SUBSTITUTED PIPERIDINES THAT INCREASE p53 ACTIVITY AND THE USES THEREOF

Field of the Invention

The present invention relates to novel compounds useful as Human Double Minute 2 ("HDM2") protein inhibitors, regulators or modulators, pharmaceutical compositions containing the compounds and methods of treatment using the compounds and compositions to treat diseases such as, for example, cancer, diseases involving abnormal cell proliferation, and diseases caused by inadequate p53 levels. This invention specifically discloses substituted piperidines as inhibitors of the HDM2 protein.

Background of the Invention

The tumor suppressor protein p53 plays a central role in maintaining the integrity of the genome in a cell by regulating the expression of a diverse array of genes responsible for DNA repair, cell cycle and growth arrest, and apoptosis [May *et al.*, Oncogene 18 (53) (1999) p. 7621-7636; Oren, Cell Death Differ. 10 (4) (2003) p. 431-442 , Hall and Peters, Adv. Cancer Res., 68: (1996) p. 67-108; Hainaut et al., Nucleic Acid Res., 25: (1997) p.151-157; Sherr, Cancer Res., 60: (2000) p. 3689-95]. In response to oncogenic stress signals, the cell triggers the p53 transcription factor to activate genes implicated in the regulation cell cycle, which thereby initiates either apoptosis or cell cycle arrest. Apoptosis facilitates the elimination of damaged cells from the organism, while cell cycle arrest enables damaged cells to repair genetic damage [reviewed in Ko et al., Genes & Devel. 10: (1996) p.1054-1072; Levine, Cell 88: (1997) p. 323-331]. The loss of the safeguard functions of p53 predisposes damaged cells to progress to a cancerous state. Inactivating p53 in mice consistently leads to an unusually high rate of tumors [Donehower et al., Nature, 356: (1992) p. 215-221].

The p53 transcription factor promotes the expression of a number of cell cycle regulatory genes, including its own negative regulator, the gene encoding the Mouse Double Minute 2 (MDM2) protein [Chene, Nature Reviews Cancer 3: (2003) p. 102-109; Momand, Gene 242 (1-2): (2000) p. 15-29; Zheleva et al.

Mini. Rev. Med. Chem. 3 (3): (2003) p. 257-270]. The MDM2 protein (designated HDM2 in humans) acts to down-regulate p53 activity in an auto-regulatory manner [Wu et al, Genes Dev., 7: (1993) p. 1126-1132; Bairak et al., EMBO J, 12: (1993) p. 461-468]. In the absence of oncogenic stress signals, i.e., under normal cellular conditions, the MDM2 protein serves to maintain p53 activity at low levels [Wu et al, Genes Dev., 7: (1993) p.1126-1132; Barak et al., EMBO J, 12: (1993) p. 461-468]. However, in response to cellular DNA damage or under cellular stress, p53 activity increases helping to prevent the propagation of permanently damaged clones of cells by induction of cell cycle and growth arrest or apoptosis.

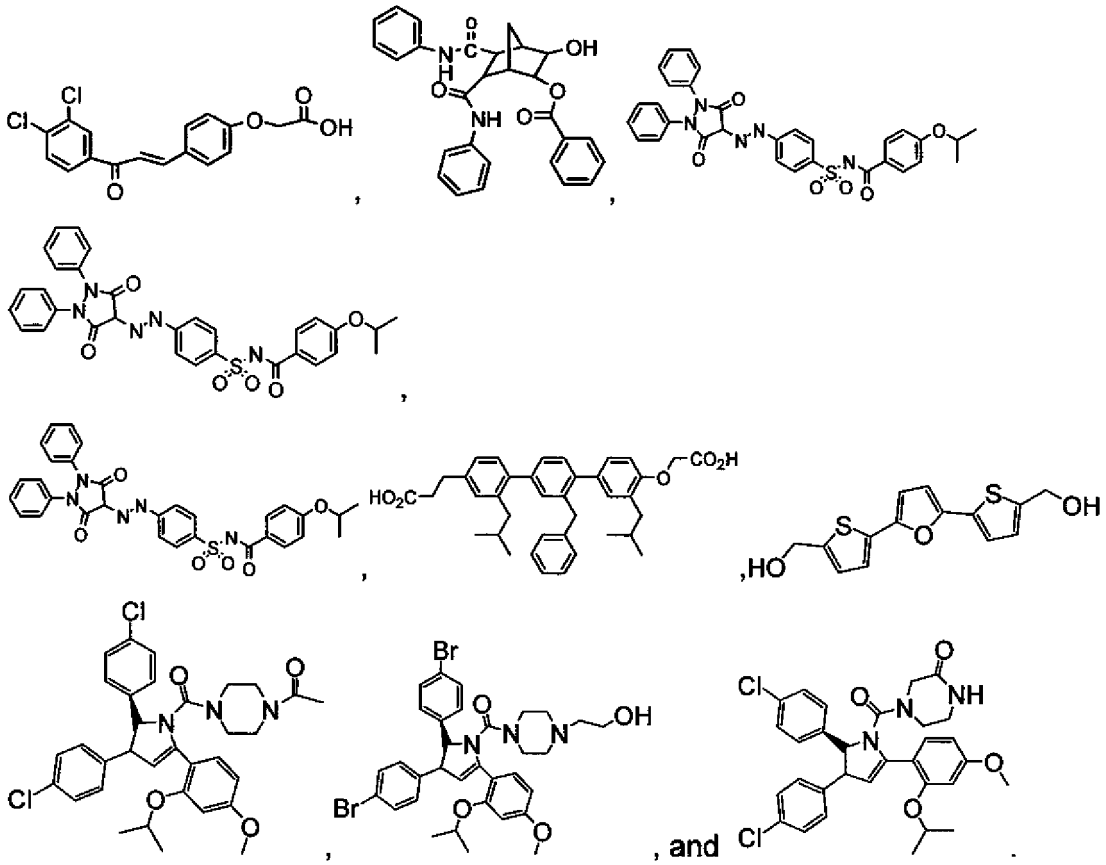
The regulation of p53 function relies on an appropriate balance between the two components of this p53-MDM2 auto-regulatory system. Indeed, this balance appears to be essential for cell survival. There are at least three ways that MDM2 acts to down-regulate p53 activity. First, MDM2 can bind to the N-terminal transcriptional activation domain of p53 to block expression of p53-responsive genes [Kussie et al., Science, 274: (1996) p. 948-953; Oliner et al., Nature, 362: (1993) p. 857-860; Momand et al, Cell, 69: (1992) p. 1237-1245]. Second, MDM2 shuttles p53 from the nucleus to the cytoplasm to facilitate the proteolytic degradation of p53 [Roth et al, EMBO J, 17: (1998) p. 554-564; Freedman et al., Mol Cell Biol, 18: (1998) p. 7288-7293; Tao and Levine, Proc. Natl. Acad. Sci. 96: (1999) p. 3077-3080]. Finally, MDM2 possesses an intrinsic E3 ligase activity for conjugating ubiquitin to p53 for degradation within the ubiquitin-dependent 26S proteosome pathway [Honda et al., FEBS Lett, 420: (1997) p. 25-27; Yasuda, Oncogene 19: (2000) p. 1473-1476]. Thus, MDM2 impedes the ability of the p53 transcription factor to promote the expression of its target genes by binding p53 in the nucleus. Attenuating the p53-MDM2 auto-regulatory system can have a critical effect on cell homeostasis. Consistently, a correlation between the overexpression of MDM2 and tumor formation has been reported [Chene, Nature 3: (2003) p. 102-109]. Functional inactivation of wild type p53 is found in many types of human tumors. Restoring the function of p53 in tumor cells by anti-MDM2 therapy would result in slowing the tumor

proliferation and instead stimulate apoptosis. Not surprisingly then, there is currently a substantial effort being made to identify new anticancer agents that hinder the ability of HDM2 to interact with p53 [Chene, Nature 3: (2003) p. 102-109]. Antibodies, peptides, and antisense oligonucleotides have been demonstrated to destroy the p53 –MDM2 interaction, which would release p53 from the negative control of MDM2, leading to activation of the p53 pathway allowing the normal signals of growth arrest and/or apoptosis to function, which offers a potential therapeutic approach to treating cancer and other diseases characterized by abnormal cell proliferation. [See, e.g., Blaydes et al., Oncogene 14: (1997) p. 1859-1868; Bottger et al., Oncogene 13 (10): (1996) p. 2141-2147].

U.S. Pub. No. 2005/0037383 A1 describes modified soluble HDM2 protein, nucleic acids that code for this HDM2 protein, the crystals of this protein that are suitable for X-ray crystallization analysis, the use of the proteins and crystals to identify, select, or design compounds that may be used as anticancer agents, and some of the compounds themselves that bind to modified HDM2. (Schering-Plough Corp.).

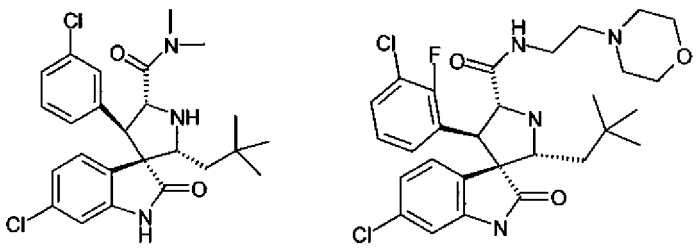
Small molecules, said to antagonize the p53-MDM2 interaction, have been described. WO 00/15657 (Zeneca Limited) describes piprizine-4-phenyl derivatives as inhibitors of the interaction between MDM2 and p53. Grasberger et al. (J. Med. Chem., 48 (2005) p. 909-912) (Johnson & Johnson Pharmaceutical Research & Development L.L. C.) describes discovery and co-crystal structure of benzodiazepinedione as HDM2 antagonists that activate p53 in cells. Galatin et al. (J. Med. Chem. 47 (2004) p. 4163-4165) describes a nonpeptidic sulfonamide inhibitor of the p53-MDM2 interaction and activator of p53 dependent transcription in MDM2-overexpressing cells.

Vassilev (J. Med. Chem. (Perspective) Vol. 48 No. 14, (2005) p. 1-8) (Hoffmann-LaRoche Inc.) describes several small molecule p53 activators as an application in oncology, including the following formulas:

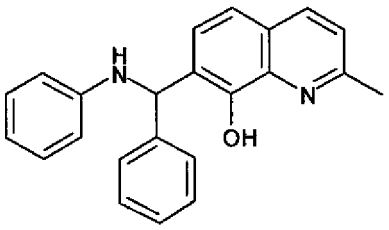


The first four compounds listed above were also described in Totouhi et al. (Current Topics in Medicinal Chemistry Vol. 3, No. 2 (2005) p. 159-166, at 161) (Hoffmann La Roche Inc.). The last three compounds listed above were also described in Vassilev et al. (Science Vol. 303 (2004): p. 844-848) (Hoffmann La Roche Inc.) and their implications on leukemia activity were investigated in Kojima et al. (Blood, , Vol. 108 No. 9 (Nov. 2005) p. 3150-3159).

Ding et. al. (J. Am. Chem. Soc. Vol. 127 (2005): 10130-10131) and (J. Med. Chem. Vol. 49 (2006): 3432-3435) describes several spiro-oxindole compounds as MDM2-p53 inhibitors.



Lu, et. al. (J. Med. Chem. Vol. 49 (2006): 3759-3762) described 7-[anilino(phenyl)methyl]-2-methyl-8-quinolinol as a small molecule inhibitor of MDM2-p53 interaction.



Chène (Molecular Cancer Research Vol. 2: (January 2006) p. 20-28) describes inhibition of the p53 –MDM2 interaction by targeting the protein-protein interface. U.S. Pub. No. 2004/0259867 A1 and 2004/0259884 A1 describes Cis-imidazoles (Hoffmann La Roche Inc.) and WO2005/110996A1 and WO 03/051359 describes Cis-Imidazolines (Hoffmann La Roche Inc.) as compounds that inhibit the interaction of MDM2 with p53-like peptides resulting in antiproliferation. WO 2004/080460 A1 describes substituted piperidine compounds as MDM2-p53 inhibitors for treating cancer (Hoffmann La Roche Inc.). EP 0947494 A1 describes phenoxy acetic acid derivatives and phenoxy methyltetrazole that act as antagonists of MDM2 and interfere with the protein-protein interaction between MDM2 and p53, which results in anti-tumor properties (Hoffmann La Roche Inc.). Duncan et al., J. Am. Chem. Soc. 123 (4): (2001) p. 554-560 describes a p-53-MDM2 antagonist, chlorofusin, from a Fusarium Sp.. Stoll et al., Biochemistry 40 (2) (2001) p. 336-344 describes chalcone derivatives that antagonize interactions between the human oncoprotein MDM2 and p53.

There is a need for effective inhibitors of the HDM2 or MDM2 protein in order to treat or prevent cancer, other disease states associated with cell proliferation, diseases associated with HDM2, or diseases caused by inadequate p53 activity. The present application discloses compounds that have potency in inhibiting or antagonizing the HDM2-p53 and MDM2-p53 interaction and/or activating p53 proteins in cells.

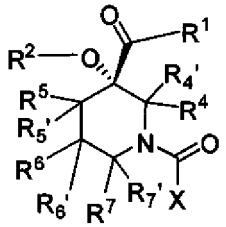
In its many embodiments, the present invention provides novel compounds having HDM2 or MDM2 antagonist activity, methods of preparing such compounds, pharmaceutical compositions comprising one or more of such compounds, methods of preparing pharmaceutical formulations comprising one or more of such compounds, methods of treatment or prevention of one or more diseases associated with HDM2, MDM2, p53, or p53 peptides by administering such compounds or pharmaceutical compositions.

WO2008/005268 (equivalent of US Patent Publication US 2008/0004287 A1) discloses substituted piperidine compounds as HDM2 inhibitors.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of substituted piperidine compounds, pharmaceutical compositions comprising one or more said compounds, and methods for using said compounds for treating or preventing a disease associated with the HDM2 protein.

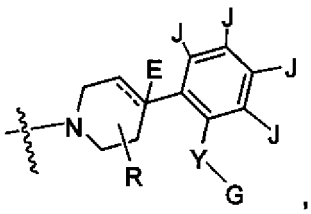
Accordingly, in one aspect the present invention provides a compound of Formula 1



Formula 1

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:



, wherein:

E is either present or absent, and when present is selected from the group consisting of H, halo, OH, CN, -O(C_1-C_6)alkyl, -(C_1-C_6)alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -(C_1-C_6)alkyl-C(O)OH, -(C_1-C_6)alkyl-OH, -(C_1-C_6)alkyl-C(O)$NR^8R^{8'}$, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, heterocyclyl, and heteroaryl;

each J independently is selected from the group consisting of H and halogen;

G, Y and R may or may not be present, wherein: when Y is not present, G is not present; when Y is present, it is selected from the group consisting of O, S, NR^8, SO_2, and $CR^8R^{8'}$;

R when present is one or more moieties independently selected from the group consisting of -(C_1-C_6)alkyl, and –$(CR^8R^{8'})_n$-C(O)OH;

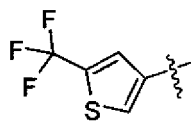
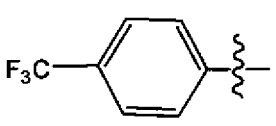
G when present is selected from the group consisting of –$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-P(O)$OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-P(O)O_2, and —$(CR^8R^{8'})_n$-OH; wherein:

each R^8 and $R^{8'}$ is independently selected from the group consisting of H, D, and (C_1-C_6)alkyl; or wherein R^8 and $R^{8'}$ together with the carbon to which each is attached form (C_3-C_8)cycloalkyl;

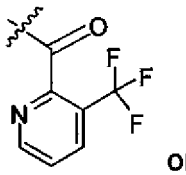
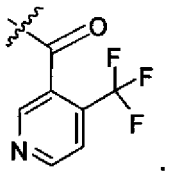
each R^9 independently is SO_2(C_1-C_6)alkyl or SO_2(C_3-C_8)cycloalkyl;

each n independently is 0-10; providing that when n is 0, any oxygen, nitrogen or sulfur atom of Y is not directly linked to any oxygen, nitrogen, sulfur or phosphorus atom of G;

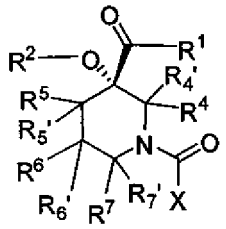
⎓ represents a single or a double bond, providing that when E is present, ⎓ represents a single bond;

R^2 is  or ;

R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, and $R^{7'}$ independently are selected from the group consisting of hydrogen and $(C_1\text{-}C_6)$alkyl; and

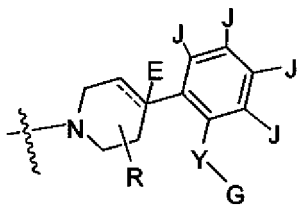
X is  or .

In another aspect, the present invention provides a compound represented by Formula 2 below:



Formula 2

wherein R^1, R^2, R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, $R^{7'}$ and X, are selected independently of each other and wherein R^1 is:



wherein E is selected from the group consisting of H, halo, OH, CN, -O-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -$(C_1\text{-}C_6)$alkyl-C(O)OH, -$(C_1\text{-}C_6)$alkyl-C(O)$NR^8R^{8'}$, -$(C_2\text{-}C_6)$alkenyl, -$(C_2\text{-}C_6)$alkynyl and heterocyclyl,

J is independently selected from the group consisting of H and halogen,

G, Y and R may or may not be present,

wherein when Y is not present, G is not present,

when Y is present it is selected from the group consisting of O,S, NR^8, SO_2, and $CR^8R^{8'}$,

further wherein, when R is present, it is one or more moieties independently selected from the group consisting of halogen, -CN, -OH, -SH, $(C_1$-$C_6)$alkoxy, -$(C_2$-$C_6)$alkenoxy, -$(C_1$-$C_6)$alkyl, -$(C_2$-$C_6)$alkenyl, haloalkoxy, -$C(O)NR^{10}R^{11}$, -$C(O)OR^{10}$, -$OC(O)R^{10}$, -$NR^{10}C(O)R^{11}$, -$NR^{10}R^{11}$, -S-alkyl, -S-alkenyl, -S-haloalkyl, $(C_2$-$C_6)$alkynyl, haloalkyl, haloalkenyl–,–$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-heteroaryl, –$(CR^8R^{8'})_n$-$C(O)NR^8R^9$, –$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$C(O)NR^8R^9$, –$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, and —$(CR^8R^{8'})_n$-OH,

G is selected from the group consisting of –$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-heteroaryl, –$(CR^8R^{8'})_n$-$C(O)NR^8R^9$, –$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$C(O)NR^8R^9$, –$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-CH_3, –$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, —$(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and $(C_1$-$C_6)$alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form $(C_3$-$C_8)$spirocycloalkyl,

R^9 is $SO_2(C_1$-$C_6)$alkyl or $SO_2(C_3$-$C_8)$cycloalkyl,

n is 0-10,

providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

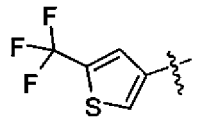
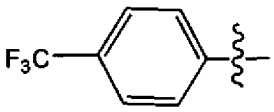
further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more $(C_1$-$C_6)$alkyl groups,

still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom,

wherein said ===== represents an optional double bond, providing that when E is present, ===== represents a single bond,

R^2 is  or ;

R^4 or $R^{4'}$, which may be the same or different, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, hydroxyalkyl, -alkylCO_2R^{12}, alkylOCOR^{12}, -alkyl$NR^{10}COR^{12}$, hydroxyalkenyl, alkoxyalkyl, alkoxyalkenyl, aminoalkyl, aminoalkenyl, alkyl$NR^{10}R^{11}$, alkenyl$NR^{10}R^{11}$, cycloalkylalkyl, cycloalkylalkenyl, cyclenylalkyl, cyclenylalkenyl, cycloalkylalkynyl, cyclenylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocylenylalkyl, heterocyclenylalkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl, wherein each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, hydroxyalkyl, -alkylCO_2R^{12}, alkylOCOR^{12}, -alkyl$NR^{10}COR^{9}$, hydroxyalkyl, hydroxyalkenyl, alkoxyalkyl, alkoxyalkenyl, aminoalkyl, aminoalkenyl, alkyl$NR^{10}R^{11}$, alkenyl$NR^{10}R^{11}$, cycloalkylalkyl, cycloalkylalkenyl, cyclenylalkyl, cyclenylalkenyl, cycloalkylalkynyl, cyclenylalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocylenylalkyl,

heterocyclenylalkenyl, arylalkyl, arylalkenyl, heteroarylalkyl, and heteroarylalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of trihaloalkyl, dihaloalkyl, monohaloalkyl, trihaloalkenyl, dihaloalkenyl, monohaloalkenyl, halogen, CN, hydroxyl, thiohydroxyl, amine, alkoxy, alkenoxy, aryloxy, cyclenyloxy, cycloalkyloxy, heteroaryloxy, heterocyclenyloxy, heterocyclyloxy, alkyl, alkenyl, trifluroalkoxy, difluroalkoxy , monofluroalkoxy, heteroalkyl, heteroalkenyl, carboxyl, -$CONR^{10}R^{11}$, -$COOR^{12}$, -$OCOR^{12}$, -$NR^{10}COR^{12}$, cycloalkyl, heterocyclyl, -$NR^{10}R^{11}$, -S-alkyl, -S-alkenyl, -S-cycloalkyl, -S-cyclenyl, -S-aryl, -S-heterocyclyl, -S-heterocyclenyl, -S-heteroaryl, -S-trifluroalkyl, -S-difluroalkyl, -S-monofluroalkyl, cyclenyl, heterocyclenyl, aryl, heteroaryl, and alkynyl;

or

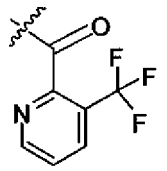
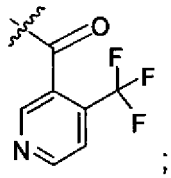
wherein R^4 and $R^{4'}$ or R^5 and $R^{5'}$ or R^6 and $R^{6'}$ or R^7 and $R^{7'}$, together with the carbon to which each is attached, independently form a spirocyclic group, wherein said spirocyclic group can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of trihaloalkyl, dihaloalkyl, monohaloalkyl, trihaloalkenyl, dihaloalkenyl, monohaloalkenyl, halogen, CN, hydroxyl, thiohydroxyl, amine, alkoxy, alkyl, alkenyl, trifluroalkoxy, difluroalkoxy , monofluroalkoxy, heteroalkyl, heteroalkenyl, carboxyl, -$CONR^{10}R^{11}$, -$COOR^{12}$, -$OCOR^{12}$, -$NR^{10}COR^{12}$, cycloalkyl, heterocyclyl, -$NR^{10}R^{11}$, alkylthio, trifluroalkylthio, difluroalkylthio, monofluroalkylthio, cyclenyl, heterocyclenyl, aryl, heteroaryl, and alkynyl;

R^5, $R^{5'}$, R^7 or $R^{7'}$, which may be the same or different, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxyl, -S-alkyl, heteroalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, alkyl$NR^{10}R^{11}$, trihaloalkyl, dihaloalkyl, monohaloalkyl, aryl, heteroaryl, cycloalkyl, cyclenyl, heterocyclyl, heterocyclenyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, cyclenylalkyl, heterocyclylalkyl, or heterocyclenylalkyl,

wherein each of said aryl, heteroaryl, cycloalkyl, cyclenyl, heterocyclyl, heterocyclenyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, cyclenylalkyl, heterocyclylalkyl, heterocyclenylalkyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of alkyl, alkenyl, hydroxyl, -SH, $-NH_2$, halogen, trifluroalkyl, difluroalkyl, and monofluroalkyl;

R^6 or $R^{6'}$, which may be the same or different, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkoxyl, trihaloalkyl, dihaloalkyl, and monohaloalky;

R^6 and R^7 or R^5 and R^6 or R^5 and R^7 together with the carbon to which each is attached, can independently cyclicize to form a fused cycloalkyl, cyclenyl, heterocyclyl, or heterocyclenyl together with the parent ring;

X is  or ;

R^{10} and R^{11}, which can be the same or different, are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, alkoxyalkyl, alkenoxyalkyl, alkynoxyalkyl, cycloalkoxyalkyl, cycloalkenoxyalkyl, aryloxyalkyl, heterocycloalkoxyalkyl, heterocycloalkenoxyalkyl, heteroaryloxyalkyl, cycloalkylalkoxyalkyl, cyclenylalkoxyalkyl, arylalkoxyalkyl, heterocyclylalkoxyalkyl, heterocyclenylalkoxyalkyl, heteroarylalkoxyalkyl, -alkyl-S-alkyl, -alkyl-S-alkenyl, -alkyl-S-alkynyl, -alkyl-S-cycloalkyl, -alkyl-S-cyclenyl, -alkyl-S-aryl, -alkyl-S-heterocyclyl, -alkyl-S-heterocyclenyl, -alkyl-S-heteroaryl, -alkyl-S-cycloalkylalkyl, -alkyl-S-cyclenylalkyl, -alkyl-S-arylalkyl, -alkyl-S-heterocyclylalkyl, -alkyl-S-heterocyclenylalkyl, -alkyl-S-heteroarylalkyl, hydroxyalkyl, hydroxyalkenyl, -alkyl-SH, -alkenyl-SH, -alkylNH_2, -alkenylNH_2, $-COR^{12}$, $-CO_2$alkyl, $-CO_2$alkenyl,-alkylN(alkoxy)$_2$, -

alkylNHalkoxy, -CONHSO$_2$alkyl, -CONHSO$_2$alkenyl, -CONalkylSO$_2$alkyl, -CONHalkyl, -CONHalkenyl, -alkylCO$_2$alkyl, -alkylCONHalkyl, -alkylCONH$_2$, -alkylCON(alkyl)$_2$, -alkylCON(alkenyl)$_2$, -alkylCO$_2$H, -alkylN(alkyl)$_2$, -alkylNHalkyl, -alkyl-NH$_2$, -alkenyl-N(alkyl)$_2$, -alkyl-N(alkenyl)$_2$, -alkyl-Nalkyl(alkenyl), -alkenyl-NH$_2$,

wherein each of said cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, cycloalkoxyalkyl, cycloalkenoxyalkyl, aryloxyalkyl, heterocycloalkoxyalkyl, heterocycloalkenoxyalkyl, heteroaryloxyalkyl, cycloalkylalkoxyalkyl, cyclenylalkoxyalkyl, arylalkoxyalkyl, heterocyclylalkoxyalkyl, heterocyclenylalkoxyalkyl, heteroarylalkoxyalkyl, can be unsubstituted or substituted with one or more moieties, which may be the same or different, each moiety being independently selected from the group consisting of alkyl, alkenyl, alkynyl, -CN, hydroxyl, -SH, -NH$_2$, -N(alkyl)$_2$, -N(alkenyl)$_2$, -N(alkoxyalkyl)$_2$, trifluroalkyl, difluroalkyl, monofluroalkyl, alkoxy, -S-alkyl, halogen, hydroxyalkyl, hydroxyalkenyl, -alkylSH, -COR^{12}, -SO$_2$R^{12}, heteroalkyl, alkoxyalkoxy, -S-alkyl-S-alkyl, -alkylNH$_2$, -alkyl-N(alkyl)$_2$, and -alkylNHalkyl,

further wherein, in any –NR^{10}R^{11} in Formula 2, said R^{10} and R^{11} can optionally be joined together with the N of said –NR^{10}R^{11} to form a cyclic ring;

R^{12} is selected from the group consisting of hydrogen, hydroxyl,-NH$_2$, -N(alkyl)$_2$, -N(alkenyl)$_2$, -NHalkyl, -NHalkenyl, -NH-alkyl-O-alkyl, -NH-alkenyl-O-alkyl, -alkyl-S-alkyl, -alkyl-O-alkyl, -alkenyl-O-alkenyl, -alkyl-O-alkenyl, -alkenyl-S-alkyl, -alkenyl-S-alkenyl, trifluroalkyl, difluroalkyl, monofluroalkyl, alkoxy, -S-alkyl, -alkyl-S-alkyl, alkoxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, heteroalkyl, heteroalkenyl, -alkylN(alkyl)$_2$, -alkylNHalkyl, -alkyl-NH$_2$, -alkenyl-N(alkyl)$_2$, -alkyl-N(alkenyl)$_2$, -alkyl-Nalkyl(alkenyl), -alkenyl-NH$_2$, hydroxyalkyl, hydroxyalkenyl, -alkyl-SH, -alkenyl-SH, -

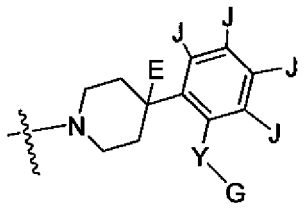
alkylCO_2H, -alkylCO_2alkyl, -alkylCONHalkyl, -alkyl$CONH_2$, -alkylCON(alkyl)$_2$, -alkylCON(alkenyl)$_2$, wherein each of said cycloalkyl, cyclenyl, aryl, heterocyclyl, heterocyclenyl, heteroaryl, cycloalkylalkyl, cyclenylalkyl, arylalkyl, heterocyclylalkyl, heterocyclenylalkyl, heteroarylalkyl, heteroalkyl, heteroalkenyl can be unsubstituted or substituted with one or more moieties, which can be the same or different, independently selected from the group consisting of alkyl, heteroalkyl, heteroalkenyl, alkenyl, alkynyl, alkoxyalkoxy, -S-alkyl-S-alkyl, hydroxyalkyl, -alkylSH, hydroxyalkenyl, -alkyl-NH_2, -alkyl-N(alkyl)$_2$, and –alkylNHalkyl.

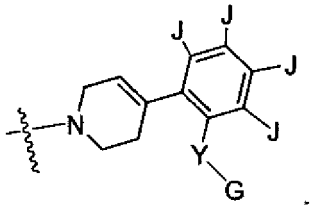
In the assay for HDM2 inhibitory activity (fluorescence polarization assay) [Zhang et al., J. Analytical Biochemistry 331: 138-146 (2004)] the compounds of the present invention exhibit FP IC_{50}, values of less than 0.5 μM. Also, the cytochrome P450 3A4 enzyme inhibition studies of the compounds of the present invention indicate that these compounds have an IC_{50} CYP3A4 (pre and co incubation) of more than 1 μM. The compounds of the present invention by themselves or in combination with one or more other suitable agents disclosed later in this application can be useful as HDM2 or MDM2 inhibitors and can be useful in the treatment and prevention of proliferative diseases such as cancers.

Such treatment or prevention can be done with the inventive compound as well as with pharmaceutical compositions or formulations comprising the compound.

Detailed description of the invention

In one embodiment, the present invention provides compounds illustrated as Formula 1, as described above, or pharmaceutically acceptable salts, solvates, esters, or prodrugs thereof, wherein the various moieties are as described above.

In another embodiment, in Formula 1, R is absent and E is present, i.e., R^1 in Formula 1 is .

In another embodiment, in Formula 1, both R and E are absent, i.e., R^1 in Formula 1 is .

In another embodiment, in Formula 1, each n independent is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

In another embodiment, in Formula 1, E is present and is selected from the group consisting of H, halo, OH, CN, -O(C_1-C_6)alkyl, (C_1-C_6)alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -(C_1-C_6)alkyl-C(O)OH, -(C_1-C_6)alkyl-OH, -(C_1-C_6)-C(O)$NR^8R^{8'}$, and heteroaryl.

In another embodiment, in Formula 1, E is present and is selected from the group consisting of H, halo, OH, CN, -O(C_1-C_6)alkyl, (C_1-C_6)alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -(C_1-C_6)alkyl-C(O)OH, -(C_1-C_6)alkyl-OH, -(C_1-C_6)-C(O)$NR^8R^{8'}$, and heteroaryl; wherein -(C_1-C_6)alkyl-OH is hydroxymethyl; said -(C_1-C_6)alkyl-C(O)$NR^8R^{8'}$ is –C(O)NH_2; said -(C_1-C_6)alkyl-C(O)OH is –$(CH_2)_4$C(O)OH; said halo is –F; said -O(C_1-C_6)alkyl is methoxy; said -(C_1-C_6)alkyl is methyl; and said heteroaryl is tetrazolyl.

In another embodiment, in Formula 1, each J independently is H or Fluoro.

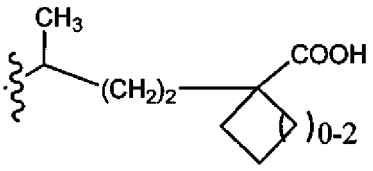
In another embodiment, in Formula 1, Y is present and is selected from the group consisting of O, S, SO_2, and $CR^8R^{8'}$.

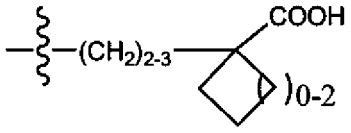
In another embodiment, in Formula 1, Y is $CR^8R^{8'}$, wherein R^8 and R^8 are both H, i.e., Y is CH_2.

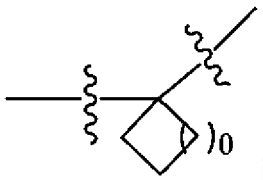
In another embodiment, in Formula 1, G is present, and is selected from the group consisting of –$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, –

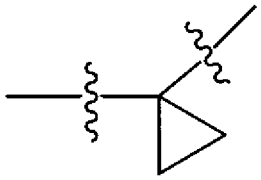
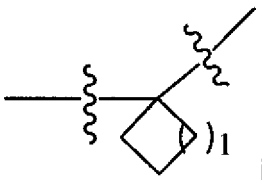
$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, and —$(CR^8R^{8'})_n$-OH.

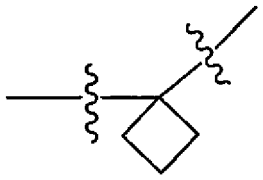
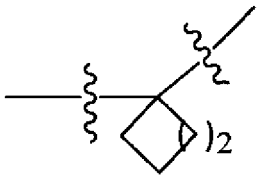
In another embodiment, in Formula 1, G is present and is –$(CR^8R^{8'})_n$-C(O)OH, wherein n is 1-6, and in one embodiment, 1, 2, 3, 4, 5, or 6.

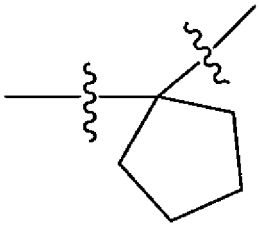
In another embodiment, in Formula 1, G is present and is –$(CR^8R^{8'})_n$-C(O)OH, which is selected from the group consisting of –$(CH_2)_{1\text{-}5}$C(O)OH, –$CH(CH_3)$-$(CH_2)_{2\text{-}3}$-C(O)OH, –$(CH_2)_{1\text{-}3}C(CH_3)_2$C(O)OH, –$(CH_2)_3CH(CH(CH_3)_2)$-C(O)OH –$(CD_2)_3$C(O)OH, –$(CH_2)_{1\text{-}2}$-$CH(CH_3)$-$(CH_2)_{1\text{-}2}$-C(O)OH, $CH(CH_3)$-$(CH_2)_2$-

$_3$-C(O)OH, 

. Here, 

is  ; 

is  ; and 

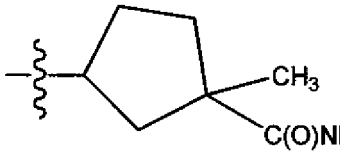
is  .

In another embodiment, in Formula 1, G is present and is –$(CR^8R^{8'})_n$-$C(O)NR^8R^9$ wherein n is 1-6, and in one embodiment, 1, 2, 3, 4, 5, or 6.

In another embodiment, in Formula 1, G is present and is –$(CR^8R^{8'})_n$-$C(O)NR^8R^9$ which is –$(CH_2)_{1\text{-}4}$-C(O)NH-$S(O)_2CH_3$ or –$(CH_2)_{3\text{-}4}$-C(O)NH-$S(O)_2$-cyclopropyl.

In another embodiment, in Formula 1, G is present and is –$(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$C(O)NR^8R^9$ wherein said $(C_3$-$C_8)$cycloalkyl is unsubstituted $(C_3$-$C_8)$cycloalkyl or $(C_3$-$C_8)$cycloalkyl that is substituted with an alkyl group. In

another embodiment, said $-(CR^8R^{8'})_n-(C_3-C_8)$cycloalkyl-$C(O)NR^8R^9$ is –

cyclopentyl-$C(O)NH-S(O)_2-CH_3$ or 

In another embodiment, in Formula 1, G is present and is $-(CR^8R^{8'})_n-(C_3-C_8)$cycloalkyl-$(CR^8R^{8'})_n-C(O)OH$ wherein each n is independently 0 or 1. In another embodiment, said $-(CR^8R^{8'})_n-(C_3-C_8)$cycloalkyl-$(CR^8R^{8'})_n-C(O)OH$ is selected from the group consisting of $-CH_2$-cyclopentyl-C(O)OH, -cyclobutyl-C(O)OH, -cyclopentyl-C(O)OH, -cyclohexyl-C(O)OH, and -cyclopentyl-CH_2-C(O)OH.

In another embodiment, in Formula 1, G is present and is $-(CR^8R^{8'})_n-O-(CR^8R^{8'})_n-(C_3-C_8)$cycloalkyl-$(CR^8R^{8'})_n-C(O)OH$ wherein each n is 0. In another embodiment, said $-(CR^8R^{8'})_n-O-(CR^8R^{8'})_n-(C_3-C_8)$cycloalkyl-$(CR^8R^{8'})_n-C(O)OH$ is –O-cyclopenyl-C(O)OH or –O-cyclobutyl-C(O)OH.

In another embodiment, in Formula 1, G is present and is $—(CR^8R^{8'})_n-O-(CR^8R^{8'})_n-C(O)OH$ wherein the first n is 0 or 1, and the second n is 3. In another embodiment, said $—(CR^8R^{8'})_n-O-(CR^8R^{8'})_n-C(O)OH$ is selected from the group consisting of $-CH_2-O-(CH_2)_3-C(O)OH$, $-O-(CH_2)_2-C(CH_3)_2-C(O)OH$, and $-O-(CH_2)_3-C(O)OH$.

In another embodiment, in Formula 1, G is present and is $—(CR^8R^{8'})_n-NH-(CR^8R^{8'})_n-C(O)OH$ wherein the first n i 0 and the second n is 3. In another embodiment, said $—(CR^8R^{8'})_n-NH-(CR^8R^{8'})_n-C(O)OH$ is $-NH(CH_2)_3C(O)OH$.

In another embodiment, in Formula 1, G is present and is $—(CR^8R^{8'})_n-O-(CR^8R^{8'})_n-CH_3$ wherein the first n is 0 and the second n i s 0. In another embodiment, said $—(CR^8R^{8'})_n-O-(CR^8R^{8'})_n-CH_3$ is $-(CH_2)_2-O-CH_3$.

In another embodiment, in Formula 1, G is present and is $—(CR^8R^{8'})_n-CH_3$ wherein n is 0. In another embodiment, said $—(CR^8R^{8'})_n-CH_3$ is $-CH_3$.

In another embodiment, in Formula 1, G is present and is $—(CR^8R^{8'})_n-$heteroaryl wherein said n is 2. In another embodiment, said heteroaryl is

pyrazolyl which is unsubstituted or substituted with an alkyl. In another embodiment, said —$(CR^8R^{8'})_n$-heteroaryl is –$(CH_2)_2$-(alkyl substituted pyrazolyl).

In another embodiment, in Formula 1, G is present and is —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$ wherein said n is 3. In another embodiment, said —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$ is –$(CH_2)_3P(O)(OH)(OH)$ or –$(CH_2)_3P(O)(OCH_3)(OCH_3)$.

In another embodiment, in Formula 1, G is present and is —$(CR^8R^{8'})_n$-OH wherein n is 2. Inother embodiment, said —$(CR^8R^{8'})_n$-OH is –$(CH_2)_2$-OH.

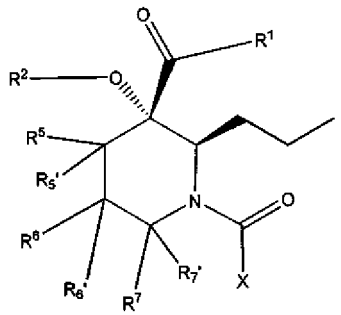
In another embodiment, in Formula 1, Y is O and G is selected from the group consisting of –$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-$C(O)NR^8R^9$, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$C(O)NR^8R^9$, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, and —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$.

In another embodiment, in Formula 1, Y is S and G is –$(CR^8R^{8'})_n$-C(O)OH or –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH.

In another embodiment, in Formula 1, Y is SO_2 and G is —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH.

In another embodiment, in Formula 1, Y is $CR^8R^{8'}$ and G is selected from the group consisting of —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-OH, —$(CR^8R^{8'})_n$-heteroaryl, and –$(CR^8R^{8'})_n$-$C(O)NR^8R^9$.

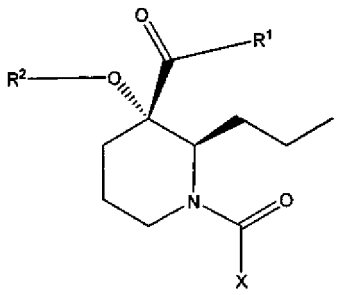
In another embodiment, in Formula 1, R^4 is hydrogen and $R^{4'}$ is 1-propyl, such that Formula 1 is represented by Formula 1A:



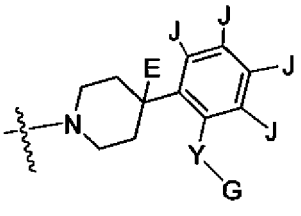
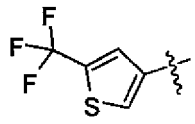
Formula 1A

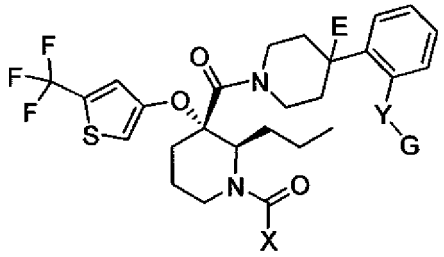
wherein R^1, R^2, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, $R^{7'}$, and X are as set forth in Formula 1.

In another embodiment, in Formula 1A, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, and $R^{7'}$ are all hydrogen, i.e., Formula 1 or 1A is represented by Formula 1B:

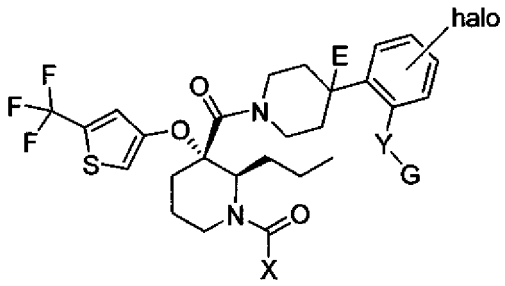


Formula 1B

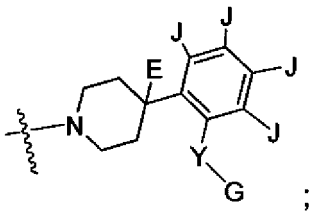
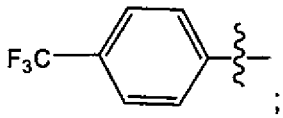
In another embodiment, in Formula 1B, R^1 is  ; R^2 is  ; and either (i) each J in R^1 is H, or (ii) one J in R^1 is halo, and the remaining three Js are H, i.e., Formula 1, 1A, or 1B is represented by Formula 1C or 1D as set forth below:

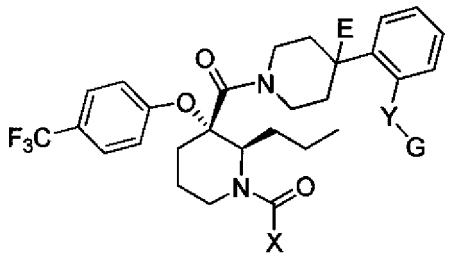


Formula 1C



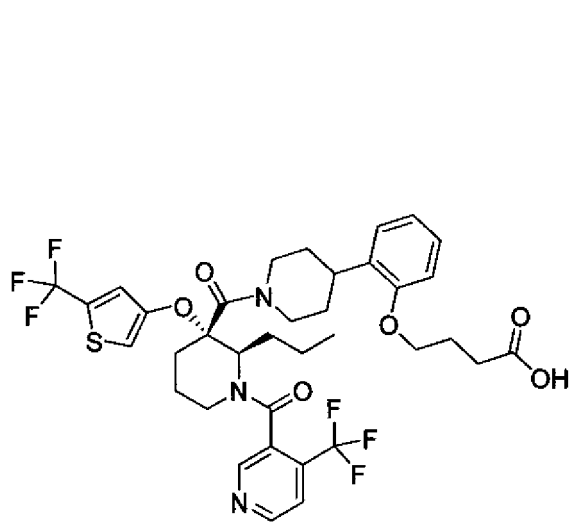
Formula 1D.

In another embodiment, in Formula 1B, R^1 is  ; R^2 is  ; and each J in R^1 is H; i.e., i.e., Formula 1, 1A, or 1B is represented by Formula 1E as set forth below:

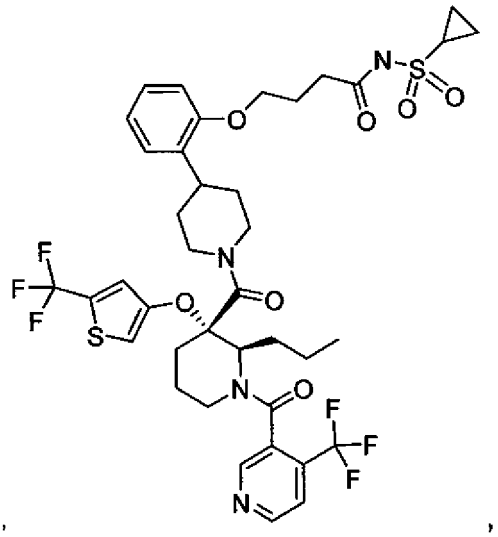


Formula 1E.

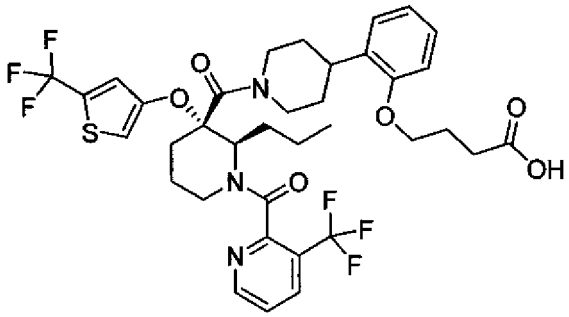
Non-limiting examples of compounds of Formula 1 include:



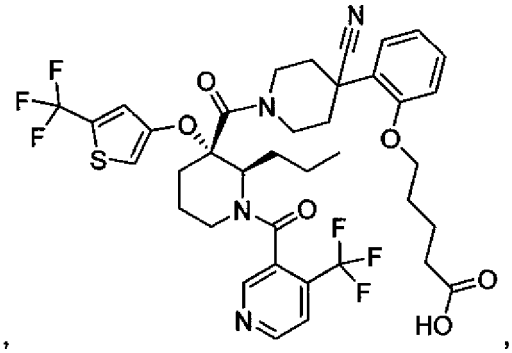
,



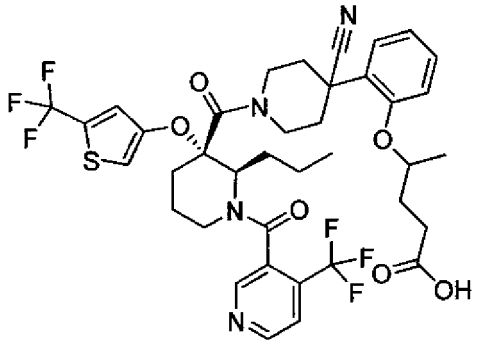
,



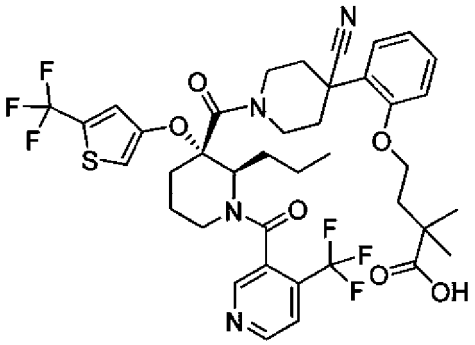
,



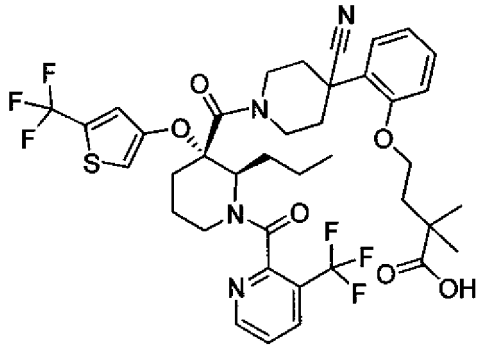
,



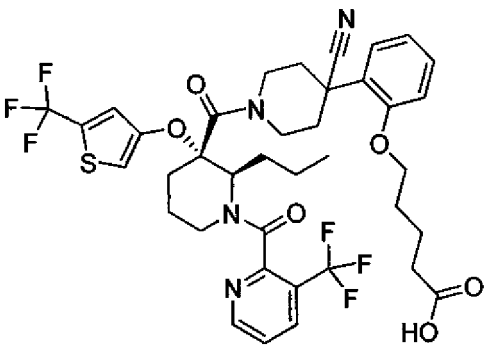
,



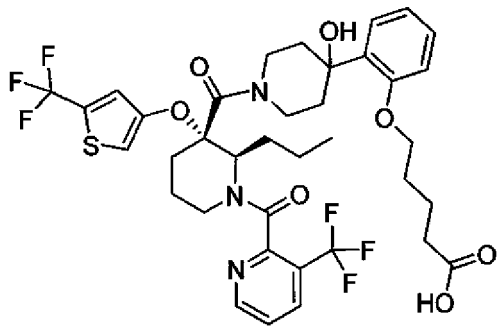
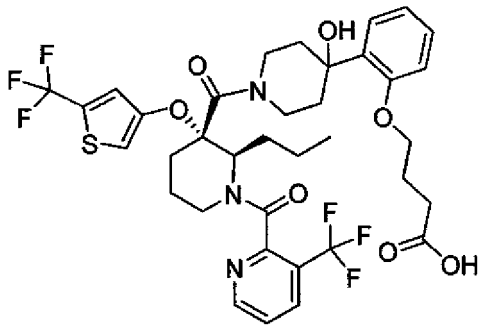
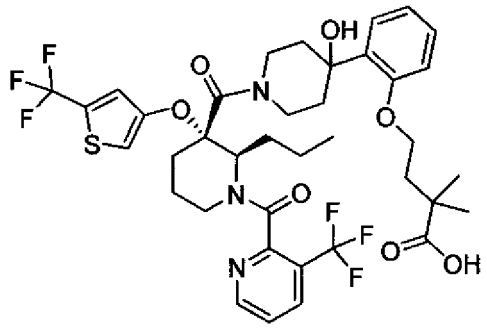
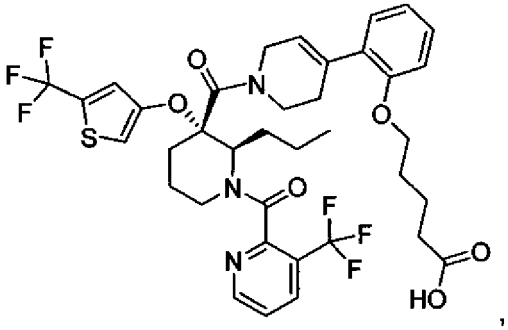
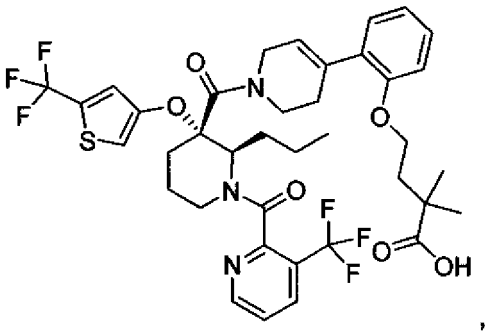
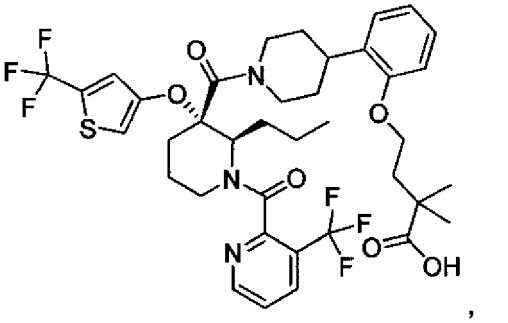
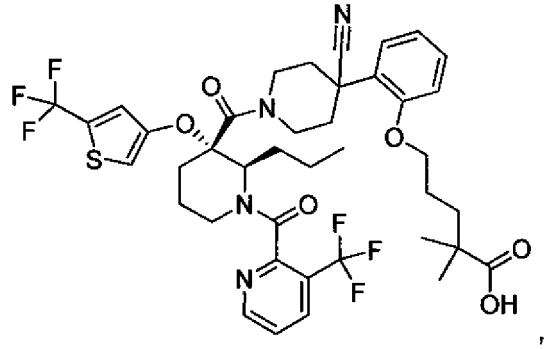
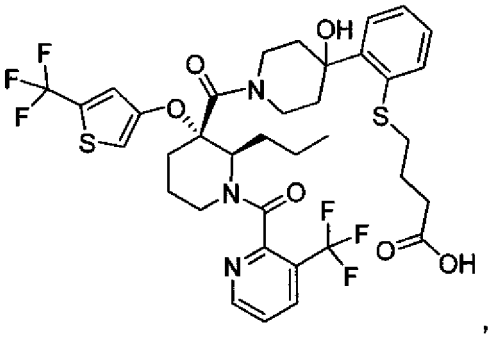
,

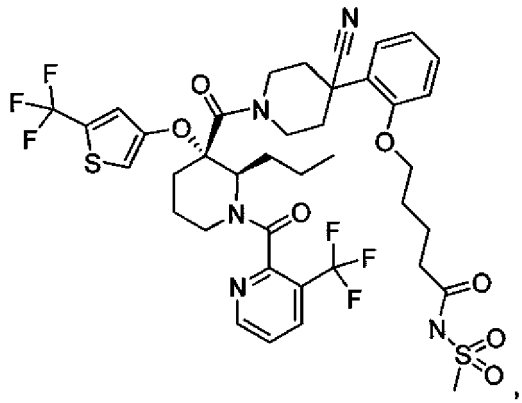


,

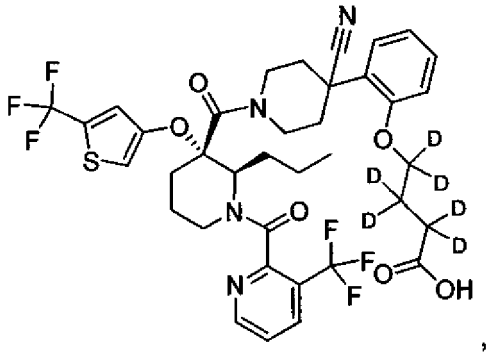


,

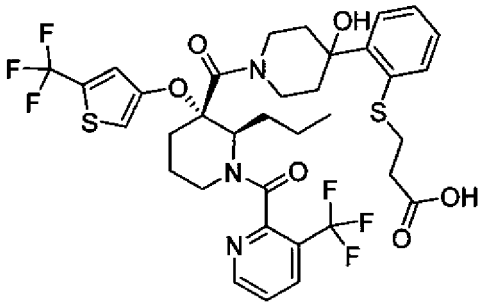

,


,

,

,

,

,

,



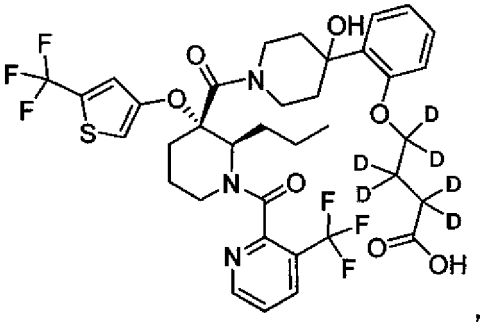
,



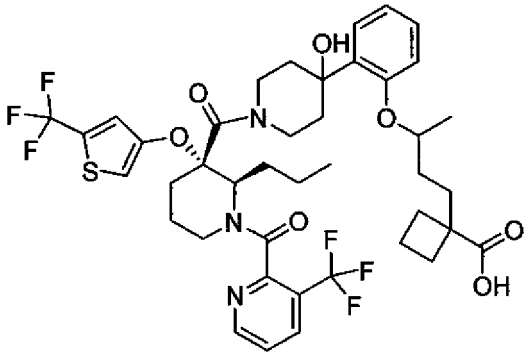
,



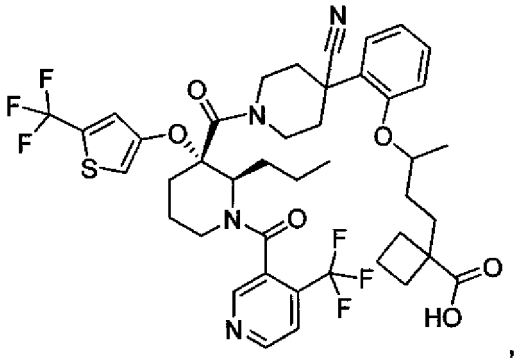
,



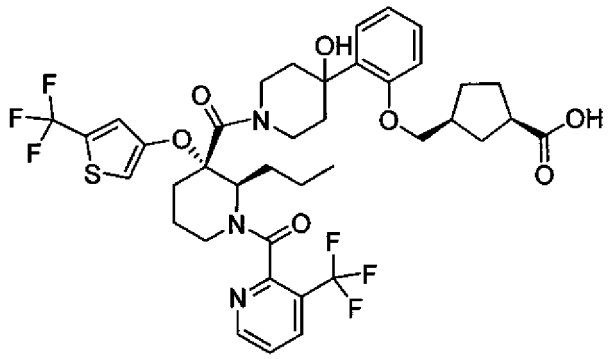
,



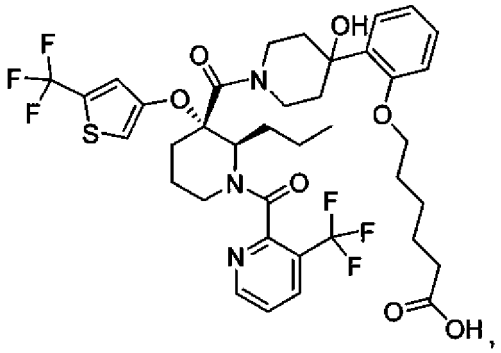
,



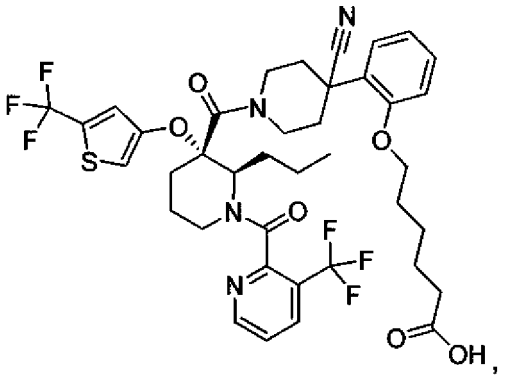
,



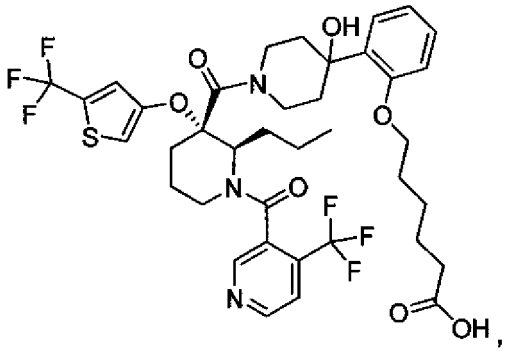
,



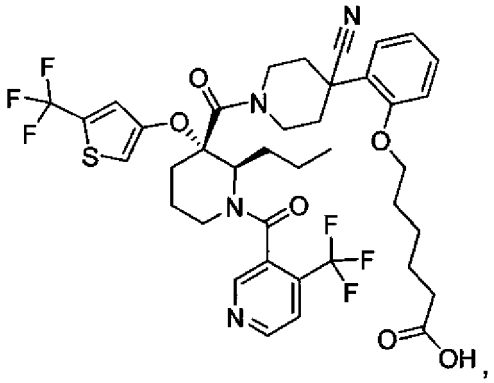
,



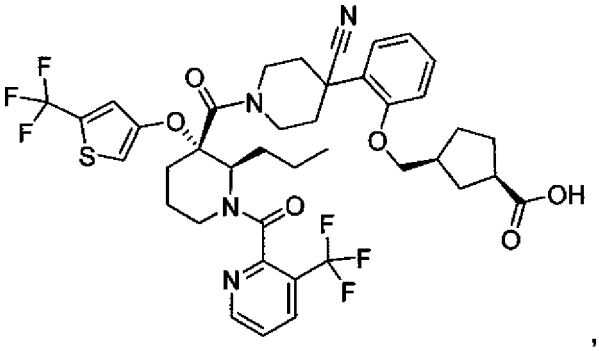
,



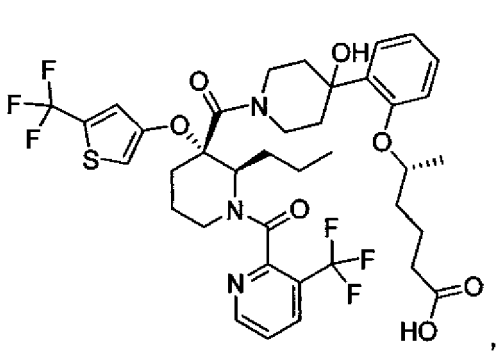
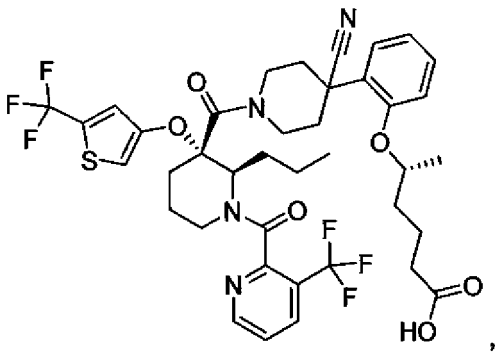
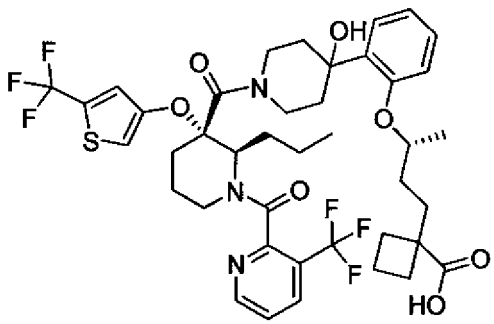
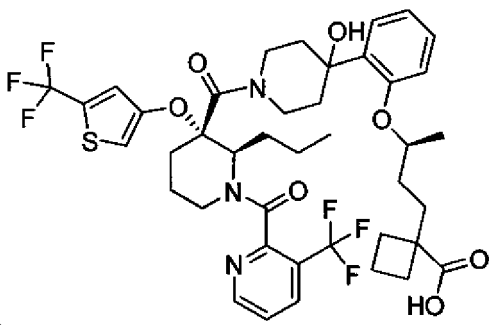
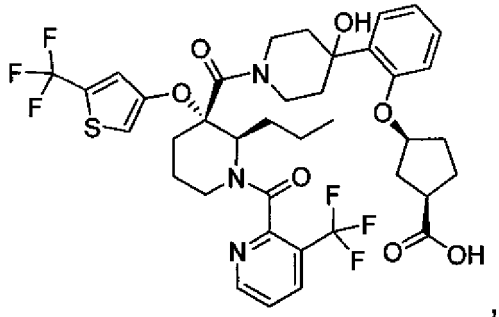
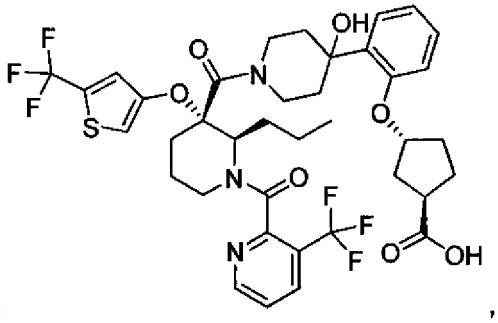
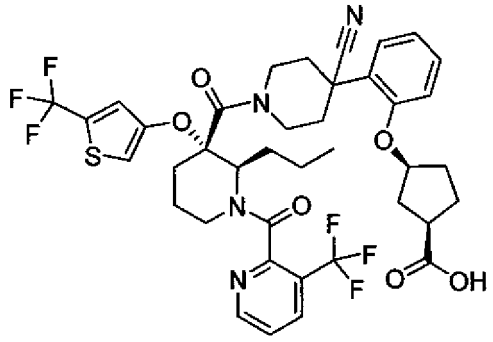
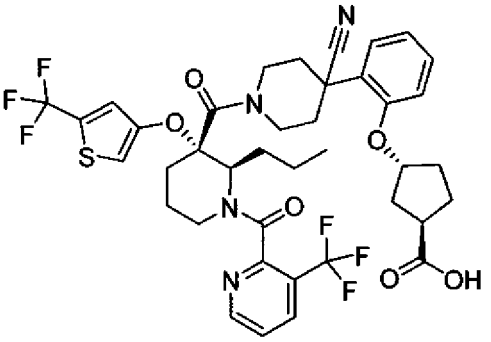
,

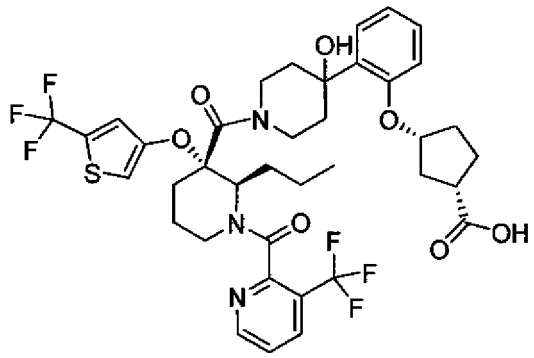
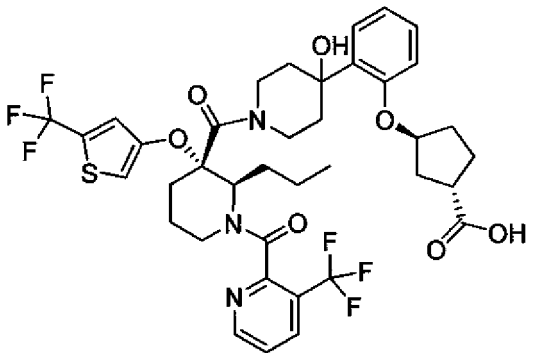
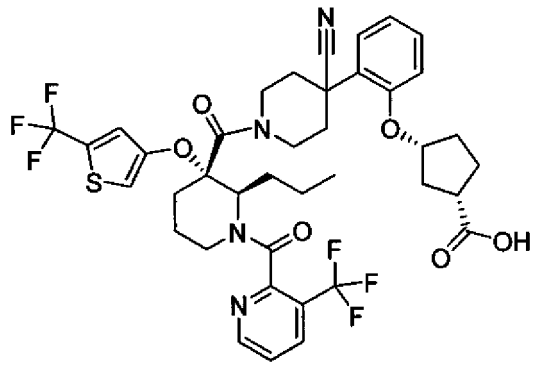
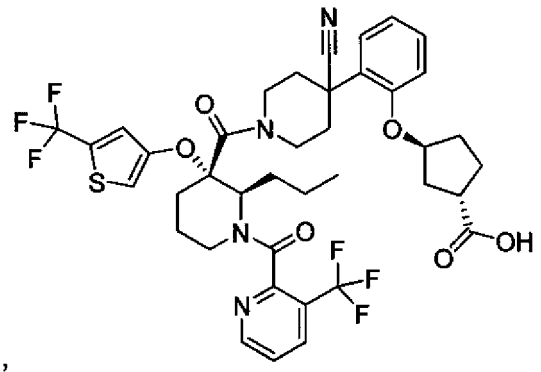
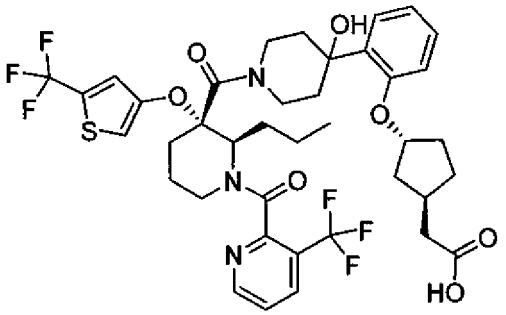
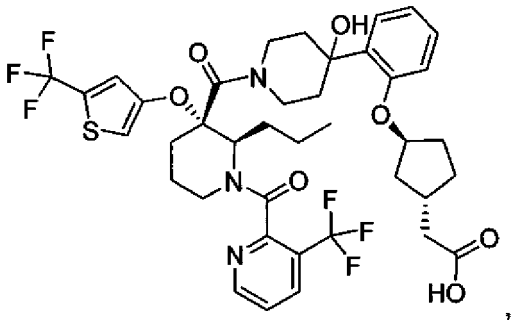
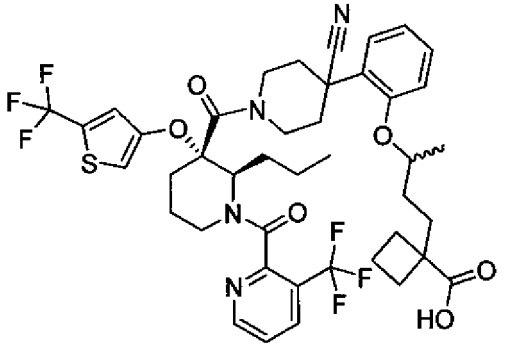
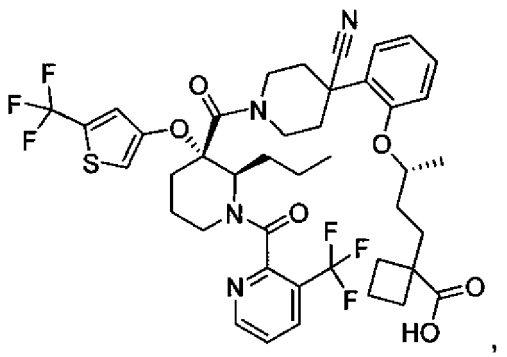


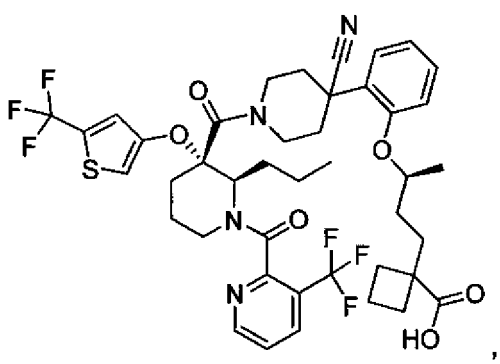
,



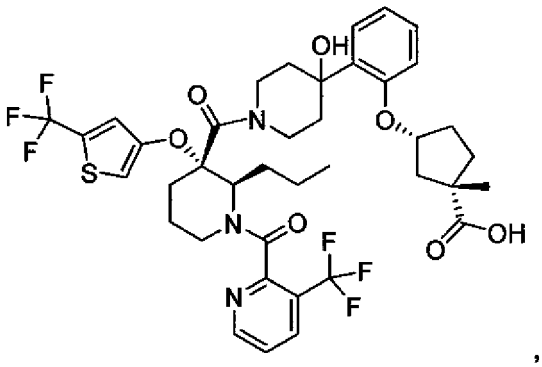
,


,

,

,

,

,

,

,

,

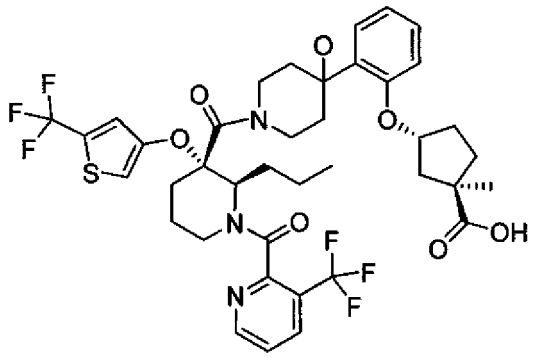

,

,

,

,

,

,

,

,



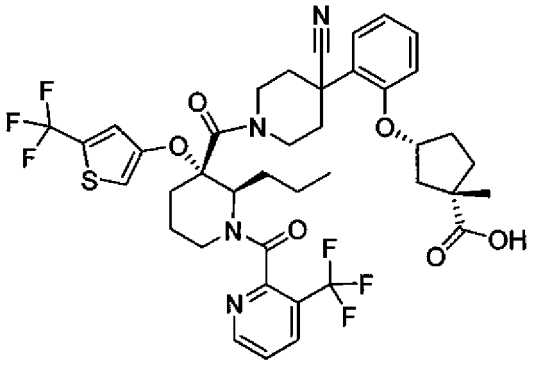
,



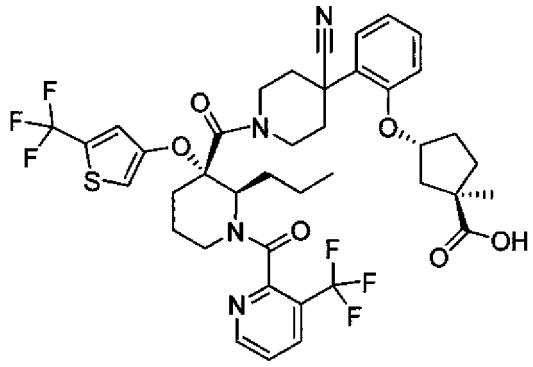
,



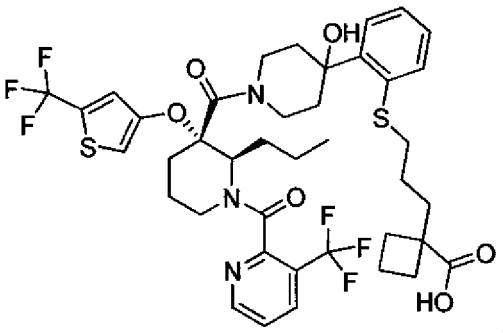
,



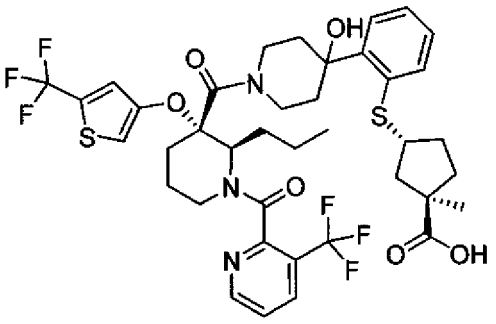
,



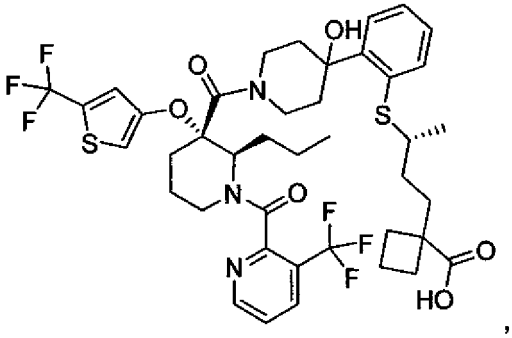
,



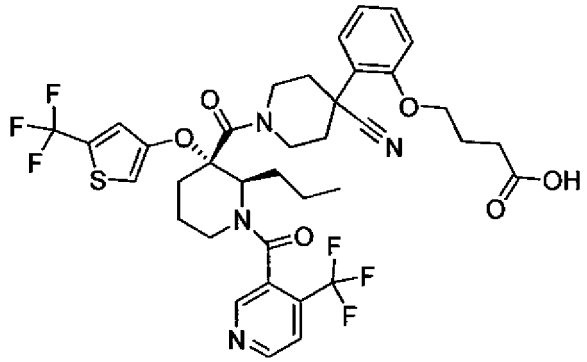
,



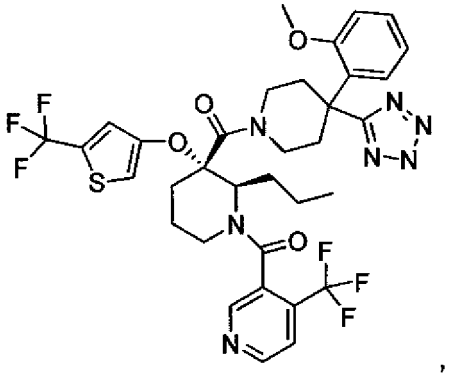
,



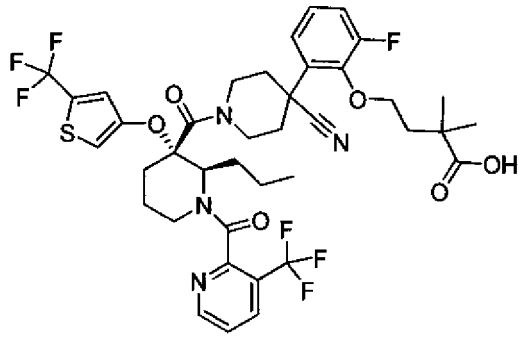
,



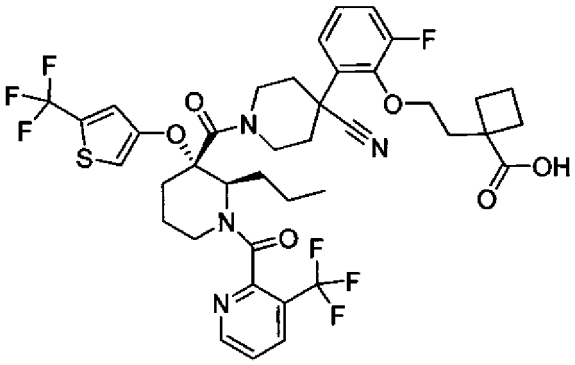
,



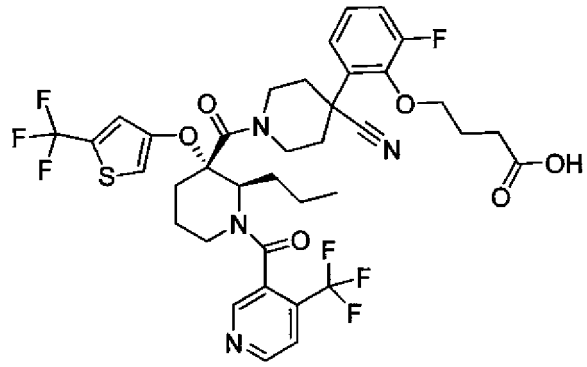
,



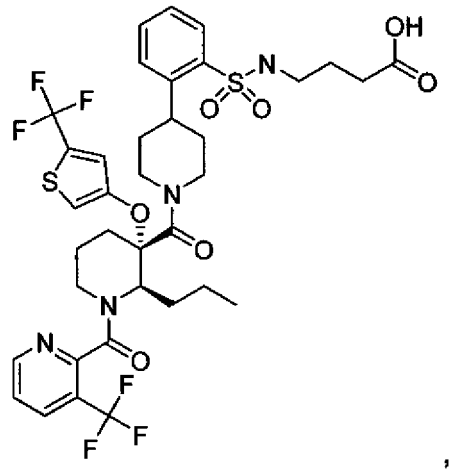
,



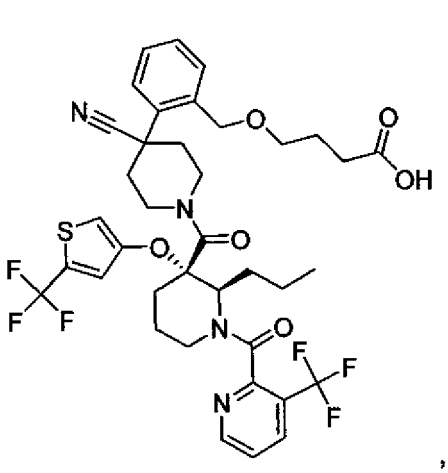
,



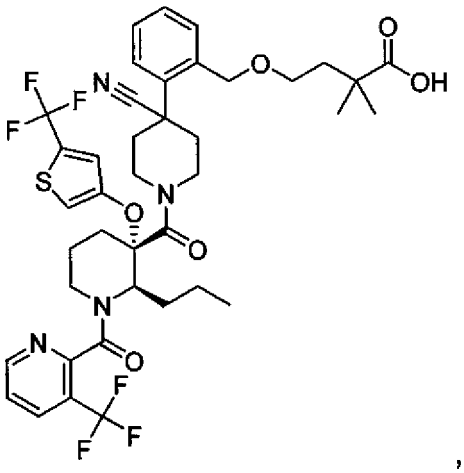
,



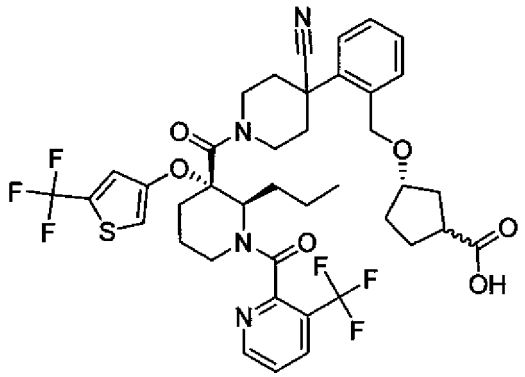
,



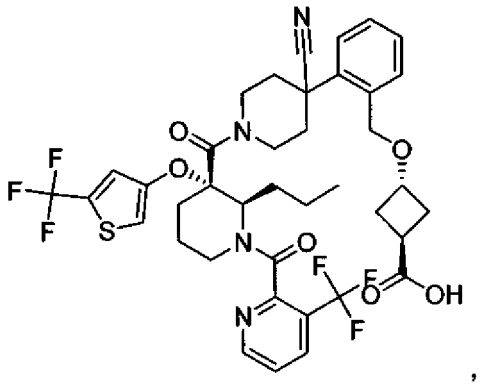
,



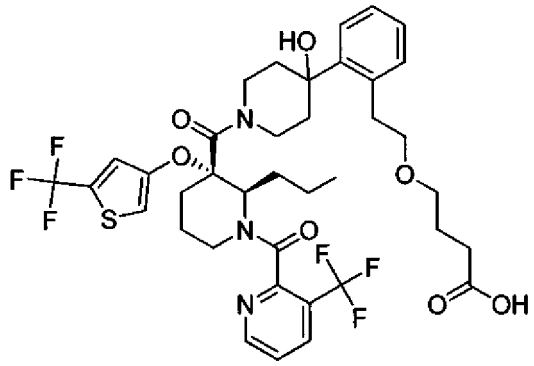
,



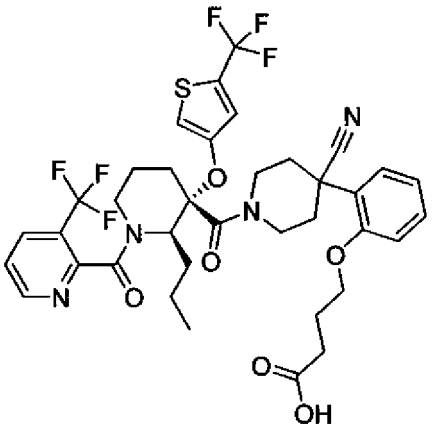
,



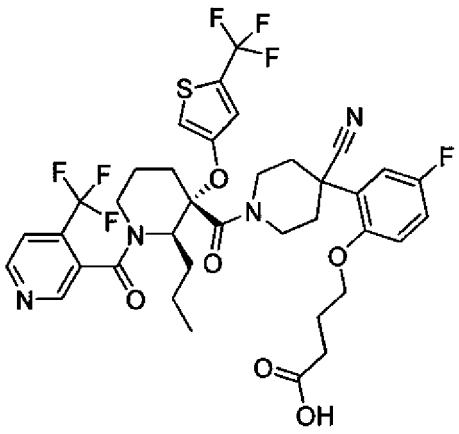
,



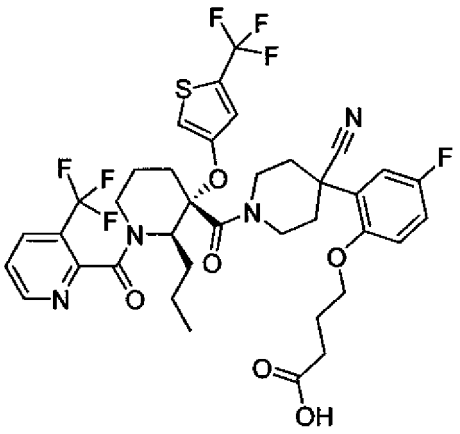
,



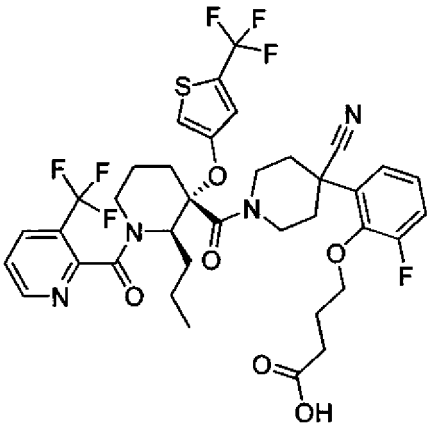
,



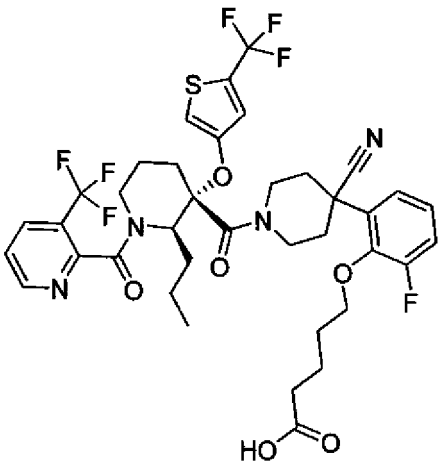
,



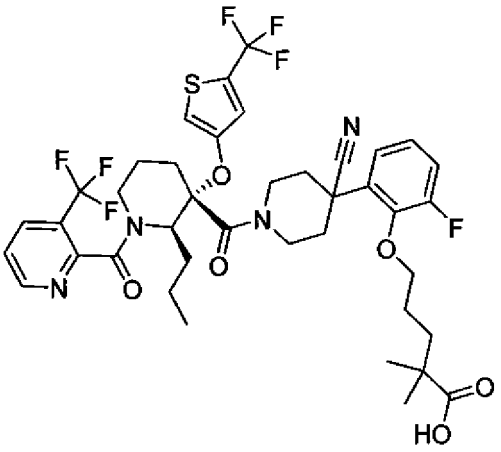
,



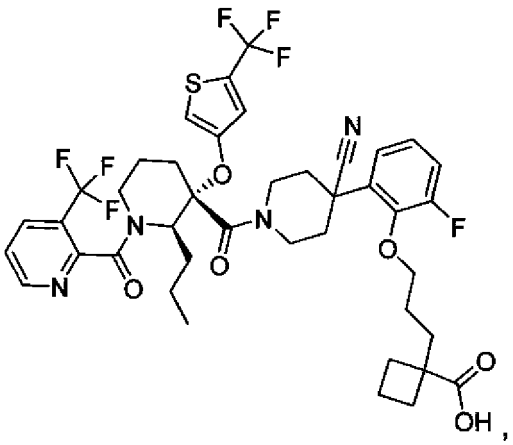
,



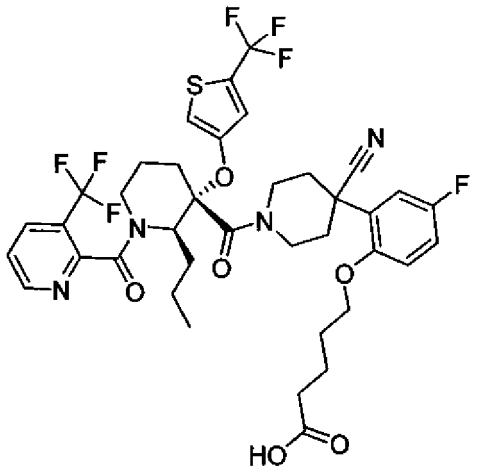
,



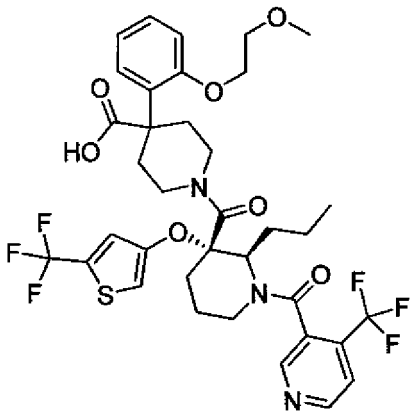
,



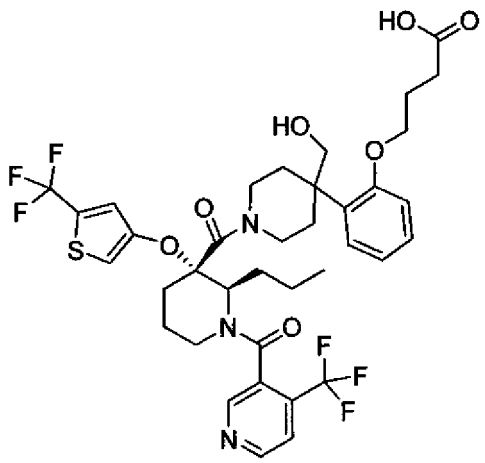
,



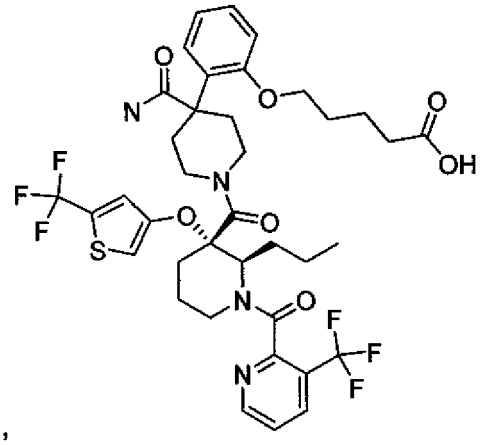
,



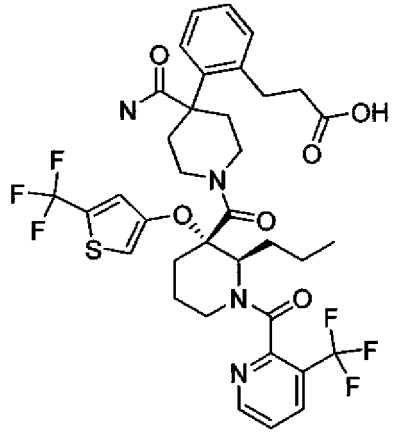
,



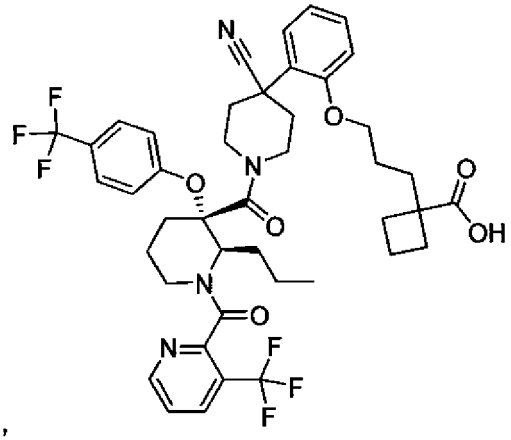
,



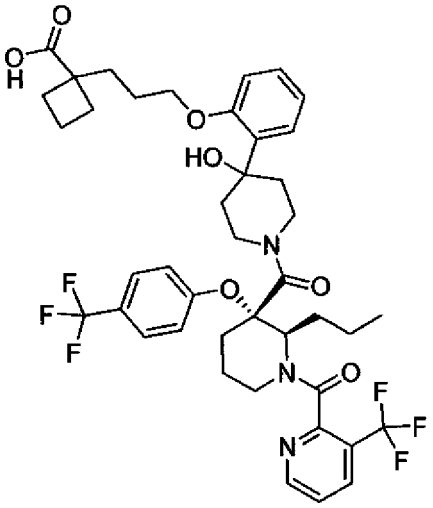
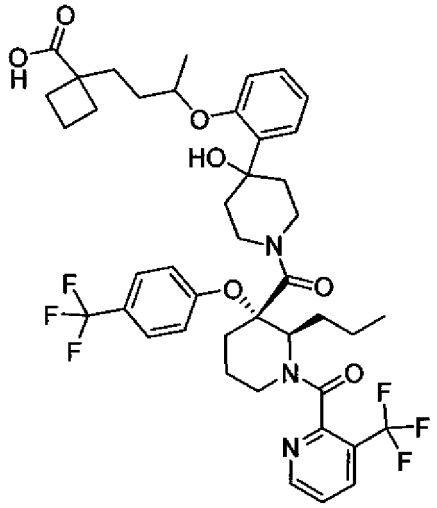
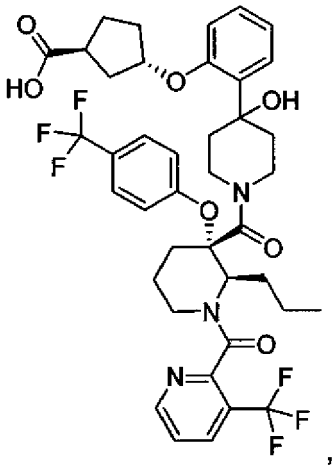
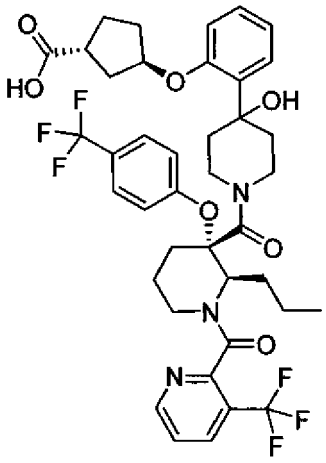
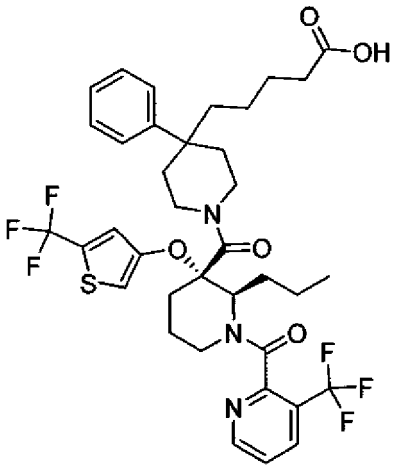
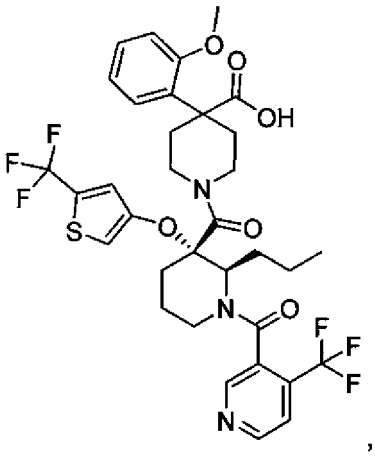
,

