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(54) **TRICYCLIC SULFONES AS RORγ MODULATORS**

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(51) **Int. Cl.**

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C07D 215/36	(2006.01)
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C07D 417/04	(2006.01)

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CPC ***C07F 9/65742*** (2013.01); ***C07D 209/30*** (2013.01); ***C07D 209/60*** (2013.01); ***C07D 209/70*** (2013.01); ***C07D 215/36*** (2013.01); ***C07D 221/10*** (2013.01); ***C07D 401/06*** (2013.01); ***C07D 401/12*** (2013.01); ***C07D 403/06*** (2013.01); ***C07D 403/12*** (2013.01); ***C07D 405/06*** (2013.01); ***C07D 409/04*** (2013.01); ***C07D 409/06*** (2013.01); ***C07D 413/06*** (2013.01); ***C07D 413/10*** (2013.01); ***C07D 413/12*** (2013.01); ***C07D 417/04*** (2013.01); ***C07D 417/06*** (2013.01); ***C07D 417/12*** (2013.01); ***C07D 417/14*** (2013.01); ***C07D 471/04*** (2013.01); ***C07D 491/052*** (2013.01); ***C07D 491/107*** (2013.01); ***C07D 493/08*** (2013.01); ***C07D 495/04*** (2013.01); ***C07D 495/08*** (2013.01)

(58) **Field of Classification Search**

USPC 514/110, 557, 568, 572

See application file for complete search history.

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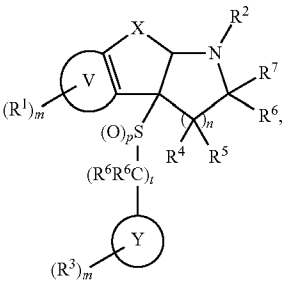
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(57) **ABSTRACT**

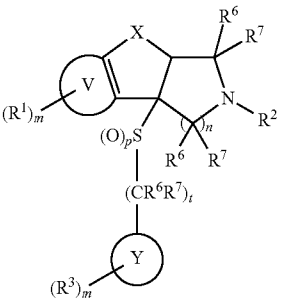
There are described RORγ modulators of the formula (I),

(I)



and formula (II)

(II)



or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein all substituents are defined herein. Also provided are pharmaceutical compositions comprising the same. Such compounds and compositions are useful in methods for modulating RORγ activity in a cell and methods for treating a subject suffering from a disease or disorder in which the subject would therapeutically benefit from modulation of RORγ activity, for example, autoimmune and/or inflammatory disorders.

15 Claims, No Drawings

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TRICYCLIC SULFONES AS RORγ MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application No. 62/158,178 filed May 7, 2015, the disclosures of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to modulators of the retinoid-related orphan receptor RORγ and methods for using said modulators. The compounds described herein can be particularly useful for diagnosing, preventing, or treating a variety of diseases and disorders in humans and animals. Exemplary disorders include, but are not limited to, psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, acute graft-versus-host disease, psoriatic arthritis, ankylosing spondylitis and multiple sclerosis.

BACKGROUND OF THE INVENTION

The retinoid-related orphan receptors, RORα, RORβ, and RORγ, play an important role in numerous biological processes including organ development, immunity, metabolism, and circadian rhythms. See, for example, Dussault et al. in Mech. Dev. (1998) vol. 70, 147-153; Andre et al. in EMBO J. (1998) vol. 17, 3867-3877; Sun et al. in Science (2000) vol. 288, 2369-2373; and Jetten in Nucl. Recept. Signal. (2009) vol. 7, 1-32.

RORγ is expressed in several tissues including the thymus, kidney, liver, and muscle. Two isoforms of RORγ have been identified: RORγ1 and RORγ 2 (also known, respectively, as RORγ and RORγt). See, for example, Hirose et al. in Biochem. Biophys. Res. Commun. (1994) vol. 205, 1976-1983; Oritz et al. in Mol. Endocrinol. (1995) vol. 9, 1679-1691; and He et al. in Immunity (1998) vol. 9, 797-806. Expression of RORγt is restricted to lymphoid cell types including CD_4+CD_8+ thymocytes, IL-17 producing T helper (Th17) cells, lymphoid tissue inducer (LTi) cells, and γδ cells. RORγt is essential for the development of lymph nodes and Peyer's patches and for the normal differentiation of Th17, γδ, and LTi cells. See, for example, Sun et al. in Science (2000) vol. 288, 2369-2373; Ivanov et al. in Cell (2006) vol. 126, 1121-1133; Eberl et al. in Nat. Immunol. (2004) vol. 5, 64-73; Ivanov et al. in Semin. Immunol. (2007) vol. 19, 409-417; and Cua and Tato in Nat. Rev. Immunol. (2010) vol. 10, 479-489.

Proinflammatory cytokines such as IL-17A (also referred to as IL-17), IL-17F, and IL-22 produced by Th17 cells and other RORγ+ lymphocytes activate and direct the immune response to extracellular pathogens. See, for example, Ivanov et al. in Semin. Immunol. (2007) vol. 19: 409-417; and Marks and Craft in Semin. Immunol. (2009) vol. 21, 164-171. RORγ directly regulates IL-17 transcription and disruption of RORγ in mice attenuates IL-17 production. See, for example, Ivanov et al. in Cell (2006) vol. 126, 1121-1133.

Dysregulated production of IL-17 has been implicated in several human autoimmune and inflammatory diseases including multiple sclerosis, rheumatoid arthritis, psoriasis, inflammatory bowel disease (IBD), and asthma. See, for example, Lock et al. in Nat. Med. (2002) vol. 8, 500-508; Tzartos et al. in Am. J. Pathol. (2008) vol. 172, 146-155; Kotake et al. in J. Clin. Invest. (1999) vol. 103, 1345-1352; Kirkham et al. in Arthritis Rheum. (2006) vol. 54, 1122-1131; Lowes et al. in J. Invest. Dermatol. (2008) vol. 128, 1207-1211; Leonardi et al. in N. Engl. J. Med. (2012) vol. 366, 1190-1199; Fujino et al. in Gut (2003) vol. 52, 65-70; Seiderer et al. in Inflamm. Bowel Dis. (2008) vol. 14, 437-445; Wong et al. in Clin. Exp. Immunol. (2001) vol. 125, 177-183; and Agache et al. in Respir. Med. (2010) 104: 1131-1137. In murine models of these diseases, inhibition of IL-17 function by neutralizing antibodies or genetic disruption of IL-17 or IL-17 receptor ameliorates the disease course or clinical symptoms. See, for example, Hu et al. in Ann. N.Y. Acad. Sci. (2011) vol. 1217, 60-76.

Disruption of RORγ in mice also attenuates disease progression or severity in animal models of autoimmunity and inflammation including experimental autoimmune encephalomyelitis (EAE), imiquimod induced psoriasis, colitis, and allergic airway disease. See, for example, Ivanov et al. in Cell (2006) vol. 126, 1121-1133; Yang et al. in Immunity (2008) vol. 28, 29-39; Pantelyushin et al. in J. Clin. Invest. (2012) vol. 122, 2252-2256; Leppkes et al. in Gastroenterology (2009) vol. 136, 257-267; and Tilley et al. in J. Immunol. (2007) vol. 178, 3208-3218.

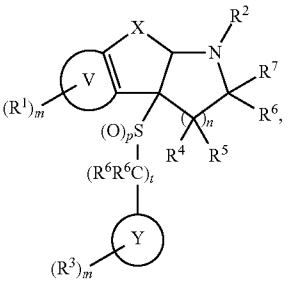
Each of the references in this Background section is hereby incorporated herein by reference in its entirety for all purposes.

Therapeutic agents exist to treat a variety of inflammatory and autoimmune diseases, but there still remains a significant unmet medical need in these therapeutic areas. Given the role of IL-17 in human disease and the validation of IL-17 and RORγ as targets in murine disease models, compounds capable of modulating RORγt activity are contemplated to provide a therapeutic benefit in the treatment of multiple immune and inflammatory disorders.

SUMMARY OF THE INVENTION

In one aspect, the invention comprises compounds of the formula (I),

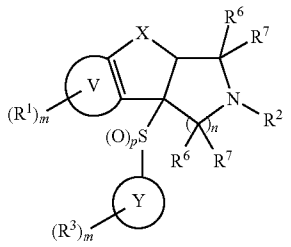
(I)



or pharmaceutically acceptable salts thereof, wherein all substituents are defined herein. The invention includes stereoisomers, tautomers, solvates, or prodrugs thereof.

In another aspect, the invention comprises compounds of the formula (II),

(II)



or pharmaceutically acceptable salts thereof, wherein all substituents are defined herein. The invention includes stereoisomers, tautomers, solvates, or prodrugs thereof.

In another aspect, the invention comprises pharmaceutical compositions comprising a compound according to formula (I), stereoisomeric form or pharmaceutically acceptable salt, as described herein, and a pharmaceutically acceptable carrier, excipient, or diluent.

In another aspect, the invention comprises methods for modulating RORγ in a cell comprising contacting the cell with an effective amount of a compound according to formula (I), stereoisomeric form or pharmaceutically acceptable salt, as described herein. This aspect may be conducted in vitro or in vivo.

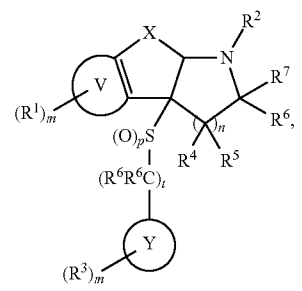
In another aspect, the invention comprises methods for treating a subject suffering from a disease or disorder modulated by RORγ, the method comprising administering to a subject a therapeutically effective amount of a compound according to formula (I), stereoisomeric form, pharmaceutically acceptable salt or pharmaceutical composition as described herein.

In another aspect, the invention comprises a method for treating a disease or disorder selected from an inflammatory disease or disorder, an autoimmune disease or disorder, an allergic disease or disorder, a metabolic disease or disorder, and/or cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a compound according to formula (I), or a stereoisomeric form, pharmaceutically acceptable salt or pharmaceutical composition as described herein.

DETAILED DESCRIPTION OF THE INVENTION

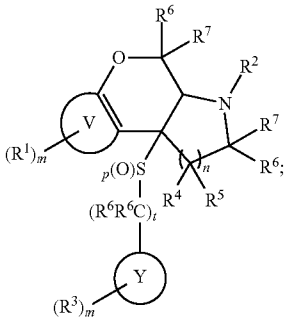
In one aspect, the invention comprises compounds of formula (I),

I



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

X is $—CR^4R^5—$, $—(CR^4R^5)_2$, $—OCR^6R^7—$, $—S(O)_pCR^6R^7—$ or $—NR^6CR^6R^7—$; wherein when X is $—OCR^6R^7—$, $—S(O)_pCR^6R^7—$ or $—NR^6CR^6R^7—$; the structure contemplated, for e.g. when X is $—OCR^6R^7—$, would be



V and Y are independently 5 or 6-membered aromatic or heteroaromatic rings;

R^1 is, independently at each occurrence, selected from hydrogen, CD_3, halo, OCF_3, CN, $—O(C_1$-$C_6)$alkyl, $—O(C_1$-$C_6)$alkyl-OH, -alkoxyalkoxy (e.g. $—O—CH_2CH_2OCH_3$), $S(O)_p(C_1$-$C_6)$alkyl, $—S(O)_p$ $(C_1$-$C_6)$alkyl-OH, -thioalkoxy-alkoxy (e.g. $—SCH_2CH_2OCH_3$), $NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{1a}, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} and $—(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, $—(CR^{2e}R^{2f})$r-OR^b, $—(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $—(CR^{2e}R^{2f})$r-$C(O)R^b$, $—(CR^{2e}R^{2f})$r-$C(O)OR^b$, $—(CR^{2e}R^{2f})$r-$OC(O)R^b$, $—(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^2 is selected from hydrogen, CN, $—(CR^{2e}R^{2f})$r-$C(O)R^{2d}$, $—(CR^{2e}R^{2f})$r-$C(O)OR^{2b}$, $—(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$S(O)_2R^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, $—(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-4 R^a, and $—(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, $—(CR^{2e}R^{2f})$r-OR^b, $—(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $—(CR^{2e}R^2)$r-$C(O)R^b$, $—(CR^{2e}R^2)$r-$C(O)OR^b$, $—(CR^{2e}R^{2f})$r-$OC(O)R^b$, $—(CR^{2e}R^{2f})$r-$OC(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$OC(O)OR^c$, $—(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, $—(CR^{2e}R^{2f})_qOR^b$, $—(CR^{2e}R^{2f})_qS(O)_pR^b$, $—(CR^{2e}R^{2f})$r-C(O)R^{1d}, $—(CR^{2e}R^{2f})$r-C(O)OR^b, $—(CR^{2e}R^{2f})_qOC(O)R^b$, $—(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, $—(CR^{2e}R^{2f})_qNR^bC(O)R^c$, $—(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $—(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $—(CR^{2e}R^{2f})_qNR^bS(O)_{2R}{}^c$, $C_{1\text{-}6}$ alkyl substituted with 0-2 R^a, $C_{1\text{-}6}$ haloalkyl, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^a, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^a, $C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^a, $C_{6\text{-}10}$ aryl substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-2 R^d, $C_{1\text{-}6}$ haloalkyl, $C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a $—(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or $C_{1\text{-}6}$ alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, $—(CR^{2e}R^{2f})$r-OR^{3b}, $—(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^{3a}, $C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $—(CR^{2e}R^{2f})$r-OR^b, $—(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $—(CR^{2e}R^{2f})$r-$C(O)R^b$, $—(CR^{2e}R^{2f})$r-$C(O)OR^b$, $—(CR^{2e}R^{2f})$r-$OC(O)R^b$, $—(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^a, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^a, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^a, $C_{1\text{-}6}$ haloalkyl, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, $—(CR^{2e}R^2)_qOR^b$, $(CR^{2e}R^{2f})_qS(O)_pR^b$, $—(CR^{2e}R^{2f})$r-C(O)R^{1d}, $—(CR^{2e}R^{2f})$r-C(O)OR^b, $—(CR^{2e}R^{2f})_qOC(O)R^b$, $—(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, $(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $—(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $—(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^a, $C_{1\text{-}6}$ haloalkyl, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, $C_{1\text{-}6}$ alkyl or $C_{1\text{-}6}$ haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, $C(=O)C_{1\text{-}4}$ alkyl, $C(=O)OC_{1\text{-}4}$ alkyl, $C_{1\text{-}6}$ alkyl or $C_{1\text{-}6}$ haloalkyl; or

R^6 and R^7 taken together are =O;

R^{11} is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, CF_3, $C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^f, $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, $—(CR^{2e}R^{2f})$r-OR^b, $—(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $—(CR^{2e}R^{2f})$r-$C(O)R^b$, $—(CR^{2e}R^{2f})$r-$C(O)OR^b$, $—(CR^{2e}R^{2f})$r-$OC(O)R^b$, $—(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $C_{1\text{-}6}$ haloalkyl, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^e, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^e, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^d, $C_{1\text{-}6}$ haloalkyl, $C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^d, $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or $—(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $—(CR^{2e}R^{2f})$r-$C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^f, or $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, $—OR^e$, $—(CR^{2e}R^{2f})$r-$C(O)R^c$, $—NR^eR^e$, $—NR^eC(O)OR^c$, $C(O)NR^eR^e$, $—NR^eC(O)R^c$, CO_2H, CO_2R^c, $—NR^eSO_2R^c$, SO_2R^c, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^f, $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, selected from hydrogen, $C(O)NR^fR^f$, $C_{1\text{-}6}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, -5-7 membered heterocycle or $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1\text{-}6}$ alkyl), $N(C_{1\text{-}6}$ alkyl)$_2$, $SO_2(C_{1\text{-}6}$ alkyl), CO_2H, $CO_2(C_{1\text{-}6}$ alkyl), OH, $C_{3\text{-}6}$ cycloalkyl, CF_3, $O(C_{1\text{-}6}$ alkyl), or

an optionally substituted $—(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, phenyl or $C_{3\text{-}6}$ cycloalkyl, each group optionally substituted with halo, CN, CF_3, $C_{1\text{-}6}$ alkyl or $O(C_{1\text{-}6}$ alkyl);

m is 0, 1, 2 or 3

n is 0, 1 or 2;

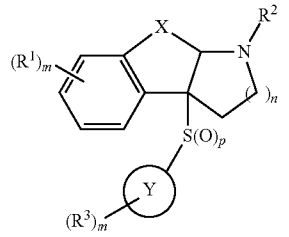
p and q are, independently at each occurrence, 0, 1, or 2;

r is 0, 1, 2, 3, or 4; and

t is 0 or 1.

In a second aspect, the invention comprises compounds of formula Ia

(Ia)



wherein

X is —CR^4R^5—, —$(CR^4R^5)_2$, —OCR^6R^7—, —$S(O)_pCR^6R^7$— or —$NR^6CR^6R^7$—;

Y is a 5 or 6-membered aromatic or heteroaromatic ring;

R^1 is, independently at each occurrence, selected from hydrogen, CD_3, halo, C_{1-6} alkyl substituted with 0-3 R^{1a}, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} and —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^2 is selected from hydrogen, —$(CR^{2e}R^{2f})$r-$C(O)R^{2d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^{2b}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$S(O)_2R^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, —$(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-3 R^a, and —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$OC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$OC(O)OR^c$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, —$(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_{2R}{}^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C_{3-10} cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a —$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C_{1-6} alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, $(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substi-

tuted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^f, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^e, C_{2-6} alkynyl substituted with 0-3 R^e, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-3 R^d, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or —$(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C_{1-6} alkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-C_{3-6} cycloalkyl substituted with 0-3 R^f, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, —OR^e, —$(CR^{2e}R^{2f})$r-$C(O)R^c$, —NR^eR^e, —$NR^eC(O)OR^c$, $C(O)NR^eR^e$, —$NR^eC(O)R^c$, CO_2H, CO_2R^c, —$NR^eSO_2R^c$, SO_2R^c, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, selected from hydrogen, $C(O)NR^fR^f$, C_{1-6} alkyl, C_{3-6} cycloalkyl, -5-7 membered heterocycle or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $SO_2(C_{1-6}$ alkyl), CO_2H, $CO_2(C_{1-6}$ alkyl), OH, C_{3-6} cycloalkyl, CF_3, $O(C_{1-6}$ alkyl); or

an optionally substituted —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, phenyl or C_{3-6} cycloalkyl, each group optionally substituted with halo, CN, CF_3, C_{1-6} alkyl or $O(C_{1-6}$ alkyl);

m is 0, 1, 2 or 3

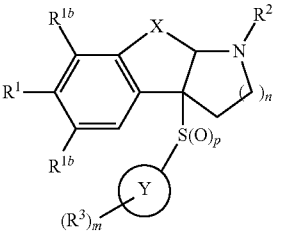
n is 0, 1 or 2;

p and q are, independently at each occurrence, 0, 1, or 2; and

r is 0, 1, 2, 3, or 4;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a third aspect, the invention comprises compounds of the formula



wherein

X is —CR^4R^5—, —$(CR^4R^5)_2$, —OCR^6R^7—, —$S(O)_pCR^6R^7$— or —$NR^6CR^6R^7$—;

Y is a 5 or 6-membered aromatic or heteroaromatic ring;

R^1 is selected from halo, C_1 alkyl substituted with 0-3 R^{1a}, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} and —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is selected from hydrogen, —$(CR^{2e}R^{2f})$r-$C(O)R^{2d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^{2b}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$S(O)_2R^2$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, —$(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-3 R^a, and —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$OC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$OC(O)OR^c$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, —$(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_{2R}{}^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-

5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C_{3-10} cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a —$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C_{1-6} alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, $(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^f, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^e, C_{2-6} alkynyl substituted with 0-3 R^e, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-3 R^d, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or —$(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C_{1-6} alkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-C_{3-6} cycloalkyl substituted with 0-3 R^f, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, —OR^e, —$(CR^{2e}R^{2f})$r-$C(O)R^c$, —NR^eR^e, —$NR^eC(O)OR^c$, $C(O)NR^eR^e$, —$NR^eC(O)R^c$, CO_2H, CO_2R^c, —$NR^eSO_2R^c$, SO_2R^c, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, selected from hydrogen, $C(O)NR^fR^f$, C_{1-6} alkyl, C_{3-6} cycloalkyl, -5-7 membered heterocycle or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $SO_2(C_{1-6}$ alkyl), CO_2H, $CO_2(C_{1-6}$ alkyl), OH, C_{3-6} cycloalkyl, CF_3, $O(C_{1-6}$ alkyl); or

an optionally substituted —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, phenyl or C_{3-6} cycloalkyl, each group optionally substituted with halo, CN, CF_3, C_{1-6} alkyl or $O(C_{1-6}$ alkyl);

m is 0, 1, 2 or 3

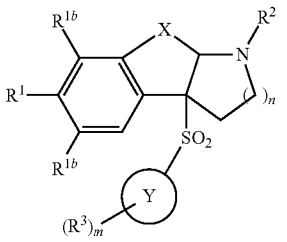
n is 0, 1 or 2;

p and q are, independently at each occurrence, 0, 1, or 2; and

r is 0, 1, 2, 3, or 4;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a 4th aspect, the invention comprises compounds of the formula



wherein

X is —CR^4R^5—, —$(CR^4R^5)_2$, —OCR^6R^7—, —$S(O)_pCR^6R^7$— or —$NR^6CR^6R^7$—;

Y is a 5 or 6-membered aromatic or heteroaromatic ring;

R^1 is selected from halo, C_{1-6} alkyl substituted with 0-3 R^{1a}, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} and —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})_r$—$S(O)_pR^b$, —$(CR^{2e}R^{2f})_r$—$C(O)R^b$, —$(CR^{2e}R^{2f})_r$—$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl; R^2 is selected from hydrogen, —$(CR^{2e}R^{2f})$r-$C(O)R^{2d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^{2b}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$S(O)_2R^2$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, —$(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-3 R^a, and —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$OC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$OC(O)OR^c$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_q$—OR^b, —$(CR^{2e}R^{2f})_q$—$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f}$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_q$—$OC(O)R^b$, —$(CR^{2e}R^{2f})_q$—$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$—$NR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})_q$—$NR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_q$—$NR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$—$S(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$—$NR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C_{3-10} cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a —$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C_{1-6} alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_q$—OR^b, —$(CR^{2e}R^{2f})_q$—$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_q$—$OC(O)R^b$, —$(CR^{2e}R^{2f})_q$—$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$—$NR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})_q$—$NR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_q$—$NR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$—$S(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$—$NR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-4 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising

carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, $—(CR^{2e}R^{2f})r\text{-}OR^b$, $—(CR^{2e}R^{2f})r\text{-}S(O)_pR^b$, $—(CR^{2e}R^{2f})r\text{-}C(O)R^b$, $—(CR^{2e}R^{2f})r\text{-}C(O)OR^b$, $—(CR^{2e}R^{2f})r\text{-}OC(O)R^b$, $—(CR^{2e}R^{2f})r\text{-}NR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}NR^bC(O)R^c$, $—(CR^{2e}R^{2f})r\text{-}NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $C_{1\text{-}6}$ haloalkyl, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^e, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^e, $—(CR^{2e}R^{2f})r$-3-14 membered carbocycle, or $—(CR^{2e}R^{2f})r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^d, $C_{1\text{-}6}$ haloalkyl, $C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^d, $—(CR^{2e}R^{2f})r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or $—(CR^{2e}R^{2f})r$-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $—(CR^{2e}R^{2f})r\text{-}C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^f, or $—(CR^{2e}R^{2f})r$-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, $—OR^e$, $—(CR^{2e}R^{2f})r\text{-}C(O)R^c$, $—NR^eR^e$, $—NR^eC(O)OR^c$, $C(O)NR^eR^e$, $—NR^eC(O)R^c$, CO_2H, CO_2R^c, $—NR^eSO_2R^c$, SO_2R^c, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^f, $—(CR^{2e}R^{2f})r$-phenyl substituted with 0-3 R^f or $—(CR^{2e}R^{2f})r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, selected from hydrogen, $C(O)NR^fR^f$, $C_{1\text{-}6}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, -5-7 membered heterocycle or $—(CR^{2e}R^{2f})r$-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1\text{-}6}$ alkyl), $N(C_{1\text{-}6}$ alkyl)$_2$, $SO_2(C_{1\text{-}6}$ alkyl), CO_2H, $CO_2(C_{1\text{-}6}$ alkyl), OH, $C_{3\text{-}6}$ cycloalkyl, CF_3, $O(C_{1\text{-}6}$ alkyl), or

an optionally substituted $—(CR^{2e}R^{2f})r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, phenyl or $C_{3\text{-}6}$ cycloalkyl, each group optionally substituted with halo, CN, CF_3, $C_{1\text{-}6}$ alkyl or $O(C_{1\text{-}6}$ alkyl);

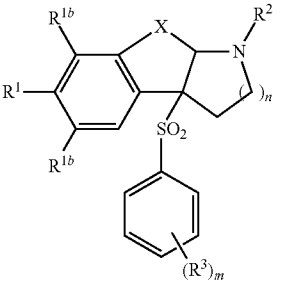
m is 0, 1, 2 or 3

n is 0, 1 or 2;

p and q are, independently at each occurrence, 0, 1, or 2; and

r is 0, 1, 2, 3, or 4, or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a 5th aspect, the invention comprises compounds of the formula



wherein

X is $—CR^4R^5—$, $—(CR^4R^5)_2$, $—OCR^6R^7—$, $—S(O)_pCR^6R^7—$ or $—NR^6CR^6R^7—$;

R^1 is selected from halo, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^{1a}, $—(CR^{2e}R^{2f})r$-3-14 membered carbocycle substituted with 0-3 R^{1a} and $—(CR^{2e}R^{2f})r$-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, $—(CR^{2e}R^{2f})r\text{-}OR^b$, $—(CR^{2e}R^{2f})_r—S(O)_pR^b$, $—(CR^{2e}R^{2f})_r—C(O)R^b$, $—(CR^{2e}R^{2f})_r—C(O)OR^b$, $—(CR^{2e}R^{2f})r\text{-}OC(O)R^b$, $—(CR^{2e}R^{2f})r\text{-}NR^{11}R^{11}$, $(CR^{2e}R^{2f})r\text{-}C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}NR^bC(O)R^c$, $—(CR^{2e}R^{2f})r\text{-}NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^a, $C_{1\text{-}6}$ haloalkyl, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^a, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})r$-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})r$-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is selected from hydrogen, $—(CR^{2e}R^{2f})r\text{-}C(O)R^{2d}$, $—(CR^{2e}R^{2f})r\text{-}C(O)OR^{2b}$, $—(CR^{2e}R^{2f})r\text{-}C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}S(O)_2R^2$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^{2a}, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^{2a}, $—(CR^{2e}R^{2f})r$-3-10 membered carbocycle substituted with 0-3 R^a, and $—(CR^{2e}R^{2f})r$-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, $—(CR^{2e}R^{2f})r\text{-}OR^b$, $—(CR^{2e}R^{2f})r\text{-}S(O)_pR^b$, $—(CR^{2e}R^{2f})r\text{-}C(O)R^b$, $—(CR^{2e}R^{2f})r\text{-}C(O)OR^b$, $—(CR^{2e}R^{2f})r\text{-}OC(O)R^b$, $—(CR^{2e}R^{2f})r\text{-}OC(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}OC(O)OR^c$, $—(CR^{2e}R^{2f})r\text{-}NR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}NR^bC(O)R^c$, $—(CR^{2e}R^{2f})r\text{-}NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^a, $C_{1\text{-}6}$ haloalkyl, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^a, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})r$-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})r$-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, $—(CR^{2e}R^{2f})_qOR^b$, $—(CR^{2e}R^{2f})_qS(O)_pR^b$, $—(CR^{2e}R^{2f})r\text{-}C(O)R^{1d}$, $—(CR^{2e}R^{2f})r\text{-}C(O)OR^b$, $—(CR^{2e}R^{2f})_qOC(O)R^b$, $—(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $—(CR^{2e}R^{2f})r\text{-}C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $—(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $—(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, $C_{1\text{-}6}$ alkyl substituted with 0-2 R^a, $C_{1\text{-}6}$ haloalkyl, $—(CR^{2e}R^{2f})r$-3-14 mem-

bered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C_{3-10} cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a —$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C_{1-6} alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, $(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$ $S(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^f, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^e, C_{2-6} alkynyl substituted with 0-3 R^e, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-3 R^d, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or —$(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C_{1-6} alkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-C_{3-6} cycloalkyl substituted with 0-3 R^f, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, —OR^e, —$(CR^{2e}R^{2f})$r-$C(O)R^c$, —NR^eR^e, —$NR^eC(O)OR^c$, $C(O)NR^eR^e$, —$NR^eC(O)R^c$, CO_2H, CO_2R^c, —$NR^eSO_2R^c$, SO_2R^c, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, selected from hydrogen, $C(O)NR^fR^f$, C_{1-6} alkyl, C_{3-6} cycloalkyl, -5-7 membered heterocycle or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $SO_2(C_{1-6}$ alkyl), CO_2H, $CO_2(C_{1-6}$ alkyl), OH, C_{3-6} cycloalkyl, CF_3; $O(C_{1-6}$ alkyl), or

an optionally substituted —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, phenyl or C_{3-6} cycloalkyl, each group optionally substituted with halo, CN, CF_3, C_{1-6} alkyl or $O(C_{1-6}$ alkyl);

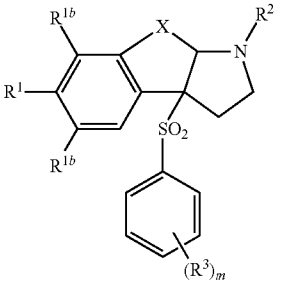
m is 0, 1, 2 or 3

n is 0, 1 or 2;

p and q are, independently at each occurrence, 0, 1, or 2; and

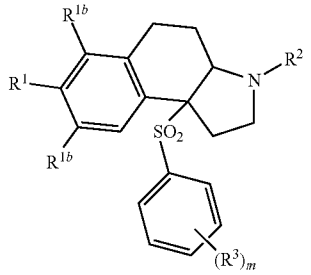
r is 0, 1, 2, 3, or 4,

or a stereoisomer or pharmaceutically-acceptable salt thereof.



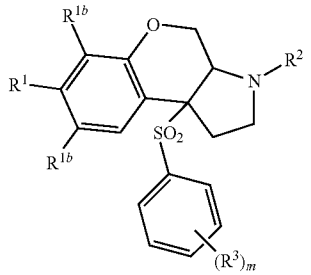
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a 7th aspect, the invention comprises compounds of the formula



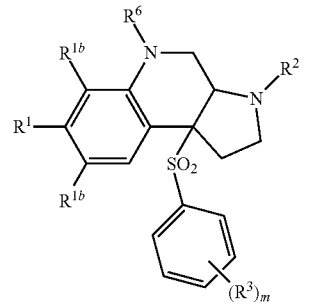
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In an 8th aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

In an 9th aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a 10th aspect, the invention comprises compounds within the 7th aspect, wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-OR^b, and —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a,

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —$C(O)R^{2d}$, —$C(O)NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a,

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10-membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, —NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_r$—$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In an 11th aspect, the invention comprises compounds within the 8th aspect, wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-OR^b, and —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a,

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —$C(O)R^{2d}$, —$C(O)NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a,

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroa-

toms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10-membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, —NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a 12th aspect, the invention comprises compounds within the 10th aspect, wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a,

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —$C(O)R^{2d}$ or —$C(O)NR^{11}R^{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is hydrogen, halo, cyclopropyl or C_{1-6} alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a 13th aspect, the invention comprises compounds within the 11th aspect, wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a;

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —$C(O)R^{2d}$ or —$C(O)NR^{11}R^{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

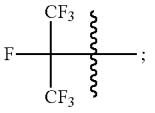
R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is hydrogen, halo, cyclopropyl or C_{1-6} alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a further aspect, the invention comprises compounds according to the 12th aspect, wherein

R^1 is



R^2 is —$C(O)R^{2d}$;

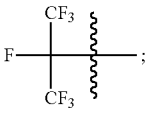
R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is F, Cl, cyclopropyl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a further aspect, the invention comprises compounds according to the 12th aspect, wherein

R^1 is



R^2 is —$C(O)R^2$;

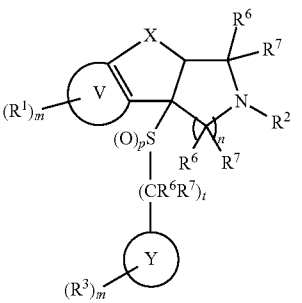
R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is F, Cl, cyclopropyl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, there is provided a compound of Formula (II), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein:

(II)



X is —CR^4R^5—, —O—, —NR^6—, —$S(O)_p$—, —$(CR^4R^5)_2$—, —OCR^6R^7—, —CR^6R^7O—, —$S(O)_pCR^6R^7$—, —$CR^6R^7S(O)_p$—, —$NR^6CR^6R^7$— or —$CR^6R^7NR^6$—;

V and Y are independently 5 or 6-membered aromatic or heteroaromatic rings;

R^1 is, independently at each occurrence, selected from halo, C_{1-6} alkyl substituted with 0-3 R^{1a}, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} and —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^2 is selected from hydrogen, —$(CR^{2e}R^2)$r-$C(O)R^{2d}$, —$(CR^{2e}R^2)$r-$C(O)OR^{2b}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$S(O)_2R^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, —$(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-3 R^a, and —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$OC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$OC(O)OR^c$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, —$(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C_{3-10} cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a —$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-3 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C_{1-6} alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, $(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f}$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^f, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^e, C_{2-6} alkynyl substituted with 0-3 R^e, —$(CR^{2e}R^{2f})$r-3-14

membered carbocycle, or —(CR^{2e}R^{2f})r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, C$_{1-6}$ alkyl substituted with 0-3 R^d, C$_{1-6}$ haloalkyl, C$_{3-6}$ cycloalkyl substituted with 0-3 R^d, —(CR^{2e}R^{2f})r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$ substituted with 0-4 R^f, or —(CR^{2e}R^{2f})r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C$_{1-6}$ alkyl substituted with 0-3 R^f, —(CR^{2e}R^{2f})r-C$_{3-6}$ cycloalkyl substituted with 0-3 R^f, or —(CR^{2e}R^{2f})r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF$_3$, CF$_3$, CN, NO$_2$, —OR^e, —(CR^{2e}R^{2f})r-C(O)R^c, —NR^{e}R^e, —NR^{e}C(O)OR^c, C(O)NR^{e}R^e, —NR^{e}C(O)R^c, CO$_2$H, CO$_2$R^c, —NR^{e}SO$_2$R^c, SO$_2$R^c, C$_{1-6}$ alkyl substituted with 0-3 R^f, C$_{3-6}$ cycloalkyl substituted with 0-3 R^f, —(CR^{2e}R^{2f})r-phenyl substituted with 0-3 R^f or —(CR^{2e}R^{2f})r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$ substituted with 0-3 R^f;

R^e is, independently at each occurrence, selected from hydrogen, C(O)NR^{f}R^f, C$_{1-6}$ alkyl, C$_{3-6}$ cycloalkyl, -5-7 membered heterocycle or —(CR^{2e}R^{2f})r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH$_2$, NH(C$_{1-6}$ alkyl), N(C$_{1-6}$ alkyl)$_2$, SO$_2$(C$_{1-6}$ alkyl), CO$_2$H, CO$_2$(C$_{1-6}$ alkyl), OH, C$_{3-6}$ cycloalkyl, CF$_3$, O(C$_{1-6}$ alkyl), or

an optionally substituted —(CR^{2e}R^{2f})r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$, phenyl or C$_{3-6}$ cycloalkyl, each group optionally substituted with halo, CN, CF$_3$, C$_{1-6}$ alkyl or O(C$_{1-6}$ alkyl);

m is 0, 1, 2 or 3

n is 1 or 2;

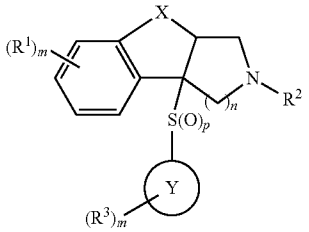
p and q are, independently at each occurrence, 0, 1, or 2;

r is 0, 1, 2, 3, or 4; and

t is 0 or 1.

