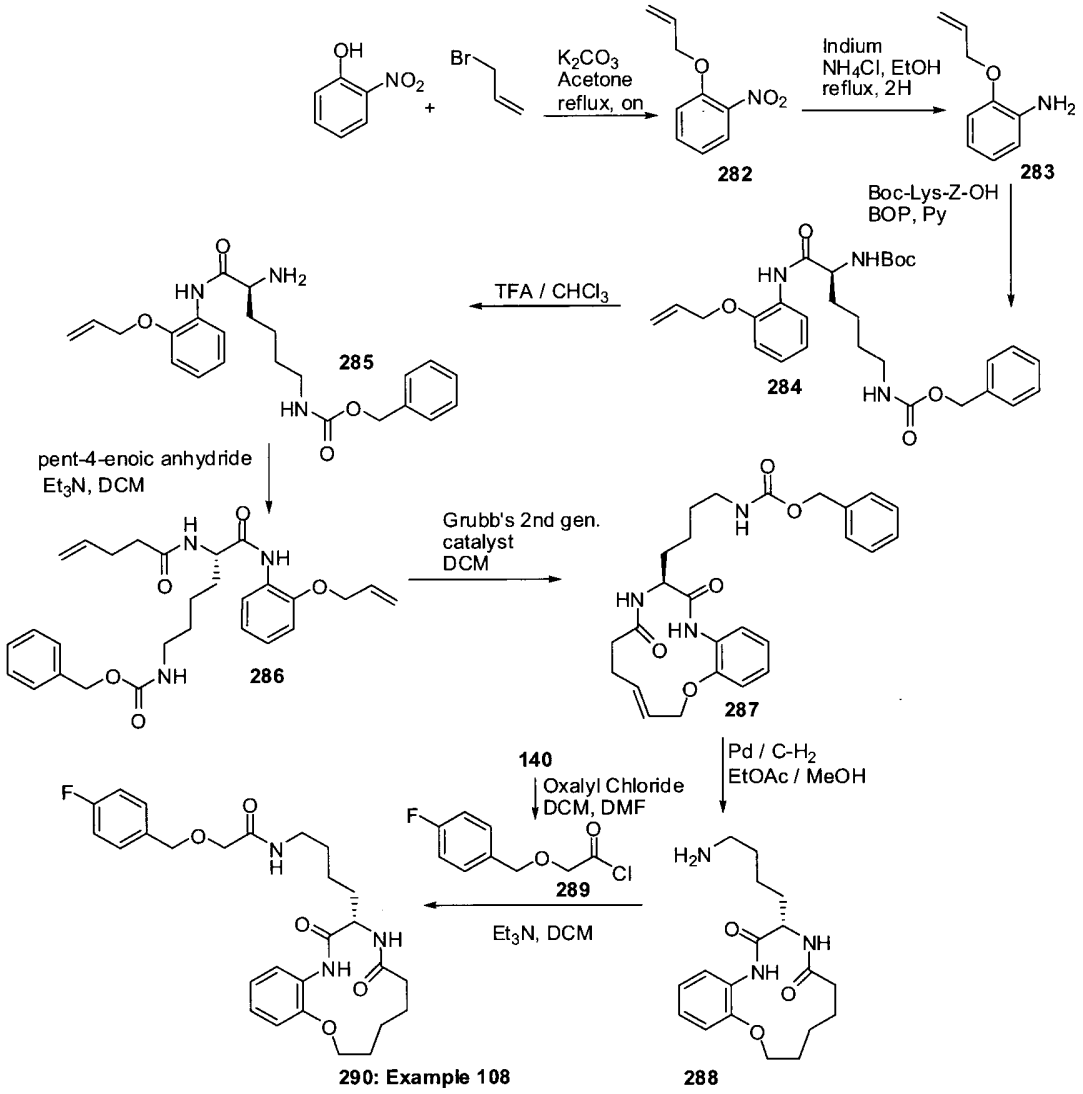
Step 5: (4S,7R,E)-4-(4-aminobutyl)-7-benzyl-1-oxa-3,6,9-triazacyclotetradec-12-ene-2,5,8-trione (**280**)

[0389] Following the same procedure as described for compound **265** (scheme **43**, example 105a, step 2) but substituting **279** for **264** to afford **280** (25 mg, quant.). LRMS (ESI): (calc) 402.2; (found) 403.1 $(MH)^+$.

Step 6: N-(4-((4S,7R,E)-7-benzyl-2,5,8-trioxo-1-oxa-3,6,9-triazacyclotetradec-12-en-4-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**281**)

[0390] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting **140** for *N*-Boc-caproic acid and **280** for 3-phenyl aniline to afford **281** (4 mg, 11%). (MeOD-*d*4) δ(ppm) ^{1}H: 7.44-7.38 (m, 2H), 7.29-7.17 (m, 5H), 7.12-7.06 (m, 2H), 5.80-5.68 (m, 1H), 5.50-5.40 (m, 1H), 5.01-4.62 (m, 3H), 4.62-4.52 (m, 2H), 4.28-4.19 (m, 1H), 4.00-3.79 (m, 3H), 3.74-360 (m, 1H), 3.42-3.34 (m, 1H), 3.22-3.02 (m, 3H), 2.88-2.72 (m, 2H), 2.40-2.26 (m, 1H), 2.10-2.02 (m, 1H), 1.44-0.82 (m, 8H). LRMS (ESI): (calc) 568.3 (found) 569.7 $(MH)^+$.

Scheme 46



Example 108

(S)-N-(4-(2,5-dioxo-1,2,3,4,5,6,7,8,9,10-decahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**288**)

Step 1: 1-(allyloxy)-2-nitrobenzene (**282**)

[0391] Following the same procedure as described for compound **171** (scheme 22, example 81a, step 1) but substituting 2-nitrophenol for 5-amino-1,3,4-thiadiazole-2-thiol and allyl bromide for 2-(3-bromopropyl)isoindoline-1,3-dione to afford **282** (6.0 g, 95%) as a yellow oil. LRMS (ESI): (calc) 176.1 (found) 177.2 $(MH)^+$.

Step 2: 2-(allyloxy)aniline (**283**)

[0392] To a stirred suspension of compound **282** (3.0 g, 17 mmol) and ammonium chloride saturated solution (8 mL) in refluxing ethanol (35 mL) was added indium (11.8 g,

102 mmol). The mixture was stirred 2 hours, filtered, concentrated, diluted with ethyl acetate, and extracted with 3N HCl solution. The aqueous layer was basified with 10% NaOH solution and extracted with ethyl acetate. The organics layer was extracted from brine, dried (Na_2SO_4), treated with activated charcoal, filtered, and concentrated to afford **283** (1.1 g, 44%) as a black oil. LRMS (ESI): (calc) 149.1 (found) 149.9 $(MH)^+$.

Step 3: (S)-benzyl 6-(2-(allyloxy)phenylamino)-5-tert-butyl carbamate-6-oxohexylcarbamate (**284**)

[0393] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting Boc-L-Lys-Z-OH for *N*-Boc-caproic acid, **283** for 3-phenyl aniline and pyridine for triethylamine-DMF to afford **284** (1.24 g, 91%). LRMS (ESI): (calc) 511.27; (found) 512.7 $(MH)^+$.

Step 4: (S)-benzyl 6-(2-(allyloxy)phenylamino)-5-amino-6-oxohexylcarbamate (**285**)

[0394] Following the same procedure as described for compound **9** (scheme 1, example 4, step 5) but substituting compound **284** for compound **7a** and chloroform for DCM to afford **285** (1.1 g, quantitative yield). LRMS (ESI): (calc) 411.2; (found) 412.3 $(MH)^+$.

Step 5: (S)-benzyl 6-(2-(allyloxy)phenylamino)-6-oxo-5-pent-4-enamidohexylcarbamate (**286**)

[0395] Following the same procedure as described for compound **54** (scheme 2, example 47, step 1) but substituting pent-4-enoic anhydride for 3-bromopropanoyl chloride and DCM for THF to afford **286** (0.23 g, 54%) as white solid. LRMS (ESI): (calc) 493.3; (found) 494.1 $(MH)^+$.

Step 6: (S,E)-benzyl 4-(2,5-dioxo-1,2,3,4,5,6,7,10-octahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butylcarbamate (**287**)

[0396] Following the same procedure as described for compound **279** (scheme 45, example 107, step 4) but substituting compound **286** for compound **278** and Grubb's 2nd generation catalyst for Grubb's 1st generation catalyst to afford **287** (0.065 g, 30%). LRMS (ESI): (calc) 465.2; (found) 466.6 $(MH)^+$.

Step 7: (S)-3-(4-aminobutyl)-3,4,7,8,9,10-hexahydrobenzo[b][1,4,7]oxadiazacyclotridecine-2,5(1H,6H)-dione (**288**)

[0397] Following the same procedure as described for compound **74** (scheme 5, example 55) but substituting **287** for **73** to afford **288** (0.055 g, quant.). LRMS (ESI): (calc) 333.2; (found) 334.4 $(MH)^+$.

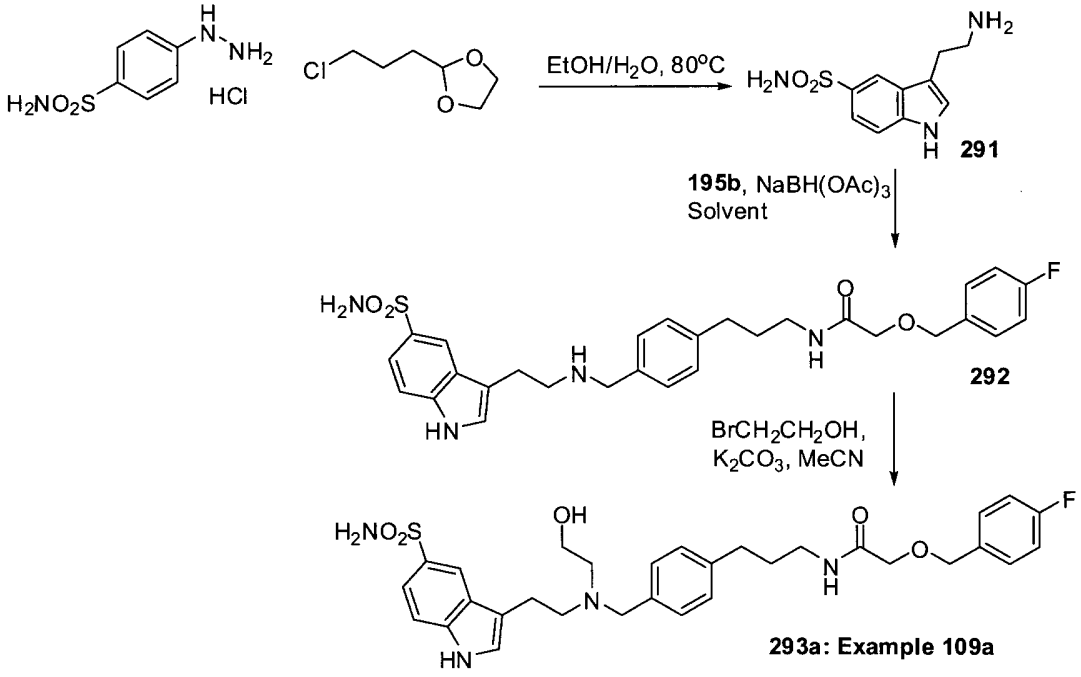
Intermediate: 2-(4-fluorobenzyloxy)acetyl chloride (**289**)

[0398] Following the same procedure as described for compound **255** (scheme 41, example 103a, step 3-1)) but substituting **140** for **254** to afford **289**. The product was used without further purification.

Step 8: (S)-N-(4-(2,5-dioxo-1,2,3,4,5,6,7,8,9,10-decahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**290**)

[0399] Following the same procedure as described for compound **3a** (scheme 1, example 1) but substituting **289** for chloroacetyl chloride, compound **288** for amine compound **2** and DCM for THF to afford **290** (0.02 g, 44%). (MeOD-*d*4) δ(ppm) ^{1}H: 8.12 (dd, J=8.0, 1.5Hz, 1H), 7.42-7.38 (m, 2H), 7.1-7.0 (m, 3H), 6.99-6.89 (m, 2H), 4.56 (s, 2H), 4.42-4.38 (m, 1H), 4.35-4.30 (m, 1H), 3.93 (s, 2H), 3.83 (td, J=9.4, 3.6Hz, 1H), 3.28-3.23 (m, 2H), 2.6-2.5 (m, 1H), 2.29-2.14 (m, 1H), 2.05-1.89 (m, 2H), 1.88-1.39 (m, 10H). LRMS (ESI): (calc) 499.3 (found) 500.6 $(MH)^+$.

Scheme 47



Example 109a

2-(4-fluorobenzyloxy)-N-(3-(4-((2-(5-sulfamoyl-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)acetamide (**293a**)

Step 1: 3-(2-aminoethyl)-1H-indole-5-sulfonamide (**291**)

[0400] To a stirred solution of 4-hydrazinylbenzenesulfonamide hydrochloride (740 mg, 3.32 mmol) in a 5 : 1 ethanol – water mixture (18 mL), was added 2-(3-chloropropyl)-1,3-dioxolane (500 mg, 3.32 mmol). The solution was heated to 80°C and stirred for 2 h. The solvent was removed via rotary evaporation. The residue was purified with silica gel column

chromatography employing a 20 : 48 : 2 methanol : dichloromethane : ammonium hydroxide moving to 33 : 63 : 2 methanol : dichloromethane : ammonium solvent gradient to afford **291** (400 mg, 51%) as a red solid.

(DMSO-*d6*) δ(ppm): 11.56 (s, 1H), 8.08 (d, J=1.6 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.51 – 7.48 (m, 1H), 7.42 (d, J=2.3 Hz, 1H), 7.13 (s, 2H), 3.15 (d, J=5.1 Hz, 2H), 3.05 (s, 4H).

Step 2: 3-(2-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylamino)ethyl)-1H-indol-5-yl sulfite (**292**)

[0401] Following the same procedure as described for compound **196b** (step 5, scheme 27, example 87b) but substituting **291** for tryptamine to afford **292** (60 mg, 17%) as a colourless oil.

(MeOD-*d4*) δ(ppm): 8.17 (d, J=1.6 Hz 1H), 7.66 (dd, J=8.6, 1.8 Hz, 1H), 7.45 (d, J=8.6 Hz, 1H), 7.38 (dd, J=8.6, 5.5 Hz, 2H), 7.20 - 7.04 (m, 7H), 4.53 (s, 2H), 3.90 (s, 2H), 3.74 (s, 2H), 3.23 (t, J=7.2 Hz, 2H), 3.01 - 2.89 (m, 4H), 2.58 (t, J=7.6 Hz, 2H), 1.79 (quintet, J=7.4 Hz, 2H).

Step 3: 2-(4-fluorobenzyloxy)-N-(3-(4-((2-(5-sulfamoyl-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)acetamide (**293a**)

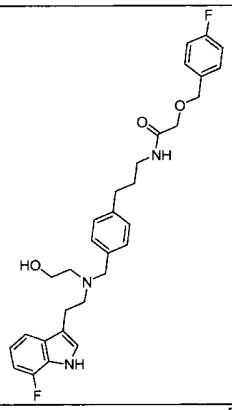
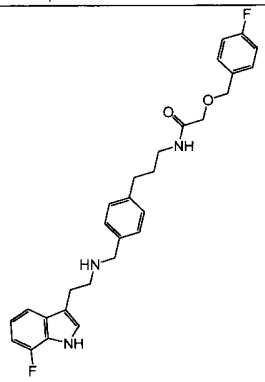
[0402] Following the same procedure as described for compound **197b** (step 1, scheme 27, example 88b) but substituting **292** for **196b** to afford 293a (15 mg, 31%) as a colourless oil.

(MeOD-*d4*) δ(ppm): 8.12 (d, J=1.8 Hz, 1H), 7.63 (dd, J=8.6, 1.8 Hz, 1H), 7.45 - 7.37 (m, 3H), 7.23 (d, J=8.0 Hz, 2H), 7.16 - 7.04 (m, 5H), 4.55 (s, 2H), 3.91 (s, 2H), 3.71 (s, 2H), 3.62 (t, J=6.2 Hz, 2H), 3.24 (t, J=7.0 Hz, 2H), 2.96 (t, J=6.8 Hz, 2H), 2.85 - 2.80 (m, 2H), 2.73 (t, J=6.3 Hz, 2H), 2.60 (t, J=7.4 Hz, 2H), 1.81 (quintet, J=7.4 Hz, 2H).

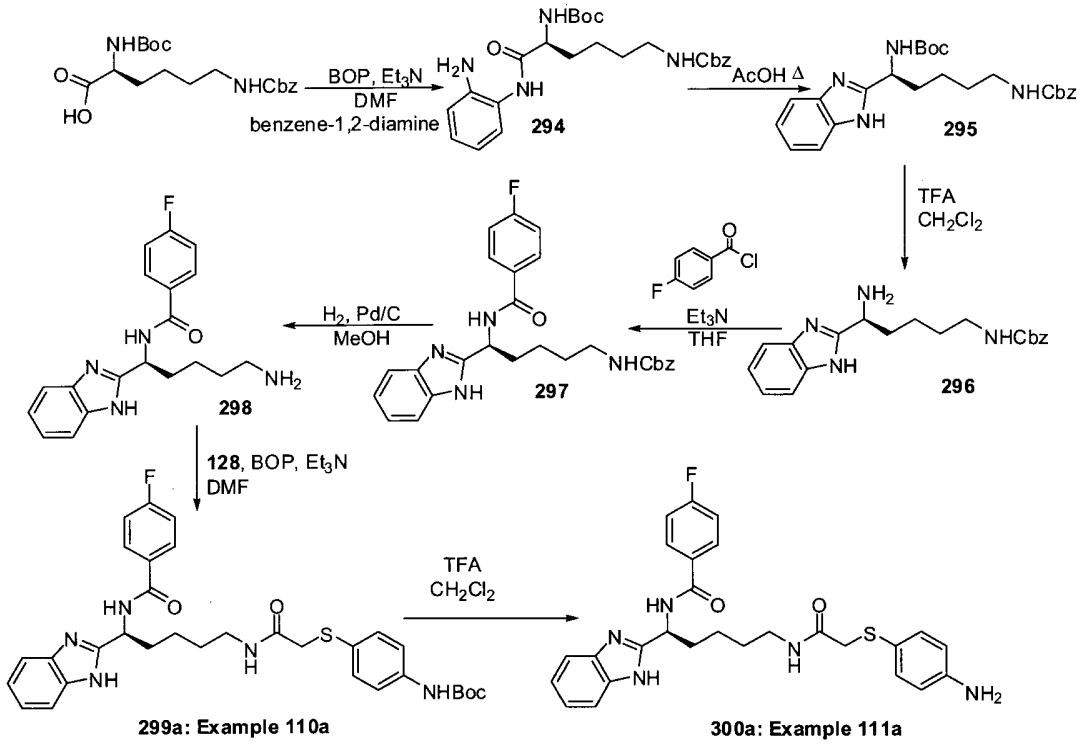
Example 109b,c

[0403] Example 109b describes the preparation of compound **293b,** using the same procedures as described for compound **293a** in Example 109a. Characterization data are presented in a Table 23.

Table 23

Ex	Cpd	structure	Name	Characterization	Scheme (steps)
109b	293b		*N*-(3-(4-(((2-(7-fluoro-1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) δ(ppm) 1H: 7.38 (dd, J=8.8, 5.8 Hz, 2H), 7.24 (d, J=8.2 Hz, 2H), 7.16 - 7.02 (m, 6H), 6.88 - 6.83 (m, 1H), 6.79 - 6.73 (m, 1H), 4.54 (s, 2H), 3.91 (s, 2H), 3.69 (s, 2H), 3.62 (t, J=6.5 Hz, 2H), 3.24 (t, J=7.0 Hz, 2H), 2.92 - 2.88 (m, 2H), 2.80 - 2.76 (m, 2H), 2.72 (t, J=6.3 Hz, 2H), 2.60 (t, J=7.6 Hz, 2H), 1.81 (quintet, J=7.2 Hz, 2H). LRMS(ESI): (calc.) 535.3 (found) 536.3 (MH)+	47
109c	293c		*N*-(3-(4-((2-(7-fluoro-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) δ(ppm) 1H: 7.36 (dd, J=8.4, 5.5 Hz, 2H), 7.28 (d, J=7.8 Hz, 1H), 7.18 (d, J=8.0 Hz, 2H), 7.13 - 7.02 (m, 5H), 6.94 - 6.88 (m, 1H), 6.83 - 6.77 (m, 1H), 4.51 (s, 2H), 3.90 (s, 2H), 3.77 (s, 2H), 3.22 (t, J=7.0 Hz, 2H), 3.00 - 2.90 (m, 4H), 2.57 (t, J=7.4 Hz, 2H), 1.78 (quintet, J=7.4 Hz, 2H). LRMS(ESI): (calc.) 491.2 (found) 492.3 (MH)+	47 (step1-2)

Scheme 48



Example 110a

(S)-tert-butyl 4-(2-(5-(1H-benzo[d]imidazol-2-yl)-5-(4-fluorobenzamido)pentylamino)-2-oxoethylthio)phenylcarbamate (**299a**)

Step 1 (S)-6-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)hexanoic -2-aminobenzamide (**294**):

[0404] Following the same procedure as described for compound **1** (step1, scheme1, example1) but substituting acid (S)-6-(benzyloxycarbonylamino)-2-(tert-butoxycarbonylamino)hexanoic acid and benzene-1,2-diamine for N-Boc-caproic acid and 3-phenyl aniline, respectively, to afford **294** (1.32g, 99%) as a yellow oil. LRMS (ESI): (calc.) 470.2; (found) 471$(MH)^+$.

Step 2: (S)-benzyl 5-(tert-butoxycarbonylamino)-5-(1H-benzo[d]imidazol-2-yl)pentylcarbamate (**295**)

[0405] Acetic acid (6mL) was added to **294** (1.55g, 3.3 mmol) and heated at 90°C for 20 minutes. The solvent was evaporated under reduced pressure. The residue was then purified by silica gel column chromatography with gradient of EtOAc (20-100%) in hexane to afford **295** (1.49g, 99%) as a light yellow oil. LRMS (ESI): (calc.) 452.2; (found) 453.2 $(MH)^+$.

Step 3: (S)-benzyl 5-amino-5-(1H-benzo[d]imidazol-2-yl)pentylcarbamate (**296**)

[0406] Following the same procedure as described for compound **2** (scheme 1, example1, step 2) but substituting **295** for **1** to afford **296** (1.1g, 95%) as a yellow oil. LRMS (ESI): (calc.) 352.2; (found) 353.1$(MH)^+$.

Step 4 (**297**) (S)-benzyl 5-(1H-benzo[d]imidazol-2-yl)-5-(4-fluorobenzamido)pentylcarbamate:

[0407] Following the same procedure as described for compound **54** (scheme 2, example 47, step 1) but substituting **296** for **2** and 4-fluorobenzoyl chloride for 3-bromopropanoyl chloride to afford **297** (165mg, 81%) as a deep yellow oil. LRMS (ESI): (calc.) 474.2; (found) 475 $(MNa)^+$.

Step 5 (**298**) (S)-N-(5-amino-1-(1H-benzo[d]imidazol-2-yl)pentyl)-4-fluorobenzamide: Following the same procedure as described for compound **74** (step 8, scheme 5, example 55) but substituting **297** for **73** to afford **298** (119mg, 99%) as a yellow oil. LRMS (ESI): (calc.) 340.1; (found) 341.2 $(MH)^+$.

Step 6: (S)-tert-butyl 4-(2-(5-(1H-benzo[d]imidazol-2-yl)-5-(4-fluorobenzamido)pentylamino)-2-oxoethylthio)phenylcarbamate (**299a**)

[0408] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting acid **128** and amine **298** for N-Boc-caproic acid and 3-phenyl aniline,respectively, to afford **299a** (175mg, 99%) as a yellow oil. LRMS (ESI): (calc.) 605.2 (found) 606.7 $(MH)^+$.

Example 111a

(S)-N-(5-(2-(4-aminophenylthio)acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)-4-fluorobenzamide (**300a**)

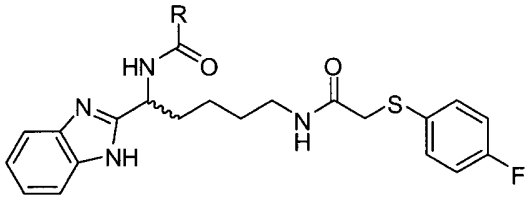
Step 7: (S)-N-(5-(2-(4-aminophenylthio)acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)-4-fluorobenzamide (**300a**)

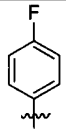
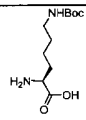
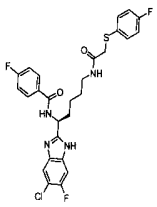
[0409] Following the same procedure as described for compound **2** (scheme 1, example 1, step 2) but substituting **299a** for **1** to afford **300a** (15mg, 9%) as a yellow oil. (MeOD-*d4*) δ (ppm):7.98 (qobs, J = 6.0, 9.0 Hz, 2H); 7.55-7.53 (m, 2H); 7.24-7.15 (m, 6H); 6.61(d, J = 9 Hz, 2H); 5.34 (qobs, J = 6.0, 9.0 Hz, 1H); 3.31 (s, 2H); 3.15-3.11 (m, 2H); 2.18-2.02 (m, 2H); 1.52-1.27 (m, 4H) LRMS (ESI): (calc.) 505.1; (found) 506.5$(MH)^+$.

Example 110b,c,d

[0410] Example 110b,c,d describe the preparation of compound **299b,c,d** using the same procedures as described for compound **299a** in Example 111a. Characterization data are presented in a Table 24.

Table 24

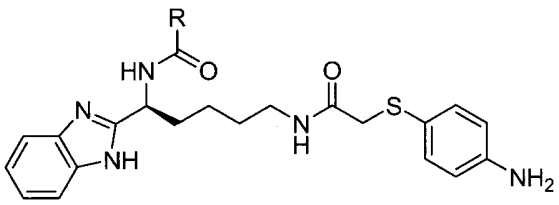


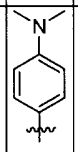
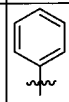
Ex	Cpd	R	Stereo chemistry	Name	Characterization	Scheme (step)
110b	299 b		S	(*S*)-*N*-(5-acetamido-5-(1*H*-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorophenylthio)acetamide	(MeOD-*d4*) δ(ppm):7.52 (bs, 2H); 7.39 (m, 2H); 7.20 (m, 2H); 7.02 (t, 2H, J = 8.8 Hz); 5.09 (dd, J = 6.3, 8.6 Hz, 1H); 3.50 (s, 2H); 3.14 (t, J = 6.8, 13.6 Hz, 2H); 2.10-2.01 (m, 4H); 1.93-1.83 (m, 1H); 1.50-1.43 (m, 2H); 1.37-1.24 (m, 2H) LRMS(ESI): 428.1 (calc) 429.8 (found)	48 (1-6)
110c	299 c		R	(*S*)-*N*-(1-(1H-benzo[d]imidazol-2-yl)-5-(2-(4-fluorophenylthio)acetamido)pentyl)-4-fluorobenzamide	(MeOD-*d4*) δ(ppm): 7.98 (q, J = 5.5, 9.0 Hz, 2H); 7.53 (m, 2H); 7.38 (q, J = 5.3, 9.0 Hz, 2H); 7.21 (m, 4H); 7.01 (t, J = 8.6 Hz, 2H); 5.35 (dd, J = 6.0, 8.8 Hz, 1H); 3.48 (s, 2H); 3.15 (t, J = 6.6 Hz, 2H); 2.11 (m, 2H); 1.42 (m, 4H) LRMS(ESI): 508.1 (calc) 509.8 (found)	48 (1-6)
110d	299 d			(*S*)-*N*-(1-(5-chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)-5-(2-(4-fluorophenylthio)acetamido)pentyl)-4-fluorobenzamide	(MeOD-*d4*) δ (ppm):7.28 (t, J = 5.5 Hz, 2H); 7.58 (d, J = 6.7 Hz, 1H); 7.37 (m, 3H); 7.18 (t, J = 9.8 Hz, 2H); 7.02 (t, J = 8.8 Hz, 2H); 5.31(t, J = 9.6 Hz, 1H); 3.48 (s, 2H); 3.16 (t, J = 6.7 Hz, 2H, J = 6.7 Hz); 2.11 (m, 2H); 1.51 (m, 2H); 1.38 (m, 2H) LRMS (ESI): 560.3 (calc) 561.1 $(MH)^+$.	48 (1) 48(1-4)

Example 111e,f,g

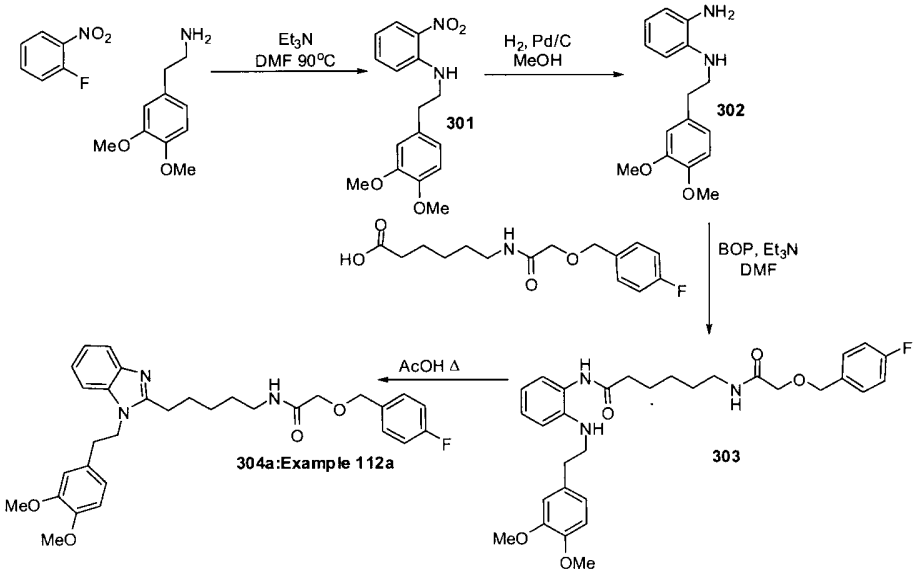
[0411] Example 111e,f,g describe the preparation of compound **300e.f,g** using the same procedures as described for compound **300a** in Example 111a. Characterization data are presented in a Table 25.

Table 25



Ex	Cpd	R	Name	Characterization	Scheme (step)
111e	300e		(*S*)-*N*-(5-(2-(4-aminophenylthio) acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)nicotinamide	(MeOD-*d4*) d(ppm):9.09 (s, 1H); 8.69 (d, J = 5.0 Hz, 1H); 8.34 (d, J = 8Hz, 1H); 7.54 (m, 3H); 7.21 (m, 2H); 7.16 (d, J = 8Hz, 2H); 6.61 (d, J = 8 Hz, 2H); 5.35 (qobs, J = 6, 9 Hz, 1H); 3.31 (s, 2H); 3.14 (m, 2H); 2.20-2.04 (m, 2H); 1.52-1.28 (m, 4H) LRMS (ESI): 488.2 (calc) 489.5 (found)	48
111f	300f		(*S*)-*N*-(5-(2-(4-aminophenylthio) acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)-4-(dimethylamino)benzamide	(MeOD-*d4*) d(ppm):7.81 (d, J = 9Hz, 2H); 7.52 (m, 2H); 7.19 (m, 4H); 6.74 (d, J = 9 Hz, 2H); 6.61 (d, J = 9 Hz, 2H); 5.35 (qobs, J = 6, 8 Hz, 1H); 3.13 (m, 2H); 3.02 (s, 6H); 2.16-1.88 (m, 2H); 1.50-1.28 (m, 4H) LRMS(ESI): 530.2 (calc) 531.2 (found)	48
111g	300g		(*S*)-*N*-(5-(2-(4-aminophenylthio) acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)benzamide	(MeOD-*d4*) d(ppm):7.91 (d, J = 7 Hz, 2H); 7.56-7.52 (m, 2H); 7.49-7.45 (m, 2H); 7.22-7.19 (m, 2H); 7.16 (d, J = 9 Hz, 2H); 6.61 (d, J = 9 Hz, 2H); 5.35 (qobs, J = 6.0, 9.0 Hz, 1H); 3.34 (s, 2H); 3.15-3.11 (m, 2H), 2.18-2.06 (m, 2H), 1.48-1.29 (m, 4H) LRMS (ESI): 487.6 (calc) 488.5 (found)	48

Scheme 49



Example 112a

N-(5-(1-(3,4-dimethoxyphenethyl)-1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**304a**)

Step 1: *N*-(3,4-dimethoxyphenethyl)-2-nitroaniline (**301**)

[0412] 2-(3,4-dimethoxyphenyl)ethanamine (0.83 mL, 4.96mmol) was added to a solution of 1-fluoro-2-nitrobenzene (700mg, 4.96mmol) and Et_3N (2.0 mL, 15 mmol) in DMF (10mL) and the reaction heated at 90°C overnight. The reaction was then concentrated under reduced pressure and the resulting residue was partitioned between EtOAc and H_2O. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was then purified by way of a silica plug to afford **301** (1.31g, 87%) as bright yellow oil. LRMS (ESI): 302.1(calc) 325.1 (MNa)+.

Step 2: *N*-1-(3,4-dimethoxyphenethyl)benzene-1,2-diamine (**302**)

[0413] Following the same procedure as described for compound **74** (scheme 5, example 55, step 1) but substituting **301** for **73** to afford **302** (725mg, 62%) as a yellow oil. LRMS (ESI): (calc.) 272.1; (found) 273 (MH)+.

Intermadiate: 6-(2-(4-fluorobenzyloxy)acetamido)hexanoic acid:

[0414] Following the same procedure as described for compound **61** (scheme 3, example 52, step1 and 2-1)) but substituting **140** for 2-(benzyloxy)acetic acid to afford 6-(2-(4-fluorobenzyloxy)acetamido)hexanoic acid (1.42g, 98%) as a yellow oil. LRMS (ESI): (calc.) 297.1; (found) 304.1(MLi)+.

Step 3: *N*-(2-(3,4-dimethoxyphenethylamino)phenyl)-6-(2-(4-fluorobenzyloxy)acetamido)hexanamide (**303**)

[0415] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting amine **302** and 6-(2-(4-fluorobenzyloxy)acetamido)hexanoic acid for N-Boc-caproic acid and 3-phenyl aniline, respecectively, to afford **303** (64mg, 32%) deep yellow oil. LRMS (ESI): (calc.) 551.3; (found) 552.3 (MH)+.

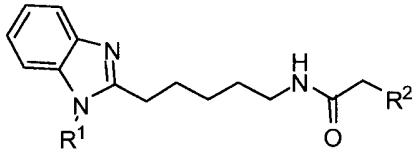
Step 4 (AA) N-(5-(1-(3,4-dimethoxyphenethyl)-1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**304a**)

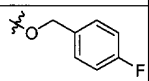
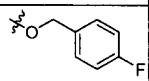
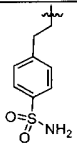
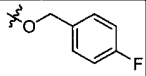
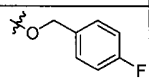
[0416] Following the same procedure as described for compound **295** (scheme 48, example 110a, step 2) but substituting **303** for **294** to afford **304a** (5.9mg, 7%) as a yellow oil. (MeOD-*d4*) δ(ppm):7.56 (d, J = 7.0 Hz, 1H); 7.47 (d, J = 7.2 Hz, 1H); 7.38 (q, J = 5.7, 8.2 Hz, 2H); 7.24 (m, 2H); 7.06 (t,J = 8.8 Hz, 2H); 6.75 (d, 1H, J = 8.2 Hz); 6.46 (d, J = 8.0 Hz, 1H); 6.20 (s, 1H); 4.53 (s, 2H); 4.42 (t, J = 6.1 Hz, 2H); 3.90 (s, 2H); 3.73 (s, 3H); 3.51 (s, 3H); 3.19 (t, J = 14.1 Hz, 2H); 3.04 (t, J = 12.1 Hz, 2H); 2.32 (t, J = 15 Hz, 2H); 1.56 (m, 2H); 1.45 (m, 2H);1.26 (m, 2H) LRMS (ESI): (calc.) 533.2; (found) 534.3 (MH)+.

Example 112b-e

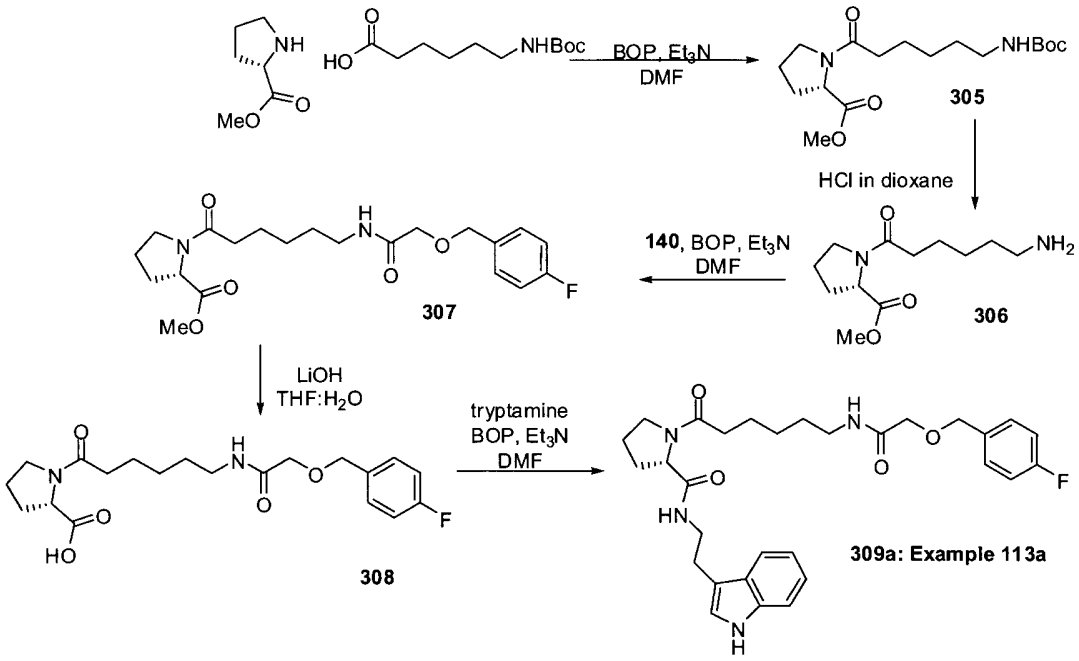
[0417] Examples 112b-d describe the preparation of compounds **304b-d** using the same procedures as described for compound **304a** in Example 112a. Characterization data are presented in a Table 26.

Table 26



Ex	Cpd	R^1	Name	Characterization	R^2	Scheme (step)
112b	304b		2-(4-fluorobenzyloxy)-N-(5-(1-methyl-1H-benzo[d]imidazol-2-yl)pentyl)acetamide	(MeOD-*d4*) d(ppm):7.55 (d, J = 7.6 Hz, 1H); 7.44 (d, J = 8.9 Hz, 1H); 7.36 (m, 2H); 7.23 (m, 2H); 7.06 (t, J = 8.8 Hz, 2H); 4.50 (s, 2H); 3.87 (s, 2H); 3.79 (s, 3H); 3.24 (t, J = 6.8 Hz, 2H); 2.94 (t, J = 7.6 Hz, 2H); 1.85 (m, 2H); 1.57 (m, 2H); 1.44 (m, 2H) LRMS: 383.2 (calc) 384.30 (found)		49
112c	304c		2-(4-fluorobenzyloxy)-N-(4-(1-phenyl-1H-benzo[d]imidazol-2-yl)butyl)acetamide	(MeOD-*d4*) d(ppm): 7.53 (m, 4H); 7.35 (d, J = 7.0 Hz, 2H); 7.26 (q, J = 5.5, 7.8 Hz, 2H); 7.15 (m, 2H); 6.97 (m, 3H); 4.41 (s, 2H); 3.77 (s, 2H); 3.05 (t, J = 7.0 Hz, 2H); 2.72 (t, J = 7.4 Hz, 2H); 1.6 (m, 2H); 1.34 (m, 2H); 1.18 (m, 4H) LRMS: 445.5 (calc) 446.2 (found)		49
112d	304d		2-(4-fluorobenzyloxy)-N-(5-(1-(4-sulfamoylphenethyl)-1H-benzo[d]imidazol-2-yl)pentyl)acetamide	(MeOD-*d4*) d(ppm):7.72 (d, J = 8.4 Hz, 2H); 7.56 (d, J = 5.5 Hz, 1H); 7.49 (d, J = 7.2 Hz, 1H); 4.53 (s, 2H); 4.49 (t, J = 13.1 Hz, 2H); 3.89 (s, 2H), 3.20 (t, J = 7.2 Hz, 4H); 2.40 (t, J = 15.4 Hz, 2H); 1.60 (m, 2H); 1.48 (m, 2H); 1.29 (m, 2H) LRMS: 552.22(calc) 553.26 (found)		49
112e	304e	H	N-(5-(1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) d(ppm): 7.47 (m, 2H); 7.37 (m, 2H); 7.17 (m, 2H); 7.06 (t, J = 8.9 Hz, 2H); 4.50 (s, 2H); 3.88 (s, 2H); 3.22 (t, J = 7.0 Hz, 2H); 2.89 (t, J = 7.4 Hz, 2H); 1.86 (m, 2H); 1.57 (m, 2H); 1.38 (m, 2H) LRMS: 369.1 (calc) 370.2 (found)		49

Scheme 50



Example 113a

(S)-N-(2-(1H-indol-3-yl)ethyl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxamide (**309a**)

Step 1: (*S*)-methyl 1-(6-(tert-butoxycarbonylamino)hexanoyl)pyrrolidine-2-carboxylate (**305**)

[0418] Following the same procedure as described for compound **1**(step1, scheme1, example1) but substituting proline methyl ester for 3-phenyl aniline to afford **305** (1.7g, 56%yield) as a pale yellow oil. LRMS (ESI): (calc.) 342.2; (found) 343.2$(MH)^+$.

Step 2: (*S*)-methyl 1-(6-aminohexanoyl)pyrrolidine-2-carboxylate (**306**)

[0419] Following the same procedure as described for compound **213** (scheme 31, example 92, step 3-1)) but substituting **305** for **212** to afford **306** (1g, 71%) as a white solid. LRMS (ESI): (calc.) 242.1; (found) 243.0$(MH)^+$.

Step 3: (*S*)-methyl 1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxylate (**307**)

[0420] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting **140** and **306** for N-Boc-caproic acid and 3-phenyl aniline,respectively, to afford **307** (998mg, 68%) as a pale yellow oil. LRMS (ESI): (calc.) 408.2; (found) 409.3 $(MH)^+$. .

Step 4: (*S*)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxylic acid (**308**)

[0421] Following the same procedure as described for compound **5** (scheme 1, example 1, step 5) but substituting **307** for **4** to afford **308** (737mg, 76%) as a yellow oil. LRMS (ESI): (calc.) 394.1; (found) 401(MLi)$^+$.

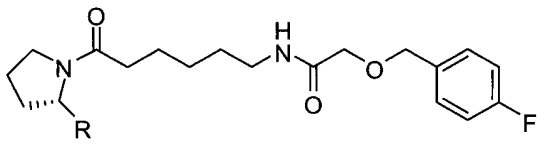
Step 5: (*S*)-N-(2-(1H-indol-3-yl)ethyl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxamide (**309a**)

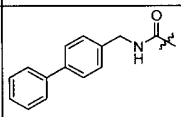
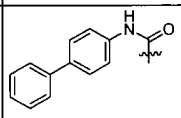
[0422] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting acid **308** and tryptamine for N-Boc-caproic acid and 3-phenyl aniline,respectively, to afford **309a** (11mg, 12%) as a yellow oil. (MeOD-*d4*) δ(ppm):7.55 (d, J = 7.6 Hz, 1H); 7.35 (m, 3H); 7.03 (m, 5H); 4.54 (s;rotamer 4.47ppm, 2H); 4.31(m, 1H); 3.91 (s,rotamer 3.85ppm, 2H); 3.50 (m, 4H); 3.19 (m, 2H); 2.30-1.80 (m, 6H); 1.58-1.17 (m, 6H) LRMS (ESI): 536.2 (calc) 537.4 (found).

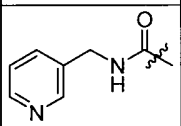
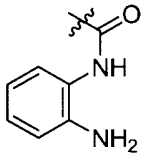
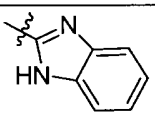
Examples 113b-f

[0423] Examples 113b-f describe the preparation of compounds **309b-f** using the same procedures as described for compound **309a** in Example 113a Characterization data are presented in a Table 27.

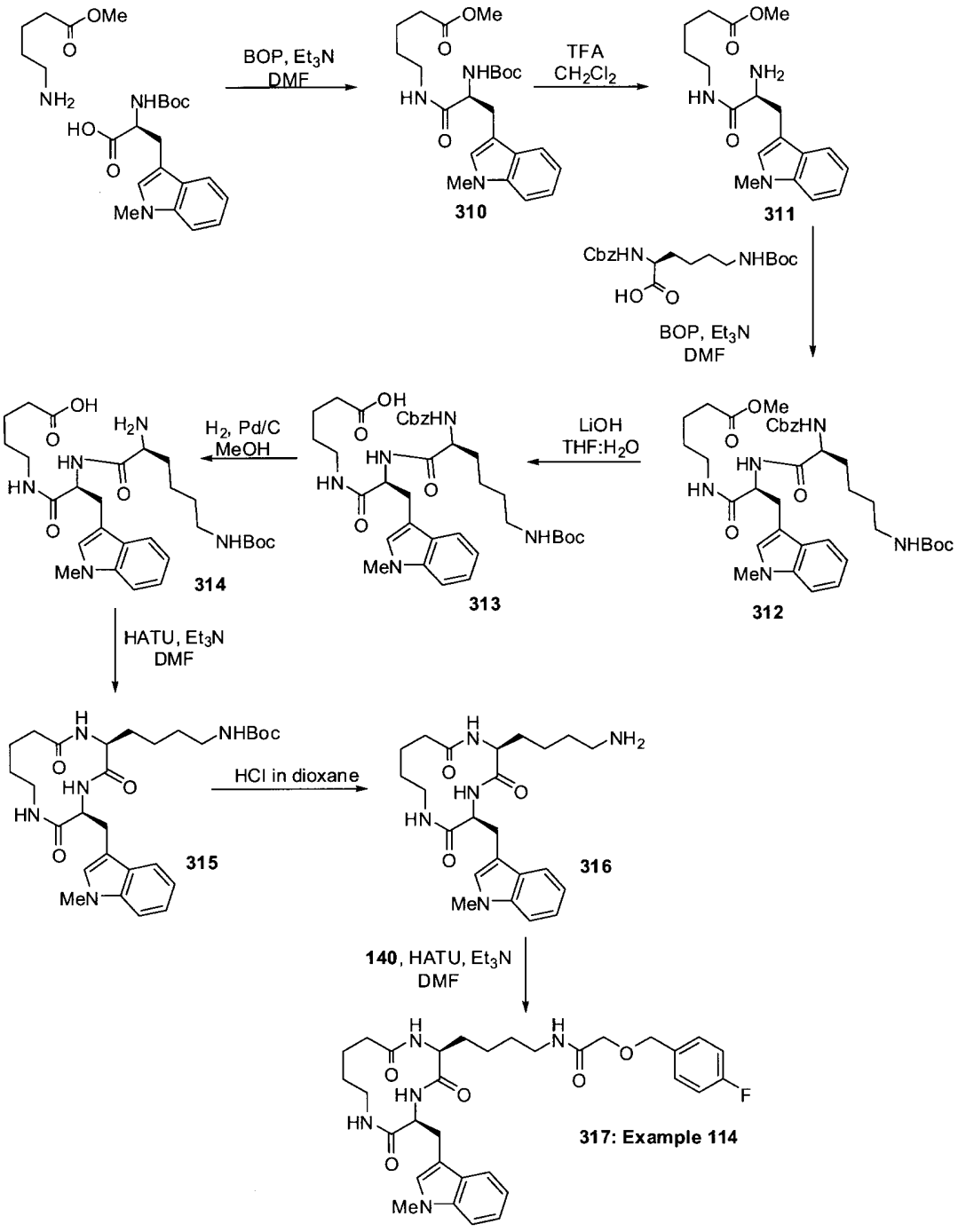
Table 27



Ex	Cpd	R	Name	Characterization	Scheme (step)
113b	309b		(S)-N-(biphenyl-4-ylmethyl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl) pyrrolidine-2-carboxamide	(MeOD-*d4*) d(ppm): 7.57 (m, 4H); 7.37 (m, 7H); 7.06 (m, 2H); 4.54 (m, 2H); 4.42 (m, 3H); 3.90 s,2H;rotamer 3.86ppm); 3.66-3.56 (m, 2H); 3.21-3.12 (m, 2H); 2.42-1.97 (m, 6H); 1.64-1.36 (m, 6H) LRMS: 559.2 (calc) 560.6 (found)	50
113c	309c		(S)-N-(biphenyl-4-yl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl) pyrrolidine-2-carboxamide	(MeOD-*d4*) d(ppm): 7.62-7.56 (m, 6H); 7.37-7.28 (m, 5H); 7.06 (m, 2H); 4.57-4.47 (m, 3H); 3.90 (s, 2H;rotamer 3.67ppm); 3.67-3.58 (m, 2H); 3.22-3.14 (m, 2H); 2.40-2.02 (m, 6H); 1.62-1.29 (m, 6H) LRMS: 545.2 (calc) 546.6 (found)	50

Ex	Cpd	R	Name	Characterization	Scheme (step)
113d	309d		(S)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)-N-(pyridin-3-ylmethyl)pyrrolidine-2-carboxamide	(MeOD-*d4*) d(ppm):8.45 (bm, 2H); 7.91-7.79 (m, 1H); 7.39 (t, J = 12 Hz, 3H); 7.08 (t, J = 8.8 Hz, 2H); 4.56 (s, 2H); 4.41 (m, 3H); 3.92 (s, 2H); 3.58 (m, 2H); 3.21 (m, 2H); 2.38 (t, J = 7.6 Hz, 2H); 2.19-1.93 (m, 4H); 1.63-1.33 (m, 6H) LRMS: 484.2 (calc) 485.3 (found)	50
113e	309e		(S)-N-(2-aminophenyl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxamide	(MeOD-*d4*) d(ppm):7.41(m,2H), 7.10-7.01 (m, 4H); 6.79 (d, J = 7.2 Hz, 1H); 6.65 (d, J = 7.2 Hz, 1H); 4.54 (s, 2H); 4.50 (m, 1H); 3.90 (s, 2H); 3.66 (m, 2H); 3.22 (m, 2H); 2.41-2.01 (m, 6H); 1.65-1.35 (m, 6H) LRMS: 484.2 (calc) 485.3 (found)	50
113f	309f		(S)-N-(6-(2-(1H-benzo[d]imidazol-2-yl)pyrrolidin-1-yl)-6-oxohexyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) d(ppm):7.49 (m, 2H); 7.38 (m, 2H); 7.18 (m, 2H); 7.07 (m, 2H); 5.27 (d, J = 8 Hz, 1H); 4.53 (s, 2H); 3.90 (s, 2H); 3.90 (s,2H;rotamer3.87); 3.63 (m, 1H); 3.22 (t, J = 4.4 Hz, 2H); 3.02 (m, 1H); 2.60-2.00 (m, 6H); 1.64-1.08 (m, 6H) LRMS: 466.2 (calc) 467.3 (found)	50 48 (2)

Scheme 51


BOP, Et3N
DMF
TFA
CH2Cl2
310
311
BOP, Et3N
DMF
312
LiOH
THF:H2O
313
H2, Pd/C
MeOH
314
HATU, Et3N
DMF
315
HCl in dioxane
316
140, HATU, Et3N
DMF
317: Example 114

Example 114

2-(4-fluorobenzyloxy)-N-(4-((2S,5S)-5-((1-methyl-1H-indol-3-yl)methyl)-3,6,12-trioxo-1,4,7-triazacyclododecan-2-yl)butyl)acetamide (**317**)

Step 1: (*S*)-methyl 5-(2-(tert-butoxycarbonylamino)-3-(1-methyl-1H-indol-3-yl)propanamido)pentanoate (**310**)

[0424] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting (*S*)-2-(tert-butoxycarbonylamino)-3-(1-methyl-1H-indol-3-yl)propanoic acid and methyl 5-aminopentanoate for *N*-Boc-caproic acid and 3-phenyl aniline, respectively, to afford **310** (1.42g, 96%) as a yellow oil. LRMS (ESI): (calc.) 431.2; (found) 432.1$(MH)^+$.

Step 2: (*S*)-methyl 5-(2-amino-3-(1-methyl-1H-indol-3-yl)propanamido)pentanoate (**311**) Following the same procedure as described for compound **2** (scheme 1, example 1, step 2) but substituting **310** for **1** to afford amine **311** (1.05g, 96%) as a white foam. LRMS (ESI): (calc.) 331.1; (found) 332.1$(MH)^+$.

Step 3: (10S,13S)-methyl 10-(benzyloxycarbonylamino)-2,2-dimethyl-13-((1-methyl-1H-indol-3-yl)methyl)-4,11,14-trioxo-3-oxa-5,12,15-triazaicosan-20-oate (**312**)

[0425] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting (S)-2-(benzyloxycarbonylamino)-6-(tert-butoxycarbonylamino)hexanoic acid and amine **311** for N-Boc-caproic acid and 3-phenyl aniline,respectively, to afford **312** (2.16g, 98%) as a yellow foam. LRMS (ESI): (calc.) 693.3; (found) 694.4$(MH)^+$.

Step 4: (10S,13S)-10-(benzyloxycarbonylamino)-2,2-dimethyl-13-((1-methyl-1H-indol-3-yl)methyl)-4,11,14-trioxo-3-oxa-5,12,15-triazaicosan-20-oic acid (**313**)

[0426] Following the same procedure as described for compound **5** (scheme 1, example 1, step 5) but substituting **312** for **4** to afford **313** (997mg, 99%) as a clear oil. LRMS (ESI): (calc.) 679.3; (found) 680.4$(MH)^+$.

Step 5: (10S,13S)-10-amino-2,2-dimethyl-13-((1-methyl-1H-indol-3-yl)methyl)-4,11,14-trioxo-3-oxa-5,12,15-triazaicosan-20-oic acid (**314**)

[0427] Following the same procedure as described for compound **74** (scheme 5, example 55, step 3) but substituting **313** for **73** to afford **314** (759mg, 96%) as a yellow oil. LRMS (ESI): (calc.) 545.3; (found) 546.6$(MH)^+$.

Step 6: *tert*-butyl 4-((2S,5S)-5-((1-methyl-1H-indol-3-yl)methyl)-3,6,12-trioxo-1,4,7-triazacyclododecan-2-yl)butylcarbamate (**315**)

[0428] A solution of HATU (43mg, 0.11mmol) in DMF (1mL) was added to a solution of **314** (20mg, 0.04mmol) and Et_3N (53μL) in DMF (3mL).The reaction was stirred for 3h, and then partitioned between EtOAc and H_2O. The organic phase was separated, dried

(Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by trituration with Et_2O to afford **315** (11mg, 52%) as a white solid. LRMS (ESI): (calc.) 527.3; (found) 528.4$(MH)^+$.

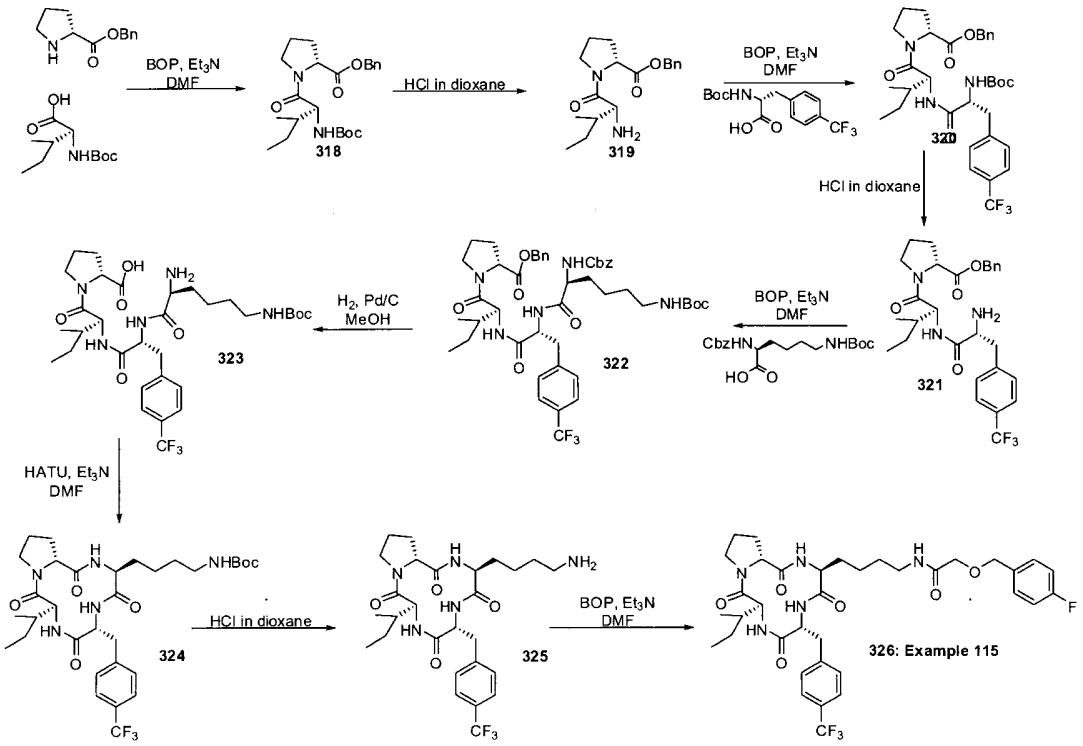
Step 7: (3S,6S)-6-(4-aminobutyl)-3-((1-methyl-1H-indol-3-yl)methyl)-1,4,7-triazacyclododecane-2,5,8-trione (**316**)

[0429] Following the same procedure as described for compound **213** (scheme 31, example 92, step 3-1)) but substituting **315** for **212** to afford amine **316** (8mg, 97%) as a white solid. LRMS (ESI): (calc.) 427.2; (found) 428.4$(MH)^+$.

Step 8: 2-(4-fluorobenzyloxy)-N-(4-((2S,5S)-5-((1-methyl-1H-indol-3-yl)methyl)-3,6,12-trioxo-1,4,7-triazacyclododecan-2-yl)butyl)acetamide (**317**)

[0430] Following the same procedure as described for compound **315** (scheme 51, example **114**, step 6) but substituting **316** and 2-(4-fluorobenzyloxy)acetic acid for **314** to afford **317** (2mg, 19%) as a white solid. (DMSO-d_6) δ (ppm): 8.00 (d, J = 8.4 Hz, 1H); 7.84 (d, J = 8. Hz, 1H); 7.76 (t, J = 6.0 Hz, 1H); 7.50 (d, J = 8.0 Hz, 1H); 7.39 (m, 2H); 7.32 (d, J 8.2 Hz, 1H); 7.17 (t, J = 6.4 Hz, 2H); 7.08 (t, J = 7.0 Hz, 1H); 6.98 (m, 2H); 6.89 (m, 1H); 4.47 (s, 2H); 4.27 (m, 1H); 3.86 (m, 3H); 3.68 (s, 3H); 3.20 (m, 2H); 2.96 (m, 3H); 2.28 (m, 1H); 1.86 (t, J = 11.5 Hz, 1H); 1.70-1.02 (m, 11H) LRMS (ESI): (calc.) 593.3; (found) 428.4$(MH)^+$. LRMS: 593.3 (calc) 594.6 (found)

Scheme 52



Example 115

N-(4-((3S,6R,9S,14aR)-9-sec-butyl-1,4,7,10-tetraoxo-6-(4-(trifluoromethyl)benzyl)-tetradecahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**326**)

Step 1: (R)-benzyl 1-((2S,3R)-2-(tert-butoxycarbonylamino)-3-methylpentanoyl)pyrrolidine-2-carboxylate (**318**)

[0431] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting (2S,3R)-2-(*tert*-butoxycarbonylamino)-3-methylpentanoic acid and (R)-benzyl pyrrolidine-2-carboxylate for N-Boc-caproic acid and 3-phenyl aniline,respectively, to afford **318** (1.8g, 82%) as a viscous clear oil. LRMS (ESI): (calc.) 418.2; (found) 419.3$(MH)^+$.

Step 2: (R)-benzyl 1-((2S,3R)-2-amino-3-methylpentanoyl)pyrrolidine-2-carboxylate (**319**)

[0432] Following the same procedure as described for compound **213** (scheme 31, example 92, step 3-1)) but substituting **318** for **212** to afford **319** (1.26g, 98%) as a white foam. LRMS (ESI): (calc.) 318.1; (found) 319.2$(MH)^+$.

Step 3: (R)-benzyl 1-((2S,3R)-2-((R)-2-(tert-butoxycarbonylamino)-3-(4-(trifluoromethyl)phenyl)propanamido)-3-methylpentanoyl)pyrrolidine-2-carboxylate (**320**)

[0433] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting (R)-2-(tert-butoxycarbonylamino)-3-(4-(trifluoromethyl)phenyl)propanoic acid and **319** for N-Boc-caproic acid and 3-phenyl aniline, respectively, to afford **320** (1.5g, 99%) as a viscous pale yellow oil. LRMS (ESI): (calc.) 633.3; (found) 634.2$(MH)^+$.

Step 4: (R)-benzyl 1-((2S,3R)-2-((R)-2-amino-3-(4-(trifluoromethyl)phenyl)propanamido)-3-methylpentanoyl)pyrrolidine-2-carboxylate (**321**)

[0434] Following the same procedure as described for compound **213** (scheme 31, example 92, step 3-1)) but substituting **320** for **212** to afford **321** (450mg, 99%) as a white solid. LRMS (ESI): (calc.) 533.2; (found) 534.2$(MH)^+$.

Step 5: (R)-benzyl 1-((10R,13R,16S)-10-(benzyloxycarbonylamino)-16-sec-butyl-2,2-dimethyl-4,11,14-trioxo-13-(4-(trifluoromethyl)benzyl)-3-oxa-5,12,15-triazaheptadecane)pyrrolidine-2-carboxylate (**322**)

[0435] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting (S)-2-(benzyloxycarbonylamino)-6-(tert-butoxycarbonylamino)hexanoic acid and **321** for N-Boc-caproic acid and 3-phenyl aniline, respectively, to afford **322** (705mg, 99%) as a viscous clear oil. LRMS (ESI): (calc.) 895.4; (found) 896.3$(MH)^+$.

Step 6: (R)-1-((10S,13R,16S)-10-amino-16-sec-butyl-2,2-dimethyl-4,11,14-trioxo-13-(4-(trifluoromethyl)benzyl)-3-oxa-5,12,15-triazaheptadecane)pyrrolidine-2-carboxylic acid (**323**)

[0436] Following the same procedure as described for compound **74** (scheme 5, example 55, step 3) but substituting **322** for **73** to afford **323** (67mg, 36%) as a white solid. LRMS (ESI): (calc.) 671.3; (found) 672.2$(MH)^+$.

Step 7: tert-butyl 4-((3S,6R,9S,14aR)-9-sec-butyl-1,4,7,10-tetraoxo-6-(4-(trifluoromethyl)benzyl)-tetradecahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)butylcarbamate (**324**)

[0437] Following the same procedure as described for compound **315** (scheme 51, example **114**, step 6) but substituting **323** for **314** to afford **324** (36mg, 56%) as a white solid. LRMS (ESI): (calc.) 653.3; (found) 654.4$(MH)^+$.

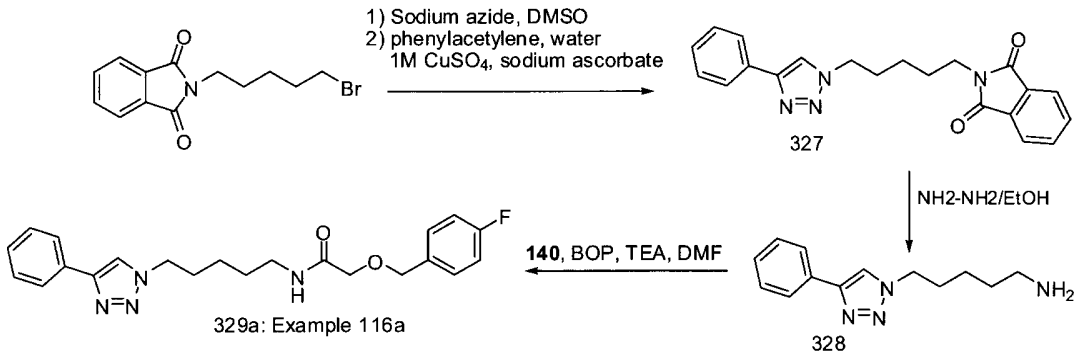
Step 8: (3S,6R,9S,14aR)-3-(4-aminobutyl)-9-sec-butyl-6-(4-(trifluoromethyl)benzyl)-decahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecine-1,4,7,10-tetraone (**325**)

[0438] Following the same procedure as described for compound **213** (scheme 31, example 92, step 3-1)) but substituting **324** for **212** to afford **214** (31mg, 99%) as a white solid. LRMS (ESI): (calc.) 533.2; (found) 534.2$(MH)^+$.

Step 9: N-(4-((3S,6R,9S,14aR)-9-sec-butyl-1,4,7,10-tetraoxo-6-(4-(trifluoromethyl)benzyl)-tetradecahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**326**)

[0439] Following the same procedure as described for compound **1** (scheme 1, example 1, step 1) but substituting **140** and amine **325** for N-Boc-caproic acid and 3-phenyl aniline, respectively, to afford **326** (15mg, 36%) as a white solid. (MeOD-d_4) δ (ppm): 7.54 (d, J = 7.8 Hz, 2H); 7.40 (m, 4H); 7.08 (t, J = 8.8 Hz, 2H); 4.79 (d, J = 7.2 Hz, 1H); 4.75 (t, J = 7.8 Hz, 1H); 4.55(s, 2H); 4.46 (d, J = 10.9 Hz, 1H); 4.29 (t, J = 7.4 Hz, 1H); 3.98 (t, J = 9.7 Hz, 1H); 3.91 (s, 2H); 3.19 (m, 3H); 2.94 (dd, J = 8.2, 14.2 Hz, 1H); 2.32 (m, 1H); 2.19 (m, 1H); 2.01 (m, 1H); 1.90 (m, 1H); 1.81 (m, 1H); 1.68 (m, 1H); 1.64-1.42 (m, 4H); 1.32-1.06 (m, 3H); 0.85 (m, 6H). LRMS (ESI): (calc.) 719.3; (found) 720.3$(MH)^+$.

Scheme 53



Example 116a

2-(4-fluorobenzyloxy)-*N*-(5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pentyl)acetamide (**329a**)

Step 1: 2-(5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pentyl)isoindoline-1,3-dione (**327**)

[0440] *N*-(5-Bromopentyl)phthalimide (0.750 g, 2.54 mmol) was dissolved in a 0.5M solution of sodium azide in DMSO (5.0 mL, 2.5 mmol). After stirring 6 hours at room temperature, water (10.0 mL), sodium ascorbate (0.050 g, 0.25 mmol), phenylacetylene (0.255 g, 2.50 mmol) and a 1M aqueous solution of copper sulfate (0.50 mL, 5.0 mmol) were added in that order. The reaction mixture was stirred at room temperature 16 hours and water (10.0 mL) was added until the product precipitated from the solution. The product was collected by filtration and then triturated in isopropyl ether to give **327** (0.530 g, 58%) as a green solid. LRMS (ESI): (calc) 381.2 (found) 382.3 $(MH)^+$.

Step 2: 5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pentan-1-amine (**328**)

[0441] Following the same procedure as described for compound **139** (step 5, scheme 16, example 73a) but substituting **327** for **138** to give **328** (0.350 g, 82%) as a beige solid. LRMS (ESI): (calc) 230.2 (found) 231.2 $(MH)^+$.

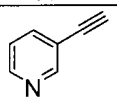
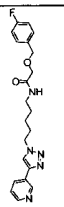
Step 3: 2-(4-fluorobenzyloxy)-*N*-(5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pentyl)acetamide (**329a**)

[0442] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting 2-(4-fluorobenzyloxy)acetic acid for *N*-Boc-caproic acid and **328** for 3-phenyl aniline to afford **329a** (190 mg, 63%) as a white solid. (MeOD-*d*4) δ(ppm): 8.32 (s, 1H), 7.82-7.80 (m, 2H), 7.43 (t, J = 7.4H, 2H), 7.41-7.33 (m, 3H), 7.06 (t, J = 8.6Hz, 2H), 4.51 (s, 2H), 4.46 (t, J = 6.8Hz, 2H), 3.89 (s, 2H), 3.24 (t, J = 6.8Hz, 2H), 2.03-1.95 (m, 2H), 1.62-1.55 (m, 2H), 1.39-1.31 (m, 2H). LRMS (ESI): (calc) 396.2 (found) 397.3 $(MH)^+$.

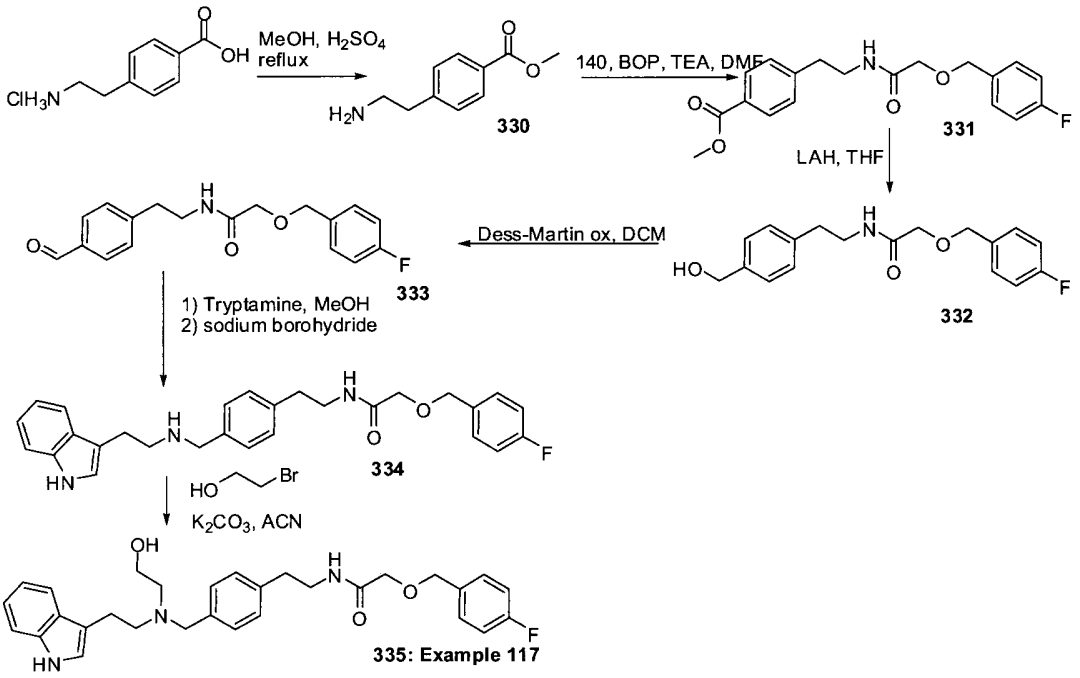
Example 116b

[0443] Example 116b describe the preparation of compound **329b** using the same procedures as described for compound **329a** in Example 116a Characterization data are presented in a Table 28.

Table 28

Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
116b	329b			2-(4-fluorobenzyloxy)-*N*-(5-(4-(pyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)pentyl)acetamide	(MeOD-δ4) d(ppm): 9.00-9.01 (m, 1H), 8.49-8.52 (m, 2H), 8.26-8.28 (m, 1H), 7.50-7.53 (m, 1H), 7.35-7.38 (m, 2H), 7.04-7.09 (m, 2H), 4.47-4.52 (m, 4H), 3.90 (s, 2H), 3.22-3.26 (m, 2H), 1.98-2.02 (m, 2H), 1.57-1.60 (m, 2H), 1.35-1.37 (m, 2H). LRMS(ESI): (calc) 397.2 (found) 398.2	PG(1 (exB1) 16(5 (Ex73a) 1(1 (ex1)

Scheme 54



Example 117

N-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**335**)

Step 1: methyl 4-(2-aminoethyl)benzoate (**330**)

[0444] 4-(2-aminoethyl)benzoic acid hydrochloride (1.00 g, 4.97 mmol) was dissolved in methanol (50.0 mL) and 6 drops of concentrated sulfuric acid ware added. After refluxing

16h, the solution was concentrated under reduced pressure and the residue was dissolved in ethyl acetate. The organic phase was washed with sodium bicarbonate (ss), water and brine. The organic layer was dried over sodium sulfate, filtered and evaporated. The product was purified by silica gel column chromatography with 75% ethyl acetate in hexanes as to afford **330** (0.808 g, 91%) as a colorless oil. LRMS (ESI): (calc) 179.1 (found) 180.2 $(MH)^+$.

Step 2: methyl 4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)benzoate (**331**)

[0445] Following the same procedure as described for compound **1** (step 1, scheme 1, example 1) but substituting 2-(4-fluorobenzyloxy)acetic acid for *N*-Boc-caproic acid and **330** for 3-phenyl aniline to afford **331** (0.753 g, 72%) as a yellow solid. LRMS (ESI): (calc) 345.1 (found) 346.2 $(MH)^+$.

Step 3: 2-(4-fluorobenzyloxy)-*N*-(4-(hydroxymethyl)phenethyl)acetamide (**332**)

[0446] Following the same procedure as described for compound **12** (step 5, scheme 1, example 7) but substituting **331** for **7c** to afford **332** (0.880 g, 74%) as an off white solid. LRMS (ESI): (calc) 317.1 (found) 318.2 $(MH)^+$.

Step 4: 2-(4-fluorobenzyloxy)-*N*-(4-formylphenethyl)acetamide (**333**)

[0447] Following the same procedure as described for compound **195a** (step 4, scheme 27, example 87a) but substituting alcohol **332** for alcohol **194a** to afford **333** (0.672 g, 77%) as clear colorless oil. LRMS (ESI): (calc) 315.1 (found) 316.2 $(MH)^+$.

Step 5: *N*-(4-((2-(1*H*-indol-3-yl)ethylamino)methyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**334**)

[0448] Following the same procedure as described for compound **103** (step 1, scheme 11, example 66) but substituting **333** for *p*-cyanobenzaldehyde to afford **334** (0.135 g, 14%) as a yellow solid. (MeOH-*d*4) δ(ppm): 7.49 (d, J=8.0Hz, 1H), 7.33-7.29 (m, 3H), 7.19 (dd, J = 12.9, 8.2Hz, 4H), 7.08-6.98 (m, 5H), 4.45 (s, 2H), 3.87 (s, 2H), 3.80 (s, 2H), 3.45 (t, J = 7.34Hz, 2H), 3.01-2.91 (m, 4H), 2.80 (t, J = 7.34Hz, 2H). LRMS (ESI): (calc) 459.2 (found) 460.3 $(MH)^+$.

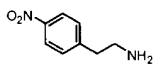
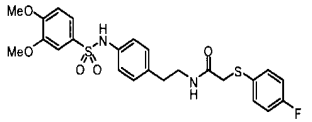
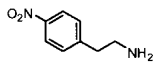
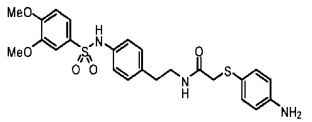
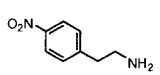
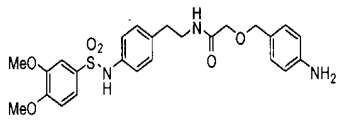
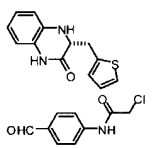
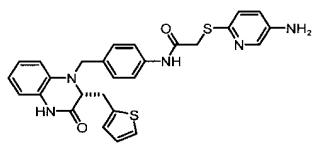
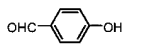
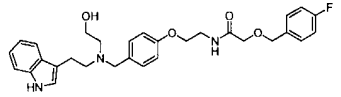
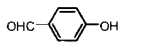
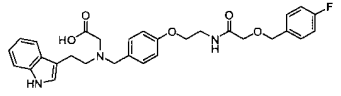
Step 6: *N*-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**335**)

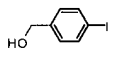
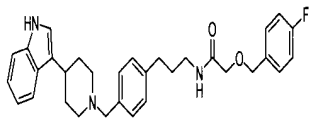
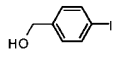
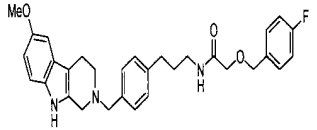
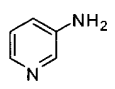
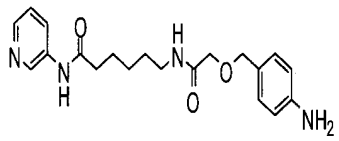
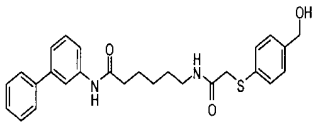
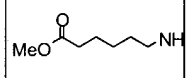
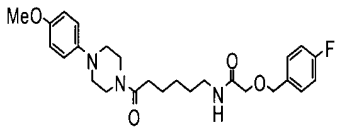
[0449] Following the same procedure as described for compound **197b** (step 1, scheme 27, example 88b) but substituting amine **334** for amine **196a** to afford **335** (40 mg, 27%) as a yellow oil after purification by silica gel column chromatography with ethyl acetate. (MeOH-*d*4) δ(ppm): 7.37 (d, J = 7.8Hz, 1H), 7.30-7.27 (m, 5H), 7.17 (d, J = 8.0Hz, 2H), 7.07-7.02 (m, 3H), 6.97 (s, 1H), 6.95-6.91 (m, 1H), 4.43 (s, 2H), 3.87 (s, 2H), 3.73 (s, 2H), 3.64 (t, J = 6.3Hz, 2H), 3.48 (t, J = 7.2Hz, 2H), 2.95-2.91 (m, 2H), 2.83-2.73 (m, 6H). LRMS (ESI): (calc) 503.3 (found) 504.3 $(MH)^+$.

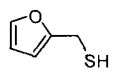
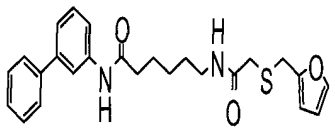
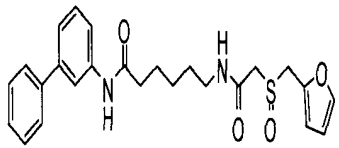
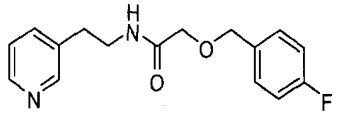
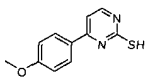
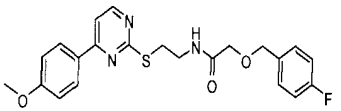
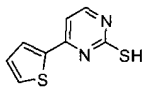
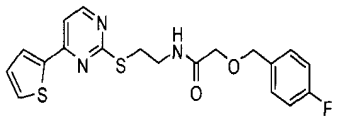
Example 300-354

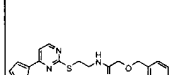
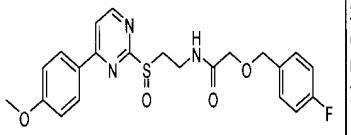
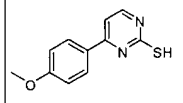
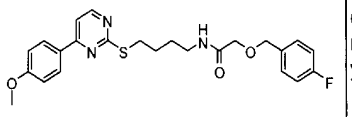
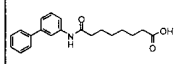
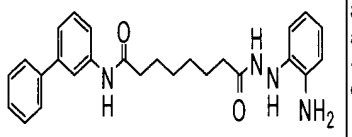
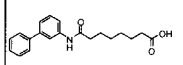
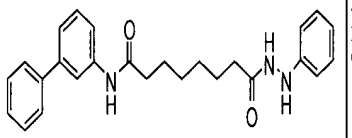
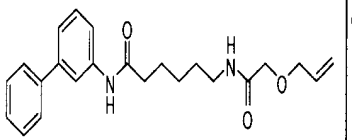
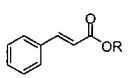
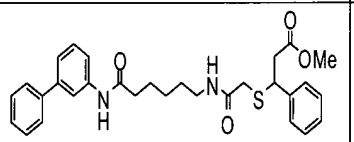
[0450] Example 300-354 describe the preparation of compound **500-554** using the same procedures as described for in the scheme column in the table below Characterization data are presented in a Table 29.