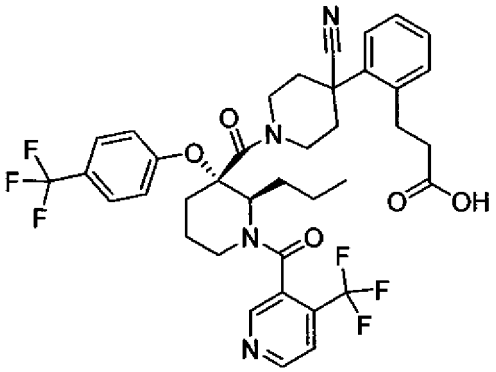


,

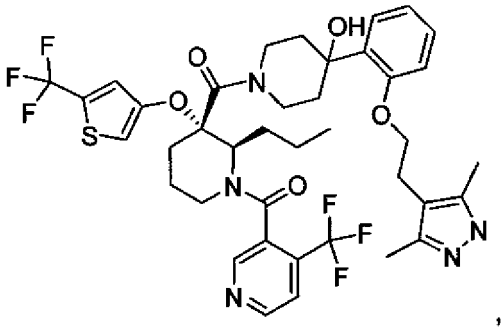


,

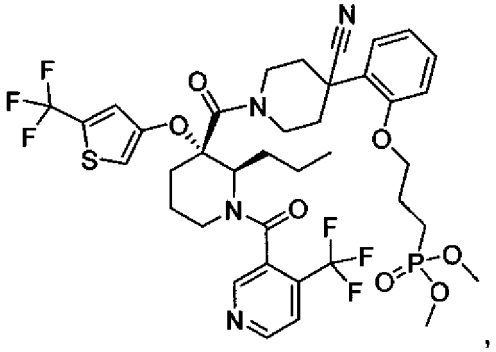

,

,

,

,

,

,



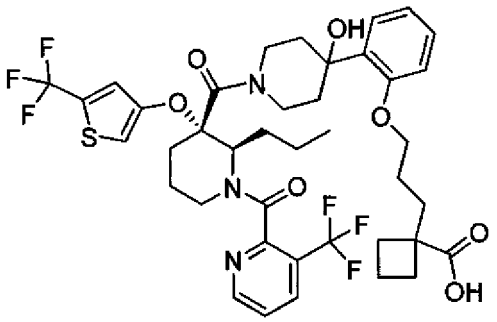
,

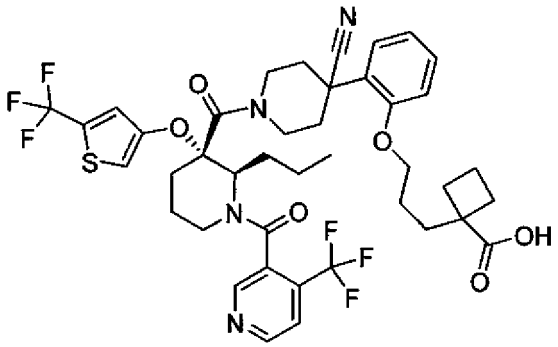


,

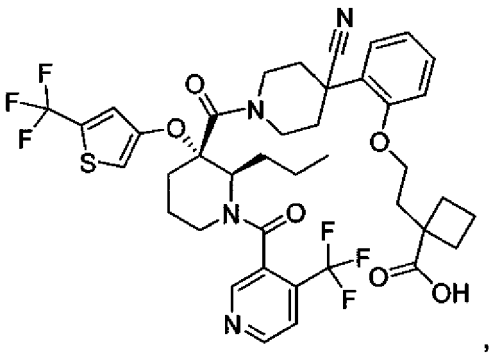


,

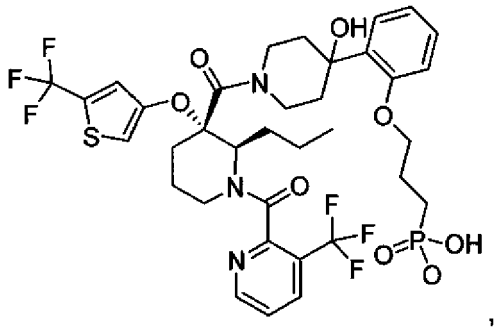




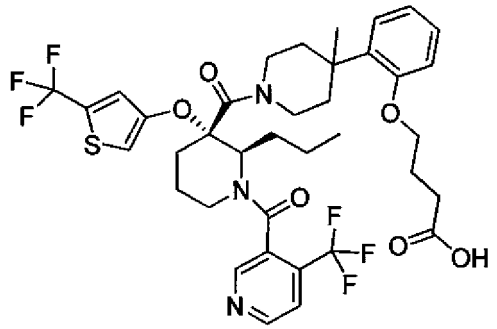
,

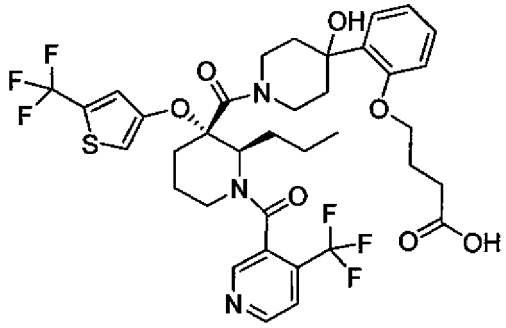
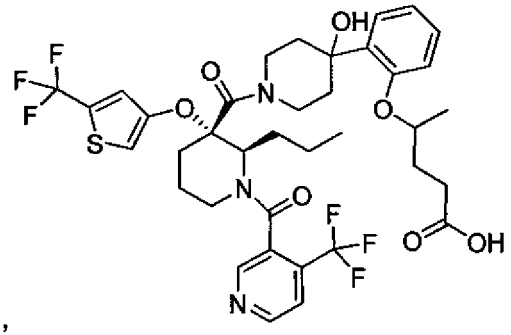
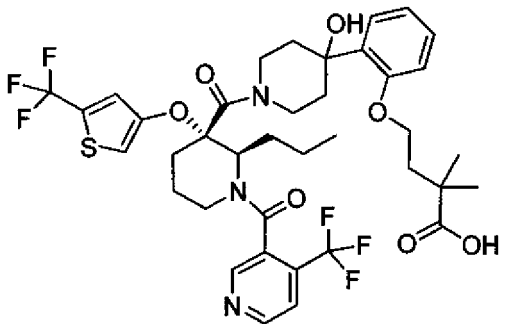
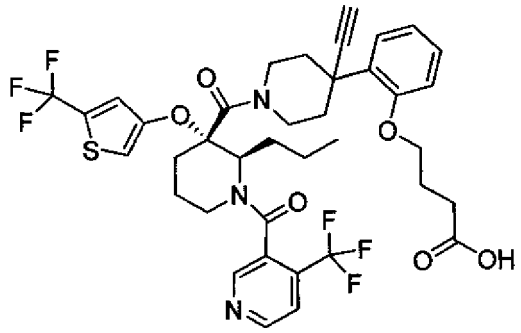
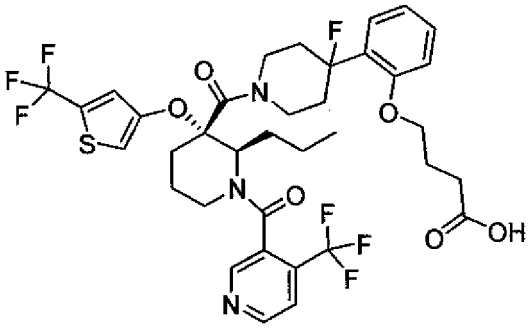
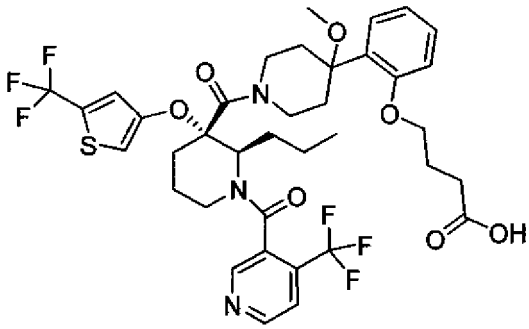
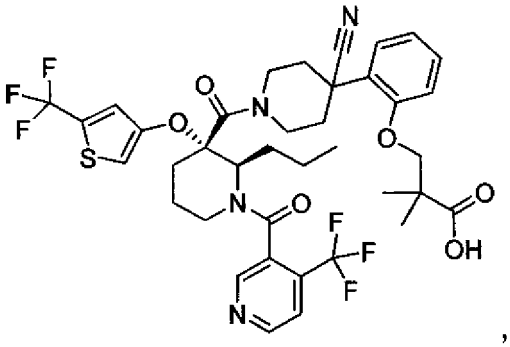


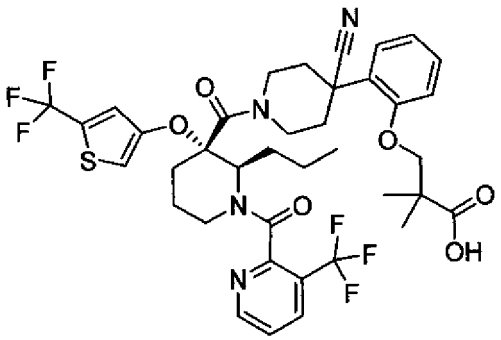
,



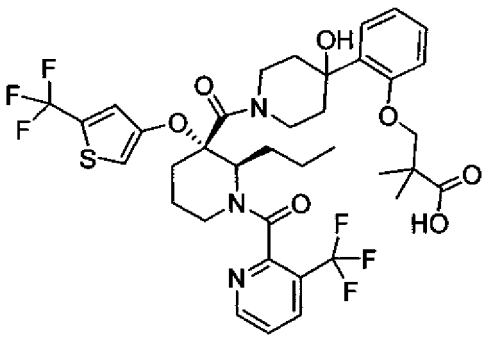
,



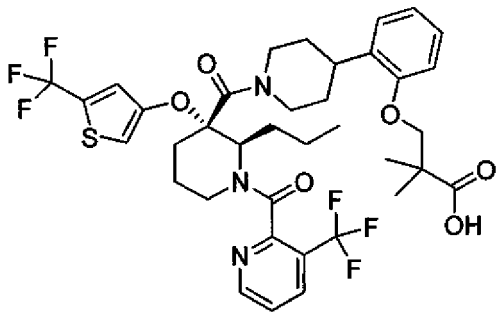

,

,

,

,

,

,

.



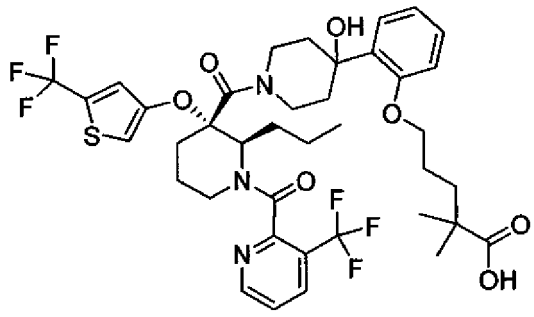
,



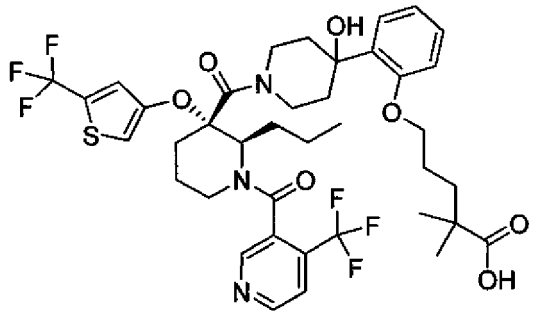
,



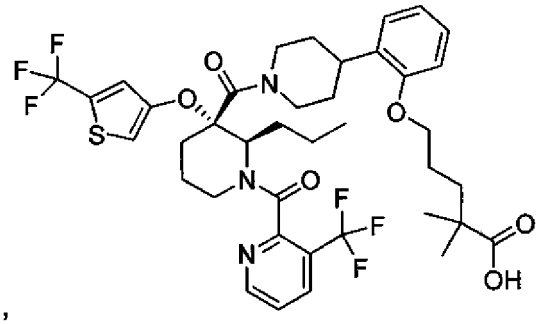
,



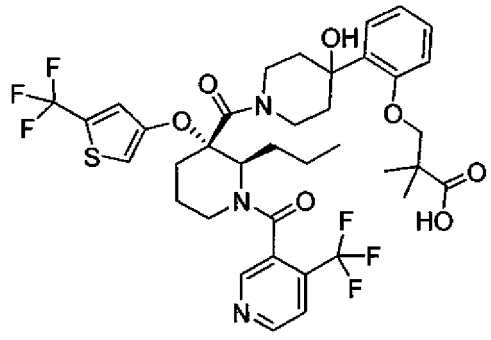
,



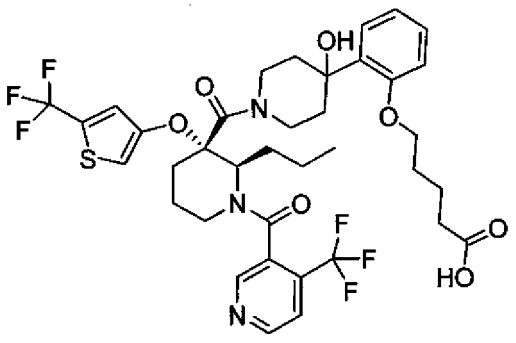
,



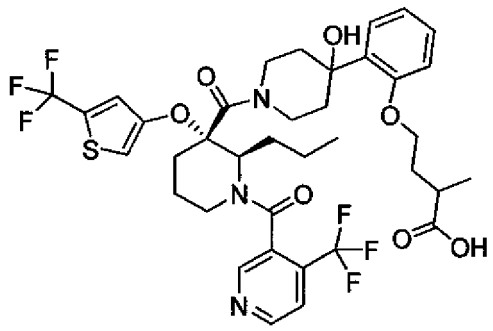
,



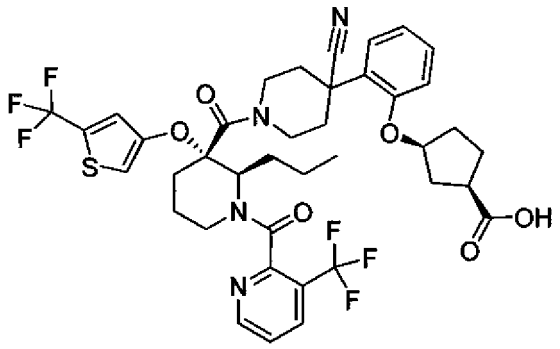
,



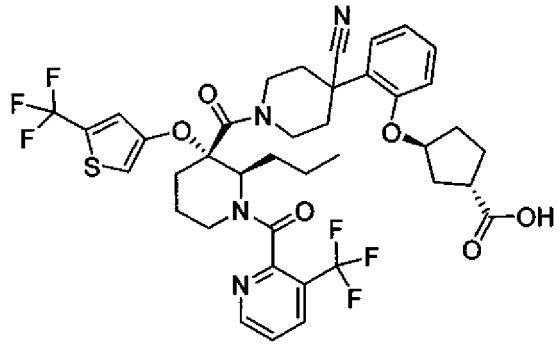
,



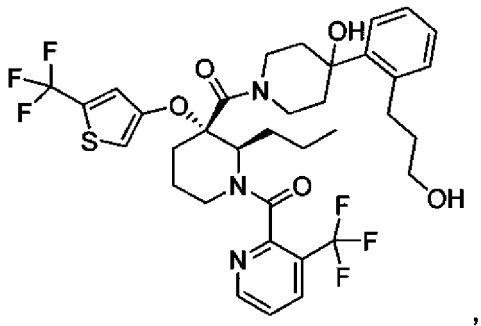
,



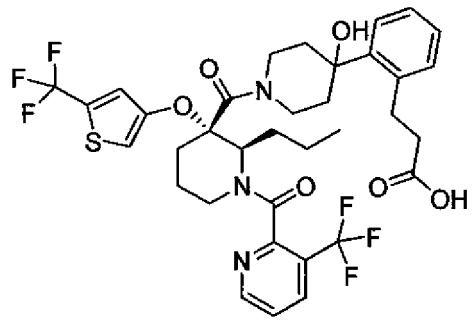
,



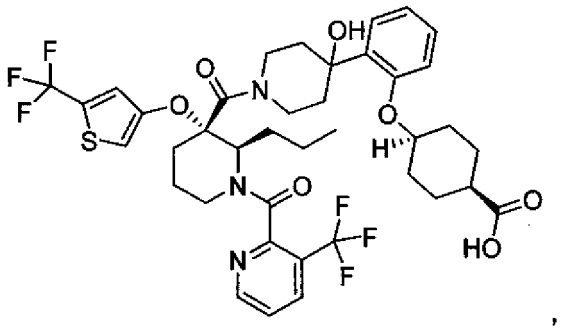
,



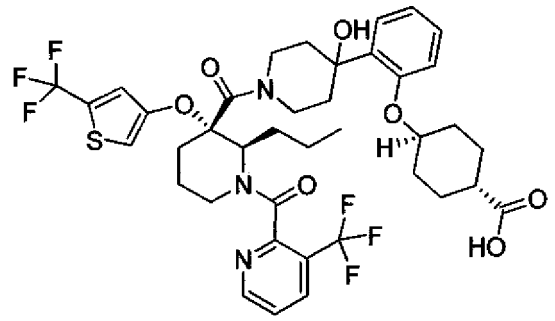
,



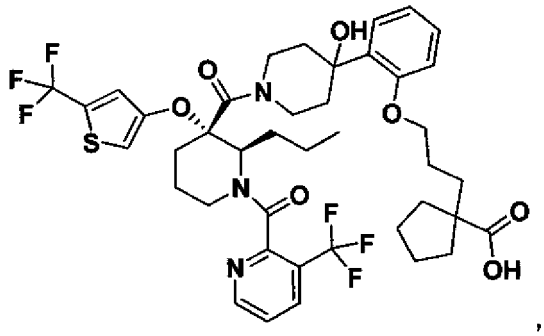
,



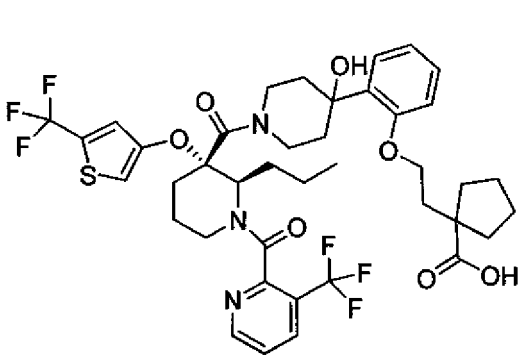
,



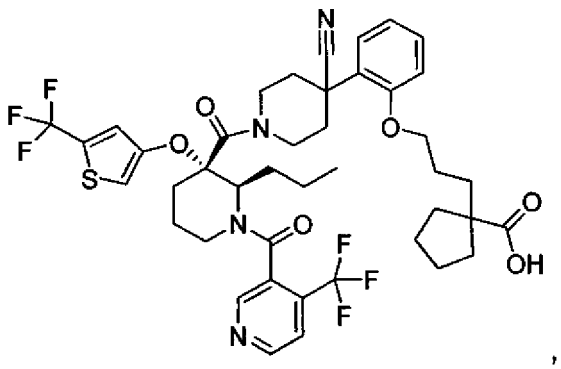
,



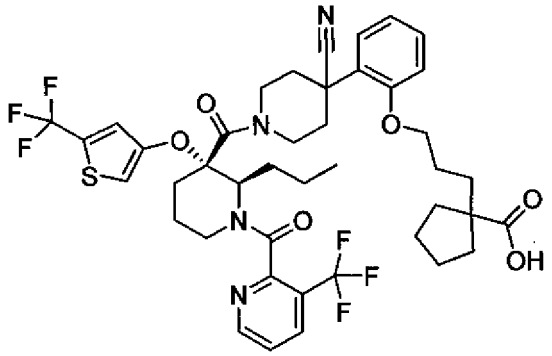
,



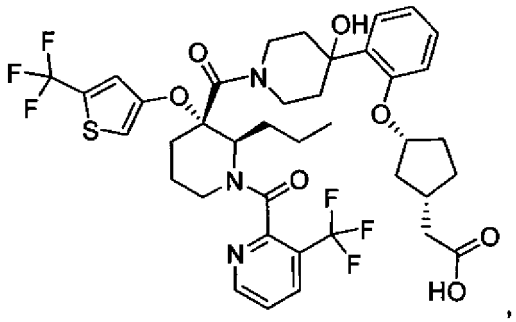
,



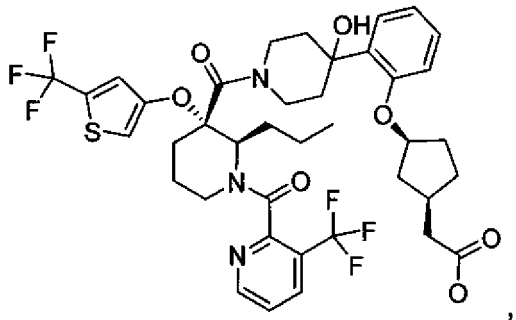
,



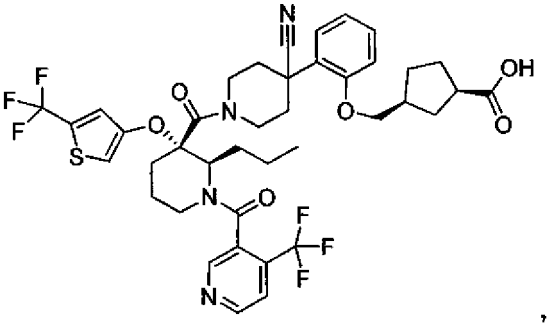
,



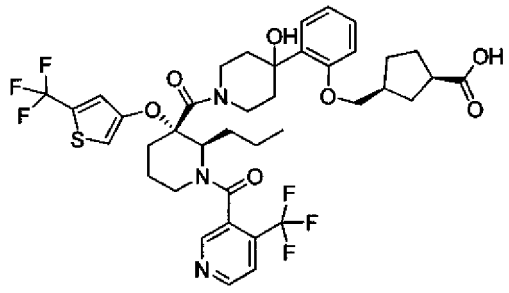
,



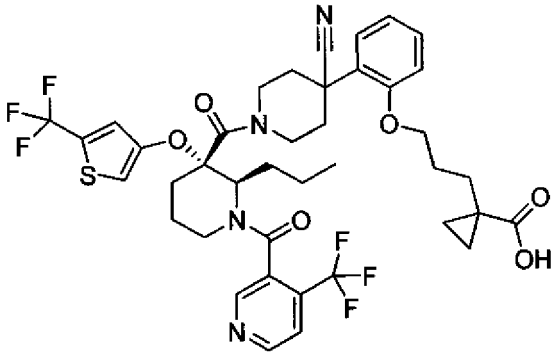
,



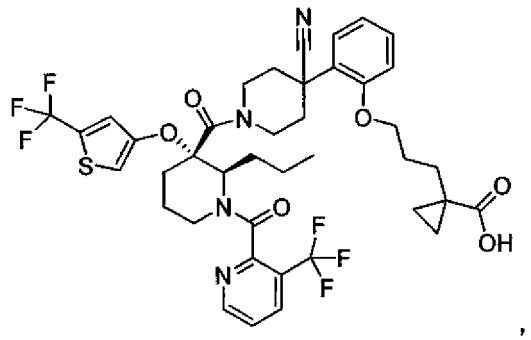
,



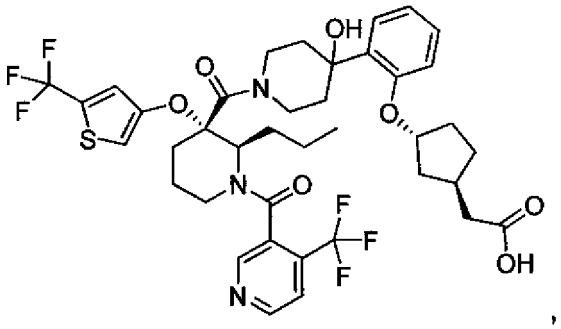
,



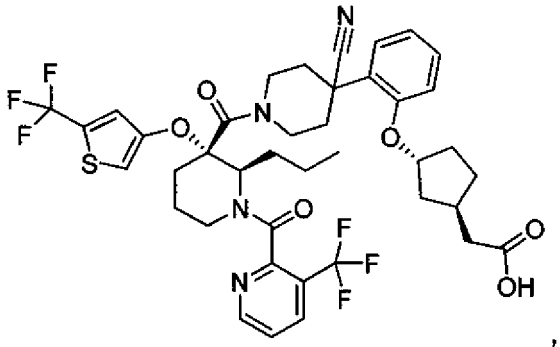
,



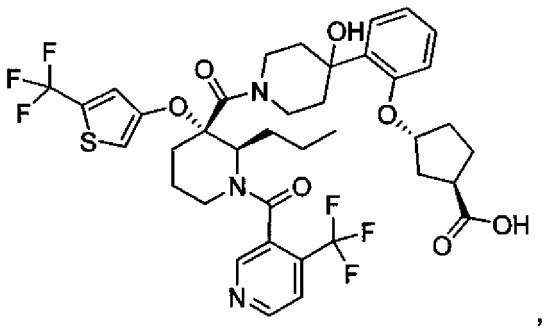
,



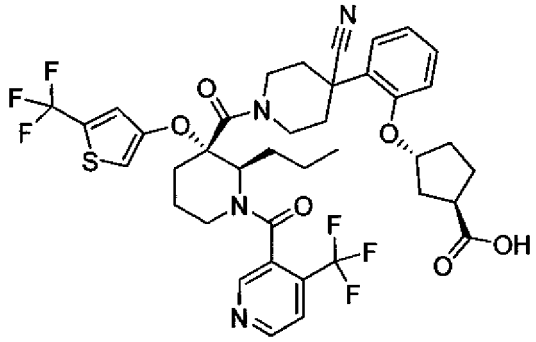
,



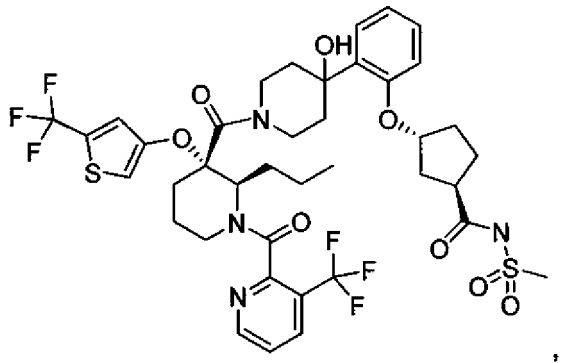
,



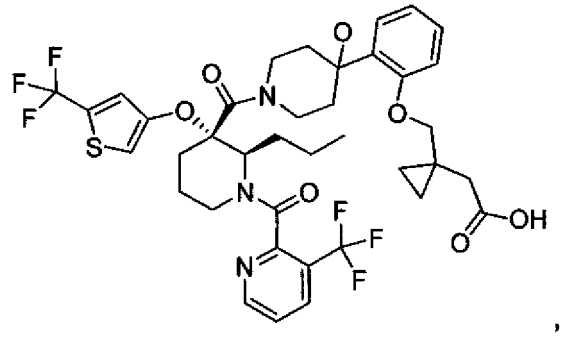
,



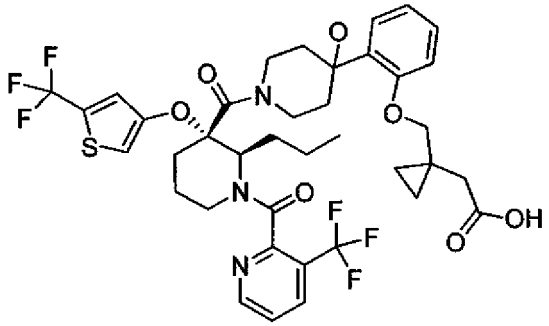
,



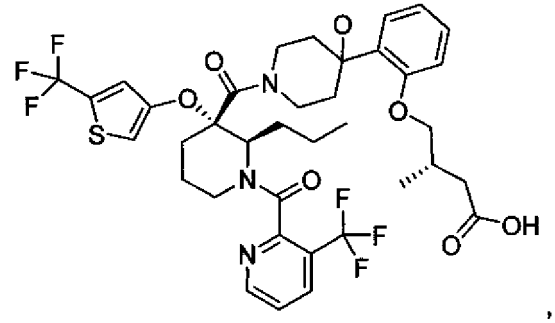
,



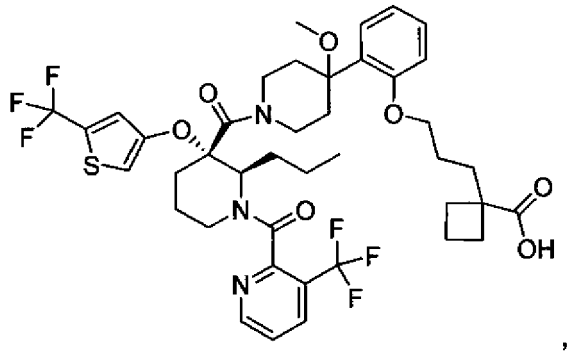
,



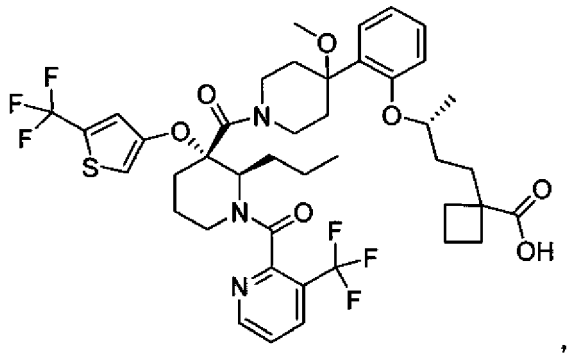
,



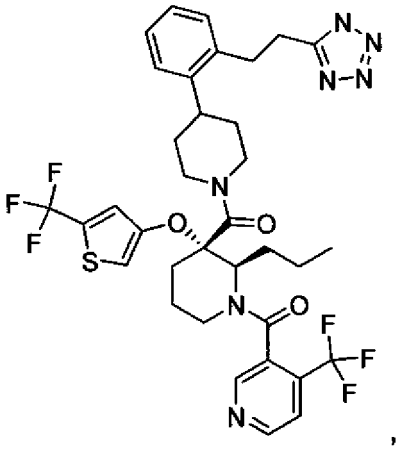
,



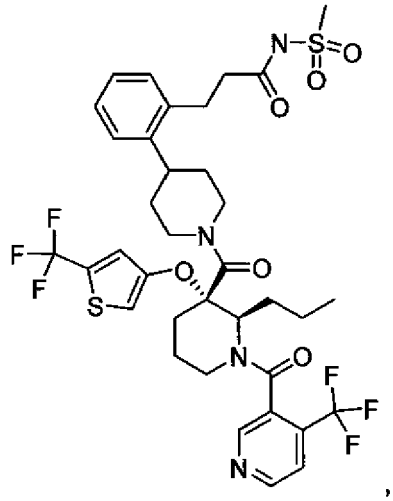
,



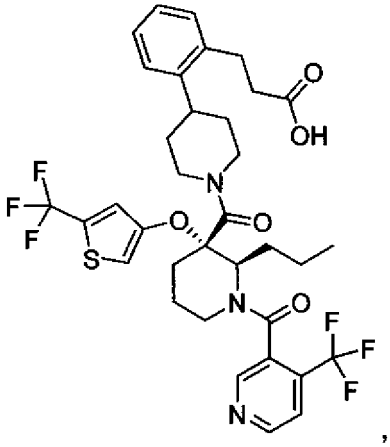
,



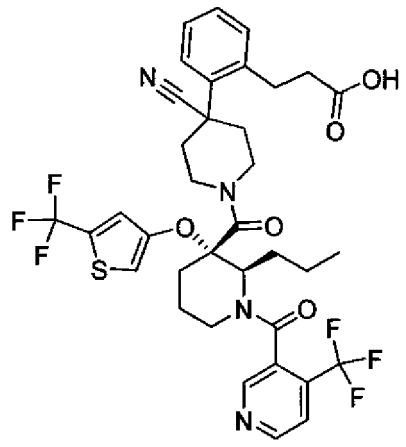
,



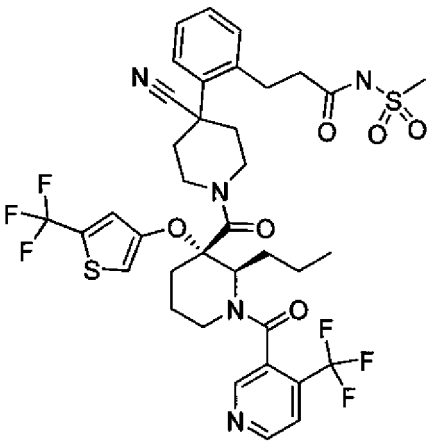
,



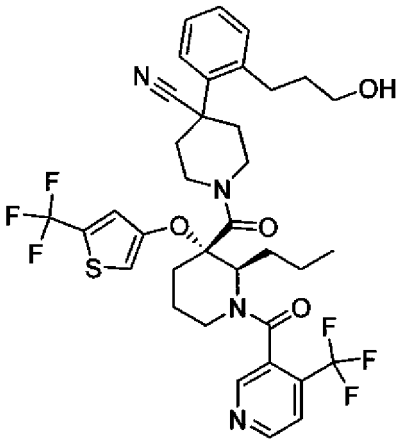
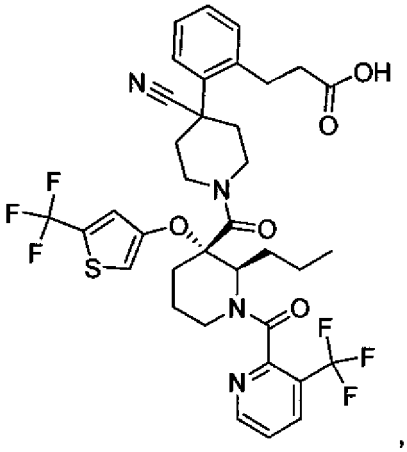
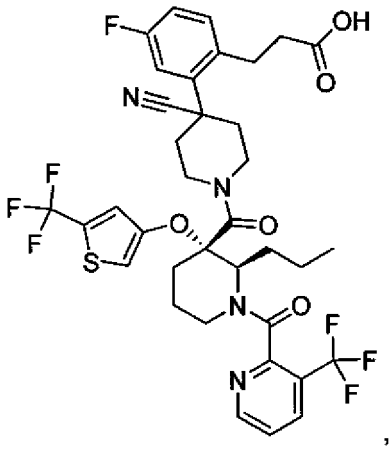
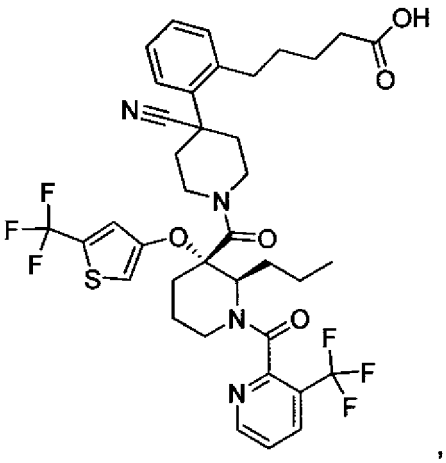
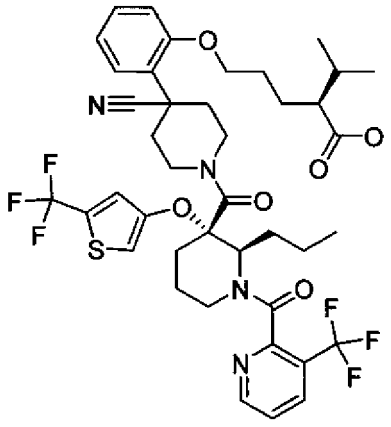
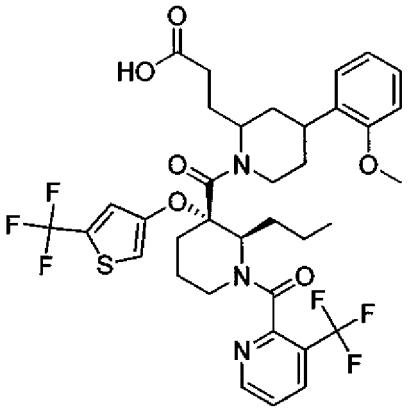
,

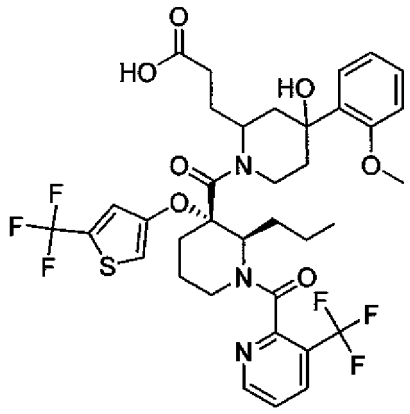


,

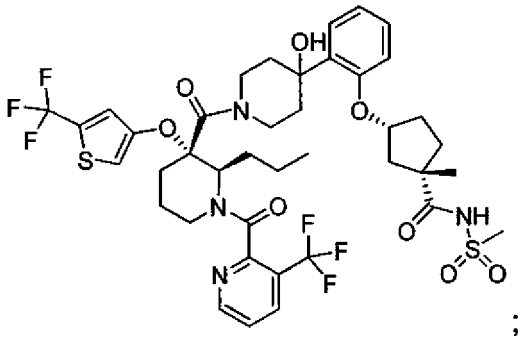


,


,

,

,

,

,

,



, and



;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides compounds illustrated as Formula 2, as described above, or pharmaceutically acceptable salts, solvates, esters, or prodrugs thereof, wherein the various moieties are as described above.

In another embodiment the compound of Formula 2 wherein R^4 or $R^{4'}$, which may be the same or different, are independently selected from the group consisting of hydrogen and alkyl,

In another embodiment the compound of Formula 2, wherein R^5, $R^{5'}$, R^6, $R^{6'}$, R^7 and $R^{7'}$ are each independently H.

In another embodiment the compound of Formula 2, wherein J may or may not be present, when J is present it is halo.

In another embodiment the compound of Formula 2, G is selected from the group consisting of $-(CR^8R^{8'})_n$-C(O)OH, $-(CR^8R^{8'})_n$-heteroaryl, $-(CR^8R^{8'})_n$-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, $—(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-heteroaryl, $—(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, $—(CR^8R^{8'})_n$-$P(O)O_2$, $—(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and (C_1-C_6)alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form $(C_3\text{-}C_8)$spirocycloalkyl,

R^9 is $SO_2(C_1\text{-}C_6)$alkyl or $SO_2(C_3\text{-}C_8)$cycloalkyl,

n is 0-10,

providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more $(C_1\text{-}C_6)$alkyl groups,

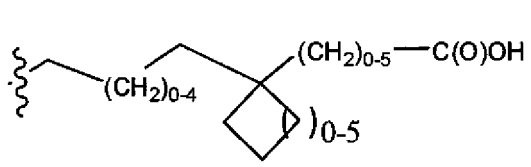
still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom.

In another embodiment the compound of Formula 2, wherein R^8 and $R^{8'}$ are independently H or $(C_1\text{-}C_6)$alkyl.

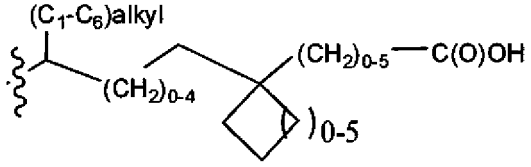
In another embodiment the compound of Formula 2, wherein R^9 is $SO_2(C_1\text{-}C_6)$alkyl or $SO_2(C_3\text{-}C_8)$cycloalkyl.

In another embodiment the compound of Formula 2, wherein G is selected from the group consisting of:

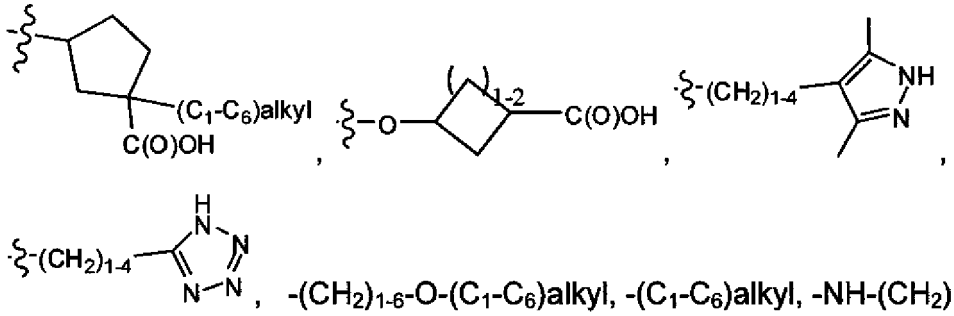
$-(CH_2)_{1\text{-}6}\text{-}C(O)OH$, $-(CH_2)_{0\text{-}4}CH((C_1\text{-}C_6)\text{alkyl})\text{-}(CH_2)_{1\text{-}5}\text{-}C(O)OH$, $-(CH_2)_{1\text{-}5}\text{-}CH((C_1\text{-}C_6)\text{alkyl})\text{-}C(O)OH$, $-(CH_2)_{0\text{-}5}\text{-}(C_3\text{-}C_8)\text{cycloalkyl-}C(O)OH$, $-(CH_2)_{0\text{-}5}\text{-}(C_3\text{-}C_8)\text{cycloalkyl-}(CH_2)_{1\text{-}6}\text{-}C(O)OH$, $-(CH_2)_{1\text{-}6}\text{-}C(O)\text{-}NH\text{-}SO_2\text{-}(C_3\text{-}C_8)\text{cycloalkyl}$, $-(CH_2)_{1\text{-}6}\text{-}C(O)\text{-}N\text{-}SO_2\text{-}(C_1\text{-}C_6)\text{alkyl}$, $-(CD_2)_{1\text{-}6}\text{-}C(O)OH$,



,



,



, -$(CH_2)_{1-6}$-O-(C_1-C_6)alkyl, -(C_1-C_6)alkyl, -NH-$(CH_2)_{1-3}$-C(O)OH, -O-(C_3-C_8)cycloalkyl-C(O)OH, -$(CH_2)_{1-6}$-O-$(CH_2)_{1-4}$-C(O)OH, -$(CH_2)_{1-5}$-(O)O$((C_1-C_6)alkyl)_2$, -$(CH_2)_{1-6}$-OH, (C_3-C_8)(cycloalkyl)-C(O)-N$(SO_2)(C_1-C_6)$alkyl, and -(C_3-C_8)cycloalkyl

providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that G is not attached to Y such that N is linked to O, S or N, and

still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

In another embodiment the compound of Formula 2, wherein J is F.

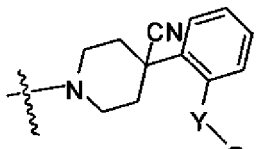
In another embodiment the compound of Formula 2, wherein R is selected from the group consisting of halogen, -CN, -OH, -SH, (C_1-C_6)alkoxy, -(C_2-C_6)alkenoxy, -(C_1-C_6)alkyl, -(C_2-C_6)alkenyl, haloalkoxy, -C(O)$NR^{10}R^{11}$, -C(O)OR^{10}, -OC(O)R^{10}, -$NR^{10}C(O)R^{11}$, -$NR^{10}R^{11}$, -S-alkyl, -S-alkenyl, -S-haloalkyl, (C_2-C_6)alkynyl, haloalkyl, haloalkenyl–, G is selected from the group consisting of –$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-heteroaryl, –$(CR^8R^{8'})_n$-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, ––$(CR^8R^{8'})_n$-P(O)$OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, —$(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and (C_1-C_6)alkyl; or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form (C_3-C_8)spirocycloalkyl,

R^9 is $SO_2(C_1\text{-}C_6)$alkyl or $SO_2(C_3\text{-}C_8)$cycloalkyl,

n is 0-10,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more $(C_1\text{-}C_6)$alkyl groups.

In another embodiment, in Formula 2, R^1 is 

, wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of $-(CR^8R^{8'})_n$-C(O)OH, $-(CR^8R^{8'})_n$-heteroaryl, $-(CR^8R^{8'})_n$-C(O)NR^8R^9, $-(CR^8R^{8'})_n$-$(C_3\text{-}C_8)$cycloalkyl-C(O)NR^8R^9, $-(CR^8R^{8'})_n$-$(C_3\text{-}C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-P(O)$OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, —$(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and $(C_1\text{-}C_6)$alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form $(C_3\text{-}C_8)$spirocycloalkyl,

R^9 is $SO_2(C_1\text{-}C_6)$alkyl or $SO_2(C_3\text{-}C_8)$cycloalkyl,

n is 0-10,

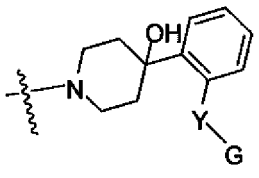
providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more $(C_1\text{-}C_6)$alkyl groups,

still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom.

In another embodiment, in Formula 2, R^1 is 

, wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of $-(CR^8R^{8'})_n$-C(O)OH, $-(CR^8R^{8'})_n$-heteroaryl, $-(CR^8R^{8'})_n$-C(O)NR^8R^9, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, —$(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-P(O)$OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, —$(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and (C_1-C_6)alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form (C_3-C_8)spirocycloalkyl,

R^9 is SO_2(C_1-C_6)alkyl or SO_2(C_3-C_8)cycloalkyl,

n is 0-10,

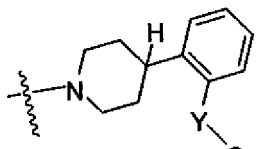
providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more (C_1-C_6)alkyl groups,

still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom.

In another embodiment, in Formula 2, R^1 is , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of $-(CR^8R^{8'})_n$-C(O)OH, $-(CR^8R^{8'})_n$-heteroaryl, $-(CR^8R^{8'})_n$-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, $—(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-heteroaryl, $—(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, $—(CR^8R^{8'})_n$-$P(O)O_2$, $—(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and (C_1-C_6)alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form (C_3-C_8)spirocycloalkyl,

R^9 is SO_2(C_1-C_6)alkyl or SO_2(C_3-C_8)cycloalkyl,

n is 0-10,

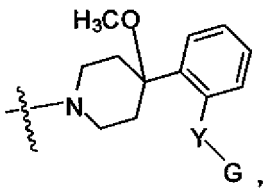
providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more (C_1-C_6)alkyl groups,

still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom.

In another embodiment, in Formula 2, R^1 is  , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of $-(CR^8R^{8'})_n$-C(O)OH, $-(CR^8R^{8'})_n$-heteroaryl, $-(CR^8R^{8'})_n$-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, —$(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, —$(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and $(C_1$-$C_6)$alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form $(C_3$-$C_8)$spirocycloalkyl,

R^9 is $SO_2(C_1$-$C_6)$alkyl or $SO_2(C_3$-$C_8)$cycloalkyl,

n is 0-10,

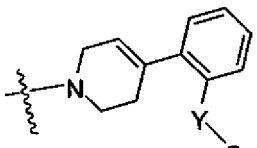
providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more $(C_1$-$C_6)$alkyl groups,

still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom.

In another embodiment, in Formula 2, R^1 is  , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of $-(CR^8R^{8'})_n$-C(O)OH, $-(CR^8R^{8'})_n$-heteroaryl, $-(CR^8R^{8'})_n$-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, —$(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, —$(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and (C_1-C_6)alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form (C_3-C_8)spirocycloalkyl,

R^9 is SO_2(C_1-C_6)alkyl or SO_2(C_3-C_8)cycloalkyl,

n is 0-10,

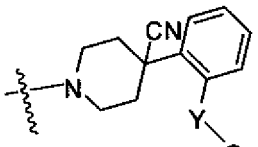
providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

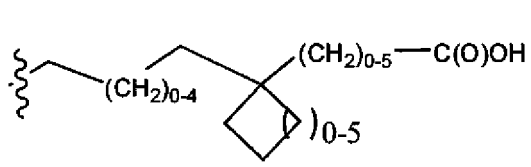
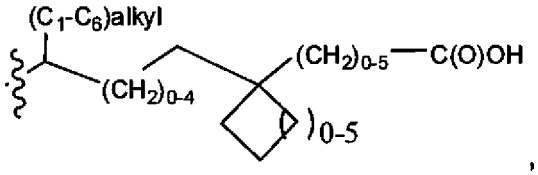
still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

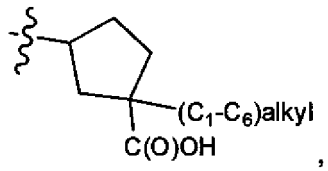
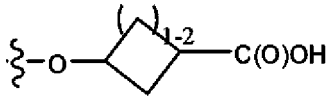
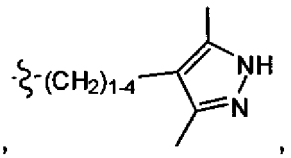
further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more (C_1-C_6)alkyl groups,

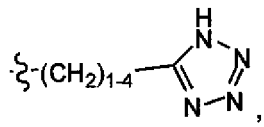
still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom.

In another embodiment, in Formula 2, R^1 is , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of:

$-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{0-4}CH((C_1-C_6)alkyl)-(CH_2)_{1-5}-C(O)OH$, $-(CH_2)_{1-5}-CH((C_1-C_6)alkyl)-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{1-6}-C(O)-NH-SO_2-(C_3-C_8)cycloalkyl$, $-(CH_2)_{1-6}-C(O)-N-SO_2-(C_1-C_6)alkyl$, $-(CD_2)_{1-6}-C(O)OH$,

, ,

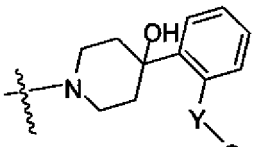
, , ,

, $-(CH_2)_{1-6}-O-(C_1-C_6)alkyl$, $-(C_1-C_6)alkyl$, $-NH-(CH_2)_{1-3}-C(O)OH$, $-O-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{1-6}-O-(CH_2)_{1-4}-C(O)OH$, $-(CH_2)_{1-5}-(O)O((C_1-C_6)alkyl)_2$, $-(CH_2)_{1-6}-OH$, $(C_3-C_8)(cycloalkyl)-C(O)-N(SO_2)(C_1-C_6)alkyl$, and $-(C_3-C_8)cycloalkyl$

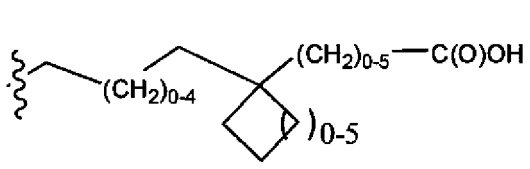
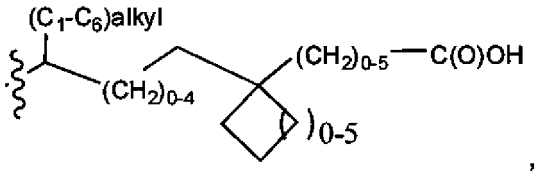
providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

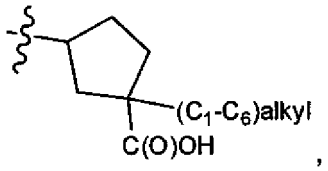
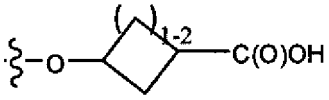
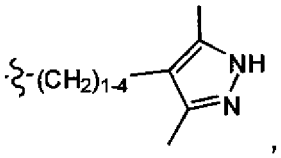
further providing that G is not attached to Y such that N is linked to O, S or N, and

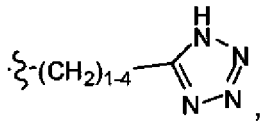
still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

In another embodiment, in Formula 2, R^1 is , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of:

$-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{0-4}CH((C_1-C_6)alkyl)-(CH_2)_{1-5}-C(O)OH$, $-(CH_2)_{1-5}-CH((C_1-C_6)alkyl)-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{1-6}-C(O)-NH-SO_2-(C_3-C_8)cycloalkyl$, $-(CH_2)_{1-6}-C(O)-N-SO_2-(C_1-C_6)alkyl$, $-(CD_2)_{1-6}-C(O)OH$,

, ,

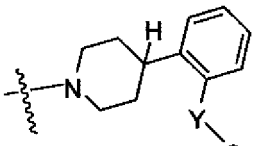
, , ,

, $-(CH_2)_{1-6}-O-(C_1-C_6)alkyl$, $-(C_1-C_6)alkyl$, $-NH-(CH_2)_{1-3}-C(O)OH$, $-O-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{1-6}-O-(CH_2)_{1-4}-C(O)OH$, $-(CH_2)_{1-5}-(O)O((C_1-C_6)alkyl)_2$, $-(CH_2)_{1-6}-OH$, $(C_3-C_8)(cycloalkyl)-C(O)-N(SO_2)(C_1-C_6)alkyl$, and $-(C_3-C_8)cycloalkyl$

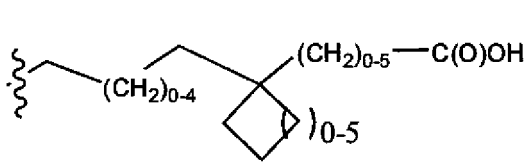
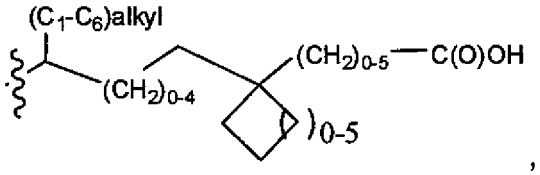
providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

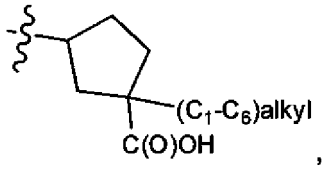
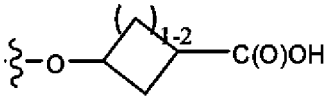
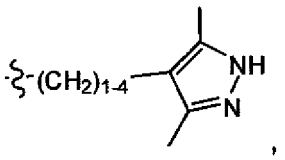
further providing that G is not attached to Y such that N is linked to O, S or N, and

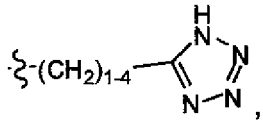
still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

In another embodiment, in Formula 2, R^1 is , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of:

$-(CH_2)_{1-6}$-C(O)OH, $-(CH_2)_{0-4}CH((C_1-C_6)alkyl)-(CH_2)_{1-5}$-C(O)OH, $-(CH_2)_{1-5}$-CH((C_1-C_6)alkyl)-C(O)OH, $-(CH_2)_{0-5}$-(C_3-C_8)cycloalkyl-C(O)OH, $-(CH_2)_{0-5}$-(C_3-C_8)cycloalkyl-$(CH_2)_{1-6}$-C(O)OH, $-(CH_2)_{1-6}$-C(O)-NH-SO_2-(C_3-C_8)cycloalkyl, $-(CH_2)_{1-6}$-C(O)-N-SO_2-(C_1-C_6)alkyl, $-(CD_2)_{1-6}$-C(O)OH,

, ,

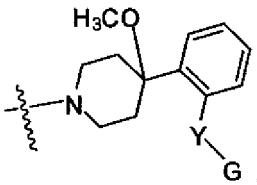
, , ,

, $-(CH_2)_{1-6}$-O-(C_1-C_6)alkyl, $-(C_1-C_6)$alkyl, -NH-$(CH_2)_{1-3}$-C(O)OH, -O-(C_3-C_8)cycloalkyl-C(O)OH, $-(CH_2)_{1-6}$-O-$(CH_2)_{1-4}$-C(O)OH, $-(CH_2)_{1-5}$-(O)O((C_1-C_6)alkyl)$_2$, $-(CH_2)_{1-6}$-OH, (C_3-C_8)(cycloalkyl)-C(O)-N(SO_2)(C_1-C_6)alkyl, and $-(C_3-C_8)$cycloalkyl

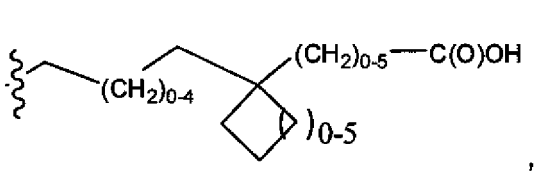
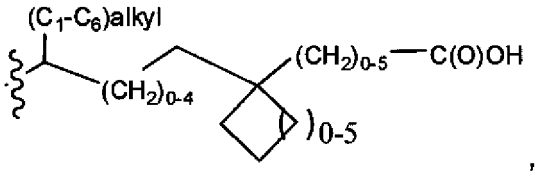
providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

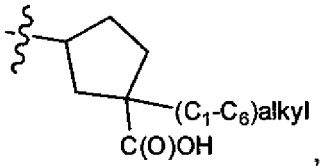
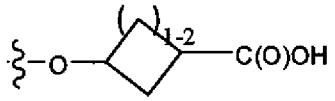
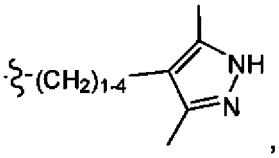
further providing that G is not attached to Y such that N is linked to O, S or N, and

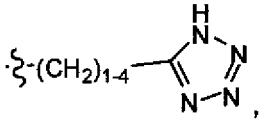
still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

In another embodiment, in Formula 2, R^1 is , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of:

$-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{0-4}CH((C_1-C_6)alkyl)-(CH_2)_{1-5}-C(O)OH$, $-(CH_2)_{1-5}-CH((C_1-C_6)alkyl)-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{1-6}-C(O)-NH-SO_2-(C_3-C_8)cycloalkyl$, $-(CH_2)_{1-6}-C(O)-N-SO_2-(C_1-C_6)alkyl$, $-(CD_2)_{1-6}-C(O)OH$,

, ,

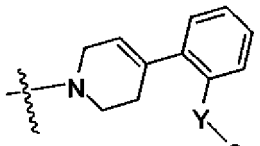
, , ,

, $-(CH_2)_{1-6}-O-(C_1-C_6)alkyl$, $-(C_1-C_6)alkyl$, $-NH-(CH_2)_{1-3}-C(O)OH$, $-O-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{1-6}-O-(CH_2)_{1-4}-C(O)OH$, $-(CH_2)_{1-5}-(O)O((C_1-C_6)alkyl)_2$, $-(CH_2)_{1-6}-OH$, $(C_3-C_8)(cycloalkyl)-C(O)-N(SO_2)(C_1-C_6)alkyl$, and $-(C_3-C_8)cycloalkyl$

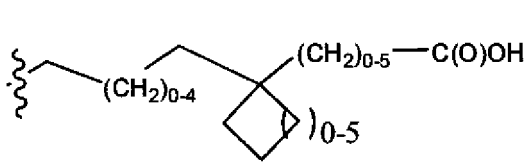
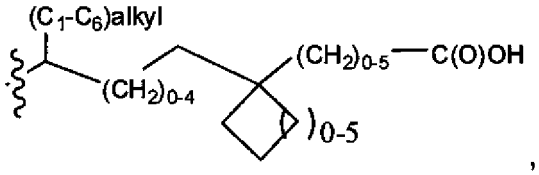
providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

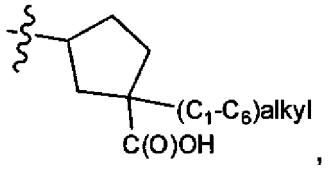
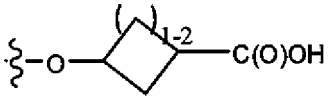
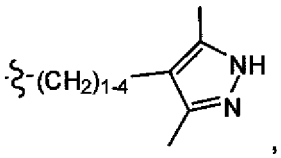
further providing that G is not attached to Y such that N is linked to O, S or N, and

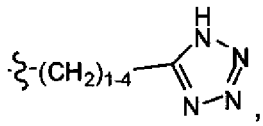
still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

In another embodiment, in Formula 2, R^1 is , wherein Y is selected from the group consisting of O, S, NR^8, SO_2 and CH_2 and G is selected from the group consisting of:

$-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{0-4}CH((C_1-C_6)alkyl)-(CH_2)_{1-5}-C(O)OH$, $-(CH_2)_{1-5}-CH((C_1-C_6)alkyl)-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{1-6}-C(O)-NH-SO_2-(C_3-C_8)cycloalkyl$, $-(CH_2)_{1-6}-C(O)-N-SO_2-(C_1-C_6)alkyl$, $-(CD_2)_{1-6}-C(O)OH$,

, ,

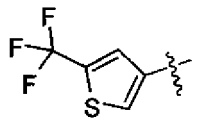
, , ,

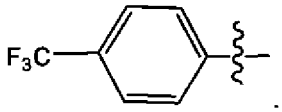
, $-(CH_2)_{1-6}-O-(C_1-C_6)alkyl$, $-(C_1-C_6)alkyl$, $-NH-(CH_2)_{1-3}-C(O)OH$, $-O-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{1-6}-O-(CH_2)_{1-4}-C(O)OH$, $-(CH_2)_{1-5}-(O)O((C_1-C_6)alkyl)_2$, $-(CH_2)_{1-6}-OH$, $(C_3-C_8)(cycloalkyl)-C(O)-N(SO_2)(C_1-C_6)alkyl$, and $-(C_3-C_8)cycloalkyl$

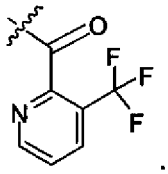
providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

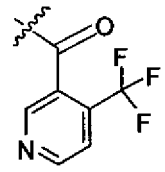
further providing that G is not attached to Y such that N is linked to O, S or N, and

still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

In another embodiment, in Formula 2, R^2 is .

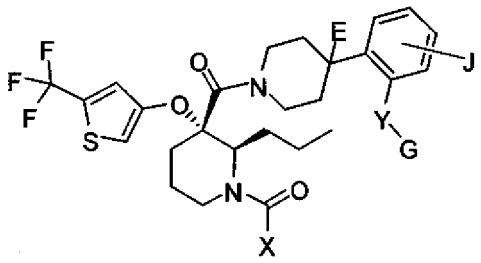
In another embodiment, in Formula 2, R^2 is .

In another embodiment, in Formula 2, X is .

In another embodiment, in Formula 2, X is .

In another embodiment, in Formula 2, Y is O, S, NR^8, SO_2, or $CR^8R^{8'}$.

In another embodiment, the compounds are represented by Formula 2A below:



Formula 2A

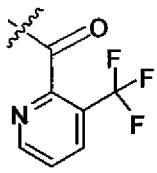
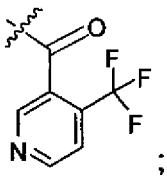
wherein E, Y, G and X, are selected independently of each other and wherein:

E is selected from the group consisting of H, halo, OH, CN, -O-(C_1-C_6)alkyl, (C_1-C_6)alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -(C_1-C_6)-C(O)OH, -(C_1-C_6)-C(O)$NR^8R^{8'}$, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl or heterocyclyl;

J, G and Y may or may not be present,

wherein when Y is not present, G is not present,

when Y is present it is selected from the group consisting of O,S, NR^8, SO_2, and $CR^8R^{8'}$, further wherein, when J is present, it is one or more moieties independently selected from the group consisting of halo;

X is  or ;

G is selected from the group consisting of $-(CR^8R^{8'})_n$-C(O)OH, $-(CR^8R^{8'})_n$-heteroaryl, $-(CR^8R^{8'})_n$-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$C(O)NR^8R^9$, $-(CR^8R^{8'})_n$-$(C_3$-$C_8)$cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-C(O)OH, $—(CR^8R^{8'})_n$-O-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-S-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-NH-$(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-CH_3, $—(CR^8R^{8'})_n$-heteroaryl, $—(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, $—(CR^8R^{8'})_n$-$P(O)O_2$, $—(CR^8R^{8'})_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and $(C_1$-$C_6)$alkyl; or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form $(C_3$-$C_8)$spirocycloalkyl,

R^9 is $SO_2(C_1$-$C_6)$alkyl or $SO_2(C_3$-$C_8)$cycloalkyl,

n is 0-10,

providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

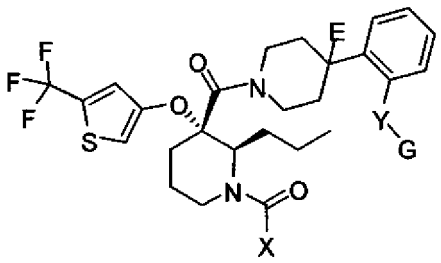
further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2A, can be unsubstituted or substituted with one or more $(C_1$-$C_6)$alkyl groups,

still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2A, can be replaced by a Deuterium atom.

In another embodiment, the compounds are represented by Formula 2B below:



Formula 2B

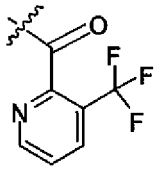
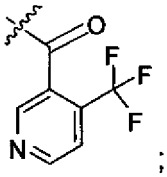
wherein E, Y, G and X, are selected independently of each other and wherein:

E is selected from the group consisting of H, OH, CN, -O-(C_1-C_6)alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -(C_1-C_6)-C(O)OH, and -(C_1-C_6)-C(O)$NR^8R^{8'}$;

G and Y may or may not be present,

wherein when Y is not present, G is not present,

when Y is present it is selected from the group consisting of O,S, SO_2, NR^8 and $CR^8R^{8'}$;

X is  or ;

G is selected from the group consisting of –($CR^8R^{8'}$)$_n$-C(O)OH, –($CR^8R^{8'}$)$_n$-heteroaryl, –($CR^8R^{8'}$)$_n$-C(O)NR^8R^9, –($CR^8R^{8'}$)$_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, –($CR^8R^{8'}$)$_n$-(C_3-C_8)cycloalkyl-($CR^8R^{8'}$)$_n$-C(O)OH, —($CR^8R^{8'}$)$_n$-O–($CR^8R^{8'}$)$_n$-C(O)OH, —($CR^8R^{8'}$)$_n$-S–($CR^8R^{8'}$)$_n$-C(O)OH, C(O)OH, —($CR^8R^{8'}$)$_n$-NH–($CR^8R^{8'}$)$_n$-C(O)OH, —($CR^8R^{8'}$)$_n$-O–($CR^8R^{8'}$)$_n$-CH_3, —($CR^8R^{8'}$)$_n$-S–($CR^8R^{8'}$)$_n$-CH_3, —($CR^8R^{8'}$)$_n$-NH–($CR^8R^{8'}$)$_n$-CH_3, —($CR^8R^{8'}$)$_n$-CH_3, —($CR^8R^{8'}$)$_n$-heteroaryl, —($CR^8R^{8'}$)$_n$-P(O)$OR^8OR^{8'}$, —($CR^8R^{8'}$)$_n$-P(O)O_2, —($CR^8R^{8'}$)$_n$-OH,

wherein each R^8 and $R^{8'}$ is independently selected from the group consisting of H and (C_1-C_6)alkyl,

or further wherein R^8 and $R^{8'}$ together with the carbon to which each is attached can cyclicize to form (C_3-C_8)spirocycloalkyl,

R^9 is SO_2(C_1-C_6)alkyl or SO_2(C_3-C_8)cycloalkyl,

n is 0-10,

providing that when n is 0, G is not attached to Y such that O is linked to O, S, N, or SO_2,

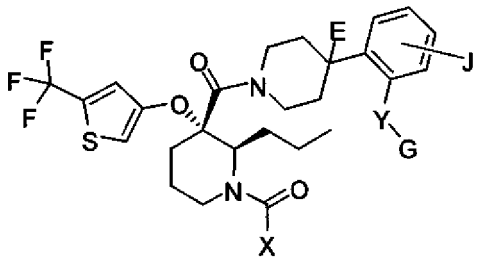
further providing that when n is 0, G is not attached to Y such that N is linked to O, S or N, and

still further providing that when n is 0, G is not attached to Y such that S is linked to O, N or SO_2,

further wherein, any spirocycloalkyl or cycloalkyl in Formula 2, can be unsubstituted or substituted with one or more $(C_1$-$C_6)$alkyl groups,

still further wherein, any Hydrogen atom that is substituted on any alkyl, cycloalkyl, heterocycloalkyl or spirocycloalkyl, in Formula 2, can be replaced by a Deuterium atom.

In another embodiment, the compounds are represented by Formula 2C below:



Formula 2C

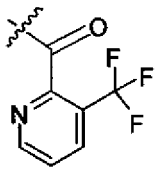
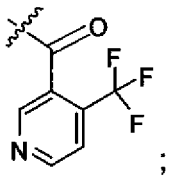
wherein E, Y, G and X, are selected independently of each other and wherein:

E is selected from the group consisting of H, halo, OH, CN, -O-$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -$(C_1$-$C_6)$-C(O)OH, -$(C_1$-$C_6)$-C(O)$NR^8R^{8'}$, -$(C_2$-$C_6)$alkenyl, -$(C_2$-$C_6)$alkynyl or heterocyclyl;

J, G and Y may or may not be present,

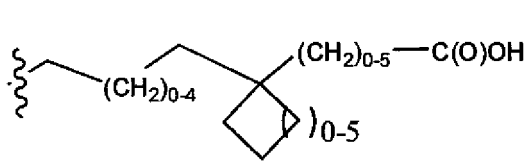
wherein when Y is not present, G is not present,

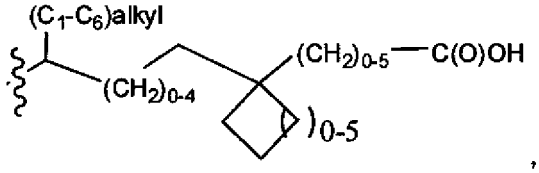
when Y is present it is selected from the group consisting of O,S, NR^8, SO_2, and $CR^8R^{8'}$, further wherein, when J is present, it is one or more moieties independently selected from the group consisting of halo;

X is  or  ;

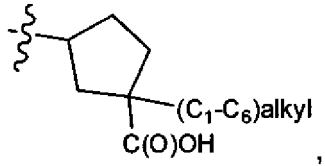
G is selected from the group consisting of:

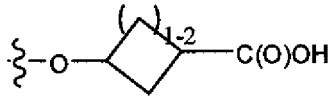
$-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{0-4}CH((C_1-C_6)alkyl)-(CH_2)_{1-5}-C(O)OH$, $-(CH_2)_{1-5}-CH((C_1-C_6)alkyl)-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{0-5}-(C_3-C_8)cycloalkyl-(CH_2)_{1-6}-C(O)OH$, $-(CH_2)_{1-6}-C(O)-NH-SO_2-(C_3-C_8)cycloalkyl$, $-(CH_2)_{1-6}-C(O)-N-SO_2-(C_1-C_6)alkyl$, $-(CD_2)_{1-6}-C(O)OH$,

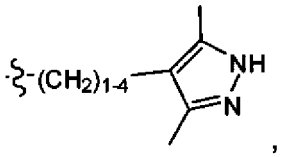


,


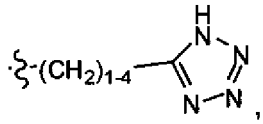
,



,


,


,



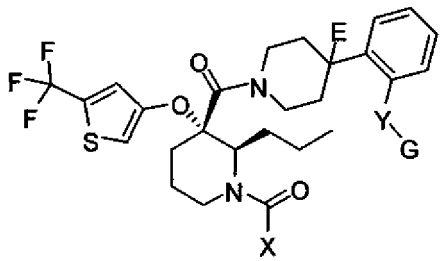
, $-(CH_2)_{1-6}-O-(C_1-C_6)alkyl$, $-(C_1-C_6)alkyl$, $-NH-(CH_2)_{1-3}-C(O)OH$, $-O-(C_3-C_8)cycloalkyl-C(O)OH$, $-(CH_2)_{1-6}-O-(CH_2)_{1-4}-C(O)OH$, $-(CH_2)_{1-5}-(O)O((C_1-C_6)alkyl)_2$, $-(CH_2)_{1-6}-OH$, $(C_3-C_8)(cycloalkyl)-C(O)-N(SO_2)(C_1-C_6)alkyl$, and $-(C_3-C_8)cycloalkyl$

providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

further providing that G is not attached to Y such that N is linked to O, S or N, and

still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

In another embodiment, the compounds are represented by Formula 2D below:



Formula 2D

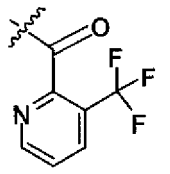
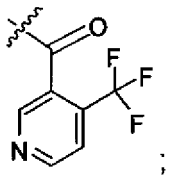
wherein E, Y, G and X, are selected independently of each other and wherein:

E is selected from the group consisting of H, OH, CN, -O-(C_1-C_6)alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -(C_1-C_6)-C(O)OH, and -(C_1-C_6)-C(O)$NR^8R^{8'}$;

G and Y may or may not be present,

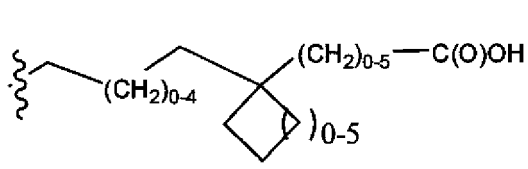
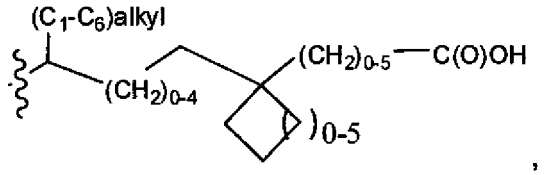
wherein when Y is not present, G is not present,

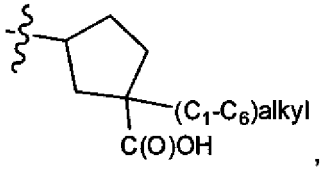
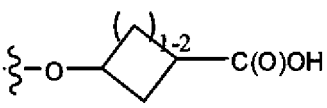
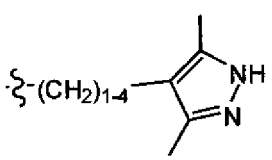
when Y is present it is selected from the group consisting of O,S, SO_2, NR^8 and $CR^8R^{8'}$;

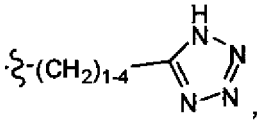
X is  or ;

G is selected from the group consisting of:

-$(CH_2)_{1-6}$-C(O)OH, -$(CH_2)_{0-4}$CH((C_1-C_6)alkyl)-$(CH_2)_{1-5}$-C(O)OH, -$(CH_2)_{1-5}$-CH((C_1-C_6)alkyl)-C(O)OH, -$(CH_2)_{0-5}$-(C_3-C_8)cycloalkyl-C(O)OH, -$(CH_2)_{0-5}$-(C_3-C_8)cycloalkyl-$(CH_2)_{1-6}$-C(O)OH, -$(CH_2)_{1-6}$-C(O)-NH-SO_2-(C_3-C_8)cycloalkyl, -$(CH_2)_{1-6}$-C(O)-N-SO_2-(C_1-C_6)alkyl, -$(CD_2)_{1-6}$-C(O)OH,

, ,

, , ,

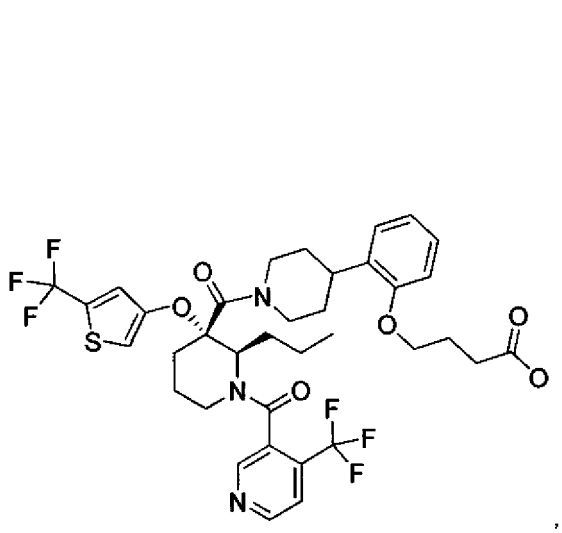

, $-(CH_2)_{1-6}-O-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkyl, $-NH-(CH_2)_{1-3}-C(O)OH$, $-O-(C_3-C_8)$cycloalkyl-$C(O)OH$, $-(CH_2)_{1-6}-O-(CH_2)_{1-4}-C(O)OH$, $-(CH_2)_{1-5}-(O)O((C_1-C_6)alkyl)_2$, $-(CH_2)_{1-6}-OH$, (C_3-C_8)(cycloalkyl)-$C(O)-N(SO_2)(C_1-C_6)$alkyl, and $-(C_3-C_8)$cycloalkyl

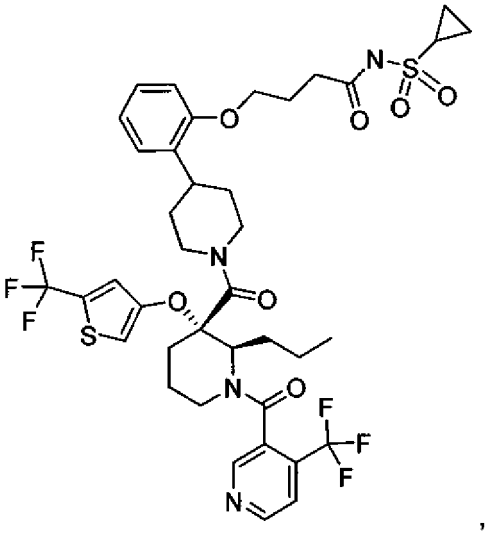
providing that G is not attached to Y such that O is linked to O, S, N, or SO_2,

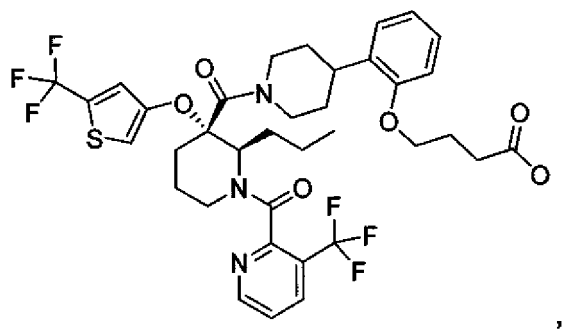
further providing that G is not attached to Y such that N is linked to O, S or N, and

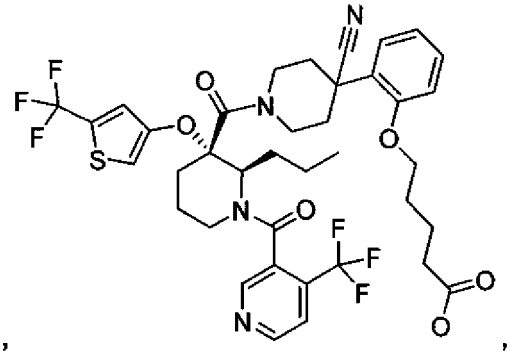
still further providing that G is not attached to Y such that S is linked to O, N or SO_2.