In another aspect, the invention comprises compounds of formula IIa

(IIa)



wherein

X is —CR^{4}R^5—, —O—, —NR^6—, —S(O)$_p$—, —(CR^{4}R^5)$_2$—, —OCR^{6}R^7—, —CR^{6}R^{7}O—, —S(O)$_p$CR^{6}R^7—, —CR^{6}R^{7}S(O)$_p$—, —NR^{6}CR^{6}R^7— or —CR^{6}R^{7}NR^6—;

Y is a 5 or 6-membered aromatic or heteroaromatic ring;

R^1 is, independently at each occurrence, selected from halo, C$_{1-6}$ alkyl substituted with 0-3 R^{1a}, —(CR^{2e}R^{2f})r-3-14 membered carbocycle substituted with 0-3 R^{1a} and —(CR^{2e}R^{2f})r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and S(O)$_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF$_3$, OCF$_3$, CN, NO$_2$, —(CR^{2e}R^{2f})r-OR^b, —(CR^{2e}R^{2f})r-S(O)$_p$R^b, —(CR^{2e}R^{2f})r-C(O)R^b, —(CR^{2e}R^{2f})r-C(O)OR^b, —(CR^{2e}R^{2f})r-OC(O)R^b, —(CR^{2e}R^{2f})r-NR^{11}R^{11}, (CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}, —(CR^{2e}R^{2f})r-NR^{b}C(O)R^c, —(CR^{2e}R^{2f})r-NR^{b}C(O)OR^c, —NR^{b}C(O)NR^{11}R^{11}, —S(O)$_p$NR^{11}R^{11}, —NR^{b}S(O)$_p$R^c, C$_{1-6}$ alkyl substituted with 0-3 R^a, C$_{1-6}$ haloalkyl, C$_{2-6}$ alkenyl substituted with 0-3 R^a, C$_{2-6}$ alkynyl substituted with 0-3 R^a, —(CR^{2e}R^{2f})r-3-14 membered carbocycle substituted with 0-3 R^a, or —(CR^{2e}R^{2f})r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and S(O)$_p$ substituted with 0-3 R^a;

R^2 is selected from hydrogen, —(CR^{2e}R^{2f})r-C(O)R^{2d}, —(CR^{2e}R^{2f})r-C(O)OR^{2b}, —(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}, —(CR^{2e}R^{2f})r-S(O)$_2$R^{2c}, C$_{1-6}$ alkyl substituted with 0-3 R^{2a}, C$_{2-6}$ alkenyl substituted with 0-3 R^{2a}, —(CR^{2e}R^{2f})r-3-10 membered carbocycle substituted with 0-3 R^a, and —(CR^{2e}R^{2f})r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$ substituted with 0-4 R^a; R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF$_3$, CN, NO$_2$, —(CR^{2e}R^{2f})r-OR^b, —(CR^{2e}R^{2f})r-S(O)$_p$R^b, —(CR^{2e}R^{2f})r-C(O)R^b, —(CR^{2e}R^{2f})r-C(O)OR^b, —(CR^{2e}R^{2f})r-OC(O)R^b, —(CR^{2e}R^{2f})r-OC(O)NR^{11}R^{11}, —(CR^{2e}R^{2f})r-OC(O)OR^c, —(CR^{2e}R^{2f})r-NR^{11}R^{11}, (CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}, —(CR^{2e}R^{2f})r-NR^{b}C(O)R^c, —(CR^{2e}R^{2f})r-NR^{b}C(O)OR^c, —NR^{b}C(O)NR^{11}R^{11}, —S(O)$_p$NR^{11}R^{11}, —NR^{b}S(O)$_p$R^c, C$_{1-6}$ alkyl substituted with 0-3 R^a, C$_{1-6}$ haloalkyl, C$_{2-6}$ alkenyl substituted with 0-3 R^a, C$_{2-6}$ alkynyl substituted with 0-3 R^a, —(CR^{2e}R^{2f})r-3-14 membered carbocycle substituted with 0-3 R^a, or —(CR^{2e}R^{2f})r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF$_3$, —(CR^{2e}R^{2f})$_q$OR^b, —(CR^{2e}R^{2f})$_q$S(O)$_p$R^b, —(CR^{2e}R^{2f})r-C(O)R^{1d}, —(CR^{2e}R^{2f})r-C(O)OR^b, —(CR^{2e}R^{2f})$_q$OC(O)R^b, —(CR^{2e}R^{2f})$_q$NR^{11}R^{11}, —(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}, —(CR^{2e}R^{2f})$_q$NR^{b}C(O)R^{1c}, —(CR^{2e}R^{2f})$_q$NR^{b}C(O)OR^c, —(CR^{2e}R^{2f})$_q$NR^{b}C(O)NR^{11}R^{11}, —(CR^{2e}R^{2f})$_q$S(O)$_2$NR^{11}R^{11}, —(CR^{2e}R^{2f})$_q$NR^{b}S(O)$_2$R^c, C$_{1-6}$ alkyl substituted with 0-2 R^a, C$_{1-6}$ haloalkyl, —(CR^{2e}R^{2f})r-3-14 membered carbocycle substituted with 0-3 R^a, or —(CR^{2e}R^{2f})r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C$_{1-6}$ alkyl substituted with 0-3 R^a, C$_{2-6}$ alkenyl substituted with 0-3 R^a, C$_{3-10}$ cycloalkyl substituted with 0-3 R^a, C$_{6-10}$ aryl substituted with 0-3 R^a, or —(CR^{2e}R^{2f})r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C$_{1-6}$ alkyl substituted with 0-2 R^d, C$_{1-6}$ haloalkyl, C(O)NR^{11}R^{11}, —(CR^{2e}R^{2f})r-C$_{3-10}$ cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —(CR^{2e}R^{2f})r-phenyl substituted with 0-2 R^a, or a —(CR^{2e}R^{2f})r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and S(O)$_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C$_{1-6}$ alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, $(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^f, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^e, C_{2-6} alkynyl substituted with 0-3 R^e, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^f;

R^b is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-3 R^d, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or —$(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C_{1-6} alkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-C_{3-6} cycloalkyl substituted with 0-3 R^f, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, —OR^e, —$(CR^{2e}R^{2f})$r-$C(O)R^c$, —NR^eR^e, —$NR^eC(O)OR^c$, $C(O)NR^eR^e$, —$NR^eC(O)R^c$, CO_2H, CO_2R^c, —$NR^eSO_2R^c$, SO_2R^c, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, selected from hydrogen, $C(O)NR^fR^f$, C_{1-6} alkyl, C_{3-6} cycloalkyl, -5-7 membered heterocycle or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $SO_2(C_{1-6}$ alkyl), CO_2H, $CO_2(C_{1-6}$ alkyl), OH, C_{3-6} cycloalkyl, CF_3, $O(C_{1-6}$ alkyl), or

an optionally substituted —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, phenyl or C_{3-6} cycloalkyl, each group optionally substituted with halo, CN, CF_3, C_{1-6} alkyl or $O(C_{1-6}$ alkyl);

m is 0, 1, 2 or 3

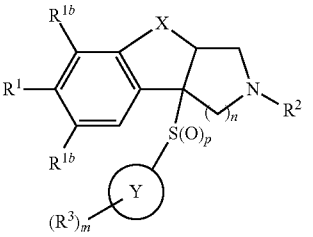
n is 1 or 2;

p and q are, independently at each occurrence, 0, 1, or 2; and

r is 0, 1, 2, 3, or 4;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



wherein

X is —CR^4R^5—, —O—, —NR^6—, —$S(O)_p$—, —$(CR^4R^5)_2$—, —OCR^6R^7—, —CR^6R^7O—, —$S(O)_pCR^6R^7$—, —$CR^6R^7S(O)_p$—, —$NR^6CR^6R^7$— or —$CR^6R^7NR^6$—;

Y is a 5 or 6-membered aromatic or heteroaromatic ring;

R^1 is selected from halo, C_{1-6} alkyl substituted with 0-3 R^{1a}, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} and —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-

$NR^{11}R^{11}$, $(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, $(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is selected from hydrogen, —$(CR^{2e}R^{2f})$r-C(O)R^{2d}, —$(CR^{2e}R^{2f})$r-C(O)OR^{2b}, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$S(O)_2R^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, —$(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-3 R^a, and —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)R^b, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})$r-OC(O)R^b, —$(CR^{2e}R^{2f})$r-OC(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-OC(O)OR^c, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, —$(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)$R^{1d}$, —$(CR^{2e}R^{2f})$r-C(O)$OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C_{3-10} cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a —$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C_{1-6} alkyl;

R^3 is, independently at each occurrence, selected from hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from N, O and $S(O)_p$, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)R^b, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})$r-OC(O)R^b, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})_qOR^b$, $(CR^{2e}R^{2f})_qS(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)$R^{1d}$, —$(CR^{2e}R^{2f})$r-C(O)$OR^b$, —$(CR^{2e}R^{2f})_qOC(O)R^b$, —$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently H, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)R^b, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})$r-OC(O)R^b, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^f, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^e, C_{2-6} alkynyl substituted with 0-3 R^e, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-3 R^d, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms

selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or —$(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C_{1-6} alkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-C_{3-6} cycloalkyl substituted with 0-3 R^f, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, —OR^e, —$(CR^{2e}R^{2f})$r-$C(O)R^c$, —NR^eR^e, —$NR^eC(O)OR^c$, $C(O)NR^eR^e$, —$NR^eC(O)R^c$, CO_2H, CO_2R^c, —$NR^eSO_2R^c$, SO_2R^c, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, selected from hydrogen, $C(O)NR^fR^f$, C_{1-6} alkyl, C_{3-6} cycloalkyl, -5-7 membered heterocycle or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, $SO_2(C_{1-6}$ alkyl), CO_2H, $CO_2(C_{1-6}$ alkyl), OH, C_{3-6} cycloalkyl, CF_3, $O(C_{1-6}$ alkyl), or

an optionally substituted —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, phenyl or C_{3-6} cycloalkyl, each group optionally substituted with halo, CN, CF_3, C_{1-6} alkyl or $O(C_{1-6}$ alkyl);

m is 0, 1, 2 or 3

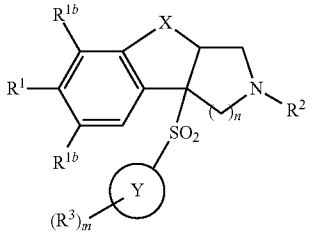
n is 1 or 2;

p and q are, independently at each occurrence, 0, 1, or 2; and

r is 0, 1, 2, 3, or 4;

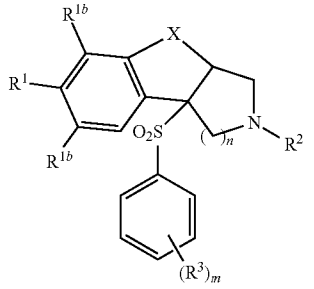
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



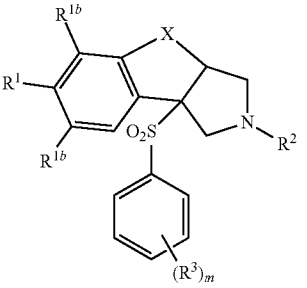
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



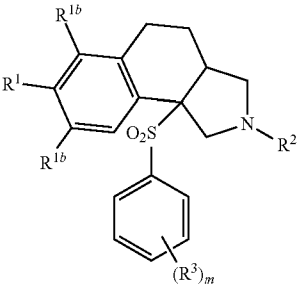
or a stereoisomer or pharmaceutically acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



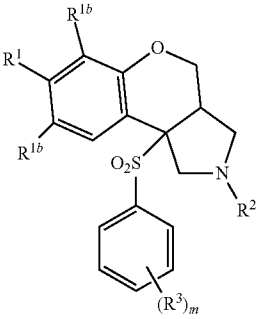
or a stereoisomer or pharmaceutically acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



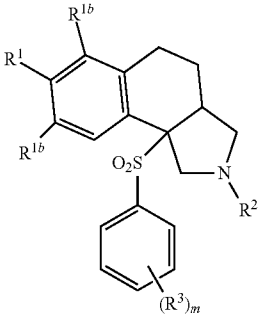
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-OR^b, and —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a,

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —$C(O)R^{2d}$, —$C(O)NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a,

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10-membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

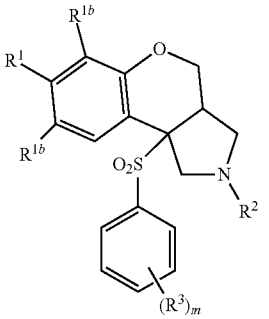
R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, —NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-OR^b, and —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a,

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —$C(O)R^{2d}$, —$C(O)NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a,

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10-membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, —NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

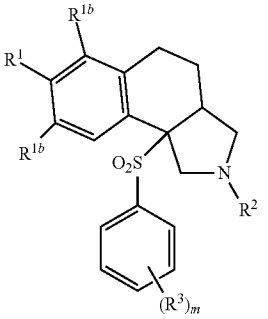
R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-$C(O)R^b$, —$(CR^{2e}R^{2f})$r-$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered hetero-

cycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —C(O)R^{2d} or —C(O)$NR^{11}R^{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

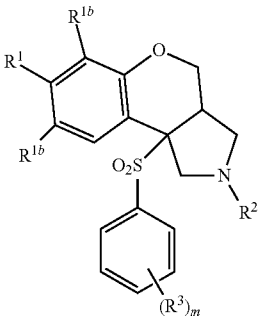
R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is hydrogen, halo or C_{1-6} alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —C(O)R^{2d} or —C(O)$NR^{11}R^{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

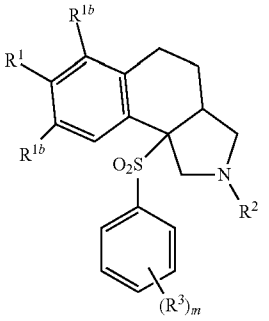
R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is hydrogen, halo or C_{1-6} alkyl;

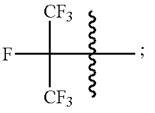
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



wherein

R^1 is



R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

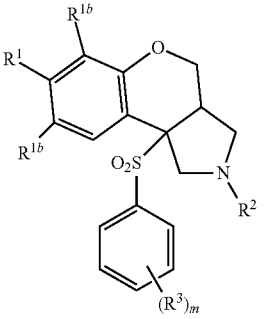
R^2 is —C(O)R^{2d}

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

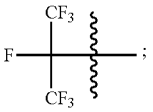
R^3 is F, Cl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



wherein
R^1 is



R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

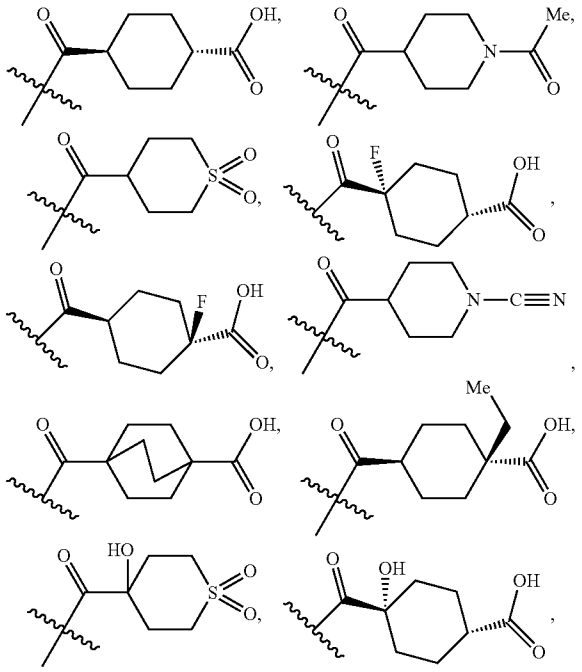
R^2 is —C(O)R^{2d}

R^{2d} is, independently at each occurrence, $C_{3\text{-}10}$ cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

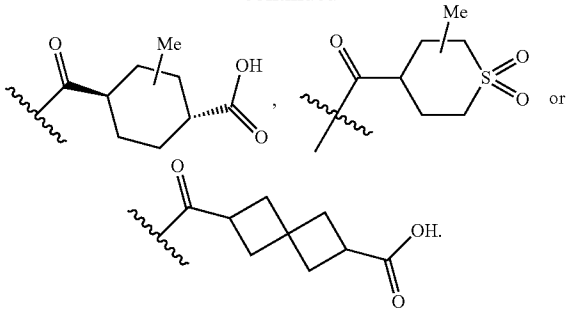
R^3 is F, Cl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, there is provided a compound of Formula (I), or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof,
wherein R^2 is:



-continued



In another aspect, there is provided a compound selected from the exemplified examples within the scope of the first aspect, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

In another aspect, there is provided a compound selected from the exemplified examples within the scope of formula II, or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

In another aspect, there is provided a compound selected from any subset list of compounds within the scope of any of the above aspects.

In another embodiment, the invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the invention provides a process for making a compound of the invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

In another embodiment, the invention provides a compound of the present invention for use in therapy.

In another embodiment, the invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

In another embodiment, the invention provides a compound of the present invention for use in treating diseases (or a method of treating diseases) in which inflammation is a component including, without limitation, diseases such as psoriasis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, acute graft-versus-host disease, psoriatic arthritis, ankylosing spondylitis and multiple sclerosis.

The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. It is well known in the art how to

prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (e.g., R^3) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^3, then said group may optionally be substituted with up to two R^3 groups and R^3 at each occurrence is selected independently from the definition of R^3. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are nitrogen atoms (e.g., amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

In accordance with a convention used in the art,



is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

A dash "-" that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, —$CONH_2$ is attached through the carbon atom.

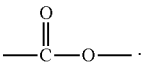
The term "optionally substituted" in reference to a particular moiety of the compound of Formula I (e.g., an optionally substituted heteroaryl group) refers to a moiety having 0, 1, 2, or more substituents. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

As used herein, the term "at least one chemical entity" is interchangeable with the term "a compound."

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-10} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or substituted so that one or more of its hydrogens are replaced by another chemical group, for example, aryl or heteroaryl groups which are optionally substituted for example with alkyl, halo or haloalkyl. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, t-butyl), pentyl (e.g., n-pentyl, isopentyl, neopentyl), and the like.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

One skilled in the field will understand that, when the designation "CO_2" is used herein, this is intended to refer to the group



When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C_{0-4})alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, i.e., aryl(C_0)alkyl. The term "heteroarylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is a heteroaryl.

When reference is made to a substituted alkenyl, alkynyl, alkylene, alkenylene, or alkynylene group, these groups are substituted with one to three substituents as defined above for substituted alkyl groups.

The term "alkoxy" refers to an oxygen atom substituted by alkyl or substituted alkyl, as defined herein. For example, the term "alkoxy" includes the group —O—C_{1-6}alkyl such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

It should be understood that the selections for all groups, including for example, alkoxy, thioalkyl, and aminoalkyl, will be made by one skilled in the field to provide stable compounds.

The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo, or keto, (i.e., =O) then 2 hydrogens on the atom are replaced. Keto substituents are

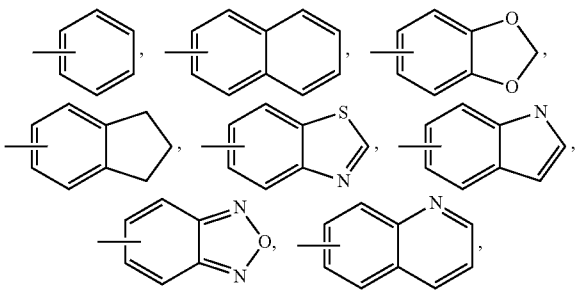
not present on aromatic moieties. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C═C, C═N, or N═N).

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture to a useful degree of purity, and subsequent formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

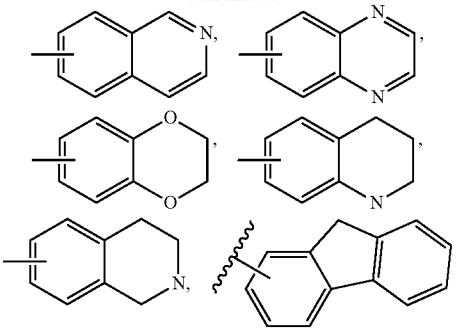
The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbomyl, and the like. As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0] bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a bicyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, and naphthyl groups, each of which may be substituted.

Thus, examples of aryl groups include:

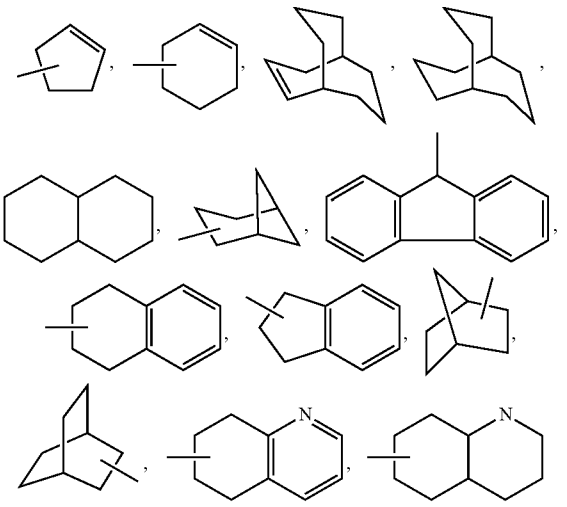


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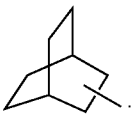


(fluorenyl) and the like, which optionally may be substituted at any available carbon or nitrogen atom. A preferred aryl group is optionally-substituted phenyl.

Accordingly, in compounds of formula I, the term "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclooctyl, etc., as well as the following ring systems:



and the like, which optionally may be substituted at any available atoms of the ring(s). Preferred cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, and



The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

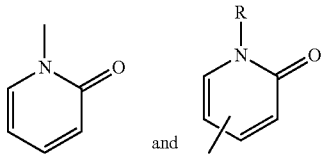
The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, di, and trifluoromethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

The terms "heterocycle", "heterocycloalkyl", "heterocyclo", "heterocyclic", or "heterocyclyl" may be used interchangeably and refer to substituted and unsubstituted 3- to 7-membered monocyclic groups, 7- to 11-membered bicy-

clic groups, and 10- to 15-membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or fully unsaturated. The heterocyclo group may be attached at any available nitrogen or carbon atom. As used herein the terms "heterocycle", "heterocycloalkyl", "heterocyclo", "heterocyclic", and "heterocyclyl" include "heteroaryl" groups, as defined below.

In addition to the heteroaryl groups described below, exemplary monocyclic heterocycle groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 1-pyridonyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl. Additional monocyclic heterocyclyl groups include



The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-membered tricyclic groups which have at least one heteroatom (0, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. As valence allows, if said further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

Unless otherwise indicated, when reference is made to a specifically-named aryl (e.g., phenyl), cycloalkyl (e.g., cyclohexyl), heterocyclo (e.g., pyrrolidinyl, piperidinyl, and morpholinyl) or heteroaryl (e.g., tetrazolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, and furyl) the reference is intended to include rings having 0 to 3, preferably 0 to 2, substituents selected from those recited above for the aryl, cycloalkyl, heterocyclo and/or heteroaryl groups, as appropriate.

The terms "carbocycle, carbocyclyl or "carbocyclic" refers to a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of mono- and bicyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl and naphthyl. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful as pharmaceutically-acceptable compounds and/or intermediate compounds useful in making pharmaceutically-acceptable compounds.

The compounds of formula I may exist in a free form (with no ionization) or can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to the free form and to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s) may include zwitterions (inner salts), e.g., when a compound of formula I, contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, e.g., in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula I may be formed, for example, by reacting a compound of the formula I 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 (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, hydrogen sulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

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; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others. Preferred salts include monohydrochloride, hydrogen sulfate, methanesulfonate, phosphate or nitrate salts.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

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

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, Easton, Pa. (1990), the disclosure of which is hereby incorporated by reference.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. Stereoisomers may include compounds which are optical isomers through possession of one or more chiral atoms, as well as compounds which are optical isomers by virtue of limited rotation about one or more bonds (atropisomers). The definition of compounds according to the invention embraces all the possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates from the conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization. One enantiomer of a compound of Formulas I and II may display superior activity compared with the other.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, and/or a salt and/or solvate thereof. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound for formula I) is a prodrug within the scope and spirit of the invention. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula I compounds per se. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester per se is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6}alkanoyloxy-C_{1-6}alkyl, e.g., acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, e.g., methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycy-

loxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology,* 112:309-396, Academic Press (1985);

b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs", Krosgaard-Larsen, P. et al., eds., *A Textbook of Drug Design and Development*, pp. 113-191, Harwood Academic Publishers (1991); and

c) Bundgaard, H., *Adv. Drug Deliv. Rev.,* 8:1-38 (1992), each of which is incorporated herein by reference.

Compounds of the formula I and salts thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have trans and cis isomers.

It should further be understood that solvates (e.g., hydrates) of the compounds of Formula I are also with the scope of the present invention. Methods of solvation are generally known in the art.

Another aspect of the invention is a pharmaceutical composition including a compound, stereoisomeric form, pharmaceutical salt, solvate or hydrate as described herein. The pharmaceutical compositions described herein generally comprise a combination of a compound described herein and a pharmaceutically acceptable carrier, diluent, or excipient. Such compositions are substantially free of non-pharmaceutically acceptable components, i.e., contain amounts of non-pharmaceutically acceptable components lower than permitted by U.S. regulatory requirements at the time of filing this application. In some embodiments of this aspect, if the compound is dissolved or suspended in water, the composition further optionally comprises an additional pharmaceutically acceptable carrier, diluent, or excipient. In other embodiments, the pharmaceutical compositions described herein are solid pharmaceutical compositions (e.g., tablet, capsules, etc.).

These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

Also, pharmaceutical compositions can contain, as the active ingredient, one or more of the compounds described herein above in combination with one or more pharmaceutically acceptable carriers. In making the compositions described herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions described herein can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual subject, the severity of the subject's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of a compound described herein.

The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former.

The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a subject will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the subject, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a subject already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the subject, and the like.

The compositions administered to a subject can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the subject, and the judgment of the prescribing physician. The proportion or concentration of a compound described herein in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration.

For example, the compounds described herein can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 rtg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular subject, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

The compounds of the present invention are useful to prevent, diagnose, and treat various medical disorders in humans or animals. The compounds are used to inhibit or reduce one or more activities associated with RORγ receptors, relative to RORγ receptors in the absence of the same compounds. Thus, in one aspect of the invention, a method for treating a disease or disorder selected from an autoimmune disease or disorder, asthma, an allergic disease or disorder, a metabolic disease or disorder, and cancer in a subject comprises administering to the subject a therapeutically effective amount of compound according to formula (I), stereoisomeric form, N-oxide, pharmaceutically acceptable salt, solvate, hydrate or pharmaceutical composition as described herein. See, e.g., L. A. Solt et al., "Action of RORs and their ligands in (patho)physiology," *Trends Endocrinol. Metab.* 2012, 23 (12): 619-627; M. S. Maddur et al., "Th17 cells: biology, pathogenesis of autoimmune and inflammatory diseases, and therapeutic strategies," *Am. J. Pathol.* 2012 July; 181(1):8-18; and A. M. Jetten, "Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism," *Nucl. Recept. Signal.* 2009; 7:e003, each of which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section. In certain embodiments, the autoimmune disease or disorder is selected from rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis, multiple sclerosis, inflammatory bowel diseases and lupus. In certain embodiments, the allergic disease or disorder is selected from allergic rhinitis and dermatitis. In certain embodiments, the metabolic disease or disorder is selected from obesity, obesity-induced insulin resistance and type II diabetes.

In certain embodiments, the disease or disorder is rheumatoid arthritis. See, e.g., L. A. Solt et al., referenced above, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is multiple sclerosis. See, e.g., L. Codarri et al., "RORγt drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation," *Nat. Immunol.,* 2011 June; 12(6):560-7, which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is ankylosing spondylitis. See, e.g., E. Toussirot, "The IL23/Th17 pathway as a therapeutic target in chronic inflammatory diseases," *Inflamm. Allergy Drug Targets,* 2012 April; 11(2): 159-68, which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is inflammatory bowel disease. See, e.g., M. Leppkes et al., "RORgamma-expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F," *Gastroenterology,* 2009 January; 136(1):257-67,

which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is lupus. See, e.g., K. Yoh et al., "Overexpression of RORγt under control of the CD_2 promoter induces polyclonal plasmacytosis and autoantibody production in transgenic mice," *Eur. J. Immunol.,* 2012 August; 42(8): 1999-2009, which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is psoriasis. See, e.g., S. Pantelyushin et al., "RORγt+ innate lymphocytes and γδ T cells initiate psoriasiform plaque formation in mice," *J. Clin. Invest.,* 2012 Jun. 1; 122(6):2252-6; and S. P. Raychaudhuri, "Role of IL-17 in Psoriasis and Psoriatic Arthritis," Clin. Rev. Allergy Immunol., 2013; 44(2): 183-193, each of which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is psoriatic arthritis. See, e.g., S. P. Raychaudhuri, referenced above, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is graft-vs.-host disease (GVHD). Y. Yu et al., "Prevention of GVHD while sparing GVL effect by targeting Th1 and Th17 transcription factor T-bet and RORγt in mice," *Blood,* 2011 Nov. 3; 118(18):5011-20, which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is autoimmune uveitis. See, e.g., R. Horai et al., "Cytokines in autoimmune uveitis," *J. Interferon Cytokine Res.,* 2011 October; 31(10):733-44, which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is obesity and/or insulin resistance. See, e.g., B. Meissburger et al., "Adipogenesis and insulin sensitivity in obesity are regulated by retinoid-related orphan receptor gamma," *EMBO Mol. Med.,* 2011 November; 3(11):637-51, which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In other embodiments, the disease or disorder is melanoma. See, e.g., Purwar R, et al. Robust tumor immunity to melanoma mediated by interleukin-9-producing T cells. Nat. Med., 2012 July: 18:1248-53, which is hereby incorporated herein by reference in its entirety, as well as the references discussed in the Background section.

In certain aspects, the medical disorder being diagnosed, treated, or prevented by use of the presently disclosed compounds can be, for example, an autoimmune disorder. In other embodiments, the disorder being diagnosed, treated or prevented by use of the presently disclosed compounds can be an inflammatory disorder. For example, in certain embodiments, the disorder is selected from arthritis, diabetes, multiple sclerosis, uveitis, rheumatoid arthritis, psoriasis, asthma, bronchitis, allergic rhinitis, chronic obstructive pulmonary disease, atherosclerosis, *H. pylori* infection and inflammatory bowel disease. In other embodiments, the disorder is selected from Crohn's disease, ulcerative colitis, sprue and food allergies. In other embodiments, the disorder is experimental autoimmune encephalomyelitis, imiquimod-induced psoriasis, colitis or allergic airway disease.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

In certain embodiments, a therapeutically effective amount can be an amount suitable for (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; or (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

As used here, the terms "treatment" and "treating" means (i) ameliorating the referenced disease state, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing or improving the pathology and/or symptomatology) such as decreasing the severity of disease; (ii) eliciting the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician; or (iii) inhibiting the referenced disease state; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder.

Methods of Preparation

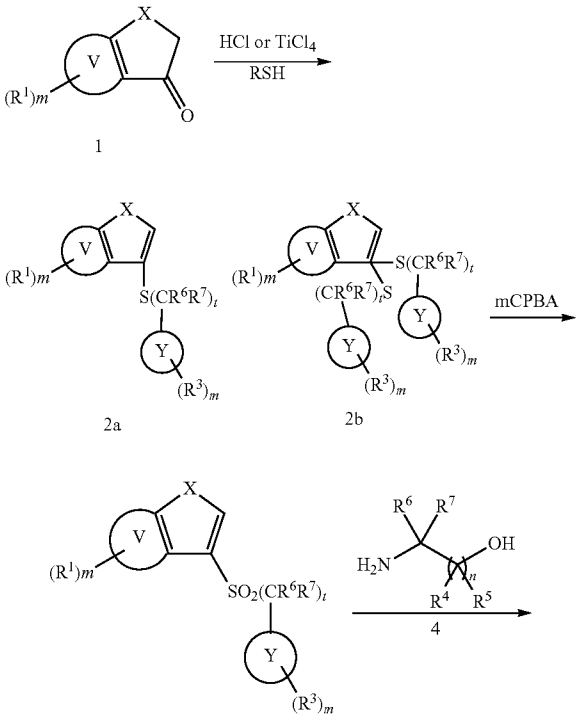
The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry. General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Examples of compounds of the present invention prepared by methods described in the general schemes are given in the Examples section set out hereinafter. Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example, homochiral compounds may be prepared by separation of racemic products or diastereomers by chiral phase preparative HPLC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically or diastereomerically enriched products.