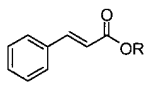
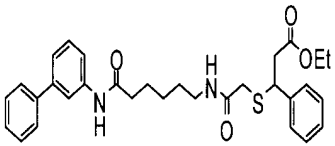
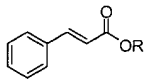
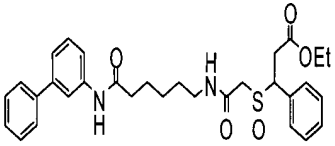
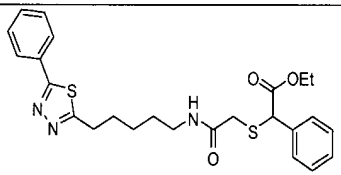
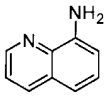
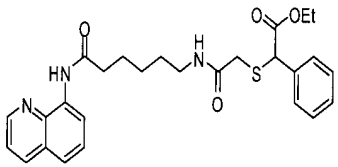
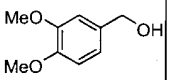
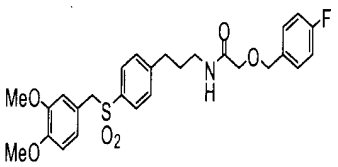
Table 29

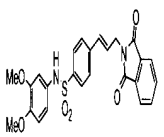
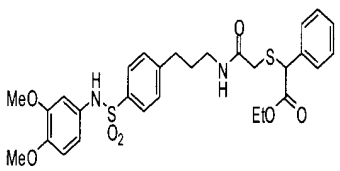
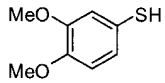
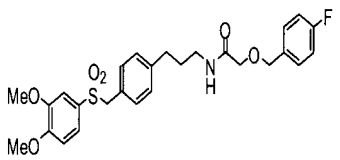
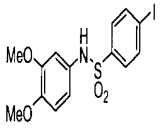
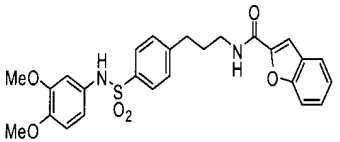
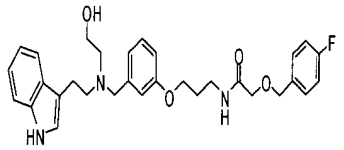
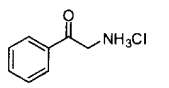
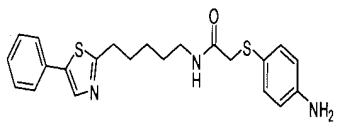
Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
300	500			N-(4-(3,4-dimethoxyphenylsulfonamido)phenethyl)-2-(4-fluorophenylthio)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.32-7.26 (m,3H), 7.18 (d, J = 2.2 Hz, 1H), 7.01-6.94 (m,6H), 6.88 (d, J = 8.6 Hz, 1H), 3.77 (s,3H), 3.72 (s,3H), 3.47 (s,2H), 3.30 (t, J = 7.2 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H) LRMS (ESI): (calc) 504.6; (found) 505.0 $(MH)^+$.	1 (3) 2 (1) 18 (4) 2 (1 (ex 47))
301	501			2-(4-aminophenylthio)-N-(4-(3,4-dimethoxyphenylsulfonamido)phenethyl)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 10.02 (s,1H), 7.98 (t, J = 5.7 Hz, 1H), 7.33 (dd, J = 8.6,2.2 Hz, 1H), 7.26 (d, J = 2.3 Hz, 1H), 7.16-7.02 (m,7H), 6.58-6.49 (m,2H), 5.29 (br s,2H), 3.81 (s,3H), 3.77 (s,3H), 3.33 (s,2H), 3.24-3.16 (m,2H), 2.61-2.53 (m,2H) LRMS (ESI): (calc) 501.6; (found) 502.7 $(MH)^+$.	1 (1) 15 (3) 2 (1 (ex 47)) 1 (5 (ex 4))
302	502			2-(4-aminobenzyloxy)-*N*-(4-(3,4-dimethoxyphenylsulfonamido)phenethyl)acetamide	(MeOD-*d4*) δ(ppm): 7.30 (dd, J=8.4, 2.1 Hz, 1H), 7.18 (d, J=2.2 Hz, 1H), 7.08 - 7.00 (m, 6H), 6.92 (d, J=8.6 Hz, 1H), 6.68 (d, J=8.4 Hz, 2H), 4.33 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.37 (t, J=7.2 Hz, 2H), 2.70 (t, J=7.2 Hz, 2H).	28 (1) 5 (3) (ex 55) 2(1(ex 47)) 1 (2) 1(1) 5 (3) (ex 55)
303	503			(R)-2-(5-aminopyridin-2-ylthio)-N-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenyl)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.97 (dd, J = 2.9,0.6 Hz, 1H), 7.45-7.40 (m,2H), 7.24-7.07 (m,4H), 7.02-6.98 (m,1H), 6.95-6.86 (m,2H), 6.82-6.70 (m,4H), 5.49 (s,1H), 4.54 (d, J = 15.1 Hz, 1H), 4.12-4.02 (m,2H), 4.00 (d, J = 14.9 Hz, 1H), 3.77 (s, 2H), 3.09-2.99 (m,2H) LRMS (ESI): (calc) 515.7; (found) 516.7 $(MH)^+$.	5 (1-3, 6) 15 (3) 1(3,4 (ex 1))
304	504			N-(2-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenoxy)ethyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.42-7.26 (m,6H), 7.10-6.86 (m,7H), 4.55 (s,2H), 4.07 (t, J = 5.7 Hz, 2H), 3.99 (s,2H), 3.72 (s,2H), 3.69-3.62 (m,4H), 2.99-2.93 (m,2H), 2.87-2.81 (m,2H), 2.77 (t, J = 6.3 Hz, 2H) LRMS (ESI): (calc) 519.6; (found) 520.6 $(MH)^+$.	22 (1) 27 (5) 22 (1) 1 (2) 1 (1) 27 (5)
305	505			2-((2-(1H-indol-3-yl)ethyl)(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethoxy)benzyl)amino)acetic acid	(MeOD-*d4*) δ (ppm) ^{1}H: 7.44-7.33 (m,4H), 7.28 (d, J = 8.6 Hz, 2H), 7.18-7.03 (m,4H), 6.94 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 4.58 (s,2H), 4.31 (s,2H), 4.02 (t, J = 5.7 Hz, 2H), 4.01 (s,2H), 3.76 (s,2H), 3.66 (t, J = 5.5 Hz, 2H), 3.45 (t, J = 7.6 Hz, 2H), 3.20 (t, J = 7.2 Hz, 2H) LRMS (ESI): (calc) 533.6; (found) 534.6 $(MH)^+$.	22 (1) 27 (5) 22 (1) 1 (2) 1 (1) 1 (5 (ex 1))

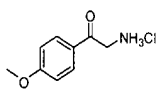
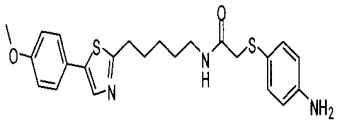
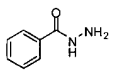
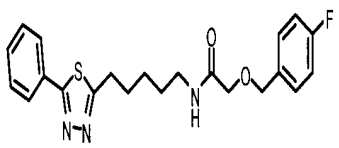
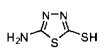
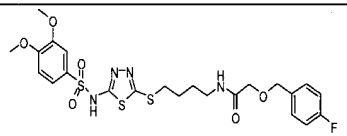
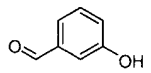
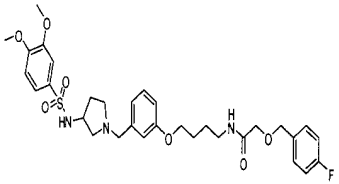
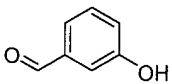
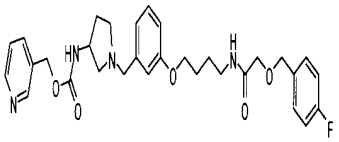
Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
306	506			N-(3-(4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.58 (d, J = 8.0 Hz, 1H), 7.41-7.31 (m,3H), 7.29-7.24 (m,2H), 7.20-7.15 (m,2H), 7.12-7.04 (m,3H), 7.02-6.97 (m,2H), 4.53 (s,2H), 3.93 (s,2H), 3.52 (s,2H), 3.26 (t, J = 7.2 Hz, 2H), 3.03-2.94 (m,2H), 2.86-2.75 (m,1H), 2.62 (t, J = 8.0 Hz, 2H), 2.22-2.10 (m,2H), 2.04-1.94 (m,2H), 1.90-1.76 (m,4H) LRMS (ESI): (calc) 513.6; (found) 514.7 $(MH)^+$.	27 (1 (ex 196b))
307	507			2-(4-fluorobenzyloxy)-N-(3-(4-((6-methoxy-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methyl)phenyl)propyl)acetamide	(MeOD-*d4*) δ (ppm) ^{1}H: 7.44-7.37 (m,2H), 7.34-7.30 (m,2H), 7.23-7.06 (m,5H), 6.91 (d, J = 2.5 Hz, 1H), 6.71 (dd, J = 8.8,2.3 Hz, 1H), 4.57 (s,2H), 3.94 (s,2H), 3.81 (s,3H), 3.73 (s,2H), 3.63 (s,2H), 3.3.28 (t, J = 7.2 Hz, 2H), 2.90-2.83 (m,2H), 2.82-2.74 (m,2H), 2.65 (t, J = 7.8 Hz, 2H), 1.90-1.80 (m,2H) LRMS (ESI): (calc) 515.6; (found) 516.4 $(MH)^+$.	27 (1 (ex 196b))
308	508			6-(2-(4-aminobenzyloxy)acetamido)-*N*-(pyridin-3-yl)hexanamide	(MeOD-*d4*) δ(ppm): 8.71 (d, J=6.6 Hz, 1H), 8.22 (dd, J=4.9, 1.6 Hz, 1H), 8.11 - 8.08 (m, 1H), 7.39 - 7.35 (m, 1H), 7.09 (d, J=8.6 Hz, 2H), 6.69 (d, J=8.6 Hz, 2H), 4.43 (s, 2H), 3.85 (s, 2H), 3.23 (t, J=7.0 Hz, 2H), 2.42 (t, J=7.4 Hz, 2H), 1.74 (quintet, J=7.4 Hz, 2H), 1.56 (quintet, J=7.2 Hz, 2H), 1.44 - 1.38 (m, 2H). LRMS (ESI): (calc) 370.2; (found) 371.2 $(MH)^+$.	1(1) 1(2) 1(1) 5 (3) (ex 55)
309	509	**3b**		*N*-(biphenyl-3-yl)-6-(2-(4-(hydroxymethyl)phenylthio)acetamido)hexanamide	(MeOD-*d4*) δ(ppm): 7.84 (s, 1H), 7.60 - 7.58 (m, 2H), 7.53 - 7.50 (m, 1H), 7.44 - 7.27 (m, 9H), 4.56 (s, 2H), 3.58 (s, 2H), 3.18 (t, J=6.8 Hz, 2H), 2.35 (t, J=7.4 Hz, 2H), 1.69 - 1.63 (m, 2H), 1.49 - 1.43 (m, 2H), 1.33 - 1.27 (m, 2H). LRMS (ESI): (calc) 462.2; (found) 485.1 $(MNa)^+$.	1(4(Ex 1))
310	510	 + **140**		2-(4-fluorobenzyloxy)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide	(MeOD-*d4*) δ(ppm): 7.42 - 7.37 (m, 2H), 7.08 (t, J=8.8 Hz, 2H), 6.94 (d, J=9.0 Hz, 2H), 6.83 (d, J=9.2 Hz, 2H), 4.55 (s, 2H), 3.92 (s, 2H), 3.73 (s, 3H), 3.68 (dt, J=15.6, 5.1 Hz, 4H), 3.24 (t, J=7.0 Hz, 2H), 3.00 (dt, J=21.3, 5.1 Hz, 4H), 2.42 (t, J=7.6 Hz, 2H), 1.53 (quintet, J=7.4 Hz, 2H), 1.55 (quintet, J=7.2 Hz, 2H), 1.40 - 1.32 (m, 2H). LRMS (ESI): (calc) 471.3; (found) 472.5 $(MH)^+$.	1(1) 1(5(Ex 1)) 1(1)

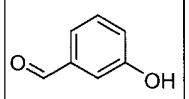
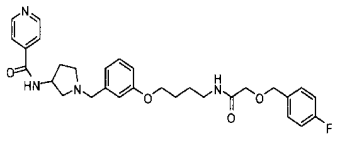
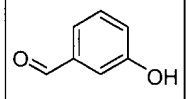
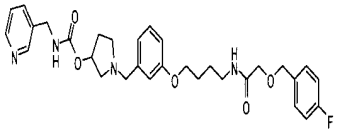
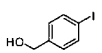
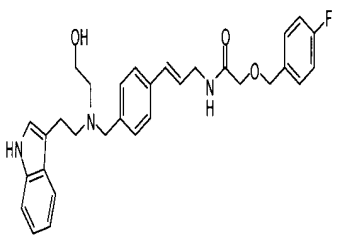
Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
311	511			*N*-(biphenyl-3-yl)-6-(2-(furan-2-ylmethylthio)acetamido)hexanamide	(MeOD-*d4*) δ(ppm): 7.38 (dd, J=8.6, 5.3 Hz, 2H), 7.19 (t, J=7.8 Hz, 1H), 7.05 (t, J=8.8 Hz, 2H), 6.90 - 6.87 (m, 2H), 6.81 - 6.77 (m, 1H), 4.57 (s, 2H), 4.02 (t, J=6.1 Hz, 2H), 3.94 (s, 2H), 3.46 - 3.42 (m, 4H), 2.39 (br s, 4H), 1.99 (quintet, J=6.3 Hz, 2H), 1.57 (quintet, J=5.5 Hz, 4H), 1.45 - 1.44 (m, 2H). LRMS (ESI): (calc) 436.2; (found) 437.2 $(MH)^+$.	2(2 (ex 47)) MeOH/RT 1(1)
312	512	**511**		*N*-(biphenyl-3-yl)-6-(2-(furan-2-ylmethylsulfinyl)acetamido)hexanamide	(DMSOD6) δ(ppm): 9.96 (s, 1H), 8.28 (t, J=5.5 Hz, 1H), 7.91 (s, 1H), 7.67 - 7.66 (m, 1H), 7.59 - 7.54 (m, 3H), 7.45 (t, J=7.2 Hz, 2H), 7.38 - 7.33 (m, 2H), 7.30 - 7.28 (m, 1H), 6.46 (dd, J=3.1, 1.7 Hz, 1H), 6.42 (d, J=2.7 Hz, 1H), 4.31 (d, J=14.1 Hz, 1H), 4.12 (d, J=14.1 Hz, 1H), 3.68 (d, J=13.3 Hz, 1H), 3.50 (d, J=13.3 Hz, 1H), 3.08 (q, J=6.8 Hz, 2H), 2.30 (t, J=7.2 Hz, 2H), 1.59 (quintet, J=7.4 Hz, 2H), 1.43 (quintet, J=7.6 Hz, 2H), 1.33 - 1.27 (m, 2H). LRMS (ESI): (calc) 452.2; (found) 453.4 $(MH)^+$.	1(6 (ex 2))
313	513	**140**		2-(4-fluorobenzyloxy)-*N*-(2-(pyridin-3-yl)ethyl)acetamide	(DMSOD6) δ(ppm):8.40-8.39 (m, 2H), 7.88 (t, J=6.1Hz, 1H), 7.61 (dt, J=7.6, 2.2Hz, 1H), 7.39-7.35 (m, 2H), 7.30-7.27 (dd, J=7.6, 4.7Hz, 1H), 7.17 (t, J=9.0Hz, 2H), 4.44 (s, 2H), 3.83 (s, 2H), 3.35 (q, J=7.0Hz, 2H), 2.76 (t, J=7.0Hz, 2H), 2.49-2.47 (m, 1H). LRMS (ESI): (calc) 288.1; (found) 289.1 $(MH)^+$.	1(1)
314	514			2-(4-fluorobenzyloxy)-*N*-(2-(4-(4-methoxyphenyl)pyrimidin-2-ylthio)ethyl)acetamide	(DMSOD6) δ(ppm): 8.56 (d, J=5.3 Hz, 1H), 8.18 (d, J=9.0 Hz, 2H), 8.08 (t, J=5.3 Hz, 1H), 7.69 (d, J=5.3 Hz, 1H), 7.38 (m, 2H), 7.15 (t, J=9.0 Hz, 2H), 7.05 (d, J=9.0 Hz, 2H), 4.47 (s, 2H), 3.87 (s, 2H), 3.82 (s, 3H), 3.52-3.47 (m, 2H), 3.38-3.28 (m, 2H). LRMS (ESI): (calc) 427.1; (found) 428.6 $(MH)^+$.	6 (1(Ex 56)) DMF 16 (5) EtOH 1(1)
315	515			2-(4-fluorobenzyloxy)-*N*-(2-(4-(thiophen-2-yl)pyrimidin-2-ylthio)ethyl)acetamide	(DMSOD6) δ(ppm): 8.56 (d, J=5.3Hz, 1H), 8.07-8.06 (m, 1H), 8.05 (t, J=5.7Hz, 1H), 7.84 (d, J=4.9Hz, 1H), 7.65 (d, J=5.3Hz, 1H), 7.40-7.37 (m, 2H), 7.25-7.23 (m, 1H), 7.15 (t, J=8.8Hz, 2H), 4.47 (s, 2H), 3.87 (s, 2H), 3.48 (q, J=6.5, 12.5Hz, 2H), 3.29-3.25 (m, 2H). LRMS (ESI): (calc) 403.1; (found) 404.1 $(MH)^+$.	6 (1(Ex 56)) DMF 16 (5) EtOH 1(1)

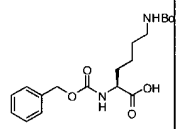
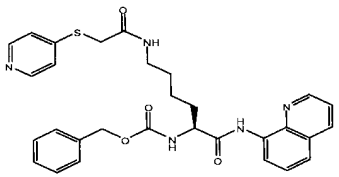
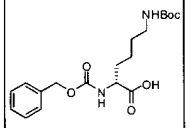
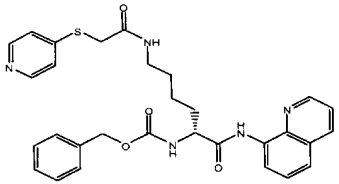
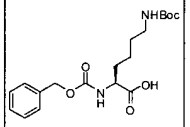
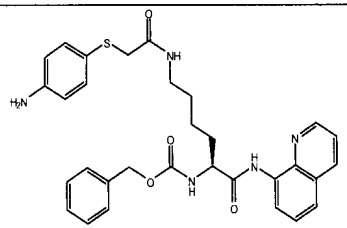
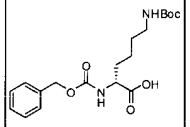
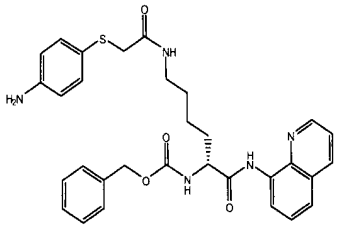
Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
316	516			2-(4-fluorobenzyloxy)-*N*-(2-(4-(4-methoxyphenyl)pyrimidin-2-ylsulfinyl)ethyl)acetamide	(MeOD-*d4*) δ(ppm): 8.80 (d, J= 5.3Hz, 1H), 8.23 (d, J=8.6Hz, 2H), 7.95 (d, J=5.5Hz, 1H), 7.33 (dd, J=8.6, 5.7Hz, 2H), 7.08-7.02 (m,4H), 4.45 (s, 2H), 3.88 (s, 3H), 3.83-3.70 (m, 4H), 3.60-3.43 (m, 2H). LRMS (ESI): (calc) 443.1; (found) 444.5 $(MH)^+$.	1(6 (ex 2))
317	517			2-(4-fluorobenzyloxy)-*N*-(4-(4-(4-methoxyphenyl)pyrimidin-2-ylthio)butyl)acetamide	(MeOD-*d4*) δ(ppm): 8.43 (d, J=5.3Hz, 1H), 8.11 (d, J=8.0Hz, 2H), 7.49 (d, J=5.3Hz, 1H), 7.34-7.30 (m, 2H), 7.06-7.00 (m, 4H), 4.47 (s, 2H), 3.87 (s, 2H), 3.86 (s, 3H), 3.34-3.28 (m, 2H), 3.24 (t, J=7.0Hz, 2H), 1.84-1.79 (m, 2H), 1.75-1.69 (m, 2H). LRMS (ESI): (calc) 455.2; (found) 456.2 $(MH)^+$.	6 (1(Ex 56)) DMF 16 (5) EtOH 1(1)
318	518			8-(2-(2-aminophenyl)hydrazinyl)-*N*-(biphenyl-3-yl)-8-oxooctanamide	(MeOD-*d4*) δ(ppm): 7.84 (t, J=1.6 Hz, 1H), 7.61 - 7.58 (m, 2H), 7.53 (dt, J=7.4, 2.0 Hz, 1H), 7.44 - 7.30 (m, 5H), 6.79 - 6.61 (m, 4H), 2.40 (t, J=7.2 Hz, 2H), 2.28 (t, J=7.2 Hz, 2H), 1.76 - 1.68 (m, 4H), 1.46 - 1.42 (m, 4H). LRMS (ESI): (calc) 430.2; (found) 431.2 $(MH)^+$.	1(1) With Molecular Sieves 5 (3, ex 55)
319	519			*N*-(biphenyl-3-yl)-8-oxo-8-(2-phenylhydrazinyl)octanamide	(MeOD-*d4*) δ(ppm): 7.85 (t, J=1.8 Hz, 1H), 7.61 - 7.58 (m, 2H), 7.53 (dt, J=7.5, 2.0 Hz, 1H), 7.45 - 7.31 (m, 5H), 7.16 (t, J=7.6 Hz, 2H), 6.79 - 6.76 (m, 3H), 2.41 (t, J=7.2 Hz, 2H), 2.28 (t, J=7.2 Hz, 2H), 1.72 (quintet, J=7.6 Hz, 4H), 1.45 (quintet, J=3.5 Hz, 4H). LRMS (ESI): (calc) 415.2; (found) 416.2 $(MH)^+$.	1(1)
320	520	**2**		6-(2-(allyloxy)acetamido)-*N*-(biphenyl-3-yl)hexanamide	(MeOD-*d4*) δ(ppm): 7.85 (t, J=1.7 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.53 (dt, J=7.5, 1.8 Hz, 1H), 7.42 - 7.28 (m, 5H), 5.93 - 5.83 (m, 1H), 5.30 - 5.24 (m, 1H), 5.19 - 5.15 (m, 1H), 4.01 - 3.98 (m, 2H), 3.23 (t, J=7.0 Hz, 2H), 2.38 (t, J=7.3 Hz, 2H), 1.72 (quintet, J=7.5 Hz, 2H), 1.56 (quintet, J=7.5 Hz, 2H), 1.43 - 1.36 (m, 2H). LRMS (ESI): (calc) 380.2; (found) 381.2 $(MH)^+$.	1(1) Pyridine
321	521			methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-3-phenylpropanoate	(MeOD-*d4*) δ(ppm): 7.85 (t, J=1.8 Hz, 1H), 7.60 - 7.56 (m, 2H), 7.52 (dt, J=7.2, 2.0 Hz, 1H), 7.43 - 7.20 (m, 10H), 4.32 (t, J=7.9 Hz, 1H), 3.56 (s, 3H), 3.17 - 3.13 (m, 2H), 3.09 - 2.81 (m, 4H), 2.41 (t, J=7.2 Hz, 2H), 1.74 (quintet, J=7.4 Hz, 2H), 1.56 - 1.50 (m, 2H), 1.45 - 1.39 (m, 2H).	1(4(Ex 1)) 70°C 1(1)

Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
322	522			ethyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-3-phenylpropanoate	(MeOD-*d4*) δ(ppm): 7.85 (t, J=1.6 Hz, 1H), 7.60 - 7.57 (m, 2H), 7.53 (dt, J=7.3, 2.0 Hz, 1H), 7.44 - 7.20 (m, 10H), 4.32 (t, J=8.4 Hz, 1H), 4.04 - 3.98 (m, 2H), 3.18 - 2.78 (m, 6H), 2.42 (t, J=7.2 Hz, 2H), 1.74 (quintet, J=7.6 Hz, 2H), 1.55 (quintet, J=7.2 Hz, 2H), 1.46 - 1.40 (m, 2H), 1.11 (t, J=7.0 Hz, 3H). LRMS (ESI): (calc) 532.3; (found) 533.3 $(MH)^+$.	1(4(Ex 1)) 70°C 1(1)
323	523			ethyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-3-phenylpropanoate	(MeOD-*d4*) δ(ppm): 7.84(t,J=1.8 Hz,1H),7.61-7.58(m,2H),7.54-7.48(m,2H),7.44-7.30(m,9H),5.07,5.27(s,s,1H),4.30-4.19(m,2H),3.89-3.38(m,2H),3.20(q,J=6.8Hz,2H),2.38(td,J=7.5,1.4Hz,2H),1.75-1.67(m,2H)1.57-1.50(m,2H)1.44-1.38(m,2H),1.26-1.27(m,3H). LRMS (ESI): (calc) 534.2; (found) 535.2 $(MH)^+$.	1(6 (ex 2))
324	524	**177**		ethyl 2-(2-oxo-2-(5-(5-phenyl-1,3,4-thiadiazol-2-yl)pentylamino)ethylthio)-2-phenylacetate	(MeOD-*d4*) δ(ppm): 7.94 - 7.90 (m, 3H), 7.55 - 7.47 (m, 3H), 7.43 - 7.40 (m, 2H), 7.35 - 7.26 (m, 3H), 4.83 (s, 1H), 4.20 - 4.08 (m, 2H), 3.23 - 3.05 (m, 6H), 1.86 (quintet, J=7.8 Hz, 2H), 1.59 - 1.53 (m, 2H), 1.49 - 1.41 (m, 2H), 1.19 (t, J=7.0 Hz, 3H). LRMS (ESI): (calc) 483.2; (found) 484.3 $(MH)^+$.	1(1)
325	525			ethyl 2-(2-oxo-2-(6-oxo-6-(quinolin-8-ylamino)hexylamino)ethylthio)-2-phenylacetate	(MeOD-*d4*) δ(ppm): 8.85 (dd, J=4.1, 1.6 Hz, 1H), 8.62 (dd, J=7.6, 1.2 Hz, 1H), 8.29 (dd, J=8.4, 1.7 Hz, 1H), 7.60 (dd, J=8.2, 1.2 Hz, 1H), 7.55 - 7.50 (m, 2H), 7.43 - 7.40 (m, 2H), 7.34 - 7.30 (m, 3H), 4.82 (s, 1H), 4.18 - 4.09 (m, 2H), 3.22 - 3.04 (m, 4H), 2.60 (t, J=7.4 Hz, 2H), 1.79 (quintet, J=7.4 Hz, 2H), 1.58 - 1.52 (m, 2H), 1.49 - 1.42 (m, 2H), 1.18 (t, J=7.2 Hz, 3H). LRMS (ESI): (calc) 493.2; (found) 494.3 $(MH)^+$.	1(1)
326	526			*N*-(3-(4-(3,4-dimethoxybenzylsulfonyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(DMSOD6) δ(ppm): 7.89 (t, J=5.7 Hz, 1H), 7.57 (d, J=8.4 Hz, 2H), 7.44 - 7.38 (m, 4H), 7.12 (t, J=9.0 Hz, 2H), 6.84 (d, J=8.4 Hz, 2H), 6.68 (dd, J=8.4, 2.1 Hz, 1H), 6.53 (d, J=2.0 Hz, 1H), 4.50 (d, J=5.8 Hz, 2H), 3.87 (s, 2H), 3.69 (s, 3H), 3.51 (s, 3H), 3.10 (q, J=6.8 Hz, 2H), 2.64 (t, J=7.4 Hz, 2H), 1.72 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 515.2; (found) 516.2 $(MH)^+$.	31 (1&2) THF /thiol 1-pot RT 1(5(ex 3)) 25(2 (ex 85a)) 5 (3 (ex 55))

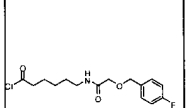
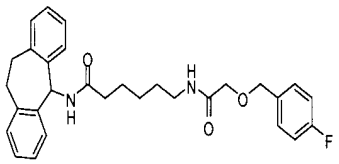
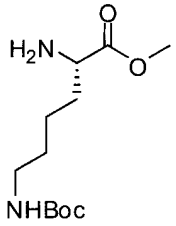
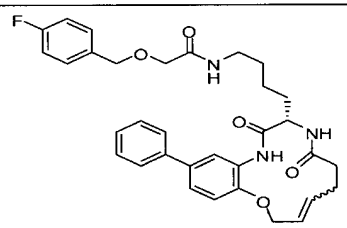
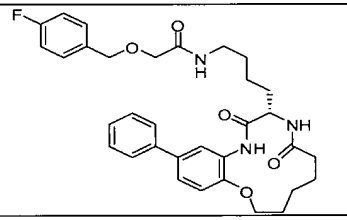
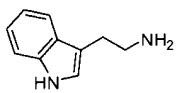
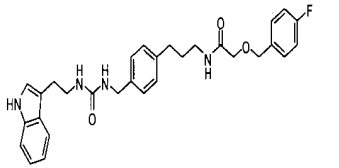
Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
327	527			ethyl 2-(2-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl) phenyl)propylamino)-2-oxoethylthio)-2-phenylacetate	(MeOD-*d4*) d(ppm): 8.54 (s, 1H), 7.60 (d, J=8.2 Hz, 2H), 7.43 - 7.39 (m, 2H), 7.33 - 7.24 (m, 5H), 6.76 (d, J=8.6 Hz, 1H), 6.67 (d, J=2.3 Hz, 1H), 6.56 (dd, J=8.0, 2.3 Hz, 1H), 4.83 (s, 1H), 4.17 - 4.09 (m, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 3.22 - 3.05 (m, 4H), 2.67 (t, J=7.5 Hz, 2H), 1.76 (quintet, J=7.7 Hz, 2H), 1.17 (t, J=7.0 Hz, 3H). LRMS (ESI): (calc) 586.2; (found) 587.3 $(MH)^+$.	16 (5) ETOH 1(1)
328	528			ethyl 2-(2-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl) phenyl)propylamino)-2-oxoethylthio)-2-phenylacetate	(MeOD-*d4*) d(ppm): 8.54 (s, 1H), 7.60 (d, J=8.2 Hz, 2H), 7.43 - 7.39 (m, 2H), 7.33 - 7.24 (m, 5H), 6.76 (d, J=8.6 Hz, 1H), 6.67 (d, J=2.3 Hz, 1H), 6.56 (dd, J=8.0, 2.3 Hz, 1H), 4.83 (s, 1H), 4.17 - 4.09 (m, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 3.22 - 3.05 (m, 4H), 2.67 (t, J=7.5 Hz, 2H), 1.76 (quintet, J=7.7 Hz, 2H), 1.17 (t, J=7.0 Hz, 3H). LRMS (ESI): (calc) 515.2; (found) 516.1 $(MH)^+$.	1(4 (Ex 1)) 1(5 (Ex 3)) 25(2 (Ex 84a)) 5 (3) (ex 55)
329	529			*N*-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl) phenyl)propyl)benzofuran-2-carboxamide	(MeOD-*d4*) d(ppm): 7.71 (dt, J=5.8, 1.2 Hz, 1H), 7.62 - 7.56 (m, 3H), 7.47 - 7.42 (m, 2H), 7.37 - 7.29 (m, 3H), 6.76 (d, J=8.6 Hz, 1H), 6.65 (d, J=2.4 Hz, 1H), 6.55 (dd, J=8.6, 2.3 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.41 (t, J=7.0 Hz, 2H), 2.75 (t, J=7.6 Hz, 2H), 1.94 (quintet, J=7.4 Hz, 2H). LRMS (ESI): (calc) 494.2; (found) 495.2 $(MH)^+$.	25(2 (Ex 84a)) 5 (3) (ex 55) 1(1)
330	530	**214**		*N*-(3-(3-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl) phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) d(ppm): 7.39 - 7.28 (m, 4H), 7.16 (t, J=7.6 Hz, 1H), 7.06 - 6.97 (m, 4H), 6.94 - 6.89 (m, 3H), 6.76 - 6.73 (m, 1H), 4.49 (s, 2H), 3.93 (t, J=5.9 Hz, 2H), 3.89 (s, 2H), 3.69 (s, 2H), 3.61 (t, J=6.2 Hz, 2H), 3.41 (t, J=6.6 Hz, 2H), 2.94 - 2.90 (m, 2H), 2.83 - 2.79 (m, 2H), 2.72 (t, J=6.3 Hz, 2H), 1.95 (quintet, J=6.3 Hz, 2H). LRMS (ESI): (calc) 533.3; (found) 534.4 $(MH)^+$.	32(1) 27 (5(Ex 87a)) 27 (1(Ex 88b)) 16 (5) ETOH 1(1)
331	531			2-(4-aminophenylthio)-*N*-(5-(5-phenylthiazol-2-yl)pentyl)acetamide	(MeOD-*d4*) d(ppm) ^{1}H: 7.89 (s, 1H), 7.60-7.57 (m, 2H), 7.42-7.38 (m, 2H), 7.35-7.30 (m, 1H), 7.22-7.18 (m, 2H), 6.65-6.61 (m, 2H), 3.35 (s, 2H), 3.13 (t, J = 6.8Hz, 2H), 2.99 (t, J = 7.6Hz, 2H), 1.81-1.74 (m, 2H), 1.49-1.42 (m, 2H), 1.34-1.26 (m, 2H) LRMS (ESI): (calc) 411.2 (found) 412.69 $(MH)^+$	23 (1-4(ex82)) 1 (step 2) Ex 1

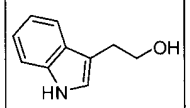
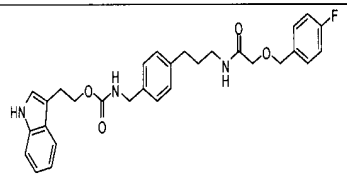
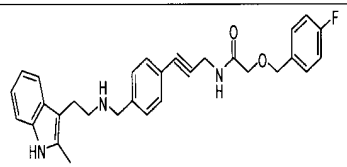
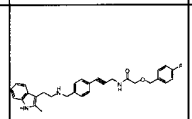
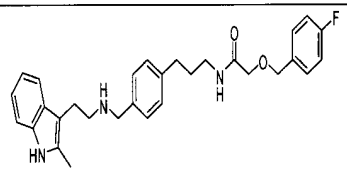
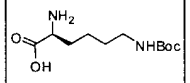
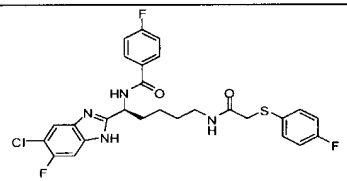
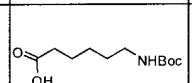
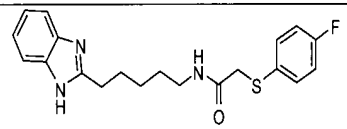
Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
332	532			2-(4-aminophenylthio)-*N*-(5-(5-(4-methoxyphenyl)thiazol-2-yl)pentyl)acetamide	(MeOH-d4) δ(ppm) ^{1}H: 7.76 (s, 1H), 7.51 (d, J = 9.0Hz, 2H), 7.19 (d, J = 8.4Hz, 2H), 6.96 (d, J = 9.0Hz, 2H), 6.63 (d, J = 8.4Hz, 2H), 3.82 (s, 3H), 3.34 (s, 2H), 3.13 (t, J = 6.8Hz, 2H), 2.97 (t, J = 7.6Hz, 2H), 1.80-1.73 (m, 2H), 1.49-1.41 (m, 2H), 1.34-1.26 (m, 2H) LRMS (ESI): (calc) 441.15 (found) 442.36 $(MH)^+$	23 (steps 1-4) Ex 82 (step 2) Ex 1
333	533			2-(4-fluorobenzyloxy)-*N*-(5-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)acetamide	(MeOH-d4) δ(ppm) ^{1}H: 7.94-7.92 (m, 2H), 7.54-7.49 (m, 3H), 7.39-7.36 (m, 2H), 7.08-7.04 (t, J=8.8Hz, 2H), 4.54 (s, 2H), 3.30-3.23 (t, J=6.8Hz, 2H), 3.18-3.14 (t, J=7.4Hz, 2H), 1.91-1.84 (m, 2H), 1.63-1.56 (m, 2H), 1.49-1.43 (m, 2H) LRMS (ESI): (calc) 413.16 (found) 414.21 $(MH)^+$	23 (steps 1-3) Ex 82 11 (step 4)
334	534			*N*-(4-(5-(3,4-dimethoxyphenylsulfonamido)-1,3,4-thiadiazol-2-ylthio)butyl)-2-(4-fluorobenzyloxy)acetamide	(MeOH-d4) δ(ppm) ^{1}H: 7.50-7.33 (m, 4H), 7.10-7.03 (m, 3H), 4.89 (s, 2H), 3.92 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.25 (t, J = 6.7Hz, 2H), 3.18 (t, J = 7.1Hz, 2H), 1.76-1.62 (m, 4H) LRMS (ESI): (calc) 570.1 (found) 571.1 $(MH)^+$	22 (Steps 1-4) Ex 81a
335	535			*N*-(4-(3-((3-(3,4-dimethoxyphenylsulfonamido)pyrrolidin-1-yl)methyl)phenoxy)butyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d4*) δ(ppm) ^{1}H: 7.43-7.38 (m, 3H), 7.31 (d, J = 2.2Hz, 1H), 7.17 (t, J = 7.8Hz, 1H), 7.10-7.02 (m, 3H), 6.82-6.78 (m, 3H), 4.56 (s, 2H), 3.94 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.75-3.68 (m, 1H), 3.52 (d, J = 12.5Hz, 1H), 3.45 (d, J = 12.7Hz, 1H), 3.35-3.30 (m, 2H), 2.59-2.46 (m, 3), 2.18 (dd, J = 10.0, 5.9Hz, 1H), 2.09-1.99 (m, 1H), 1.82-1.67 (m, 4H), 1.58-1.50 (m, 1H) LRMS (ESI): (calc) 629.3 (found) 630.88 $(MH)^+$.	32 (1-4) 1(5(ex5)) 16 (1)
336	536			pyridin-3-ylmethyl 1-(3-(4-(2-(4-fluorobenzyloxy)acetamido)butoxy)benzyl)pyrrolidin-3-ylcarbamate	(MeOH-d4) δ(ppm) ^{1}H: 8.54 (s, 1H), 8.47 (d, J = 3.9Hz, 1H), 7.84 (d, J = 7.2Hz, 1H), 7.44-7.38 (m, 3H), 7.20 (t, J = 8.2Hz, 1H), 7.10-7.05 (m, 2H), 6.90-6.80 (m, 3H), 5.11 (s, 2H), 4.56 (s, 2H), 4.12-4.11 (m, 1H), 3.99 (t, J = 5.9Hz, 2H), 3.93 (s, 2H), 3.57 (s, 2H), 3.32-3.29 (m, 2H), 2.84-2.80 (m, 1H), 2.67-2.64 (m, 1H), 2.56-2.51 (m, 1H), 2.40 (dd, J = 14.7, 8.0Hz, 1H), 2.25-2.19 (m, 1H), 1.82-1.61 (m, 5H) LRMS (ESI): (calc) 564.3 (found) 565.95 (MH^+)	32 (1-4) 1(5(ex5)) 26 (Step 2) Ex 81a

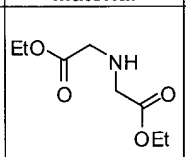
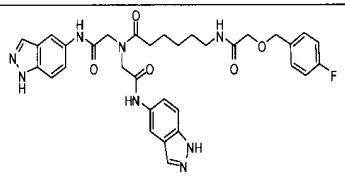
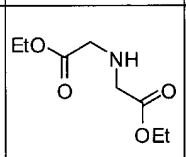
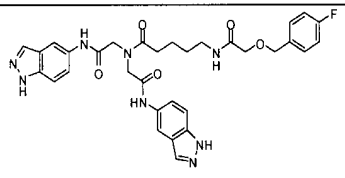
Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
337	537			*N*-(1-(3-(4-(2-(4-fluorobenzyloxy)acetamido) butoxy)benzyl)pyrrolidin-3-yl)isonicotinamide	(MeOH-d4) δ(ppm) ^{1}H: 8.68-8.67 (m, 2H), 7.77-7.76 (m, 2H), 7.42-7.38 (m, 2H), 7.22 (t, J = 8.0Hz, 1H), 7.10-7.05 (m, 2H), 6.93-6.90 (m, 2H), 6.82 (dd, J = 8.2, 2.3Hz, 1H), 4.56-4.53 (m, 3H), 3.99 (t, J = 6.1Hz, 2H), 3.93 (s, 2H), 3.63 (s, 2H), 3.32-3.29 (m, 2H), 2.91-2.87 (m, 1H), 2.84-2.78 (m, 1H), 2.62-2.54 (m, 2H), 2.40-2.31 (m, 1H), 1.87-1.65 (m, 5H) LRMS (ESI): (calc) 534.3 (found) 535.77 $(MH)^+$	32 (1-4) 1(5(ex5)) 1 (step 3) Ex 1
338	538			1-(3-(4-(2-(4-fluorobenzyloxy)acetamido) butoxy)benzyl)pyrrolidin-3-yl pyridin-3-ylmethylcarbamate	(MeOH-d4) δ(ppm) ^{1}H: 8.47-8.42 (m, 2H), 7.75 (d, J = 7.8Hz, 1H), 7.42-7.37 (m, 3H), 7.20 (t, J = 7.8Hz, 1H), 7.10-7.05 (m, 2H), 6.91-6.87 (m, 2H), 6.82 (ddd, J = 8.2, 2.5, 0.8Hz, 1H), 5.10-5.06 (m, 1H), 4.56 (s, 2H), 4.30 (s, 2H), 3.99 (d, J = 5.9Hz, 2H), 3.93 (s, 2H), 3.65 (d, J = 12.7Hz, 1H), 3.53 (d, J = 12.7Hz, 1H), 3.33-3.29 (m, 2H), 2.83-2.63 (m, 3H), 2.48-2.42 (m, 1H), 2.27-2.22 (m, 1H), 1.88-1.68 (m, 5H) LRMS (ESI): (calc) 564.3 (found) 565.61 $(MH)^+$	32 (1-4) 1(5(ex5)) 26 (step 1) Ex 86a 16 (Step 5) Ex 73a 1 (Step 1) Ex 1
339	539			(*E*)-*N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl) phenyl)allyl)-2-(4-fluorobenzyloxy)acetamide	(MeOH-d4) δ(ppm) ^{1}H: 7.44-7.28 (m, 8H), 7.10-6.98 (m, 4H), 6.91 (t, J = 7.8Hz, 1H), 6.53 (d, J = 16.0Hz, 1H), 6.21 (dt, J = 16.0, 5.9Hz, 1H), 4.60 (s, 2H), 4.01-3.99 (m, 4H), 3.73 (s, 2H), 3.63 (t, J = 6.3Hz, 2H), 2.95-2.92 (m, 2H), 2.84-2.80 (m, 2H), 2.74 (t, J = 6.1Hz, 2H) LRMS (ESI): (calc) 515.3 (found) 516.2 $(MH)^+$	11 (step 1) Ex 66 27 (step 1) Ex 88b 25 (step 2) Ex 85a 16 (step 5) Ex 73a 1 (step 1) Ex 1

Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
340	540			(S)-benzyl 1-oxo-6-(2-(pyridin-4-ylthio)acetamido)-1-(quinolin-8-ylamino)hexan-2-ylcarbamate	(MeOD-*d*4) δ(ppm) ^{1}H: 8.75 (dd, J=4.1, 1.6Hz, 1H), 8.64 (d, J=6.8Hz, 1H), 8.37-8.25 (m, 3H), 7.62 (d, J=8.3Hz, 1H), 7.56-7.5 (m, 2H), 7.4-7.2 (m, 6H), 5.22 and 5.11 (ab doublet, J=2.1Hz, 2H), 4.38-4.2 (m, 1H), 3.78 (s, 2H), 3.23 (t, J=6.4Hz, 2H), 2.1-1.95 (m, 1H), 1.85-1.75 (m, 1H), 1.6-1.4 (m, 4H). LRMS (ESI): (calc) 557.2 (found) 558.8 $(MH)^+$.	43 (1-2) 1 (3(ex1)) 1(4(ex1)) DIPEA at 50C
341	541			(R)-benzyl 1-oxo-6-(2-(pyridin-4-ylthio)acetamido)-1-(quinolin-8-ylamino)hexan-2-ylcarbamate	(MeOD-*d*4) δ(ppm) ^{1}H: 8.74 (dd, J=4.2, 1.6Hz, 1H), 8.64 (d, J=6.8Hz, 1H), 8.37-8.2 (m, 4H), 7.65-7.6 (m, 1H), 7.55-7.5 (m, 2H), 7.39 (dd, J=5.3, 1.6Hz, 2H), 7.3-7.25 (m, 4H), 5.22 and 5.11 (ab doublet, J=2.5Hz, 2H), 4.34-4.30 (m, 1H), 3.76 (s, 2H), 3.22 (t, J=6.6Hz, 2H), 2.05-1.95 (m, 1H), 1.81-1.75 (m, 1H), 1.6-1.4 (m, 4H,). LRMS (ESI): (calc) 557.2 (found) 558.4 $(MH)^+$.	43 (1-2) 1 (3(ex1)) 1(4(ex1)) DIPEA at 50C
342	542			(S)-benzyl 6-(2-(4-aminophenylthio)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate	(MeOD-*d*4) δ(ppm) ^{1}H: 8.76 (dd, J=4.2, 1.6Hz, 1H), 8.62 (d, J=7.5Hz, 1H), 8.29 (dd, J=8.2, 1.6Hz, 1H), 7.62 (d, J=8.4Hz, 1H), 7.56-7.51 (m, 2H), 7.4-7.36 (m, 1.5H), 7.3-7.25 (m, 2.5H), 7.19 (d, J=8.6Hz, 2H), 6.63 (d, J=8.4Hz, 2H), 5.21 and 5.11 (ab doublet, J=12.3Hz, 2H), 4.33-4.28 (m, 1H), 3.34 (s, 2H), 3.13 (t, J=6.5Hz, 2H,), 2.0-1.84 (m, 1H), 1.8-1.61 (m, 1H), 1.5-1.2 (m, 1H). LRMS (ESI): (calc) 571.2; (found) 572.8 $(MH)^+$.	43 (1-2) 1 (3(ex1)) 1(4(ex1)) DIPEA at 50C
343	543			(R)-benzyl 6-(2-(4-aminophenylthio)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate	(MeOD-*d*4) δ(ppm) ^{1}H: 8.76 (dd, J=4.2, 1.7Hz, 1H), 8.64 (d, J=7.4Hz, 1H), 8.29 (dd, J=8.3, 1.5Hz, 1H), 7.62 (d, J=8.3Hz, 1H), 7.56-7.51 (m, 2H), 7.4-7.37 (m, 1.5H), 7.3-7.20 (m, 2.5H), 7.19 (d, J=8.6Hz, 2H), 6.63 (d, J=8.4Hz, 2H), 5.21 and 5.11 (ab doublet, J=12.7Hz, 2H), 4.33-4.22 (m, 1H), 3.34 (s, 2H), 3.13 (t, J=6.5Hz, 2H), 2.0-1.84 (m, 1H), 1.8-1.71 (m, 1H), 1.5-1.22 (m, 1H). LRMS (ESI): (calc) 571.2 (found) 572.9 $(MH)^+$.	43 (1-2) 1 (3(ex1)) 1(4(ex1)) DIPEA at 50C

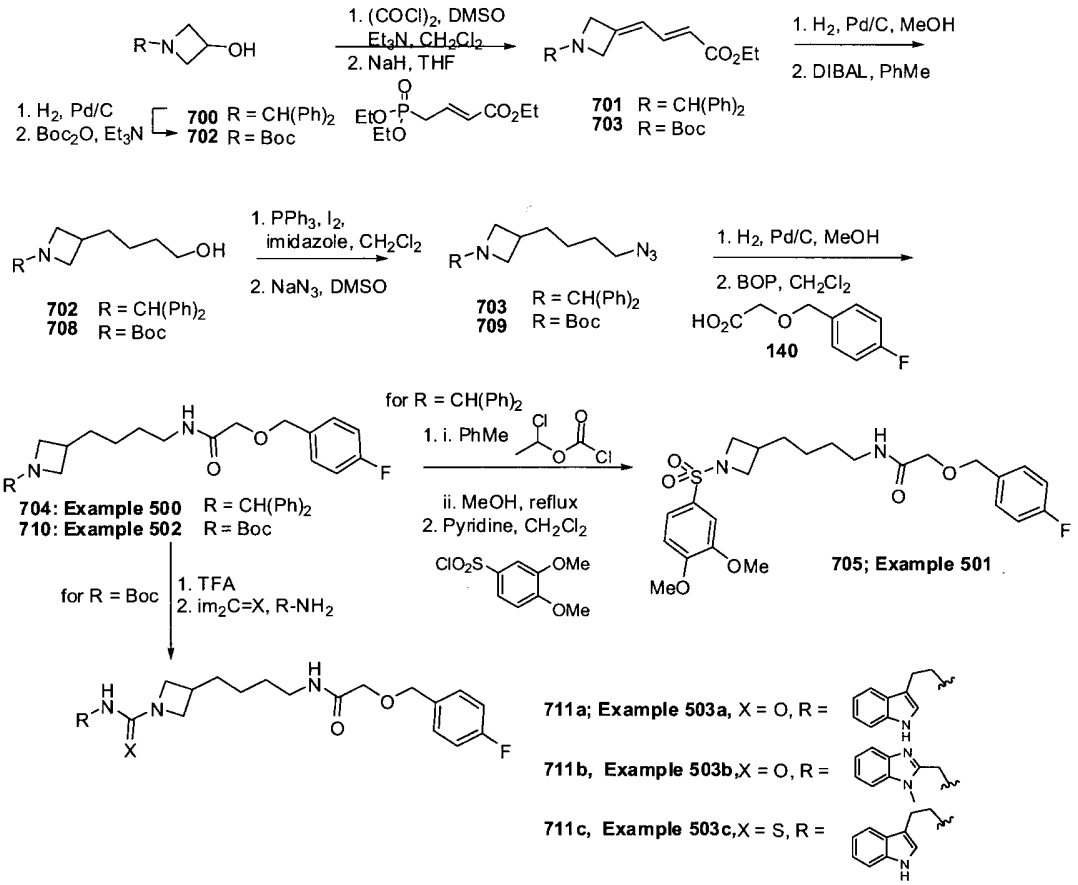
WO 2006/102760 PCT/CA2006/000483

Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
344	544			*N*-(10, 11-dihydro-5*H*-dibenzo[a,a]cyclohepten-5-yl)-6-(2-(4-fluorobenzyloxy)acetamido)-hexanamide	(CDCl3-*d*) δ(ppm) ^{1}H: 7.45-7.38 (m, 2H), 7.33-7.25 (m, 2H), 7.24-7.11 (m, 4H), 7.10-7.02 (m, 2H), 6.53 (br s, 1H), 6.36-6.30 (m, 1H), 6.27-6.21 (m, 1H), 4.50 (s, 2H), 3.91 (s, 2H), 3.39-3.16 (m, 5H), 3.14-3.02 (m, 2H), 2.17 (t, J=7.4Hz, 2H), 1.71-1.58 (m, 2H), 1.52-1.40 (m, 2H), 1.32-1.20 (m, 2H). LRMS (ESI): (calc) 488.2 (found) 489.3 $(MH)^+$.	1 (3 (ex1))
345	545			(S,E / Z (7:3))-N-(4-(2,5-dioxo-14-phenyl-1,2,3,4,5,6,7,10-octahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD--*d*4) δ(ppm) ^{1}H: 8.66 (dd, J=2.4hHz, 0.6H), 8.40 (dd, J=1.8Hz, 0.3H), 7.57-7.54 (m, 2H), 7.45-7.25 (m, 7H), 7.22 (d, J=8.4Hz, 1H), 7.09-7.02 (m, 2H), 6.12-6.02 (m, 0.7H), 5.78-5.65 (m, 1.3H), 4.68-4.42 (m, 4H), 4.25-4.15 (m, 2H), 3.94-3.89 (m, 2H), 2.5-2.38 (m, 4H), 2.05-1.65 (m, 2H), 1.64-1.38 (m, 4H). LRMS (ESI): (calc) 573.3 (found) 574.2 $(MH)^+$.	2(1(ex47)) 43(2(ex105a)) 1(1(ex1)) 1(5(ex1)) 46(1,2(ex108)) 45(4(ex107))
346	546	89284		(S)-N-(4-(2,5-dioxo-14-phenyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide	(MeOD-*d*4) δ(ppm) ^{1}H: 8.45 (d, J=2.2Hz, 0.7H), 8.16 (s, 0.3H), 7.54 (d, J=7.5Hz, 2H), 7.42-7.34 (m, 4H), 7.33-7.25 (m, 3H), 4.56-4.50 (m, 2H), 3.95-3.85 (m, 3H), 3.30-3.22 (m, 2H), 2.64-2.52 (m, 1H), 2.32-2.24 (m, 1H), 2.10-1.26 (m, 12H). LRMS (ESI): (calc) 575.3 (found) 576.3 $(MH)^+$.	5 (3(ex55))
347	547			*N*-(3-(4-((3-(2-(1H-indol-3-yl)ethyl)ureido)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(acetone-*d6*) δ(ppm):10.11 (bs, 1H); 7.58 (d, J= 7.2 Hz, 1H); 7.45-7.27 (m, 4H); 7.18 (d, J= 8.0 Hz, 2H); 7.14-7.05 (m, 5H); 7.01-6.96 (m, 1H); 4.58 (s), 4.56 (s) (2H); 4.34 (s), 4.29 (s) (2H); 3.92 (s), 3.90 (s)(2H); 3.47 (dd, J= 6.8, 7.2 Hz, 2H); 3.23 (q, J= 6.8 Hz, 2H); 2.91 (dd, J= 6.8, 7.2 Hz, 2H); 2.58 (t; J= 7.6 Hz, 2H); 1.83-1.76 (m, 2H).	26(1(ex86a)) inPy 26(3(ex86a)) 5 (3(ex55,comp74)), in AcOEt

Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
348	548			2-(1H-indol-3-yl)ethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido) propyl)benzylcarbamate	(CDCl3) δ(ppm):8.42 (bs, 1H); 7.62 (d, J= 7.6 Hz, 1H); 7.35-7.20 (m, 3H); 7.18-7.04 (m, 8H); 6.99 (bs, 1H); 6.61 (bs, 1H); 5.10 (bs, 1H); 4.51 (s, 2H); 4.38 (dd, J= 6.8, 7.2 Hz, 2H); 4.31 (bs, 2H); 3.96 (s, 2H); 3.31 (q, J= 6.8 Hz, 2H); 3.09 (dd, J= 6.8, 7.2 Hz, 2H); 2.62 (t, J= 7.6 hz, 2H); 1.87-1.80 (m, 2H).	26(1(ex86a)) inPy 26(3(ex86a)) 5 (3(ex55,comp74)), in AcOEt
349	549	**189**		2-(4-fluorobenzyloxy)-N-(3-(4-((2-(2-methyl-1H-indol-3-yl)ethylamino)methyl)phenyl)prop-2-ynyl)acetamide	(MeOD-*d4*) δ(ppm):7.39-7.35 (m, 3H); 7.30 (bd, J=8.4 Hz, 2H); 7.21 (bd, J= 7.6 Hz, 1H); 7.15 (bd, J= 8.0 Hz, 2H); 7.04 (bt, J= 8.8 Hz, 2H); 6.98 (dt, J= 1.2, 8.0 Hz, 1H); 6.91 (dt, J= 1.2, 8.0 Hz, 1H); 4.54 (s, 2H); 4.21 (s, 2H); 3.95 (s, 2H); 3.69 (s, 2H); 2.88 (t, J= 7.2 Hz, 2H); 2.76 (t, J= 7.2 Hz, 2H); 2.31 (s, 3H).	26(2(ex86a)) 27(5(ex87a))
350	550			2-(4-fluorobenzyloxy)-N-(3-(4-((2-(2-methyl-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)acetamide	(MeOD-*d4*) δ(ppm): 7.39-7.36 (m, 3H); 7.21 (bd, J= 8.0 Hz, 1H); 7.14-7.04 (m, 6H); 6.98 (td, J= 1.2, 6.8 Hz, 1H); 6.91 (td, J= 1.2, 8.0 Hz, 1H); 4.52 (s, 2H); 3.90 (s, 2H); 3.71 (s, 2H); 3.22 (t, J= 7.2 Hz, 2H); 2.90 (t, J= 6.8 Hz, 2H); 2.80 (d, J= 6.8 Hz, 2H); 2.58 (t, J= 7.2 Hz, 2H); 2.32 (s, 3H); 1.78 (t, J= 7.2 Hz, 2H).	5 (3(ex55,comp74)), in AcOEt
351	551			(*S*)-N-(1-(5-chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)-5-(2-(4-fluorophenylthio)acetamido) pentyl)-4-fluorobenzamide	(MeOD-*d4*) δ(ppm):7.28 (t, J = 5.5 Hz, 2H); 7.58 (d, J = 6.7 Hz, 1H); 7.37 (m, 3H); 7.18 (t, J = 9.8 Hz, 2H); 7.02 (t, J = 8.8 Hz, 2H); 5.31(t, J = 9.6 Hz, 1H); 3.48 (s, 2H); 3.16 (t, J = 6.7 Hz, 2H, J = 6.7 Hz); 2.11 (m, 2H); 1.51 (m, 2H); 1.38 (m, 2H) LRMS (ESI): 560.3 (calc) 561.1 $(MH)^+$.	1(1) 1(1) 48 (2) 1 (2) 1(1)
352	552			N-(5-(1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorophenylthio)acetamide	(MeOD-*d4*) d(ppm):7.55 (q, J = 3.1 ,6.1 Hz, 2H); 7.40 (m, 2H); 7.31 (q, J = 3.1, 6.1 Hz, 2H); 7.02 (t, J = 9.0 Hz, 2H); 3.50 (s, 2H); 3.14 (t, J = 6.8 Hz, 2H); 2.94 (t, J = 7.4 Hz, 2H); 1.82 (m, 2H); 1.47 (m, 2H); 1.29 (m, 2H) LRMS: 371.1 (calc) 372.5 (found)	1 (1) 48 (2) 1 (2) 1 (4, ex1)

Ex	Cpd	Starting Material	Product	Name	Characterization	Scheme (step)
353	553			*N*,*N*-bis(2-(1H-indazol-5-ylamino)-2-oxoethyl)-6-(2-(4-fluorobenzyloxy)acetamido) hexanamide	(MeOD-*d4*) d(ppm): 8.21 (s, 1H); 8.14 (s, 1H); 8.01 (m, 2H); 7.57 (m, 4H); 7.31 (m, 2H); 7.01 (m, 2H); 4.46 (m, 4H); 4.31 (s, 2H); 3.83 (s, 2H); 3.18 (m, 2H); 2.47 (m, 2H); 1.65 (m, 2H); 1.52 (m, 2H) LRMS (ESI): (calc.) 628.2; (found) 629.3$(MH)^+$.	1(1) 1(5,ex1) 1(1)
354	554			*N*,*N*-bis(2-(1H-indazol-5-ylamino)-2-oxoethyl)-5-(2-(4-fluorobenzyloxy)acetamido) pentanamide	(MeOD-*d4*) d(ppm):8.22 (s, 1H); 8.14 (s, 1H); 8.01 (d, J = 5.3 Hz, 2H); 7.53 (m, 4H); 7.30 (m, 2H); 7.03 (t, J = 8.6 Hz, 2H); 4.44 (s, 2H); 4.43 (s, 2H); 4.30 (s, 2H); 3.82 (s, 2H); 3.14 (t, J = 6.8 Hz, 2H); 2.44 (t, J = 7.2 Hz, 2H); 1.65 (m, 2H); 1.45 (m, 2H); 1.31 (m, 2H) LRMS(ESI): 642.6 (calc) 643.3 (found)	1(1) 1(5,ex1) 1(1)

Scheme 300



Example 500

N-(4-(1-benzhydrylazetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide **(704)**

Step 1: (E)-ethyl 4-(1-benzhydrylazetidin-3-ylidene)but-2-enoate (**701**)

[0451] To a stirred solution of oxalyl chloride (0.91 mL, 10.46 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added DMSO (0.74 mL, 10.46 mmol). After 20 min, a solution of 1-benzhydrylazetidin-3-ol **700** (1.0 g, 4.18 mmol) in CH_2Cl_2 (5 mL) was added. The solution was stirred at -78 °C for another 20 min and Et_3N (2.91 mL, 20.92 mmol) was added. The solution was slowly warmed to 0 °C over 1h. A mixture of 1:1 EtOAc/hexane was added and the salt was filtered through a pad of Celite-Silica gel. The solution was evaporated to dryness and the crude ketone in THF (20 mL) was cooled in an ice bath. (E)-ethyl 4-(diethoxyphosphoryl)but-2-enoate (1.11 mL, 5.02 mmol) and NaH (218 mg, 5.44 mmol) were added and the resulting mixture was slowly warmed to room temperature and stirred for 1h. H_2O was added and the mixture was extracted with EtOAc. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography with EtOAc (20%) in hexane to afford **701** (1.27 g, 99%) as a mixture of cis and trans isomers.

[0452] (CD_3CN) δ (ppm) ^1H: 7.49 (d, J= 8.4 Hz, 4H), 7.31 (t, J= 7.6 Hz, 4H), 7.22 (t, J= 4.0 Hz, 2H), 7.12 (dd. J= 4.0, 11.2 Hz, 1H), 6.06 (dt, J= 2.0, 11.2 Hz, 1H), 5.82 (d, J= 15.6 Hz, 1H), 4.62 (s, 1H), 4.13 (q, J= 6.8 Hz, 2H), 3.98 (s, 2H), 3.84 (s, 2H), 1.24 (t, J= 7.2 Hz, 3H). LRMS (ESI): (calc) 333.4; (found) 334.2 $(MH)^+$.

Step 2: 4-(1-benzhydrylazetidin-3-yl)butan-1-ol (**702**)

[0453] To a stirred solution of (E)-ethyl 4-(1-benzhydrylazetidin-3-ylidene)but-2-enoate **701** (965 mg, 2.89 mmol) in MeOH (29 mL) was carefully added palladium on charcoal (10% w/w) (30 mg). A balloon filled with hydrogen was attached to the flask and the suspension was stirred for 3h. The suspension was filtered and evaporated. To a stirred solution of the resulting ester in PhMe (14 mL) at -78 °C was added a 1.0M solution of DIBAL in PhMe (13.9 mL, 13.94 mmol). After stirring for 1h, MeOH was added and warmed to 0 °C. 3 drops of H_2O were added followed by Et_2O (10 mL) and stirred at room temperature for 10 min. The gel that was formed was filtered through Celite and washed with EtOAc to yield **702** (522 mg, 60 %). LRMS (ESI): (calc) 295.4; (found) 296.2 $(MH)^+$.

Step 3: 3-(4-azidobutyl)-1-benzhydrylazetidine (**703**)

[0454] To a stirred solution of **702** (522 mg, 1.77 mmol) in CH_2Cl_2 (4.5 mL) at 0 °C were added sequentially PPh_3 (509 mg, 1.94 mmol), imidazole (240 mg, 3.53 mmol) and a solution of iodine (494 mg, 1.94 mmol) in CH_2Cl_2 (10 mL). The yellow solution was stirred at room temperature for 1h. Saturated solutions of $NaHCO_3$ and sodium thiosulfate were added and CH_2Cl_2 extractions. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography with EtOAc (15%) in hexane to afford 1-benzhydryl-3-(4-iodobutyl)azetidine (349 mg, 49%). LRMS (ESI): (calc) 405.3; (found) 406.4 $(MH)^+$. To a stirred solution of 1-benzhydryl-3-(4-iodobutyl)azetidine (349 mg, 0.86 mmol) in DMSO (4.0 mL) was added NaN_3 (112 mg, 1.72 mmol). The solution was stirred for 0.5h and H_2O was added followed by EtOAc extractions. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography with EtOAc (15%) in hexane to afford **703** (250 mg, 91%). LRMS (ESI): (calc) 320.4; (found) 321.2 $(MH)^+$.

Step 4: N-(4-(1-benzhydrylazetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**704**)

[0455] To a stirred solution of 3-(4-azidobutyl)-1-benzhydrylazetidine **703** (250 mg, 0.78 mmol) in MeOH (5.0 mL) was carefully added palladium on charcoal (10% w/w) (20 mg). A balloon filled with hydrogen was attached to the flask and the suspension was stirred for 0.5h. The suspension was filtered and evaporated. To a stirred solution of the amine in CH_2Cl_2 (7.5 mL) at 0 °C were added 2-(4-fluorobenzyloxy)acetic acid **140** (158 mg, 0.86 mmol), Et_3N (0.24 mL, 1.72 mmol) and BOP (380 mg, 0.86 mmol). The mixture was stirred at room temperature overnight and evaporated to dryness. The residue was purified by silica

gel column chromatography with a gradient of EtOAc (50% to 70%) in hexane to afford **704** (243 mg, 68%).

[0456] (MEOD-d_4) δ (ppm) ^{1}H: 7.39-7.36 (m, 6H), 7.28-7.24 (m, 4H), 7.17 (t, J= 7.6 Hz, 2H), 7.05 (t, J= 8.4 Hz, 2H), 4.53 (s, 2H), 4.41 (s, 1H), 3.90 (s, 2H), 3.36 (t, J= 7.6 Hz, 2H), 3.19 (t, J= 7.2 Hz, 2H), 2.76 (t, J= 7.6 Hz, 2H), 2.44 (qt, J= 7.2 Hz, 1H), 1.53 (qt, J= 8.0 Hz, 2H), 1.47 (qt, J= 7.6 Hz, 2H), 1.25-1.19 (m, 2H). LRMS (ESI): (calc) 460.6; (found) 461.3 $(MH)^+$.

Example 501

N-(4-(1-(3,4-dimethoxyphenylsulfonyl)azetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide **(705)**

[0457] To a stirred solution of N-(4-(1-benzhydrylazetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide **704** (60 mg, 0.13 mmol) in $ClCH_2CH_2Cl$ (0.9 mL) at 0 °C was added 1-chloroethyl chloroformate (0.03 mL, 0.30 mmol). The solution was warmed to room temperature and was then stirred overnight at 65 °C. The solution was evaporated to dryness. The residue was dissolved in MeOH (1.3 mL) and heated at 70 °C for 6h. The solution was evaporated to dryness to yield the crude amine. To a stirred solution of the amine in CH_2Cl_2 (0.9 mL) were added sequentially pyridine (0.02 mL, 0.20 mmol) and 3,4-dimethoxybenzene-1-sulfonyl chloride (40 mg, 0.17 mmol). The mixture was stirred at room temperature overnight and evaporated to dryness. The residue was purified by silica gel column chromatography with EtOAc (80%) in hexane to afford **705** (6.5 mg, 17%). (MEOD-d_4) δ (ppm) ^{1}H: 7.43 (dd, J= 2.0, 8.4 Hz, 1H), 7.41-7.38 (m, 2H), 7.30 (d, J= 2.0 Hz, 1H), 7.18 (d, J= 8.8 Hz, 1H), 7.08 (t, J= 8.8 Hz, 2H), 4.55 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.89 (s, 2H), 3.82 (t, J= 8.4 Hz, 2H), 3.35 (t, J= 6.0 Hz, 2H), 3.14 (t, J= 7.2 Hz, 2H), 2.38 (qt, J= 7.6 Hz, 1H), 1.39 (qt, J= 7.2 Hz, 2H), 1.34-1.28 (m, 2H), 1.15-1.09 (m, 2H). LRMS (ESI): (calc) 494.6; (found) 495.2 $(MH)^+$.

Example 502

tert-butyl 3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)azetidine-1-carboxylate **((710)**

Step 1: tert-butyl 3-hydroxyazetidine-1-carboxylate (**706**).

[0458] To a stirred solution of **700** (1.0 g, 4.18 mmol) in MeOH (10 mL) was carefully added palladium on charcoal (10% w/w) (500 mg). A balloon filled with hydrogen was attached to the flask and the suspension was stirred for 2h. The suspension was filtered and evaporated. To a stirred solution of the azetidin-3-ol in MeOH (20 mL) were added Et_3N (0.70 mL, 5.01 mmol) and Boc_2O (957 mg, 4.39 mmol). The resulting mixture was stirred at

room temperature for 12h. The solution was evaporated and purified by silica gel column chromatography with EtOAc (50%) in hexane to afford **706** (624 mg, 86%) as a clear oil.

[0459] (MEOD-d_4) δ (ppm) ^{1}H: 4.50-4.47 (m, 1H), 4.10 (t, J= 7.2 Hz, 2H), 3.70 (dd, J= 4.4, 9.2 Hz, 2H), 1.43 (s, 9H). LRMS (ESI): (calc) 173.2; (found) 212.0 $(MK)^+$.

Step 2: (E)-tert-butyl 3-(4-ethoxy-4-oxobut-2-enylidene)azetidine-1-carboxylate (**707**)

[0460] Following the same procedure as described for compound **701** but substituting **700** for carbamate **706**, to afford **707** (385 mg, 40 %).

(MEOD-d_4) δ (ppm) ^{1}H: 7.14 (dd, J= 11.6, 15.2 Hz, 1H), 6.19 (d, J= 11.6 Hz, 1H), 5.88 (d, J= 15.2 Hz, 1H), 4.69 (s, 2H), 4.57 (s, 2H), 4.18 (q, J= 6.8 Hz, 2H), 1.44 (s, 9H), 1.28 (t, J= 7.2 Hz, 3H). LRMS (ESI): (calc) 267.3; (found) 290.0 $(MNa)^+$.

Step 3: tert-butyl 3-(4-hydroxybutyl)azetidine-1-carboxylate (**708**)

[0461] (E)-tert-butyl 3-(4-ethoxy-4-oxobut-2-enylidene)azetidine-1-carboxylate **707** (563 mg, 2.11 mmol) in MeOH (10.5 mL) and palladium on charcoal (10% w/w) (25 mg) was hydrogenated under 1 atm.of hydrogen gas 3h. The suspension was filtered and evaporated and the resulting ester in THF (10.5 mL) at 0 °C was added to $LiAlH_4$ (200 mg, 5.27 mmol). After 20 min, H_2O was added and the mixture was extracted with EtOAc. The organic phase was dried (Na_2SO_4) and evaporated to yield **708** (466 mg, 96%).

[0462] ($CDCl_3$) δ (ppm) ^{1}H: 3.92 (t, J= 8.0 Hz, 2H), 3.58 (t, J= 6.4 Hz, 2H), 3.46 (t, J= 5.6 Hz, 2H), 2.45-2.38 (m, 1H), 1.88 (br, 1H), 1.57-1.46 (m, 4H), 1.36 (s, 9H), 1.29-1.17 (m, 2H). LRMS (ESI): (calc) 229.3; (found) 252.1 $(MNa)^+$.

Step 4: tert-butyl 3-(4-azidobutyl)azetidine-1-carboxylate (**709**)

[0463] To a stirred solution of tert-butyl 3-(4-hydroxybutyl)azetidine-1-carboxylate **708** (298 mg, 1.30 mmol) in CH_2Cl_2 (3.5 mL) at 0° C were added sequentially PPh_3 (375 mg, 1.43 mmol), imidazole (177 mg, 2.60 mmol) and a solution of iodine (363 mg, 1.43 mmol) in CH_2Cl_2 (8.5 mL). The yellow solution was stirred at room temperature for 3h. Saturated solutions of $NaHCO_3$ and sodium thiosulfate were added and CH_2Cl_2 extractions. The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography with EtOAc (20%) in hexane to afford tert-butyl 3-(4-iodobutyl)azetidine-1-carboxylate (286 mg, 65%). (CD_3CN) δ (ppm) ^{1}H 3.94 (t, J= 7.6 Hz, 2H), 3.47 (br, 2H), 3.27 (t, J= 7.2 Hz, 2H), 2.52-2.48 (m, 1H), 1.81 (qt, J= 7.2 Hz, 2H), 1.58 (q, J= 7.6 Hz, 2H), 1.41 (s, 9H), 1.37-1.31 (m, 2H). LRMS (ESI): (calc) 339.2; (found) 362.0 $(MNa)^+$.

[0464] To a stirred solution of tert-butyl 3-(4-iodobutyl)azetidine-1-carboxylate (286 mg, 0.84 mmol) in DMSO (4.5 mL) was added NaN_3 (110 mg, 1.69 mmol). The solution was stirred for 0.5h and H_2O was added followed by EtOAc extractions. The organic phase was

dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography with EtOAc (20%) in hexane to afford **709** (189 mg, 88%).

[0465] ($CDCl_3$) δ (ppm) ^1H: 4.00 (t, J= 8.4 Hz, 2H), 3.53 (dd, J= 5.2, 8.4 Hz, 2H), 3.28 (t, J= 6.8 Hz, 2H), 2.50-2.46 (m, 1H), 1.60 (qt, J= 7.2 Hz, 4H), 1.43 (s, 9H), 1.35-1.28 (m, 2H). LRMS (ESI): (calc) 254.3; (found) 277.2 $(MNa)^+$.

Step 5: tert-butyl 3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)azetidine-1-carboxylate (**710**)

[0466] Following the same procedure as described for compound **704, Example 500** but substituting **703** for azide **709**, to afford **710** (120 mg, 41 %). (CD_3CN) δ (ppm) ^1H: 7.42 (dd, J= 5.6, 8.4 Hz, 2H), 7.14 (t, J= 8.8 Hz, 2H), 6.86 (br, 1H), 4.55 (s, 2H), 3.92 (br, 2H), 3.91 (s, 2H), 3.47 (br, 2H), 3.19 (q, J= 6.8 Hz, 2H), 2.49 (m, 1H), 1.58 (q, J= 7.6 Hz, 2H), 1.46 (qt, J= 7.2 Hz, 2H), 1.41 (s, 9H), 1.25 (m, 1H). LRMS (ESI): (calc) 394.5; (found) 417.3 $(MNa)^+$.

Example 503a

N-(2-(1H-indol-3-yl)ethyl)-3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)azetidine-1-carboxamide **(711a)**

[0467] To a stirred solution of tert-butyl 3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)azetidine-1-carboxylate **710** (110 mg, 0.28 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (0.5 mL). After stirring for 1h at room temperature, the solution was evaporated to dryness. To a stirred solution of 1,1'-carbonyldiimidazole (45 mg, 0.28 mmol) in THF (1.0 mL) was added dropwise a solution of tryptamine (45 mg, 0.28 mmol) in THF (1.0 mL). After stirring for 30 min at room temperature, a solution of the crude amine in THF (1.0 mL) was added and the resulting mixture was stirred overnight. A solution of 10% HCl was added and EtOAc extractions. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by silica gel column chromatography with MeOH (5% to 10%) in EtOAc and by HPLC to afford **711a** (40 mg, 30%).

[0468] (MEOD-d_4) δ (ppm) ^1H: 10.20 (br, 1H), 7.90 (br, 1H), 7.56 (d, J= 8.0 Hz, 1H), 7.40 (dd, J= 5.2, 8.4 Hz, 2H), 7.31 (d, J= 8.0 Hz, 1H), 7.11-7.05 (m, 4H), 6.99 (t, J= 7.2 Hz, 1H), 6.14 (br, 1H), 4.56 (s, 2H), 3.92 (s, 2H), 3.90 (t, J= 8.0 Hz, 2H), 3.44 (t, J= 5.6 Hz, 2H), 3.38 (t, J= 7.2 Hz, 2H), 3.21 (q, J= 6.4 Hz, 2H), 2.91 (t, J= 7.2 Hz, 2H), 2.53-2.46 (m, 1H), 1.59-1.47 (m, 4H), 1.28-1.21 (m, 2H). LRMS (ESI): (calc) 480.6; (found) 481.3 $(MH)^+$.

Examples 503b

3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)-N-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)azetidine-1-carboxamide (**711b**)

[0469] Compound **711b** was prepared (36 mg, 35%) according to the method desribed for compound **711a**, Example **503a**, but replacing tryptamine with (1-methyl-1H-benzo[d]imidazol-2-yl)methanamine.

(MEOD-d_4) δ (ppm) ^{1}H: 8.16 (br, 1H), 7.91 (br, 1H), 7.62 (d, J= 7.2 Hz, 1H), 7.54 (d, J= 7.2 Hz, 1H), 7.41-7.38 (m, 2H), 7.37-7.29 (m, 2H), 7.08 (t, J= 8.4 Hz, 2H), 4.64 (s, 2H), 4.56 (s, 2H), 4.05 (t, J= 8.0 Hz, 2H), 3.92 (s, 2H), 3.87 (s, 3H), 3.58 (t, J= 5.6 Hz, 2H), 3.23 (q, J= 6.8 Hz, 2H), 2.57 (qt, J= 6.0 Hz, 1H), 1.61 (q, J= 8.0 Hz, 2H), 1.52 (qt, J= 7.2 Hz, 2H), 1.31-1.24 (m, 2H). LRMS (ESI): (calc) 481.6; (found) 482.3 $(MH)^+$.

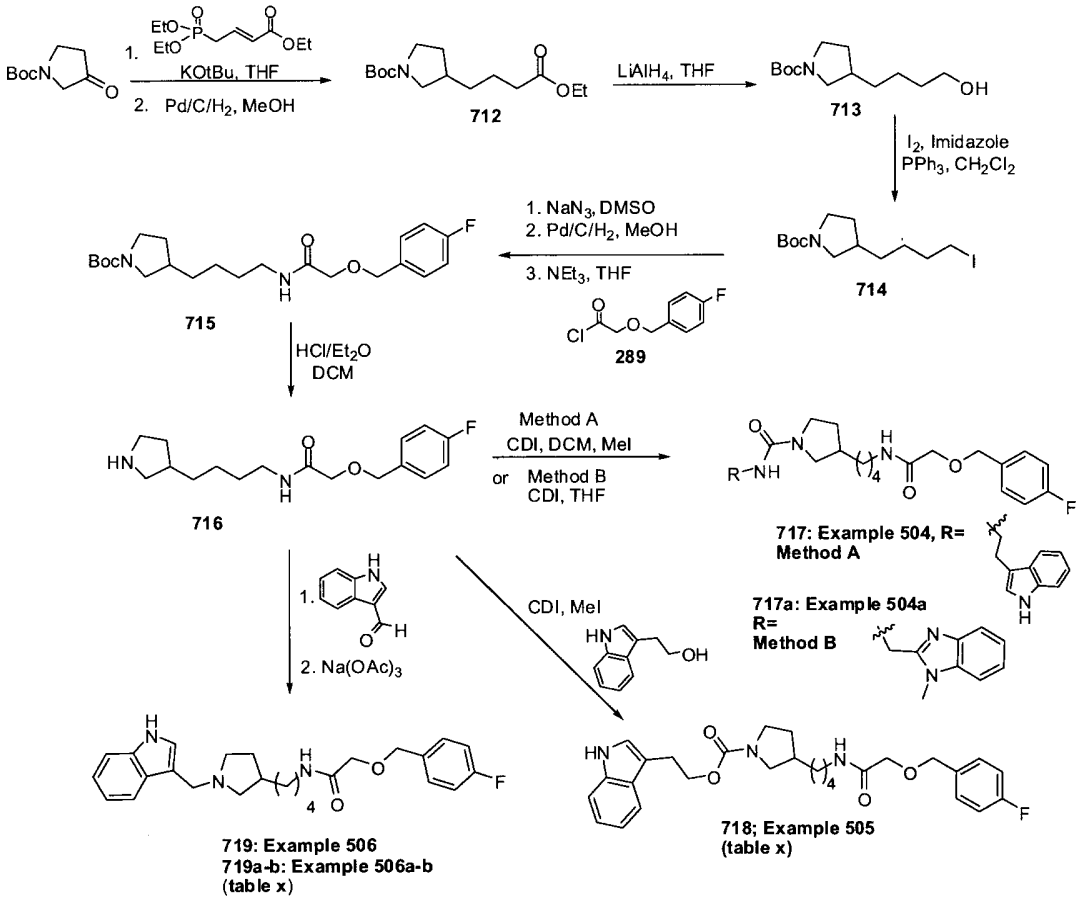
Examples 503c

N-(4-(1-(2-(1H-indol-3-yl)ethylcarbamothioyl)azetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**711c**)

[0470] Compound **711b** was prepared (26 mg, 22%) according to the method desribed for compound **711a**, Example **503a**, but replacing 1,1'-carbonyldiimidazole with 1,1'-thiocarbonyldiimidazole.

(MEOD-d_4) δ (ppm) ^{1}H: 9.18 (br, 1H), 7.67 (d, J= 7.6 Hz, 1H), 7.44-7.40 (m, 3H), 7.16-7.12 (m, 3H), 7.07 (t, J= 7.6 Hz, 1H), 6.89 (br, 1H), 6.00 (br, 1H), 4.55 (s, 2H), 4.01 (br, 2H), 3.92 (s, 2H), 3.75 (q, J= 6.4 Hz, 2H), 3.55 (br, 2H), 3.20 (q, J= 6.4 Hz, 2H), 3.00 (t, J= 7.2 Hz, 2H), 2.52-2.48 (m, 1H), 2.25 (br, 1H), 1.56 (q, J= 7.6 Hz, 2H), 1.48 (qt, J= 7.2 Hz, 2H), 1.29-1.21 (m, 2H). LRMS (ESI): (calc) 496.6; (found) 497.2 $(MH)^+$.

Scheme 301



Example 504

N-(2-(1H-indol-3-yl)ethyl)-3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)pyrrolidine-1-carboxamide (**717**)

Step 1: tert-butyl 3-(4-ethoxy-4-oxobutyl)pyrrolidine-1-carboxylate (**712**)

[0471] Triethyl 4-phosphonocrotonate (1.44g, 6.47 mmol) was added to a mixture of potassium tert-butoxide (726 mg, 6.47 mmol) in THF (10 mL) at 0 °C. After 10 min, 1-*N*-Boc-3-pyrrolidinone (1.00 g, 5.39 mmol) was added to the mixture and the reaction was warmed up slowly to room temperature, and stirred for 1.5 h. A solution of sodium carbonate was added and the aqueous mixture was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered, and evaporated. To give (E)-tert-butyl 3-((E)-4-ethoxy-4-oxobut-2-enylidene)pyrrolidine-1-carboxylate which was used without further purification. LRMS (ESI): (calc) 281.3; (found) 304.3 $(MNa)^+$.

[0472] The unsaturated ester from above (1.52 g, 5.39 mmol) and 10% Palladium on carbon (20% wt, 300 mg) in MeOH (27 mL) and EtOAc (1 mL) was hydrogenated under 1

atmosphere of H_2 for 2 h. The material was purified by silica gel column chromatography with ethyl acetate (10%) in hexane to give **712** (610 mg 40% over 2 steps).
(MEOD-d_4) δ (ppm) ^{1}H: 4.11 (q, J=7.2Hz, 2H), 3.53-3.47 (m, 1H), 3.44-3.39 (m, 1H), 3.27-3.18 (m, 1H), 3.87-3.81 (m, 1H), 2.33 (t, J=7.4Hz, 2H), 2.16-2.09 (m, 2H), 2.05-2.00 (m, 1H), 1.68-1.59 (m, 2H), 1.58-1.48 (m, 12H), 1.24 (t, J=7.2Hz, 3H).
LRMS (ESI): (calc) 285.3; (found).308.2 $(MNa)^+$
Step 2: tert-butyl 3-(4-hydroxybutyl)pyrrolidine-1-carboxylate (**713**)

[0473] A solution of ester **712** (639 mg, 2.23 mmol) in THF (3 mL) was added to a mixture of lithium aluminumhydride (254 mg, 6.71 mmol) in THF (3 mL) at room temperature. The reaction stirred for 30 min. The reaction was cooled to 0° C and slowly quenched with H_2O until the grey mixture turned white. The reaction was diluted with 10% HCl in water. The aqueous mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. Product **713** was used without further purification (522 mg, 96%).
(MEOD-d_4) δ (ppm) ^{1}H: 3.55 (t, J=6.4Hz, 2H), 3.52-3.47 (m, 1H), 3.44-3.39 (m, 1H), 3.29-3.18 (m, 1H), 2.86-2.81 (m, 1H), 2.14-2.13 (m, 1H), 2.04-1.98 (m, 2H), 1.60-1.48 (m, 3H), 1.45 (s, 9H), 1.40-1.35 (m, 4H).
LRMS (ESI): (calc) 243.3; (found) 266.2 $(MNa)^+$.
Step 3: tert-butyl 3-(4-iodobutyl)pyrrolidine-1-carboxylate (**714**)

[0474] Imidazole (160 mg, 2.36 mmol), iodine (598 mg, 2.36 mmol) and **713** (522 mg, 2.15 mmol) were added in the mentioned order to a solution of triphenylphosphine (618 mg, 2.36 mmol) in DCM (10 mL). The bright orange mixture stirred for 16 h. The formed solid was filtered off and the filtrate was evaporated. The residue was purified by silica gel column chromatography with EtOAc (20%) in Hexane to give **714** (574 mg 69%).
(MEOD-d_4) δ (ppm) ^{1}H: 3.52-3.48 (m, 1H), 3.44-3.40 (m, 1H), 3.26-3.18 (m, 3H), 3.87-3.81 (m, 1H), 2.16-2.10 (m, 1H), 2.05-2.01 (m, 1H), 1.85-1.78 (m, 2H), 1.60-1.45 (m, 14H).
LRMS (ESI): (calc) 353.2; (found).376.2 $(MNa)^+$
Step 4: tert-butyl 3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)pyrrolidine-1-carboxylate (**715**)

[0475] A solution of sodium azide (211 mg, 3.24 mmol) and **714** (574 mg, 1.62 mmol) in DMSO (8 mL) stirred at room temperature for 6 h. The reaction was diluted with H_2O. The aqueous mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated to give the crude azide, tert-butyl 3-(4-azidobutyl)pyrrolidine-1-carboxylate. LRMS (ESI): (calc) 268.3; (found) 291.2 $(MNa)^+$.

[0476] The crude azide (435 g, 1.62 mmol) in methanol (8 mL) and 10% Palladium on carbon (20% wt, 87 mg) in ethyl acetate (1 mL) was hydrogenated under 1 atmosphere of H_2 for 16 h, to give the crude amine, tert-butyl 3-(4-aminobutyl)pyrrolidine-1-carboxylate. LRMS (ESI): (calc) 242.3; (found) 243.3 $(MH)^+$.

[0477] A solution of acid chloride **289** (1.67 mmol) in THF (5 mL) was added to the crude amine from above (445 mg, 1.84 mmol) and triethylamine (0.436 mL, 3.35 mmol) in THF (5 mL). The reaction was stirred at room temperature for 3 h, then was diluted with 10% HCl in water and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated and the residue was purified by silica gel column chromatography with ethyl acetate (30%-60%) in Hexanes to give **715** (196 mg 28% over 3 steps).

[0478] ($CDCl_3$) δ (ppm) ^{1}H: 7.32-7.30 (m, 2H), 7.08-7.04 (m, 2H), 6.53 (bs, 1H), 4.53 (s, 2H), 3.96 (s, 2H), 3.56-3.37 (m, 2H), 3.29-3.20 (m, 3H), 2.88-2.77 (m, 1H), 2.07-2.00 (m, 1H), 1.99-1.91 (m, 1H), 1.56-1.48 (m, 3H), 1.45 (s, 9H), 1.43-1.29 (m, 4H).

LRMS (ESI): (calc) 408.5; (found) 431.2 (MNa)+.

Step 5: 2-(4-fluorobenzyloxy)-N-(4-(pyrrolidin-3-yl)butyl)acetamide (**716**)

[0479] A solution of dry HCl (4M, 1.19 mL, 4.79 mmol) in dioxane was added to **715** (196 mg, 0.479 mmol) in minimum amount of DCM (1 mL). The reaction stirred at room temperature for 2 h. The solvent was evaporated and the residue was triturated with ether to give the HCl salt of amine **716** (160 mg, 97%).

(MEOD-d_4) δ (ppm) ^{1}H: 7.43-7.39 (m, 2H), 7.11-7.06 (m, 2H), 4.57 (s, 2H), 3.94 (s, 2H), 3.86-3.33 (m, 2H), 3.26-3.17 (m, 3H), 2.81-2.76 (m, 1H), 2.31-2.13 (m, 2H), 1.64-1.44 (m, 7H).