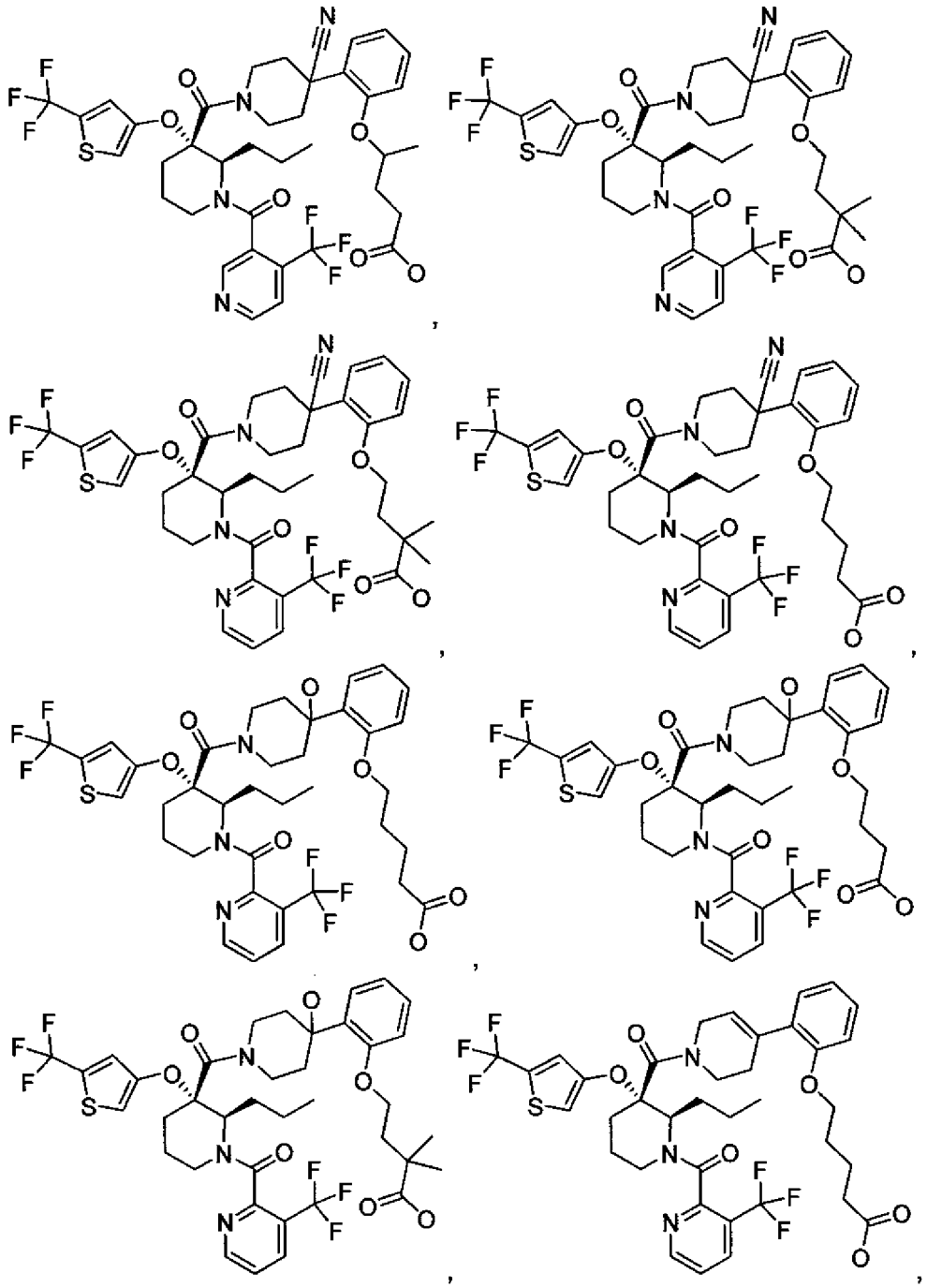
Non-limiting examples of compounds of the present invention of Formula 2 include:

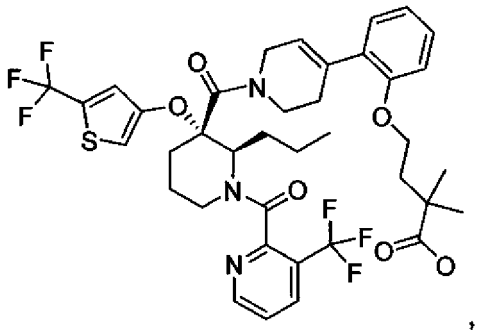

,


,

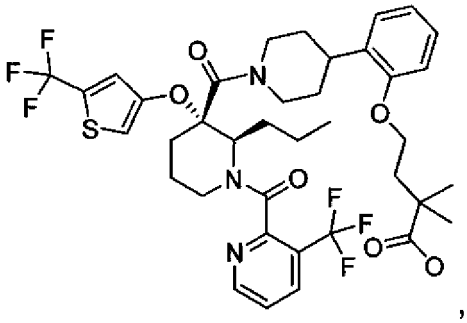

,


,

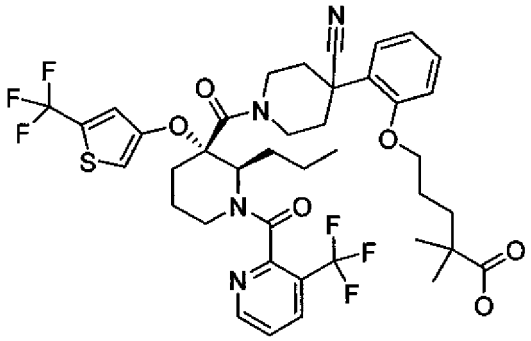




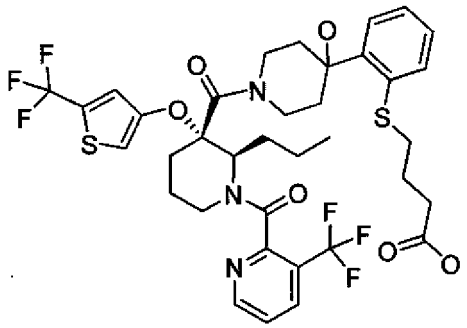
,



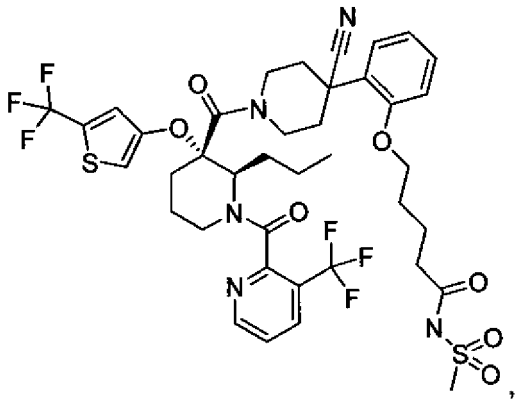
,



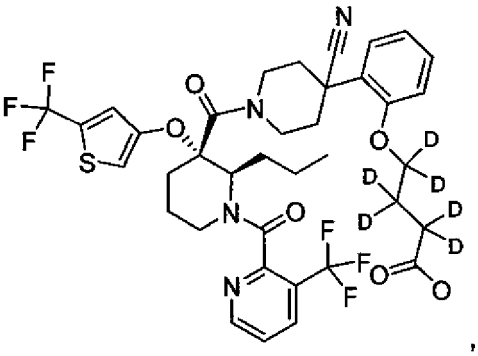
,



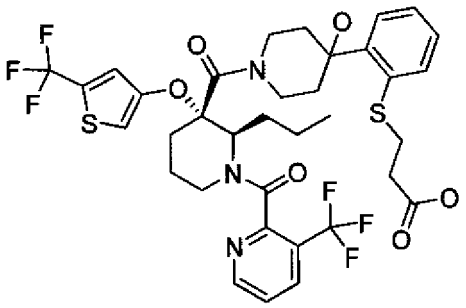
,



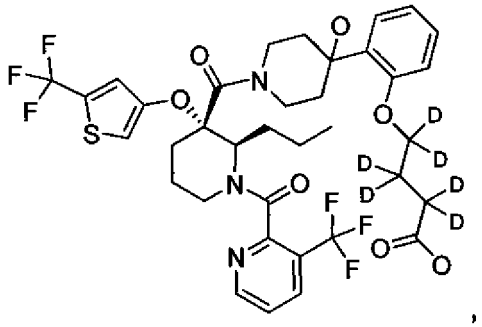
,



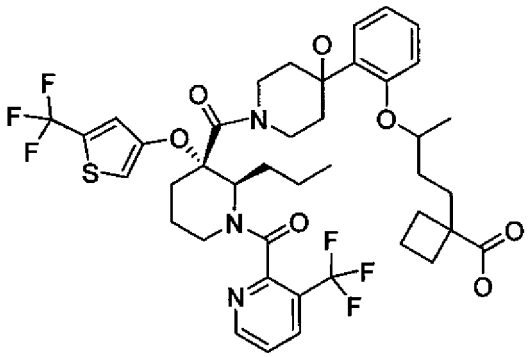
,



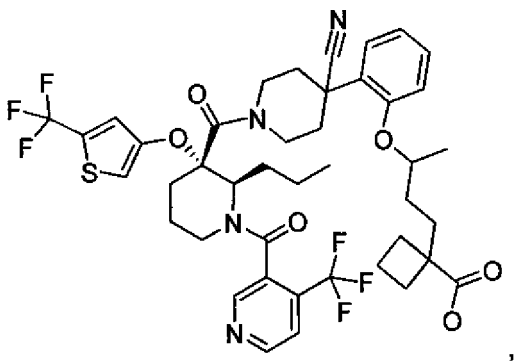
,



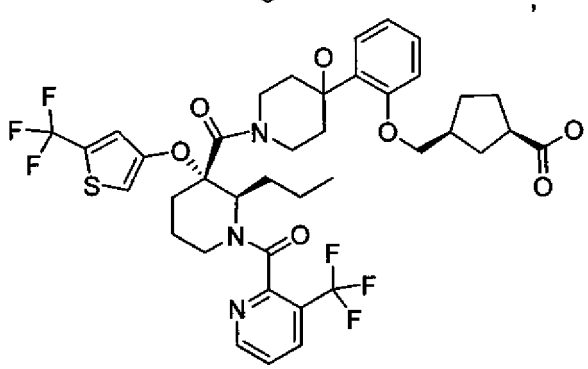
,



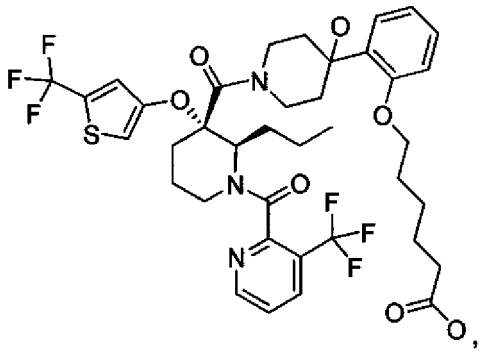
,



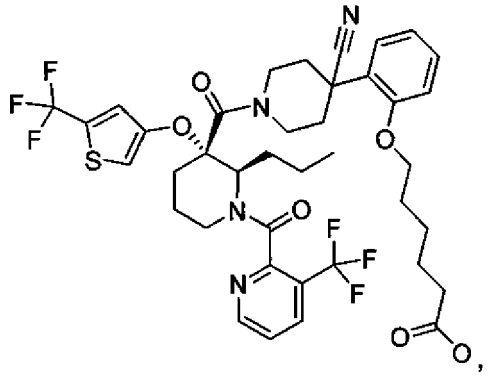
,



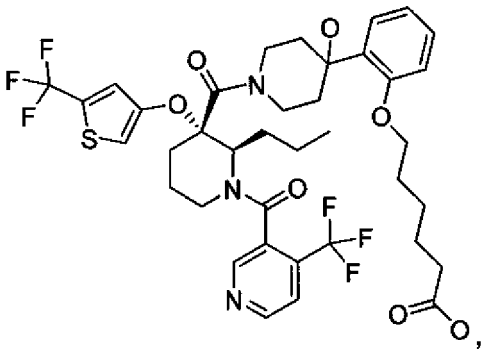
,



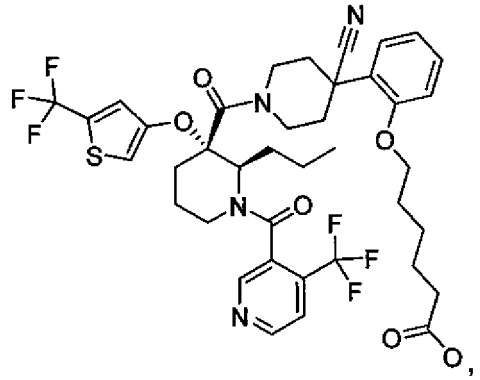
,



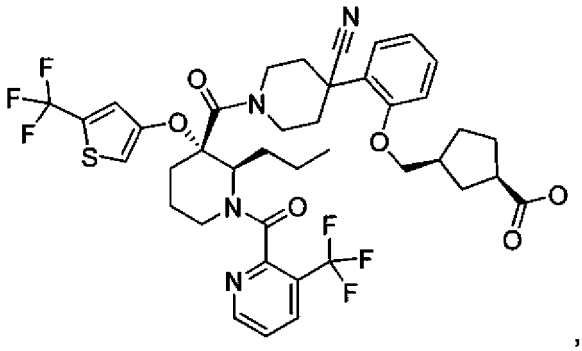
,



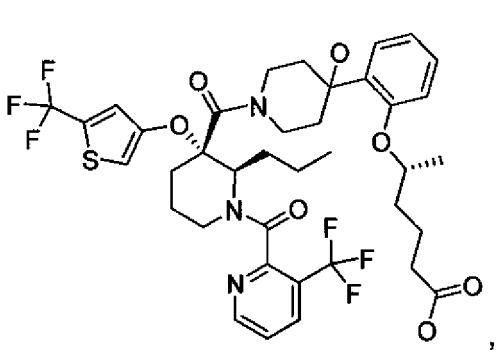
,



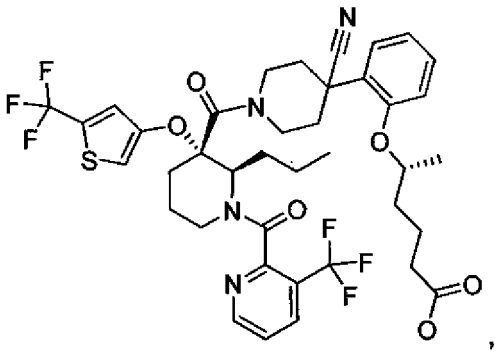
,



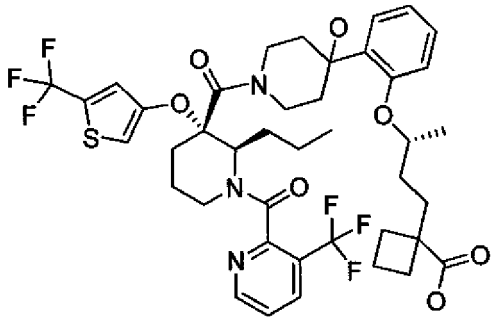
,



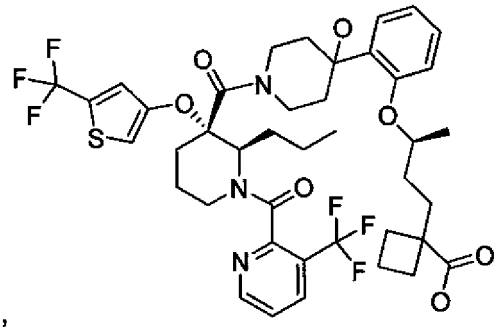
,



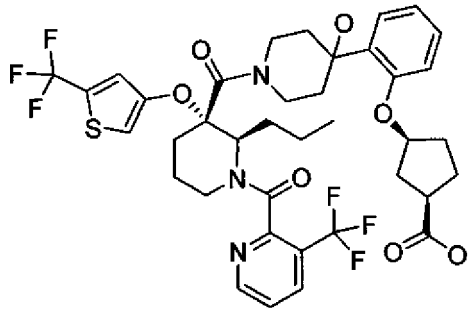
,



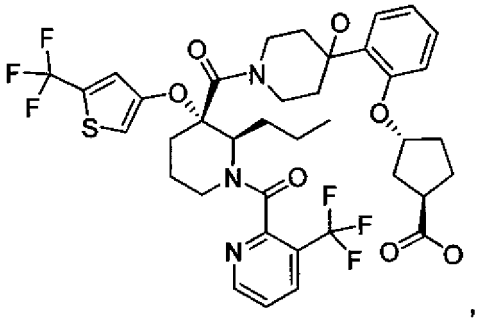
,



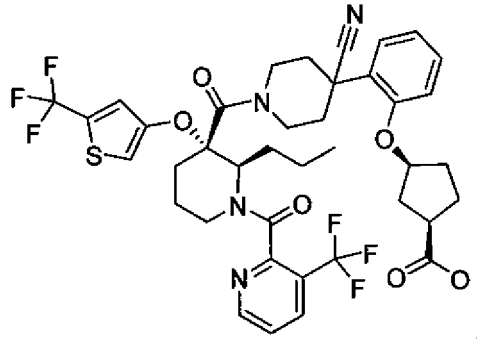
,



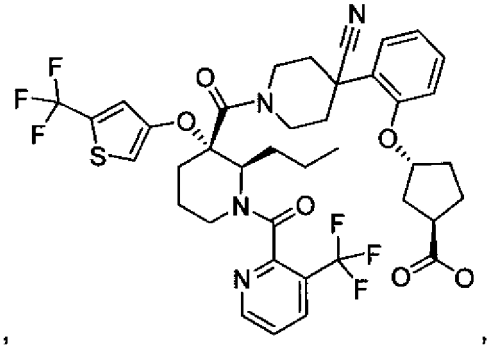
,



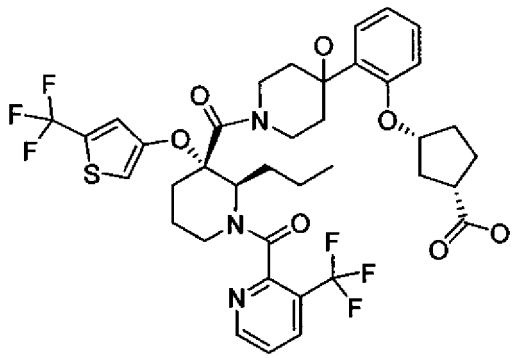
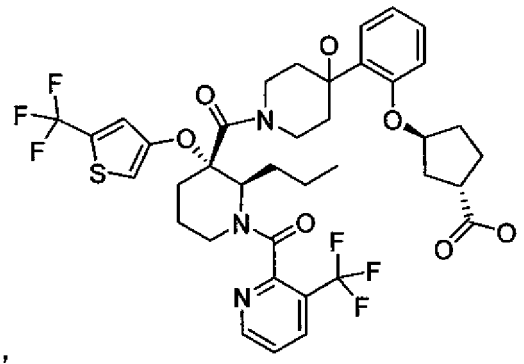
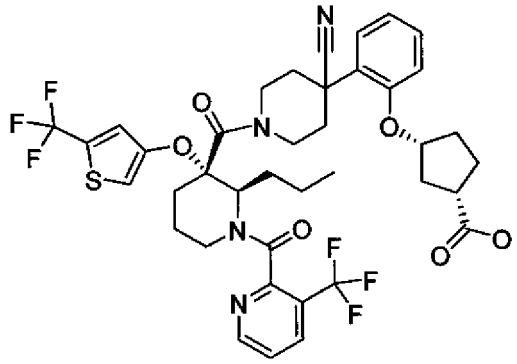
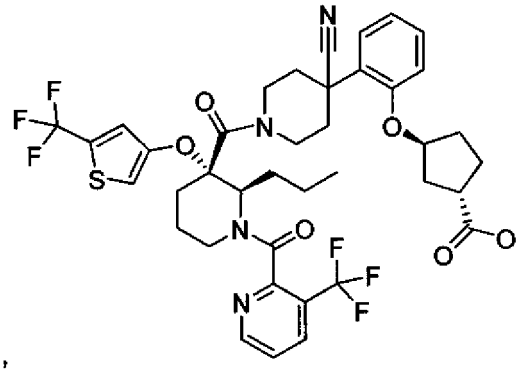
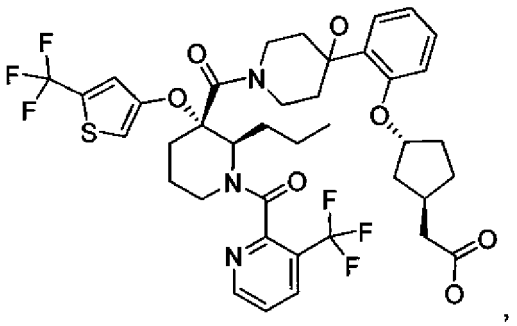
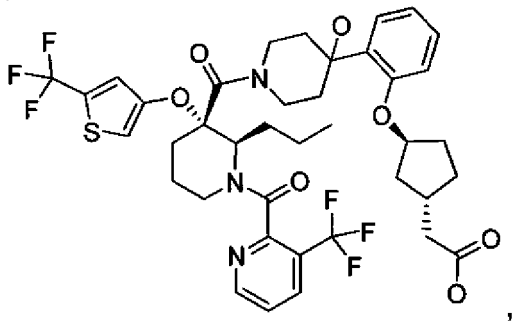
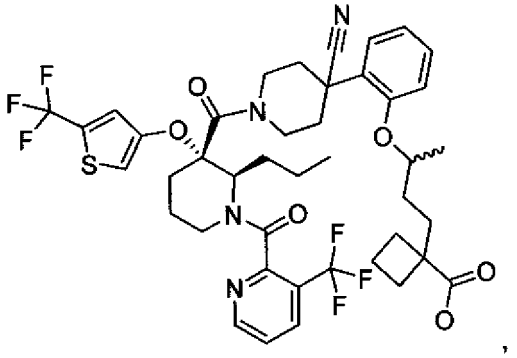
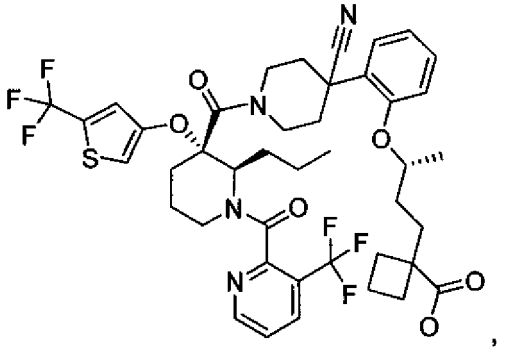
,

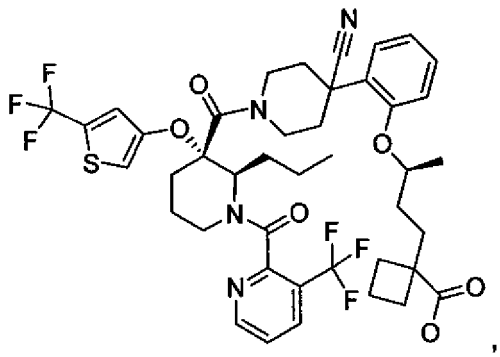


,

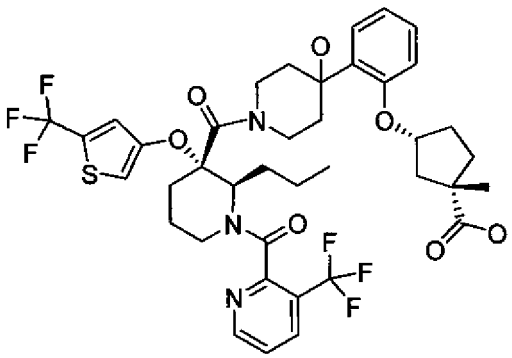


,

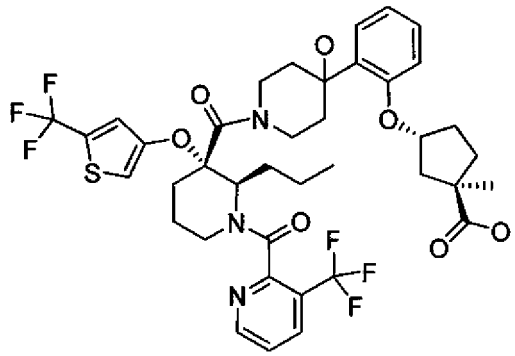

,

,

,

,

,

,

,

,



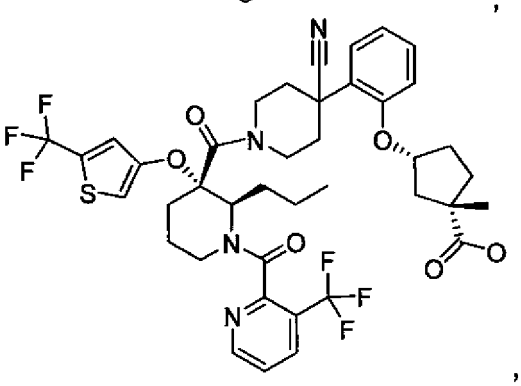
,



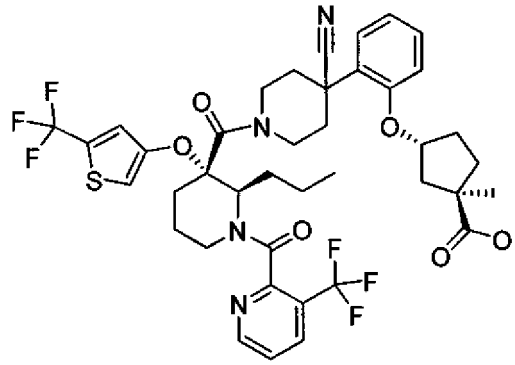
,



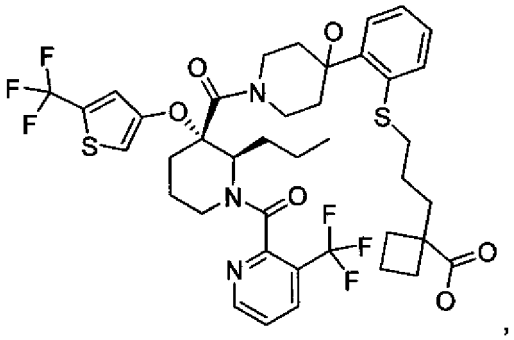
,



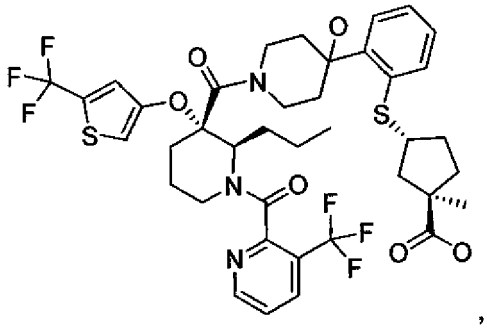
,



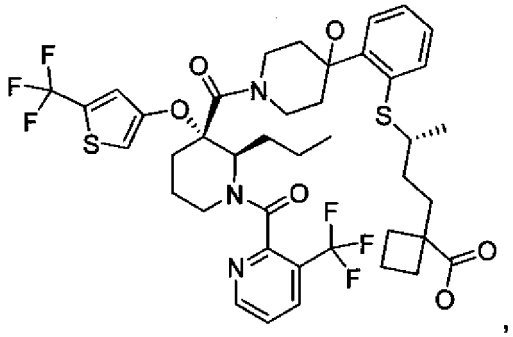
,



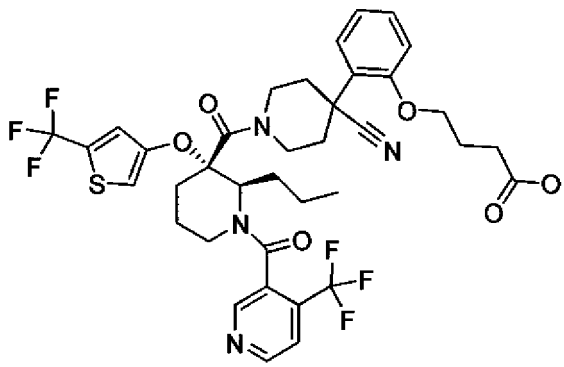
,



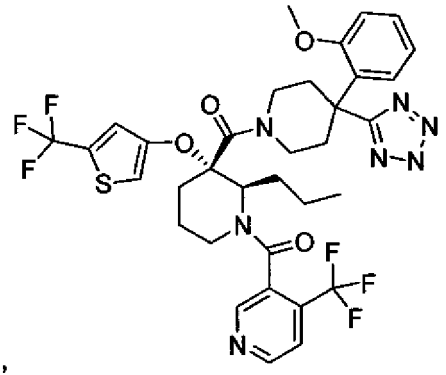
,



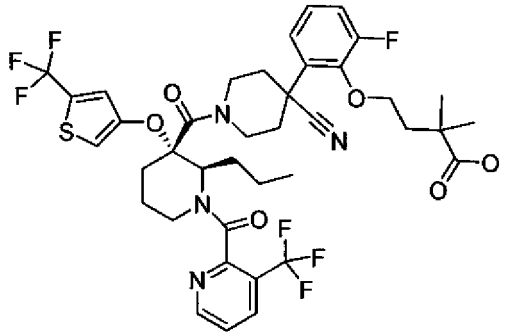
,



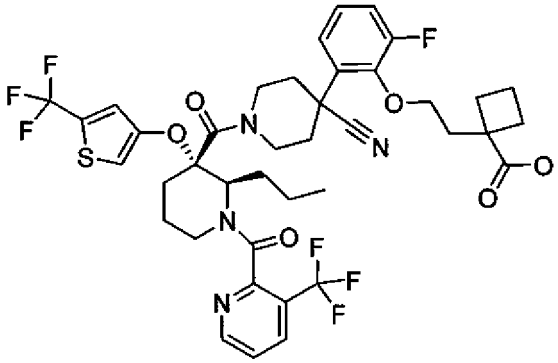
,



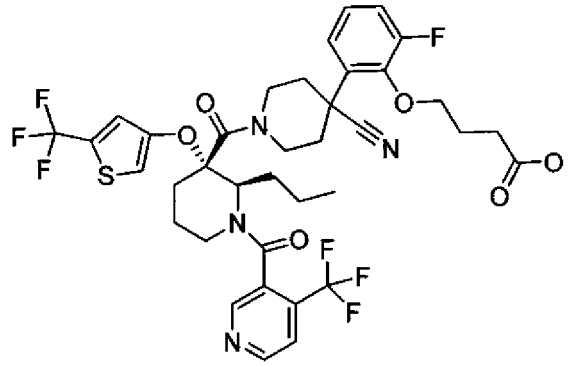
,



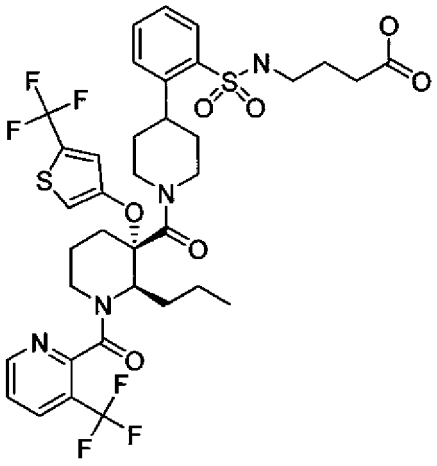
,



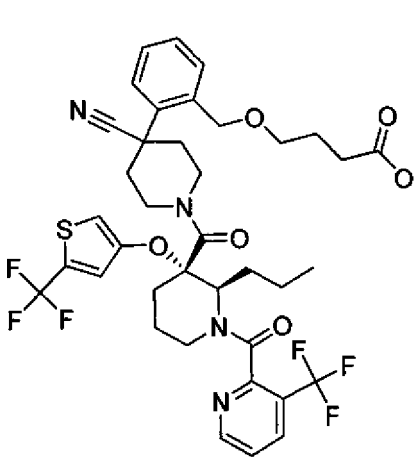
,



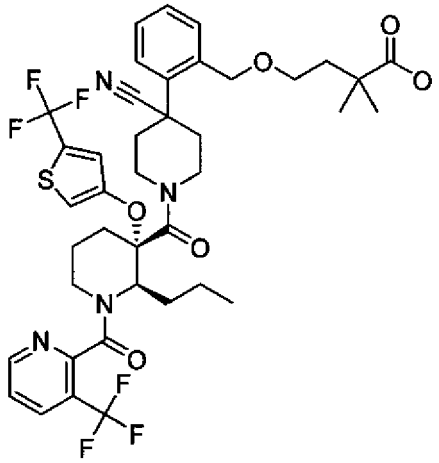
,



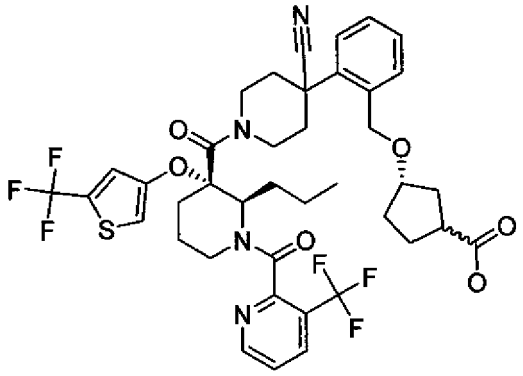
,



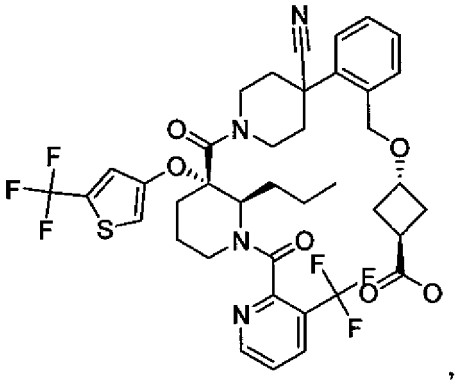
,



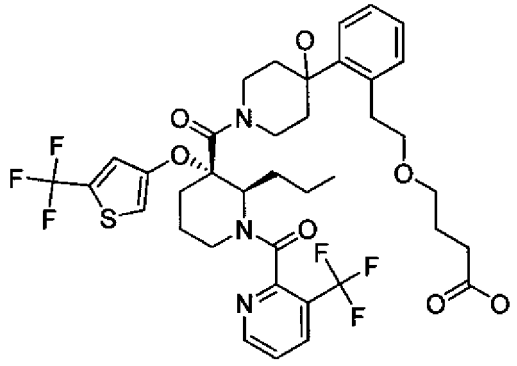
,



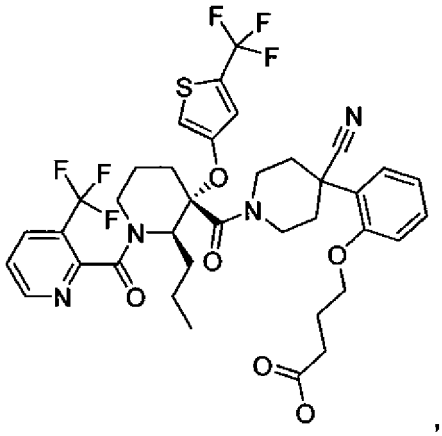
,



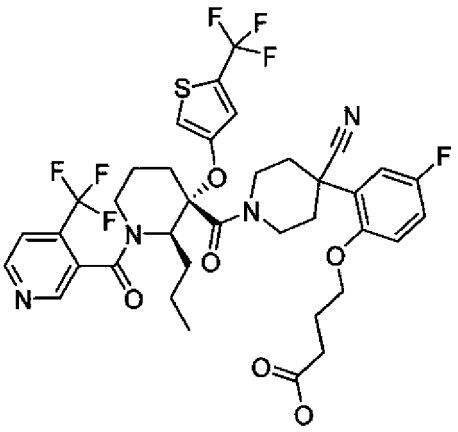
,



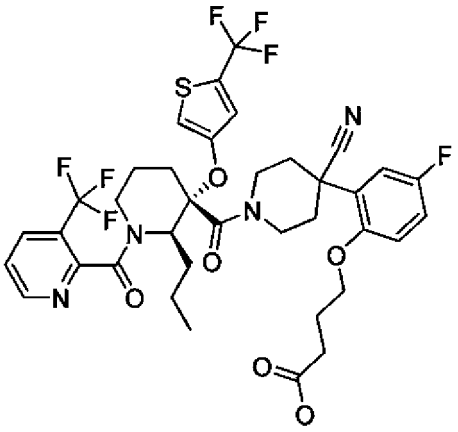
,



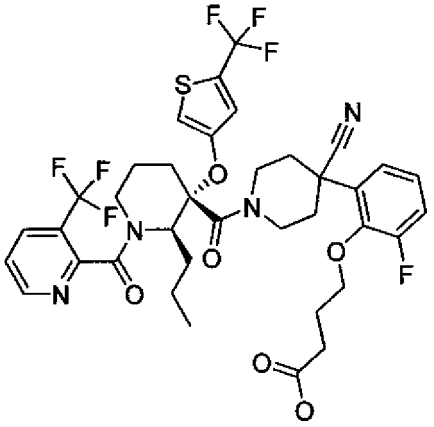
,



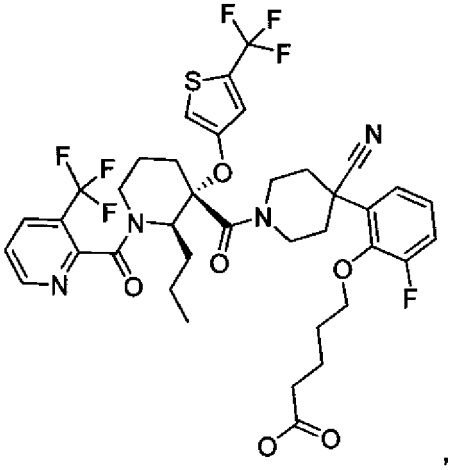
,



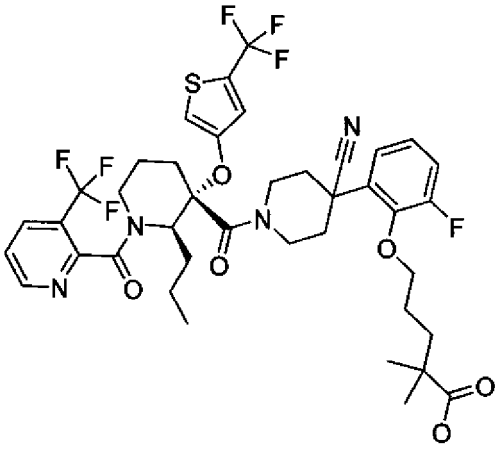
,



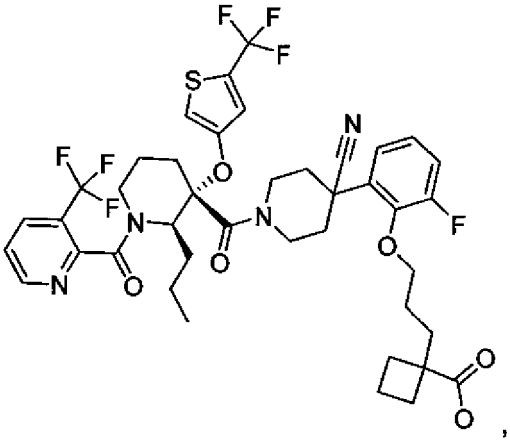
,



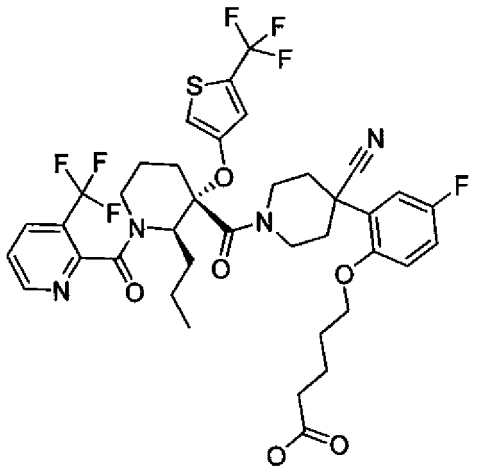
,



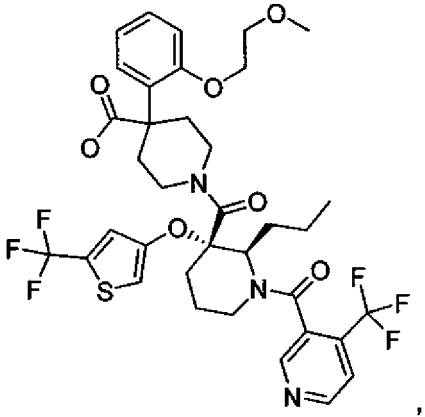
,



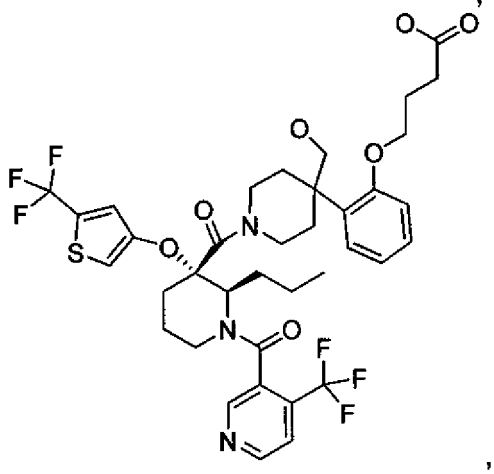
,



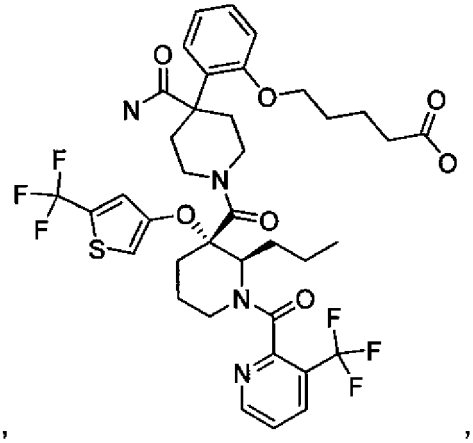
,



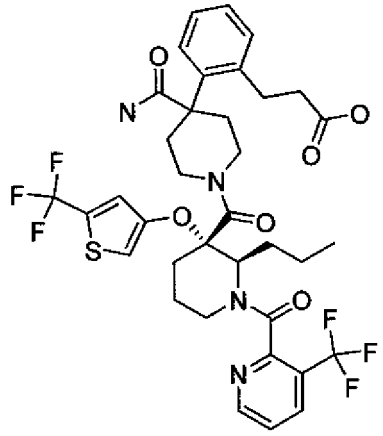
,



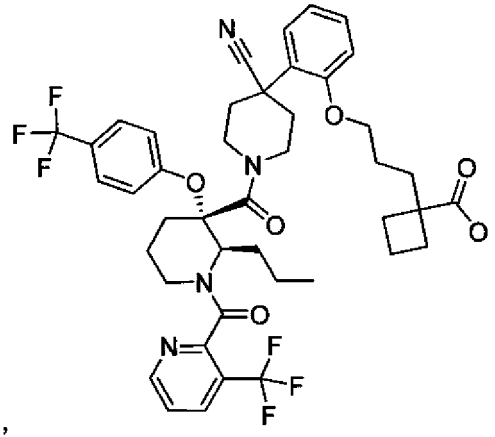
,



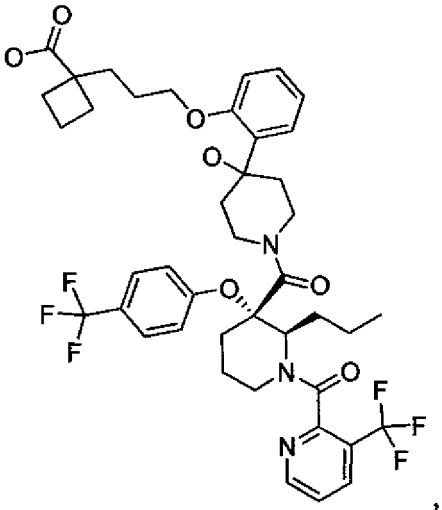
,



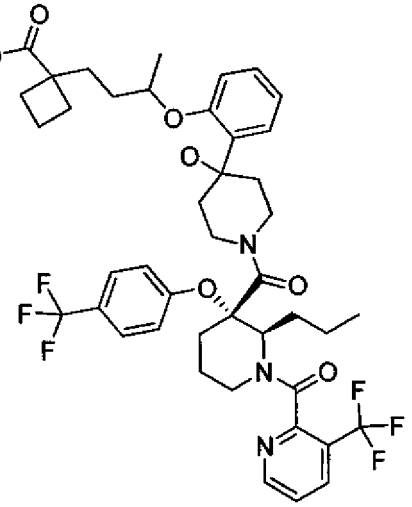
,



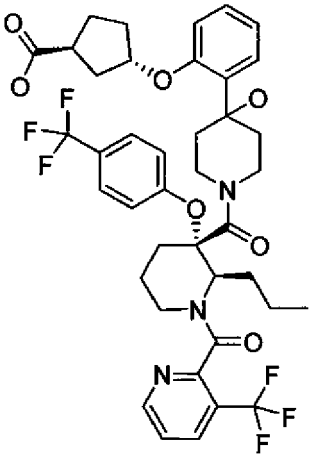
,



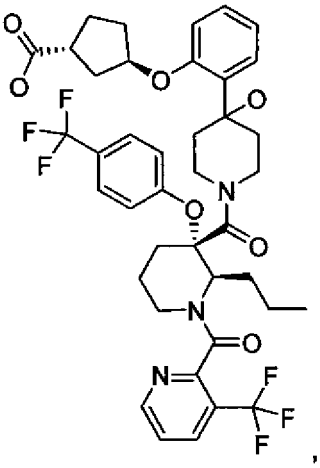
,



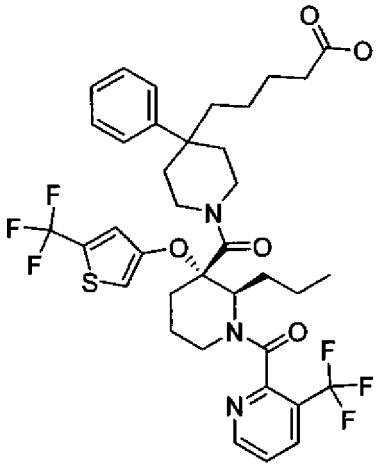
,



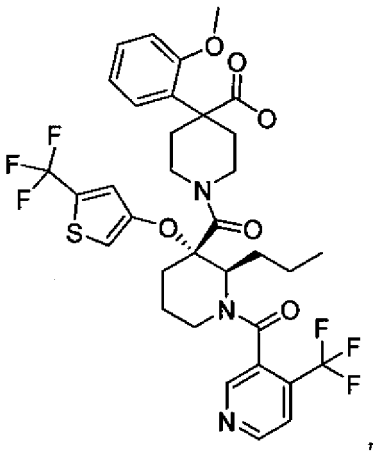
,



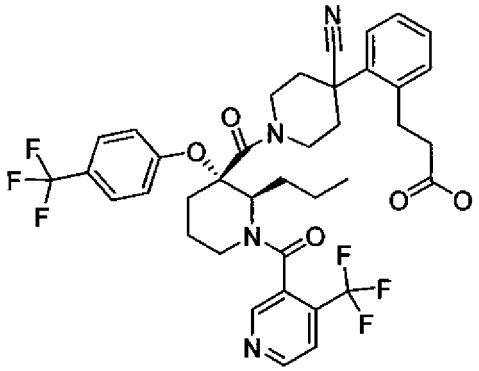
,



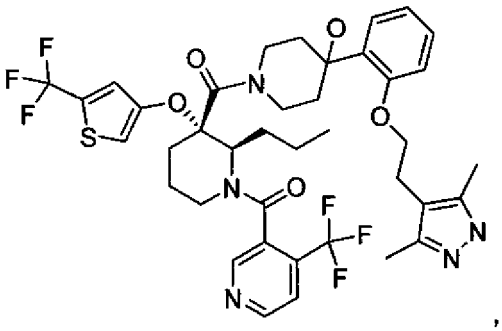
,



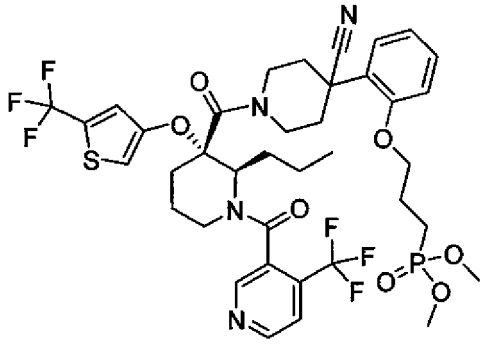
,



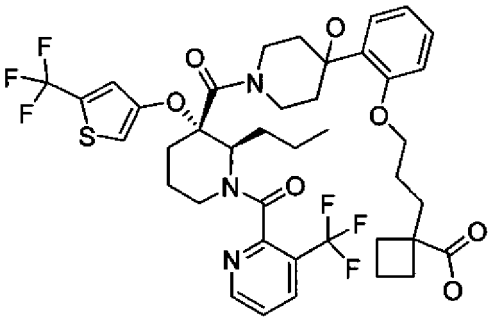
,

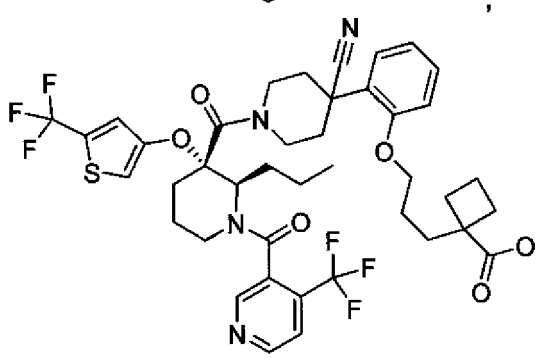


,

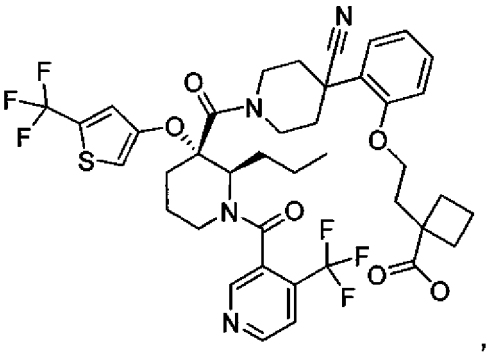


,

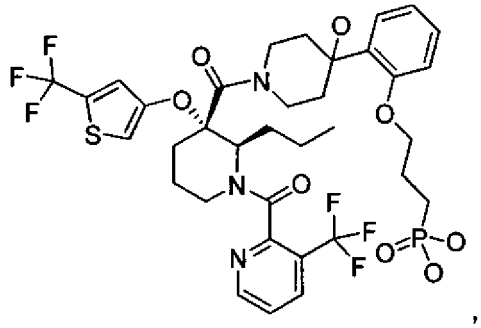




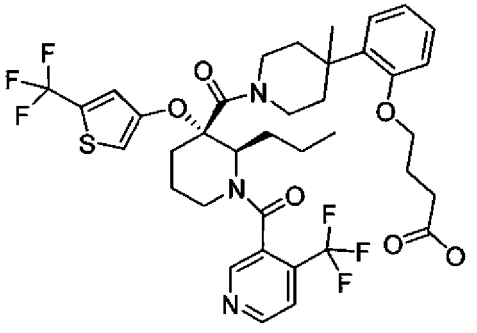
,

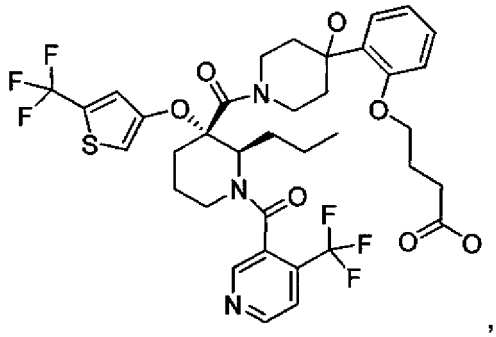


,

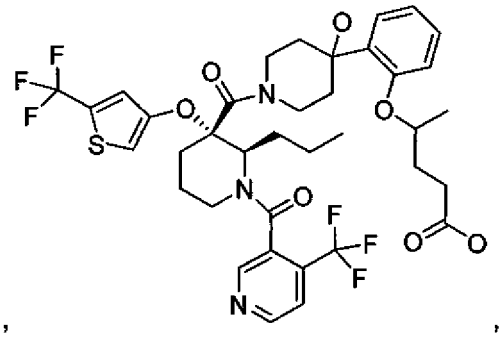


,

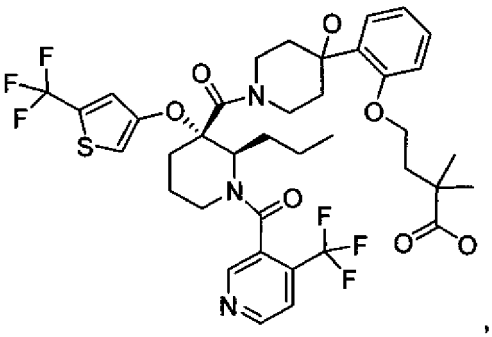




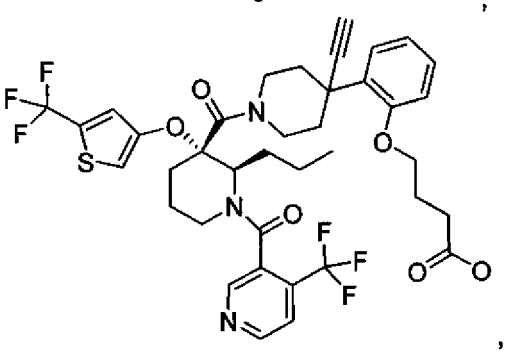
,



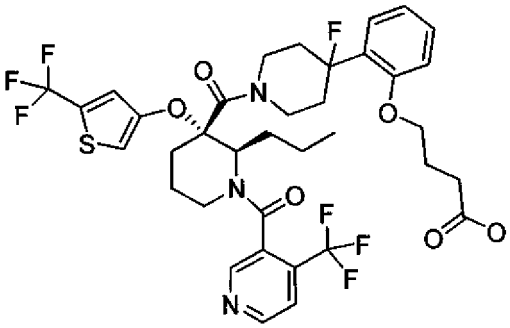
,



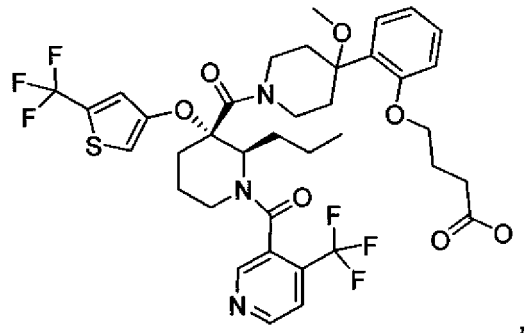
,



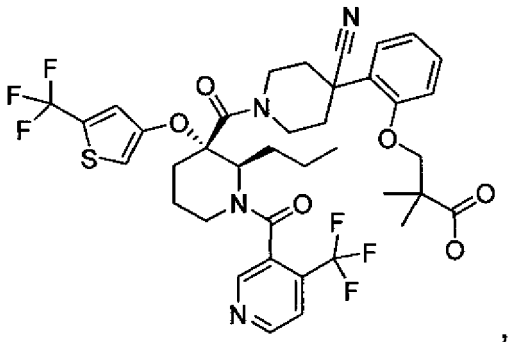
,



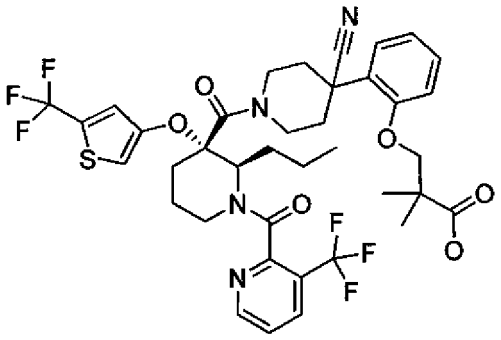
,



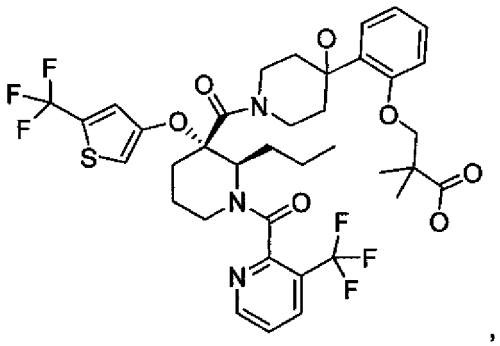
,



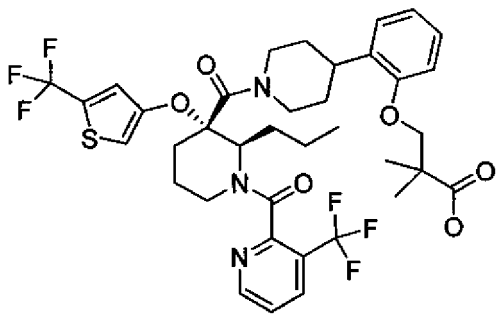
,



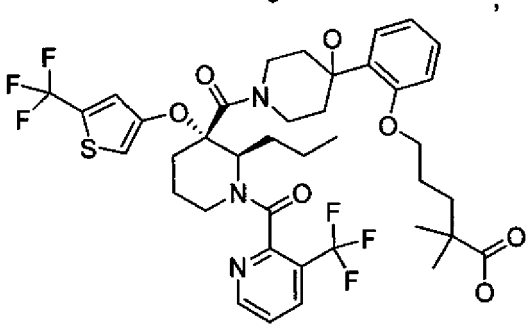
,



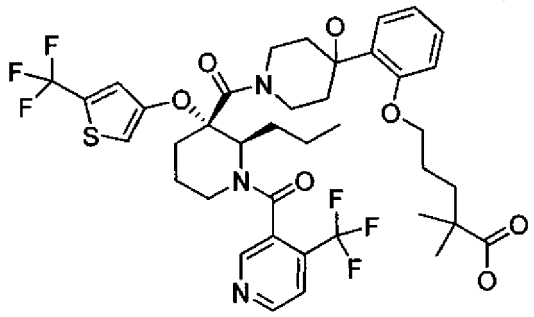
,



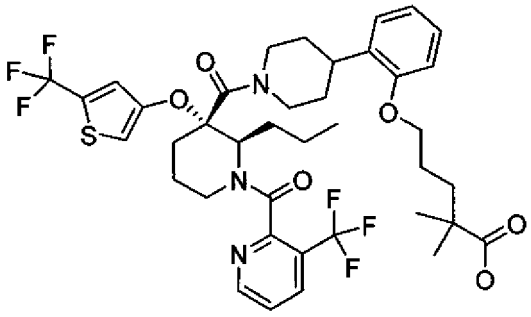
,



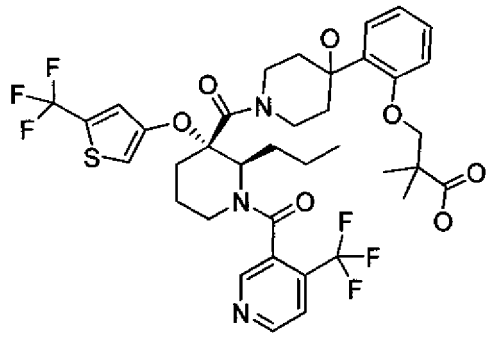
,



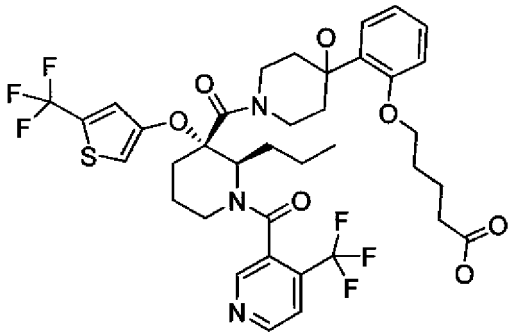
,



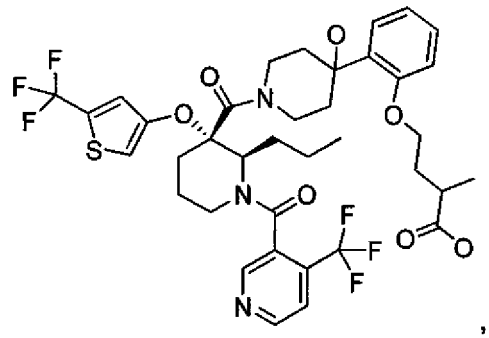
,



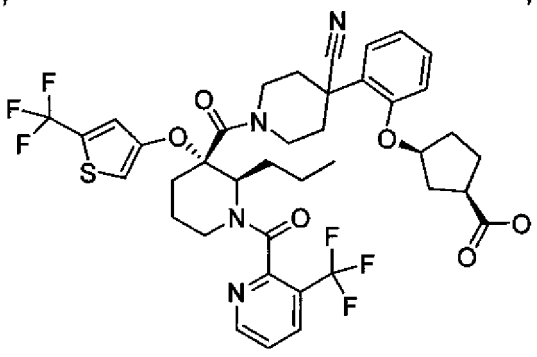
,



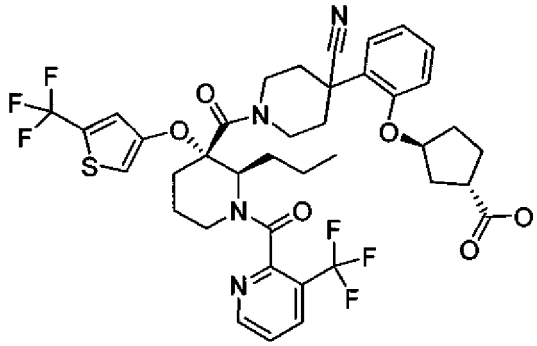
,



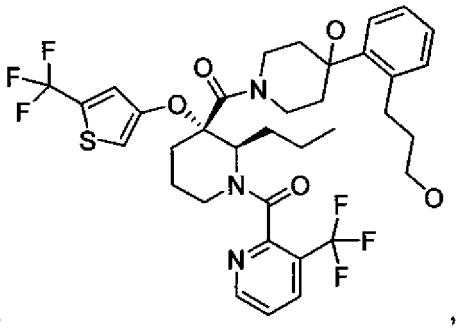
,



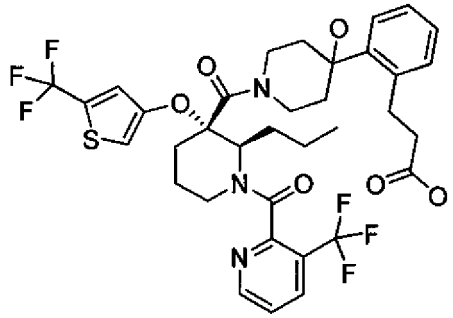
,



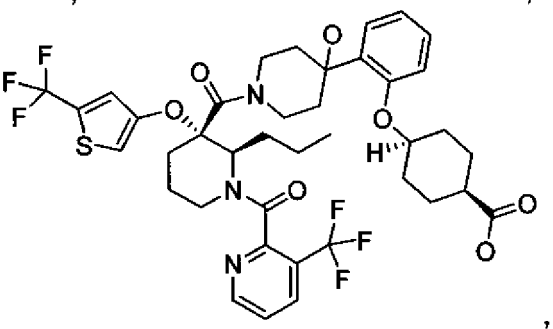
,



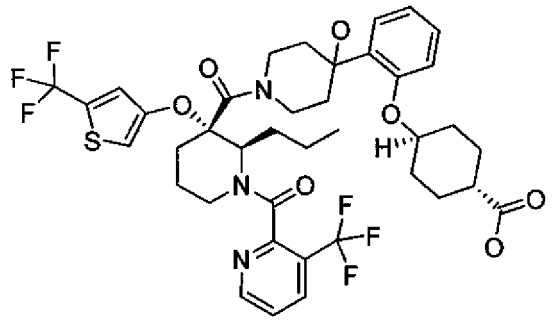
,



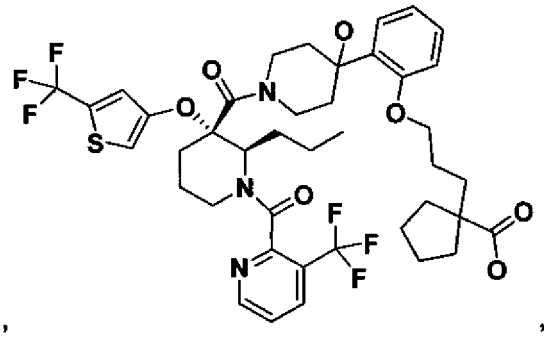
,



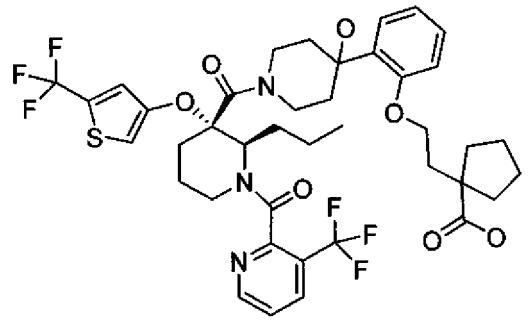
,



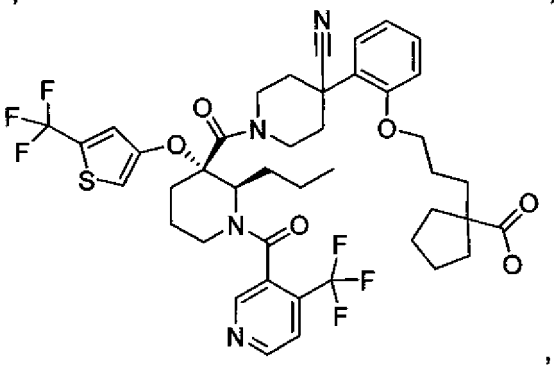
,



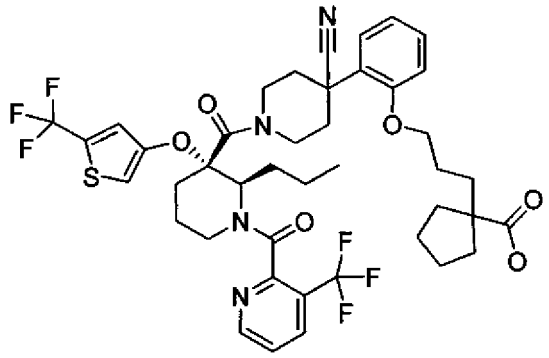
,



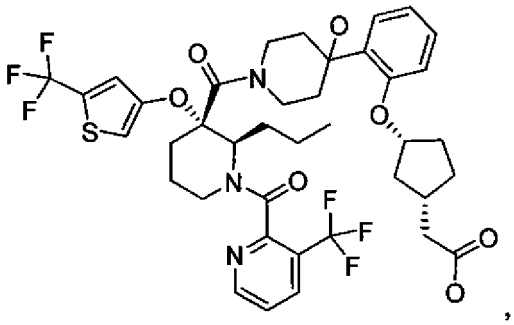
,



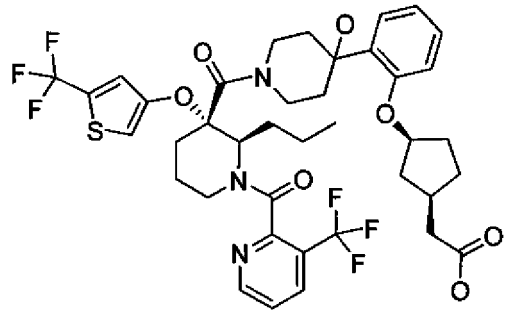
,



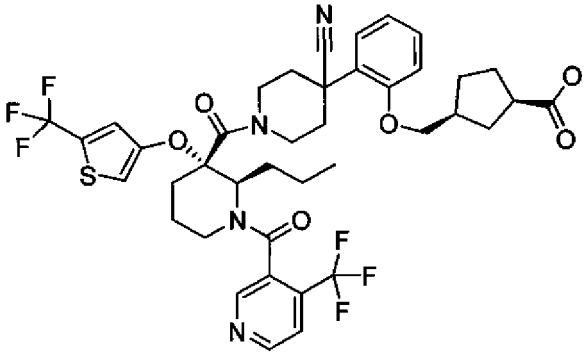
,



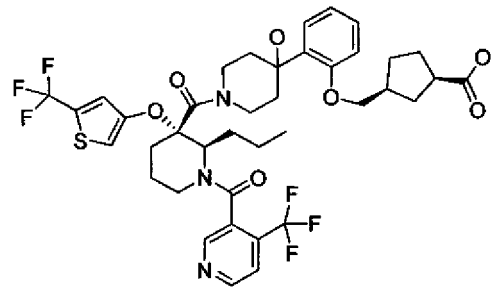
,



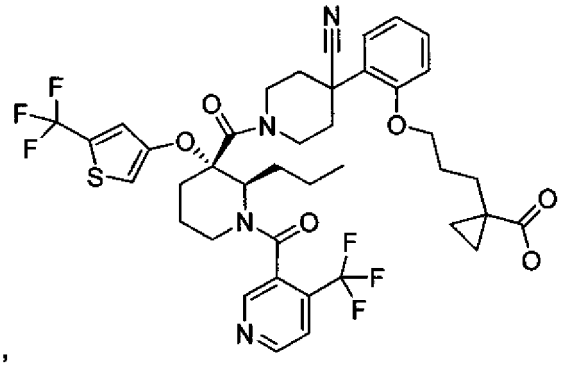
,



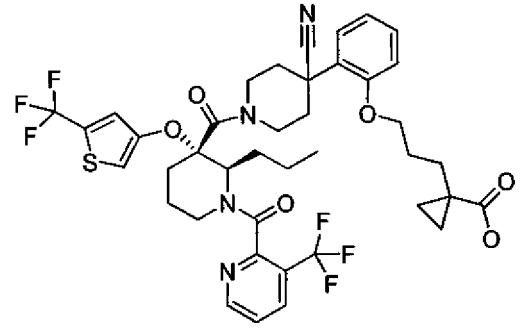
,



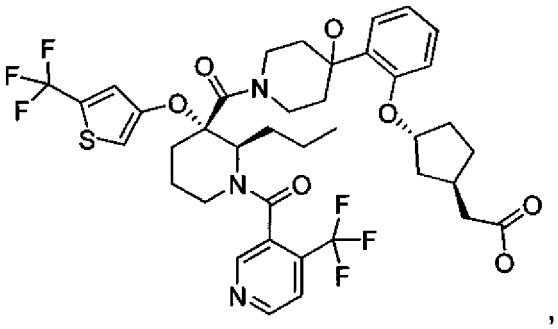
,



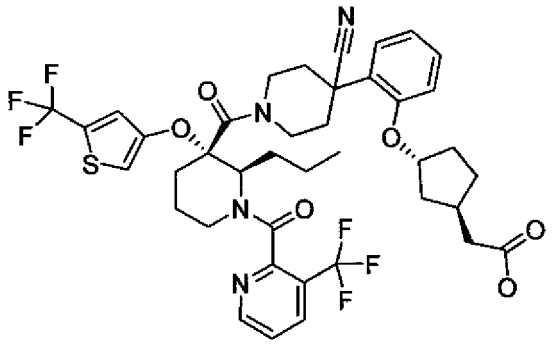
,



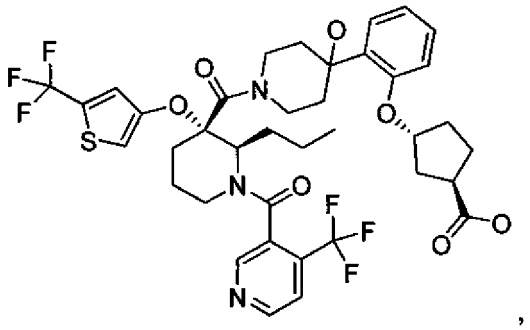
,



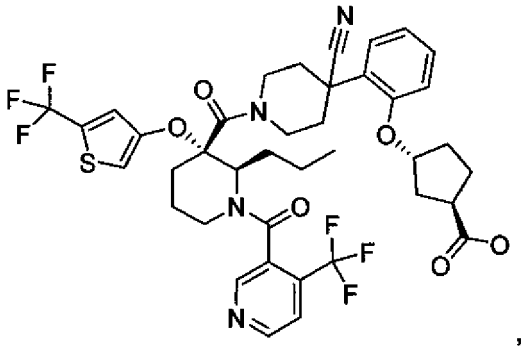
,



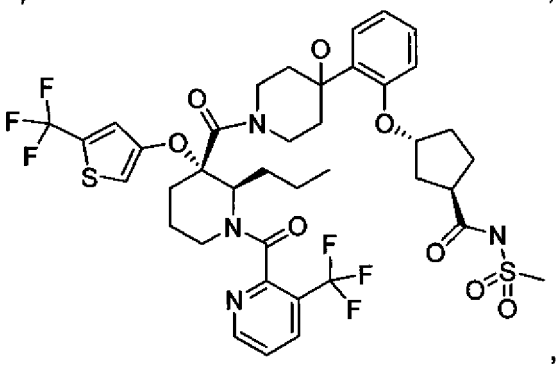
,



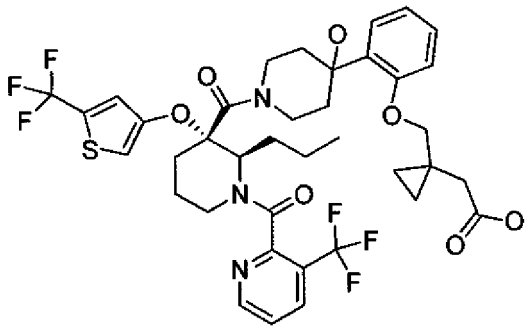
,



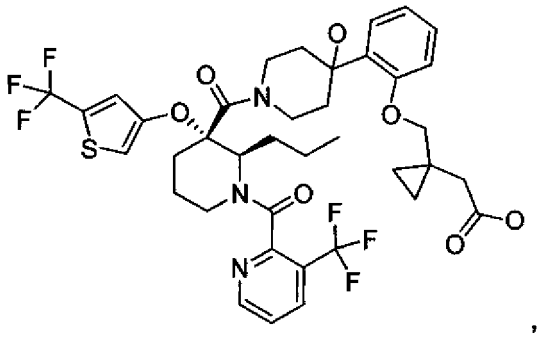
,



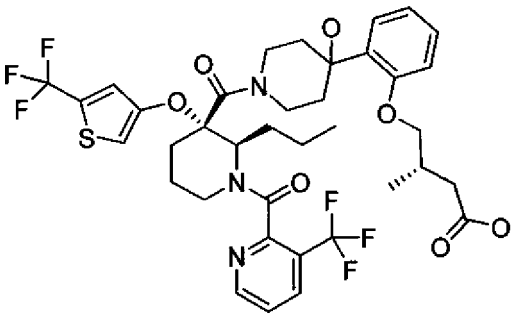
,



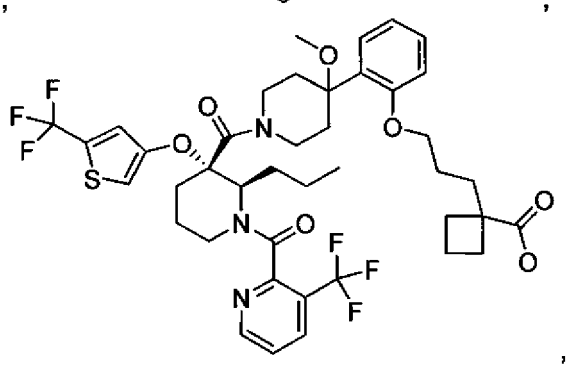
,



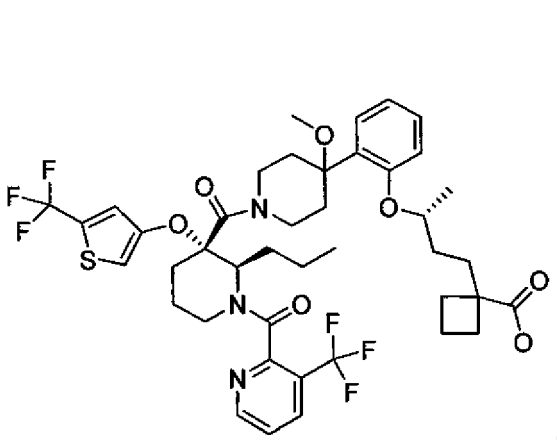
,



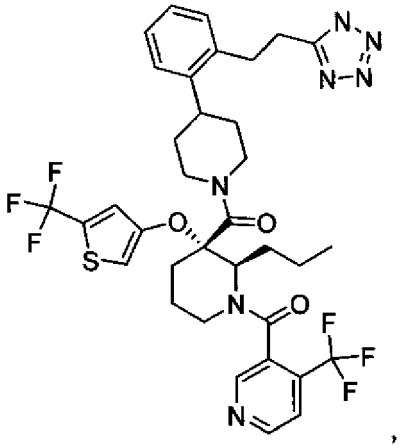
,



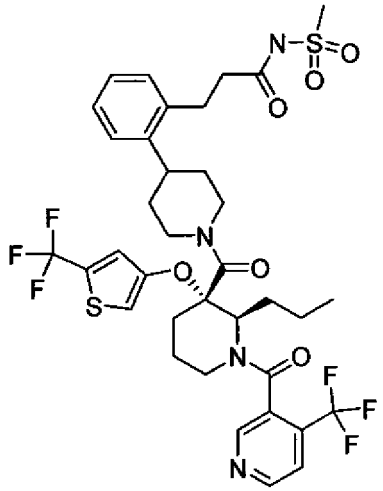
,



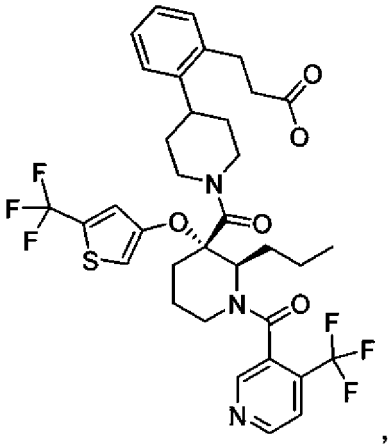
,



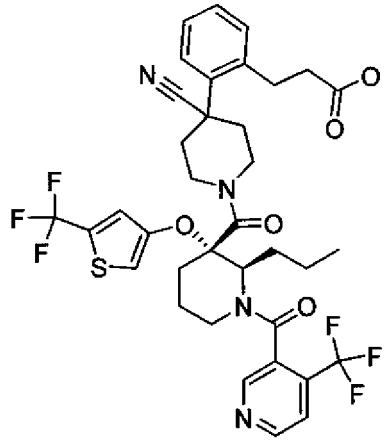
,



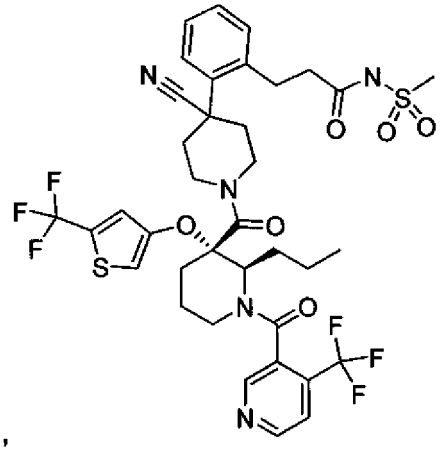
,



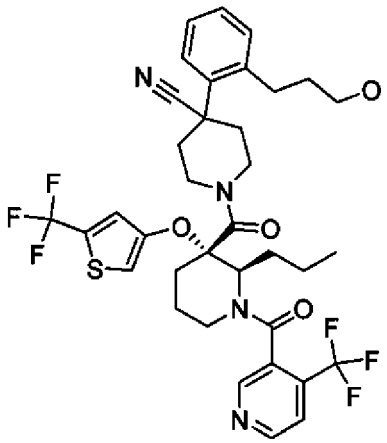
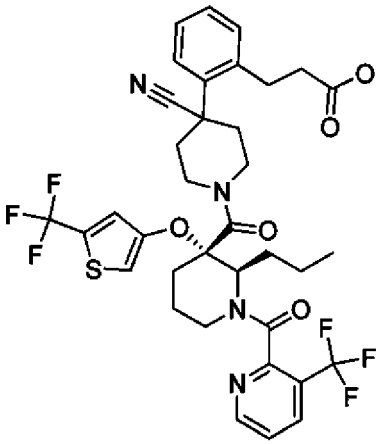
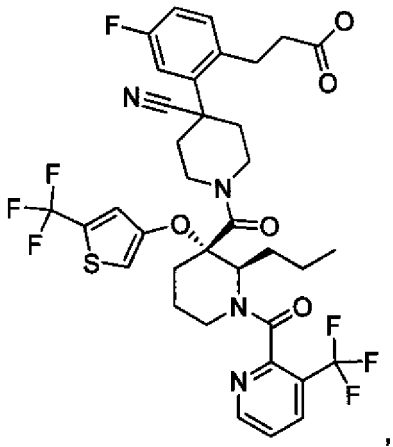
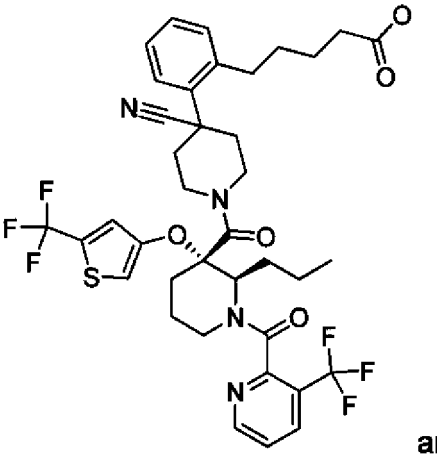
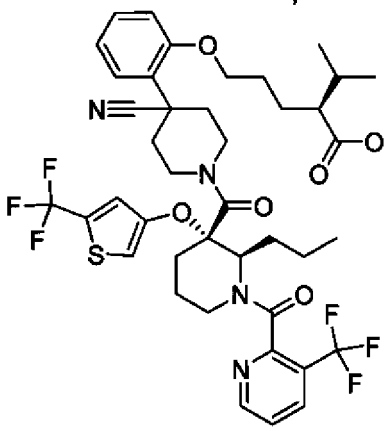
,



,



,


,

,

,

and


or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings. Any additional needed definition is understood to be the same as those disclosed in WO2008/005268 (equivalent of US Patent Publication US 2008/0004287 A1).