The reactions and techniques described in this section are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods given below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents that are compatible with the reaction conditions

will be readily apparent to one skilled in the art, with alternatives required when incompatible substituents are present. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of a protecting group used for protection of reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Wuts and Greene, Greene's Protective Groups in Organic Synthesis, Fourth Edition, Wiley and Sons (2007).

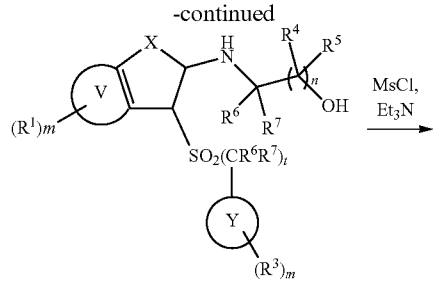
Scheme 1 illustrates a method for the preparation of compounds 7. An appropriately functionalized carbonyl compound 1 (which can be purchased or synthesized using typical conditions; see, for example: *Eur. J. Med. Chem.* 2015, 90, 834; Science of Synthesis 2077, 31a, 1097; PCT Int. Appl. 2014/138484; *Bioorg. Med. Chem. Lett.* 2012, 22, 240; *Eur. J. Med. Chem.* 2013, 69, 490; or PCT Int. Appl. 2013/178322) may be reacted with an appropriate thiol in the presence of an acid such as HCl or $TiCl_4$ to afford a vinyl sulfide 2a, a thioketal 2b, or a mixture of 2a and 2b. Oxidation of sulfide 2a, thioketal 2b, or a mixture of 2a and 2b can be accomplished using a reagent such as m-chloroperoxybenzoic acid to afford sulfone 3. A nucleophile such as an amino alcohol 4 can then be added, yielding an alcohol 5. This compound could be converted to the corresponding methanesulfonate 6 using methanesulfonyl chloride and triethylamine, followed by treatment with a base such as potassium tert-butoxide, to give tricyclic amine 7.

SCHEME 1

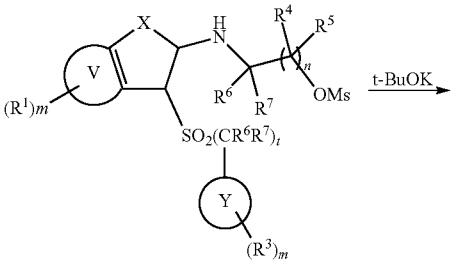


1 2a 2b 3 4

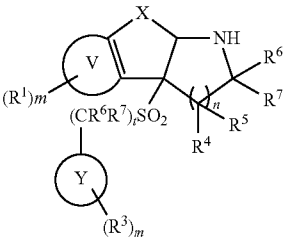
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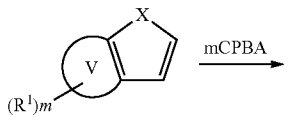
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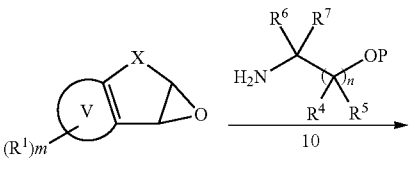
An alternative method for the preparation of compounds 7 is shown in Scheme 2. An appropriately substituted olefin 8 (which can be purchased, or prepared using typical methods; see for example US Pat. Appl. 2007/0155738 and US Pat. Appl. 2005/261310) can be converted to the epoxide 9, for example by treatment with a reagent such as m-chloroperoxybenzoic acid. The epoxide may be treated with a nucleophile such as a protected amino alcohol 10 (where P is, for example, tert-butyldimethylsilyl) to provide alcohol 11. Treatment of 11 with a suitable reagent such as triphenylphosphine and diethyl azodicarboxylate can provide the substituted aziridine 12. Treatment of the aziridine with an appropriate thiol can give 13. Protection of the amino group with a suitable protecting group P' such as tert-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz), followed by oxidation of the thiol with a reagent such as m-chloroperoxybenzoic acid, can provide the sulfone 14. Selective removal of the alcohol protecting group, followed by conversion to the corresponding methanesulfonate and treatment with a base such as potassium tert-butoxide (as in Scheme 1) can provide 15, which can be deprotected to provide the tricyclic amine 7.

SCHEME 2



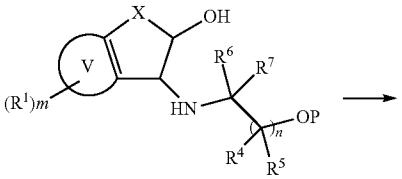
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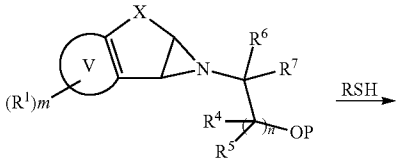


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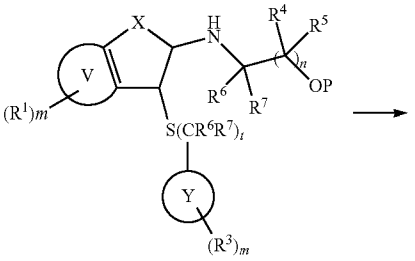


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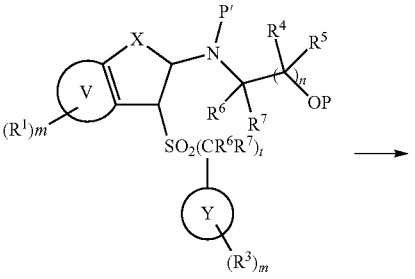


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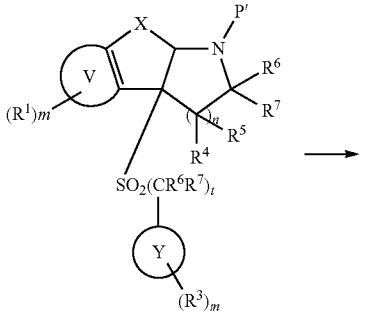
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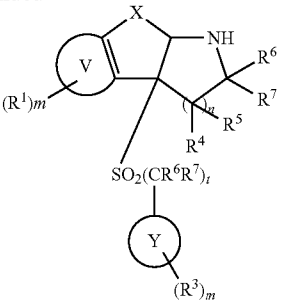


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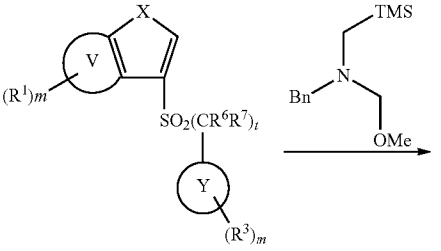
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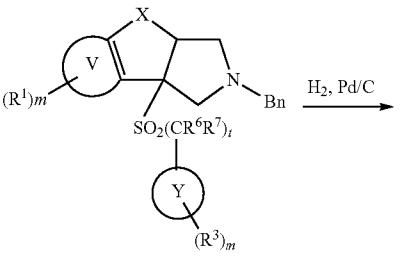
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Scheme 3 illustrates an approach to the synthesis of compounds of type 17. Appropriately functionalized vinyl sulfone 3 may undergo cycloaddition reactions with a variety of reagents. For example, reaction with N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)-methanamine in the presence of a catalytic amount of trifluoroacetic acid can provide pyrrolidine 16. Deprotection using hydrogen with catalytic palladium on carbon can give rise to pyrrolidine 17.

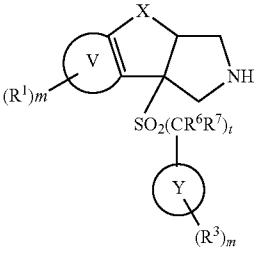
SCHEME 3



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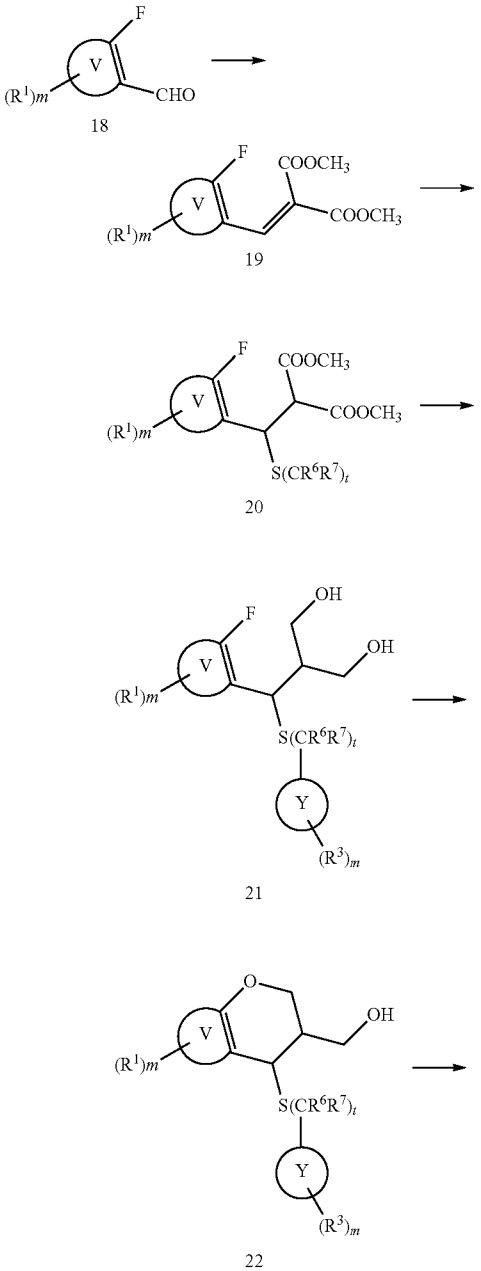


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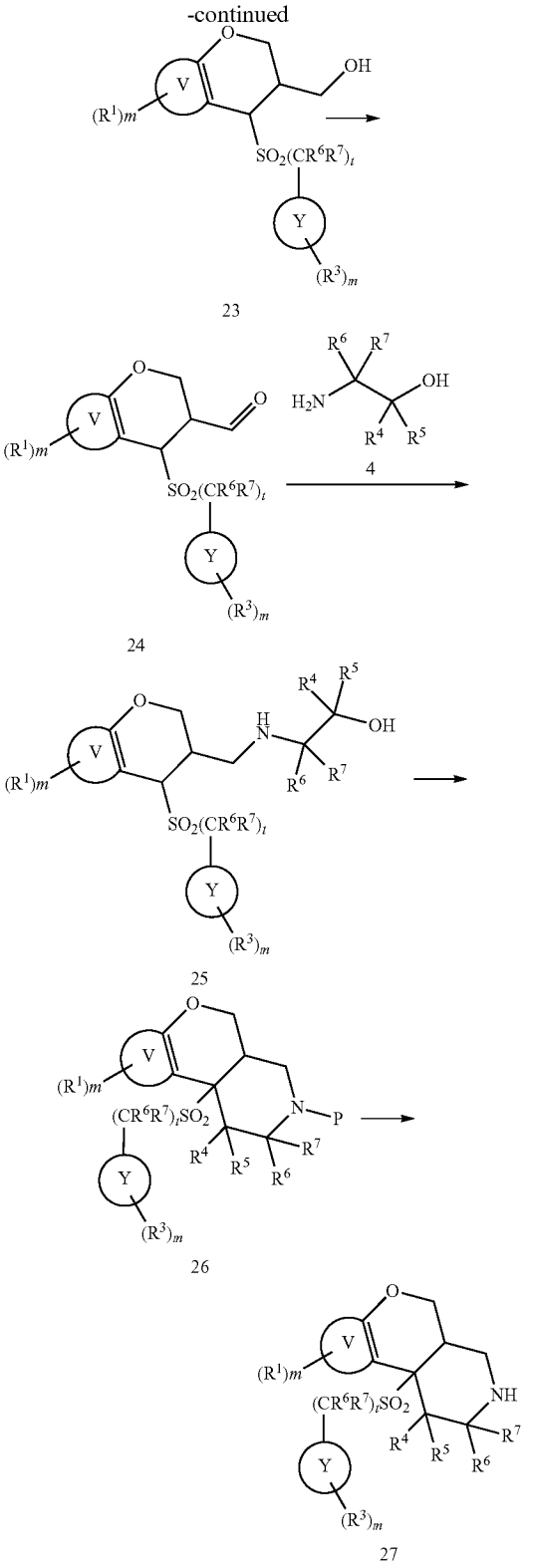
An approach to the synthesis of compounds of type 27 is shown in Scheme 4. An appropriate fluoro-substituted aldehyde 18 can be condensed with dimethyl malonate in the presence of an acid and base such as benzoic acid and piperidine to provide 19. This compound can be reacted with an appropriate thiol to provide 20. The ester groups of 20 can be reduced, for example with diisobutylaluminum hydride,

to provide the diol 21, which can be treated with a base such as sodium hydride to provide 22. The sulfide can be converted to the corresponding sulfone 23 by treatment with a reagent such as m-chloroperoxybenzoic acid. Oxidation of the carbinol of 23, for example using 1,1,1-tris(acetyloxy)-11-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinane) can provide the aldehyde 24. This material can be reacted with an amino alcohol 4 in the presence of a reducing agent such as sodium triacetoxyborohydride to give 25. Protection of the nitrogen, for example as the Boc or Cbz derivative, followed by conversion to the methanesulfonate and treatment with a base such as potassium tert-butoxide (as in Scheme 1) can provide the tricyclic compound 26. Deprotection of the amine can then provide 27.

SCHEME 4



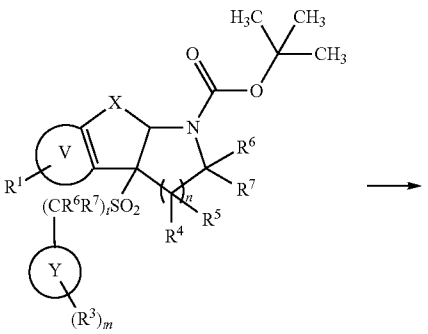
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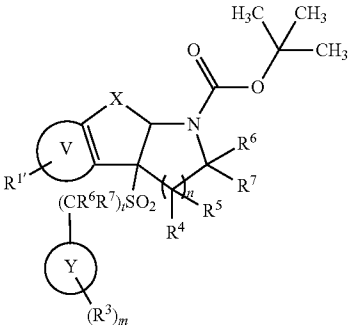
Scheme 5 illustrates methods which can provide access to amine intermediates through modification of compounds 7. (The same method can be applied to other intermediates, such as amines 17 or 27.) Amine 7, wherein R^1 is a halide such as Cl, Br or I, can be treated with di-tert-butyl dicarbonate to provide the protected amine 28. Any of a number of well-known methods for converting an aromatic halide to

a different group can then be applied to convert 28 into 29, where $R^{1'}$ is a different substituent. Some examples, not meant to be limiting, are: (1) treatment with an aryl or alkenyl boronic acid or boronate ester in the presence of a suitable palladium catalyst, commonly known as the Suzuki coupling (see, for example, *Chem. Rev.* 1979, 95, 2457; *J. Organometallic Chem.* 1999, 576, 147), to give 29 where $R^{1'}$ can be aryl, heteroaryl or alkenyl (the latter of which can be further converted to the corresponding alkyl by catalytic reduction); (2) treatment with a zinc reagent such as zinc(II) cyanide or an alkyl- or cycloalkylzinc halide in the presence of a suitable palladium catalyst, commonly known as the Negishi coupling (see, for example, *Metal-Catalyzed Cross-Coupling Reactions* (2nd edition), 2004, 815), to give 29 where $R^{1'}$ can be, for example, alkyl, cycloalkyl or cyano; (3) treatment with an amine or amide in the presence of a suitable palladium catalyst, commonly known as the Buchwald-Hartwig coupling (see, for example, *Chem. Sci.* 2011, 2, 27; *Acc. Chem. Res.* 1998, 31, 805; *Angew. Chem. Int. Ed.* 2008, 47, 6338), to give 29 where $R^{1'}$ can be, for example, dialkylamino; (4) treatment with an organomagnesium halide in the presence of a suitable iron catalyst (see, for example, *Org. React.* 2014, 83, 1; *J. Am. Chem. Soc.*, 2002, 13856), to give 29 where $R^{1'}$ can be, for example, methyl or trideuteromethyl; (5) treatment with a fluorinated alkyl halide in the presence of a copper catalyst (see, for example, *Tetrahedron* 1969, 25, 5921; *Angew. Chem. Int. Ed.* 2011, 50, 3793), to give 29 where $R^{1'}$ can be, for example, trifluoromethyl, heptafluoropropyl, heptafluoroisopropyl, or the like; or (6) treatment with copper(I) halide to give 29 where $R^{1'}$ is a different halide from R^1 in 28. Removal of the Boc protecting group can be achieved by treatment with a strong acid such as HCl or trifluoroacetic acid. The same or similar methods can also be applied to a protected amine 30 (or a protected amine derived from amines 17 or 27) wherein R^3 is a halide such as Cl, Br or I to give the corresponding 31 where $R^{3'}$ is a different group, as described above.

SCHEME 5

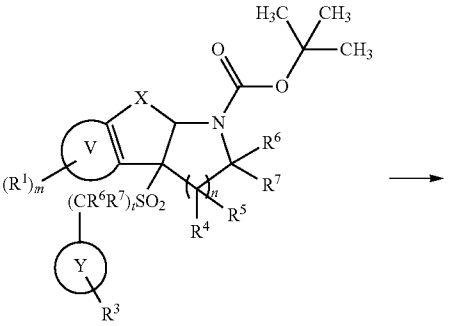


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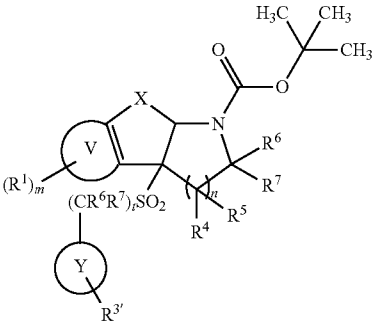


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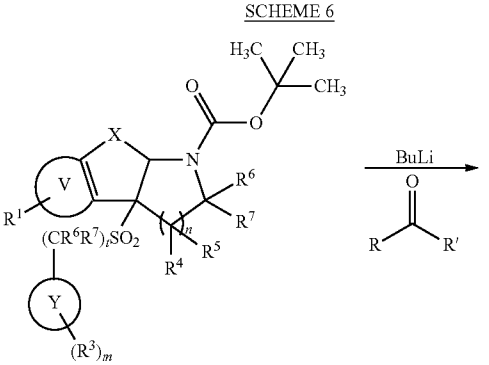
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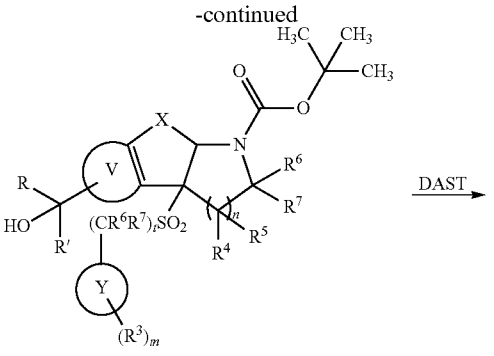
An alternative method for the conversion of a compound 28 where R^1 is Br or I to a compound 32 or 33 is shown in Scheme 6. Compound 28 can be treated with an organometallic reagent such as n-butyllithium, and then reacted with a carbonyl containing compound RC(=O)R' to provide alcohol 32. Optionally, alcohol 32 may be treated with a fluorinating agent such as (diethylamino)sulfur trifluoride, affording a fluorinated analog such as 33. Treatment of 32 or 33 with a strong acid such as HCl or trifluoroacetic acid would then remove the Boc protecting group.

SCHEME 6

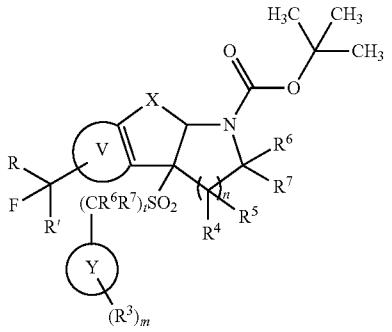


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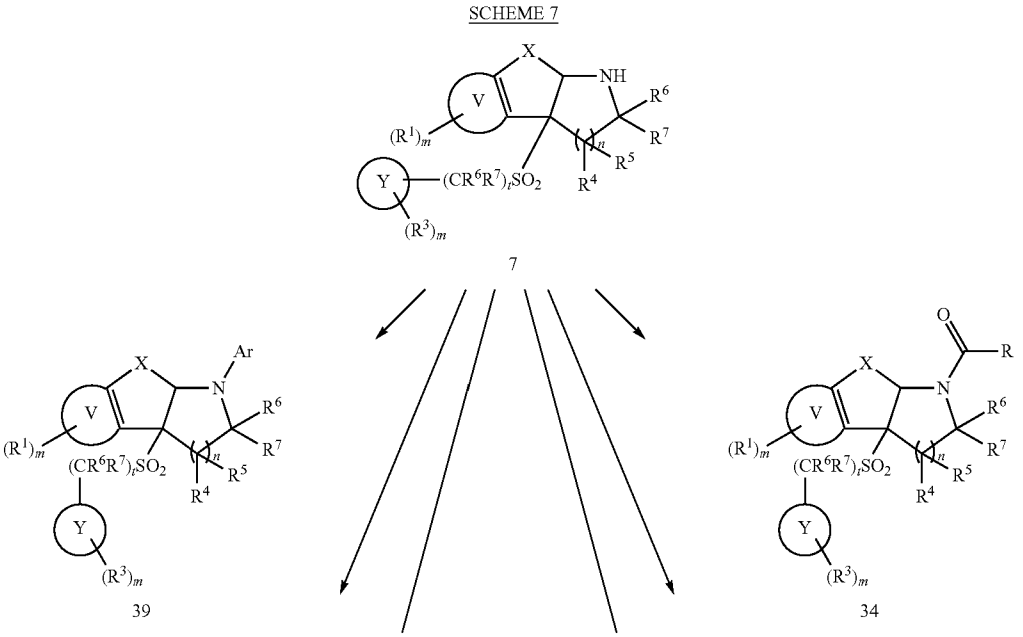
32



33

A variety of methods well known in the literature can be used for conversion of amines 7 to compounds of the present invention. (Such methods can also be used for similar conversions of amines 17 and 27 to compounds of the present invention.) Some examples are shown in Scheme 7. An amine 7 can be treated with an acid anhydride $(RC(=O))_{20}$ or an acid chloride RC(=O)Cl in the presence of a base such as triethylamine or pyridine to provide an amide 34. Alternatively, an amine 7 can be treated with an acid RC(=O)OH in the presence of a suitable base and a coupling reagent such as (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), or a combination of 1-hydroxybenzotriazole (HOBT) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) to provide an amide 34. An amine 7 can also be treated with a sulfonyl chloride RSO_2Cl in the presence of a suitable base to provide a sulfonamide 35. An amine 7 can also be treated with an isocyanate RN=C=O to provide a urea 36 (where R' is H), or with an aminocarbonyl chloride RN(R')C(=O)Cl to provide a urea 36. Alternatively, an amine 7 can be treated with phosgene or triphosgene to provide the intermediate N-chlorocarbonyl derivative, which can then be treated with an amine RN(R')H to provide a urea 36. An amine 7 can be treated with a sulfamyl chloride $RN(R')SO_2Cl$ to provide a sulfamide 37. An amine 7 can be treated with an appropriate substituted or unsubstituted alkyl halide, cycloalkyl halide, or arylalkyl halide RC(R')(H)X' where X' is Br, I or Cl, or with a related alkyl group containing another leaving group X' such as methanesulfonate or trifluoromethanesulfonate, in the presence of a suitable base, to provide an alkylated amine 38. Alternatively, an amine 7 can be treated with an aldehyde RCHO or a ketone RC(=O)R', in the presence of a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride, to provide an alkylated amine 38 (where R' is H if an aldehyde is used). An amine 7 can be treated with an aryl or heteroaryl iodide ArI, an aryl or heteroaryl bromide ArBr, an aryl or heteroaryl chloride ArCl, or an aryl or heteroaryl trifluoromethanesulfonate $ArOS(=O)_2CF_3$ in the presence of a suitable palladium catalyst to provide an arylamine 39 (a reaction commonly known as the Buchwald-Hartwig coupling; see, for example, *Chem. Sci.* 2011, 2, 27; *Acc. Chem. Res.* 1998, 31, 805; *Angew. Chem. Int. Ed.* 2008, 47, 6338).

SCHEME 7

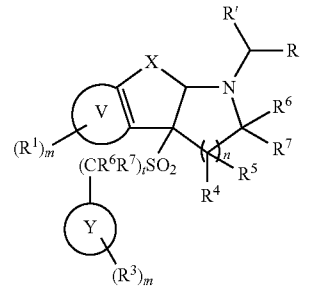


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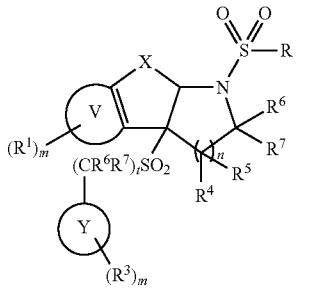
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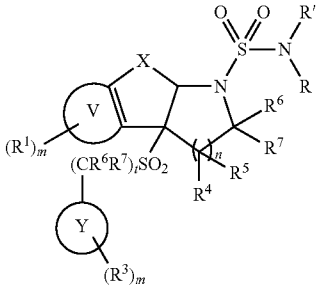
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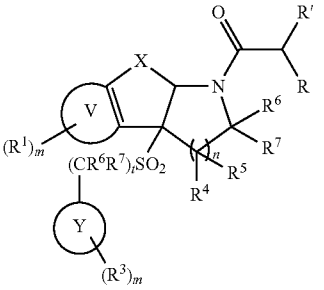
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35



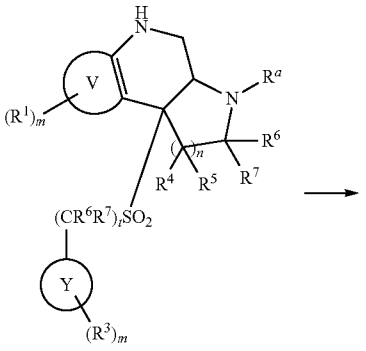
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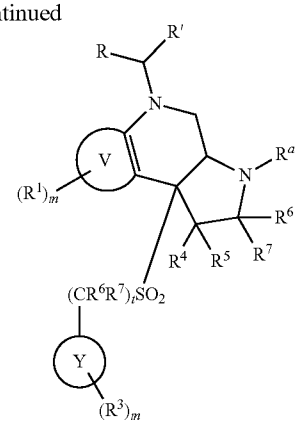
A method for preparing certain compounds 41 is shown in Scheme 8. An amine 40 can be treated with an aldehyde RCHO or a ketone RC(=O)R' the presence of a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride to provide the alkylated amine 41. Alternatively, an amine 40 can be treated with an alkyl chloride, alkyl bromide, alkyl iodide or other activated alkyl derivatives such as an alkyl methanesulfonate or alkyl trifluoromethanesulfonate, in the presence of a suitable base, to provide the alkylated amine 41. If R^a in 41 is a protecting group such as Boc, it can be removed using standard methods and the resulting amine reacted as desired, for example as shown in Scheme 7.

SCHEME 8



40

-continued



41

A variety of available methods may be used for conversion of intermediates or compounds of the invention to other intermediates or compounds of the invention. Some examples, well known to those skilled in the art of organic chemistry, include but are not limited to: conversion of a carboxylic acid ester to a carboxylic acid; conversion of a carboxylic acid to an amide; conversion of an amine to an amide, a urea, or a sulfonamide; alkylation or arylation of an amine; replacement of an aryl halide by an alkyl group, an aryl group or an amino group; and electrophilic substitution of an aromatic ring.

It will be appreciated by one skilled in the art of organic chemistry that various steps in a synthesis may be performed in an alternative sequence from that described in order to give a desired compound or compounds.

EXAMPLES

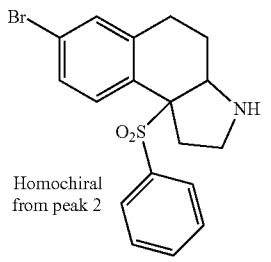
The following examples illustrate the particular and preferred embodiments of the present invention and do not limit

the scope of the present invention. Chemical abbreviations and symbols as well as scientific abbreviations and symbols have their usual and customary meanings unless otherwise specified. Additional abbreviations employed in the Examples and elsewhere in this application are defined below. Common Intermediates are generally useful for the preparation of more than one Example and are identified sequentially by the Intermediate number and step in which they were prepared (e.g., Intermediate 1, Step A), or by the Intermediate number only where the compound is the title compound. Compounds of the Examples are identified by the Example number and step in which they were prepared (e.g., Example 1, Step A) if the compound is an intermediate, or by the Example number only where the compound is the title compound of the Example. In some instances alternative preparations of Intermediates or Examples are described. Frequently chemists skilled in the art of synthesis may devise alternative preparations which may be desirable based on one or more considerations such as shorter reaction time, less expensive starting materials, ease of operation or isolation, improved yield, suitability to catalysis, avoidance of toxic reagents, accessibility of specialized instrumentation, decreased number of linear steps, etc. The intent of describing alternative preparations is to further enable the preparation of the Examples of this invention. In some instances some functional groups in the outlined Examples and claims may be replaced by well known bioisosteric replacements known in the art, for example, replacement of a carboxylic acid group with a tetrazole or a phosphate moiety. Starting materials and intermediates for which no preparation is explicitly shown are available commercially, are known in the literature, or may be prepared by analogy to similar compounds which are known in the literature.

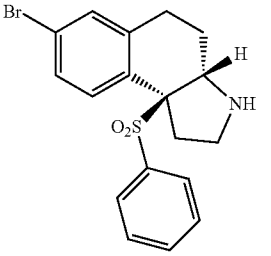
Heating of a reaction mixture via microwave irradiation was done in sealed vials using a Biotage® Initiator Microwave Synthesizer. Solvent removal was performed by concentration under reduced pressure. Column chromatography was generally performed using the flash chromatography technique (*J. Org. Chem.* 1978, 43, 2923), or with prepacked silica gel cartridges using a CombiFlash® automated chromatography apparatus (Teledyne Isco), eluting with the solvent or solvent mixture indicated. Analytical and preparative high performance liquid chromatography (HPLC) was generally performed using a reverse phase column of a size appropriate to the quantity of material being separated, generally eluting with a gradient of increasing concentration of methanol or acetonitrile in water, also containing 0.05% or 0.1% trifluoroacetic acid or 10 mM ammonium acetate, at a rate of elution suitable to the column size and separation to be achieved. Chiral super-critical fluid chromatographic (SFC) separation of enantiomers or diastereomers was performed using conditions described for the individual cases. Mass spectral data were obtained by liquid chromatography mass spectroscopy (LCMS) using electrospray ionization.

Many Intermediates and Examples are homochiral (entirely or mostly a single enantiomer), but in some cases the absolute configuration has not been proven. In those cases, a text notation to the left of the structure will indicate that the compound is homochiral, and indicates whether the compound was obtained from (or is derived from an intermediate which was obtained from) the specified peak eluting during chiral SFC separation. However, in all cases, the stereochemistry within the tricyclic ring system is cis. Thus, for example, the structure 42 shown below indicates that, while the material is homochiral, the absolute stereochemistry of the material, which was derived from the second-eluting peak during SFC separation, is not known, but is either the absolute stereochemistry shown in 42a or that shown in 42b.

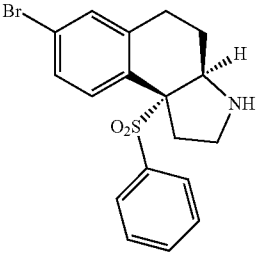
42



42a

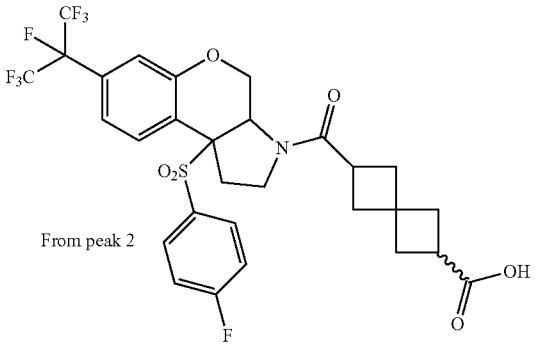


42b



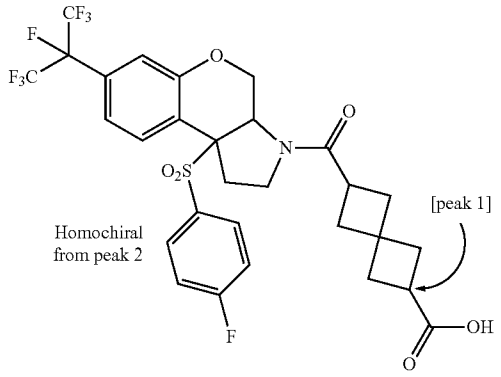
In some cases, an Intermediate or Example is derived from combining a homochiral starting material with a non-homochiral or racemic starting material, yielding a mixture of two or more diastereomers. In such cases, if the absolute stereochemistry of the homochiral starting material is not known, a text notation to the left of the structure will indicate that the chiral centers of the tricyclic moiety are those of the homochiral tricyclic intermediate derived from the indicated peak eluting during chiral SFC separation (as above), while the non-homochiral asymmetric center or centers are indicated by a wavy line, for example as shown in structure 43 below.

43



In some cases, a diastereomeric mixture resulting from combining a homochiral starting material with a non-homochiral starting material (such as structure 43 above) has been separated by a method such as chiral SFC to give a homochiral product wherein the absolute stereochemistry at none of the asymmetric centers is known. In such cases, a text notation to the left of the structure (as above) will indicate that the chiral centers of the tricyclic moiety are those of the tricyclic intermediate derived from the indicated peak eluting during chiral SFC separation of the intermediate, and a text notation in brackets to the right of the structure will indicate the peak (from the separation of the diastereomeric mixture such as structure 43 above) from which the product was isolated. An example is shown in Structure 44 below, which indicates that the tricyclic moiety is derived from peak 2 eluting during chiral separation of a tricyclic intermediate used to prepare 43, while the final product 44 is derived from peak 1 eluting during chiral separation of the diastereomeric mixture 43.