LRMS (ESI): (calc) 308.3; (found) 309.2 $(MNa)^+$.

Step 6: N-(2-(1H-indol-3-yl)ethyl)-3-(4-(2-(4-fluorobenzyloxy)acetamido)-butyl)pyrrolidine-1-carboxamide (**717**)

[0480] Method A: Tryptamine (104 mg, 0.648 mmol) and CDI (420 mg, 2.59 mmol) in DCM (2 mL) were stirred at room temperature for 2 h. The reaction was diluted with H_2O, and the aqueous mixture was extracted with EtOAc and the organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in acetonitrile (0.5 mL) and a solution of methyliodide (0.045 mL, 0.486 mmol) was added and the reaction was stirred for 2 h, concentrated and a solution of amine **716** (100 mg, 0.324 mmol) in acetonitrile (0.5 mL) was added. The reaction was stirred for 16h, and then it was diluted with 10% NaOH in water and the aqueous mixture was extracted with ethyl acetate and the organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with methanol (1%-2%) in DCM to give **717** (65 mg, 40%).

[0481] (MEOD-d_4) δ (ppm) ^{1}H: 7.55 (d, J=8Hz, 1H), 7.42-7.38 (m, 2H), 7.31 (d, J=8Hz, 1H), 7.10-7.05 (m, 4H), 6.99-6.95 (m, 1H), 4.56 (s, 2H), 3.93 (s, 2H), 3.44-3.34 (m, 4H), 3.24-3.17 (m, 3H), 2.95-2.91(m, 2H), 2.80-2.76 (m, 1H), 2.14-2.10 (m, 1H), 2.03-1.99 (m, 1H), 1.55-1.44 (m, 3H), 1.40-1.30 (m, 4H).

LRMS (ESI): (calc) 494.6; (found) 495.3 $(MH)^+$.

Example 504a

3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)-N-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)pyrrolidine-1-carboxamide (**717a**)

[0482] Method B: A solution of (1-methyl-1H-benzo[d]imidazol-2-yl)methanamine (39 mg, 0.243 mmol) in THF (0.5 mL) was added to CDI (39 mg, 0.243 mmol) in THF (1 mL). The reaction was stirred for 30 min then a solution of **716** (75 mg, 0.243 mmol) in DMF (0.5 mL) was added and the mixture was stirred for 16 h. The reaction was diluted with H_2O and the aqueous layer was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with methanol (1%-3%) in dichloromethane to give **717a** (45 mg, 37%).

[0483] (MEOD-d_4) δ (ppm) ^{1}H: 7.59 (d, J=7.6Hz, 1H), 7.47 (d, J=8.0Hz, 1H), 7.41-7.38 (m, 2H), 7.29-7.21 (m, 2H), 7.10-7.05 (m, 2H), 4.63 (s, 2H), 4.55 (s, 2H), 3.92 (s, 2H), 3.84 (s, 3H), 3.61-3.52 (m, 1H), 3.51-3.45 (m, 1H), 3.34-3.29 (m, 1H), 3.23 (t, J=7.0Hz, 2H), 2.92 (t, J=9.2Hz, 1H), 2.19-2.06 (m, 2H), 1.55-1.47 (m, 3H), 1.45-1.33 (m, 4H).
LRMS (ESI): (calc) 495.5; (found) 496.3 $(MH)^+$.

Example 505

2-(1H-indol-3-yl)ethyl 3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)pyrrolidine-1-carboxylate (**718**)

Compound **718**, Example **505,** was prepared using method A of Example **504** replacing tryptamine with 2-(1H-indol-3-yl)ethanol.

[0484] (MEOD-d_4) δ (ppm) ^{1}H: 7.53 (d, J=8.4Hz, 1H), 7.39-7.36 (m, 2H), 7.31 (d, J=8.0Hz, 1H), 7.08-7.03 (m, 4H), 6.98-6.96 (m, 1H), 4.56 (s, 2H), 4.27 (t, J=6.8Hz, 2H), 3.91 (s, 2H), 3.51-3.29 (m, 2H), 3.24-3.13 (m, 3H), 3.05 (t, J=6.8Hz, 2H), 2.85-2.70 (m, 1H), 2.05-1.90 (m, 2H), 1.52-1.22 (m, 7H).
LRMS: (calc) 495.6; (found) 496.3 $(MH)^+$.

Example 506

N-(4-(1-((1H-indol-3-yl)methyl)pyrrolidin-3-yl)butyl)-2-(4-fluorobenzyloxy)-acetamide (**719**)

[0485] A solution of 1H-indole-3-carbaldehyde (38 mg, 0.243 mmol) and **716** (75 mg, 0.243 mmol) in THF (2 ml) was stirred at room temperature for 1 h. Sodium triacetoxyborohydride (51 mg, 0.243 mmol) was added and the mixture stirred for 16 h. The reaction was diluted with 10% NaOH in water. The aqueous mixture was extracted with ethyl

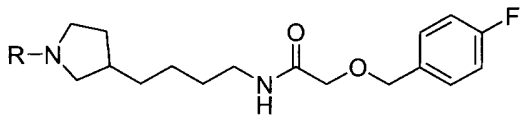
acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by prep-hplc with gradient of methanol (20%-95%) in water to give **719** (50 mg, 47%).

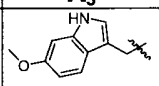
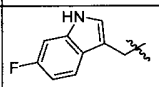
(MEOD-d_4) δ (ppm) ^{1}H: 8.50 (s, 1H), 7.71 (d, J=8.0Hz, 1H), 7.51 (s, 1H), 7.43 (d, J=8.0Hz, 1H), 7.39-7.35 (m, 2H), 7.20-7.11 (m, 2H), 7.08-7.04 (m, 2H), 4.53 (s, 2H), 4.50 (s, 2H), 3.90 (s, 2H), 3.51-3.46 (m, 1H), 3.36-3.31 (m, 2H), 3.19 (t, J=7.0Hz, 2H), 2.93-2.88 (m, 1H), 2.34-2.26 (m, 1H), 2.19-2.11 (m, 1H), 1.66-1.57 (m, 1H), 1.51-1.38 (m, 4H), 1.36-1.26 (m, 2H).

LRMS: 437.5 (calc) 438.3 (found, M+1)

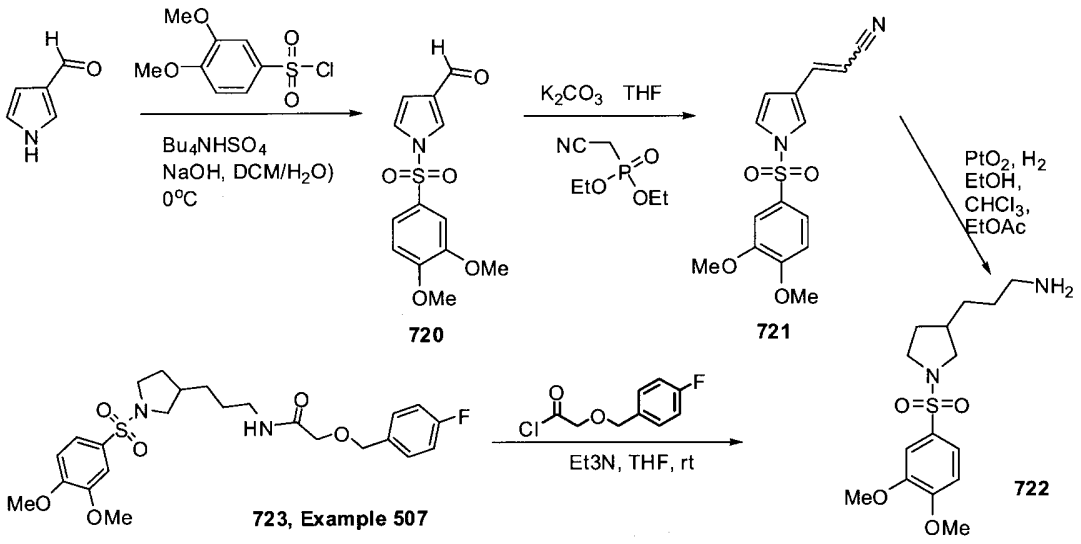
[0486] Examples **506a-b** describe the preparation of compounds **719a-b** using the same procedure as described for compound **719**, Example **506**, in scheme **301**, replacing 1H-indole-3-carbaldehyde with 6-methoxy-1H-indole-3-carbaldehyde and 6-fluoro-1H-indole-3-carbaldehyde respectively. Characterization data are presented in **Table 30.**

Table 30



Ex	Cpd	R_3	Name	Characterization	Scheme
506a	719a		2-(4-fluorobenzyloxy)-N-(4-(1-((5-methoxy-1H-indol-2-yl)methyl)pyrrolidin-3-yl)butyl)acetamide	^{1}H NMR: (MEOD-d_4) δ (ppm): 8.52 (s, 1H), 7.46 (s, 1H), 7.40-7.36 (m, 2H), 7.31 (d, J=8.8Hz, 1H), 7.22 (d, J=2.4Hz, 1H), 7.09-7.05 (m, 2H), 6.84 (dd, J=8.8, 2.4Hz, 1H), 4.54 (s, 2H), 4.50 (s, 2H), 3.90 (s, 2H), 3.84 (s, 3H), 3.53-3.49 (m, 1H), 3.38-3.34 (m, 2H), 3.20 (t, J=7.2Hz, 2H), 2.95-2.90 (m, 1H), 2.37-2.29 (m, 1H), 2.22-2.14 (m, 1H), 1.70-1.60 (m, 1H), 1.53-1.37 (m, 4H), 1.35-1.22 (m, 2H).	301 example 506
506b	719b		N-(4-(1-((5-fluoro-1H-indol-2-yl)methyl)pyrrolidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide	^{1}H NMR: (MEOD-d_4) δ (ppm): 8.49 (s, 1H), 7.58 (s, 1H), 7.47 (dd, J=10, 2.4Hz, 1H), 7.42-7.36 (m, 3H), 7.09-7.04 (m, 2H), 6.96 (td, J=6.9, 1.8Hz, 1H), 4.54 (s, 2H), 4.50 (s, 2H), 3.91 (s, 2H), 3.52-3.47 (m, 1H), 3.36-3.34 (m, 2H), 3.20 (t, J=7.0Hz, 2H), 2.96-2.88 (m, 1H), 3.39-3.32 (m, 1H), 2.20-2.15 (m, 1H), 1.67-1.62 (m, 1H), 1.53-1.39 (m, 4H), 1.35-1.23 (m, 2H).	301 example 506

Scheme 302



Example 507

N-(3-(1-(3,4-dimethoxyphenylsulfonyl)pyrrolidin-3-yl)propyl)-2-(4-fluorobenzyloxy)acetamide (**723**)

Step 1: 1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrole-3-carbaldehyde (**720**)

[0487] 3,4-dimethoxybenzene-1-sulfonyl chloride (755mg,3.2 mmol, 1.1 eq.) in DCM (3.8 ml) was added to an ice cold mixture of 50% NaOH (3 ml), Bu_4NHSO_4 (17 mg), DCM (3.4 ml) and 1H-pyrrole-3-carbaldehyde (276 mg, 2.9 mmol, prepared according to the method of Brian L. Bray et al, JOC, 1990, 55, 6317-6328; Brian L. Bray et al, JOC, 1988, 53, 6115-8). The reaction was allowed to warm-up to room temperature over 2h and was stirred at room temperature for 16h. Saturated $NaHCO_3$ was added and the organic layer was separated and the aqueous layer extracted with DCM (X2). The organic extracts were washed with sat'd $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated leaving a beige solid which was triturated from ether to give **720** (85% yield).

($CDCl_3$) δ (ppm) ^1H: 9.81 (s, 1H0, 7.76 (m, 1H), 7.58 (dxd, J= 2.3, 8.6 Hz, 1H), 7.31 (d, J= 2.3 Hz, 1H), 7.17 (m, 1H), 6.95 (d, J= 8.6 Hz, 1H), 6.7 (m, 1H), 3.94 (s, 3H), 3.93 (s, 3H).

LRMS (ESI): (calc.)295.3; (found) 295.9 $(MH)^+$

Step 2: 3-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)acrylonitrile (**721**)

[0488] A mixture of diethyl cyanomethylphosphonate (330 mg/ 302 uL,1.83 mmol, 1.2 eq.) and K_2CO_3 (211 mg, 1.53 mmol) in THF (6 ml) was stirred at room temperature for 10 min, then at 70°C for 20 min after which aldehyde **720** (450 mg, 1.52 mmol) was added and the mixture was stirred at 70°C for 16h. The material was taken to dryness and the residue

was purified by silica gel column chromatography with EtOAc (30-40%) in Hexane to afford **721** (298 mg, 61.6% yield, as a mixture of 4:1 trans: cis isomers)

LRMS (ESI): (calc.) 318.4; (found) 319.0 $(MH)^+$

Step 3: 3-(1-(3,4-dimethoxyphenylsulfonyl)pyrrolidin-3-yl)propan-1-amine (**722**)

[0489] Nitrile **721** (298 mg, 0.94 mmol), platinum oxide (36 mg) in EtOH (8 ml), $CHCl_3$ (0.6 ml), and EtOAc (1.6 ml) (to help solublise the compound) were placed under H_2 atmosphere. The material was not fully soluble. After 16h a sample checked by MS indicated the presence of the ring reduced amine **722**. The catalyst was filtered through Celite, and the filtrate was concentrated and triturated from ether, leaving **722** as white solid (119 mg, 38.5% yield, ~ 85% pure by HPLC).

LRMS (ESI): (calc.) 328.4; (found) 329.0 $(MH)^+$

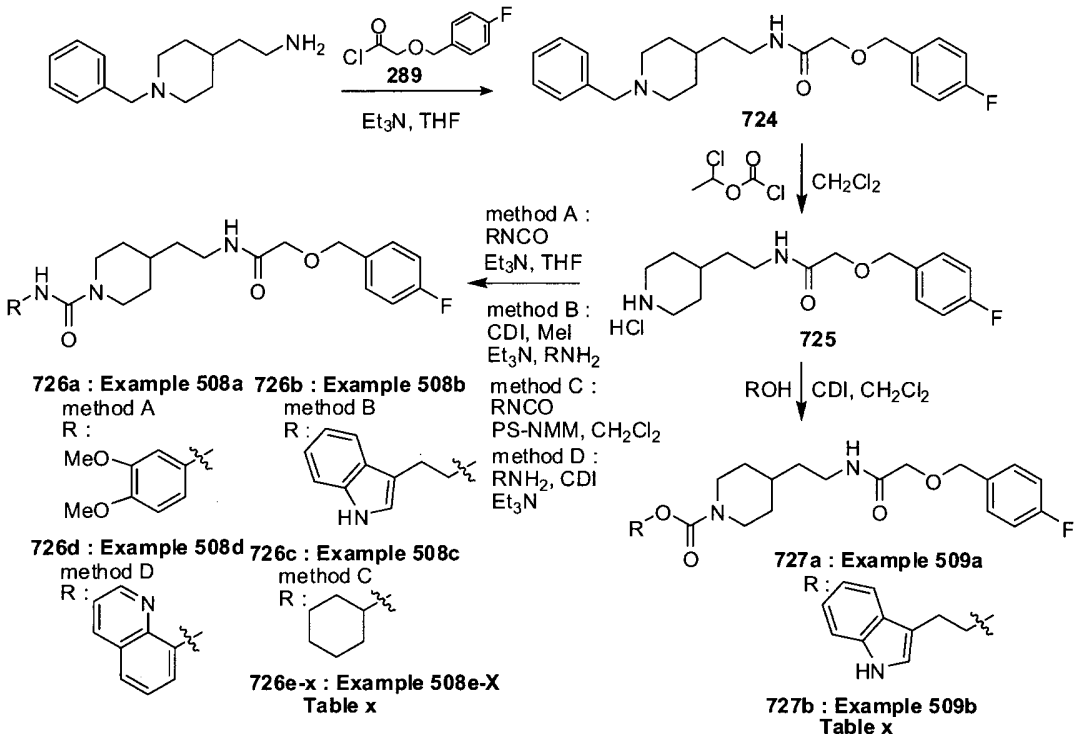
Step 4: N-(3-(1-(3,4-dimethoxyphenylsulfonyl)pyrrolidin-3-yl)propyl)-2-(4-fluorobenzyloxy)acetamide (**723**)

[0490] Amine **722** (100mg, 0.30 mmol) was added to acid chloride **289** (0.4 mmol) in THF (3 ml) followed by TEA (0.101 g/ 139.4 uL, 1 mmol). After 16h at room temperature, EtOAc and sat'd $NaHCO_3$ were added and the organic layer was separated, washed with H_2O, 0.5 N HCl, brine, dried ($MgSO_4$), filtered and concentrated leaving a white solid. Trituration from ether, then from EtOAc/hexanes gave **723** as white solid (77 mg, 52% yield).

(CD_3CN) δ (ppm) ^1H: 7.41 (m,m, 2H), 7.27 (d, J=2.2 Hz, 1H), 7.11 (m, 3H), 6.83 (bs, 1H), 4.53 (s, 2H), 3.89 (s, 5H), 3.88 (s, 3H), 3.4 (dxd, J=7.5, 9.9 Hz, 1H), 3.3 (m, 1H), 3.13 (m, 3H), 2.75 (dxd, J= 7.9, 9.9 Hz, 1H), 1.93 (m, 1H), 1.38 (m, 3H), 1.2 (m, 2H).

LRMS (ESI): (calc.) 494.6; (found) 495.0 $(MH)^+$

Scheme 303



Example 508a

4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(3,4-dimethoxyphenyl)piperidine-1-carboxamide (**726a**)

Step 1: 2-(4-fluorobenzyloxy)-N-(2-(1-benzylpiperidin-4-yl)ethyl)acetamide (**724**)

[0491] To a stirred solution of acid chloride **289** (16.5 mmol) and triethylamine (4.6 mL, 33 mmol) in THF (60 mL) at 0°C was added a solution of 4-(2-aminoethyl)-1-benzylpiperidine (4.0 mL, 18.1 mmol) in THF (6 mL) dropwise. The reaction was stirred at room temperature for 16h. The reaction mixture was quenched with a saturated solution of sodium carbonate in water. The aqueous mixture was extracted with ethyl acetate. The organic extract was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of methanol (0-10%) in dichloromethane to give **724** (4.87 g, 70%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.75 (t, J=5.9Hz, 1H), 7.40 (dd, J=8.4and5.7Hz, 2H), 7.30-7.09 (m, 7H), 4.48 (s, 2H), 3.84 (s, 2H), 3.39 (s, 2H), 3.10 (q, J=7.2Hz, 2H), 2.73 (bd, J=12Hz, 2H), 1.83 (bt, J=9.8Hz, 2H), 1.59 (bd, J=12Hz, 2H), 1.33 (q, J=7.4Hz, 2H), 1.28-1.13 (m, 1H), 1.08 (qd, J=12and3.5Hz, 2H). LRMS (ESI): (calc) 384.2; (found) 385.2 $(MH)^+$.

Step 2: 2-(4-fluorobenzyloxy)-N-(2-(piperidin-4-yl)ethyl)acetamide hydrochloride (**725**)

[0492] To a stirred solution of **724** (4.87 g, 12.7 mmol) in dichloromethane (64 mL) was added 1-chloroethyl chloroformate (2.74 mL, 25.4 mmol). The reaction was stirred at room temperature for 1.5h. All the solvent was evaporated then the residue was stirred in methanol (40 mL) at 50°C for 45 min. The solvent was evaporated then the residue was purified by silica gel column chromatography with gradient of methanol (0-20%) in dichloromethane to give **725** (3.10 g, 74%).

[0493] (DMSO-d_6) δ (ppm) ^{1}H: 8.97-8.87 (m, 1H), 8.76-8.63 (m, 1H), 7.84 (t, J=5.9Hz, 1H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.18 (t, J=8.8Hz, 2H), 4.50 (s, 2H), 3.86 (s, 2H), 3.19 (bd, J=13Hz, 2H), 3.12 (q, J=6.8Hz, 2H), 2.76 (bq, J=11Hz, 2H), 1.79 (bd, J=13Hz, 2H), 1.58-1.42 (m, 1H), 1.36 (q, J=7.0Hz, 2H), 1.30-1.25 (m, 2H). LRMS (ESI): (calc) 330.2; (found) 295.2 $(M-Cl)^+$.

Step 3: 4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(3,4-dimethoxyphenyl)piperidine-1-carboxamide (**726a**)

Method A:

[0494] To a stirred solution of **725** (40 mg, 0.12 mmol) in THF (1 mL) was added triethylamine (0.10 mL, 0.69 mmol), then 3,4-dimethoxyphenylisocyanate (18 uL, 0.12 mmol). The reaction was stirred at room temperature for 16h. More 3,4-dimethoxyphenylisocyanate (18 uL, 0.12 mmol) was added. The reaction was stirred at room temperature for 1h. The reaction mixture was quenched with water. The aqueous mixture was extracted with dichloromethane. The organic extract was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by prep-hplc with gradient of methanol (20-100% in water to give **726a** (27 mg, 49%).

(DMSO-d_6) δ (ppm) ^{1}H: 8.24 (s, 1H), 7.81 (t, J=5.9Hz, 1H), 7.42 (d, J=5.7Hz, 1H), 7.40 (d, J=5.7Hz, 1H), 7.17 (t, J=9.0Hz, 2H), 7.13 (d, J=2.3Hz, 1H), 6.94 (dd, J=8.8and2.5Hz, 1H), 6.78 (d, J=8.8Hz, 1H), 4.49 (s, 2H), 4.05 (bd, J=13Hz, 2H), 3.85 (s, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.13 (q, J=6.7Hz, 2H), 2.67 (bt, J=12Hz, 2H), 1.66 (bd, J=11Hz, 2H), 1.40-1.33 (m, 3H), 1.04-0.96 (m, 2H). LRMS (ESI): (calc) 473.2; (found) 474.1 $(MH)^+$.

Example 508b

N-(2-(1H-indol-3-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide (**726b**)

Method B:

[0495] To a stirred solution of **725** (53 mg, 0.18 mmol) in THF (3.6 mL) was added 1,1'-carbonyldiimidazole (117 mg, 0.72 mmol). The mixture was stirred for 4h at 60°C. The solvent was evaporated, and the residue diluted with dichloromethane and washed with

brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated. Acetonitrile (1.0 mL) and iodomethane (0.25 mL) were added to the residue. The reaction was stirred at room temperature for 16h. The solvent was evaporated and the residue was put in dichloromethane (1.0 mL), then tryptamine (87 mg, 0.54 mmol) was added, followed by triethylamine (0.25 mL). The reaction was stirred for 16h at room temperature. The solvent was evaporated and the residue was purified by prep-hplc with gradient of methanol (20-100%) in water to give **726b** (32 mg, 37%).

(DMSO-d_6) δ (ppm) ^{1}H: 10.76 (s, 1H), 7.78 (t, J=5.9Hz, 1H), 7.52 (d, J=7.8Hz, 1H), 7.41 (dd, J=8.8and5.7Hz, 2H), 7.30 (d, J=8.0Hz, 1H), 7.17 (t, J=9.0Hz, 2H), 7.09 (d, J=2.3Hz, 1H), 7.03 (td, J=7.0and1.2Hz, 1H), 6.94 (t, J=6.8Hz, 1H), 6.52 (t, J=5.3Hz, 1H), 4.49 (s, 2H), 3.91 (bd, J=13Hz, 2H), 3.85 (s, 2H), 3.27-3.22 (m, 2H), 3.12 (q, J=6.3Hz, 2H), 2.78 (t, J=8.4Hz, 2H), 2.56 (t, J=12Hz, 2H), 1.59 (bd, J=12Hz, 2H), 1.35-1.30 (m, 3H), 0.96-0.88 (m, 2H). LRMS (ESI): (calc) 480.3; (found) 481.2 $(MH)^+$.

Example 508c

N-cyclohexyl-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide (**726c**)

Method C:

[0496] To a stirred solution of PS-NMM (300 mg, 0.68 mmol) in dichloromethane (1.0 mL) was added **725** (83 mg, 0.25 mmol) in dichloromethane (1.5 mL), followed by cyclohexyl isocyanate (29 uL, 0.23 mmol). The reaction was stirred at room temperature for 16h. PS-NMM was filtered, solvent evaporated and the residue was purified by prep-hplc with gradient of methanol (20-100%) in water to give **726c** (54 mg, 56%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.78 (t, J=5.9Hz, 1H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.18 (t, J=8.8Hz, 2H), 6.03 (d, J=7.6Hz, 1H), 4.49 (s, 2H), 3.91 (bd, J=13Hz, 2H), 3.85 (s, 2H), 3.40-3.33 (m, 1H), 3.12 (q, J=6.3Hz, 2H), 2.55-2.50 (m, 2H), 1.71-1.64 (m, 4H), 1.60-1.53 (m, 3H), 1.40-1.28 (m, 3H), 1.28-1.00 (m, 5H), 1.00-0.88 (m, 2H). LRMS (ESI): (calc) 419.3; (found) 420.3 $(MH)^+$.

Example 508d

4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(quinolin-8-yl)piperidine-1-carboxamide (**726d**)

Method D:

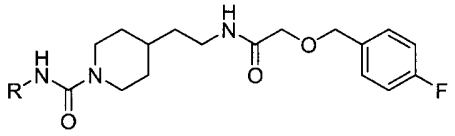
[0497] To a stirred solution of 8-aminoquinoline (36 mg, 0.25 mmol) in THF (1.0 mL) was added 1,1'-carbonyldiimidazole (40 mg, 0.25 mmol). The mixture was stirred for 1h at 60°C. To that intermediate was added **725** (90 mg, 0.30 mmol), triethylamine (0.09 mL, 0.63 mmol)

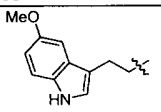
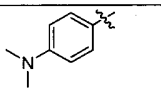
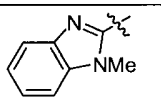
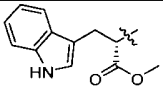
and DCM (0.5 mL). The reaction was stirred at room temperature for 16h. The solvent was evaporated and the residue was purified by prep-hplc with gradient of methanol (20-100%) in water to give **726d** (50 mg, 43%).

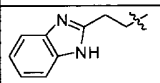
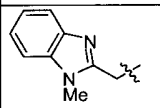
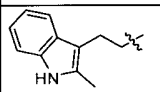
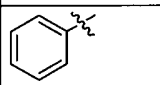
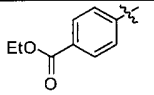
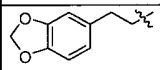
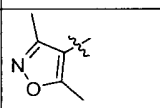
(DMSO-d_6) δ (ppm) ^{1}H: 9.32 (s, 1H), 8.88 (dd, J=4.3and1.6Hz, 1H), 8.41-8.34 (m, 2H), 7.82 (t, J=5.9Hz, 1H), 7.61 (dd, J=8.2and4.3Hz, 1H), 7.52 (d, J=4.5Hz, 2H), 7.43 (dd, J=8.4and5.7Hz, 2H), 7.18 (t, J=8.8Hz, 2H), 4.51 (s, 2H), 4.09 (bd, J=13Hz, 2H), 3.87 (s, 2H), 3.17 (q, J=6.7Hz, 2H), 1.78 (bd, J=11Hz, 2H), 1.58-1.45 (m, 1H), 1.40 (q, J=7.0Hz, 2H), 1.11 (qd, J=12and3.5Hz, 2H). LRMS (ESI): (calc) 464.2; (found)465.3 $(MH)^+$.

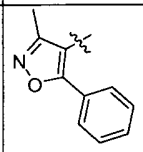
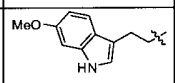
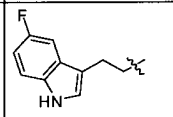
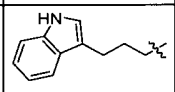
[0498] **Example 508e-p** describe the preparation of compound **726e-p** using the same procedures as described in **scheme 303**, utilizing method A, B, C or D. Characterization data are presented in **Table 31.**

Table 31



Ex	Cpd	R	Name	Characterization	Scheme
508e	726e		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.60 (s, 1H), 7.79 (t, J=5.9Hz, 1H), 7.43 (d, J=6.1Hz, 1H), 7.41 (d, J=5.7Hz, 1H), 7.20 (d, J=8.6Hz, 1H), 7.18 (t, J=9.2Hz, 2H), 7.04 (dd, J=18and 2.3Hz, 2H), 6.69 (dd, J=8.6and2.3Hz, 1H), 6.51 (t, J=5.3Hz, 1H), 4.50 (s, 2H), 3.92 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.74 (s, 3H), 3.25 (q, J=8.2Hz, 2H), 3.13 (q, J=6.3Hz, 2H), 2.75 (t, J=7.8Hz, 2H), 2.56 (t, J=12Hz, 2H), 1.60 (d, J=12Hz, 2H), 1.41-1.30 (m, 3H), 0.93 (q, J=7.6Hz, 2H). LRMS (ESI): 510.3 (calc) 511.3 (MH)+ (found).	303 Method B 508b
508f	726f		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(4-(dimethylamino)phenyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 8.10 (s, 1H), 7.80 (t, J=5.7Hz, 1H), 7.44-7.40 (m, 2H), 7.23-7.16 (m, 4H), 6.63 (d, J=9.2Hz, 2H), 4.50 (s, 2H), 4.06 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.15 (q, J=6.7Hz, 2H), 2.80 (s, 6H), 2.66 (t, J=12Hz, 2H), 1.66 (d, J=12Hz, 2H), 1.48-1.33 (m, 3H), 1.05-0.96 (m, 2H). LRMS (ESI): 456.2 (calc) 457.2 (MH)+ (found)	303 Method A 508a
508g	726g		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(1-methyl-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 11.91 (s, 1H), 7.80 (t, J=6.1Hz, 1H), 7.42 (dd, 8.4and5.7Hz, 2H), 7.32 (d, J=6.7Hz, 1H), 7.25 (d, J=7.4Hz, 1H), 7.18 (t, J=8.8Hz, 2H), 7.11-7.03 (m, 2H), 4.75-4.60 (m, 1H), 4.50 (s, 2H), 4.42-4.25 (s, 1H), 3.86 (s, 2H), 3.45 (s, 3H), 3.15 (q, J=7.2Hz, 2H), 2.82-2.54 (m, 2H), 1.66 (bd, J=11Hz, 2H), 1.50-1.40 (m, 1H), 1.37 (q, J=6.8Hz, 2H), 1.03-0.95 (m, 2H). LRMS (ESI): 467.2 (calc) 468.3 (MH)+ (found)	303 Method D 508d
508h	726h		(S)-methyl 2-(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamido)-3-(1H-indol-3-	(DMSO-d_6) δ (ppm) ^{1}H: 10.82 (s, 1H), 7.78 (t, J=5.9Hz, 1H), 7.49 (d, J=7.8Hz, 1H), 7.41 (dd, J=8.4and5.7Hz, 2H), 7.32 (d, J=7.8Hz, 1H), 7.18 (t, J=9.0Hz, 2H), 7.14 (d, J=2.3Hz, 1H), 7.05 (t, J=6.8Hz, 1H), 6.96 (t, J=7.0Hz, 1H), 6.63 (d, J=7.6Hz, 1H), 4.50 (s, 2H), 4.28 (q, J=8.6Hz, 1H), 3.91-3.85 (m, 2H), 3.86 (s, 2H),	303 Method D 508d

			yl)propanoate	3.56 (s, 3H), 3.14-3.02 (m, 4H), 2.66-2.50 (m, 2H), 1.57 (bd, 14Hz, 2H), 1.41-1.29 (m, 3H), 0.98-0.80 (m, 2H). LRMS (ESI): 538.2 (calc) 539.3 (MH)+ (found)	
508i	726i		N-(2-(1H-benzo[d]imidazol-2-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 8.18 (s, 1H), 7.78 (t, J=5.1Hz, 1H), 7.55-7.32 (m, 4H), 7.18 (t, J=9.0Hz, 2H), 7.09 (dd, J=6.1and2.9Hz, 2H), 6.65 (t, J=5.7Hz, 1H), 4.50 (s, 2H), 3.89 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.44 (q, J=6.3Hz, 2H), 3.12 (q, J=6.7Hz, 2H), 2.93 (t, J=7.4Hz, 2H), 2.57 (bt, J=13Hz, 2H), 1.59 (bd, J=12Hz, 2H), 1.42-1.29 (m, 3H), 1.00-0.87 (m, 2H). LRMS (ESI): 481.2 (calc) 482.3 (MH)+ (found)	303 Method B 508b
508j	726j		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 8.14 (s, 1H), 7.79 (t, J=5.9Hz, 1H), 7.55 (d, J=7.8Hz, 1H), 7.49 (d, J=7.4Hz, 1H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.23-7.13 (m, 4H), 7.05 (t, J=5.3Hz, 1H), 4.50-4.46 (m, 4H), 3.96 (bd, J=13Hz, 2H), 3.85 (s, 2H), 3.76 (s, 3H), 3.12 (q, J=6.7Hz, 2H), 2.61 (bt, J=12Hz, 2H), 1.61 (bd, J=12Hz, 2H), 1.45-1.32 (m, 3H), 0.96 (bq, J=13Hz, 2H). LRMS (ESI): 481.2 (calc) 482.3 (MH)+ (found)	303 Method B 508b
508k	726k		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-(2-methyl-1H-indol-3-yl)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.66 (s, 1H), 7.79 (t, J=5.7Hz, 1H), 7.44-7.40 (m, 3H), 7.18 (t, J=8.6Hz, 3H), 6.94 (t, J=6.8Hz, 1H), 6.89 (t, J=7.4Hz, 1H), 6.50 (t, J=5.3Hz, 1H), 4.50 (s, 2H), 3.91 (db, J=13Hz, 2H), 3.86 (s, 2H), 3.20-3.10 (m, 4H), 2.72 (t, J=8.2Hz, 2H), 2.55 (bt, J=12Hz, 2H), 2.29 (s, 3H), 1.60 (bd, J=13Hz, 2H), 1.42-1.32 (m, 3H), 1.00-0.88 (m, 2H). LRMS (ESI): 494.3 (calc) 495.3 (MH)+ (found)	303 Method B 508b
508l	726l		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-phenylpiperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 8.41 (s, 1H), 7.81 (t, J=5.7Hz, 1H), 7.44-7.40 (m, 4H), 7.22-7.15 (m, 4H), 6.90 (t, J=7.2Hz, 1H), 4.50 (s, 2H), 4.09 (bd, J=13Hz, 2H), 3.87 (s, 2H), 3.15 (q, J=6.5Hz, 2H), 2.71 (bt, J=11Hz, 2H), 1.68 (bd, J=11Hz, 2H), 1.50-1.34 (m, 3H), 1.02 (qd, J=12and2.5Hz, 2H). LRMS (ESI): 413.2 (calc) 414.3 (MH)+ (found)	303 Method C 508c
508m	726m		ethyl 4-(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamido)benzoate	(DMSO-d_6) δ (ppm) ^{1}H: 8.83 (s, 1H), 7.81 (d, J=8.6Hz, 2H), 7.59 (d, J=8.8Hz, 2H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.18 (t, J=9.0Hz, 2H), 4.50 (s, 2H), 4.25 (q, J=7.0Hz, 2H), 4.10 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.15 (q, J=7.0Hz, 2H), 2.74 (t, J=12Hz, 2H), 1.69 (bd, J=11Hz, 2H), 1.50-1.42 (m, 1H), 1.37 (q, J=7.0Hz, 2H), 1.29 (t, J=7.0Hz, 3H), 1.03 (qd, J=13and3.5Hz, 2H). LRMS (ESI): 485.2 (calc) 486.3 (MH)+ (found)	303 Method C 508c
508n	726n		N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 7.78 (t, J=5.7Hz, 1H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.18 (t, J=8.8Hz, 2H), 6.79 (d, J=7.8Hz, 1H), 6.73 (d, J=1.6Hz, 1H), 6.61 (dd, J=8.0and1.6Hz, 1H), 6.44 (t, J=5.5Hz, 1H), 5.94 (s, 2H), 4.50 (s, 2H), 3.89 (bd, J=15Hz, 2H), 3.86 (s, 2H), 3.19-3.09 (m, 4H), 2.60 (t, J=8.0Hz, 2H), 2.55-2.50 (m, 2H), 1.58 (bd, J=13Hz, 2H), 1.42-1.30 (m, 3H), 0.89 (bq, J=8.2Hz, 2H) LRMS (ESI): 485.2 (calc) 486.3 (MH)+ (found)	303 Method C 508c
508o	726o		N-(3,5-dimethylisoxazol-4-yl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H: 7.82-7.78 (m, 2H), 7.42 (dd, J=8.6and5.7Hz, 2H), 7.18 (t, J=8.8Hz, 2H), 4.50 (s, 2H), 4.00 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.14 (q, J=6.7Hz, 2H), 2.71 (bt, J=11Hz, 2H), 2.19 (s, 3H), 2.02 (s, 3H), 1.66 (bd, J=11Hz, 2H), 1.50-1.40 (m, 1H), 1.37 (q, J=6.8Hz, 2H), 1.01 (qd, J=13and4.1Hz, 2H).	303 Method C 508c

				LRMS (ESI): 432.2 (calc) 433.3 (MH)+ (found)	
508p	726p		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(3-methyl-5-phenylisoxazol-4-yl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H:8.17 (s, 1H), 7.82 (t, J=5.9Hz, 1H), 7.77 (d, J=6.8Hz, 1H), 7.54-7.47 (m, 3H), 7.43 (dd, J=8.4and5.7Hz, 2H), 7.19 (t, J=8.8Hz, 2H), 4.51 (s, 2H), 4.05 (bd, J=13Hz, 2H), 3.87 (s, 2H), 3.16 (q, J=6.8Hz, 2H), 2.11 (s, 3H), 1.69 (bd, J=11Hz, 2H), 1.57-1.42 (m, 1H), 1.39 (q, J=7.0Hz, 2H), 1.03 (qd, J=12and2.7Hz, 2H). LRMS (ESI): 494.2 (calc) 495.3 (MH)+ (found)	303 Method C 508c
508q	726q		4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-(6-methoxy-1H-indol-3-yl)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H:10.56 (s, 1H), 7.79 (t, J=5.3Hz, 1H), 7.44-7.37 (m, 3H), 7.18 (t, J=8.8Hz, 2H), 6.95 (d, J=2.2Hz, 1H), 6.81 (d, J=2.2Hz, 1H), 6.62 (dd, J=8.4and2.3Hz, 1H), 6.51 (t, J=5.5Hz, 1H), 4.50 (s, 2H), 3.91 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.73 (s, 3H), 3.30-3.21 (m, 2H), 3.13 (q, J=6.3Hz, 2H), 2.74 (t, J=8.0Hz, 2H), 2.57 (bt, J=12Hz, 2H), 1.59 (bd, J=13Hz, 2H), 1.42-1.30 (m, 3H), 1.00-0.92 (m, 2H). LRMS (ESI): 510.3 (calc) 511.3 (MH)+ (found)	303 Method D 508d
508r	726r		N-(2-(5-fluoro-1H-indol-3-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H:10.87 (s, 1H), 7.79 (t, J=5.9Hz, 1H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.31-7.25 (m, 2H), 7.20-7.16 (m, 3H), 6.87 (td, J=9.4and2.3Hz, 1H), 6.53 (t, J=5.3Hz, 1H), 4.50 (s, 2H), 3.91 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.31-3.20 (m, 2H), 3.13 (q, J=6.1Hz, 2H), 2.75 (t, J=7.6Hz, 2H), 2.59-2.51 (m, 2H), 1.59 (bd, J=11Hz, 2H), 1.42-1.30 (m, 3H), 1.00-0.88 (m, 2H). LRMS (ESI): 498.2 (calc) 499.3 (MH)+ (found)	303 Method D 508d
508s	726s		N-(3-(1H-indol-3-yl)propyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide	(DMSO-d_6) δ (ppm) ^{1}H:10.73 (s, 1H), 7.79 (t, J=5.9Hz, 1H), 7.46 (d, J=7.6Hz, 1H), 7.41 (dd, J=8.4and5.7Hz, 2H), 7.31 (d, J=8.2Hz, 1H), 7.18 (t, J=9.0Hz, 2H), 7.11 (d, J=2.0Hz, 1H), 7.04 (t, J=8.0Hz, 1H), 6.94 (t, J=7.8Hz, 1H), 6.41 (t, J=5.3Hz, 1H), 4.49 (s, 2H), 3.90 (bd, J=13Hz, 2H), 3.85 (s, 2H), 3.12 (q, J=6.3Hz, 2H), 3.06 (q, J=6.5Hz, 2H), 2.64 (t, J=7.4Hz, 2H), 2.55 (bt, J=12Hz, 2H), 1.75 (qt, J=7.2Hz, 2H), 1.59 (bd, J=12Hz, 2H), 1.42-1.30 (m, 3H), 0.92 (bq, J=12Hz, 2H). LRMS (ESI): 494.3 (calc) 495.3 (MH)+ (found)	303 Method D 508d

Example 509a

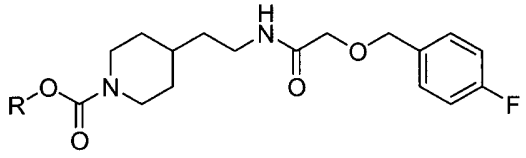
2-(1H-indol-3-yl)ethyl 4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxylate (**727a**)

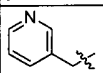
[0499] To a stirred solution of 1,1'-carbonyldiimidazole (58 mg, 0.36 mmol) in dichloromethane (1 mL) at 0°C was added a solution of tryptophol (58 mg, 0.36 mmol) in dichloromethane (1.0 mL). The mixture was stirred for 1h at room temperature. The amine **725** (106 mg, 0.36 mmol) was added, and the reaction stirred for 2h at room temperature. The solvent was evaporated and the residue was purified by silica gel column chromatography with gradient of methanol (0-10%) in dichloromethane. The collected product was re-purified by prep-hplc with gradient of methanol (20-100%) in water to give **727a** (20 mg, 23%).

(DMSO-d_6) δ(ppm) ^{1}H: 10.83 (s, 1H), 7.78 (t, J=5.7Hz, 1H), 7.51 (d, J=8.0Hz, 1H), 7.43-7.38 (m, 2H), 7.31 (d, J=8.0Hz, 1H), 7.20-7.14 (m, 3H), 7.04 (t, J=6.8Hz, 1H), 6.95 (t, J=7.0Hz, 1H), 4.49 (s, 2H), 4.17 (t, J=7.0Hz, 2H), 4.00-3.85 (m, 2H), 3.85 (s, 2H), 3.11 (q, J=6.7Hz, 2H), 2.96 (t, J=6.8Hz, 2H), 2.75-2.60 (m, 2H), 1.65-1.53 (m, 2H), 1.42-1.30 (m, 3H), 1.00-0.83 (m, 2H). LRMS (ESI): (calc) 481.2; (found) 482.1 $(MH)^+$

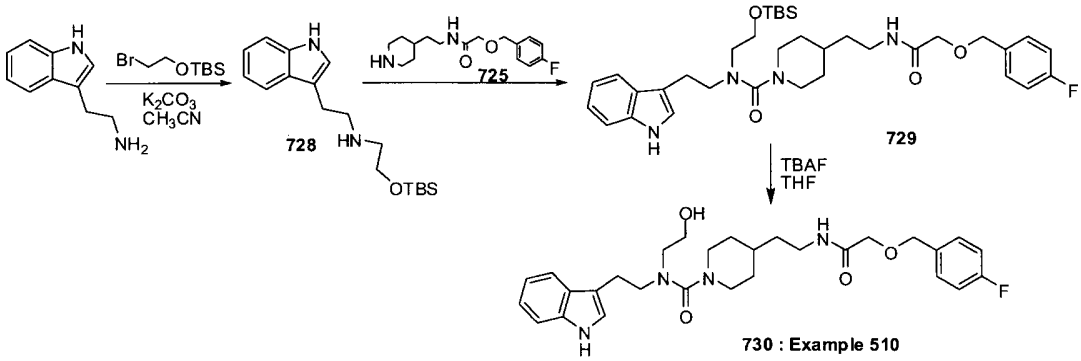
[0500] **Table 32** presents the characterization data for **example 509b** prepared according to the method described for compound **727a**, example **509a,** in scheme **303**

Table 32



Ex	Cpd	R	Name	Characterization	Scheme
509b	727b		pyridin-3-ylmethyl 4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxylate	(DMSO-d_6) δ(ppm) ^{1}H: 8.67 (s, 1H), 8.63 (d, J=3.7Hz, 1H), 7.91-7.86 (m, 2H), 7.55-7.48 (m, 3H), 7.28 (t, J=8.8Hz, 2H), 5.19 (s, 2H), 4.60 (s, 2H), 4.06 (bd, J=13Hz, 2H), 3.96 (s, 2H), 3.23 (q, J=6.7Hz, 2H), 2.95-2.73 (m, 2H), 1.76 (bd, J=13Hz, 2H), 1.59-1.48 (m, 1H), 1.45 (q, J=7.2Hz, 2H), 7.08 (qd, J=12and4.1Hz, 2H). LRMS (ESI): 429.2 (calc) 430.1 (MH)+ (found)	303 727a

Scheme 304



Example 510

N-(2-(1H-indol-2-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-hydroxyethyl)piperidine-1-carboxamide (**730**)

Step 1: N-(2-(1H-indol-3-yl)ethyl)-2-(tert-butyldimethylsilyloxy)ethanamine (**728**)

[0501] To a stirred solution of tryptamine (896 mg, 5.59 mmol) in acetonitrile (23 mL) at 0°C was added potassium carbonate (1.93 g, 13.98 mmol), followed by (2-bromoethoxy)-tert-butyldimethylsilane (1 mL, 4.66 mmol). The reaction was stirred for 2h at room temperature, and then for 16h at 60°C. The solvent was evaporated, a solution of saturated

sodium carbonate in water was added, and the residue was extracted with ethyl acetate. The organic extract was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of methanol (0-20%) in dichloromethane to give **728** (560 mg, 38%).

(DMSO-d_6) δ (ppm) ^{1}H: 10.80 (s, 1H), 7.52 (d, J=8.0Hz, 1H), 7.33 (d, J=8.2Hz, 1H), 7.12 (d, J=2.3Hz, 1H), 7.06 (t, J=7.0Hz, 1H), 6.97 (t, J=8.0Hz, 1H), 3.63 (t, J=5.7Hz, 2H), 3.19 (d, J=3.7Hz, 1H), 2.83 (s, 4H), 2.65 (t, J=5.7Hz, 2H), 0.82 (s, 9H), 0.00 (s, 6H). LRMS (ESI): (calc) 318.2; 9found) 319.2 $(MH)^+$.

Step 2: N-(2-(1H-indol-2-yl)ethyl)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide (**729**)

[0502] Compound **729** (14 mg, 9%) was prepared starting from **725** (89 mg, 0.28 mmol) and following the same procedures as described for compound **726b**, Example **508b**, scheme **303**, method B,

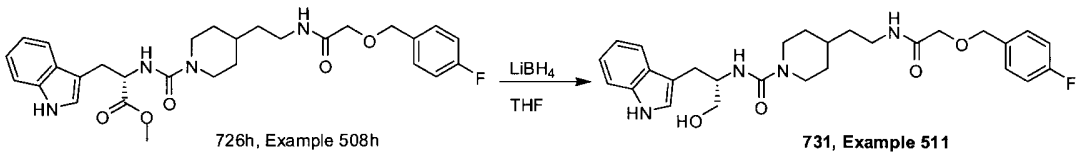
LRMS (ESI): (calc) 638.4; (found) 639.4 $(MH)^+$.

Step 3: N-(2-(1H-indol-2-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-hydroxyethyl)piperidine-1-carboxamide (**730**)

[0503] To a stirred solution of **729** (14 mg, 0.02 mmol) in THF (0.5 ml) at 0°C was added tetrabutylammonium fluoride (26 uL of 1M solution in THF, 0.03 mmol). The mixture was stirred for 16h at room temperature. The solvent was evaporated and the residue was purified by prep-hplc with gradient of methanol (10-100%) in water to give **730** (5 mg, 37%).

(MEOD-d_4) δ (ppm) ^{1}H: 7.55 (d, J=7.8Hz, 1H), 7.40 (dd, J=8.4and5.5Hz, 2H), 7.31 (d, J=8.2Hz, 1H), 7.12-7.04 (m, 3H), 7.02-6.97 (m, 2H), 4.56 (s, 2H), 3.92 (s, 2H), 3.64 (t, J=6.1Hz, 2H), 3.55 (t, J=6.8Hz, 2H), 3.42-3.35 (m, 4H), 3.21 (t, J=6.8Hz, 2H), 2.97 (t, J=6.8Hz, 2H), 2.53 (t, J=11Hz, 2H), 1.52 (d, J=12Hz, 2H), 1.40-1.27 (m, 3H), 0.86 (q, J=13Hz, 2H). LRMS (ESI): (calc) 524.3; (found).525.3 $(MH)^+$.

Scheme 305



Example 511

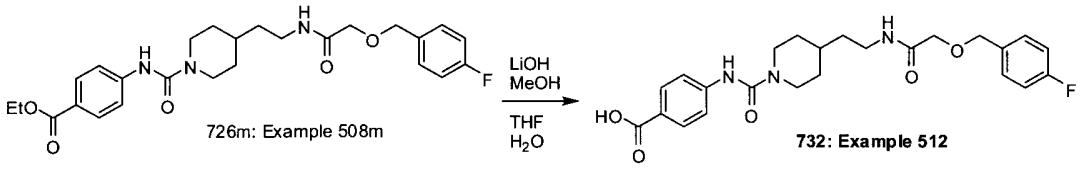
(S)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(1-hydroxy-3-(1H-indol-3-yl)propan-2-yl)piperidine-1-carboxamide (**731**)

[0504] To a stirred solution of (S)-methyl 2-(4-(2-(2-(4-fluorobenzyloxy)acetamido)-ethyl)piperidine-1-carboxamido)-3-(1H-indol-3-yl)propanoate **726h** (33 mg, 0.06 mmol) in

THF (0.5 mL) was added lithium borohydride (2 mg, 0.07 mmol). The mixture was stirred for 1h at 50°C. Lithium borohydride was filtered, and the solvent was evaporated. The residue was purified by prep-hplc with gradient of methanol (20-100%) in water to give **731** (15 mg, 48%).

(DMSO-d_6) δ (ppm) ^{1}H: 10.73 (s, 1H), 7.78 (t, J=6.1Hz, 1H), 7.60 (d, J=7.4Hz, 1H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.29 (d, J=8.0Hz, 1H), 7.18 (t, J=8.8Hz, 2H), 7.07 (d, J=2.2Hz, 1H), 7.03 (t, J=7.0Hz, 1H), 6.94 (t, J=7.8Hz, 1H), 5.98 (d, J=7.6Hz, 1H), 4.64 (t, J=5.5Hz, 1H), 4.50 (s, 2H), 3.98-3.80 (m, 5H), 3.41-3.33 (m, 1H), 3.12 (q, J=6.1Hz, 2H), 2.87 (dd, J=14and6.5Hz, 1H), 2.76 (dd, J=14and7.4Hz, 1H), 2.60-2.51 (m, 2H), 1.61-1.53 (m, 2H), 1.40-1.28 (m, 3H), 0.98-0.80 (m, 2H). LRMS (ESI): (calc) 510.2; (found) 511.3 $(MH)^+$.

Scheme 306



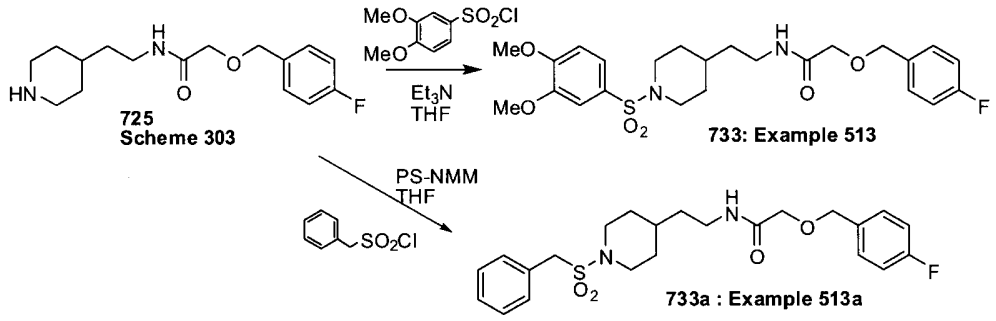
Example 512

4-(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamido)benzoic acid (**732**)

[0505] To a stirred solution of **726m,** example **508,** Table **31** (41 mg, 0.08 mmol) in methanol (0.25 mL), water (0.25 mL) and THF (0.25 mL) was added lithium hydroxide monohydrate (18 mg, 0.42 mmol). The reaction was stirred at room temperature for 2h. Tetrahydrofuran was evaporated, and the residue was purified by prep-hplc with gradient of methanol (20-100%) in water to give **732** (27 mg, 71%).

(DMSO-d_6) δ (ppm) ^{1}H: 8.77 (s, 1H), 7.81 (t, J=6.1Hz, 1H), 7.79 (d, J=8.8Hz, 2H), 7.55 (d, J=8.8Hz, 2H), 7.42 (dd, J=8.4and5.7Hz, 2H), 7.18 (t, J=8.8Hz, 2H), 4.50 (s, 2H), 4.09 (bd, J=13Hz, 2H), 3.86 (s, 2H), 3.15 (q, J=6.1Hz, 2H), 2.74 (t, J=12Hz, 2H), 1.69 (bd, J=12Hz, 2H), 1.50-1.40 (m, 1H), 1.37 (q, J=7.0Hz, 2H), 1.03 (qd, J=14and3.9Hz, 2H). LRMS (ESI): (calc) 457.2; (found) 458.3 $(MH)^+$.

Scheme 307



Example 513

N-(2-(1-(3,4-dimethoxyphenylsulfonyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide (**733**)

[0506] To a stirred solution of 2-(4-fluorobenzyloxy)-N-(2-(piperidin-4-yl)ethyl)acetamide **725**, scheme **303** (0.12 mmol) in THF (1.0 mL) was added triethylamine (0.10 mL, 0.69 mmol), followed by 3,4-dimethoxybenzenesulfonyl chloride (29 mg, 0.12 mmol). The mixture was stirred for 16h at room temperature. More 3,4-dimethoxybenzenesulfonyl chloride (29 mg, 0.12 mmol) was added, and the mixture was stirred for 1h more. The reaction mixture was quenched with water. The aqueous mixture was extracted with dichloromethane. The organic extract was dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized from diethyl ether to give **733** (31 mg, 54%). (DMSO-d_6) d(ppm) ^{1}H: 7.75 (t, J=5.9Hz, 1H), 7.38 (d, J=5.7Hz, 1H), 7.36 (d, J=5.7Hz, 1H), 7.28 (dd, J=8.4and2.2Hz, 1H), 7.16-7.10 (m, 4H), 4.44 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.57 (bd, J=12Hz, 2H), 3.06 (bq, J=6.8Hz, 2H), 2.10 (bt, J=10Hz, 2H), 1.69 (bd, J=10Hz, 2H), 1.29 (bq, J=6.8Hz, 2H), 1.17-1.04 (m, 3H). LRMS (ESI): 494.2 (calc) 495.0 (MH)+ (found)

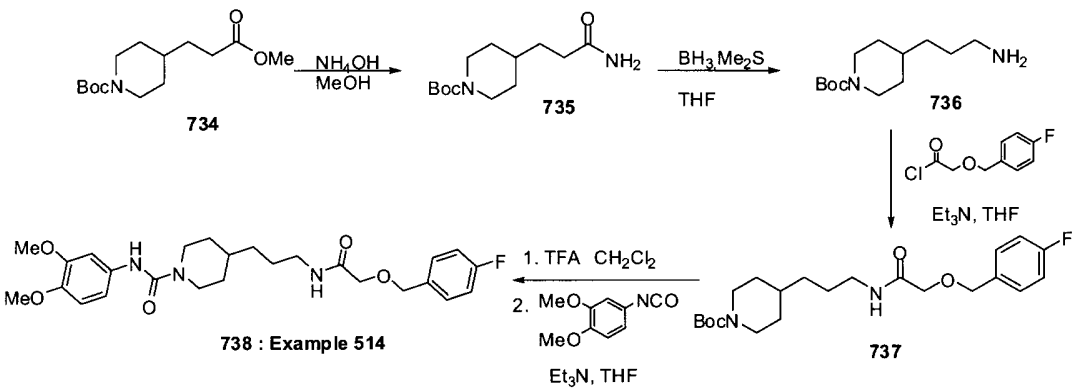
Example 513a

N-(2-(1-(benzylsulfonyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide (**733a**)

[0507] To a stirred solution of PS-NMM (329 mg, 0.75 mmol) in DCM (2.5 mL) was added 2amine **725** (83 mg, 0.25 mmol) followed by α-toluenesulfonyl chloride (44 mg, 0.23 mmol). The reaction was stirred at room temperature for 16h. More α-toluenesulfonyl chloride (44 mg, 0.23 mmol) was added, and the mixture stirred for 1h at room temperature, and 1.5h at 50°C. PS-NMM was filtered, solvent evaporated and the residue was purified by prep-hplc with gradient of methanol (20-100%) in water to give **733a** (19 mg, 18%). (DMSO-d_6) δ (ppm) ^{1}H: 7.80 (t, J=5.7Hz, 1H), 7.44-7.33 (m, 7H), 7.18 (t, J=9.0Hz, 2H), 4.50 (s, 2H), 4.35 (s, 2H), 3.85 (s, 2H), 3.50 (bd, J=12Hz, 2H), 3.11 (q, J=6.8Hz, 2H), 2.60 (td,

J=12and2.3Hz, 2H), 1.67 (bd, J=11Hz, 2H), 1.40-1.23 (m, 3H), 1.02 (qd, J=12and4.1Hz, 2H). LRMS (ESI): (calc) 448.2; (found) 449.2 $(MH)^+$.

Scheme 308



Example 514

4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)-N-(3,4-dimethoxyphenyl)piperidine-1-carboxamide (**738**)

Step 1: tert-butyl 4-(3-amino-3-oxopropyl)piperidine-1-carboxylate (**735**)

[0508] Ammonium hydroxide (3 mL of 28% in H_2O) was added to a stirred solution of tert-butyl 4-(3-methoxy-3-oxopropyl)piperidine-1-carboxylate **734** (646 mg, 2.38 mmol, prepared from N-boc-4-piperidinemethanol by oxidation followed by the sequence desribed by Klein, Scott I. et al.; J. Med. Chem. 1998, 41; 14; 2492-2502) in methanol (3 mL). The mixture was stirred for 45 min at room temperature, and then for 16h at 50°C. The solvent was evaporated. The residue was purified by silica gel column chromatography with gradient of methanol (0-10%) in DCM to give **735** (490 mg, 80%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.23 (s, 1H), 6.69 (s, 1H), 3.88 (bd, J=9.8Hz, 2H), 2.78-2.50 (m, 2H), 2.03 (t, J=7.2Hz, 2H), 1.58 (bd, J=12Hz, 2H), 1.44-1.20 (m, 3H), 1.36 (s, 9H), 0.91 (qd, J=12and4.3Hz, 2H). LRMS (ESI): (calc) 256.2; (found) 256.0 $(M)^+$.

Step 2: tert-butyl 4-(3-aminopropyl)piperidine-1-carboxylate (**736**)

[0509] To **735** (490 mg, 1.91 mmol) was added borane methyl sulfide complex (7.6 mL of a 2M solution in THF, 15.3 mmol). The mixture was stirred at 60°C for 4h. The reaction mixture was quenched with a saturated solution of sodium carbonate in water. The aqueous mixture was extracted with dichloromethane. The organic extract was dried ($MgSO_4$), filtered, and evaporated. The crude product was used without purification.

Step 3: tert-butyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)piperidine-1-carboxylate (**737**)

[0510] Compound **736** (0.96 mmol) in THF (3 mL) and triethylamine (0.25 mL, 1.8 mmol), was reacted with 2-(4-fluorobenzyloxy)acetyl chloride (0.90 mmol) in THF (1.5 mL) as described for the synthesis of compound **723**, **example 507**, step 4, scheme 302.

Purification by silica gel column chromatography with gradient of ethyl acetate (60-80%) in hexane gave **737** (65 mg, 17%).

LRMS (ESI): (calc) 408.2; (found) 431.1 $(M+Na)^+$.

Step 4: 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)-N-(3,4-dimethoxyphenyl)piperidine-1-carboxamide (**738**)

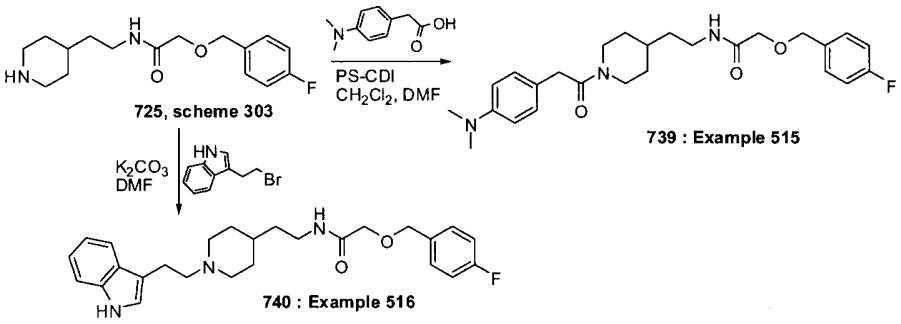
[0511] To a stirred solution of **737** (65 mg, 0.16 mmol) in DCM (0.7 mL) was added trifluoroacetic acid (0.1 mL). The mixture was stirred for 4.5h at room temperature. The solvent was evaporated giving the crude amine, 2-(4-fluorobenzyloxy)-N-(3-(piperidin-4-yl)propyl)acetamide. LRMS (ESI): 308.2 (calc) 309.1 $(MH)^+$ (found).

[0512] To the crude amine (0.16 mmol) in THF (1 mL) at 0°C was added triethylamine (0.07 mL, 0.48 mmol), then 3,4-dimethoxyphenylisocyanate (24 uL, 0.16 mmol). The reaction was stirred at room temperature for 16h. More 3,4-dimethoxyphenylisocyanate (18 uL, 0.12 mmol) was added. The reaction was stirred at room temperature for 1h. The reaction mixture was quenched with brine. The aqueous mixture was extracted with dichloromethane. The organic extract was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of methanol (0-5%) in dichloromethane to give **738** (33 mg, 42%).

(DMSO-d_6) δ (ppm) ^1H: 8.24 (s, 1H), 7.79 (t, J=5.5Hz, 1H), 7.41 (dd, J=8.6and5.7Hz, 2H), 7.19-7.13 (m, 3H), 6.94 (dd, J=8.6and2.5Hz, 1H), 6.78 (d, J=8.8Hz, 1H), 4.49 (s, 2H), 4.07 (bd, J=13Hz, 2H), 3.85 (s, 2H), 3.67 (s, 3H), 3.66 (s, 3H), 3.07 (q, J=6.5Hz, 2H), 2.65 (bt, J=12Hz, 2H), 1.64-1.61 (m, 2H), 1.45-1.39 (m, 3H), 1.19-1.16 (m, 2H), 1.02-0.93 (m, 2H).

LRMS (ESI): (calc) 487.2; (found) 488.1 $(MH)^+$.

Scheme 309



Example 515

N-(2-(1-(2-(4-(dimethylamino)phenyl)acetyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide (**739**)

[0513] To a stirred solution of PS-CDI (424 mg, 0.5 mmol) in DCM (2.5 mL) was added 4-(dimethylamino)phenylacetic acid (67 mg, 0.37 mmol), and the mixture was stirred for 10 min. Then a solution of amine **725** (83 mg, 0.25 mmol) in DMF (1 mL) was added. The reaction was stirred at room temperature for 16h. PS-CDI was filtered, solvent evaporated and the residue was purified by prep-hplc with gradient of methanol (20-100%) in water to give **739** (36 mg, 32%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.77 (t, J=5.7Hz, 1H), 7.41 (dd, J=8.2and5.7Hz, 2H), 7.17 (t, J=8.8Hz, 2H), 7.01 (d, J=8.6Hz, 2H), 6.65 (d, J=8.8Hz, 2H), 4.49 (s, 2H), 4.33 (bd, J=13Hz, 1H), 3.88 (bd, J=13Hz, 1H), 3.84 (s, 2H), 3.52 (s, 2H), 3.10 (q, J=6.8Hz, 2H), 2.89-2.84 (m, 1H), 2.83 (s, 6H), 2.50-2.41 (m, 1H), 1.65-1.56 (M, 2H), 1.44-1.40 (m, 1H), 0.83 (sxd, 12and3.9Hz, 2H). LRMS (ESI): (calc) 455.3; (found) 456.3 $(MH)^+$.

Example 516

N-(2-(1-(2-(1H-indol-3-yl)ethyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide (**740**)

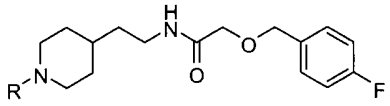
[0514] To a stirred solution of amine **725** (50 mg, 0.17 mmol) in dimethylformamide (1.7 mL) was added potassium carbonate (94 mg, 0.68 mmol) followed by 3-(2-bromoethyl)indole (38 mg, 0.17 mmol). The reaction was stirred at 90°C for 2h. The reaction mixture was quenched with a saturated solution of sodium carbonate in water. The aqueous mixture was extracted with ethyl acetate, and the organic extract was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of methanol (0-10%) in dichloromethane to give **740** (25 mg, 34%).

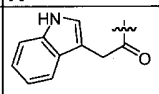
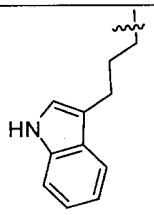
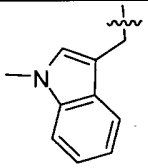
(DMSO-d_6) δ (ppm) ^{1}H: (10.76 (s, 1H), 7.77 (t, J=5.9Hz, 1H), 7.48 (d, J=7.8Hz, 1H), 7.41 (dd, J=8.6and5.7Hz, 2H), 7.30 (d, J=8.0Hz, 1H), 7.17 (t, J=9.0Hz, 2H), 7.12 (s, 1H), 7.03 (t, J=7.8Hz, 1H), 6.94 (t, J=7.0Hz, 1H), 4.49 (s, 2H), 3.85 (s, 2H), 3.12 (q, J=7.0Hz, 2H), 3.02-2.90 (m, 2H), 2.90-2.78 (m, 2H), 2.65-2.50 (m, 2H), 2.05-1.80 (m, 2H), 1.73-1.60 (m, 2H), 1.35 (q, J=7.0Hz, 2H), 1.31-1.08 (m, 3H). LRMS (ESI): (calc) 437.2; (found) 438.1 $(MH)^+$.

[0515] Example **515a** compound **740a** was prepared as describer for Example **515**, compound **739**, and scheme **309**. Characterization data is presented in **Table** 33

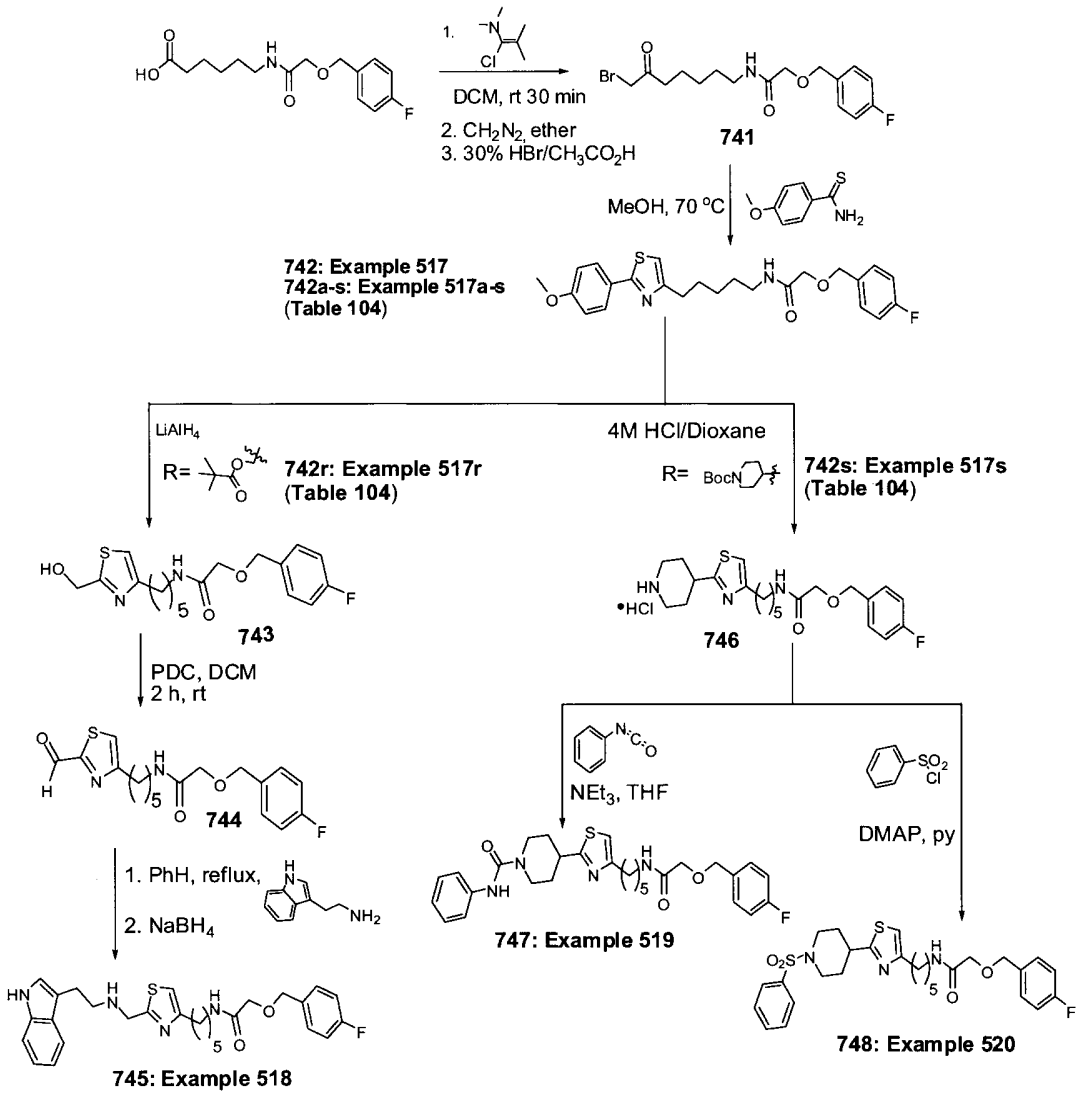
[0516] Examples **516a-b**, compounds **740a-b,** were prepared as described for Example **516**, compound **740**. Characterization data is presented in **Table** 33.

Table 33



Ex	Cpd	R	Name	Characterization	Scheme
515a	739a		N-(2-(1-(2-(1H-indol-3-yl)acetyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy) acetamide	(DMSO-d_6) δ(ppm) ^{1}H: 10.86 (s, 1H), 7.76 (t, J=5.7Hz, 1H), 7.54 (d, J=8.0Hz, 1H), 7.40 (t, J=8.4Hz, 2H), 7.32 (d, J=8.2Hz, 1H), 7.20-7.14 (m, 3H), 7.05 (t, J=7.0Hz, 1H), 6.95 (t, J=6.8Hz, 1H), 4.48 (s, 2H), 4.36 (bd, J=13Hz, 1H), 3.98 (bd, J=13Hz, 1H), 3.84 (s, 2H), 3.72 (s, 2H), 3.08 (q, J=6.7Hz, 2H), 2.88 (bt, J=12Hz, 1H), 2.50-2.43 (m, 1H), 1.64-1.54 (m, 2H), 1.50-1.34 (m, 1H), 1.26 (q, J=7.4Hz, 2H), 0.90-0.73 (m, 2H). LRMS (ESI): (calc) 451.2; (found) 452.3 $(MH)^+$.	309 Ex 515
516a	740a		N-(2-(1-(3-(1H-indol-3-yl)propyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy) acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.73 (s, 1H), 7.77 (t, J=5.7Hz, 1H), 7.49-7.39 (m, 2H), 7.30 (d, J=8.0Hz, 1H), 7.17 (t, J=9.0Hz, 2H), 7.08 (d, J=2.2Hz, 1H), 7.03 (t, J=7.6Hz, 1H), 6.94 (t, J=7.8Hz, 1H), 4.49 (s, 2H), 3.85 (s, 2H), 3.11 (q, J=7.0Hz, 2H), 2.88-2.79 (m, 2H), 2.66 (t, J=7.4Hz, 2H), 2.38-2.24 (m, 2H), 1.88-1.70 (m, 4H), 1.62 (bd, J=11Hz, 2H), 1.34 (q, J=7.2Hz, 2H), 1.25-1.05 (m, 3H). LRMS(ESI): (calc) 451.3; (found) 452.3 $(MH)^+$	309 Ex 516
516b	740b		2-(4-fluorobenzyloxy)-N-(2-(1-((1-methyl-1H-indol-3-yl)methyl)piperidin-4-yl)ethyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 8.47 (s, 1H), 7.70 (d, J=8.0Hz, 1H), 7.46 (d, J=10Hz, 1H), 7.44 (s, 1H), 7.39 (dd, J=8.4and5.7Hz, 2H), 7.28 (t, J=7.2Hz, 1H), 7.19 (t, J=8.0Hz, 1H), 7.07 (t, J=8.6Hz, 1H), 4.55 (s, 2H), 4.45 (s, 2H), 3.91 (s, 2H), 3.86 (s, 3H), 3.51 (bd, J=12Hz, 2H), 3.26 (t, J=7.2Hz, 2H), 3.02-2.93 (m, 2H), 1.98 (bd, J=13Hz, 2H), 1.61-1.32 (m, 5H). LRMS: 437.2 (calc) 438.3 (MH)+ (found)	309 Ex 516

Scheme 310



Example 517

2-(4-fluorobenzyloxy)-N-(5-(2-(4-methoxyphenyl)thiazol-4-yl)pentyl)acetamide (**742**)

Step 1: 2: N-(7-bromo-6-oxoheptyl)-2-(4-fluorobenzyloxy)acetamide (**741**)

[0517] 1-Chloro-*N,N*,2-trimethyl-1-propenylamine (0.450 mL, 3.39 mmol) was added to a solution of 6-(2-(4-fluorobenzyloxy)acetamido)hexanoic acid (842 mg, 2.83 mmol, as described for the synthesis of compound **303**, Example **112a**, step 3,scheme **49**) in DCM (30 mL). The reaction stirred for 1 h at room temperature. The solvent was evaporated and crude 6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl chloride, was diluted with 10 mL of diethyl ether. Diazomethane (0.5M, 14.1 mmol) in diethyl ether (from *N*-nitroso-*N*-methylurea, 1.45 g) was added to the reaction at 0°C and reaction mixture was stirred for 30

min. A solution of hydrogen bromide in acetic acid (1.14 mL, 4.24 mmol) was added drop-wise at 0°C and the orange mixture stirred for 2 h. The solvent was evaporated and the residue was purified by silica gel column chromatography with ethyl acetate (60%) in hexane to give **741** (850 mg, 81%) as white crystals. The product was contaminated with *N,N*-dimethylisobutyramide and was used as is without further purification..

(CD_3CN) δ (ppm) ^1H: 7.44 (m, 2H), 7.16-7.11 (m, 2H), 6.85 (bs, 1H), 4.54 (s, 2H), 4.09 (s, 2H), 3.90 (m, 2H), 3.20 (q, J=6.8Hz, 2H), 2.60 (t, J=7.2Hz, 2H), 1.61-1.56 (m, 2H), 1.50-1.45 (m, 2H), 1.33-1.29 (m, 2H).

LRMS (ESI): (calc) 374.2; (found) 376.1 $(MH)^+$.

Step 2: 2-(4-fluorobenzyloxy)-N-(5-(2-(4-methoxyphenyl)thiazol-4-yl)pentyl)acetamide (**742**)

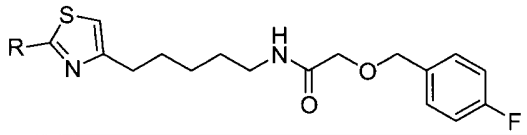
[0518] 4-Methoxybenzothioamide (73 mg, 0.439 mmol) was added to a solution of **741** (137 mg, 0.366 mmol) in methanol (5 mL). The reaction was heated to 70 °C and stirred for 16 h. The solvent was evaporated and the residue was purified by silica gel column chromatography with gradient of ethyl acetate (40% - 60%) in hexane to give **742** (20 mg, 12%) as a clear oil.

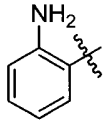
^1H NMR: ($CDCl_3$) d(ppm): 7.86 (d, J=8.8Hz, 2H),7.29 (dd, J=6.0,2.4Hz, 2H), 7.05 (t, J=8.6Hz, 2H), 6.93 (d, J=8.8Hz, 2H), 6.78 (s, 1H), 6.54 (bs, 1H), 4.51 (s, 2H), 3.95 (s, 2H), 3.85 (s, 3H), 3.30 (q, J=6.8Hz, 2H), 2.79 (t, J=7.4Hz, 2H), 1.82-1.74 (m, 2H), 1.60-1.54 (m, 2H), 1.45-1.40 (m, 2H).

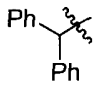
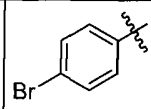
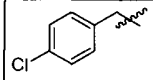
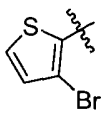
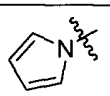
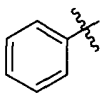
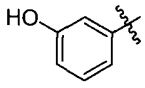
LRMS (ESI): 442.6 (calc) 443.1 (MH)+ (found).

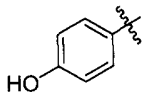
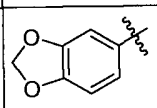
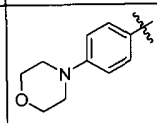
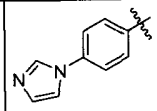
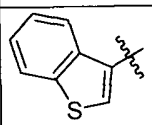
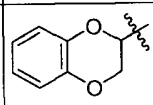
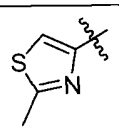
[0519] Examples **517a-s** describe the preparation of compounds **742a-s** using the same procedures as described for compound **742**, Example **517**, scheme **310**. Characterization data are presented in Table **34**.