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkoxyalkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. "Alkenyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl,

1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl, carbazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

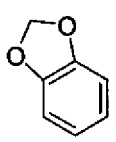
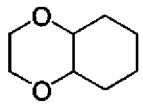
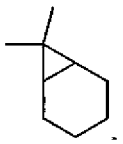
"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred

cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:

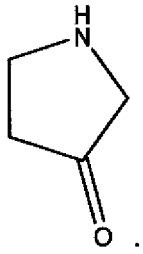


and


"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heteroalkyl" is a saturated or unsaturated chain (unsaturated chain may also be interchangeably referred to as heteroalkenyl) containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 2 to 15 member atoms (carbon and heteroatoms) in the chain, preferably 2 to 10, more preferably 2 to 5. For example, alkoxy (i.e., --O-alkyl or --O-heteroalkyl) radicals are included in heteroalkyl. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more carbon-carbon double bonds and/or one or more carbon-carbon triple bonds. Preferred unsaturated heteroalkyls have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or tri-substituted. Heteroalkyl may be substituted with lower alkyl, haloalkyl, halo, hydroxy, aryloxy, heteroaryloxy, acyloxy, carboxy, monocyclic aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycle, amino, acylamino, amido, keto, thioketo, cyano, or any combination thereof.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH

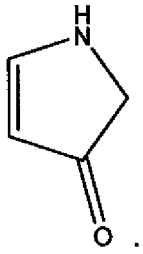
in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. Non-limiting examples of suitable bicyclic heterocyclyl rings include decahydro-isoquinoline, decahydro-[2,6]naphthyridine, and the like. "Heterocyclyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:



"Heterocyclylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

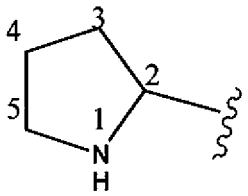
"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 15 ring atoms, preferably about 5 to about 14 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 13 ring atoms. The prefix aza, oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is

present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 1,2,3,4-tetrahydro-isoquinolinyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like. "Heterocyclenyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidinone:



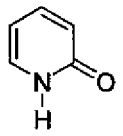
"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

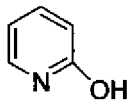
It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



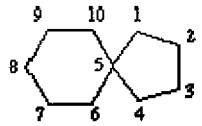
and


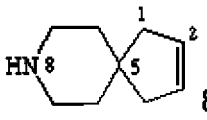
are considered equivalent in certain embodiments of this invention.

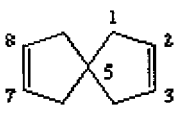
"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Spiro ring systems" have two or more rings linked by one common atom. Preferred spiro ring systems include spiroheteroaryl, spiroheterocyclenyl, spiroheterocyclyl, spirocycloalkyl, spirocyclenyl, and spiroaryl. The spiro ring systems can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. Non-limiting examples of suitable spiro ring systems include 

spiro[4.5]decane, 

8-azaspiro[4.5]dec-2-ene, and 

spiro[4.4]nona-2,7-diene.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen. An alkoxy linked directly to another alkoxy is an "alkoxyalkoxy".

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" or "thioalkoxy" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization and the like) , in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is

assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula 1 or 2, its definition on each occurrence is independent of its definition at every other occurrence.

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

Prodrugs and solvates of the compounds of the invention are also contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula 1 or 2 or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula 1 or 2 or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid

functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula 1 or 2 contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula 1 or 2 incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl

and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula 1 or 2 can form salts which are also within the scope of this invention. Reference to a compound of Formula 1 or 2 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula 1 or 2 contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula 1 or 2 may be formed, for example, by reacting a compound of Formula 1 or 2 with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of Formula 1 or 2, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

The compounds of Formula 1 or 2 may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula 1 or 2 as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula 1 or 2 incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula 1 or 2 may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula 1 or 2 may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). (For example, if a

compound of Formula 1 or 2 incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.) Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled compounds of Formula 1 or 2 (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances.

The term "Deuterated" in describing the compounds of this invention means that the deuterium-to-hydrogen ratio in the deuterated areas of the molecule substantially exceeds the naturally occurring deuterium-to-hydrogen

ratio. Wikipedia (http://en.wikipedia.org/wiki/Deuterium) suggests that deuterium has a natural abundance in the oceans of Earth of approximately one atom in 6500 of hydrogen (~154 PPM). Deuterium thus accounts for approximately 0.015% (on a weight basis, 0.030%) of all naturally occurring hydrogen in the oceans on Earth. However, other sources suggest a much higher abundance of e.g. $6 \cdot 10^{-4}$ (6 atoms in 10,000 or 0.06% atom basis).

Deuteration of molecules and preparation of deuterated drugs are known. See, for example, M. Tanabe et al, "The Pharmacologic Effect of Deuterium Substitution on 5-n-Butyl-5-ethyl Barbituric Acid', *Life Sciences* (1969) Vol. 8, part I, pp. 1123-1128; N. J. Haskins, "The Application of Stable Isotopes in Biomedical Research", *Biomedical Mass Spectrometry* (1981), Vol. 9 (7), pp. 2690277; and the announcements from Concert Pharma (http://www.concertpharma.com/ConcertAnnouncesPreclinicalResultsICAAC.htm) regarding preclinical results of their deuterated antibiotic, C-20081, and http://www.concertpharma.com/news/ConcertBeginsCTP347PhaseI.htm regarding Phase I clinical trials of their deuterium-containing serotonin modulator, CTP-347.

Isotopically labelled compounds of Formula 1 or 2 can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent. For example, deuteration is specifically exemplified in representative Examples 63 and 64.

Polymorphic forms of the compounds of Formula 1 or 2, and of the salts, solvates, esters and prodrugs of the compounds of Formula 1 or 2, are intended to be included in the present invention.

HDM2, Hdm2, hDM2, and hdm2 are all equivalent representations of the Human Double Minute 2 protein. Likewise, MDM2, Mdm2, mDM2, and mdm2 are all equivalent representations mouse Double Minute 2 protein.

The compounds of Formula 1 or 2 can be inhibitors or antagonists of the Human or Mouse Double Minute 2 protein interaction with p53 protein and it can be activators of the p53 protein in cells. Furthermore, the pharmacological properties of the compounds of Formula 1 or 2 can be used to treat or prevent

cancer, treat or prevent other disease states associated with abnormal cell proliferation, and treat or prevent diseases resulting from inadequate levels of p53 protein in cells.

Those skilled in the art will realize that the term "cancer" to be the name for diseases in which the body's cells become abnormal and divide without control.

Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma) colorectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma,

chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

In one embodment, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: lung cancer, pancreatic cancer, colon cancer, colorectal cancer, myeloid leukemias, acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelomonocytic leukemia, thyroid cancer, myelodysplastic syndrome, bladder carcinoma, epidermal carcinoma, melanoma, breast cancer, prostate cancer, head and neck cancers, ovarian cancer, brain cancers, cancers of mesenchymal origin, sarcomas, tetracarcinomas, nuroblastomas, kidney carcinomas,

hepatomas, non-Hodgkin's lymphoma, multiple myeloma, and anaplastic thyroid carcinoma.

In another embodiment, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: breast, prostate, colon, colorectal, lung, brain, testicular, stomach, pancrease, skin, small intestine, large intestine, throat, head and neck, oral, bone, liver, bladder, kidney, thyroid and blood.

In another embodiment, cancers that may be treated by the compounds, compositions and methods of the invention include breast, prostate, colon, ovary, endometrium and thyroid.

In another embodiment, cancers that may be treated by the compounds, compositions and methods of the invention include breast and prostate.

The compounds of the invention are also useful in preparing a medicament that is useful in treating cancer.

The instant compounds are also useful in combination with therapeutic, chemotherapeutic and anti-cancer agents. Combinations of the presently disclosed compounds with therapeutic, chemotherapeutic and anti-cancer agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, inhibitors of cell proliferation and survival signaling, bisphosphonates, aromatase inhibitors, siRNA therapeutics, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and agents that interfere with cell cycle checkpoints.

The instant compounds are particularly useful when co-administered with radiation therapy.

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

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

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, histone deacetylase inhibitors, inhibitors of kinases involved in mitotic progression, inhibitors of kinases involved in growth factor and cytokine signal transduction pathways, antimetabolites, biological response modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteosome inhibitors, ubiquitin ligase inhibitors, and aurora kinase inhibitors.

Examples of cytotoxic/cytostatic agents include, but are not limited to, platinum coordinator compounds, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteosome inhibitors include but are not limited to lactacystin and MLN-341 (Velcade).

Examples of microtubule inhibitors/microtubule-stabilising agents include taxanes in general. Speicific compounds include paclitaxel (Taxol®), vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol (Taxotere®), rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. In an embodiment the epothilones are not included in the microtubule inhibitors/microtubule-stabilising agents.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-

amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in Publications WO03/039460, WO03/050064, WO03/050122, WO03/049527, WO03/049679, WO03/049678, WO04/039774, WO03/079973, WO03/099211, WO03/105855, WO03/106417, WO04/037171, WO04/058148, WO04/058700, WO04/126699, WO05/018638, WO05/019206, WO05/019205, WO05/018547, WO05/017190, US2005/0176776. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamflatin, PXD101, MG98 and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. *J. Med. Chem.* 46(24):5097-5116 (2003).

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in

particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an "aurora kinase inhibitor" is VX-680.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and

5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO

96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Opthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin, Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature, 362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see

review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the CHK11 and CHK12 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

"Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs as described by Bume-Jensen and Hunter, *Nature*, 411:355-365, 2001.

"Inhibitors of cell proliferation and survival signalling pathway" refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469), inhibitors of Raf kinase (for example PLX-4032), inhibitors of MEK (for example Arry-162, RO-4987655 and GSK-1120212), inhibitors of mTOR (for example AZD-8055, BEZ-235 and everolimus), and inhibitors of PI3K (for example GDC-0941, BKM-120).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possesses an IC_{50} for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, U.S. Patent 5,861,419, U.S. Patent 6,001,843, U.S. Patent 6,020,343, U.S. Patent 5,409,944, U.S. Patent 5,436,265, U.S. Patent 5,536,752, U.S. Patent 5,550,142, U.S. Patent 5,604,260, U.S. 5,698,584, U.S. Patent 5,710,140, WO 94/15932, U.S. Patent 5,344,991, U.S. Patent 5,134,142, U.S. Patent 5,380,738, U.S. Patent 5,393,790, U.S. Patent 5,466,823, U.S. Patent 5,633,272 and U.S. Patent 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following: parecoxib, BEXTRA® and CELEBREX® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-

naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$,$\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in

angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am. J. Hum. Genet.* 61:785-789, 1997) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 2000;164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In another embodiment, conjunctive therapy with an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is disclosed for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170,

93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with P450 inhibitors including: xenobiotics, quinidine, tyramine, ketoconazole, testosterone, quinine, methyrapone, caffeine, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafyline, cimetidine, dextromethorphan, ritonavir, indinavir, amprenavir, diltiazem, terfenadine, verapamil, cortisol, itraconazole, mibefradil, nefazodone and nelfinavir.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with Pgp and/or BCRP inhibitors including: cyclosporin A, PSC833, GF120918, cremophorEL, fumitremorgin C, Ko132, Ko134, Iressa, Imatnib mesylate, EKI-785, CI1033, novobiocin, diethylstilbestrol, tamoxifen, resperpine, VX-710, tryprostatin A, flavonoids, ritonavir, saquinavir, nelfinavir, omeprazole, quinidine, verapamil, terfenadine, ketoconazole, nifidepine, FK506, amiodarone, XR9576, indinavir, amprenavir, cortisol, testosterone, LY335979, OC144-093, erythromycin, vincristine, digoxin and talinolol.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

A compound of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with siRNA therapeutics.

The compounds of the instant invention may also be administered in combination with γ-secretase inhibitors and/or inhibitors of NOTCH signaling. Such inhibitors include compounds described in WO 01/90084, WO 02/30912, WO 01/70677, WO 03/013506, WO 02/36555, WO 03/093252, WO 03/093264, WO 03/093251, WO 03/093253, WO 2004/039800, WO 2004/039370, WO 2005/030731, WO 2005/014553, USSN 10/957,251, WO 2004/089911, WO 02/081435, WO 02/081433, WO 03/018543, WO 2004/031137, WO 2004/031139, WO 2004/031138, WO 2004/101538, WO 2004/101539 and WO 02/47671 (including LY-450139).

Inhibitors of Akt, as disclosed in the following publications; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, and including compounds of the instant invention, are also useful in combination with potassium salts, magnesium salts, beta-blockers (such as atenolol) and endothelin-a (ETa)antagonists with the goal of maintaining cardiovascular homeostasis.

Inhibitors of Akt, as disclosed in the following publications; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, and including compounds of the instant invention, are also useful in combination with insulin, insulin secretagogues, PPAR-gamma agonists, metformin, somatostatin receptor agonists such as octreotide, DPP4 inhibitors,

sulfonylureas and alpha-glucosidase inhibitors with the goal of maintaining glucose homeostasis.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with PARP inhibitors: olaparib, MK-4827 and veliparib.

A compound of the instant invention may also be useful for treating cancer in combination with the following chemotherapeutic agents: abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bendamustine hydrochloride (Treanda®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); brefeldin A; busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); dalteparin sodium injection (Fragmin®); Darbepoetin alfa (Aranesp®); dasatinib (Sprycel®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); degarelix (Firmagon®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); dexrazoxane hydrochloride (Totect®); didemnin B; 17-DMAG; docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal

(Doxil®); dromostanolone propionate (Dromostanolone ®); dromostanolone propionate (Masterone Injection®); eculizumab injection (Soliris®); Elliott's B Solution (Elliott's B Solution®); eltrombopag (Promacta®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); ethinyl estradiol; etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); everolimus tablets (Afinitor®); exemestane (Aromasin®); ferumoxytol (Feraheme Injection®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); geldanamycin; gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); iobenguane I 123 injection (AdreView®); irinotecan (Camptosar®); ixabepilone (Ixempra®); lapatinib tablets (Tykerb®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); 8-methoxypsoralen; mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); mitramycin; nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); nilotinib (Tasigna®); Nofetumomab (Verluma®); ofatumumab (Arzerra®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); panitumumab (Vectibix®); pazopanib tablets (Votrienttm®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®);

Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plerixafor (Mozobil®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); pralatrexate injection (Folotyn®); procarbazine (Matulane®); quinacrine (Atabrine®); rapamycin; Rasburicase (Elitek®); raloxifene hydrochloride (Evista®); Rituximab (Rituxan®); romidepsin (Istodax®); romiplostim (Nplate®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); temsirolimus (Torisel®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiopurine; thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); trans-retinoic acid; Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); triethylenemelamine; Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); vorinostat (Zolinza®); wortmannin; and zoledronate (Zometa®).

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA), the Physician's Desk Reference, 56th Edition, 2002 (published by Medical Economics company, Inc. Montvale, NJ 07645-1742), and the Physician's Desk Reference, 57th Edition, 2003 (published by Thompson PDR, Montvale, NJ 07645-1742); the disclosures of which is incorporated herein by reference thereto.

The compounds of Formula 1 or 2 can be useful to the treatment of a variety of cancers, including, but not limited to: carcinoma, including, but not limited to, of the bladder, breast, colon, rectum, endometrium, kidney, liver, lung,

head and neck, esophagus, gall bladder, cervix, pancreas, prostrate, larynx, ovaries, stomach, uterus, sarcoma and thyroid cancer;

hematopoietic tumors of the lymphoid lineage, including leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, mantle cell lymphoma, myeloma, and Burkett's lymphoma;

hematopoetic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; and

other tumors, including melanoma, skin (non-melanomal) cancer, mesothelioma (cells), seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of p53 in the regulation of cellular apoptosis (cell death), the compounds of Formula 1 or 2 could act as agent to induce cell death which may be useful in the treatment of any disease process which features abnormal celllular proliferation eg, cancers of various origin and tissue types, inflammation, immunological disorders.

Due to the key role of HDM2 and p53 in the regulation of cellular proliferation, the compounds of Formula 1 or 2 could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal celllular proliferation, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cell proliferation, e.g., benign prostrate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty, or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of Formula 1 or 2 may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of Formula 1 or 2 may also be useful in inhibiting tumor angiogenesis and metastasis.

Another aspect of this invention is a method of treating a mammal (e.g., human) having a disease or condition associated with HDM2 by administering a therapeutically effective amount of at least one compound of Formula 1 or 2, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound to the mammal.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula 1 or 2. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula 1 or 2, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more of anti-cancer treatments such as radiation therapy, and/or one or more anti-cancer agents different from compound of Formula 1 or 2. The compounds of the present invention can be present in the same dosage unit as the anticancer agent or in separate dosage units.

Another aspect of the present invention is a method of treating one or more diseases associated with HDM2, comprising administering to a mammal in need of such treatment an amount of a first compound, which is a compound of the present invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; and an amount of at least one second compound, the second compound being an anti-cancer agent different from the compounds of the present invention, wherein the amounts of the first compound and the second compound result in a therapeutic effect.

Non-limiting examples of suitable anti-cancer agents include cytostatic agents, cytotoxic agents, targeted therapeutic agents (small molecules, biologics, siRNA and microRNA) against cancer and neoplastic diseases,

1) anti-metabolites (such as methoxtrexate, 5-fluorouracil, gemcitabine, fludarabine, capecitabine);
2) alkylating agents, such as temozolomide, cyclophosphamide,
3) DNA interactive and DNA damaging agents, such as cisplatin, oxaliplatin, doxorubicin,
4) Ionizing irradiation, such as radiation therapy,
5) topoisomerase II inhibitors, such as etoposide, doxorubicin,
6) topoisomerase I inhibitors, such as irinotecan, topotecan,
7) tubulin interacting agents, such as paclitaxel, docetaxel, Abraxane, epothilones,
8) kinesin spindle protein inhibitors,
9) spindle checkpoint inhibitors,
10) Poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, MK-4827 and veliparib
11) Matrix metalloprotease (MMP) inhibitors
12) Protease inhibitors, such as cathepsin D and cathepsin K inhibitors
13) Proteosome or ubiquitination inhibitors, such as bortezomib,
14) Activator of mutant p53 to restore its wild-type p53 activity
15) Adenoviral-p53
16) Bcl-2 inhibitors, such as ABT-263
17) Heat shock protein (HSP) modulators, such as geldanamycin and 17-AAG
18) Histone deacetylase (HDAC) inhibitors, such as vorinostat (SAHA),
19) sex hormone modulating agents,
    a. anti-estrogens, such as tamoxifen, fulvestrant,
    b. selective estrogen receptor modulators (SERM), such as raloxifene,
    c. anti-androgens, such as bicalutamide, flutamide
    d. LHRH agonists, such as leuprolide,
    e. 5α-reductase inhibitors, such as finasteride,

f. Cytochrome P450 C17 lyase (CYP450c17, also called 17α-hydroxylase/17,20 lysase) inhibitors, such as Abiraterone acetate, VN/124-1, TAK-700

g. aromatase inhibitors, such as letrozole, anastrozole, exemestane,

20) EGFR kinase inhibitors, such as geftinib, erlotinib, laptinib

21) dual erbB1 and erbB2 inhibitors, such as Lapatinib

22) multi-targeted kinases (serine/threonine and/or tyrosine kinase) inhibitors,

a. ABL kinase inhibitors, imatinib and nilotinib, dasatinib

b. VEGFR-1, VEGFR-2, PDGFR, KDR, FLT, c-Kit, Tie2, Raf, MEK and ERK inhibitors, such as sunitinib, sorafenib, Vandetanib, pazopanib, PLX-4032, Axitinib, PTK787, GSK-1120212

c. Polo-like kinase inhibitors,

d. Aurora kinase inhibitors,

e. JAK inhibitor

f. c-MET kinase inhibitors

g. Cyclin-dependent kinase inhibitors, such as CDK1 and CDK2 inhibitor SCH 727965

h. PI3K and mTOR inhibitors, such as GDC-0941, BEZ-235, BKM-120 and AZD-8055

i. Rapamycin and its analogs, such as Temsirolimus, everolimus, and deforolimus

23) and other anti-cancer (also know as anti-neoplastic) agents include but are not limited to ara-C, adriamycin, cytoxan, Carboplatin, Uracil mustard, Clormethine, Ifosfsmide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Vinblastine, Vincristine, Vindesine, Vinorelbine, Navelbine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, teniposide, cytarabine, pemetrexed, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17□-

Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Flutamide Medroxyprogesteroneacetate, Toremifene, goserelin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Drolloxafine, Hexamethylmelamine, Bexxar, Zevalin, Trisenox, Profimer, Thiotepa, Altretamine, Doxil, Ontak, , Depocyt, Aranesp, Neupogen, Neulasta, Kepivance.

24) Farnesyl protein transferase inhibitors, such as, SARASAR™(4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6, 11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl-]-1-piperidinyl]-2-oxoethyl]-piperidinecarboxamide, tipifarnib

25) interferons, such as Intron A, Peg-Intron,

26) anti-erbB1 antibodies, such as cetuximab, panitumumab,

27) anti-erbB2 antibodies, such as trastuzumab,

28) anti-CD52 antibodies, such as Alemtuzumab,

29) anti-CD20 antibodies, such as Rituximab

30) anti-CD33 antibodies, such as Gemtuzumab ozogamicin

31) anti-VEGF antibodies, such as Avastin,

32) TRIAL ligands, such as Lexatumumab, mapatumumab, and AMG-655

33) Anti-CTLA-4 antibodies, such as ipilimumab

34) antibodies against CTA1, CEA, CD5, CD19, CD22, CD30, CD44, CD44V6, CD55, CD56, EpCAM, FAP, MHCII, HGF, IL-6, MUC1, PSMA, TAL6, TAG-72, TRAILR, VEGFR, IGF-2, FGF,

35) anti-IGF-1R antibodies, such as dalotuzumab (MK-0646) and robatumumab (SCH 717454)

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range. Compounds of Formula 1 or 2 may also be administered sequentially with known

anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of Formula 1 or 2 may be administered either concurrent with, prior to or after administration of the known anticancer or cytotoxic agent. Such techniques are within the skills of the persons skilled in the art as well as attending physicians.

Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of Formula 1 or 2, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and an amount of one or more anti-cancer treatments and anti-cancer agents listed above wherein the amounts of the compounds/ treatments result in desired therapeutic effect.

Another aspect of the invention is a method of protecting normal, healthy cells of a mammal from cytotoxic induced side-effects comprising administering at least one compound of the invention or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof to a cancer patient, in particular those carrying mutated p53, prior to administration of anticancer agents other than the compounds of the invention, such as paclitaxel.

A method of inhibiting one or more HDM2 proteins in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Another aspect of the present invention is a method of treating, or slowing the progression of a disease associated with one or more HDM2 proteins in a patient, comprising administering to a patient in need thereof, a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Another aspect of the present invention is a method of treating, or slowing the progression of a disease associated with inadequate p53 levels in a patient, comprising administering to a patient in need thereof, a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Yet another aspect of the present invention is a method of treating one or more diseases associated with HDM2, comprising administering to a mammal in need of such treatment an amount of a first compound, which is a compound of the present invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; and an amount of at least one second compound, the second compound being an anti-cancer agent, wherein the amounts of the first compound and the second compound result in a therapeutic effect.

Another aspect of the present invention is a method of treating one or more diseases associated with inadequate p53 levels, comprising administering to a mammal in need of such treatment an amount of a first compound, which is a compound of the present invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; and an amount of at least one second compound, the second compound being an anti-cancer agent, wherein the amounts of the first compound and the second compound result in a therapeutic effect.

Another aspect of the present invention is a method of treating, or slowing the progression of, a disease associated with a HDM2 protein comprising administering to a patient in need thereof, a therapeutically effective amount of a pharmaceutical composition comprising in combination at least one pharmaceutically acceptable carrier and at least one compound according to the present invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Another aspect of the present invention is a method of treating, or slowing the progression of, a disease associated with inadequate p53 levels in a patient, comprising administering to a patient in need thereof, a therapeutically effective amount of a pharmaceutical composition comprising in combination at least one pharmaceutically acceptable carrier and at least one compound according to the present invention, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

The term "pharmaceutical composition" is also intended to encompass both the bulk composition and individual dosage units comprised of more than

one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

Another embodiment of the invention discloses a method of making the substituted compounds disclosed above. The compounds may be prepared by several processes well known in the art. In one method, the starting material, 1-benzyl-3-(4-trifluoromethyl-phenoxy)-piperidine-3-carboxylic acid is converted to its diisopropylethyl ammonium salt of the dicarboxylic acid ester. This ester is combined with 1-(2-methoxy-phenyl)-piperazine forming the HCL salt of 4-(2-methoxy-phenyl)-piprazinl-yl]-[3-(4-trifluormethylphenoxy)-piperidin-3-yl]-methanone, which combined with 4-trifluromethyl-nicotinic acid to form the target compound. Other substituted compounds of this invention can be made.

Isolation of the compound at various stages of the reaction may be achieved by standard techniques such as, for example, filtration, evaporation of solvent and the like. Purification of the product, intermediate and the like, may also be performed by standard techniques such as recrystallization, distillation, sublimation, chromatography, conversion to a suitable derivative, which may be recrystallized and converted back to the starting compound, and the like. Such techniques are well known to those skilled in the art.

The compounds of this invention may be analyzed for their composition and purity as well as characterized by standard analytical techniques such as, for example, elemental analysis, NMR, mass spectroscopy, and IR spectra.

In another embodiment, this invention provides pharmaceutical compositions comprising the above-described inventive substituted compounds as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HDM2 or MDM2 antagonist activity, such pharmaceutical compositions possess utility in treating cancer, abnormal cell proliferation, and the like diseases.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Lubricants in these dosage forms include boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like.

Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. anti-cell proliferation activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. For example, water or water-propylene glycol solutions may be included for parenteral injections or sweeteners and pacifiers may be added for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool to solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula 1l or 2, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formulas 1 or 2, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one anticancer therapy and /or anti-cancer agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gels- refer to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powders for constitution refer to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrants - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2

to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binders - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d,l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glidents - materials that prevent caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

The following abbreviations have the following meanings unless defined otherwise:

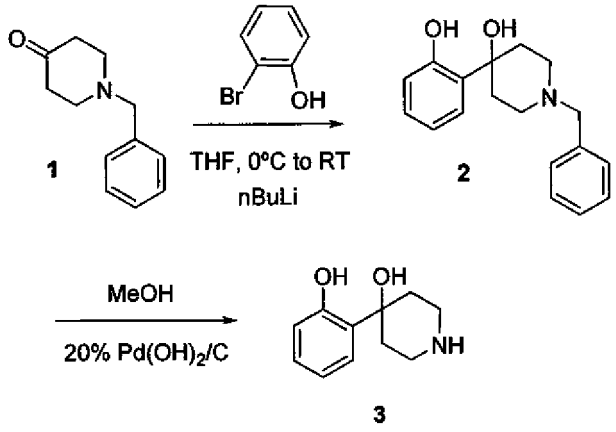
ACN	Acetonitrile
AcOH	Acetic acid
DAST	(diethylamino)sulfur trifluoride
DCC	Dicyclohexylcarbodiimide
DCU	Dicyclohexylurea
DCM	Dichloromethane
DI	Deionized water
DIAD	Diisopropylazodicarboxylate
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane

DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMSO	Dimethyl sulfoxide
DTT	Dithiothreitol
EDCI	1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HOBt	1-Hydroxylbenzotriazole
HPLC	High pressure liquid chromatography
LCMS	Liquid chromatography mass spectrometry
LDA	Lithium diisopropylamide
mCPBA	*meta*-Chloroperoxybenzoic acid
MeOH	Methanol
MTT	(3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide, Thiazolyl blue)
NMR	Nuclear magnetic resonance
PFP	Pentafluorophenol
PMB	p-methoxybenzyl
Pyr	Pyridine
Rb	Round bottom flask
Rbt	Round bottom flask
RT	Room temperature
SEMCl	2-(Trimethylsily)ethoxy methyl chloride
TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TEA	Triethylamine
Tr	Triphenyl methane

Trt	Triphenyl methane
TrCl	Triphenyl methane chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

Representative procedures to prepare substituted piperidines used in the synthesis of HDM2 inhibitors included in table 1

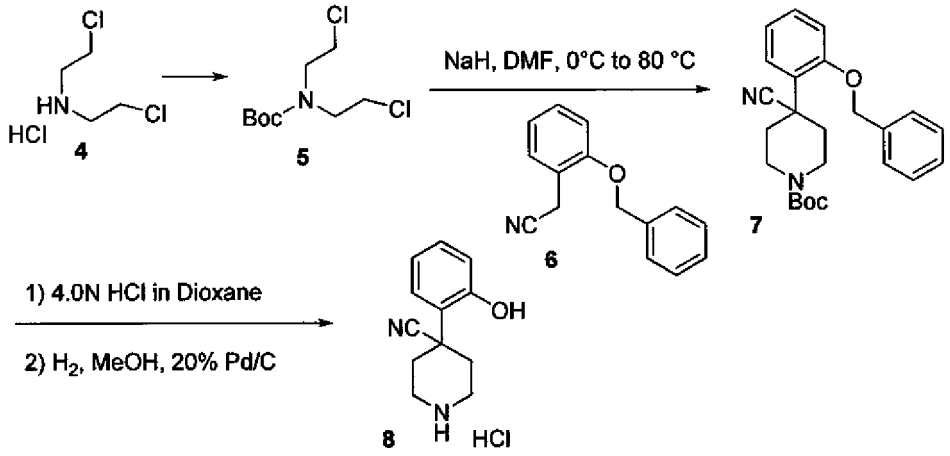
Representative example 1: Preparation of 4-(2-hydroxyphenyl)piperidin-4-ol **3**.



Step1: At RT, n-BuLi (1.6M, 20 mL, 32 mmol, in hexanes) was added to Et2O (30 mL). At RT, was added dropwise 2-Bromophenol (1.8 mL, 16 mmol). During addition, refluxed was observed. Large condenser was placed on to flask and addition was resumed. After addition, stirring was maintained for 45 min. At RT, n-Benzyl piperidione (3 mL, 16 mmol) was added fast. After 1.5 h, NH4Cl was added and reaction extracted with EtOAc. Organic layer was washed with brine and dried over MgSO4, filtered and concentrated down to a viscous oil that crystallized upon standing. Hexanes was added and crystalline material filtered off. Boilling Hexanes was added to the first drop of crystalline **2.** Slurry was stirred and crystalline material filtered off and dried under Nitrogen. After drying, 2.32g of crystalline product was obtained with LCMS purity >99.5%.

Step2: To **2** (2.04g, 5.46mmol) in 25mL of MeOH was added 20% Pd(OH)2/C (1g, 50%w/w). The mixture was stirred at RT under H_2 overnight. The reaction was filtered through a pad of celite and filtrate was concentrated to dryness to give 1.03g (100% yield) of solid product **3**.

Representative example 2: Preparation of 4-(2-hydroxyphenyl)piperidine-4-carbonitrile hydrochloride **8**.



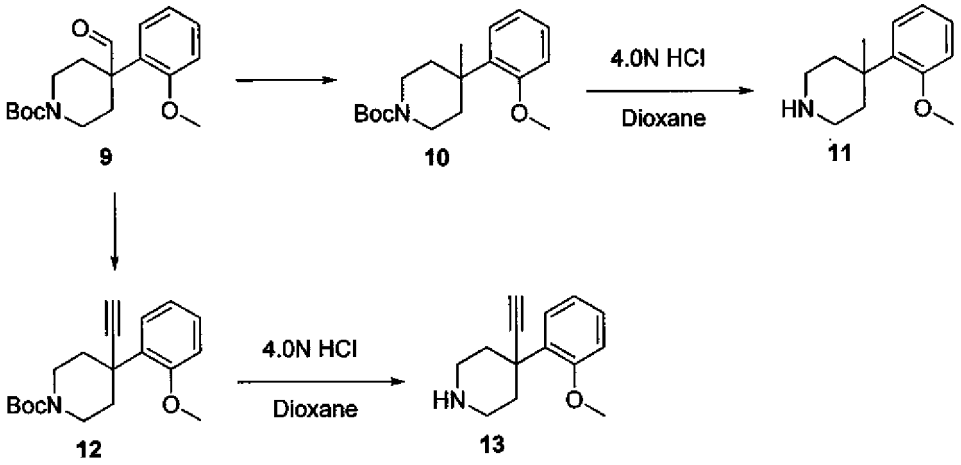
Step 1: To the amine, **4** (80g, 45 mmol, 1 equi.) dissolved in acetonitrile/ water (800/80mL) was added sodium hydroxide (2 equi., 291 mmol, 36g) and to the stirring solution, Boc anhydride (1.02 equi, 46 mmol, 101g) dissolved in acetonitrile (200mL) was added drop wise and stirred for 18 hours at room temperature. Volatile was removed to 300mL and solid residue was filtered out. Washed the solid with dichloromethane and evaporated off the solvent to provide 102g of intermediate **5**.

Step 2: Nitrile **6** (15g, 1equi.) was dissolved in DMF (100 mL) and was cooled to 0 °C. NaH (60% in mineral oil, 2.1 equi.) was added and the reaction was warmed to 23 °C and stirred for 10 min. Dichloride. **5** (1equi) was added and the reaction was heated to 80 °C and stirred overnight. The reaction was cooled to 23 °C and was quenched with aqueous saturated. NH_4Cl (20 mL). The mixture was extracted with EtOAc (3x100mL). The organic layers were washed with brine (1x50ml), dried over Na_2SO_4, filtered and concentrated down to dryness. The residue was purified by silica gel chromatography (10% to 80% ethyl acetate/hexanes) to provide 21.4 g of intermediate **7** (74% yield).

Step 3: Intermediate **7** (15.6gm, 1equiv.) dissolved in MeOH (150 mL). The solution was degassed with N_2 few times. Pd/C (20%, 3 mg) was added and H_2

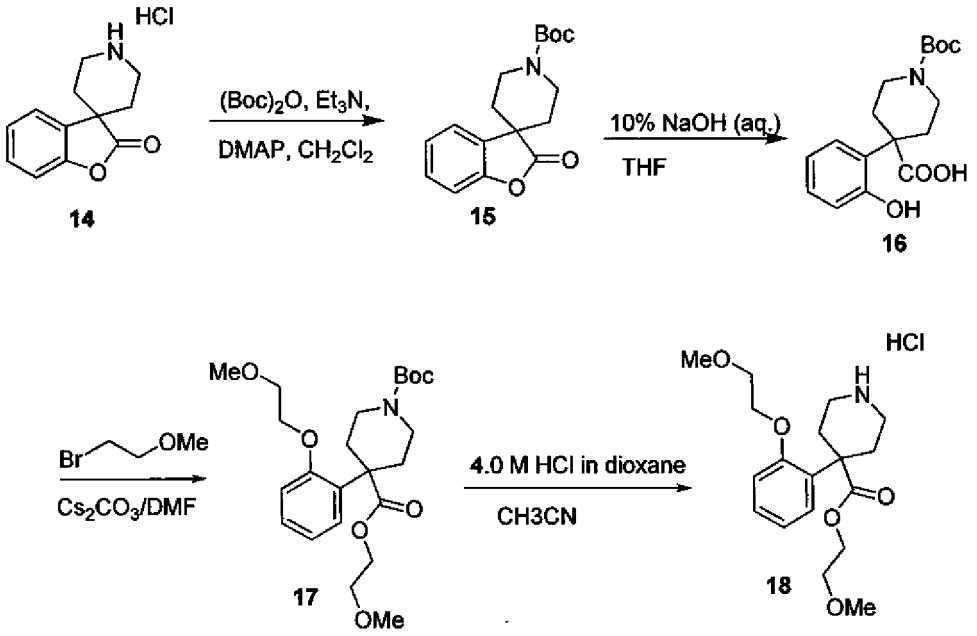
was bubbled in for a few minutes. The reaction was stirred under a H_2 balloon at 23 °C for 4hrs. The reaction was filtered through a pad of celite and filtrate was concentrated to dryness to give 11.8g (98% yield) of product to which 4 M HCl/dioxane (120 mL) was added. Slurry was stirred at 23 °C for 1.5 h. The solution was concentrated to yield hydrochloride **8** (9g, 96% yield over 2 steps).

Representative example 3: Preparation of 4-(2-methoxyphenyl)-4-methylpiperidine 11 and 4-ethynyl-4-(2-methoxyphenyl)piperidine **13.**



Intermediate **10** was prepared according a published procedure (*J.Org.Chem.*, **2001**, *4*, 1434) from corresponding aldehyde **9**. Piperidine **11** was obtained following same procedure described in example 2, step3. Intermediate **12** was prepared from same aldehyde **9** using Ohira's phosphonate. Piperidine **13** was obtained following same procedure described in example 2, step3.

Representative example 4: Preparation of 2-methoxyethyl 4-(2-(2-methoxyethoxy)phenyl)piperidine-4-carboxylate hydrochloride **18.**



Step 1: To a stirring suspension of **14** (3.3 mmol, 0.8 g) in dichloromethane and triethylamine (8.25mmol, 1.15ml) at room temperature was added di-t-butyl dicarbonate (4.0 mmol, 0.87 g) followed by DMAP (0.33mmol, 40 mg). The reaction mixture was stirred at room temperature for 6 hours and then diluted with EtOAc (200ml), washed with water (2x40ml), brine (40ml), then dried (Na2SO4). The solvent was removed *in vacuo*. The crude product **15** (0.97 g) was obtained as colorless oil, which was used in the next step without further purification.

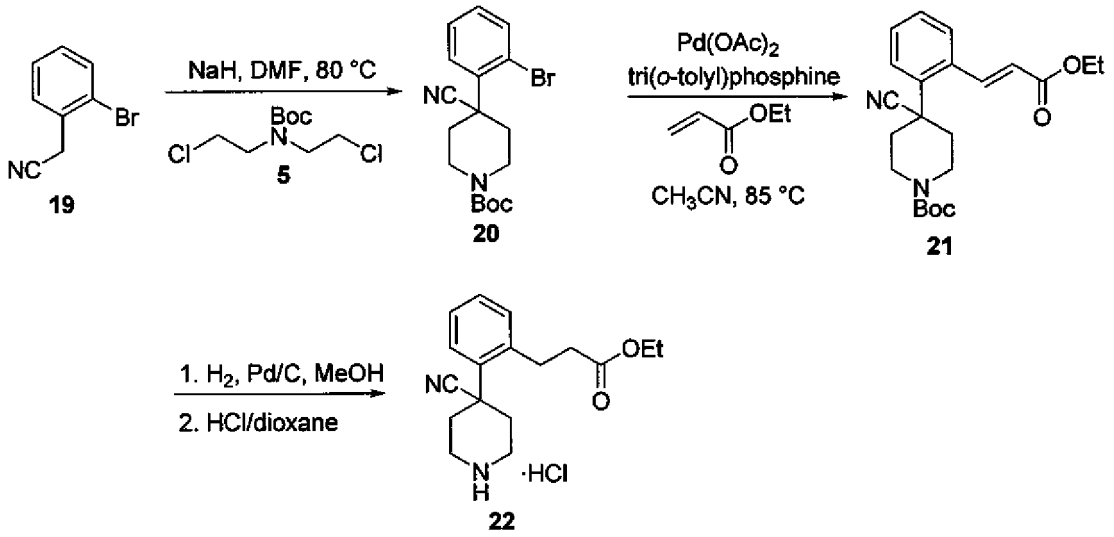
Step 2: To a stirring solution of **15** (0.33 mmol, 100 mg) in THF (1ml) was added 10% NaOH (2ml) and the solution was stirred at room temperature overnight. The reaction mixture was neutralized with 0.5 N HCl to PH ~4, then extracted with EtOAc (2x25ml). The combined organic layer was dried and concentrated. The crude product **16** (110 mg) was obtained as white solid, which was used in the next step without further purification.

Step 3: To a stirring solution of **16** (0.44 mmol, 0.140 g) in DMF (5ml) at room temperature was added cesium carbonate (4.4 mmol, 1.43 g) followed by 2-Bromoethyl methyl ether (4.4 mmol, 0.42 ml). The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue

was dissolved in EtOAc (50ml), washed with water (2x10ml), brine (10ml), and dried (Na2SO4). The solvent was removed *in vacuo*. The crude product was purified by Biotage (EtOAc in hexane: 0~25%) to yield pure **17**.

Step4: To a solution of **17** in acetonitrile at room temperature was added 4.0 M hydrochloride in 1,4-dioxane. After 10 min, the solvent and volatile were removed by lyophilization, to give **18** as yellowish oil.

Representative example 5: Preparation of ethyl 3-(2-(4-cyanopiperidin-4-yl)phenyl)propanoate hydrochloride **22.**



Step 1: Nitrile **19** (1.0 g, 5.10 mmol) was dissolved in DMF (20 mL) and was cooled to 0 °C. NaH (60% in mineral oil, 449 mg, 11.22 mmol) was added and the reaction was warmed to 23 °C and was stirred for 10 min. Dichloride (**5**, 1.3 g, 5.36 mmol) was added and the reaction was heated at 80 °C overnight. The reaction was cooled to 23 °C and was quenched with aqueous sat'd NH_4Cl (5 mL). The mixture was extracted with EtOAc (3x). The organic layers were washed with brine (1x), dried over $MgSO_4$, filtered and concentrated. The crude residue was recrystallized with EtOAc/hexanes to obtain pure *tert*-butyl 4-(2-bromophenyl)-4-cyanopiperidine-1-carboxylate as an off-white solid (**20,** 1.1 g, 59% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.70-7.68 (m, 1H), 7.39-7.37 (m, 2H),

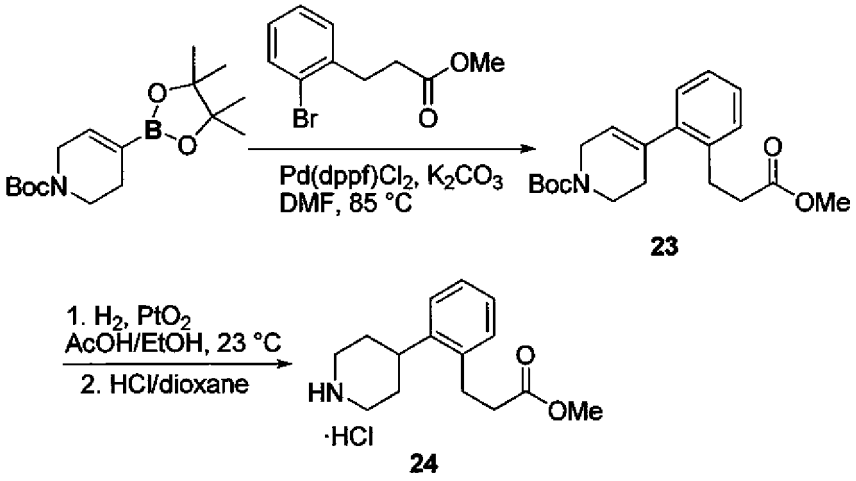
7.25-7.21 (m, 2H), 4.31-4.27 (m, 2H), 3.29 (bt, 2H), 2.58-2.52 (m, 2H), 1.98 (td, 2H), 1.48 (s, 9H).

Step 2: *Tert*-butyl 4-(2-bromophenyl)-4-cyanopiperidine-1-carboxylate (**20,** 100 mg, 0.28 mmol) and $Pd(OAc)_2$ (7.0 mg, 0.030 mmol) were added to a vial, followed by tri(*o*-tolyl)phosphine (14 mg, 0.047 mmol). The reaction vial was purged with Ar (3x). Dry CH_3CN (1.4 mL) and Et_3N (103 µL, 0.74 mmol) were added, followed by ethylacrylate (36 µL, 0.33 mmol). The reaction mixture was heated at 85 °C overnight. The reaction was concentrated. Et_2O (2 mL) was added to the mixture and was then filtered through Celite. The crude residue was purified by silica gel chromatography (gradient, 10% to 20% EtOAc/hexanes) to yield (*E*)-*tert*-butyl 4-cyano-4-(2-(3-ethoxy-3-oxoprop-1-enyl)phenyl)piperidine-1-carboxylate as a pale yellow oil (**21,** 102 mg, 96% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, 1H), 7.58 (dd, 1H), 7.41 (td, 1H), 7.38-7.34 (m, 1H), 6.31 (d, 1H), 4.29 (q, 1H), 3.29 (bt, 2H), 2.35-2.31 (m, 2H), 1.90 (dt, 2H), 1.47 (s, 9H), 1.35 (t, 3H).

Step 3: (*E*)-*tert*-butyl 4-cyano-4-(2-(3-ethoxy-3-oxoprop-1-enyl)phenyl)piperidine-1-carboxylate (**21,** 278 mg, 0.72 mmol) was dissolved in MeOH (7 mL). The solution was degassed with Ar for 2 min. Pd/C (10%, 30 mg) was added and H_2 was bubbled in for a few minutes. The reaction was stirred under a H_2 balloon at 23 °C overnight. The solution was filtered through Celite and was concentrated to yield *tert*-butyl 4-cyano-4-(2-(3-ethoxy-3-oxopropyl)phenyl)piperidine-1-carboxylate. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (m, 2H), 7.26-7.24 (m, 2H), 4.28 (bd, 2H), 4.17 (q, 2H), 3.29-3.25 (m, 4H), 2.78-2.74 (m, 2H), 2.34-2.30 (m, 2H), 1.91 (td, 2H), 1.48 (s, 9H), 1.26 (t, 3H). LC/MS RT (5 min method) = 2.19 min. Mass observed: 287.22 (M-Boc+H).

Step 4: 4 M HCl/dioxane (905 µL, 3.62 mmol) was added to neat *tert*-butyl 4-cyano-4-(2-(3-ethoxy-3-oxopropyl)phenyl)piperidine-1-carboxylate at 23 °C and was stirred for 2 h. The solution was concentrated to yield ethyl 3-(2-(4-cyanopiperidin-4-yl)phenyl)propanoate hydrochloride (**22,** 230 mg, 99% yield over 2 steps).

Representative example 6: Synthesis of ethyl 3-(2-(piperidin-4-yl)phenyl)propanoate hydrochloride **24.**



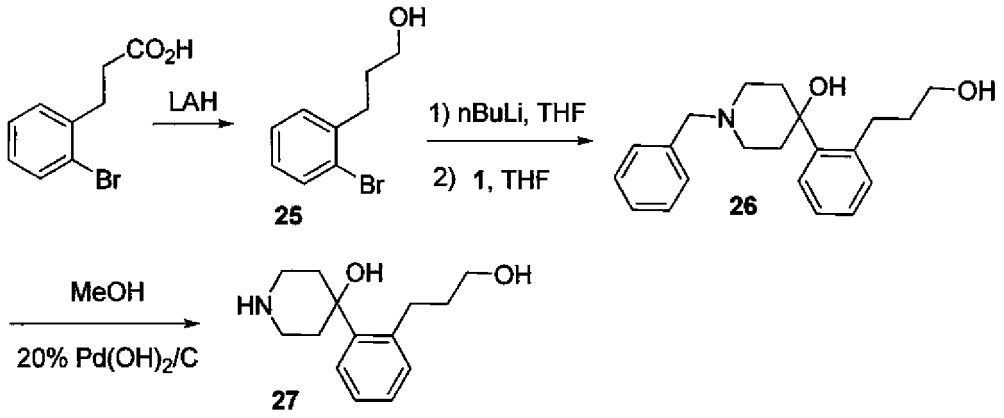
Step 1: To Methyl 3-(2-bromophenyl)propanoate (715 mg, 2.94 mmol) and 3,6-dihydro-2H-pyridine-1-*N*-Boc-4-boronic acid pinacol ester (1.0 g, 3.23 mmol) were added to a flask, followed by $Pd(dppf)Cl_2$ (151 mg, 0.21 mmol) and K_2CO_3 (1.22 g, 8.82 mmol). The reaction flask was purged with Ar (3x). Dry DMF (22 mL) was added and the solution was degassed for 10 min. The reaction mixture was heated to 85 °C overnight. The mixture was filtered through Celite and was concentrated. The crude residue was purified by silica gel chromatography (gradient, 10% to 30% EtOAc/hexanes) to give *tert*-butyl 4-(2-(3-methoxy-3-oxopropyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate **(23)** as a pale yellow oil (970 mg, 96% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.21-7.16 (m, 3H), 7.09-7.06 (m, 1H), 5.57-5.55 (m, 1H), 4.03 (q, 2H), 3.67 (s, 3H), 3.63 (t, 2H), 2.95-2.91 (m, 2H), 2.59-2.55 (m, 2H), 2.37-2.33 (m, 2H), 1.50 (s, 9H). LC/MS RT (5 min method) = 2.10 min. Mass observed: 246.19 (M-Boc+H).

Step 2: 23 (310 mg, 0.90 mmol) was dissolved in EtOH/AcOH (4 mL/4 mL). The solution was degassed with Ar for 2 min. PtO_2 (61 mg, 0.27 mmol) was added to the mixture and H_2 was bubbled in for 2 min. The reaction was stirred under a H_2 balloon overnight. The reaction mixture was filtered through Celite and was concentrated to yield *tert*-butyl 4-(2-(3-methoxy-3-oxopropyl)phenyl)piperidine-1-

carboxylate. LC/MS RT (5 min method) = 2.47 min. Mass observed: 248.21 (M-Boc+H).

4 M HCl/dioxane (2.2 mL, 8.97 mmol) was added to neat *tert*-butyl 4-(2-(3-methoxy-3-oxopropyl)phenyl)piperidine-1-carboxylate at 23 °C and was stirred overnight. The reaction mixture was concentrated to yield methyl 3-(2-(piperidin-4-yl)phenyl)propanoate hydrochloride (**24,** 250 mg, 98% yield). LC/MS RT (5 min method) = 1.14 min. Mass observed: 248.16 (M+H).

Representative example 7: Preparation of 4-(2-(3-hydroxypropyl)phenyl)piperidin-4-ol **27**.



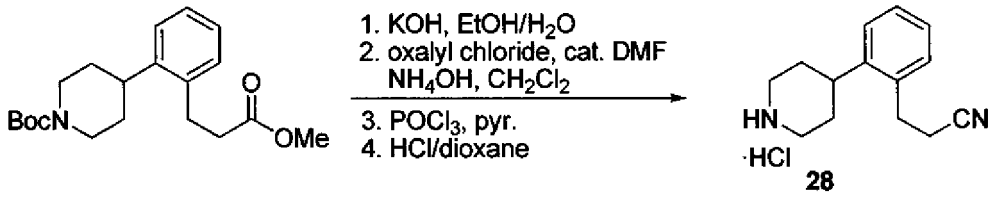
Step 1: To 3-(2-Br-phenyl)propionic acid (2.0g, 8.73mmol) in THF was added LAH (8.73mL, 8.73mmol, 1eq.) at 0°C. The mixture was stirred at 0°C for 1 hour. Reaction was quenched by addition of $Na_2SO_4.10H_2O$ and stirred for 15min. The reaction mixture was diluted with EtOAc and washed with 1N HCl and brine. Filtered and concentrated to dryness to give 1.16g of crude product alcohol **25** (62% yield).

Step 2: To **25** (0.46g, 2.14mmol) in 8mL of THF was added nBuLi (2.9mL, 4.28mmol, 2.0eq.) slowly at -78°C. The mixture was stirred at -78°C for 30min, followed by the addition of 1-Benzy-4-piperidone **1** (405mg, 2.14mmol, 1eq.) in 3mL of THF. The mixture was stirred at -78°C and warmed up to -10°C in 1 hour, then stirred at room temperature for 2 hours. Reaction mixture was MS

showed the reaction quenched with water. Reaction was diluted with EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated down. The residue was purified by silica gel chromatography (10% to 60% ethyl acetate/hexanes) to provide 0.154g of product **26** (22% yield).

Step 3: To **26** (90mg, 0.28mmol) in 2mL of MeOH at room temperature was added 20% Pd(OH)/C (72mg, 80%w/w). . The reaction was stirred under a H_2 balloon overnight. The reaction mixture was filtered through Celite and was concentrated to yield 57mg of product **27** (85% yield).

Representative example 8: Synthesis of 3-(2-(piperidin-4-yl)phenyl)propanenitrile hydrochloride **28**.



28

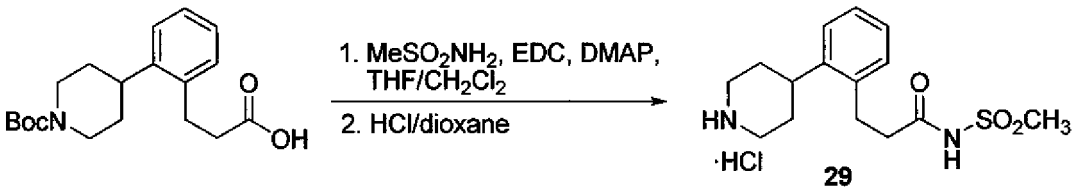
Step 1: *tert*-butyl 4-(2-(3-methoxy-3-oxopropyl)phenyl)piperidine-1-carboxylate obtained in step 3 of representative example 6 (300 mg, 0.86 mmol) was dissolved in $EtOH/H_2O$ (6.0 mL/5 drops). KOH (121 mg, 2.16 mmol) was added and the reaction was heated at 70 °C for 3 h. The reaction mixture was cooled and then concentrated. The residue was dissolved in H_2O and acidified to pH ~ 4 with 1 M HCl. The solution was extracted with EtOAc (3 x 15 mL), dried over Na_2SO_4 and concentrated.

Step 2: The crude acid (100 mg, 0.30 mmol) was dissolved in CH_2Cl_2 (3.0 mL) and then DMF (2 drops) was added. Oxalyl chloride (34 μL, 0.36 mmol) was added dropwise and the reaction was stirred at 23 °C under Ar for 1 h. NH_4OH (28%) was added to the reaction mixture and was stirred for 15 min. The mixture was extracted with EtOAc (2 x 15 mL). The organic layer was washed with water (1 x 20 mL), and brine (1 x 20 mL). The solution was dried over Na_2SO_4 and concentrated.

Step 3: The crude amide (96 mg, 0.29 mmol) was dissolved in pyridine (700 μL) under Ar. The mixture was cooled to 0 °C and $POCl_3$ (28 μL, 0.30 mmol) was added dropwise. The mixture was warmed to 23 °C and was further stirred for 3 h. The reaction mixture was quenched with 2 M HCl (~1 mL) and was extracted with EtOAc (2 x 15 mL). The organic layer was washed with sat'd $CuSO_4$ (2 x 15 mL) and brine (1 x 15 mL). The solution was dried over Na_2SO_4 and concentrated.

Step 4: To the crude Boc-piperidine nitrile, 4 M HCl/dioxane (725 μL, 2.90 mmol) was added under Ar at 23 °C and was stirred for 1 h. The reaction mixture was concentrated to obtain 3-(2-(piperidin-4-yl)phenyl)propanenitrile hydrochloride **28**. LC/MS RT (5 min method) = 0.92 min. Mass observed: 215.15 (M+H).

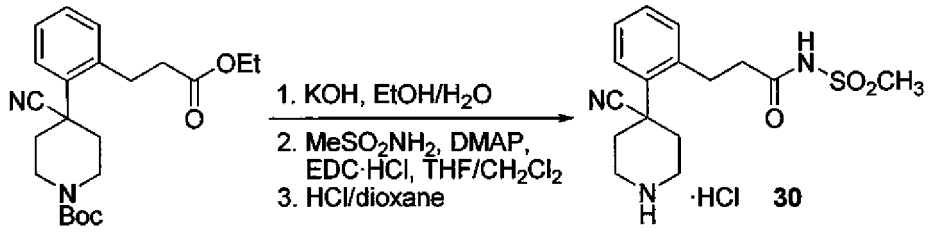
Representative example 9: Synthesis of *N*-(methylsulfonyl)-3-(2-(piperidin-4-yl)phenyl)propanamide hydrochloride **29**.



29

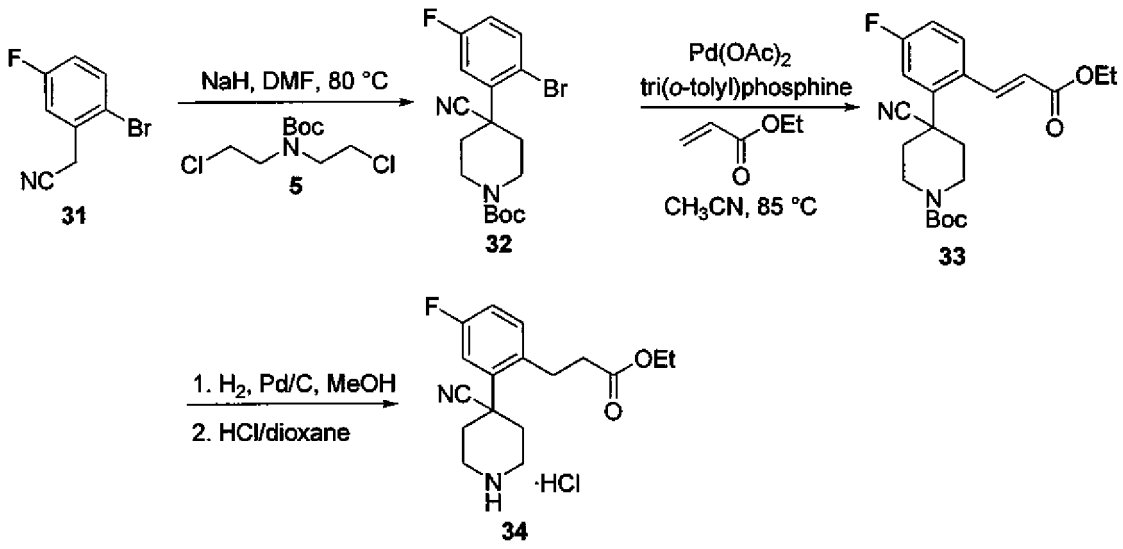
Acid 3-(2-(1-(tert-butoxycarbonyl)piperidin-4-yl)phenyl)propanoic acid obtained in step 1 of representative example 8 (40 mg, 0.12 mmol) and methane sulfonamide (17 mg, 0.18 mmol) were dissolved in THF/CH_2Cl_2 (0.5 mL/1.0 mL). DMAP (22 mg, 0.18 mmol) and EDC•HCl (35 mg, 0.18 mmol) were added and the reaction was stirred at 23 °C overnight. Water was added to the reaction mixture and was extracted with EtOAc (2 x 10 mL). The organic layers were dried over Na_2SO_4 and concentrated.

Representative example 10: Synthesis of 3-(2-(4-cyanopiperidin-4-yl)phenyl)-N-(methylsulfonyl)propanamide hydrochloride **30**.



Hydrolysis of the ester tert-butyl 4-cyano-4-(2-(3-ethoxy-3-oxopropyl)phenyl)piperidine-1-carboxylate obtained from representative example 5, step3, to the carboxylic acid *tert*-butyl 4-cyano-4-(2-(3-ethoxy-3-oxopropyl)phenyl)piperidine-1-carboxylate was followed similarly to the aforementioned procedures. Acylsulfonamide formation, followed by Boc-deprotection was followed by the synthesis of amine **29** to yield 3-(2-(4-cyanopiperidin-4-yl)phenyl)-*N*-(methylsulfonyl)propanamide hydrochloride **30**.

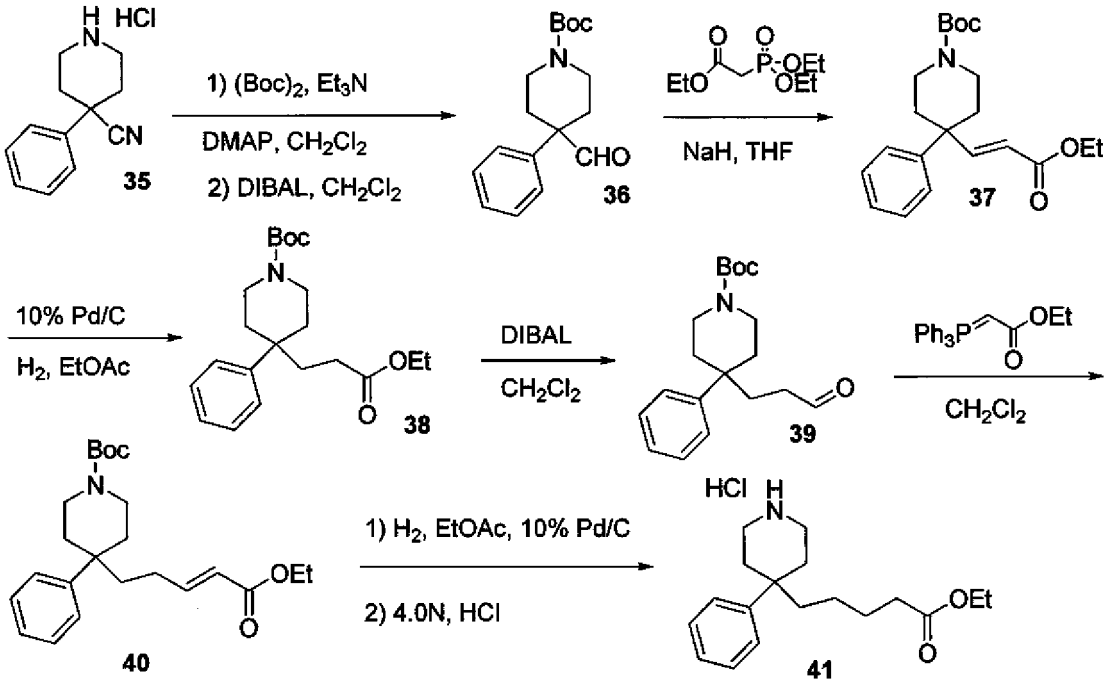
Representative example 11: Synthesis of ethyl 3-(2-(4-cyanopiperidin-4-yl)-4-fluorophenyl)propanoate hydrochloride **34**.



Procedure to prepare ethyl 3-(2-(4-cyanopiperidin-4-yl)-4-fluorophenyl)propanoate hydrochloride **34** (LC/MS RT (5 min method) = 1.19 min. Mass observed: 305.16 (M +H). is identical to the procedure used to prepare

ethyl 3-(2-(4-cyanopiperidin-4-yl)phenyl)propanoate hydrochloride **22** from Representative example 5 by replacing in step 1, nitrile **19** with nitrile **31**.

Representative example 12: Preparation of ethyl 5-(4-phenylpiperidin-4-yl)pentanoate hydrochloride **41**.



Step 1: To a stirring suspension of **35** (4.5 mmol, 1.0 g) in dichloromethane and triethylamine (11mmol, 1.6ml) at room temperature was added di-t-butyl dicarbonate (5.4 mmol, 1.2 g) followed by DMAP (0.45mmol, 55 mg). The reaction mixture was stirred at room temperature overnight and then diluted with EtOAc (50ml), washed with water (2x10ml), brine (10ml), then dried (MgSO4). The solvent was removed *in vacuo*. The crude product (1.3 g) was obtained as brownish oil. To a solution of this crude product (4.5 mmol, 1.2 g) in dichloromethane at 0°C was added diisobutylaluminum hydride (1.0 M in DCM, 5.0 ml, 5.0mmol). The reaction mixture was stirred at room temperature for 2 hours Then Rochelle Salt solution was added and the mixture was stirred vigorously for 1 hour, then diluted with EtOAc. The organic phase was separated

and the aqueous was extracted with EtOAc. The combined organic layer was washed with brine, dried (MgSO4), concentrated. The crude product **36** was obtained as slightly yellow oil (~1.2g), which was used in the next step without further purification.

Step 2: Sodium hydride (60% in mineral oil, 200mg, 5mmol) was washed with hexane twice, then added THF, cooled to 0°C. Triethylphosphoro acetate (1ml, 5.4 mmol) was added and the mixture was stirred for 30 min, then a solution of **36** in THF was added, warmed to room temperature, and stirred at rt overnight. The reaction was quenched with saturated NH4Cl, extracted with EtOAc. The combined organic layer was washed with brine, dried (MgSO4), concentrated, purified on Biotage (EtOAc in hexane: 10~25%) to give **37** as colorless oil (0.6g).

Step 3: To a stirring solution of **37** (1.67 mmol, 0.6 g) in EtOAc at room temperature was added catalytical amount of 10% palladium on carbon and the reaction mixture was purged with Hydrogen gas. After stirring at room temperature for 4h, the mixture was filtered through celite and concentrated *in vacuo*, to give **38** (0.5 g) as orange oil, which was used in the next step without further purification.

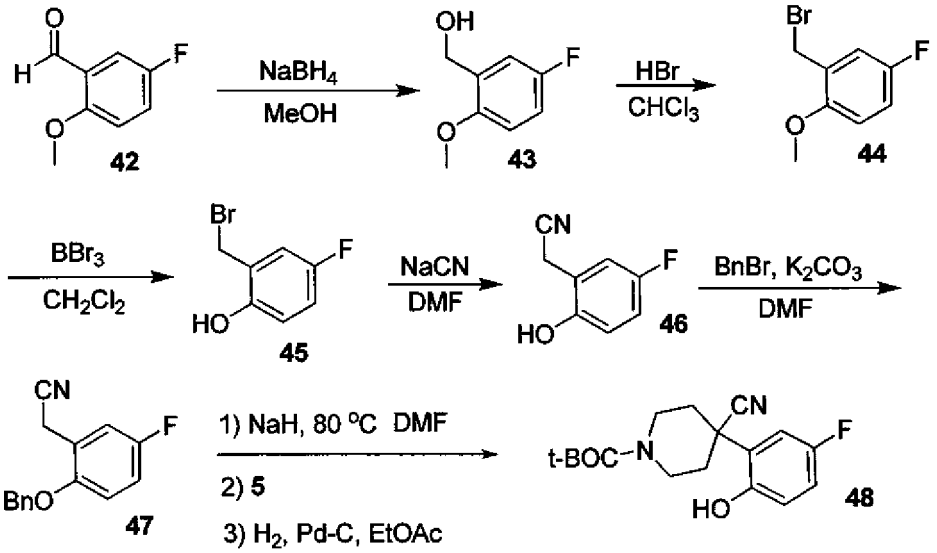
Step 4: To a solution of **38** in dichloromethane at 0°C was added diisobutylaluminum. The reaction mixture was stirred at -78°C for 1h. Then Rochelle Salt solution was added and the mixture was stirred vigorously for 30min, then extracted with EtOAc. The organic phase was separated and the aqueous was extracted with EtOAc, dried (MgSO4), concentrated. The crude product **39** was used in the next step without further purification.

Step 5: To a stirring solution of **39** in DCM at room temperature was added (carbethoxymethylene) triphenylphosphorane and the reaction mixture was stirred at reflux overnight. The solvent was removed in vacuo. The crude product was purified on Biotage (EtOAc in hexane: 10~25%) to give **40** as colorless oil.

Step 6: To a stirring solution of **40** in EtOAc was added catalytical amount of 10% palladium on carbon and the reaction mixture was purged with Hydrogen gas. After stirring at room temperature overnight, the mixture was filtered through celite and concentrated *in vacuo*, to give a colorless oil to which was added 4.0

M hydrochloride in 1,4-dioxane. After 1h, the solvent and volatile were removed by lyophilization, to give **41** as yellowish oil.

Representative example 13: Synthetic route to fluorinated cyanophenylpiperidines (5-Fluoro regioisomer) tert-butyl 4-cyano-4-(5-fluoro-2-hydroxyphenyl)piperidine-1-carboxylate **48**.



Step 1: To **42** (1 eq, 17.1 mmol, 2.6 g) in MeOH (68 mL) at room temperature, added $NaBH_4$ (1.2 eq, 20.5 mmol, 775 mg) and the reaction mixture stirred 18h, then concentrated *in vacuo*. The crude residue was diluted with ethyl acetate, washed with 1N aqueous HCl then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **43** (2.8 g) as a pale yellow oil

Step 2: To **43** (1 eq, 17.9 mmol, 2.8 g) in $CHCl_3$ (18 mL) at room temperature, added HBr (22 mL) and the reaction mixture was stirred 2h, then diluted with dichloromethan, washed with water then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **44** (3.3 g) as an off-white solid.

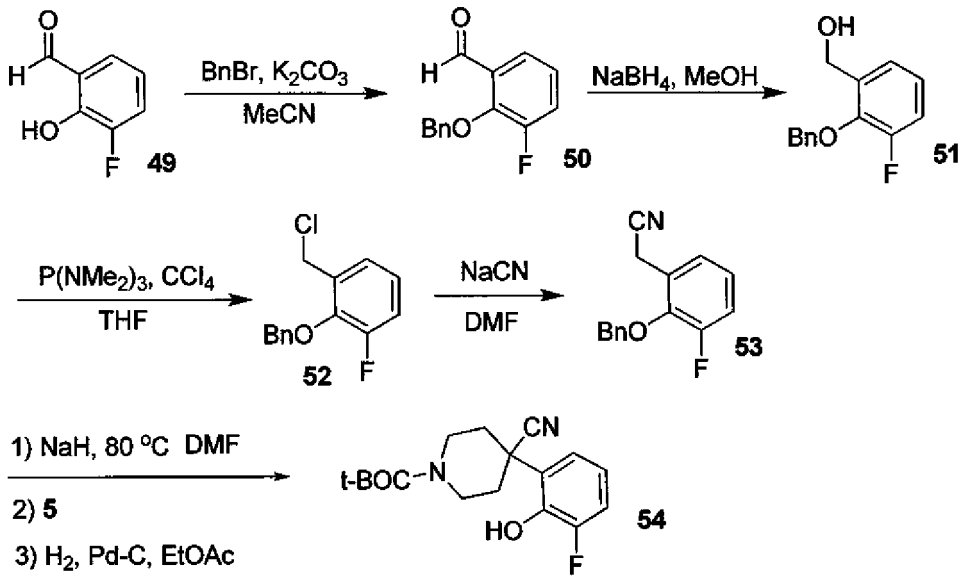
Step 3: To **44** (1 eq, 8.67 mmol, 1.9 g) in CH_2Cl_2 (58 mL) at -78 °C, added BBr_3 solution (1.5 eq, 13 mmol, 13 mL) dropwise over 5 min, stirred at -78 °C 3h, then warmed to room temperature and stirred 18h. The reaction was quenched with

water (10 mL), extracted with dichloromethane then ethyl acetate, the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to give **45** (~2 g) as a brown oily solid.

Step 4: To **45** (1 eq, 8.5 mmol, 1.75 g) in DMF (43 mL) at room temperature, added NaCN (1.1 eq, 9.30 mmol, 460 mg) and stirred at room temperature 3 days. The reaction mixture was diluted with water, extracted with ethyl acetate, washed with water (3X) then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **46** (1.47 g) as a brown oil

Step 5: To NaH (2.2 eq, 2.05 mmol, 82 mg) under argon at room temperature with stirring, added a solution of **46** (1 eq, 0.93 mmol, 225 mg) and amine **5** (1.0 eq, 0.93 mmol, 225 mg) in DMF (9 mL) and stirred at room temperature 0.5h, then heated at 80 °C for 5h. The reaction was cooled to room temperature, quenched with water (~10 mL), extracted with ethyl acetate, washed with water (3X) then brine, dried over sodium sulfated, and concentrated *in vacuo*. Purification by flash silica gel chromatography (10% → 20% → 50% EtOAc/hexane) gave tert-butyl 4-(2-(benzyloxy)-5-fluorophenyl)-4-cyanopiperidine-1-carboxylate (236 mg) as a sticky brown oil. To tert-butyl 4-(2-(benzyloxy)-5-fluorophenyl)-4-cyanopiperidine-1-carboxylate (1 eq, 0.9 mmol, 370 mg) in ethyl acetate (9 mL), added Pd-C (100 mg), purged the reaction vessel with H_2, and stirred at room temperature under an H_2 atmosphere (balloon) for 3 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to give **48** (250 mg) as an orange foam.

Representative example 14: Synthetic route to fluorinated cyanophenylpiperidines (3-Fluoro regioisomer) tert-butyl 4-cyano-4-(5-fluoro-2-hydroxyphenyl)piperidine-1-carboxylate **54**.



Step 1: To **49** (1 eq, 21 mmol, 3 g) in MeCN (107 mL) at room temperature, added BnBr (1.1 eq, 24 mmol, 2.8 mL) followed by K_2CO_3 (1.5 eq, 32 mmol, 4.4 g) and the reaction mixture stirred at room temperature 18h, filtered through celite, and the solvent removed *in vacuo*. The crude residue was dissolved in ether, washed with water then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **50** as a pale yellow oil (5 g).

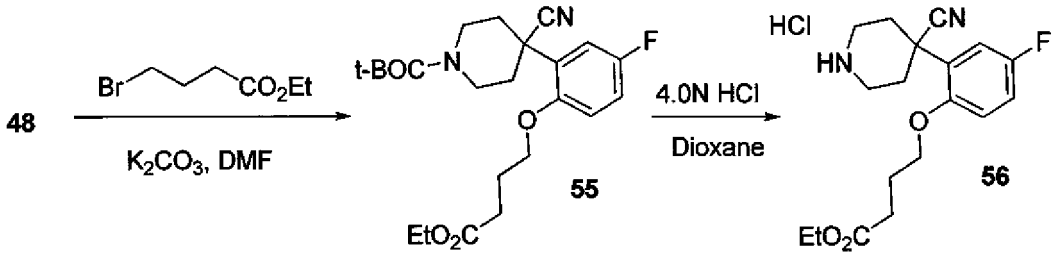
Step 2: To **50** (1 eq, 22 mmol, 5 g) in MeOH (109 mL) at 0 °C, added $NaBH_4$ (1.2 eq, 26 mmol, 0.99 g) and the reaction mixture was warmed to room temperature, stirred 18h, then concentrated *in vacuo*. The crude residue was diluted with ethyl acetate, washed with 1N aqueous HCl then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **51** (4.1 g) as a colorless oil.

Step 3: To **51** (1 eq, 4.15 mmol, 963 mg) and CCl_4 (1.1 eq, 4.56 mmol, 441 uL) in THF (28 mL) at 0 °C under argon, added $P(NMe_2)_3$ (1.1 eq, 4.56 mmol, 829 uL) dropwise and the reaction mixture was warmed to room temperature over 2h, and stirred an additional 2h. After **51** was consumed as observed by TLC, the solvent was removed *in vacuo*, the crude residue **52** was dissolved in DMF (15 mL) and NaCN (1.1 eq, 4.56 mmol, 224 mg) was added and the reaction mixture stirred at room temperature 18h. The mixture was diluted with ethyl acetate,

washed with water (3X) then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **53** (733 mg) as a dark red oil.

Step 4: To NaH (2.2 eq, 2.74 mmol, 109 mg) under argon at room temperature with stirring, added a solution of **53** (1 eq, 1.24 mmol, 300 mg) and **5** (1.1 eq, 1.24 mmol, 300 mg) in DMF (10 mL) and stirred at room temperature 0.5h, then heated at 80 °C for 5h. The reaction was cooled to room temperature, quenched with water (~10 mL), extracted with ethyl acetate, washed with water (3X) then brine, dried over sodium sulfated, and concentrated *in vacuo.* Purification by flash silica gel chromatography (10% → 20% → 40% EtOAc/hexane) gave tert-butyl 4-(2-(benzyloxy)-3-fluorophenyl)-4-cyanopiperidine-1-carboxylate (189 mg) as an orange oil. To tert-butyl 4-(2-(benzyloxy)-3-fluorophenyl)-4-cyanopiperidine-1-carboxylate (1 eq, 5 mmol, 1.86 g) in ethyl acetate (45 mL), added Pd-C (300 mg), purged the reaction vessel with H_2, and stirred at room temperature under an H_2 atmosphere (balloon) for 3 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to give **54** (1.45 g) as a colorless oil.

Representative example 15: Preparation of ethyl 4-(2-(4-cyanopiperidin-4-yl)-4-fluorophenoxy)butanoate **56**.

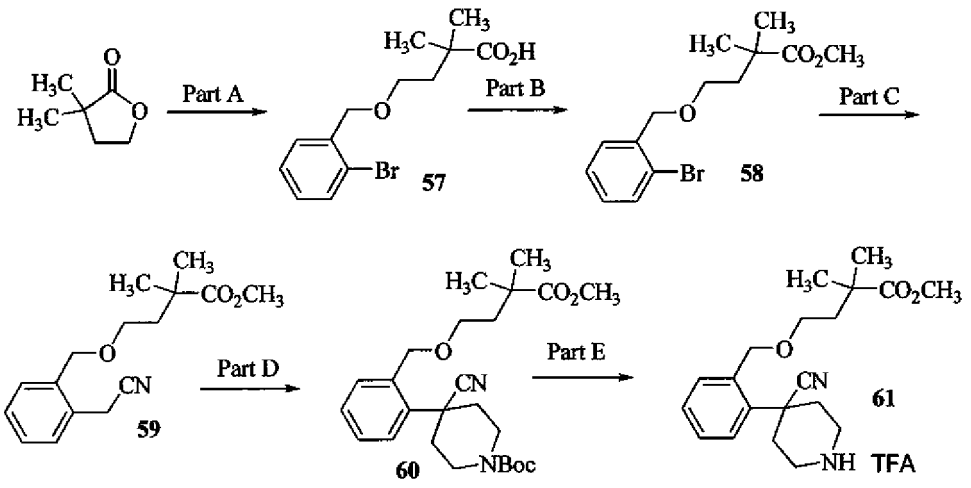


Step 1: To a stirring solution of **48** (1 eq, 0.78 mmol, 250 mg) and ethyl 4-bromobutanoate (1.1 eq, 0.86 mmol, 167 mg) in DMF at room temperature, added K_2CO_3 (2.5 eq, 2.34 mmol, 324 mg) and stirred the reaction mixture 18h. The mixture was diluted with water, extracted with ethyl acetate, washed with

water (3X) then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **55** (151 mg) as an orange oil.

Step 2: A solution of **55** (1 eq, 0.348 mmol, 151 mg) was stirred in HCl/dioxane (1 mL) at room temperature 2h, then concentrated to dryness *in vacuo*. The crude reside was dissolved in dichloromethane, washed with sodium bicarbonate (aqueous) then brine, dried over sodium sulfate, and concentrated *in vacuo* to give **56** (80 mg) as a pale brown oil.

Representative example 16: Preparation of methyl 4-(2-(4-cyanopiperidin-4-yl)benzyloxy)-2,2-dimethylbutanoate 2,2,2-trifluoroacetate **61**.



Part A: Powdered potassium hydroxide (3.99 g, 60.5 mmol) was added in one portion to 3,3-dimethyldihydrofuran-2(3H)-one (2.76 g, 24.2 mmol) and 2-bromobenzylbromide (13.3 g, 53.2 mmol) in anhydrous toluene (100 mL) under nitrogen. The reaction mixture was heated to reflux for 3 h, cooled to room temperature, transferred to a separatory funnel and extracted with 1 N aqueous sodium hydroxide (2 × 50 mL). The combined aqueous layers were washed with ether (50 mL, discard) then the pH was adjusted to ~1 with 2 N hydrochloric acid and extracted with ether (3 × 60 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Compound **57** (2.10 g, 29% yield) was isolated as a

light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.51 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.33-7.26 (m, 1H), 7.12 (td, *J* = 7.7, 1.4 Hz, 1H), 4.53 (s, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.49 (s, 1H), 1.97 (t, *J* = 6.8 Hz, 2H), 1.25 (s, 6H).

Part B: Thionyl chloride (0.83 g, 6.97 mmol) was added dropwise to **57** (2.10 g, 6.97 mmol) in methanol (75 mL) and stirred at room temperature for 15 h. The solvent was removed by evaporation and the residue taken up in ether (100mL) then washed with water (25 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography (ethyl acetate/hexanes) to provide **58** (1.23 g, 56% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.51 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.12 (td, *J* = 7.7, 1.4 Hz, 1H), 4.52 (s, 2H), 3.63-3.56 (m, 5H), 1.94 (t, *J* = 6.8 Hz, 2H), 1.23 (s, 6H).

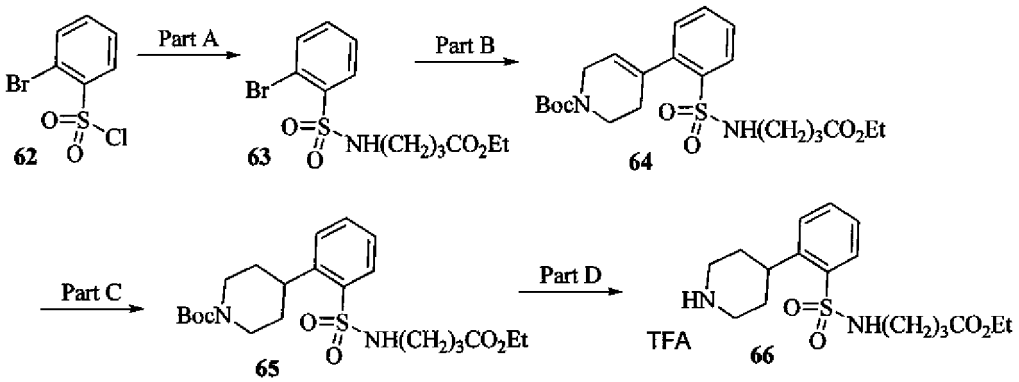
Part C: Zinc fluoride (159 mg, 1.53 mmol) was added in one portion to **58** (646 mg, 2.05 mmol), tris(dibenzylideneacetone)dipalladium(0) (75 mg, 0.082 mmol), tri-*t*-butylphosphonium tetrafluoroborate (48 mg, 0.164 mmol), potassium carbonate (23 mg, 0.164 mmol), and trimethylsilyacetonitrile (348 mg, 3.07 mmol) in anhydrous DMF (2 mL) in a heavy walled test tube with a threaded cap. The tube was sealed and the reaction mixture was heated at 90 °C for 14 h. The reaction mixture was diluted with ether (50 mL) then washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography (ethyl acetate/hexanes) to provide **59** (300 mg, 53% yield) as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.46-7.27 (m, 4H), 4.84 (s, 2H), 3.85 (s, 2H), 3.54 (s, 3H), 3.49 (t, *J* = 6.8 Hz, 2H), 1.88 (t, *J* = 6.8 Hz, 2H), 1.19 (s, 6H).