44



If the absolute configuration at an asymmetric center of an Intermediate or Example is known, or that asymmetric center is derived from a precursor whose absolute configuration is known, this is explicitly shown in the structure of the Intermediate or Example. If no absolute configuration is explicitly shown at an asymmetric center in a structure, and no text notation is present with the structure (as above), that chiral center is either racemic or of undefined stereochemistry.

Chemical names were determined using ChemBioDraw Ultra, version 14.0.0.126 (PerkinElmer Inc.). The following abbreviations are used:

ABBREVIATION	NAME
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Boc	tert-butyloxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
$CDCl_3$	deuterated chloroform
DAST	diethylaminosulfur trifluoride
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-d_6	deuterated dimethyl sulfoxide
Et_3N	triethylamine
EtOAc	ethyl acetate
h	hours

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ABBREVIATION	NAME
HATU	O-(7-azabenzotriazol-l-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
LCMS	liquid chromatography - mass spectrometry
MeCN	acetonitrile
MeOH	methanol
MeOH-d_4	deuterated methanol
mCPBA	meta-chloroperoxybenzoic acid
min	minutes
MsCl	methanesulfonyl chloride
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
rt	room temperature
SFC	super-critical fluid chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	chromatographic retention time
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

HPLC Methods

Method A: (Analytical)

Column: Kinetex® XB-C_{18} 3×75 mm, 2.6 m (Phenomenex Inc.); mobile phase A: 10 mM ammonium acetate in water-MeCN (98:2); mobile phase B: 10 mM ammonium acetate in water-MeCN (2:98); flow rate 1 mL/min; gradient 4.7 min.

Method B: (Analytical)

Column: Acquity UPLC® BEH C_{18} 2.1×50 mm, 1.7 m (Waters Corp.); mobile phase A: water with 0.05% TFA; mobile phase B: MeCN with 0.05% TFA; temperature: 50° C.; flow rate 0.80 mL/min; gradient: 2-98% B over 1 min, then 0.5 min isocratic at 98% B.

Method C: (analytical)

Column: Acquity UPLC® BEH C_{18} 2.1×50 mm, 1.7 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 10 mM ammonium acetate; mobile phase B: 95:5 MeCN-water with 10 mM ammonium acetate; temperature: 50° C.; flow rate 1.0 mL/min; gradient: 0-100% B over 3 min, then 0.75 min isocratic at 100% B.

Method D: (analytical)

Column: Acquity UPLC® BEH C_{18} 2.1×50 mm, 1.7 μm (Waters Corp.); mobile phase A: 5:95 MeCN-water with 0.1% TFA; mobile phase B: 95:5 MeCN-water with 0.1% TFA; temperature: 50° C.; flow rate 1.0 mL/min; gradient: 0-100% B over 3 min, then 0.75 min isocratic at 100% B.

Method E: (preparative)

Column: XBridge™ C_{18} 19×200 mm, 5 m (Waters Corp.); mobile phase A: 5:95 MeCN-water with 10 mM ammonium acetate; mobile phase B: 95:5 MeCN-water with 10 mM ammonium acetate; flow rate 20 mL/min; gradient: increasing B, then isocratic.

Method F: (preparative)

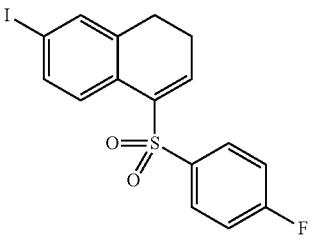
Column: XBridge™ C_{18} 19×200 mm, 5 m (Waters Corp.); mobile phase A: 5:95 MeCN-water with 0.1% TFA; mobile phase B: 95:5 MeCN-water with 0.1% TFA; flow rate 20 mL/min; gradient: increasing B, then isocratic.

Method G: (preparative)

Column: Luna® C_{18} 30×100 mm, 5 m (Phenomenex Inc.); mobile phase A: water with 0.1% TFA; mobile phase B: MeCN with 0.1% TFA; flow rate 30 mL/min; gradient: increasing B, then isocratic.

Intermediate 1

4-((4-fluorophenyl)sulfonyl)-7-iodo-1,2-dihydronaphthalene



A solution of 6-iodo-3,4-dihydronaphthalen-1(2H)-one (13.3 g, 48.9 mmol) and $TiCl_4$ (1 M in DCM, 48.9 mL, 48.9 mmol) in THF (326 mL) in an ice-water bath was treated with a solution of 4-fluorobenzenethiol (6.3 mL, 58.7 mmol) and Et_3N (13.6 mL, 98 mmol) in THF (25 mL) at a rate such that the temperature remained below 10° C. The solution was stirred at rt for 60 min, then was treated with water (200 mL) and concentrated to remove the bulk of the organic solvents. The aqueous residue was extracted with diethyl ether (2×250 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide crude (4-fluorophenyl)(6-iodo-3,4-dihydronaphthalen-1-yl)sulfane (20 g) as a mixture with the corresponding thioketal, which was used directly. HPLC t_R 1.36 min (method B).

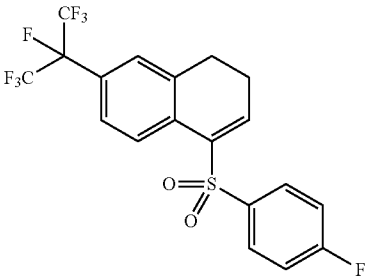
A solution of (4-fluorophenyl)(6-iodo-3,4-dihydronaphthalen-1-yl)sulfane and its thioketal (the mixture from the above reaction, 18.69 g) in DCM (978 mL) in an ice-water bath was treated portionwise with mCPBA (21.92 g, 98 mmol). The mixture was allowed to reach rt and was stirred for 1 h, when LCMS showed consumption of the starting material and 4-((4-fluorophenyl)sulfinyl)-7-iodo-1,2-dihydronaphthalene as the major product. Additional mCPBA (10.96 g, 48.9 mmol) was added at rt. The reaction was stirred for 30 min, when LCMS showed very little sulfoxide (t_R 1.00 min, method B). The mixture was washed twice with saturated aqueous $NaHCO_3$, and the organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography, eluting with EtOAc-hexanes (gradient from 0-10%). The resulting material was dissolved in EtOAc and washed twice with saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4 and concentrated to provide 4-((4-fluorophenyl)sulfonyl)-7-iodo-1,2-dihydronaphthalene as a white foamy solid (12 g, 59% yield over two steps). LCMS m/z 455.9 $(M+H+MeCN)^+$, HPLC t_R 1.09 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.89 (m, 2H), 7.64 (d, J=8.8 Hz, 1H), 7.57-7.47 (m, 3H), 7.22-7.13 (m, 2H), 2.79-2.68 (m, 2H), 2.61-2.50 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.7 (s, 1F).

Alternative Procedure:

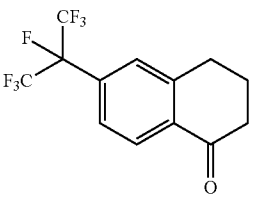
A solution of 6-iodo-3,4-dihydronaphthalen-1(2H)-one (5.0 g, 18.38 mmol), 4-fluorobenzenethiol (4.11 mL, 38.6 mmol) and absolute ethanol (20 mL) was cooled with an ice-water bath and bubbled with HCl gas until saturation was reached (observed by the formation of a white precipitate). The mixture was allowed to warm to rt and stirred overnight. The mixture was dissolved in ether (250 mL) and washed sequentially with water (2×125 mL), 0.5 M aqueous Na_2CO_3 (3×100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated to provide a solid (9.2 g) which was a mixture of thioketal and vinyl sulfide. The solid was dissolved in chloroform (150 mL) and cooled in an ice-water bath. A solution of mCPBA (35 g, 156 mmol) in DCM (200 mL) was washed with brine (50 mL), dried over Na_2SO_4, filtered, and the filter cake was washed with DCM (50 mL). The combined filtrates were added dropwise in portions to the chloroform solution of the products from above until the reaction was completed as judged by LCMS (175 mL of the mCPBA solution was needed). The mixture was cooled in an ice bath, filtered to remove the insoluble material, and the filtrate was stirred with 10% aqueous $Na_2S_2O_3$ (120 mL) for 5 min. The organic phase was separated, washed sequentially with 10% aqueous $Na_2S_2O_3$ (2×120 mL), 10% aqueous Na_2CO_3 (3×200 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 0-20%) to give 4-((4-fluorophenyl)sulfonyl)-7-iodo-1,2-dihydronaphthalene (5.3 g, 70% yield) as a white foamy solid.

Intermediate 2

4-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2-dihydronaphthalene



Step A: 6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1(2H)-one

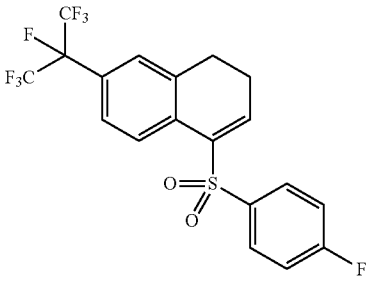


Activated copper was prepared by adding zinc dust (24.57 g, 376 mmol) portionwise with stirring to a solution of copper(II) sulfate (45.09 g, 283 mmol) in water (250 mL) over 10 min. The mixture was stirred 10 min longer, then the supernatant was decanted from the red precipitate. This was washed twice with water by decantation, then was stirred with 1 M aqueous HCl (400 mL) for 2.5 h. The supernatant was decanted and the precipitate was washed with water by decantation until the pH of the supernatant was about 7. The

solid was stored under water and an inert atmosphere (nitrogen or argon). For use the solid was washed twice by decantation with MeOH, then twice with diethyl ether, and dried under vacuum.

Dried activated copper (10.13 g, 159 mmol) was combined with 6-iodo-3,4-dihydronaphthalen-1(2H)-one (4.20 g, 15.44 mmol) and dry DMF (85 mL), bubbled with argon, and treated with 1,1,1,2,3,3,3-heptafluoro-2-iodopropane (8.78 mL, 61.7 mmol). The reaction vessel was sealed under argon and heated at 120° C. for 3 h. The mixture was cooled to rt, diluted with EtOAc and filtered through Celite. The solids were washed with additional EtOAc and the combined filtrates were concentrated. The residue was dissolved in EtOAc, shaken with water, and the mixture was filtered through Celite. The solids were washed with additional EtOAc, and the organic phase of the combined filtrates was separated, washed twice with 5% aqueous LiCl, then with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 5-30%), to provide 6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1(2H)-one as an orange oil (3.32 g, 68% yield). LCMS m/z 356.0 $(M+H+MeCN)^+$, HPLC t_R 1.13 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J=8.4 Hz, 1H), 7.58 (d, J=8.6 Hz, 1H), 7.55 (s, 1H), 3.07 (t, J=6.1 Hz, 2H), 2.77-2.71 (t, J=6.6 Hz, 2H), 2.22 (quintet, 6.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.38 (d, J=7.2 Hz, 6F), −182.41 (septet, J=7.2 Hz, 1F).

Step B: 4-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2-dihydronaphthalene



Following the alternative procedure used to prepare Intermediate 1, 6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1(2H)-one was converted into 4-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2-dihydronaphthalene in quantitative yield, with minor impurities present, and was used without further purification. LCMS m/z 457.3 $(M+H)^+$, HPLC t_R 1.12 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dt, J=8.9, 4.3 Hz, 3H), 7.58 (t, J=4.8 Hz, 1H), 7.44 (d, J=8.6 Hz, 1H), 7.39 (s, 1H), 7.22 (t, J=8.6 Hz, 2H), 2.92-2.84 (m, 2H), 2.65 (td, J=8.0, 5.0 Hz, 2H).

The Intermediates in Table 1 were prepared using the same methods or similar methods used to prepare Intermediates 1 and 2, by employing the appropriate ketone and substituted thiophenol.

TABLE 1

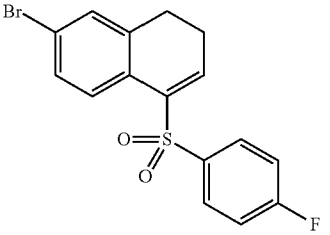
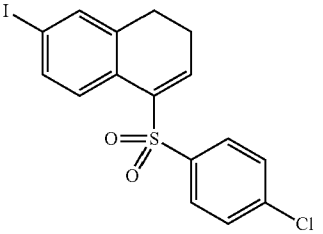
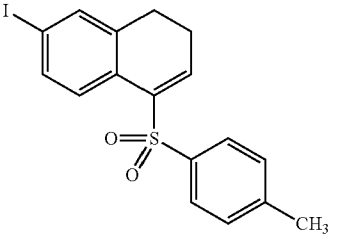
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
3		364.8 $(M + H + MeCN)^+$	1.09	B
4		493.8 $(M + Na + MeCN)^+$	1.13	B
5		451.9 $(M + H + MeCN)^+$	1.12	B

TABLE 1-continued

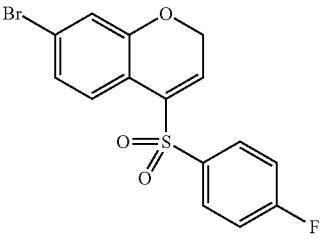
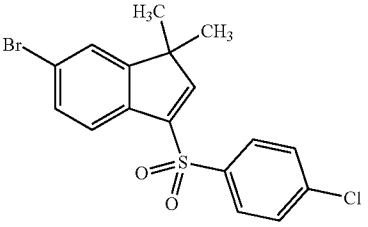
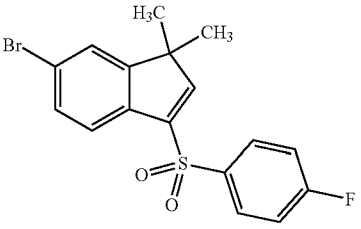
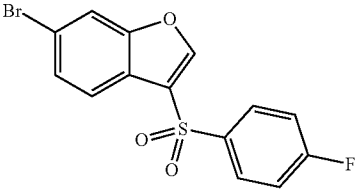
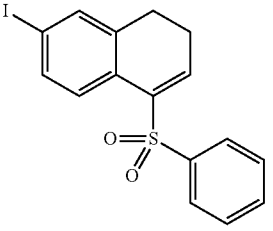
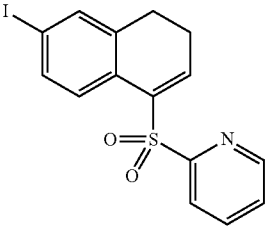
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
6		410.0 $(M + H + MeCN)^+$	1.08	B
7		438.0 $(M + H + MeCN)^+$	1.18	B
8		422.1 $(M + H + MeCN)^+$	1.13	B
9		396.1 $(M + H + MeCN)^+$	1.08	B
10		438.0 $(M + H + MeCN)^+$	1.11	B
11		398.4 $(M + H)^+$	1.01	B

TABLE 1-continued

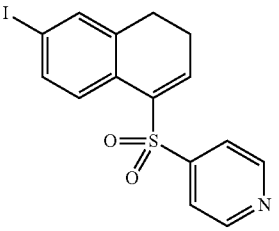
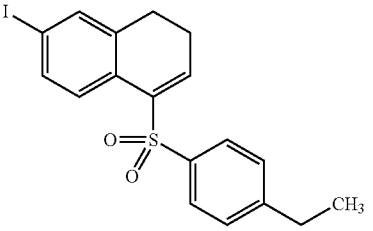
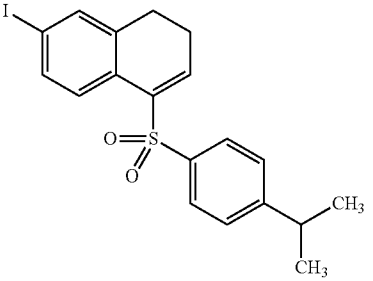
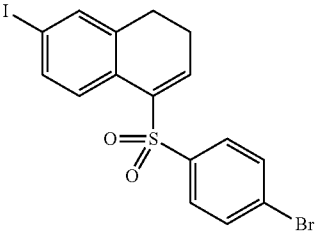
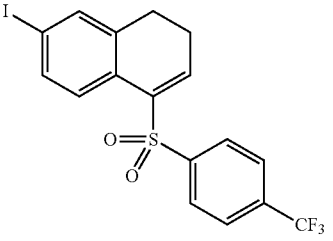
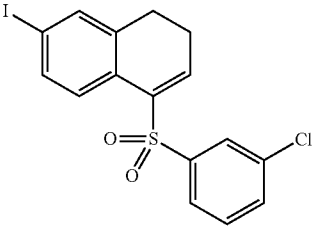
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
12		398.0 $(M + H)^+$	1.01	B
13		466.0 $(M + H + MeCN)^+$	1.17	B
14		480.0 $(M + H + MeCN)^+$	1.20	B
15		516.0 $(M + H + MeCN)^+$	1.19	B
16		506.0 $(M + H + MeCN)^+$	1.17	B
17		472.1 $(M + H + MeCN)^+$	1.13	B

TABLE 1-continued

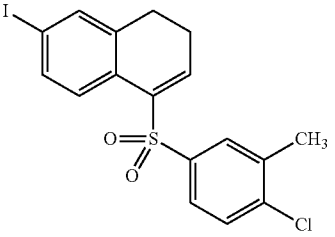
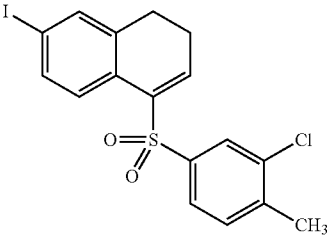
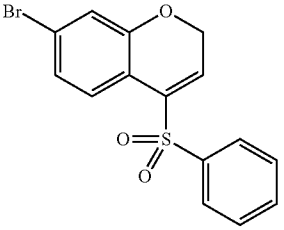
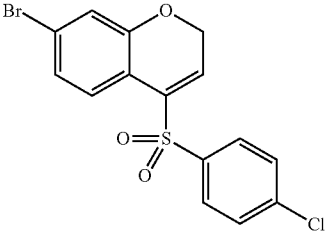
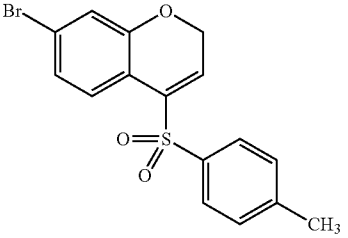
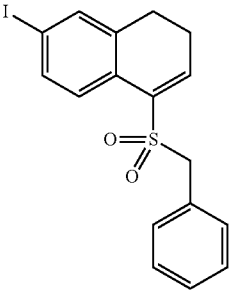
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
18		486.0 $(M + H + MeCN)^+$	1.21	B
19		486.0 $(M + H + MeCN)^+$	1.21	B
20		350.9 $(M + H)^+$	1.06	B
21		447.9 $(M + Na + MeCN)^+$	1.10	B
22		365.0 $(M + H)^+$	1.06	B
23		452.0 $(M + H + MeCN)^+$	1.11	B

TABLE 1-continued

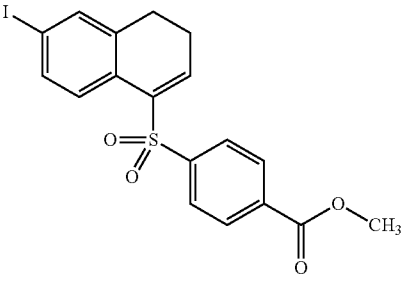
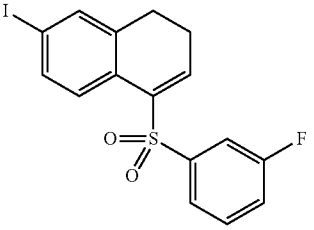
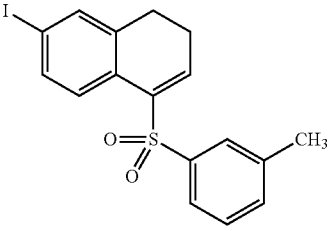
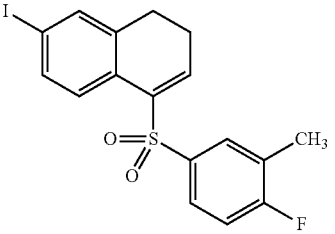
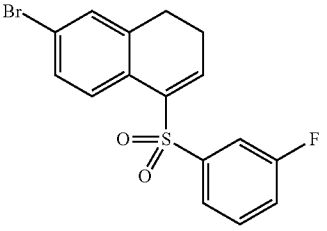
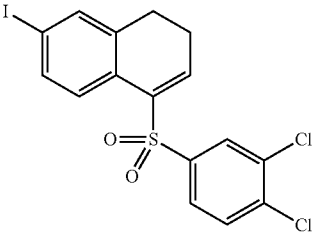
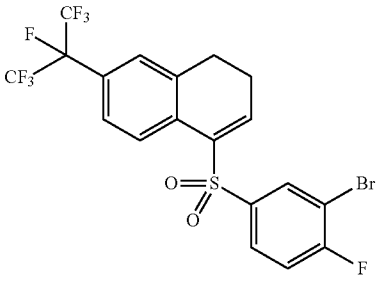
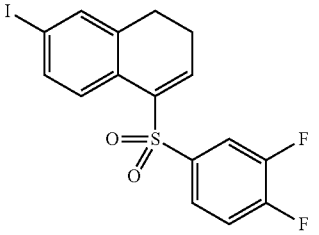
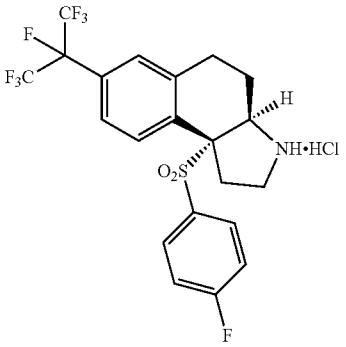
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
24		496.1 $(M + H + MeCN)^+$	1.12	B
25		455.9 $(M + H + MeCN)^+$	1.09	B
26		411.0 $(M + H)^+$	1.10	B
27		428.9 $(M + H)^+$	1.10	B
28		407.8 $(M + H + MeCN)^+$	1.11	B
29		465.1 $(M + H)^+$	1.18	B

TABLE 1-continued

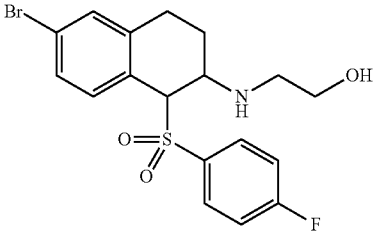
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
30		576.2 $(M + H + MeCN)^+$	1.16	B
31		474.0 $(M + H + MeCN)^+$	1.09	B

Intermediate 32

(3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride

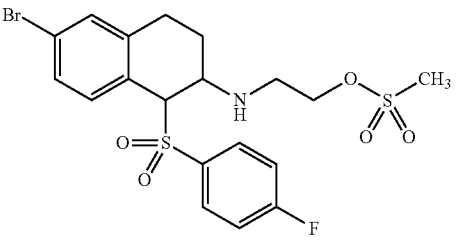


Step A: 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethan-1-ol



A solution of 7-bromo-4-((4-fluorophenyl)sulfonyl)-1,2-dihydronaphthalene (Intermediate 3; 5.7 g, 15.52 mmol) in THF (259 mL) in an ice-water bath was treated with 2-aminoethanol (13.42 mL, 233 mmol). The mixture was stirred at about 5° C. for 30 min, when LCMS showed complete consumption of the starting material. The mixture was concentrated and the resulting oil was dissolved in EtOAc (250 mL), washed with saturated aqueous $NaHCO_3$, then twice with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc, to provide 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethanol (2.8 g, 42% yield. LCMS m/z 427.8 $(M+H)^+$, HPLC t_R 0.71 min (method B).

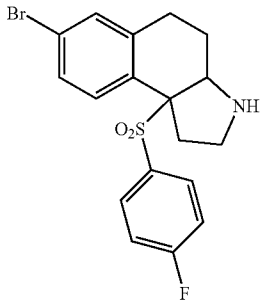
Step B: 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethyl methanesulfonate



A solution of 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethanol (2.8 g, 6.54 mmol) in DCM (654 mL) was treated at rt with MsCl (0.611 mL, 7.84 mmol) followed by Et_3N (1.093 mL, 7.84 mmol). The mixture was stirred for 1 h, when LCMS showed complete consumption of the starting material. The mixture was washed with a 1:1 mixture of brine and water, and the organic layer was dried over Na_2SO_4, filtered and concentrated to provide 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethyl

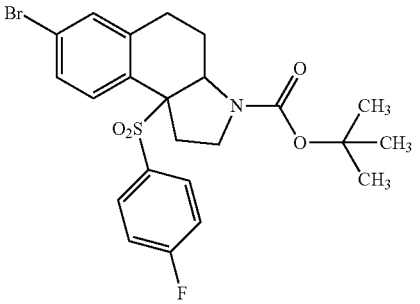
methanesulfonate (2.9 g, 88% yield), used without further purification. LCMS m/z 505.9 $(M+H)^+$, HPLC t_R 0.76 min (method B).

Step C: 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole



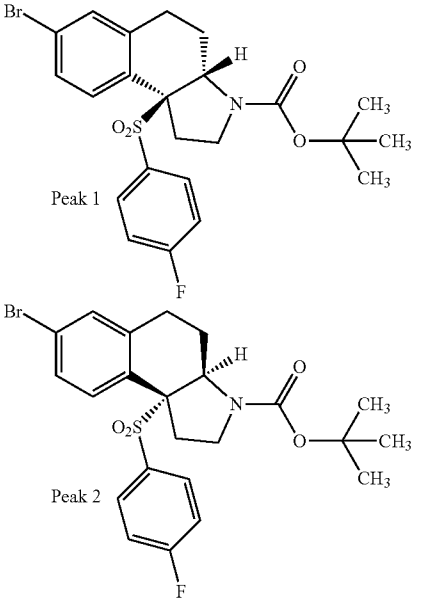
A solution of 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethyl methanesulfonate (2.9 g, 5.73 mmol) in THF (286 mL) was treated portionwise with potassium tert-butoxide ((3.21 g, 28.6 mmol) at rt, such that the temperature of the reaction mixture did not exceed 25.5° C. The mixture was stirred for 1 h, when LCMS showed complete consumption of starting material. The mixture was treated with 100 mL of a 1:1 mixture of water and brine and partially concentrated. The aqueous residue was extracted with EtOAc (2×125 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to provide crude 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (2.1 g), used without further purification. LCMS m/z 409.9 $(M+H)^+$, HPLC t_R 0.76 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.43 (m, 1H), 7.42-7.35 (m, 1H), 7.32-7.27 (m, 2H), 7.11 (s, 1H), 7.02 (t, J=8.78 Hz, 2H), 3.97 (dd, J=12.0, 6.0 Hz, 1H), 3.32 (dd, J=11.5, 4.0 Hz, 1H), 3.27-3.13 (m, 1H), 3.02 (d, J=12.0 Hz, 1H), 2.50-2.30 (m, 2H), 2.05-1.95 (m, 1H), 1.77-1.56 (m, 1H), 1.34-1.20 (m, 1H).

Step D: tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carboxylate



A solution of 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (2.1 g, 5.12 mmol) in DCM (50 mL) was treated with di-tert-butyl dicarbonate (1.426 mL, 6.14 mmol) and Et_3N (1.427 mL, 10.24 mmol). The mixture was stirred at rt for 1 h, when LCMS showed complete consumption of starting material. The mixture was diluted with DCM (100 mL) and washed sequentially with 1 M aqueous HCl and 1 M aqueous NaOH. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to afford tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carboxylate (1.6 g, 61% yield for 3 steps). LCMS m/z 453.9 $(M+H—C_4H_8)^+$, HPLC t_R 1.15 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.51 (m, 1H), 7.46-7.32 (m, 3H), 7.16-6.91 (m, 3H), 4.49-4.45 (m, 1H), 3.76-3.73 (m, 1H), 3.59-3.38 (m, 2H), 2.43-2.34 (m, 3H), 1.73 (t, J=14.8 Hz, 1H), 1.49 (s, 9H), 1.34-1.12 (m, 1H). ^{19}F NMR (376 MHz) δ −102.6.

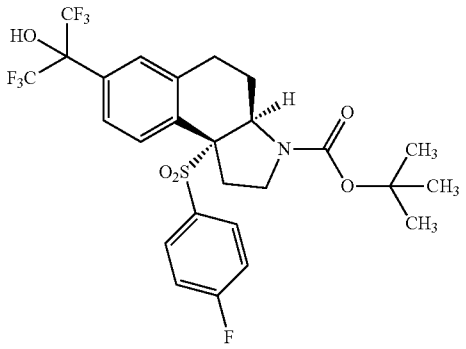
Step E: (3aS,9bS)-tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate and (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-bromo-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate



A sample of tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-bromo-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (1.6 g, 3.13 mmol) was separated by chiral SFC using the following conditions: Column: Lux® Cellulose-4 (4.6×250) mm, 5 μm (Phenomenex Inc.); column temperature 24.9° C.; CO_2 flow rate: 2.10 mL/min; co-solvent: 30% of 0.2% diethylamine in MeOH, flow rate 0.9 mL/min; injection volume: 10 mL. Peak 1 ((3aS,9bS)-tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate) was eluted with t_R 2.79 min. Peak 2 ((3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-bromo-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate, 0.7 g) was eluted with t_R 3.92 min (100%). The absolute configurations of peaks 1 and 2 were determined based on single crystal X-ray analysis from the anomalous dispersion signal using the FLACK method. Analytical data for Peak 2: LCMS m/z 453.9 $(M+H—C_4H_8)^+$, HPLC t_R 1.15 min (method B); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.51 (m, 1H), 7.46-7.32 (m, 3H), 7.16-6.91 (m, 3H), 4.49-4.45

(m, 1H), 3.76-3.73 (m, 1H), 3.59-3.38 (m, 2H), 2.43-2.34 (m, 3H), 1.73 (t, J=14.8 Hz, 1H), 1.49 (s, 9H), 1.34-1.12 (m, 1H). ^{19}F NMR (376 MHz) δ −102.6.

Step F: (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl) sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate

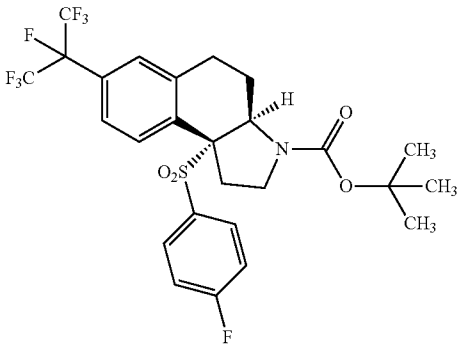


tert-Butyllithium (3 M in heptane, 376 μL, 0.940 mmol) was added dropwise to a stirred solution of (3aR,9bR)-tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (240 mg, 0.470 mmol) (which had been dried by concentration from toluene three times) in diethyl ether (8.2 mL) under nitrogen in a dry ice acetone bath. The resulting brownish solution was stirred for 15 min at −78° C. Gaseous $CF_3C(O)CF_3$ (3.28 g. 19.73 mmol) was slowly added via a needle by placing the tip of the needle just above the cold solution to allow the gas to condense (about 2 min; the weight of reagent added was estimated by weighing the gas cylinder before and after the addition). The resulting mixture was stirred under nitrogen for 30 min at −78° C., then at rt for 30 min. The mixture was treated with saturated aqueous NH_4Cl (15 mL) and diluted with EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography on silica gel, eluting with hexanes followed by a gradient to 30% EtOAc-hexanes, to provide (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (200 mg, 71% yield, about 75% purity). LCMS m/z 541.8 $(M+H—C_4H_8)^+$, HPLC t_R 1.08 min (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=8.4 Hz, 1H), 7.61 (d, J=8.1 Hz, 1H), 7.41 (dd, J=8.3, 5.2 Hz, 2H), 7.38-7.32 (m, 1H), 7.04 (t, J=8.3 Hz, 2H), 4.55-4.38 (m, 1H), 3.81-3.66 (m, 1H), 3.57-3.32 (m, 2H), 2.52-2.29 (m, 3H), 1.74 (t, J=13.2 Hz, 1H), 1.52 (br. s., 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.5 (s, 1F), −75.5 (s, 6F).

Alternative preparation of (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate

The same procedure was used, but starting with (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-iodo-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (prepared by following the procedures of Steps A through E above, but starting from Intermediate 1 instead of Intermediate 3; 1.1 g, 1.973 mmol) to provide (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (0.7 g, 70% yield, about 80% purity).

Step G: (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate

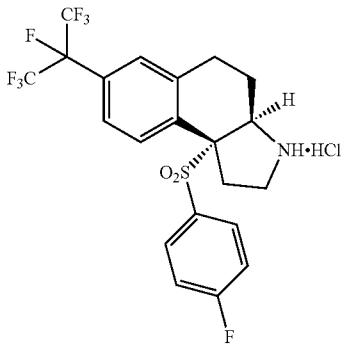


DAST (2.92 mL, 22.09 mmol) was added to a stirred solution of (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (1.1 g, 1.841 mmol) in 1,2-dichloroethane (18.41 mL) under N_2 at rt. The reaction vessel was sealed and heated with stirring at 60° C. After 15 h, LCMS showed only partial consumption of the starting material. Additional DAST (2.92 mL, 22.09 mmol) was added and the mixture was stirred at 60° C. for 4 h more. The mixture was cooled to rt, carefully quenched with MeOH (1 mL), diluted with EtOAc (160 mL) and washed with saturated aqueous $NaHCO_3$. The aqueous phase was separated and extracted with EtOAc (100 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 5-40%), to provide (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (800 mg, 72.5% yield). LCMS m/z 544.0 $(M+H—C_4H_8)^+$, HPLC t_R 1.21 min (method B).

Alternative preparation of (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate

A mixture of activated copper (prepared as outlined in Step A of the preparation of Intermediate 2; 3.5 g, 55 mmol) and (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-iodo-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (prepared by following the procedures of Steps A through E above, but starting from Intermediate 1 instead of Intermediate 3; 4 g, 7.2 mmol) in dry DMF (18 mL) was purged with nitrogen, treated with 1,1,1,2,3,3,3-heptafluoro-2-iodopropane (4.6 mL, 32 mmol) and heated at 120° C. in a sealed reaction vessel. After 4 h the mixture was cooled to rt, diluted with EtOAc and filtered through Celite. The filtrate was washed 4 times with brine, dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica, eluting with EtOAc-hexanes, to provide (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (3.6 g, 84% yield).