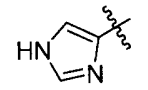
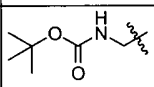
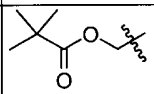
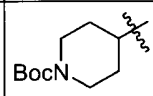
Table 34



Ex	Cpd	R_3	Name	Characterization	Scheme
517a	742a		N-(5-(2-(2-aminophenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm): 7.60 (dd, J=8.2, 1.4Hz, 1H), 7.29-7.26 (m, 2H), 7.16-7.12 (m, 1H), 7.06-7.02 (m, 2H), 6.75-6.66 (m, 3H), 6.54 (bs, 1H), 6.16 (bs, 2H), 4.49 (s, 2H), 3.94 (s, 2H), 3.29 (q, J=6.8Hz, 2H), 2.78 (t, J=7.4Hz, 2H), 1.81-1.73 (m, 2H), 1.59-1.53 (m, 2H), 1.44-1.36 (m, 2H).	310 Step 1-4 Ex 517

Ex	Cpd	R_3	Name	Characterization	Scheme
517b	742b		N-(5-(2-benzhydrylthiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm): 7.32-7.21 (m, 12H), 7.07-7.03 (m, 2H), 6.79 (s, 1H), 6.53 (bs, 1H), 5.81 (s, 1H), 4.51 (s, 2H), 3.94 (s, 2H), 3.27 (q, J=6.8Hz, 2H), 2.75 (t, J=7.6Hz, 2H), 1.75-1.67 (m, 2H), 1.58-1.50 (m, 2H), 1.40-1.35 (m, 2H).	310 Step 1-4 Ex 517
517c	742c		N-(5-(2-(4-bromophenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm): 7.82 (d, J=6.8, 2Hz, 2H), 7.55 (d, J=6.8, 2Hz, 2H), 7.30-7.27 (m, 2H), 7.07-7.03 (m, 2H), 6.54 (bs, 1H), 4.51 (s, 2H), 3.30 (quartet, J=6.8Hz, 2H), 2.83 (t, J=7.8Hz, 2H), 1.78 (quintet, J=7.6Hz, 2H), 1.60-1.54 (m, 2H), 1.45-1.40 (m, 2H).	310 Step 1-4 Ex 517
517d	742d		N-(5-(2-(4-chlorobenzyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm): 7.30-7.27 (m, 3H), 7.23-7.21 (m, 2H), 7.07-7.03 (m, 2H), 6.73 (s, 1H), 6.54 (bs, 1H), 4.51 (s, 2H), 4.25 (s, 2H), 3.95 (s, 2H), 3.27 (quartet, J=6.8Hz, 2H), 2.73 (t, J=7.6Hz, 2H), 1.75-1.67 (m, 2H), 1.57-1.51 (m, 2H), 1.41-1.35 (m, 2H).	310 Step 1-4 Ex 517
517e	742e		N-(5-(2-(3-bromothiophen-2-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm): 7.31-7.26 (m, 3H), 7.07-7.03 (m, 3H), 6.93 (s, 1H), 6.55 (bs, 1H). 4.51 (s, 2H), 3.95 (s, 2H), 3.30 (q, J=6.8Hz, 2H), 2.80 (t, J=7.4Hz, 2H), 1.80-1.72 (m, 2H), 1.60-1.53 (m, 2H), 1.44-1.38 (m, 2H).	310 Step 1-4 Ex 517
517f	742f		N-(5-(2-(4-(1H-pyrrol-1-yl)phenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm): 7.99 (t, J=1.8Hz, 1H), 7.77 (dt, J=5.7, 1.2Hz, 1H), 7.49-7.41 (m, 2H), 7.30-7.26 (m, 2H), 7.17 (t, J=2.0Hz, 2H), 7.07-7.02 (m, 2H), 6.91 (s, 1H), 6.54 (bs, 1H), 6.37 (t, J=2.4Hz, 2H), 4.51 (s, 2H), 3.95 (s, 2H), 3.31 (q, J=7.2Hz, 2H), 2.83 (t, J=7.6Hz, 2H), 1.84-1.76 (m, 2H), 1.62-1.55 (m, 2H), 1.46-1.39 (m, 2H).	310 Step 1-4 Ex 517
517g	742g		2-(4-fluorobenzyloxy)-N-(5-(2-phenylthiazol-4-yl)pentyl)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.94-7.90 (m, 2H), 7.44-7.39 (m, 3H), 7.30-7.25 (m, 2H), 7.08-7.02 (m, 2H), 6.86 (s, 1H), 6.54 (bs, 1H), 4.50 (s, 2H), 3.95 (s, 2H), 3.30 (q, J=6.8Hz, 2H), 2.82 (t, J=7.6Hz, 2H), 1.83-1.75 (m, 2H), 1.62-1.54 (m, 2H), 1.46-1.40 (m, 2H).	310 Step 1-4 Ex 517
517h	742h		2-(4-fluorobenzyloxy)-N-(5-(2-(3-hydroxyphenyl)thiazol-4-yl)pentyl)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.69 (bs, 1H), 7.62-7.61 (m, 1H), 7.33-7.31 (m, 1H), 7.27-7.22 (m, 3H), 7.05-7.01 (m, 2H), 6.90-6.88 (m, 1H), 6.84 (s, 1H), 6.66 (bs, 1H), 4.48 (s, 2H), 3.97 (s, 2H), 3.36 (q, J=6.8Hz, 2H), 2.81 (t, J=7.2Hz, 2H), 1.76 (quintet, J=7.6Hz, 2H), 1.67-1.61 (m, 2H), 1.46-1.40 (m, 2H).	310 Step 1-4 Ex 517

Ex	Cpd	R_3	Name	Characterization	Scheme
517i	742i		2-(4-fluorobenzyloxy)-N-(5-(2-(4-hydroxyphenyl)thiazol-4-yl)pentyl)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 8.40 (bs, 1H), 7.72 (d, J=8.8Hz, 2H), 7.28-7.25 (m, 2H), 7.06-7.01 (m, 2H), 6.80 (d, J=8.8Hz, 2H), 6.61 (bs, 1H), 4.49 (s, 2H), 3.95 (s, 2H), 3.28 (q, J=7.2Hz, 2H), 2.77 (t, J=7.2Hz, 2H), 1.77-1.70 (m, 2H), 1.58-1.51 (m, 2H), 1.41-1.35 (m, 2H).	310 Step 1-4 Ex 517
517j	742j		N-(5-(2-(benzo[d][1,3]dioxol-5-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.43-7.40 (m, 2H), 7.30-7.26 (m, 2H), 7.06-7.02 (m, 2H), 6.82 (d, J=8Hz, 1H), 6.78 (s, 1H), 6.55 (bs, 1H), 6.00 (s, 2H), 4.50 (s, 2H), 3.94 (s, 2H), 3.29 (q, J=6.8Hz, 2H), 2.77 (t, J=7.6Hz, 2H), 1.80-1.72 (m, 2H), 1.59-1.53 (m, 2H), 1.44-1.38 (m, 2H).	310 Step 1-4 Ex 517
517k	742k		2-(4-fluorobenzyloxy)-N-(5-(2-(4-morpholinophenyl)thiazol-4-yl)pentyl)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.82 (d, J=8.8Hz, 2H), 7.30-7.25 (m, 2H), 7.07-7.03 (m, 2H), 6.90 (d, J=9.2Hz, 2H), 6.76 (s, 1H), 6.54 (bs, 1H), 4.50 (s, 2H), 3.95 (s, 2H), 3.88-3.85 (m, 4H), 3.29 (q, J=7.2Hz, 2H), 3.24-3.22 (m, 4H), 2.79 (t, J=7.6Hz, 2H), 1.81-1.73 (m, 2H), 1.60-1.54 (m, 2H), 1.45-1.39 (m, 2H).	310 Step 1-4 Ex 517
517l	742l		N-(5-(2-(4-(1H-imidazol-1-yl)phenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm) ^{1}H: 8.03 (d, J=8.8Hz, 2H), 7.90 (s, 1H), 7.44 (d, J=8.8Hz, 2H), 7.32 (s, 1H), 7.30-7.26 (m, 2H), 7.22 (s, 1H), 7.07-7.02 (m, 2H), 6.91 (s, 1H), 6.56 (bs, 1H), 4.51 (s, 2H), 3.95 (s, 2H), 3.30 (q, J=6.8Hz, 2H), 2.82 (t, J=7.6 Hz, 2H), 1.83-1.75 (m, 2H), 1.62-1.54 (m, 2H), 1.46-1.38 (m, 2H).	310 Step 1-4 Ex 517
517m	742m		N-(5-(2-(benzo[b]thiophen-3-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm) ^{1}H: 8.70-8.68 (m, 1H), 7.93 (s, 1H), 7.89-7.87 (m, 1H), 7.51-7.47 (m, 1H), 7.43-7.39 (m, 1H), 7.28-7.25 (m, 2H), 7.06-7.01 (m, 2H), 6.88 (s, 1H), 6.56 (bs, 1H), 3.31 (q, J=6.8Hz 2H), 2.87 (t, J=7.6Hz, 2H), 1.88-1.80 (m, 2H), 1.64-1.56 (m, 2H), 1.49-1.41 (m, 2H).	310 Step 1-4 Ex 517
517n	742n		N-(5-(2-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.31-7.27 (m, 2H), 7.07-6.99 (m, 3H), 6.94-6.88 (m, 3H), 6.55 (bs, 1H), 5.48 (dd, J=7.4, 2.8Hz, 1H), 4.60 (dd, J=11.4, 2.8Hz, 1H), 4.52 (s, 2H), 4.22 (dd, J=11.6, 7.2Hz, 1H), 3.95 (s, 2H), 3.28 (q, J=6.8Hz, 2H), 2.77 (t, J=8.0Hz, 2H), 1.77-1.69 (m, 2H), 1.58-1.52 (m, 2H), 1.41-1.36 (m, 2H).	310 Step 1-4 Ex 517
517o	742o		2-(4-fluorobenzyloxy)-N-(5-(2'-methyl-2,4'-bithiazol-4-yl)pentyl)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.76 (s, 1H), 7.30-7.26 (m, 2H), 7.08-7.03 (m, 2H), 6.88 (s, 1H), 6.54 (bs, 1H), 4.51 (s, 2H), 3.95 (s, 2H), 3.29 (q, J=7.2Hz, 2H), 2.80 (t, J=7.6Hz, 2H), 2.76 (s, 3H), 1.81-1.73 (m, 2H), 1.61-1.53 (m, 2H).	310 Step 1-4 Ex 517

Ex	Cpd	R_3	Name	Characterization	Scheme
517p	742p		N-(5-(2-(1H-imidazol-4-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	(MEOD-d_4) δ (ppm) ^{1}H: 9.01 (d, J=1.2Hz, 1H), 8.11 (d, J=1.2Hz, 1H), 7.40-7.36 (m, 2H), 7.34 (s, 1H), 7.09-7.05 (m, 2H), 4.54 (s, 2H), 3.91 (s, 2H), 3.23 (t, J=7.2Hz, 2H), 2.84 (t, J=7.6Hz, 2H), 1.83-1.76 (m, 2H), 1.60-1.53 (m, 2H), 1.42-1.32 (m, 2H).	310 Step 1-4 Ex 517
517q	742q		tert-butyl (4-(5-(2-(4-fluorobenzyloxy) acetamido)pentyl)thiazol-2-yl)methylcarbamate	(CD_3CN) δ (ppm) ^{1}H: 7.43-7.39 (m, 2H), 7.16-7.11 (m, 2H), 6.94 (s, 1H), 6.85 (bs, 1H), 6.05 (bs, 1H), 4.54 (s, 2H), 4.43 (d, J=6.0Hz, 2H), 3.90 (s, 2H), 3.20 (q, J=6.8Hz, 2H), 2.70 (t, J=7.6Hz, 2H), 2.17 (s, 1H), 1.72 (m, 2H), 1.55-1.48 (m, 2H), 1.44 (s, 9H), 1.37-1.32 (m, 2H).	310 Step 1-4 Ex 517 Except used ethanol as solvent In step 4
517r	742r		(4-(5-(2-(4-fluorobenzyloxy) acetamido)pentyl)thiazol-2-yl)methyl pivalate	(CD_3CN) δ (ppm) ^{1}H: 7.30-7.25 (m, 2H), 7.07-7.03 (m, 2H), 6.86 (s, 1H), 6.54 (bs, 1H), 5.34 (s, 2H), 4.51 (s, 2H), 3.94 (s, 2H), 3.28 (q, J=6.8Hz, 2H), 2.74 (t, J=7.8Hz, 2H), 1.75-1.68 (m, 2H), 1.58-1.51 (m, 2H), 1.41-1.33 (m, 2H), 1.24 (s, 9H).	310 Step 1-4 Ex 517 Except used ethanol as solventin step 4
517s	742s		tert-butyl 4-(4-(5-(2-(4-fluorobenzyloxy) acetamido)pentyl)thiazol-2-yl)piperidine-1-carboxylate	($CDCl_3$) δ (ppm) ^{1}H: 7.31-7.27 (m, 2H), 7.07-7.03 (m, 2H), 6.73 (s, 1H), 6.55 (bs, 1H), 4.52 (s, 2H), 4.18 (bs, 2H), 3.95 (s, 2H), 3.27 (q, J=7.2Hz, 2H), 3.13-3.07 (m, 1H), 2.87-2.81 (m, 2H), 2.72 (t, J=7.6Hz, 2H), 2.07-2.04 (m, 2H), 1.74-1.63 (m, 3H), 1.58-1.51 (m, 2H), 1.46 (s, 9H), 1.40-1.35 (m, 2H).	310 Step 1-4 Ex 517

Example 518

N-(5-(2-((2-(1H-indol-3-yl)ethylamino)methyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**745**)

Step 1: 2-(4-fluorobenzyloxy)-N-(5-(2-(hydroxymethyl)thiazol-4-yl)pentyl)acetamide (**743**)

[0520] A solution of compound **742r**, scheme **310**, example **517r**, (800 mg, 1.77 mmol) in THF (2 mL) was added to a solution of $LiAlH_4$ (131 mg, 3.55 mmol) in THF (2 mL) at room temperature. The reaction was stirred for 10 min., and then it was cooled to 0°C and slowly quenched with H_2O until the grey mixture turned white. The reaction was diluted with 10% HCl in water. The aqueous mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The alcohol, **743** was used without further purification (615 mg, 95%, clear oil).

(MEOD-d_4) δ(ppm) ^{1}H: 7.88 (bs, 1H), 7.42-7.38 (m, 2H), 7.42 (s, 1H), 7.41-7.38 (m, 2H), 4.88 (s, 2H), 4.79 (s, 1H), 4.55 (s, 2H), 3.92 (s, 2H), 3.24-3.20 (m, 2H), 2.72 (t, J=7.4Hz, 1H), 1.72-1.67 (m, 1H), 1.58-1.50 (m, 3H), 1.38-1.31 (m, 3H).

LRMS (ESI): (calc) 366.4; (found) 367.1 $(MH)^+$.

Step 2: 2-(4-fluorobenzyloxy)-N-(5-(2-formylthiazol-4-yl)pentyl)acetamide (**744**)

[0521] Pyridinium dichromate (1.26 g, 3.36 mmol) was added to a solution of **743** (615 mg, 1.60 mmol) in dichloromethane (1 ml). The reaction stirred at room temperature for 5 h. The mixture was filtered over a pad of silica, washing with ethyl acetate. The filtrate was evaporated and the residue was purified by silica gel column chromatography with gradient of methanol (0% - 2%) in ethyl acetate to give **744** (100 mg, 17%) as a clear film.

LRMS (ESI): (calc) 364.4; (found) 387.1 $(MNa)^+$.

Step 3: N-(5-(2-((2-(1H-indol-3-yl)ethylamino)methyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**745**)

[0522] Tryptamine (87 mg, 0.548 mmol) and **744** (100 mg, 0.274 mmol) in benzene (5 ml, the flask equipped with a condenser and a Dean-Stark trap) was heated to 90 ^{0}C for 16 h. The reaction was cooled to room temperature and sodium triacetoxyborohydride (58 mg, 0.274 mmol) was added. The mixture stirred for 3 h at room temperature. The reaction was diluted with 10% NaOH in water and the aqueous mixture was extracted with ethyl acetate and the organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was first purified by prep-hplc with gradient of methanol (20%-95%) in water, and the product was re-purified by prep-TLC plate, eluting with methanol (4%) in DCM to give **745** (6 mg, 4%) as a yellow film.

($CDCl_3$) δ(ppm) ^{1}H: 7.40 (d, J=8.0Hz, 1H), 7.30-7.26 (m, 2H), 7.12 (d, J=8.0Hz, 1H), 6.99-6.94 (m, 4H), 6.88-6.85 (m, 4H), 4.43 (s, 2H), 3.97 (s, 2H), 3.80 (s, 2H), 3.09 (t, J=7.0Hz, 2H), 2.87 (s, 3H), 2.60 (t, J=7.4Hz, 2H), 1.62-1.54 (m, 2H), 1.46-1.38 (m, 2H), 1.26-1.18 (m, 2H).

LRMS (ESI): (calc) 508.6; (found) 509.3 $(MH)^+$.

Example 519

4-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)-N-phenylpiperidine-1-carboxamide (**747**)

Step 1: 2-(4-fluorobenzyloxy)-N-(5-(2-(piperidin-4-yl)thiazol-4-yl)pentyl)acetamide (**746**)

[0523] Compound **742s** (570 mg, 1.09 mmol, scheme **310**, example **517s**) was dissolved in a minimum amount of DCM. A solution of HCl (4M, 10.9 mmol) in ether was added to the solution and the reaction stirred at room temperature for 16 h. The solvent was evaporated and the hydrochrloride salt **746** was triturated with ether to give the product as a white solid. LRMS (ESI): (calc) 456.0; (found) 457.0 $(MH)^+$.

Step 2: 4-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)-N-phenylpiperidine-1-carboxamide (**747**)

[0524] Phenylisocyanate (52 mg, 0.438 mmol) was added to a solution of **746** (100 mg, 0.219 mmol) and triethylamine (0.057 mL, 0.438 mmol) in THF (2 mL) and the reaction stirred at room temperature for 16 h, then it was diluted with a saturated solution of sodium carbonate in water. The aqueous mixture was extracted with EtOAc and the extracts were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of methanol (1%-10%) in diethyl ether to give **747** (60 mg, 51%) as a clear oil.

($CDCl_3$) δ(ppm) ^{1}H: 7.37-7.34 (m, 2H), 7.31-7.25 (m, 2H), 7.07-7.00 (m, 3H), 6.79 (s, 1H), 6.59-6.56 (m, 2H), 4.51 (s, 2H), 4.19-4.15 (m, 2H), 3.94 (s, 2H), 3.27 (q, J=6.8Hz, 3H), 3.07-3.00 (m, 2H), 2.75 (t, J=7.6Hz, 2H), 2.18-2.16 (m, 2H), 1.85-1.68 (m, 4H), 1.59-1.51 (m, 2H), 1.42-1.33 (m, 2H). LRMS: (calc) 538.6; (found) 539.1 $(MH)^+$.

Example 520

2-(4-fluorobenzyloxy)-N-(5-(2-(1-(phenylsulfonyl)piperidin-4-yl)thiazol-4-yl)pentyl)acetamide (**748**)

[0525] Phenylsulfonylchloride (77 mg, 0.438 mmol) was added to a solution of **746,** scheme 310 (100 mg, 0.219 mmol) and catalytic amounts of dimethylaminopyridine in pyridine (2 mL). The reaction stirred at room temperature for 16 h. The reaction was diluted with 10% HCl in water. The aqueous mixture was extracted with ethyl acetate, and the organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with pure diethyl ether to give **748** (15 mg, 12%) as clear oil.

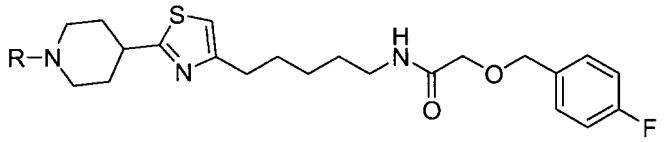
($CDCl_3$) δ (ppm) ^{1}H: 7.81-7.79 (m, 2H), 7.70-7.60 (m, 3H), 7.41-7.60 (m, 2H), 7.10-7.05 (m, 2H0, 6.98 (s, 1H), 4.55 (s, 2H), 3.91 (s, 2H), 3.85-3.82 (m, 2H), 3.20 (t, J=7.2Hz, 2H), 2.96-2.90 (m, 2H), 2.69 (t, J=7.6Hz, 2H), 2.46 (td, J=12, 2.4Hz, 2H), 2.11-2.09 (m, 2H), 1.84-1.76 (m, 2H), 1.71-1.63 (m, 2H), 1.56-1.50 (m, 2H), 1.39-1.30 (m, 2H).

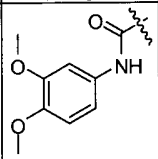
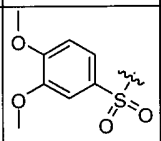
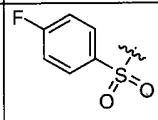
LRMS (ESI): (calc) 559.7; (found) 560.0 $(MH)^+$.

[0526] Example **519a** describes the preparation of compound **747a** using the same procedure as described for compound **747** in Example **519**, scheme **310**. Characterization data is presented in Table 35.

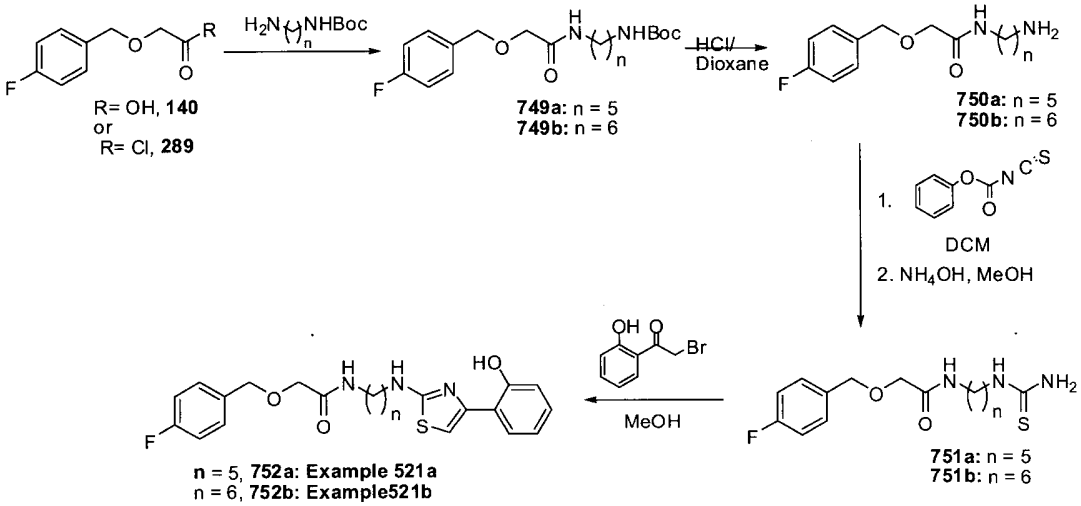
[0527] Examples **520a-b** describe the preparation of compounds **748a-b** using the same procedures as described for compound **748** in Example **520**, scheme **310**. Characterization data are presented in **Table 35**.

Table 35



Ex	Cpd	R_3	Name	Characterization	Scheme
519a	747a		N-(3,4-dimethoxyphenyl)-4-(4-(5-(2-(4-fluorobenzyloxy) acetamido)pentyl)thiazol-2-yl)piperidine-1-carboxamide	($CDCl_3$) δ(ppm) ^{1}H: 7.30-7.27 (m, 2H), 7.07-7.02 (m, 2H), 6.77 (s, 1H), 6.64 (s, 1H), 6.63 (d, J=2.4Hz, 2H), 6.56 (bs, 1H), 6.15 (t, J=2.0Hz, 1H), 4.51 (s, 2H), 4.17-4.13 (m, 2H), 3.94 (s, 2H), 3.75 (s, 6H), 3.29-3.23 (m, 3H), 3.06-2.99 (m, 2H), 2.73 (t, J=7.6Hz, 2H), 2.17-2.14 (m, 2H), 1.84-1.67 (m, 4H), 1.58-1.50 (m, 2H), 1.42-1.32 (m, 2H).	310 Ex 519
520a	748a		N-(5-(2-(1-(3,4-dimethoxyphenyl sulfonyl)piperidin-4-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy) acetamide	($CDCl_3$) δ(ppm) ^{1}H: 7.39 (dd, J=8.4, 2.4Hz, 1H), 7.30-7.27 (m, 2H), 7.22 (d, J=2.4Hz, 1H), 7.07-7.02 (m, 2H), 6.96 (d, J=8.8Hz, 1H), 6.75 (s, 1H), 6.53 (bs, 1H), 4.51 (s, 2H), 3.95 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.87-3.84 (m, 2H), 3.26 (q, J=6.8Hz, 2H), 2.96-2.94 (m, 1H), 2.70 (t, J=7.6Hz, 2H), 2.43 (td, J=12, 2.4Hz, 2H), 2.17-2.14 (m, 2H), 1.94-1.83 (m, 2H), 1.72-1.64 (m, 2H), 1.57-1.50 (m, 2H), 1.39-1.33 (m, 2H).	310 Ex 520
520b	748b		2-(4-fluorobenzyloxy)-N-(5-(2-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)thiazol-4-yl)pentyl)acetamide	($CDCl_3$) δ(ppm) ^{1}H: 7.81-7.77 (m, 2H), 7.31-7.27 (m, 2H), 7.24-7.20 (m, 2H), 7.07-7.03 (m, 2H), 6.75 (s, 1H), 6.54 (bs, 1H), 4.52 (s, 2H), 3.94 (s, 2H), 3.87-3.84 (m, 2H), 3.26 (q, J=6.8Hz, 2H), 2.98-2.93 (m, 1H), 2.70 (t, J=7.6Hz, 2H), 2.44 (td, J=12, 2.4Hz, 2H), 2.18-2.15 (m, 2H), 1.94-1.84 (m, 2H), 1.72-1.64 (m, 2H), 1.57-1.50 (m, 2H), 1.39-1.32 (m, 2H).	310 Ex 520

Scheme 311



Examples 521a

2-(4-fluorobenzyloxy)-N-(5-(4-(2-hydroxyphenyl)thiazol-2-ylamino)pentyl)acetamide (**752a**)

Step 1: tert-butyl 5-(2-(4-fluorobenzyloxy)acetamido)pentylcarbamate (**749a**)

[0528] A solution of acid chloride **289** (2.71 mmol) in THF (3 mL) was added to a solution of *N*-boc-1,5-diaminopentane (0.376 mL, 1.80 mmol) and diisopropylethylamine (0.627 mL, 3.60 mmol) in THF (3 mL). The reaction stirred at room temperature for 1 h. The reaction was diluted with 10% HCl in water. The aqueous mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The crude product **749a**, an orange solid, was used without further purification (883 mg, 88% crude).
LRMS (ESI): (calc) 368.4; (found) 369.0 $(MH)^+$.

Step 2: N-(5-aminopentyl)-2-(4-fluorobenzyloxy)acetamide (**750a**)

[0529] A solution of dry HCl (4M, 7.19 mmol) in dioxane was added to a solution of **749a** in dioxane (1.80 mL). The reaction stirred at room temperature for 1 h. The reaction was quenched with a saturated solution of sodium carbonate in water. The aqueous mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The crude product **750a**, yellow oil, was used without further purification (420 mg, 65% crude).
LRMS (ESI): (calc) 268.3; (found) 269.0 $(MH)^+$.

Step 3: 2-(4-fluorobenzyloxy)-N-(5-thioureidopentyl)acetamide (**751a**)

[0530] Benzoyl isothiocyanate (0.126 mL, 0.938 mmol) was added to a mixture **750a** (210 mg, 0.782 mmol) in DCM (3 mL) and the reaction stirred at room temperature for 1 h. Solvent was evaporated and the residue was dissolved in methanol (2 mL). Ammonium hydroxide was added (1 mL) and the reaction stirred for 16 h. The reaction was diluted with 10% HCl in water. The aqueous mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The crude product **751a**, brown oil, was used without further purification (255 mg, 99% crude).
LRMS (ESI): (calc) 327.4; (found) 328.0 $(MH)^+$.

Step 4: 2-(4-fluorobenzyloxy)-N-(5-(5-(2-hydroxyphenyl)thiazol-2-ylamino)pentyl)acetamide (**752a**)

[0531] 2-Bromo-1-(2-hydroxyphenyl)ethanone (201 mg, 0.938 mmol) was added to a solution of **751a** (255 mg, 0.782 mmol) in methanol (5 mL). The reaction was heated to 70°C and stirred for 16 h. The solvent was evaporated and the residue was purified by silica gel column chromatography with gradient of ethyl acetate (50% - 70%) in hexane to give **752a** (39 mg, 11% over 4 steps) as an opaque oil.

(CDCl3) δ(ppm): 12.0 (bs, 1H), 7.52 (dd, J=7.6, 1.6 Hz, 1H), 7.30-7.27 (m, 2H), 7.20-7.15 (m, 1H), 7.06-7.02 (m, 2H), 6.93 (dd, J=8.4, 1.2 Hz, 1H), 6.84-6.80 (m, 1H)6.65 (s, 1H), 6.63 (bs, 1H), 5.61-5.58 (m, 1H), 4.52 (s, 2H), 3.97 (s, 2H), 3.34-3.28 (m, 4H), 1.69 (quintet, J=5.4 Hz, 2H), 1.56 (quintet, J=5.4 Hz, 2H), 1.45-1.39 (m, 2H).
LRMS (ESI): (calc) 443.5; (found) 444.1 $(MH)^+$.

Example 521b

2-(4-fluorobenzyloxy)-N-(6-(4-(2-hydroxyphenyl)thiazol-2-ylamino)hexyl)acetamide (**752b**)

Step 1: tert-butyl 6-(2-(4-fluorobenzyloxy)acetamido)hexylcarbamate (**749b**)

[0532] Prepared by the reaction of acid **140** (500 mg, 2.71 mmol) and EDC (779 mg, 4.06 mmol) in dimethylformamide (6 mL). After 5 min, *N*-boc-1,6-aminohexane (753 mg, 2.98 mmol) and catalytic amount of DMAP was added to the solution and the reaction was stirred for 32 h. The mixture was diluted with 10% HCl in water and the aqueous layer was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography with diethyl ether (70%) in hexane to give **749b** (1.03 mg, 28%) as a white solid.
LRMS (ESI): (calc) 382.4; (found) 405.0 $(MNa)^+$.

Step 2: N-(6-aminohexyl)-2-(4-fluorobenzyloxy)acetamide (**750b**)

[0533] Was prepared following the same procedure as described for compound **750a** (scheme**311**, example **521a**) to give **750b** (611 mg, 100% crude, yellow oil).
LRMS (ESI): (calc) 282.3; (found) 283.0 $(MH)^+$.

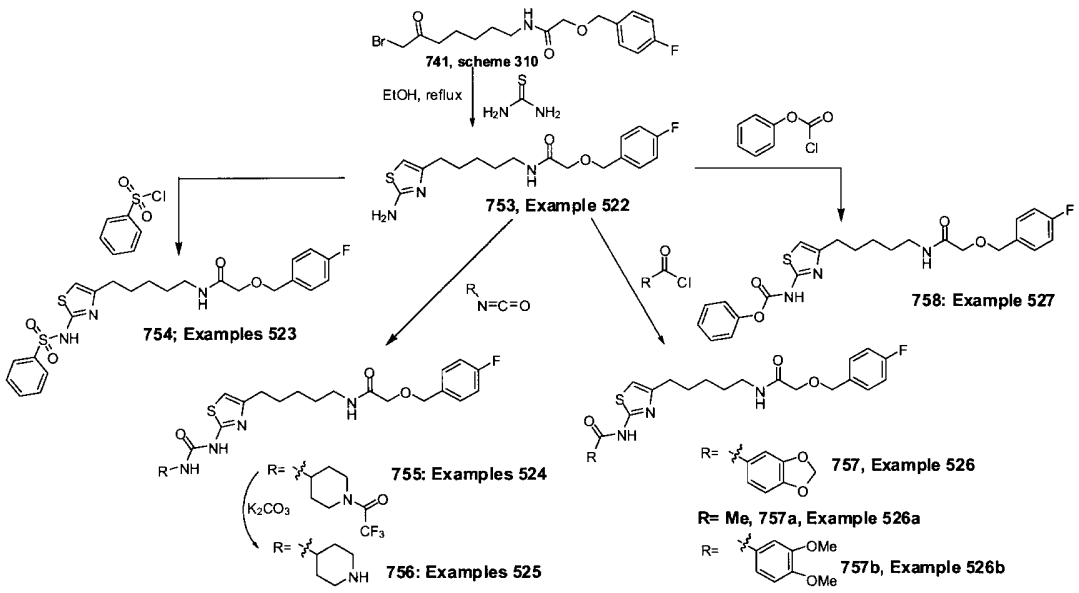
Step 3: 2-(4-fluorobenzyloxy)-N-(6-thioureidohexyl)acetamide (**751b**)

[0534] Was prepared following the same procedure as described for compound **751a** (scheme 311, Example **521a**) to give **751b** (263 mg, 100% crude) as yellow solid.

Step 4: 2-(4-fluorobenzyloxy)-N-(6-(4-(2-hydroxyphenyl)thiazol-2-ylamino)hexyl)acetamide (**752b**)

[0535] Was prepared following the same procedure as described for compound **752a** (scheme**311**, example **521a**) except that the residue was purified by silica gel column chromatography with gradient of ethyl acetate (40% - 70%) in hexane to give **752b** (8 mg, 2% yield over 4 steps) as a clear oil.
(CDCl3) δ (ppm) ^{1}H: 7.52 (dd, J=7.6, 1.6Hz, 1H), 7.31-7.27 (m, 2H), 7.21-7.16 (m, 1H), 7.07-7.02 (m, 2H), 6.97-6.82 (m, 1H), 6.68 (s, 1H), 6.60 (bs, 1H), 6.15 (bs, 1H), 4.52 (s, 2H), 3.97 (s, 2H), -3.34-3.27 (m, 4H), 1.73-1.66 (m, 2H), 1.57-1.50 (m, 2H), 1.48-1.33 (m, 4H).
LRMS (ESI): (calc) 457.5; (found) 458.0 $(MH)^+$.

Scheme 312



Example 522

N-(5-(2-aminothiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**753**)

[0536] A mixture of alpha-bromoketone **741**, scheme 310 (90 mg, 0.24), and thiourea (36.6 mg, 0.48 mmol) in EtOH (5 ml) was refluxed for 48h. The mixture was taken to dryness and the residue was purified by silica gel column chromatography with gradient of EtOAc (30-60%) in Hexanes then with gradient of MeOH (1-10%) in EtOAc. To give compound **753** (83% yield) as clear oil.

(MEOD-d_4) δ (ppm) ^{1}H 7.39 (m, 2H), 7.07 (m, 2H), 6.08 (s, 1H), 4.55 (s, 2H), 3.92 (s, 2H), 3.22 (t, J= 7Hz, 2H), 2.47, J= 0.7, 7 Hz, 2H), 1.62 (m, 2H), 1.52 (m, 2H), 1.34 (m, 2H).

LRMS (ESI): (calc.) 351.4, (found) 352.1 $(MH)^+$.

Example 523

2-(4-fluorobenzyloxy)-N-(5-(2-(phenylsulfonamido)thiazol-4-yl)pentyl)acetamide (**754**)

[0537] Aminothiazole **753** (40mg, 0.114mmol) and benzene sulfonylchloride (44□L, 0.343mmol) was dissolved in 0.5mL of pyridine, and a solution of 4-dimethylaminopyridine (4mg, 0.03mmol) in pyridine 90.5mL) was added and the mixture was shaken for 22 hours. The orange solution was, concentrated, diluted with 1M Na_2CO_3(aq.) and extracted with DCM. The organic layer was washed with 1N HCl(aq), dried (anhydrous Na_2SO_4) and concentrated. The crude material was purified by silica gel flash chromatography through a Biotage 12M column using a gradient of methanol (0 to 20%) in DCM. It was then further

purified by preparative HPLC (Aquasil C18 20×250mm, 50/50 to 100/0 methanol/water (0.1% formic acid) in 45min at 10mL/min) to give **754** as a white solid after lyophilization (17.2mg, 31%).

(DMSO-d_6) δ (ppm) ^{1}H: 12.7 (s, 1H), 7.77-7.53 (m, 3H), 7.55-7.48 (m, 3H), 7.42-7.38 (m 2H), 7.17 (t, J = 8.8Hz, 2H), 6.37 (s, 1H), 4.48 (s, 2H), 3.83 (s, 2H), 3.02 (q, J = 6.4Hz, 2H), 2.36 (t, J = 7.2Hz, 2H), 1.49 (quint, J = 7.6Hz, 2H), 1.38 (quint, J = 7.6Hz, 2H), 1.21-1.17 (m 2H). LRMS (ESI): (calc) 491.1; (found) 492.1 $(MH)^+$, 514.0 $(MNa)^+$.

Example 524

2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-(1-(2,2,2-trifluoroacetyl)piperidin-4-yl)ureido)thiazol-4-yl)pentyl)acetamide (**755**)

[0538] A solution of the aminothiazole **753** (62.5mg, 0.178mmol) and *N*-(trifluroacetyl)-piperidine-4-isocyanate (79mg, 0.356mmol) in 1mL THF inside a sealed vial was shaken on a mechanical shaker for 5.5 hours at 50°C. The reaction was cooled and PS-trisamine was added. The suspension was shaken for an additional 2.5 hours. It was filtered and the resin washed with CH_2Cl_2. The filtrate was concentrated and purified by silica gel flash chromatography through a Biotage 12M column using a gradient of MeOH (0-15%) in ethyl acetate, the material was further purified by preparative HPLC (Aquasil C18 20×250mm, methanol (0-50%) in water (0.1% formic acid) in 45min at 10mL/min) to give pure **755** (29 mg) as a semi-crystalline solid.

(DMSO-d_6) δ (ppm) ^{1}H: 10.25 (s, 1H), 7.77 (t, J = 6.0Hz, 1H), 7.41-7.38 (m, 2H), 7.19-7.14 (m, 2H), 6.61 (d, J = 7.6Hz, 1H), 6.53 (s, 1H), 4.48 (s, 2H), 4.15-4.10 (m, 1H), 3.84 (s, 2H), 3.79-3.76 (m, 2H), 3.10-3.03 (m, 3H), 1.94-1.89 (m, 2H), 1.56 (quint, J = 7.2 Hz, 2H), 1.44-1.37 (m, 4H) 1.26-1.20 (m, 2H). LRMS (ESI): (calc) 573.2; (found) 574.0 $(MH)^+$, 596.0 $(MNa)^+$

Example 525

2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-piperidin-4-ylureido)thiazol-4-yl)pentyl)acetamide hydrochloride (**756**)

[0539] To a solution of **755, scheme 312** (52mg, 0.091mmol) in methanol (1mL) of and H_2O (0.5mL) was added potassium carbonate (50mg, 0.364mmol). The reaction was stirred at room temperature for 2 h, and then it was concentrated, diluted with water (10mL) and extracted into EtOAc (3×7mL). The combined organic extracts were washed with brine, dried (anhydrous Na_2SO_4) and concentrated. Addition of HCl in CH_2Cl_2 to the crude gave the hydrochloride salt of **756** as a semi-crystalline material. The compound was further

purified by trituration with methanol and diethyl ether and then with acetonitrile to give **756** as white powder (23mg 49%).

(MEOD-d_4) δ (ppm) ^{1}H: 7.42-7.38 (m, 2H), 7.11-7.06 (m, 2H), 6.91 (s, 1H), 4.56 (s, 2H), 3.98-3.95 (m, 1H), 3.92 (s, 2H), 3.43 (ddd, J = 3.6, 3.6, 13.6Hz, 2H), 3.24 (t, J = 6.8Hz, 2H), 3.18-3.11 (m, 2H), 2.71 (t, J = 7.6Hz, 2H), 2.20-2.16 (m, 2H), 1.86-1.76 (m, 2H), 1.72 (quint, J = 7.6Hz, 2H), 1.56 (quint, J = 7.26Hz, 2H), 1.41-1.36 (m, 2H). LRMS (ESI): (calc) 477.2; (found) 478.1 $(MH)^+$, 500.0 $(MNa)^+$.

Example 526

N-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)benzo[d][1,3]dioxole-5-carboxamide (**757**)

[0540] Piperonyloyl chloride (19.1 mg, 0.1 mmol) was added to amine **753** (24.3 mg, 0.07 mmol) and dimethylaniline (12.6 mg, 0.1 mmol) in THF (1 ml). After 16 at room temperature the reaction was slow so DMAP (cat. amount) was added and immediate reaction was observed and a precipitate formed. Sat'd $NaHCO_3$, and EtOAc were added and the mixture was stirred for 30 min, then the organic layer was separated and extracted with H_2O, then 1 N HCl, dried ($MgSO_4$), filtered and concentrated and purified by silica gel column chromatography with gradient of EtOAc (60-80%) in Hexanes to give amide **757** (23.7% yield) as clear oil.

($CDCl_3$) δ (ppm) ^{1}H:7.52 (d, J=8 Hz, 1H), 7.45 (s, 1H), 7.28 (mk, 2H), 7.04 (m, 2H), 6.87 (dxd, J= 8.2, 2.7 Hz, 1H0, 6.61 (bs, 1H), 6.55 (s, 1H), 6.06 (s, 2H), 4.52 (s, 2H), 4.0 (s, 2H), 3.27 (m, 2H), 2.58 (m, 2H), 1.67 (m, 2H), 1.52 (m, 2H), 1.33 (m, 2H). LRMS (ESI): (calc.) 499.6; (found) 500.0 $(MH)^+$.

Example 526a

N-(5-(2-acetamidothiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**757a**)

[0541] Amine **753** (47.5 mg, 0.135 mmol) and 3,4-dimethoxybenzene-1-sulfonyl chloride (32 mg, 0.135 mmol), pyridine (54 uL) and acetic anhydride (0.27 ml) were heated at 100°C for 16h according to the procedure of A. S. Gupta *et al.* (Indian J. Chem. Sec. B, 1996, 967-969). The progress of the reaction was followed by MS. The only signal observed is that of the acetylated amine. The mixture was taken to dryness, EtOAc and sat'd $NaHCO_3$ were added and the organic layer was washed with H_2O, and 1 N HCl, dried ($MgSO_4$) filtered, concentrated and purified by silica gel column chromatography with gradient of EtOAc (20-100%) in Hexanes, then with MeOH (3%) in EtOAc. Amide **757a** was obtained as clear semi-crystalline solid (56.6 % yield).

($CDCl_3$) δ (ppm) ^1H: 9.2 (bs, 1H), 7.29 (m, 2H), 7.05 (m, 2H), 6.61 (bs, 1H), 6.5 (s, 1H), 4.52 (s, 2H), 3.98 (s, 2H), 3.28 (m, 2H), 2.53 (m, 2H), 2.21 (s, 3H), 1.65 (m, 2H), 1.55 (m, 2H), 1.37 (m, 2H). LRMS (ESI): (calc.) 393.5; (found) 394.1 $(MH)^+$.

Example 526b

N-(4-(5-(2-(4-fluorobenzyloxy)acetamido)-pentyl)thiazol-2-yl)-3,4-dimethoxybenzamide (**757b**)

[0542] 3,4-Dimethoxybenzoylchloride (69mg, 0.344mmol) was added to a suspension of aminothiazole **753** (41mg, 0.117mmol), 4-dimethy-laminopyridine (4mg 0.032mmol), and PS-DIEA (0.468mmol) in THF (1mL). The suspension was heated to 50°C for 2hours on a mechanical shaker. The reaction was cooled and PS-trisamine (0.468mmol) was added. The suspension was shaken for a further 2 hours at room temperature, then the resin was filtered, and the filtrate was concentrated and purified by silica gel flash chromatography through a Biotage 12M column using a gradient of EtOAc (50-100%) in CH_2Cl_2 and then a gradient of MeOH (0-15%) in EtOAc to obtain **757b** as an oily white solid (25 mg 42 %).

[0543] (DMSO-d_6) δ(ppm) ^1H: 12.43 (s, 1H), 7.78 (t, J = 6.0Hz, 1H), 7.74-7.71 (m, 2H), 7.41-7.38 (m, 2H), 7.19-7.14 (m, 2H), 7.07 (d, J = 8.4Hz, 1H), 6.78 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.08 (q, J = 6.8Hz, 2H), 2.60 (t, J = 7.6Hz, 2H), 1.64 (quint, J = 7.6Hz, 2H), 1.44 (quint, J = 7.6Hz, 2H), 1.28-1.24 (m, 2H). LRMS (ESI): (calc.) 515.2; (found0 516.0 $(MH)^+$, 538.0 $(MNa)^+$

Example 527

Phenyl 4-(5-(2-(4-fluorobenzyloxy)acetamido)-pentyl)thiazol-2-ylcarbamate (**758**)

[0544] To a solution of amine **753** (22mg, 0.063mmol) in THF (1mL) was added PS-DIEA (52mg, 0.189mmol) followed by phenylchloroformate (16uL, 0.125mmol). The suspension was stirred for 3.5 h at room temperature before the addition of PS-trisamine (31mg, 0.125mmol) to scavenge the excess phenylchloroformate. The suspension was shaken overnight on a mechanical shaker and then filtered. The resin was washed with DCM and then the filtrate concentrated to give the crude material. The crude was purified by preparative TLC using EtOAc (60%) in DCM to give **758** as a semi-crystalline white solid (15mg, 49%).

(DMSO-d_6) δ (ppm) ^1H: 12.21 (s, 1H), 7.78 (t, J = 5.6Hz, 1H), 7.44-7.39 (m, 4H), 7.27 (t, J = 7.2Hz, 1H), 7.22-7.15 (m, 4H), 6.76 (s, 1H), 4.48 (s, 2H), 3.85 (s, 2H), 3.07 (q, J = 6.4Hz,

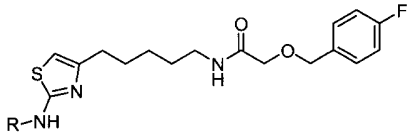
2H), 2.55 (t, J = 7.6Hz, 2H), 1.60 (quint, J = 7.2Hz, 2H), 1.43 (quint, J = 7.2Hz, 2H), 1.30-1.23 (m, 2H). LRMS (ESI): (calc) 471.2; (found) 472.0 $(MH)^+$, 494.0 $(MNa)^+$.

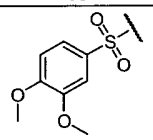
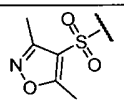
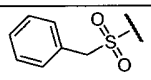
[0545] Examples **523a-d** describe the preparation of compounds **754a-d** using the same procedures as described for compound **754**, Example **523**, scheme **312**. Characterization data are presented in **Table 36**

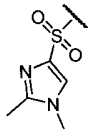
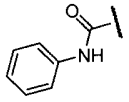
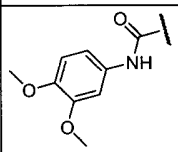
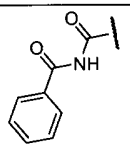
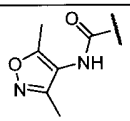
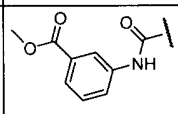
[0546] Examples **524a-** describe the preparation of compounds **755a-** using the same procedure as described for compound **755**, Example **524**, scheme **312**. Characterization data are presented in **Table 36.**

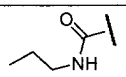
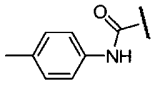
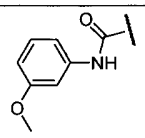
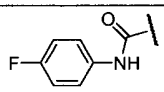
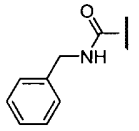
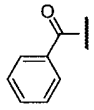
[0547] Example **526c** describe the preparation of compound **757c** using the same procedure as described for compound **757b**, Example **526b**, scheme **312**. Characterization data are presented in **Table 36.**

Table 36

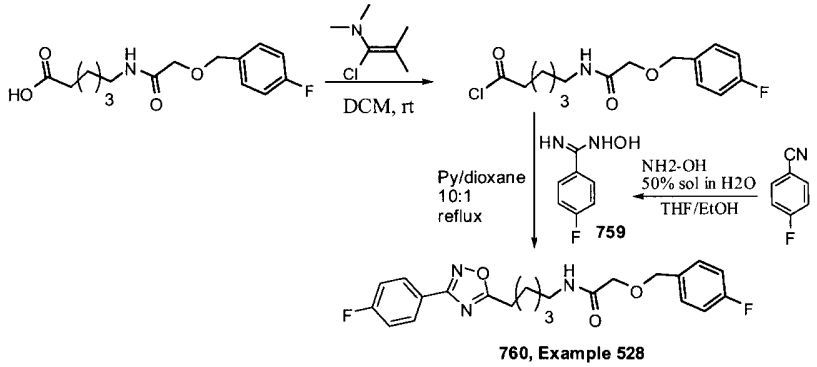


Ex	Cpd	R	Name	Characterization	Scheme
523a	754a		*N*-(5-(2-(3,4-dimethoxyphenylsulfonamido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 7.756 (t, J = 6.0Hz, 1H), 7.42-7.38 (m, 2H), 7.34 (dd, J = 2.0, 8.4Hz, 1H), 7.22 (d, J = 2.0Hz, 1H), 7.19-7.14 (m, 2H), 7.02 (d, J = 8.4Hz, 1H), 6.31 (s, 1H), 4.48 (s, 2H), 3.83 (s, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.05 (q, J = 6.8Hz, 2H), 2.48 (t, J = 7.6Hz, 2H), 1.49 (quint, J = 7.6Hz, 2H), 1.39 (quint, J = 7.2Hz, 2H), 1.21-1.17 (m, 2H). LRMS (ESI): (calc) 551.2; (found) 552.1 $(MH)^+$, 574.01 $(MNa)^+$.	312 Ex 523
523b	754b		*N*-(5-(2-(3,5-dimethylisoxazole-4-sulfonamido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.32-7.28 (m, 2H), 7.08-7.03 (m, 2H), 6.51 (t, J = 6.0Hz, 1H), 6.08 (s, 1H), 4.53 (s, 2H), 4.00 (s, 2H), 3.29 (q, J = 6.8Hz, 2H), 2.67 (s, 3H), 2.60 (t, J = 7.6Hz, 2H), 2.36 (s, 3H), 1.67 (quint. J = 7.6Hz, 2H), 1.55 (quint. J = 7.2Hz, 2H), 1.37-1.33 (m 2H). LRMS (ESI): calc 510.1; (found) 511.1 $(MH)^+$, 533.0 $(MNa)^+$.	312 Ex 523
523c	754c		2-(4-fluorobenzyloxy)-*N*-(5-(2-(phenylmethylsulfonamido)thiazol-4-yl)pentyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 12.4 (s, 1H), 7.72 (t, J = 6.0Hz, 1H), 7.37-7.34 (m, 2H), 7.28-7.21 (m, 5H), 7.14-7.10 (m, 2H), 6.22 (s, 1H), 4.44 (s, 2H), 4.20 (s, 2H), 3.02 (q, J = 6.0Hz, 2H), 2.33 (t, J = 7.6Hz, 2H), 1.47 (quint, J = 7.6Hz, 2H), 1.37 (quint, J = 7.2Hz, 2H), 1.17-1.14 (m 2H). LRMS (ESI): calc 505.2; (found) 506.1 $(MH)^+$, 528.1 $(MNa)^+$.	312 Ex 523

523d	754d		*N*-(5-(2-(1,2-dimethyl-1H-imidazole-4-sulfonamido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 7.78 (t, J = 6.0Hz, 1H), 7.48 (s, 1H), 7.42-7.38 (m, 2H), 7.19-7.15 (m, 2H), 6.27 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.52 (s, 3H), 3.05 (q, J = 6.8Hz, 2H), 2.36 (t, J = 7.2Hz, 2H), 1.50 (quint, J = 7.2Hz, 2H), 1.40 (quint, J = 7.6Hz, 2H), 1.21-1.17 (m 2H). LRMS (ESI): calc 509.2; (found) 510.22 $(MH)^+$,	312 Ex 523
524a	755a		2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-phenylureido)thiazol-4-yl)pentyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.42 (s, 1H), 8.90 (s, 1H), 7.77 (t, J = 5.6Hz, 1H), 7.45-7.38 (m , 4H), 7.29 (t, J = 7.6Hz, 2H), 7.18-7.14 (m, 2H), 7.00 (t, J = 7.2Hz, 1H), 6.62 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.07 (q, J = 6.8Hz, 2H), 2.52 (t, J = 7.2Hz, 2H), 1.59 (quint, J = 7.2Hz, 2H), 1.43 (quint, J = 7.2Hz, 2H), 1.29-1.23 (m, 2H) LRMS (ESI): calc 470.2; (found) 471.1 $(MH)^+$, 493.1 $(MNa)^+$.	312 Ex 524
524b	755b		*N*-(5-(2-(3-(3,4-dimethoxyphenyl)ureido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.38 (s, 1H), 8.75 (s, 1H), 7.77 (t, J = 6.0Hz, 1H), 7.42-7.38 (m , 2H), 7.19-7.14 (m, 3H), 6.87 (s, 2H), 6.60 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.72 (s, 3H), 6.70 (s, 3H), 3.07 (q, J = 6.8Hz, 2H), 2.48 (t, J = 7.2Hz, 2H), 1.59 (quint, J = 7.2Hz, 2H), 1.43 (quint, J = 7.2Hz, 2H), 1.26-1.23 (m, 2H). LRMS (ESI): calc 530.2; (found) 531.2 $(MH)^+$, 553.1 $(MNa)^+$.	312 Ex 524
524c	755c		*N*-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-ylcarbamoyl)benzamide	(DMSO-d_6) δ (ppm) ^{1}H: 11.86 (s, 1H), 11.46 (s, 1H), 8.00 (d, J = 7.6Hz, 2H), 7.79 (t, J = 5.6, 1H), 7.66 (t, J = 7.2Hz, 1H), 7.54 (t, J = 8.0Hz, 2H), 7.42-7.38 (m, 2H), 7.19-7.14 (m, 2H), 6.82 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.07 (q, J = 6.4Hz, 2H), 2.56 (t, J = 7.6Hz, 2H), 1.60 (quint, J = 7.6Hz, 2H), 1.43 (quint, J = 7.6Hz, 2H), 1.29-1.21(m, 2H) LRMS (ESI): calc 498.2; (found) 499.2 $(MH)^+$, 521.2 $(MNa)^+$.	312 Ex 524
524d	755d		*N*-(5-(2-(3-(3,5-dimethylisoxazol-4-yl)ureido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.80 (s, 1H), 8.06 (s, 1H), 7.78 (t, J = 5.6, 1H), 7.42-7.37 (m, 2H), 7.20-7.14 (m, 2H), 6.60 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.06 (q, J = 6.4Hz, 2H), 2.50 (t, J = 8.0Hz, 2H), 2.73 (s, 3H), 2.07 (s, 3H), 1.57 (quint, J = 7.2Hz, 2H), 1.42 (quint, J = 7.2Hz, 2H), 1.25-1.21 (m, 2H) LRMS (ESI): calc 489.2; (found) 490.2 $(MH)^+$,	312 Ex 524
524e	755e		methyl 3-(3-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)ureido)benzoate	(DMSO-d_6) δ (ppm) ^{1}H: 10.51 (s, 1H), 9.15 (s, 1H), 8.19 (s, 1H), 7.77 (t, J = 5.6Hz, 1H), 7.64 (d, J = 6.8Hz, 1H), 7.59 (d, J = 7.6Hz, 1H), 7.45-7.38 (m, 3H), 7.19-7.14 (m, 2H), 6.63 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.07 (q, J = 6.4 Hz, 2H), 2.52 (t, J = 7.2Hz, 2H), 1.59 (quint, J = 7.6 Hz, 2H), 1.43 (quint, J =6.8 Hz, 2H), 1.27-1.23 (m, 2H) LRMS (ESI): calc 528.2; (found) 529.2 $(MH)^+$, 551.2 $(MNa)^+$.	312 Ex 524

524f	755f		2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-propylureido)thiazol-4-yl)pentyl)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.30-7.27 (m, 2H), 7.08-7.02 (m, 2H), 6.59 (t, J = 5.6Hz, 1H), 6.31 (s, 1H), 4.51(s, 2H), 3.96 (s, 2H), 3.3-3.25 (m, 4H), 2.60 (t, J = 7.6Hz, 2H), 1.66 (quint, J = 7.6 Hz, 2H), 1.62-1.52 (m, 4H), 1.37-1.32 (m, 2H), 0.95 (t, J = 7.2Hz, 3H). LRMS (ESI): calc 436.2; (found) 437.2 $(MH)^+$, 459.2 $(MNa)^+$.	312 Ex 524
524g	755g		2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-p-tolylureido)thiazol-4-yl)pentyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.40 (s, 1H), 8.82 (s, 1H), 7.78 (t, J = 5.6Hz, 1H), 7.42-7.38 (m, 2H), 7.32 (d, J = 8.0Hz, 2H), 7.19-7.14 (m, 2H), 7.09 (d, J = 8.8Hz, 2H), 6.76 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.07 (q, J = 7.2Hz, 2H), 2.51 (t, J = 7.2Hz, 2H), 2.31 (s, 3H), 1.59 (quint, J = 7.6Hz, 2H), 1.43 (quint, J = 7.2Hz, 2H), 1.30-1.23 (m, 2H) LRMS (ESI): calc 484.2; (found) 485.0 $(MH)^+$, 507.0 $(MNa)^+$.	312 Ex 524
524h	755h		2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-(3-methoxyphenyl)ureido)thiazol-4-yl)pentyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.41 (s, 1H), 8.92 (s, 1H), 7.78 (t, J = 5.6Hz, 1H), 7.42-7.38 (m, 2H), 7.20-7.14 (m, 4H), 6.93 (d, J = 8.0Hz, 1H), 6.62 (s, 1H), 6.58 (dd, J = 2.4, 8.4Hz, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.72 (s, 3H), 3.07 (q, J = 6.0Hz, 2H), 2.52 (t, J = 7.2Hz, 2H), 1.59 (quint, J = 7.6Hz, 2H), 1.43 (quint, J = 7.2Hz, 2H), 1.30-1.23 (m, 2H) LRMS (ESI): calc 500.2; (found) 501.0 $(MH)^+$, 523.0 $(MNa)^+$.	312 Ex 524
524i	755i		2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-(4-fluorophenyl)ureido)thiazol-4-yl)pentyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.43 (s, 1H), 8.95 (s, 1H), 7.78 (t, J = 6.0Hz, 1H), 7.48-7.44 (m, 2H), 7.42-7.38 (m, 2H), 7.19-7.11 (m, 4H), 6.62 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.07 (q, J = 6.0Hz, 2H), 2.52 (t, J = 7.2Hz, 2H), 1.59 (quint, J = 7.6Hz, 2H), 1.43 (quint, J = 7.2Hz, 2H), 1.28-1.23 (m, 2H) LRMS (ESI): calc 488.2; (found) 489.0 $(MH)^+$, 511.0 $(MNa)^+$.	312 Ex 524
524j	755j		*N*-(5-(2-(3-benzylureido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	(CD_3OD) δ (ppm) ^{1}H: 7.41-7.37 (m, 2H), 7.32-7.30 (m, 4H), 7.26-7.22 (m, 1H), 7.07-7.05 (m, 2H), 6.51 (s, 1H), 4.54 (s, 2H), 4.42 (s, 2H), 3.91 (s,2H), 3.21 (t, J = 7.2Hz, 2H), 2.58 (t, J = 7.2Hz, 2H), 1.54 (quint, J = 8.0Hz, 2H), 1.52 (quint, J = 7.2Hz, 2H), 1.36-1.30 (m, 2H) LRMS (ESI): calc 484.2; (found) 485.1 $(MH)^+$, 507.0 $(MNa)^+$.	312 Ex 524
526c	757c		*N*-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)benzamide	(DMSO-d_6) δ (ppm) ^{1}H: 12.43 (s, 1H), 7.78 (t, J = 6.0Hz, 1H), 7.74-7.71 (m, 2H), 7.41-7.38 (m, 2H), 7.19-7.14 (m, 2H), 7.07 (d, J = 8.4Hz, 1H), 6.78 (s, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.08 (q, J = 6.8Hz, 2H), 2.60 (t, J = 7.6Hz, 2H), 1.64 (quint, J = 7.6Hz, 2H), 1.44 (quint, J = 7.6Hz, 2H), 1.28-1.24 (m, 2H) LRMS (ESI): calc 515.2; (found) 516.0 $(MH)^+$, 538.0 $(MNa)^+$.	312 Ex 526b

Scheme 313



760, Example 528

Example 528

2-(4-fluorobenzyloxy)-N-(5-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)pentyl)acetamide (**760**)

Step 1: 4-fluoro-N-hydroxybenzimidamide (**759**)

[0548] Hydroxylamine (0.35 ml, 50% solution in H_2O, 5.7 mmol) was added to a solution of 4-fluorobenzonitrile (0.59 g, 4.87 mmol) in THF (5 ml) and EtOH (1 ml) and the mixture was stirred at room temperature for 1h. The reaction mixture was concentrated and triturated from hexanes leaving **759** as a white solid (0.598 g, 79.6% yield). (DMSO-$d6_3$) δ (ppm) ^{1}H: 9.63 (s, 1H), 7.68 (m, 2H), 7.19 (m, 2H), 5.84 (bs, 2H). LRMS (ESI): (calc.) 154.1; (found) 155.1 $(MH)^+$.

Step 2: 2-(4-fluorobenzyloxy)-N-(5-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)pentyl)acetamide (**760**)

[0549] 1-chloro-N,N,2-trimethylprop-1-en-1-amine (133.6 mg/ 140 uL, 1 mmol) was added to a solution of 6-(2-(4-fluorobenzyloxy)acetamido)hexanoic acid (230 g, 0.77 mmol) in DCM (2 ml) at room temperature under N_2. After 3 h, amidine **759** (118.7 mg, 0.77 mmol), pyridine (1 ml) and dioxane (10 ml) were addded and the mixture was refluxed for 16h. The mixture was cooled to room temperature and H_2O was added (20 ml) and the oil that formed was extracted with EtOAc and the organic layer was separated, dried ($MgSO_4$), filtered, concentrated and purified by silica gel column chromatography with gradient of EtOAc (30-100%) in Hexanes. Compound **760** was obtained as a clear semi-crystalline solid (78% yield).

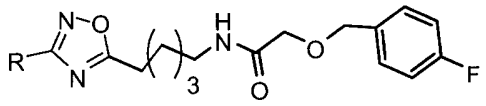
($CDCl_3$) δ (ppm) ^{1}H: 8.06 (m, 2H), 7.28 (m, 2H), 7.16(m, 2H), 7.05 (m, 2H), 6.57 (bs, 1H), 4.51 (s, 2H), 3.96 (s, 2H), 3.31 (q, J= 6.8 Hz, 2H), 2.94 (t, J= 7.5, 2H), 1.90 (m, 2H), 1.61 (m, 2H), 1.46 (m, 2H). LRMS (ESI): (calc.) 415.4; (found) 416.1 $(MH)^+$.

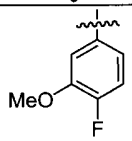
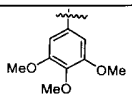
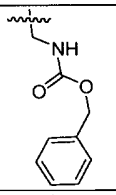
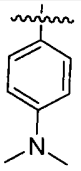
[0550] Following the procedure in **scheme 313, example 528,** step 1 the following intermediates: 4-fluoro-N-hydroxy-3-methoxybenzimidamide **759a**, N-hydroxy-3,4,5-trimethoxybenzimidamide **759b**, benzyl 2-(hydroxyamino)-2-iminoethylcarbamate **759c**, and

4-(dimethylamino)-N-hydroxybenzimidamide **759d**, were obtained in 78%, 73%, 94% and 29% respectively, replacing 4-fluorobenzonitrile with 4-fluoro-3-methoxybenzonitrile, 3,4,5-trimethoxybenzonitrile, benzyl cyanomethylcarbamate, and 4-(dimethylamino)benzonitrile in the order indicated.

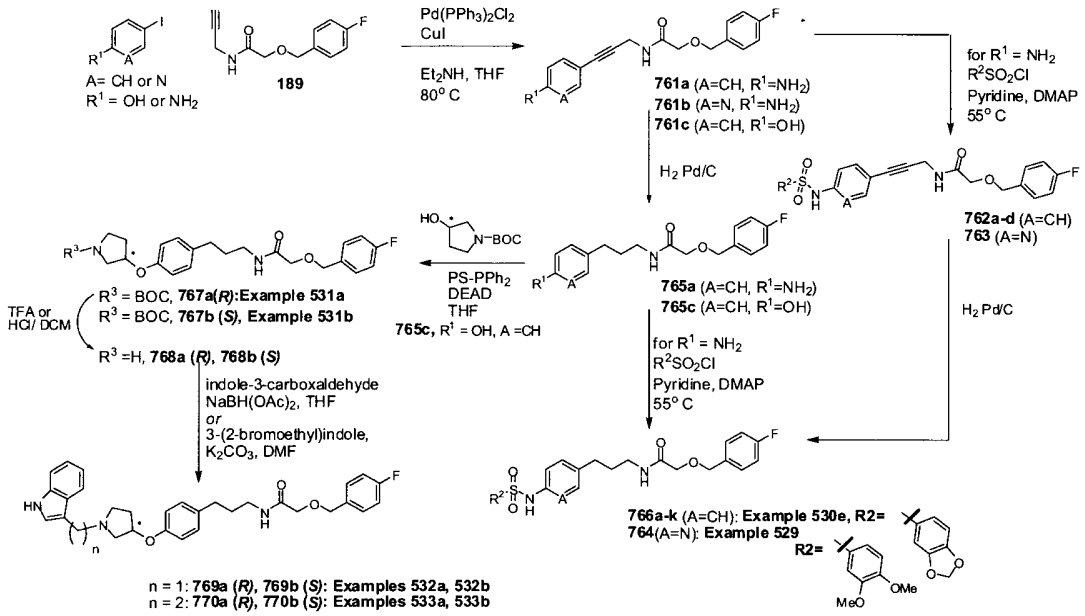
[0551] Examples **528a-d** describe the preparation of compound **760a-d** using the same procedure as described for Example **528**. Characterization data are presented in Table **37**.

Table 37



Ex	Cpd	R_3	Name	Characterization	Scheme
528a	760a		N-(5-(3-(4-fluoro-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.65 (m, 2H), 7.28 (m, 2H), dxd, J= Hz, 1H), 7.06 (m, 2H), 6.57 (bs, 1H), 4.51 (s, 2H), 3.96 (s, 3H), 3.95 (s, 2H), 3.31 (q, J= 6.9 Hz, 2H), 2.4 (t, J= 7.5, 2H), 1.9 (quint, J= 7.6 Hz, 2H), 1.6 (m, 2H), 1.45 (m, 2H). LRMS (ESI): (calc.) 445.5; (found) 446.1 $(MH)^+$	313 Int. 759a Ex 528
528b	760b		2-(4-fluorobenzyloxy)-N-(5-(3-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazol-5-yl)pentyl)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.31 (s, 2H), 7.28 (m, 2H), 7.05 (m, 2H), 6.58 (bs, 1H), 4.51 (s, 2H), 3.96 (s, 2H), 3.93 (s, 6H), 3.9 (s, 3H), 3.31 (q, J= 7 Hz, 2H), 2.95 (t, J= 7.6 Hz, 2H), 1.91 (quint, J= 7.6 Hz, 2H), 1.58 (m, 2H), 1.45 (m, 2H) LRMS (ESI): (calc.) 487.5; (found) 488.1 $(MH)^+$	313 Int. 759b Ex 528
528c	760c		benzyl (5-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)-1,2,4-oxadiazol-3-yl)methylcarbamate	($CDCl_3$) δ (ppm) ^{1}H:7.36-7.25 (m, 7H), 7.06 (m, 2H), 6.56 (bs, 1H), 5.37 (bs, 1H), 5.14 (s, 2H), 4.5 (overlapped d and s, 4H), 3.95 (s, 2H), 3.28 (q, J= 6.8 Hz, 2H), 2.87 (t, J= 7.3 Hz, 2H), 1.82 (m, 2H), 1.55 (m, 2H), 1.41 (m, 2H). LRMS (ESI): (calc.) 484.5; (found) 485.1 $(MH)^+$	313 Int. 759c Ex 528
528d	760d		N-(5-(3-(4-(dimethylamino)phenyl)-1,2,4-oxadiazol-5-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide	($CDCl_3$) δ (ppm) ^{1}H:7.93 (d, J= 9 Hz, 2H), 7.28 (m, 2H), 7.05 (m, 2H), 6.78 (poorly resolved doublet, 2H), 6.57 (poorly resolved triplet, 1H),4.51 (s, 2H), 3.95 (s, 2H), 3.30 (q, J= 6.7 Hz, 2H), 3.04 (s, 6H), 2.92 (t, J= 7.4H, 2H),1.89 (m, 2H), 1.58 (m, 2H), 1.45 (m, 2H). LRMS (ESI): (calc.) 440.5; (found) 441.3 $(MH)^+$	313 Int. 759d Ex 528

Scheme 314



Example 529

N-(3-(6-(3,4-dimethoxyphenylsulfonamido)pyridin-3-yl)propyl)-2-(4-fluorobenzyloxy)acetamide (**764**)

Step 1: *N*-(3-(6-aminopyridin-3-yl)prop-2-ynyl)-2-(4-fluoro-benzyloxy)acetamide (**761b**)

[0552] A solution of alkyne **189** (100mg, 0.452mmol), 2-amino-5-iodopyridine (99.5mg, 0.452mmol), $Pd(PPh_3)_2Cl_2$ (16mg, 0.023mmol), and copper iodide (9mg, 0.45mmol) in diethylamine (0.23mL, 2.3mmol) and THF (2mL) was stirred at room temperature under nitrogen for 1 hour. An additional amount of 2-amino-5-iodopyridine (10mg, 0.045mmol) was tadded and the reaction stirred for another 30 min. The reaction was concentrated and purified by silica gel flash chromatography using a Biotage 12M column and a stepwise gradient of EtOAc (50-100%) in hexanes, then a gradient of MeOH (0-10%) in EtOAc to give **761b** as yellow solid (117mg, 83%).

(DMSO-d_6) δ (ppm) ^{1}H: 8.31 (t, J = 5.6Hz, 1H), 7.94 (d, J = 1.6Hz, 1H), 7.44-7.40 (m, 2H), 7.34 (dd, J = 2.4, 8.8Hz, 1H), 7.19-7.13 (m, 2H), 6.36 (d, J = 8.8Hz, 1H), 6.31 (s, 2H), 4.50 (s, 2H), 4.10-4.08 (m, 2H), 3.92 (s, 2H).

LRMS (ESI): (calc.) 313.3; (found) 314.0 $(MH)^+$.

Step 2: *N*-(3-(6-(3,4-dimethoxyphenyl-sulfonamido)pyridin-3-yl)prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide (**763**)

[0553] Amine **761b** (134mg, 0.428mmol), 3,4-dimethoxybenzenesulfonyl chloride (152mg, 0.642mmol) and 4-dimethyl-aminoaniline (16mg, 0.128mmol) were heated at 60°C

in pyridine (2mL) inside a sealed vial for 24 hours as described for Example **523**, scheme **312**. Purification by silica gel flash chromatography through a Biotage 25M column using a gradient of EtOAc (50-100%) in DCM gave **763** as a white fluffy solid (53mg, 24%).
(MEOD-d_4) δ (ppm) ^{1}H: 8.16 (d, J = 2.4Hz, 1H), 7.34 (dd, J = 2.0, 8.4Hz, 1H), 7.52 (dd, J = 2.4, 8.4Hz, 1H), 7.45 (s, 1H), 7.41-7.38 (m, 2H), 7.12 (d, J = 8.4Hz, 1H), 7.08-7.04 (m, 2H), 7.00 (d, J = 8.4Hz, 1H), 4.56 (s, 2H), 4.20 (s, 2H), 3.96 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H).
LRMS (ESI): (calc.) 513.14; (found) 514.0 $(MH)^+$, 536.0 $(MNa)^+$.

Step 3: N-(3-(6-(3,4-dimethoxyphenylsulfonamido)pyridin-3-yl)propyl)-2-(4-fluorobenzyloxy)acetamide (**764**)

[0554] Compound **763** (50mg, 0.097mmol) in MeOH (0.3mL), *N,N*-dimethylacetamide (0.3mL) and palladium on activated charcoal (5% wt, 30mg) was hydrogenated under an 1 atmosphere of hydrogen gas. Thematerial was purified by silica gel flash chromatography using a Biotage 12S column using a gradient of EtOAc (20-100%) in DCM followed by a gradient of MeOH (0-15%) in EtOAc. Trituration with methanol and pentane gave **764** as an off-white powder (21mg, 42%).
(MEOD-d_4) δ (ppm) ^{1}H: 7.87 (d, J = 1.6Hz, 1H), 7.57 (dd, J = 2.4, 8.8Hz, 1H), 7.50 (dd, J = 2.0, 8.0Hz, 1H), 7.24 (d, J = 2.0Hz, 1H), 7.41-7.37 (m, 2H), 7.16 (dd, J = 0.8, 8.8Hz, 1H), 7.10-7.05 (m, 2H), 7.00 (d, J = 8.4Hz, 1H), 4.53 (s, 2H), 3.88 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.22 (t, J = 6.8Hz, 2H), 2.52 (t, J = 7.6Hz, 2H), 1.76 (quint. J = 7.6Hz, 2H).
LRMS (ESI): (calc.) 517.17; (found) 518.0 $(MH)^+$, 540.0 $(MNa)^+$.

Example 530e

N-(3-(4-(benzo[d][1,3]dioxole-5-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)-acetamide (**766e**)

Step 1: N-(3-(4-aminophenyl)prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide (**761a**)

[0555] A solution of alkyne **189** (1.00g, 4.52mmol), 4-iodoaniline (0.991g, 4.52mmol), $Pd(PPh_3)_2Cl_2$ (0.159g, 0.226mmol), and copper iodide (86mg, 0.452mmol) in diethylamine (2.3mL, 22.6mmol) and THF (20mL) was reacted as described for **761b**, Example **529**, step 1. After 1h, the mixture was concentrated and purified by silica gel flash chromatography using a stepwise gradient of EtOAc (20-80%) in hexanes to afford **761a** as an orange oil (1.13g, 80%). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.28 (t, J = 5.6Hz, 1H), 7.44-7.40 (m, 2H), 7.19-7.13 (m, 2H), 7.02 (d, J = 8.8Hz, 2H), 6.46 (d, J= 8.8Hz, 2H), 5.44 (s, 2H), 4.50 (s, 2H), 4.07 (d, J= 5.6Hz, 2H) 3.91 (s, 2H).

Step 2: *N*-(3-(4-aminophenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**765a**)

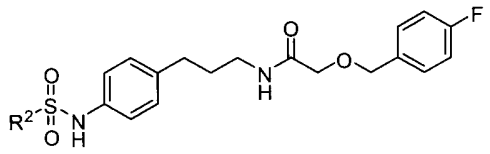
[0556] Compound **761a** (0.721g, 2.31mmol) in methanol (8mL) and palladium on charcoal (5% wt, 150mg) was hydrogenated under an atmosphere of hydrogen gas as described for **763**, Example **529**, step 3. Purification by chromatography using a stepwise gradient of EtOAc (40-100%) in hexanes gave **765a** as pinkish solid (0.470g, 64%). ^{1}H NMR (DMSO-d_6) δ (ppm) ^{1}H: 7.87 (t, J = 6.0Hz, 1H), 7.42-7.39 (m, 2H), 7.19-7.14 (m, 2H), 6.80 (d, J = 8.0Hz, 2H), 6.44(d, J= 8.0 2H), 4.80 2H), 4.48(s, 2H), 3.85 (s, 2H), 3.06 (q, J = 6.8Hz, 2H), 2.51 (t, J = 8.0Hz, 2H), 1.61 (quint., J = 7.6Hz, 2H). LRMS (ESI): (calc.) 316.4; (found) 317.1 $(MH)^+$, 339.0 $(MNa)^+$.

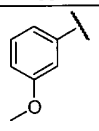
Step 3: *N*-(3-(4-aminophenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**766e**)

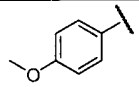
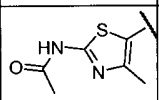
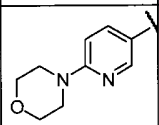
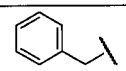
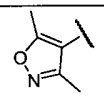
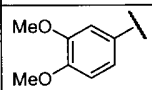
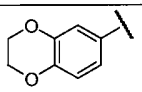
[0557] Reaction of **765a** (80mg, 0.253mmol) with1,3-benzodioxole-5-sulfonylchloride (61.4mg, 0.278mmol) and 4-dimethylaminoaniline (9mg, 0.076mmol) at 55°C in pyridine (1mL) inside a sealed vial for 6 hours as described for compound **754**, Example **523**, scheme **312**. Purification by silica gel flash chromatography using a Biotage 12M column and a gradient of EtOAc (20-90%) in DCM gave ***766e*** as a white solid (86mg, 68%). (DMSO-d_6) δ (ppm): 10.0 (s, 2H), 7.81 (t, J = 5.6Hz, 1H), 7.415-7.38 (m, 2H), 7.23 (dd, J = 1.6, 8.0Hz, 1H), 7.18-7.14 (m, 3H), 7.04-6.94 (m, 5H), 6.10 (s, 2H), 4.48 (s, 2H), 3.84 (s, 2H), 3.04 (q, J = 6.4Hz, 2H), 2.42 (t, J = 8.0Hz, 2H), 1.62 (quint., J = 7.2Hz, 2H). LRMS (ESI): (calc.) 500.14; (found) 501.0 $(MH)^+$, 523.0 (MNa^+).

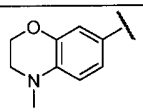
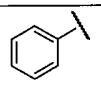
[0558] Examples **530a-k** describe the preparation of compound **766a-k** using the same procedure as described either for for Example **529 or 530e,** scheme **314.** Characterization data are presented in Table **38**.

Table 38



Ex	No.	R^2	Name	Characterization	Scheme
530a	766a		2-(4-fluorobenzyloxy)-*N*-(3-(4-(3-methoxyphenylsulfonamido)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 6.60-6.56 (m, 2H), 6.53 (d, J = 8.4Hz, 1H), 6.47 (m, 1H), 6.39-6.37 (m, 1H), 6.29-6.23 (m, 5H), 6.17 (d, J = 8.8Hz, 2H), 3.74 (s, 2H), 3.09 (s, 2H), 2.93 (s, 3H), 2.39 (t, J = 7.2Hz, 2H), 1.73 (t, J = 7.6Hz, 2H), 0.946 (quint, J = 7.2Hz, 2H). LRMS (ESI): (calc) 486.2; (found) 487.0 $(MH)^+$, 509.0 $(MNa)^+$.	314 Ex 529, step1-3

530b	766b		2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methoxyphenylsulfonamido)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.99 (s, 1H), 7.81 (t, J = 6.0Hz, 1H), 7.62 (d, J = 8.8Hz, 2H), 7.41-7.38 (m, 2H), 7.18-7.14 (m, 2H), 7.02 (m, 4H), 6.95 (d, J = 8.8Hz, 2H), 4.47 (s, 2H), 3.83 (s, 2H), 3.76 (s, 3H), 3.03 (q, J = 6.8Hz, 2H), 2.42 (t, J = 7.2Hz, 2H), 1.61 (quint. J = 7.6Hz, 2H). LRMS (ESI): calc 486.2; (found) 487.0 $(MH)^+$, 509.0 $(MNa)^+$.	314 Ex 529, step1-3
530c	766c		*N*-(3-(4-(2-acetamido-4-methylthiazole-5-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(MEOD-d_4) δ (ppm) ^{1}H: 7.42-7.38 (m, 2H), 7.11-7.02 (m, 6H), 4.55 (s, 2H), 3.61 (s, 2H), 3.20 (t, J = 7.2Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.34 (s, 3H), 2.17 (s, 3H), 1.77 (quint. J = 7.2Hz, 2H). LRMS (ESI): calc 534.1; (found) 535.0 $(MH)^+$, 557.0 $(MNa)^+$.	314 Ex 529, step1-3
530d	766d		2-(4-fluorobenzyloxy)-*N*-(3-(4-(6-morpholinopyridine-3-sulfonamido)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.98 (s, 1H), 8.24 (d, J = 2.4Hz, 1H), 7.82 (t, J = 6.0Hz, 1H), 7.68 (dd, J = 2.4, 9.2Hz, 1H), 7.42-7.38 (m, 2H), 7.18-7.14 (m, 2H), 7.04 (d, J = 8.8Hz, 2H), 6.97 (d, J = 8.4Hz, 2H), 6.85 (d, J = 9.2Hz, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.63-3.60 (m, 4H), 3.54-3.51 (m, 4H), 3.04 (t, J = 6.4Hz, 2H), 2.43 (t, J = 6.4Hz, 2H), 1.62 (quint. J = 7.2Hz, 2H). LRMS (ESI): calc 542.2; (found) 543.1 $(MH)^+$, 565.0 $(MNa)^+$.	314 Ex 529, step1-3
530f	766f		2-(4-fluorobenzyloxy)-*N*-(3-(4-(phenylmethylsulfonamido)phenyl)propyl)acetamide	(MEOD-d_4) δ (ppm) ^{1}H: 7.14-7.38 (m, 2H), 7.31-7.28 (m, 3H), 7.27-7.29 (m, 2H), 7.15-7.05 (m, 6H), 4.55 (s, 2H), 4.33 (s, 2H), 3.91 (s, 2H), 3.25 (t, J = 6.8Hz, 2H), 2.56 (t, J = 7.2Hz, 2H), 1.81 (quint. J = 7.2Hz, 2H). LRMS (ESI): calc 470.2; (found) 471.0 (MH^+), 493.0$(MNa)^+$.	314 Ex 530e, step1-3
530g	766g		*N*-(3-(4-(3,5-dimethylisoxazole-4-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(MEOD-d_4) δ (ppm) ^{1}H: 7.23-7.39 (m,2H), 7.14 (d, J = 8.8Hz, 2H), 7.11-7.06 (m, 2H), 7.02 (d, J = 8.4Hz, 2H), 4.57 (s, 2H), 3.92 (s, 2H), 3.23 (t, J = 7.2Hz, 2H), 2.59 (t, J = 8.0Hz, 2H), 2.36 (m, 3H), 2.19 (S, 3H), 1.79 (quint, J = 7.6Hz, 2H) LRMS (ESI): calc 475.2; (found) 476.0 $(MH)^+$, 498.0 $(MNa)^+$.	314 Ex 530e, step1-3
530h	766h		*N*-(3-(4-(3,4-dimethoxyphenylsulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.92 (s, 1H), 7.81 (t, J = 6.0Hz, 1H), 7.41-7.38 (m, 2H), 7.26 (dd, J = 2.4, 8.4Hz, 1H), 7.18-7.14 (m, 3H), 7.04-7.01 (m, 3H), 6.96 (d, J = 8.4Hz, 2H), 4.47 (s, 2H), 3.84 (s, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.04 (q, J = 6.4Hz, 2H), 2.42 (t, J = 7.6Hz, 2H), 1.61 (quint, J = 7.2Hz, 2H). LRMS (ESI): calc 516.2; (found) 517.0 $(MH)^+$, 539.0 $(MNa)^+$.	314 Ex 530e, step1-3
530i	766i		*N*-(3-(4-(2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.03 (s, 1H), 7.82 (t, J = 6.0Hz, 1H), 7.42-7.38 (m, 2H), 7.18-7.14 (m, 4H), 7.03 (d, J = 8.8Hz, 2H), 6.98-6.94 (m, 3H), 4.47 (s, 2H), 4.26-4.23 (m, 4H), 3.84 (s, 2H), 3.04 (q, J = 6.4Hz, 2H), 2.424 (t, J = 7.6Hz, 2H), 1.62 (quint, J = 7.2Hz, 2H). LRMS (ESI): calc 514.2; obs 515.0 $(MH)^+$, 537.0 $(MNa)^+$.	314 Ex 530e, step1-3

530j	766j		2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-sulfonamido)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.90 (s, 1H), 7.82 (t, J = 6.0Hz, 1H), 7.42-7.38 (m, 2H), 7.18-7.14 (m, 2H), 7.03 (d, J = 8.4Hz, 2H), 6.97 (d, J = 8.8Hz, 2H), 6.93-6.90 (m, 2H), 6.70 (d, J = 8.8Hz, 1H), 4.48 (s, 2H), 4.23-4.21 (m, 2H), 3.84 (s, 2H), 3.23-3.21 (m, 2H), 3.04 (q, J = 7.2Hz, 2H), 2.76 (s, 3H), 2.42 (t, J = 7.6Hz, 2H), 1.62 (quint, J = 7.6Hz, 2H). LRMS (ESI): calc 527.2; (found) 528.0 $(MH)^+$, 550.0 $(MNa)^+$.	314 Ex 530e, step1-3
530k	766k		2-(4-fluorobenzyloxy)-*N*-(3-(4-(phenylsulfonamido)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.15 (s, 1H), 7.81 (t, J = 6.0Hz, 1H), 7.72-7.69 (m, 2H), 7.59-7.55 (m, 1H), 7.53-7.49 (m, 2H), 7.41-7.38 (m, 2H), 7.18-7.14 (m, 2H), 7.02 (d, J = 8.4Hz, 2H), 6.95 (d, J = 8.4Hz, 2H), 4.47 (s, 2H), 3.83 (s, 2H), 3.03 (q, J = 6.4Hz, 2H), 2.41 (t, J = 7.6Hz, 2H), 1.61 (quint, J = 7.6Hz, 2H). LRMS (ESI): (calc) 456.2; (found) 457.0 $(MH)^+$, 479.0 $(MNa)^+$.	314 Ex 530e, step1-3

Example 531a

(R)-tert-butyl 3-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenoxy)pyrrolidine-1-carboxylate (**767a**)

Step 1: 2-(4-fluorobenzyloxy)-N-(3-(4-hydroxyphenyl)prop-2-ynyl)acetamide (**761c**)

[0559] A solution of alkyne **189** (2.01g, 9.10mmol), 4-iodophenol (2.00g, 9.10mmol), $Pd(PPh_3)_2Cl_2$ (0.319g, 0.455mmol), and copper iodide (173mg, 0.910mmol) in diethylamine (4.7mL, 46mmol) and THF (30mL) was stirred at room temperature under nitrogen for 1 hour as described for **761b**, Example **530e**, step 1. The crude material was purified by silica gel flash chromatography using a stepwise gradient of EtOAc (50-80%) in hexanes to afford **761c** as orange oil (2.0g, 71%). LRMS (ESI): (calc.) 313.3; (found) 314.0 $(MH)^+$, 336.0 (MNa^+).

Step 2: 2-(4-fluorobenzyloxy)-N-(3-(4-hydroxyphenyl)propyl)acetamide (**765c**)

[0560] Palladium on charcoal (5% wt, 400mg) was added to a solution of **761c** (2.0g, 6.4mmol) in methanol (20mL) and the reaction was carried out as described for **765a**, Example **530e**, step 2. The crude material was purified by silica gel flash chromatography using a stepwise gradient of EtOAc (50-80%) in hexanes to obtain **765c** as a white solid (1.72g, 85%). LRMS (ESI): (calc.) 317.4; (found) 318.1 $(MH)^+$, 340.0 (MNa^+).

Step 3: (R)-tert-butyl 3-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenoxy)-pyrrolidine-1-carboxylate (**767a**)

[0561] To a flask containing a suspension of PS-PPh_2 (1.54g, 3.32mmol) in THF (20mL) under nitrogen was added compound **765c** (0.700g, 2.21mmol). The suspension was stirred for 15 minutes before the addition of DEAD (1.15g of 40% solution in toluene, 2.65mmol). After 45 minutes, (S)-(-)-*N*-BOC-3-pyrrolidinol (0.413g, 2.21mmol) was added as a solid. The suspension was stirred for 20 hours and then filtered, and the resin was washed with

DCM and the filtrate was concentrated and purified by silica gel chromatography using a stepwise gradient of EtOAc (50-100%) in hexanes to obtain **767a** as clear oil (0.302g, 28%).

[0562] (MEOD-d_4) δ (ppm) ^{1}H: 7.42-7.38 (m, 2H), 7.12-7.09 (m, 2H), 7.07 (d, J = 8.8Hz, 2H), 6.82 (d, J = 8.8Hz, 2H), 4.93 (br s, 1H), 4.56 (s, 2H), 3.91 (s, 2H), 3.54-3.43 (m, 4H), 3.24 (t, J = 6.8Hz, 2H), 2.56 (t, J = 7.6Hz, 2H), 2.15-2.10 (m, 2H), 1.79 (quint. J = 7.2Hz, 2H), 1.46-1.44 (m, 9H). LRMS (ESI): (calc.) 486.3; (found) 487.1 $(MH)^+$, 509.1 (MNa^+).

Example 532a

R)-*N*-(3-(4-(1-((1H-indol-3-yl)methyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**769a**)

Step 1: (*R*)-2-(4-fluorobenzyloxy)-N-(3-(4-(pyrrolidin-3-yloxy)phenyl)propyl)acetamide (**768a**).

[0563] Compound **767a** (0.264g, 0.543mmol) was stirred in a solution of trifluoroacetic acid (1mL) in DCM (1mL) for 2 hours. The mixture was concentrated and dissolved in EtOAc and washed with saturated $NaHCO_3$(aq.) (X3), dried (Na_2SO_4) and concentrated to a give amine **768a** as brown solid (0.209g, 99%).

LRMS (ESI): (calc.) 386.5; (found) 387.2 $(MH)^+$, 409.1 (MNa^+).

Step 2:(*R*)-*N*-(3-(4-(1-((1H-indol-3-yl)methyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**769a**)

[0564] Amine **768a** (84mg, 0.22mmol) and indole-3-carboxaldehyde (32mg, 0.22mmol) were stirred in THF (1mL) at room temperature for 1 hour. $NaBH(OAc)_3$ (46mg, 0.22mmol) was added and the reaction was stirred for 20 hours, concentrated, re-dissolved in dichloromethane and washed with water. The organic phase was dried (Na_2SO_4) and concentrated, and the crude material was purified by silica gel flash chromatography using a Biotage 12M column and a slow gradient of MeOH (2-15% methanol) in DCM. It was then further purified by washing the compound in DCM with saturated $NaHCO_3$ (aq.) (X3), and the organic layer was dried (Na_2SO_4) and concentrated to give pure **769a** as a white solid (65mg, 58%).