Part D: *t*-Butyl bis(2-chloroethyl)carbamate (572 mg, 2.36 mmol) and **59** (650 mg, 2.36 mmol) in DMF (8 mL) were added dropwise to sodium hydride (60% in mineral oil, 208 mg, 5.19 mmol) suspended in DMF (20 mL) at 0 °C. After 30 min at 0 °C the ice bath was removed and the reaction mixture allowed to warm to room temperature for 1.5 h. The reaction was heated to 75 °C for 3 h and cooled back to room temperature. The reaction was quenched by addition of saturated

ammonium chloride (50 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were washed with water (3 × 20 mL) and brine (40 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography (ethyl acetate/hexanes) to provide **60** (683 mg, 65% yield) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.57-7.52 (m, 1H), 7.39-7.37 (m, 3H), 4.78 (s, 2H), 4.39-4.16 (m, 2H), 3.64-3.52 (m, 5H), 3.36-3.18 (m, 2H), 2.35-2.26 (m, 2H), 1.99-1.85 (m, 4H), 1.48 (s, 9H), 1.22 (s, 6H).

Part E: Trifluoroacetic acid (2 mL) was added to **60** (222 mg, 0.50 mmol) in methylene chloride (2 mL). The reaction was stirred at ambient temperature for 3 h then concentrated down to yield methyl 4-(2-(4-cyanopiperidin-4-yl)benzyloxy)-2,2-dimethylbutanoate 2,2,2-trifluoroacetate **61**.

Representative example 17: Preparation of ethyl 4-(2-(piperidin-4-yl)phenylsulfonamido)butanoate 2,2,2-trifluoroacetate **66**.



Part A: A mixture of 2-bromobenzenesulfonyl chloride (**62**, 1.39 g, 5.43 mmol), ethyl-4-aminobutyrate•HCl (1.27 g, 7.60 mmol), and triethylamine (1.54 g, 15.2 mmol) in methylene chloride (27.1 mL) was stirred at room temperature for 21 h. The mixture was diluted with EtOAc (300 mL), washed with sat'd aq. NH_4Cl (3 × 100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide sulfonamide **63** (1.67 g, 88%) as a yellow solid which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$ 8.13 (dd, J = 7.4, 1.7 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.52–7.37 (m, 2H),

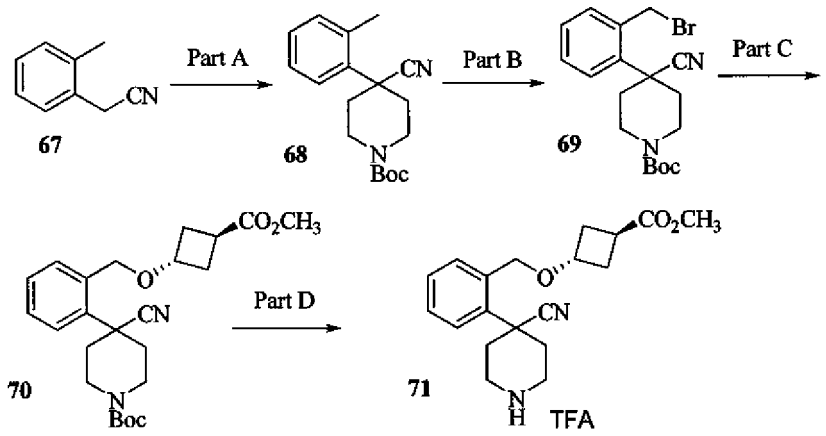
5.30 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.96 (q, *J* = 7.1 Hz, 2H), 2.36 (t, *J* = 7.1 Hz, 2H), 1.81 (pentet, *J* = 7.1 Hz, 2H), 1.30–1.19 (t, *J* = 7.1 Hz, 3H).

Part B: A mixture of *tert*-butyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (264 mg, 0.854 mmol), compound **63** (272 mg, 0.776 mmol), $Pd(PPh_3)_4$ (44.8 mg, 38.8 umol), 2 M aq. Na_2CO_3 (1.17 mL), and DME (5.17 mL) we place in a sealed microwave vial and heated at 80 °C for 3 d. The mixture was diluted with EtOAc (250 mL), washed with sat'd aq. NH_4Cl (3 × 100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by CombiFlash (40 g, Hex/EtOAc) to provide pure product **64** (325 mg, 93%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$ 7.97 (d, *J* = 7.6 Hz, 1 H), 7.52, (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 5.62 (s, 1H), 5.30 (s, 1H), 4.62 (d, *J* = 5.9 Hz, 1H), 4.20–4.02 (m, 2H), 3.66 (t, *J* = 5.5 Hz, 2H), 2.91 (q, *J* = 6.6 Hz, 2H), 2.52–2.41 (m, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.79 (pentet, *J* = 6.8 Hz, 2H), 1.63–1.46 (m, 10H), 1.30–1.19 (m, 3H).

Part C: A solution of compound **64** (320 mg, 0.708 mmol) in ethanol (200 mL) was degassed with nitrogen, added 10% Pd/C (75.3 mg, 35.4 □mol) then hydrogenated at 45 psi overnight. The Pd/C was removed by filtration through Celite, washing with methanol. The filtrate was concentrated under reduced pressure to provide compound **65** (277 mg, 86%) as a yellow oil which was used in the next step without further purification: ^1H NMR (300 MHz, $CDCl_3$ 7.93 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.58–7.49 (m, 1H), 7.47–7.40 (m, 1H), 7.36–7.27 (m, 1H), 4.85 (t, *J* = 6.2 Hz, 1H), 4.40–4.05 (m, 4H), 3.80–3.53 (m, 1H), 3.06 (q, *J* = 6.7 Hz, 2H), 2.86 (t, *J* = 12.8 Hz, 2H), 2.37 (t, *J* = 6.7 Hz, 2H), 1.90–1.76 (m, 4H), 1.75–1.40 (m, 11H), 1.24 (t, *J* = 7.1 Hz, 3H).

Part D: Trifluoroacetic acid was added to **65** in methylene chloride (2 mL). The reaction was stirred at ambient temperature for 3 h then concentrated down to yield 4-(2-(piperidin-4-yl)phenylsulfonamido)butanoate 2,2,2-trifluoroacetate **66**.

Representative example 18: Preparation of ethyl (1R,3R)-methyl 3-(2-(4-cyanopiperidin-4-yl)benzyloxy)cyclobutanecarboxylate 2,2,2-trifluoroacetate **71**.



Part A: Sodium hydride (60% in mineral oil, 8.51 g, 212 mmol) was added in portions to **67** (10.0g, 76.2 mmol) and *t*-butyl bis(2-chloroethyl)carbamate (20.3 g, 83.8 mmol) in DMF (150 mL) over a 3 h period under nitrogen. After the addition was complete the reaction was stirred for 1 h at room temperature then 2 h at 70 °C. The reaction was cooled to room temperature and the volume was reduced to ~60 mL in vacuo. Saturated ammonium chloride (100 mL) was added with vigorous stirring. The aqueous layer was decanted and the oily solid residue taken up in methylene chloride. The reaction was repeated and combined for purification by chromatography on silica gel (methylene chloride/ethyl acetate) to provide **68** (15.0 g, 33% yield) as a light brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.22 (m, 4H), 4.42-4.18 (m, 2H), 3.37-3.20 (m, 2H), 2.65 (s, 3H), 2.36-2.28 (m, 2H), 1.90 (td, J = 9.8, 3.1 Hz, 2H), 1.48 (s, 9H).

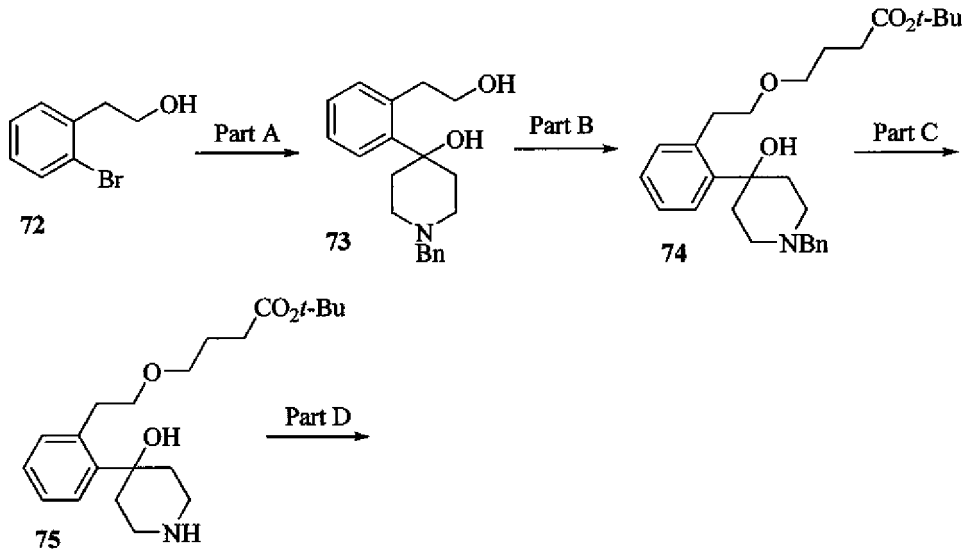
Part B: Bromine (0.72 g, 4.49 mmol) was added to **68** (300 mg, 1.00 mmol) in a mixture of water/chlorobenzene (4:1, 5 mL) at 0 °C in a heavy walled screw cap test tube. Six identical sealed tubes were set up and irradiated with a tungsten lamp for 1 h. The lamp was turned off and stirring was continued for 20 min. The crude reaction mixtures were combined and partitioned between ethyl acetate (100 mL) and saturated sodium thiosulfate (50 mL). The ethyl acetate solution was dried over $MgSO_4$, filtered, evaporated and purified by silica gel chromatography (ethyl acetate/hexanes) to provide compound **69** (0.84 g, 37% yield) as light brown oil contaminated with **68** (~15%): ^{1}H NMR (300 MHz, $CDCl_3$)

7.61-7.56 (m, 1H), 7.42-7.33 (m, 3H), 4.91 (s, 2H), 4.48-4.17 (m, 2H), 3.29 (t, *J* = 12.9 Hz, 2H), 2.45-2.33 (m, 2H), 2.03-1.86 (m, 2H), 1.48 (s, 9H).

Part C: Potassium *t*-butoxide (1M in THF, 0.4 mL, 0.4 mmol) was added dropwise to methyl *trans*-3-hydroxycyclobutanecarboxylate (52 mg, 0.399 mmol) and **69** (150 mg, 0.395 mmol) in anhydrous THF (3.6 mL). After 2.5 h the reaction mixture was cooled to 0–5 °C and quenched with 0.5 M hydrochloric acid to a pH of ~2. The reaction mixture was partitioned between water/ethyl acetate (1:1, 20 mL) and extracted further with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography (ethyl acetate/hexane) to provide **70** (36 mg, 21 % yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.58-7.53 (m, 1H), 7.41-7.27 (m, 3H), 4.76 (s, 2H), 4.39-4.14 (m, 2H), 4.07 (quint, *J* = 7.3 Hz, 1H), 3.69 (s, 3H), 3.27 (t, *J* = 12.8 Hz, 2H), 2.75-2.51 (m, 3H), 2.40-2.23 (m, 4H), 2.02-1.86 (m, 2H), 1.48 (s, 9H).

Part D: Trifluoroacetic acid was added to **70** in methylene chloride (2 mL). The reaction was stirred at ambient temperature for 3 h then concentrated down to yield (1R,3R)-methyl 3-(2-(4-cyanopiperidin-4-yl)benzyloxy)cyclobutanecarboxylate 2,2,2-trifluoroacetate **71**.

Representative example 19: Preparation of ethyl tert-butyl 4-(2-(4-hydroxypiperidin-4-yl)phenethoxy)butanoate **75**.



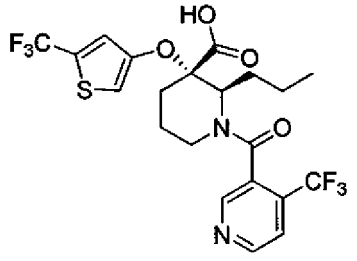
Part A: *n*-Butyl lithium (1.6 M in hexanes, 65.2 mL, 104 mmol) was added dropwise to **72** (10 g, 49.7 mmol) in a mixture of ether/THF (1:1, 150 mL) at -78 °C. After the addition was complete stirring was continued at -78 °C for 3 h. 1-Benzyl-4-piperidone (10.2 g, 53.6 mmol) in a mixture of ether/THF (1:1, 50 mL) was added dropwise to the reaction mixture and after addition is completed the reaction was allowed to warm to room temperature over 4 h. The reaction was quenched with ice cold water (200 mL) then extracted with ether (3 × 150 mL). The combined extracts were washed with brine (100 mL) and dried over Na_2SO_4 and filtered. The volume of the solvent was reduced by 80% in vacuo at which time a white solid precipitates. The remaining mixture was cooled in an ice water bath and the white solid was filtered to give **73** (7.00 g, 46% yield) as a crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.40-7.15 (m, 9H), 3.91 (t, *J* = 6.0 Hz, 2H), 3.57 (s, 2H), 3.29 (t, *J* = 6.0 Hz, 2H), 2.81-2.74 (m, 2H), 2.57-2.50 (m, 2H), 2.17 (t, *J* = 12.8, 4.3 Hz, 2H), 1.93-1.87 (m, 2H), 1.74 (br, 2H).

Part B: 18-Crown-6 (896 mg, 3.39 mmol) was added to **73** (480 mg, 1.54 mmol) in anhydrous THF (25 mL) and the resulting mixture was cooled to 0 °C. The reaction was allowed to warm to room temperature over 1.5 h then continue stirring for an additional 20 h. The reaction mixture was cooled to 0 °C and quenched with saturated ammonium chloride (10 mL). Extract with ethyl acetate

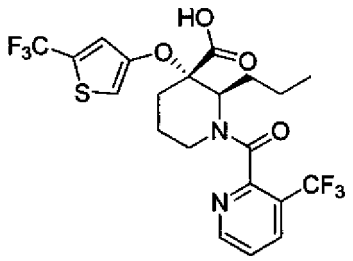
(3 × 20 mL) and the combined extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography (methanol/methylene chloride) to provide **74** (50 mg, 7% yield) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) 7.40-7.24 (m, 6H), 7.20-7.14 (m, 3H), 3.88 (br, 1H), 3.68 (t, *J* = 5.9 Hz, 2H), 3.41-3.30 (m, 4H), 2.84-2.71 (m, 2H), 2.57 (t, *J* = 10.8 Hz, 2H), 2.23-2.06 (m, 4H), 1.84 (dd, *J* = 13.7, 2.3 Hz, 2H), 1.74 (quint, *J* = 7.0 Hz, 2H), 1.67-1.52 (m, 2H), 1.40 (s, 9H).

Part C: A solution of palladium hydroxide (25 mg) and **74** (66 mg, 0.145 mmol) in methanol (4 mL) was hydrogenated under a hydrogen balloon for 6 h. The reaction mixture was flushed with nitrogen and the catalyst was removed by filtration. The solvent was removed in vacuo to provide **75** (55 mg, quantitative) as a clear oil: ^{1}H NMR (300 MHz, MeOD-d_3) 7.45-7.34 (m, 1H), 7.27-7.20 (m, 1H), 7.20-7.11 (m, 2H), 3.67 (t, *J* = 6.9 Hz, 2H), 3.45 (t, *J* = 6.2 Hz, 2H), 3.35-3.18 (m, 4H), 3.05-2.87 (m, 2H), 2.23 (t, *J* = 2.5 Hz, 2H), 2.17-2.01 (m, 2H), 2.00-1.88 (m, 2H), 1.78 (quint, *J* = 6.8 Hz, 2H), 1.43 (s, 9H).

Representative procedures for amide formation, sidechain modification, and ester formation or hydrolysis



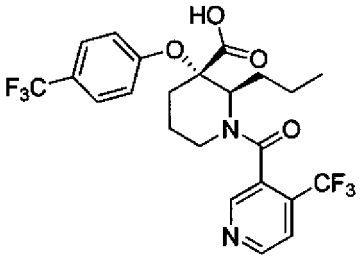
76



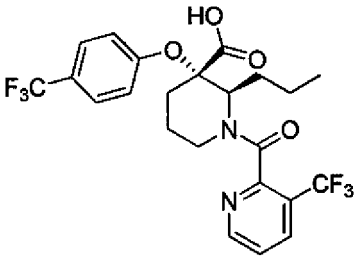
77

Preparation of (2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carboxylic acid **76** has been described in the previous publication (US 2008/0004287 A1). (2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-

carboxylic acid **77** was prepared in a similar manner to **76** by replacing CF3-nicotinic acid with commercially available CF3-picolinic acid.



76-A

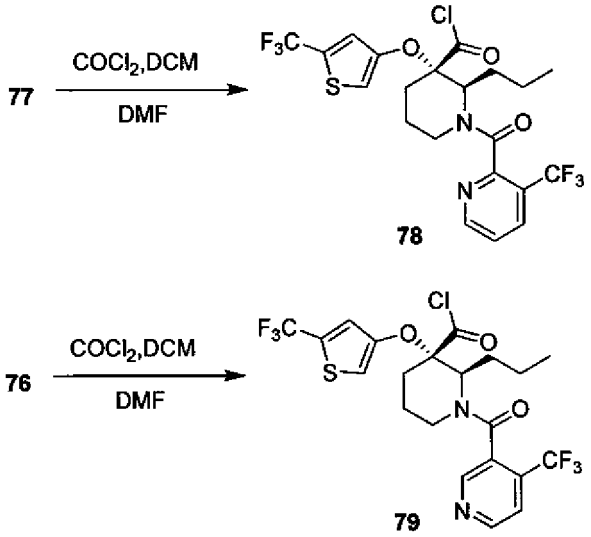


77-A

Preparation of (2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(4-(trifluoromethyl)phenoxy)piperidine-3-carboxylic acid **76-A** has been described in the previous publication (US 2008/0004287 A1). (2R,3S)-2-propyl-3-(4-(trifluoromethyl)phenoxy)-1-(3-(trifluoromethyl)picolinoyl)piperidine-3-carboxylic acid **77-A** was prepared in a similar manner to acid **76-A** by replacing CF3-nicotinic acid with commercially available CF3-picolinic acid.

Generale procedure 1:

Representative example 20: Synthesis of (2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl chloride **78** and (2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl chloride **79**

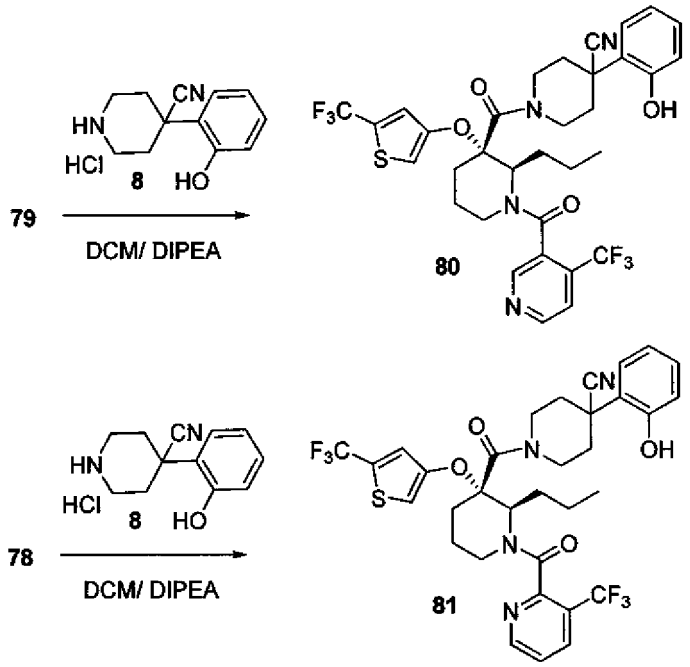


To a 0°C solution of acid **77** (1.71 mmol, 0.9g) in DCM (10 mL) was added oxalylchloride (2 equiv, 3.5 mmol, 0.3 mL) followed by DMF (2 drops). Reaction was stirred at 0°C for 30 min then concentrated to dryness and stored under high vacuum. The resulting (2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl chloride **78** was used without further purification.

(2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl chloride **79** was prepared in similar fashion using acid **76** as starting material instead of acid **77**.

General procedure 2:

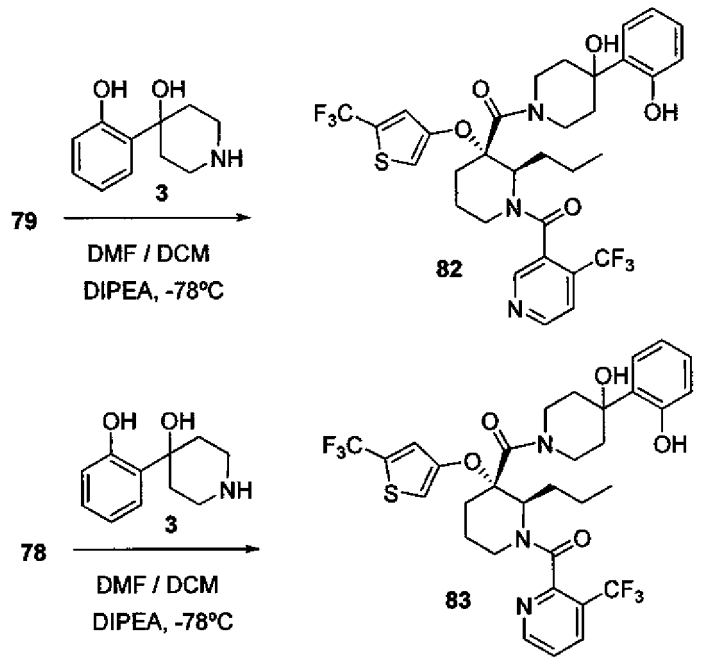
Representative example 21: Synthesis of 4-(2-hydroxyphenyl)-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidine-4-carbonitrile **80** and4-(2-hydroxyphenyl)-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl) thiophen-3-yloxy)piperidine-3-carbonyl)piperidine-4-carbonitrile **81**



To the phenol **8** (1.36gm, 5.69mmol, 1.5 equi.) in DCM(100 mL) was added the DIPEA (10 equi., 7mL) followed by the acid chloride **79** (2gm, 1 equi., 4.54mmol) under nitrogen. Reaction was stirred at room temperature for 18 hours and diluted with ethyl acetate, then washed with sat ammonium chloride, sodium bicarbonate and brine. Dried over Na_2SO_4, .filtered and concentrated to dryness. The residue was purified by silica gel chromatography (10% to 80% ethyl acetate/hexanes) to provide 2.49 g of intermediate **80**. Intermediate **81** was prepared in similar fashion using acid chloride **78** as starting material instead of acid chloride **79**.

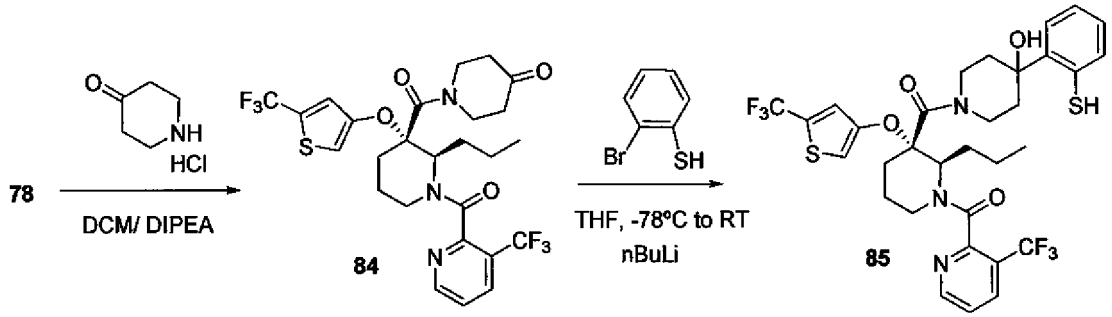
General procedure 3:

Representative example 22: Synthesis of (4-hydroxy-4-(2-hydroxyphenyl)piperidin-1-yl)((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone **82** and (4-hydroxy-4-(2-hydroxyphenyl)piperidin-1-yl)((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone **83**.



To a -50°C internal temp solution of piperidine **3** (1.5 equiv, 22.5 mmol, 4.4g) in DMF (100 mL) and DIPEA (5 equiv, 12.4 mL) was added dropwise a DMF solution (100 mL) of acid chloride **78** (15 mmol). Cooling bath was removed and reaction was warmed-up to 23°C overnight. The reaction mixture was diluted withEtOAc, wash with HCl 1.0N. dried over MgSO4, filtered and concentrated down. The residue was purified by silica gel chromatography (10% to 60% ethyl acetate/hexanes) to provide 7.6 g (74% yield) of intermediate **83** as a white foam. Intermediate **82** was prepared in similar fashion using acid chloride **79** as starting material instead of acid chloride **78**.

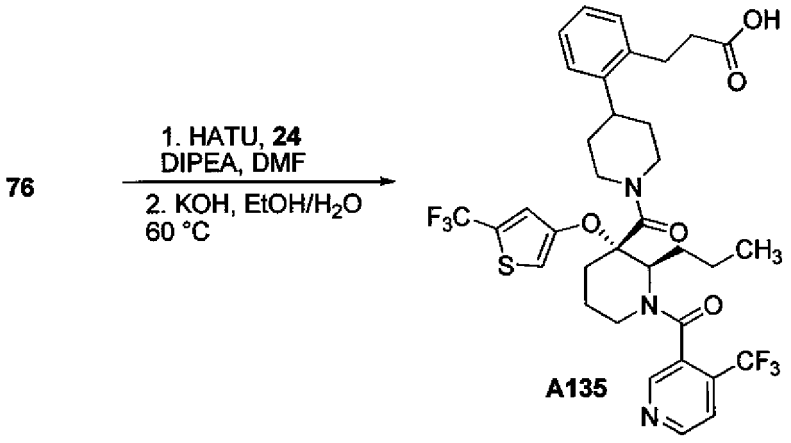
Representative example 23: Synthesis of (4-hydroxy-4-(2-mercaptophenyl)piperidin-1-yl)((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone **85**.



Step 1: Acid chloride **78** (2 mmol) was diluted in DCM (10 mL) and added DIPEA (1 mL) followed by piperidin-4-one hydrochloride (3 mmol, 400 mg). After 15' MS MS analysis showed that all starting material had been consumed. Reaction was diluted with EtOAc, washed with HCl 1.0N and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated down. The residue was purified by C18 column using 60-95% CH3CN in water over 10 minutes. The product was lyophilized to yield 63% of 1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-one **84**.

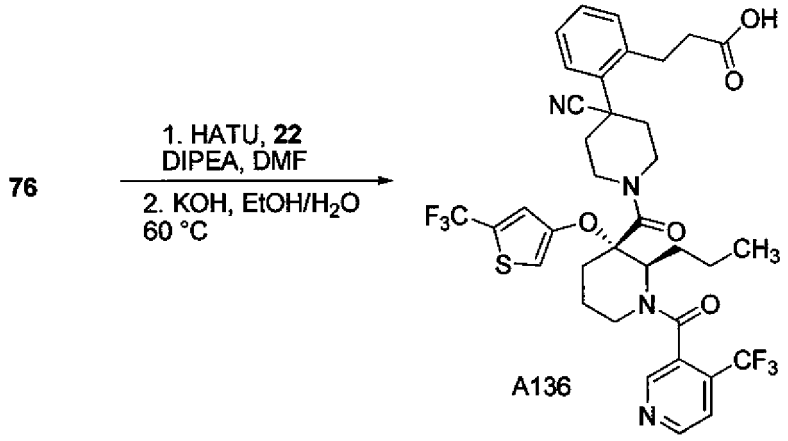
Step 2; To a -78°C solution of Bromothiophenol (0.6 g, 3 mmol) in THF (5 mL) was added n-BuLi (6 mmol, 2.4mL). After 30 min, reaction was added to **84** (2 mmol, in THF) at -78°C. After addition, reaction was warmed-up to RT. After 1 hours, NH_4Cl was added and reaction was extracted with EtOAc. Organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated down. The residue was purified by silica gel chromatography 40g, 20-100% EtOAc in hexanes to provide 390 mg of **85** (30% yield).

General procedure 4: Representative example 24: Synthesis of 3-(2-(1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanoic acid **A135**.



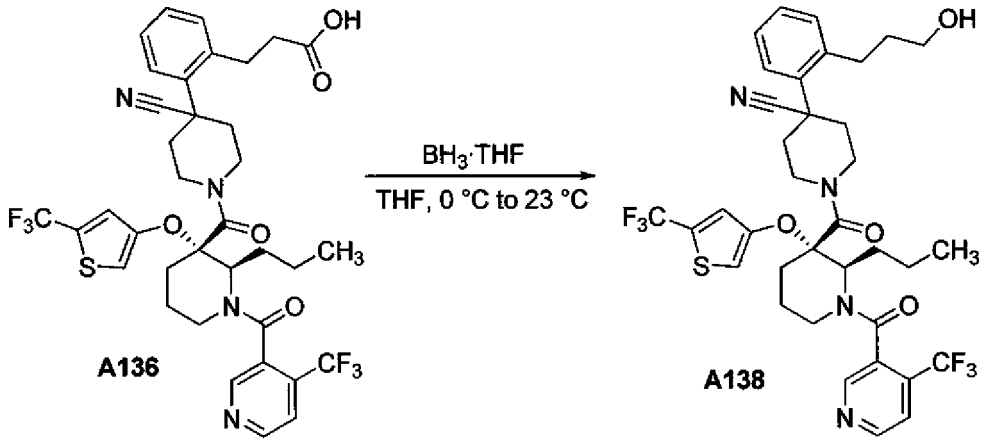
76 (80 mg, 0.16 mmol) and 3-(2-(piperidin-4-yl)phenyl)propanoate hydrochloride **24** (66 mg, 0.20 mmol) were dissolved in DMF (1 mL). HATU (119 mg, 0.31 mmol) and DIPEA (280 µL, 1.57 mmol) were added. The reaction was stirred at 23 °C overnight. The reaction mixture was concentrated. The crude residue was dissolved in EtOH (1 mL). KOH (26 mg, 0.47 mmol) and water (5 drops) were added and the reaction was heated at 65 °C for 2 h. The reaction was concentrated and the residue was dissolved in H_2O (3 mL) and was acidified to pH ~ 4 with aqueous 1 M HCl. The crude residue was purified by reverse phase preparative HPLC to yield 3-(2-(1-((2*R*,3*S*)-2-propyl-1-(4-trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanoic acid **A135**. LC/MS RT (10 min method) = 6.31 min. Mass observed: 726.23 (M+H).

Representative example 25: Synthesis of 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanoic acid **A136**.



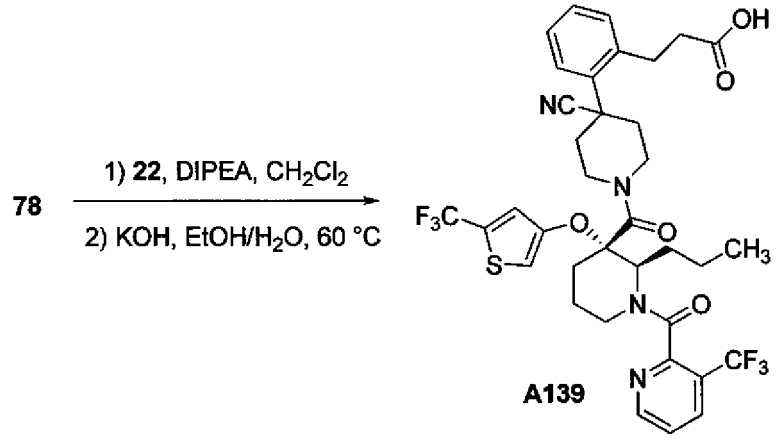
Amide coupling of **76** and 3-(2-(4-cyanopiperidin-4-yl)phenyl)propanoate hydrochloride **22** followed by hydrolysis were performed by following ***general procedure 4***. Reverse phase preparative HPLC purification yielded 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl) nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanoic acid **A136**. LC/MS RT (10 min method) = 4.55 min. Mass observed: 751.23 (M+H).

Representative example 26: Synthesis of 4-(2-(3-hydroxypropyl)phenyl)-1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidine-4-carbonitrile **A138**.



Acid **A136** 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanoic acid (10 mg, 13.3 μmol) was dissolved in THF (0.5 mL). The mixture was cooled to 0 °C and BH_3•THF (30 μL, 27.9 μmol) was added dropwise under Ar. The reaction was warmed to 23 °C and was stirred overnight. The reaction mixture was quenched with 1 M NaOH and was concentrated. The crude residue was purified by reverse phase preparative HPLC to yield 4-(2-(3-hydroxypropyl)phenyl)-1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidine-4-carbonitrile **A138**. LC/MS RT (10 min method) = 6.04 min. Mass observed: 737.25 (M+H).

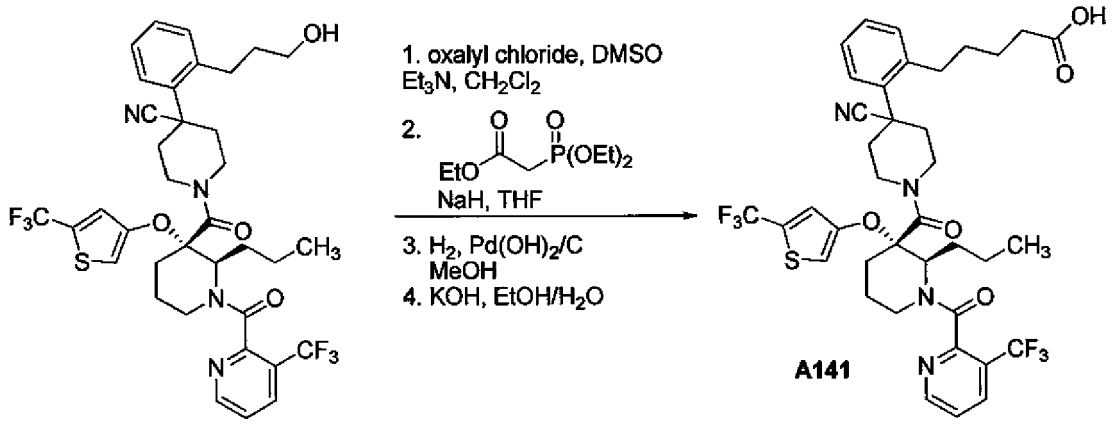
Representative example 27: Synthesis of 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanoic acid **A139**.



Amide bond formation was followed by ***general procedure 2***. Hydrolysis of the ester to the carboxylic acid was followed as described in ***general procedure 4***. The crude product was purified by reverse phase preparative HPLC to yield 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-

yl)phenyl)propanoic acid **A139**. LC/MS RT (10 min method) = 4.54 min. Mass observed: 751.23 (M+H).

Representative example 28: Synthesis of 5-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)pentanoic acid **A141**.



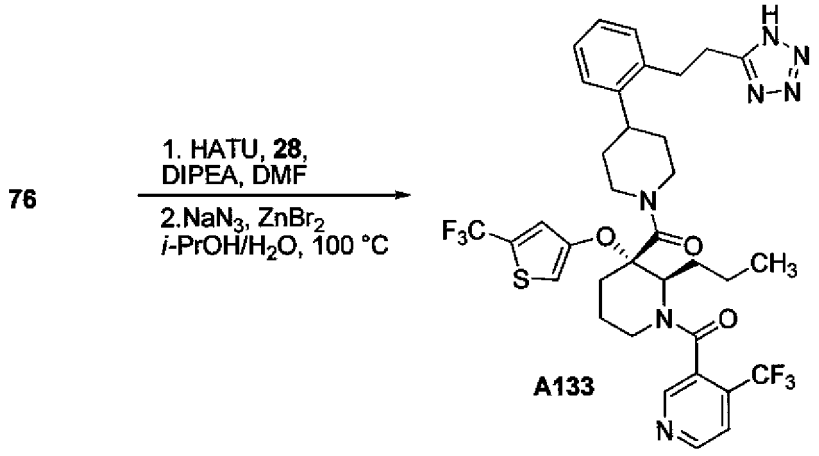
Step 1: A mixture of DMSO (69 µL, 0.98 mmol) in CH_2Cl_2 (2.0 mL) was cooled to –78 °C. Oxalylchloride (46 µL, 0.49 mmol) was added to the mixture and was stirred for 10 min at –78 °C. A solution of alcohol **A139** 4-(2-(3-hydroxypropyl)phenyl)-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidine-4-carbonitrile (180 mg, 0.24 mmol) obtained following a similar procedure used to prepare hydroxypropyl)phenyl)-1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidine-4-carbonitrile from 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanoic acid in CH_2Cl_2 (1.0 mL) was added and was stirred at the same temperature for 1 h. Et_3N (204 µL, 1.46 mmol) was added slowly at –78 °C and was warmed to 23 °C. The reaction was further stirred at 23 °C for 3 h. The mixture was diluted with CH_2Cl_2 (10 mL) and was washed with aqueous sat'd

$NaHCO_3$ (1 x 15 mL), and brine (1 x 15 mL). The organic layer was dried over Na_2SO_4 and was concentrated to yield the aldehyde.

Step 2: NaH (60% in mineral oil, 10 mg, 0.26 mmol) was washed with hexanes (2x) and was kept under Ar. THF (2.0 mL) was added and the mixture was cooled to 0 °C. Triethyl phosphonoacetate (56 µL, 0.28 mmol) was added and was further stirred at 0 °C for 30 min. A solution of the crude aldehyde (172 mg, 0.23 mmol) in THF (1.0 mL) was added at 0 °C. The reaction was warmed to 23 °C and was stirred overnight. The reaction was quenched with aqueous sat'd NH_4Cl (2 mL) and the solution was extracted with EtOAc (3 x 15 mL). The organic layers were washed with brine (1 x 15 mL), dried over Na_2SO_4 and was concentrated. The crude residue was purified by silica gel chromatography (gradient, 20% to 50% EtOAc/hexanes) to yield the enone as a pale yellow oil. LC/MS RT (5 min method) = 2.78 min. Mass observed: 805.28 (M+H).

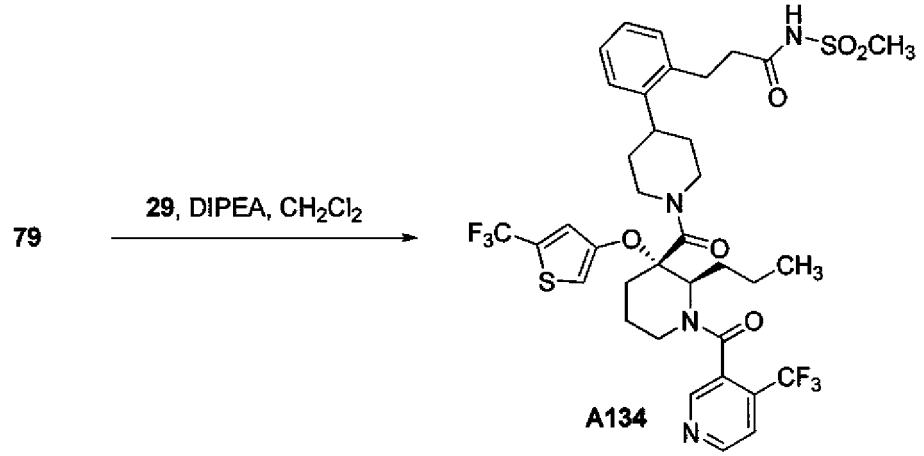
Step 3: Hydrogenation, followed by hydrolysis of the ester to the carboxylic acid was followed similarly as shown above. Reverse phase preparative HPLC purification yielded 5-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl) thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)pentanoic acid **A141**. LC/MS RT (10 min method) = 4.51 min. Mass observed: 779.26 (M+H).

Representative example 29: Synthesis of (4-(2-(2-(1H-tetrazol-5-yl)ethyl)phenyl)piperidin-1-yl)((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone **A133**.



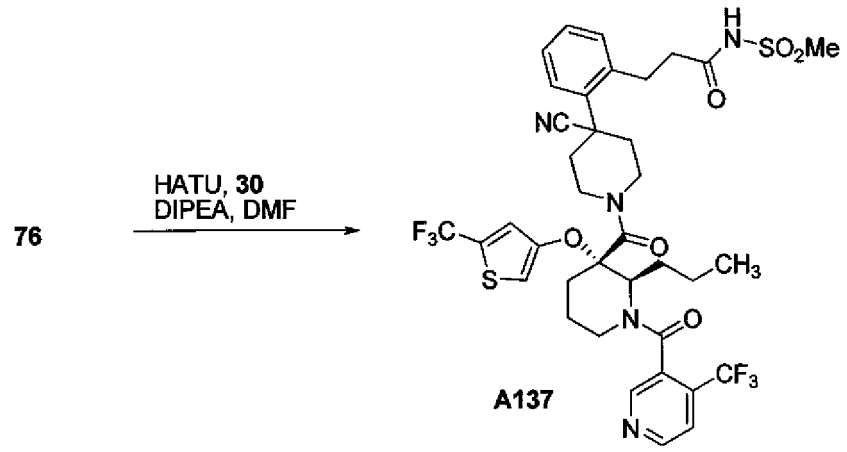
Amine **28** (26 mg, 0.10 mmol) was dissolved in DMF (0.5 mL) and reacted with acid **76** following ***general procedure 4***. The nitrile obtained (10 mg, 14.2 μmol) was dissolved in *i*-PrOH/H_2O (50μL/150μL). NaN_3 (1.0 mg, 15.6 μmol) and $ZnBr_2$ (3.0 mg, 14.2 μmol) were added. The reaction was heated at 100 °C overnight. The reaction was quenched with 1 M HCl (5 drops) and was then concentrated. The crude residue was purified by preparative HPLC to yield (4-(2-(2-(1H-tetrazol-5-yl)ethyl)phenyl)piperidin-1-yl)((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone. LC/MS RT (10 min method) = 5.97 min. Mass observed: 750.26 (M+H) **A133**.

Representative example 30: Synthesis of *N*-(methylsulfonyl)-3-(2-(1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanamide **A134**.



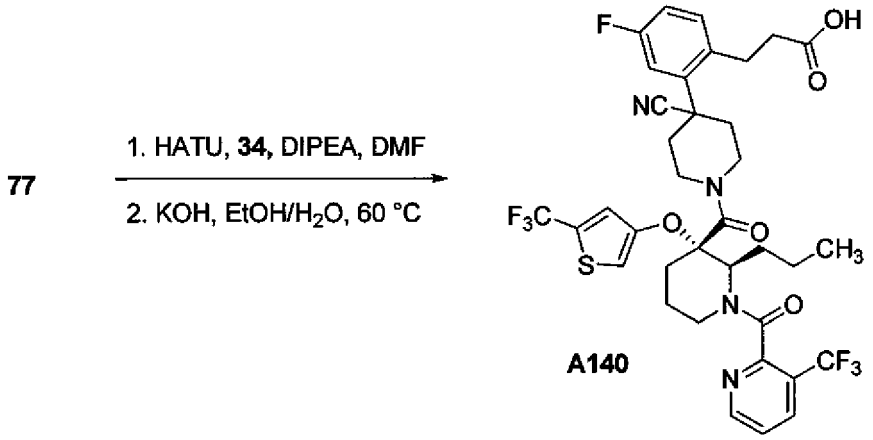
N-(methylsulfonyl)-3-(2-(piperidin-4-yl)phenyl)propanamide hydrochloride **29** (13 mg, 42.5 µmol) was used as described in **general procedure 2** using intermediate 79. The reaction was stirred overnight at 23 °C. The reaction mixture was concentrated and was purified by reverse phase preparative HPLC to yield *N*-(methylsulfonyl)-3-(2-(1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)propanamide **A134**. LC/MS RT (10 min method) = 4.56 min. Mass observed: 803.23 (M+H).

Representative example 31: Synthesis of 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(4 (trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)-N-(methylsulfonyl)propanamide **A137**.



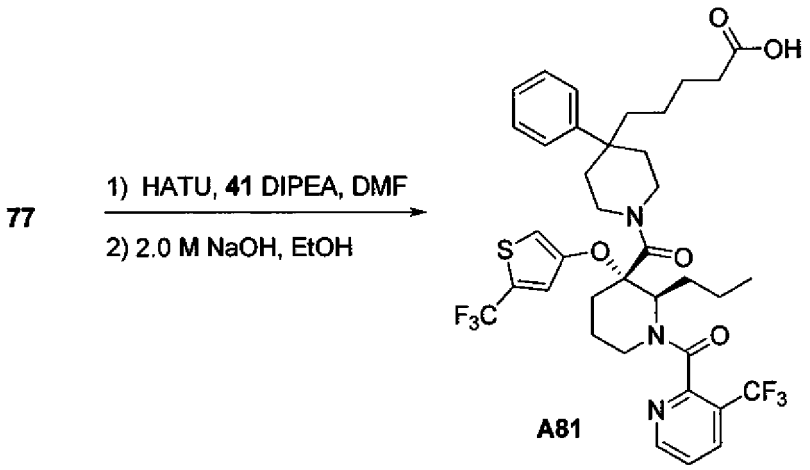
Amide coupling of **76** and 3-(2-(4-cyanopiperidin-4-yl)phenyl)-N-(methylsulfonyl)propanamide hydrochloride **30** was followed by **general procedure 4**. Reverse phase preparative HPLC purification yielded 3-(2-(4-cyano-1-((2*R*,3*S*)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenyl)-N-(methylsulfonyl)propanamide **A137**. LC/MS RT (10 min method) = 5.89 min. Mass observed: 828.22 (M+H).

Representative example 32: Synthesis of 3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)-4-fluorophenyl)propanoic acid **A140**.



Amide coupling of **77** and 3-(2-(4-cyanopiperidin-4-yl)-4-fluorophenyl)propanoate hydrochloride **34**, followed by hydrolysis were performed by following **general procedure 4** replacing in step 1, **76** by **77**. Reverse phase preparative HPLC purification yielded 3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)-4-fluorophenyl)propanoic acid **A140**. LC/MS RT (10 min method) = 4.34 min. Mass observed: 769.22 (M+H).

Representative example 33: Synthesis of 5-(4-phenyl-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)pentanoic acid **A81**.

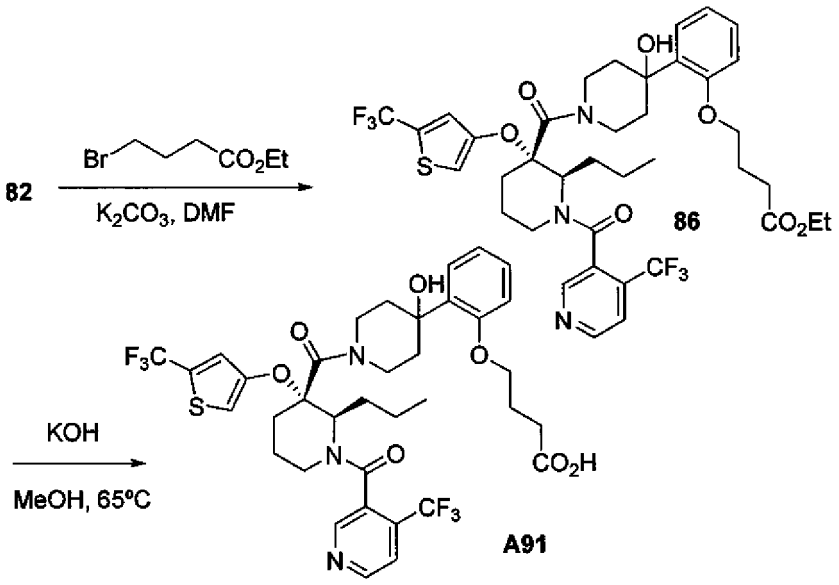


Step 1: Amide coupling of **77** and **9** (0.2 mmol, 70 mg) was performed by following **general procedure 4** replacing in step 1, acid **76** by acid **77**. The crude product was purified on Biotage (EtOAc in hexane: 25~50%), to give ethyl 5-(4-phenyl-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)pentanoate as white solid.

Step 2: To ethyl 5-(4-phenyl-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)pentanoate in ethanol was added 2.0 M NaOH aqueous solution and the mixture was stirred at 70 °C for 1 h. Then the solvent was removed *in vacuo*. The residue was redissolved in water, acidified with 6N HCl to PH ~4, then extracted with EtOAc (2x30ml), dried (MgSO4), concentrated, purified on Gilson, treated with 4.0 M HCl in dioxane (2~3 drops), lyophilized, to give 5-(4-phenyl-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)pentanoic acid **A81** as white solid.

General procedure 5:

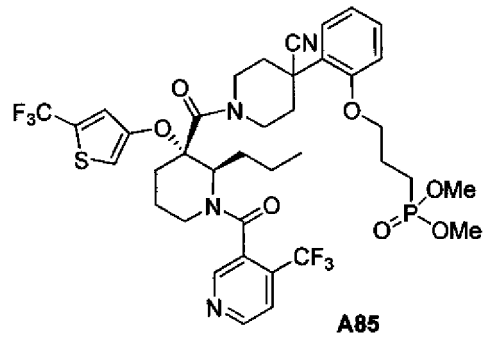
Representative example 34: Synthesis of 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butanoic acid **A91**.



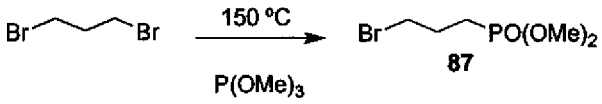
Step1: To intermediate **82** (prepared according the aforementioned **general procedure 3**, 300mg, 0.44mmol) in 5mL of DMF was added K_2CO_3 (608mg, 4.4mmol, 10eq.) followed by ethyl 4-bromobutyrate (94uL, 0.66mmol, 1.5eq.). The mixture was stirred at 60°C for 18 hours then diluted with EtOAc, washed with water and brine. Organic layer was dried over MgSO4, filtered and concentrated down. Purified by SiO2 column using a gradient 10~40% EtOAc in hexane to give 0.246g of ethyl 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butanoate **86**.

Step2: To **86** (40mg, 0.05mmol, 1eq) in MeOH was added KOH (3.5N, 5 equiv). Reaction was brought to 65 °C for 1 hour then cooled down to 23°C. Reaction was diluted with EtOAc, washed with sat. NH_4Cl and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated down. HPLC purification, C18, CH_3CN/H2O, 70% to 100% CH_3CN provided 37 mg (100% yield) of product **A91**.

Representative example 35: Synthesis of dimethyl 3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propylphosphonate **A85**.



A85



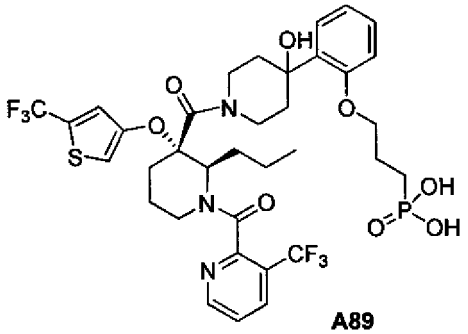
87

Step 1: To trimethyl phosphate (2.38ml, 20.1mmol) was added dibromopropane (10.2ml, 5 equi., 0.105mol). Reaction mixture was brought to 150 °C for 30min. Volatile were evaporated off excess dibromide was removed by distillation. 4.5g of dimethyl 3-bromopropylphosphonate **87** was isolated (98% yield).

Step 2: NaH (2 equiv.) was added to a DMF (2 mL) solution of intermediate **80** (prepared in **general procedure 2**, 60mg, 0.086 mmol). Reaction was stirred under nitrogen atmosphere for 10 minutes. To this was added **87** (3 equiv.). Reaction was brought to 60 °C and stirred overnight. Volatiles were removed and the residue was purified by reverse phase HPLC (10% to 100 % acetonitrile/water (0.1 % TFA) over 40min. Flow rate of 10mL/min), using a C18, 10 micron (19x250mm) column. Sample was lyophilized to yield 42 mg of product **A85**.

Generale procedure 6:

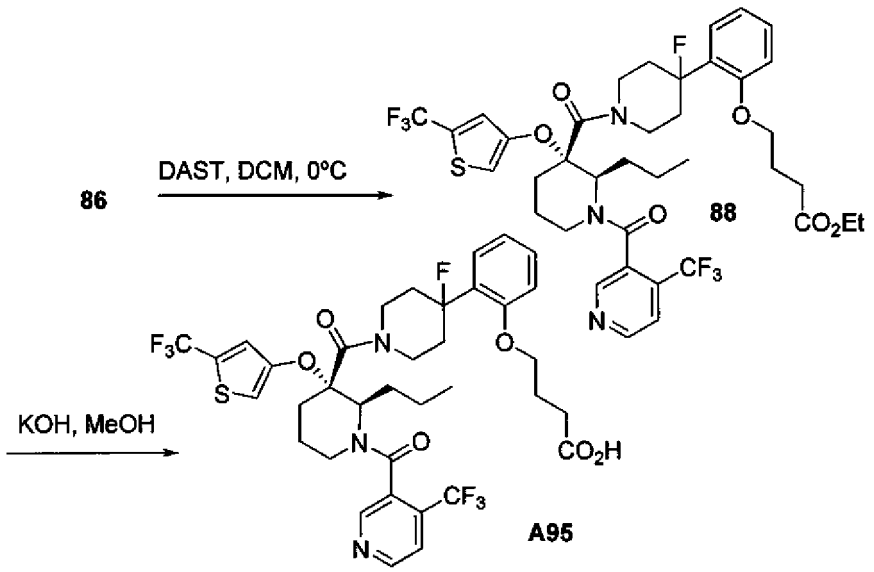
Representative example 36: Synthesis of 3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propylphosphonic acid **A89**.



A89

To intermediate **83** (prepared according the aforementioned **general procedure 3**, 120mg, 1 equi.) dissolved in DMF (5mL added bromo phosphonate **87** (1.5 equi.) and potassium carbonate (10equiv.). Reaction mixture was stirred at room temperature overnight. Reaction was diluted with ethyl acetate and washed with water and brine. Volatiles were removed and the residue was purified by reverse phase HPLC (10% to 100 % acetonitrile/water (0.1 % TFA) over 40min. Flow rate of 10mL/min), using a C18, 10 micron (19x250mm) column. Sample was lyophilized to yield 66 mg of product **A89**.

Representative example 37: Synthesis of 4-(2-(4-fluoro-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butanoic acid **A95**.

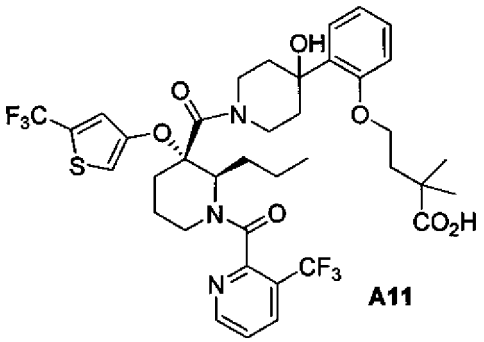


A95

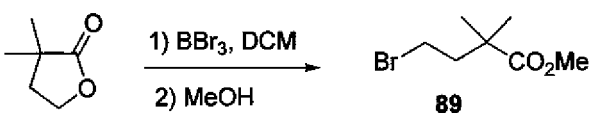
Step 1: To ethyl 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl) nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butanoate **86** (40mg, 0.05mmol, 1eq) in DCM at 0°C was added DAST (7.4uL, 0.06mmol, 1.2eq.). The reaction was stirred at room temperature for overnight. The reaction mixture was diluted with EtOAc and washed with saturated aqueous NH4Cl and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated down. HPLC purification, C18, CH3CN/H2O, 60% to 90% CH3CN provided 38 mg (99% yield) of ester ethyl 4-(2-(4-fluoro-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butanoate **88**.

Step 2: To ester **88** (38mg, 0.047mmol) in 1.0mL of MeOH was added aqueous KOH (0.2mL, 0.71mmol, 15equiv). Reaction was stirred at 45°C for 15 hours. Reaction was concentrated to a lower and 3mL of EtOAc was added. Water (5 mL) was added and the mixture was acidified with aqueous 1N HCl to PH=3.5. EtOAc layer was separated and washed with brine. The Organic later was dried over $MgSO_4$ filtered and concentrated to dryness to give 36mg of product **A95** (100% yield).

Representative example 38: Synthesis of 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-2,2-dimethylbutanoic acid **A11**.



A11

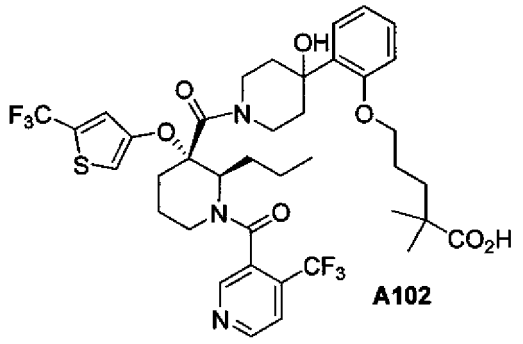


89

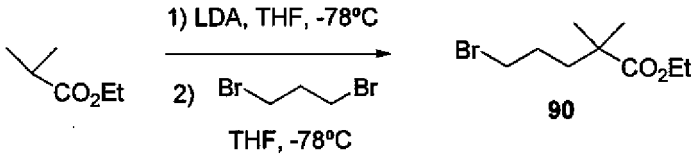
Step 1: To alpha,alpha-dimethyl-gamma-butyrolactone (1.49g, 13.05mmol) in 10mL of anhydrous DCM was added BBr3 (3.7mL, 13.7mmol, 1.05eq.) slowly at 0°C. The mixture was stirred at room temperature over night. Reaction was quenched by addition of MeOH (1 mL) at 0°C. Reaction was further stirred at room temperature for 20min then diluted with saturated aqueous NaHCO3 and extracted with DCM. Organic layer was washed with aqueous $Na_2S_2O_4$, brine and dried over $MgSO_4$, filtered and concentrated down. The residue was purified by silica gel chromatography (100% DCM) to provide 1.9 g (68% yield) of methyl 4-bromo-2,2-dimethylbutanoate **89**.

Step 2: **89** was reacted as described in **general procedure 6** to yield 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-2,2-dimethylbutanoic acid. Hydrolysis of 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-2,2-dimethylbutanoic acid was performed as described in **general procedure 5**, step 2 to yield **A11**.

Representative example 39: Synthesis of 5-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-2,2-dimethylpentanoic acid **A102**.



A102

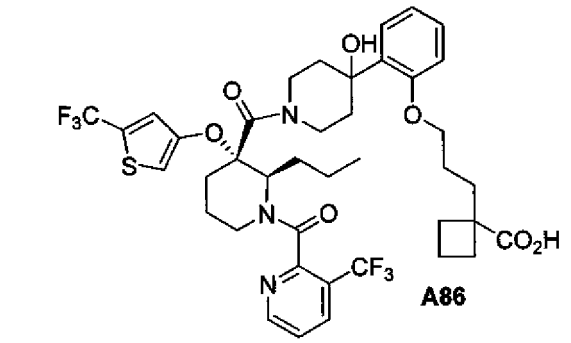


90

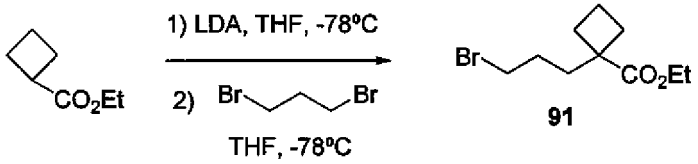
Step 1: To a 0°C solution of diisopropylamine (14.35mL, 0.102mol) in 70mL of THF was added n-BuLi (68mL, 0.102mol). The mixture was stirred at 0~5°C for 30min. After the mixture was cooled to -78°C, ethyl isobutyrate (13.7mL, 0.102mol, 1eq.) was added drop wise and stirring was maintained at -78°C for 1h. 1,3-Dibromopropane (1.01 equiv, 10.5 mL) was added drop wise at -78°C and stirring was maintained at -78°C for 1h. Reaction was then warmed up to 23°C over 2 hrs. Reaction mixture was added to an aqueous NH4Cl solution and extracted with EtOAc. The organic layer was washed with 1N HCl and brine, dried over $MgSO_4$, filtered and concentrated down to give 23g of crude product. The residue was purified by silica gel chromatography (5% to 30% EtOAc in hexanes) to provide 17.4 g (73% yield) of ethyl 5-bromo-2,2-dimethylpentanoate **90**.

Step 2: 90 was reacted as described in **general procedure 5** to yield **A102**.

Representative example 40: Synthesis of 1-(3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclobutanecarboxylic acid **A86**.



A86

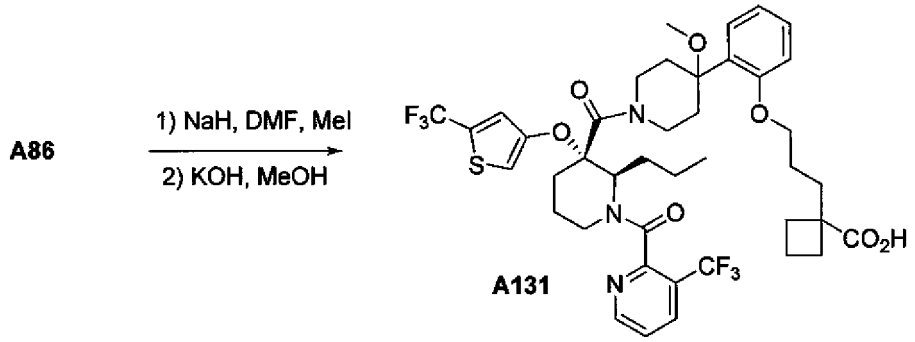


91

Step1: Procedure described in **representative example A102** was used by replacing in step1, ethyl isobutyrate with Ethyl cyclobutanecarboxylate to prepare ethyl 1-(3-bromopropyl)cyclobutanecarboxylate **91**.

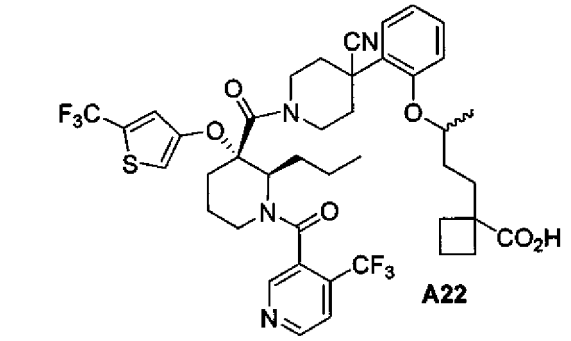
Step 2: **91** was reacted with intermediate **83** as described in **general procedure 6** to give ethyl 1-(3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclobutanecarboxylate. Hydrolysis of ethyl 1-(3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclobutanecarboxylate was performed as described in **general procedure 5**, step 2 to yield **A86**.

Representative example 41: Synthesis of 1-(3-(2-(4-methoxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclobutanecarboxylic acid **A131**.

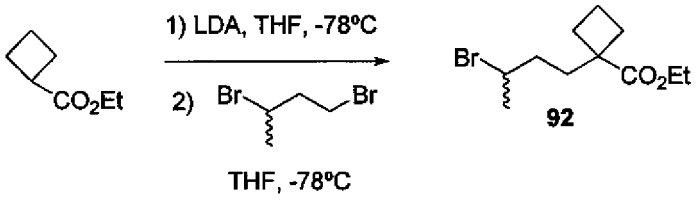


To **A86** prepared in representative example 40 (0.15g, 0.18mmol) in THF at 0°C was added NaH (35 mg, 1.5 mmol, 8eq.). After 5 minutes, MeI (45uL, 0.72mmol, 4eq.) was added slowly. Reaction was stirred for 2 hours then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated down to yield 1-(3-(2-(4-methoxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclobutanecarboxylic acid. Hydrolysis of 1-(3-(2-(4-methoxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclobutanecarboxylic acid was performed as described in **general procedure 5**, step2 to yield, after HPLC purification, C18, CH3CN/H2O, 60% to 90% CH3CN, 39.6 mg (26% yield) of product **A131**.

Representative example 42: Synthesis of 1-(3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butyl)cyclobutanecarboxylic acid **A22**.



A22



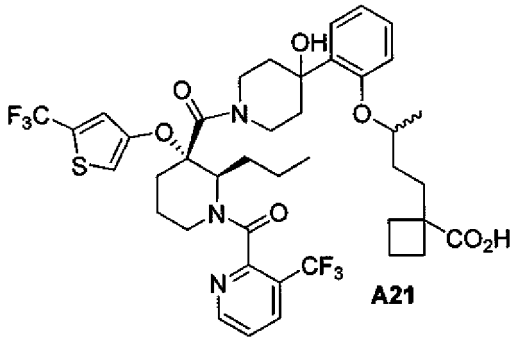
92

THF, -78°C

Step 1: To a 0°C solution of DIPA (14.3 mL,102 mmol) in THF (100 mL) was added n-BuLi (2.5M, 102 mmol). The Rx was stirred for 30-45 min then cooled to -78°C. Ethyl cyclobutane carboxylate (102 mmol, 1 equiv) was added slowly and the enolate was allowed to form for ~ 30 min. At -78°C, above enolate was poured into 1,3-dibromobutane (2 equiv, 200 mmol) and Rx stirred at -78°C for 1h then warmed-up to RT. After 3 hours, NH4Cl was added and reaction extracted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated down to give 25g of crude product. The residue was purified by silica gel chromatography (0% to 10% EtOAc in hexanes) to provide 11 g (42% yield) of racemic ethyl 1-(3-bromobutyl)cyclobutanecarboxylate **92**.

Step 2: Ethyl 1-(3-bromobutyl)cyclobutanecarboxylate **92** was used as described in **general procedure 5** by replacing in step 1, intermediate **82** by intermediate **80**. Ethyl 1-(3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butyl)cyclobutanecarboxylate obtained was hydrolyzed following the conditions of **general procedure 5**, step 2 to yield **A22** as a mixture of 2 diastereomers.

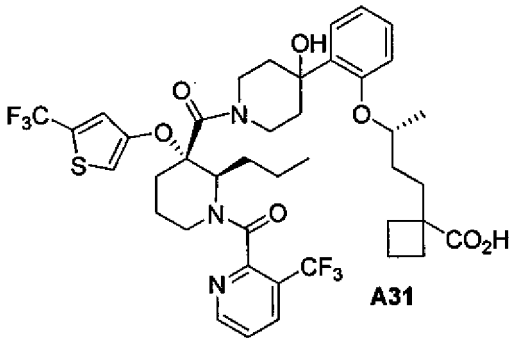
Representative example 43: Synthesis of 1-(3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butyl)cyclobutanecarboxylic acid **A21**.



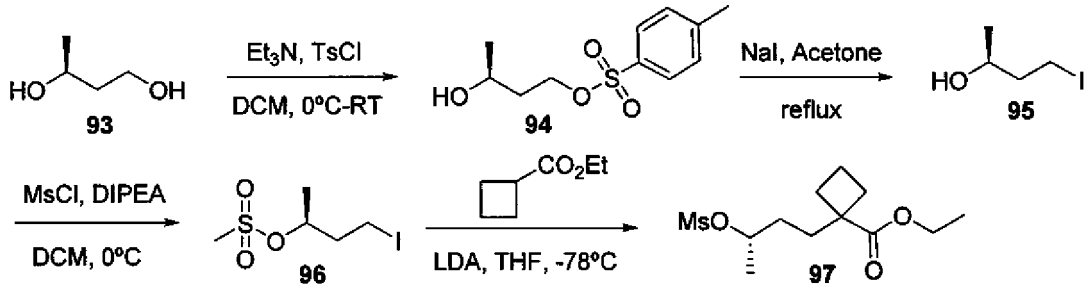
A21

Compound **A21** was synthesized in a fashion analogous to compound **A22** of **representative example 42** starting with intermediate **83** of general procedure 3.

Representative example 44: Synthesis of 1-((R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butyl)cyclobutanecarboxylic acid **A31**.



A31



Step 1: To a 0°C DCM (100 mL) solution of (S)-(+)-1,3-Butanol (7g, 77.6 mmol) containing Et_3N (14 mL, 1.3equiv) was added drop wise a DCM solution (60 mL) of TsCl (1.05 equiv, 15g). Reaction was warmed-up to Rt and stirred overnight. After 18 hours, the DCM layer was washed with HCl 1.0N (X2), then $NaHCO_3$, then brine. Organic layer was dried over MgSO4, filtered and concentrated down to 15 g of crude oil. The residue was purified by silica gel chromatography (10% to 40% EtOAc in hexanes) to provide 13 g (69% yield) of (S)-3-hydroxybutyl 4-methylbenzenesulfonate **94**.

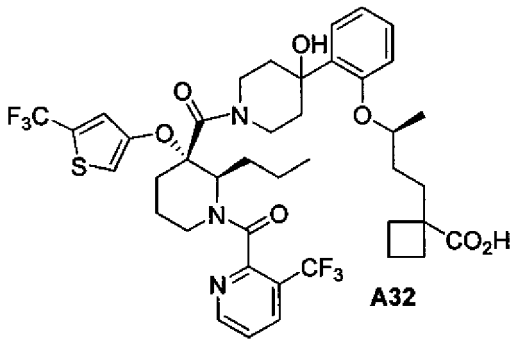
Step 2: To a RT solution of **94** (4 mmol, 1g) in acetone (10 mL) was added NaI (5 equiv, 20mmol, 3g) and the reaction was brought to reflux. After 2 hours, TLC showed that reaction was completed. Insoluble was filtered off trough pad of celite. Filtrate was concentrated down and diluted with EtOAc and water. EtOAc layer was washed with $NaHCO_3$, then Na_2S2O_3 and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated down to a yellow oil. The residue was purified by silica gel chromatography (10% to 50% EtOAc in hexanes) to provide 0.7 g (88% yield) of (S)-4-iodobutan-2-ol **95**.

Step 3: To a 0ºC solution of alchool **95** (2.5 mmol, 0.5g) in DCM (10 mL) was added DIPEA (5 mmol, 0.83 ml) followed by CH_3SO_2Cl (1.2 equiv, 3mmol, 0.25 mL). After 10 min, TLC showed showed that reaction was completed. Reaction was poured into water and EtOAc. Washed with HCl (1.0N) and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated down to a yellow oil. The residue was purified by silica gel chromatography (10% to 50% EtOAc in hexanes) to provide 0.64g (92% yield) of (S)-4-iodobutan-2-yl methanesulfonate **96**.

Step 4: To a solution of diisopropylamine (9.1 mL, 65 mmol) in 43 mL of THF was added n-BuLi (26mL, 65 mmol) at 0°C slowly (5min). The mixture was stirred at 0~5°C for 30min. After the mixture was cooled to -78°C (10min), Ethylcyclobutanecarboxylate (8 mL, 59.6 mmol, 1.1 eq.) was added dropwise and stirred at -78°C for 30min. The enolate was added into the solution of (S)-4-iodobutan-2-yl methanesulfonate **96** (15g, 54mmol) in 100mL of THF at -78°C. Cooling bath was removed to allow the reaction to warm up to RT. After 30 min at RT, reaction was quenched by addition of water and extracted with EtOAc. The organic layer was washed with brine then dried over $MgSO_4$, filtered and concentrated down. The residue was purified by silica gel chromatography first with (5% to 30% EtOAc in hexanes) then 100% DCM to (98% DCM/2% EtOAc) to provide 5.3g (36% isolated yield) of (S)-ethyl 1-(3-(methylsulfonyloxy)butyl)cyclobutanecarboxylate **97**.

Step 5: **97** was reacted as described in **general procedure 6** to yield ethyl 1-((R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butyl)cyclobutanecarboxylate Hydrolysis of ethyl 1-((R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butyl)cyclobutanecarboxylate was performed as described in **general procedure 5**, step2 to yield **A31**.

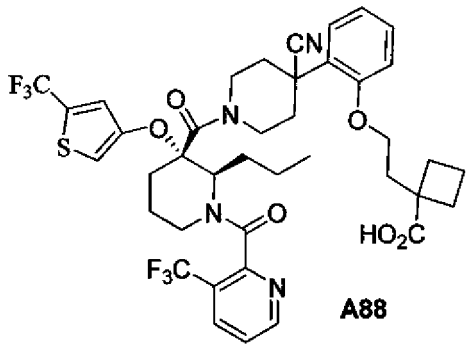
Representative example 45: Synthesis of 1-((S)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butyl)cyclobutanecarboxylic acid **A32**.



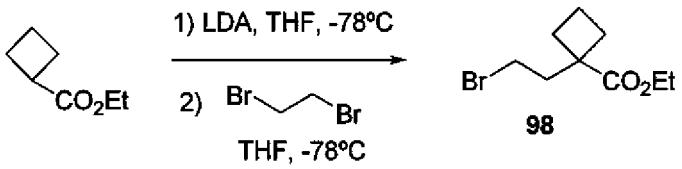
A32

Compound **A32** can be prepared in a sequence analogous to the preparation of example **A31** from (R)-(-)-1,3-Butanol instead of (S)-(+)-1,3-Butanol **93** in **representative example 44**, step 1.

Representative example 46: Synthesis of 1-(2-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)ethyl)cyclobutanecarboxylic acid **A88**.



A88

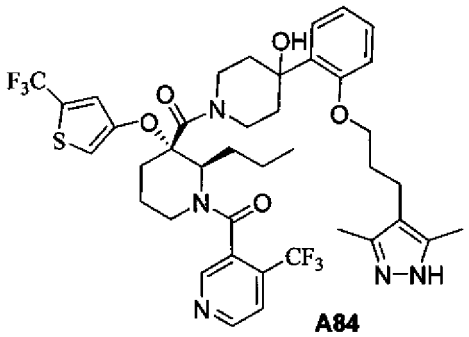


98

Step1: Procedure described in representative example 40, step 1, was used by replacing 1,3-Dibromopropane by 1,3-Dibromoethane to prepare ethyl 1-(2-bromoethyl)cyclobutanecarboxylate **98**.

Step 2: **98** was reacted according the **general procedure 6** by replacing intermediate **83** with intermediate **81** to give ethyl 1-(2-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)ethyl)cyclobutanecarboxylate. Hydrolysis of ethyl 1-(2-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)ethyl)cyclobutanecarboxylate was performed as described in **general procedure 5**, step 2 to yield **A88**.

Representative example 47: Synthesis of (4-(2-(3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy)phenyl)-4-hydroxypiperidin-1-yl)((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone **A84**.

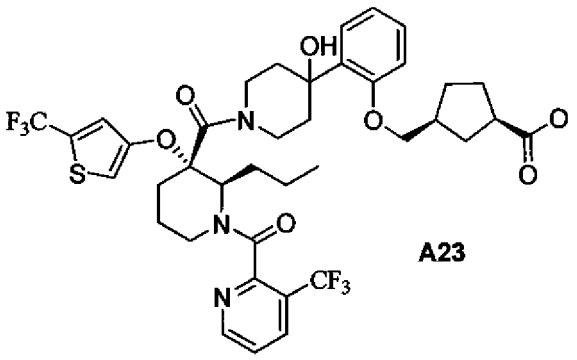


A84

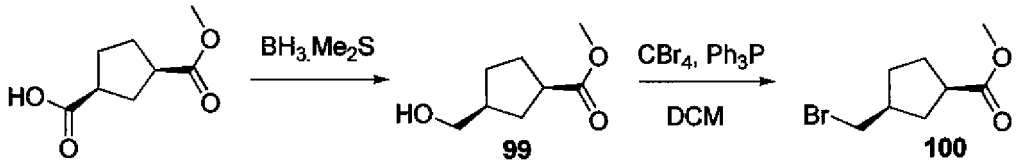
Intermediate **82** was reacted with commercially available 4-(2-bromoethyl)-3,5-dimethyl-1H-pyrazole according the **general procedure 5**, step 1, to yield **A84**.

Representative example 48: Synthesis of (1R,3S)-3-((2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-

yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)methyl)cyclopentanecarboxylic acid **A23**.



A23



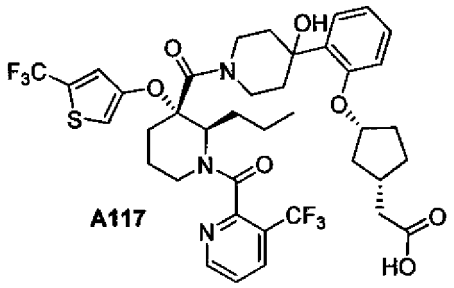
Step 1: (1S,3R)-3-(methoxycarbonyl)cyclopentanecarboxylic acid (15.9gm, 92.3mmol, 1 equi.) was dissolved in anhydrous THF (250mL) and cooled down to -78°C under nitrogen atmosphere. To this wass added borane dimethyl sulfide complex (2M solution in THF, 1.66 equi., 147.7mmol, 74mL) and stirring was maintained for one hour allowing the temperature to raise to 0°C temperature and stirred at room temperature for another three hours. The mixture was cooled down to -20 °C and quenched with a slow addition of 1M KH_2PO_4. Reaction was warmed up to room temperature and stirred for further 20 min and extracted with ether. Organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by silica gel chromatography with (10% to 80% EtOAc in hexanes) to provide 13g of (1R,3S)-methyl 3-(hydroxymethyl)cyclopentanecarboxylate **99**.

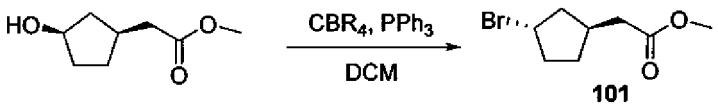
Step 2: To a 0°C solution of **99** (6.6gm, 50mmol, 1 equi.) in 60mL of DCM was added triphenyl phosphine (60mmol, 1.2 equi, 15.72gm) followed by carbon tetrabromide (60mmol, 1.2 equi. 19.86gm). The reaction mixture was stirred overnight allowing the temperature to rise to room temperature. Reaction was

concentrated to dryness and the residue was diluted with ether/DCM (1:1, 20ml) and filtered through a pad of celite. The filtrate was concentrated to dryness and the residue was purified by silica gel chromatography with (5% to 20% EtOAc in hexanes) to provide 3.5g of (1R,3S)-methyl 3-(bromomethyl)cyclopentanecarboxylate **100**.

Step 3: 100 was reacted as described in **general procedure 5** to yield **A23**.

Representative example 49: Synthesis of 2-((1S,3R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)cyclopentyl)acetic acid **A117**.



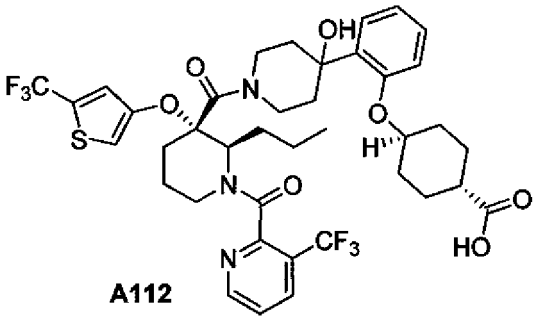


101

Step 1: To (1S,3R)-(3-hydroxy-cyclopentyl)acetic acid methyl ester (2.0g, 12.6mmol) in 10mL of DCM at 0°C was added PPh_3 (3.49g, 13.3mmol, 1.05eq.), followed by CBr_4 (4.41g, 13.3mmol, 1.05eq.) slowly. The mixture was stirred at room temperature overnight. The reaction mixture was filtered through a thin layer silica gel and the filtrate was concentrated down. The residue was purified by silica gel chromatography with (15% EtOAc in hexanes) to provide 1.96g of methyl 2-((1R,3S)-3-bromocyclopentyl)acetate **101**.

Step 2: 101 was reacted as described in **general procedure 5** to yield **A117**.

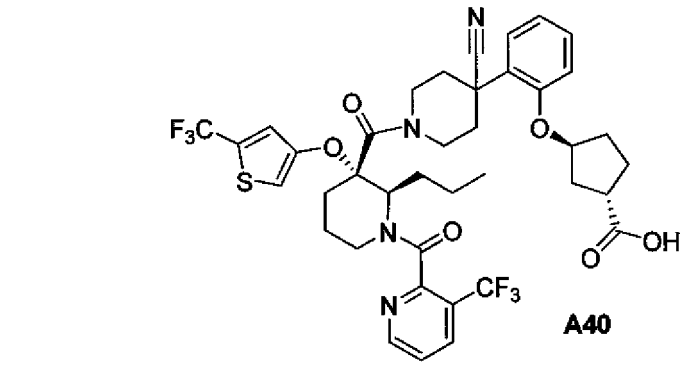
Representative example 50: Synthesis of (1S,4r)-4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)cyclohexanecarboxylic acid **A112**.



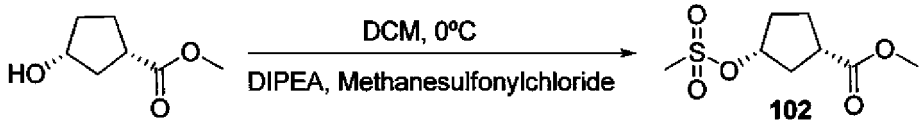
A112

Compound **A112** was prepared according the procedure described in representative example 49 by replacing in step 1, (1S,3R)-(3-hydroxy-cyclopentyl)acetic acid methyl ester with trans- ethyl 4-hydroxy-cyclohexanecarboxylate.

Representative example 51: Synthesis of (1S,3S)-3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)cyclopentanecarboxylic acid **A40**.



A40

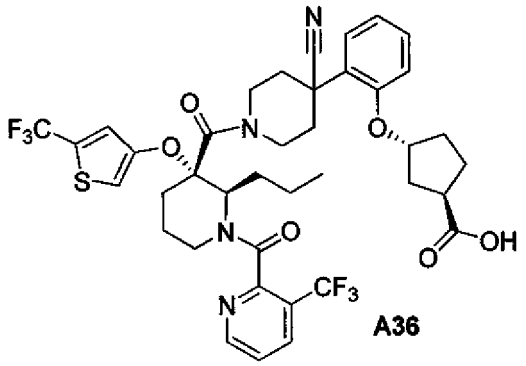


102

Step1: To a 0°C solution of (1S,3R)-methyl 3-hydroxycyclopentanecarboxylate (10 mmol, 1.45g) in DCM (10 mL) was added DIPEA (15 mmol,) followed by CH_3SO_2Cl (1.2 equiv, 12 mmol, 0.93 mL) and cat DMAP. After 3h. reaction was washed with NH_4Cl, then HCl (0.5N) then brine. Organic layer dried over $MgSO_4$, filtered and concentrated down to provide **102** as a yellowish oil that was used as it is for step 2.

Step 2: **102** was reacted according the **general procedure 6** by replacing intermediate **83** with intermediate **81** to give. Hydrolysis of was performed as described in **general procedure 5**, step 2 to yield **A40**.

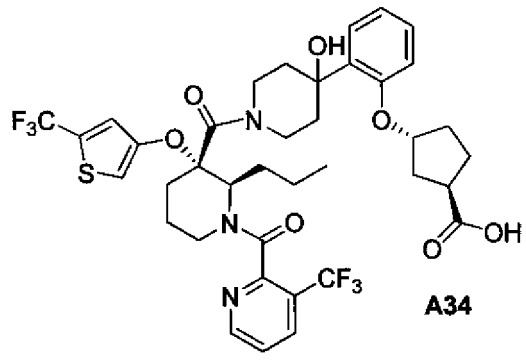
Representative example 52: Synthesis of (1R,3R)-3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)cyclopentanecarboxylic acid **A36**.



A36

Compound **A36** was prepared according the procedure described in representative example 51 by replacing in step1, (1S,3R)-methyl 3-hydroxycyclopentanecarboxylate with (1R,3S)-methyl 3-hydroxycyclopentanecarboxylate.

Representative example 53: Synthesis of (1R,3R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)cyclopentanecarboxylic acid **A34**.