Step H: (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride



A solution of (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (250 mg, 0.417 mmol) in DCM (4.2 mL) was treated with HCl (4 M in 1,4-dioxane, 4.2 mL, 16.68 mmol). After 1 h at rt, the mixture was concentrated to provide (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole, HCl (225 mg). LCMS m/z 500.0 $(M+H)^+$, HPLC t_R: 0.88 min (method B).

The Intermediates in Table 2 were prepared using procedures (or similar procedures) used in the preparation of Intermediate 32, starting from an appropriate vinylic sulfone, an appropriate aminocarbinol, and other appropriate reagents. In the preparation of some of the Intermediates in Table 2, one or more steps used in the preparation of Intermediate 32 were omitted, or applied in a different order, as appropriate.

TABLE 2

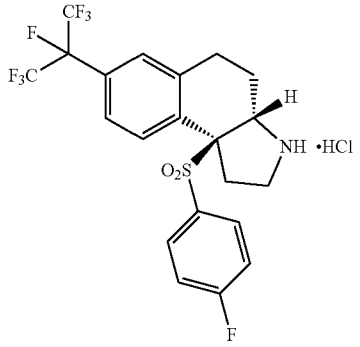
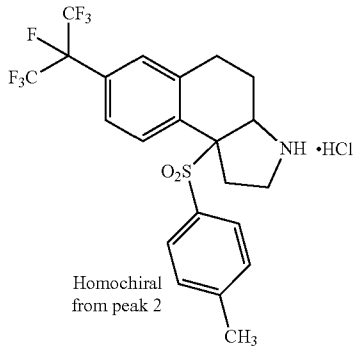
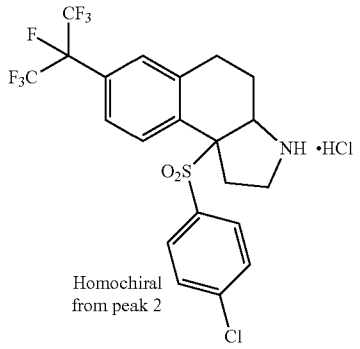
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
33		500.0 $(M + H)^+$	0.88	B
34		496.1 $(M + H)^+$	0.92	B
35		516.0 $(M + H)^+$	0.94	B

TABLE 2-continued

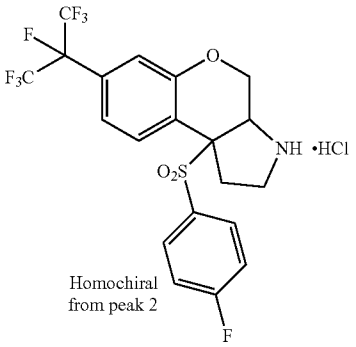
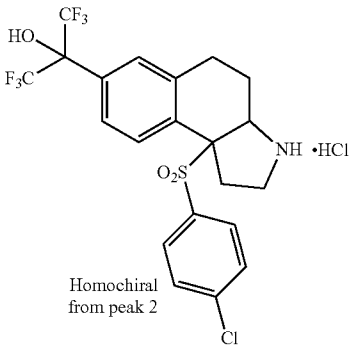
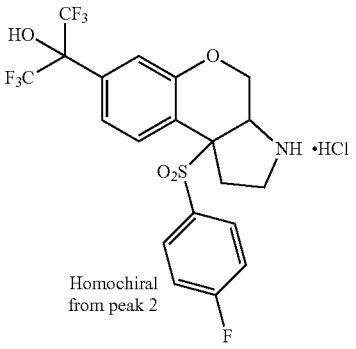
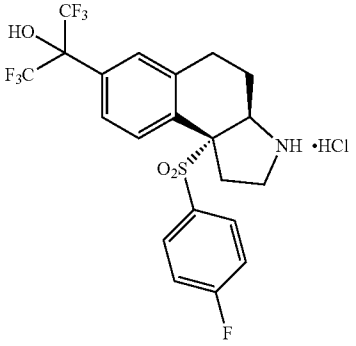
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
36		502.1 $(M + H)^+$	0.84	B
37		513.3 $(M + H)^+$	0.81	B
38		500.5 $(M + H)^+$	0.78	B
39		498.0 $(M + H)^+$	0.85	B

TABLE 2-continued

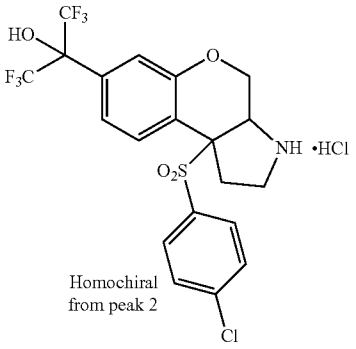
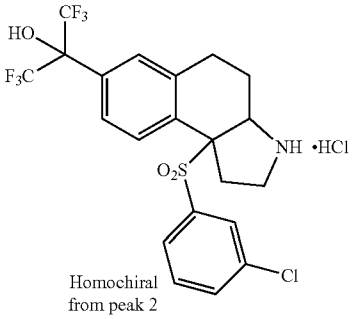
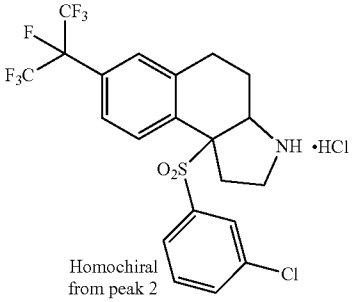
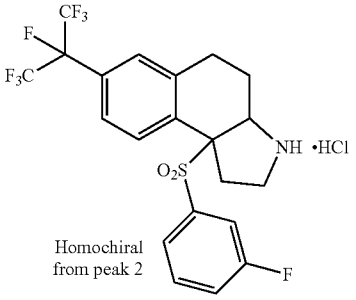
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
40		516.0 $(M + H)^+$	0.79	B
41		514.0 $(M + H)^+$	0.80	B
42		516.2 $(M + H)^+$	0.88	B
43		500.0 $(M + H)^+$	0.82	B

TABLE 2-continued

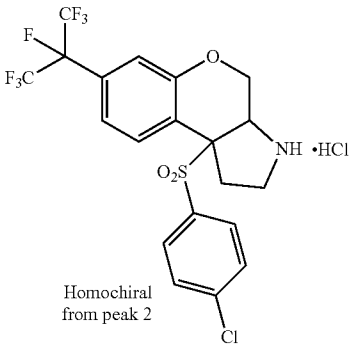
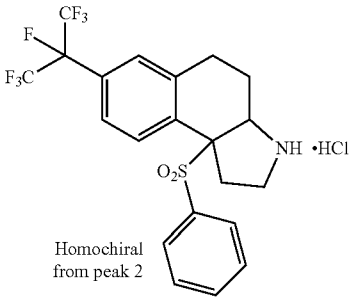
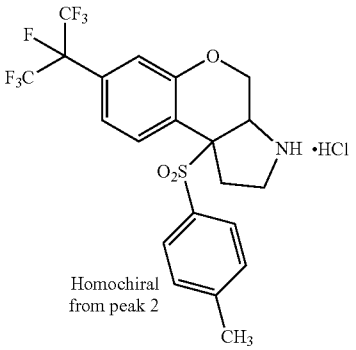
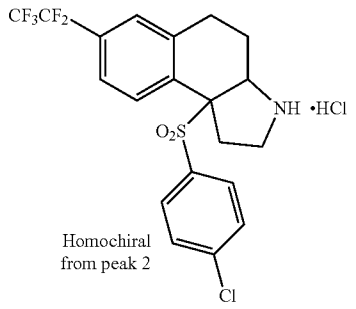
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
44		518.0 $(M + H)^+$	0.92	B
45		482.0 $(M + H)^+$	0.87	B
46		498.0 $(M + H)^+$	0.89	B
47		466.0 $(M + H)^+$	0.87	B

TABLE 2-continued

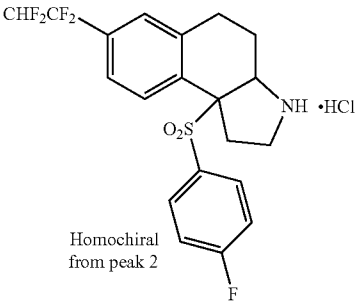
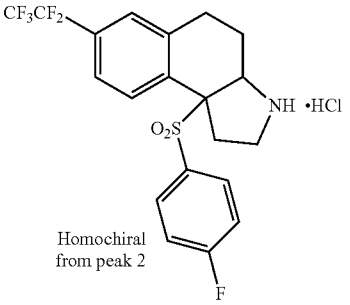
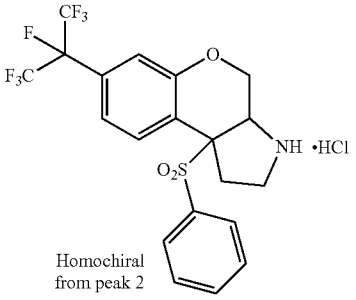
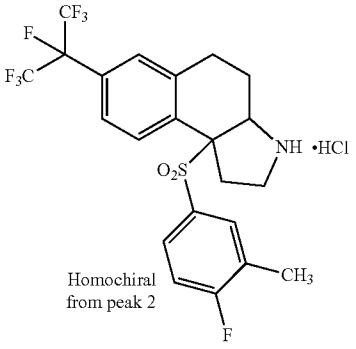
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
48		432.1 $(M + H)^+$	0.77	B
49		450.1 $(M + H)^+$	0.83	B
50		484.0 $(M + H)^+$	0.85	B
51		514.0 $(M + H)^+$	0.87	B

TABLE 2-continued

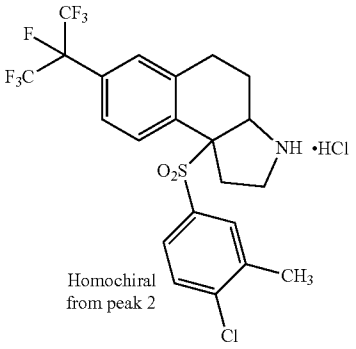
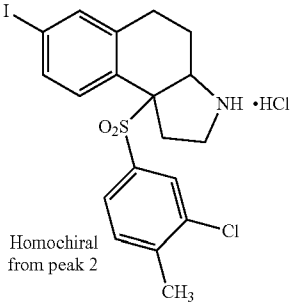
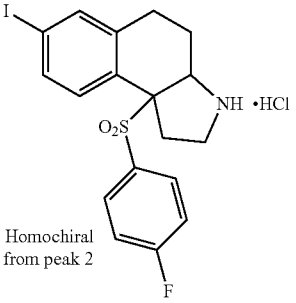
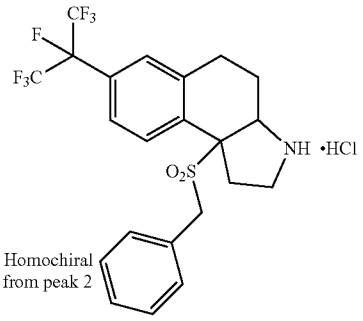
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
52	 Homochiral from peak 2	530.2 $(M + H)^+$	0.97	B
53	 Homochiral from peak 2	488.0 $(M + H)^+$	0.84	B
54	 Homochiral from peak 2	500.0 $(M + H)^+$	0.88	B
55	 Homochiral from peak 2	496.1 $(M + H)^+$	0.87	B

TABLE 2-continued

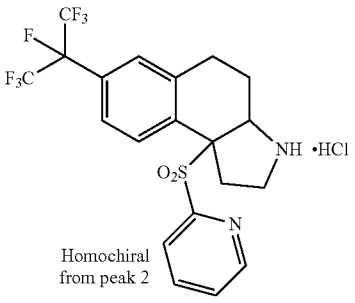
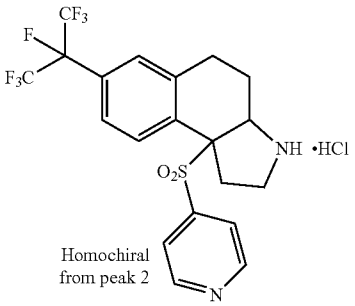
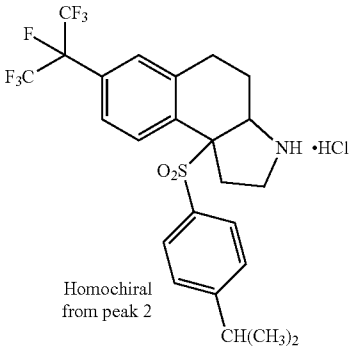
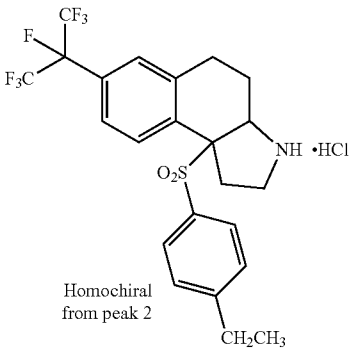
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
56		483.2 $(M + H)^+$	0.77	B
57		483.3 $(M + H)^+$	0.76	B
58		524.1 $(M + H)^+$	0.96	B
59		510.3 $(M + H)^+$	0.90	B

TABLE 2-continued

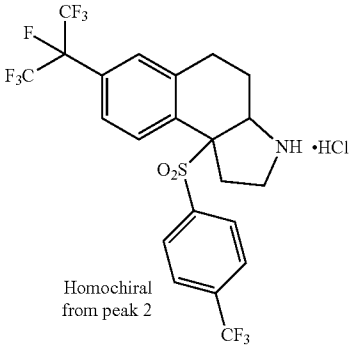
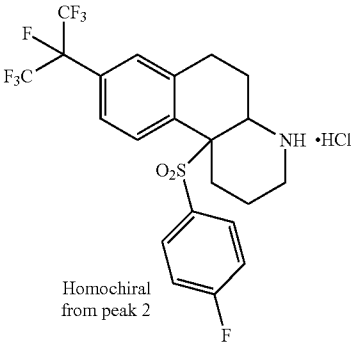
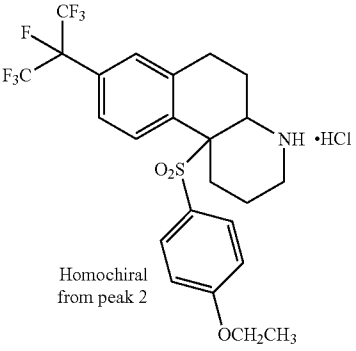
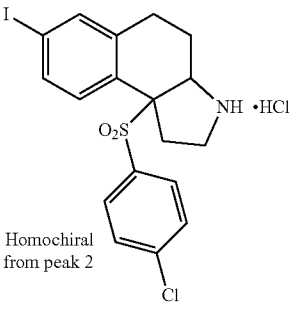
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
60		550.3 $(M + H)^+$	1.01	B
61		514.5 $(M + H)^+$	0.86	B
62		540.4 $(M + H)^+$	0.88	B
63		473.9 $(M + H)^+$	0.83	B

TABLE 2-continued

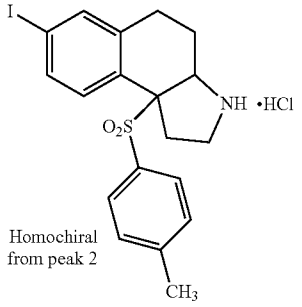
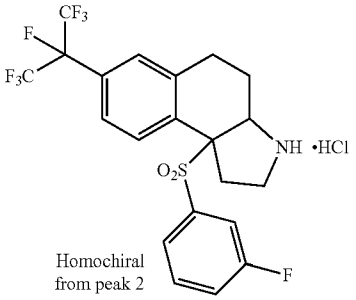
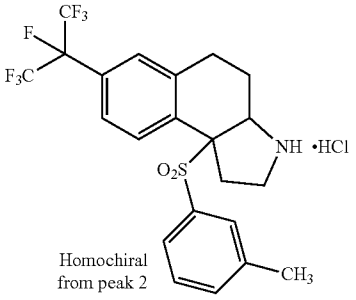
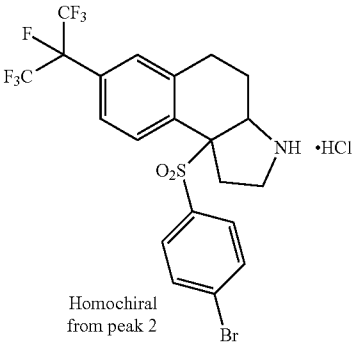
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
64		453.8 $(M + H)^+$	0.76	B
65		500.0 $(M + H)^+$	0.89	B
66		496.2 $(M + H)^+$	0.86	B
67		558.4 $(M + H + MeCN)^+$	1.22	B

TABLE 2-continued

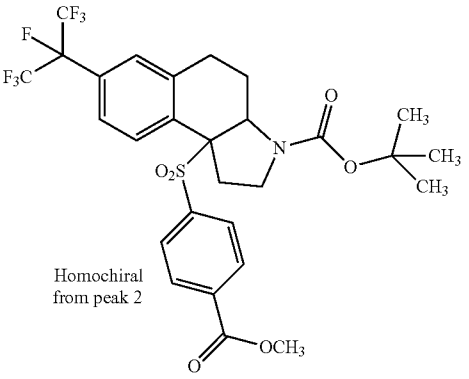
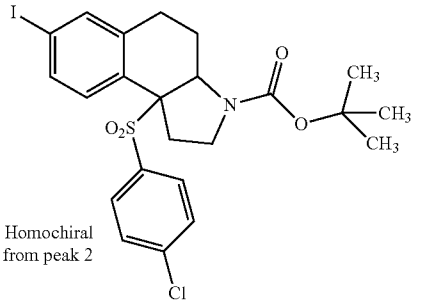
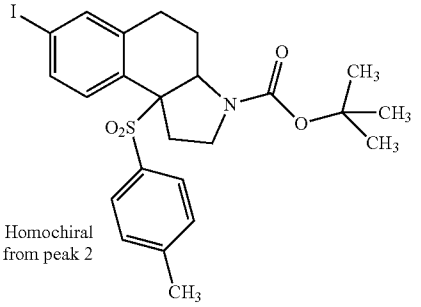
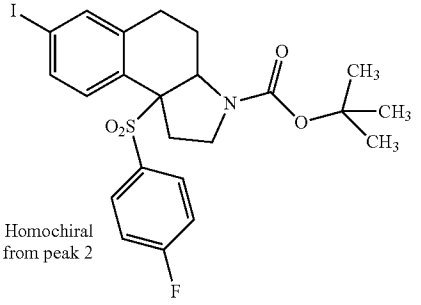
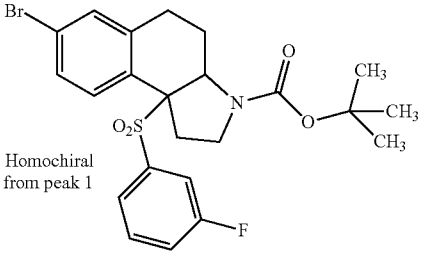
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
68	 Homochiral from peak 2	584.4 $(M + H - C_4H_8)^+$	1.17	B
69	 Homochiral from peak 2	517.8 $(M + H - C_4H_8)^+$	1.22	B
70	 Homochiral from peak 2	497.7 $(M + H - C_4H_8)^+$	1.18	B
71	 Homochiral from peak 2	501.8 $(M + H - C_4H_8)^+$	2.45	C
72	 Homochiral from peak 1	495.0 $(M + H - C_4H_8)^+$	1.19	B

TABLE 2-continued

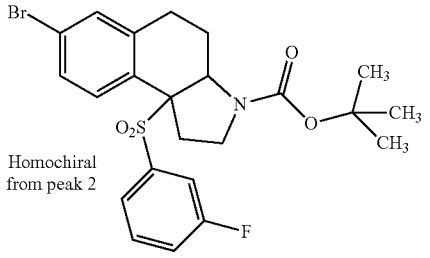
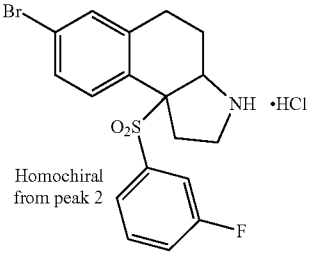
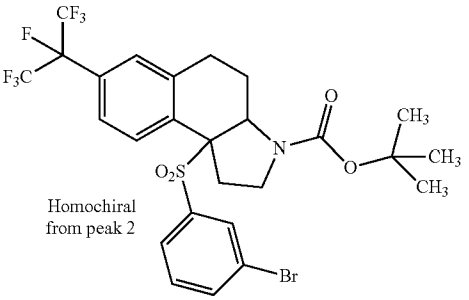
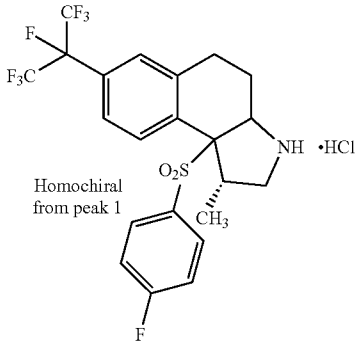
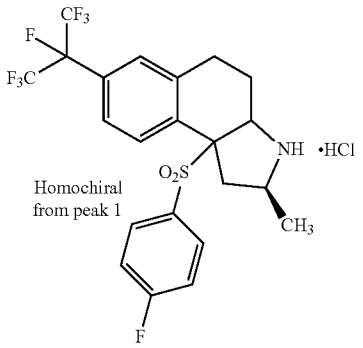
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
73		495.0 $(M + H - C_4H_8)^+$	1.19	B
74		409.9 $(M + H)^+$	0.73	B
75		645.0 $(M + H + MeCN - C_4H_8)^+$	1.27	B
76		514.1 $(M + H)^+$	0.90	B
77		514.0 $(M + H)^+$	0.88	B

TABLE 2-continued

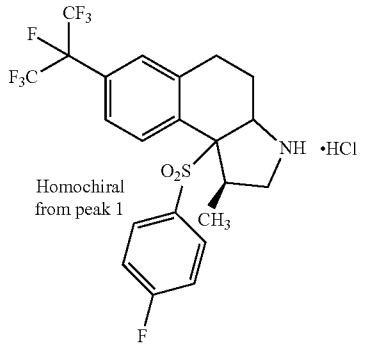
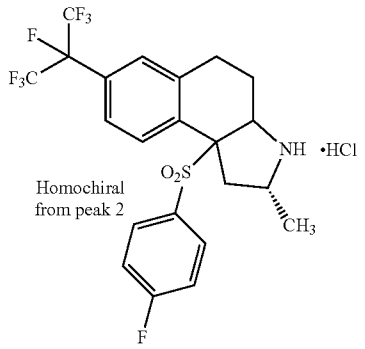
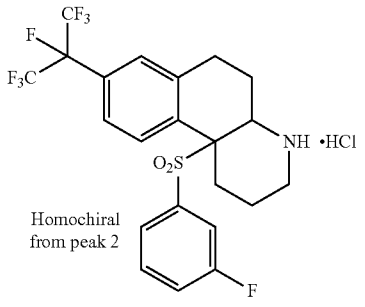
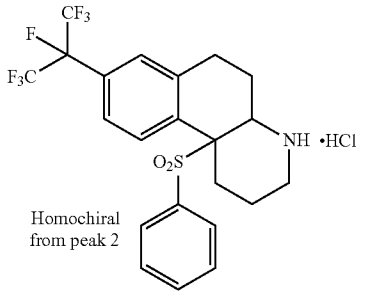
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
78		514.1 $(M + H)^+$	0.90	B
79		514.0 $(M + H)^+$	0.89	B
80		514.1 $(M + H)^+$	0.92	B
81		496.1 $(M + H)^+$	0.89	B

TABLE 2-continued

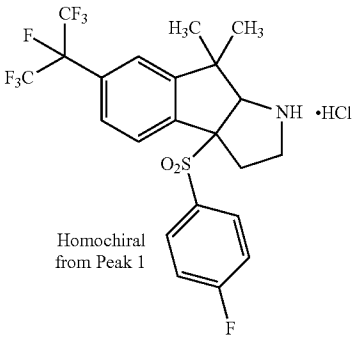
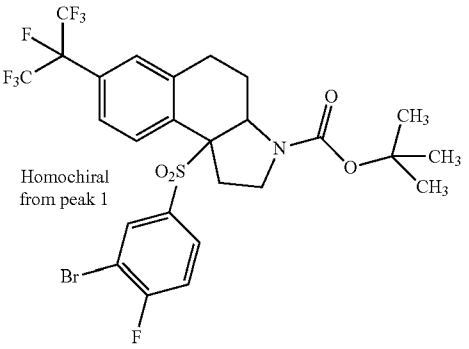
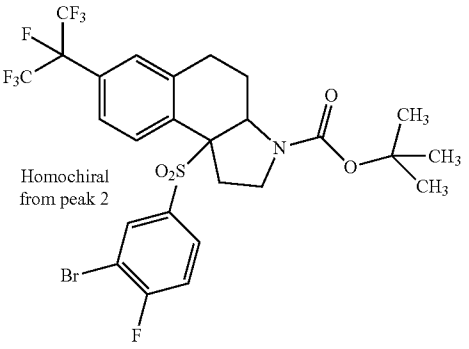
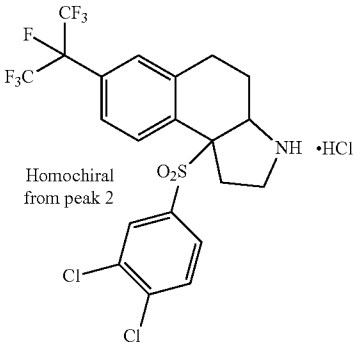
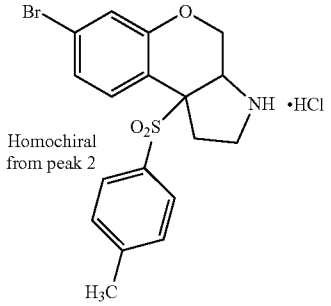
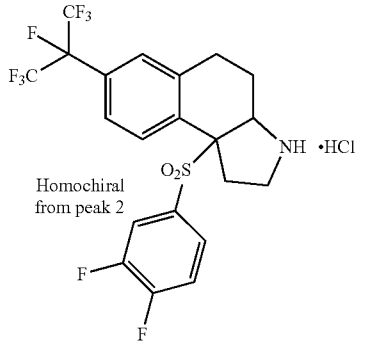
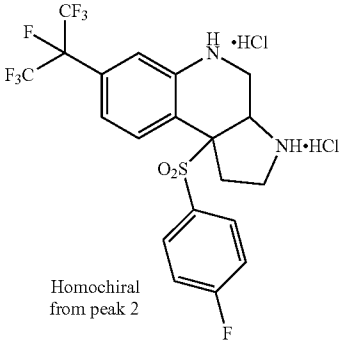
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
82		514.2 $(M + H)^+$	0.90	B
83		663.2 $(M + H + MeCN - C_4H_8)^+$	1.22	B
84		663.2 $(M + H + MeCN - C_4H_8)^+$	1.22	B
85		550.0 $(M + H)^+$	0.91	B

TABLE 2-continued

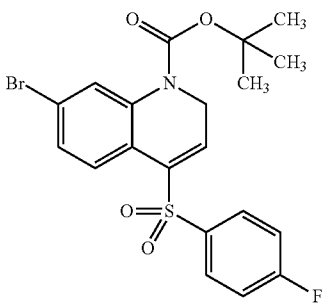
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
86		408.0 $(M + H)^+$	0.73	B
87		518.0 $(M + H)^+$	0.88	B

Intermediate 88

9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline dihydrochloride



Step A: tert-butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)quinoline-1 (2H)-carboxylate

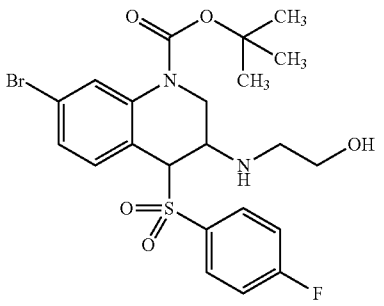


A solution of 7-bromo-2,3-dihydroquinolin-4(1H)-one (8 g, 35 mmol), 4-fluorobenzenethiol (7.9 mL, 74 mmol) and absolute ethanol (44 mL) was cooled with an ice-water bath. HCl gas was bubbled through the mixture until saturation was reached (as indicated by the formation of a white precipitate). The mixture was stirred on the ice-water bath for 1 h and at rt for 1 h more. The mixture was concentrated and the resulting oil was dissolved in DCM (250 mL) and washed with 1 M aqueous NaOH. The organic phase was dried over Na_2SO_4 and concentrated to give crude 7-bromo-4,4-bis((4-fluorophenyl)thio)-1,2,3,4-tetrahydroquinoline as a solid (16.4 g, 100% yield). HPLC t_R 1.27 min (method B).

This material was dissolved in 1,4-dioxane (180 mL) and treated with 4-dimethylaminopyridine (13 g, 106 mmol) and di-tert-butyl dicarbonate (25 mL, 106 mmol). The mixture was stirred at rt for 16, then was diluted with EtOAc and washed twice with 1 M aqueous HCl. The organic phase was dried over Na_2SO_4 and concentrated to afford tert-butyl 7-bromo-4,4-bis((4-fluorophenyl)thio)-3,4-dihydroquinoline-1(2H)-carboxylate (20 g, 100% yield). HPLC t_R 1.37 min (method B).

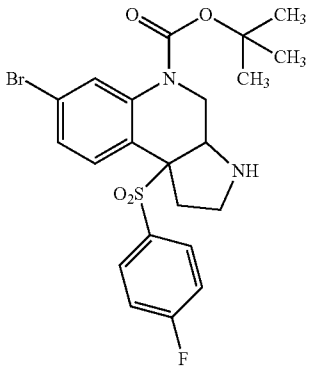
This material was dissolved in DCM (350 mL) and cooled with an ice-water bath. mCPBA (22 g, 172 mmol) was added and the mixture was stirred for 1 h. Additional mCPBA (22 g, 172 mmol) was added, and stirring was continued for 1 h more. The mixture was filtered to remove the insoluble material, and the filtrate was treated with 10% aqueous $Na_2S_2O_3$ (120 mL) and stirred for 5 min. The organic phase was separated, washed sequentially with 10% aqueous $Na_2S_2O_3$ (2×120 mL), 10% aqueous Na_2CO_3 (3×200 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated to give crude tert-butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)quinoline-1(2H)-carboxylate (17 g) which was used without further purification. LCMS m/z 468.0 $(M+H+MeCN)^+$, HPLC t_R 1.16 min (method B).

Step B: tert-butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)-3-((2-hydroxyethyl)amino)-3,4-dihydroquinoline-1 (2H)-carboxylate



A solution of tert-butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)quinoline-1(2H)-carboxylate (16.6 g, 35 mmol) in THF (700 mL) was stirred on an ice-water bath and treated with 2-aminoethanol (11 mL, 177 mmol). The mixture was stirred at about 5° C. for 30 min, then was concentrated. The resulting oil was dissolved in EtOAc (750 mL) and the solution washed three times with brine, dried over Na_2SO_4 and concentrated to provide tert-butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)-3-((2-hydroxyethyl)amino)-3,4-dihydroquinoline-1(2H)-carboxylate (19.5 g) which was used without further purification. LCMS m/z 529.0 $(M+H)^+$, HPLC t_R 0.89 min (method B).

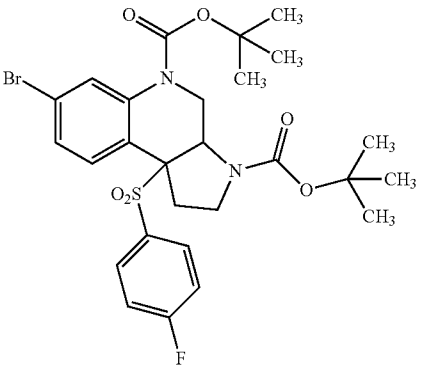
Step C: tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-1,2,3,3a,4,9b-hexahydro-5H-pyrrolo[2,3-c]quinoline-5-carboxylate



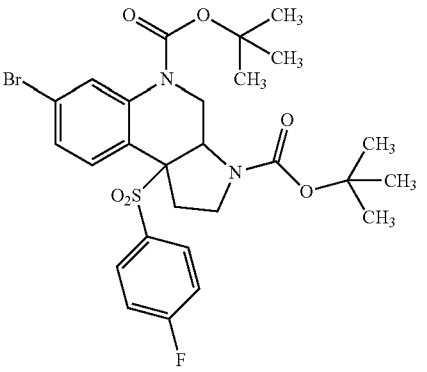
A solution of tert-butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)-3-((2-hydroxyethyl)amino)-3,4-dihydroquinoline-1 (2H)-carboxylate (19 g, 35 mmol) in DCM (650 mL) was treated with MsCl (3.3 mL, 43 mmol), then with Et_3N (5.9 mL, 43 mmol) at rt. The mixture was stirred for 30 min, when LCMS showed complete conversion to the methanesulfonate derivative; LCMS m/z 607.0 $(M+1)^+$, HPLC t_R 0.94 min (method B). The mixture was treated with a solution of potassium tert-butoxide (20 g, 180 mmol) in THF (150 mL) and stirred for 30 min. The mixture was then treated with a 1:1 mixture of water and saturated brine (100 mL) and diluted with EtOAc (1 μL). The organic phase was separated and washed 3 times with brine, dried over Na_2SO_4 and concentrated to give crude tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-c]quinoline-5-carboxylate (19 g), used without further purification. LCMS m/z 511.0 $(M+1)^+$, HPLC t_R 0.85 min (method B).

Step D: di-tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-1,3a,4,9b-tetrahydro-3H-pyrrolo[2,3-c]quinoline-3,5(2H)-dicarboxylate, two homochiral enantiomers

Peak 1



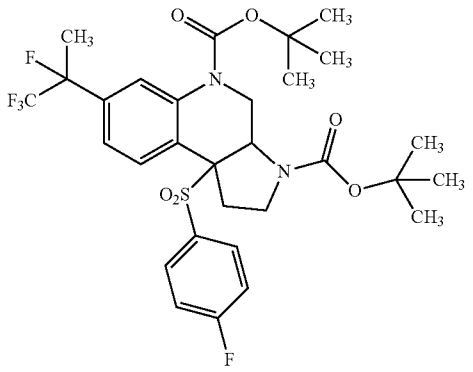
Peak 2



A solution of tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-c]quinoline-5-carboxylate (18 g, 35 mmol) in DCM (350 mL) was treated with di-tert-butyl dicarbonate (12 mL, 53 mmol) and diisopropylethylamine (18.5 mL, 106 mmol). The mixture was stirred at rt for 1 h, then was diluted with DCM (100 mL) and washed sequentially with 1 M aqueous HCl and 1 M aqueous NaOH. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to provide di-tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-1,3a,4,9b-tetrahydro-3H-pyrrolo[2,3-c]quinoline-3,5(2H)-dicarboxylate (7.6 g, 35% overall yield from 7-bromo-2,3-dihydroquinolin-4(1H)-one).