(MEOD-d_4) δ (ppm) ^{1}H: 7.62 (d, J = 7.6Hz, 1H), 7.40-7.37 (m, 2H), 7.34 (d, J = 8.0Hz, 1H), 7.21 (s, 1H), 7.11-7.00 (m, 6H), 6.72 (d, J = 8.4Hz, 2H), 4.78 (br s, 1H), 4.53 (s, 2H), 3.90 (s, 2H), 3.91 (d, J = 13.6Hz, 1H), 3.86 (d, J = 13.2Hz, 1H), 3.22 (t, J = 7.2Hz, 2H), 2.95 (dd, J = 6.4, 10.8Hz, 1H), 2.88-2.80 (m, 2H), 2.65-2.59 (m, 1H), 2.53 (t, J = 8.0Hz, 2H), 2.29-2.22 (m, 1H), 1.94-1.86 (m, 1H), 1.77 (quint. J = 7.2Hz, 2H).

LRMS (ESI): (calc.) 515.3; (found) 516.2 $(MH)^+$, 538.2 (MNa^+).

Example 533a

(*R*)-*N*-(3-(4-(1-(2-(1H-indol-3-yl)ethyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**770a**)

[0565] A suspension of amine **768a** (82mg, 0.21mmol), 3-(2-bromoethylindole (48mg, 0.21mmol) and potassium carbonate (88mg, 0.639mmol) was heated to 90°C in DMF (1mL) for 3 hours. The suspension was then cooled and filtered and the filtrate taken to dryness. The residue was purified by silica gel flash chromatography using a gradient of MeOH (1-5%) in DCM to afford **770a** as yellow oil (39mg, 35%).

(MEOD-d_4) δ (ppm) ^{1}H: 7.53 (d, J = 7.6Hz, 1H), 7.41-7.38 (m, 2H), 7.31 (d, J = 8.4Hz, 1H), 7.11-7.05 (m, 6H), 6.99 (t, J = 7.6Hz, 1H), 6.79 (d, J = 8.4Hz, 2H), 4.87 (br s, 1H), 4.55 (s, 2H), 3.91 (s, 2H), 3.24 (t, J = 7.2Hz, 2H), 3.00-2.92 (m, 5H), 2.87-2.80 (m, 2H), 2.68-2.59 (m, 2H), 2.56 (t, J = 7.2Hz, 2H), 2.35-2.28 (m, 1H), 2.00-1.96 (m, 1H), 1.79 (quint. J = 7.2Hz, 2H).

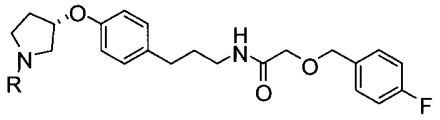
LRMS (ESI): (calc.) 529.3; (found) 530.2 $(MH)^+$, 552.2 (MNa^+).

[0566] Example **531b** describes the preparation of compound **767b** using the same procedures as described for compound **767a**, example **531a**, step 3, scheme 314, replacing (S)-(-)-*N*-BOC-3-pyrrolidinol, with (R)-(-)-*N*-BOC-3-pyrrolidinol. Characterization data are presented in Table **38**.

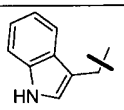
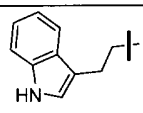
[0567] Example **532b** describes the preparation of compound **769b** using the same procedures as described for compound **769a**, example **532a**, step 2, scheme **314**, replacing **768a**, for **768b**. Characterization data are presented in Table **38**.

[0568] Example **533b** describes the preparation of compound **770b** using the same procedure as described for compound **770a**, example **533a**, scheme **314**, replacing **768a**, for **768b**. Characterization data are presented in Table **39**.

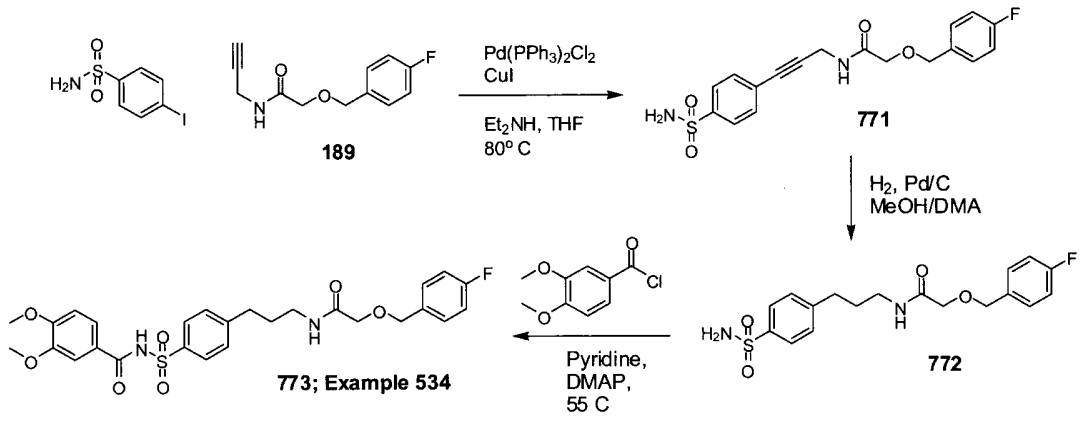
Table 39



Ex	No.	R^2	Name	Characterization	Scheme
531b	767b		(S)-tert-butyl 3-(4-(3-(2-(4-fluorobenzyloxy) acetamido)propyl)phenoxy)pyrrolidine-1-carboxylate	(MEOD-d_4) δ (ppm) ^{1}H: 7.42-7.38 (m, 2H), 7.12-7.08 (m, 2H), 7.07 (d, J = 8.8Hz, 2H), 6.82 (d, J = 8.8Hz, 2H), 4.92 (br s, 1H), 4.55 (s, 2H), 3.91 (s, 2H), 3.54-3.43 (m, 4H), 3.24 (t, J = 6.8Hz, 2H), 2.56 (t, J = 7.6Hz, 2H), 2.15-2.10 (m, 2H), 1.79 (quint. J = 7.2Hz, 2H), 1.46-1.44 (m, 9H). LRMS (ESI): (calc.) 486.3; (found) 487.1 $(MH)^+$, 509.1 (MNa^+).	314 Ex 531a, step3

532b	769b		(S)-N-(3-(4-(1-((1H-indol-3-yl)methyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(MEOD-d_4) δ (ppm) ^{1}H: 7.62 (d, J = 7.6Hz, 1H), 7.41-7.37 (m, 2H), 7.34 (d, J = 8.0Hz, 1H), 7.21 (s, 1H), 7.11-7.00 (m, 6H), 6.73 (d, J = 8.4Hz, 2H), 4.80 (br s, 1H), 4.54 (s, 2H), 3.90 (s, 2H), 3.91 (d, J = 13.6Hz, 1H), 3.86 (d, J = 13.2Hz, 1H), 3.22 (t, J = 7.2Hz, 2H), 2.96 (dd, J = 6.4, 10.8Hz, 1H), 2.90-2.81 (m, 2H), 2.65-2.62 (m, 1H), 2.54 (t, J = 8.0Hz, 2H), 2.32-2.23 (m, 1H), 1.95-1.87 (m, 1H), 1.78 (quint. J = 7.2Hz, 2H). LRMS (ESI): (calc.) 515.26 ; (found) 516.2 (MH^+), 538.2 (MNa^+)	314 Ex 532a, step2
533b	770b		(S)-*N*-(3-(4-(1-(2-(1H-indol-3-yl)ethyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy) acetamide	(MEOD-d_4) δ (ppm) ^{1}H: 7.53 (d, J = 7.6Hz, 1H), 7.39-7.36 (m, 2H), 7.32 (d, J = 8.4Hz, 1H), 7.09-7.05 (m, 6H), 6.99 (t, J = 7.6Hz, 1H), 6.78 (d, J = 8.4Hz, 2H), 4.85 (br s, 1H), 4.53 (s, 2H), 3.90 (s, 2H), 3.21 (t, J = 7.2Hz, 2H), 3.00-2.92 (m, 5H), 2.89-2.83 (m, 2H), 2.68-2.62 (m, 2H), 2.55 (t, J = 8.0Hz, 2H), 2.33-2.28 (m, 1H), 2.00-1.96 (m, 1H), 1.78 (quint. J = 7.6Hz, 2H). LRMS (ESI): (calc.) 529.3; (found) 530.2 (MH^+), 552.2 (MNa^+);	314 Ex 533a

Scheme 315



Example 534

N-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylsulfonyl)-3,4-dimethoxybenzamide (**773**)

Step 1:2-(4-fluorobenzyloxy)-*N*-(3-(4-sulfamoylphenyl)prop-2-ynyl)acetamide (**771**)

[0569] A solution of alkyne **189** (78mg, 0.35mmol), 4-iodobenzenesulfonamide (100mg, 0.35mmol), $Pd(PPh_3)_2Cl_2$ (12mg, 0.018mmol), and copper iodide (7mg, 0.04mmol) in diethylamine (0.18mL, 1.8mmol) and THF (1.5mL) was stirred under nitrogen for 1 hour at room temperature as described for **761b**, Example **530e**, step 1, scheme **314**. The crude material was purified by column chromatography eluting with a gradient of acetone (25%) in DCM to afford **771** as a white solid (80mg, 60%).

(DMSO-d_6) δ (ppm) ^{1}H: 8.41 (t, J = 5.6Hz, 1H), 7.77 (d, J = 8.8Hz, 2H), 7.57 (d, J = 8.4Hz, 2H), 7.45-7.41 (m, 4H), 7.19-7.17 (m, 2H), 4.51 (s, 2H), 4.17 (d, J = 6.0Hz, 2H), 3.94 (s, 2H). LRMS (ESI): (calc.) 376.4; (found) 377.0 $(MH)^+$,

Step 2: 2-(4-fluorobenzyloxy)-*N*-(3-(4-sulfamoylphenyl)propyl)acetamide (**772**)

[0570] Compound **771** (78mg, 0.21mmol) in methanol (1mL), *N,N*-dimethylacetamide (1mL) and palladium on charcoal (5% wt, 30mg) was hydrogenated as described for **765a**, Example **530e**, step 2, scheme **314**. Filtration of the catalyst and concentration gave **772** as a grey solid (61mg, 77%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.88 (t, J = 5.6Hz, 1H), 7.70 (d, J = 8.4Hz, 2H), 7.43-7.39 (m, 2H), 7.37 (d, J = 8.4Hz, 2H), 7.28 (s, 2H), 7.19-7.15 (m, 2H), 4.49 (s, 2H), 3.86 (s, 2H), 3.09 (q, J = 6.4Hz, 2H), 2.61 (t, J = 7.6Hz, 2H), 1.72 (quint., J = 7.2Hz, 2H).

LRMS (ESI): (calc.) 380.4; (found) 381.0 $(MH)^+$, 409.1 (MNa^+),

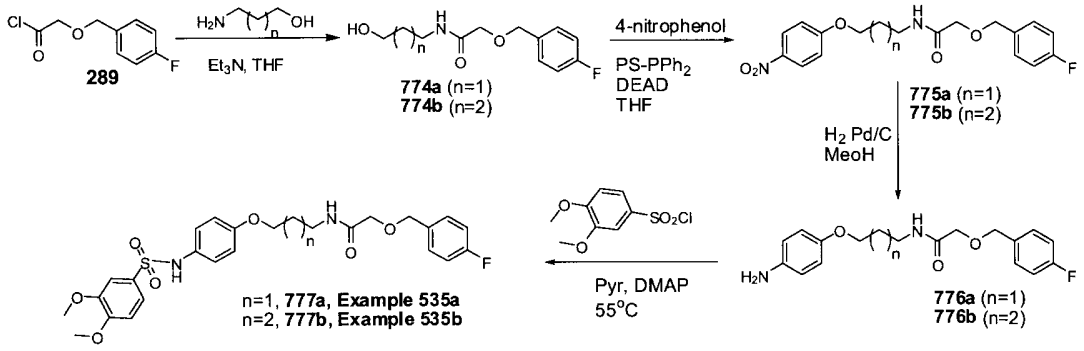
Step 3: *N*-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylsulfonyl)-3,4-dimethoxybenzamide (**773**)

[0571] A solution of Compound **772** (59mg, 0.16mmol) and 3,4-dimethoxybenzoylchloride (31mg, 0.16mmol) in pyridine (1mL) was shaken on a mechanical shaker at room temperature for 15 hours. 4-dimethylaminopyridine (6mg, 0.05mmol) was then added and the solution was shaken for an additional 12 hours at 55°C. The mixture was concentrated and suspended in DCM and the insoluble material was filtered out. The filtrate was concentrated and purified by preparative HPLC (Aquasil C18 20×250mm, 50/50 to 95/5 methanol/water (0.05% formic acid) at 10mL/min in 45 minutes) to afford **773** as an off white semi-crystalline solid (12mg, 14%).

(MEOD-d_4) □(ppm) ^{1}H: 7.97 (d, J = 8.4Hz, 2H), 7.51 (dd, J = 2.0, 8.4Hz, 1H), 7.43-7.36 (m, 5H), 7.10-7.04 (m, 2H), 6.97 (d, J = 8.4Hz, 1H), 4.54 (s, 2H), 3.89 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.27 (t, J = 6.4Hz, 2H), 2.72 (t, J = 7.6Hz, 2H), 1.88 (quint, J = 7.6 Hz, 2H).

LRMS (ESI): (calc.) 544.2; (found) 545.0 $(MH)^+$, 567.0 (MNa^+).

Scheme 316



Example 535a

N-(3-(4-(3,4-dimethoxyphenylsulfonamido)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide (**777a**)

Step 1: 2-(4-fluorobenzyloxy)-*N*-(3-hydroxypropyl)acetamide (**774a**)

[0572] A solution of 3-aminopropanol (0.83mL, 10.8mmol) and triethylamine (1.5mL, 10.8mmol) in THF (5mL) was added to a solution of acid chloride **289** (10.8mmol) in THF (20mL). The mixture was stirred at room temperature for 16 h, then it was diluted with EtOAc and washed with 1N HCl(aq), dried (Na_2SO_4) and concentrated. The crude material was purified by silica gel flash chromatography using a stepwise gradient of EtOAc (75-100%) in DCM, then a gradient of MeOH (0-15%) in EtOAc to afford **774a** as yellow oil (0.920 g, 36%).

(DMSO-d_6) □(ppm) ^{1}H: 7.81 (t, J = 6.0Hz, 1H), 7.42-7.39 (m, 2H), 7.19-7.14 (m, 2H), 4.49 (s, 2H), 4.48 (t, J = 5.2Hz, 1H), 3.85 (s, 2H), 3.39 (q, J = 6.0, 1H), 3.16 (q, J = 6.8Hz, 2H), 1.55 (quint, J = 6.8Hz, 2H).

Step 2: 2-(4-fluorobenzyloxy)-*N*-(3-(4-nitrophenoxy)propyl)acetamide (**775a**)

[0573] 4-Nitrophenol (0.124g, 0.892mmol) was added to a flask containing a suspension of PS-PPh_2 (1.338g, 1.338mmol) in THF (7mL) under nitrogen. The suspension was stirred for 10 minutes before the addition of DEAD (0.466g of 40% solution in toluene, 1.07mmol). After 45 minutes a solution of **774a** (0.215g, 0.892mmol) in THF (1.5mL) was added. The suspension was stirred 20 h, and the resin was filtered and washed with DCM and MeOH. The filtrate was concentrated and purified by silica gel chromatography using a gradient of EtOAc (50-65%) in DCM to give **775a** as yellow oil (171mg, 53%).

(DMSO-d_6) □(ppm) ^{1}H: 8.17 (d, J = 9.6Hz, 2H), 7.94 (t, J = 6.0Hz, 1H), 7.42-7.39 (m, 2H), 7.19-7.14 (m, 2H), 7.09 (d, J = 9.6Hz, 2H), 4.49 (s, 2H), 4.10 (t, J = 6.0Hz, 2H), 3.87 (s, 2H), 3.26 (q, J = 6.4Hz, 2H), 1.90 (quint. J = 6.4Hz, 2H).

LRMS (ESI): (calc.) 362.4; (found) 363.0 $(MH)^+$, 385.0 (MNa^+).

Step 3: *N*-(3-(4-aminophenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide (**776a**)

[0574] The reaction of **775a** (0.150g, 0.414mmol) in methanol with palladium on activated charcoal (5% wt, 70mg) under hydrogen gas atmosphere was carried out as described for **765a**, Example **530e**, step 2, scheme **314**. The crude was purified by silica gel chromatography using a Biotage 12M column eluting with a gradient of EtOAc (50-100%) in DCM to give **776a** (114mg, 83%).

(DMSO-d_6) □(ppm) ^{1}H: 7.87 (t, J = 5.6Hz, 2H), 7.41-7.38 (m, 2H), 7.18-7.13 (m, 2H), 6.59 (d, J = 9.2Hz, 2H), 6.46 (d, J = 9.2Hz, 2H), 4.58 (s, 2H), 4.49 (s, 2H), 3.86 (s, 2H), 3.80 (t, J = 6.4Hz, 2H), 3.22 (q, J = 6.8Hz, 2H), 1.79 (quint. J = 6.4Hz, 2H).

LRMS (ESI): (calc.) 332.4; (found) 333.0 $(MH)^+$, 355.0 (MNa^+).

Step 4: *N*-(3-(4-(3,4-dimethoxyphenylsulfonamido)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide. (**777a**)

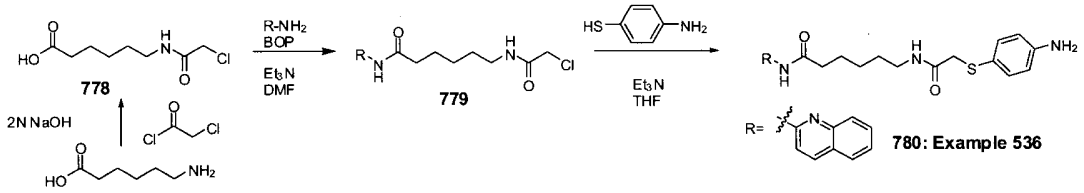
[0575] Amine **776a** (106mg, 0.319mmol) was reacted with 3,4-dimethoxybenzenesulfonyl chloride (76mg, 0.319mmol), and 4-dimethylaminopyridine (12mg, 0.096mmol) in 2.0mL of pyridine as described for compound **754**, Example **523**, scheme **312**. The crude material was purified by flash chromatography using a gradient of EtOAc (60-90%) in DCM to afford **777a** as white solid (154mg, 90%).
(DMSO-d_6) □(ppm) ^{1}H: 9.71 (s, 1H), 7.87 (t, J = 6.0Hz, 1H), 7.40-7.37 (m, 2H), 7.20-7.13 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 9.2Hz, 2H), 6.74 (d, J = 9.2Hz, 2H), 4.47 (s, 2H), 3.84 (s, 2H), 3.84 (t, J = 6.2Hz, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 3.20 (q, J = 6.4 Hz 2H), 1.80 (quint, J = 6.4Hz, 2H). LRMS (ESI): (calc.) 532.17; (found) 533.0 $(MH)^+$, 555.0 $(MNa)^+$.

Example 535b

N-(4-(4-(3,4-dimethoxyphenylsulfonamido)phenoxy)butyl)-2-(4-fluorobenzy-loxy)acetamide. (**777b**)

[0576] Compound **777b** was prepared as described for **777a**, Example **535a**, scheme **316**, except using 4-aminobutanol in step 1, in place of 3-aminopropanol. The crude material was purified by silica gel flash chromatography using a Biotage 12S column and a gradient of EtOAc (20 -80%) in DCM followed by crystallization from minimum amount of DCM in hexanes to give **777b** as white solid (52mg, 82%).
(DMSO-d_6) □(ppm) ^{1}H: 9.69 (s, 1H), 7.83 (t, J = 6.0Hz, 1H), 7.41-7.38 (m, 2H), 7.20-7.13 (m, 4H), 7.00 (d, J = 8.4Hz, 1H), 6.93 (d, J = 9.2Hz, 1H), 6.77 (d, J = 9.2Hz, 2H), 4.48 (s, 2H), 3.84 (s, 2H), 3.84 (t, J = 6.4Hz, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 3.12 (q, J = 6.0Hz, 2H), 1.63-1.59 (m, 2H), 1.52-1.48 (m, 2H).
LRMS (ESI): (calc.) 546.18; (found) 547.1 $(MH)^+$, 596.0 $(MNa)^+$.

Scheme 317



Example 536

6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-2-yl)hexanamide (**780**)

Step 1: 6-(2-chloroacetamido)hexanoic acid (**778**)

[0577] 6-aminocaproic acid (4.00g, 30.49mmol) was dissolved in 2N NaOH(aq) (20mL). The solution was cooled to 0°C and a third of the chloroacetylchloride (0.75mL, 9.24mmol) was added. After most of the precipitate had disappeared, 2N NaOH(aq) (another 5mL) was added followed by another portion of chloroacetylchloride (0.75mL, 9.24mmol). When the reaction mixture had turned clear more 2N NaOH(aq) (5mL) and the final third of chloroacetylchloride (0.75mL, 9.24mmol) were added. The reaction was warmed to room temperature and stirred for an additional hour. It was then acidified to pH~2 with 6N HCl(aq) and extracted with EtOAc (3×50mL). The organic extracts were dried (Na_2SO_4) and concentrated to give **778** as a white solid (4.5g, 78%). LRMS (ESI): (calc.) 207.7; (found) 206.0 $(M-H)^-$, 230.0(MNa^+).

Step 2: 6-(2-chloroacetamido)-N-(quinolin-2-yl)hexanamide **779**

[0578] Acid **778** (0.207g, 0.482mmol), BOP (0.213g, .483mmol), 2-aminoquinoline (84mg, 0.58mmol), and triethylamine (0.14mL, 0.966mmol) in DMF (1mL) were shaken for 20 h at room temperature. The reaction was diluted with water (45mL) and extracted with EtOAc (3×20mL). The organic extracts were washed with saturated $NaHCO_3$(aq), water, brine, dried (Na_2SO_4), filtered and concentrated. The crude material was purified by flash chromatography using a Biotage 12M column and a gradient of EtOAc (50- 100%) in hexanes to afford **779** (58.8mg, 37%). LRMS (ESI): (calc.) 333.1 (100%), 335.1 (32%); (found) 334.1, 336.1$(MH)^+$.

Step 3: 6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-2-yl)hexanamide (**780**)

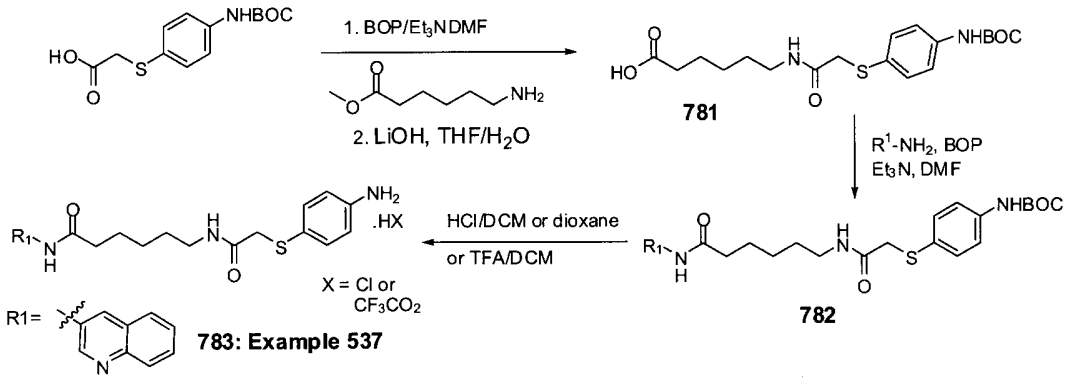
[0579] 4-aminobenzenethiol (39mg, 0.31mmol) in THF (0.22 mL) was added to **779** (51.6mg, 0.16 mmol) in THF (0.5mL) followed by triethylamine (43□L, 0.31mmol). The mixture was heated to 75°C and shaken for 1.5 hours. A small amount of additional 4-aminobenzenethiol (~10mg) was added and the mixture was shaken for 72 h at room temperature. The reaction mixture was concentrated and purified first by preparative TLC with ethyl acetate and then by preparative HPLC (Aquasil 20×250mm C18, 50/50 to 100/0 methanol/water (0.1% formic acid) in 45min at 10mL/min) to give **780** as white solid (28mg, 43%).

(DMSO-d_6) δ (ppm) ^{1}H: 10.75 (s, 1H), 8.30 (m, 2H), 7.89-7.84 (m, 2H), 7.77 (d, J = 8.4Hz, 1H), 7.68 (dt, J = 1.2, 6.8Hz, 1H), 7.46 (dt, J = 1.2, 7.2Hz, 1H), 7.07 (d, J = 8.4Hz, 2H), 6.47 (d, J = 8.8Hz, 2H), 5.24 (s,2H), 3.30 (s, 2H), 3.01 (q, J = 6.0Hz, 2H), 2.43 (t, J = 7.6Hz, 2H), 1.59 (quint, J = 7.2Hz, 2H), 1.38 (quint, J = 8.0Hz, 2H), 1.26-1.22 (m, 2H).

LRMS (ESI): (calc.) 422.2; (found) 423.1 $(MH)^+$.

[0580] Examples **536a-e**, compounds **780a-e**, were prepared as described for compound **780**, Example **536**, scheme **317**, replacing 2-aminoquinoline in step 2, with 4-phenoxyaniline, 4-(4-chlorophenyl)thiazol-2-amine, naphthalen-2-amine, biphenyl-4-ylmethanamine and benzo[d]thiazol-6-amine respectively. Characterization data are presented in Table **40**.

Scheme 318



Example 537

6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-3-yl)hexanamide dihydrochloride (**783**)

Step 1: 6-(2-(4-(tert-butoxycarbonylamino)phenylthio)acetamido)hexanoic acid (**781**)

[0581] Methyl 6-aminohexanoate hydrochloride (3.14g, 17.1mmol), BOP (5.46g, 12.4mmol), 2-(4-(tert-butoxycarbonylamino)phenylthio)acetic acid (3.50g, 12.4mmol) and triethylamine (5.8mL, 42mmol) in DMF (30mL) were stirred at room temperature for 14 hours. The aqueous work-up was divided into two equal batches of the reaction solution. Each batch was diluted with 500mL of water and then extracted with EtOAc (3×100mL). The combined organic extracts were washed with 1N HCl(aq.) (2×100mL), saturated $NaHCO_3$(aq.) (100mL), brine, dried (Na_2SO_4) and concentrated. Purification by silica gel flash chromatography with a gradient of EtOAc (50-70%) in hexanes gave the ester as a white solid (4.53g, 89%). LRMS (ESI): (calc.) 410.5; (found) 411 (MH^+), 433(MNa^+)

[0582] The ester from above (3.58g, 8.73mmol) in THF (40mL) H_2O (10mL) was treated with lithium hydroxide monohydrate (0.733g, 17.5mmol) in H_2O (10mL) and the mixture was stirred for 2 hours at room temperature, then it was acidified to pH 2 with 1N HCl(aq), diluted with H_2O (200mL) and extracted with EtOAc (3×50mL). The organic extracts were washed with brine and concentrated to afford **781** as a white solid (3.33g, 96%). LRMS (ESI): (calc.) 396.5; (found) 403.2 (MLi^+), 395.1$(M-H)^-$.

Step 2: tert-butyl 4-(2-oxo-2-(6-oxo-6-(quinolin-3-ylamino)hexylamino)ethylthio)phenyl-carbamate **782**

[0583] Acid **781** (0.125g, 0.316mmol) was reacted with BOP (0.140g, 0.316mmol), 3-aminoquinoline (55mg, 0.379mmol) and triethylamine (0.088mL, 0.632mmol) in DMF (1mL) as described for compound **779**, Example **536**, step 2, scheme **317**. The crude material was purified by silica gel flash chromatography using a Biotage 25M column and a gradient of EtOAc (60-100%) in hexanes to afford **782** (0.83g, 77%). LRMS (ESI): (calc.) 522.7; (found) 523.3$(MH)^+$.

Step 3: 6-(2-(4-aminophenylthio)acetamido)-N-(quinolin-3-yl)hexanamide **783**

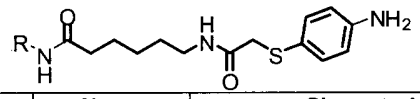
[0584] Compound **782** (83mg, 0.159mmol) was stirred in 3mL of a freshly prepared solution of HCl in DCM. After 5 hours, the resulting precipitate was filtered and washed with DCM to give **783** as an off-white solid as the HCl salt (55mg, 70%).

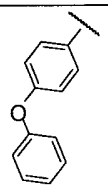
(DMSO-d_6) δ (ppm) ^{1}H: 11.0 (s, 1H), 9.23 (d, J = 2.0Hz, 1H), 8.99 (d, J= 2.4Hz, 1H), 8.19 (t, J = 5.6Hz, 1H), 8.10 (d, J = 4.4Hz, 1H), 8.11-8.08 (m, 2H), 7.80 (dt, J = 1.2, 7.2Hz, 1H), 7.71 (dt, J = 1.2, 8..0Hz, 1H), 7.40 (d, J = 8.4Hz, 2H), 7.28 (d, J = 8.8Hz, 2H), 3.65 (s, 2H), 3.05 (q, J = 6.4Hz, 2H), 2.43 (t, J = 7.2Hz, 2H), 1.62 (quint, J = 7.2Hz, 2H), 1.42 (quint, J = 6.8Hz, 2H), 1.32-1.26 (m, 2H).

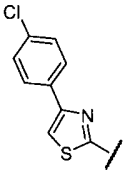
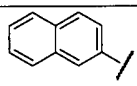
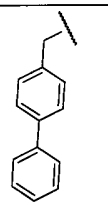
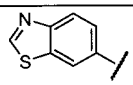
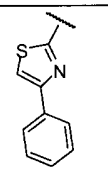
LRMS (ESI): (calc.) 422.5; (found) 423.2 $(MH)^+$.

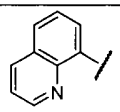
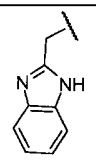
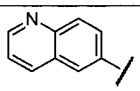
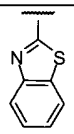
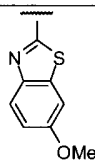
[0585] Examples **537a-h**, compounds **783a-h**, were prepared as described for compound **783**, Example **537**, scheme **318,** replacing 3-aminoquinoline in step 2, with 4-phenylthiazol-2-amine, quinolin-8-amine, (1H-benzo[d]imidazol-2-yl)methanamine, quinolin-6-amine, benzo[d]thiazol-2-amine, 6-methoxybenzo[d]thiazol-2-amine, 4,6-difluorobenzo[d]thiazol-2-amine, and 4-(4-methoxyphenyl)thiazol-2-amine respectively. Characterization data are presented in Table **40**.

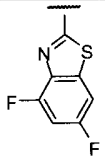
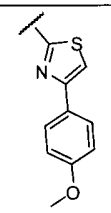
Table 40



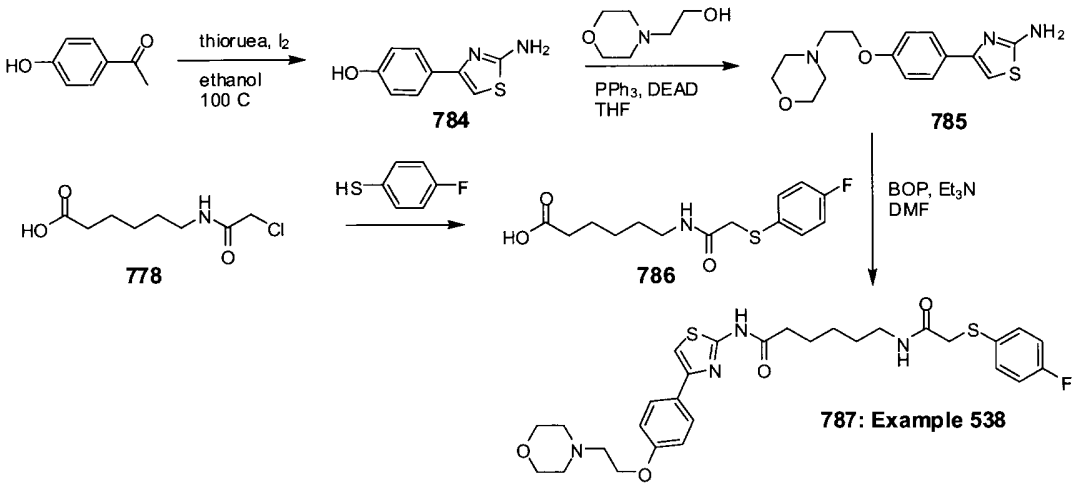
Ex	No.	R	Name	Characterization	Scheme
536a	780a		6-(2-(4-aminophenylthio)acetamido)-*N*-(4-phenoxyphenyl)hexanamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.86 (s, 1H), 7.87 (t, J = 5.6Hz, 1H), 7.58 (d, J = 8.8Hz, 2H), 7.36-7.31 (m, 2H), 7.08-7.05 (m, 3H), 6.96-6.91 (m, 4H), 6.47 (d, J = 8.4Hz, 2H), 5.24 (s, 2H), 3.30 (s, 2H), 3.01 (q, J = 6.0Hz, 2H), 2.27 (t, J = 7.2Hz, 2H), 1.56 (quint, J = 7.6Hz, 2H), 1.38 (quint, J = 7.6Hz, 2H), 1.24 (quint, J = 6.8Hz, 2H). LRMS (ESI): (calc) 463.2; (found) 464.2 $(MH)^+$.	317 Ex 536

536b	780b		6-(2-(4-aminophenylthio)acetamido)-*N*-(4-(4-chlorophenyl)thiazol-2-yl)hexanamide	(DMSO-d_6) δ (ppm) ^{1}H: 12.2 (s, 1H), 7.89-7.84 (m, 3H), 7.65 (s, 1H), 7.46 (d, J = 8.8Hz, 2H), 7.07 (d, J = 8.4Hz, 2H), 6.47 (d, J = 8.4Hz, 2H), 5.24 (s,2H), 3.30 (s, 2H), 3.01 (q, J = 6.0Hz, 2H), 2.43 (t, J = 7.6Hz, 2H), 1.58 (quint, J = 8.0Hz, 2H), 1.36 (quint, J = 8.0Hz, 2H), 1.22 (m, 2H). LRMS (ESI): (calc) 488.1; (found) 489.1 $(MH)^+$.	317 Ex 536
536c	780c		6-(2-(4-aminophenylthio)acetamido)-*N*-(naphthalen-2-yl)hexanamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.04 (s, 1H), 8.28 (m, 1H), 7.87 (t, J = 4.8Hz, 1H), 7.82-7.76 (m, 3H), 7.55 (dd, J = 8.8, 2.0Hz, 1H), 7.43 (dt, J = 1.2, 6.4Hz, 1H), 7.36 (dt, J = 1.6, 6.8Hz, 1H), 7.07 (d, J = 8.8Hz, 2H), 6.47 (d, J = 8.4Hz, 2H), 5.24 (s,2H), 3.31 (s, 2H), 3.01 (q, J = 6.0Hz, 2H), 2.36 (t, J = 7.2Hz, 2H), 1.61 (quint, J = 7.6Hz, 2H), 1.40 (quint, J = 7.6Hz, 2H), 1.31-1.25 (m, 2H). LRMS (ESI): (calc) 421.2; (found) 422.1 $(MH)^+$.	317 Ex 536
536d	780d		6-(2-(4-aminophenylthio)acetamido)-N-(biphenyl-4-ylmethyl)hexanamide	(DMSO-d_6) δ(ppm) ^{1}H: 8.32 (t, J = 5.6Hz, 1H), 7.84 (t, J = 5.6Hz, 1H), 7.60 (d, J = 7.2Hz, 2H), 7.51-7.33 (m, 6H), 7.21 (d, J = 8.0Hz, 1H), 7.07 (d, J = 8.8Hz, 2H), 6.47 (J = 8.4Hz, 2H), 5.24 (s,2H), 4.32 (d, J = 5.6Hz, 2H), 3.30 (s, 2H), 2.98 (q, J = Hz, 2H), 2.13 (t, J = 7.6Hz, 2H), 1.51 (quint, J = 7.2Hz, 2H), 1.36 (quint, J = 7.6Hz, 2H), 1.24-1.18 (m, 2H). LRMS (ESI): (calc) 461.2; (found) 462.2 $(MH)^+$.	317 Ex 536
536e	780e		6-(2-(4-aminophenylthio)acetamido)-*N*-(benzo[d]thiazol-6-yl)hexanamide	(DMSO-d_6) δ(ppm) ^{1}H: 10.12 (s, 1H), 9.22 (s, 1H), 8.53 (d, J = 1.6Hz, 1H), 7.97 (d, J = 8.8Hz, 1H), 7.87 (t, J = 5.6Hz, 1H), 7.56 (dd, J = 2.0, 8.8Hz, 1H), 7.07 (d, J = 8.4Hz, 2H), 6.47 (dd, J = 8.4Hz, 2H), 5.24 (s, 2H), 3.31 (s, 2H), 3.01 (q, J = 6.4Hz, 2H), 2.33 (t, J = 7.6Hz, 2H), 1.59 (quint, J = 7.2Hz, 2H), 1.39 (quint, J = 7.2Hz, 2H), 1.30-1.24 (m, 2H). LRMS (ESI): (calc) 428.1; (found) 429.2 $(MH)^+$.	317 Ex 536
537a	783a		6-(2-(4-aminophenylthio)acetamido)-*N*-(4-phenylthiazol-2-yl)hexanamide hydrochloride	(DMSO-d_6) δ (ppm) ^{1}H: 10.12 (s, 1H), 8.12 (t, J = 5.2Hz, 1H), 7.87 (dd, J = 0.8, 7.2Hz, 2H), 7.58 (s, 1H), 7.43-7.38 (m, 4H), 7.30 (t, J = 7.2Hz, 1H), 7.19 (d, J = 8.0Hz, 2H), 3.61 (s, 2H), 3.03 (q, J = 6.4Hz, 2H), 2.44 (t, J = 7.2Hz, 2H), 1.59 (quint, 7.2Hz, 2H), 1.40 (quint, J = 7.2Hz, 2H), 1.29-1.23 (m, 2H). LRMS (ESI): (calc) 454.2; (found) 455.2 $(MH)^+$.	318 Ex 537

537b	783b		6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-8-yl)hexanamide dihydrochloride	(DMSO-d_6) δ (ppm) ^{1}H: 10.0 (s, 1H), 8.91 (dd, J = 1.6, 4.4 Hz, 1H), 8.59 (d, J = 7.6Hz, 1H), 8.41 (dd, J = 1.2, 8.4Hz, 1H), 8.12 (t, J = 5.6Hz, 1H), 7.67-7.62 (m, 2H), 7.56 (t, J = 8.0Hz, 1H), 7.39 (d, J = 8.4Hz, 2H), 7.21 (d, J = 8.4Hz, 2H), 3.61 (s, 2H), 3.05 (q, J = 6.0Hz, 2H), 2.56 (t, J = 7.6Hz, 2H), 1.63 (quint, J = 7.2Hz, 2H), 1.42 (quint, J = 7.2Hz, 2H), 1.34-1.28 (m, 2H). LRMS (ESI): (calc) 422.2; (found) 423.2 $(MH)^+$.	318 Ex 537
537c	783c		6*N*-((1H-benzo[d]imidazol-2-yl)methyl)-6-(2-(4-aminophenylthio)acetamido)hexanamide dihydrochloride	(DMSO-d_6) δ (ppm) ^{1}H: 8.89 (t, J = 5.6Hz, 1H), 8.13 (t, J = 5.2Hz 1H), 7.78-7.75 (m, 2H), 7.52-7.50 (m, 2H), 7.36 (d, J = 8.4Hz, 2H), 7.15 (d, J = 8.0Hz, 2H), 4.72 (d, J = 5.2Hz, 2H), 3.60 (s, 2H), 3.02 (q, J = 6.4Hz, 2H), 2.23 (t, J = 7.2Hz, 2H), 1.51 (quint, J = 7.2Hz, 2H), 1.36 (quint, J = 7.6Hz, 2H), 1.25-1.17 (m, 2H) LRMS (ESI): (calc) 425.2; (found) 460.3 (MCl^-),	318 Ex 537
537d	783d		6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-6-yl)hexanamide dihydrochloride	(DMSO-d_6) δ (ppm) ^{1}H: 10.6 (s, 1H), 9.00 (d, J = 5.2Hz, 1H), 8.83 (d, J= 8.4Hz, 1H), 8.66 (d, J = 2.0Hz, 1H), 8.20 (d, J = 8.8Hz, 1H), 8.13 (t, J = 5.2Hz, 1H), 8.06 (dd, J = 2.0, 9.2Hz, 2H), 7.83 (dd, J = 5.2, 8.4Hz, 1H), 3.58 (s, 2H), 3.04 (q, J = 6.0Hz, 2H), 2.42 (t, J = 7.2Hz, 2H), 1.61 (quint, J = 7.2Hz, 2H), 1.41 (quint, J = 7.2Hz, 2H), 1.28-1.24 (m, 2H) LRMS (ESI): (calc) 422.2; (found) 423.2 $(MH)^+$.	318 Ex 537
537e	783e		6-(2-(4-aminophenylthio)acetamido)-N-(benzo[d]thiazol-2-yl)hexanamide trifluoroacetic acid	(DMSO-d_6) δ (ppm) ^{1}H: 12.3 (s, 1H), 7.99 (t, J = 5.6Hz, 1H), 7.94 (d, J= 8.0Hz, 1H), 7.70 (d, J = 8.0Hz, 1H), 7.41 (dt, J = 1.2, 8.4Hz, 1H), 7.28 (dt, J = 1.2, 8.0Hz, 1H), 7.24 (d, J = 8.4Hz, 2H), 6.85 (d, J = 8.4Hz, 2H), 3.47 (s, 2H), 3.02 (q, J = 6..0Hz, 2H), 2.47 (t, J = 7.6Hz, 2H), 1.60 (quint, J = 7.6Hz, 2H), 1.38 (quint, J = 7.6Hz, 2H), 1.29-1.23 (m, 2H) LRMS (ESI): (calc) 428.1; (found) 428.9 (MH^+), 450.9 $(MNa)^+$	318 Ex 537
537f	783f		6-(2-(4-aminophenylthio)acetamido)-N-(6-methoxybenzo[d]thiazol-2-yl)hexanamide hydrochloride	(DMSO-d_6) δ (ppm) ^{1}H: 8.15 (t, J = 5.2Hz, 1H), 7.59 (d, J = 8.8Hz, 1H), 7.53 (d, J = 2.8Hz, 1H), 7.40 (d, J = 8.8Hz, 2H), 7.25 (d, J = 8.4Hz, 2H), 6.99 (dd, J = 2.8, 8.8Hz, 1H), 3.79 (s, 3H), 3.64 (s, 2H), 3.04 (q, J = 6.4Hz, 2H), 2.45 (t, J = 7.6Hz, 2H), 1.59 (quint, J = 6.0Hz, 2H), 1.39 (quint, J = 7.2Hz, 2H), 1.29-1.23 (m, 2H) LRMS (ESI): (calc) 458.1; (found) 458.9 (MH^+), 480.9 $(MNa)^+$	318 Ex 537

537g	783g		6-(2-(4-aminophenylthio)acetamido)-*N*-(4,6-difluorobenzo[d]thiazol-2-yl)hexanamide trifluoroacetic acid	(DMSO-d_6) δ (ppm) ^{1}H: 8.15 (t, J = 5.2Hz, 1H), 7.59 (d, J = 8.8Hz, 1H), 7.53 (d, J = 2.8Hz, 1H), 7.40 (d, J = 8.8Hz, 2H), 7.25 (d, J = 8.4Hz, 2H), 6.99 (dd, J = 2.8, 8.8Hz, 1H), 3.79 (s, 3H), 3.64 (s, 2H), 3.04 (q, J = 6.4Hz, 2H), 2.45 (t, J = 7.6Hz, 2H), 1.59 (quint, J = 6.0Hz, 2H), 1.39 (quint, J = 7.2Hz, 2H), 1.29-1.23 (m, 2H) LRMS (ESI): calc 458.1; (found) 458.9 $(MH)^+$, 480.9 $(MNa)^+$	318 Ex 537
537h	783h		6-(2-(4-aminophenylthio)acetamido)-N-(4-(4-methoxyphenyl)thiazol-2-yl)hexanamide hydrochloride	(DMSO-d_6) δ (ppm) ^{1}H: 12.6 (s,1H), 8.11 (t, J = 5.6Hz, 1H), 7.89 (d, J = 8.8Hz, 2H), 7.41 (s, 1H), 7.38 (d, J = 8.8Hz, 2H), 7.18 (d, J = 8.4Hz, 2H), 6.96 (d, J = 8.8Hz, 2H), 3.76 (s, 3H), 3.59 (s, 2H), 3.02 (q, J = 6.0Hz, 2H), 2.40 (t, J = 7.6Hz, 2H), 1.56 (quint, J = 8.0Hz, 2H), 1.36 (quint, J = 8.0Hz, 2H), 1.24-1.18 (m, 2H) LRMS (ESI): (calc) 484.2; (found) 485.0 $(MH)^+$, 507.0 $(MNa)^+$.	318 Ex 537

Scheme 319



Example 538

(6-(2-(4-fluorophenylthio)acetamido)-*N*-(4-(4-(2-morpholinoethoxy)phenyl)thiazol-2-yl)hexanamide) (**787**)

Step 1: 4-(2-aminothiazol-4-yl)phenol (**784**)

[0586] Thiourea (2.16g, 28.3mmol), 4-hydroxyacephenone (1.93g, 14.2mmol) and iodine (3.60g, 14.2mmol) were heated to 100°C in ethanol (15mL) inj a pressure tube for 24 hours. The dark colored reaction mixture was cooled and concentrated. The residue was taken up in EtOAc (100mL) and washed with saturated $NaHCO_3$(aq) (2×50mL) and water, dried (Na_2SO_4) and concentrated. The crude material was purified by silica gel flash chromatography using a stepwise gradient of EtOAc (50-70%) in hexanes to afford

compound **784** as light yellow oil (1.10g, 40%). LRMS (ESI): (calc.) 192.2; (found) 193.0 $(MH)^+$.

Step 2: 4-(4-(2-morpholinoethoxy)phenyl)thiazol-2-amine (**785**)

[0587] To a solution of **784** (0.200g, 1.04mmol) and 2-hydroxy-ethylmorphorine (0.13mL, 1.04mmol) in THF (5mL) under nitrogen was added triphenylphosphine (0.327g, 1.25mmol) followed by DEAD (0.21mL, 1.35mmol). The reaction was stirred at room temperature for 20 hours and was concentrated. The residue was diluted with EtOAc and washed with water and then 1N HCl(aq). The acidic wash was basified to pH 8 with by the addition of solid $NaHCO_3$ to give a cloudy suspension which was extracted into EtOAc and the extracts were dried (Na_2SO_4), concentrated and purified by silica gel flash chromatography using a Biotage 12M column and a gradient of MeOH (5-10%) in DCM to give compound **785** as white solid (0.197g, 62%). LRMS (ESI): (calc.) 305.4; (found) 306.1 $(MH)^+$.

Step 3: 6-(2-(4-fluorophenylthio)acetamido)hexanoic acid (**786**)

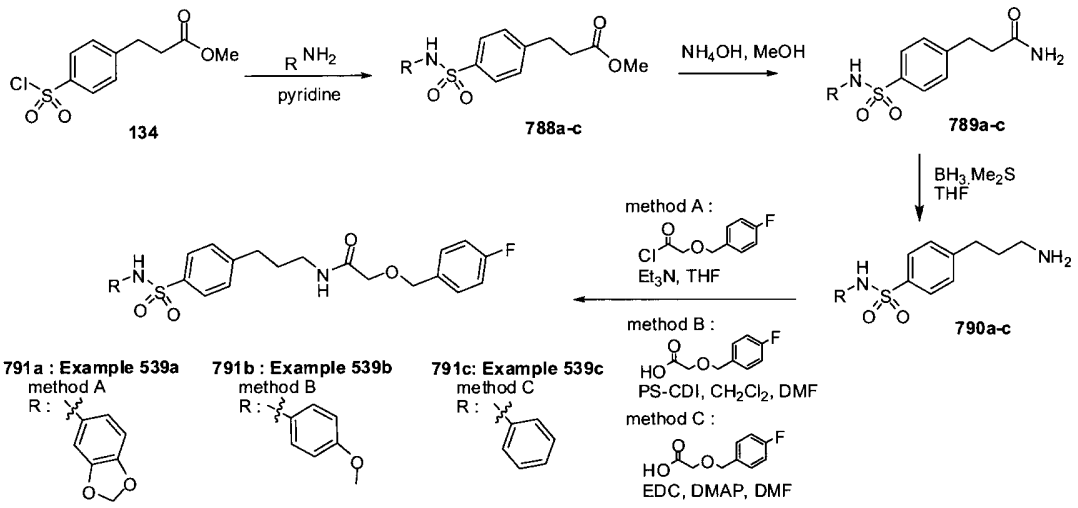
[0588] To a solution of compound **778,** Example **536,** step 1, scheme **317** (0.377g, 1.82mmol) and triethylamine (0.63mL, 4.55mmol) in THF (4mL) was added 4-fluorobenzenethiol (0.29mL, 2.73mmol). The white precipitate that formed was filtered off and the filtrate was diluted with EtOAc, and the organic phase was washed with 1N HCl(aq) and extracted with saturated $NaHCO_3$(aq). The $NaHCO_3$ extracts were acidified to pH 2 with concentrated HCl (aq) and the aqueous layer was extracted with EtOAc, and the organic extracts were dried (Na_2SO_4), filtered and concentrated to give acid **786** as semi-crystalline white solid (0.485g, 89%). LRMS (ESI): (calc.) 299.4; (found) 298.0 $(M-H)^-$.

Step 4: 6-(2-(4-fluorophenylthio)acetamido)-N-(4-(4-(2-morpholinoethoxy)phenyl)thiazol-2-yl)hexanamide (**787**)

[0589] A solution of compound **786** (0.101g, 0.338mmol), **785** (0.103g, 0.338mmol), BOP (0.149g, 0.338mmol), and triethylamine (0.094mL, 0.676mmol) was stirred in DMF (1.0mL) at room temperature for 17 h as described for compound **781**, Example **537**, scheme **318**. The crude material was purified by silica gel flash chromatography using a Biotage 12M column and a gradient of MeOH (1-10%) in DCM containing 1% acetic acid. The material was further purified by preparative HPLC (Aquasil 20×250mm C18, 40/60 to 90/10 methanol/water (0.05% formic acid) in 45min at 10mL/min) to give pure **787** as a white solid (51mg, 26%). ^1H NMR: (DMSO-d_6) □(ppm): 12.3 (s,1H), 8.15 (t, J = 5.6Hz, 1H), 7.88 (d, J = 8.8Hz, 2H), 7.50-7.46 (m, 3H), 7.27-7.22 (m, 2H), 7.06 (d, J = 8.8Hz, 2H), 4.19 (t, J = 6.0 Hz, 2H), 3.67-3.64 (m, 6H), 3.11 (q, J = 6.0Hz, 2H), 2.77 (t, J = 5.6Hz, 2H), 2.56-2.54 (m, 4H), 2.49 (t, J = 7.2Hz, 2H), 1.64 (quint, J = 7.6Hz, 2H), 1.44 (quint, 7.6Hz, 2H), 1.32-1.27 (m, 2H).

LRMS (ESI): (calc.) 586.2; (found) 587.2 $(MH)^+$, 609.0 $(MNa)^+$.

Scheme 320



Example 539a

N-(3-(4-(N-benzo[d][1,3]dioxol-5-ylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**791a**)

Step 1: methyl 3-(4-(N-benzo[d][1,3]dioxol-5-ylsulfamoyl)phenyl)propanoate **788a**

[0590] Methyl 3(4-chlorosulphonyl) phenylpropionate **134** (1.00 g, 3.81 mmol) was added drop-wise to a stirred solution of 3,4-(methylenedioxy)aniline (522 mg, 3.81 mmol) in pyridine (4 mL) at 0°C, and was stirred at room temperature for 16h. The reaction mixture was quenched with a saturated solution of ammonium chloride in water, and pyridine was evaporated, and the aqueous mixture was extracted with EtOAc. The organic extract was dried ($MgSO_4$), filtered, and evaporated. Crude **788a** was used without further purification. ($CDCl_3$) δ (ppm) ^{1}H: 7.64 (d, J=8.4Hz, 2H), 7.27-7.24 (m, 2H), 6.66 (d, J=2.2Hz, 1H), 6.63 (d, J=8.2Hz, 1H), 6.52 (bs, 1H), 6.40 (dd, J=8.2and2.2Hz, 1H), 5.94 (s, 2H), 3.66 (s, 3H), 2.99 (t, J=7.6Hz, 2H), 2.63 (t, J=7.8Hz, 2H). LRMS (ESI): (calc) 363.1; (found) 362.0 $(M-H)^-$.

Step 2: 3-(4-(N-benzo[d][1,3]dioxol-5-ylsulfamoyl)phenyl)propanamide **789a**

[0591] To a stirred solution of **788a** (0.30 mmol) in MeOH (2 mL) was added ammonium hydroxide (2 mL). The reaction was stirred at room temperature for 16h, then it was taken to dryness and triturated with ethyl ether to give **789a** (67 mg, 64%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.58 (d, J=8.4Hz, 2H), 7.35 (d, J=8.6Hz, 2H), 7.26 (bs, 1H), 6.76 (bs, 1H), 6.72 (d, J=8.4Hz, 1H), 6.63 (d, J=2.2Hz, 1H), 6.44 (dd, J=8.4and2.2Hz, 1H), 5.93 (s, 2H), 2.82 (t, J=7.8Hz, 2H), 2.33 (t, J=8.0Hz, 2H). LRMS (ESI): (calc) 348.0; (found) 346.9 $(M-H)^-$.

Step 3: 4-(3-aminopropyl)-N-(benzo[d][1,3]dioxol-5-yl)benzenesulfonamide (**790a**)

[0592] To a stirred solution of **789a** (127 mg, 0.36 mmol) in THF (1.8 mL) was added borane-methyl sulfide (1.5 mL of 2.0M in THF) and the reaction was stirred at 65°C for 16h as described for compound **736**, example **514**, scheme **308**, step 2. Crude **790a** was used without further purification. LRMS (ESI): (calc) 334.1; (found).335.1 $(MH)^+$

Step 4: N-(3-(4-(N-benzo[d][1,3]dioxol-5-ylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**791a**)

Method A:

[0593] To a stirred solution of **790a** (0.27 mmol) in THF (0.5 mL) was added triethylamine (0.11 mL, 0.81 mmol). The solution was cooled to 0°C, and then a solution of acid chloride **289** (0.32 mmol) in THF (0.5 mL) was added as described for compound **723**, example **507**, scheme **302**, step 4. The crude material was purified by silica gel column chromatography with gradient of EtOAc (60-100%) in hexane. The isolated product was purified again by prep-hplc with gradient of methanol (50-100%) in water to give **791a** (6 mg, 5%).

(CD_3CN) δ (ppm) ^1H: 7.63 (d, J=8.4Hz, 2H), 7.42 (dd, J=8.8and5.3Hz, 2H), 7.35 (d, J=8.4Hz, 2H), 7.13 (tt, J=9.0and2.9Hz, 2H), 6.91 (bs, 1H), 6.69-6.67 (m, 2H), 6.47 (dd, J=6.1and2.2Hz, 2H), 5.93 (s, 2H), 4.54 (s, 2H), 3.90 (s, 2H), 3.21 (q, J=7.4Hz, 2H), 2.68 (t, J=7.4Hz, 2H), 1.79 (qi, J=7.4Hz, 2H). LRMS (ESI): (calc) 500.1; (found).499.0 $(M-H)^-$.

Example 539b

2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide (**791b**)

[0594] Steps 1 to 3 to prepare 4-(3-aminopropyl)-N-(4-methoxyphenyl)benzenesulfonamide **790b**, were carried-out following the same procedures as desribed for **790a**, in example **539a**, scheme **320**, except in step 1 *p*-anisidine was used in place of 3,4-(methylenedioxy)aniline.

Step 4: 2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-methoxyphenyl)sulfamoyl)phenyl)propyl)-acetamide **791b**

Method B:

[0595] To a stirred solution PS-CDI (428 mg, 0.60 mmol) in DCM (3 mL) was added acid **140** (83 mg, 0.45 mmol). The mixture was stirred for 10 minutes at room temperature. A solution of amine **790b** (97 mg, 0.30 mol) in DMF (1 mL) was added. The reaction was stirred at room temperature for 16h. The resin was filtered and rinsed with DCM. The solvent was evaporated and the residue was purified by prep-hplc with gradient of methanol (40-100% in water to give **791b** (10 mg, 7%).

(CD_3CN) □ (ppm) ^1H: 7.60 (d, J=8.6, 2H), 7.42 (dd, J=8.8and5.5Hz, 2H), 7.33 (d, J=8.6Hz, 2H), 7.13 (t, J=9.0Hz, 2H), 6.99 (d, J=9.2Hz, 2H), 6.91 (bs, 1H), 6.80 (d, J=9.0Hz, 2H), 4.54 (s, 2H), 3.90 (s, 2H), 3.72 (s, 3H), 3.21 (q, J=6.5Hz, 2H), 2.67 (t, J=7.6Hz, 2H), 1.78 (qi, J=7.2Hz, 2H). LRMS (ESI): (calc) 486.1; (found) 485.0 $(M-H)^-$.

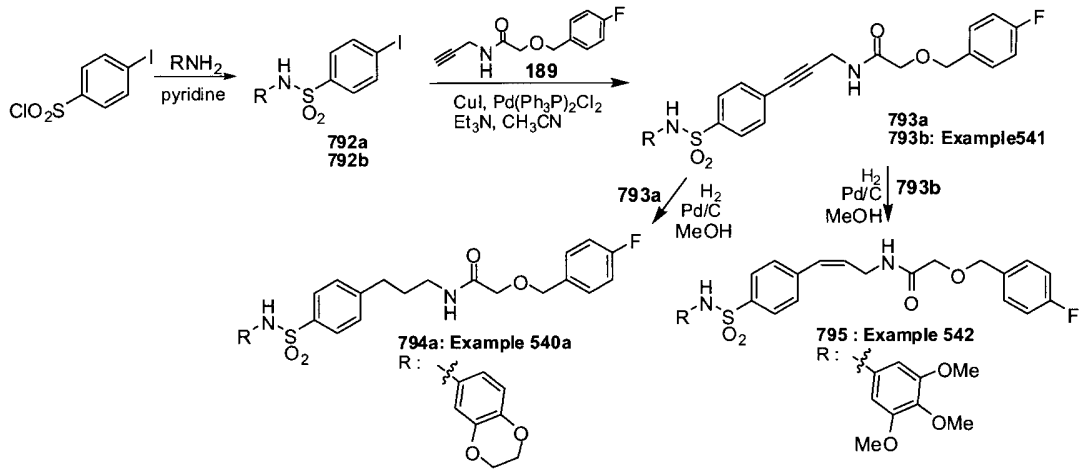
Example 539c

2-(4-fluorobenzyloxy)-N-(3-(4-(N-phenylsulfamoyl)phenyl)propyl)acetamide (**791c**)

[0596] Steps 1 to 3 to prepare 4-(3-aminopropyl)-N-phenylbenzenesulfonamide **790c**, were carried out following the same procedures as desribed for **790a**, in example **539a**, scheme **320**, except in step 1 aniline was used in place of 3,4-(methylenedioxy)aniline.
Step 4: 2-(4-fluorobenzyloxy)-N-(3-(4-(N-phenylsulfamoyl)phenyl)propyl)acetamide (**791c**)
Method C:

[0597] To a stirred solution of acid **140** (47 mg, 0.26 mmol) in dimethylformamide (1 mL) was added N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (81 mg, 0.42 mmol). The mixture was stirred for 5 minutes at room temperature. 4-Dimethylaminopyridine (34 mg, 0.26 mmol) was added. A solution of amine **790c** (82 mg, 0.26 mol) in dimethylformamide (0.7 mL) was added. The reaction was stirred at room temperature for 16h. The reaction mixture was quenched with a saturated solution of sodium carbonate in water. The aqueous mixture was extracted with EtOAc, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by prep-hplc with gradient of methanol (40-100% in water to give **791c** (5 mg, 4%).
(CD_3CN) δ (ppm) ^1H: 7.69 (d, J=8.2Hz, 2H), 7.12 (dd, J=8.6and5.7Hz, 2H), 7.34 (d, J=8.2Hz, 2H), 7.26 (dd, J=8.6and7.0Hz, 2H), 7.16-7.08 (m, 5H), 6.90 (bs, 1H), 4.54 (s, 2H), 3.89 (s, 2H), 3.20 (q, J=7.4Hz, 2H), 2.66 (t, J=7.6Hz, 2H), 1.77 (qi, J=7.4Hz, 2H). LRMS (ESI): (calc) 456.2; (found) 455.0 $(M-H)^-$.

Scheme 321



Example 540a

N-(3-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**794a**)

Step 1: N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-iodobenzenesulfonamide (**792a**)

[0598] To a stirred solution of 1,4-benzodioxan-6-amine (0.34 mL, 2.74 mmol) in pyridine (4 mL) was added 4-iodobenzenesulfonyl chloride (830 mg, 2.74 mmol) as described for compound **788a**, example **539a**, step1, scheme **320**. The crude was purified by silica gel column chromatography with gradient of EtOAc (20-60%) in hexane to give **792a** (937 mg, 82%).

(DMSO-d_6) δ (ppm) ^{1}H: 10.03 (s, 1H), 7.92 (d, J=8.6Hz, 2H), 7.43 (d, J=8.6Hz, 2H), 6.70 (d, J=8.6Hz, 1H), 6.54 (d, J=2.5Hz, 1H), 6.49 (dd, J=8.8and2.5Hz, 1H), 4.15-4.12 (m, 4H). LRMS (ESI): (calc0 417.0; (found) 415.8 $(M-H)^-$.

Step 2: N-(3-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide (**793a**)

[0599] To a stirred solution of **792a** (209 mg, 0.50 mmol) in acetonitrile (1.5 mL) was added alkyne **189** (133 mg, 0.60 mmol), triethylamine (0.10 mL, 0.75 mmol), dichlorobis(triphenylphosphine)palladium(II) (18 mg, 0.03 mmol), and copper(I) iodide (10 mg, 0.05 mmol). The mixture was stirred for 3h at room temperature. The mixture was concentrated and the residue was purified by silica gel column chromatography with gradient of ethyl acetate (40-80%) in hexane to give **793a** (202 mg, 79%).

(DMSO-d_6) δ (ppm) ^{1}H: 10.0 (s, 1H), 8.39 (t, J=6.1Hz, 1H), 7.64 (d, J=8.6Hz, 2H), 7.54 (d, J=8.6Hz, 2H), 7.42 (dd, J=8.8and5.7Hz, 2H), 7.17 (t, J=9.0Hz, 2H), 6.68 (d, J=8.6Hz, 1H), 6.52 (d, J=2.5Hz, 1H), 6.47 (dd, J=8.6and2.5Hz, 1H), 4.51 (s, 2H), 4.16-4.12 (m, 6H), 3.93 (s, 2H). LRMS (ESI): (calc) 510.1; (found) 509.0 $(M-H)^-$

Step 3: N-(3-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**794a**)

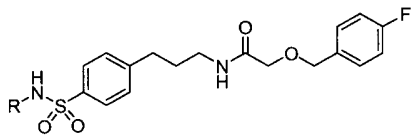
[0600] Compound **793a** (159 mg, 0.31 mmol) in methanol (1.6 mL) and 10% palladium on charcoal (16 mg) was hydrogenated under 1 atm of H_2 gas. The residue was purified by silica gel column chromatography with gradient of ethyl acetate (40-80%) in hexane to give **794a** (97 mg, 61%).

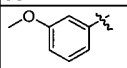
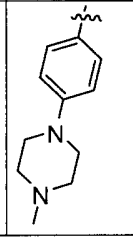
(DMSO-d_6) δ (ppm) ^{1}H: 9.91 (s, 1H), 7.86 (t, J=6.1Hz, 1H), 7.59 (d, J=8.2Hz, 2H), 7.40 (dd, J=8.4and2.0Hz, 2H), 7.35 (d, J=8.4Hz, 2H), 7.16 (t, J=9.0Hz, 2H), 6.67 (d, J=8.6Hz, 1H), 6.55 (d, J=2.5Hz, 1H), 6.49 (dd, J=8.6and2.5Hz, 1H), 4.48 (s, 2H), 4.14-4.11 (m, 4H), 3.84 (s, 2H), 3.08 (q, J=6.5Hz, 2H), 2.58 (t, J=7.2Hz, 2H), 1.69 (qi, J=7.6Hz, 2H). LRMS (ESI): (calc) 514.2; (found) 513.0 $(M-H)^-$.

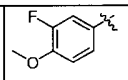
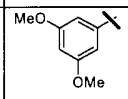
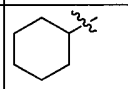
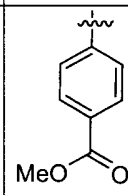
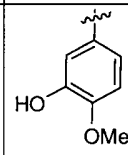
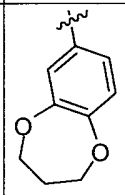
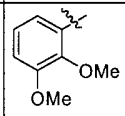
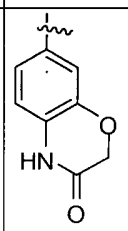
[0601] Examples **539d-e,** compounds **791d-e** were prepared as described for compound **791b** Example **539b**, scheme **320**, except in step 1 replacing *p*-anisidine with 3-methoxyaniline and 4-(4-methylpiperazin-1-yl)aniline respectively. Characterization data are presented in **Table 41**

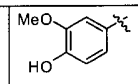
[0602] Examples **540b-j,** compounds **794b-j** were prepared as described for compound **794a** Example **540a**, scheme **321**. Characterization data are presented in **Table 41.**

Table 41



Ex	Cpd	R	Name	Characterization	Scheme
539d	791d		2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide	(CD_3CN) δ (ppm) ^{1}H: 7.71 (d, J=8.4Hz, 2H), 7.41 (dd, J=8.8and5.5Hz, 2H), 7.34 (d, J=8.4Hz, 2H), 7.17-7.07 (m, 3H), 6.92 (bs, 1H), 6.70-6.63 (m, 3H), 4.54 (s, 2H), 3.90 (s, 2H), 3.71 (s, 3H), 3.21 (q, J=6.5Hz, 2H), 2.66 (t, J=8.8Hz, 2H), 1.77 (qi, J=7.4Hz, 2H). LRMS (ESI): 486.1 (calc) 485.1 (M-) (found).	320 Ex 539b Step 1-4
539e	791e		2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-(4-methylpiperazin-1-yl)phenyl)sulfamoyl)phenyl)propyl)acetamide	(CD_3CN) δ (ppm) ^{1}H: 8.25 (s, 1H), 7.61 (d, J=8.4Hz, 2H), 7.43-7.37 (m, 2H), 7.32 (d, J=8.6Hz, 2H), 7.15-7.08 (m, 2H), 6.94 (d, J=9.0Hz, 2H), 6.79 (d, J=9.2Hz, 2H), 4.54 (s, 2H), 3.99 (s, 1H), 3.90 (s, 2H), 3.20 (q, J=6.5Hz, 2H), 3.17-3.14 (m, 4H), 2.71-2.64 (m, 6H), 2.40 (s, 3H), 1.78 (qi, J=4.2Hz, 2H). LRMS (ESI): 554.2 (calc) 555.2 (MH)+ (found).	320 Ex 539b Step 1-4

540b	794b		N-(3-(4-(N-(3-fluoro-4-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.09 (s, 1H), 7.86 (t, J=5.9Hz, 1H), 7.59 (d, J=8.7Hz, 2H), 7.40 (dd, J=8.8and5.7Hz, 2H), 7.35 (d, J=8.4Hz, 2H), 7.16 (t, J=9.0Hz, 2H), 7.00 (t, J=9.2Hz, 1H), 6.88 (dd, J=12.7and2.5Hz, 1H), 6.79-6.76 (m, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.71 (s, 3H), 3.07 (q, J=6.5Hz, 2H), 2.58 (t, J=7.6Hz, 2H), 1.69 (qi, J=7.4Hz, 2H). LRMS (ESI): 504.1 (calc) 503.0 (M-) (found)	321 Ex 540a
540c	794c		N-(3-(4-(N-(3,5-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.24 (s,1H), 7.84-7.87 (m,1H), 7.66-7.68 (m,2H), 6.24 (d,2H,J=2Hz), 6.12 (t,1H,J=2Hz), 4.47 (s,2H), 3.83 (s,3H), 3.60 (s,6H), 3.05-3.10 (m,2H), 2.56-2.60 (m,2H), 1.65-1.72 (m,2H). LRMS (ESI): 516.17 (calc) 515.0 (M-) (found)	321 Ex 540a
540d	794d		N-(3-(4-(N-cyclohexylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.76 (d,1H,J=8.4Hz), 7.28-7.31 (m,4H), 7.03-7.07 (m,2H), 6.60 (bs,1H), 4.51 (s,2H), 3.95 (s,2H), 3.30-3.35 (m,2H), 3.08-3.16 (m,1H), 2.68-2.72 (m,2H), 1.82-1.90 (m,2H), 1.60-1.67 (m,2H), 1.48-1.58 (m,1H), 1.07-1.17 (m,5H). LRMS(ESI): 462.20 (calc) 461.0(M-) (found).	321 Ex 540a
540e	794e		methyl 4-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylsulfonamido)benzoate	($CDCl_3$) δ (ppm) ^{1}H: 7.89 (d,2H,J=8.8Hz), 7.77-7.71 (m,3H), 7.27-7.30 (m,2H), 7.22 (d,2H,J=8.2Hz), 7.15 (d,2H,J=8.8Hz), 7.04 (t,2H,J=8.6Hz), 6.60-6.63 (m,1H), 4.50 (s,2H), 3.96 (s,2H), 3.86 (s,3H), 3.30 (q,2H,J=6.8Hz), 2.64 (t,2H,J=7.4Hz), 7.82 (qi,2H,J=7.4Hz). LRMS(ESI): 514.16 (calc) 513.0(M-) (found)	321 Ex 540a
540f	794f		2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-hydroxy-4-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.75 (bs,1H), 9.06 (s,1H), 7.85 (t,1H,J=6.0Hz), 7.57 (d,2H,J=8.4Hz), 7.38-7.42 (m,2H), 7.33 (d,2H,J=8.4Hz), 7.16 (t,2H,J=8.9Hz) 6.70 (d,1H,J=8.6Hz), 6.55 (d,1H,J=2.7Hz), 6.39-6.42 (m,1H), 4.47 (s,2H), 3.84 (s,2H), 3.62 (s,3H), 3.05-3.09 (m3H), 2.57 (t,2H,J=7.4Hz), 1.67-1.72 (m,2H). LRMS(ESI): 502.16 (calc) 501.0(M-) (found)	321 Ex 540a
540g	794g		N-(3-(4-(N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.05 (bs,1H), 7.85 (t,2H,J=6.0Hz), 7.60 (d,2H,J=8.2Hz), 7.33-7.41 (m,4H), 7.15 (t,2H,J=8.9Hz), 6.78 (d,1H,J=8.4Hz), 6.59-6.63 (m,2H), 4.47 (s,2H), 3.95-4.01 (m,4H), 3.83 (s,2H), 3.06 (q,2H,J=6.4Hz), 2.57 (t,2H,J=7.8Hz), 1.96-2.00 (m,2H), 1.68 (qi,2H,J=7.4Hz). LRMS(ESI): 528.17 (calc) 527.0(M-) (found)	321 Ex 540a
540h	794h		N-(3-(4-(N-(2,3-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.57 (bs), 7.88 (t,1H,J=5.8Hz), 7.66 (d,2H,J=8.4Hz), 7.38-7.44 (m,2H), 7.35 (d,2H,J=8.4Hz), 7.17 (d,2H,J=8.8Hz), 6.89-6.96 (m,2H), 6.76 (dd,1H,J=2.7and7.0Hz), 4.49 (s,2H), 3.85 (s,2H), 3.71 (s,3H), 3.35 (s,3H), 3.07 (q,2H,J=6.6Hz), 2.58 (t,2H,J=7.8Hz), 1.68 (qi,2H,J=7.2Hz). LRMS(ESI): 516.17 (calc) 515.0(M-) (found)	321 Ex 540a
540i	794i		2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)sulfamoyl)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.87 (s,1H), 10.57 (s,1H), 7.85 (s,1H), 7.60 (d,2H,J=8.2Hz), 7.33-7.41 (m,4H), 7.15 (t,2H,J=8.8Hz), 6.65 (m,3H), 4.46 (d,4H,J=5.0Hz), 3.84 (s,2H), 3.07 (q,2H,J=J=6.4Hz), 2.57 (t,2H,J=7.6Hz), 1.68 (qi,2H,J=7.2Hz). LRMS(ESI): 527.15 (calc) 526.0(M-) (found)	321 Ex 540a

540j	794j		2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-hydroxy-3-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.66 (s, 1H), 8.83 (s, 1H), 7.85 (t, J=5.9Hz, 1H), 7.56 (d, J=8.4Hz, 2H), 7.41 (dd, J=8.8and5.7Hz, 2H), 7.33 (d, J=8.4Hz, 2H), 7.16 (t, J=8.8Hz, 2H), 6.57-6.54 (m, 2H), 6.40 (dd, J=8.4and2.5Hz, 1H), 4.48 (s, 2H), 3.85 (s, 2H), 3.58 (s, 3H), 3.07 (q, J=6.3Hz, 2H), 2.58 (t, J=7.6Hz, 2H), 1.69 (qi, J=7.2Hz, 2H). LRMS (ESI): 502.1 (calc) 503.0 (MH)+ (found)	321 Ex 540a

Example 541

2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3,4,5-trimethoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)acetamide (**793b**)

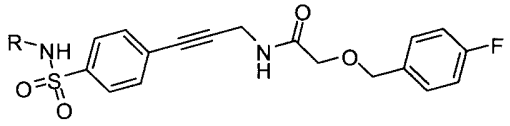
[0603] Compound **793b** was prepared according to the procedures described for compound **793a**, example **540a**, scheme **321**, steps 1 and 2, replacing 1,4-benzodioxan-6-amine with 3,4,5-trimethoxyaniline in step 1.

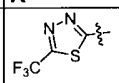
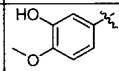
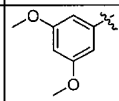
[0604] ($CDCl_3$) δ (ppm)^{1}H: 7.68 (d,2H,J=8.6Hz), 7.46 (d,2H,J=8.4Hz), 7.29-7.33 (m,2H), 7.04-7.08 (m,2H), 6.81 (s,1H), 6.34 (s,1H), 6.26 (s,1H), 4.55 (s,2H), 4.32 (d,2H,J=5.6Hz), 4.11 (d,2H,J=7.2Hz), 4.01 (s,2H), 3.78 (s,3H), 3.74 (s,6H).

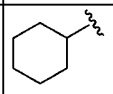
LRMS (ESI): calc 542.15; found 541.0 $(M-H)^-$

[0605] Examples **541c-f,** compounds **793c-f** were prepared as described for compound **793b** Example **541**, scheme **321**. Characterization data are presented in **Table 42.**

Table 42



Ex	Cpd	R	Name	Characterization	Scheme
541c	793c		2-(4-fluorobenzyloxy)-N-(3-(4-(N-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)prop-2-ynyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 8.40 (t, J=5.7Hz, 1H), 7.77 (d, J=8.2Hz, 2H), 7.55 (d, J=8.2Hz, 2H), 7.42 (dd, J=8.8and5.7Hz, 2H), 7.17 (t, J=8.8Hz, 2H), 4.51 (s, 2H), 4.16 (d, J=5.7Hz, 2H), 3.94 (s, 2H). LRMS (ESI): (calc) 528.0; (found) 528.9 $(MH)^+$	321 Ex 541
541d	793d		2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-hydroxy-4-methoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.85 (s, 1H), 9.11 (s, 1H), 8.39 (t, J=5.9Hz, 1H), 7.61 (d, J=8.6Hz, 2H), 7.52 (d, J=8.6Hz, 2H), 7.42 (dd, J=8.8and5.7Hz, 2H), 7.17 (t, J=9.0Hz, 2H), 6.71 (d, J=8.8Hz, 1H), 6.52 (d, J=2.7Hz, 1H), 6.37 (dd, J=8.8and2.7Hz, 1H), 4.50 (s, 2H), 4.14 (d, J=5.9Hz, 2H), 3.93 (s, 2H), 3.64 (s, 3H). LRMS (ESI): 498.1 (calc) 497.0 (M-) (found)	321 Ex 541
541e	793e		N-(3-(4-(N-(3,5-dimethoxyphenyl)sulfamoyl)phenyl) prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide	($CDCl_3$) δ (ppm) ^{1}H: 7.73 (d,2H,J=8.4Hz), 7.45 (d,2H,J=8.4Hz), 7.33-7.29 (m,2H), 7.04-7.08 (m,2H), 6.81 (s,1H), 6.5 (s,1H), 6.20 (m,3H), 4.55 (s,2H), 4.32 (d,2H,J=5.6Hz), 4.01(s,6H) LRMS (ESI): (calc) 512.1; (found)	321 Ex 541

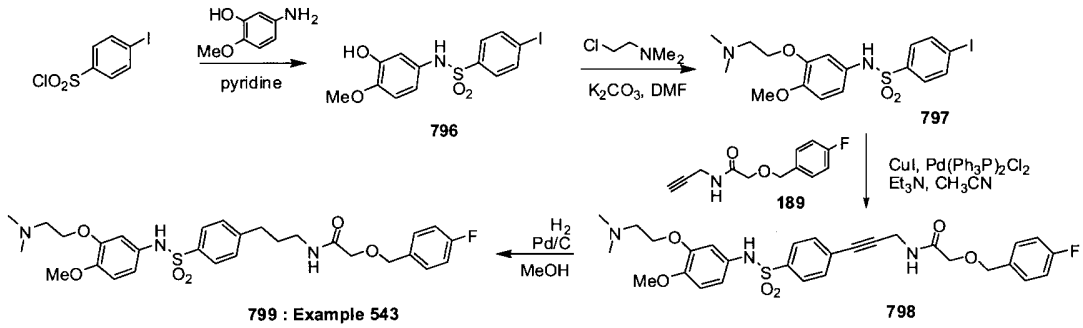
				511.0(M-H)$^-$.	
541f	793f		N-(3-(4-(N-cyclohexylsulfamoyl) phenyl)prop-2-ynyl)-2-(4-fluorobenzyl-oxy)acetamide	(MEOD-d_4) δ (ppm) ^{1}H: 7.81(m,2H), 7.56 (d,2H,J=8.4Hz), 7.40-7.44 (m,2H), 7.05-7.10 (m,2H), 4.6 (s,2H), 4.26 (s,2H), 3.99 (s,2H), 3.00 (s,1H), 1.64 (d,4H,J=9.8Hz), 1.5 (s,1H), 1.13-1.22 (m,5H). LRMS (ESI): (calc) 458.17; (found) 457.0 (M-H)-	321 Ex 541

Example 542

(Z)-2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3,4,5-trimethoxyphenyl)sulfamoyl)phenyl)allyl)acetamide (**795**)

[0606] Compound **793b** (226 mg, 04.44 mmol, example **541**, scheme **321**) in methanol (2.2 mL) and 10% palladium on charcoal (22 mg) was hydrogenated under 1 atm of H_2 for 16h at room temperature. The residue was purified by silica gel column chromatography with gradient of ethyl acetate (40-60%) in hexane to give **795** (148 mg, 62%). (DMSO-d_6) δ (ppm)^{1}H: 10.14 (s,1H), 8.16 (t,1H,J=6.0Hz), 7.74 (d,2H,J=8.4Hz), 7.48 (d,2H,J=8.4Hz), 7.38-7.42 (m,2H), 7.12-7.18 (m,2H), 6.47 (d,2H,J=12Hz), 6,36 (s,2H), 5.68-5.74 (m,1H), 4.48 (s,2H), 3.97-4.01 (m,2H), 3.87 (s,2H), 3.62 (s,6H), 3.53 (s,3H). LRMS (ESI): (calc) 544.2; (found) 543.0(M-H)$^-$.

Scheme 322



Example 543

N-(3-(4-(N-(3-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**799**)

Step 1: N-(3-hydroxy-4-methoxyphenyl)-4-iodobenzenesulfonamide (**796**)

[0607] To a stirred solution of 5-amino-2-methoxyphenol (460 mg, 3.31 mmol) in pyridine (10 mL) was added 4-iodobenzenesulfonyl chloride (1.00 g, 3.31 mmol) as described for compound **792a**, example **540a**, scheme **321**, step 1. The crude material was purified by silica gel column chromatography with gradient of ethyl acetate (20-40%) in hexane to give **796** (1.0 g, 75%).

[0608] ($CDCl_3$) δ (ppm)^{1}H: 7.78 (d, J=8.6Hz, 1H), 7.42 (d, J=8.6Hz, 2H), 6.71 (d, J=8.6Hz, 1H), 6.64 (d, J=2.5Hz, 1H), 6.56 (dd, J=8.6and2.7Hz, 1H), 6.51 (s, 1H), 5.77 (s, 1H), 3.85 (s, 3H). LRMS (ESI): (calc) 405.0; (found) 403.8 $(M-H)^-$.

Step 2: N-(3-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)-4-iodobenzenesulfonamide (**797**)

[0609] To a stirred solution of **796** (250 mg, 0.62 mmol) in dimethylformamide (4.1 mL) was added potassium carbonate (256 mg, 1.85 mmol), and 2-(dimethylamino)ethyl chloride hydrochloride (98 mg, 0.68 mmol). The mixture was stirred for 3.5h at 60°C. Brine was added and the aqueous phase was extracted with EtOAc, and the organic extract was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by silica gel column chromatography with gradient of methanol (0-5%) in dichloromethane to give **797** (123 mg, 42%).

(DMSO-d_6) δ (ppm)^{1}H: 9.21 (s, 1H), 7.94 (d, J=8.4Hz, 2H), 7.34 (d, J=8.6Hz, 2H), 6.82 (d, J=8.6Hz, 1H), 6.46 (d, J=2.5Hz, 1H), 6.38 (dd, J=8.4and2.5Hz, 1H), 3.72 (s, 3H), 3.51 (t, J=6.8Hz, 2H), 2.18 (t, J=6.8Hz, 2H), 2.07 (s, 6H). LRMS (ESI): (calc) 476.0; (found) 476.9 $(MH)^+$.

Step 3: N-(3-(4-(N-(3-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)sulfamoyl)phenyl)-prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide (**798**)

[0610] Compound **797** (123 mg, 0.26 mmol) in acetonitrile (1 mL) was added 2-(4-fluorobenzyloxy)-N-(prop-2-ynyl)acetamide (69 mg, 0.31 mmol), triethylamine (0.05 mL, 0.39 mmol), dichlorobis(triphenylphosphine)palladium(II) (9 mg, 0.01 mmol), and copper(I) iodide (5 mg, 0.03 mmol) as described for compound **793b**, example **541**, scheme **321**. The material was purified by silica gel column chromatography with gradient of methanol (0-5%) in DCM to give **798** (100 mg, 68%).

(DMSO-d_6) δ (ppm)^{1}H: 9.20 (s, 1H), 8.42 (t, J=6.1Hz, 1H), 7.58-7.53 (m, 4H), 7.43 (dd, J=8.4and5.7Hz, 2H), 7.17 (t, J=8.8Hz, 2H), 6.81 (d, J=8.8Hz, 1H), 6.42 (d, J=2.5Hz, 1H), 6.34 (dd, J=8.4and2.5Hz, 1H), 4.52 (s, 2H), 4.17 (d, J=5.9Hz, 2H), 3.95 (s, 2H), 3.72 (s, 3H), 3.55-3.51 (m, 2H), 2.28-2.03 (m, 8H). LRMS (ESI): (calc) 569.2; (found) 570.0 $(MH)^+$.