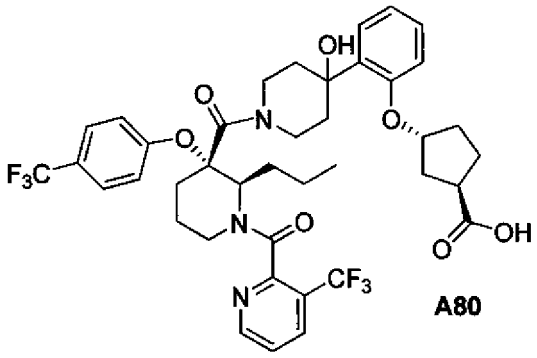


A34

Compound **A34** was prepared according the procedure described in representative example 52 by replacing intermediate **81** with intermediate **83.**

Representative example 54: Synthesis of acid (1R,3R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-3-(4-(trifluoromethyl)phenoxy)-1-(3-

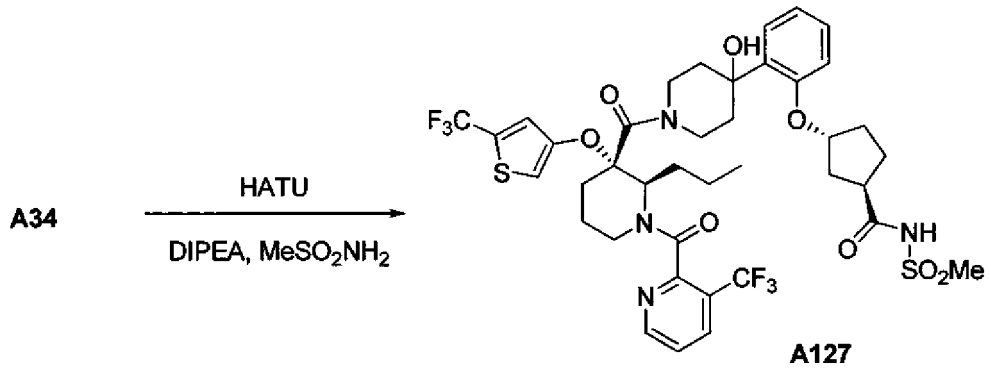
(trifluoromethyl)picolinoyl)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)cyclopentanecarboxylic acid **A80**.



A80

Compound **A80** was prepared according the procedure described in representative example 53 by replacing acid **77**, used in the preparation of intermediate **83** with acid **77-A.**

Representative example 55: Synthesis of (1R,3R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-N-(methylsulfonyl)cyclopentanecarboxamide **A127**.

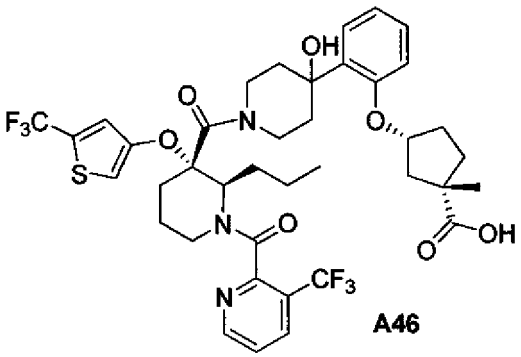


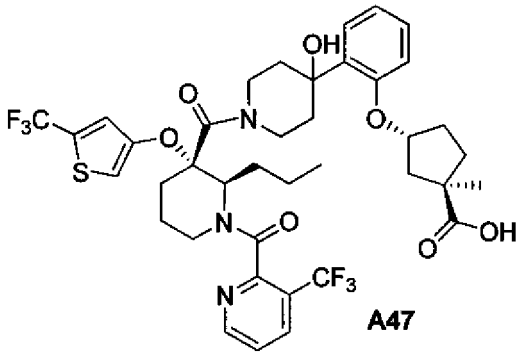
A127

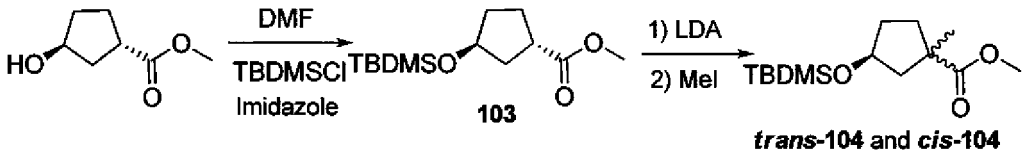
To **A34** (40mg, 0.050mmol) in DCM/DMF was added methanesulfonamide (33mg, 0.35mmol, 7eq.), HATU (23mg, 0.060mmol, 1.2eq.) and DIPEA (0.050mL, 0.30mmol, 6eq.) at room temperature. The mixture was stirred at room

temperature overnight. The reaction mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl, saturated aqueous NaHCO3 and brine. The organic layer was dried over $MgSO_4$ and filtered and concentrated down. The residue was purified by reverse phase HPLC (60-90-40 % acetonitrile/ water with 0.1 % TFA in 35min, with a flow rate of 15ml/min using a sunfire prep C18 Column, 10 micron (19x250mm). The residue was lyophilized to provide 19mg of product **A127** (43% yield).

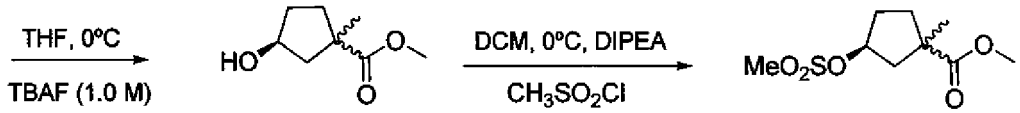
Representative example 56: Synthesis of (1S,3R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-1-methylcyclopentanecarboxylic acid **A46** and (1R,3R)-3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-1-methylcyclopentanecarboxylic acid **A47**.







***trans*-104 and *cis*-104**



***trans*-105 and *cis*-105**

***trans*-106 and *cis*-106**

Step 1: To a RT solution of (1S,3S)-methyl 3-hydroxycyclopentanecarboxylate (23.7 mmol, 3.45g) in DMF (10 mL) was added imidazole (2.5 equiv, 60 mmol, 4g) followed by TBDMSCl (1.2 equiv, 4.3g). After 24h, reaction was diluted with EtOAc and washed with HCl (1.0N), twice, then $NaHCO_3$ and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated down. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to provide 6g of **103** (100% yield).

Step 2: To a -78°C solution of ester (3.23g, 12.5 mmol) was added 15 mmol of freshly prepared LDA (23 mL). After 30 minutes, MeI (5 equiv) was added dropwise. After addition, reaction was let under stirring for 1 hour and warmed - up to RT. Reaction was diluted with EtOAc and washed with NH_4Cl and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated down to an oil. The residue was purified by silica gel chromatography (0% to 5% EtOAc in hexanes) to provide 2.67 g (71% yield) of **trans-104** and **cis-104** as an inseparable mixture of 2 diastereomers (3.4 (**trans-104**) / 1 (**cis-104**) ratio).

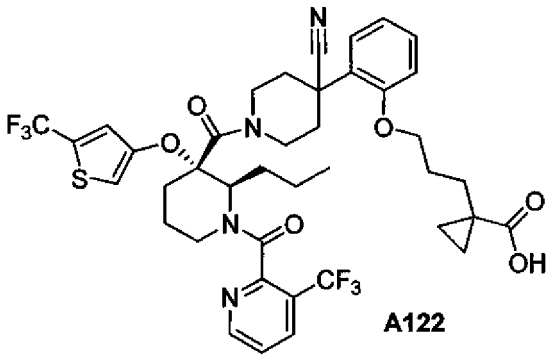
Step 3: To a 0°C solution of the diastereomeric mixture **trans-104** and **cis-104** (10 mmol, 2.65 g) in THF (30 ml) was added TBAF (1.2 equiv, 12 mmol, 12 mL). After 1h, reaction was warmed-up to RT and stir overnight. After 18 hours, reaction was diluted with EtOAc and washed with water, HCl (1.0N) and brine. Organic layer dried over $MgSO_4$, filtered and concentrated down. The residue was purified by silica gel chromatography (0% to 5% EtOAc in hexanes) to provide 1.3g (83%) **trans-105** and **cis-105** as an inseparable mixture of 2 diastereomers.

Step 4: Compounds **trans-106** and **cis-106** were prepared according the procedure described in representative **example 51** by replacing in step1, (1S,3R)-methyl 3-hydroxycyclopentanecarboxylate with **trans-105** and **cis-105**. Compounds **trans-106** and **cis-106** were used as a mixture of 2 diastereomer in a ~3.4/1 ratio for step 5.

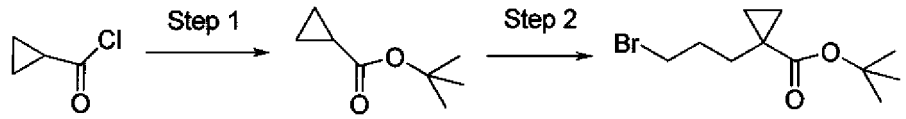
Step 5: The mixture **trans-106** and **cis-106** was reacted as described in **general procedure 5** to yield **A46** and **A47** as a mixture of 2 diastereomers that can be separated by reverse phase HPLC using C18 sunfire prep 10 micron (18x250)

column, 70% -100% CH3CN in water over 30 min at a flow rate of 15 mL.min. First pic (minor) is **A47** Second pic (major) is **A46**.

Representative example 57: Synthesis of 1-(3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclopropanecarboxylic acid **A122**.



A122



107 **108** **109**

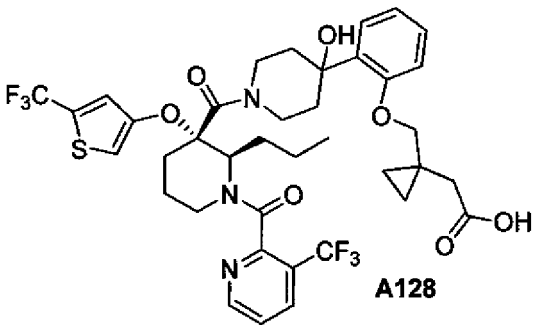
Step 1: To a solution of tert-butanol (1.16g, 15.6mmol) in THF at 0°C was added n-BuLi(10.4mL, 15.6mmol). After 15min, cyclopropanecarbonyl chloride **107** (1.5mL, 16.4mmol, 1.05eq.) was added slowly. The mixture was stirred at room temperature for 24 hours. The reaction was quenched by the addition of aqueous NH_4Cl. The mixture was diluted with EtOAc and washed with brine. Organic layer was dried over $MgSO_4$. Filtered and concentrated down to give 1.91g (86% yield) of crude product **107**.

Step 2: To a solution of diisopropylamine (2.06mL, 14.7mmol) in 20mL of THF was added n-BuLi (9.4mL, 14.07mmol) at 0°C. The mixture was stirred at 0~5°C for 30min. Then a solution of **107** (1.91g, 13.4mmol) in 5mL of THF at -78°C was added slowly, then followed by 1,3-dibromopropane (2.7mL, 26.8mmol, 2eq.). The mixture was stirred at -78°C and warmed-up to room temperature over 4 hours. The reaction mixture was added to an aqueous solution NH_4Cl and

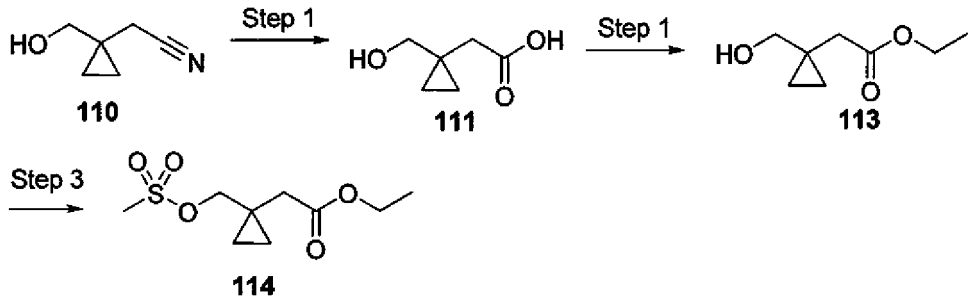
extracted with ether. The organic layer was washed with brine. Organic layer was dried over $MgSO_4$, filtered and concentrated down. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to provide 1.08g of **109**.

Step 4: **109** was reacted according the **general procedure 6** by replacing intermediate **83** with intermediate **81** to give tert-butyl 1-(3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)propyl)cyclopropanecarboxylate. To this intermediate (12mg, 0.014mmol) in DCM was added TFA. The mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$. Filtered and concentrated down. The residue was purified by reverse phase HPLC (40-90-40 % acetonitrile/ water with 0.1 % TFA in 35min, with a flow rate of 15ml/min using sunfire prep C18, 10micron (19x250mm)). The residue was lyophilized to provide 7mg of product **A122**. (61% yield).

Representative example 58: Synthesis of 2-(1-((2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)methyl)cyclopropyl)acetic acid **A128**.



A128



110 111 113

114

Step 1: To 1-(hydroxymethyl)cyclopropaneacetonitrile **110** (5.0g, 44.9mmol) in EtOH was added aqueous KOH (56mL, 56mmol, 10eq.). The mixture was heated at reflux for overnight. The reaction mixture was cooled to room temperature and concentrated to remove solvent. The remaining aqueous solution was cooled to 0°C and acidified to PH~1 with concentrated aqueous HCl dropwise, then extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to give 5.35g of product **111** (92% yield).

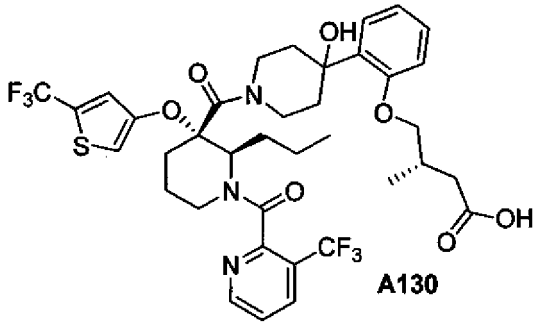
Step 2: To 2-(1-(hydroxymethyl)cyclopropyl)acetic acid **111** (5.35g, 41.1mmol) in EtOH was added concentrated sulfuric acid(1.3 mL) . The mixture was heated at reflux for 2hrs. 35mL of saturated aqueous $NaHCO_3$ was added to the cooled mixture and the mixture was extracted with CH_2Cl_2. Organic layer was dried over Na_2SO_4, filtered and concentrated to dryness to give 6.17g of product **113** (95% yield).

Step 3: To ethyl 2-(1-(hydroxymethyl)cyclopropyl)acetate **113** (1.0g, 6.3mmol) in 5mL of DCM at 0°C was added DIPEA (1.8mL, 10.7mmol, 1.7eq.), followed by MsCl (0.73mL, 9.48mmol, 1.5eq.) slowly. The mixture was stirred at 0°C for 1 hour. TLC indicated the reaction completed. The reaction mixture was diluted

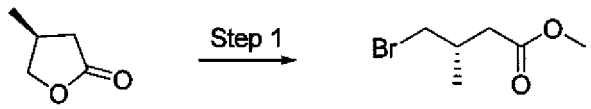
with EtOAc and washed with 1N HCl and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to give 1.33g of **114** (89% yield).

Step 4: Ethyl 2-(1-((methylsulfonyloxy)methyl)cyclopropyl)acetate **114** was reacted as described in **general procedure 5** to yield **A128**.

Representative example 59: Synthesis of (S)-4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-3-methylbutanoic acid **A130**.



A130

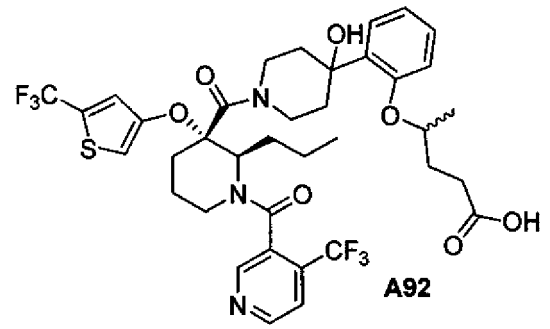


115

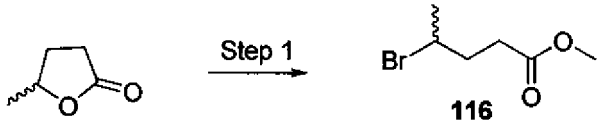
Step 1: To (S)-beta-methyl-gamma-butyrolactone (1g, 9.99mmol) in 10mL of anhydrous DCM was added BBr_3 (10.5mL, 10.5mmol, 1.05eq.) slowly at 0°C. The mixture was stirred at room temperature overnight then quenched by addition of MeOH (2 mL) at 0°C. After the addition, the mixture was stirred at room temperature for 20min then diluted with saturated aqueous. Organic layer was separated and washed with aqueous $Na_2S_2O_4$ then brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to give1.0g of crude product **115** (51% yield).

Step 2: (S)-methyl 4-bromo-3-methylbutanoate **115** was reacted as described in **general procedure 5** to yield **A130**.

Representative example 60: Synthesis of 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)pentanoic acid **A92**.



A92

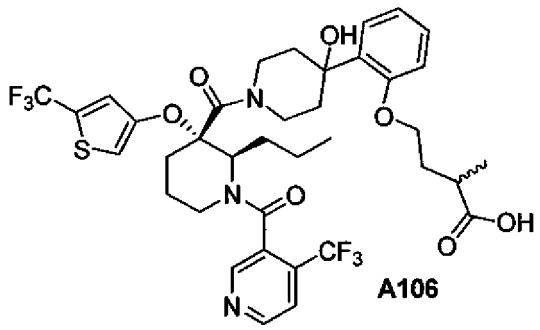


116

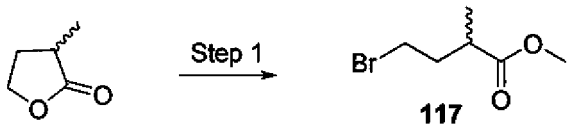
Step 1: Preparation of intermediate **116** was done according representative example 59, step 1, by replacing (S)-beta-methyl-gamma-butyrolactone with gamma-valerolactone.

Step 2: Intermediate **82** was reacted with methyl 4-bromopentanoate **116** according the **general procedure 5** to yield **A92**.

Representative example 61: Synthesis of 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(4-(trifluoromethyl)nicotinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)pentanoic acid **A106**.



A106

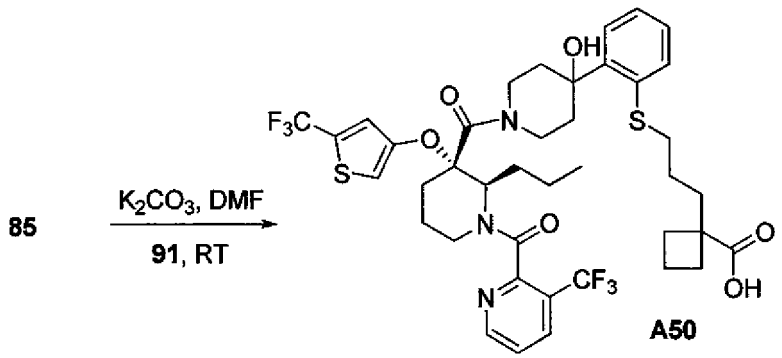


117

Step 1: Preparation of intermediate **117** was done according representative example 59, step 1, by replacing (S)-beta-methyl-gamma-butyrolactone with alpha-methyl-gamma-butyrolactone.

Step 2: Intermediate **82** was reacted with methyl 4-bromo-2-methylbutanoate **117** according the **general procedure 5** to yield **A106**.

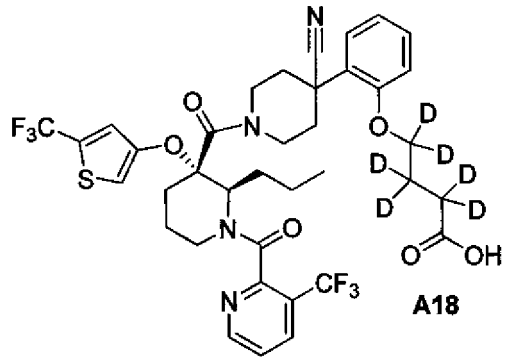
Representative example 62: Synthesis of 1-(3-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenylthio)propyl)cyclobutanecarboxylic acid **A50**.



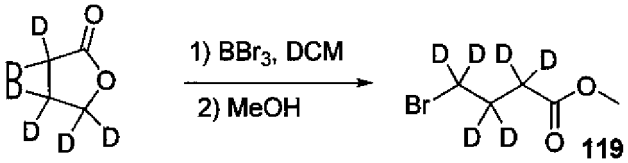
A50

Compound **A50** was prepared according the procedure described in representative example 40 by replacing in step 2, intermediate **83** with intermediate **85** of representative example 23.

Representative example 63: Synthesis of 4-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-2,2,3,3,4,4-hexadeuterobutanoic acid **A18**.



A18

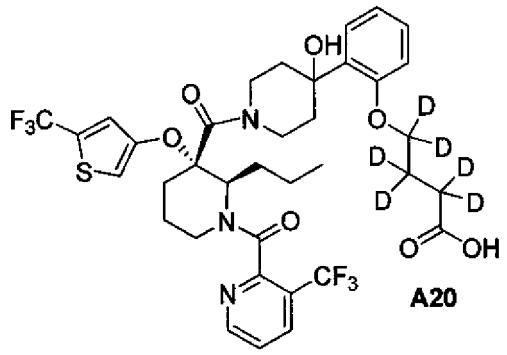


119

Step 1: Preparation of intermediate **119** was done according representative example 59, step 1, by replacing (S)-beta-methyl-gamma-butyrolactone with gama-butyrolactone-d6.

Step 2: Methyl 4-bromo-2,2,3,3,4,4-hexadeuterobutanoate **119** was reacted according the **general procedure 6** by replacing intermediate **83** with intermediate **81** to give methyl 4-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-2,2,3,3,4,4-hexadeuterobutanoate. Hydrolysis of methyl 4-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)-2,2,3,3,4,4-hexadeuterobutanoate was performed as described in **general procedure 5**, step 2 to yield **A18**.

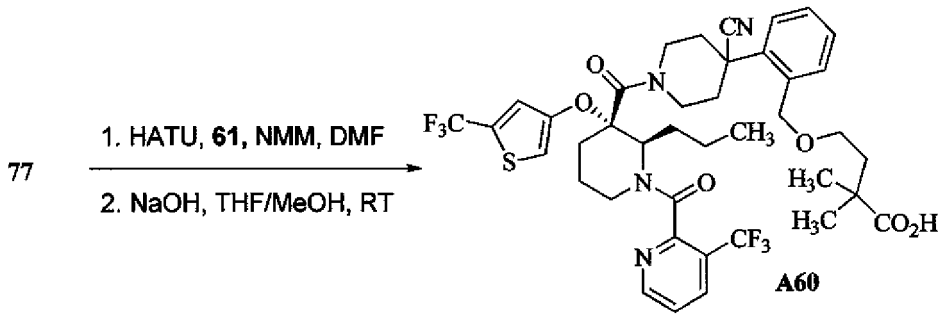
Representative example 64: Synthesis of 2,2,3,3,4,4-hexadeutero-4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenoxy)butanoic acid **A20**.



A20

(Methyl 4-bromo-2,2,3,3,4,4-hexadeuterobutanoate **119** of representative example **63** was reacted as described in **general procedure 5 with intermediate 83** to yield **A20**.

Representative example 65: Synthesis of 4-(2-(4-Cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)-2,2-dimethylbutanoic acid **A60**.



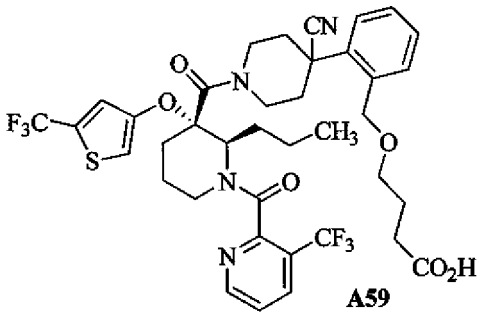
A60

Step 1: The intermediate TFA salt methyl 4-(2-(4-cyanopiperidin-4-yl)benzyloxy)-2,2-dimethylbutanoate 2,2,2-trifluoroacetate **61** (170 mg, 0.50 mmol), **77** (255

mg, 0.50 mmol) and HATU (228 mg, 0.60 mmol) were taken up in DMF (5 mL) followed by the addition of N-methyl morpholine (505 mg, 5.0 mmol). The reaction mixture was stirred at room temperature for 16 h, then diluted with ethyl acetate (50 mL). The organic phase washed with sat NH_4Cl (30 mL), sat $NaHCO_3$ (30 mL), brine (50 mL), and dried over Na_2SO_4. The reaction mixture was filtered, evaporated to dryness, then purified by silica gel chromatography (ethyl acetate/hexanes) to afford methyl 4-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)-2,2-dimethylbutanoate (312 mg, 77% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80-8.81 (d, J = 4.5 Hz, 1H), 8.05 – 8.07 (d, J = 7.8 Hz, 1H), 7.22-7.52 (m, 5H), 7.06-7.08 (m, 1H), 6.52-6.55 (m, 1H), 4.52-5.16 (m, 6H), 3.49-3.67 (m, 3H), 3.10-3.24 (m, 3H), 1.19 (s, 6H), 0.85-2.38 (m, 17H).

Step 2: 2 N Aqueous sodium hydroxide (5.5 mL) was added to methyl 4-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)-2,2-dimethylbutanoate (312 mg, 0.37 mmol) in THF/methanol (1:3, 12 mL). The reaction was stirred for 8 h at room temperature then concentrated. The residue was diluted ethyl acetate (30 mL) and the pH adjusted to 1 with 1 N hydrochloric acid. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by C18 semi-prep HPLC to obtain **A60** (300 mg, 99% yield) as a white powder after lyophilization from water/acetonitrile: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.81-8.82 (d, J = 3.9 Hz, 1H), 8.06 – 8.08 (d, J = 8.1 Hz, 1H), 7.24-7.50 (m, 5H), 6.84-6.87 (d, J = 8.1 Hz, 1H), 6.53-6.56 (m, 1H), 4.65-5.57 (m, 5H), 3.48-3.75 (m, 6H), 3.08-3.20 (m, 3H), 1.22 (s, 6H), 0.93-2.47 (m, 17H).

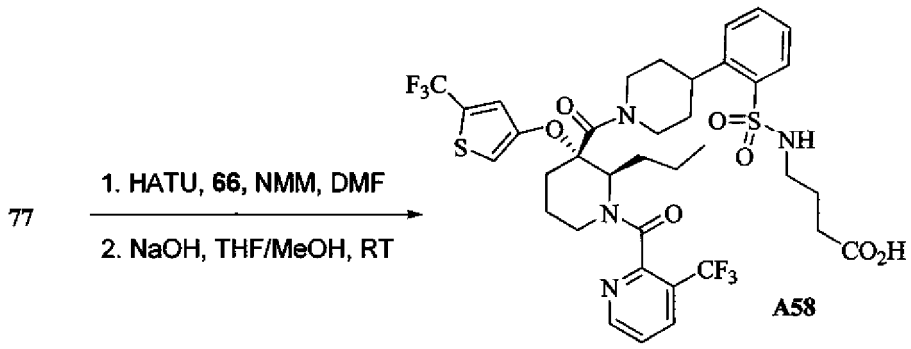
Representative example 66: Synthesis of 4-(2-(4-Cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)butanoic acid **A59**.



A59

Compound **A59** was synthesized in a fashion analogous to compound **A60** starting with dihydrofuran-2(3H)-one as starting material instead of 3,3-dimethyldihydrofuran-2(3H)-one and isolated as a white solid after lyophilization from water/acetonitrile. ^{1}H NMR (300 MHz, $CDCl_3$ 9.75 (br, s, 1H), 8.79 (d, *J* = 4.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.57–7.00 (m, 6H), 6.53 (s, 1H), 5.55–5.25 (m, 1H), 5.20–4.89 (m, 3H), 4.52–4.38 (m, 1H), 3.72–2.70 (m, 6H), 2.58–0.78 (m, 19H).

Representative example 67: Synthesis of 4-(2-(1-((2R,3S)-2-Propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenylsulfonamido)butanoic acid **A58**.



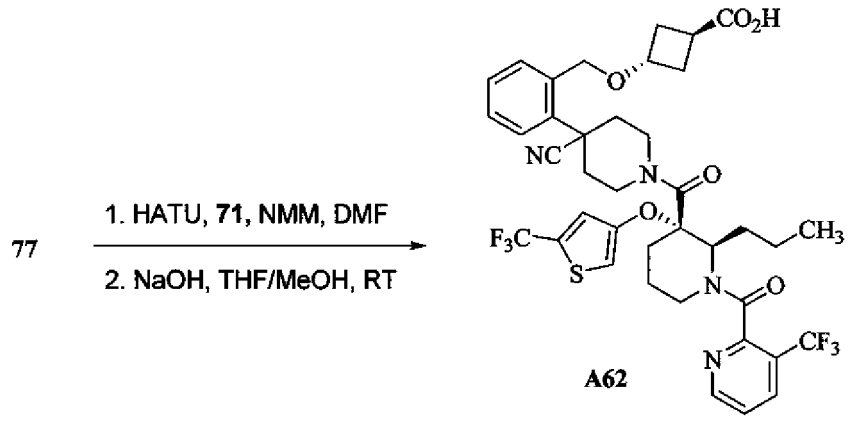
A58

Step 1: In an analogous procedure to representative example 65 step 1, **66** was coupled to **77** to provide ethyl 4-(2-(1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenylsulfonamido)butanoate: ^{1}H NMR (300 MHz,

$CDCl_3$□ 8.81 (d, *J* = 3.2 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.98–7.84 (m, 1H), 7.60–7.18 (m, 4H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.73–6.49 (m, 1H), 5.60–5.40 (m, 1H), 5.23–5.01 (m, 2H), 4.90 (d, *J* = 12.8 Hz, 1H), 4.20–4.00 (m, 2H), 3.87–3.60 (m, 1H), 3.51–1.02 (m, 28H).

Step 2: In an analogous procedure to representative example 65 step 2, ethyl 4-(2-(1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenylsulfonamido)butanoate was saponified to provide **A58** as a white solid after lyophilization from water/acetonitrile: ^{1}H NMR (300 MHz, $CDCl_3$ 8.80 (d, *J* = 4.4 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.98–7.84 (m, 1H), 7.60–7.30 (m, 4H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.72–6.50 (m, 1H), 5.61–5.30 (m, 4H), 3.90–3.67 (m, 1H), 3.43–0.70 (m, 25H).

Representative example 68: Synthesis of (1R,3R)-3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)cyclobutanecarboxylic acid **A62**.

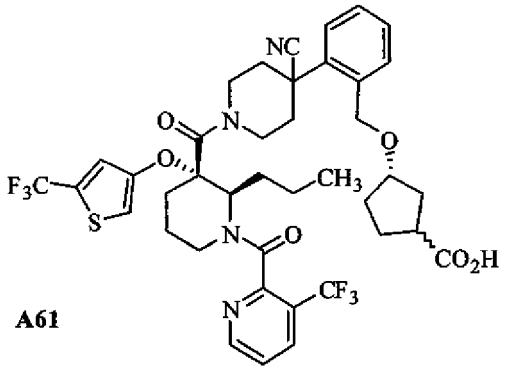


Step 1: In an analogous procedure to representative example 65 step 1, **71** was coupled to **77** to provide (1S,3R)-methyl 3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)cyclobutanecarboxylate (41 mg, 59% yield) as

a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 8.82 (d, *J* = 4.5 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.61-7.55 (m, 0.3H), 7.50-7.46 (m, 2H), 7.43-7.27 (m, 2H), 6.87 (d, *J* = 7.8 Hz, 0.7H), 6.56-6.51 (m, 1H), 5.58-5.48 (m, 0.7H), 5.42-5.34 (m, 0.3H), 5.26-5.10 (m, 1H), 4.98-4.87 (m, 1H), 4.83 (dd, *J* = 11.9, 7.4 Hz, 1H), 4.65 (t, *J* = 12.3 Hz, 1H), 4.06 (quint, *J* = 7.3 Hz, 1H), 3.73-3.64 (m, 3H), 3.38-3.02 (m, 3H), 2.73-1.20 (19H), 1.04 (t, *J* = 7.2 Hz, 2H), 0.95 (d, *J* = 7.4 Hz, 1H).

Step 2: In an analogous procedure to representative example 65 step 2, (1S,3R)-methyl 3-(2-(4-cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)cyclobutanecarboxylate was saponified to provide **A62** (36 mg, 90% yield) as a white solid after lyophilization from water/acetonitrile: ^{1}H NMR (400 MHz, $CDCl_3$) 8.81 (d, *J* = 3.0 Hz, 1H), 8.06 (d, *J* = 6.0 Hz, 1H), 7.53-7.46 (m, 1.3H), 7.44-7.18 (3H), 7.07-7.02 (m, 0.7H), 6.59-6.50 (m, 1H), 5.57-5.46 (m, 0.7H), 5.40-5.31 (m, 0.3H), 5.22-4.91 (m, 3H), 4.49 (d, *J* = 8.7 Hz, 0.3H), 4.33 (d, *J* = 8.1 Hz, 0.7H), 4.23-4.12 (m, 1H), 3.69 (t, *J* = 9.3 Hz, 0.7H), 3.52 (d, *J* = 9.9 Hz, 1H),3.33-3.04 (m, 3H), 2.95-2.05 (m, 10H), 1.99-1.82 (m, 2H), 1.72-1.44 (m, 3H), 1.43-1.28 (m, 3H), 1.08-0.83 (m, 3H).

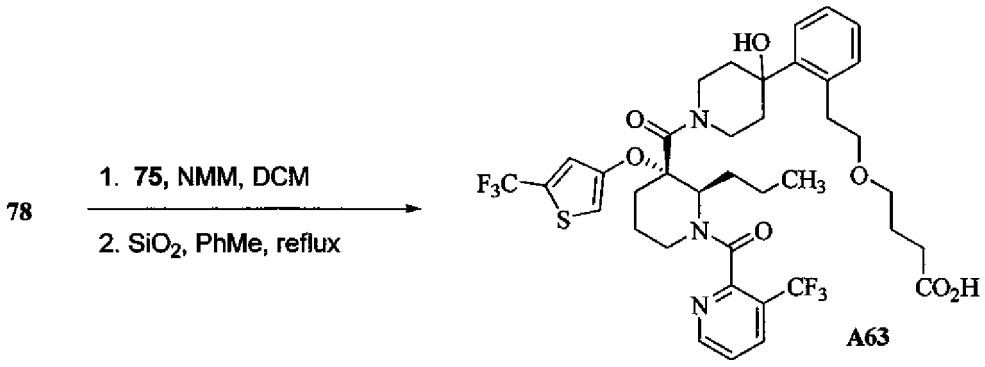
Representative example 69: Synthesis of (S)-3-(2-(4-Cyano-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)benzyloxy)cyclopentanecarboxylic acid **A61**.



A61

Compound **A61** was prepared from intermediate **69** of representative example 18 and (S)-methyl 3-hydroxycyclopentanecarboxylate in a sequence analogous to the preparation of representative example 68 and was isolated as a white powder after lyophilization from water/acetonitrile: ^{1}H NMR (300 MHz, $CDCl_3$) 8.86-8.76 (m, 1H), 8.13-8.04 (m, 1H), 7.59-6.85 (m, 5H), 6.60-6.51 (m, 1H), 5.58-5.33 (m, 1H), 5.25-4.38 (m, 7H), 4.26-4.12 (m, 1H), 3.80-3.43 (m, 1H), 3.32-1.15 (m, 20H), 1.18-0.81 (m, 3H).

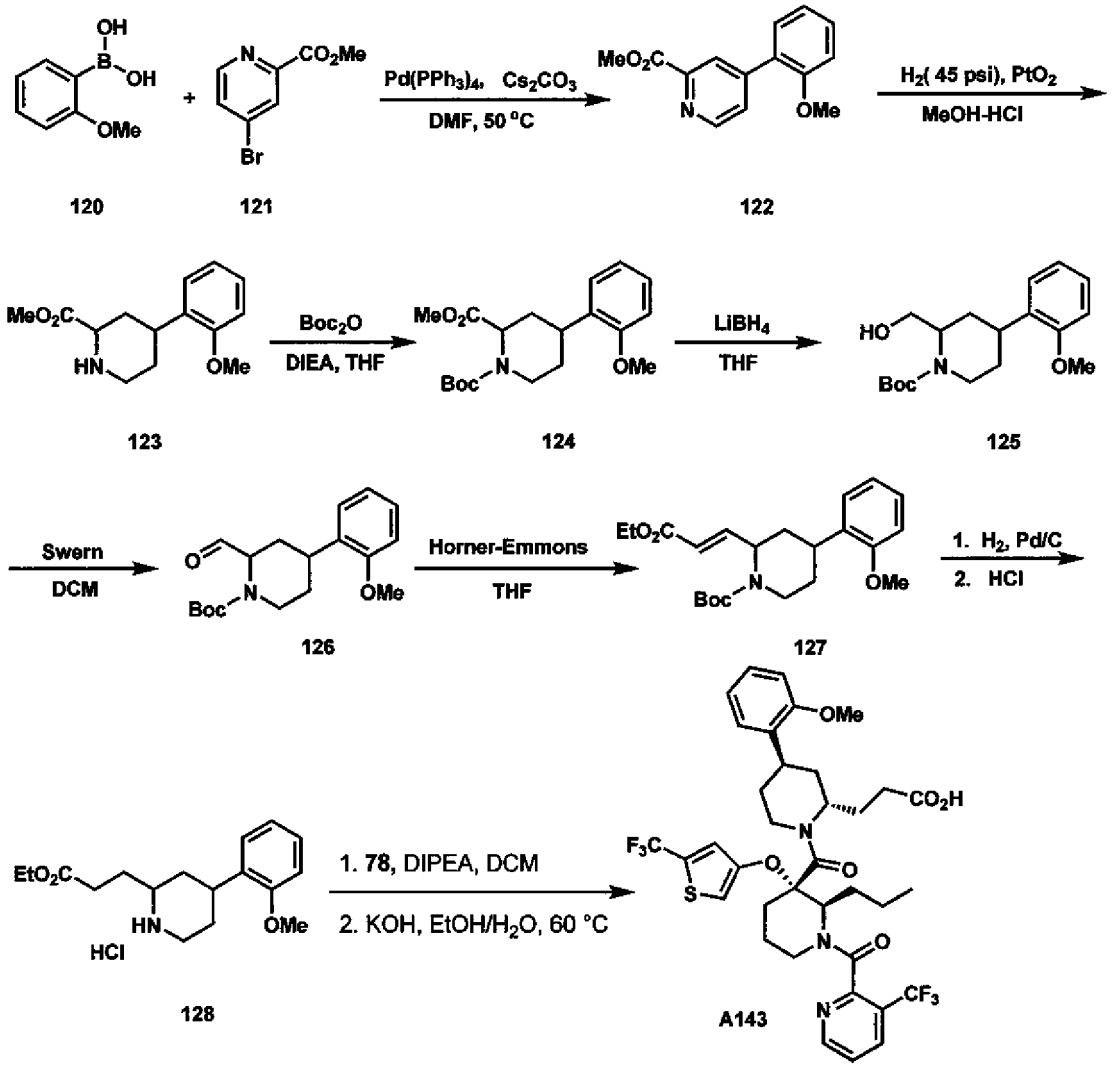
Representative example 70: Synthesis of 4-(2-(4-Hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenethoxy)butanoic acid **A63**.



Step 1: In an analogous procedure to **general procedure 2**, amine **75** was coupled to **78** to provide tert-butyl 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenethoxy)butanoate (54 mg, 60% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 8.81 (d, J = 4.5 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.48 (dd, J = 7.8, 5.0 Hz, 1H), 7.42-7.27 (m, 0.6H), 7.25-7.04 (m, 2.8H), 6.77 (d, J = 7.8 Hz, 0.6H), 6.64 (d, J = 1.8 Hz, 0.6H), 6.54 (d, J = 1.8 Hz, 0.4H), 5.57 (d, J = 10.8 Hz, 0.6H), 5.45 (d, J = 10.8 Hz, 0.4H), 4.87 (t, J = 13.4 Hz, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.59-4.53 (m, 1H), 3.60-3.49 (m, 3H), 3.43-3.01 (m, 6H), 2.59-1.20 (m, 27H), 1.02 (t, J = 7.2 Hz, 3H).

Step 2: Silica gel (230-400 mesh, 88 mg) was added to tert-butyl 4-(2-(4-hydroxy-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-4-yl)phenethoxy)butanoate (15 mg, 0.018 mmol) in toluene (0.5 mL) and heated to reflux with vigorous stirring for 6 h. Additional silica gel (44 mg) and toluene (0.5 mL) were added and reflux was continued for 18 h. The reaction mixture was cooled to room temperature and the silica gel was removed by filtration through Celite washing with methylene chloride/methanol (1:1, 10 mL) and methanol (10 mL). The solvent was removed under reduced pressure and the residue purified by silica gel chromatography (methanol/methylene chloride) to provide **A63** (9.8 mg, 70% yield) as a white solid after lyophilization from water/acetonitrile: ^{1}H NMR (300 MHz, $CDCl_3$) 8.81 (d, *J* = 4.8 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.49 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.23-7.05 (m, 3H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 1.8 Hz, 0.7H), 6.54 (d, *J* = 1.8 Hz, 0.3H), 5.57-5.40 (m, 1H), 4.93-4.73 (m, 1H), 4.70-4.45 (m, 2H), 3.95-3.01 (m, 9H), 2.81 (dt, *J* = 14.1, 3.67 Hz, 1H), 2.59-1.24 (m, 18H), 1.08-0.96 (m, 3H).

Representative example 71: Synthesis of ethyl 3-(4-(2-methoxyphenyl)piperidin-2-yl)propanoate hydrochloride (**A143**)



Step 1: A reaction mixture of 2-methoxyphenylboronic acid **120** (600 mg, 4 mmol), Cs_2CO_3 (2.6 g, 8 mmol), $Pd(PPh_3)_4$ (200 mg, 0.2 mmol) and methyl 4-bromopicolinate **121** (864 mg, 4 mmol) in DMF (4 mL), was degassed and heated to 50 °C under Argon for 5 hr. The mixture was filtered through Celite and was concentrated. The crude residue was purified by silica gel chromatography (gradient, 10% to 50% EtOAc/hexanes) to give methyl 4-(2-methoxyphenyl)picolinate **122.** LC/MS RT (5 min method) = 1.703 min. Mass observed: 244.1 (M+H).

Step 2: To a solution of methyl 4-(2-methoxyphenyl)picolinate **122** (240 mg, 1 mmol) in MeOH (10 mL) and 1M HCl in ether (2 mL), PtO_2 (10 mg) was added.

The reaction mixture was stirred under H_2 at 60 psi overnight. The mixture was filtered through Celite and was concentrated to give the crude product methyl 4-(2-methoxyphenyl)piperidine-2-carboxylate **123.** LC/MS RT (5 min method) = 1.114 min. Mass observed: 250.2 (M+H).

Step 3: To a solution of methyl 4-(2-methoxyphenyl)piperidine-2-carboxylate **123** (1.1 g, 4.1 mmol) in THF (10 mL), Boc_2O (900 mg, 4.1 mmol) and $^{i}Pr_2NEt$ (1.4 mL, 8.2 mmol) was added. The reaction mixture was stirred at r.t overnight. After removal of solvent, the crude residue was purified by silica gel chromatography (gradient, 10% to 50% EtOAc/hexanes) to give a mixture of diasteremers of 1-*tert*-butyl 2-methyl 4-(2-methoxyphenyl)piperidine-1,2-dicarboxylate **124.** LC/MS RT (5 min method) = 2.271 min. Mass observed: 250.1 (M-Boc+H).

Step 4: At 0 °C, to a solution of 1-*tert*-butyl 2-methyl 4-(2-methoxyphenyl)piperidine-1,2-dicarboxylate **124** (640 mg, 1.83 mmol) in THF (10 mL) and MeOH (0.5 mL), $LiBH_4$ (60 mg, 2.74 mmol) was added. The reaction solution was stirred at r.t overnight, The reaction was quenched with water and the mixture was extracted with ethyl acetate. After removal of solvent, the crude product of *tert*-butyl 2-(hydroxymethyl)-4-(2-methoxyphenyl)piperidine-1-carboxylate **125** was obtained without further purification. LC/MS RT (5 min method) = 2.027 min. Mass observed: 222.2 (M-Boc+H).

Step 5: At -78 °C, to a solution of Oxalyl Chloride (0.24 mL, 2.75 mmol) in DCM (4 mL), DMSO (0.43 mL, 6.04 mmol) was added. The reaction solution was stirred at the same temperature for 30 min and then a solution of *tert*-butyl 2-(hydroxymethyl)-4-(2-methoxyphenyl)piperidine-1-carboxylate **125** (580 mg, 1.8 mmol) in DCM (2 mL) was added. The reaction mixture was stirred at -78 °C for 30 min, followed by the addition of Et_3N (1.1 mL, 7.32 mmol). The reaction mixture was warmed up to r.t overnight. The reaction was quenched with water and the mixture was extracted with ethyl acetate. After removal of solvent, the crude product of *tert*-butyl 2-formyl-4-(2-methoxyphenyl)piperidine-1-carboxylate **126** was obtained without further purification. LC/MS RT (5 min method) = 2.406 min. Mass observed: 264.1 (M- Buthyl + H).

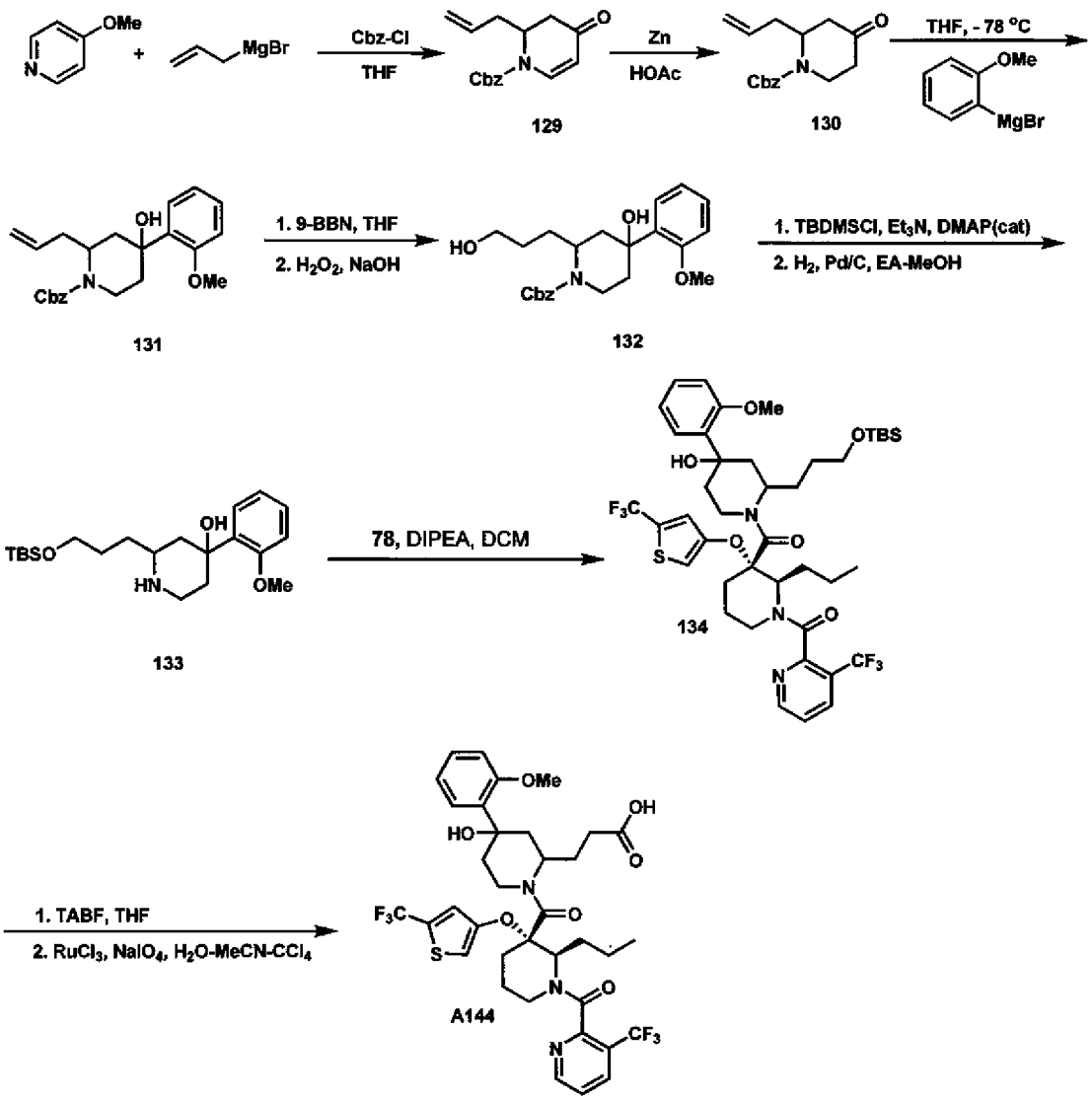
Step 6: At 0 °C, to a suspension of 60% NaH (100 mg, 2.5 mmol) in THF (3 mL), triethyl phosphono acetate (0.5 mL, 2.5 mmol) was added. After stirring at 0 °C for 30 min, a solution of *tert*-butyl 2-formyl-4-(2-methoxyphenyl)piperidine-1-carboxylate **126** (540 mg, 1.69 mmol)) in THF (2 mL) was added. The reaction mixture was warmed up to r.t for 3 hr. The reaction was quenched with water and the mixture was extracted with ethyl acetate. After removal of solvent, the crude residue was purified by silica gel chromatography (gradient, 10% to 25% EtOAc/hexanes) to give a mixture of diasteremers of *tert*-butyl 2-(3-ethoxy-3-oxoprop-1-enyl)-4-(2-methoxyphenyl)piperidine-1-carboxylate **127.** LC/MS RT (5 min method) = 2.655 min. Mass observed: 290.2 (M-Boc+H).

Step 7: To a solution of *tert*-butyl 2-(3-ethoxy-3-oxoprop-1-enyl)-4-(2-methoxyphenyl)piperidine-1-carboxylate **127** (540 mg, 1.4 mmol) in MeOH (5 mL) and EtOAc (5 mL), 10% Pd/C (50 mg) was added. The reaction mixture was stirred under H_2 overnight. LC/MS showed the completion of hydrogenation LC/MS RT (5 min method) = 2.514 min. Mass observed: 292.3 (M - Boc + H).

After the filtration through Celite and removal of solvent, the residue was treated with 4N HCl in dioxane (3 mL). The reaction mixture was stirred at r.t for 1 hr. After removal of solvent, the crude product of ethyl 3-(4-(2-methoxyphenyl)piperidin-2-yl)propanoate hydrochloride **128** was obtained without further purification. LC/MS RT (5 min method) = 1.239 min. Mass observed: 292.3 (M + H).

Step 8: Amide bond formation was done from intermediate **78** following the ***general procedure 2***. Hydrolysis of the ester to the carboxylic acid was followed as described in ***general procedure 4***. The crude product was purified by reverse phase preparative HPLC to yield ethyl 3-(4-(2-methoxyphenyl)piperidin-2-yl)propanoate hydrochloride (**A143**). LC/MS RT (7 min method) = 4.21 min. Mass observed: 756.2 (M+H).

Representative example 72: Synthesis of 3-(4-hydroxy-4-(2-methoxyphenyl)-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy) piperidine- 3-carbonyl)piperidin-2-yl)propanoic acid (**A144**)



Step 1:

At -23 °C, to a solution of 4-methoxypyridine (5.45 g, 50 mmol) in THF (50 mL), 1.0 N Allyl-MgBr (50 mL, 50 mmol) in ether was added to form a yellow suspension. 95% Cbz-Cl (7.4 mL, 50 mmol) was then added dropwise. The yellow mixture was stirred at -23 °C for 30 mins and then poured into 10% HCl (100 mL). The reaction mixture was extracted with ethyl acetate. After removal of solvent, the crude product was purified by silica gel chromatography (gradient,

10% to 25% EtOAc/hexanes) to give benzyl 2-allyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate **129.** LC/MS RT (2.25 min method) = 1.090 min. Mass observed: 272.1 (M + H).

Step 2:

To a solution of benzyl 2-allyl-4-oxo-3,4-dihydropyridine-1(2H)-carboxylate **129** (160 mg, 0.6 mmol) HOAc (2 mL), Zn powder (113 mg, 1.8 mmol) was added. The reaction mixture was heated to 50 °C for 16 hr. After removal of solvent, ethyl acetate and water was added. The reaction mixture was extracted with ethyl acetate. After removal of solvent, the crude product was purified by silica gel chromatography (gradient, 10% to 25% EtOAc/hexanes) to give benzyl 2-allyl-4-oxopiperidine-1-carboxylate **130.** LC/MS RT (2.25 min method) = 1.080 min. Mass observed: 274.0 (M + H).

Step 3:

At-78 °C, to a solution of benzyl 2-allyl-4-oxopiperidine-1-carboxylate **130** (895 mg, 3.3 mmol) in THF (5 mL), 1.0 N of 2-methoxyphenyl Grignard reagent in ether (3.6 mL, 3.6 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 2 hr, and then quenched with water. The reaction mixture was extracted with ethyl acetate. After removal of solvent, the crude product was purified by silica gel chromatography (gradient, 10% to 25% EtOAc/hexanes) to give benzyl 2-allyl-4-hydroxy-4-(2-methoxyphenyl)piperidine-1-carboxylate **131.** LC/MS RT (2.25 min method) = 1.330 min. Mass observed: 404.1 (M + Na).

Step 4:

To a solution of benzyl 2-allyl-4-hydroxy-4-(2-methoxyphenyl)piperidine-1-carboxylate **131** (220 mg, 0.58 mmol) in THF (2 mL), 0.5 M of 9-BBN in THF (3.5 mL) was added. The reaction solution was stirred at r.t for 16 hr and then 10% NaOH (3 mL) and H_2O_2 (3 mL) were added. After stirring for 30 mins, the reaction mixture was extracted with ethyl acetate. After removal of solvent, the crude product was purified by silica gel chromatography (gradient, 30% to 75%

EtOAc/hexanes) to give benzyl 4-hydroxy-2-(3-hydroxypropyl)-4-(2-methoxyphenyl)piperidine-1-carboxylate **132.** LC/MS RT (2.25 min method) = 1.228 min. Mass observed: 400.2 (M + H).

Step 5:

At 0 °C, to a solution of benzyl 4-hydroxy-2-(3-hydroxypropyl)-4-(2-methoxyphenyl)piperidine-1-carboxylate **132** (200 mg, 0.5 mmol) in DCM (2 mL), catalytic amount of DMAP and Et_3N (80 μL, 0.57 mmol) was added followed by TBDMSCl (80 mg, 0.53 mmol). After addition, the reaction solution was warmed up to r.t for 16 hr and then quenched with water. The reaction mixture was extracted with ethyl acetate. After removal of solvent, the crude product was purified by silica gel chromatography (gradient, 10% to 25% EtOAc/hexanes) to give the silyl ether: benzyl 2-(3-(tert-butyldimethylsilyloxy)propyl)-4-hydroxy-4-(2-methoxyphenyl)piperidine-1-carboxylate. LC/MS RT (2.25 min method) = 1.653 min. Mass observed: 514.1 (M + H).

To a solution of the above product in ethyl acetate (10 mL), 10% Pd/C (10 mg) was added. The reaction mixture was stirred under H_2 atmosphere for 2 hr. After filtration off the Pd/C and removal of solvent, the crude product of 2-(3-(tert-butyldimethylsilyloxy)propyl)-4-(2-methoxyphenyl)piperidin-4-ol **133** was obtained without further purification. LC/MS RT (2.25 min method) = 0.960 min. Mass observed: 380.4 (M + H).

Step 6:

To a solution of acid chloride **78** (160 mg, 0.32 mmol) in DCM (1 mL) was a solution of 2-(3-(tert-butyldimethylsilyloxy)propyl)-4-(2-methoxyphenyl)piperidin-4-ol **133** (120 mg, 0.32 mmol) and iPr_2NEt (0.17 mL, 1.0 mmol) in DCM (1 mL). The dark yellow reaction solution was stirred at r.t. for 16 hr. After removal of solvent, the residue was purified by silica gel chromatography (gradient, 30% to 50% EtOAc/hexanes) to give (2-(3-(tert-butyldimethylsilyloxy)propyl)-4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl)((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-

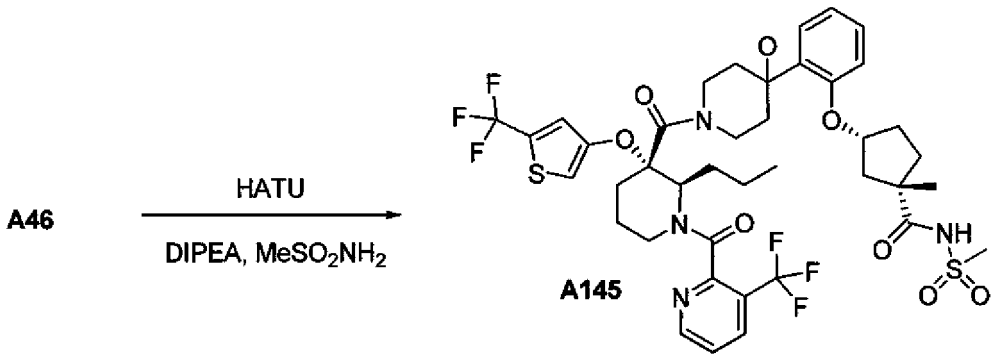
yl)methanone **134**. LC/MS RT (2.25 min method) = 1.883 min. Mass observed: 872.2 (M + H).

Step 7:

To a solution of (2-(3-(tert-butyldimethylsilyloxy)propyl)-4-hydroxy-4-(2-methoxyphenyl)piperidin-1-yl)((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone **134** (140 mg, 0.16 mmol) in THF (1 mL), 1.0 M of TBAF in THF (0.2 mL, 0.19 mmol) was added. The yellow reaction solution was stirred at r.t. for 2 hr. After removal of solvent, the residue was purified by silica gel chromatography (gradient, 30% to 50% EtOAc/hexanes) to give de-silyl product (4-hydroxy-2-(3-hydroxypropyl)-4-(2-methoxyphenyl)piperidin-1-yl)((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidin-3-yl)methanone. LC/MS RT (7 min method) = 4.352 min. Mass observed: 758.2 (M + H).

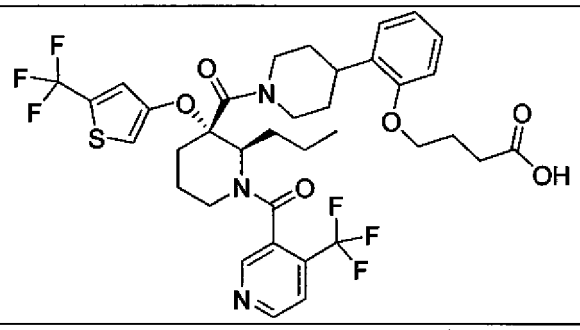
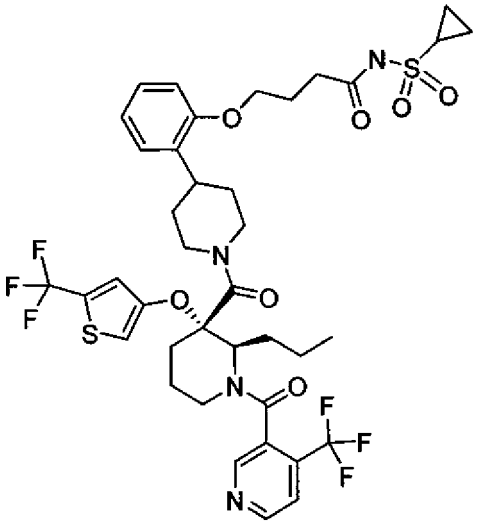
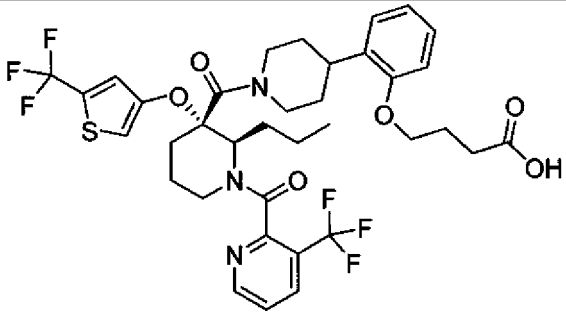
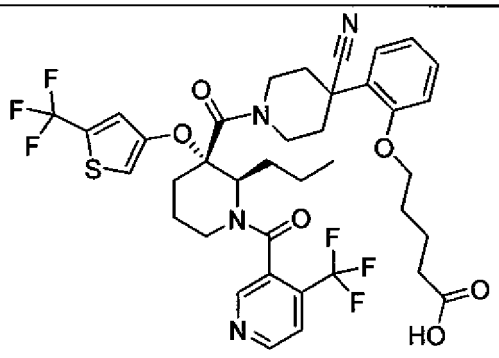
To a solution of the above alcohol (25 mg, 0.03 mmol) in MeCN (0.5 mL), CCl_4 (0.5 mL) and H_2O (0.75 mL), $RuCl_3$ (1.4 mg, 0.007 mmol) and $NaIO_4$ (14 mg, 0.07 mmol) was added. The bi-layer reaction mixture was stirred at r.t. for 16 hr. The reaction mixture was extracted with ethyl acetate. The residue was purified by reverse phase HPLC to give 3-(4-hydroxy-4-(2-methoxyphenyl)-1-((2R,3S)-2-propyl-1-(3-(trifluoromethyl)picolinoyl)-3-(5-(trifluoromethyl)thiophen-3-yloxy)piperidine-3-carbonyl)piperidin-2-yl)propanoic acid **A144**. LC/MS RT (7 min method) = 4.286 min. Mass observed: 772.1 (M + H).

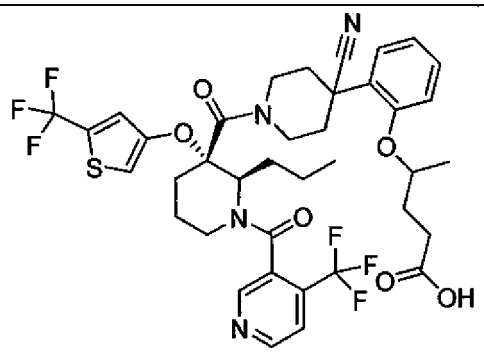
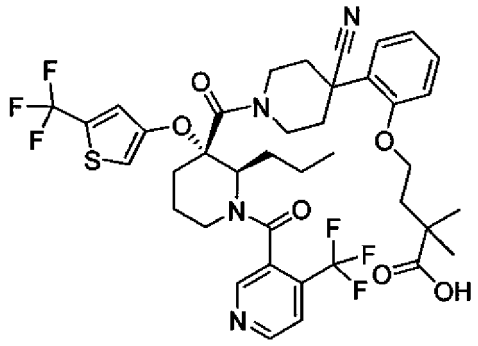
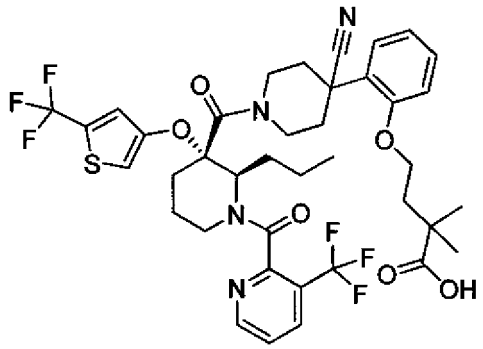
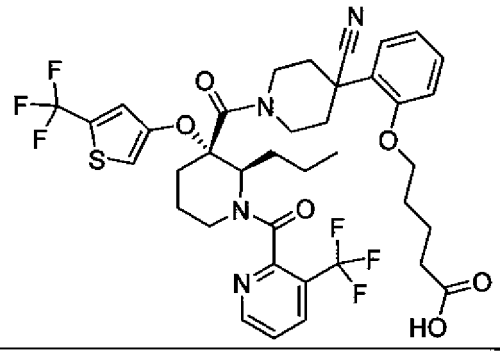
Representative example 73: Synthesis of (**A145**)

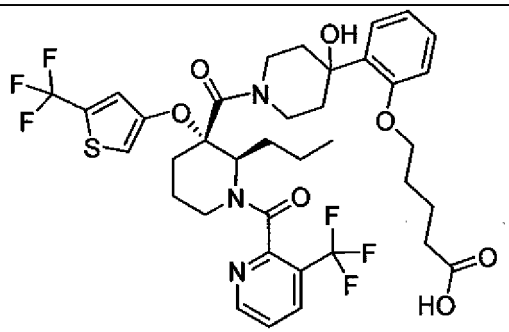
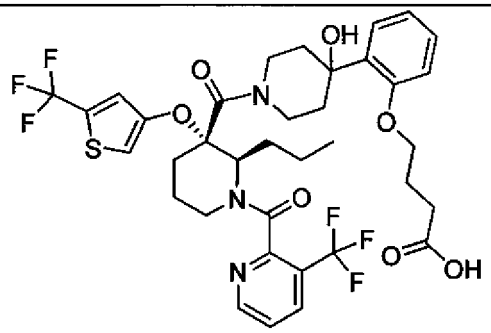
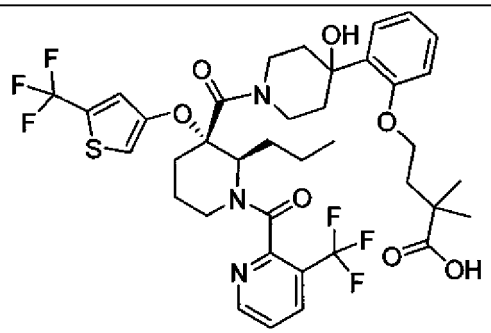
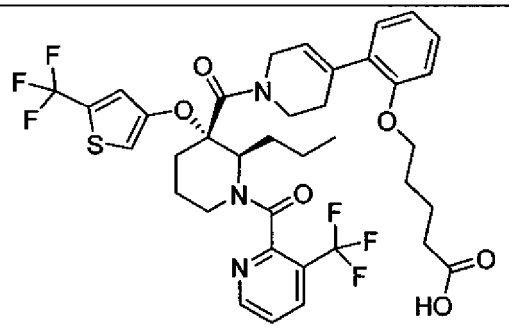
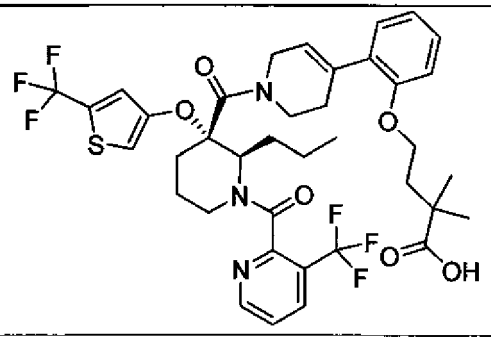


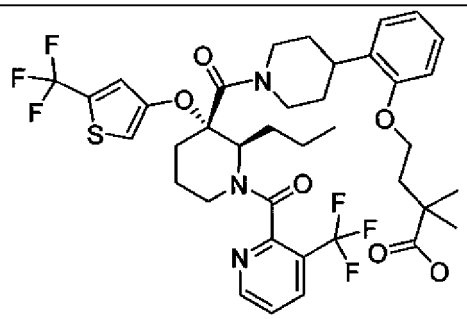
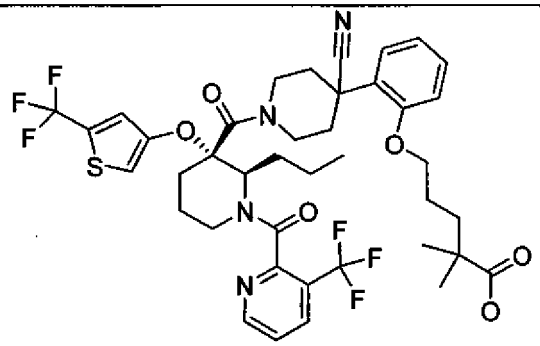
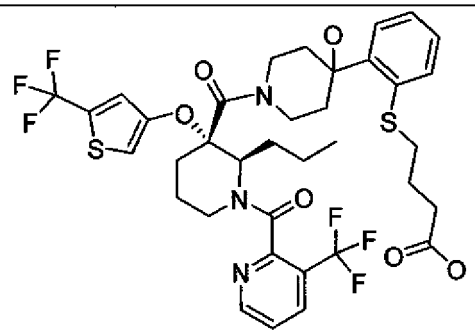
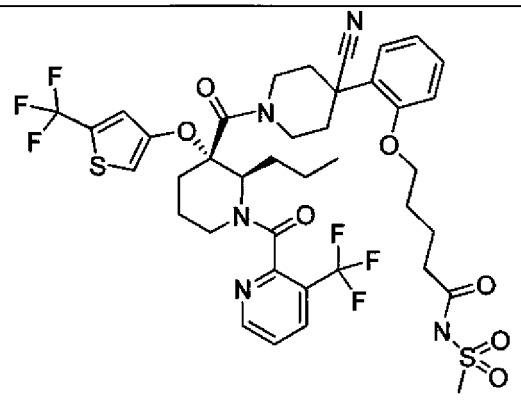
Compound **A145** was prepared according the procedure described in **representative example 55** by replacing intermediate **A34** with intermediate **A46**. LC/MS RT (4 min method) = 2.44 min. Mass observed: 889.1 (M + H).

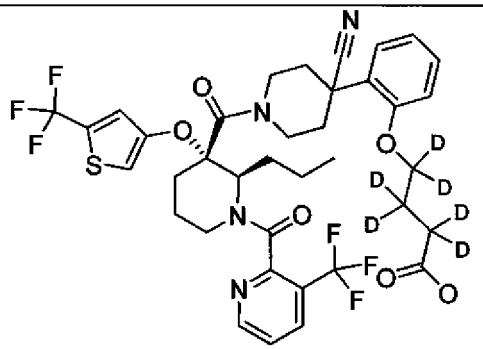
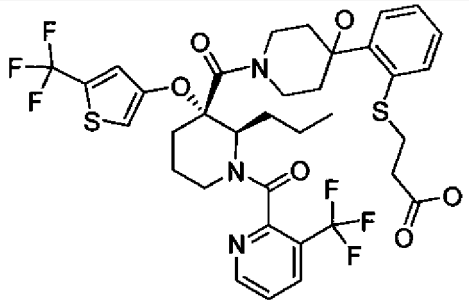
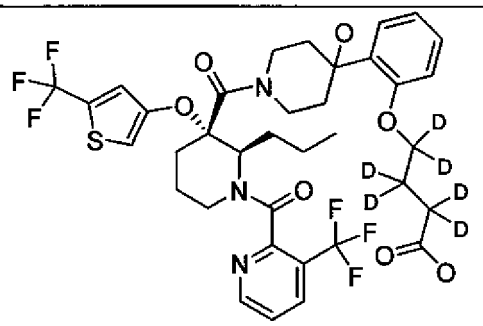
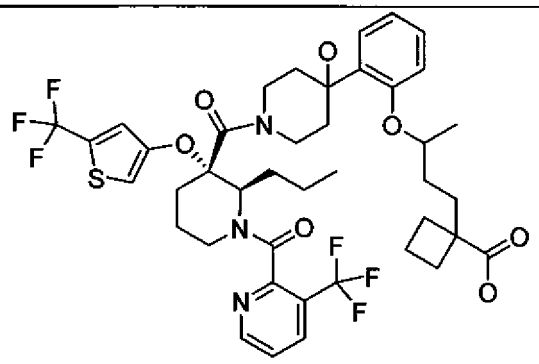
The above compounds as well as other compounds prepared by essentially the same procedures given in the preparative examples above are shown below in Table 1.

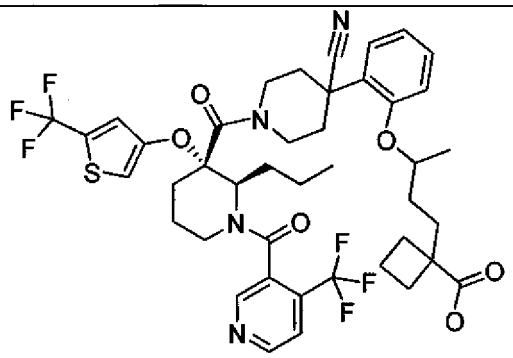
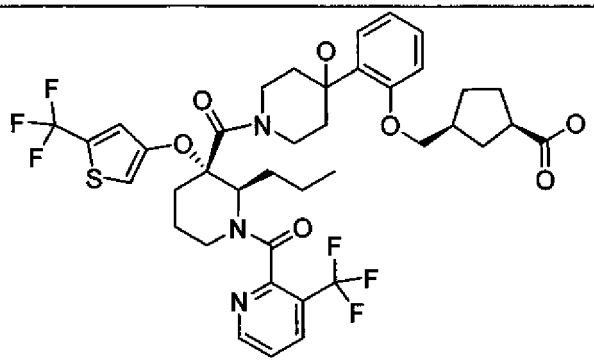
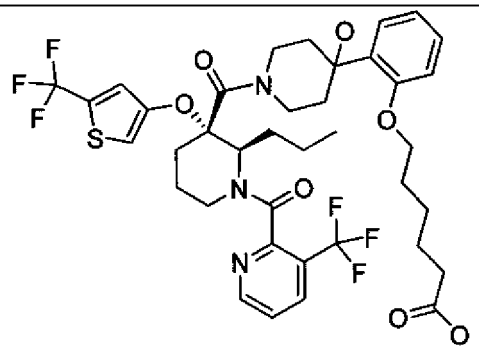
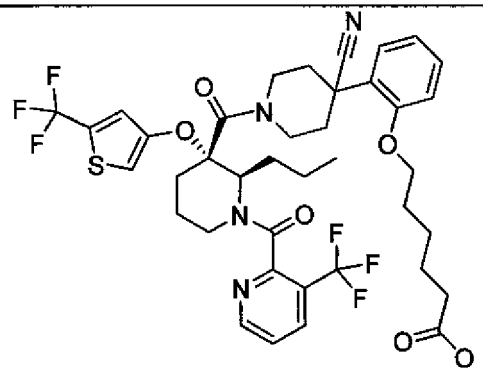
Compound number	Mol structure	Observed M+H or M+Na*	HPLC retention time (min)
A1		756.4	5.05
A2		859.5	5.19
A3		756.7	15.58
A4		795.2	2.35

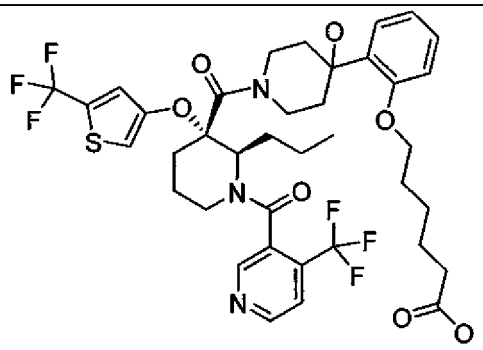
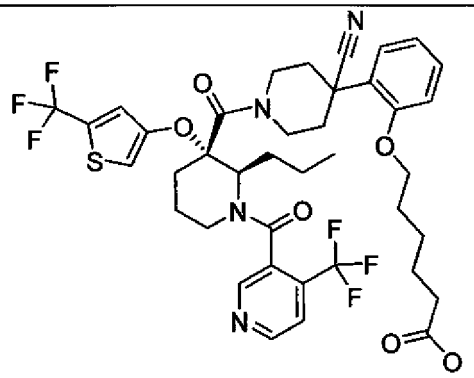
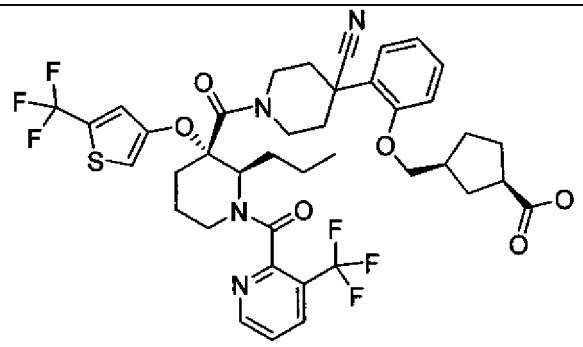
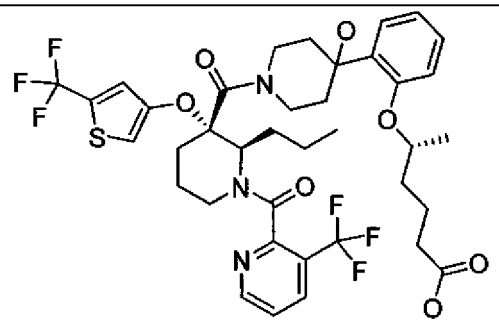
A5		795.2	2.34
A6		810.2	2.39
A7		809.2	2.43
A8		795	2.37

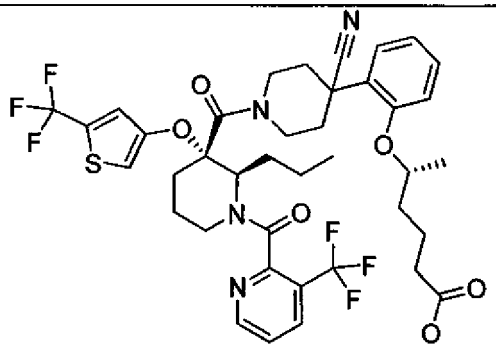
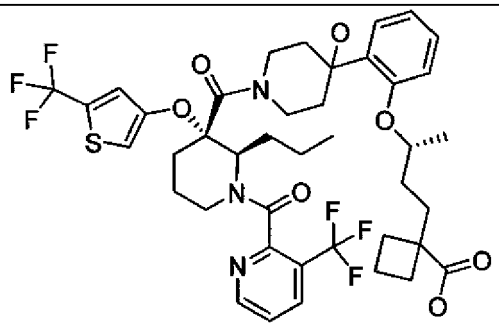
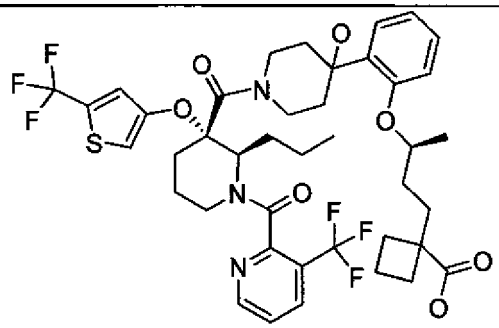
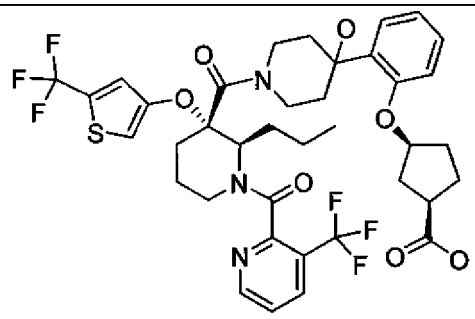
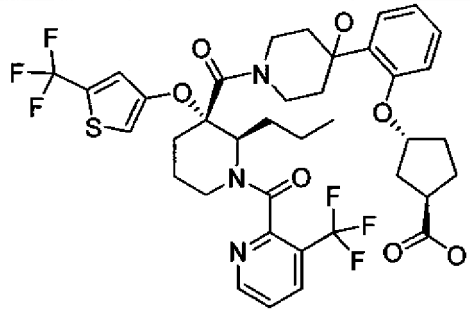
A9		808.2(Na)	2.33
A10		794(Na)	2.3
A11		822.1(Na)	2.39
A12		790(Na)	2.43
A13		804(Na)	2.48

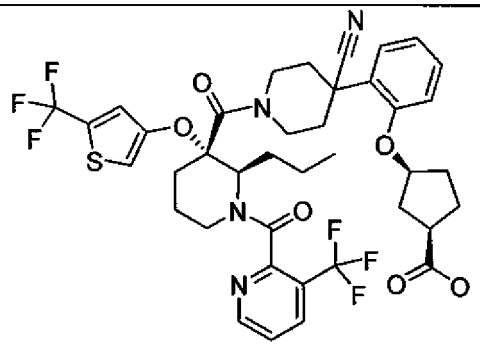
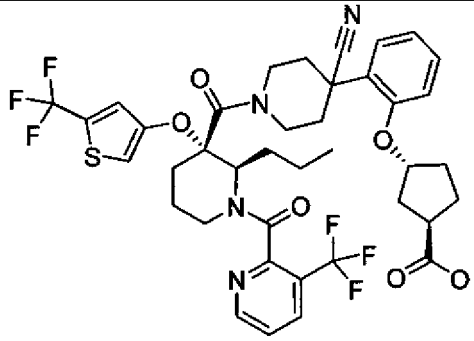
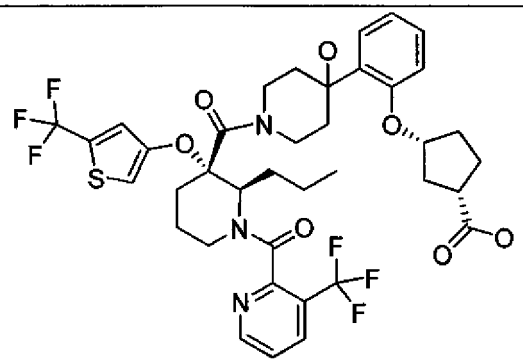
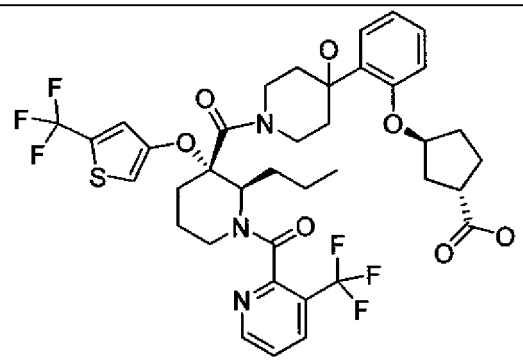
A14		800(Na)	2.49
A15		845(Na)	2.59
A16		810(Na)	2.37
A17		872	2.44

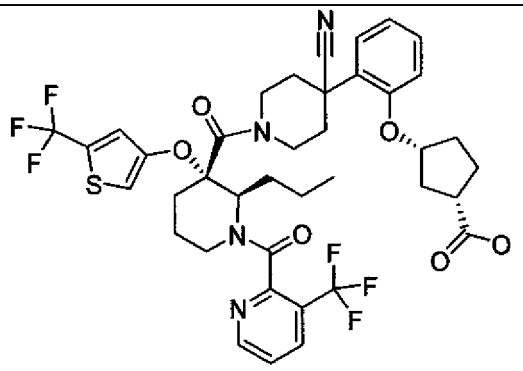
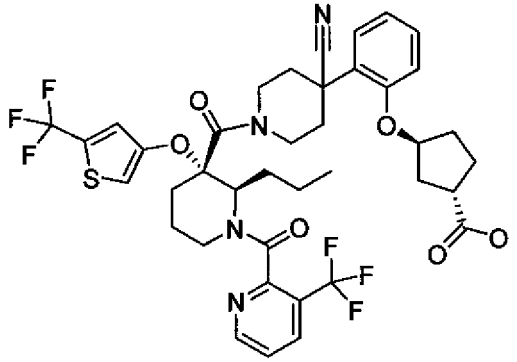
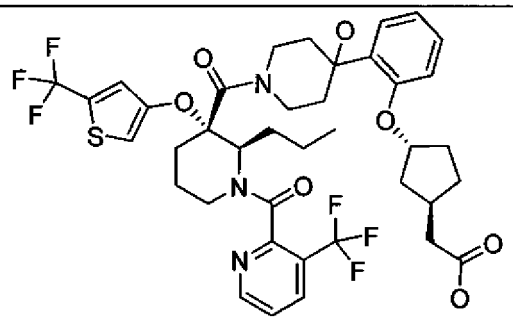
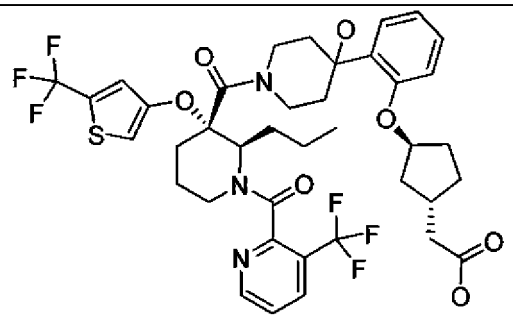
A18		809(Na)	2.41
A19		796(Na)	2.35
A20		796(Na)	2.73
A21		862(Na)	1.27