This material was separated by chiral SFC using the following conditions: Column: Chiralcel® OD-H 50×250 mm, 5 m (Chiral Technologies Inc.); column temperature 35° C.; pressure 100 bars; mobile phase CO_2-MeOH (90:10); flow rate 300 mL/min; injection volume 0.9 mL. Peak 1 was eluted with t_R 3.51 min. Peak 2 (2.6 g) was eluted with t_R 4.01 min. LCMS m/z 454.9 $(M+2H—CO_2C_4H_9—C_4H_9)^+$, HPLC t_R 1.22 min (method B).

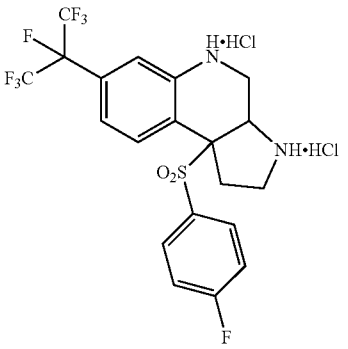
Step E: di-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,3a,4,9b-tetrahydro-3H-pyrrolo[2,3-c]quinoline-3,5(2H)-dicarboxylate (homochiral)



Homochiral from Peak 2

A sealable reaction vessel was charged with activated copper powder (prepared as outlined in Step A of the preparation of Intermediate 2; 3.5 g, 55 mmol), homochiral di-tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3a,4-dihydro-1H-pyrrolo[2,3-c]quinoline-3,5(2H)-dicarboxylate (from Peak 2; 2.9 g, 4.7 mmol) DMF (16 mL) and 1,1,1,2,3,3,3-heptafluoro-2-iodopropane (5.4 mL, 38 mmol). The sealed vial was purged with nitrogen and heated at 120° C. After 4 h, the mixture was cooled to rt, diluted with EtOAc and filtered through Celite. The filtrate was washed 4 times with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to provide homochiral di-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4-dihydro-1H-pyrrolo[2,3-c]quinoline-3,5(2H)-dicarboxylate (712 mg, 22% yield) along with recovered starting material (1.1 g). LCMS m/z 545.0 $(M+2H-CO_2C_4H_9-C_4H_9)^+$, HPLC t_R 1.27 min (method B).

Step F: 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline dihydrochloride



Homochiral from Peak 2

A solution of di-tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4-dihydro-1H-pyrrolo[2,3-c]quinoline-3,5(2H)-dicarboxylate (from Peak 2; 358 mg, 0.511 mmol) in DCM (2.5 mL) was treated with HCl (4 M in 1,4-dioxane; 2.5 mL, 10 mmol). The mixture was allowed to stand at rt for 1 h, then was concentrated to provide 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline dihydrochloride (290 mg, 99% yield). LCMS m/z 501.1 $(M+1)^+$, HPLC t_R 0.89 min (method B). ^1H NMR (500 MHz, DMSO-d_6) δ 7.52 (d, J=8.3 Hz, 1H), 7.44 (dd, J=8.3, 5.1 Hz, 2H), 7.26 (t, J=8.6 Hz, 2H), 6.85 (d, J=8.2 Hz, 1H), 6.74 (s, 1H), 6.27 (br. s., 1H), 3.77 (t, J=5.5 Hz, 1H), 3.13-3.05 (m, 1H), 3.01-2.91 (m, 1H), 2.91-2.74 (m, 3H), 2.55 (s, 1H), 2.46-2.32 (m, 1H). ^{19}F NMR (376 MHz, DMSO-d_6) δ −104.9 (s, 1F), −77.3 (m, 1F), −77.0 (s, 6F).

The Intermediates in Table 3 were prepared using the same methods or similar methods used to prepare Intermediate 88, by employing the appropriate substituted thiophenol.

TABLE 3

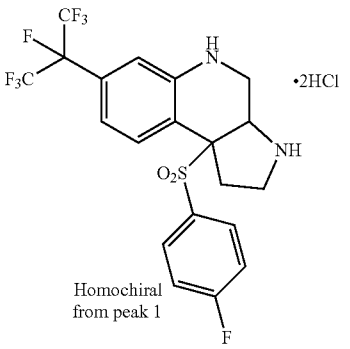
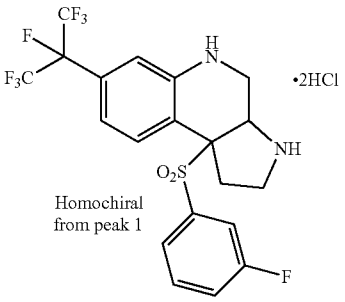
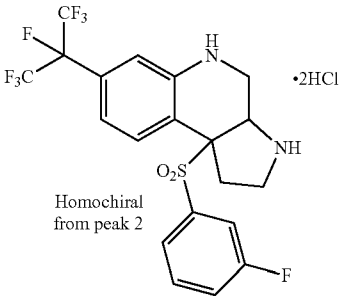
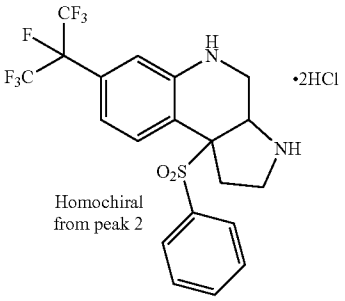
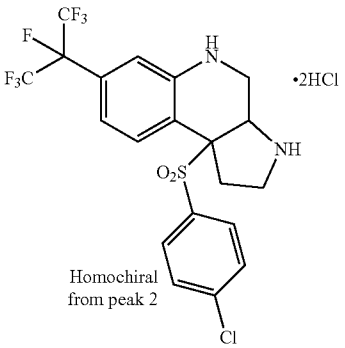
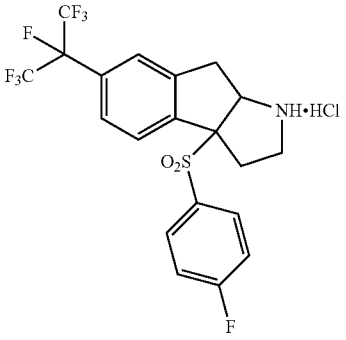
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
89	 Homochiral from peak 1	501.0 $(M+H)^+$	0.89	B

TABLE 3-continued

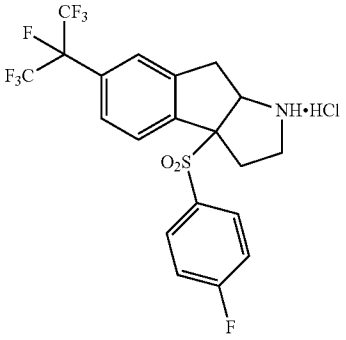
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
90		501.0 $(M + H)^+$	0.86	B
91		501.0 $(M + H)^+$	0.86	B
92		483.1 $(M + H)^+$	0.86	B
93		517.0 $(M + H)^+$	0.88	B

Intermediates 94 and 95

3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole hydrochloride (two homochiral enantiomers)

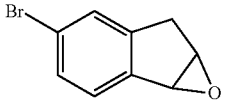


Homochiral from Peak 1



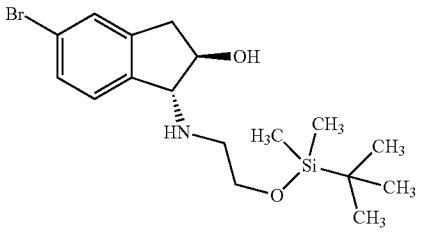
Homochiral from Peak 2

Step A:
4-bromo-1a,6a-dihydro-6H-indeno[1,2-b]oxirene



A solution of 6-bromo-1H-indene (prepared according to the procedure in U.S. Pat. No. 7,678,798; 5.30 g, 27.2 mmol) in DCM (125 mL) was treated with $NaHCO_3$ (6.85 g, 82 mmol) and stirred vigorously on an ice-water bath. The mixture was treated portionwise over 20 min with mCPBA (9.38 g, 38.0 mmol). After 3.75 h, additional mCPBA (1.675 g, 6.79 mmol) was added, and the reaction flask was stirred on an ice-water bath for 19.75 h more. The mixture was diluted with DCM (125 mL) and shaken with 10% aqueous $Na_2S_2O_3$ (100 mL). Additional DCM (250 mL), 1.5 M aqueous K_2HPO_4 (200 mL) and water (100 mL) were added, and the layers were mixed and separated. The aqueous phase was extracted twice more with DCM, and the combined organic phases were washed sequentially with 1.5 M aqueous K_2HPO_4, 10% aqueous $Na_2S_2O_3$, 1.5 M aqueous K_2HPO_4, water and brine, then dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 5-40%), to provide 4-bromo-1a,6a-dihydro-6H-indeno[1,2-b]oxirene as a white solid (4.324 g, 74%), contaminated with about 2% by weight of 5-bromo-1H-inden-2(3H)-one. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 3H), 4.29-4.23 (m, 1H), 4.15 (t, J=2.9 Hz, 1H), 3.23 (d, J=18.3 Hz, 1H), 2.99 (dd, J=18.2, 3.0 Hz, 1H).

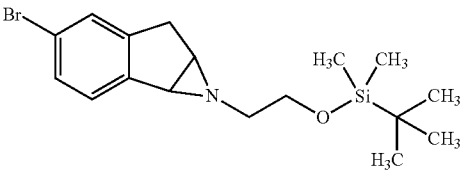
Step B: (1RS,2RS)-5-bromo-1-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)-2,3-dihydro-1H-inden-2-ol (racemic)



Racemic

A solution of 4-bromo-1a,6a-dihydro-6H-indeno[1,2-b]oxirene (4.32 g, 20.06 mmol) in MeCN (90 mL) at rt was treated with $LiClO_4$ (2.77 g, 26.1 mmol) and 2-((tert-butyldimethylsilyl)oxy)ethanamine (prepared according to *J. Org. Chem.* 2009, 74 (4), 1791 suppl.; 4.57 g, 26.1 mmol). The mixture was heated to 55° C. and stirred for 22.5 h. The mixture was cooled to rt and concentrated, and the residue was partitioned between water and EtOAc. The aqueous phase was extracted twice more with EtOAc, and the combined organic layers were washed with saturated brine, dried over Na_2SO_4 and concentrated to provide a dark brown viscous syrup. The material was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 30-100%, then isocratic) to provide (1RS,2RS)-5-bromo-1-((2-((tert-butyldimethylsilyl)oxy) ethyl)amino)-2,3-dihydro-1H-inden-2-ol (racemic) as a tan waxy solid (5.842 g, 75% yield). LCMS m/z 386.0 $(M+H)^+$, HPLC t_R 0.85 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 2H), 7.23-7.15 (m, 1H), 4.34 (q, J=6.6 Hz, 1H), 4.01 (d, J=5.7 Hz, 1H), 3.78 (t, J=5.2 Hz, 2H), 3.25 (dd, J=16.0, 6.9 Hz, 1H), 3.03-2.86 (m, 2H), 2.80 (dd, J=15.8, 6.6 Hz, 1H), 0.92 (s, 9H), 0.09 (d, J=1.1 Hz, 6H).

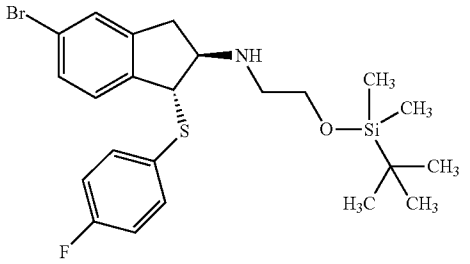
Step C: 4-bromo-1-(2-((tert-butyldimethylsilyl)oxy) ethyl)-1,1a,6,6a-tetrahydroindeno[1,2-b]azirine



A solution of racemic (1RS,2RS)-5-bromo-1-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)-2,3-dihydro-1H-inden-2-ol (5.83 g, 15.09 mmol) in THF (100 mL) was treated with triphenylphosphine (5.94 g, 22.63 mmol). The resulting solution was cooled on an ice-water bath and treated dropwise over about 20 min with diethyl azodicarboxylate (3.58

mL, 22.63 mmol). The resulting thin brown suspension was stirred while the cooling bath was allowed to warm to rt. After 16 h, the mixture was concentrated and the residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 0-25%) to provide 4-bromo-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1,1a,6,6a-tetrahydroindeno[1,2-b]azirine as a light brown-yellow syrup (4.693 g, 83% yield). LCMS m/z 368.0 $(M+H)^+$, HPLC t_R 0.91 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.27 (d, J=1.1 Hz, 2H), 3.84 (t, J=5.8 Hz, 2H), 3.16-3.06 (m, 1H), 3.04-2.93 (m, 2H), 2.69 (t, J=4.5 Hz, 1H), 2.63 (dt, J=11.8, 5.8 Hz, 1H), 2.47 (dt, J=12.0, 6.0 Hz, 1H), 0.95 (s, 9H), 0.10 (s, 6H).

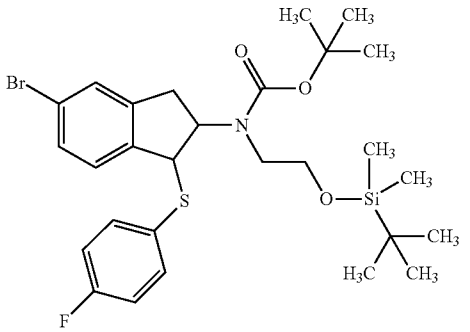
Step D: (1RS,2RS)-5-bromo-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-((4-fluorophenyl)thio)-2,3-dihydro-1H-inden-2-amine (racemic)



Racemic

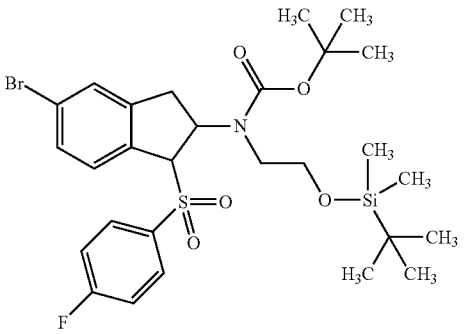
A solution of 4-bromo-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1,1a,6,6a-tetrahydroindeno[1,2-b]azirine (4.650 g, 12.62 mmol) in MeCN (60 mL) was treated rapidly dropwise with 4-fluorobenzenethiol (1.789 mL, 16.79 mmol) and the solution was stirred at rt. After 2 h, the mixture was concentrated to give a light greenish-brown oil. This was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 0-25%), to provide racemic (1RS,2RS)-5-bromo-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-((4-fluorophenyl)thio)-2,3-dihydro-1H-inden-2-amine as a yellow-tan viscous oil (5.957 g, 95% yield). LCMS m/z 496.5 $(M+H)^+$, HPLC t_R 1.04 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.37 (m, 1H), 7.36-7.31 (m, 2H), 7.17 (d, J=8.6 Hz, 1H), 7.04-6.94 (m, 2H), 4.31 (d, J=4.4 Hz, 1H), 3.74-3.63 (m, 2H), 3.46 (dt, J=6.7, 4.6 Hz, 1H), 3.18 (dd, J=16.1, 6.8 Hz, 1H), 2.75-2.63 (m, 3H), 0.90 (s, 9H), 0.07 (s, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.38 (tt, J=8.3, 5.4 Hz, 1F).

Step E: tert-butyl (5-bromo-1-((4-fluorophenyl)thio)-2,3-dihydro-1H-inden-2-yl)(2-((tert-butyldimethylsilyl)oxy)ethyl)carbamate



A solution of racemic (1RS,2RS)-5-bromo-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-((4-fluorophenyl)thio)-2,3-dihydro-1H-inden-2-amine (5.94 g, 11.96 mmol), Et_3N (2.168 mL, 15.55 mmol) and di-tert-butyl dicarbonate (3.61 mL, 15.55 mmol) in DCM (70 mL) was treated with 4-dimethylaminopyridine (0.073 g, 0.598 mmol) and stirred at rt. After 17 h, the solution was diluted with DCM, washed twice with water, then with saturated brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 0-10%). The product eluted in two peaks. Peak 1 provided one isomer of tert-butyl (5-bromo-1-((4-fluorophenyl)thio)-2,3-dihydro-1H-inden-2-yl)(2-((tert-butyldimethylsilyl)oxy)ethyl)carbamate as a colorless syrup (1.545 g, 22% yield). LCMS m/z 496.2 $(M+H—COOC_4H_9)+$, HPLC t_R 1.09 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.25 (m, 5H), 6.97 (t, J=8.6 Hz, 2H), 5.01-4.68 (br. m, 1H), 4.43 (q, J=7.9 Hz, 1H), 3.78-2.91 (br. m, 6H), 1.48-1.25 (br. m, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). Peak 2 provided another isomer of tert-butyl (5-bromo-1-((4-fluorophenyl)thio)-2,3-dihydro-1H-inden-2-yl)(2-((tert-butyldimethylsilyl)oxy)ethyl)carbamate as a pale yellowish gum (4.814 g, 67% yield). LCMS m/z 496.2 $(M+H—COOC_4H_9)+$, HPLC t_R 1.09 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 3H), 7.32-7.28 (m, 2H), 7.02-6.93 (m, 2H), 4.99 and 4.69 (2d, 1H), 4.61-4.34 (2q, 1H), 3.80-3.65 (2t, 2H), 3.49-3.01 (m, 4H), 1.60-1.48 (2s, 9H), 0.89 (s, 9H), 0.08-0.04 (2s, 6H). Both materials were combined and used in the subsequent reaction.

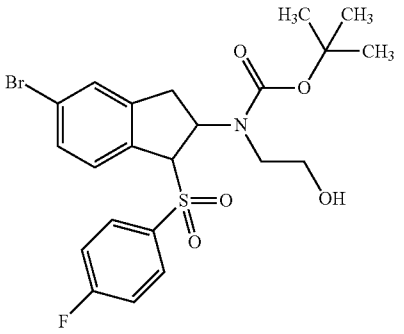
Step F: tert-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1H-inden-2-yl)(2-((tert-butyldimethylsilyl)oxy)ethyl)carbamate



A solution of tert-butyl (5-bromo-1-((4-fluorophenyl)thio)-2,3-dihydro-1H-inden-2-yl)(2-((tert-butyldimethylsilyl)oxy)ethyl)carbamate (6.34 g, 10.63 mmol) in DCM (85 mL) was stirred on an ice bath and treated with mCPBA (6.11 g, 26.6 mmol). After about 1 min the cooling bath was removed and the mixture was stirred at rt. After 4 h, the mixture was diluted with DCM, washed sequentially with 10% aqueous $Na_2S_2O_3$, 1.5 M aqueous K_2HPO_4 and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 0-20%), to provide tert-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1H-inden-2-yl)(2-((tert-butyldimethylsilyl)oxy)ethyl)carbamate as a white glassy solid (5.794 g, 87% yield). LCMS m/z 528.2 $(M+H—COOC_4H_9)+$, HPLC t_R 1.35 min (method B). ^1H NMR (400 MHz, CHLOROFORM-d) δ

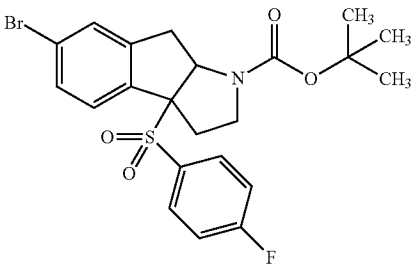
7.72 (br. m., 2H), 7.51 (br. s, 1H), 7.41 (d, J=6.2 Hz, 1H), 7.30 (s, 1H), 7.16 (t, J=8.6 Hz, 2H), 5.34-4.89 (2 br. s., 1H), 4.75 (br. d., 1H), 3.86-3.62 (br. m., 2H), 3.62-3.26 (2 br. s., 1H), 3.16-3.04 (2d, 1H), 3.04-2.70 (br. m., 2H), 1.50-1.13 (2 br. s., 9H), 0.92 (s, 9H), 0.08 (s, 6H).

Step G: tert-butyl (5-bromo-1-((4-fluorophenyl) sulfonyl)-2,3-dihydro-1H-inden-2-yl)(2-hydroxy-ethyl)carbamate



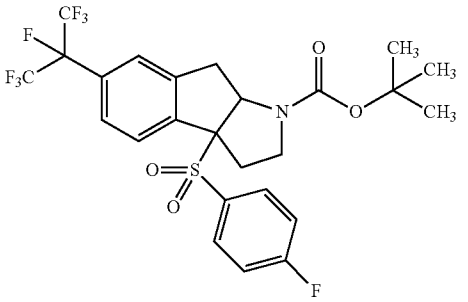
A solution of tert-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1H-inden-2-yl)(2-((tert-butyldimethylsilyl)oxy)ethyl)carbamate (5.78 g, 9.19 mmol) in THF (100 mL) was stirred on an ice-water bath and treated dropwise with tetra-n-butylammonium fluoride, 1.0 M in THF (12 mL, 12.00 mmol) over about 7 min, forming a yellow-brown solution. After 80 min, the cold mixture was treated with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc. The aqueous phase was extracted again with EtOAc and the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 0-60%), to provide tert-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1H-inden-2-yl)(2-hydroxyethyl)carbamate as a white glassy solid. (3.796 g, 80% yield). LCMS m/z 458.1 $(M+H—C_4H_8)^+$, HPLC t_R 1.04 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (br. s., 2H), 7.43-7.38 (m, 1H), 7.34 (d, J=2.4 Hz, 1H), 7.31 (s, 1H), 7.19 (t, J=8.6 Hz, 2H), 5.10 (br. s., 1H), 4.78 (br. s., 1H), 3.80 (d, J=6.2 Hz, 1H), 3.74 (br. s., 1H), 3.43 (br. s., 1H), 3.25-3.17 (m, 1H), 3.17-3.07 (m, 1H), 3.02-2.88 (m, 1H), 2.70-2.32 (m, 1H), 1.32 (br. s., 9H).

Step H: tert-butyl 6-bromo-3a-((4-fluorophenyl) sulfonyl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1 (2H)-carboxylate



A solution of tert-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1H-inden-2-yl)(2-hydroxyethyl)carbamate (3.18 g, 6.18 mmol) in DCM (160 mL) was stirred on a water bath at rt and treated in one portion with MsCl (0.626 mL, 8.04 mmol). The solution was then treated dropwise over about 30 sec with Et_3N (1.12 mL, 8.04 mmol) and the resulting solution was stirred at rt. After 60 min, the mixture was treated with potassium tert-butoxide, 1.0 M in tetrahydrofuran (24.73 mL, 24.73 mmol) over about 3 min, gradually forming a slightly cloudy light brown solution, and stirring was continued. After 35 min, the mixture was treated with saturated aqueous NH_4Cl and diluted with DCM. The layers were mixed and separated and the aqueous phase was extracted again with DCM. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 0-30%), to provide tert-butyl 6-bromo-3a-((4-fluorophenyl)sulfonyl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1 (2H)-carboxylate as a white glassy solid (2.812 g, 92% yield). LCMS m/z 481.1 $(M+H+MeCN—C_4H_8)^+$, HPLC t_R 1.18 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.02 (br. m., 7H), 4.79 (d, J=5.9 Hz, 1H), 3.98-3.77 (2 br. s., 1H), 3.15-2.85 (br. m., 3H), 2.73-2.27 (2 br. m., 2H), 1.47 (2 br. s., 9H).

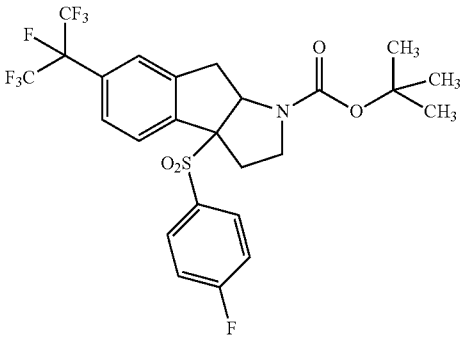
Step I: tert-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1(2H)-carboxylate



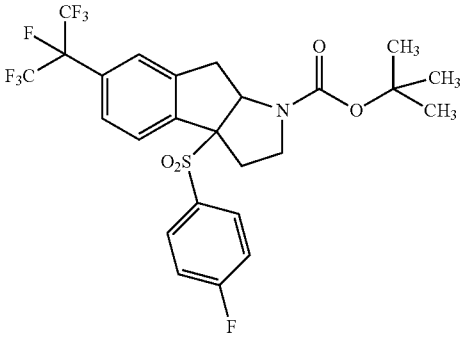
A sealable reaction vessel was charged with activated copper powder (prepared as outlined in Step A of the preparation of Intermediate 2; 3.32 g, 52.2 mmol), tert-butyl 6-bromo-3a-((4-fluorophenyl)sulfonyl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1(2H)-carboxylate (1.727 g, 3.48 mmol) and DMF (20 mL). The brick-red suspension was bubbled with argon, then treated with 1,1,1,2,3,3,3-heptafluoro-2-iodopropane (3.46 mL, 24.35 mmol), sealed under argon and heated with stirring on an oil bath at 120° C. After 4.5 h the mixture was cooled to rt, diluted with EtOAc and filtered through Celite. The solids were washed with EtOAc and the combined filtrates were washed with water. The organic phase was washed twice with 15% aqueous LiCl, then with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica

gel (220 g), eluting with EtOAc-hexanes (gradient from 0-25%), to provide tert-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1(2H)-carboxylate as a light tan glassy solid (1.566 g, 74% yield). LCMS m/z 571.3 $(M+H+MeCN—C_4H_8)^+$, HPLC t_R 1.18 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (br. s., 1H), 7.66-7.35 (br. m, 4H), 7.00 (br. s, 2H), 4.83 (d, J=6.2 Hz, 1H), 3.91 (br. s., 1H), 3.22-2.90 (br. m, 3H), 2.72-2.27 (br. m, 2H), 1.49 (br. s., 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.40--75.76 (m, 6F), −101.67 (br. s., 1F), −181.88 (m, 1F).

Step J: tert-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1 (2H)-carboxylate (two homochiral enantiomers)



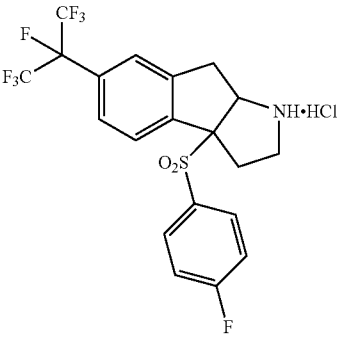
Peak 1



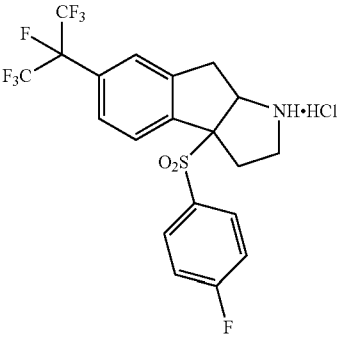
Peak 2

A sample of tert-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1(2H)-carboxylate (2.95 g, 5.04 mmol) was separated by chiral SFC using the following conditions: Column: Chiralpak® IC (30×250) mm, 5 μm (Chiral Technologies Inc.); column temperature 35° C.; pressure 100 bars; mobile phase CO_2-MeOH (90:10); flow rate 180 mL/min; injection volume: 0.75 mL. Peak 1 (white glassy solid, 1.246 g, 80%) was eluted with t_R 1.15 min. Peak 2 (white glassy solid, 1.273 g, 92%) was eluted with t_R 1.6 min. LCMS and NMR of both products were the same as those of the racemic material obtained in Step I.

Step K: 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole hydrochloride (two homochiral enantiomers)



Homochiral from Peak 1



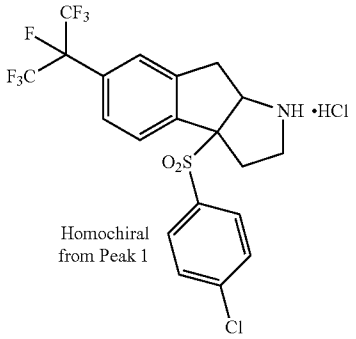
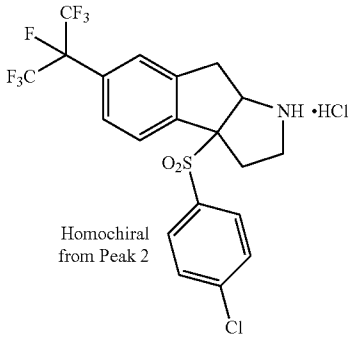
Homochiral from Peak 2

A solution of tert-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1(2H)-carboxylate (single enantiomer, Peak 1 from Step J; 1.225 g, 2.092 mmol) in DCM (20 mL) was treated with HCl, 4 M in 1,4-dioxane (16 mL, 64.0 mmol) and allowed to stand at rt. After 80 min, the solution was concentrated to provide one enantiomer of 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole hydrochloride as an off-white glassy solid (1.12 g, 97% yield). LCMS m/z 486.2 $(M+H)^+$, HPLC t_R 0.85 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 10.84-10.28 (br. m, 2H), 7.79 (d, J=8.4 Hz, 1H), 7.66 (d, J=8.4 Hz, 1H), 7.59 (dd, J=8.5, 4.7 Hz, 2H), 7.33 (s, 1H), 7.00 (t, J=8.3 Hz, 1H), 5.49 (d, J=7.0 Hz, 1H), 3.97 (d, J=7.5 Hz, 1H), 3.85-3.75 (m, 1H), 3.35 (td, J=12.3, 6.8 Hz, 1H), 3.08 (d, J=4.4 Hz, 1H), 2.92 (dd, J=19.0, 8.0 Hz, 1H), 2.70 (dd, J=13.1, 4.1 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.53 (m, 6F), −100.46 (m, 1F), −181.90 (m, 1F).

Likewise, tert-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrole-1(2H)-carboxylate (single enantiomer, Peak 2 from Step J; 1.256 g, 2.145 mmol) was converted into the other enantiomer of 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole hydrochloride as an off-white glassy solid (1.15 g, 98% yield). LCMS and NMR same as that of the material obtained from Peak 1.

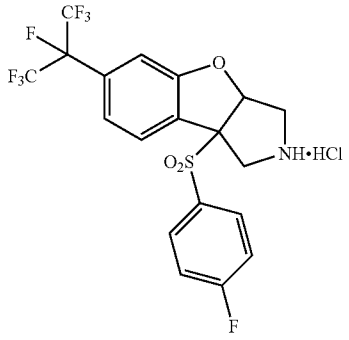
The Intermediates in Table 4 were prepared using the same or similar methods used in the preparation of Intermediates 94 and 95, by employing the appropriate thiol in Step D.

TABLE 4

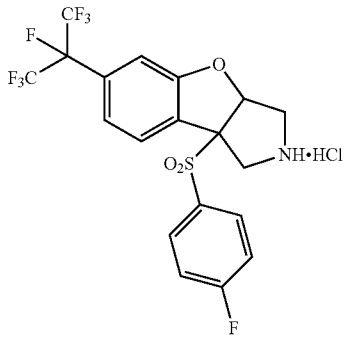
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
96		502.0 $(M + H)^+$	0.88	B
97		502.0 $(M + H)^+$	0.88	B

Intermediates 98 and 99

8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole hydrochloride (two homochiral enantiomers)

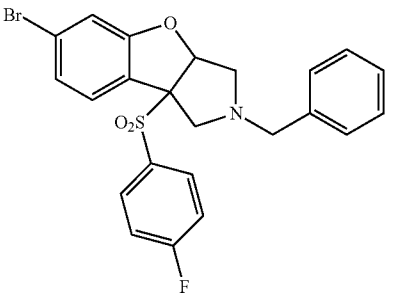


Homochiral from peak 1



Homochiral from peak 2

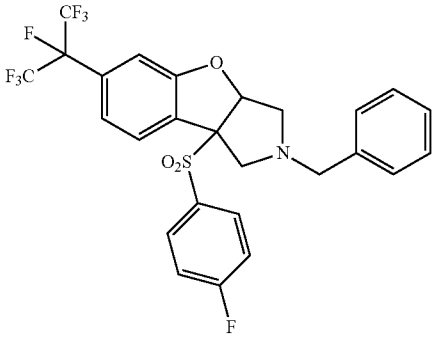
Step A: 2-benzyl-6-bromo-8b-((4-fluorophenyl)sulfonyl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole



A solution of 6-bromo-3-((4-fluorophenyl)sulfonyl)benzofuran (Intermediate 9; 1.00 g, 2.82 mmol) in dry DCM (15 mL) was treated with N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (1.80 mL, 7.04 mmol) and stirred on an ice-water bath. This solution was treated dropwise with TFA (0.5 M in DCM, 2.82 mL, 1.408 mmol) over about 6 min. The resulting solution was stirred on ice. After 5 min the mixture was warmed to rt. After 2 h, the solution was diluted with DCM, washed with 1.5 M aqueous K_2HPO_4, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with EtOAc-hexanes (gradient from 0-30%), to provide 2-benzyl-6-bromo-8b-((4-fluorophenyl)sulfonyl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole as a white glassy solid (1.27 g, 92% yield). LCMS m/z 488.1 $(M+H)^+$, HPLC t_R 1.04 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.65

(dd, J=9.0, 5.1 Hz, 2H), 7.34-7.25 (m, 4H), 7.21-7.15 (m, 2H), 7.14-7.07 (m, 3H), 6.82 (d, J=1.5 Hz, 1H), 5.37 (dd, J=5.6, 1.9 Hz, 1H), 3.73-3.60 (m, 2H), 3.45 (d, J=9.7 Hz, 1H), 3.27 (d, J=9.7 Hz, 1H), 3.14-3.08 (m, 1H), 2.84 (dd, J=10.9, 5.6 Hz, 1H).