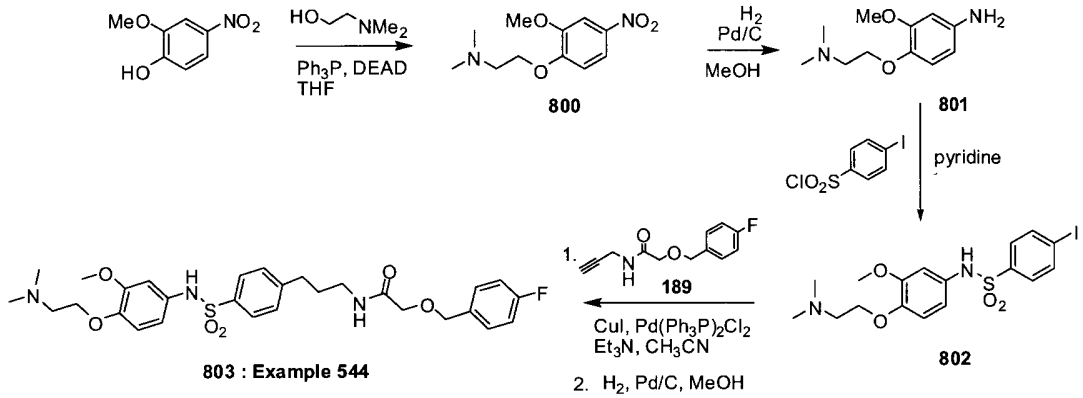
Step 4: N-(3-(4-(N-(3-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)sulfamoyl)phenyl)-propyl)-2-(4-fluorobenzyloxy)acetamide **799**

[0611] To a stirred solution of **798** (80 mg, 0.14 mmol) in methanol (1.0 mL) was added 10% palladium on charcoal (16 mg). The mixture was stirred under 1 atm of H_2 for 16h. The material was purified by silica gel column chromatography with a gradient of MeOH (0-10%) in DCM to give **799** (13 mg, 57%).

(DMSO-d_6) δ (ppm)^{1}H: 9.17 (s, 1H), 7.89 (t, J=5.7Hz, 1H), 7.49 (d, J=8.6Hz, 2H), 7.43-7.37 (m, 4H), 7.17 (t, J=9.0Hz, 2H), 6.80 (d, J=8.6Hz, 1H), 6.45 (d, J=2.5Hz, 1H), 6.34 (dd, J=8.6and2.5Hz, 1H), 4.49 (s, 2H), 3.86 (s, 2H), 3.72 (s, 3H), 3.49 (t, J=7.0Hz, 2H), 3.10 (q,

J=6.3Hz, 2H), 2.64 (t, J=8.0Hz, 2H), 2.18 (t, J=6.8Hz, 2H), 1.73 (qi, J=7.4Hz, 2H). LRMS (ESI): (calc) 573.2; (found) 574.1 $(MH)^+$.

Scheme 323



Example 544

N-(3-(4-(N-(4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**803**)

Step 1: 2-(2-methoxy-4-nitrophenoxy)-N,N-dimethylethanamine (**800**)

[0612] To a stirred solution of 4-nitroguaiacol (750 mg, 4.32 mmol) in THF (39 mL) was added N,N-dimethylethanolamine (0.40 mL, 3.92 mmol), triphenylphosphine (1.34 g, 5.10 mmol) and diethylazodicarboxylate (0.73 mL, 4.71 mmol). The mixture was stirred for 16h at room temperature. Saturated sodium carbonate (aq.) was added and the mixture was extracted with EtOAc. The organic extract was dried ($MgSO_4$), filtered, and concentrated and the residue was purified by silica gel column chromatography with gradient of MeOH (0-10%) in DCM to give **800** (310 mg, 33%).

(DMSO-d_6) δ (ppm)^{1}H: 7.87 (dd, J=8.8and2.5Hz, 1H), 7.71 (d, J=2.7Hz, 1H), 7.18 (d, J=9.0Hz, 1H), 4.16 (t, J=5.9Hz, 2H), 3.86 (s, 3H), 2.64 (t, J=5.7Hz, 2H), 2.19 (s, 6H).

Step 2: 4-(2-(dimethylamino)ethoxy)-3-methoxybenzenamine (**801**)

[0613] To a stirred solution of **800** (310 mg, 1.29 mmol) in methanol (6 mL) was added 10% palladium on charcoal (31 mg). The mixture was stirred under 1 atm of H_2 for 3.5h at room temperature. The material was purified by silica gel column chromatography with gradient of methanol (0-20%) in dichloromethane to give **801** (237 mg, 87%).

(DMSO-d_6) δ (ppm)^{1}H: 6.62 (d, J=8.4Hz, 1H), 6.23 (d, J=2.5Hz, 1H), 6.01 (dd, J=8.4and2.5Hz, 1H), 4.67 (bs, 2H), 3.82 (t, J=6.1Hz, 2H), 3.64 (s, 3H), 2.50 (t, J=6.1Hz, 2H), 2.16 (s, 6H). LRMS (ESI): (calc) 210.1; (found) 211.1 (MH)+.

Step 3: N-(4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)-4-iodobenzenesulfonamide (**802**)

[0614] To a stirred solution of **801** (237 mg, 1.13 mmol) in pyridine (3.5 mL) was added 4-iodobenzenesulfonyl chloride (341 mg, 1.13 mmol) as described for compound **792a**, example **540a**, scheme **321**, step 1. The material was purified by silica gel column chromatography with gradient of methanol (0-20%) in dichloromethane to give **802** (410 mg, 76%).

(DMSO-d_6) δ (ppm)^{1}H: 9.97 (bs, 1H), 7.91 (d, J=8.6Hz, 2H), 7.42 (d, J=8.6Hz, 2H), 6.80 (d, J=8.6Hz, 1H), 6.64 (d, J=2.3Hz, 1H), 6.48 (dd, J=8.6and2.5Hz, 1H), 3.89 (t, J=5.9Hz, 2H), 3.61 (s, 3H), 2.54 (t, J=5.9Hz, 2H), 2.16 (s, 6H). LRMS (ESI): (calc) 476.0; (found) 476.9 $(MH)^+$.

Step 4: N-(3-(4-(N-(4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)sulfamoyl)phenyl)-propyl)-2-(4-fluorobenzyloxy)acetamide (**803**)

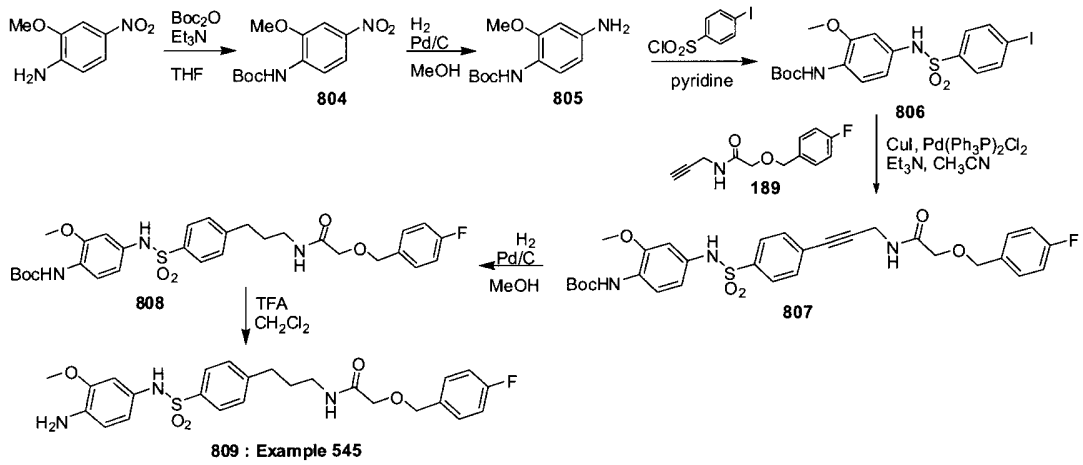
[0615] To a stirred solution of **802** (196 mg, 0.41 mmol) in acetonitrile (1.2 mL) was added 2-(4-fluorobenzyloxy)-N-(prop-2-ynyl)acetamide (100 mg, 0.45 mmol), triethylamine (0.09 mL, 0.62 mmol), dichlorobis(triphenylphosphine)palladium(II) (14 mg, 0.02 mmol), and copper(I) iodide (8 mg, 0.04 mmol) as described for example **541**, compound **793b**, scheme **321**. The material was purified by silica gel column chromatography with gradient of methanol (0-20%) in DCM to give the alkyne product (185 mg, 79%).

(DMSO-d_6) δ (ppm)^{1}H: 9.96 (s, 1H), 8.39 (t, J=5.9Hz, 1H), 7.63 (d, J=8.4Hz, 2H), 7.53 (d, J=8.4Hz, 2H), 7.42 (dd, J=8.4and5.5Hz, 2H), 7.16 (t, J=9.0Hz, 2H), 6.79 (d, J=8.6Hz, 1H), 6.63 (d, J=2.5Hz, 1H), 6.46 (dd, J=8.6and2.5Hz, 1H), 4.50 (s, 2H), 4.14 (d, J=5.9Hz, 2H), 3.93 (s, 2H), 3.89 (t, J=5.9Hz, 2H), 3.60 (s, 3H), 2.53 (t, J=5.9Hz, 2H), 2.15 (s, 6H). LRMS (ESI): (calc) 569.2; (found) 570.1 $(MH)^+$.

[0616] Reduction of the alkyne above (148 mg, 0.26 mmol) in methanol (1.0 mL) using 10% palladium on charcoal (15 mg).under 1 atm of H_2 for 16h at room temperature gave **803** (136 mg, 91%).

(DMSO-d_6) δ (ppm)^{1}H: 9.85 (s, 1H), 7.85 (t, J=5.9Hz, 1H), 7.59 (d, J=8.4Hz, 2H), 7.40 (dd, J=8.4and5.7Hz, 2H), 7.34 (d, J=8.2Hz, 2H), 7.16 (t, J=8.8Hz, 2H), 6.78 (t, J=8.6Hz, 1H), 6.63 (d, J=2.5Hz, 1H), 6.50 (dd, J=8.6and2.5Hz, 1H), 4.48 (s, 2H), 3.88 (t, J=5.9Hz, 2H), 3.84 (s, 2H), 3.59 (s, 3H), 3.07 (q, J=6.5Hz, 2H), 2.58 (t, J=7.6Hz, 2H), 2.53 (t, J=5.9Hz, 2H), 2.15 (s, 6H), 1.68 (qi, J=7.6Hz, 2H). LRMS (ESI): (calc) 573.2; (found) 574.1 (MH)+.

Scheme 324



Example 545

N-(3-(4-(N-(4-amino-3-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**809**)

Step 1: tert-butyl 2-methoxy-4-nitrophenylcarbamate (**804**)

[0617] To a stirred solution of 2-methoxy-4-nitroaniline (2.5 g, 15 mmol) in THF (75 mL) was added di-tert-butyl dicarbonate (3.89 g, 18 mmol). The mixture was stirred for 16h at reflux. Triethylamine (3 mL, 30 mmol) was added, and then the mixture was stirred for 16h at reflux. The mixture was concentrated and the residue was purified by silica gel column chromatography with 30% ethyl acetate in hexane to give **804** (987 mg, 25%).

LRMS (ESI): (calc) 268.1; (found) 269.0 $(MH)^+$.

Step 2: tert-butyl 4-amino-2-methoxyphenylcarbamate (**805**)

[0618] Compound **804** (805 mg, 3.0 mmol) in methanol (15 mL) and 10% palladium on charcoal (80 mg) was hydrogenated under 1 atm of H_2 for 16h at room temperature. The material was purified by silica gel column chromatography with gradient of methanol (0-10%) in dichloromethane to give **805** (215 mg, 30%).

(DMSO-d_6) δ (ppm)^{1}H: 7.52 (s, 1H), 7.04-6.98 (m, 1H), 6.20 (d, J=2.3Hz, 1H), 6.05 (dd, J=8.4and2.3Hz, 1H), 5.74 (s, 2H), 3.65 (s, 3H), 1.38 (s, 9H). LRMS (ESI): (calc) 238.1; (found)183.0 (MH-tBu)+.

Step 3: tert-butyl 4-(4-iodophenylsulfonamido)-2-methoxyphenylcarbamate (**806**)

[0619] To a stirred solution of **805** (215 mg, 0.90 mmol) in pyridine (3 mL) was added 4-iodobenzenesulfonyl chloride (272 mg, 0.90 mmol) as described for compound **792a**, example **540a**, scheme **321**, step 1. The material was purified by silica gel column chromatography with gradient of ethyl acetate (20-40%) in hexane to give **806** (387 mg, 85%).

($CDCl_3$) δ (ppm)^{1}H: 10.15 (s, 1H), 7.91 (d, J=8.4Hz, 2H), 7.85 (s, 1H), 7.46 (d, J=8.6Hz, 2H), 7.44-7.40 (m, 1H), 6.70 (d, J=2.3Hz, 1H), 6.53 (dd, J=8.6and2.3Hz, 1H), 3.67 (s, 3H), 1.39 (s, 9H). LRMS (ESI): (calc) 504.0; (found) 526.8 $(MNa)^+$.

Step 4: tert-butyl 4-(4-(3-(2-(4-fluorobenzyloxy)acetamido)prop-1-ynyl)phenylsulfonamido)-2-methoxyphenylcarbamate (**807**)

[0620] Compound **806** (158 mg, 0.31 mmol) in acetonitrile (1.0 mL) was reacted with 2-(4-fluorobenzyloxy)-N-(prop-2-ynyl)acetamide (82 mg, 0.37 mmol), triethylamine (0.07 mL, 0.47 mmol), dichlorobis(triphenylphosphine)palladium(II) (11 mg, 0.02 mmol), and copper(I) iodide (6 mg, 0.03 mmol) as described for compound **793b**, example **541**, scheme **321**. The material was purified by silica gel column chromatography with gradient of ethyl acetate (40-60%) in hexane to give **807** (107 mg, 57%).

($DMSO-d_6$) δ (ppm)^{1}H:10.14 (s, 1H), 8.38 (t, J=5.9Hz, 1H), 7.85 (s, 1H), 7.67 (d, J=8.6Hz, 2H), 7.53 (d, J=8.6Hz, 2H), 7.43-7.39 (m, 3H), 7.16 (t, J=9.0Hz, 2H), 6.69 (d, J=2.3Hz, 1H), 6.52 (dd, J=2.3and8.6Hz, 1H), 4.50 (s, 2H), 4.14 (d, J=5.9Hz, 2H), 3.93 (s, 2H), 3.65 (s, 3H), 1.39 (s, 9H). LRMS (ESI): (calc) 597.2; (found) 620.0 $(MNa)^+$.

Step 5: tert-butyl 4-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylsulfonamido)-2-methoxyphenylcarbamate (**808**)

[0621] Compound **807** (97 mg, 0.16 mmol) in MeOH (1.0 mL) and 10% palladium on charcoal (10 mg) was hydrogenated under 1 atm of H_2 for 16h at room temperature. The material was purified by silica gel column chromatography with gradient of ethyl acetate (40-80%) in hexane to give **808** (67 mg, 68%).

($DMSO-d_6$) δ (ppm) ^{1}H: 10.04 (s, 1H), 7.84-7.83 (m, 2H), 7.63 (d, J=8.4Hz, 2H), 7.42-7.36 (m, 3H), 7.35 (d, J=8.4Hz, 2H), 7.16 (t, J=9.0Hz, 2H), 6.70 (d, J=2.2Hz, 1H), 6.55 (dd, J=8.4and2.2Hz, 1H), 4.48 (s, 2H), 3.84 (s, 2H), 3.64 (s, 3H), 3.08 (q, J=6.5Hz, 2H), 2.58 (t, J=7.6Hz, 2H), 1.69 (qi, J=7.6Hz, 2H), 1.38 (s, 9H). LRMS (ESI): (calc) 601.2; (found) 602.1 $(MH)^+$.

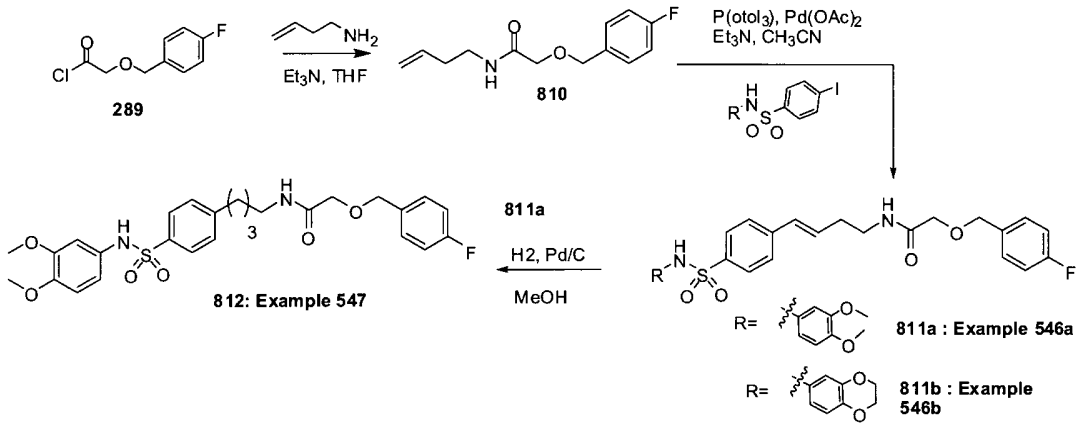
Step 6: N-(3-(4-(N-(4-amino-3-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide (**809**)

[0622] To a stirred solution of **808** (58 mg, 0.10 mmol) in DCM (0.5 mL) was added trifluoroacetic acid (0.1 mL). The mixture was stirred for 1.25 h at room temperature. The solvent was evaporated, a solution of saturated sodium carbonate in water was added, and then the residue was extracted with DCM. The organic extract was dried ($MgSO_4$), filtered, and evaporated to give **809** (38 mg, 79%).

($DMSO-d_6$) δ (ppm) ^{1}H: 9.44 (s, 1H), 7.85 (t, J=5.7Hz, 1H), 7.54 (d, J=8.4Hz, 2H), 7.41 (dd, J=8.8and5.7Hz, 2H), 7.32 (d, J=8.4Hz, 2H), 7.16 (t, J=9.0Hz, 2H), 6.42-6.38 (m, 2H), 6.31 (dd, J=8.2and2.2Hz, 1H), 4.56 (s, 2H), 4.48 (s, 3H), 3.85 (s, 2H), 3.56 (s, 3H), 3.08 (q,

J6.5Hz, 2H), 2.58 (t, J=7.4Hz, 2H), 1.69 (qi, J=7.0Hz, 2H). LRMS (ESI): (calc) 501.2; (found) 502.1 $(MH)^+$.

Scheme 325



Example 546a

(E)-N-(4-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)but-3-enyl)-2-(4-fluorobenzyloxy)acetamide (**811a**)

Step 1: 2-(4-fluorobenzyloxy)-N-(but-3-enyl)acetamide (**810**)

[0623] A solution of acid chloride **289** (5.43 mmol) in THF (4 mL) was added to 3-buten-1-amine hydrochloride (584 mg, 5.43 mmol) and triethylamine (2.3 mL, 16.3 mmol) in THF (18 mL) at 0°C as described for compound **724**, example **508a**, step 1,scheme **303**. The material was purified by silica gel column chromatography with ethyl acetate (40%) in hexane to give **810** (575 mg, 45%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.79 (bs, 1H), 7.40 (dd, J=9.1and5.5Hz, 2H), 7.17 (t, J=8.8Hz, 2H), 5.79-5.69 (m, 1H), 5.06-4.96 (m, 2H), 4.48 (s, 2H), 3.85 (s, 2H), 3.15 (q, J=7.0Hz, 2H), 2.16 (q, J=7.0Hz, 2H). LRMS (ESI): (calc) 237.1; (found) 238.0 $(MH)^+$.

Step 2: (E)-N-(4-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)but-3-enyl)-2-(4-fluorobenzyloxy)acetamide (**811a**)

[0624] To a stirred solution of N-(3,4-dimethoxyphenyl)-4-iodobenzenesulfonamide (1.01 mg, 2.42 mmol) in acetonitrile (6 mL) was added tri-*o*-tolylphosphine (74.8 mg, 0.24 mmol), palladium(II) acetate (27 mg, 0.12 mmol), **810a** (690 mg, 2.91 mmol), and triethylamine (0.63 mL, 4.84 mmol) as described for compound **761a**, example **529** , step 1, scheme **314**. The material was purified by silica gel column chromatography with gradient of ethyl acetate (0-90%) in hexane to give **811a** (211mg, 16%) as white solid.

(DMSO-d_6) δ (ppm) ^{1}H: 9.86 (s, 1H), 7.88 (broad triplet, 1H), 7.59 (d, J=8.8Hz, 2H), 7.48 (d, J=8.8Hz, 2H), 7.35-7.31 (m, 2H), 7.13-7.09 (m, 2H), 6.74 (d, J=8.8Hz, 1H), 6.65 (d, J=2.8Hz, 1H), 6.50 (dd, J=8.4, 2.4Hz, 1H), 6.46-6.34 (m, 2H), 4.45 (s, 2H), 3.84 (s, 2H), 3.62 (s, 3H), 3.59 (s, 3H), 3.25-3.21 (m, 2H), 2.36-2.31 (m, 2H).
LRMS (ESI): (calc) 528.6; (found) 529.0 $(MH)^+$.

Example 546b

(E)-N-(4-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)but-3-enyl)-2-(4-fluorobenzyloxy)acetamide (**811b**)

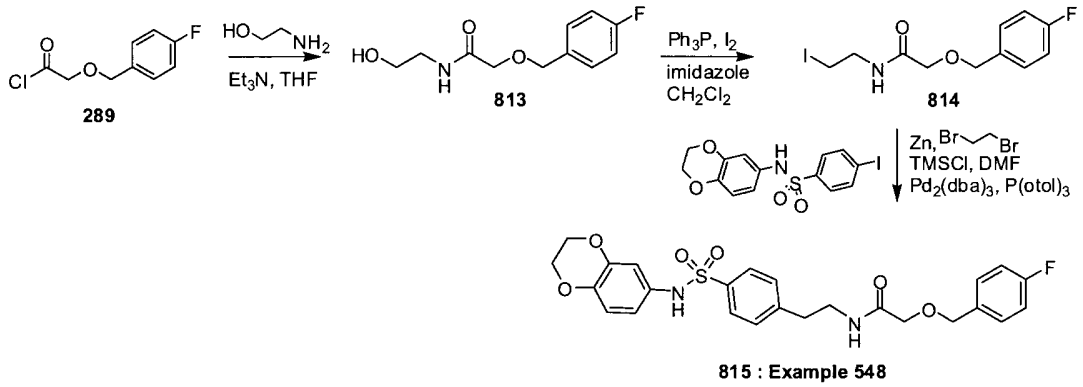
[0625] Compound **811b,** Example **546b**, was obtained in 20% overall yield following the procedures desribed for compound **811a**, Example **546a**, scheme **325**, replacing N-(3,4-dimethoxyphenyl)-4-iodobenzenesulfonamide in step 2, with N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-iodobenzenesulfonamide.
(MEOD-d_4) δ(ppm) ^{1}H: 7.60 (d, 2H, J=8.4Hz), 7.43 (d, 2H, J=8.6Hz), 7.30 (dd, 2H, J1=5.4Hz,J2=3.1Hz), 7.00 (t, 2H, J=8.8Hz), 6.62 (d, 1H, J=8.6Hz), 6.57 (d, 1H, J=2.5Hz), 6.45-6.49 (m, 2H), 6.36 (dt, 2H, J1=6.6Hz,J2=15.8Hz), 4.50 (s, 2H), 4.13 (s, 4H), 3.90 (s, 2H), 3.38 (t, 2H, J=6.8Hz), 2.44 (q, 2H, J=6.4Hz). LRMS (ESI): (calc) 526.1; (found) 525.0 $(M-H)^-$.

Example 547

N-(4-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)butyl)-2-(4-fluorobenzyloxy)acetamide (**812**)

[0626] Compound **811a** (79 mg, 0.165mmol) in MeOH (1.0 mL) and 10% palladium on charcoal (16 mg) was hydrogenated under 1 atm of H_2 for 16h at room temperature. The material was purified by silica gel column chromatography with gradient of ethyl acetate (40-80%) in hexane to give **812** (20 mg, 25%) as clear oil.
(MEOD-d_4) δ(ppm) ^{1}H:7.59 (d, J=8.4Hz, 2H), 7.39-7.36 (m, 2H), 7.28 (d, J=8.4Hz, 2H), 7.08-7.03 (m, 2H), 6.45 (d, J=8.8Hz, 1H), 6.65 (d, J=2.4Hz, 1H), 6.56 (dd, J=8.6, 2.4Hz, 1H), 4.54 (s, 2H), 3.91 (s, 2H), 3.72 (s, 3H), 3.67 (s, 2H), 3.22 (t, J=7.2Hz, 2H), 2.66 (t, J=7.6Hz, 2H), 1.63-1.56 (m, 2H), 1.52-1.45 (m, 2H).
LRMS: (calc) 530.6; (found) 531.0 $(MH)^+$.

Scheme 326



Example 548

N-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**815**)

Step 1: 2-(4-fluorobenzyloxy)-N-(2-hydroxyethyl)acetamide (**813**)

[0627] A solution of acid chloride **289** (5.43 mmol) in THF (4 mL) was added to ethanolamine (0.33 mL, 5.43 mmol) and triethylamine (1.5 mL, 10.9 mmol) in THF (18 mL) at 0°C as described for compound **724**, example **508a**, step 1, scheme **303.** The material was purified by silica gel column chromatography with gradient of EtOAc (60-100%) in hexanes to give **813** (330 mg, 27%).

(DMSO-d_6) δ (ppm) ^{1}H: 7.69 (t, J=5.1Hz, 1H), 7.41 (dd, J=8.8and5.7Hz, 2H), 7.17 (t, J=9.0Hz, 2H), 4.70 (t, J=5.5Hz, 1H), 4.49 (s, 2H), 3.86 (s, 2H), 3.39 (q, J=5.7Hz, 2H), 3.15 (q, J=6.1Hz, 2H). LRMS (ESI): (calc) 227.1; (found).228.0 (MH)+.

Step 2: 2-(4-fluorobenzyloxy)-N-(2-iodoethyl)acetamide (**814**)

[0628] To a stirred solution of triphenylphosphine (381 mg, 1.45 mmol) in DCM (5 mL) was added imidazole (100 mg, 1.45 mmol) followed by iodine (406 mg, 1.60 mmol) and a solution of **813** (330 mg, 1.45 mmol) in DCM (2 mL) was added. The reaction was stirred at room temperature for 16h. The solvent was evaporated and the residue was purified by silica gel column chromatography with gradient of EtOAc (20-40%) in hexane to give **814** (395 mg, 81%).

(DMSO-d_6) δ (ppm) ^{1}H: 8.11 (t, J=5.5Hz, 1H), 7.42 (dd, J=8.8and5.7Hz, 2H), 7.18 (t, J=9.0Hz, 2H), 4.51 (s, 2H), 3.88 (s, 2H), 3.43 (q, J=6.1Hz, 2H), 3.21 (t, J=6.8Hz, 2H). LRMS (ESI): (calc) 337.0; (found).359.9 $(MNa)^+$.

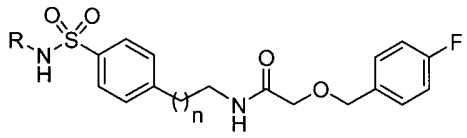
Step 3: N-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide (**815**)

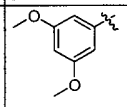
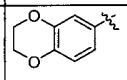
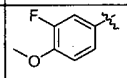
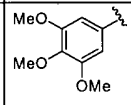
[0629] Zinc dust (294 mg, 4.50 mmol) in a round bottom flask was heated with a heat-gun for 30 sec under nitrogen. After cooling to room temperature, dimethylformamide (0.5 mL) was added, followed by 1,2-dibromoethane (30 uL, 0.36 mmol) according to the method of Hunter, C.; Jackson, R.; Rami, H. (*J. Chem. Soc. Perkin Trans 1* **2000,** 219-223). The reaction was stirred at 80°C for 1 min. After cooling to room temperature, chlorotrimethylsilane (20 uL, 0.25 mmol) was added and the reaction was stirred for 30 min. A solution of **814** (253 mg, 0.75 mmol) in dimethylformamide (0.5 mL) was added, and the mixture was stirred for another 30 min. Then tris(dibenzylideneacetone)dipalladium (23 mg, 0.03 mmol) was added, followed by tri-*o*-tolylphosphine (30 mg, 0.10 mmol) and N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-iodobenzenesulfonamide (253 mg, 0.75 mmol). The reaction was stirred for 16h at room temperature. The mixture was diluted with ethyl acetate and washed with brine twice. The organic extract was dried ($MgSO_4$), filtered, and evaporated, and the crude was purified by silica gel column chromatography with gradient of ethyl acetate (60-80%) in hexane to give **815** (130 mg, 35%).
(DMSO-d_6) δ (ppm) ^{1}H: 9.92 (s, 1H), 7.85 (t, J=5.7Hz, 1H), 7.61 (d, J=8.4Hz, 2H), 7.37-7.33 (m, 4H), 7.16 (t, J=9.0Hz, 2H), 6.65 (d, J=8.8Hz, 1H), 6.55 (d, J=2.5Hz, 1H), 6.48 (dd, J=8.8and2.5Hz, 1H), 4.42 (s, 2H), 4.13-4.10 (m, 4H), 3.81 (s, 2H), 3.32 (q, J=6.8Hz, 2H), 2.78 (t, J=7.2Hz, 2H). LRMS (ESI): (calc) 500.1; (found).499.1 $(M-H)^-$.

[0630] Example **548a** describe the preparation of compound **815a** using the same procedures as described for compound **815** in Example **548**, scheme **326**, replacing N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-iodobenzenesulfonamide in step 3 with N-(3,5-dimethoxyphenyl)-4-iodobenzenesulfonamide. Characterization data is presented in Table **43**.

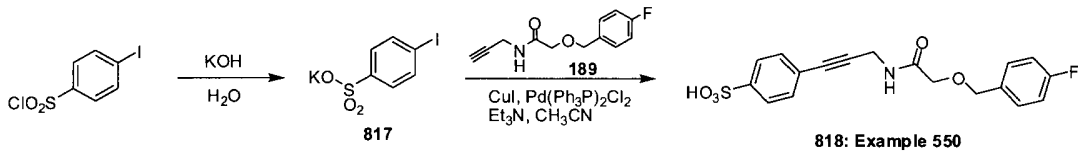
[0631] Example **549a-c** describe the preparation of compound **816a-c** using the same procedures as described for compound **815** in Example **548**, scheme **326**, except using 4-aminobutan-1-ol in place of 2-aminoethanol in step 1, and replacing N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-4-iodobenzenesulfonamide in step 3 with with N-(3-fluoro-4-methoxyphenyl)-4-iodobenzenesulfonamide for compound **816b**, and with 4-iodo-N-(3,4,5-trimethoxyphenyl)benzenesulfonamide for compound **816c**.

Table 43



Ex	Cpd	R	n	Name	Characterization	Scheme
548a	815a		1	N-(4-(N-(3,5-dimethoxyphenyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.25 (s, 1H), 7.86 (t, J=5.9Hz, 1H), 7.69 (d, J=8.4Hz, 2H), 7.37 (d, J=8.4Hz, 2H), 7.36-7.33 (m, 2H), 7.16 (t, J=9.0Hz, 2H), 6.24 (d, J=2.2Hz, 2H), 6.12 (t, J=2.2Hz, 1H), 4.41 (s, 2H), 3.81 (s, 2H), 3.60 (s, 6H), 3.32 (q, J=6.8Hz, 2H), 2.78 (t, J=7.0Hz, 2H). LRMS (ESI): (calc) 502.1; (found) 503.0 (MH)+.	326 Step 1-3 Ex 548
549a	816a		3	N-(4-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)butyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 9.90 (s, 1H), 7.80 (t, J=6.1Hz, 1H), 7.59 (d, J8.4Hz, 2H), 7.39 (dd, J=8.8and5.7Hz, 2H), 7.33 (d, J=8.6Hz, 2H), 7.15 (t, J=9.0Hz, 2H), 6.66 (d, J=8.8Hz, 1H), 6.55 (d, J=2.5Hz, 1H), 6.49 (dd, J=8.6and2.5Hz, 1H), 4.47 (s, 2H), 4.14-4.10 (m, 4H), 3.84 (s, 2H), 3.08 (q, J=6.5Hz, 2H), 2.59 (t, J=7.4Hz, 2H), 1.50 (qi, J=8.0Hz, 2H), 1.38 (qi, J=7.0Hz, 2H). LRMS (ESI): (calc) 528.1; (found) 529.0 (MH)+	326 Step 1-3 Ex 548
549b	816b		3	N-(4-(4-(N-(3-fluoro-4-methoxyphenyl)sulfamoyl)phenyl)butyl)-2-(4-fluorobenzyloxy)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 7.60 (d, J=8.6Hz, 2H), 7.38 (dd, J=9.0and5.5Hz, 2H), 7.30 (d, J=8.4Hz, 2H), 7.06 (t, J=8.8Hz, 2H), 6.91 (t, J=9.0Hz, 1H), 6.84 (dd, J=12.5and2.5Hz, 1H), 6.77-6.74 (m, 1H), 4.55 (s, 2H), 3.91 (s, 2H), 3.77 (s, 3H), 3.23 (t, J=7.0Hz, 2H), 2.67 (t, J=7.4Hz, 2H), 1.65-1.57 (m, 2H), 1.54-1.46 (m, 2H). LRMS (ESI): (calc) 518.1; (found) 519.0 (MH)+	326 Step 1-3 Ex 548
549c	816c		3	2-(4-fluorobenzyloxy)-N-(4-(4-(N-(3,4,5-trimethoxyphenyl)sulfamoyl)phenyl)butyl)acetamide	(DMSO-d_6) δ (ppm) ^{1}H: 10.04 (s, 1H), 7.79 (t, J=5.7Hz, 1H), 7.66 (d, J=8.4Hz, 2H), 7.40-7.34 (m, 4H), 7.15 (t, J=9.0Hz, 2H), 6.34 (s, 2H), 4.47 (s, 2H), 3.83 (s, 2H), 3.61 (s, 6H), 3.52 (s, 3H), 3.08 (q, J=6.3Hz, 2H), 2.60 (t, J=7.4Hz, 2H), 1.50 (qi, J=7.8Hz, 2H), 1.37 (qi, J=7.6Hz, 2H). LRMS (ESI): (calc) 560.2; (found) 561.1 $(MH)^+$	326 Step 1-3 Ex 548

Scheme 327



Example 550

4-(3-(2-(4-fluorobenzyloxy)acetamido)prop-1-ynyl)benzenesulfonic acid

Step 1: potassium 4-iodobenzenesulfonate (**817**)

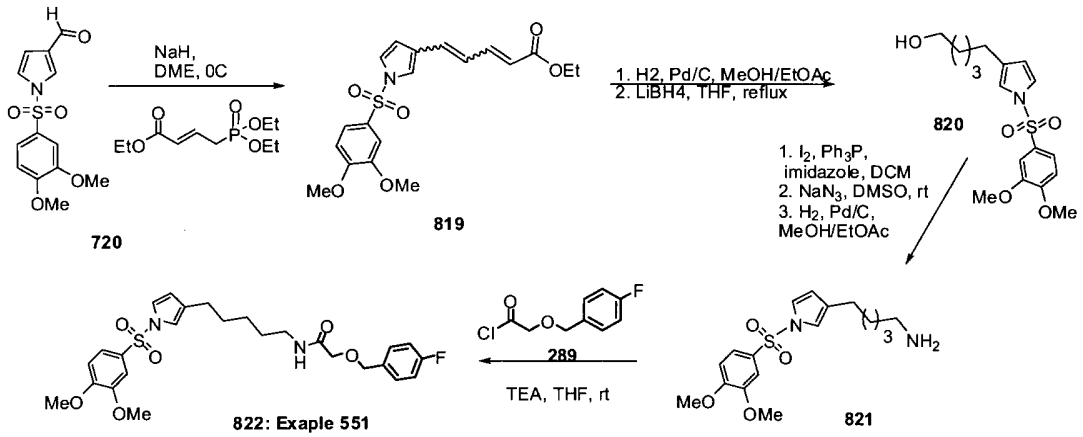
[0632] To a stirred solution of 4-iodobenzenesulfonyl chloride (500 mg, 1.65 mmol) in water (3.3 mL) was added potassium hydroxide (924 mg, 16.5 mmol). The mixture was stirred for 1.25h at 80°C. The precipitate was filtered, and ried under reduced pressure to give **817** (257 mg, 48%).

Step 2: 4-(3-(2-(4-fluorobenzyloxy)acetamido)prop-1-ynyl)benzenesulfonic acid (**818**)

[0633] Compound **818** was prepared following the procedure described for compound **793b**, example **541**, scheme 321.

(DMSO-d_6) d(ppm) ^{1}H: 8.39 (t, J=5.9Hz, 1H), 7.54 (d, J=7.8Hz, 2H), 7.43 (dd, J=8.8and5.7Hz, 2H), 7.34 (d, J=8.0Hz, 2H), 7.17 (t, J=9.0Hz, 2H), 4.51 (s, 2H), 4.14 (d, J=5.9Hz, 2H), 3.94 (s, 2H). LRMS (ESI): (calc) 377.0; (found) 375.9 $(M-H)^-$.

Scheme 328



Example 551

N-(5-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**822**)

Step 1: ethyl 5-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)penta-2,4-dienoate (**819**)

[0634] Sodium hydride (34 mg, 60% in oil, 0.85 mmol) was added to a mixture of aldehyde **720** (210 mg, 0.71 mmol), (E)-ethyl 4-(diethoxyphosphoryl)but-2-enoate (214 mg, 0.85 mmol, 1.2 eq) in DME (4 ml) in ice-bath under N_2. The reaction was allowed to warm-up s owly to room temperature and was stirred at room temperature for 16 h. Sat'd $NaHCO_3$ and EtOAc were added and the organic layer was separated, dried ($MgSO_4$), filtered and concentrated leaving brown oil. The crude material was purified by silica gel column chromatography with gradient of EtOAc (25-30%) in hexanes to give **819** as white solid (43% yield, thetrans isomer major). LRMS (ESI): (calc.) 391.4; (found) 392.0 $(MH)^+$

Step 2: 5-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)pentan-1-ol (**820**)

[0635] The unsaturated ester **819** (115 mg, 0.29 mmol) and 10% Pd/C (28 mg) in EtOAc (7 ml) and MeOH (5 ml) was hydrogenated at 1 atmosphere of H_2 gas for 6h. Ethyl 5-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)pentanoate, was obtained as clear oil (97 % yield). LRMS (ESI): (calc.) 395.5; (found) 396.1 $(MH)^+$

[0636] $LiAlH_4$ (11.4 mg, 0.3 mmol) was added to a solution of the ester above (113 mg, 0.286 mmol) in THF (3 ml) and the reaction was refluxed for 1h, then it was stirred at room temperature for 16h. The progress of the reaction was slow, so $LiBH_4$ (2M solution, 0.15 ml) was added and the mix was refluxed for 2h, then it was cooled, quenched with H_2O and extracted with EtOAc, and the organic layer separated and washed with brine, dried ($MgSO_4$), filtered and concentrated giving **820** as clear oil in almost quantitative yield. LRMS (ESI): (calc.) 353.4; (found) 354.0 $(MH)^+$

Step 3: 5-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)pentan-1-amine (**821**)

[0637] Iodine (223.4 mg, 0.88 mmol, 1.1 eq.) was added to a mixture of Ph_3P (210 mg, 0.8 mmol, 1 eq) and imidazole (54.5 mg, 0.8 mmol) in DCM (4 ml) at room temperature under N_2. The mixture became yellow. Alcohol **820** (283 mg, 0.8 mmol) in DCM (1 ml) was added and the mixture was stirred at room temperature for 16 h. The mixture was taken to dryness and the residue was purified by silica gel column chromatography with gradient of EtOAc (20-50%) in hexanes to give 1-(3,4-dimethoxyphenylsulfonyl)-3-(5-iodopentyl)-1H-pyrrole (62% yield) as a light pink oil which became dark upon standing. The material was used as is for next step. LRMS (ESI): (calc.) 463.3; (found) 464.0 $(MH)^+$

[0638] Sodium azide (65.7 mg, 1.01 mmol) was added to a solution of the iodo compound from above (234 mg, 0.51 mmol) in DMSO (2 ml) and the reaction mixture was stirred at room temperature for 16h. EtOAc was added and the organic phase was washed with H_2O (X3), brine, dried ($MgSO_4$), filtered and concentrated to give 3-(5-azidopentyl)-1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrole. LRMS (ESI): (calc.) 378.4; (found) 379.1 $(MH)^+$

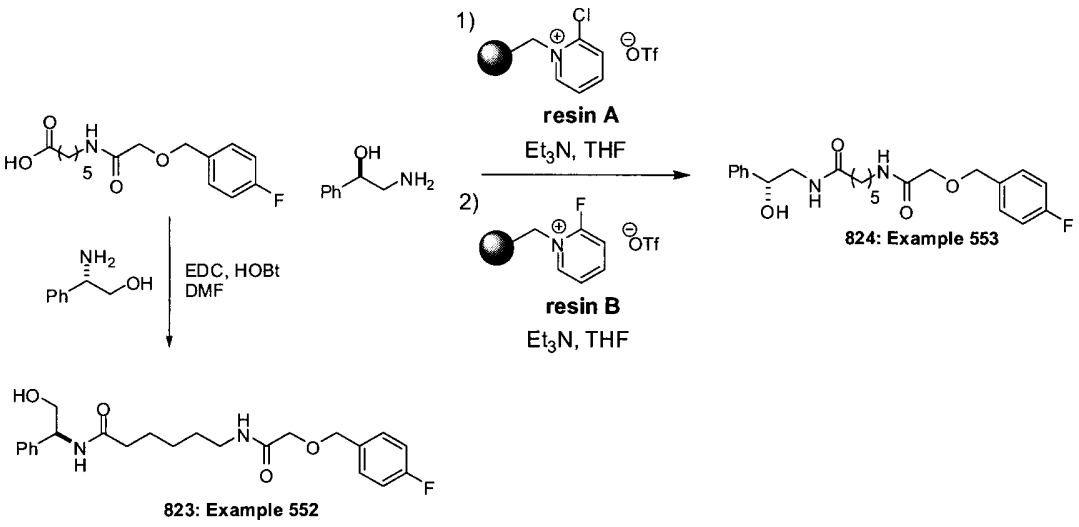
[0639] The crude azide from above and 10% Pd/C (35 mg) in MeOH (5 ml) and EtOAc (5 ml) was hydrogenated with H_2 (1 atmosphere). After 6h, the catalyst was filtered (Celite) and the material taken to dryness to give **821** (145 mg). LRMS (ESI): (calc.) 352.4; (found) 353.1 $(MH)^+$

[0640] Step 4: N-(5-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide (**822**)

[0641] Acid chloride **289** (202 mg, 1mmol, 1.3 eq.) was added to amine **821** (145 mg, 0.41 mmol) and TEA (202.4 mg/ 279 uL, 2 mmol) in THF (3 ml) as described for compound **723**, example **507**, scheme **302**, step 4. The crude material was purified by silica gel column chromatography with gradient of EtOAc (40-100%) in hexanes to give **822** (83% yield). ($CDCl_3$) δ (ppm) ^1H: 7.46 (dxd, J= 2.2, 8.6 Hz, 1H), 7.3 (m, 3H), 7.06 (m, 3H), 6.9 (d, J= 8.6 Hz, 1H), 6.88 (s, 1H), 6.54 (bs, 1H), 6.13 (s, 1H), 4.53 (s, 2H), 3.97 (s, 2H), 3.92 (s, 3H),

3.91 (s, 3H), 3.26 (quartet, J=6.8 Hz, 2H), 2.38 (t, J= 7.5 Hz, 2H), 1.52 (m, 4H), 1.32 (m, 2H). LRMS (ESI): (calc.) 518.6; (found) 519.2 $(MH)^+$

Scheme 329



Example 552

(S)-6-(2-(4-fluorobenzyloxy)acetamido)-N-(2-hydroxy-1-phenylethyl)hexanamide (**823**)

[0642] To a solution of 6-(2-(4-fluorobenzyloxy)acetamido)hexanoic acid (301mg, 1.01mmol), (*S*)-2-phenylglycinol (153mg, 1.11mmol), and HOBt (309mg, 2.02mmol) in DMF (3mL) was added EDC (387mg, 2.02mmol). The reaction was stirred for 1.75 hours at room temperature and then concentrated. The residue was partitioned between ethyl acetate and 1N HCl(aq), and the organic phase was washed with $NaHCO_3$ (sat'd), dried over (Na_2SO_4) filtered and concentrated. The residue was purified by silica gel flash chromatography using a 25M Biotage column with a gradient of methanol (0-15%) in DCM to obtain **823** as a white solid (187mg, 44%).

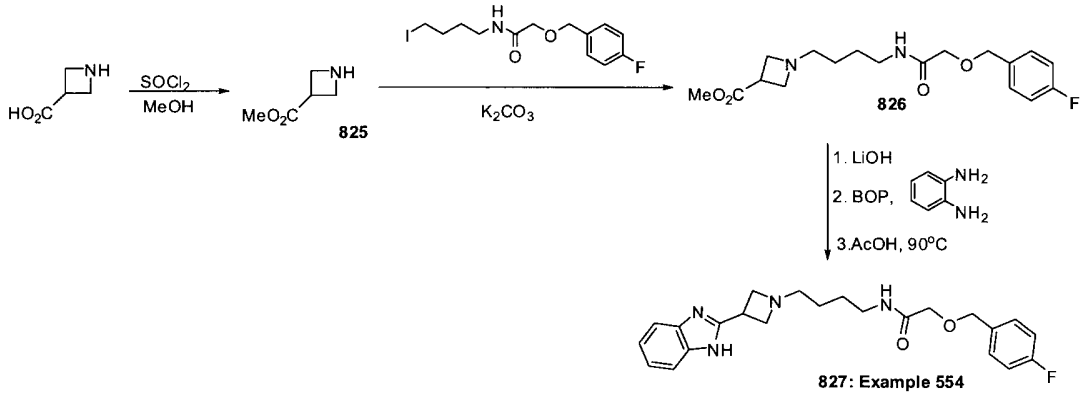
(DMSO-d_6) δ (ppm) ^{1}H: 8.14 (d, J = 8.0Hz, 1H), 7.77 (t, J = 5.6Hz, 1H), 7.42-7.39 (m, 2H), 7.30-7.25 (m, 4H), 7.20-7.15 (m, 3H), 4.83-4.77 (m, 2H), 4.48 (s, 2H), 3.84 (s, 2H), 3.51-3.48 (m, 2H), 3.04 (q, J = 6.4Hz, 2H), 2.11 (t, J = 7.6 Hz, 2H), 1.46 (quint. J = 7.6Hz, 2H), 1.37 (quint J = 7.2Hz, 2H), 1.22-1.16 (m, 2H). LRMS (ESI): (calc) 416.2; (found) 417.1 $(MH)^+$, 439.1 $(MNa)^+$.

Example 553

(R)-6-(2-(4-fluorobenzyloxy)acetamido)-N-(2-hydroxy-2-phenylethyl)hexanamide (**824**)

[0643] To a solution of 6-(2-(4-fluorobenzyloxy)acetamido)hexanoic acid (63 mg, 0.212 mmol), (*R*)-2-amino-1-phenylethanol (35 mg, 0.254 mmol) in THF (4mL) and DMF (0.5mL) was added triethylamine (90uL, 0.636 mmol) then Resin A (0.424mmol) The suspension was stirred for 2 hours before the addition of Resin B (0.424mmol) and 1.0mL of triethylamine according to the procedure of S. Crosignani and D. Swinnen (J. Comb. Chem. 2005, 7(5) 688-696). After another 3 days of stirring the suspension was filtered through an amino-functionalized SPE column (Isolute NH_2 SPE, 2g). The filterate was concentrated and then purified by silica gel flash chromatography using a 12M Biotage column and a gradient of methanol (0-20%) in DCM and then triturated with ethyl acetate and hexanes to obtain **824** as a white solid (17mg). (DMSO-d_6) δ (ppm) ^{1}H: 7.83 (t, J = 5.6Hz, 1H), 7.77 (t, J = 5.6Hz, 1H), 7.42-7.39 (m, 2H), 7.30-7.28 (m, 4H), 7.26-7.15 (m, 3H), 5.43 (d, J = 4.4Hz, 1H), 4.58-4.54 (m, 1H), 4.49 (s, 2H), 3.84 (s, 2H), 3.28-3.22 (m, 1H), 3.10-3.02 (m, 3H), 2.03 (t, J = 7.2Hz, 2H), 1.47-1.33 (m, 4H), 1.19-1.13 (m, 2H). LRMS (ESI): (calc) 416.2; (found) 417.1 $(MH)^+$, 439.1 $(MNa)^+$.

Scheme 330



Example 554

N-(4-(3-(1H-benzo[d]imidazol-2-yl)azetidin-1-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**827**)

Step 1: Methyl azetidine-3-carboxylate (**825**)

[0644] To a stirred solution of azetidine-3-carboxylic acid (325 mg, 3.21 mmol) in MeOH (15 mL) was carefully added $SOCl_2$ (0.47 mL, 6.43 mmol). The solution was stirred at room temperature for 1h and concentrated to yield **825** (365 mg, 99%) as a clear oil. LRMS (ESI): (calc) 115.1; (found) 116.2 $(MH)^+$.

Step 2: Methyl 1-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)azetidine-3-carboxylate (**826**)

[0645] The ester **825** (365 mg, 3.18 mmol) was partially dissolved in MeCN (15 mL) and K_2CO_3 (1.33 g, 9.64 mmol) was added followed by 2-(4-fluorobenzyloxy)-N-(4-iodobutyl)acetamide (1.17 g, 3.21 mmol). The suspension was stirred at room temperature for 2h, H_2O was added and the aqueous phase was extracted with EtOAc and the EtOAc extracts were filtered and evaporated to afford **826** (825 mg, 73%). LRMS (ESI): (calc) 352.4; (found) 353.2 $(MH)^+$.

Step 3: N-(4-(3-(1H-benzo[d]imidazol-2-yl)azetidin-1-yl)butyl)-2-(4-fluorobenzyloxy)acetamide (**827**)

[0646] To a stirred solution of the ester **826** (88 mg, 0.25 mmol) in a 1:1 mixture of H_2O/THF (1.3 mL) was added LiOH (12 mg, 0.50 mmol). After stirring for 1h, the mixture was filtered through a Celite-SiO_2 pad and washed with 30% MeOH in CH_2Cl_2. The filtrate was evaporated to dryness. To a stirred solution of the crude acid in DMF (2.5 mL) were added BOP (121 mg, 0.27 mmol), 1,2-phenylenediamine (27 mg, 0.25 mmol), and Et_3N (0.08 mL, 0.55 mmol). The solution was stirred overnight at room temperature. H_2O was added and the aqueous phase was extracted with EtOAc. The organic extracts were combined, dried and evaporated. The residue obtained was dissolved in AcOH (2.5 mL) and heated at 90 °C for 10 minutes. The solution was evaporated to dryness and the residue was purified by Prep-HPLC to afford **827** (11 mg, 10%) as the formate salt. (CD_3CN) δ (ppm) ^1H: 7.52 (dd, J= 3.2, 6.0 Hz, 2H), 7.39 (dd, J= 5.6, 8.8 Hz, 2H), 7.22 (dd, J= 3.2, 6.0 Hz, 2H), 7.06 (t, J= 8.8 Hz, 2H), 4.56 (s, 2H), 4.05-3.99 (m, 1H), 3.95 (t, J= 7.6 Hz, 2H), 3.93 (s, 2H), 3.68 (t, J= 7.2 Hz, 2H), 3.26 (t, J= 6.8 Hz, 2H), 2.75 (t, J= 7.6 Hz, 2H), 1.57 (qt, J= 7.2 Hz, 2H), 1.46 (qt, J= 8.4 Hz, 2H). LRMS (ESI): (calc) 410.5; (found) 411.2 $(MH)^+$.

Compositions

[0647] In a second aspect, the invention provides compositions comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route. The compositions may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal dropsa or aerosols. The compositions of the invention may be administered systemically or locally.

[0648] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

[0649] As used herein, the term "pharmaceutically acceptable salts" is intended to mean salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for Example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula -NR + Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate). As used herein, the term "salt" is also meant to encompass complexes, such as with an alkaline metal or an alkaline earth metal.

[0650] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver an inhibition effective amount without causing serious toxic effects. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0651] In certain preferred embodiments of the second aspect of the invention, the composition further comprises an antisense oligonucleotide that inhibits the expression of a

histone deacetylase gene. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10, HDAC-11, SirT1, SirT2, SirT3, SirT4, SirT5, SirT6 and SirT7 (see e.g., GenBank Accession Number U50079 for HDAC-1, GenBank Accession Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

Inhibition of Histone Deacetylase

[0652] In a third aspect, the present invention provides a method of inhibiting histone deacetylase, comprising contacting the histone deacetylase with an inhibition effective amount of an inhibitor of histone deacetylase of the present invention.

[0653] In another embodiment of the third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting the cell in which inhibition of histone deacetylase is desired with an inhibition effective amount of an inhibitor of histone deacetylase, or composition thereof, according to the present invention.

[0654] Because compounds of the invention inhibit histone deacetylase, they are useful research tools for *in vitro* study histone deacetylases and their role in biological processes.

[0655] Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For Example, Yoshida *et al.*, *J. Biol. Chem.*, 265: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated histones in trichostatin A treated cells. Taunton *et al., Science*, 272: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

[0656] In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in a cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10, HDAC-11, SirT1, SirT2, SirT3, SirT4, SirT5, SirT6 and SirT7).

[0657] The term "inhibition effective amount" is meant to denote a dosage sufficient to cause inhibition of histone deacetylase activity in a cell, which cell can be in a multicellular

organism. The multicellular organism can be a plant or an animal, preferably a mammal. If in a multicellular organism, the method according to this aspect of the invention comprises administering to the organism a compound or composition according to the present invention. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0658] In certain preferred embodiments of the thirdaspects of the invention, the method further comprises contacting a histone deacetylase enzyme or a cell expressing histone deacetylase activity with an antisense oligonucleotide that inhibits the expression of a histone deacetylase gene. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, SirT1, SirT2, SirT3, SirT4, SirT5, SirT6 and SirT7 (see e.g., GenBank Accession Number U50079 for HDAC-1, GenBank Accession Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

[0659] For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/ or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane.

[0660] For purposes of the invention the term "2'-substituted ribonucleoside" includes ribonucleosides in which the hydroxyl group at the 2' position of the pentose moiety is substituted to produce a 2'-O-substituted ribonucleoside. Preferably, such substitution is with a lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups. The term "2'-substituted ribonucleoside" also includes ribonucleosides in which the 2'-hydroxyl group is replaced with an amino group or with a halo group, preferably fluoro.

[0661] Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

[0662] For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Patent Nos. 5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

[0663] For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide contains at least three consecutive deoxyribonucleosides and also contains ribonucleosides, 2'-substituted ribonucleosides, preferably 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Metelev and Agrawal, U.S. Patent No. 5,652,355).

[0664] The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active. Useful assays for this purpose include quantitating the mRNA encoding a product of the gene, a Western blotting analysis assay for the product of the gene, an activity assay for an enzymatically active gene product, or a soft agar growth assay, or a reporter gene construct assay, or an in vivo tumor growth assay, all of which are described in detail in this specification or in Ramchandani *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94: 684-689.

[0665] Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, e.g., Pon, R.T. (1993) *Methods in Molec. Biol.* 20: 465-496).

[0666] Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides which include the nucleotide sequences shown in Table 44. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides which include the nucleotide sequences shown in Table 44.

Table 44

Oligo	Target	Accession Number	Nucleotide Position	Sequence	position within Gene	Seq ID No.
HDAC1 AS1	Human HDAC1	U50079	1585-1604	5'-GAAACGTGAGGGACTCAGCA-3'	3'-UTR	Seq ID No:1
HDAC1 AS2	Human HDAC1	U50079	1565-1584	5'-GGAAGCCAGAGCTGGAGAGG-3'	3'-UTR	Seq ID No:2
HDAC1 MM	Human HDAC1	U50079	1585-1604	5'-GTTAGGTGAGGCACTGAGGA-3'	3'-UTR	Seq ID No:3
HDAC2 AS	Human HDAC2	U31814	1643-1622	5'-GCTGAGCTGTTCTGATTTGG-3'	3'-UTR	Seq ID No:4
HDAC2 MM	Human HDAC2	U31814	1643-1622	5'-CGTGAGCACTTCTCATTTCC-3'	3'-UTR	Seq ID No:5
HDAC3 AS	Human HDAC3	AF039703	1276-1295	5'-CGCTTTCCTTGTCATTGACA-3'	3'-UTR	Seq ID No:6
HDAC3 MM	Human HDAC3	AF039703	1276-1295	5'-GCCTTTCCTACTCATTGTGT-3'	3'-UTR	Seq ID No:7
HDAC4 AS1	Human HDAC4	AB006626	514-33	5-GCTGCCTGCCGTGCCCACCC-3'	5'-UTR	Seq ID No:8
HDAC4 MM1	Human HDAC4	AB006626	514-33	5'-CGTGCCTGCGCTGCCCACGG-3'	5'-UTR	Seq ID No:9
HDAC4 AS2	Human HDAC4	AB006626	7710-29	5'-TACAGTCCATGCAACCTCCA-3'	3'-UTR	Seq ID No:10
HDAC4 MM4	Human HDAC4	AB006626	7710-29	5'-ATCAGTCCAACCAACCTCGT-3'	3'-UTR	Seq ID No:11
HDAC5 AS	Human HDAC5	AF039691	2663-2682	5'-CTTCGGTCTCACCTGCTTGG-3'	3'-UTR	Seq ID No:12
HDAC6 AS	Human HDAC6	AJ011972	3791-3810	5'-CAGGCTGGAATGAGCTACAG-3'	3'-UTR	Seq ID No:13
HDAC6 MM	Human HDAC6	AJ011972	3791-3810	5'-GACGCTGCAATCAGGTAGAC-3'	3'-UTR	Seq ID No:14
HDAC7 AS	Human HDAC7	AF239243	2896-2915	5'-CTTCAGCCAGGATGCCCACA-3'	3'-UTR	Seq ID No:15
HDAC8 AS1	Human HDAC8	AF230097	51-70	5'-CTCCGGCTCCTCCATCTTCC-3'	5'-UTR	Seq ID No:16
HDAC8 AS2	Human HDAC8	AF230097	1328-1347	5'-AGCCAGCTGCCACTTGATGC-3'	3'-UTR	Seq ID No:17

[0667] In certain preferred embodiments of the invention, the antisense oligonucleotide and the HDAC inhbitor of the present invention are administered separately to a mammal, preferably a human. For example, the antisense oligonucleotide may be administered to the mammal prior to administration to the mammal of the HDAC inhibitor of the present invention. The mammal may receive one or more dosages of antisense oligonucleotide prior to receiving one or more dosages of the HDAC inhibitor of the present invention.

[0668] In another embodiment, the HDAC inhibitor of the present invention may be administered to the mammal prior to administration of the antisense oligonucleotide. The mammal may receive one or more dosages of the HDAC inhibitor of the present invention prior to receiving one or more dosages of antisense oligonucleotide.

[0669] In certain preferred embodiments of the present invention, the HDAC inhibitor of the present invention may be administered together with other HDAC inhibitors known in the art or which will be discovered. Administration of such HDAC inhibitors may be done sequentially or concurrently. In certain preferred embodiments of the present invention thecompositions comprise an HDAC inhibitor of the present invention and/or an antisense oligonucleotide and/or another HDAC inhibitor known in the art or which will be discovered. The active ingredients of such compositions may act synergistically to produce a therapeutic effect.

[0670] In certain embodiments, the known HDAC inhibitor is selected from the group consisting of trichostatin A, depudecin, trapoxin, suberoylanilide hydroxamic acid, FR901228, MS-27-275, CI-994 sodim butyrate, and those compounds found in WO 2003/024448, WO 2001/038322, US 6,541,661, WO 01/70675, and PCT/US04/31591.

[0671] The following Examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

ASSAY EXAMPLES

Assay Example 1

Inhibition of Histone Deacetylase Enzymatic Activity

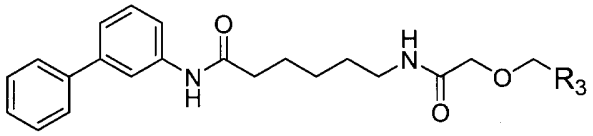
[0672] The following protocol is used to assay the compounds of the invention. In the assay, the buffer used is 25 mM HEPES, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$ and the subtrate is Boc-Lys(Ac)-AMC in a 50 mM stock solution in DMSO. The enzyme stock solution is 4.08 µg/mL in buffer.

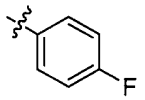
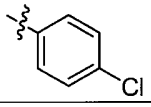
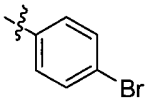
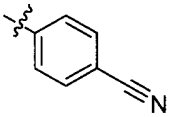
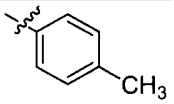
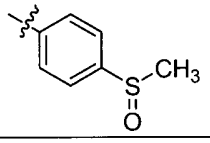
[0673] The compounds are pre-incubated (2 µl in DMSO diluted to 13 µl in buffer for transfer to assay plate) with enzyme (20 µl of 4.08 µg/ml) for 10 minutes at room temperature (35 µl pre-incubation volume). The mixture is pre-incubated for 5 minutes at room temperature. The reaction is started by bringing the temperature to 37°C and adding

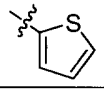
16 µl substrate. Total reaction volume is 50 µl. The reaction is stopped after 20 minutes by addition of 50 µl developer, prepared as directed by Biomol (Fluor-de-Lys developer, Cat. # KI-105). A plate is incubated in the dark for 10 minutes at room temperature before reading (λ_{Ex}=360nm, λ_{Em}=470nm, Cutoff filter at 435nm).

[0674] All compounds exemplified have an IC_{50} value less than or equal to 10 µM against one or more of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9, HDAC-10, HDAC-11, SirT1, SirT2, SirT3, SirT4, SirT5, SirT6 and SirT7. Tables 45-50, for example, show selected examples.

Table 45



Cpd	R_3
61	Ph
7b	
47	
18	
13	
14	
50	

Cpd	R_3
15	
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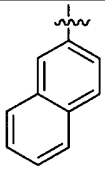
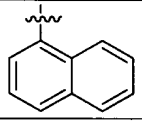
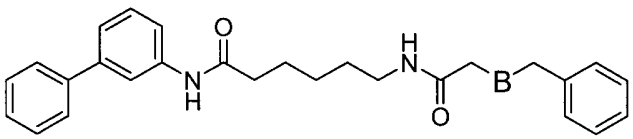
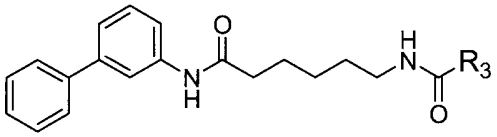
17	
45	
19	

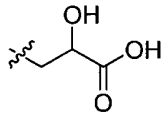
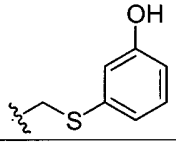
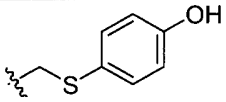
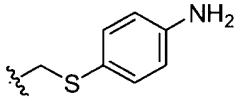
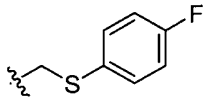
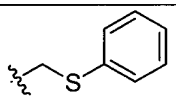
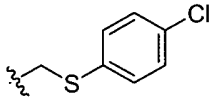
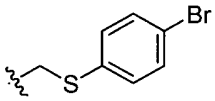
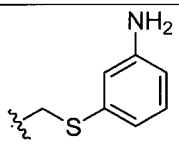
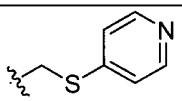
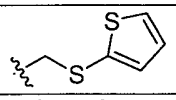
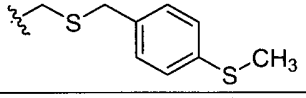
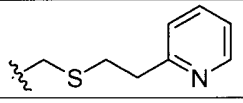
Table 46

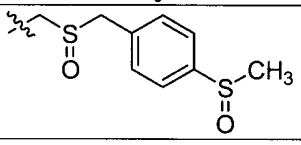
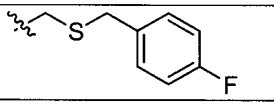
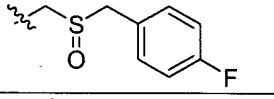
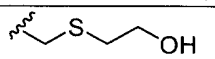
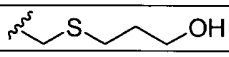
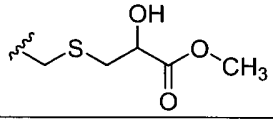
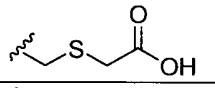
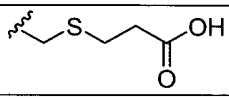
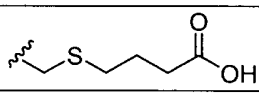
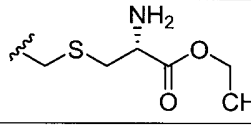
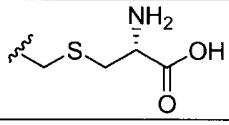
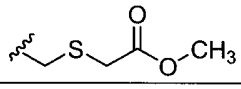
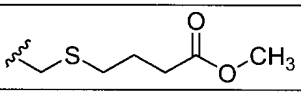
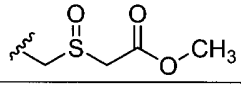
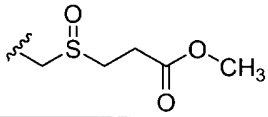
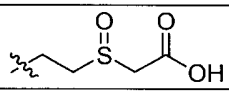


Cpd	B
51	-S-
52	-S(O)-

Table 47



Cpd	R_3
98	
33	
29	
34	
35	
36	
37	
38	
39	
40	
41	
83	
77	

Cpd	R_3
84	
56	
57	
24	
23	
100	
5	
21	
82	
26	
27	
4	
81	
30	
22	
59	

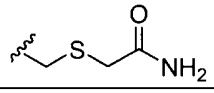
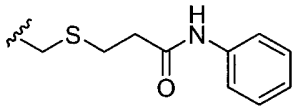
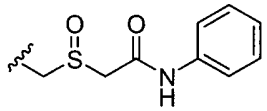
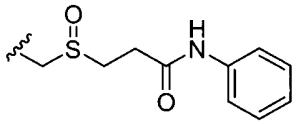
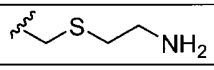
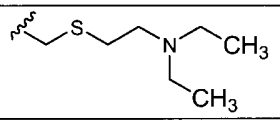
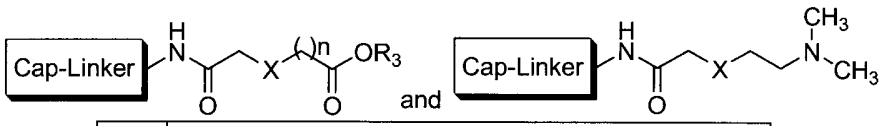
Cpd	R_3
25	
31	
20	
32	
28	
78	

Table 48



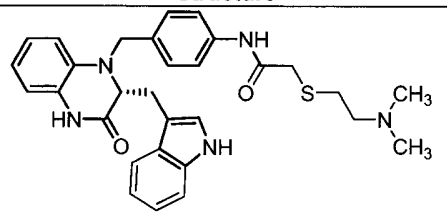
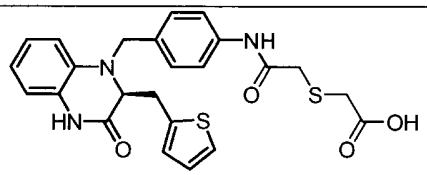
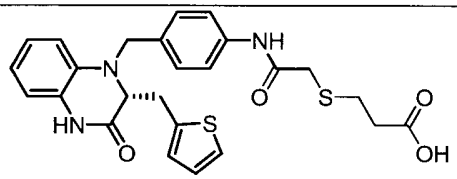
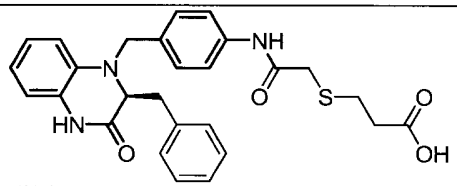
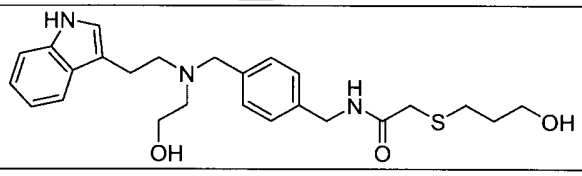
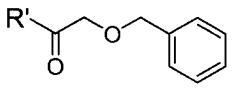
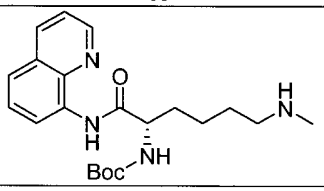
Cpd	Structure
113	
76	
91	
90	
108	

Table 49



Cpd	R'
64	

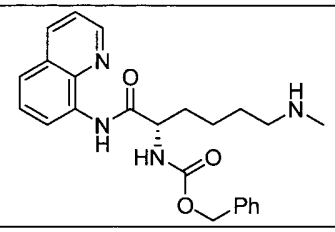
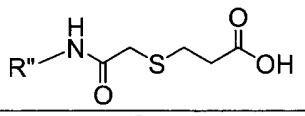
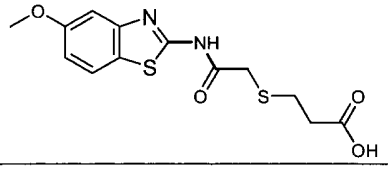
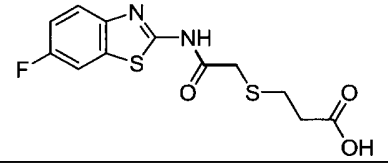
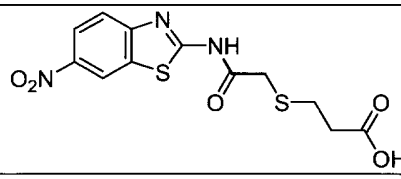
66	

Table 50

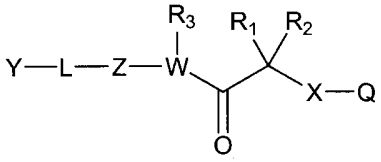


Cpd	Structure
94	
118	
119	

[0675] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

What is claimed is:

1. A compound of the formula

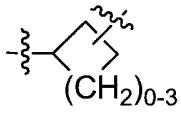


(I)

or pharmaceutically acceptable salts thereof, wherein

W is nitrogen or oxygen, wherein when W is oxygen, R_3 is absent;

X is a covalent bond, -S-, -SO-, $-SO_2-$, -O-, $-NR_3-$, $-CH_2-$, -N(OH), optionally substituted $-C_1-C_6$ alkyl, or a structure of the formula



R_1 and R_2 are independently selected from the group consisting of -H, C_1-C_6 alkyl, halo; -N(H)-C(O)-O-C_1-C_6 alkyl, -N(H)-C(O)-O-benzyl, C_3-C_6 cycloalkyl, aryl, aryl-C_1-C_6 alkyl-, and heteroaryl-C_1-C_6 alkyl, wherein the alkyl, benzyl, cycloalkyl, aryl and heteroaryl moieties of said R_1 and R_2 are optionally substituted; or

R_1 and R_2 together with the carbon atom to which they are attached form a 3 to 9-membered heterocyclyl-aryl, C_3-C_6-cycloalkyl or 3 to 9-membered heterocyclyl group, wherein each of the cycloalkyl, heterocyclyl, and heterocyclyl-aryl is optionally substituted with one or more groups selected from oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-NO_2$, $-N(R_3)(R_{3a})$, halo, -SH, mono- to per-halogenated C_1-C_6 alkyl; or

when X-Q is absent, R_1 and R_2 together with the atom to which they are attached form an aryl, heterocyclyl, cycloalkyl or heteroaryl group, wherein said aryl, heterocyclyl, cycloalkyl and heteroaryl are optionally substituted, and wherein R^3 is optionally connected to the aryl, heterocyclyl, cycloalkyl or heteroaryl by a covalent bond;

X-Q, R_3 and R_{3a} are independently selected from the group consisting of -H, -OH, -C(O)H, heterocyclyl, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_3alkynyl, C_2-C_4 alkyl-OR_3, C_2-C_6 hydroxyalkyl, heteroaryl, C_1-C_6heteroalkyl-aryl, C_0-C_6alkylheteroaryl, C_0-C_6heteroalkylheteroaryl, C_1-C_3alkyl-C(O)NR_3-heteroaryl, C_1-C_3alkyl-C(O)NR_3-aryl, C_1-C_4alkyl-C(O)OR_3, -C_1-C_6 hydroxyalkyl-C(O)-OH, -C(O)-NH-aryl, $-C(O)CF_3$, $-C(O)-NH_2$, $-CH(NH_2)$-C(O)-OH, $-NH_2$, $-CH(NH_2)$-C(O)-O-C_1-C_6 alkyl, -C(O)-OH, -C(O)-O-C_1-C_6 alkyl, C_1-C_6 heteroalkyl-C_1-C_6 alkyl-, C_3-C_6 cycloalkyl, heterocyclyl-C_1-C_6 alkyl-, -C_1-C_6 alkylaryl, aryl, -C_0-C_6 alkyl-S(O)-C_1-C_6 alkylaryl, -C_0-C_6 alkyl-O-C_0-C_6 alkylaryl, -C_0-C_6

alkyl-S-C_0-C_6 alkylaryl, -C_0-C_6 alkyl-S-C_0-C_6 alkylheteroaryl, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-OH, -C_0-C_6 alkyl-S-C_1-C_6 hydroxyalkyl-C(O)-O-C_1-C_6 alkyl, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-CH(NH_2)-C(O)-OR_4, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-OH, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-O-C_1-C_6 alkyl, -C_0-C_6 alkyl-S(O)-C_1-C_6 alkyl-C(O)-OR_4, -C_0-C_6 alkyl-S(O)-C_1-C_6 alkyl-C(O)-N(R_4)-aryl, -C_0-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-N(R_4)(R_{4a}), -C_0-C_6 alkyl-S-C_1-C_6 alkyl-N(R_4)(R_{4a}), -C_1-C_6 alkylheteroaryl and heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of the aforementioned X-Q, R^3 and R^{3a} is optionally substituted;

Q is selected from the group consisting of -H, -OH, -N(R_3)(R_{3a}), halo, -SH, -C(O)OR_3, -C(O)R_3, -C_0-C_3-alkyl-diphenyl-R_4, -C_0-C_3alky-aryl, -C_0-C_3alkyl-heteroaryl, -C_1-C_6 alkyl-N(R_3)-C(O)-C_1-C_6 alkyl-B-(CH_2)$_n$-R_3, -C_1-C_6-alkyl-N(R_3)-C(O)-C_1-C_6 alkyl-O-C_1-C_6 alkyl-R_3, -C_1-C_6-alkyl-C(O)-OR_3, -C_1-C_6-alkyl-N(R_3)(R_{3a}), -C_1-C_6-alkyl-CN, -C_1-C_6 alkyl-C(O)-N(R_3)-N(R_3)-aryl, -C_1-C_6 alkyl-N(R_3)-C_1-C_6 heteroalkyl, -C_1-C_6 alkyl-N(R_3)-C_3-C_6 cycloalkyl, -C_1-C_6 alkyl-N(R_3)-heterocyclyl, -C_1-C_6 alkyl-N(R_3)-aryl, -C_1-C_6 alkyl-N(R_3)-C_1-C_6-alkyl-aryl, -C_1-C_6 alkyl-N(R_3)-heteroaryl, -C_1-C_6 alkyl-N(R_3)-C_3-C_6 cycloalkyl, C_1-C_6 alkyl substituted with -OH, -C_1-C_6 alkyl-O-C_1-C_6 alkyl, -C_1-C_6 alkyl-O-C_3-C_6 cycloalkyl, -C_1-C_6-alkyl-O-C_1-C_6 alkyl-(C_1-C_6 heteroalkyl), -C_1-C_6-alkyl-O-C_1-C_6 alkyl-heterocyclyl, -C_1-C_6 alkyl-O-aryl, -C_1-C_6-alkyl-O-C_1-C_6 alkylaryl, -C_1-C_6 alkyl-O-heteroaryl, -C_1-C_6 alkylhydroxamate, C_1-C_6 alkyl, -C_1-C_6 alkyl-(C_1-C_6 heteroalkyl), C_3-C_6 cycloalkyl, -C_1-C_6 alkylheterocyclyl, -C_1-C_6 alkyl-C_2-C_6 alkenyl, -C_1-C_6 alkyl-C_2-C_6 alkynyl, aryl, -C_1-C_6 alkylaryl, heteroaryl, C_1-C_6 alkylheteroaryl, C_1-C_3 alkyl-CN, -C_1-C_6 alkyl-CH(OR_3)-C(O)-OR_3, -C_1-C_6 alkyl-CH(N(R_3)(R_{3a}))-C(O)-OR_3, -C_1-C_6 alkyl-C(O)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-N(R_3)-C(O)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-N(R_3)-C(O)-OR_3, -C_1-C_6 alkyl-N(R_3)-C(O)-R_3, -C_1-C_6 alkyl-N(R_3)-S(O)$_2$-R_3, -C_1-C_6 alkyl-S(O)$_2$-N(R_3)(R_{3a}), -C_1-C_6 alkyl-CH(N(R_3)(R_{3a}))-C_1-C_6 alkyl-OR_3, or -C_1-C_6 alkyl-O-C(O)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-(C=NR_3)-N(R_3)(R_{3a}), -C_1-C_6 alkyl-X-C_1-C_6 alkyl-C(O)OR_3, -C_1-C_6 alkyl-X-C_1-C_6 alkyl-OR_3, and -C_1-C_6 alkyl-X-C_1-C_6 alkyl-N(R_3)(R_{3a}), C_1-C_4 alkyl-aryl- wherein the C_1-C_4 alkyl is optionally substituted with -C_1-C_4 alkylOR_3, C_1-C_4 alkylNR_3 R_{3a}, C_0-C_4 alkylC(O)N(R_3)(R_{3a}) or C_0-C_4 alkylC(O)OR_3, C_1-C_4 alkyl-heteroaryl- wherein the C_1-C_4 alkyl is optionally substituted with -C_1-C_4 alkylOR_3, C_1-C_4 alkylN(R_3)(R_{3a}), C_0-C_4 alkylC(O)N(R_3)(R_{3a}) or C_0-C_4 alkylC(O)OR_3, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_0-C_6 alkylC(O)NR_3-N(R_3)aryl and C_0-C_6 alkylC(O)NR_3-NR_3heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of the aforementioned Q is optionally substituted;

B is selected from the group consisting of -O-, -S(O)-, -S- and -S(O)$_2$-,

n is 0 or an interger from 1 to 3;

R_4 and R_{4a} are independently selected from the group consisting of -H, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6 alkyl-R_3, -C_0-C_6 alkyl-OR_3, -C_0-C_6 alkyl-C(O)-OR_3, -C_0-C_6 alkyl-C(O)NR_3 R_{3a}, -CH=CH-C(O)-OR_3, -CH=CH-C(O)-N(R_3)(R_{3a}), -N(R_3)-C(O)-CF_3, -N(R_3)-C_2-C_6 alkyl-N(R_3)(R_{3a}), -C_0-C_6 alkyl-N(R_3)(R_{3a}), -N(R_3)-C(O)-C_1-C_6 alkyl-R_3, -N(R_3)-$S(O)_2$-C_1-C_6 alkyl-R_3, - $S(O)_2$- N(R_3)R_{3a}, -O-C_2-C_6 alkyl-N(R_3)(R_{3a}), -S-R_3, -S(O)-C_1-C_6 alkyl-R_3, -$S(O)_2$-C_1-C_6 alkyl-R_3, C_3-C_6 cycloalkyl, heterocyclyl, C_4-C_7heterocyclyl-R_3, -O-C_2-C_4alkyl-heterocyclyl, -O-heterocyclyl-C(O)-OR_3, -NR_3-C_2-C_4alkyl-heterocyclyl, halo, -CF_3,-SO_3H, -CN, -C_1-C_6 alkylaryl, aryl, heteroaryl, -C_1-C_6 alkylheteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moeity of the aformentioned R_4 and R_{4a} are optionally substituted;

Z is selected from the group consisting of C_1-C_8 alkyl, C_1-C_8 alkenyl, C_1-C_8 alkynyl, C_1-C_8 heteroalkyl, -C_0-C_3alkyl-alkenyl-C_0-C_3-alkyl, -C_0-C_3alkyl-alkynyl-C_0-C_3-alkyl, -C_0-C_3alkyl-heteroalkyl-C_0-C_3-alkyl, aryl, -C_1-C_6 alkylaryl-, -C_0-C_6 alkylaryl-C_0-C_6-alkyl-,-C_0-C_6 alkylaryl-C_2-C_6-heteroalkyl-,-C_2-C_6 heteroalkylaryl-C_0-C_6-alkyl-,-C_4-C_6 heterocyclylaryl-C_0-C_6-alkyl-, -C_0-C_6 alkylaryl-C_4-C_6-heterocyclyl-, -C_0-C_6 alkylheteroaryl-, -C_0-C_6-alkylheteroaryl-C_0-C_6-alkyl-, heteroaryl, -C_0-C_6 alkylheteroaryl-C_2-C_6-heteroalkyl-,-C_2-C_6 heteroalkyl-heteroaryl-C_0-C_6-alkyl-,-C_4-C_6 heterocyclyl-heteroaryl-C_0-C_6-alkyl-, -C_0-C_6 alkyl-heteroaryl-C_4-C_6-heterocyclyl-, -C_3-C_6 alkynyl-aryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-aryl-C_3-C_6-alkynyl, -C_3-C_6 alkynyl-heteroaryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-heteroaryl-C_3-C_6-alkynyl, -C_3-C_6 alkenyl-aryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-aryl-C_3-C_6-alkenyl, -C_3-C_6 alkenyl-heteroaryl-C_0-C_6-alkyl, -C_0-C_6 alkyl-heteroaryl-C_3-C_6-alkenyl, -C_0-C_6 alkylaryl-aryl-, -C_0-C_6 alkylaryl-aryl-C_0-C_6-alkyl-, -C_0-C_6 alkylaryl-heteroaryl-, -C_0-C_6 alkylaryl-heteroaryl-C_0-C_6-alkyl-, -C_0-C_6 alkyl-C_3-C_6 cycloalkyl-, -C_0-C_6 alkyl-C_3-C_6 cycloalkyl-C_0-C_6-alkyl-, -C_1-C_6 alkyl-X-C_3-C_6 cycloalkyl-, -C_1-C_6 alkyl-X-C_3-C_6 cycloalkyl-C_0-C_6-alkyl-, -C_1-C_6 alkyl-N(R_3)-C_1-C_6 alkyl-C_3-C_6 cycloalkyl-, -C_1-C_6 alkyl-N(R_3)-C_1-C_6 alkyl-C_3-C_6 cycloalkyl-C_0-C_6-alkyl-, and -C_1-C_6 alkyl-S-S-C_1-C_6 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, heterocyclyl, and cycloalkyl moiety is optionally substituted;

L is selected from the group consisting of a covalent bond, -C_0-C_6alkyl-aryl-C_0-C_3alkyl-X-C_0-C_3alkyl, C_0-C_6alkyl-heteroaryl-C_0-C_3alkyl-X-C_0-C_3alkyl, C_0-C_3alkyl-X-C_0-C_3alkyl, C_0-C_6alkyl-N(R_3)-C(O)-N(R_3)-$S(O)_2$-C_0-C_3alkyl-aryl, -C_0-C_3alkyl-$S(O)_2$-N(R_3)-C_0-C_3alkyl-aryl-C_0-C_3alkyl-C(O)-N(R_3)-C_0-C_3alkyl, -C_0-C_3alkyl-N(R_3)-C(O)-O-heterocyclyl-C_0-C_3alkyl, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl-N(R_3)-C_0-C_3alkyl, -C_0-C_6 alkyl-N(R_3)C(O)heterocyclyl-C_0-C_3alkyl, -C_0-C_6 alkyl-$S(O)_2$heterocyclyl-C_0-C_3alkyl-, -C_0-C_6 alkyl-N(R_3)$S(O)_2$heterocyclyl-C_0-C_3alkyl, -C_0-C_6 alkyl-, -C_2-C_6 alkenyl-, -C_2-C_6 alkynyl-, -C_0-C_6 alkyl-N(R_3)C(O)-C_0-C_3 alkyl, -C_0-C_6 alkyl-N(R_3)C(S)-C_0-C_3 alkyl, -C_0-C_6 alkyl-C(O)N(R_3)C(O)-C_0-C_3 alkyl, -C_2-C_6 heteroalkyl-N(R_3)C(O)-C_0-C_3 alkyl, -C_0-C_6 alkyl-C(O)-N(R_3)-C_0-C_3 alkyl, -C_0-C_6 alkyl-