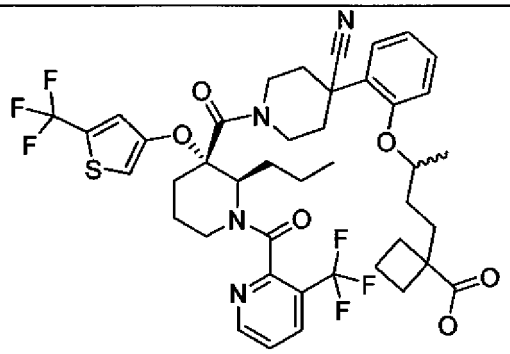
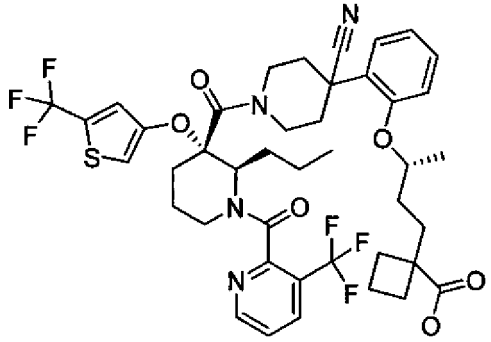
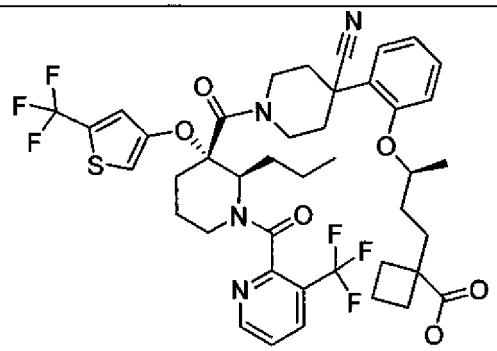
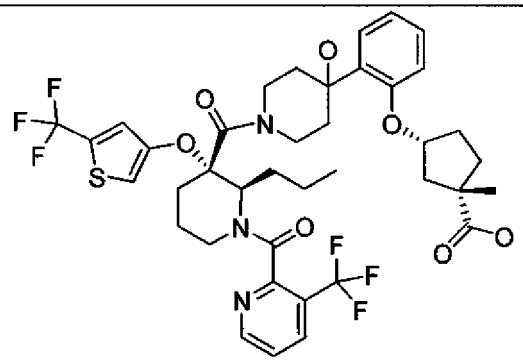
A22		849	1.27
A23		834(Na)	1.22
A24		822(Na)	1.21
A25		831(Na)	1.24

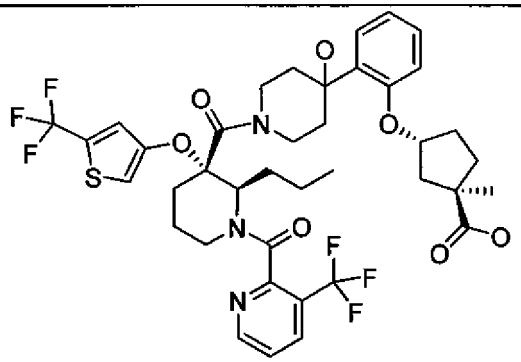
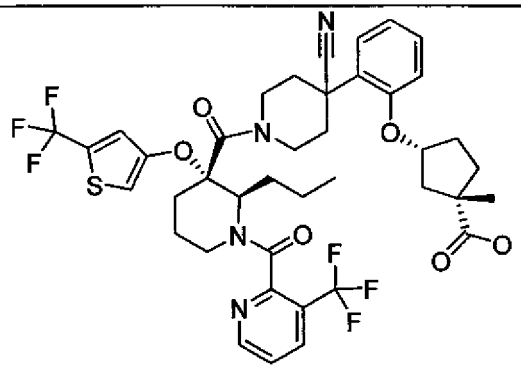
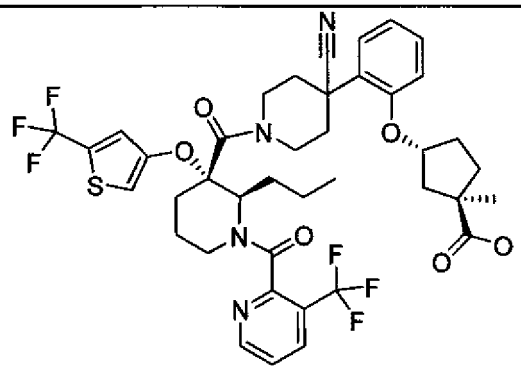
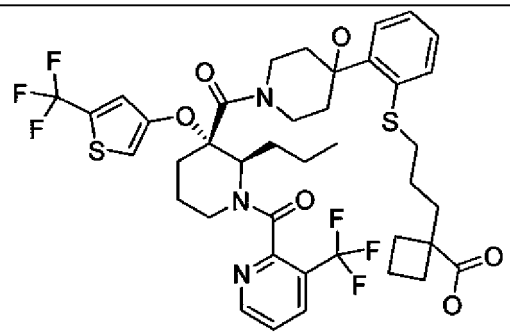
A26		822(Na)	1.19
A27		809	1.21
A28		843(Na)	1.24
A29		822(Na)	5.02

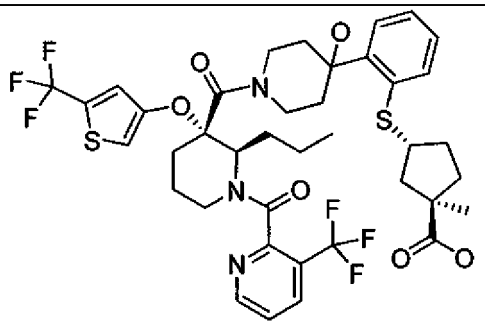
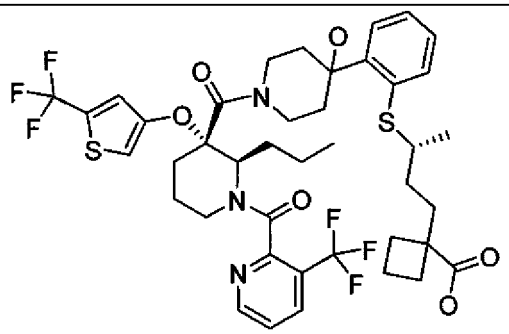
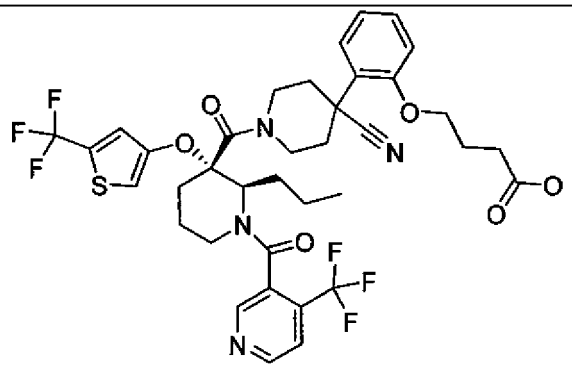
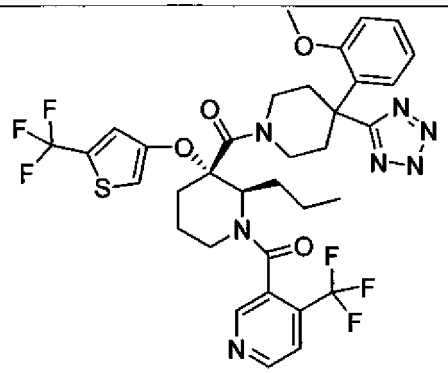
A30		809	5.06
A31		862(Na)	5.34
A32		862(Na)	5.37
A33		821(Na)	5
A34		821(Na)	4.89

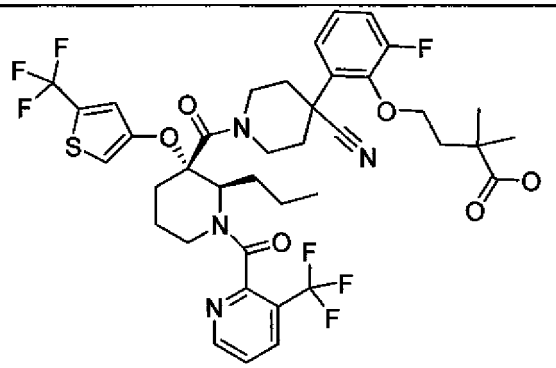
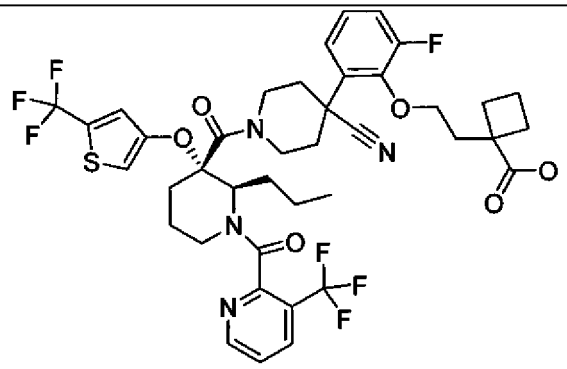
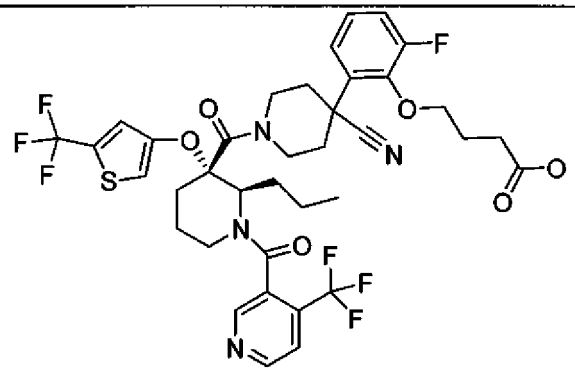
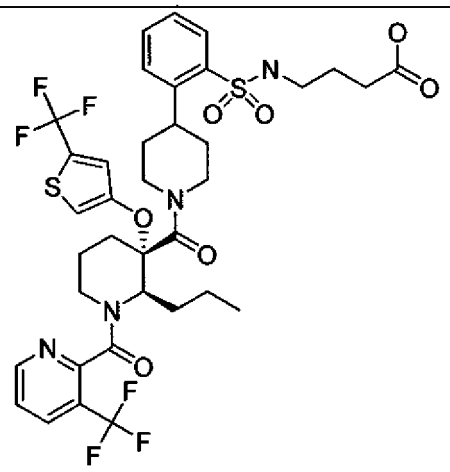
A35		807	5.1
A36		807	4.9
A37		821(Na)	4.99
A38		821(Na)	4.89

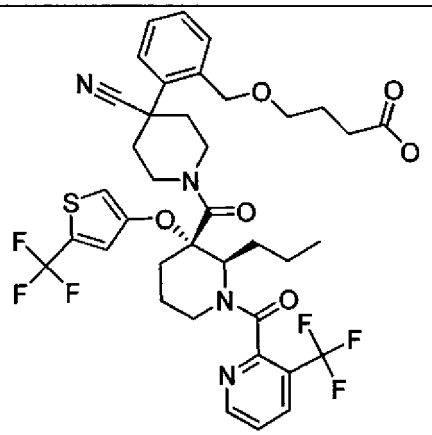
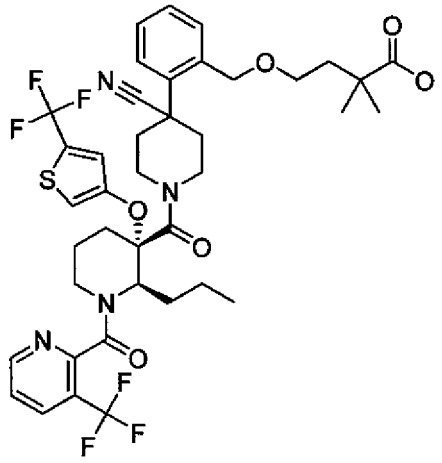
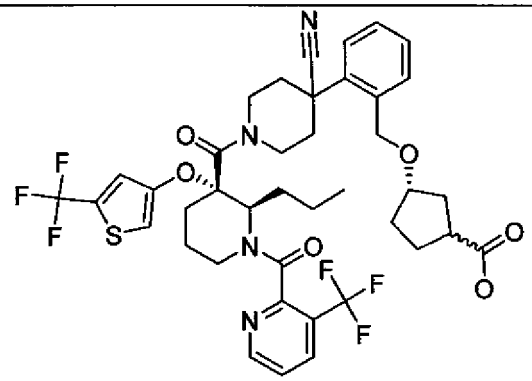
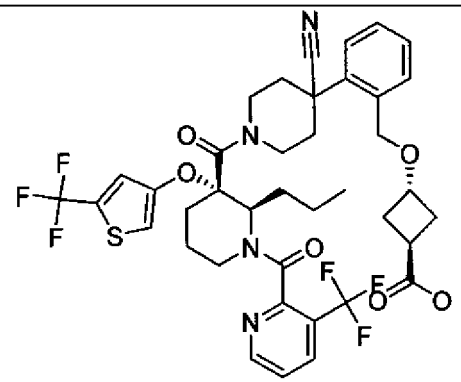
A39		807	5.06
A40		807	5.01
A41		834(Na)	4.97
A42		834(Na)	2.33

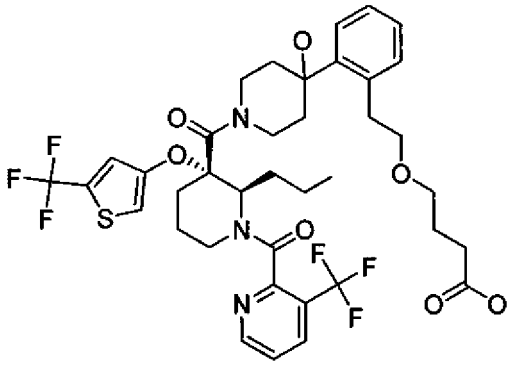
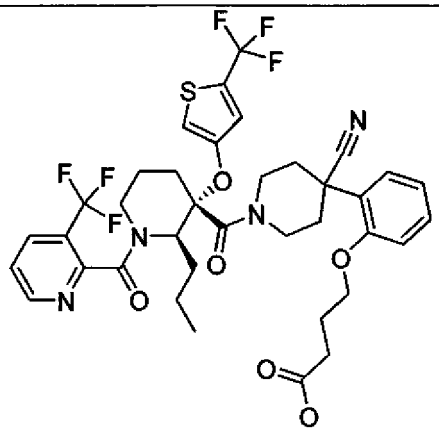
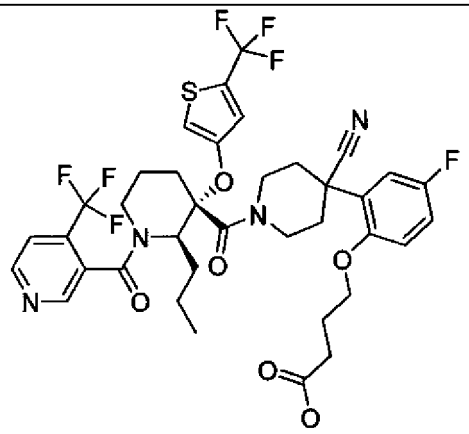
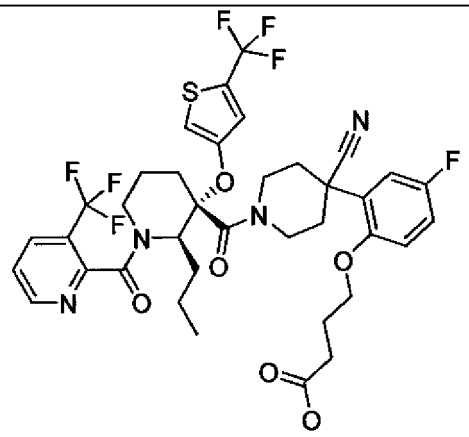
A43		871(Na)	5.37 and 5.40
A44		871(Na)	5.37
A45		871(Na)	5.4
A46		834(Na)	4.54

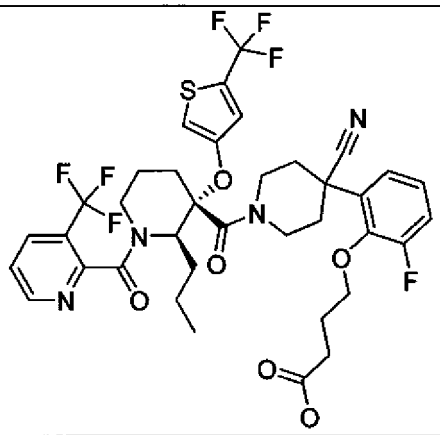
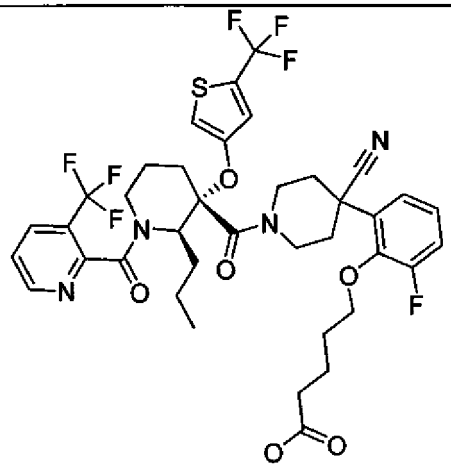
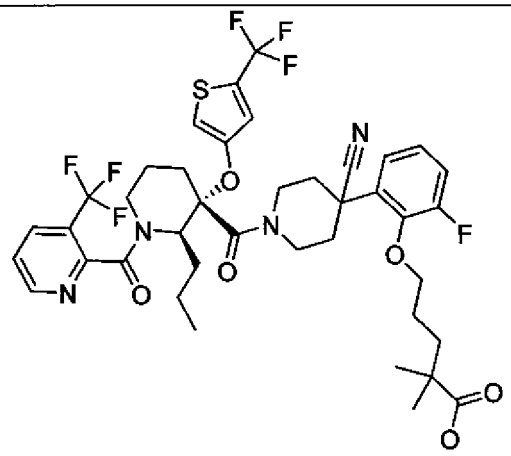
A47		834(Na)	4.43
A48		821	2.45
A49		821	2.51
A50		864(Na)	2.47

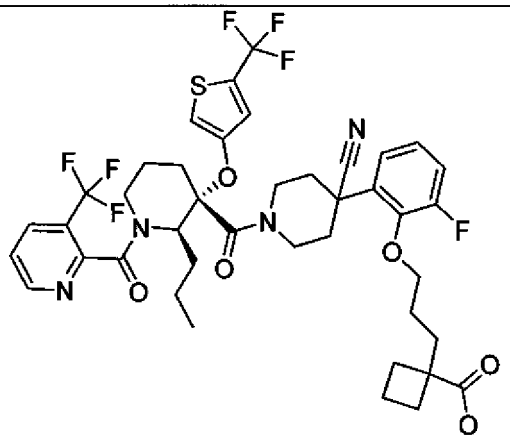
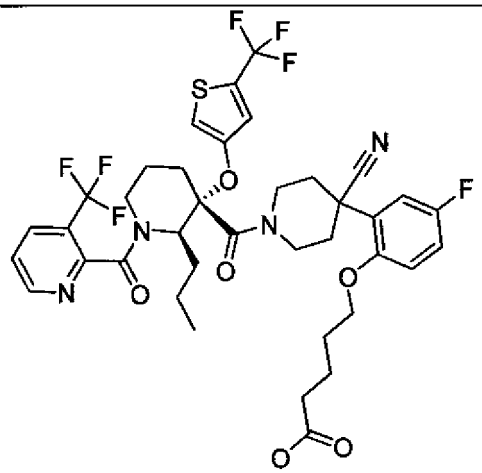
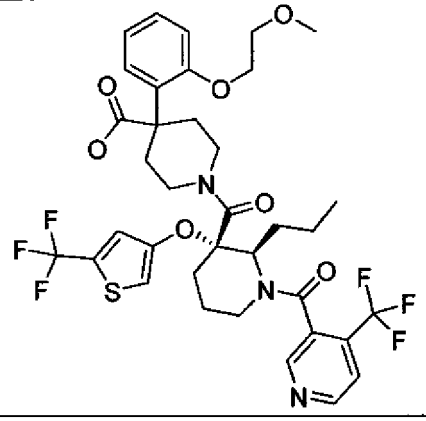
A51		850(Na)	2.43
A52		878(Na)	5.27
A53		781.24	5.81
A54		752.24	5.50

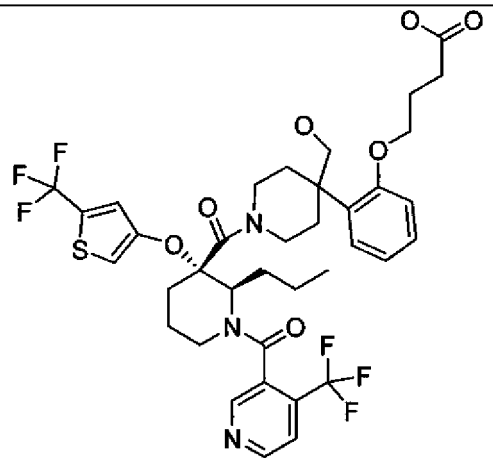
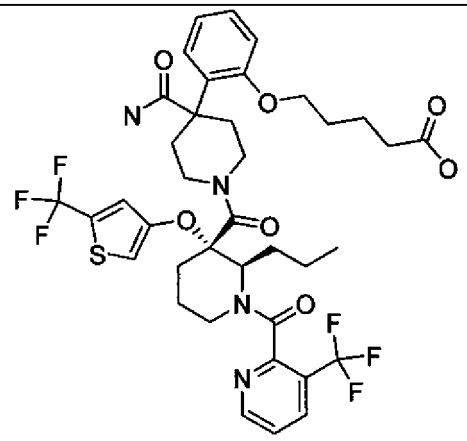
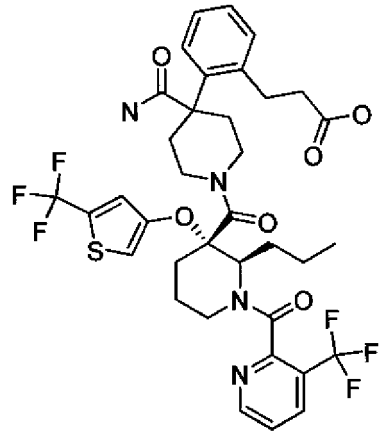
A55		827.20	4.71
A56		839.00	6.61
A57		799.00	5.94
A58		ESI, m/z [M-H]- = 817	7.5

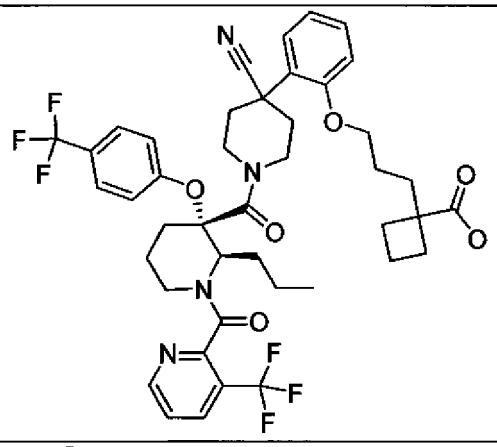
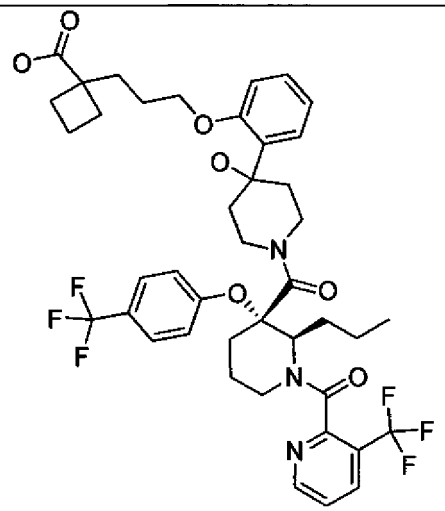
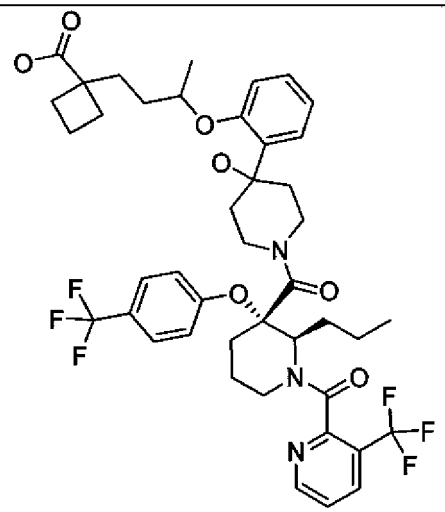
A59		ESI, m/z [M+H]+ = 795	9.72
A60		ESI, m/z [M+H]+ = 823	9.44
A61		ESI, m/z [M+H]+ = 821	9.68
A62		ESI, m/z [M+H]+ = 807	10.69

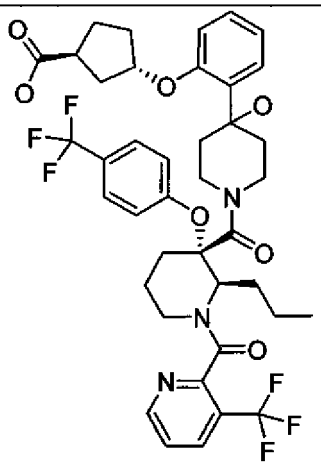
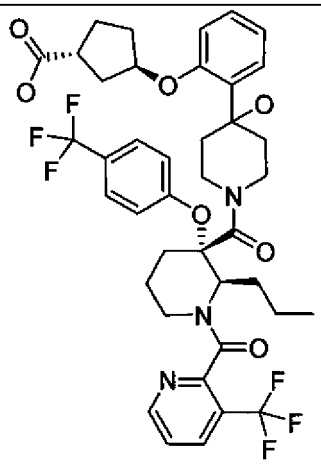
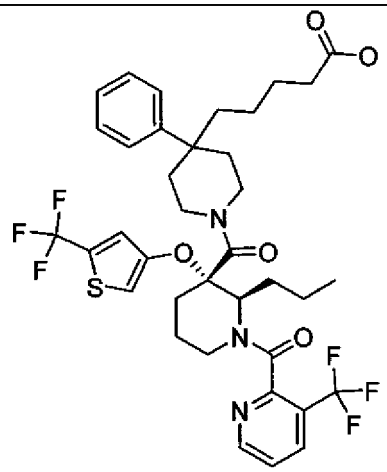
A63		ESI, m/z [M-H]- = 798	9.64
A64		781.2	6.19
A65		799.2	4.55
A66		799.2	4.66

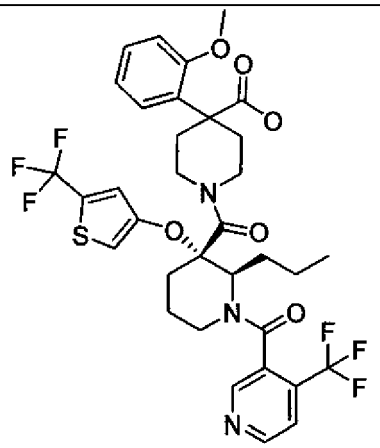
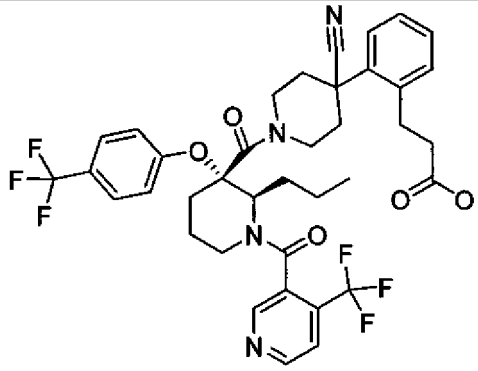
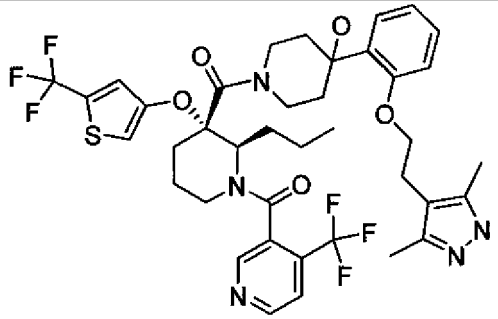
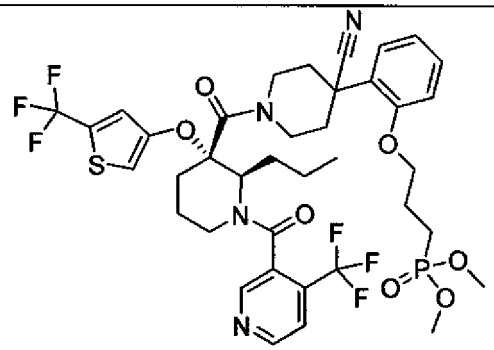
A67		799.37	5.91
A68		813.40	5.80
A69		841.20	6.70

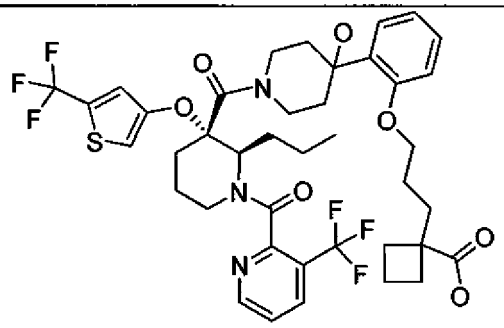
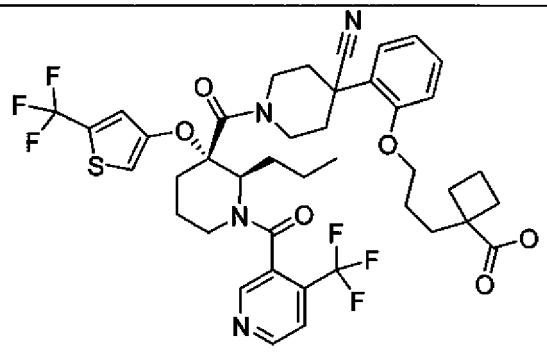
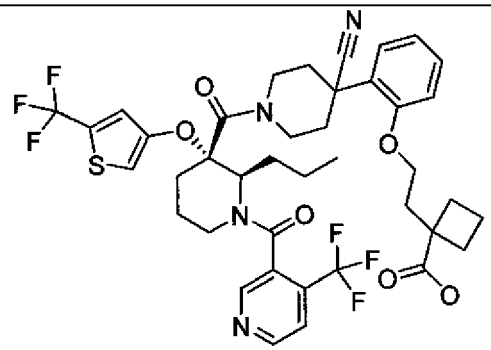
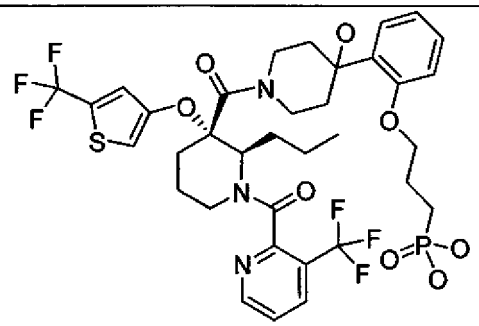
A70		853.20	6.74
A71		813.20	4.46
A72		772.24	4.62

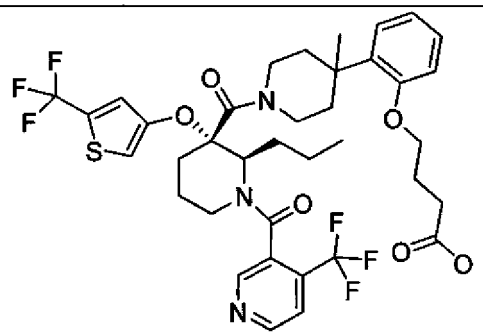
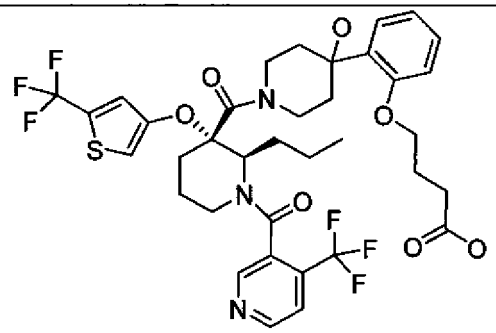
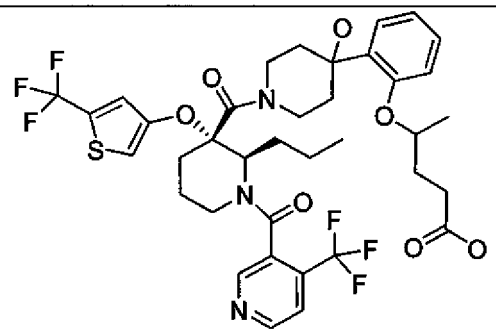
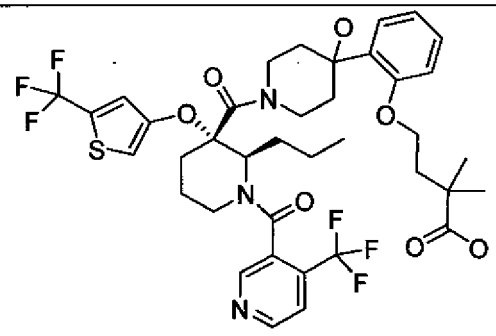
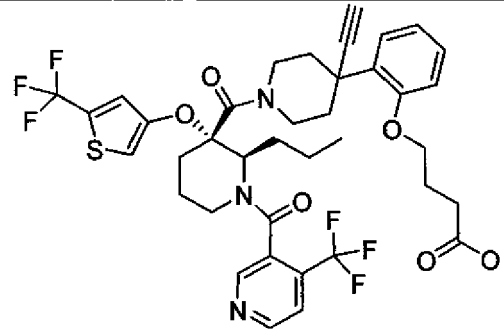
A73		786.26	5.62
A74		813.27	5.67
A75		769.24	5.46

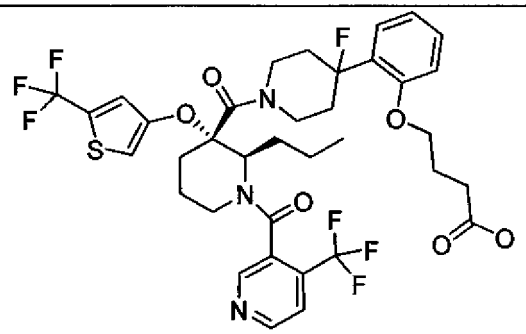
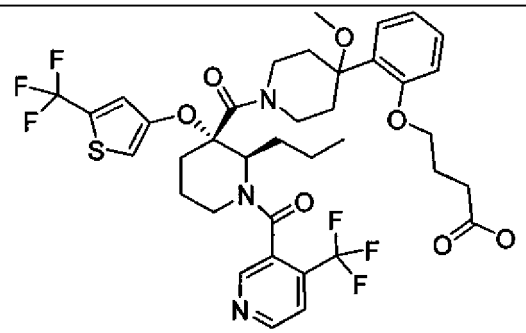
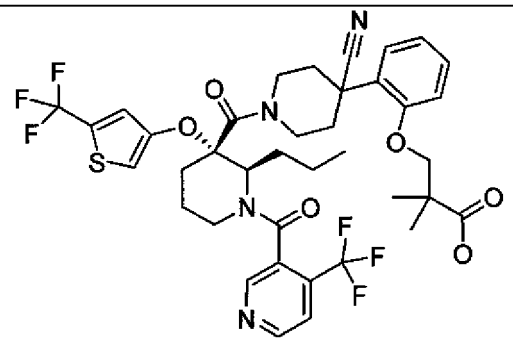
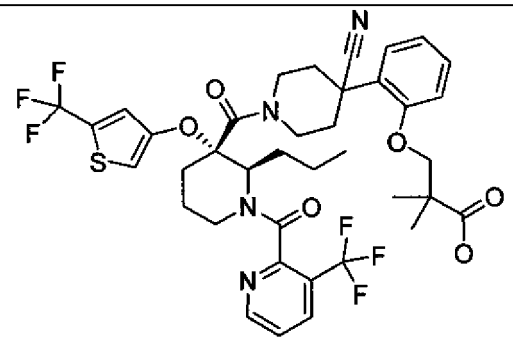
A76		829.33	6.60
A77		820.33	6.41
A78		834.34	4.65

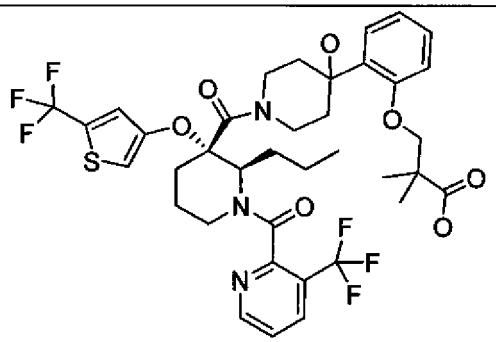
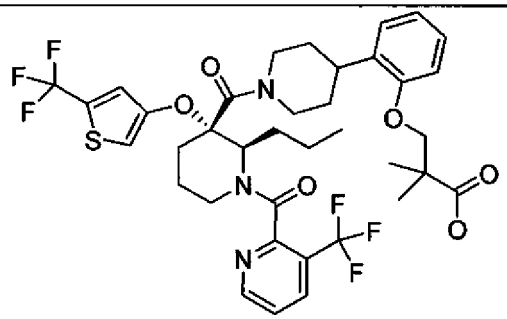
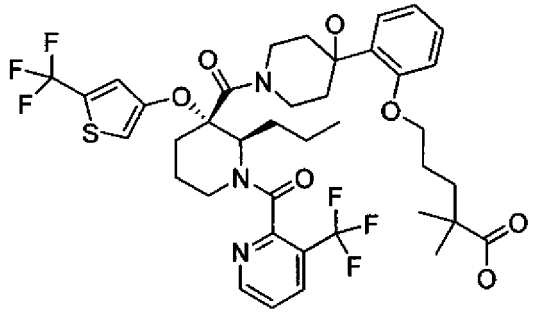
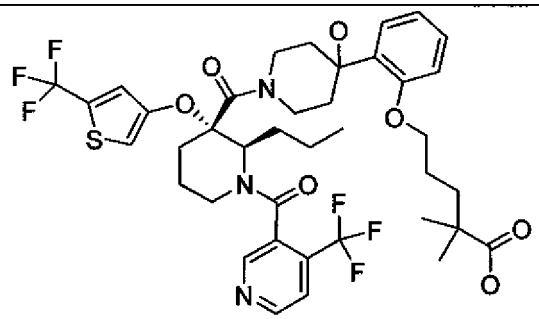
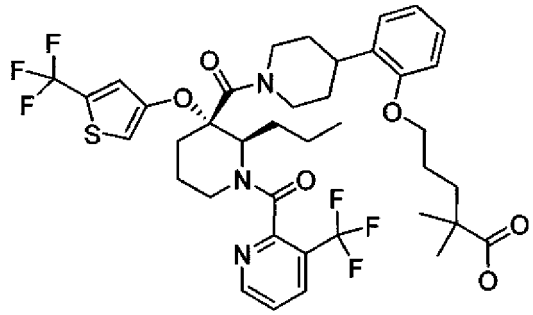
A79		792.30	4.27
A80		792.30	4.26
A81		754.27	6.12

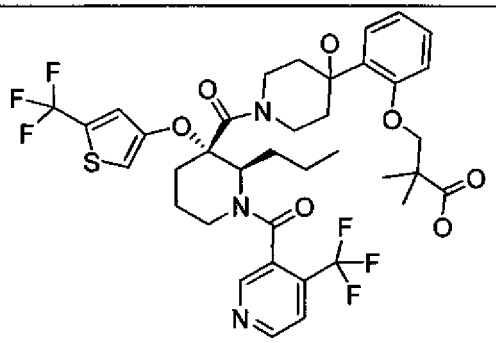
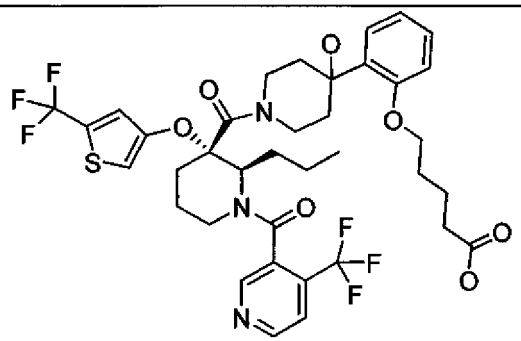
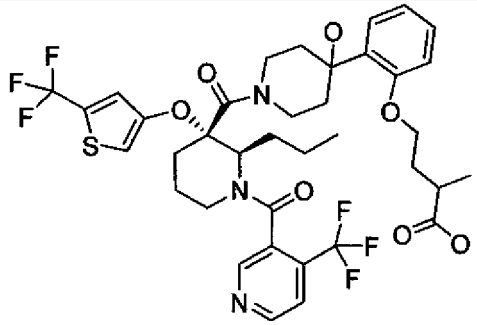
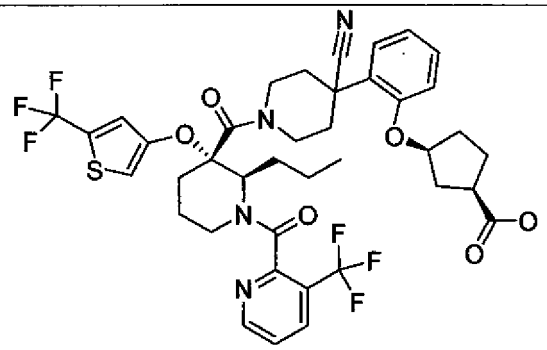
A82		728.20	6.11
A83		745.30	5.46
A84		808.4(M+H)	5.02
A85		845.5(M+H)	6.24

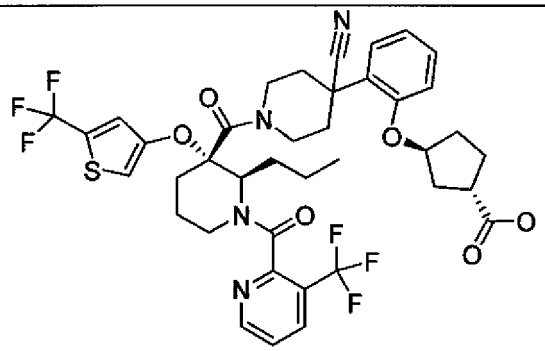
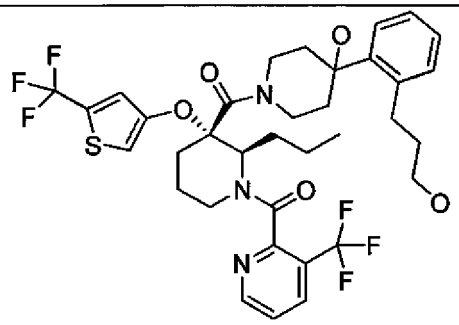
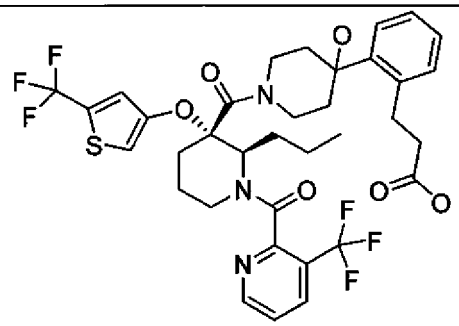
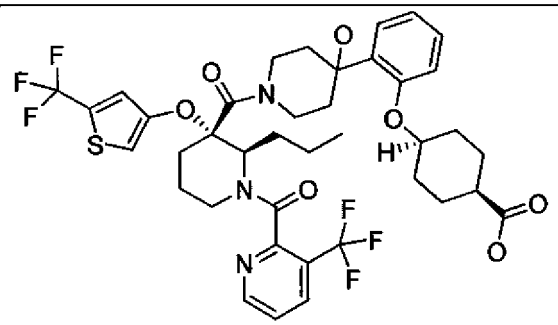
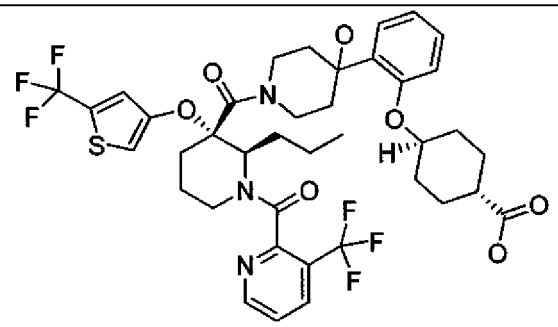
A86		826.4(M+H)	6.41
A87		835.5(M+H)	6.58
A88		821.5(M+H)	6.42
A89		830.0(M+Na)	1.27

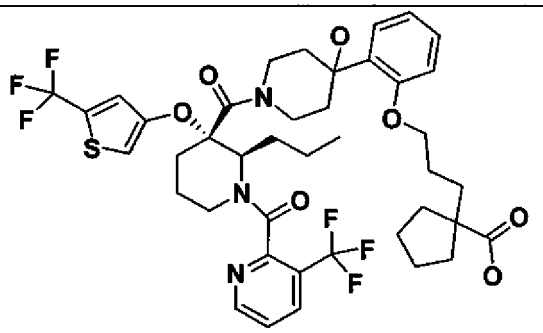
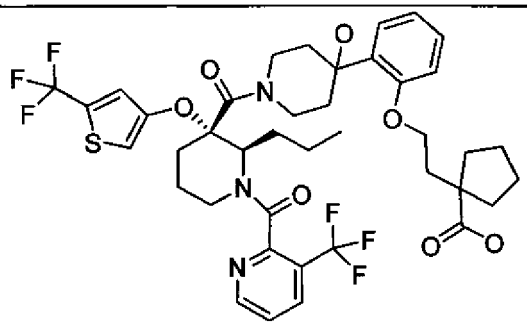
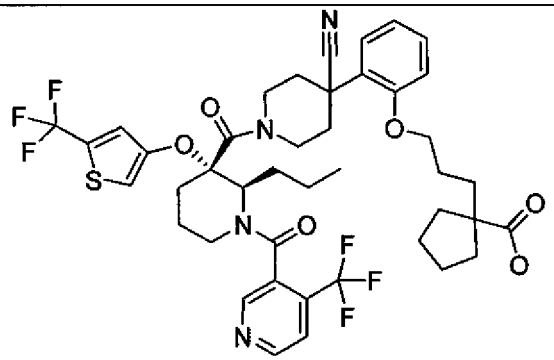
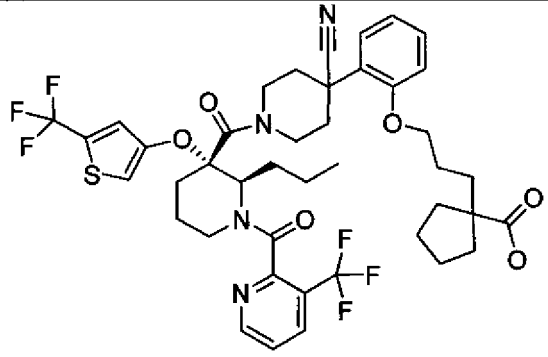
A90		770.4	5.32
A91		772	2.34
A92		786.2	2.38
A93		754.4	4.87
A94		800.4	4.6

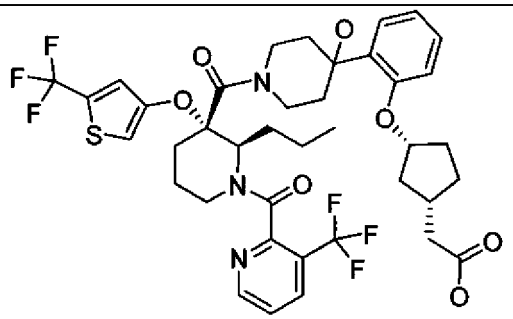
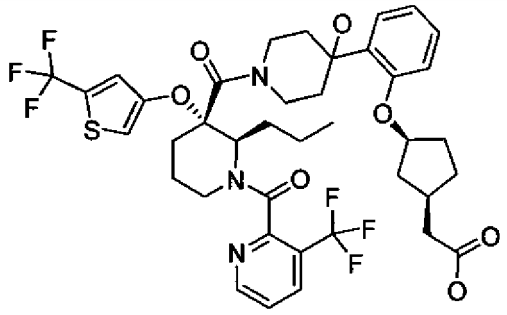
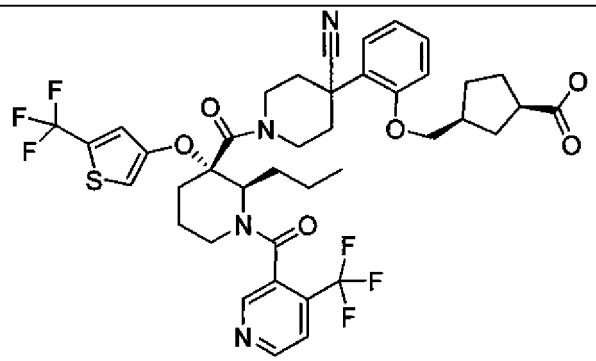
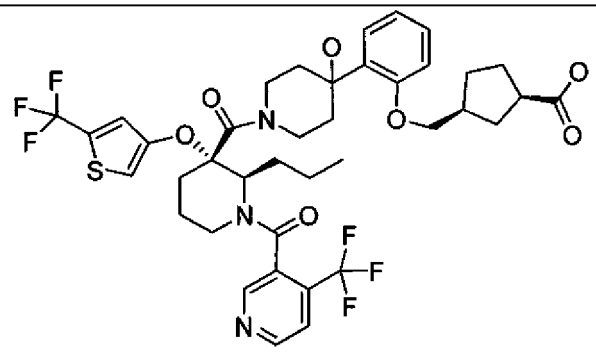
A95		774.4	5.21
A96		786.4	5.13
A97		795.4	5.21
A98		795.2	2.51

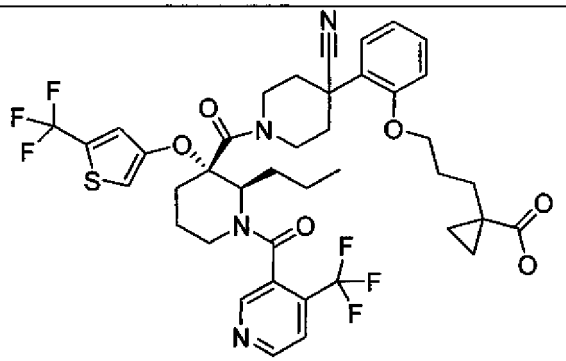
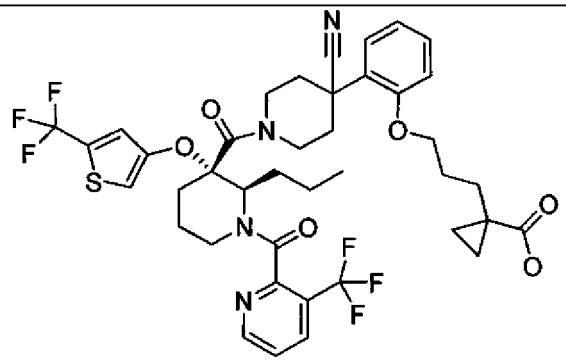
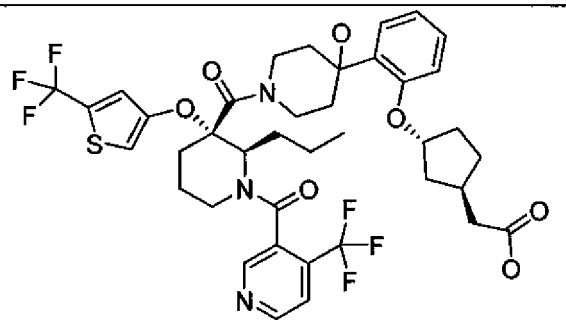
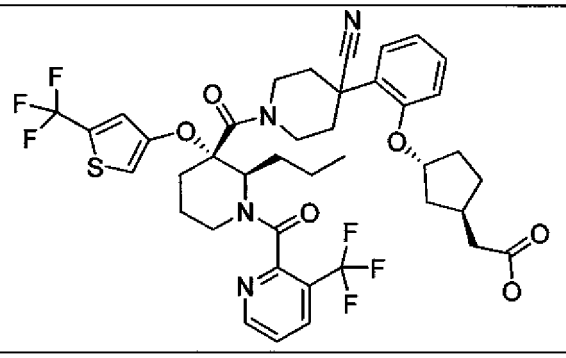
A99		808.2 (Na)	2.51
A100		770.6	13.08
A101		836.4 (Na)	2.44
A102		836.2 (Na)	2.4
A103		797.8	2.74

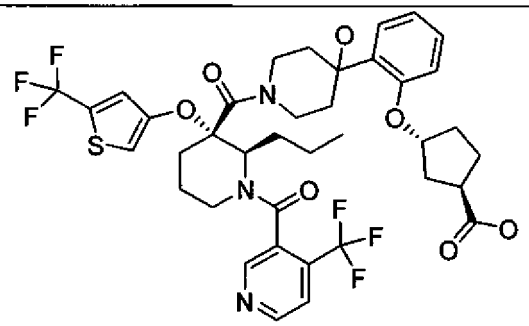
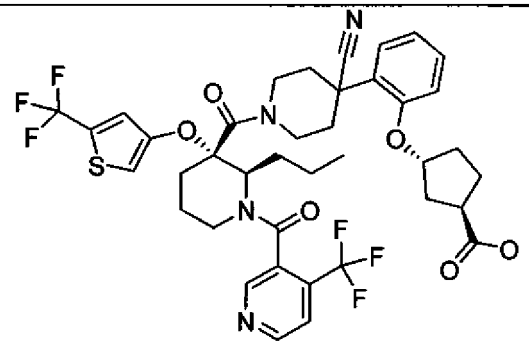
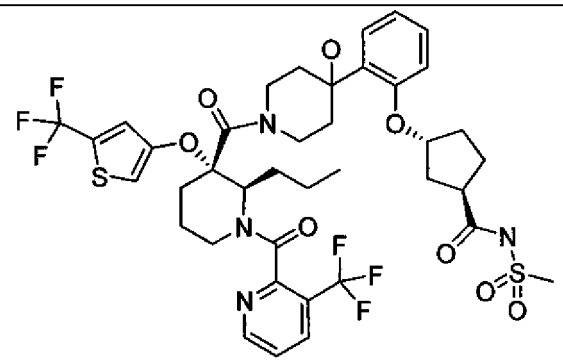
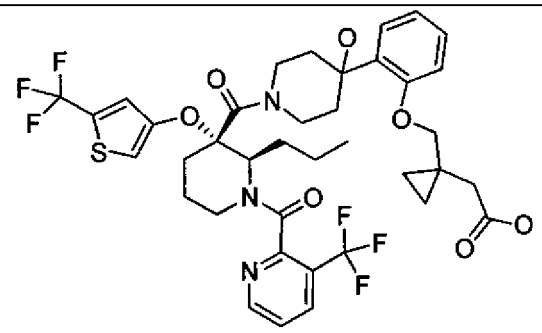
A104		807.8 (Na)	2.46
A105		807.8 (Na)	2.39
A106		808.0 (Na)	2.4
A107		807.4	10.34

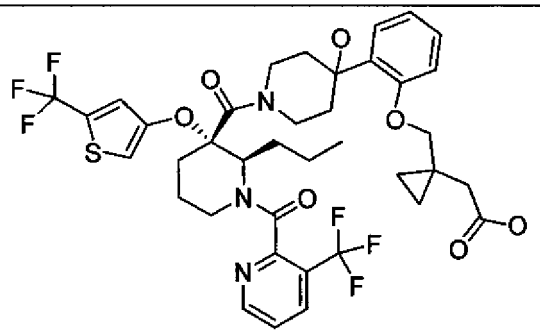
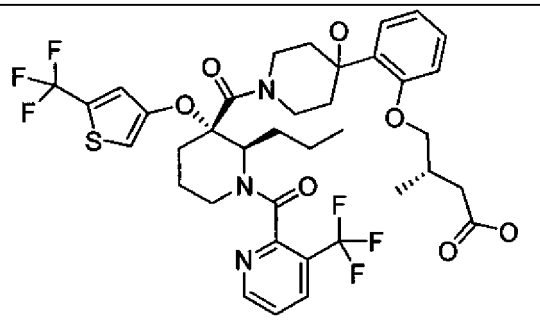
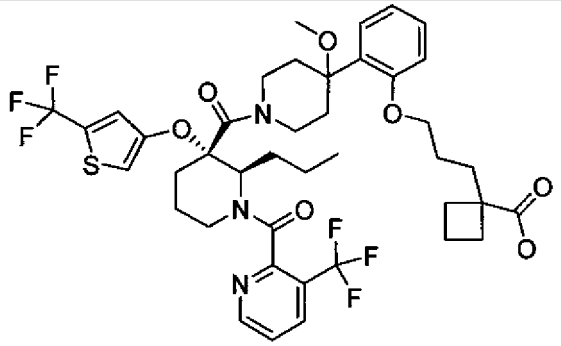
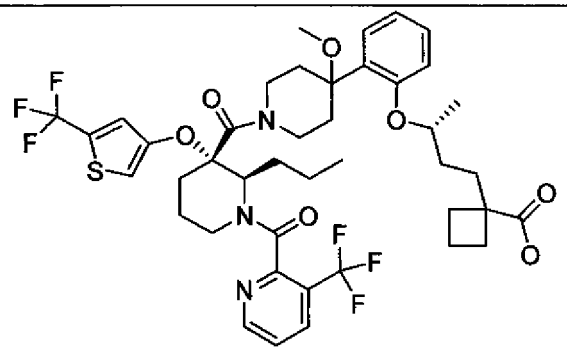
A108		807.4	11.06
A109		750.2 (Na)	2.59
A110		764.1 (Na)	2.35
A111		834.2 (Na)	2.44
A112		834.2 (Na)	2.49

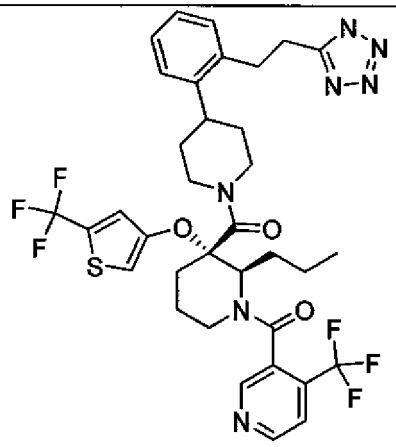
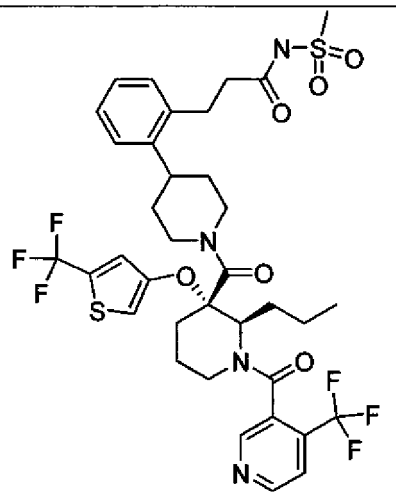
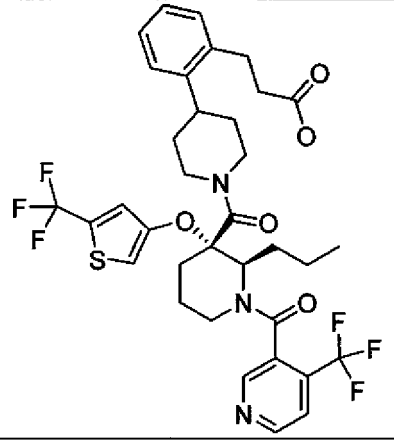
A113		862.0 (Na)	2.51
A114		848.1 (Na)	2.46
A115		849.2	2.49
A116		871.2 (Na)	1.28

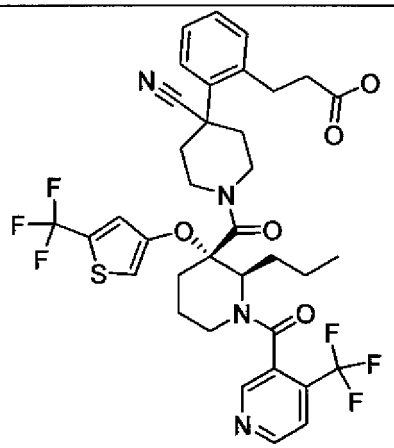
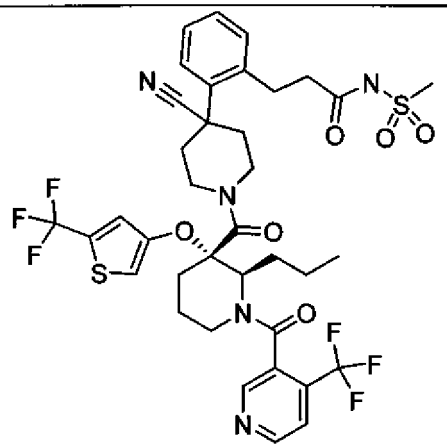
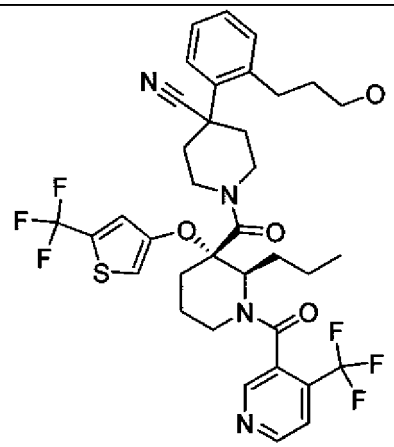
A117		835.2 (Na)	4.98
A118		835.2 (Na)	4.98
A119		821.2	1.19
A120		834.2 (Na)	1.17

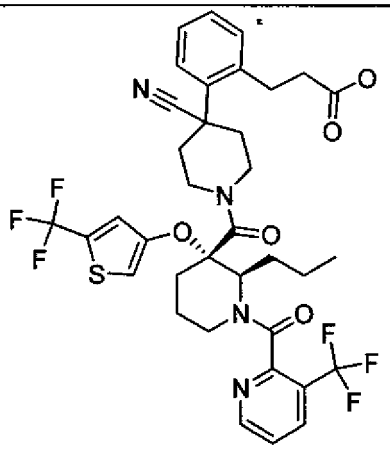
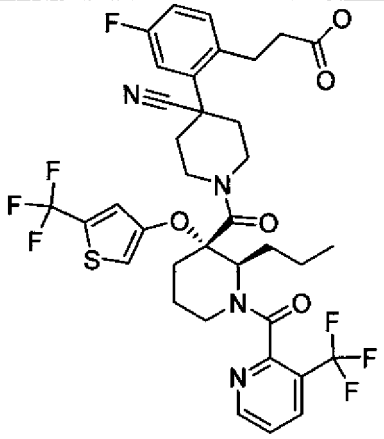
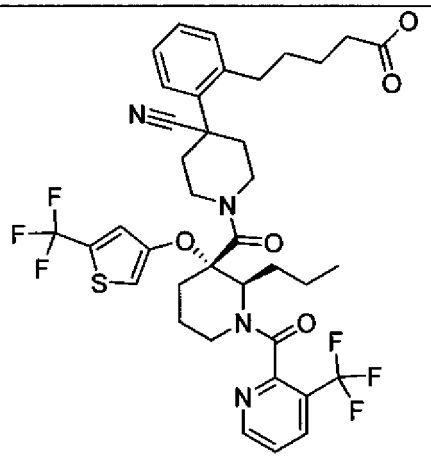
A121		843.2 (Na)	1.2
A122		821.5	11.13
A123		834.2 (Na)	1.18
A124		821.2	1.22

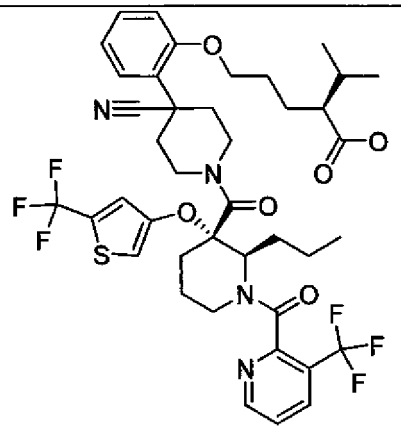
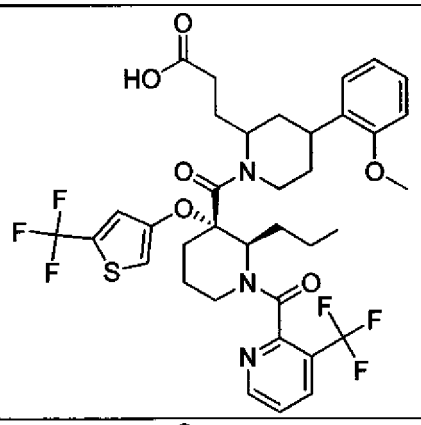
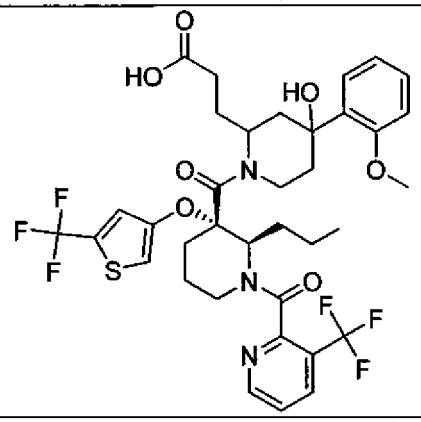
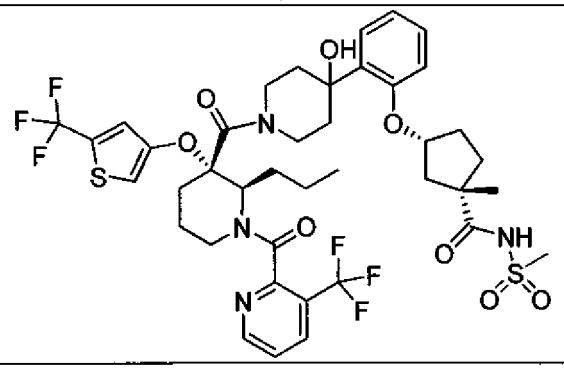
A125		798.2	2.34
A126		807.2	2.37
A127		875.2	2.23
A128		821.1 (Na)	2.39

A129		834.2 (Na)	2.43
A130		806.2 (Na)	2.4
A131		862.2 (Na)	2.62
A132		876.1 (Na)	2.62

A133		750.26	5.97
A134		803.23	4.56
A135		726.23	6.31

A136		751.23	4.56
A137		828.22	5.89
A138		737.25	6.04

A139		751.23	4.54
A140		769.22	4.34
A141		779.26	4.51

A142		837.10	6.74
A143		756.2	4.21
A144		772.1	4.28
A145		881	2.44

The inventive compounds can readily be evaluated to determine activity at the HDM2 protein by known methods such as the fluorescence polarization screening assay that measures the inhibitory concentration that achieves 50% of maximal activity (FP IC_{50}) and the dissociation constant for inhibitor binding (FP Ki). [Zhang et al., J. Analytical Biochemistry 331: 138-146 (2004)].

Additionally, compounds are tested for activity at the HDM2 protein using the Cell Viability Assay, which measures the number of viable cells in culture after treatment with the inventive compound for a certain period of time *e.g.* 72 hours based on quantitation of the ATP present (Cell Viability. IC_{50}). [CellTiter-Glo® Luminescent Cell Viability Assay from Promega].

The compounds of the present invention have unexpectedly superior potency over the compounds disclosed in WO2008/005268 (equivalent to U.S. Patent Publication US 2008/0004287). They exhibit FP IC_{50} values of less than 0.5 μM. In one embodiment, the compounds of the present invention exhibit FP IC_{50} values of less than 0.1 μM. Representative FP IC_{50} values for some of the compounds from Table 1 are shown in Table 2:

Table 2

Compound number	FP (IC 50 uM)	Compound number	FP (IC 50 uM)
A2	0.009	**A89**	0.011
A4	0.014	**A109**	0.018
A54	0.019	**A133**	0.011
A83	0.013	**A145**	0.008

In order to assess the potential for inhibition of Cytochrome P450s (CYPs) and therefore possible drug interactions, human liver microsomes were incubated with several concentrations (0.2, 2, and 20 uM) of compound of the present invention, 1 mM reduced nicotinamide adenine dinucleotide phosphate (NADPH) and substrates for various CYPs at 37°C for 13 mins. The substrate concentration was kept near the Km value for each CYP reaction. They were 100 μM testosterone (6β-hydroxylase reaction) for CYP3A4. The concentrations of the metabolites formed from each substrate after incubation were determined by LC/MS/MS using a standard curve. The concentrations at which 50% of the

initial enzyme activity was inhibited (IC_{50}) were determined from the graph of the concentrations versus percent of inhibition.

The cytochrome P450 3A4 enzyme inhibition studies of the compounds of the present invention also have an improved CYP3A4 profile. They have an IC_{50} CYP3A4 (pre and co incubation) or more than 1 μM, which is unexpectedly superior to the compounds disclosed in WO2008/005268 (U.S. Patent Publication 2008/0004287).

From these test results, it would be apparent to the skilled artisan that the compounds of the invention have utility in treating cancer, diseases involving abnormal cell proliferation and diseases caused by inadequate functioning p53.

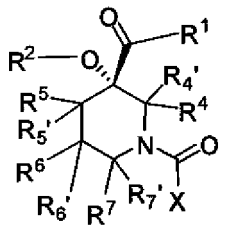
While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Each and every reference, whether a published patent application, a granted/issued patent or a nonpatent scientific publication, mentioned herein is incorporated by reference for all purposes.

CLAIMS

What is claimed is:

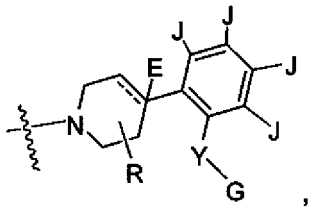
1. A compound of Formula 1:



Formula 1

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is:



, wherein:

E is either present or absent, and when present is selected from the group consisting of H, halo, OH, CN, -O(C_1-C_6)alkyl, -(C_1-C_6)alkyl, -C(O)OH, -C(O)$NR^8R^{8'}$, -(C_1-C_6)alkyl-C(O)OH, -(C_1-C_6)alkyl-OH, -(C_1-C_6)alkyl-C(O)$NR^8R^{8'}$, -(C_2-C_6)alkenyl, -(C_2-C_6)alkynyl, heterocyclyl, and heteroaryl;

each J independently is selected from the group consisting of H and halogen;

G, Y and R may or may not be present, wherein: when Y is not present, G is not present; when Y is present, it is selected from the group consisting of O, S, NR^8, SO_2, and $CR^8R^{8'}$;

R when present is one or more moieties independently selected from the group consisting of -(C_1-C_6)alkyl, and –($CR^8R^{8'}$)$_n$-C(O)OH;

G when present is selected from the group consisting of –($CR^8R^{8'}$)$_n$-C(O)OH, –($CR^8R^{8'}$)$_n$-C(O)NR^8R^9, –($CR^8R^{8'}$)$_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, –($CR^8R^{8'}$)$_n$-(C_3-C_8)cycloalkyl-($CR^8R^{8'}$)$_n$-C(O)OH, –($CR^8R^{8'}$)$_n$-O–($CR^8R^{8'}$)$_n$-(C_3-C_8)cycloalkyl-($CR^8R^{8'}$)$_n$-C(O)OH, —($CR^8R^{8'}$)$_n$-O–($CR^8R^{8'}$)$_n$-C(O)OH, —($CR^8R^{8'}$)$_n$-

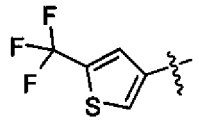
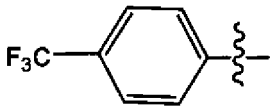
S–$(CR^8R^{8'})_n$-C(O)OH, C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-S–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-$P(O)OR^8OR^{8'}$, —$(CR^8R^{8'})_n$-$P(O)O_2$, and —$(CR^8R^{8'})_n$-OH; wherein:

each R^8 and $R^{8'}$ is independently selected from the group consisting of H, D, and $(C_1$-$C_6)$alkyl; or wherein R^8 and $R^{8'}$ together with the carbon to which each is attached form $(C_3$-$C_8)$cycloalkyl;

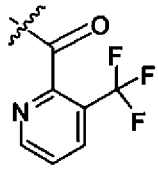
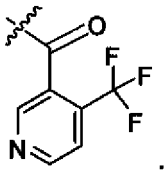
each R^9 independently is $SO_2(C_1$-$C_6)$alkyl or $SO_2(C_3$-$C_8)$cycloalkyl;

each n independently is 0-10; providing that when n is 0, any oxygen, nitrogen or sulfur atom of Y is not directly linked to any oxygen, nitrogen, sulfur or phosphorus atom of G;

----- represents a single or a double bond, providing that when E is present, ----- represents a single bond;

R^2 is  or ;

R^4, $R^{4'}$, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, and $R^{7'}$ independently are selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl; and

X is  or .

2. The compound of claim 1, wherein R is absent and E is present.

3. The compound of claim 1, wherein both R and E are absent.

4. The compound of claim 1, wherein E is present and is selected from the goup consisting of H, halo, OH, CN, -O$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl, -C(O)OH, -$C(O)NR^8R^{8'}$, -$(C_1$-$C_6)$alkyl-C(O)OH, -$(C_1$-$C_6)$alkyl-OH, -$(C_1$-$C_6)$-$C(O)NR^8R^{8'}$, and heteroaryl.

5. The compound of claim 4, wherein said -$(C_1$-$C_6)$alkyl-OH is hydroxymethyl; said -$(C_1$-$C_6)$alkyl-$C(O)NR^8R^{8'}$ is –$C(O)NH_2$; said -$(C_1$-$C_6)$alkyl-

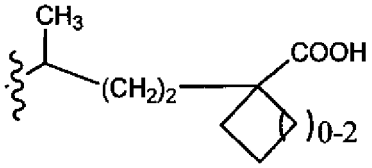
C(O)OH is –$(CH_2)_4$COOH; said halo is –F; said -O(C_1-C_6)alkyl is methoxy; said -(C_1-C_6)alkyl is methyl; and said heteroaryl is tetrazolyl.

6. The compound of claim 1, wherein each J independently is H or Fluoro.

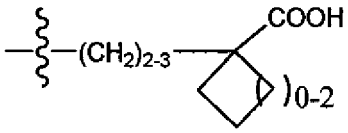
7. The compound of claim 1, wherein Y is present and is selected from the group consisting of O, S, SO_2, and $CR^8R^{8'}$.

8. The compound of claim 1, wherein G is present, and is selected from the group consisting of –$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, —$(CR^8R^{8'})_n$-P(O)$OR^8OR^{8'}$, and —$(CR^8R^{8'})_n$-OH.

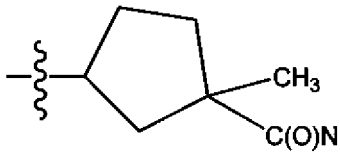
9. The compound of claim 9, wherein said –$(CR^8R^{8'})_n$-C(O)OH is selected from the group consisting of –$(CH_2)_{1-5}$C(O)OH, –$CH(CH_3)$-$(CH_2)_{2-3}$-C(O)OH, –$(CH_2)_{1-3}C(CH_3)_2$C(O)OH, –$(CH_2)_3CH(CH(CH_3)_2)$-C(O)OH –$(CD_2)_3$C(O)OH, –$(CH_2)_{1-2}$-$CH(CH_3)$-$(CH_2)_{1-2}$-C(O)OH, $CH(CH_3)$-$(CH_2)_{2-3}$-C(O)OH,



, and



; wherein said –$(CR^8R^{8'})_n$-C(O)NR^8R^9 is –$(CH_2)_{1-4}$-C(O)NH-$S(O)_2CH_3$ or –$(CH_2)_{3-4}$-C(O)NH-$S(O)_2$-cyclopropyl; said –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9 is –cyclopentyl-C(O)NH-$S(O)_2$-CH_3 or



; said –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH is selected from the group consisting of –CH_2-cyclopentyl-C(O)OH, -cyclobutyl-C(O)OH, -cyclopentyl-C(O)OH, -cyclohexyl-C(O)OH, and -cyclopentyl-CH_2-C(O)OH; said –$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH is –O-cyclopenyl-C(O)OH or –O-cyclobutyl-C(O)OH; said —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH is selected from the group consisting of -CH_2-O-$(CH_2)_3$-C(O)OH, -O-$(CH_2)_2$-$C(CH_3)_2$-C(O)OH, and -O-

$(CH_2)_3$-C(O)OH; said —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH is –NH$(CH_2)_3$C(O)OH; said —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3 is –$(CH_2)_2$-O-CH_3; said —$(CR^8R^{8'})_n$-CH_3 is –CH_3; said —$(CR^8R^{8'})_n$-heteroaryl is –$(CH_2)_2$-(alkyl substituted pyrazolyl); said —$(CR^8R^{8'})_n$-P(O)$OR^8OR^{8'}$ is –$(CH_2)_3$P(O)(OH)(OH) or –$(CH_2)_3$P(O)$(OCH_3)(OCH_3)$; and said —$(CR^8R^{8'})_n$-OH is –$(CH_2)_2$-OH.

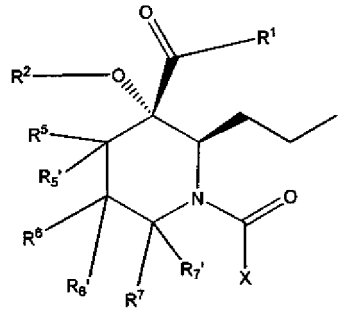
10. The compound of claim 1, wherein Y is O and G is selected from the group consisting of –$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-C(O)NR^8R^9, –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-CH_3, —$(CR^8R^{8'})_n$-heteroaryl, and —$(CR^8R^{8'})_n$-P(O)$OR^8OR^{8'}$.

11. The compound of claim 1, wherein Y is S and G is –$(CR^8R^{8'})_n$-C(O)OH or –$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH.

12. The compound of claim 1, wherein Y is SO_2 and G is —$(CR^8R^{8'})_n$-NH–$(CR^8R^{8'})_n$-C(O)OH.

13. The compound of claim 1, wherein Y is $CR^8R^{8'}$ and G is selected from the group consisting of —$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-O–$(CR^8R^{8'})_n$-(C_3-C_8)cycloalkyl-$(CR^8R^{8'})_n$-C(O)OH, –$(CR^8R^{8'})_n$-C(O)OH, —$(CR^8R^{8'})_n$-OH, —$(CR^8R^{8'})_n$-heteroaryl, and –$(CR^8R^{8'})_n$-C(O)NR^8R^9.

14. The compound of claim 1, wherein R^4 is hydrogen and $R^{4'}$ is 1-propyl, such that Formula 1 is represented by Formula 1A:

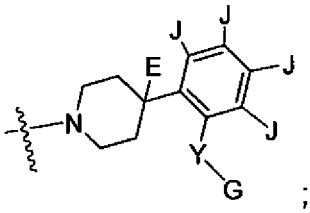


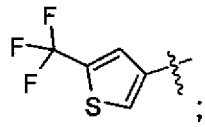
Formula 1A

wherein R^1, R^2, R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, $R^{7'}$, and X are as set forth in Formula 1.

15. The compound of claim 15, wherein R^5, $R^{5'}$, R^6, $R^{6'}$, R^7, and $R^{7'}$ are all hydrogen.

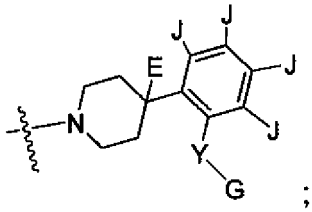
16. The compound of claim 16, wherein:

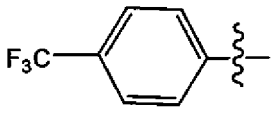
R^1 is  ;

R^2 is  ; and

either (i) each J in R^1 is H, or (ii) one J in R^1 is halo, and the reminaing three Js are H.

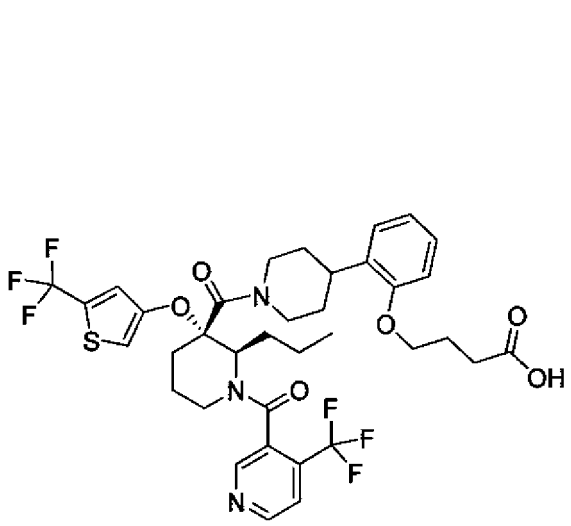
17. The compound of claim 16, wherein:

R^1 is  ;

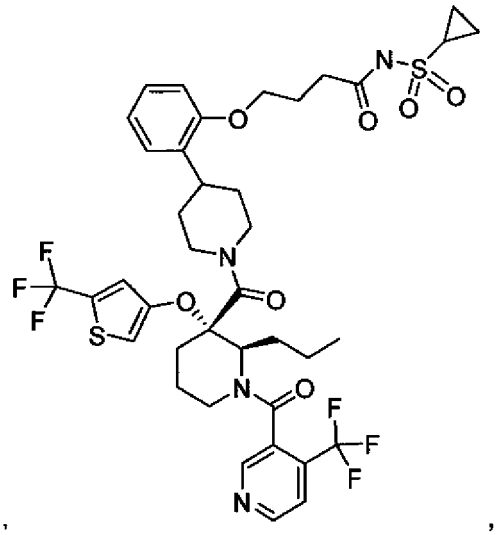
R^2 is  ; and

each J in R^1 is H.