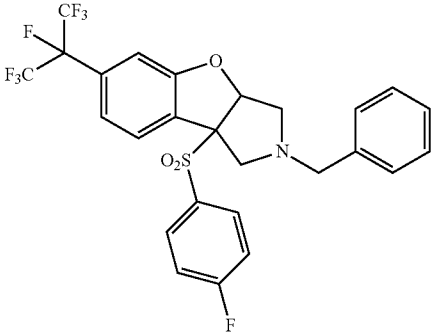
Step B: 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole



Following the procedure used in Step A of the preparation of Intermediate 2, 2-benzyl-6-bromo-8b-((4-fluorophenyl) sulfonyl)-2,3,3a, 8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole (800 mg, 1.638 mmol) was converted into 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a, 8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole as a white glassy solid (646 mg, 68% yield). LCMS m/z 578.2 $(M+H)^+$, HPLC t_R 1.16 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.55 (m, 3H), 7.35-7.26 (m, 3H), 7.24 (d, J=8.1 Hz, 1H), 7.21-7.15 (m, 2H), 7.03 (t, J=8.5 Hz, 2H), 6.86 (s, 1H), 5.42 (dd, J=5.8, 2.1 Hz, 1H), 3.76-3.63 (m, 2H), 3.50 (d, J=9.7 Hz, 1H), 3.35 (d, J=9.7 Hz, 1H), 3.13 (d, J=9.5 Hz, 1H), 2.90 (dd, J=10.8, 5.7 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.63 (d, J=7.2 Hz, 6F), −101.83 (m, 1F), −181.37 (m, 1F).

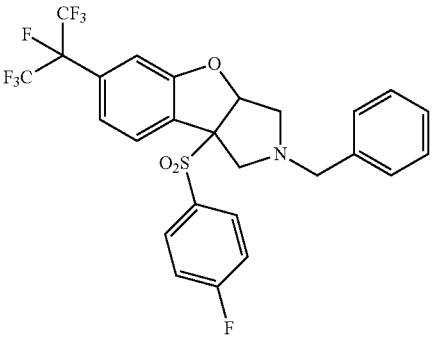
Step C: 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole (two single enantiomers)

Peak 1



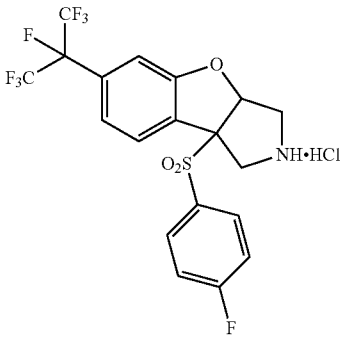
-continued

Peak 2

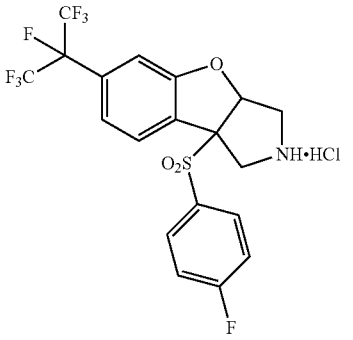


A sample of 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a, 8b-tetrahydro-1H-benzofuro [2,3-c]pyrrole (640 mg, 1.109 mmol) was separated by chiral SFC using the following conditions: Column: Chiralcel® OD-H 50×250 mm, 5 m (Chiral Technologies Inc.); column temperature 35° C.; pressure 100 bars; mobile phase CO_2-MeOH (90:10); flow rate 250 mL/min; injection volume: 0.5 mL. Peak 1 (pale yellow glassy solid, 280 mg, 88%) was eluted with t_R 5.7 min. Peak 2 (pale yellow glassy solid, 291 mg, 91%) was eluted with t_R 6.2 min (100%). LCMS and NMR of both products were the same as those of the racemic material obtained in Step B.

Step D: 8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole hydrochloride (two single enantiomers)



Homochiral from Peak 1



Homochiral from Peak 2

A solution of 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro

[2,3-c]pyrrole (single enantiomer, Peak 1 from Step C; 276 mg, 0.478 mmol) in MeOH (10 mL) was treated with 1.0 M aqueous HCl (0.574 mL, 0.574 mmol) and Pearlman's Catalyst (276 mg, 0.393 mmol). The flask was subjected to 5 evacuate-fill cycles with hydrogen, then was stirred under a hydrogen balloon at rt. After 16.5 h, the mixture was filtered through Celite, the solids were washed with MeOH and the combined filtrates were concentrated to provide one enantiomer of 8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a, 8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole hydrochloride as an off-white solid (250 In mg, quantitative yield). LCMS m/z 488.1 $(M+H)^+$, HPLC t_R 0.87 min (method B). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (br. s., 2H), 7.83-7.75 (m, 2H), 7.72 (d, J=8.4 Hz, 1H), 7.43-7.32 (m, 3H), 7.03 (s, 1H), 6.01 (d, J=4.8 Hz, 1H), 4.26 (d, J=12.3 Hz, 1H), 4.00 (d, J=12.5 Hz, 1H), 3.69 (d, J=13.4 Hz, 1H), 3.65-3.55 (dd, J=13.6, 6.5 Hz, 1H).

Likewise, 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole (single enantiomer, Peak 2 from Step C; 298 mg, 0.516 mmol) was converted into the other enantiomer of 8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a, 8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole hydrochloride as a pale yellow solid (246 mg, 91% yield). LCMS and NMR same as that of the material obtained from Peak 1.

The Intermediates in Table 5 were prepared using the same or similar methods used in the preparation of Intermediates 98 and 99, by employing the appropriate vinylic sulfone as the starting material.

TABLE 5

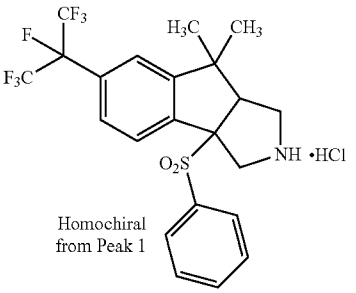
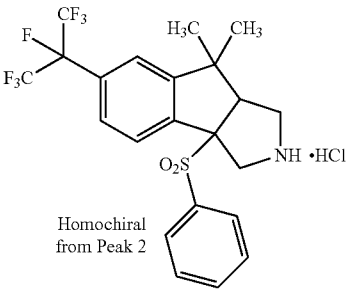
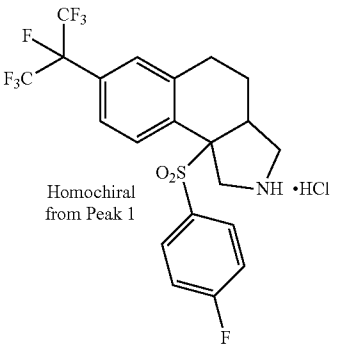
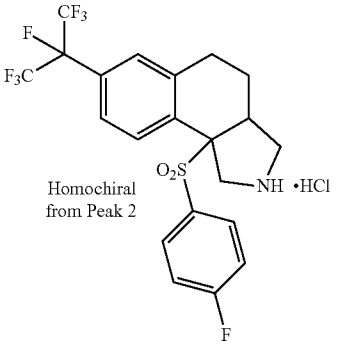
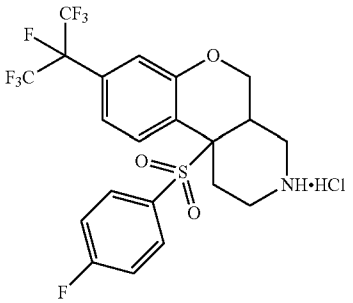
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
100		496.1 $(M+H)^+$	0.88	B
101		496.1 $(M+H)^+$	0.88	B
102		500.2 $(M+H)^+$	0.85	B

TABLE 5-continued

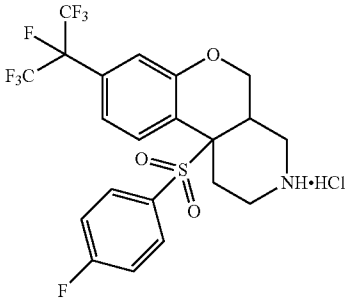
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
103	 Homochiral from Peak 2	500.3 $(M + H)^+$	0.85	B

Intermediates 104 and 105

10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,3,4,4a,5,10b-hexahydro-2H-chromeno[3,4-c]pyridine hydrochloride (two homochiral enantiomers)

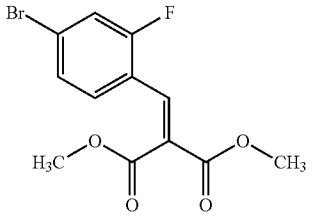


Homochiral from Peak 1



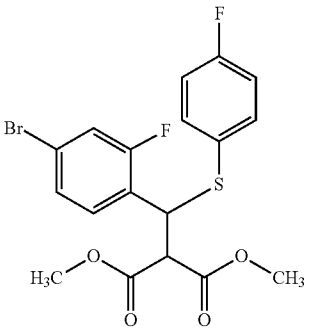
Homochiral from Peak 2

Step A: dimethyl 2-(4-bromo-2-fluorobenzylidene)malonate



A solution of 4-bromo-2-fluorobenzaldehyde (20.07 g, 99 mmol), dimethyl malonate (14.73 mL, 129 mmol), benzoic acid (1.207 g, 9.89 mmol), and piperidine (1.953 mL, 19.77 mmol) in toluene (198 mL) was heated to reflux under a Dean-Stark water trap. After 4 h, the mixture was cooled to rt and concentrated The residue was dissolved in EtOAc, washed sequentially with saturated aqueous NH_4Cl, 1.5 M aqueous K_2HPO_4 and brine, dried over Na_2SO_4, filtered and concentrated to afford dimethyl 2-(4-bromo-2-fluorobenzylidene)malonate as an light brown oil in quantitative yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.35-7.28 (m, 3H), 3.87 (s, 3H), 3.83 (s, 3H).

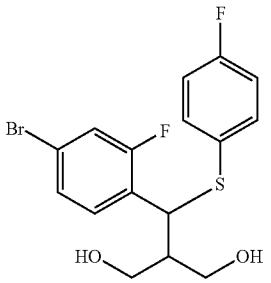
Step B: dimethyl 2-((4-bromo-2-fluorophenyl)((4-fluorophenyl)thio)methyl)malonate



A mixture of dimethyl 2-(4-bromo-2-fluorobenzylidene) malonate (19.29 g, 54.7 mmol), 4-fluorobenzenethiol (8.19 mL, 77 mmol), and K_2CO_3 (12.11 g, 88 mmol) in THF (238 mL) was heated at 60° C. for 4 h. The mixture was cooled to rt, filtered through Celite, and the solids were washed with EtOAc. The combined filtrates were concentrated and purified by column chromatography on silica gel (220 g), eluting with EtOAc-hexanes (5:95). A solid which formed in the effluent fractions was removed by filtration, and the combined filtrates were concentrated and re-purified by column chromatography on silica gel to provide dimethyl 2-((4-bromo-2-fluorophenyl)((4-fluorophenyl)thio)methyl)malonate as a yellow syrup (16.14 g, 66% yield). LCMS m/z 467.1 $(M+Na)^+$, HPLC t_R 1.10 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.16 (m, 3H), 7.12 (dd, J=8.3, 1.2

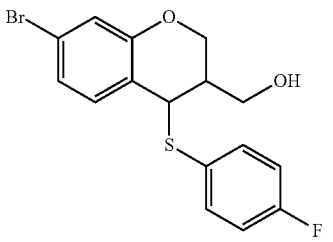
Hz, 1H), 6.95 (t, J=8.7 Hz, 2H), 6.78 (t, J=8.0 Hz, 1H), 4.90 (d, J=11.7 Hz, 1H), 4.08 (dd, J=11.6, 0.6 Hz, 1H), 3.85 (s, 3H), 3.55 (s, 3H).

Step C: 2-((4-bromo-2-fluorophenyl)((4-fluorophenyl)thio)methyl)propane-1,3-diol



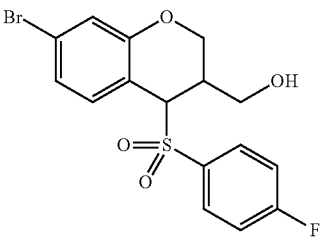
A solution of dimethyl 2-((4-bromo-2-fluorophenyl)((4-fluorophenyl)thio)methyl)malonate (16.14 g, 36.2 mmol) in THF (300 mL) was cooled in an ice-water bath and treated slowly with DIBAL-H (1 M in toluene; 149 mL, 149 mmol). The resulting mixture was stirred at rt overnight. After 17 h, the mixture was treated with ice and water, then with 1 M aqueous HCl (210 mL), and diluted with EtOAc. The organic phase was separated, washed sequentially with 1.5 M aqueous K_2HPO_4 and brine, dried over Na_2SO_4, filtered, and concentrated to afford 2-((4-bromo-2-fluorophenyl)((4-fluorophenyl)thio)methyl)propane-1,3-diol as a yellow syrup (13.65 g, 97% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.18 (m, 3H), 7.17-7.10 (m, 2H), 6.91 (t, J=8.7 Hz, 2H), 4.60 (d, J=10.3 Hz, 1H), 4.28-4.14 (m, 2H), 3.79 (dd, J=10.9, 3.2 Hz, 1H), 3.53 (dd, J=11.0, 5.7 Hz, 1H), 2.46-1.89 (m, 3H).

Step D: (7-bromo-4-((4-fluorophenyl)thio)chroman-3-yl)methanol



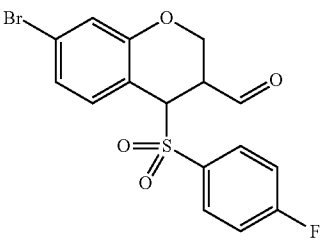
A solution of 2-((4-bromo-2-fluorophenyl)((4-fluorophenyl)thio)methyl)propane-1,3-diol (13.65 g, 35.1 mmol) in THF (501 mL) was treated portionwise at rt with NaH (60% in mineral oil; 5.51 g, 138 mmol). The resulting mixture was then heated at 60° C. After 4.5 h, the mixture was cooled to rt and treated with ice-water and 1 M aqueous HCl (100 mL). The layers were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (220 g), eluting with EtOAc-hexanes (10-20%), to provide (7-bromo-4-((4-fluorophenyl)thio) chroman-3-yl)methanol as a dark yellow syrup (5.14 g, 40% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J=8.8, 5.3 Hz, 2H), 7.14 (d, J=8.1 Hz, 1H), 7.07-6.98 (m, 4H), 4.51 (dd, J=11.2, 2.4 Hz, 1H), 4.30-4.20 (m, 2H), 3.70 (dd, J=10.8, 7.3 Hz, 1H), 3.54 (dd, J=10.8, 7.5 Hz, 1H), 2.19 (tq, J=7.3, 2.6 Hz, 1H).

Step E: (7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-yl)methanol



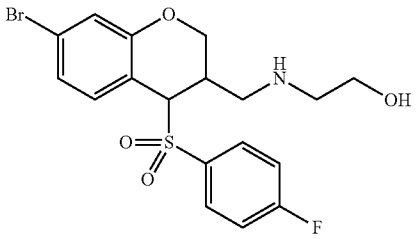
A solution of (7-bromo-4-((4-fluorophenyl)thio)chroman-3-yl)methanol (4.65 g, 12.59 mmol) in DCM (252 mL) was treated with mCPBA (6.77 g, 30.2 mmol) and stirred at rt. After 18 h, the mixture was diluted with DCM, washed sequentially with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and 1.5 M aqueous K_2HPO_4. The organic phase was dried over Na_2SO_4 and concentrated to afford (7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-yl)methanol as a yellow glassy solid (3.94 g, 78% yield). LCMS m/z 422.9 $(M+Na)^+$, HPLC t_R 0.91 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (m, 2H), 7.24 (t, J=8.5 Hz, 2H), 7.05 (d, J=2.0 Hz, 1H), 6.98 (dd, J=8.4, 2.0 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H), 4.43 (dd, J=11.7, 3.3 Hz, 1H), 4.31 (s, 1H), 4.19-4.11 (m, 1H), 3.70 (dd, J=10.7, 6.7 Hz, 1H), 3.50 (dd, J=10.7, 8.5 Hz, 1H), 2.80-2.69 (m, 1H).

Step F: 7-bromo-4-((4-fluorophenyl)sulfonyl)chromane-3-carbaldehyde



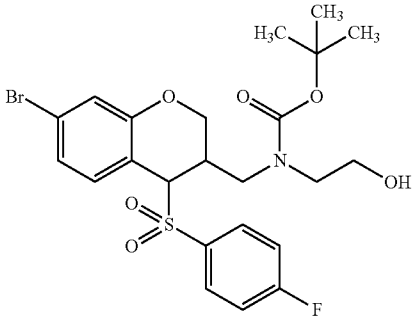
A solution of (7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-yl)methanol (3.93 g, 9.79 mmol) in DCM (122 mL) was treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one (Dess-Martin periodinane; 4.15 g, 9.79 mmol) and stirred at rt. After 2 h, the mixture was concentrated, and the residue was dissolved in EtOAc, washed sequentially with 5% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to afford 7-bromo-4-((4-fluorophenyl)sulfonyl)chromane-3-carbaldehyde as a light yellow glassy solid (3.97 g, quantitative yield). ^1H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.79 (dd, J=8.8, 5.1 Hz, 2H), 7.34-7.21 (m, 2H), 7.03 (d, J=2.0 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 6.62 (d, J=8.4 Hz, 1H), 4.82-4.58 (m, 3H), 3.52 (dt, J=3.3, 1.9 Hz, 1H).

Step G: 2-(((7-bromo-4-((4-fluorophenyl)sulfonyl) chroman-3-yl)methyl)amino)ethanol



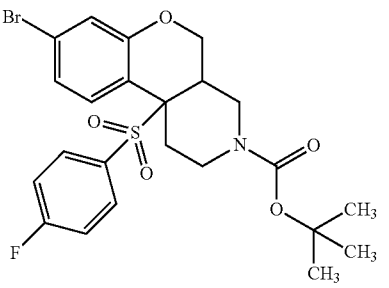
A solution of 7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-carbaldehyde (3.97 g, 9.94 mmol) in 1,2-dichloroethane (301 mL) was treated with 2-aminoethanol (1.020 mL, 16.90 mmol), then with sodium triacetoxyborohydride (5.56 g, 26.3 mmol). The resulting suspension was stirred at rt for 4.5 h, then was diluted with DCM, water and saturated aqueous $NaHCO_3$. The organic phase was separated and washed with brine, dried over Na_2SO_4 and concentrated to afford 2-(((7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-yl)methyl)amino)ethanol as a yellow glassy solid (3.61 g, 82% yield). LCMS m/z 444.0 $(M+H)^+$, HPLC t_R 0.71 min (method B).

Step H: tert-butyl ((7-bromo-4-((4-fluorophenyl) sulfonyl)chroman-3-yl)methyl)(2-hydroxyethyl)carbamate



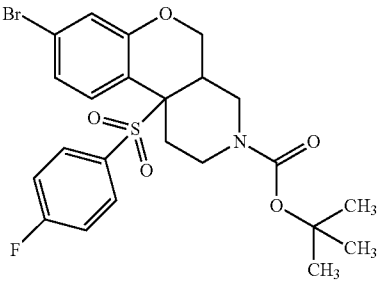
A solution of 2-(((7-bromo-4-((4-fluorophenyl)sulfonyl) chroman-3-yl)methyl)amino)ethanol (3.61 g, 8.12 mmol) in DCM (135 mL) was treated with di-tert-butyl dicarbonate (2.264 mL, 9.75 mmol), then with Et_3N (2.038 mL, 14.62 mmol). The mixture was stirred at rt for 5 h, then was diluted with DCM and washed with water. The organic phase was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford tert-butyl ((7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-yl)methyl)(2-hydroxyethyl) carbamate as a yellow sticky solid in quantitative yield. LCMS m/z 566.3 $(M+Na)^+$, HPLC t_R 1.01 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J=8.8, 5.1 Hz, 2H), 7.26-7.22 (m, 2H), 7.07 (d, J=2.0 Hz, 1H), 6.97 (d, J=7.9 Hz, 1H), 4.42 (d, J=11.7 Hz, 1H), 4.08-4.00 (m, 1H), 3.79-3.57 (m, 3H), 3.41-3.14 (m, 5H), 3.05-2.94 (m, 1H), 1.56 (s, 9H).

Step I: tert-butyl 8-bromo-10b-((4-fluorophenyl) sulfonyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-c] pyridine-3(4H)-carboxylate



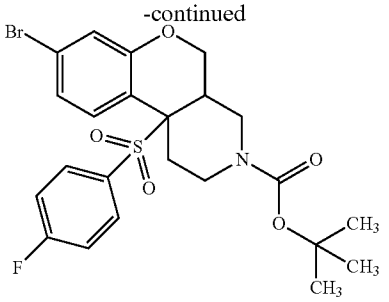
A solution of tert-butyl ((7-bromo-4-((4-fluorophenyl) sulfonyl)chroman-3-yl)methyl)(2-hydroxyethyl)carbamate (4.73 g, 8.08 mmol) in DCM (269 mL) at rt was treated with MsCl (0.630 mL, 8.08 mmol), then with Et_3N (1.464 mL, 10.50 mmol). The mixture was stirred at rt for 1 h, then potassium tert-butoxide (4.08 g, 36.4 mmol) was added and stirring was continued for 2 h more. The mixture was treated with half-saturated brine and diluted with additional DCM. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc-hexanes (10-20%) to provide tert-butyl 8-bromo-10b-((4-fluorophenyl)sulfonyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-c]pyridine-3(4H)-carboxylate as a white solid (1.78 g, 42% yield). LCMS m/z 548.2 $(M+Na)^+$, HPLC t_R 1.12 (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67-7.60 (m, 2H), 7.21 (t, J=8.6 Hz, 2H), 7.11 (d, J=2.0 Hz, 1H), 7.01 (dd, J=8.6, 2.0 Hz, 1H), 6.72 (br. s., 1H), 4.95 (br. s., 1H), 4.21-3.85 (m, 3H), 2.83-2.10 (m, 5H), 1.44 (s, 9H).

Step J: tert-butyl 8-bromo-10b-((4-fluorophenyl) sulfonyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-c] pyridine-3(4H)-carboxylate (two homochiral enantiomers)



peak 1

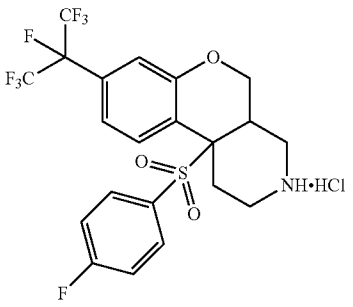
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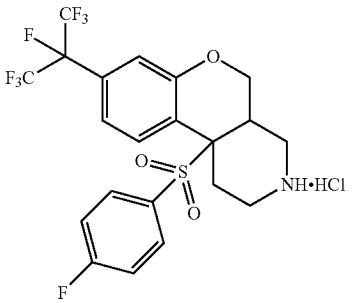
peak 2

A sample of racemic tert-butyl 8-bromo-10b-((4-fluorophenyl)sulfonyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-c]pyridine-3 (4H)-carboxylate (1.96 g) was separated by chiral SFC using the following conditions: Column: Lux® Cellulose-4 46×250 mm, 5 m (Phenomenex Inc.); column temperature 30° C.; pressure 100 bars; mobile phase CO_2-MeOH (84:16); flow rate 160 mL/min; injection volume 0.5 mL. Peak 1 (off-white solid, 0.81 g, 83%) was eluted with t_R 5.2 min. Peak 2 (off-white solid, 0.867 g, 88%) was eluted with t_R 5.9 min. LCMS and NMR of both products were the same as those of the racemic material obtained in Step I.

Step K: 10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,3,4,4a,5,10b-hexahydro-2H-chromeno[3,4-c]pyridine hydrochloride (two homochiral enantiomers)



Homochiral
from Peak 1



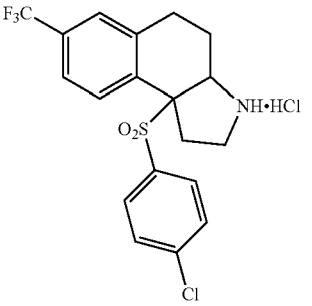
Homochiral
from Peak 2

Following the procedures used in Steps I and K of the preparation of Intermediates 94 and 95, tert-butyl 8-bromo-10b-((4-fluorophenyl)sulfonyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-c]pyridine-3(4H)-carboxylate (homochiral, from Peak 1) was converted into one enantiomer of 10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,3,4,4a,5,10b-hexahydro-2H-chromeno[3,4-c]pyridine hydrochloride. LCMS m/z 516.1 $(M+H)^+$, HPLC t_R 0.83 min (method B).

Likewise, tert-butyl 8-bromo-10b-((4-fluorophenyl)sulfonyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-c]pyridine-3 (4H)-carboxylate (homochiral, from Peak 2) was converted into the other enantiomer of 10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,3,4,4a,5,10b-hexahydro-2H-chromeno[3,4-c]pyridine hydrochloride. LCMS m/z 516.3 $(M+H)^+$, HPLC t_R 0.83 min (method B).

Intermediate 106

9b-((4-chlorophenyl)sulfonyl)-7-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole Hydrochloride

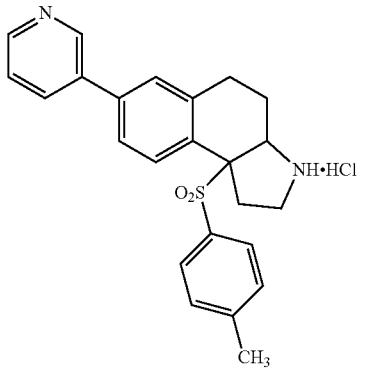


Homochiral
from peak 2

A mixture of tert-butyl 9b-((4-chlorophenyl)sulfonyl)-7-iodo-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 69; 100 mg, 0.17 mmol), CuI (33 mg, 0.17 mmol) and KF (30 mg, 0.52 mmol) was placed in a sealed vial which was evacuated and filled with nitrogen 3 times. DMF (2 mL) was added and the vessel was again evacuated and filled with nitrogen 3 times. Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (167 mg, 0.87 mmol) was added and the mixture was heated to 80° C. After 2 days, LCMS showed 70% conversion of the starting material. The mixture was cooled to rt, diluted with EtOAc, washed sequentially with 1.5 M aqueous K_2HPO_4, 10% aqueous LiCl and brine, dried over Na_2SO_4 and concentrated. The resulting oil was dissolved in DCM (2 mL) and treated with 4N HCl in 1,4-dioxane (2 mL). After 1 h the mixture was concentrated, affording 9b-((4-chlorophenyl)sulfonyl)-7-(trifluoromethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (single enantiomer, 83 mg, >100% yield). This material was used without further purification. LCMS m/z 416.0 $(M+H)^+$, HPLC t_R 0.83 min (method B).

Intermediate 107

7-(pyridin-3-yl)-9b-tosyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride

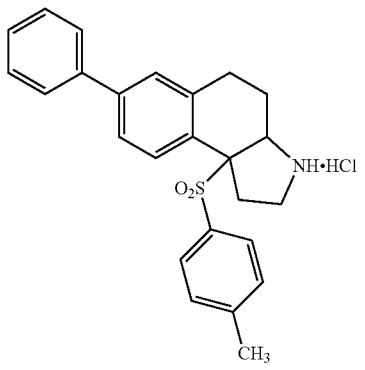


Homochiral
from peak 2

A mixture of tert-butyl 7-iodo-9b-tosyl-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 70; 50 mg, 0.090 mmol), chloro(2-dicyclohexyl-phosphino-2',4',6'-triisopropyl-1,1'-biphenyl) [2-(2'-amino-1, 1'-biphenyl)]palladium(II) (second generation Xphos precatalyst; 1.4 mg, 1.8 μmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (1.7 mg, 3.6 μmol), tetrahydroxydiboron (12 mg, 0.14 mmol), and potassium acetate (26.6 mg, 0.27 mmol) was placed in a pressure vial which was purged with nitrogen 4 times. Ethanol (bubbled with nitrogen to remove dissolved oxygen; 903 μL) and ethylene glycol (15 μL, 0.27 mmol) were added and the mixture was heated at 80° C. for 1.5 h. The mixture was cooled to rt and treated with 1 M aqueous K_3PO_4 (271 μL, 0.271 mmol) and 3-bromopyridine (13.4 mg, 0.085 mmol). The resulting mixture was warmed to 80° C. and stirred for 1 h. The mixture was cooled to rt and partitioned between EtOAc and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was treated with 4 M HCl in 1,4-dioxane (0.5 mL) and allowed to stand at rt for 1 h. The mixture was concentrated affording crude 7-(pyridin-3-yl)-9b-tosyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (single enantiomer) which was used without further purification. LCMS m/z 405.2 $(M+H)^+$, HPLC t_R 0.53 min (method B).

Intermediate 108

7-phenyl-9b-tosyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride

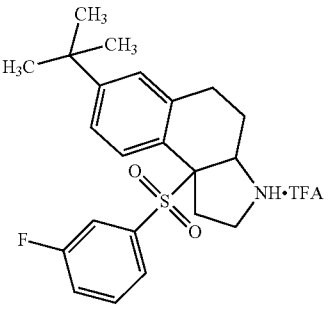


Homochiral
from peak 2

A solution of tert-butyl 7-iodo-9b-tosyl-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 70; 20 mg, 0.036 mmol) in DMF (1 mL) was treated with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (15 mg, 0.072 mmol), [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (2.6 mg, 3.6 mol), and 2 M aqueous K_3PO_4 (0.036 mL, 0.072 mmol), and the mixture was heated at 80° C. for 16 h. The mixture was cooled to rt and partitioned between EtOAc and brine. The organic phase was dried over Na_2SO_4 and concentrated. The residue was treated with 4 N HCl in 1,4-dioxane (0.5 mL) and allowed to stand at rt for 1 h. The mixture was concentrated to provide crude 7-phenyl-9b-tosyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride which was used without further purification. LCMS m/z 404.2 $(M+H)^+$, HPLC t_R 0.82 min (method B).

Intermediate 109

7-(tert-butyl)-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole trifluoroacetate

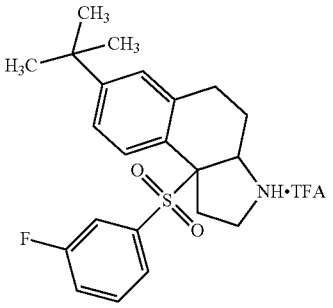


Homochiral
from peak 2

A mixture of tert-butyl 7-bromo-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 73; 0.15 g, 0.294 mmol), THF (2.45 mL) and tert-butylzinc bromide (0.5 M in THF; 2.94 mL, 1.469 mmol) in a reaction vial was flushed with nitrogen. Tetrakis(triphenylphosphine)palladium (3.04 mg, 2.94 mol) was added, and the vial was sealed and heated by microwave irradiation at 130° C. for 10 min. The cooled mixture was diluted with EtOAc (30 mL) and filtered. The filtrate was washed sequentially with water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in DCM-TFA (2:1, 5 mL) and stirred at rt for 15 min. The mixture was concentrated to provide crude 7-(tert-butyl)-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole trifluoroacetate (120 mg, about 75% purity, 79% yield) as a single enantiomer, used without further purification. LCMS m/z 388.0 $(M+H)^+$, HPLC t_R 0.88 min (method B).

Intermediate 110

7-(tert-butyl)-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole trifluoroacetate

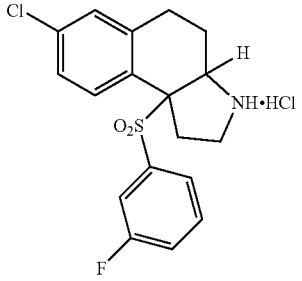


Homochiral from peak 1

Following the procedure used to prepare Intermediate 109, tert-butyl 7-bromo-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 1, Intermediate 72) was converted into crude 7-(tert-butyl)-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole trifluoroacetate as a single enantiomer, used without further purification. LCMS m/z 388.0 $(M+H)^+$, HPLC t_R 0.87 min (method B).

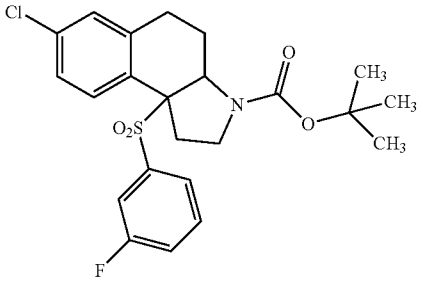
Intermediate 111

7-chloro-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride



Homochiral from peak 2

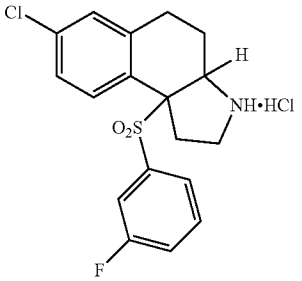
Step A: tert-butyl 7-chloro-9b-((3-fluorophenyl)sulfonyl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carboxylate



Homochiral from peak 2

A mixture of copper(I) chloride (0.159 g, 1.607 mmol) and activated copper powder (prepared as outlined in Step A of the preparation of Intermediate 2; 0.102 g, 1.607 mmol) was placed in a sealable vial which was flushed with nitrogen. The mixture was treated with a solution of tert-butyl 7-bromo-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 73; 0.082 g, 0.161 mmol) in anhydrous pyridine (1.5 mL) and the vial was sealed and heated at 120° C. for 5.5 days. The mixture was cooled to rt and taken up in EtOAc (75 mL). The mixture was washed sequentially with 1 M aqueous HCl (2×50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated to give tert-butyl 7-chloro-9b-((3-fluorophenyl)sulfonyl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carboxylate as an off-white foam (65 mg, 87% yield), used without further purification. LCMS m/z 451.0 $(M+H+MeCN—C_4H_8)^+$, HPLC t_R 1.17 min (method B). ^1H NMR (400 MHz, MeOH-d_4) δ 7.67 (d, J=8.4 Hz, 1H), 7.56-7.36 (m, 2H), 7.35-7.17 (m, 2H), 7.12-6.94 (m, 2H), 4.65-4.33 (m, 1H), 3.71-3.57 (m, 1H), 3.57-3.34 (m, 2H), 2.59-2.43 (m, 2H), 2.41-2.15 (m, 1H), 1.86 (t, J=13.6 Hz, 1H), 1.60-1.43 (m, 9H), 1.40-1.26 (m, 1H).