$C(S)$-$N(R_3)$-C_0-C_3 alkyl, -C_0-C_6 alkyl-$OC(O)$-, -C_0-C_6 alkyl-$C(O)$-O-, -C_0-C_6 alkyl-$C(O)$-C_0-C_3 alkyl, -C_0-C_6 alkyl-SO_2-$N(R_3)$-C_0-C_3 alkyl, -C_0-C_6 alkyl-$N(R_3)$-SO_2-C_0-C_3 alkyl, -C_0-C_6 alkyl-$C(O)$-$N(R_3)$-SO_2-C_0-C_3 alkyl, -C_0-C_6 alkyl-$C(O)$-$N(R_3)$-SO_2-C_0-C_3 alkyl-aryl, -C_0-C_6 alkyl-$C(O)$-$N(R_3)$-SO_2-C_0-C_3 alkyl-heteroaryl, -C_0-C_6 alkyl-$N(R_3)$-C_0-C_3 alkyl, -C_0-C_6 alkyl-$N(R_7)$-C_0-C_3 alkyl, -C_0-C_6 alkyl-S-C_0-C_3 alkyl, -C_0-C_6 alkyl-O-C_0-C_3 alkyl -, -C_0-C_6 alkyl-$S(O)$-C_0-C_3 alkyl, -C_0-C_6 alkyl-$S(O)_2$-C_0-C_3 alkyl, -C_0-C_6 alkyl-$(CR_3{=}CR_3)_{1\text{-}2}$-$C_1$-$C_6$ alkyl-, -C_0-C_6 alkyl-$(C{\equiv}C)_{1\text{-}2}$-$C_1$-$C_6$ alkyl-, -C_0-C_6 alkyl-$N(R_3)$-$C(O)$-$N(R_3)$-C_0-C_3 alkyl, -C_0-C_6 alkyl-$N(R_3)$-$C(O)$-O-C_0-C_3 alkyl, -C_0-C_6 alkyl-O-$C(O)$-$N(R_3)$-C_0-C_3 alkyl, -C_0-C_3 alkyl $N(R_3)C(O)$-C_0-C_3 alkyl-heterocyclyl-$C(O)$-C_0-C_6 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_2-C_4 alkenyl- C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl-O-C_0-C_3 alkyl, -C_0-C_3 alkyl-O-C_0-C_3 alkyl heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl-$N(R_3)$-C_0-C_3 alkyl, -C_0-C_3 alkyl-$N(R_3)$-C_0-C_3 alkyl heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl-S-, -C_0-C_3 alkyl $S(O)_2N(R_3)$-C_0-C_3 alkyl heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $S(O)_2$-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-$C(O)N(R_3)$-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-$C(S)N(R_3)$-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $C(O)$-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $OC(O)N(R_3)$-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-$OC(S)N(R_3)$-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-$OC(O)$-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $N(R_3)C(O)N(R_3)$-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $N(R_3)C(S)N(R_3)$-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $N(R_3)C(O)$-heterocyclyl-C_0-C_3alkyl, -C_0-C_3 alkyl $N(R_3)C(S)$-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl $N(R_3)S(O)_2N(R_3)$-C_0-C_3 alkyl-heterocyclyl-C_0-C_3 alkyl, -C_0-C_3 alkyl-$C{=}N$-O-C_0-C_3 alkyl, -C_0-C_3 alkyl $N(R_3)C(O)$-C_1-C_3 alkyl-$N(R_3)C(O)$-C_0-C_3 alkyl, -C_0-C_3 alkyl $N(R_3)C(S)$-C_1-C_3 alkyl-$N(R_3)C(S)$-C_0-C_3 alkyl, -$S(O)_2$-$N(R_3)$-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-$N(R_3)C(O)$-C_1-C_3 alkyl-, -$S(O)_2$-$N(R_3)$-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-$N(R_3)C(S)$-C_1-C_3 alkyl-,-$N(R_3)$-$S(O)_2$-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-$N(R_3)C(O)$-C_1-C_3 alkyl-, -$N(R_3)$-$S(O)_2$-C_0-C_3 alkyl-aryl-C_0-C_3 alkyl-$N(R_3)C(S)$-C_1-C_3 alkyl-,-$S(O)_2$-$N(R_3)$-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-$N(R_3)C(O)$-C_1-C_3 alkyl-, -$S(O)_2$-$N(R_3)$-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-$N(R_3)C(S)$-C_1-C_3 alkyl-, -$N(R_3)$-$S(O)_2$-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-$N(R_3)C(O)$-C_1-C_3 alkyl- and -$N(R_3)$-$S(O)_2$-C_0-C_3 alkyl-heteroaryl-C_0-C_3 alkyl-$N(R_3)C(S)$-C_1-C_3 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl moiety of the aforementioned L are optionally substituted,

-(C_0-C_3alkyl)$(R_3)N$-$S(O)_2$-$N(R_3)$-C_2-C_4alkyl-O-C_0-C_3alkyl, when Y is absent,

-$R_3R_{3a}NS(O)_2N(R_3)$-C_2-C_4alkyl-O-C_0-C_6 alkyl-, when Y is absent, and

-$R_3R_{3a}NS(O)_2N(R_3)$-C_2-C_4alkyl, when Y is absent,

wherein the right end attaches to Z and the left end attaches to Y;

Y is selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocyclyl, alkylcycloalkyl, alkylheterocyclyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, aryl-heteroaryl, alkylaryl-heteroaryl, heteroaryl-alkylaryl, aryl-aryl, alkylaryl-aryl, aryl-alkylaryl, heteroaryl-heteroaryl, heteroaryl-aryl, alkylheteroaryl-aryl, aryl-alkylheteroaryl, heteroaryl-aryl-aryl, aryl-aryl-heteroaryl, alkylheteroaryl-aryl-aryl, aryl-aryl-alkylheteroaryl, heteroaryl-aryl-heteroaryl, alkylheteroaryl-aryl-heteroaryl, heteroaryl-aryl-alkylheteroaryl, alkylheteroaryl-heteroaryl, heteroaryl-alkylheteroaryl, heterocyclyl-heteroaryl, heteroaryl-heterocyclyl, heterocyclyl-aryl, aryl-heterocyclyl, heterocyclyl-alyl-aryl, aryl-alkyl-heterocyclyl, aryl-C_1-C_3alkyl-aryl, -(O)C-C_0-C_3alkyl-aryl, C_0-C_3alkyl-aryl, -C_0-C_3alkyl-aryl-O-C_2-C_4alkyl-N(R_3)(R_{3a}), -C_0-C_3alkyl-heteroaryl-O-C_2-C_4alkyl-N(R_3)(R_{3a}), -C_0-C_3alkyl-aryl-C_0-C_3alkyl, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl and aryl-C_1-C_3alkyl-heteroaryl, each optionally substituted with one or more groups selected from R_3, R_4 or R_7; or

Y-L-Z- is selected from the group consisting of aryl-C_2-C_6 alkynyl-C_1-C_4alkyl, heteroaryl-C_2-C_6-alkynyl-C_1-C_4alkyl, R_3-heterocyclyl-C_0-C_3 alkyl-$NR_3C(O)NR_3$-heteroaryl-C_2-C_7alkyl; R_3-heterocyclyl-C_o-C_3 alkyl-$NR_3C(O)NR_3$-aryl-C_2-C_7alkyl; aryl-C_0-C_6 alkyl-, heteroaryl-C_1-C_6 alkyl-N(R_4)-C_1-C_6-alkyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_6-alkyl, heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkenyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkenyl-, heteroaryl-C_0-C_6 alkynyl-heteroaryl-C_0-C_6 alkynyl-, heteroaryl-

C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_3-alkyl, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_3-alkyl, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-heteroaryl-, aryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-heteroaryl-C_0-C_3-alkyl, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_3-alkyl, heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-, heteroaryl-C_0-C_6 alkyl-aryl-C_0-C_7 alkyl-, heteroaryl-C(O)-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-, heteroaryl-C(O)-C_0-C_6 alkyl-aryl-C_0-C_7 alkyl-, heteroaryl-$S(O)_2$-C_0-C_6 alkyl-heteroaryl-, heteroaryl-C_0-C_6 alkyl-$N(R_3)$-C(O)-C_1-C_7 alkyl-, aryl-C_0-C_6 alkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, heteroaryl-C_0-C_6 alkyl- C(O)-$N(R_3)$-C_1-C_7 alkyl-, C_1-C_6 alkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, heterocyclyl-C_0-C_6 alkyl- C(O)-$N(R_3)$-C_1-C_7 alkyl-, C_1-C_6 cycloalkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, $(R_3)(R_{3a})$N-C_0-C_6alkyl-C(O)-$N(R_3)$-C_1-C_7alkyl, aryl-C_0-C_6alkyl-O-C(O)-$N(R_3)$-C_1-C_7alkyl, aryl-C_1-C_3 alkyl-$N(R_3)$-C(O)-C_1-C_7 alkyl-, C_1-C_3 alkyl-$N(R_3)$- C(O)- C_1-C_7 alkyl-, heteroaryl-$S(O)_2$-C_0-C_6 alkyl-aryl-, aryl-C_0-C_6 alkyl-$N(R_3)$-C(O)-C_1-C_7 alkyl-, -R_3-O-C(O)NR_3-C_0-C_3alkyl-heteroaryl-C_1-C_7alkyl-, R_3-C(O)-C_0-C_3alkyl-heteroaryl-C_1-C_7alkyl-, R_3-C(O)-heterocyclyl-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl-, R_3-heterocyclyl-C_0-C_3alkyl-$N(R_3)$C(O)$N(R_3)$-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl-, R_3-heterocyclyl-C_0-C_3alkyl-$N(R_3)$C(O)-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl- and R_3-heterocyclyl-C_0-C_3alkyl-$N(R_3)S(O)_2$-C_0-C_3alkyl-heteroaryl-C_0-C_7alkyl-, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heterocyclyl and heteroaryl moieties of the aforementioned Y-L-Z are optionally substituted,

A_{2a}-aryl-C_0-C_3 alkyl-$N(R_3)$-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –NR_3-C(O)-C_1-C_5 alkyl-C_2-C_4 alkenyl-C_1-C_3 alkyl-O-A_{2b}, or –$N(R_3)$-C(O)-C_1-C_7alkyl-O-A_{2b},

A_{2a}-heteroarylene-C_0-C_3 alkyl-$N(R_3)$-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –NR_3-C(O)-C_1-C_5 alkyl-C_2-C_4 alkenyl-C_1-C_3 alkyl-O-A_{2b},

A_{1a}-O-aryl-C_0-C_3alkyl-$N(R_3)$-C(O)-C_1-C_7alkyl, wherein the C_1-C_7 alkyl is optionally substituted with –$N(R_3)$-C(O)-C_1-C_7alkyl-A_{1b}, and

B_2-B_1-$N(R_3)$-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –NR_3-B_3 and the amine of B_3 is conected with the acid of B_2 to form a peptide bond; wherein

A_{1a} and A_{1b} are independently selected from the group consisting of alkyl, alkenyl and a protecting group; or

A_{1a} and A_{1b} together via a –C_2-C_6alkylene, –C_2-C_6alkenylene or –C_2-C_6alkynylene linker, form an optionally substituted ring;

A_{2a} and A_{2b} together are a covalent bond and are attached to form a ring; and

B_1, B_2 and B_3 are each independently a natural or synthetic amino acid; or

L is a covalent bond and Z is C_0-C_6alkyl, heteroalkyl, -C_0-C_6 alkyl-heterocyclyl-C_0-C_6 alkyl-, -heterocyclyl-C(O)-C_2-C_6 alkenyl-C_1-C_3 alkyl-, - C_0-C_7 alkyl-N(R_3)-C(O)-heterocyclyl-C_0-C_7 alkyl-, -C_0-C_7 alkyl-N(R_3)-C(S)-heterocyclyl-C_0-C_7 alkyl-, -C_0-C_7 alkyl-,O-C(O)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_7 alkyl-O-C(S)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-C(O)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-C(S)-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-$S(O)_2$-heterocyclyl-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-C(O)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-C(S)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-$S(O)_2$-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-N(R_3)C(O)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-O-C(O)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-N(R_3)C(S)-C_0-C_6 alkyl-, -C_0-C_6 alkyl-heterocyclyl-O-C(S)-C_0-C_6 alkyl-, and -X-C_1-C_6 alkyl-C(R_3)=C(R_3)-C_1-C_6 alkyl-, wherein each alkyl, alkenyl and heterocyclyl of the aforementioned Z is optionally substituted;

R_6 is selected from the group consisting of -H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, heterocyclyl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-, heteroaryl-C_0-C_6 alkyl-, C_3-C_6 cycloalkyl-C_0-C_6 alkyl-, N(R_3)(R_{3a})-C_1-C_6 alkyl- and N(R_3)(R_{3a})-C(O)-C_1-C_6 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteoralkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl moiety is optionally substituted; and

R_7 and R_{7a} are independently selected from the group consisting of -H, C_1-C_6 alkyl-, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, R_3-O-C_1-C_6 alkyl-, N(R_3)(R_{3a})-C_1-C_6 alkyl-, a protecting group, -C(O)-O-C_1-C_6 alkyl, -C(O)-O-benzyl and heterocyclyl-C_1-C_6 alkyl-, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, benzyl and heterocyclyl moiety is independently optionally substituted; or

R_7 is -OR_3 when attached to the N atom of an indolyl moiety;

wherein in a -N(R_3)(R_{3a}) group, optionally the R_3 and R_{3a} together with the nitrogen atom to which they are attached form a heterocyclyl group; or

wherein in a -N(R_4)(R_{4a}) group, optionally the R_4 and R_{4a} together with the nitrogen atom to which they are attached form a heterocyclyl group; and

provided that

when R_3, R_{3a}, R_4 and R_{4a} are present in -N(R_3)(R_{3a}), -N(R_4)(R_{4a}), -NR_3, -OR_3, -SR_3, -alkyl-R_3, -$NR_3S(O)_2R_3$, -S(O)CH_2R_3, -$NR_3S(O)_2CH_2R_3$, -$NR_3C(O)CH_2R_3(C{=}NR_3)N(R_3)(R_{3a})$, -C(O)$R_3$, -$NR_4$ and -$CR_3{=}CR_3$, then R_3, R_{3a}, R_4 and R_{4a} are independently H, -C_1-C_6-alkyl, -C_3-C_6-cycloalkyl, heteroalkyl, aryl, alkyl-aryl, heteroaryl or alkyl-heteroary;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1 and R_2 are -H, and Q is -C_1-C_6-alkyl-C(O)-OR_3, then R_3 is not -H;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1 and R_2 are -H, and Q is -C_1-C_6-alkyl-N(R_3)(R_{3a}), and R_3 is -H, then R_{3a} is not -H;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1 and R_2 are -H, Q is -C_1-C_6 alkyl-C(O)-N(R_3)(R_{3a}), and R_3 is -H, then R_{3a} is not -H, -OH, or phenyl substituted with -NH_2 or -OH;

when Y-L-Z- is phenyl or phenyl-CH_2-, W is nitrogen, X is a covalent bond or -CH_2-, R_1 and R_2 are -H, and Q is -C_1-C_6 alkyl-N(H)-S(O)$_2$-R_3, then R_3 is not -CH_3;

when Y-L-Z- is aryl-C_1-C_6 alkyl- or heteroaryl-C_1-C_6 alkyl-, W is nitrogen, X is a covalent bond or -CH_2-, R_1 and R_2 are -H, Q is -C_1-C_6 alkyl-C(O)-N(R_3)(R_{3a}), and R_3 is -H, then R_{3a} is not –OH;

when Y-L-Z- is aryl-C_1-C_6 alkyl-, aryl, cycloalkyl, heterocyclyl, heteroaryl, or heteroaryl-C_1-C_6 alkyl-, W is nitrogen, X is a covalent bond or -CH_2-, R_1, R_2 and R_3 are -H, Q is not -C_1-C_6 alkyl-N(H)-C(O)-CH_2-SH;

when Y-L-Z- is aryl-C_1-C_6 alkyl-, aryl, or heteroaryl, W is nitrogen, R_1, R_2 and R_3 are -H, -X-Q is not -C_1-C_6 alkyl-SH;

when Y-L-Z- is phenyl optionally para substituted with -N(CH_3)$_2$, naphthyl, indolyl, or benzofuranyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1, R_2 and R_3 are -H, then Q is not -C_1-C_6 alkyl-OH;

when Y-L-Z- is phenyl optionally para substituted with -N(CH_3)$_2$, quinolinyl, biphenyl or benzyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1, R_2 and R_3 are -H, then Q is not -C_1-C_6 alkyl-N(H)-S(O)$_2$-CH_3, -C_1-C_6 alkyl-S(O)$_2$-N(H)-OH, -C_1-C_6 alkyl-N(H)-C(O)-NH_2, -C_1-C_6 alkyl-N(H)-C(O)-C_1-C_2 alkyl-SH, -C_1-C_6 alkyl-C(O)-N(H)-OH, -C_1-C_6 alkyl-C(O)-OH, or -C_1-C_6 alkyl-N(H)-C(O)-O-t-butyl;

when Y-L-Z- is phenyl optionally para substituted with -N(CH_3)$_2$, biphenyl, substituted pyrrolyl, or substituted pyrrolidinyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1, R_2 and R_3 are -H, then Q is not -C_1-C_6 alkyl-C(O)-N(H)-OH;

when Y-L-Z- is phenyl, benzyl, or quinolinyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1 is -H, R_2 is -N(H)-C(O)-O-t-butyl or -N(H)-C(O)-O-benzyl, then Q is not -C_1-C_6 alkyl-C(O)-N(H)-OH, -C_1-C_6 alkyl-imidazolyl, -C_1-C_6 alkyl-SO_2-NH_2, -C_1-C_6 alkyl-C(O)-N(H)-imidazolyl, -C_1-C_6 alkyl-C(O)-N(H)-thiazolyl, -C_1-C_6 alkyl-C(O)-N(H)-pyridinyl, -C_1-C_6 alkyl-C(O)-N(H)-anilinyl, -C_1-C_6 alkyl-NH_2, -C_1-C_6 alkyl-N(H)-S(O)$_2$-CH_3, or -C_1-C_6 alkyl-C(O)-O-R_3, wherein R_3 is -CH_3, -t-butyl, or -H;

when Y-L-Z- is phenyl, W is nitrogen, X is a covalent bond or -CH_2-, R_1, R_2 and R_3 are -H, then Q is not C_1-C_6-alkyl-NH-$S(O)_2$-CH_3, C_1-C_6-alkyl-$S(O)_2$-NH-OH, C_1-C_6-alkyl-NH-C(O)-NH_2, -C_1-C_6-alkyl-NH_2, -C_1-C_6-alkyl-NH-C(O)-C_1-C_2-alkyl-halo, -C_1-C_6-alkyl-NH-C(O)-C_1-C_2-alkyl-NH_2 or -C_1-C_6-alkyl-NH-C(O)-CH_2-OH; or

when Y is phenyl optionally para substituted with -$N(CH_3)_2$, L is -C(O)-NH-CH_2-, Z is phenyl-CH_2, W is N, R_1, R_2 and R_3 are -H, and X is a covalent bond, Q is not -SH; and

further provided that Formula (I) excludes those compounds wherein

X is S;

Q is selected from the group consisting of H, methyl, ethyl, phenyl, benzyl and acetyl; and

Y-L-Z is selected from the group consisting of R^a-$(CH_2)_{4-6}$ and R^b-Ar-$(CH_2)_{1-2}$-, wherein

R^a is selected from the group consisting of $R^c$$NR^d$C(O)-, R^cNHC(O)NH-, R^cNHC(S)NH-, $R^c$$SO_2$NH- and R^cC(O)NH-;

R^b is selected from the group consisting of $R^c$$NR^d$C(O)$(CH_2)_{1-2}$-, R^cNHC(O)NH$(CH_2)_{1-2}$-, R^cNHC(S)NH$(CH_2)_{1-2}$, $R^c$$SO_2NH(CH_2)_{1-2}$- and R^cC(O)NH$(CH_2)_{1-2}$-;

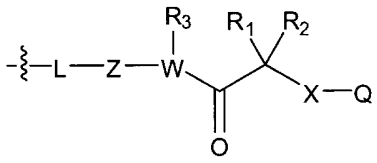
R^c is selected from the group consisting of C_{0-2}alkyl, aryl, heteroaryl, carbocyclyl, -heteroaryl-heteroaryl, -heteroaryl-C_{1-4}alkyl, -heteroaryl-OCH_3, -heteroaryl-aryl-halogen, -heteroaryl-aryl, aryl-aryl, -aryl-SCH_3, -aryl-OCH_3, -aryl-CF_3, -aryl-O-C_2alkyl-heterocyclyl, -C_{3-10}cycloalkyl-aryl, -C_{0-2}alkyl-heterocyclyl, -C_{0-2}alkyl-heteroaryl, -C_{0-2}alkyl-aryl, -C_{0-1}alkyl-heteroaryl, -aryl-OCH_2-aryl, -aryl-CH_2O-aryl, -aryl-carbonyl-aryl, -aryl-C(O)CH_3, -aryl-O-aryl, -aryl-O-heterocyclyl, -aryl-C_{1-4}alkyl, -aryl-O-C_{2-3}alkyl-$N(CH_3)(CH_3)$, C_{0-1}alkyl-heterocyclyl-C_{0-1}allkyl, C_{0-1}alkyl-heteroaryl-C_{0-1}alkyl, -heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl, -aryl-heterocyclyl, -aryl-heteroaryl and –CH(aryl)(aryl), any of which is optionally substituted with one or more of R^e or R^f;

R^e or R^f are C_{0-4}alkyl, halogen, -OH, -CF_3, -SCH_3, -OCH_3, -NH_2, -$O(CH_2)_2N(CH_3)(CH_3)$, -OCH_2-aryl, -$O(CH_2)_2$-heterocyclyl, -C(O)CH_3, -O-heterocyclyl, aryloxy-C_{0-1}alkyl-, aryl or heterocyclyl; and

R^d is C_{0-1}alkyl, or R^c and R^d taken together form a heterocyclic or carbocyclic ring, any of which is optionally substituted with one or more independent C_{0-4}alkyl, halogen, -OH, -SCH_3, OCH_3, -NH_2, aryl, or heterocyclyl substituents; and

Ar is aryl optionally substituted with one or more independent C_{1-4}alkyl, halogen, -OH, -SCH_3, -OCH_3, -NH_2, aryl or heterocyclyl substituents, and

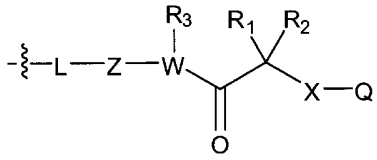
further provided that Formula (I) excludes those compounds wherein



is -$(CH_2)_{3-4}$-NH(CO)-CH_2-O-CH_2-phenyl or –$(CH_2)_{3-4}$-NHC(O)-CH_2-S-phenyl and

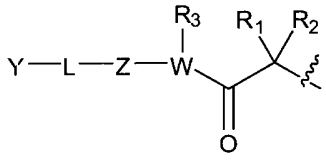
Y is selected from the group consisting of optionally substituted imidazopyridinyl or optionally substituted imidazonaphthyridine; and

further provided that Formula (I) excludes those compounds wherein

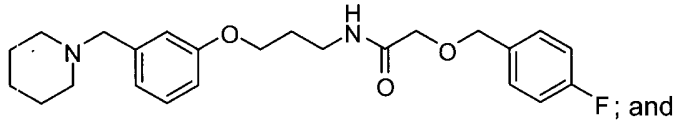


is -$(CH_2)_{2-3}$-NHC(O)-CH_2-O-CH_2-phenyl or -$(CH_2)_{2-3}$-NHC(O)-CH_2-S-phenyl, wherein the phenyl is optionally substituted with halogen, and Y is dimethyoxyphenyl; and

further provided that Formula (I) excludes those compounds wherein

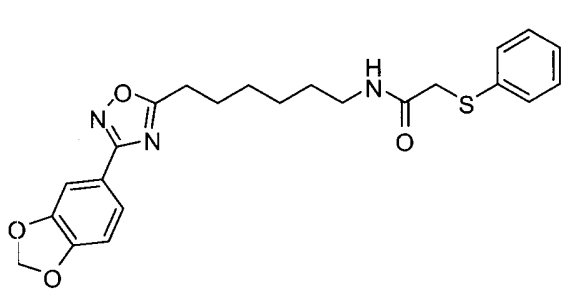


is 3-(R^t)(R^{tt})CH-phenyl-1-O-C_3-C_4alkyl-NHC(O)-, 3-(R^t)(R^{tt})CH-phenyl-1-O-C_3-C_4alkenyl-NHC(O)-, (R^t)(R^{tt})CH-thiophene-O-C_3-C_4alkyl-NHC(O)-, (R^t)(R^{tt})CH-thiophene-O-C_3-C_4alkenyl-NHC(O)-, (R^t)(R^{tt})CH-pyridine-O-C_3-C_4alkyl-NHC(O)- and (R^t)(R^{tt})CH-pyridinyl-O-C_3-C_4alkenyl-NHC(O)-, wherein R^t is selected from the group consisting of H, halogen, OH, Me, optionally substituted piperidino, dimethylamino, 1-pyrrolidinyl and 1-perhydroazepinyl, and R^{tt} is H or Me, or R^t is oxo and R^{tt} is absent, with the exception the this proviso does not include the compound



F; and

further provided that Formula (I) excludes indol-$(CH_2)_2$-NHC(O)-CH_2-O-CH_2-phenyl, indol-$(CH_2)_2$-NHC(O)-CH_2-S(O)$_2$-phenyl-Me, phenyl-$(CH_2)_2$-NHC(O)-CH_2-S(O)2-phenyl, phenyl-$(CH_2)_2$-NHC(O)-CH_2-S(O)$_2$-phenyl-Me, T-$(CH_2)_{2-5}$-NHC(O)-CH_2-S-phenyl (wherein T is pheny, fluro-phenyl, pyridine, methyl-pyrrolidine or methyl), NH_2-S(O)$_2$-phenyl-$(CH_2)_2$-NHC(O)-CH_2-S-phenyl, CH_3-$(CH_2)_2$-NHC(O)-CH_2-O-CH_2-phenyl, CH_3-$(CH_2)_2$-NHC(O)-CH_2-S(O)$_2$-phenyl, CH_3-$(CH_2)_2$-NHC(O)-CH_2-S-phenyl, N-[[[[(aryloxy- or –thio)alkyl]carbonyl]amino]alkyl]-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamide,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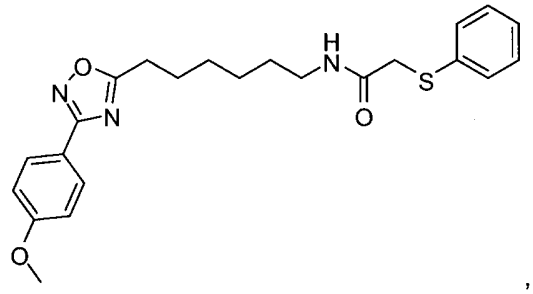
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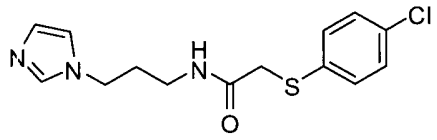
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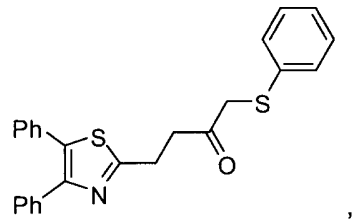
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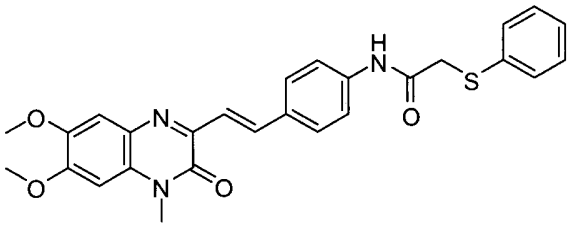
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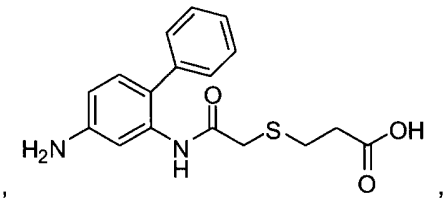
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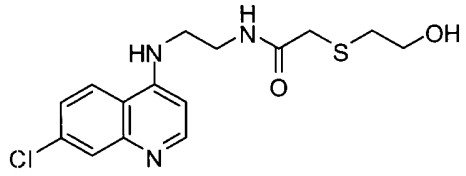
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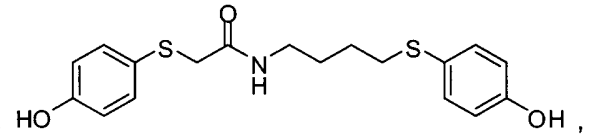
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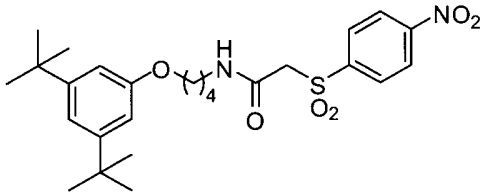
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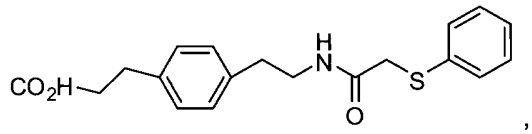
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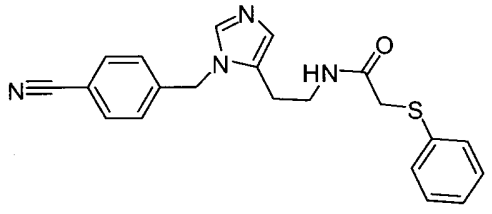

and

,

and

further provided that Formula (I) excludes compounds of formula (R^v)(R^{vv})pyrimidine-$NHS(O)_2$-phenyl-C_0-C_4alkyl-NHC(O)-A, wherein A is aryloxylalkyl or arylmercaptoalkyl, R^v is a lower alkyl, and R^{vv} is selected from the group consisting of H, unsubstituted or substituted alkyl, cycloalkyl, aryl, aralkyl, alkoxy, alkoxyalkyl and alkoxyalkoxy, or

wherein R^v and R^{vv} taken together form a ring of 3 to 5 methylene groups which can contain oxygen or sulfur atoms.

2. The compound according to claim 1, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of X-Q, Q, L, Z, R^3 and R^{3a} is independently optionally substituted with one or more groups independently selected from R^4.

3. The compound according to claim 2, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl moiety of X-Q, Q, R^3 and R^{3a} is independently optionally substituted with one or more groups independently selected from oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2, -$N(R_4)(R_{4a})$, halo, -SH, -S-C_1-C_6 alkyl, -S(O)-C_1-C_6 alkyl, -S-C(O)-C_1-C_6 alkyl and mono- to per-halogenated C_1-C_6 alkyl.

4. The compound according to claim 1, wherein C_1-C_6 alkyl of R_4 and R_{4a} is optionally substituted with -OH, -NO_2 or C_0-C_6 alkyl-C(O)-$N(R_3)(R_{3a})$.

5. The compound according to claim 1, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl moiety of Z is independently optionally substituted with one or more groups independently selected from oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2, -$N(R_3)(R_{3a})$, halo, -SH and mono- to per-halogenated C_1-C_6 alkyl.

6. The compound according to claim 1, wherein L is selected from the group consisting of

-C_1-C_6 alkyl-$N(R_3)$-C_0-C_3 alkyl wherein the C_1-C_6 alkyl is optionally substituted with -C_1-C_4 alkyl-OR_3, or –C_0-C_4 alkyl-$C(O)OR_3$,

-C_0-C_6 alkyl-$N(R_3)$-C(O)-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-$C(O)O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-,

-C_0-C_6 alkyl-$N(R_3)$-C(S)-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-$C(O)O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-,

-C_0-C_6 alkyl-C(O)-$N(R_3)$-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-$C(O)O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-,

-C_0-C_6 alkyl-C(S)-$N(R_3)$-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-$C(O)O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-, and

-C_0-C_6 alkyl-$N(R_3)$-C_0-C_3 alkyl- wherein the C_1-C_6 alkyl is optionally substituted with –C_0-C_6 alkyl-$O(R_3)$-, –C_0-C_6 alkyl-$C(O)O(R_3)$- or –C_0-C_6 alkyl-$N(R_3)(R_{3a})$-.

7. The compound according to claim 1, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl moiety of Y-L-Z is independently optionally substituted with one or more groups independently selected from oxo, $-NO_2$, C_1-C_6 alkoxy, halo, R_3, R_4 and R_6.

8. The compound according to claim 1, wherein Y-L-Z- is selected from the group consisting of

heteroaryl-C_0-C_6 alkyl-$N(R_3)$-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with $-N(R_7)(R_{7a})$ or $-N(R_3)$-C(O)-C_1-C_6 alkyl-R_3,

aryl-C_0-C_6 alkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with $-N(R_7)(R_{7a})$, aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

heteroaryl-C_0-C_6 alkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with $-N(R_7)(R_{7a})$, aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

C_1-C_6 alkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with $-N(R_7)(R_{7a})$, aryl-aryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

heterocyclyl-C_0-C_6 alkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with $-N(R_7)(R_{7a})$, aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl or heteroaryl,

C_1-C_6 cycloalkyl- C(O)-$N(R_3)$- C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with $-N(R_7)(R_{7a})$, aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl, heteroaryl-aryl, or heteroaryl,

C_1-C_3 alkyl-$N(R_3)$-C(O)- C_1-C_7 alkyl-, wherein the C_1-C_3 alkyl is optionally substituted with –C(O)NR_3-C_1-C_3 alkyl-A_{1a} and the C_1-C_7 alkyl is optionally substituted with $-NR_3$-C(O)O-C_1-C_3 alkyl-A_{1b}, $-NR_3$-C(O)-C_1-C_3 alkyl-A_{1b}, $-NR_3$-$S(O)_2$-C_1-C_3 alkyl-A_{1b}, $-NR_3$-C(O)-NR_3-C_1-C_3 alkyl-A_{1b} or $-NR_3$-$S(O)_2$-NR_3-C_1-C_3 alkyl-A_{1b}, and

aryl-C_1-C_3 alkyl-$N(R_3)$-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_3 alkyl is optionally substituted with –C(O)NR_3-C_1-C_3 alkyl-A_{1a} and the C_1-C_7 alkyl is optionally substituted with $-N(R_3)$-C(O)O-C_1-C_3 alkyl-A_{1b}, $-N(R_3)$-C(O)-C_1-C_3 alkyl-A_{1b}, $-NR_3$-$S(O)_2$-C_1-C_3 alkyl-A_{1b}, $-NR_3$-C(O)-NR_3-C_1-C_3 alkyl A_{1b} or $-NR_3$-$S(O)_2$-NR_3-C_1-C_3 alkyl-A_{1b}.

9. The compound according to claim 1, wherein B_1, B_2 and B_3 are independently selected from the group consisting of D-Gly, L-Gly, D-Pro, L-Pro, D-Tyr, L-Tyr, D-Tyr(OR_3), L-Tyr(OR_3), D-Phe, L-Phe, D-PheR_4, L-PheR_4, D-Aib, L-Aib, D-Ala, L-Ala, D-ProR_3, L-ProR_3, D-Ile, L-Ile, D-Leu, L-Leu D-PheR_3, L-PheR_3, D-Pip and L-Pip.

10. The compound according to claim 1, wherein each alkyl, alkenyl and heterocyclyl moiety of Y-Z is independently optionally substituted with one or more groups independently selected from R^4.

11. The compound according to claim 1, wherein each alkyl, alkenyl, alkynyl, heteoralkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl moiety of R_6 is independently optionally substituted with one or more groups independently selected from R_3 and R_4.

12. The compound according to claim 1, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, benzyl and heterocyclyl moiety of R_7 and R_{7a} is independently optionally substituted with one or more groups independently selected oxo, -OH, -CN, C_1-C_6 alkyl, C_1-C_6 alkoxy, -NO_2, -$N(R_3)(R_{3a})$, halo, -SH and mono- to per-halogenated C_1-C_6 alkyl.

13. The compound according to claim 1, wherein Y is selected from the group consisting of aromatic polycycle, non-aromatic polycycle, mixed aryl and non-aryl polycycle, polyheteroaryl, non-aromatic polyheterocycle, mixed aryl and non-aryl polyheterocycle, each of which is optionally substituted.

14. The compound according to claim 1, wherein Y is selected from the group consisting of -(O)C-C_0-C_3alkyl-aryl, -C_0-C_3alkyl-aryl, -C_0-C_3alkyl-aryl-O-C_2-C_4alkyl-$N(R_3)(R_{3a})$, -C_0-C_3alkyl-heteroaryl-O-C_2-C_4alkyl-$N(R_3)(R_{3a})$, -C_0-C_3alkyl-aryl-C_0-C_3alkyl, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl and aryl-C_1-C_3alkyl-aryl, each of which is optionally substituted.

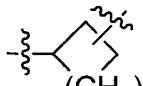
15. The compound according to claim 1, wherein Y is aryl-C_1-C_3alkyl-aryl , wherein C_1-C_3 alkyl is optionally substituted with C_0-C_3alkyl.

16. The compound according to claim 1, wherein L is a covalent bond and Z is selected from the group consisting of

-C_0-C_7 alkyl-$N(R_3)$-C(O)-heterocyclyl-C_0-C_6 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –C_0-C_3alkyl-C(O)OR_3 or –C_0-C_3alkyl-OR_3,

- C_0-C_7 alkyl-O-C(O)-heterocyclyl-C_0-C_6 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with –C_0-C_3alkyl-C(O)OR_3 or –C_0-C_3alkyl-OR_3, and

-C_1-C_4alkyl-$N(R_3)$C(O)-heteorcyclyl-C_1-C_7alkyl, wherein the C_1-C_4alkyl is optionally substituted with C_0-C_3alkyl-C(O)OR_3 or C_0-C_3alkyl-OR_3.

17. The compound according to claim 1, wherein X is -S-, -SO-, -SO_2-, -O-, -NR_3-, -N(OH)--CH_2-, -CH(OH)-, or  .

18. The compound according to claim 1, wherein R_1 and R_2 are independently -H, halo; C_1-C_3 alkyl, C_3-C_6 cycloalkyl, aryl, heteroaryl, or aryl-C_1-C_3 alkyl-.

19. The compound according to claim 3, wherein R_1 and R_2 are independently -CH_3, -CH_2CH_3, phenyl, benzyl or benzofuran.

20. The compound according to claim 1, wherein R_1 and R_2 together with the carbon atom to which they are attached form a aryl or heteroaryl and 3- to 6-membered cycloalkyl or heterocyclyl group.

21. The compound according to claim 1, wherein R_3 and R_{3a} are independently -H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, -C(O)CF_3, -C(O)H, C_1-C_4alkyl -C(O)OR_3; heterocyclyl; C_2-C_4 alkyl-OR_3, C_1-C_3alkylene; C_2-C_6alkenyl; C_2-C_6 hydroxyalkyl -C_1-C_6 alkylaryl, aryl; heteroaryl, C_0-C_6alkylheteroaryl; or C_1-C_3alkyl -C(O)NR_3-heteroaryl;.

22. The compound according to claim 6, wherein R_3 and R_{3a} are independently -C_1-C_6 alkylaryl, or aryl.

23. The compound according to claim 7, wherein R_3 and R_{3a} are independently ethanol; tetrahydro-2H-pyran; phenyl or benzyl.

24. The compound according to claim 6, wherein R_3 and R_{3a} are independently C_1-C_4 alkyl.

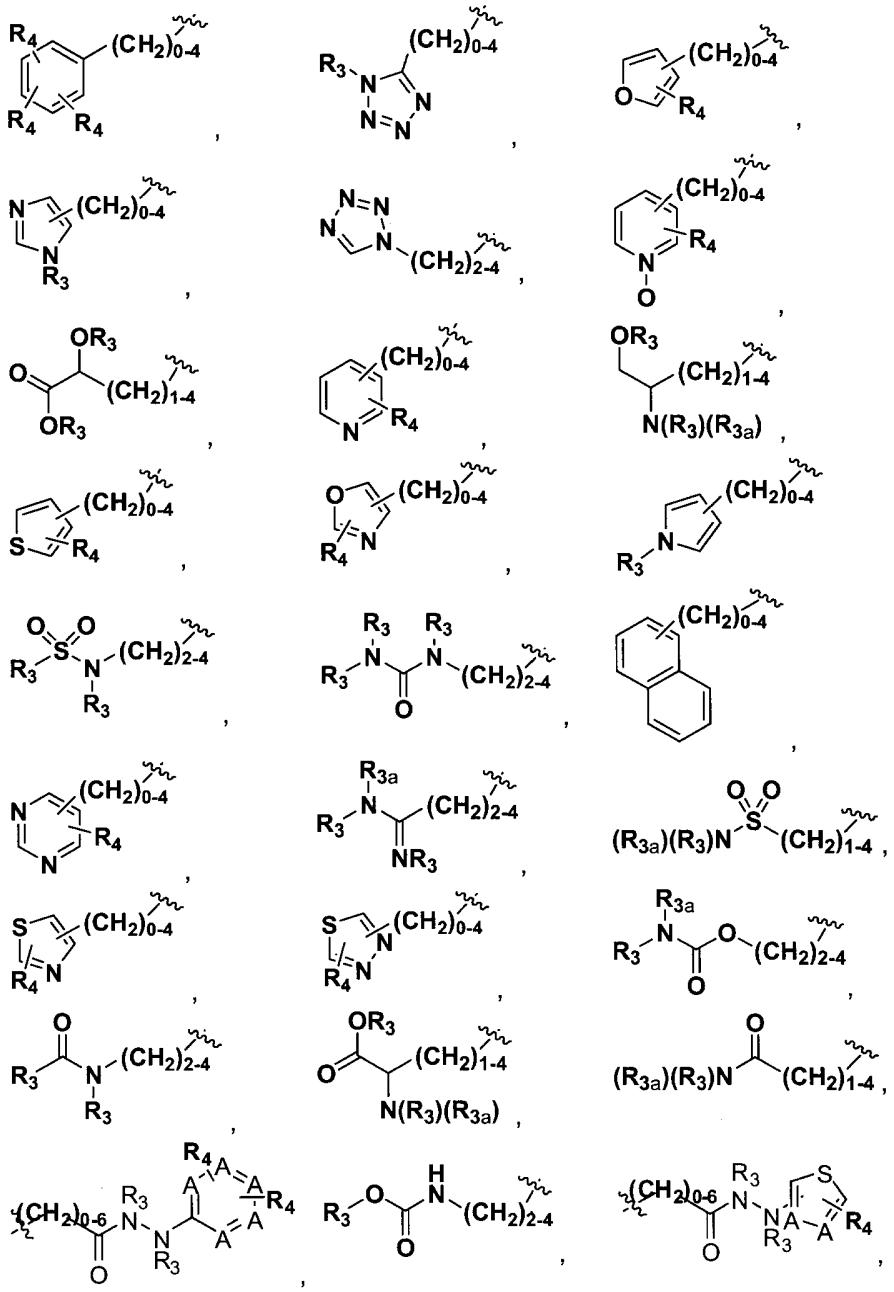
25. The compound according to claim 9, wherein R_3 and R_{3a} are independently t-butyl or i-propyl.

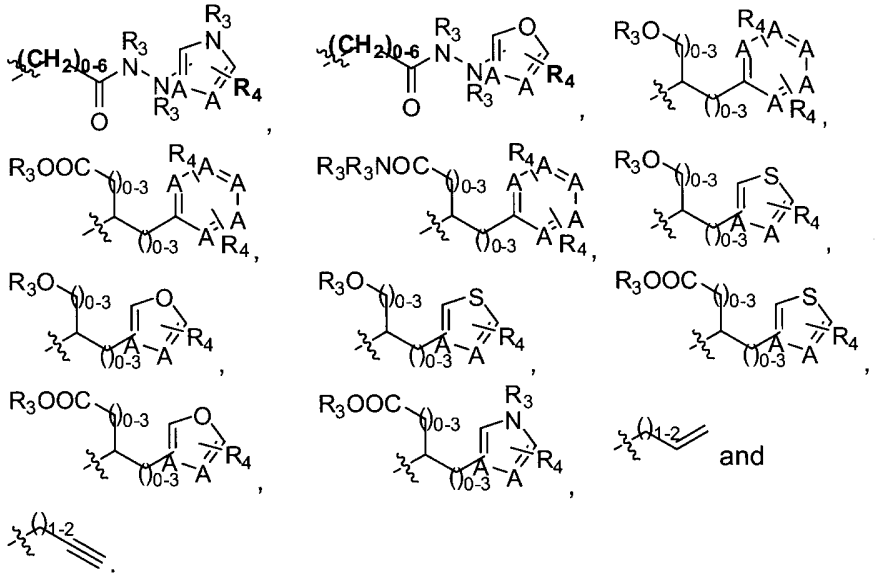
26. The compound according to claim 1, wherein in a NR_3R_{3a} group or a NR_4R_{4a} group, optionally the R_3 together or the R_4 together with the nitrogen atom to which they are attached form a group selected from morpholinyl, piperazinyl ,piperidinyl, pyrrolydinyl, and azetidinyl

27. The compound according to claim 1, wherein X-Q is -OH, -NH_2, -Cl, -F, -SH or -Br.

28. The compound according to claim 1, wherein X-Q is absent and R_1 and R_2 together with the carbon atom to which they attached form a 5- to 6-membered aromatic or heteroaromatic ring.

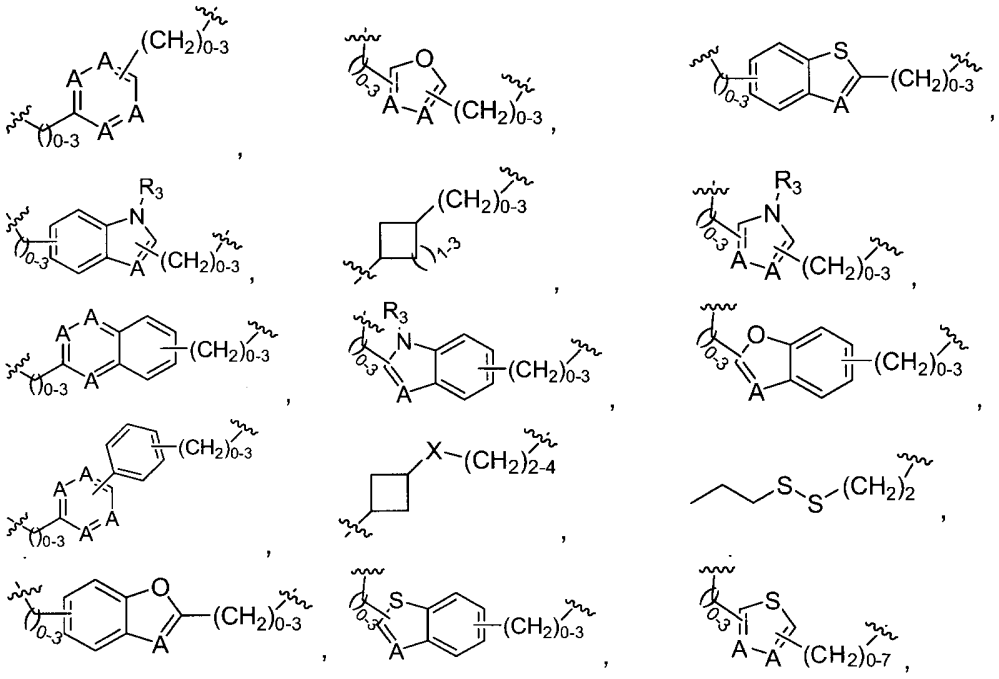
29. The compound according to claim 1, Q is selected from the group consisting of

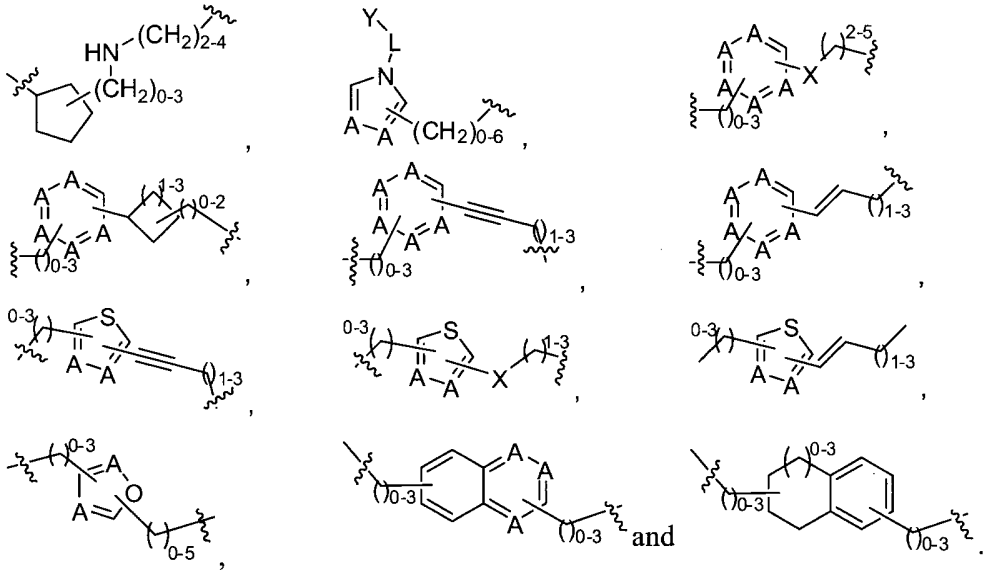




30. The compound according to claim 1, wherein R_4 is -H, $-CH_3$, , $-S(O)_2-N(R_3)R_{3a}$, $-SO_3H$, $-O-C_2-C_4$alkyl-heterocyclyl, $-NR_3-C_2-C_4$alkyl-heterocyclyl, $-(CH_2)_{0-4}OR_3$, $-(CH_2)_{0-4}N(R_3)(R_{3a})$, -F, -Cl, -Br, $-CF_3$, -CN, $-CH_2OH$, $-NO_2$, $-N(R_3)C(O)CH_2R_3$, $-N(R_3)SO_2CH_2R_3$, $-O(CH_2)_{2-4}N(R_3)(R_{3a})$, $-SR_3$, $-S(O)CH_2R_3$, $-SO_2CH_2R_3$, $-(CH_2)_{0-4}C(O)OR_3$, $-CH=CHC(O)OR_3$, $-CH=CHC(O)N(R_3)(R_{3a})$, $-N(R_3)C(O)CF_3$ or $-N(R_3)(CH_2)_2N(R_3)(R_{3a})$.

31. The compound according to claim 1, wherein Z is one of the following structures

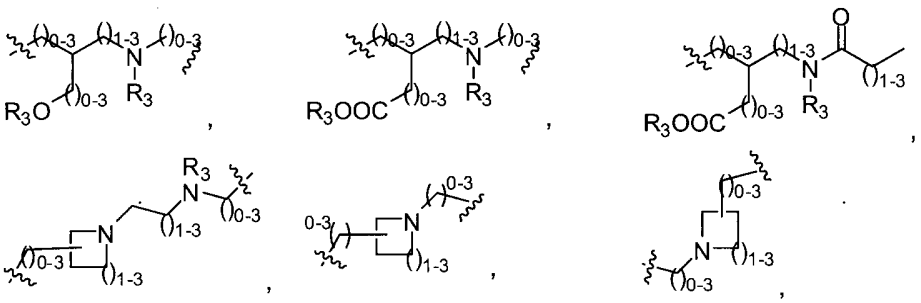


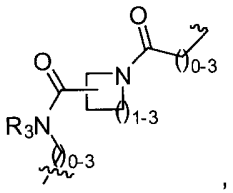


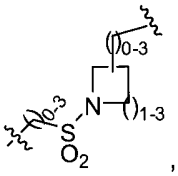
wherein A is -CH= or -N=.

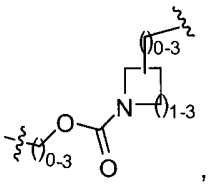
32. The compound according to claim 1, wherein L is selected from the group consisting of a covalent bond, $-(CH_2)_{0-3}N(R_3)C(O)-$, $-(CH_2)_{0-3}C(O)N(R_3)-$, $-(CH_2)_{0-3}OC(O)-$, $-(CH_2)_{0-3}C(O)O-$, $-C_0-C_6$ alkyl-$N(R_3)C(O)$heterocyclyl-C_0-C_3alkyl, $-C_0-C_6$ alkyl-$S(O)_2$heterocyclyl-C_0-C_3alkyl,-, $-(CH_2)_{0-3}C(O)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}SO_2N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}NR_3S(O)_2-(CH_2)_{0-3}$, $-(CH_2)_{0-3}N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}N(R_7)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}S-(CH_2)_{0-3}$, $-(CH_2)_{0-3}O-(CH_2)_{0-3}$, $-(CH_2)_{0-3}S(O)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}S(O)_2-(CH_2)_{0-3}$, $-(CH_2)_{0-3}CH=CH-(CH_2)_{2-3}-$, $-(CH_2)_{0-3}N(R_3)C(O)N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}N(R_3)C(O)O-(CH_2)_{0-3}$ and $-(CH_2)_{0-3}OC(O)N(R_3)-(CH_2)_{0-3}$, $-(CH_2)_{0-3}NR_3C(O)NR_3S(O)_2-(CH_2)_{0-3}$, $-(CH_2)_{0-3}NR_3C(O)NR_3C(O)-(CH_2)_{0-3}$, and $-(CH_2)_{0-3}-C(O)-N(R_3)-C(O)N(R_3)-(CH_2)_{0-3}$ and $-(C_0-C_3alkyl)(R_3)N-S(O)_2-N(R_3)-C_2-C_4alkyl-O-C_0-C_3alkyl$, -and $R_3R_{3a}NS(O)_2NR_3-C_2-C_4alkyl-O-C_0-C_6$ alkyl- , when Y is absent, and $-R_3R_{3a}NS(O)_2NR_3-C_2-C_4alkyl$, when Y is absent.

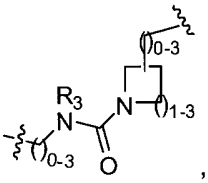
33. The compound according to claim 1, wherein L is selected from the group consisting of

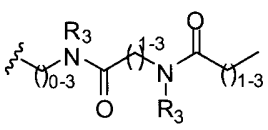


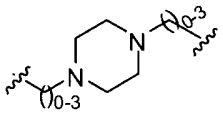


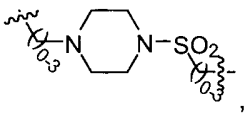


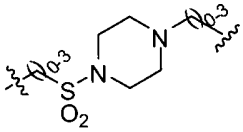


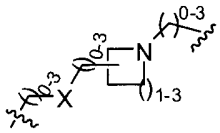


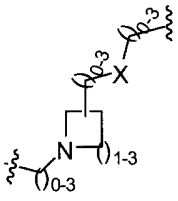


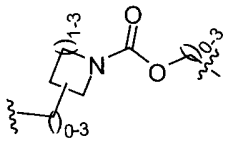


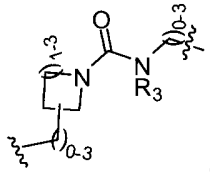


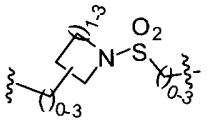


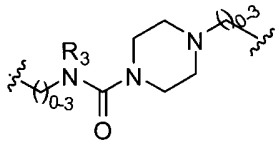


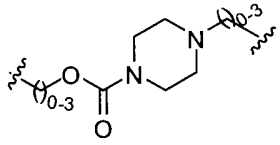


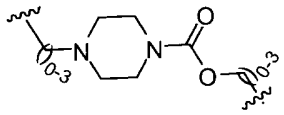


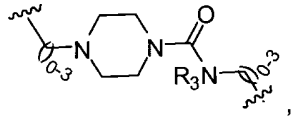


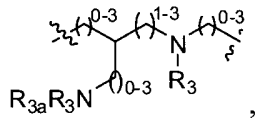


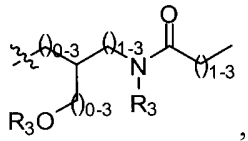


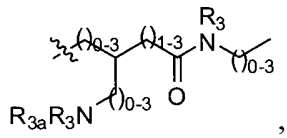


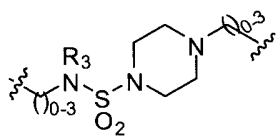


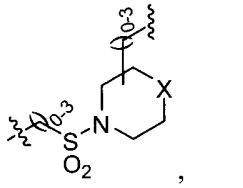


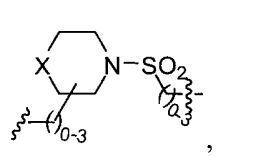


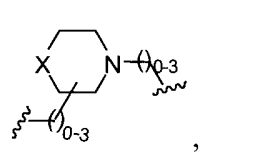


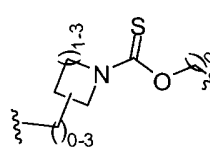


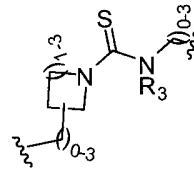


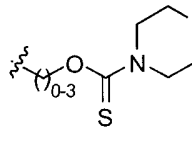


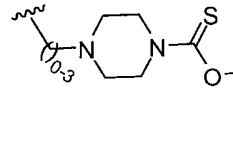


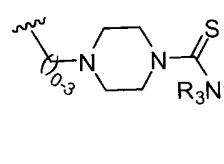


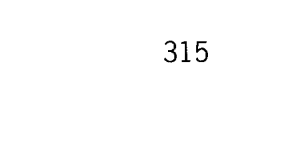












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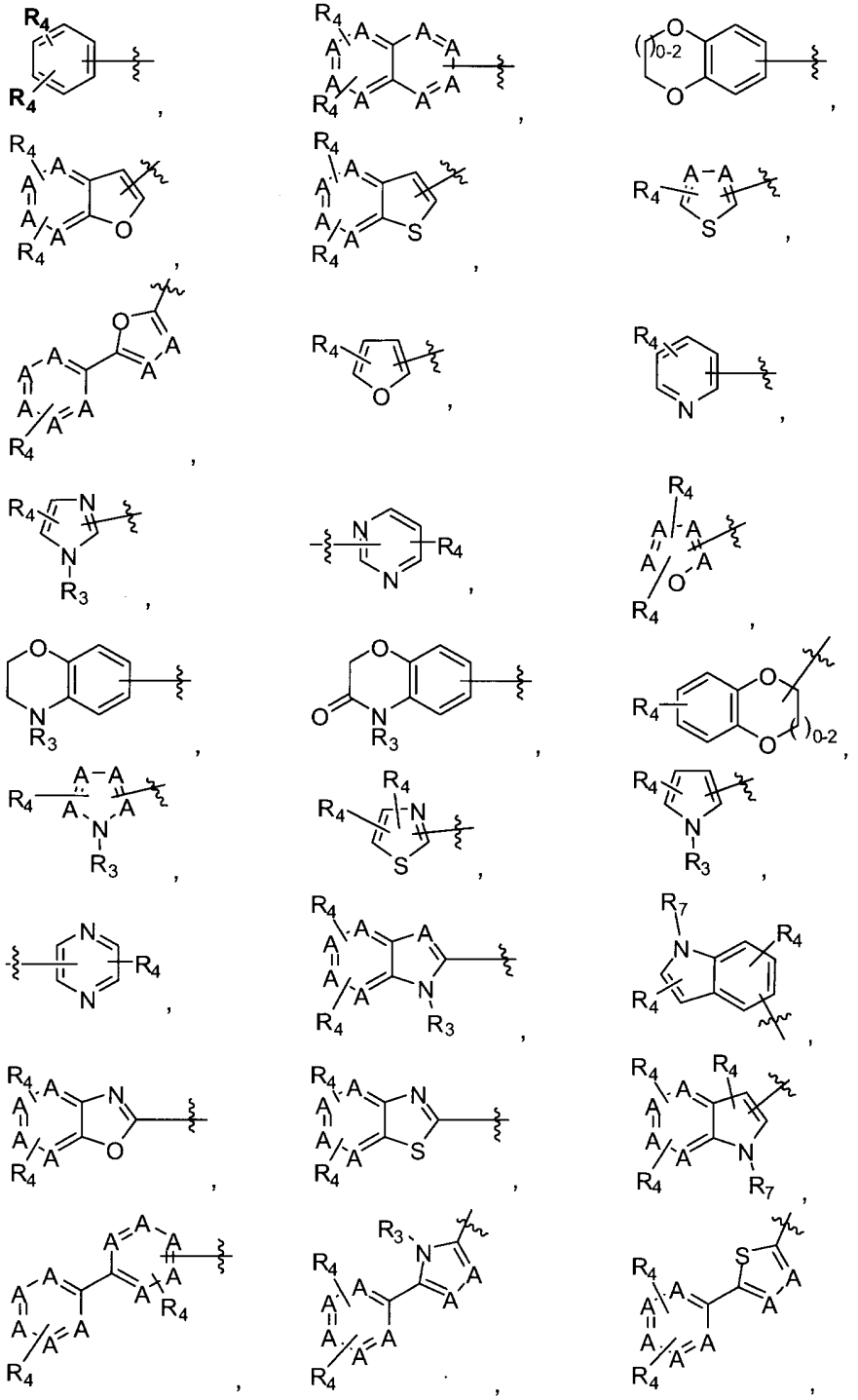
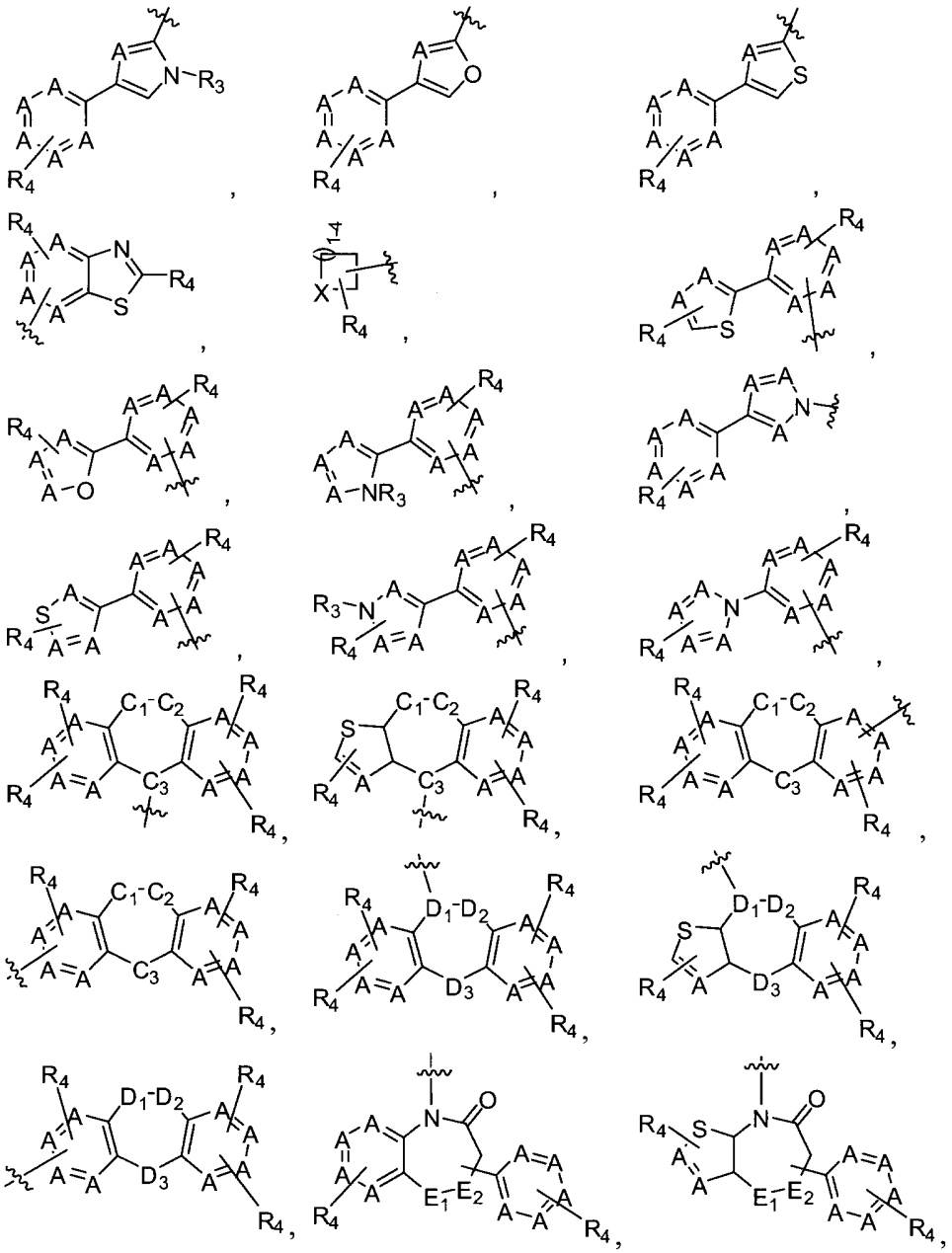
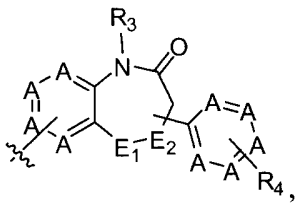
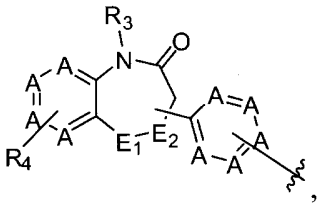
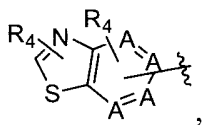
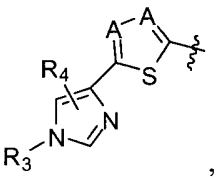
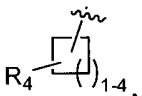
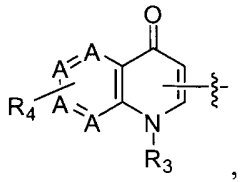
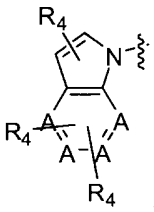
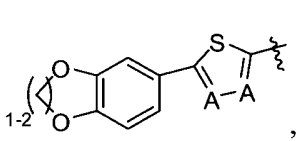
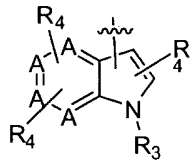
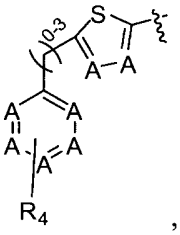
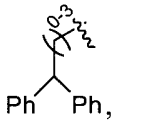
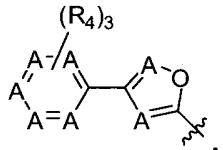
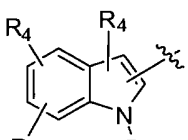
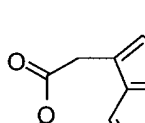
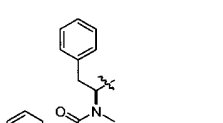
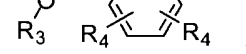
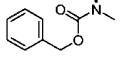
34. The compound according to claim 1, wherein Y is selected from the group consisting of





and

wherein A is -CH= or -N=;

C_1 is selected from the group consisting of absent, a covalent bond, CH, CH_2, S, O, SO_2, C(O) and CR_3R_3;

C_2 is selected from the group consisting of absent, a covalent bond, CH, CH_2 and NR_3;

C_3 is selected from the group consisting of CH, N and NR_3;

D_1 is selected from the group consisting of N, CO and CH_2;

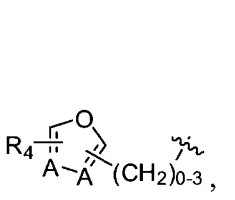
D_2 is selected from the group consisting of C, N and CH;

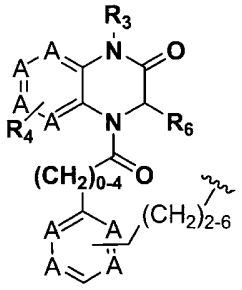
D_3 is selected from the group consisting of O, NR_3, SO and S;

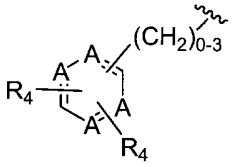
E_1 is selected from the group consistingof S, C and N; and

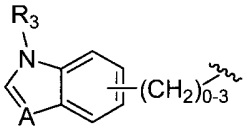
E_2 is selected from the group consisting of CH, N and C(O).

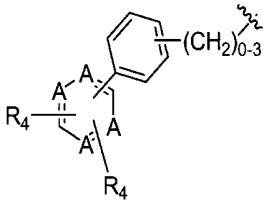
35. The compound according to claim 1, wherein Y-L-Z- is one of the following structures

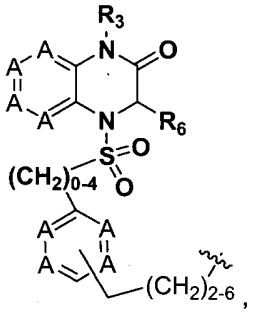


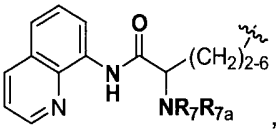


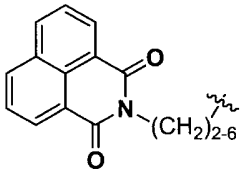


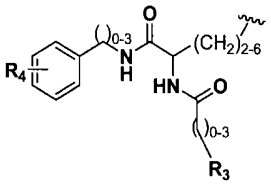


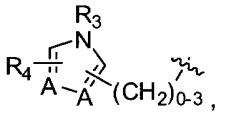


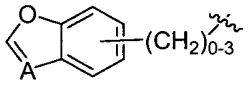


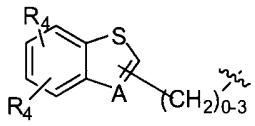


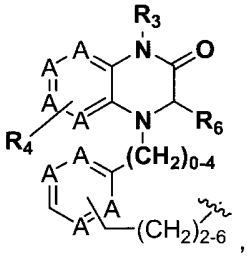


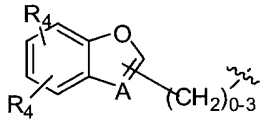


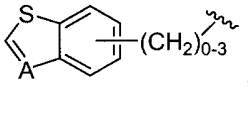


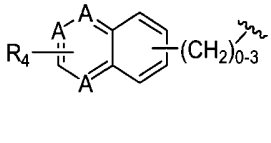


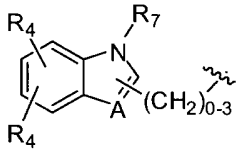


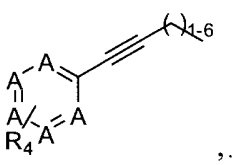


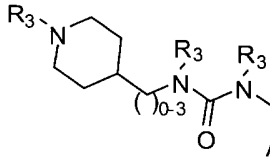












R4
O
A
A
(CH2)0-3
,

R3
N
O
R4
N
R6
(CH2)0-4
O
(CH2)2-6
,

(CH2)0-3
R4
R4
,

R3
N
A
(CH2)0-3
,

(CH2)0-3
R4
R4
,

R3
N
O
N
R6
S
O
O
(CH2)0-4
(CH2)2-6
,

O
N
H
N
(CH2)2-6
NR7R7a
,

O
N
O
(CH2)2-6
,

R4
()0-3
N
H
O
(CH2)2-6
HN
O
()0-3
R3
,

R3
N
R4
A
A
(CH2)0-3
,

O
A
(CH2)0-3
,

R4
S
R4
A
(CH2)0-3
,

R3
N
O
R4
N
R6
(CH2)0-4
(CH2)2-6
,

R4
O
R4
A
(CH2)0-3
,

S
R4
A
A
(CH2)0-3
,

S
A
(CH2)0-3
,

R4
(CH2)0-3
,

R4
R7
N
R4
A
(CH2)0-3
,

()1-6
R4
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R3
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N
R3
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O
S
A
A
(CH2)0-3
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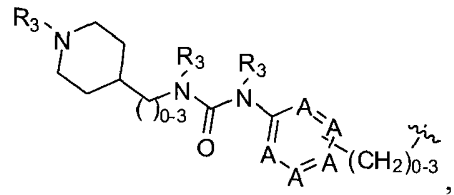
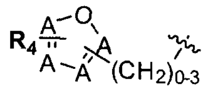
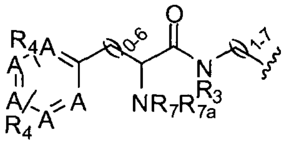
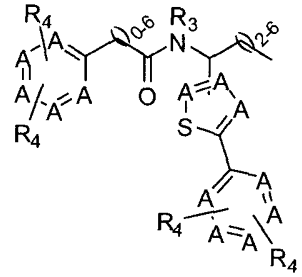
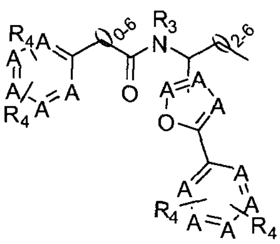
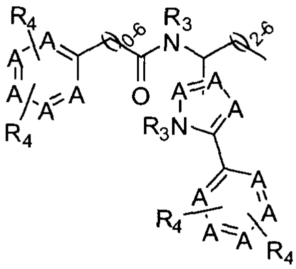
 ,

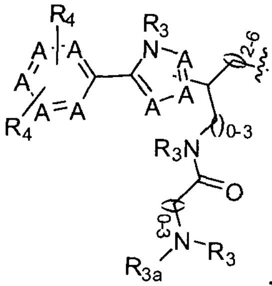
 ,

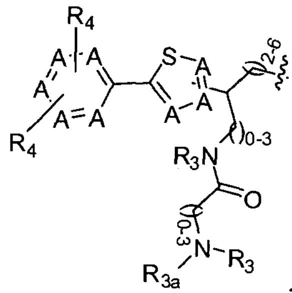
 ,

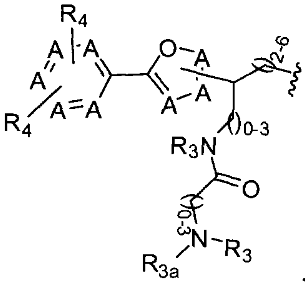
 ,

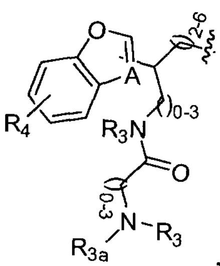
 ,

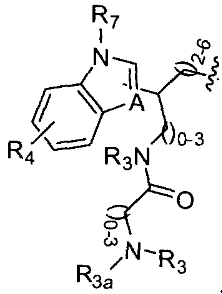
 ,

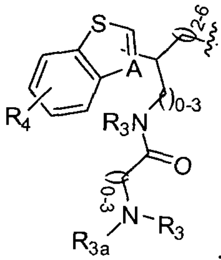
 ,

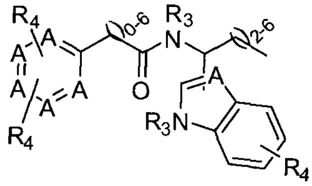
 ,

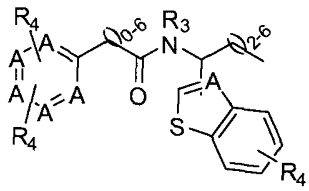
 ,

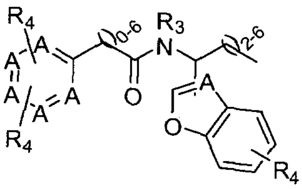
 ,

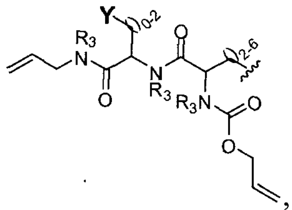
 ,

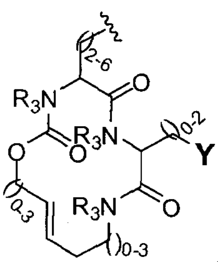
 ,

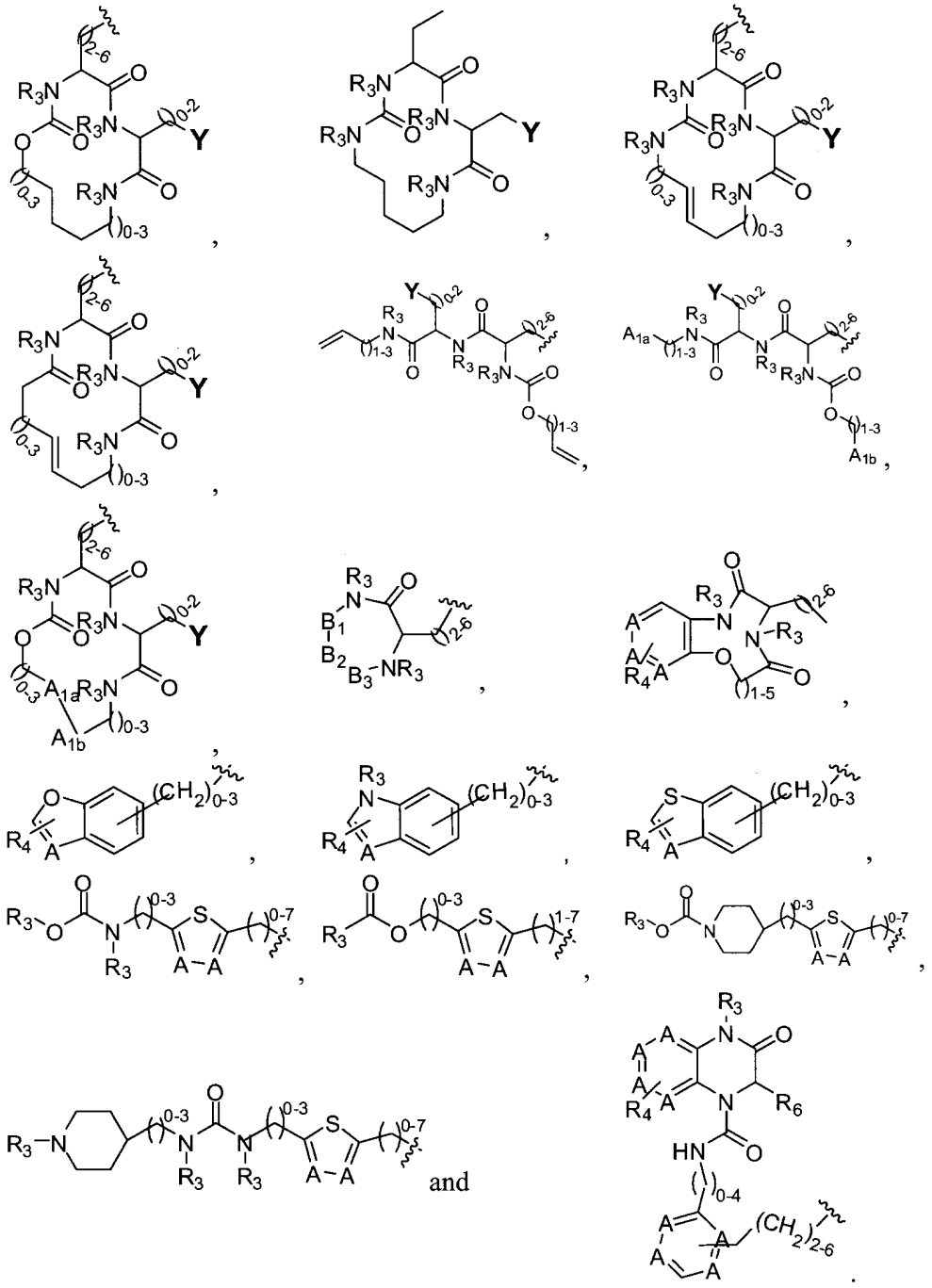
 ,

 ,

 ,

 ,

 ,



wherein A is -CH= or -N=;

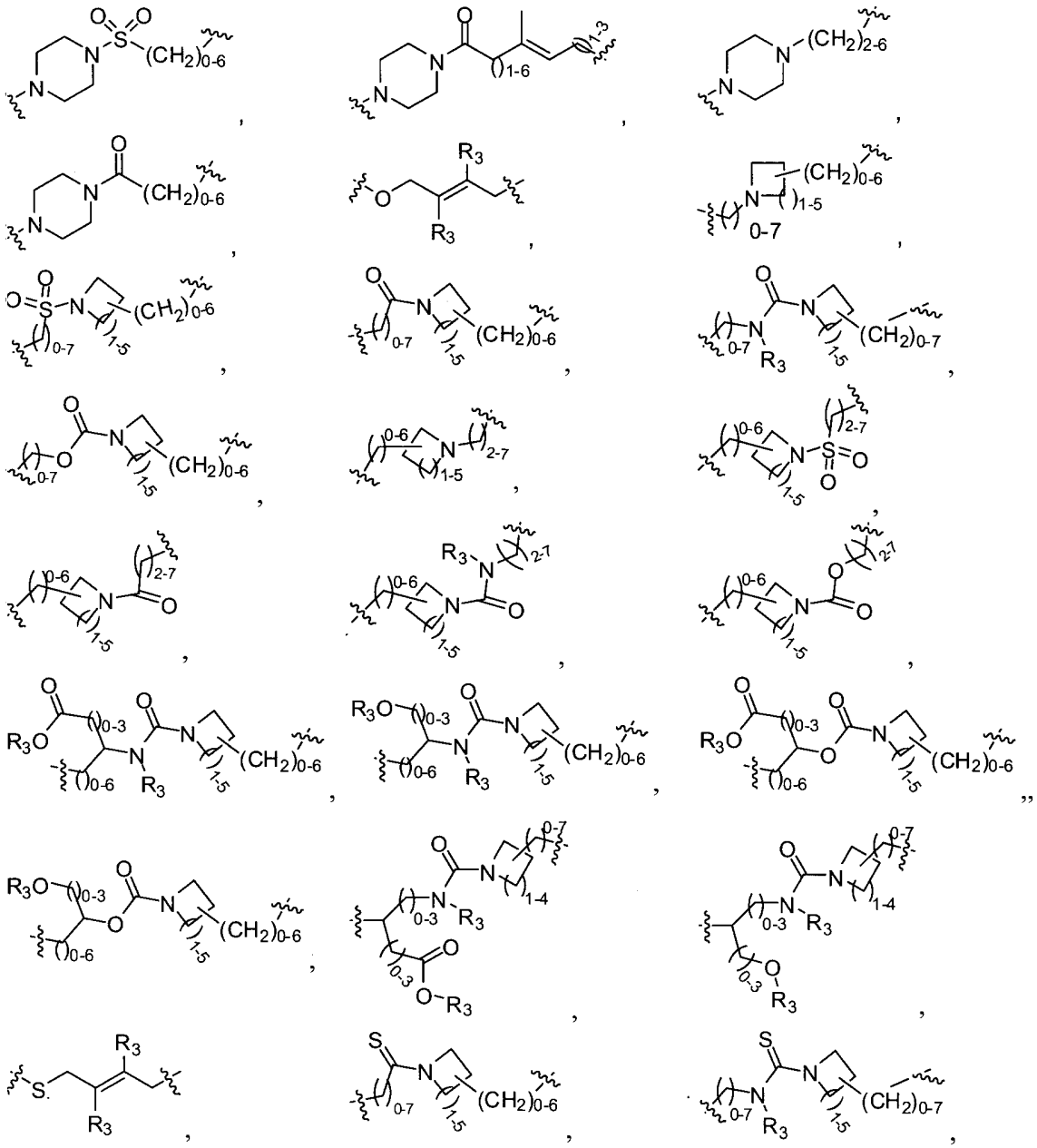
A_{1a} and A_{1b} are independently selected from the group consisting of alkyl, alkenyl and protecting group; or

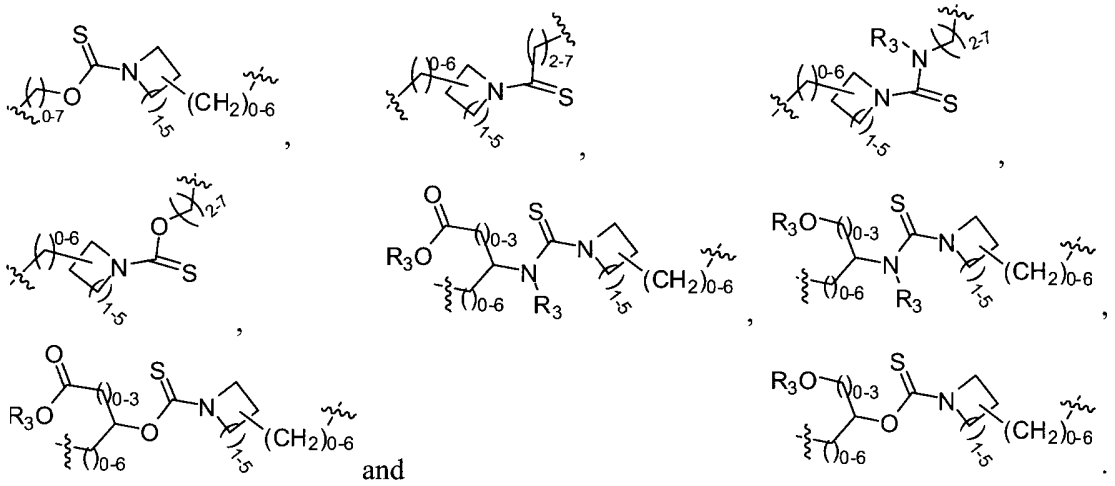
A_{1a} and A_{1b} together via a $-C_2$-C_6alkylene, $-C_2$-C_6alkenylene or $-C_2$-C_6alkynylene linker, form an optionally substituted ring; and

B_1, B_2 and B_3 are each independently a natural or synthetic amino acid.