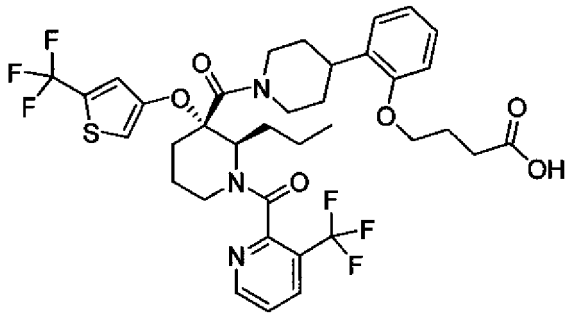
18. A compound selected from the group consisting of:



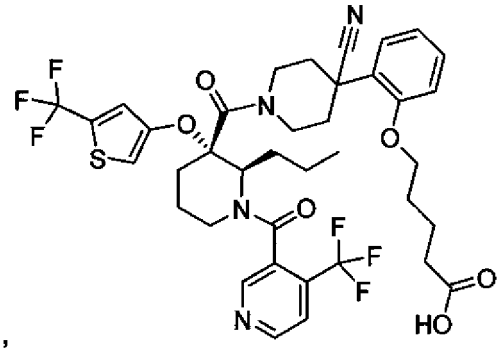
,



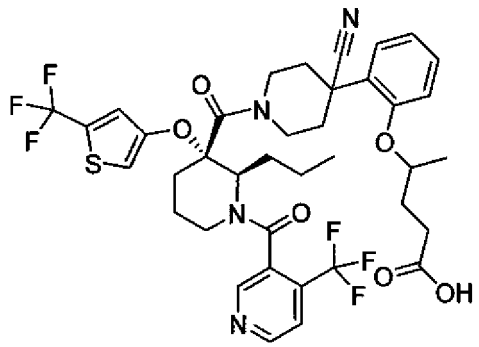
,



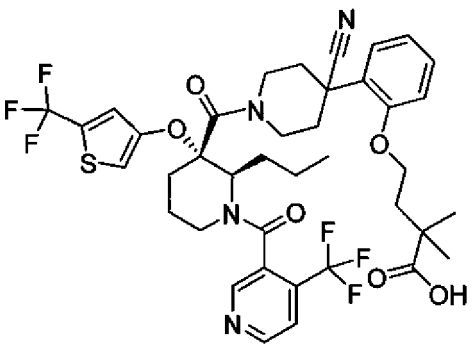
,



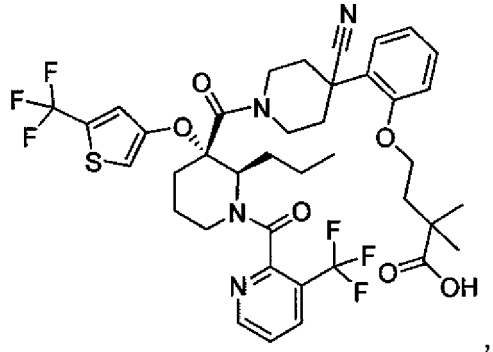
,



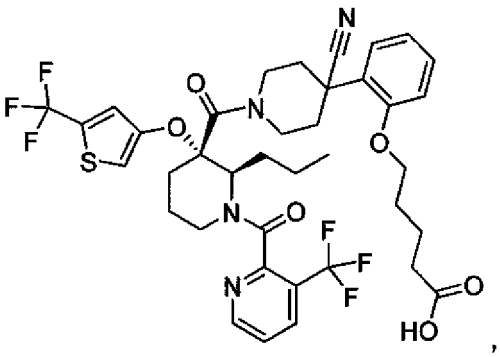
,



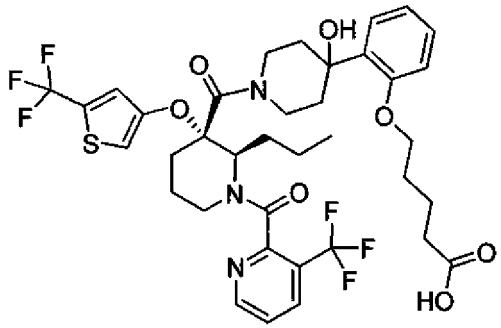
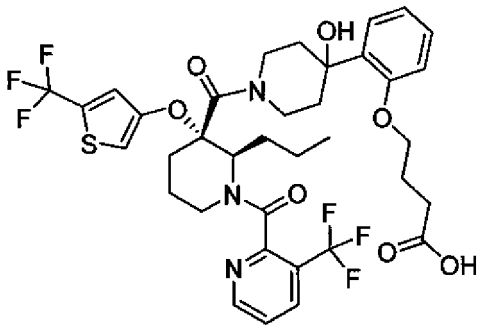
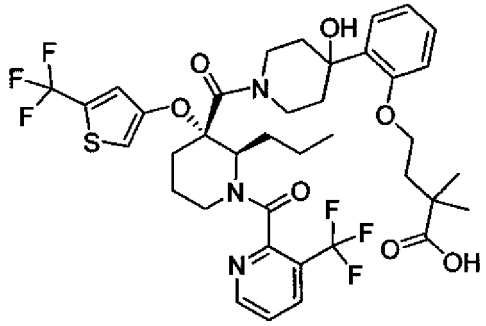
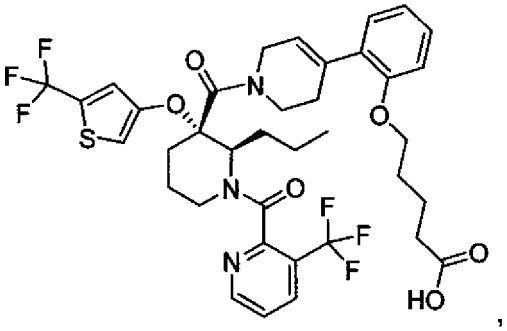
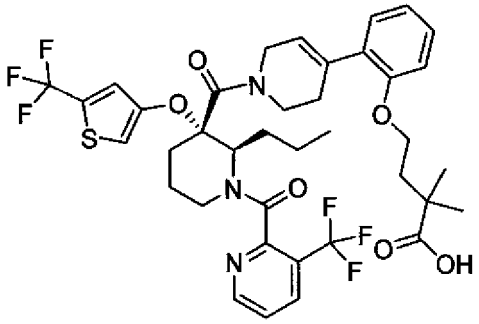
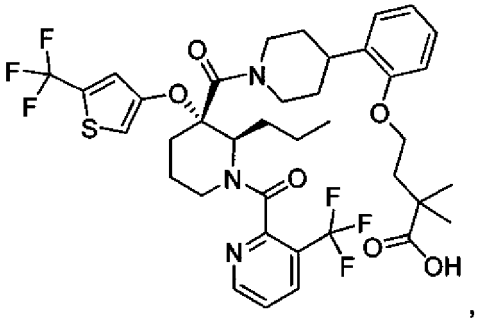
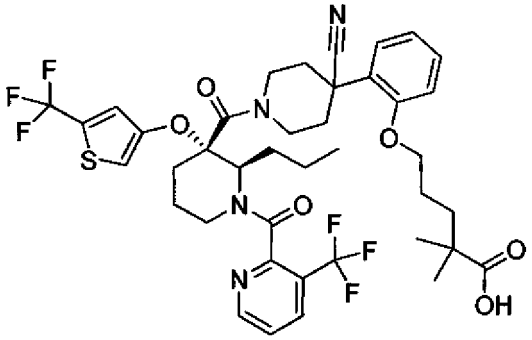
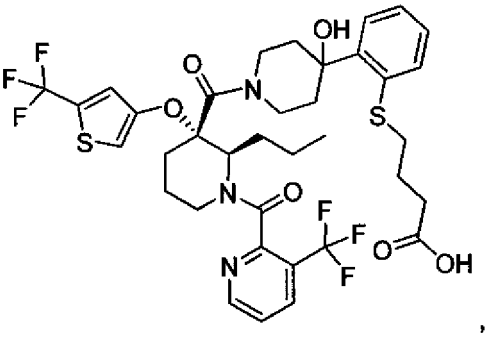
,

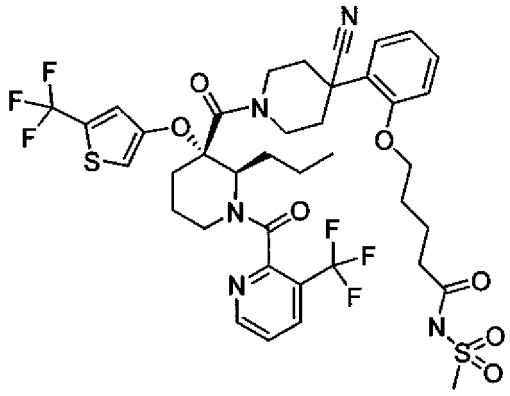


,

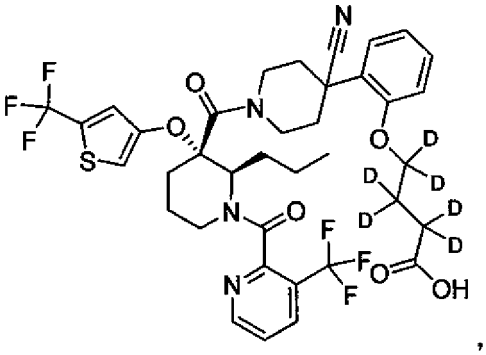


,

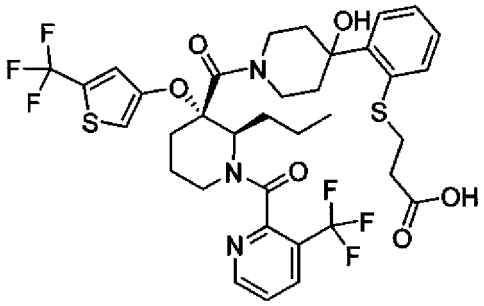

,


,

,

,

,

,

,



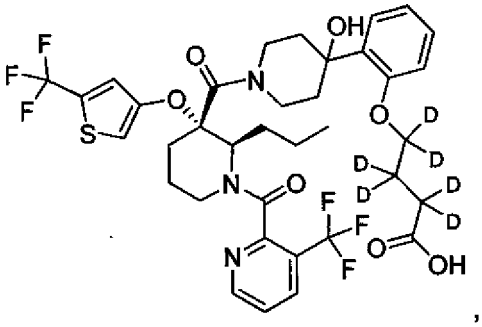
,



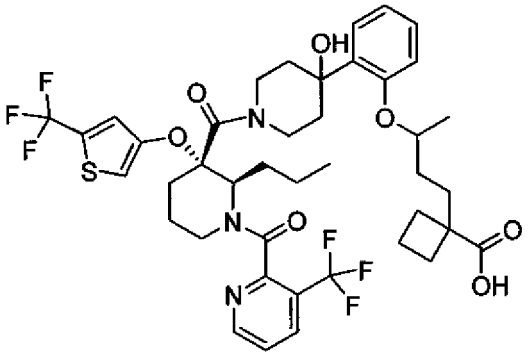
,



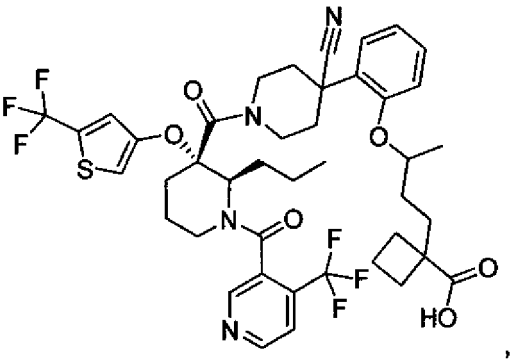
,



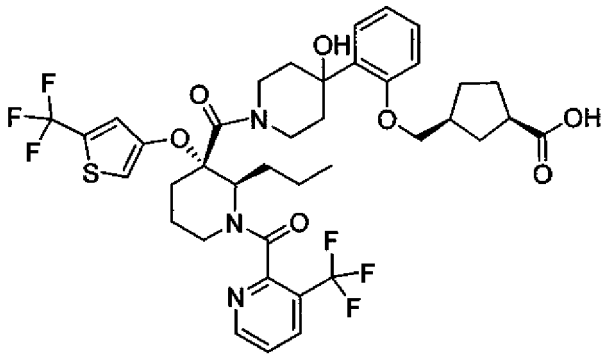
,



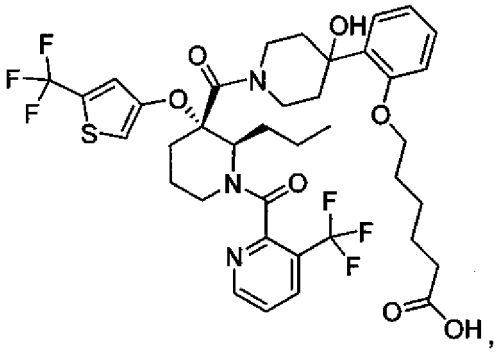
,



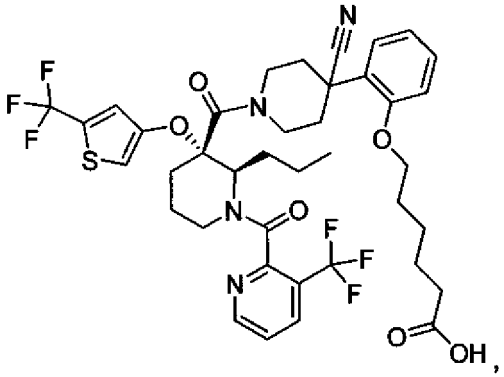
,



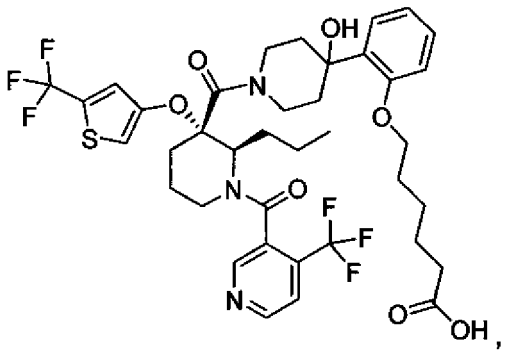
,



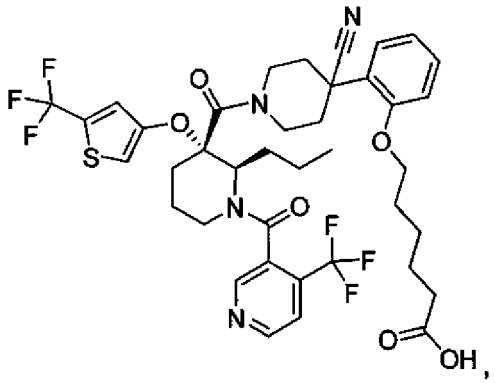
,



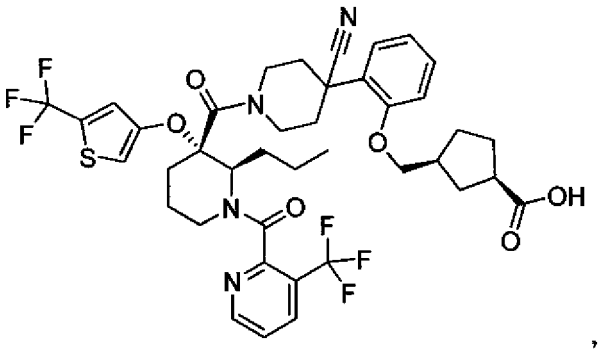
,



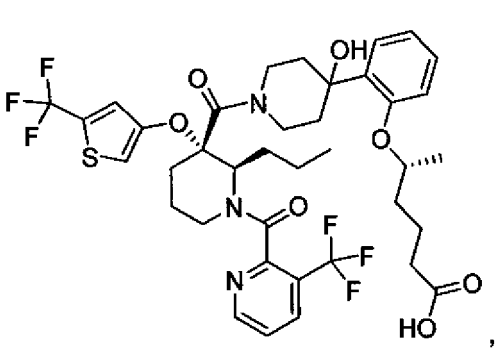
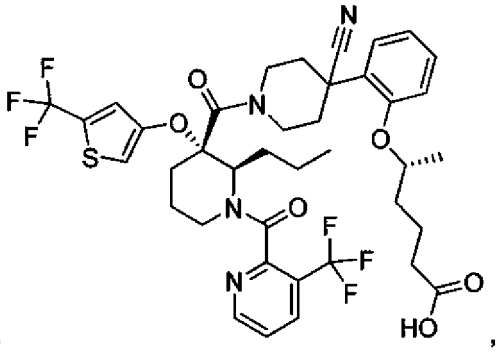
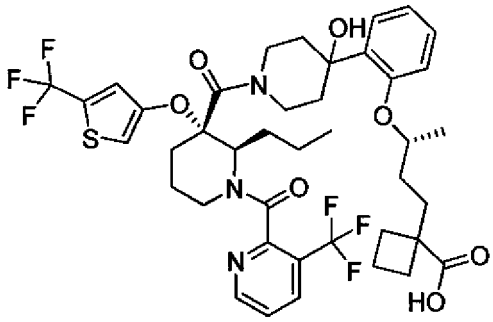
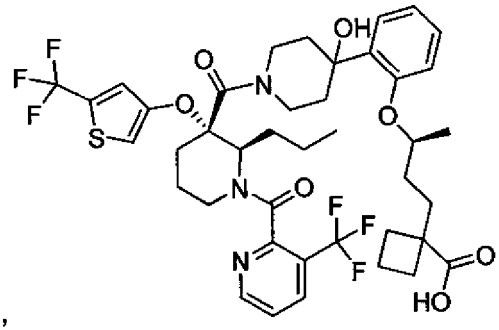
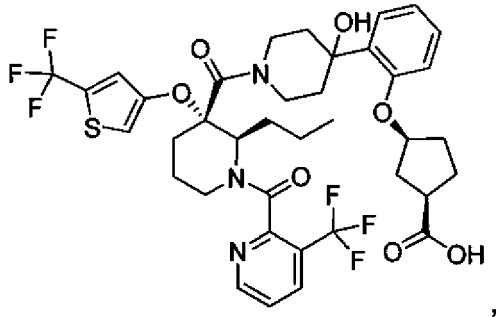
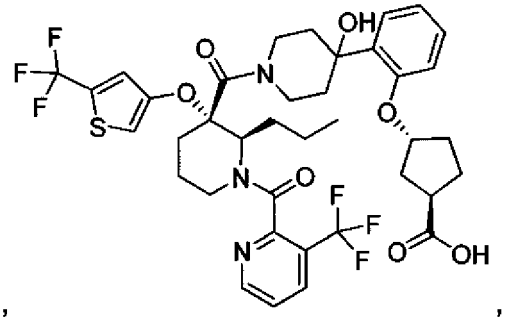
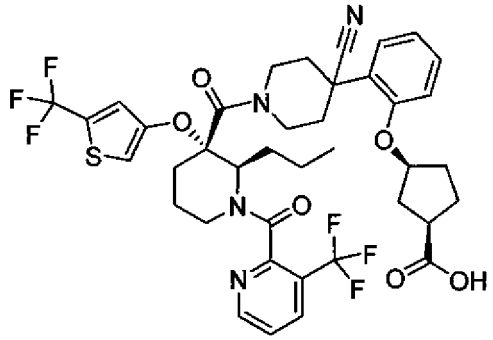
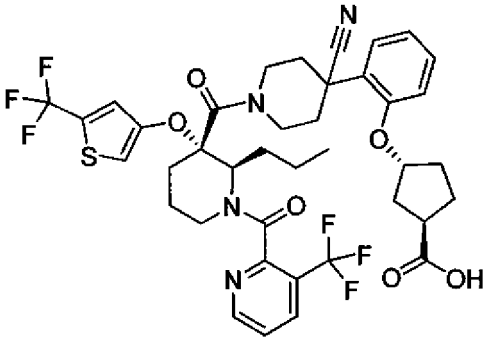
,

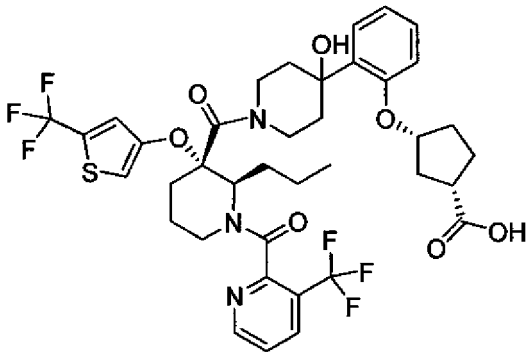
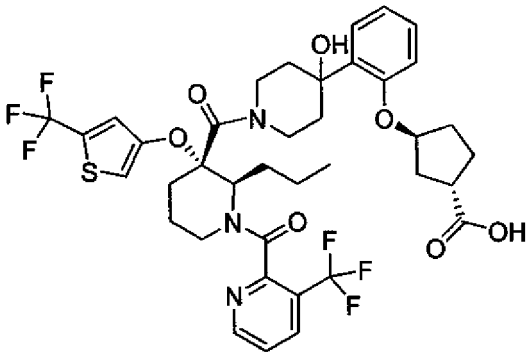
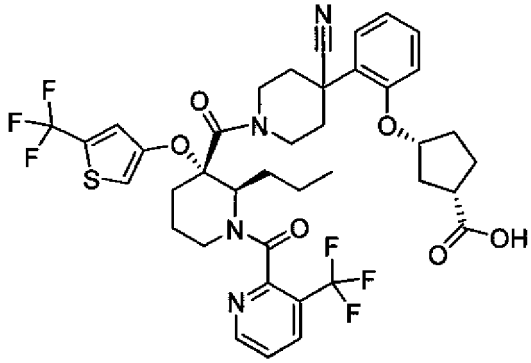
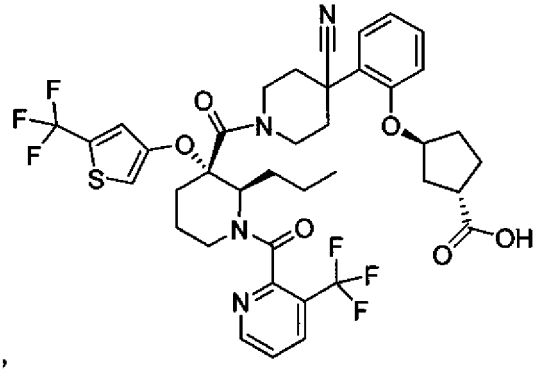
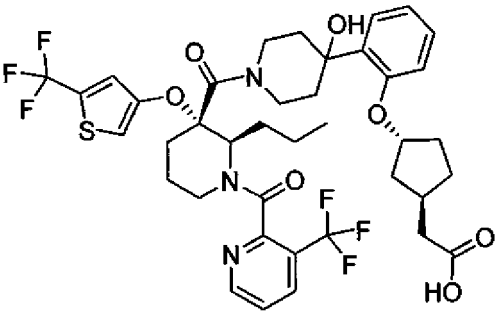
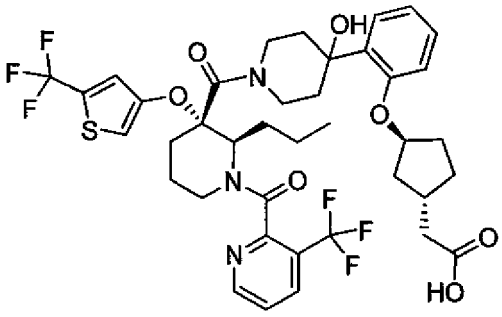
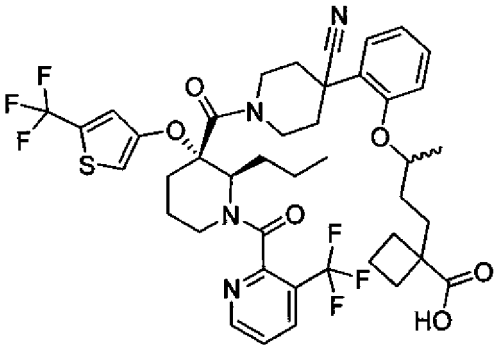
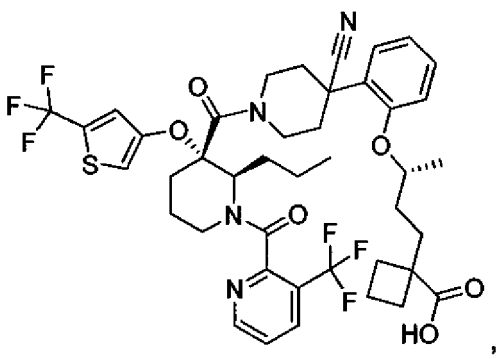


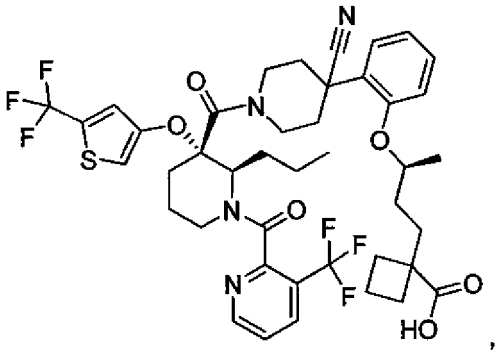
,



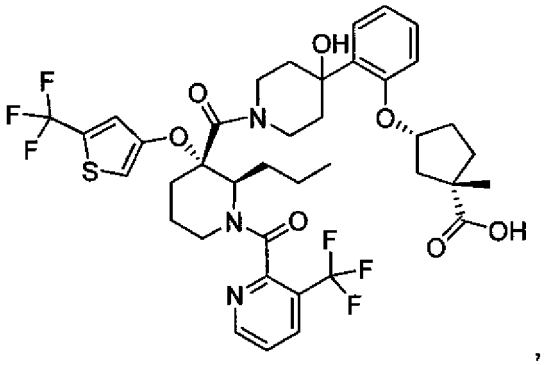
,


,

,

,


,

,

,

,

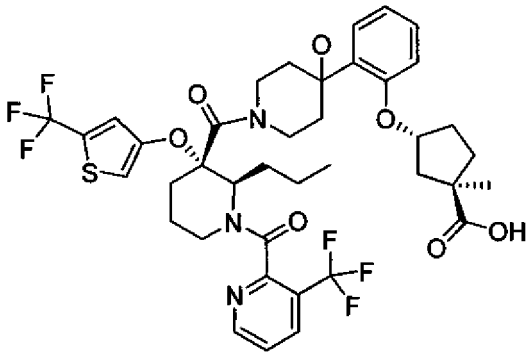

,

,

,

,

,

,

,

,



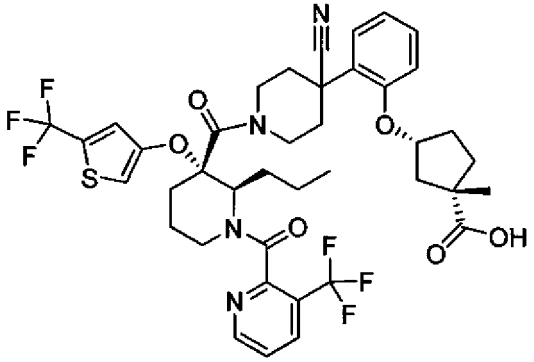
,



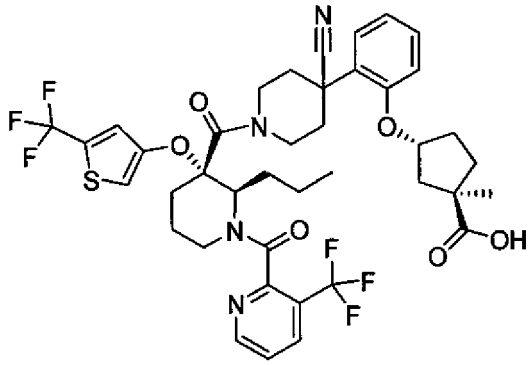
,



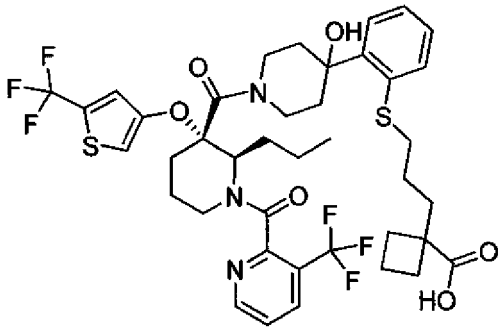
,



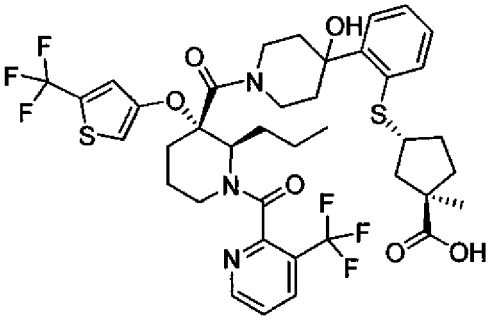
,



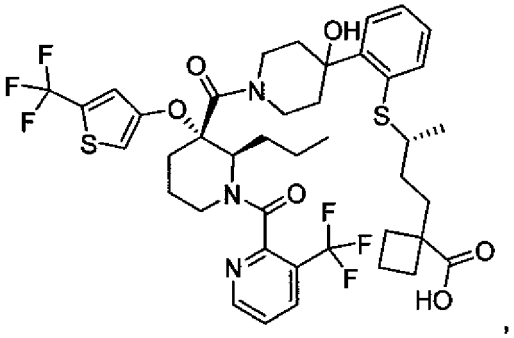
,



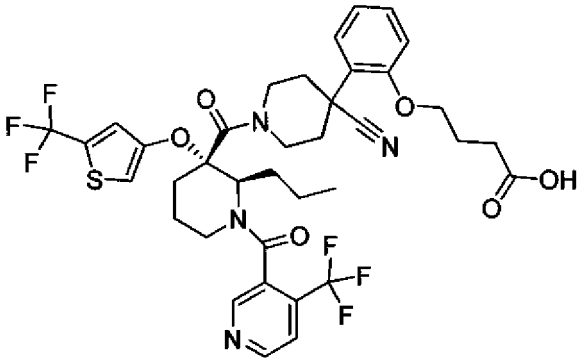
,



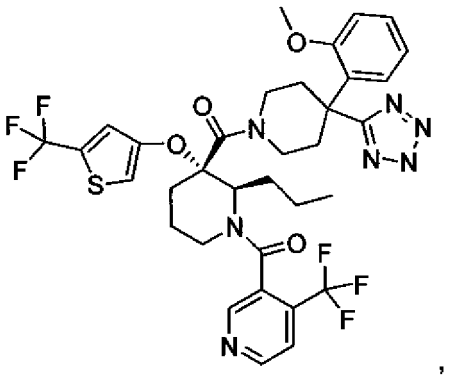
,



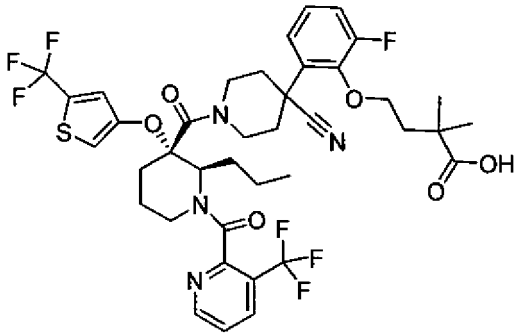
,



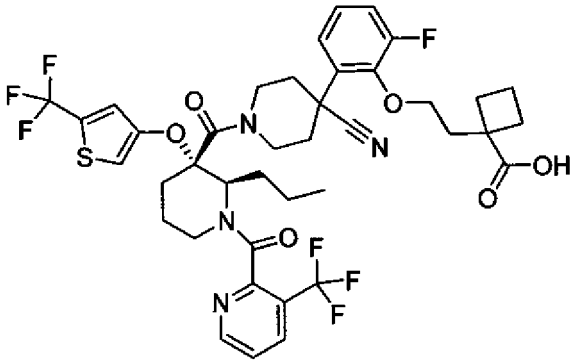
,



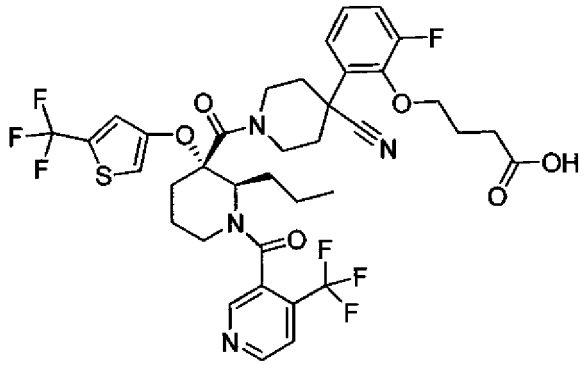
,



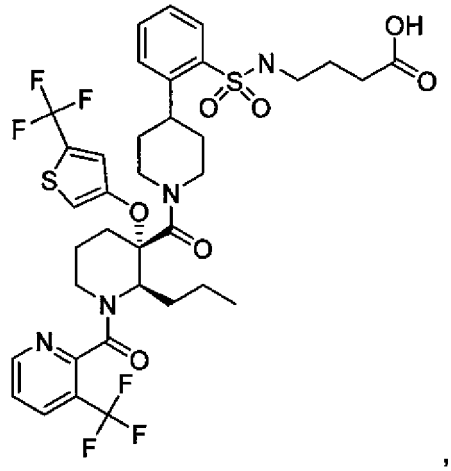
,



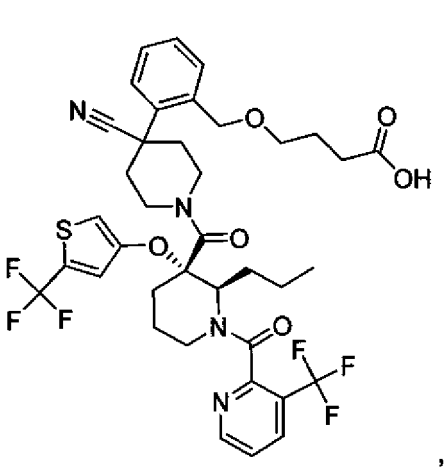
,



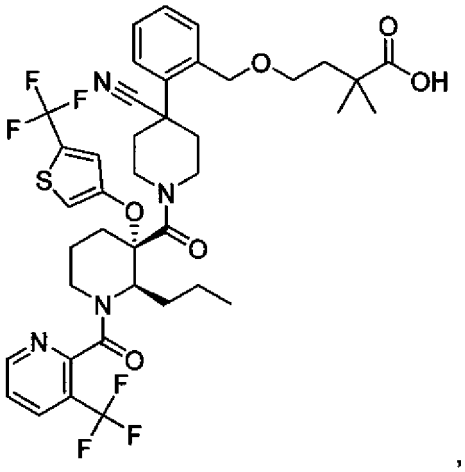
,



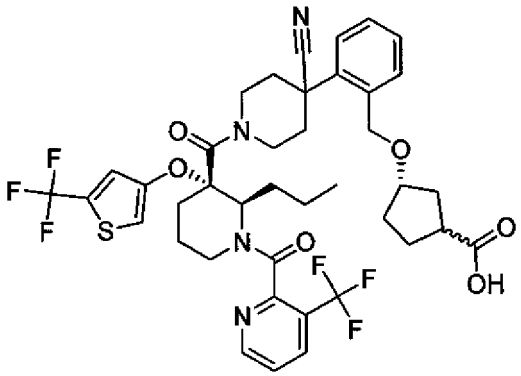
,



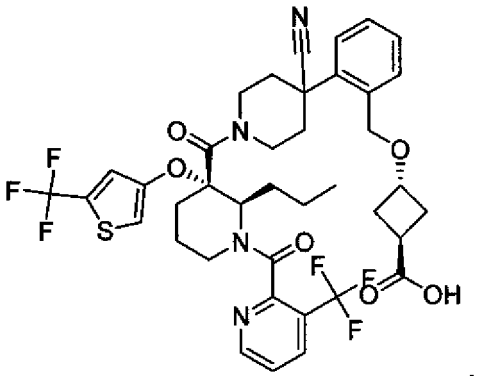
,



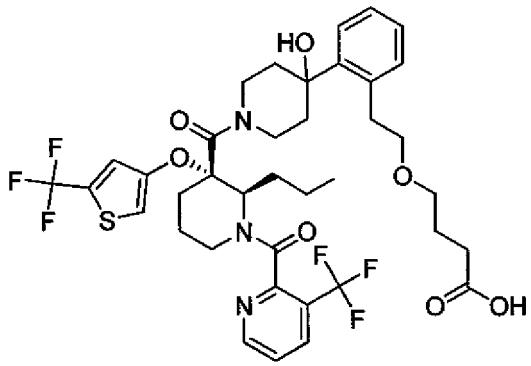
,



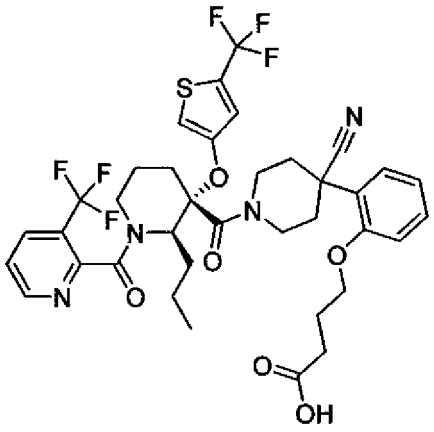
,



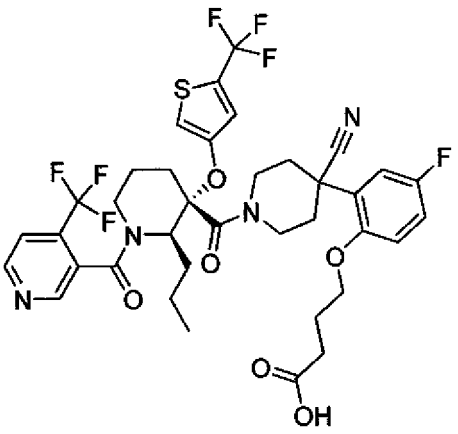
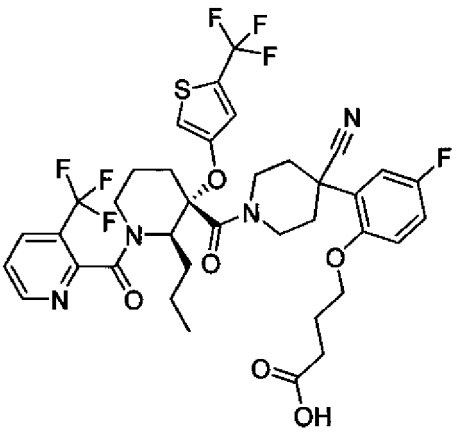
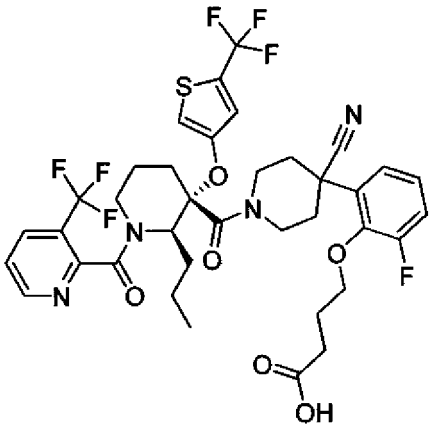
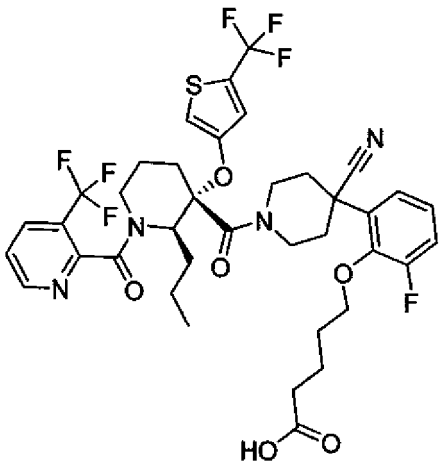
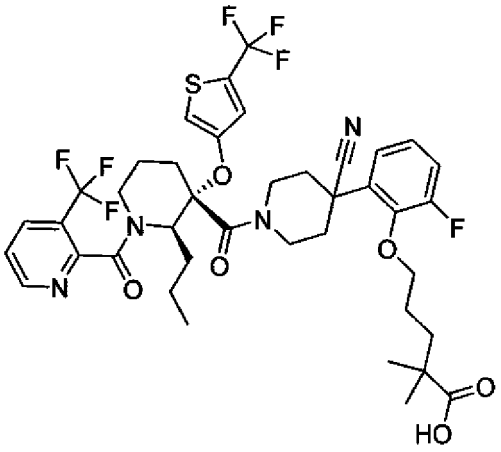
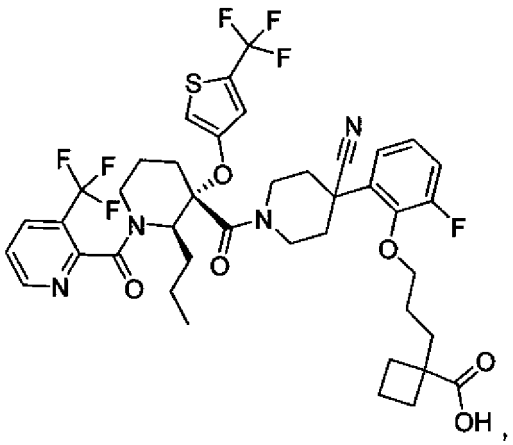
,

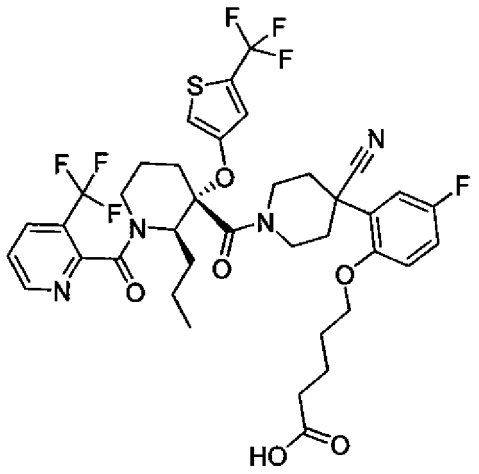


,

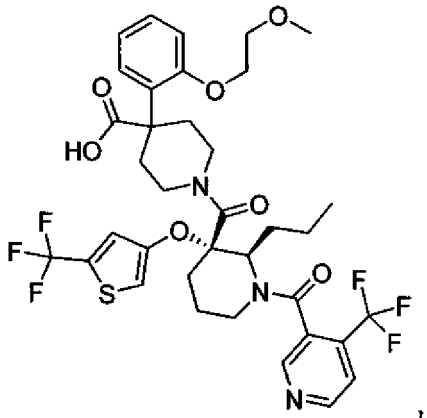


,

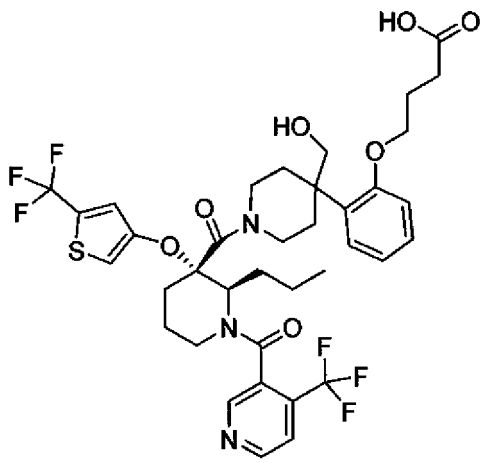

,

,

,

,

,

,



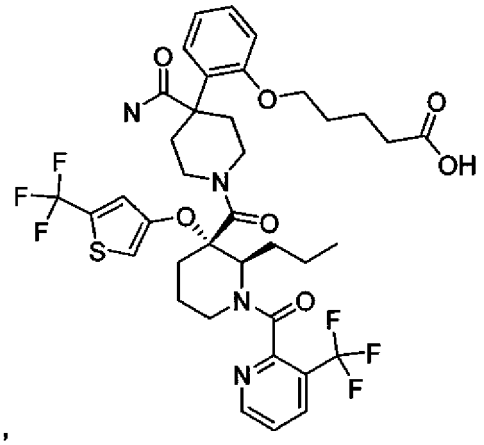
,



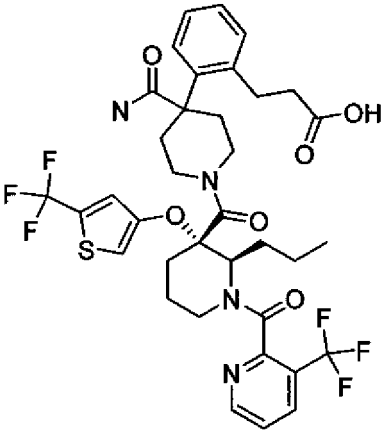
,



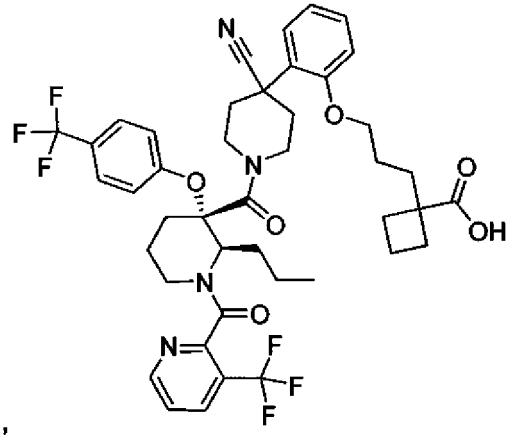
,



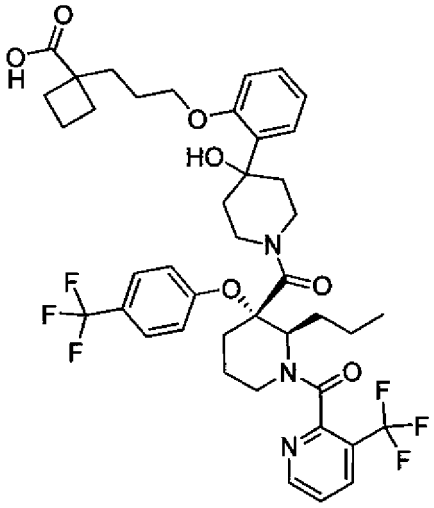
,



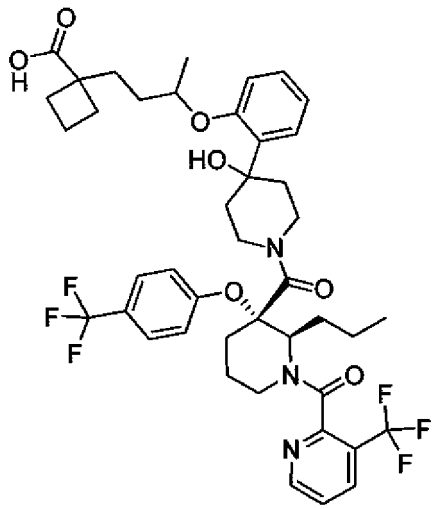
,



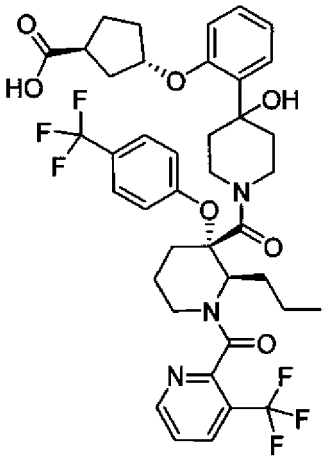
,



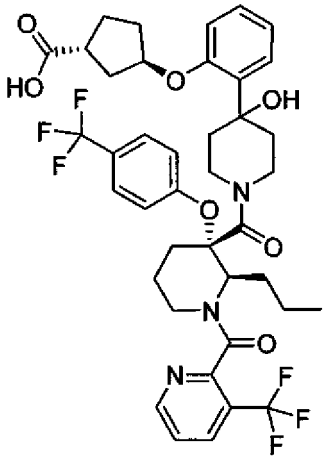
,



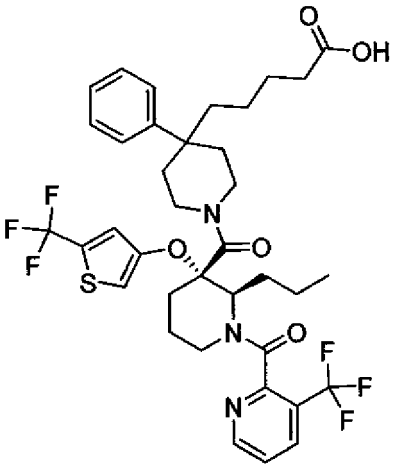
,



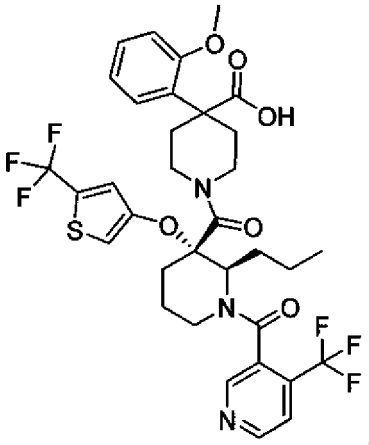
,



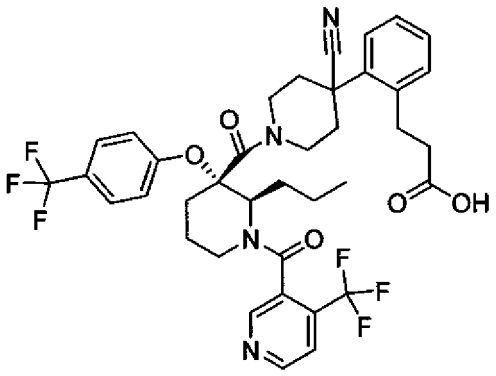
,



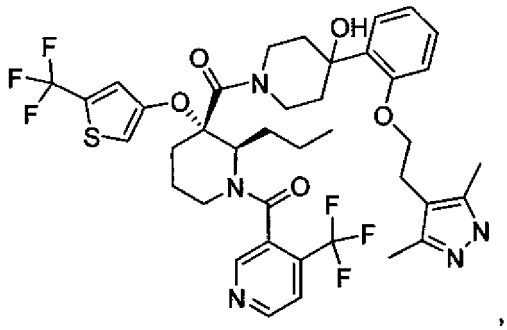
,



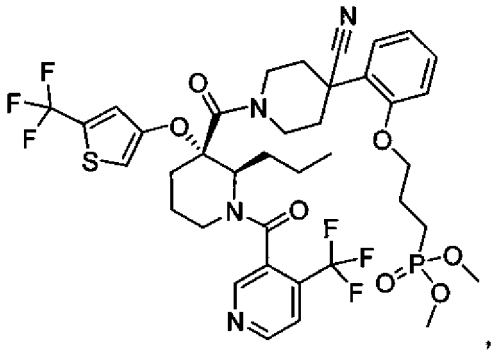
,



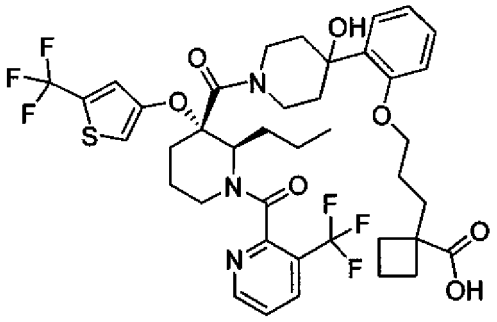
,

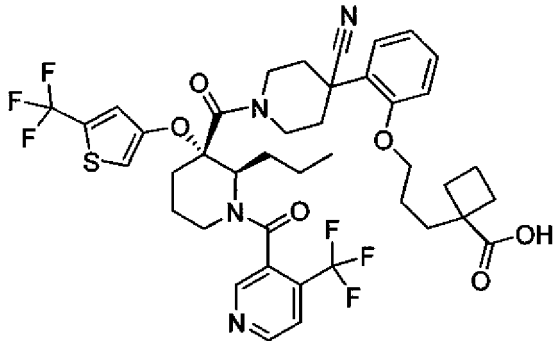


,

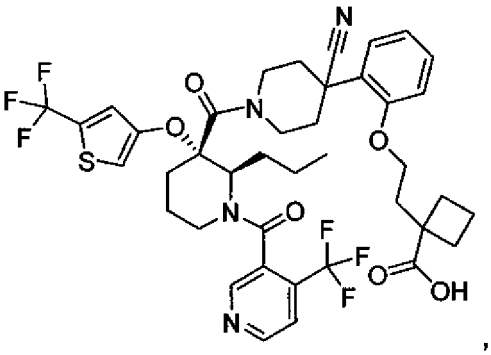


,

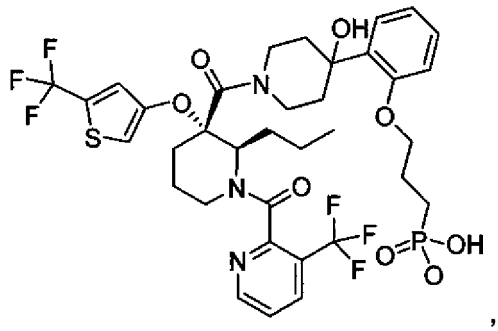




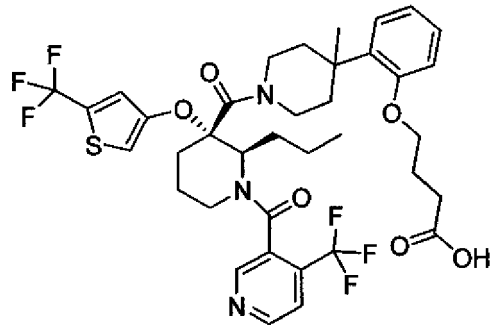
,

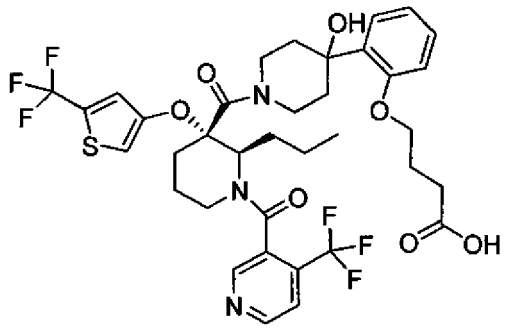
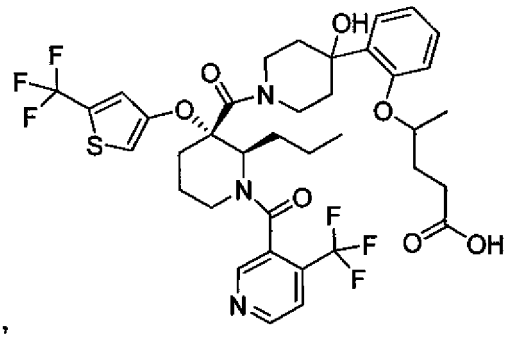
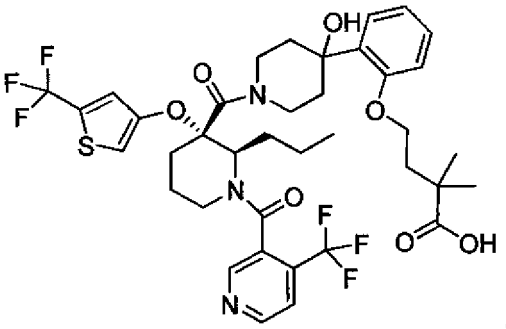
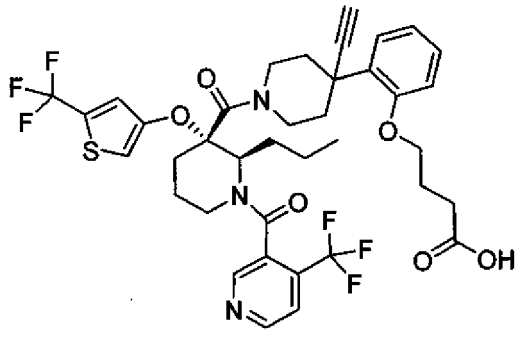
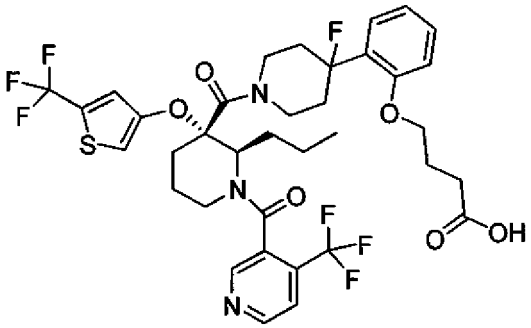
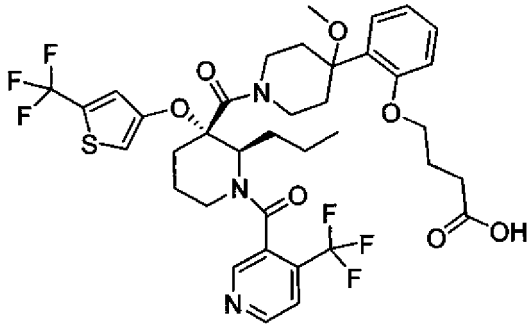
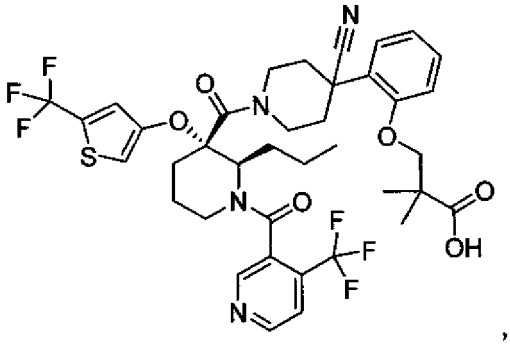


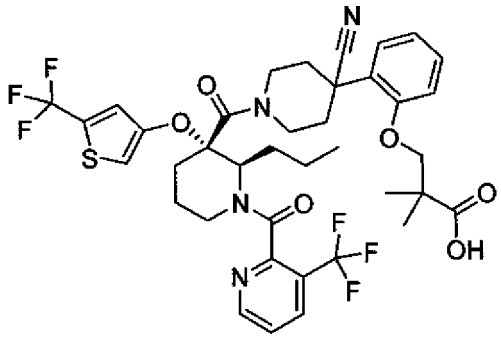
,



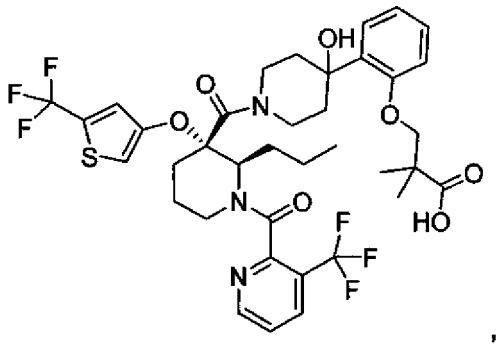
,



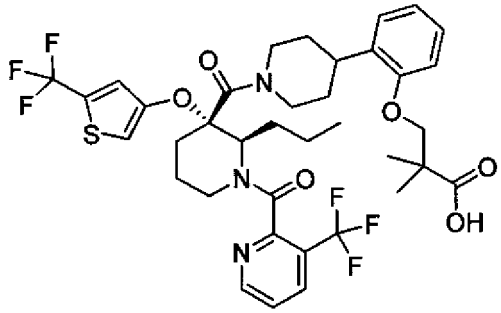

,

,

,

,

,

,

,



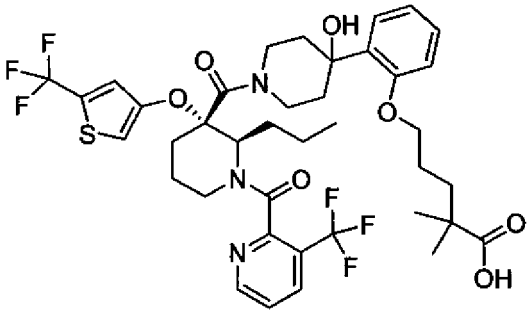
,



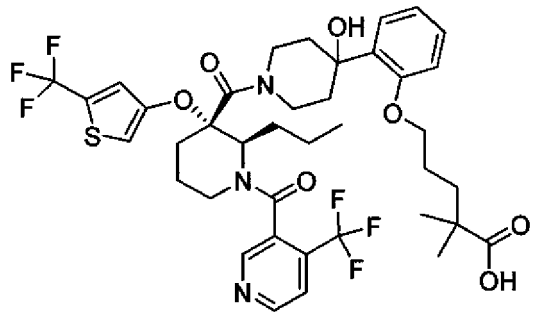
,



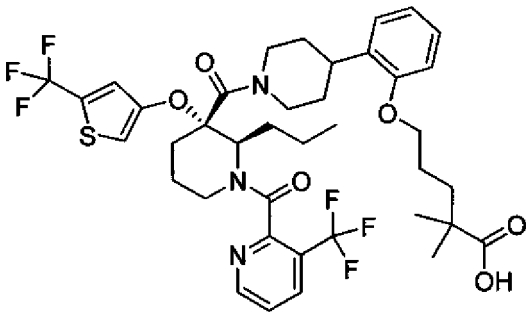
,



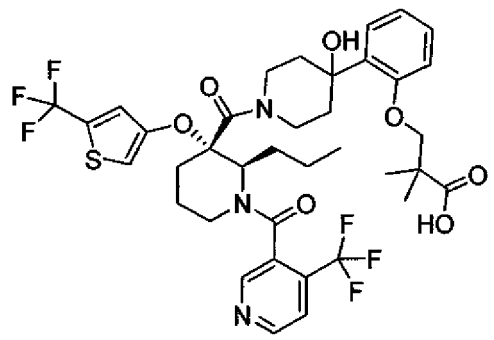
,



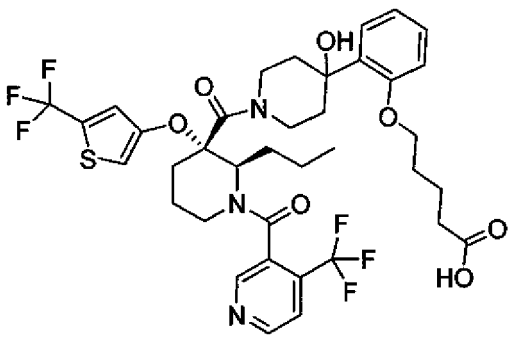
,



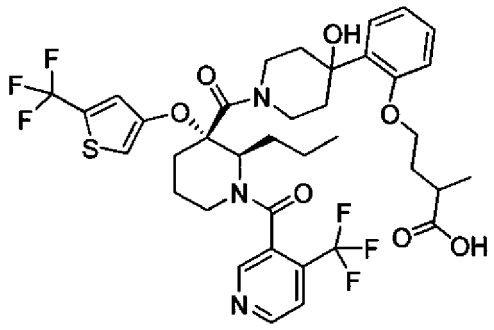
,



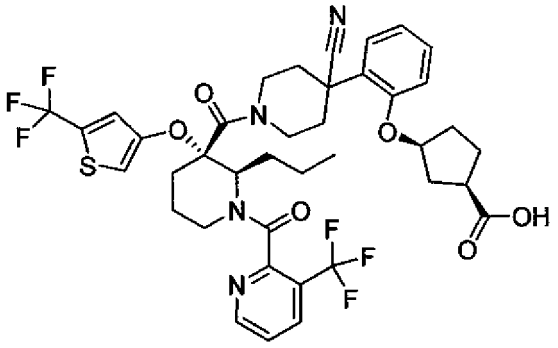
,



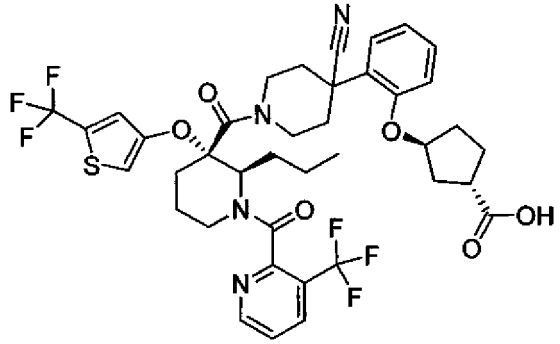
,



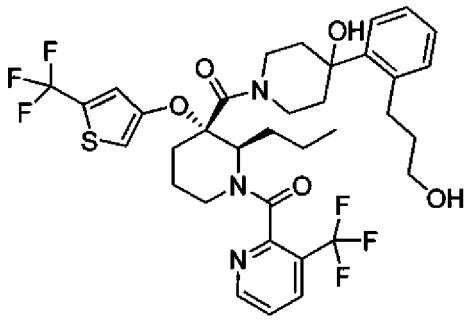
,



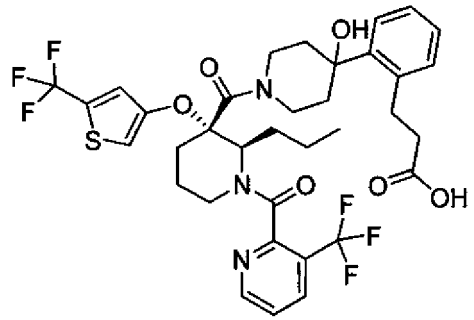
,



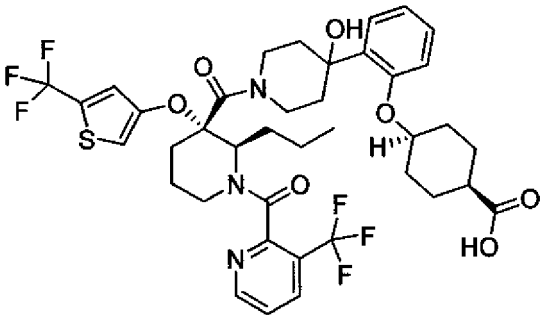
,



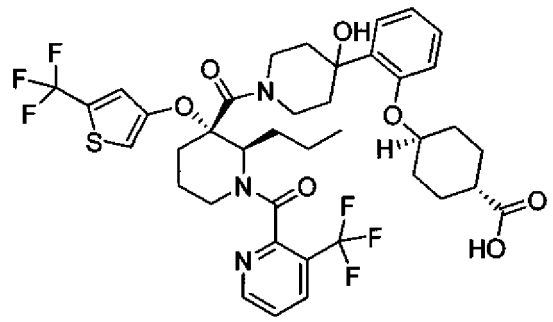
,



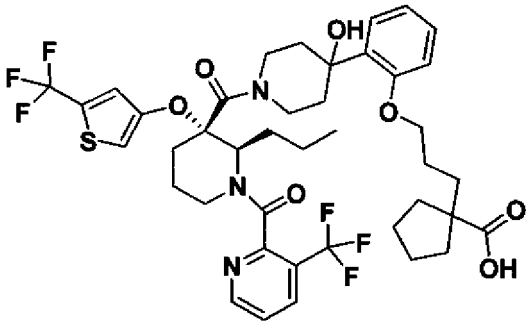
,



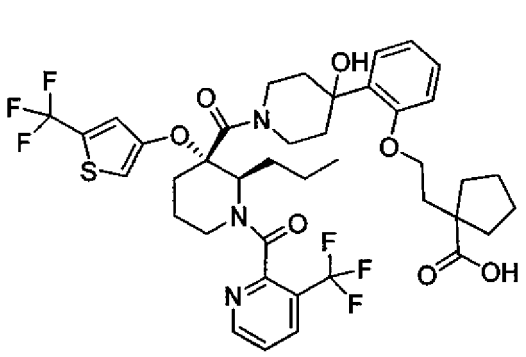
,



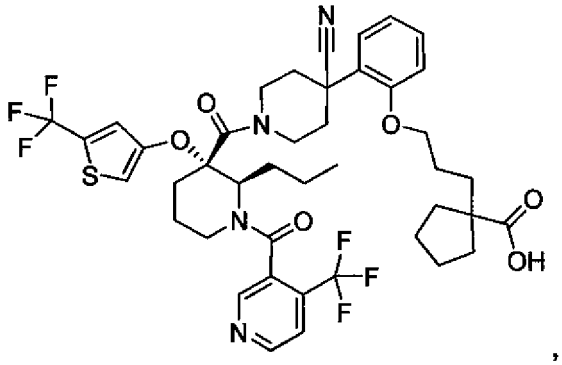
,



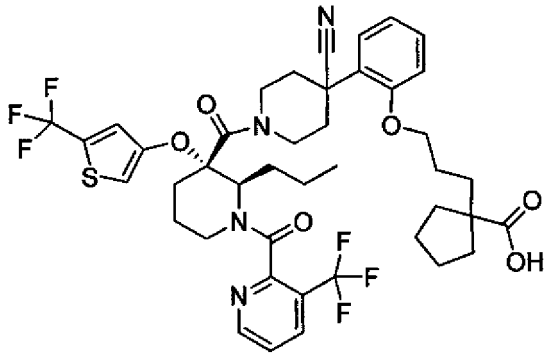
,



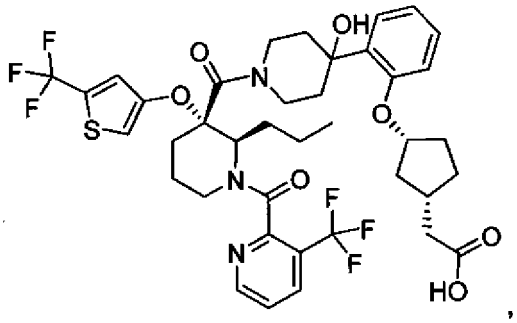
,



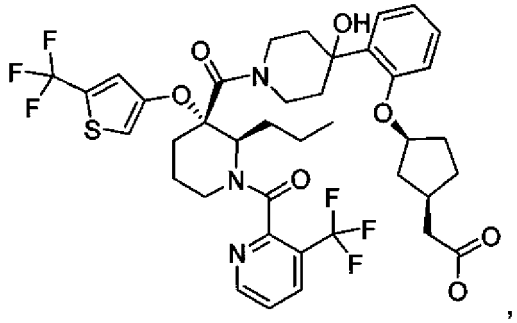
,



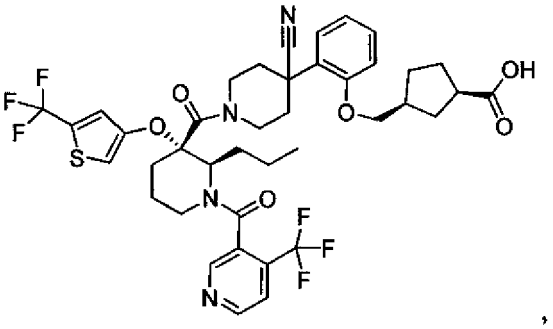
,



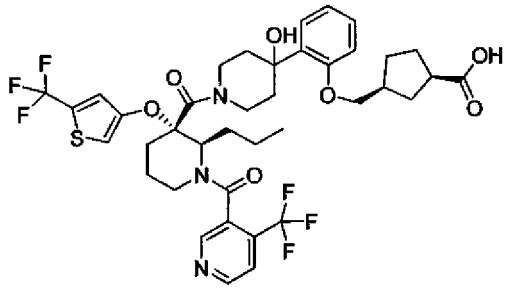
,



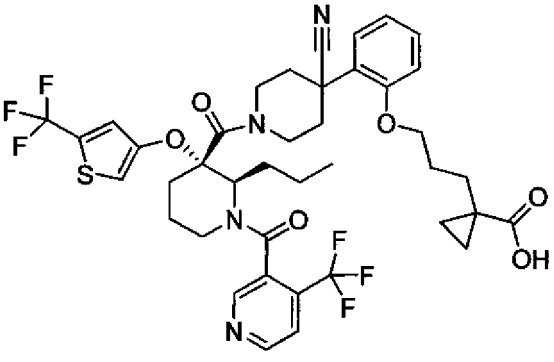
,



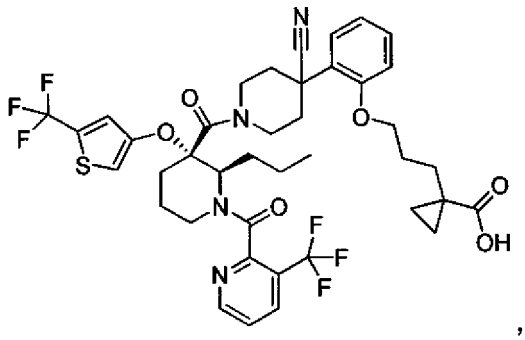
,



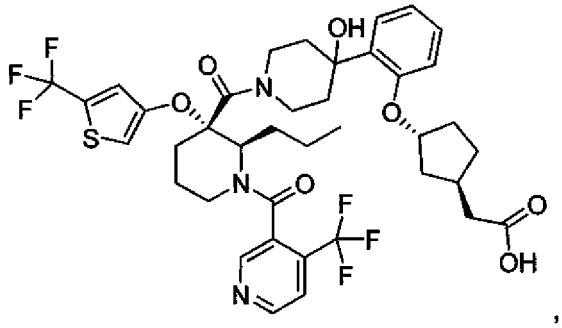
,



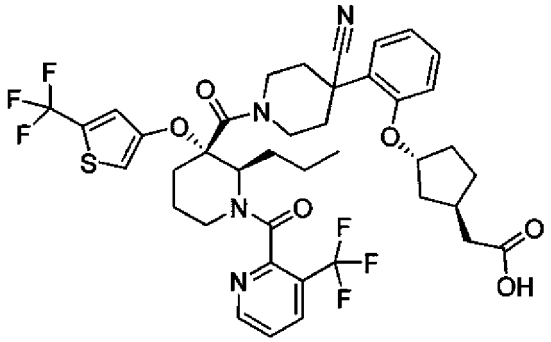
,



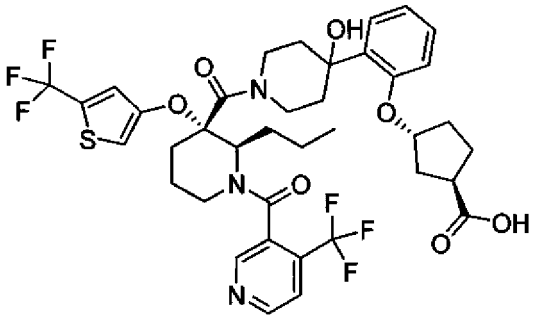
,



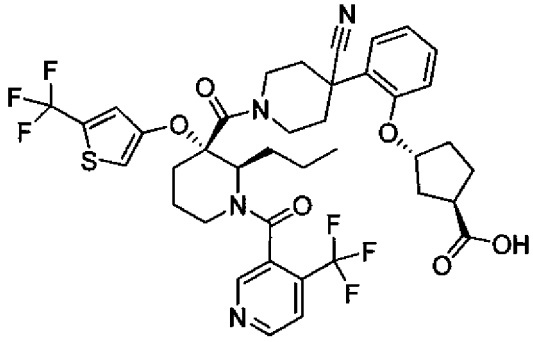
,



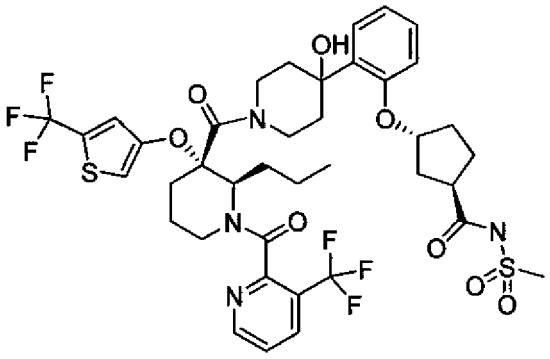
,



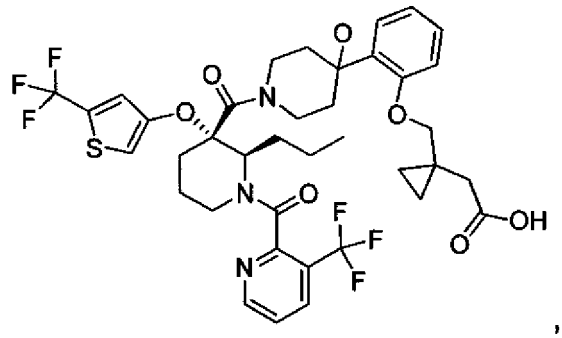
,



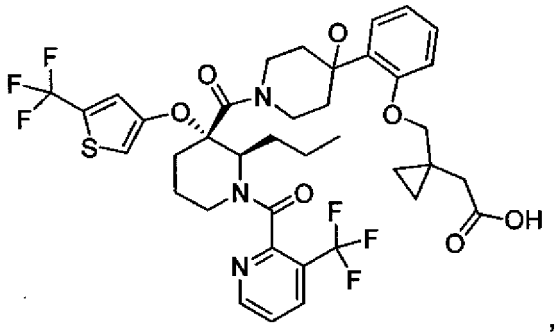
,



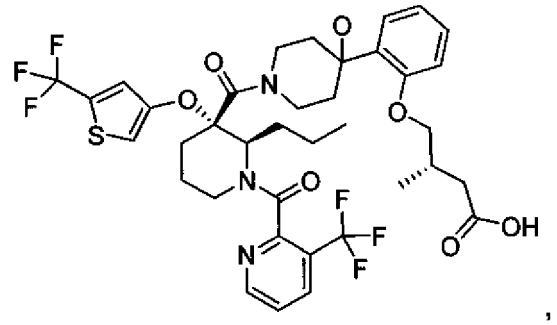
,



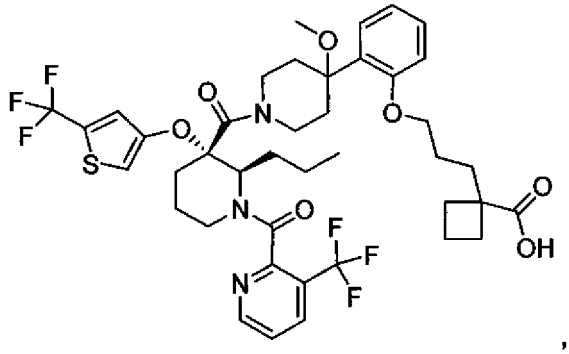
,



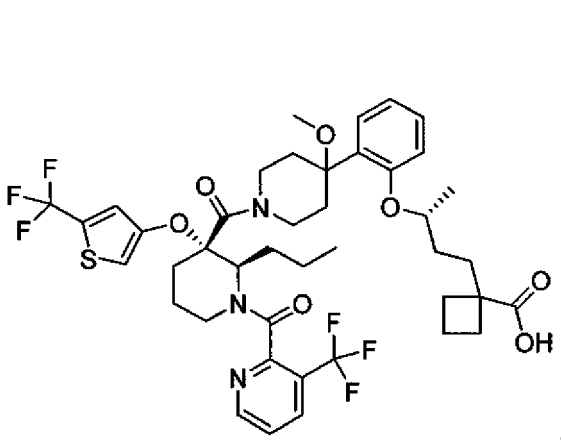
,



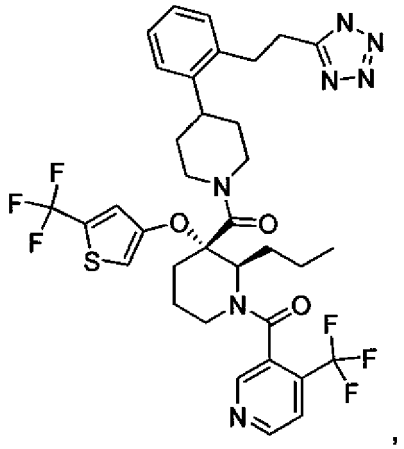
,



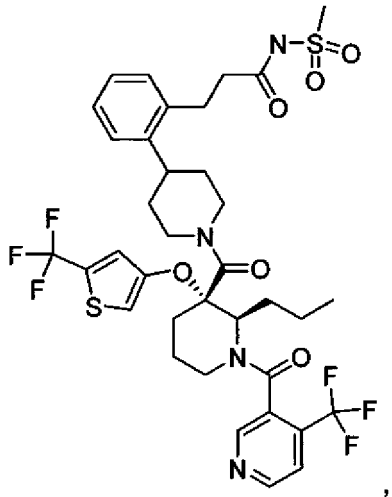
,



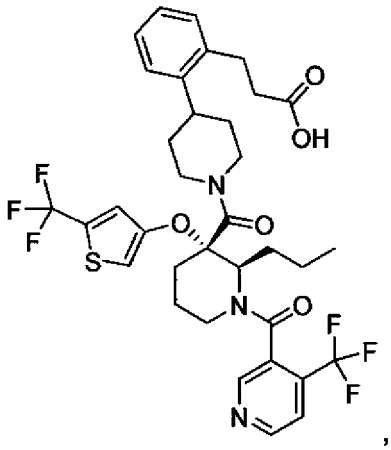
,



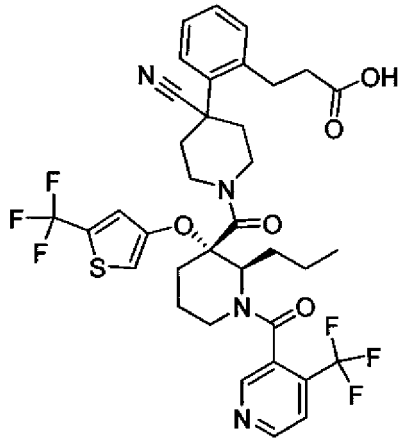
,



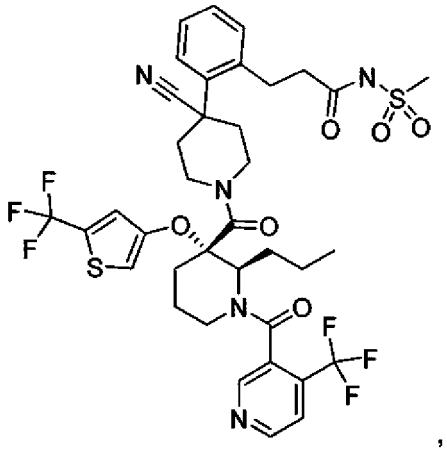
,



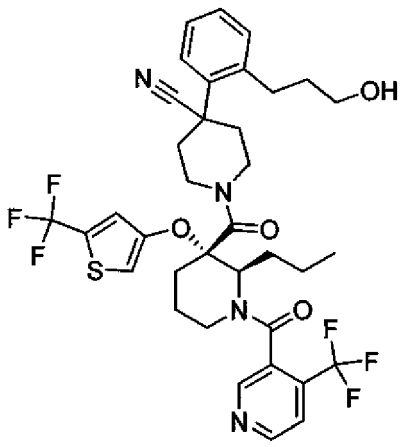
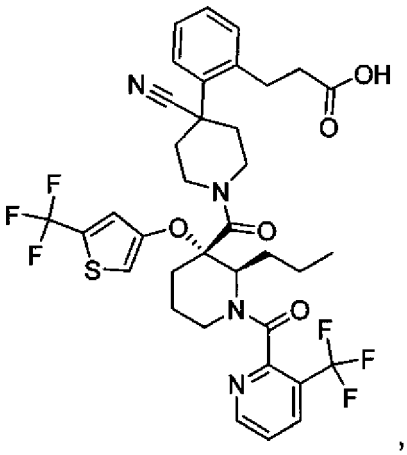
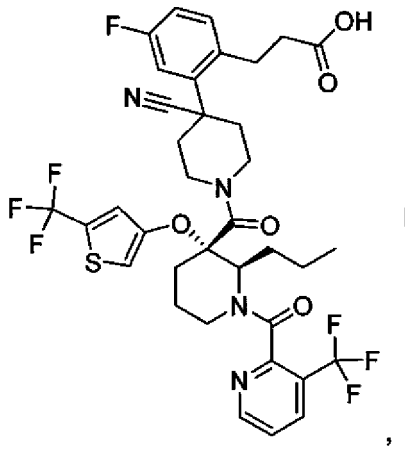
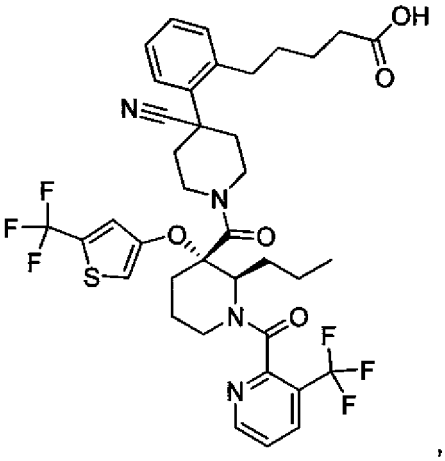
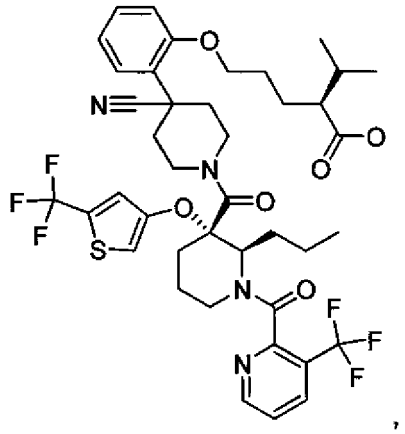
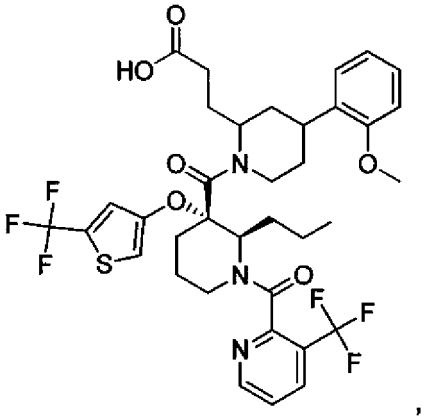
,

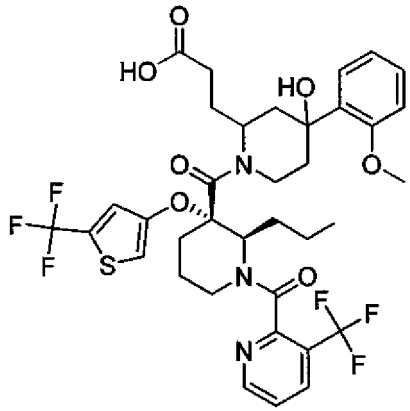


,

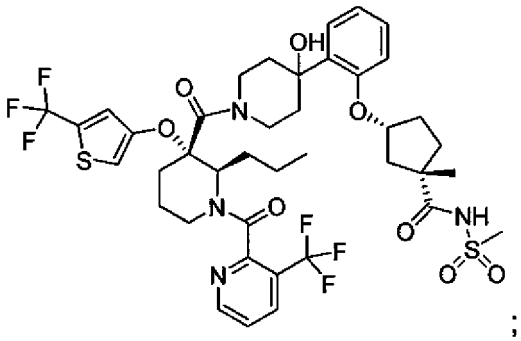


,


,

,

,

,

,

,



, and



;

or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof, in combination with at least one pharmaceutically acceptable carrier.

20. A method of treating a cancer selected from the group consisting of selected from the group consisting of cancer of bladder, breast, colon, rectum, endometrium, kidney, liver, lung, head and neck, esophagus, gall bladder, cervix, pancreas, prostrate, larynx, ovaries, stomach, uterus, sarcoma, osteosarcoma, liposarcoma, thyroid cancer, hematopoietic tumors of the lymphoid lineage, hematopoetic tumors of myeloid lineage, myelogenous leukemias, myelodysplastic syndrome, promyelocytic leukemia, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, skin (non-melanomal) cancer, mesothelioma (cells), seminoma, teratocarcinoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma, in a patient in need of such treatment, comprising administering an effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt thereof.