36. The compound according to claim 29, wherein B_1, B_2 and B_3 are independently selected from the group consisting of D-Gly, L-Gly, D-Pro, L-Pro, D-Tyr, L-Tyr, D-Tyr(OR_3), L-Tyr(OR_3), D-Phe, L-Phe, D-PheR_4, L-PheR_4, D-Aib, L-Aib, D-Ala, L-Ala, D-ProR_3, L-ProR_3, D-Ile, L-Ile, D-Leu, L-Leu D-PheR_3, L-PheR_3, D-Pip and L-Pip.

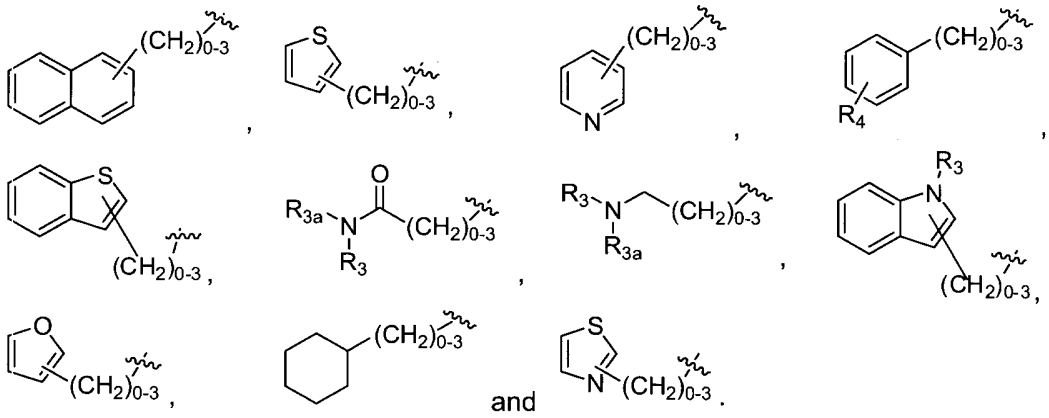
37. The compound according to claim 1, wherein L is a covalent bond and Z- is selected from the group consisting of





and

38. The compound according to claim 1, wherein R_6 is selected from the group consisting of



and

39. The compound according to claim 1, wherein R_7 is selected from the group consisting of -H, optionally substituted C_1-C_6 alkyl, -$(CH_2)_{2-4}OR_3$, -$(CH_2)_{2-4}N(R_3)(R_{3a})$, -C(O)Ot-butyl, -C(O)O-benzyl, -$(CH_2)_2$-morpholinyl or -$(CH_2)_2$-piperazynnyl.

40. The compound according to claim 1, wherein then Q is -C(O)-OR_3 and X is -$N(R_3)$-, -$C(H)_2$- -CH(OH)-.

41. The compound according to claim 1, wherein Q is -$C(O)R_3$ and X is -S-, -O- or -$N(R_3)$-.

42. The compound according to claim 1, wherein X is -CH_2-and Q is selected from the group consisting of -$(CH_2)_{0-3}$-X-$(CH2)_{1-3}$-$C(O)OR_3$, -$(CH_2)_{0-3}$-X-$(CH_2)_{2-3}$-OR_3 and -$(CH_2)_{0-3}$-X-$(CH_2)_{2-3}$-$N(R_3)(R_{3a})$.

43. The compound according to claim1, wherein

W is nitrogen;

X is a covalent bond or $-CH_2-$;

R_1 and R_2 are -H

R_3 is -H, -OH, -C(O)-NH-aryl, $-C(O)-NH_2$, $-C(NH_2)-C(O)-OH$, NH_2, $-C(NH_2)-C(O)-O-C_1-C_6$ alkyl, -C(O)-OH, $-C(O)-O-C_1-C_6$ alkyl, aryl, heteroaryl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from -OH, -CN, C_1-C_6 alkyl, $-N(R_4)(R_{4a})$, halo;

Q is $-C_1-C_6$ alkyl-$N(R_3)-C(O)-C_1-C_6$ alkyl-B-$(CH_2)_n-R_3$;

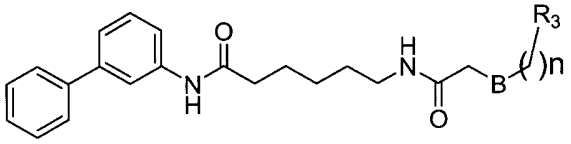
B is -O-, -S(O)-, or -S-;

n is 0 or an interger from 1 to 3;

R_4 and R_{4a} are -H; and

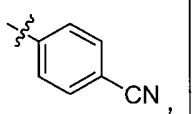
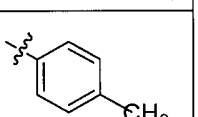
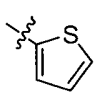
Y-L-Z- is aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkenyl-aryl-C_0-C_6 alkynyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkenyl-, aryl-C_0-C_6 alkynyl-aryl-C_0-C_6 alkynyl-.

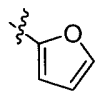
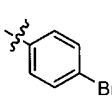
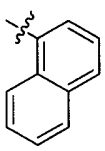
44. The compound according to claim 43 of the formula

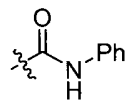
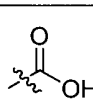
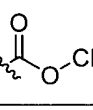


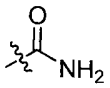
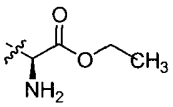
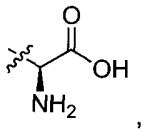
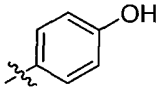
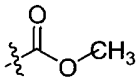
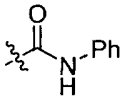
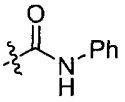
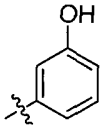
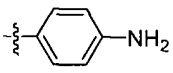
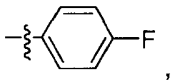
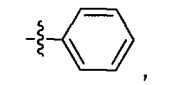
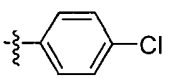
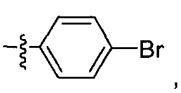
(II)

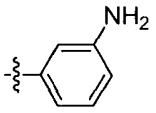
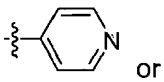
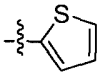
or a pharmaceutically acceptable salt thereof, wherein B, n and R_3 are any one of the following combination:

n	B	R_3
1	O	 ,
1	O	 ,
1	O	 ,
1	O	 ,

n	B	R_3
1	O	 ,
1	O	 ,
1	O	 ,

n	B	R_3
1	S O	 ,
2	S	 ,
2	S O	 ,
3	S	-OH,
2	S	-OH,

n	B	R_3
1	S	 ,
1	S	 ,
1	S	 ,
2	S	-NH2
0	S	 ,
1	S O	 ,
2	S	 ,
2	S O	 ,
0	S	 ,
0	S	 ,
0	S	 ,
0	S	 ,
0	S	 ,
0	S	 ,

n	B	R_3
0	S	 ,
0	S	 or
0	S	 .

45. The compound according to claim1, wherein

W is nitrogen;

X is a covalent bond or $-CH_2-$;

R_1 and R_2 are -H;

R_3 is H, aryl or heteroaryl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from -CN, -S(O)- C_1-C_6 alkyl, C_1-C_6 alkyl, or halo;

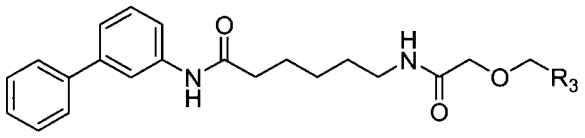
Q is -C_1-C_6 alkyl-N(R_3)-C(O)-C_1-C_6 alkyl-B-C_1-C_6 alkyl-R_3;

B is -S-, -S(O)- or -O-;

and

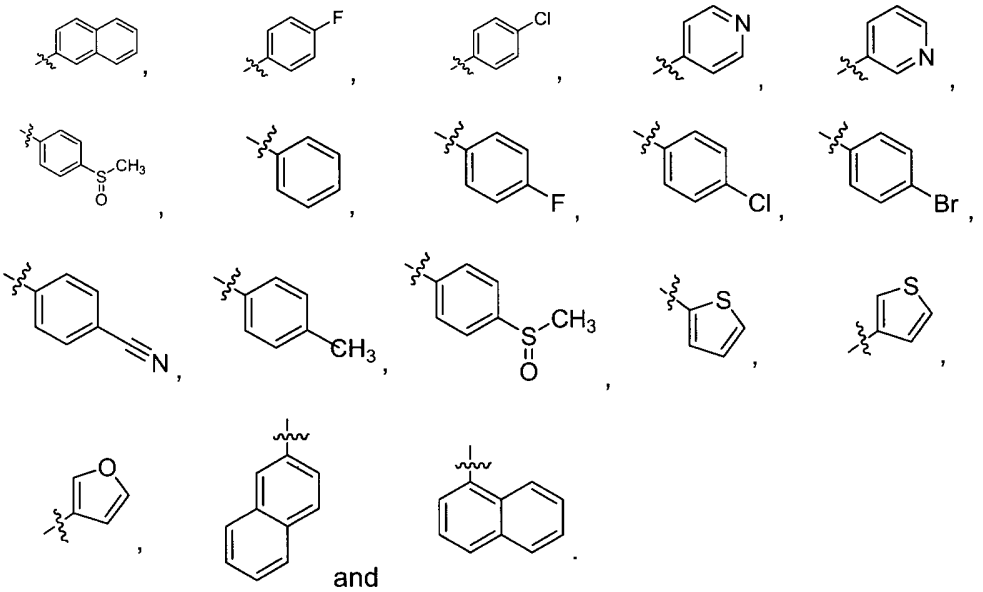
Y-L-Z- is aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-,.

46. The compound according to claim 45 of the formula



(III)

or a pharmaceutically acceptable salt thereof, wherein R_3 is selected from the group consisting of



and

R_1 and R_2 are -H;

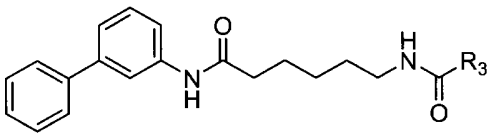
R_3 is -H, -C_1-C_6 hydroxyalkyl-C(O)-OH, -C_1-C_6 alkyl-S-C_1-C_6 alkyl-C(NH_2)-C(O)-OR_4, -C_1-C_6 alkyl-S(O)-C_1-C_6 alkylaryl, -C_1-C_6 alkyl-S-C_0-C_6 alkylaryl, -C_1-C_6 alkyl-S-C_0-C_6 alkylheteroaryl, -C_1-C_6 alkyl-S-C_1-C_6 alkyl-OH, -C_1-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-OH, -C_1-C_6 alkyl-S-C_1-C_6 hydroxyalkyl-C(O)-O-C_1-C_6 alkyl, -C_1-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-O-C_1-C_6 alkyl, -C_1-C_6 alkyl-S(O)-C_1-C_6 alkyl-C(O)-OR_4, -C_1-C_6 alkyl-S-C_1-C_6 alkyl-C(O)-N(R_4)(R_{4a}), -C_1-C_6 alkyl-S(O)-C_1-C_6 alkyl-C(O)-N(R_4)-aryl, -C_1-C_6 alkyl-S-C_1-C_6 alkyl-N(R_4)(R_{4a}), and -C_1-C_6-alkylheteroaryl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from oxo, -OH, -N(R_4)(R_{4a}), halo, -S-C_1-C_6 alkyl, or -S(O)-C_1-C_6 alkyl;

Q is -C_1-C_6 alkyl-N(R_3)-C(O)-R_3;

R_4 and R_{4a} are independently -H, C_1-C_6 alkyl, or aryl; and

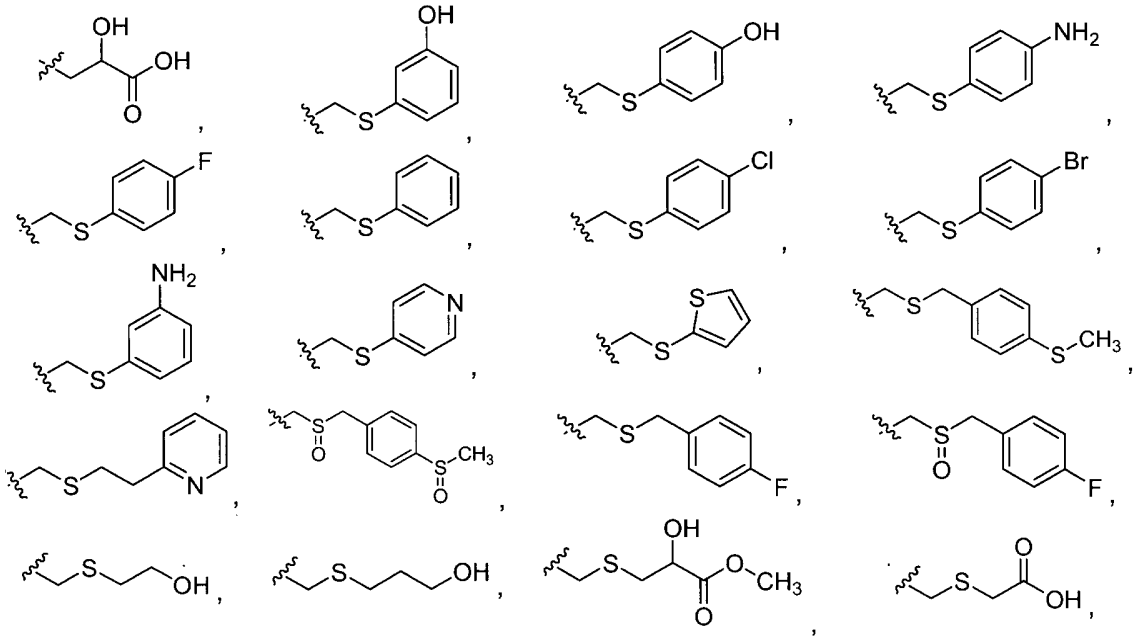
Y-L-Z- is aryl-C_0-C_6 alkyl-aryl-C_0-C_6 alkyl-.

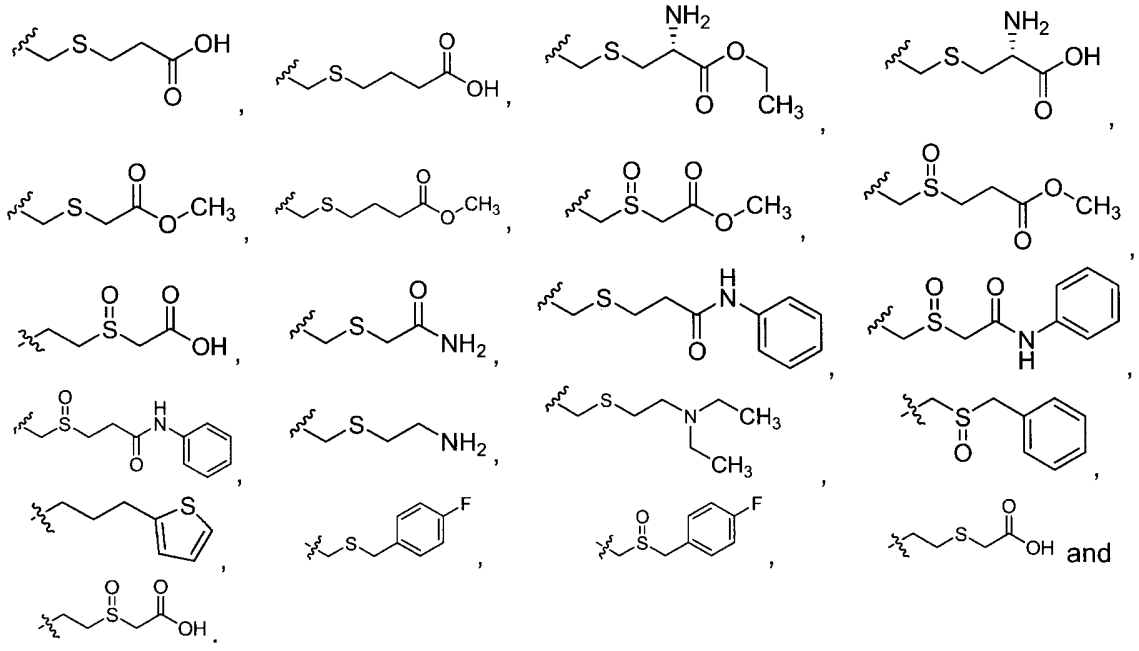
48. The compound according to claim 47 of the formula



(IV)

or a pharmaceutically acceptable salt thereof, wherein R_3 is selected from the group consisting of





49. The compound according to claim 1, wherein

W is nitrogen;

X is -S-;

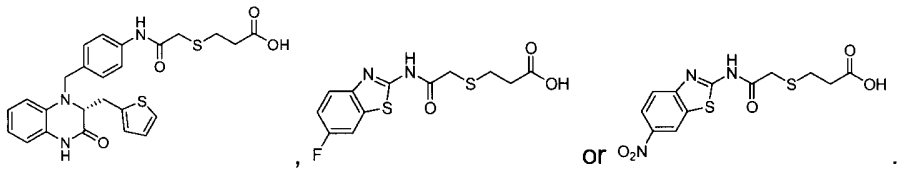
R_1 and R_2 are -H;

R_3 is -H;

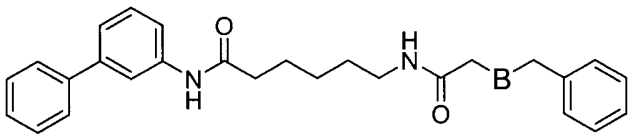
Q is -C_1-C_6-alkyl-C(O)-OR_3; and

Y-L-Z- is heteroaryl-C_0-C_6 alkyl- or heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_6-alkyl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from oxo or halo.

50. The compound according to claim 49 that is one of the following structures:



51. The compound according to claim 45 of the formula



(VI)

wherein B is -S- or -S(O)-.

52. The compound according to claim 1, wherein

W is nitrogen;

X is -S-;

R_1 and R_2 are -H;

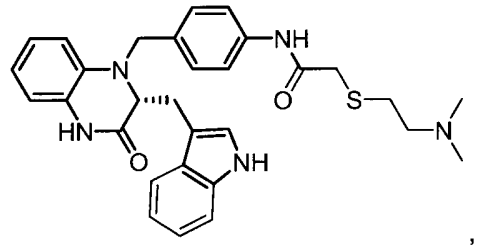
R_3 is -H or C_1-C_6 alky;

R_4 is C_1-C_6 alkyl-OR_3;

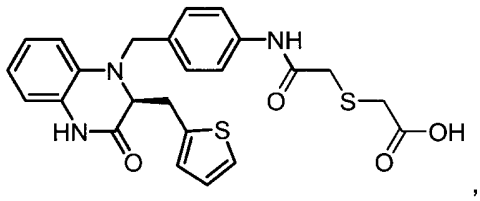
Q is -C_1-C_6-alkyl-C(O)-OR_3, -C_1-C_6-alkyl-N(R_3)(R_{3a}), C_1-C_6 alkyl substituted with -OH; and

Y-L-Z- is heteroaryl-C_1-C_6 alkyl-N(R_4)-C_1-C_6-alkyl-aryl-C_0-C_6 alkyl- or heteroaryl-C_0-C_6 alkyl-heteroaryl-C_0-C_7 alkyl-aryl-C_0-C_6-alkyl, wherein each of the aryl and heteroaryl is optionally substituted with one or more groups selected from oxo.

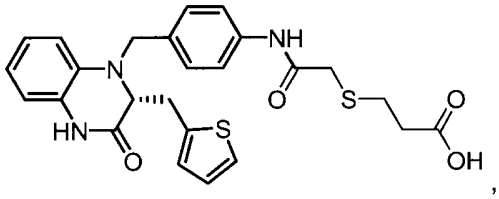
53. The compound according to claim 52 that is one of the following structures:



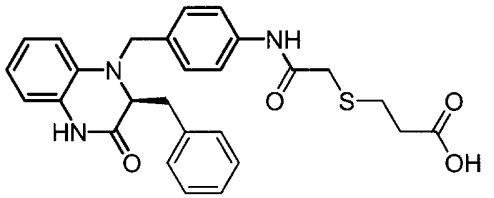
,



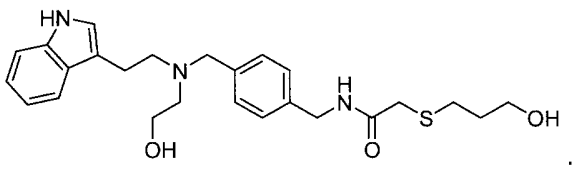
,



,



or



.

54. The compound according to claim 1, wherein

W is nitrogen;

X is a covalent bond or -CH_2-;

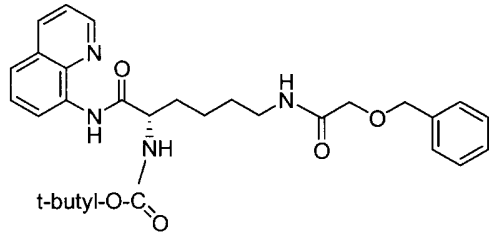
R_1 and R_2 are independently -H, -N(H)-C(O)-O-C_1-C_6 alkyl or -N(H)-C(O)-O-benzyl;

R_3 is -H or -C_1-C_6 alkyl-O-C_0-C_6 alkylaryl;

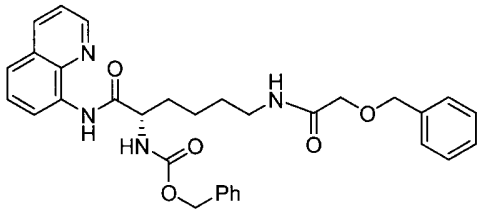
Q is -C_1-C_6 alkyl-N(R_3)-C(O)-R_3; and

Y-L-Z- is heteroaryl-C_0-C_6 alkyl-.

55. The compound according to claim 54 that is one of the following structures:



or



.

56. The compound according to claim 1, wherein

W is nitrogen;

X is -S-;

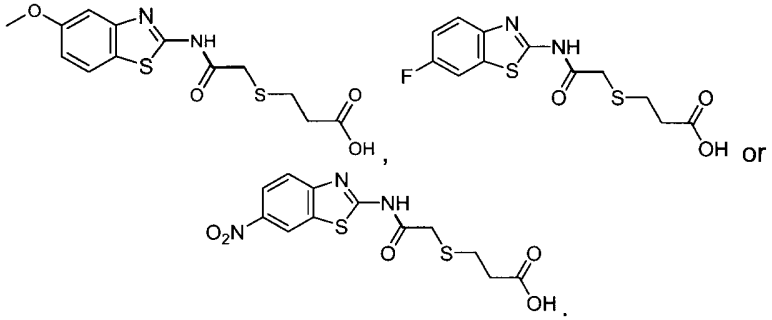
R_1 and R_2 are -H;

R_3 is -H;

Q is -C_1-C_6-alkyl-C(O)-OR_3; and

Y-L-Z- is heteroaryl-C_0-C_6 alkyl-, wherein the heteroaryl is optionally substituted with one or more groups selected from C_1-C_6 alkoxy, halo or -NO_2.

57. The compound according to claim 56 that is one of the following structures:



.

58. The compound according to claim 1, wherein

W is nitrogen;

X is selected from the group consisting of S, O, SO and SO_2;

R_1 and R_2 are H or halogen;

Q is selected from the group consisting of aryl-NH_2, C_1-C_6alkyl-aryl, C_1-C_6alkyl-heteroaryl, C_1-C_6alkyl-CN, wherein the alkyl, aryl and heteroaryl are each independently optionally substituted;

Z is selected from the group consisting of -C_1-C_6alkyl-, -C_1-C_8heteroalkyl-, -C_0-C_6alkyl-aryl-C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-heteroaryl-C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-heteroaryl-C_2-C_6heteroalkyl-, -C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-aryl-C_3-C_6alkynyl- and -C_0-C_6alkyl-aryl-C_3-C_6alkenyl-, wherein the alkyl, heteroalkyl, aryl, heteroaryl and alkenyl are each independently optionally substituted;
L is selected from the group consisting of -C_0-C_6alkyl-$S(O)_2$-$N(R_3)$-C_0-C_6alkyl-, -C_0-C_6alkyl-O-C(O)-$N(R_3)$-C_0-C_3alkyl-, -C_0-C_6alkyl-$N(R_3)$-$S(O)_2$-C_0-C_3alkyl-, -heterocyclyl-C(O)-C_0-C_3alkyl-, -C_0-C_6alkyl-$N(R_3)$-C(O)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-$N(R_3)$-C_0-C_3alkyl-, covalent bond, -C_0-C_6alkyl-$N(R_3)$-C_0-C_3alkyl-, -C_0-C_6alkyl-, -$S(O)_2$-$N(R_3)$-C_0-C_3alkyl-aryl-C_0-C_3alkyl-C(O)-$N(R_3)$-C_1-C_3alkyl-, -C_0-C_6alkyl-$S(O)_2$-C_0-C_3alkyl-, -C_0-C_3alkyl-$S(O)_2$-$N(R_3)$-C_0-C_3alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-O-C(O)-$N(R_3)$-C_0-C_3alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-C(O)-$N(R_3)$-C_0-C_3alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-$N(R_3)$-C(O)-O-heterocyclyl-C_0-C_3alky- and -C_0-C_6alkyl-C(O)-$N(R_3)$-C(O)-C_0-C_3alkyl-, wherein the alkyl, heterocyclyl and aryl are each independently optionally substituted; and
Y is selected from the group consisting of aryl-aryl, aryl, heterocyclyl-aryl, heteroaryl, heteroaryl-aryl, heterocyclyl, alkylaryl, alkylheterocyclyl, aryl-alkylheterocyclyl, heterocyclyl-alkyl-aryl, alkyl, heteroaryl-heteroaryl and heterocyclyl-heteroaryl, wherein each said Y is independently optionally substituted.

59. The compound according to claim 58, wherein Q is C_1-C_6alkyl-heteroaryl, wherein said C_1-C_6alkyl is optionally substituted with -CH_2-C(O)-O-C_1-C_6alkyl.

60. The compound according to claim 1, wherein
W is nitrogen;
X is –O- or –S-;
R_1, R_2 are H;
Q is selected from the group consisting of C_0-C_6alkyl-aryl and heteroaryl, wherein said alkyl, aryl and heteroaryl are independently optionally substituted;
Y-L-Z is selected from the group consisting of aryl-C_0-C_6alkyl-C(O)-$N(R_3)$-C_1-C_7alkyl-, $(R_3)(R_{3a})$N-C_0-C_6alkyl-C(O)-$N(R_3)$-C_1-C_7alkyl-, aryl-C_0-C_6alkyl-O-C(O)-$N(R_3)$-C_1-C_7alkyl-, C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl-$N(R_3)$-C(O)-C_1-C_7alkyl-, C_1-C_7alkyl-$N(R_3)$-C(O)-C_0-C_6alkyl-, heteroaryl-C_0-C_6alkyl-C(O)-$N(R_3)$-C_1-C_7alkyl-, wherein each of said aryl, alkyl and heteroaryl are independently optionally substituted.

61. The compound according to claim 60, wherein said C_1-C_7alkyl is optionally substituted with a substituent selected from the group consisting of heteroaryl-aryl, -C(O)-

$N(R_3)$-heteroaryl, $-N(R_3)$-C(O)-O-alkenyl, heteroaryl and $-N(R_3)$-C(O)-O-C_0-C_3alkyl-aryl, and said C_0-C_3alkyl is optionally substituted with $-C(O)-N(R_3)$alkenyl.

62. The compound according to claim 1, wherein

W is nitrogen;

X is -O- or -S-;

R_1 and R_2 are H;

Q is alkyl-aryl; and

Y-L-Z is selected from the group consisting of aryl-C_0-C_3alkyl-$N(R_3)$-C(O)-C_1-C_7alkyl-, A_{2a}-aryl-C_0-C_3alkyl-$N(R_3)$-C(O)-C_1-C_7alkyl- and heteroaryl-C_0-C_3alkyl-$N(R_3)$-C(O)-C_1-C_7alkyl-, wherein said aryl and heteroaryl are each independently optionally substituted, and wherein said C_0-C_3alkyl is optionally substituted with $-C(O)-N(R_3)-C_1$-C_6alkyl-A_{1a} or $-C(O)-N(R_3)-C_0$-C_6alkyl-C(O)-A_{2a}; and

said C_1-C_7alkyl is optionally substituted with a substituent selected from the group consisting of $-N(R_3)$-C(O)-O-C_1-C_3alkyl-A_{1b}, $-N(R_3)$-C(O)-C_1-C_7alkyl-O-A_{2b}, $-N(R_3)$-C(O)-heteorcyclyl-A_{2b} and $-N(R_3)$-C(O)-C_2-C_7alkenyl-O-A_{2b}, wherein

A_{1a} and A_{1b} optionally together via a C_2-C_6alkylene, C_2-C_6alkenylene or C_2-C_6alkynylene linker, form an optionally substituted ring system; and

A_{2a} and A_{2b} together are a covalent bond and are attached to form a ring, or

Y-L-Z is B_2-B_1-$N(R_3)$-C(O)-C_1-C_7 alkyl-, wherein the C_1-C_7 alkyl is optionally substituted with $-NR_3$-B_3 and the amine of B_3 is conected with the acid of B_2 to form a peptide bond; wherein

B_1, B_2 and B_3 are each independently a natural or synthetic amino acid.

63. The compound according to claim 1, wherein

W is nitrogen;

X is –O-;

R_1 and R_2 are H;

Q is optionally substituted alkyl-aryl;

Z is optionally substituted C_1-C_8alkyl;

L is selected from the group consisting of $-C_0$-C_3alkyl-$N(R_3)$-C(O)-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-$N(R_3)$-C(S)-heterocyclyl-C_0-C_3alkyl-, -C_0-C_7alkyl-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-O-C(O)-heterocyclyl-C_0-C_3alkyl-, C_0-C_3alkyl-$S(O)_2$-heterocyclyl-C_0-C_3alkyl- and -C_0-C_3alkyl-C(O)-heterocyclyl-C_0-C_3alkyl, wherein said alkyl and heterocyclyl are independently optionally subsituted; and

Y is selected from the group consisting of heteroaryl, aryl, cycloalkyl and heteroaryl-aryl, each of which is optionally substituted.

64. The compound according to claim 1, wherein

W is nitrogen;

X is -O-;

R_1 and R_2 are H;

Q is optionally substituted alkyl-aryl;

Z is optionally substituted $-C_0$-C_6alkyl-heteroaryl-C_0-C_6alkyl and optionally substituted C_1-C_8alkyl;

L is selected from the group consisting of $-C_0$-C_6alkyl-$S(O)_2$-heterocyclyl-C_0-C_3alkyl, covalent bond, -C_0-C_6alkyl- , -C_0-C_6alkyl-O-C(O)-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-O-, -C_0-C_6alkyl-N(R_3)-C(O)-heterocyclyl-C_0-C_3alkyl-, -C_0-C_3alkyl-heteroaryl-C_0-C_3alkyl-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-N(R_3)-C(O)-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-$S(O)_2$-N(R_3)-C_0-C_3alkyl-, -C_0-C_6alkyl-C(O)-N(R_3)-C(O)-N(R_3)-C_0-C_6alkyl- and -C_0-C_6alkyl-$S(O)_2$-C_0-C_3alkyl, wherein the alkyl, heterocyclyl, heteroaryl are independently optionally substituted; and

Y is selected from the group consisting of aryl, alkylaryl, heteroaryl, aryl-heterocyclyl, aryl-heteroaryl, alkyl and heterocyclyl, each of which is independently optionally substituted.

65. The compound according to claim 1, wherein

W is nitrogen;

X is -O-;

R_1 and R_2 are H;

Q is optionally substituted alkyl-aryl;

Z is selected from the group consisting of -C_0-C_6alkyl-aryl-C_0-C_6alkyl-, -C_0-C_6alkyl-aryl-C_0-C_3alkyl-X-C_0-C_3alkyl-, -C_0-C_6alkyl-aryl-C_3-C_6alkenyl-C_0-C_3alkyl and $-C_0$-C_6alkyl-aryl-C_3-C_6alkynyl-C_0-C_3alkyl, wherein the alkyl, aryl and alkynyl are each independently optionally substituted;

L is selected from the group consisting of -C_0-C_3alkyl-N(R_3)-C_0-C_3alkyl, $-C_0$-C_3alkyl-heterocyclyl-C_0-C_3alkyl-O-C_0-C_3alkyl-, -C_0-C_6alkyl-$S(O)_2$-N(R_3)-C_0-C_6alkyl-, -C_0-C_6alkyl-O-C(O)-, -C_0-C_6alkyl-C(O)-N(R_3)-$S(O)_2$-C_0-C_3alkyl- and $-C_0$-C_6alkyl-N(R_3)-$S(O)_2$-C_0-C_3alkyl, wherein said alkyl and heterocyclyl are each independently optionally substituted; and

Y is selected from the group consisting of heteroaryl, aryl, heteroaryl-hetercyclyl, alkyl, aryl-heterocyclyl and cycloalky, each of which is independently optionally substituted.

66. The compound according to claim 1, wherein

W is nitrogen;

X is -O-;

R_1 and R_2 are H;

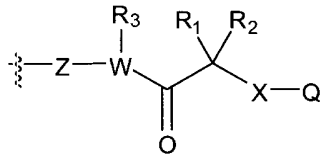
Q is optionally substituted alkyl-aryl;

Z is optionally substituted C_1-C_6alkyl;

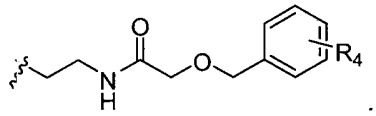
L is $-C_0$-C_3alkyl-N(R_3)-C(O)-C_0-C_3alkyl-heterocyclyl-C(O)-C_0-C_3alkyl, wherein the alkyl and heterocyclyl are independently optionally substituted; and

Y is selected from the group consisting of aryl-aryl, alkyl-heteroaryl, aryl and heteroaryl, each of which is independently optionally substituted.

67. The compound according to claim 1, wherein



is the structure



68. A compound according to claim 1 that is selected from the group consisting of

2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)acetic acid,

N-(biphenyl-3-yl)-6-(2-(4-(methylthio)benzylthio)acetamido)hexanamide,

methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-hydroxypropanoate,

methyl 4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)butanoate,

methyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)acetate,

(S)-tert-butyl 6-(2-(benzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate;

N-(biphenyl-3-yl)-6-(2-(2-oxo-2-(phenylamino)ethylthio)acetamido)hexanamide,

2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)acetic acid,

methyl 2-(2-(2-(biphenyl-3-ylamino)-2-oxoethylamino)-2-oxoethylsulfonyl)acetate,

6-(2-(2-aminoethoxy)acetamido)-N-(biphenyl-3-yl)hexanamide,

N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)ethanethioamido)hexanamide,

4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)benzoic acid,

N-(biphenyl-3-yl)-6-(2-(4-(hydroxymethyl)benzyloxy)acetamido)hexanamide,

N-(biphenyl-3-yl)-6-(2-(4-cyanobenzyloxy)-acetamido)-hexanamide,

N-(biphenyl-3-yl)-6-(2-(4-methylbenzyloxy)-acetamido)-hexanamide,

N-(biphenyl-3-yl)-6-(2-(thiophen-2-ylmethoxy)-acetamido)-hexanamide,

N-(biphenyl-3-yl)-6-(2-(thiophen-3-ylmethoxy)-acetamido)-hexanamide,

N-(biphenyl-3-yl)-6-(2-(furan-3-ylmethoxy)-acetamido)-hexanamide,

N-(biphenyl-3-yl)-6-(2-(4-bromobenzyloxy)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(naphthalen-1-ylmethoxy)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(2-oxo-2-(phenylamino)-ethylsulfinyl)-acetamido)-hexanamide,
3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoic acid,
methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-propanoate,
N-(biphenyl-3-yl)-6-(2-(3-hydroxypropylthio)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(2-hydroxyethylthio)-acetamido)-hexanamide,
6-(2-(2-amino-2-oxoethylthio)-acetamido)-N-(biphenyl-3-yl)hexanamide,
(R)-ethyl 2-amino-3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoate,
(R)-2-amino-3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-propanoic acid,
6-(2-(2-aminoethylthio)-acetamido)-N-(biphenyl-3-yl)hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-hydroxyphenylthio)-acetamido)-hexanamide,
methyl 2-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-acetate,
N-(biphenyl-3-yl)-6-(2-(3-oxo-3-(phenylamino)-propylthio)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(3-oxo-3-(phenylamino)-propylsulfinyl)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(3-hydroxyphenylthio)-acetamido)-hexanamide,
6-(2-(4-aminophenylthio)-acetamido)-N-(biphenyl-3-yl)hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-fluorophenylthio)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(phenylthio)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-chlorophenylthio)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-bromophenylthio)-acetamido)-hexanamide,
6-(2-(3-aminophenylthio)-acetamido)-N-(biphenyl-3-yl)hexanamide,
N-(biphenyl-3-yl)-6-(2-(pyridin-4-ylthio)acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(thiophen-2-ylthio)acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-(methylthio)benzyloxy)acetamido)hexanamide),
N-(biphenyl-3-yl)-6-(2-(naphthalen-2-ylmethoxy)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyloxy)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-chlorobenzyloxy)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(pyridin-4-ylmethoxy)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(pyridin-3-ylmethoxy)-acetamido)-hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-(methylsulfinyl)-benzyloxy)-acetamido)-hexanamide,
6-(2-(benzylthio)acetamido)-N-(biphenyl-3-yl)hexanamide,
6-(2-(benzylsulfinyl)acetamido)-N-(biphenyl-3-yl)hexanamide,
N-(biphenyl-3-yl)-6-(4-(thiophen-2-yl)butanamido)-hexanamide,
N-(biphenyl-3-yl)-6-(3-(4-fluorobenzylthio)propanamido)hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyl-thio)acetamido)-hexanamide,

N-(biphenyl-3-yl)-6-(2-(4-fluorobenzyl-sulfinyl)-acetamido)-hexanamide,
2-(3-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-3-oxopropylthio)-acetic acid,
2-(3-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-3-oxopropyl-sulfinyl)acetic acid,
6-(2-(benzyloxy)acetamido)-N-(biphenyl-3-yl)hexanamide,
(S)-2-amino-6-(2-(benzyloxy)acetamido)hexanoic acid,
(S)-benzyl 6-(2-(benzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate,
(S)-2-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)ethylthio)acetic acid,
N-(biphenyl-3-yl)-6-(2-(2-(pyridin-2-yl)ethylthio)acetamido)hexanamide,
N-(biphenyl-3-yl)-6-(2-(2-(diethylamino)ethylthio)acetamido)hexanamide,
4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)butanoic acid,
N-(biphenyl-3-yl)-6-(2-(4-(methylsulfinyl)benzylthio)acetamido)hexanamide,
N-(biphenyl-3-yl)-6-(2-(2-(dimethylamino)ethylthio)-acetamido)-hexanamide,
(S)-3-(2-(4-((2-benzyl-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenylamino)-2-oxoethylthio)propanoic acid,
(R)-3-(2-oxo-2-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)-phenylamino-)ethylthio)-propanoic acid,
3-(2-(6-methoxybenzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid,
4-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-hydroxy-4-oxobutanoic acid,
3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-2-hydroxypropanoic acid,
N-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)benzyl)-2-(3-hydroxypropylthio)acetamide,
(R)-N-(4-((2-((1H-indol-3-yl)methyl)-3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenyl)-2-(2-(dimethylamino)ethylthio)acetamide,
3-(2-(benzo[d]thiazol-2-ylamino)-2-oxoethylthio)propanoic acid,
3-(2-(6-fluorobenzo[d]-thiazol-2-ylamino)-2-oxoethylthio)-propanoic acid,
3-({2-[(6-nitro-1,3-benzothiazol-2-yl)amino]-2-oxoethyl}thio)propanoic acid,
3-(2-(6-nitrobenzo[d]-thiazol-2-ylamino)-2-oxoethylthio)-propanoic acid,
3-(2-oxo-2-(6-oxo-6-(3-(pyridin-3-yl)phenylamino)hexylamino)ethylthio)-propanoic acid,
N-biphenyl-3-yl-6-({[(4-fluorobenzyl)oxy]acetyl}amino)hexanamide,
2-(4-aminophenylthio)-*N*-(4-(biphenyl-4-ylsulfonamido)phenethyl)acetamide,
benzyl 4-(2-(2-(4-aminophenylthio)acetamido)ethyl)phenylcarbamate,
2-(4-aminophenylthio)-*N*-(2-(4-(biphenyl-4-ylsulfonamido)phenylthio)ethyl)acetamide,
N-(3-(4-(N-(3,4-dimethoxyphenyl)-*N*-methylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(pyridin-4-ylthio)acetamide,

2-(4-aminophenylthio)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide,
2-(4-fluorophenylthio)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide,
6-(2-(4-aminophenylthio)acetamido)-*N*-phenylhexanamid,
6-(2-(4-aminophenylthio)acetamido)-*N*-(pyridin-3-yl)hexanamide,
2-(4-aminophenylthio)-*N*-(4-(biphenyl-4-ylsulfonamido)butyl)acetamide,
2-(4-aminophenylthio)-*N*-(5-(biphenyl-4-ylsulfonamido)pentyl)acetamide,
5-(2-(4-aminobenzyloxy)acetamido)-*N*-(biphenyl-3-yl)pentanamide,
N-(biphenyl-3-yl)-5-(2-(4-fluorobenzyloxy)acetamido)pentanamide,
4-((2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethoxy)methyl)pyridine 1-oxide,
4-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfonyl)pyridine 1-oxide,
5-(2-(5-aminopyridin-2-ylthio)acetamido)-*N*-(biphenyl-3-yl)pentanamide,
6-(2-(5-aminopyridin-2-ylthio)acetamido)-*N*-(biphenyl-3-yl)hexanamide,
5-methoxy-*N*-(5-(2-(thiophen-2-ylthio)acetamido)pentyl)-1*H*-indole-2-carboxamide,
N-(5-(2-(4-aminophenylthio)acetamido)pentyl)-4-(dimethylamino)benzamide,
5-chloro-*N*-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)-1*H*-indole-2-carboxamide,
5-fluoro-*N*-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)-1*H*-indole-2-carboxamide,
(*S*)-benzyl 1-(5-(2-(4-fluorobenzyloxy)acetamido)pentylamino)-1-oxo-3-phenylpropan-2-yl(methyl)carbamate,
N-(5-(2-(4-aminophenylthio)acetamido)pentyl)-1*H*-indole-2-carboxamide,
N-(2-(5-(biphenyl-4-ylsulfonamido)-1,3,4-thiadiazol-2-ylthio)ethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(5-(3,4-dimethoxyphenylsulfonamido)-1,3,4-thiadiazol-2-ylthio)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(5-(biphenyl-4-ylsulfonamido)-1,3,4-thiadiazol-2-ylthio)butyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methoxyphenyl)pyrimidin-2-ylthio)propyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methoxyphenyl)pyrimidin-2-ylsulfinyl)propyl)acetamide,
N-(5-(5-(4-bromophenyl)-1,3,4-thiadiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(*N*-(cyclohexylcarbamoyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide,
3-(2-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propylamino)-2-oxoethylthio)propanoic,
N-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)-2-(pyridin-4-ylmethoxy)acetamide,
N-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)-2-(pyridin-4-ylthio)acetamide,
N-(3-(4-(*N*-(2-(1*H*-indol-3-yl)ethyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(*N*-(2-(1*H*-indol-3-yl)ethyl)-*N*-(2-hydroxyethyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,

N-(3-(4-(*N*-(3,4-dimethoxybenzyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(3,4-dimethoxyphenylsulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
pyridin-3-ylmethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylcarbamate,
pyridin-3-ylmethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylcarbamate,
N-(3-(4-(2-(2-(1*H*-indol-3-yl)ethylamino)ethyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
(*S*)-2-(4-fluorobenzyloxy)-*N*-(3-(4-((1-hydroxy-3-(1*H*-indol-3-yl)propan-2-ylamino)methyl)phenyl)propyl)acetamide,
(*S*)-2-(4-fluorobenzyloxy)-*N*-(3-(4-(((1-hydroxy-3-(1*H*-indol-3-yl)propan-2-yl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-((2-(5-methoxy-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)acetamide,
N-(3-(4-((2-(5-(benzyloxy)-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((2-(5-fluoro-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((2-(1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(((2-hydroxyethyl)(2-(5-methoxy-1H-indol-3-yl)ethyl)amino)methyl)phenyl)propyl)acetamide,
N-(3-(4-(((2-(5-(benzyloxy)-1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(5-fluoro-1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(1H-indol-3-yl)ethyl)(cyclohexyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(1H-indol-3-yl)ethyl)(tetrahydro-2H-pyran-4-yl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(1H-indol-3-yl)ethyl)(3-hydroxypropyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2,3-dihydroxypropyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((2-(benzo[d][1,3]dioxol-5-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((2-(4-benzylpiperidin-1-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(benzo[d][1,3]dioxol-5-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,

N-(3-(4-(((2-(4-benzylpiperidin-1-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((2-(1H-benzo[d]imidazol-2-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(1H-benzo[d]imidazol-2-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(((2-hydroxyethyl)(2-(1-(2-hydroxyethyl)-1H-benzo[d]imidazol-2-yl)ethyl)amino)methyl)phenyl)propyl)acetamide,
N-(3-(4-(((2-(1*H*-indol-3-yl)ethyl)(methyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((2-(benzofuran-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((2-(benzofuran-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((1*H*-indol-3-yl)methylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((((1*H*-indol-3-yl)methyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(((5-fluoro-1*H*-indol-3-yl)methylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((((5-fluoro-1*H*-indol-3-yl)methyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(biphenyl-3-yl)-6-(2,2-difluoro-2-(4-fluorophenylthio)acetamido)hexanamide,
N-(5-(4,5-diphenyl-1H-imidazol-1-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(3-(piperidin-1-ylmethyl)phenoxy)propyl)acetamide,
N-(3-(3-((4-benzylpiperidin-1-yl)methyl)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(3-((4-phenylpiperidin-1-yl)methyl)phenoxy)propyl)acetamide,
N-(3-(3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(3-((4-benzylpiperazin-1-yl)methyl)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(3-((4-benzylpiperidin-1-yl)methyl)phenoxy)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(3-((2-(1H-indol-3-yl)ethylamino)methyl)phenoxy)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(6-(bis(pyridin-3-ylmethyl)amino)benzo[d]thiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(6-(3,4-dimethoxyphenylsulfonamido)benzo[d]thiazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(3-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,

(E)-2-(4-chlorobenzyloxy)-N-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)allyl)acetamide,
2-(4-chlorobenzyloxy)-N-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)acetamide,
N-(biphenyl-3-yl)-6-(2-(2-hydroxy-1-phenylethylthio)acetamido)hexanamide,
N-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzyl)-2-(phenylmethylsulfonamido)benzamide,
N-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3,4-dimethoxyphenyl)-4-(3-(1-oxoisoindolin-2-yl)propyl)benzenesulfonamide,
N-(biphenyl-3-yl)-6-(2-(2-cyanoethylthio)acetamido)hexanamide,
2-(4-aminophenylthio)-*N*-(5-(5-(4-(pyridin-3-yl)phenyl)oxazol-2-yl)pentyl)acetamide,
2-(4-fluorophenylthio)-*N*-(5-(2-phenylthiazol-4-yl)pentyl)acetamide,
2-(4-fluorophenylthio)-*N*-(5-(2-(pyridin-3-yl)thiazol-4-yl)pentyl)acetamide,
2-(4-fluorophenylthio)-*N*-(5-(2-(pyridin-3-yl)thiazol-4-yl)pentyl)acetamide,
(S)-*N*-(5-(2-(4-fluorobenzyloxy)acetamido)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)nicotinamide,
(*S*)-2-(dimethylamino)-*N*-(5-(2-(4-fluorobenzyloxy)acetamido)-1-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)acetamide,
(*S*)-benzyl 6-(2-(4-aminobenzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate,
(R)-benzyl 6-(2-(4-aminobenzyloxy)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate,
allyl (*S*)-1-((S)-1-(allylamino)-3-(1-methyl-1H-indol-3-yl)-1-oxopropan-2-ylamino)-6-(2-(4-aminophenylthio)acetamido)-1-oxohexan-2-ylcarbamate,
N-(4-((4S,7R,E)-7-benzyl-2,5,8-trioxo-1-oxa-3,6,9-triazacyclotetradec-12-en-4-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
(S)-N-(4-(2,5-dioxo-1,2,3,4,5,6,7,8,9,10-decahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-((2-(5-sulfamoyl-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)acetamide,
N-(3-(4-(((2-(7-fluoro-1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
(S)-tert-butyl 4-(2-(5-(1H-benzo[d]imidazol-2-yl)-5-(4-fluorobenzamido)pentylamino)-2-oxoethylthio)phenylcarbamate,
(S)-N-(5-acetamido-5-(1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorophenylthio)acetamide,
(R)-N-(1-(1H-benzo[d]imidazol-2-yl)-5-(2-(4-fluorophenylthio)acetamido)pentyl)-4-fluorobenzamide,

(S)-N-(1-(5-chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)-5-(2-(4-fluorophenylthio)acetamido)pentyl)-4-fluorobenzamide,
(S)-N-(5-(2-(4-aminophenylthio)acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)nicotinamide,
(S)-N-(5-(2-(4-aminophenylthio)acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)benzamide,
(S)-N-(5-(2-(4-aminophenylthio)acetamido)-1-(1H-benzo[d]imidazol-2-yl)pentyl)-4-(dimethylamino)benzamide,
N-(5-(1-(3,4-dimethoxyphenethyl)-1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(1-methyl-1H-benzo[d]imidazol-2-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-N-(4-(1-phenyl-1H-benzo[d]imidazol-2-yl)butyl)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(1-(4-sulfamoylphenethyl)-1H-benzo[d]imidazol-2-yl)pentyl)acetamide,
N-(5-(1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
(S)-N-(2-(1H-indol-3-yl)ethyl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxamide,
(S)-N-(biphenyl-4-ylmethyl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxamide,
(S)-N-(biphenyl-4-yl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxamide,
(S)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)-N-(pyridin-3-ylmethyl)pyrrolidine-2-carboxamide,
(S)-N-(2-aminophenyl)-1-(6-(2-(4-fluorobenzyloxy)acetamido)hexanoyl)pyrrolidine-2-carboxamide,
(S)-N-(6-(2-(1H-benzo[d]imidazol-2-yl)pyrrolidin-1-yl)-6-oxohexyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(4-((2S,5S)-5-((1-methyl-1H-indol-3-yl)methyl)-3,6,12-trioxo-1,4,7-triazacyclododecan-2-yl)butyl)acetamide,
N-(4-((3S,6R,9S,14aR)-9-sec-butyl-1,4,7,10-tetraoxo-6-(4-(trifluoromethyl)benzyl)-tetradecahydropyrrolo[1,2-a][1,4,7,10]tetraazacyclododecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(4-(pyridin-3-yl)-1*H*-1,2,3-triazol-1-yl)pentyl)acetamide,
N-(4-(3,4-dimethoxyphenylsulfonamido)phenethyl)-2-(4-fluorophenylthio)acetamide,
2-(4-aminophenylthio)-N-(4-(3,4-dimethoxyphenylsulfonamido)phenethyl)acetamide,
2-(4-aminobenzyloxy)-*N*-(4-(3,4-dimethoxyphenylsulfonamido)phenethyl)acetamide,
(R)-2-(5-aminopyridin-2-ylthio)-N-(4-((3-oxo-2-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-1(2H)-yl)methyl)phenyl)acetamide,

N-(2-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenoxy)ethyl)-2-(4-fluorobenzyloxy)acetamide,
2-((2-(1H-indol-3-yl)ethyl)(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethoxy)benzyl)amino)acetic acid,
N-(3-(4-((4-(1H-indol-3-yl)piperidin-1-yl)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-((6-methoxy-3,4-dihydro-1H-pyrido[3,4-b]indol-2(9H)-yl)methyl)phenyl)propyl)acetamide,
6-(2-(4-aminobenzyloxy)acetamido)-*N*-(pyridin-3-yl)hexanamide,
N-(biphenyl-3-yl)-6-(2-(4-(hydroxymethyl)phenylthio)acetamido)hexanamide,
2-(4-fluorobenzyloxy)-*N*-(6-(4-(4-methoxyphenyl)piperazin-1-yl)-6-oxohexyl)acetamide,
N-(biphenyl-3-yl)-6-(2-(furan-2-ylmethylthio)acetamido)hexanamide,
N-(biphenyl-3-yl)-6-(2-(furan-2-ylmethylsulfinyl)acetamido)hexanamide,
2-(4-fluorobenzyloxy)-*N*-(2-(pyridin-3-yl)ethyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(2-(4-(4-methoxyphenyl)pyrimidin-2-ylthio)ethyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(2-(4-(thiophen-2-yl)pyrimidin-2-ylthio)ethyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(2-(4-(4-methoxyphenyl)pyrimidin-2-ylsulfinyl)ethyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(4-(4-(4-methoxyphenyl)pyrimidin-2-ylthio)butyl)acetamide,
8-(2-(2-aminophenyl)hydrazinyl)-*N*-(biphenyl-3-yl)-8-oxooctanamide,
N-(biphenyl-3-yl)-8-oxo-8-(2-phenylhydrazinyl)octanamide,
6-(2-(allyloxy)acetamido)-*N*-(biphenyl-3-yl)hexanamide,
methyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-3-phenylpropanoate,
ethyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylthio)-3-phenylpropanoate,
ethyl 3-(2-(6-(biphenyl-3-ylamino)-6-oxohexylamino)-2-oxoethylsulfinyl)-3-phenylpropanoate,
ethyl 2-(2-oxo-2-(5-(5-phenyl-1,3,4-thiadiazol-2-yl)pentylamino)ethylthio)-2-phenylacetate,
ethyl 2-(2-oxo-2-(6-oxo-6-(quinolin-8-ylamino)hexylamino)ethylthio)-2-phenylacetate,
N-(3-(4-(3,4-dimethoxybenzylsulfonyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
ethyl 2-(2-(3-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propylamino)-2-oxoethylthio)-2-phenylacetate,
ethyl 2-(2-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propylamino)-2-oxoethylthio)-2-phenylacetate,
N-(3-(4-(*N*-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)propyl)benzofuran-2-carboxamide,
N-(3-(3-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-aminophenylthio)-*N*-(5-(5-phenylthiazol-2-yl)pentyl)acetamide,
2-(4-aminophenylthio)-*N*-(5-(5-(4-methoxyphenyl)thiazol-2-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(5-phenyl-1,3,4-thiadiazol-2-yl)pentyl)acetamide,

N-(4-(5-(3,4-dimethoxyphenylsulfonamido)-1,3,4-thiadiazol-2-ylthio)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(3-((3-(3,4-dimethoxyphenylsulfonamido)pyrrolidin-1-yl)methyl)phenoxy)butyl)-2-(4-fluorobenzyloxy)acetamide,
pyridin-3-ylmethyl 1-(3-(4-(2-(4-fluorobenzyloxy)acetamido)butoxy)benzyl)pyrrolidin-3-ylcarbamate,
N-(1-(3-(4-(2-(4-fluorobenzyloxy)acetamido)butoxy)benzyl)pyrrolidin-3-yl)isonicotinamide,
1-(3-(4-(2-(4-fluorobenzyloxy)acetamido)butoxy)benzyl)pyrrolidin-3-yl pyridin-3-ylmethylcarbamate,
(*E*)-*N*-(3-(4-(((2-(1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenyl)allyl)-2-(4-fluorobenzyloxy)acetamide,
(S)-benzyl 1-oxo-6-(2-(pyridin-4-ylthio)acetamido)-1-(quinolin-8-ylamino)hexan-2-ylcarbamate,
(R)-benzyl 1-oxo-6-(2-(pyridin-4-ylthio)acetamido)-1-(quinolin-8-ylamino)hexan-2-ylcarbamate,
(S)-benzyl 6-(2-(4-aminophenylthio)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate,
(R)-benzyl 6-(2-(4-aminophenylthio)acetamido)-1-oxo-1-(quinolin-8-ylamino)hexan-2-ylcarbamate,
N-(10, 11-dihydro-5*H*-dibenzo[a,a]cyclohepten-5-yl)-6-(2-(4-fluorobenzyloxy)acetamido)-hexanamide,
(S,E / Z (7:3))-N-(4-(2,5-dioxo-14-phenyl-1,2,3,4,5,6,7,10-octahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
(S)-N-(4-(2,5-dioxo-14-phenyl-1,2,3,4,5,6,7,8,9,10-decahydrobenzo[b][1,4,7]oxadiazacyclotridecin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-((3-(2-(1H-indol-3-yl)ethyl)ureido)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(1H-indol-3-yl)ethyl 4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylcarbamate,
2-(4-fluorobenzyloxy)-N-(3-(4-((2-(2-methyl-1H-indol-3-yl)ethylamino)methyl)phenyl)prop-2-ynyl)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-((2-(2-methyl-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)acetamide,
(*S*)-N-(1-(5-chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)-5-(2-(4-fluorophenylthio)acetamido)pentyl)-4-fluorobenzamide,
N-(5-(1H-benzo[d]imidazol-2-yl)pentyl)-2-(4-fluorophenylthio)acetamide,
N,*N*-bis(2-(1H-indazol-5-ylamino)-2-oxoethyl)-6-(2-(4-fluorobenzyloxy)acetamido)hexanamide,

N,*N*-bis(2-(1H-indazol-5-ylamino)-2-oxoethyl)-5-(2-(4-fluorobenzyloxy)acetamido)pentanamide,
N-(4-(1-benzhydrylazetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(1-(3,4-dimethoxyphenylsulfonyl)azetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
tert-butyl 3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)azetidine-1-carboxylate,
N-(2-(1H-indol-3-yl)ethyl)-3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)azetidine-1-carboxamide,
3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)-N-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)azetidine-1-carboxamide,
N-(4-(1-(2-(1H-indol-3-yl)ethylcarbamothioyl)azetidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(2-(1H-indol-3-yl)ethyl)-3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)pyrrolidine-1-carboxamide ,
3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)-N-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)pyrrolidine-1-carboxamide,
2-(1H-indol-3-yl)ethyl 3-(4-(2-(4-fluorobenzyloxy)acetamido)butyl)pyrrolidine-1-carboxylate,
N-(4-(1-((1H-indol-3-yl)methyl)pyrrolidin-3-yl)butyl)-2-(4-fluorobenzyloxy)-acetamide,
2-(4-fluorobenzyloxy)-N-(4-(1-((5-methoxy-1H-indol-2-yl)methyl)pyrrolidin-3-yl)butyl)acetamide,
N-(4-(1-((5-fluoro-1H-indol-2-yl)methyl)pyrrolidin-3-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(1-(3,4-dimethoxyphenylsulfonyl)pyrrolidin-3-yl)propyl)-2-(4-fluorobenzyloxy)acetamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(3,4-dimethoxyphenyl)piperidine-1-carboxamide,
N-(2-(1H-indol-3-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide,
N-cyclohexyl-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(quinolin-8-yl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(4-(dimethylamino)phenyl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(1-methyl-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxamide,
(S)-methyl 2-(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamido)-3-(1H-indol-3-yl)propanoate,
N-(2-(1H-benzo[d]imidazol-2-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide,

4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-((1-methyl-1H-benzo[d]imidazol-2-yl)methyl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-(2-methyl-1H-indol-3-yl)ethyl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-phenylpiperidine-1-carboxamide,
ethyl 4-(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamido)benzoate,
N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide,
N-(3,5-dimethylisoxazol-4-yl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(3-methyl-5-phenylisoxazol-4-yl)piperidine-1-carboxamide,
4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-(6-methoxy-1H-indol-3-yl)ethyl)piperidine-1-carboxamide,
N-(2-(5-fluoro-1H-indol-3-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide,
N-(3-(1H-indol-3-yl)propyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamide,
2-(1H-indol-3-yl)ethyl 4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxylate,
pyridin-3-ylmethyl 4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxylate,
N-(2-(1H-indol-2-yl)ethyl)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(2-hydroxyethyl)piperidine-1-carboxamide,
(S)-4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)-N-(1-hydroxy-3-(1H-indol-3-yl)propan-2-yl)piperidine-1-carboxamide,
4-(4-(2-(2-(4-fluorobenzyloxy)acetamido)ethyl)piperidine-1-carboxamido)benzoic acid,
N-(2-(1-(3,4-dimethoxyphenylsulfonyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(2-(1-(benzylsulfonyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide,
4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)-N-(3,4-dimethoxyphenyl)piperidine-1-carboxamide,
N-(2-(1-(2-(4-(dimethylamino)phenyl)acetyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(2-(1-(2-(1H-indol-3-yl)acetyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(2-(1-(2-(1H-indol-3-yl)ethyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(2-(1-(3-(1H-indol-3-yl)propyl)piperidin-4-yl)ethyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(2-(1-((1-methyl-1H-indol-3-yl)methyl)piperidin-4-yl)ethyl)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2-(4-methoxyphenyl)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(2-aminophenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,

N-(5-(2-benzhydrylthiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(2-(4-bromophenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(2-(4-chlorobenzyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(2-(3-bromothiophen-2-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(2-(4-(1H-pyrrol-1-yl)phenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2-phenylthiazol-4-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2-(3-hydroxyphenyl)thiazol-4-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2-(4-hydroxyphenyl)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(benzo[d][1,3]dioxol-5-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2-(4-morpholinophenyl)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(4-(1H-imidazol-1-yl)phenyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(2-(benzo[b]thiophen-3-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(5-(2-(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2'-methyl-2,4'-bithiazol-4-yl)pentyl)acetamide,
N-(5-(2-(1H-imidazol-4-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
tert-butyl (4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)methylcarbamate,
(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)methyl pivalate,
tert-butyl 4-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)piperidine-1-carboxylate,
N-(5-(2-((2-(1H-indol-3-yl)ethylamino)methyl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
4-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)-N-phenylpiperidine-1-carboxamide,
N-(3,4-dimethoxyphenyl)-4-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)piperidine-1-carboxamide,
2-(4-fluorobenzyloxy)-N-(5-(2-(1-(phenylsulfonyl)piperidin-4-yl)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(1-(3,4-dimethoxyphenylsulfonyl)piperidin-4-yl)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2-(1-(4-fluorophenylsulfonyl)piperidin-4-yl)thiazol-4-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(4-(2-hydroxyphenyl)thiazol-2-ylamino)pentyl)acetamide,
2-(4-fluorobenzyloxy)-N-(6-(4-(2-hydroxyphenyl)thiazol-2-ylamino)hexyl)acetamide,
N-(5-(2-aminothiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(2-(phenylsulfonamido)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(3,4-dimethoxyphenylsulfonamido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,

N-(5-(2-(3,5-dimethylisoxazole-4-sulfonamido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(phenylmethylsulfonamido)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(1,2-dimethyl-1H-imidazole-4-sulfonamido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-(1-(2,2,2-trifluoroacetyl)piperidin-4-yl)ureido)thiazol-4-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-phenylureido)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(3-(3,4-dimethoxyphenyl)ureido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-ylcarbamoyl)benzamide,
N-(5-(2-(3-(3,5-dimethylisoxazol-4-yl)ureido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
methyl 3-(3-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)ureido)benzoate,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-propylureido)thiazol-4-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-p-tolylureido)thiazol-4-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-(3-methoxyphenyl)ureido)thiazol-4-yl)pentyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-(4-fluorophenyl)ureido)thiazol-4-yl)pentyl)acetamide,
N-(5-(2-(3-benzylureido)thiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(5-(2-(3-piperidin-4-ylureido)thiazol-4-yl)pentyl)acetamide hydrochloride,
N-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)benzo[d][1,3]dioxole-5-carboxamide,
N-(5-(2-acetamidothiazol-4-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(5-(2-(4-fluorobenzyloxy)acetamido)-pentyl)thiazol-2-yl)-3,4-dimethoxybenzamide,
N-(4-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)thiazol-2-yl)benzamide,
Phenyl 4-(5-(2-(4-fluorobenzyloxy)acetamido)-pentyl)thiazol-2-ylcarbamate,
2-(4-fluorobenzyloxy)-N-(5-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)pentyl)acetamide,
N-(5-(3-(4-fluoro-3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(5-(3-(3,4,5-trimethoxyphenyl)-1,2,4-oxadiazol-5-yl)pentyl)acetamide,
benzyl (5-(5-(2-(4-fluorobenzyloxy)acetamido)pentyl)-1,2,4-oxadiazol-3-yl)methylcarbamate,
N-(5-(3-(4-(dimethylamino)phenyl)-1,2,4-oxadiazol-5-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(6-(3,4-dimethoxyphenylsulfonamido)pyridin-3-yl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(3-methoxyphenylsulfonamido)phenyl)propyl)acetamide,

2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methoxyphenylsulfonamido)phenyl)propyl)acetamide,
N-(3-(4-(2-acetamido-4-methylthiazole-5-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(6-morpholinopyridine-3-sulfonamido)phenyl)propyl)acetamide,
N-(3-(4-(benzo[d][1,3]dioxole-5-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)-acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(phenylmethylsulfonamido)phenyl)propyl)acetamide,
N-(3-(4-(3,5-dimethylisoxazole-4-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(3,4-dimethoxyphenylsulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamido)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-sulfonamido)phenyl)propyl)acetamide,
2-(4-fluorobenzyloxy)-*N*-(3-(4-(phenylsulfonamido)phenyl)propyl)acetamide,
(R)-tert-butyl 3-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenoxy)pyrrolidine-1-carboxylate,
(S)-tert-butyl 3-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenoxy)pyrrolidine-1-carboxylate,
R)-*N*-(3-(4-(1-((1H-indol-3-yl)methyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
(S)-N-(3-(4-(1-((1H-indol-3-yl)methyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
(*R*)-*N*-(3-(4-(1-(2-(1H-indol-3-yl)ethyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
(S)-*N*-(3-(4-(1-(2-(1H-indol-3-yl)ethyl)pyrrolidin-3-yloxy)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)phenylsulfonyl)-3,4-dimethoxybenzamide,
N-(3-(4-(3,4-dimethoxyphenylsulfonamido)phenoxy)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(4-(3,4-dimethoxyphenylsulfonamido)phenoxy)butyl)-2-(4-fluorobenzy-loxy)acetamide,
6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-2-yl)hexanamide,
6-(2-(4-aminophenylthio)acetamido)-*N*-(4-phenoxyphenyl)hexanamide,
6-(2-(4-aminophenylthio)acetamido)-*N*-(4-(4-chlorophenyl)thiazol-2-yl)hexanamide,
6-(2-(4-aminophenylthio)acetamido)-*N*-(naphthalen-2-yl)hexanamide,
6-(2-(4-aminophenylthio)acetamido)-N-(biphenyl-4-ylmethyl)hexanamide,
6-(2-(4-aminophenylthio)acetamido)-*N*-(benzo[d]thiazol-6-yl)hexanamide,
6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-3-yl)hexanamide dihydrochloride,

6-(2-(4-aminophenylthio)acetamido)-*N*-(4-phenylthiazol-2-yl)hexanamide hydrochloride,
6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-8-yl)hexanamide dihydrochloride,
6*N*-((1H-benzo[d]imidazol-2-yl)methyl)-6-(2-(4-aminophenylthio)acetamido)hexanamide dihydrochloride,
6-(2-(4-aminophenylthio)acetamido)-*N*-(quinolin-6-yl)hexanamide dihydrochloride,
6-(2-(4-aminophenylthio)acetamido)-N-(benzo[d]thiazol-2-yl)hexanamide trifluoroacetic acid,
6-(2-(4-aminophenylthio)acetamido)-N-(6-methoxybenzo[d]thiazol-2-yl)hexanamide hydrochloride,
6-(2-(4-aminophenylthio)acetamido)-*N*-(4,6-difluorobenzo[d]thiazol-2-yl)hexanamide trifluoroacetic acid,
6-(2-(4-aminophenylthio)acetamido)-N-(4-(4-methoxyphenyl)thiazol-2-yl)hexanamide hydrochloride,
(6-(2-(4-fluorophenylthio)acetamido)-*N*-(4-(4-(2-morpholinoethoxy)phenyl)thiazol-2-yl)hexanamide),
N-(3-(4-(N-benzo[d][1,3]dioxol-5-ylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-phenylsulfamoyl)phenyl)propyl)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-(4-methylpiperazin-1-yl)phenyl)sulfamoyl)phenyl)propyl)acetamide,
N-(3-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-(4-methylpiperazin-1-yl)phenyl)sulfamoyl)phenyl)propyl)acetamide,
N-(3-(4-(N-(3,5-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(N-cyclohexylsulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
methyl 4-(4-(3-(2-(4-fluorobenzyloxy)acetamido)
propyl)phenylsulfonamido)
benzoate,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-hydroxy-4-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide,
N-(3-(4-(N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(N-(2,3-dimethoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)sulfamoyl)phenyl)-propyl)acetamide,

2-(4-fluorobenzyloxy)-N-(3-(4-(N-(4-hydroxy-3-methoxyphenyl)sulfamoyl)phenyl)propyl)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3,4,5-trimethoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)sulfamoyl)phenyl)prop-2-ynyl)acetamide,
2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3-hydroxy-4-methoxyphenyl)sulfamoyl)phenyl)prop-2-ynyl)acetamide,
N-(3-(4-(N-(3,5-dimethoxyphenyl)sulfamoyl)phenyl) prop-2-ynyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(N-cyclohexylsulfamoyl)phenyl)prop-2-ynyl)-2-(4-fluorobenzyl-oxy)acetamide,
(Z)-2-(4-fluorobenzyloxy)-N-(3-(4-(N-(3,4,5-trimethoxyphenyl)sulfamoyl)phenyl)allyl)acetamide,
N-(3-(4-(N-(3-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(N-(4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
N-(3-(4-(N-(4-amino-3-methoxyphenyl)sulfamoyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
(E)-N-(4-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)but-3-enyl)-2-(4-fluorobenzyloxy)acetamide,
(E)-N-(4-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)but-3-enyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(4-(N-(3,4-dimethoxyphenyl)sulfamoyl)phenyl)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(N-(3,5-dimethoxyphenyl)sulfamoyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(4-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)phenyl)butyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(4-(N-(3-fluoro-4-methoxyphenyl)sulfamoyl)phenyl)butyl)-2-(4-fluorobenzyloxy)acetamide,
2-(4-fluorobenzyloxy)-N-(4-(4-(N-(3,4,5-trimethoxyphenyl)sulfamoyl)phenyl)butyl)acetamide,
N-(5-(1-(3,4-dimethoxyphenylsulfonyl)-1H-pyrrol-3-yl)pentyl)-2-(4-fluorobenzyloxy)acetamide,
N-(4-(((2-(1*H*-indol-3-yl)ethyl)(2-hydroxyethyl)amino)methyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide,

N-(4-((2-(1*H*-indol-3-yl)ethylamino)methyl)phenethyl)-2-(4-fluorobenzyloxy)acetamide,
4-(3-(2-(4-fluorobenzyloxy)acetamido)prop-1-ynyl)benzenesulfonic acid,
N-(4-(3-(1H-benzo[d]imidazol-2-yl)azetidin-1-yl)butyl)-2-(4-fluorobenzyloxy)acetamide,
3-(2-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylamino)ethyl)-1H-indol-5-yl sulfite,
N-(3-(4-((2-(7-fluoro-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide,
3-(2-(4-(3-(2-(4-fluorobenzyloxy)acetamido)propyl)benzylamino)ethyl)-1H-indol-5-yl sulfite and
N-(3-(4-((2-(7-fluoro-1H-indol-3-yl)ethylamino)methyl)phenyl)propyl)-2-(4-fluorobenzyloxy)acetamide, or
a pharmaceutically acceptable salt thereof.

69. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

70. A method of inhibiting histone deacetylase, the method comprising contacting the histone deacetylase with an inhibiting effective amount of a compound according to claim 1.

71. A method of inhibiting histone deacetylase, the method comprising contacting the histone deacetylase with an inhibiting effective amount of a composition according to claim 69.

72. A method of inhibiting histone deacetylase in a cell, the method comprising contacting the cell with an inhibiting effective amount of compound according to claim 1.

73. A method of inhibiting histone deacetylase in a cell, the method comprising contacting the cell with an inhibiting effective amount of a composition according to claim 69.

SEQUENCE LISTING

<110> Methylgene Inc.
Leit de Moradei, Silvana Marcela
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Mancuso, John
Therrien, Eric
Allan, Martin
Chantigny, Yves Andre
Ajamian, Alain
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000483

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07D 417/04*** (2006.01) , ***A61K 31/18*** (2006.01) , ***A61K 31/166*** (2006.01) , ***A61K 31/195*** (2006.01) , ***A61K 31/34*** (2006.01) , ***A61K 31/404*** (2006.01) (more IPCs on the last page)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[8]: A61K, C07D, C07C

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

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

STN structure search (across all IPC classes), Canadian Patent Database, Delphion, Scopus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Novel Histone Deacetylase Inhibitors: Design, Synthesis, Enzyme Inhibition, and Binding Mode Study of SAHA-Based Non-hydroxamates"; *Bioorg. Med. Chem. Lett.*, (2003), vol. 13, pp. 4321-4326 (SUZUKI ET AL.)	43-48, 51, 54, 55 and 68 (in part)
X	WO 05/009392 A2 (BRISTOL-MEYERS SQUIBB COMPANY) 3 February 2005	58, 63, 65, 67 and 68 (in part)
X	WO 01/02424 A2 (DUPONT PHARMACEUTICALS COMPANY) 11 January 2001	58, 60, 61, 65, 67 and 68 (in part)
X	WO 99/15490 A1 (SMITHKLINE BEECHAM CORPORATION) 1 April 1999	58, 60, 61, 65, 67 and 68 (in part)
X	WO 98/33795 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 6 August 1998	58, 60, 61, 65, 67 and 68 (in part)
X	EP 808 838 A1 (HOECHST AKTIENGESELLSCHAFT) 26 November 1997	58, 60-62, 65, 67 and 68 (in part)

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2006 (10-08-2006)	18 August 2006 (18-08-2006)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	Ryan Jaecques (819) 953-6570

A61K 31/4184 (2006.01) , ***A61K 31/4192*** (2006.01) , ***A61K 31/426*** (2006.01) , ***A61K 31/427*** (2006.01) , ***A61K 31/433*** (2006.01) , ***A61K 31/44*** (2006.01) , ***A61K 31/4427*** (2006.01) , ***A61K 31/47*** (2006.01) , ***A61K 31/495*** (2006.01) , ***A61K 31/505*** (2006.01) , ***C07C 237/38*** (2006.01) , ***C07C 311/21*** (2006.01) , ***C07C 323/33*** (2006.01) , ***C07C 323/60*** (2006.01) , ***C07D 207/16*** (2006.01) , ***C07D 209/30*** (2006.01) , ***C07D 209/42*** (2006.01) , ***C07D 211/22*** (2006.01) , ***C07D 215/38*** (2006.01) , ***C07D 217/12*** (2006.01) , ***C07D 235/04*** (2006.01) , ***C07D 239/08*** (2006.01) , ***C07D 241/40*** (2006.01) , ***C07D 277/82*** (2006.01) , ***C07D 285/12*** (2006.01) , ***C07D 317/46*** (2006.01) , ***C07D 319/14*** (2006.01) , ***C07D 333/32*** (2006.01) , ***C07D 403/06*** (2006.01) , ***C07D 409/06*** (2006.01) , ***C07D 413/04*** (2006.01)

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 808 628 A2 (HOECHST AKTIENGESELLSCHAFT) 26 November 1997	58, 60-62, 65, 67 and 68 (in part)
X	EP 808 627 A2 (HOECHST AKTIENGESELLSCHAFT) 26 November 1997	58, 60-62, 65, 67 and 68 (in part)
X	"Proglumide Analogues: Potent Cholecystokinin Receptor Antagonists" *American Journal of Physiology* (1985), 249(2, Pt. 1), G214-G220 (JENSEN ET AL.)	58, 60, 61, 65, 67 and 68 (in part)
X	DE 2 515 091 A1 (CIBA-GEIGY AKTIENGESELLSCHAFT) 23 October 1975	58, 64, 65, 67 and 68 (in part)
X	DE 1 927 692 A (BEECHAM GROUP LTD.) 11 December 1969	58, 60, 61, 65, 67 and 68 (in part)
X	CAS RN: 796121-07-8 (Entered STN: 10 Dec 2004)	58, 64, 65, 67 and 68 (in part)
X	CAS RN: 748148-96-1 (Entered STN: 20 Sep 2004)	58, 64, 65, 67 and 68 (in part)
X	CAS RN: 722476-36-0 (Entered STN: 05 Aug 2004)	58, 64, 65, 67 and 68 (in part)
X	CAS RN: 684241-04-1 (Entered STN: 21 May 2004)	58, 65-67 and 68 (in part)
X	CAS RN: 337366-70-8 (Entered STN: 22 May 2001)	58, 65-67 and 68 (in part)
X	CAS RN: 337356-86-2 (Entered STN: 22 May 2001)	58, 65-67 and 68 (in part)
X	CAS RN: 337355-24-5 (Entered STN: 22 May 2001)	58, 65-67 and 68 (in part)
X	CAS RN: 336880-45-6 (Entered STN: 21 May 2001)	58, 65-67 and 68 (in part)
X	CAS RN: 331419-47-7 (Entered STN: 16 Apr 2001)	58, 65-67 and 68 (in part)
X	CAS RN: 57837-70-4 (Entered STN: 16 Nov 1984)	58, 64, 65, 67 and 68 (in part)
X	CAS RN: 69516-77-4 (Entered STN: 16 Nov 1984)	58, 64, 65, 67 and 68 (in part)
A	CA 2 463 552 A1 (SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH) 24 April 2004	43-48, 51, 54, 55 and 68 (in part)
A	CA 2 391 952 A1 (METHYLGENE INC.) 31 May 2001	43-48, 51, 54, 55 and 68 (in part)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000483

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [ ] Claim Nos. :
because they relate to subject matter not required to be searched by this Authority, namely :

2. [X] Claim Nos. : 1-42 and 69-73
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

see Extra Sheet

3. [ ] Claim Nos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

See Extra Sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

43-48, 51, 54, 55, 58 and 60-68 (see Extra Sheet)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest
[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
[X] No protest accompanied the payment of additional search fees.

Continuation of **Box No. II**

Claims 1-42 are directed to a vast number of different compounds and are thus so broad as to preclude any meaningful search being performed across their full scope. Claims 69-73 are directed to compositions and medical methods employing a compound of claim 1 and are thus also too broad to be searched under Article 17(2)(a) PCT.

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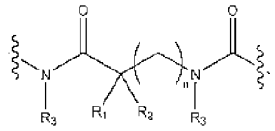
Continuation of **Box No. III**

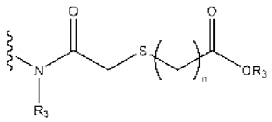
Claims 1-42 and 69-73 were excluded from the search due to the breadth of these claims precluding any reasonable search being performed. The remaining claims, claims 43-68 are directed to four separate alleged inventions. This was determined by considering the common structural elements of each of the compounds in light of the fact that the compounds of each invention must share a *significant* structural element.

Group A — comprises compounds defined in claims 43-48, 51, 54, 55 and 68 (partially) containing the structural element:



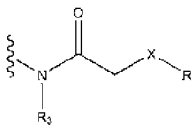
Specifically, where there is an amide group spaced apart from a second one by a hydrocarbon chain. This *bis*-amide is considered one significant structural element because any fragment smaller that this is little more than a single functional group, which is insufficient to unify the various structures.

Group B — comprises compounds defined in claims 49, 50, 52 (partially), 53 (partially), 56, 57 and 68 (partially) containing the structural element:



Specifically, where there is an amide group linked to a carboxylate group (acid or ester) via a hydrocarbon chain interrupted by a sulphur atom at the position β to the amide carbonyl. The difference between this group and Group A is that there is the presence of the Lewis basic sulphur atom and the amide has been changed to a carboxylic acid or ester. Considering the relatively small size of the structural element in these compounds, these differences are considered substantial.

Group C — comprises compounds defined in claims 58 and 60 (both partially), 61-67 and 68 (partially) containing the structural element:



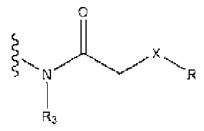
Wherein X=O, S, SO or SO_2

Specifically, where the 'R' is a hydrocarbon, alkyl-aryl etc. group such that the result is a hydrophobic carbon chain. Because 'heteroaryl' can encompass systems with a basic nitrogen group (see the exemplified compounds), these are excluded from this group. Even when X is a sulphur atom, it is clear that the 'R' would be significantly different from the $COOR_3$ group defined in **Group B**, both structurally and electronically. The common amide-β-sulphur moiety (not actually required in all the compounds of this group) is not sufficiently significant to unite these two structures, especially in light of the possible overall size of the compounds when all the variables are considered.

(Continued on Extra Sheet)

Continuation of Extra Sheet

Group D — comprises compounds defined in claims 52, 53 and 58 (each partially), 59 and 60 and 68 (both partially) containing the structural element:

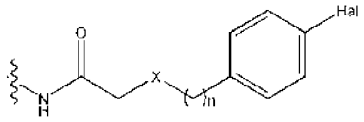


Wherein X=O, S, SO or SO_2

Specifically, where the structure is substantially the same as **Group C**, except that instead of a hydrocarbon 'R' group, there is a basic group and/or an available lone pair on a particular atom (i.e. this includes the heteroaryl, the aryl-NH_2 and the alkyl-CN groups). This difference from **Group C** and **Group D** is considered substantial because of the great electronic differences expected by changing this group.

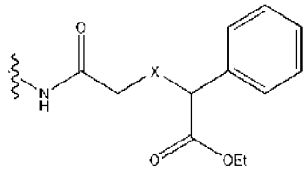
As used herein, reference to claims 58 and 60 applies only to embodiments in these claims which fall within **Group C**, and claim 68, inasmuch as it falls within **Group A** or **Group C**, since these were the groups for which an international search was established. References to claim 68 were made on the assumption that the numerous listed compounds fall within the scope of the prior art relating to the broader claims. Therefore, the *International Search Report* was based on claims 43-48, 51, 54, 55, 58 and 60-68, with the conditions discussed elsewhere being applied.

In regard to **Group C**, the claims of this group (58 and 60-68) encompass a wide range of compounds, the complete scope of which would be impossible to search across. In particular, the description indicates that the various terms in the claims (alkyl, aryl etc.) can be optionally substituted, but the scope of said substitution is very broad, with no restrictions and an extensive list of preferred substituents. Further, R_3 is not restricted in these claims, but is the broad definition provided in claim 1, and the 'left side' of the molecules of claim 67 rely on the definition of Y–L–Z in excluded claim 1. The end result is that the range of compounds encompassed by these claims is so broad that no exhaustive search could be done for these claims. Consequently, the search of the prior art was performed based on a structural feature present in the examples given in the description. In particular, the structure:



Wherein X=S or O

appears in the majority of the compounds exemplified in the description. The moiety:



Wherein X=S or SO

also appears in a few of the compounds; however, there were too many examples provided for each to be individually searched.

Because these structural motifs appear in all of the compounds exemplified, the search of claims 58 and 60-67 was restricted to compounds in which these moieties appear. The 'left side' of each molecule was tailored to be within the definition of structure Y–L–Z, as defined in claims 60-66, but not claim 58 or 67, since these claims were deemed too broad to properly search, although many of the compounds in claims 60-66 fall within their scope. Claim 68 is only relevant insofar as it defines compounds which were included in the search of the other claims included in the search of **Group A** and **Group C**.

A further restriction placed on the search was necessitated by the limitations of the structure searching software and the breadth of the claims. For claim 64, when the 'right side' of the molecule is the *para*-halogen moiety defined above and n=0, too many hits were produced, making proper citation unreasonable. Claim 65 was not able to be searched at all because of software limitations and claim breadth. Therefore, only the compounds of this claim that fall within the scope of other of the searched claims were included in the search.

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		DK808628T T3	26-06-2000
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