Step B: 7-chloro-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride

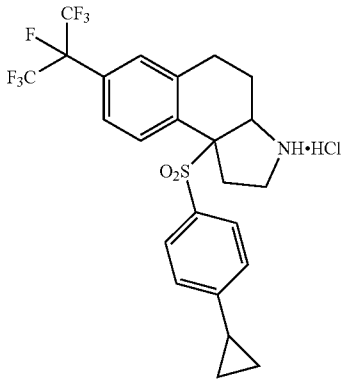


Homochiral from peak 2

A mixture of tert-butyl 7-chloro-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (65 mg, 0.139 mmol) and HCl (4 M in 1,4-dioxane; 2.0 mL, 8.00 mmol) was stirred at rt for 1.5 h. The mixture was concentrated to give 7-chloro-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride as a white solid which was used without further purification. LCMS m/z 366.0 $(M+H)^+$, HPLC t_R 0.74 min (method B).

Intermediate 112

9b-((4-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,59b-hexahydro-1H-benzo[e]indole Hydrochloride

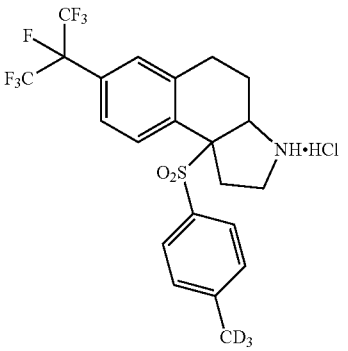


Homochiral
from peak 2

A solution of 9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (homochiral, from peak 2, Intermediate 67; 100 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium (8.8 mg, 7.6 mol) in THF (1 mL) was placed in a sealed tube which was evacuated and filled with nitrogen three times. Cyclopropylzinc(II) bromide (0.6 mL, 0.3 mmol) was added and the mixture was heated at 70° C. for 2.5 h. The mixture was cooled to rt and partitioned between EtOAc and brine. The organic phase was dried over Na_2SO_4 and concentrated. The residue was treated with 4 M HCl in 1,4-dioxane (0.5 mL) and allowed to stand at rt for 1 h. The mixture was concentrated, affording crude 9b-((4-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (homochiral), which was used without further purification. LCMS m/z 522.1 $(M+H)^+$, HPLC t_R 0.96 min (method B).

Intermediate 113

9b-((4-(methyl-d_3)phenyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride



Homochiral
from peak 2

A solution of tert-butyl 9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 67; 200 mg, 0.3 mmol) and iron(III) acetylacetonate (5.4 mg, 0.015 mmol) in THF (2 mL) was placed in a sealed tube which was evacuated and filled with nitrogen three times. The resulting dark red solution was treated dropwise with methyl-d_3-magnesium iodide (1.0 M in diethyl ether; 0.3 mL, 0.3 mmol) dropwise and the mixture was stirred at rt for 30 min. The mixture was partitioned between EtOAc and brine, and the organic phase was dried over Na_2SO_4 and concentrated. The residue was treated with 4 M HCl in 1,4-dioxane (0.5 mL) for 1 h. The mixture was concentrated, affording crude 9b-((4-(methyl-d_3)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (210 mg, >100%) which was used without further purification. LCMS m/z 499.1 $(M+H)^+$, HPLC t_R 0.92 min (method B).

The Intermediates in Table 6 were prepared using the same methods or similar methods used to prepared Intermediate 113, by employing the appropriate bromine-substituted starting material.

TABLE 6

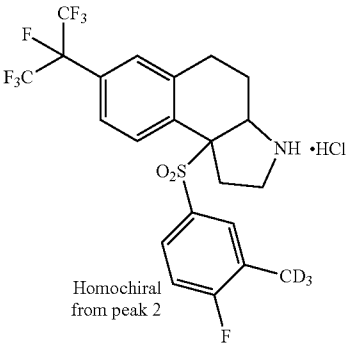
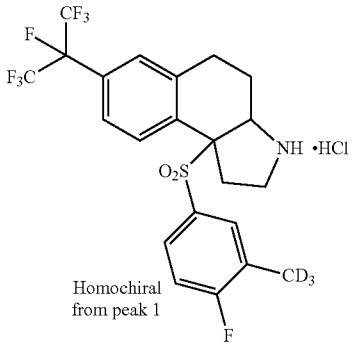
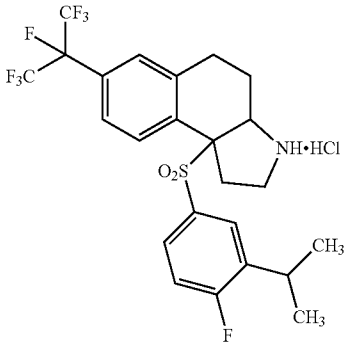
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
114	 Homochiral from peak 2	517.0 $(M + H)^+$	0.90	B

TABLE 6-continued

Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
115	 Homochiral from peak 1	517.1 $(M + H)^+$	0.91	B

Intermediate 116

9b-((4-fluoro-3-isopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride

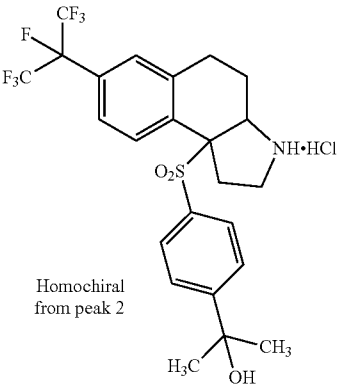


Homochiral from peak 2

A mixture of tert-butyl 9b-((3-bromo-4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 84; 113 mg, 0.167 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (28.0 mg, 0.167 mmol) and 2 M aqueous K_3PO_4 (0.167 mL, 0.333 mmol) in THF (2 mL) was subjected to 3 evacuate-fill cycles with nitrogen. 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (5.43 mg, 8.33 μmol) was added, and the mixture was again subjected to 3 evacuate-fill cycles with nitrogen. The mixture was stirred overnight, then was diluted with EtOAc, washed sequentially with 1.5 M aqueous K_2HPO_4 and water, dried and concentrated. The residue was dissolved in MeOH (5 mL), treated with Pd on charcoal (53.2 mg) and stirred at rt overnight under a hydrogen atmosphere (balloon pressure). The mixture was filtered and concentrated, and the residue was treated with HCl (4 M in 1,4-dioxane) followed by concentration to provide 9b-((4-fluoro-3-isopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride. LCMS m/z 542.4 $(M+H)^+$, HPLC t_R 1.30 min (method B).

Intermediate 117

2-(4-((7-(perfluoropropan-2-yl)-1,2,3,3a,4,5-hexahydro-9bH-benzo[e]indol-9b-yl)sulfonyl)phenyl) propan-2-ol hydrochloride

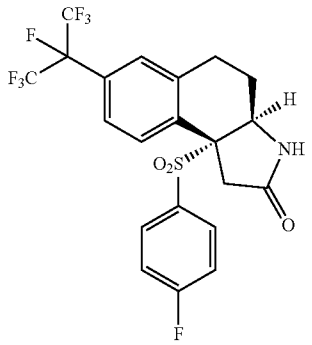


Homochiral from peak 2

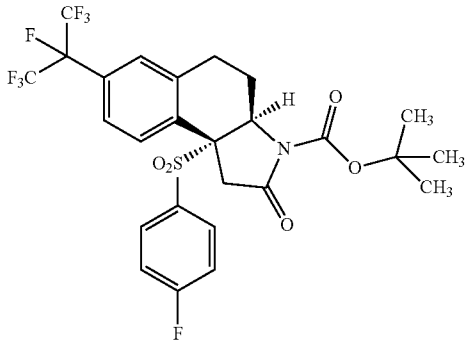
A solution of tert-butyl 9b-((4-(methoxycarbonyl)phenyl) sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 68; 150 mg, 0.24 mmol) in THF (5 mL) was cooled in a dry ice-acetone bath and treated dropwise with methyllithium (3.1 M in 1,2-diethoxyethane; 0.23 mL, 0.7 mmol). The mixture was stirred at −78° C. for 30 min, then was treated with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted twice with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residue was treated with 4 M HCl in 1,4-dioxane (0.5 mL) and allowed to stand at rt for 1 h. The mixture was concentrated, affording crude 2-(4-((7-(perfluoropropan-2-yl)-1,2,3,3a,4,5-hexahydro-9bH-benzo[e]indol-9b-yl)sulfonyl)phenyl) propan-2-ol which was used without further purification. LCMS m/z 540.3 $(M+H)^+$, HPLC t_R 0.80 min (method B).

Intermediate 118

(3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,3,3a,4,5,9b-hexahydro-2H-benzo[e]indol-2-one

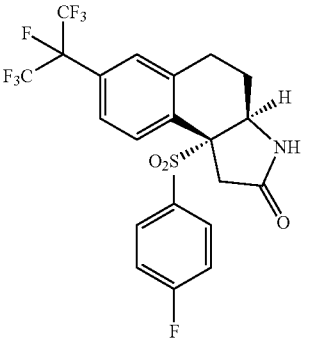


Step A: tert-butyl (3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-2-oxo-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-carboxylate



A solution of (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (Intermediate 32 Step G; 0.70 g, 1.168 mmol) in EtOAc (6 mL) was added dropwise over 3 min to a mixture of ruthenium(III) chloride (0.242 g, 1.168 mmol) and sodium periodate (1.498 g, 7.01 mmol) in water (18.00 mL). The mixture was stirred at rt for 1 h, treated with additional ruthenium (III) chloride (24.2 mg, 0.117 mmol) and stirring was continued at rt for 1 h. The mixture was treated dropwise with 2-propanol (25 mL). The resulting mixture was filtered through Celite and the solids were washed with EtOAc. The combined filtrates were concentrated and the residue was partitioned between EtOAc (100 mL) and brine (100 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (40 g), eluting with EtOAc-hexanes (gradient from 0-30%), to give (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl) sulfonyl)-2-oxo-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate as a white glassy solid (0.50 g, 70% yield). LCMS m/z 599.0 (M+H+MeCN—C_4H_9)+, HPLC t_R 1.16 min (method B).

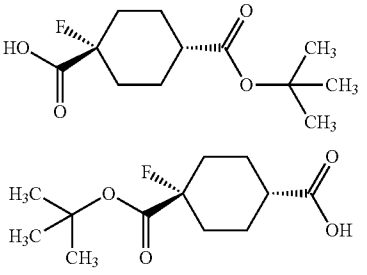
Step B: (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,3,3a,4,5,9b-hexahydro-2H-benzo[e]indol-2-one



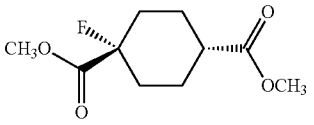
A solution of (3aR,9bR)-tert-butyl 9b-((4-fluorophenyl) sulfonyl)-2-oxo-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (0.47 g, 0.766 mmol) in EtOAc (2 mL) was treated with HCl (2 M in diethyl ether; 1.915 mL, 3.83 mmol) and the mixture was stirred at rt for 15 h. The deprotection was incomplete so the mixture was concentrated, the residue was dissolved in DCM (5 mL), treated with TFA (1 mL) and stirred at rt for 10 min. The mixture was diluted with 1.5 M aqueous K_2HPO_4 (20 mL) and extracted with DCM (2×20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to give (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,3,3a,4,5,9b-hexahydro-2H-benzo[e]indol-2-one as a pale yellow solid (0.40 g, 92% yield). LCMS m/z 555.0 $(M+H+MeCN)^+$, HPLC t_R 1.01 min (method B). ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J=8.4 Hz, 1H), 7.57 (d, J=8.7 Hz, 1H), 7.32 (dd, J=8.6, 5.0 Hz, 2H), 7.25 (s, 1H), 7.06-6.98 (m, 2H), 4.42 (ddd, J=11.4, 5.3, 0.8 Hz, 1H), 3.78 (d, J=18.3 Hz, 1H), 2.98 (d, J=18.3 Hz, 1H), 2.61 (dt, J=16.3, 3.7 Hz, 1H), 2.29-2.10 (m, 1H), 1.98-1.79 (m, 1H), 1.54-1.43 (m, 1H).

Intermediate 119

Mixture of (1s,4s)-4-(tert-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid and (1s,4s)-4-(tert-butoxycarbonyl)-4-fluorocyclohexane-1-carboxylic acid

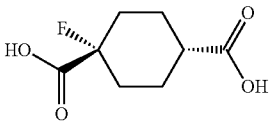


Step A: dimethyl (1s,4s)-1-fluorocyclohexane-1,4-dicarboxylate



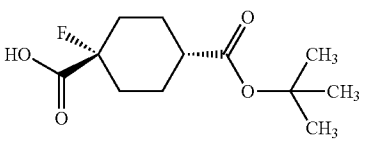
A solution of diisopropylamine (1.4 mL, 10.2 mmol) in THF (30 mL) was treated with n-butyllithium (2.5 M in hexanes, 4.1 mL, 10.2 mmol) at −78° C. and stirred at 0° C. for 30 min. The mixture was cooled to −78° C. and was treated with a solution of (1r,4r)-dimethyl cyclohexane-1,4-dicarboxylate (1.85 g, 9.24 mmol) in THF (15 mL) dropwise over 10 min. The resulting mixture was stirred at −78° C. for 30 min, then was treated with a solution of N-fluorobenzenesulfonimide (3.06 g, 9.70 mmol) in THF (15 mL). The mixture was warmed to rt and stirred for 2 h. After quenching with saturated aqueous NH_4Cl (20 mL), the mixture was diluted with EtOAc (300 mL), washed sequentially with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography, eluting with EtOAc-hexanes (gradient from 0-10%), to give dimethyl (1s,4s)-1-fluorocyclohexane-1,4-dicarboxylate as the second peak from the column (330 mg, 16% yield, minor isomer). ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.66 (s, 3H), 2.44-2.29 (m, 1H), 2.26-1.73 (m, 8H).

Step B: (1s,4s)-1-fluorocyclohexane-1,4-dicarboxylic acid

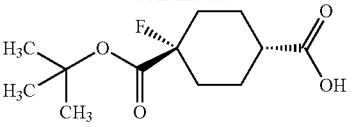


A mixture of dimethyl (1s,4s)-1-fluorocyclohexane-1,4-dicarboxylate (180 mg, 0.83 mmol) in THF (6 mL) was treated with 1 M aqueous LiOH (4.95 mL, 4.95 mmol). After stirring at rt for 15 h, the mixture was acidified to pH 2-3 with 1 M aqueous HCl. After evaporation of organic solvents, the residue was treated with EtOAc (100 mL), washed sequentially with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to give (1s,4s)-1-fluorocyclohexane-1,4-dicarboxylic acid (142 mg), used without further purification. ^1H NMR (400 MHz, MeOH-d_4) δ 2.55-2.33 (m, 1H), 2.33-2.11 (m, 1H), 2.10-1.80 (m, 5H), 1.72 (qd, J=12.6, 3.6 Hz, 2H).

Step C: mixture of (1s,4s)-4-(tert-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid and (1s,4s)-4-(tert-butoxycarbonyl)-4-fluorocyclohexane-1-carboxylic acid



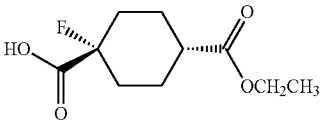
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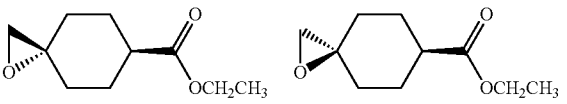
4-Dimethylaminopyridine (9.6 mg, 0.079 mmol) was added to a solution of (1s,4s)-1-fluorocyclohexane-1,4-dicarboxylic acid (50 mg, 0.263 mmol) and di-tert-butyl dicarbonate (73 μL, 0.316 mmol) in tert-butanol (2 mL). After stirring at rt for 15 h, the mixture was treated with EtOAc (60 mL), washed sequentially with 0.2 M aqueous HCl (5 mL), water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated to give crude (1s,4s)-4-(tert-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid (55 mg), contaminated with (1s,4s)-4-(tert-butoxycarbonyl)-4-fluorocyclohexane-1-carboxylic acid, which was used without further purification. LCMS m/z 244.9 $(M-H)^-$, HPLC t_R 0.94 min (method B).

Intermediate 120

(1s,4s)-4-(ethoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid

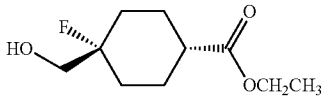


Step A: mixture of ethyl (3r,6r)-1-oxaspiro[2.5]octane-6-carboxylate and ethyl (3s,6s)-1-oxaspiro[2.5]octane-6-carboxylate



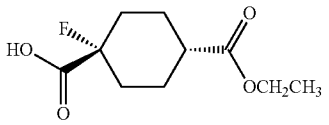
A suspension of potassium tert-butoxide (5.03 g, 44.8 mmol) in dry THF (100 mL) was treated with trimethylsulfoxonium iodide (10.21 g, 46.4 mmol) and the mixture was stirred at reflux under nitrogen for 2 h. The mixture was cooled to rt, treated dropwise over 2 min with a solution of ethyl 4-oxocyclohexanecarboxylate (5.3 g, 31.1 mmol) in THF (30 mL), then heated at reflux for 2.5 h. The mixture was cooled to rt, partitioned between EtOAc (250 mL) and water (150 mL) and the aqueous phase was extracted with EtOAc (2×50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc-hexanes (gradient from 0-15%), to give a mixture of ethyl (3r,6r)-1-oxaspiro[2.5]octane-6-carboxylate and ethyl (3s,6s)-1-oxaspiro[2.5]octane-6-carboxylate (3.8 g, 66% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, J=7.2 Hz, 2.2H), 2.63 (s, 2H), 2.60 (s, 0.2H), 2.47-2.29 (m, 1.2H), 2.13-2.04 (m, 0.2H), 2.02-1.94 (m, 1.2H), 1.93-1.89 (m, 0.2H), 1.89-1.81 (m, 9.6H), 1.81-1.78 (m, 1.6H), 1.77-1.70 (m, 0.4H), 1.56-1.45 (m, 0.2H), 1.42-1.33 (m, 2H), 1.25 (t, J=7.2 Hz, 3.2H).

Step B: ethyl (1s,4s)-4-fluoro-4-(hydroxymethyl) cyclohexane-1-carboxylate



Hydrogen fluoride (70% in pyridine; 5 mL, 5.43 mmol) was cooled to −78° C. in a polypropylene vial and treated with a solution of the mixture of ethyl (3r,6r)-1-oxaspiro [2.5]octane-6-carboxylate and ethyl (3s,6s)-1-oxaspiro[2.5] octane-6-carboxylate from Step A (1.0 g, 5.43 mmol) in DCM (5 mL). The mixture was stirred at −78° C. for 4.5 h, then was poured into ice-cold 2 M aqueous NH_4OH (25 mL) and DCM (25 mL). The mixture was adjusted to pH 8 using concentrated aqueous NH_4OH and extracted with DCM (2×50 mL). The combined organic phases were washed sequentially with 1 M aqueous HCl (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (24 g), eluting with EtOAc-hexanes (gradient from 0-30%), to give (1s,4s)-ethyl 4-fluoro-4-(hydroxymethyl)cyclohexanecarboxylate as a solid (390 mg, 35% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 4.21-4.07 (m, 2H), 3.57 (dd, J=19.6, 5.7 Hz, 2H), 2.36-2.20 (m, 1H), 2.05 (dd, J=12.4, 9.4 Hz, 2H), 1.96-1.86 (m, 2H), 1.86-1.73 (m, 2H), 1.47-1.28 (m, 2H), 1.26 (t, J=7.2 Hz, 3H). (1r,4r)-ethyl 4-fluoro-4-(hydroxymethyl)cyclohexanecarboxylate was also isolated. ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (q, J=7.1 Hz, 2H), 3.72-3.55 (m, 2H), 2.62-2.46 (m, 1H), 1.99-1.87 (m, 2H), 1.85-1.72 (m, 6H), 1.26 (t, J=7.2 Hz, 3H).

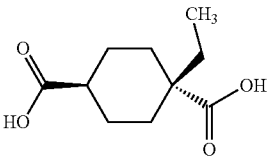
Step C: (1s,4s)-4-(ethoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid



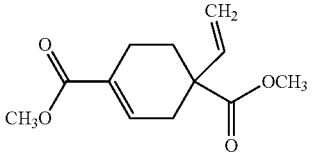
A solution of (1s,4s)-ethyl 4-fluoro-4-(hydroxymethyl) cyclohexanecarboxylate (0.76 g, 3.72 mmol) in MeCN (8 mL) and tetrachloromethane (8.00 mL) was treated with a solution of periodic acid (3.48 g, 15.26 mmol) in water (12.00 mL), then with ruthenium(III) chloride hydrate (0.034 g, 0.149 mmol). The mixture was stirred at rt for 1.5 h, then was diluted with diethyl ether (60 mL) and stirred at rt for 10 min. The mixture was filtered and the phases were separated, and the aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic phases were washed with brine (2×30 mL), dried over Na_2SO_4 and concentrated to give crude (1s,4s)-4-(ethoxycarbonyl)-1-fluorocyclohexanecarboxylic acid as a solid (0.74 g, 91% yield), used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, J=7.3 Hz, 2H), 2.45-2.31 (m, 1H), 2.23-2.11 (m, 2H), 2.04-1.94 (m, 3H), 1.94-1.72 (m, 3H), 1.27 (t, J=7.2 Hz, 3H).

Intermediate 121

(1r,4r)-1-ethylcyclohexane-1,4-dicarboxylic acid

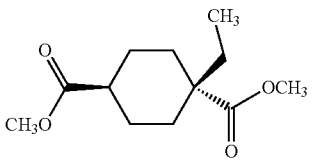


Step A: dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate



A stirred solution of methyl 3-hydroxy-2-methylenebutanoate (2.56 g, 21.13 mmol) in DCM (150 mL) at 0° C. under a nitrogen atmosphere was treated Et_3N (11.8 mL, 85 mmol) followed by MsCl (2.1 mL, 27.5 mmol). The reaction mixture was allowed to reach rt and stirring was continued for 12 h. The mixture was treated with water (50 mL) and extracted with DCM (3×50 mL). The combined organic layers were washed with 1.5 M aqueous HCl (2×50 mL) followed by 50 mL saturated brine, dried over Na_2SO_4, filtered and concentrated to provide a pale yellow liquid (3.7 g). The material was purified by column chromatography (24 g silica gel), eluting with EtOAc-petroleum ether (gradient from 5-7%), to yield dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (1.9 g, 40% yield) as colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (m, 1H), 5.89 (dd, J=18, 9 Hz, 1H), 5.02-5.20 (m, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 2.92-2.72 (m, 1H), 2.45-2.25 (m, 3H), 2.20-2.02 (m, 1H), 1.92-1.72 (m, 1H).

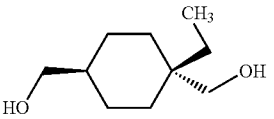
Step B: dimethyl (1r,4r)-1-ethylcyclohexane-1,4-dicarboxylate



A solution of dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (1 g, 4.46 mmol) in DCM (100 mL) was treated with iridium(I) hexafluorophosphate (1,5-cyclooctadiene)-(pyridine)-(tricyclohexylphosphine) (Crabtree's catalyst; 72 mg, 0.089 mmol). The solution was stirred under a hydrogen atmosphere (balloon pressure). The progress of the reaction was monitored by ^1H NMR. After 24 h, another portion of Crabtree's catalyst (72 mg, 0.089 mmol) was added and stirring was continued for another 24 hours. The mixture

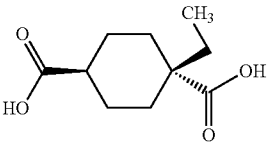
was concentrated to yield a brownish gummy solid which was triturated with diethyl ether (30 mL) to produce a solid. The mixture was filtered and the solids were washed with diethyl ether (2×15 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography (12 g silica gel), eluting with 5% EtOAc in petroleum ether, to yield dimethyl (1r,4r)-1-ethylcyclohexane-1,4-dicarboxylate (1 g, 98% yield) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 6H), 2.52-2.28 (m, 1H), 1.90-1.50 (m, 10H), 0.82 (t, J=3.9 Hz, 3H).

Step C:
((1r,4r)-1-ethylcyclohexane-1,4-diyl)dimethanol



A solution of dimethyl (1r,4r)-1-ethylcyclohexane-1,4-dicarboxylate (200 mg, 0.876 mmol) in toluene (25 mL) was cooled to −78° C. under an argon atmosphere. The mixture was treated dropwise over 10 min with DIBAL-H (1.0 M in toluene, 4.4 mL, 4.38 mmol). The mixture was allowed to reach rt and stirred for 1 h, monitoring the reaction by TLC (silica gel, 10% EtOAc in hexanes). After complete conversion, the mixture was cooled to 0° C. and slowly treated with saturated aqueous NH_4Cl (about 5 mL). The mixture was further diluted with additional saturated aqueous NH_4Cl (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated to yield ((1r,4r)-1-ethylcyclohexane-1,4-diyl)dimethanol as a colorless liquid (150 mg, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52-3.45 (m, 2H), 3.35-3.29 (m, 2H), 1.67-1.50 (m, 3H), 1.43 (q, J=7.6 Hz, 2H), 1.28-1.05 (m, 6H), 0.79 (t, J=7.6 Hz, 3H).

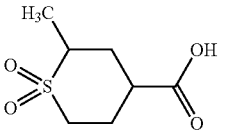
Step D: (1r,4r)-1-ethylcyclohexane-1,4-dicarboxylic acid



A solution of ((1r,4r)-1-ethylcyclohexane-1,4-diyl)dimethanol (150 mg, 0.871 mmol) in acetone (15 mL) at 0° C. was slowly treated with freshly prepared aqueous chromic acid [prepared by adding H_2SO_4 (0.278 mL, 5.22 mmol) to a cold solution of sodium dichromate dihydrate (1.04 g, 3.48 mmol) in water (5 mL) at 0° C. with stirring for 10 min]. The resulting mixture was stirred at rt for 3 h. After completion of the reaction (monitored by TLC), the mixture was partially concentrated and the aqueous residue was extracted with EtOAc (3×10 mL). The combined organic layers (light red in color) were repeatedly washed with brine (15 mL in each wash) until colorless, then was dried over Na_2SO_4 and concentrated to give (1r,4r)-1-ethylcyclohexane-1,4-dicarboxylic acid as a white solid (117 mg, 67% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br. s, 2H), 2.35-2.24 (m, 1H), 1.73-1.57 (m, 6H), 1.55-1.40 (m, 4H), 0.75 (t, J=8.0 Hz, 3H).

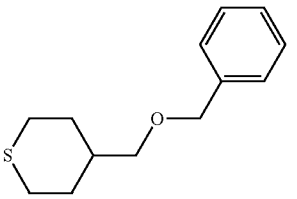
Intermediate 122

(2RS,4RS)-2-methyltetrahydro-2H-thiopyran-4-carboxylic acid 1,1-dioxide



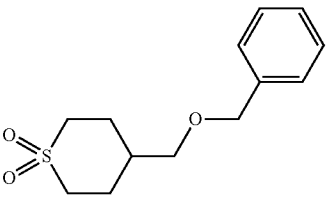
(racemic cis)

Step A:
4-((benzyloxy)methyl)tetrahydro-2H-thiopyran



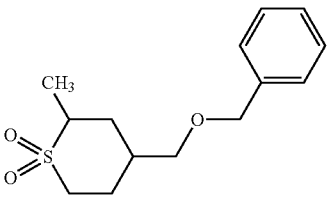
A suspension of NaH (60% in mineral oil; 1.234 g, 30.9 mmol) in DMF (50 mL) at 0° C. was treated portionwise with a solution of (tetrahydro-2H-thiopyran-4-yl)methanol (3.4 g, 25.7 mmol) in DMF (2 mL) and the mixture was stirred for 15 min. Benzyl bromide (3.36 mL, 28.3 mmol) was added dropwise over 2 min, and the mixture was left to warm to rt. After 1.5 h, the mixture was treated with saturated aqueous NH_4Cl (20 mL), diluted with water (50 mL) and extracted with EtOAc (75 mL). The organic phase was washed sequentially with 10% aqueous LiCl (3×30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with EtOAc-hexanes (gradient from 0-10%), to give 4-((benzyloxy)methyl)tetrahydro-2H-thiopyran as a colorless oil (3.4 g, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 4.50 (s, 2H), 3.31 (d, J=6.4 Hz, 2H), 2.75-2.66 (m, 2H), 2.66-2.57 (m, 2H), 2.16-2.07 (m, 2H), 1.79-1.62 (m, 1H), 1.51-1.34 (m, 2H).

Step B:
4-((benzyloxy)methyl)tetrahydro-2H-thiopyran 1,1-dioxide



A solution of 4-((benzyloxy)methyl)tetrahydro-2H-thiopyran (4.7 g, 21.14 mmol) in DCM (125 mL) at 0° C. was treated portionwise with mCPBA (77%; 9.95 g, 44.4 mmol) and the ice bath was removed to allow the mixture to warm to rt. After 2 h, the mixture was cooled to 0° C., filtered and the filtrate was stirred at rt for 10 min with 10% aqueous $Na_2S_2O_3$ (120 mL). The organic phase was separated and washed with 10% aqueous K_2CO_3 (2×150 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with EtOAc-hexanes (gradient from 0-60%), to give 4-((benzyloxy)methyl)tetrahydro-2H-thiopyran 1,1-dioxide as a white solid (4.9 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 4.51 (s, 2H), 3.43-3.30 (m, 2H), 3.14-2.87 (m, 4H), 2.20 (d, J=11.9 Hz, 2H), 2.00-1.76 (m, 3H).

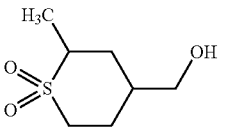
Step C: (2RS,4RS)-4-((benzyloxy)methyl)-2-methyltetrahydro-2H-thiopyran 1,1-dioxide



(racemic cis)

A solution of diisopropylamine (0.579 mL, 4.13 mmol) in THF (12 mL) under nitrogen was cooled to −78° C. and treated dropwise with n-butyllithium (2.4 M in hexanes; 1.556 mL, 3.74 mmol) and the mixture was stirred for 30 min, then at rt for 15 min. The mixture was cooled to −78° C., treated over 3 min with a solution of 4-((benzyloxy)methyl)tetrahydro-2H-thiopyran 1,1-dioxide (1.0 g, 3.93 mmol) in THF (5 mL) and stirred for 1 h. The mixture was then treated with a solution of iodomethane (0.257 mL, 4.13 mmol) in THF (0.5 mL). After 45 min, the cooling bath was removed and the mixture was allowed to warm to rt, then was stirred for 1 h. The mixture was treated with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2×50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc-hexanes (gradient from 0-35%) to give racemic cis-4-((benzyloxy)methyl)-2-methyltetrahydro-2H-thiopyran 1,1-dioxide as a white solid (450 mg, 43% yield). LCMS m/z 290.8 $(M+Na)^+$, HPLC t_R 0.81 min (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (m, 5H), 4.51 (s, 2H), 3.33 (d, J=6.2 Hz, 2H), 3.12 (dt, J=14.3, 3.4 Hz, 1H), 3.04-2.87 (m, 2H), 2.23-2.12 (m, 1H), 2.11-2.03 (m, 1H), 2.00-1.76 (m, 2H), 1.69-1.59 (m, 1H), 1.35 (d, J=6.8 Hz, 3H). The dimethylated side product (2R,4r,6S)-4-((benzyloxy)methyl)-2,6-dimethyltetrahydro-2H-thiopyran 1,1-dioxide was also isolated in 75% purity (250 mg, 23% yield). LCMS m/z 283.1 $(M+H)^+$, HPLC t_R 0.88 min (method B).

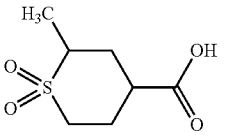
Step D: (2RS,4RS)-4-(hydroxymethyl)-2-methyltetrahydro-2H-thiopyran 1,1-dioxide



(racemic cis)

A solution of (2RS,4RS)-4-((benzyloxy)methyl)-2-methyltetrahydro-2H-thiopyran 1,1-dioxide (0.45 g, 1.677 mmol) in MeOH (2 mL) and ethanol (10 mL) was treated with palladium on carbon (160 mg, 0.075 mmol) and stirred under a hydrogen atmosphere (balloon pressure) for 1.5 h. The mixture was filtered to remove the catalyst and the filtrate was concentrated to give (2RS,4RS)-4-(hydroxymethyl)-2-methyltetrahydro-2H-thiopyran 1,1-dioxide as a white solid (280 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (d, J=5.7 Hz, 1H), 3.20-3.09 (m, 1H), 3.06-2.85 (m, 2H), 2.24-2.12 (m, 1H), 2.10-2.00 (m, 2H), 1.92-1.73 (m, 2H), 1.67-1.52 (m, 1H), 1.36 (d, J=6.8 Hz, 3H).

Step E: (2RS,4RS)-2-methyltetrahydro-2H-thiopyran-4-carboxylic acid 1,1-dioxide

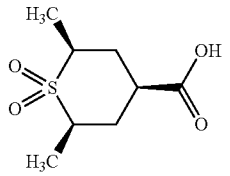


(racemic cis)

A solution of (2RS,4RS)-4-(hydroxymethyl)-2-methyltetrahydro-2H-thiopyran 1,1-dioxide (0.275 g, 1.543 mmol) in MeCN (0.9 mL) and CCl_4 (0.9 mL) was treated with a solution of sodium periodate (1.353 g, 6.33 mmol) in water (1.3 mL), then with ruthenium(III) chloride hydrate (0.014 g, 0.062 mmol), and the mixture was stirred at rt. After 30 min, the mixture was a yellow emulsion, and stirring was continued at rt for 30 min more with periodic sonication. An additional portion of ruthenium(III) chloride hydrate (0.014 g, 0.062 mmol) was added, and stirring was continued for 1 h with occasional sonication. The mixture was diluted with EtOAc (125 mL), the organic phase was separated and washed with water (25 mL), dried over Na_2SO_4 and concentrated. The residue was treated with EtOAc (125 mL) and MeOH (10 mL), filtered (Acrodisk syringe filter, 25 mm, 0.45 m) and concentrated to give (2RS,4RS)-2-methyltetrahydro-2H-thiopyran-4-carboxylic acid 1,1-dioxide as a gray solid (165 mg, 56% yield), used without further purification. ^{1}H NMR (400 MHz, MeOH-d_4) δ 3.28-3.04 (m, 3H), 2.69 (tt, J=12.4, 3.3 Hz, 1H), 2.37 (d quin, J=14.1, 3.5 Hz, 1H), 2.28 (dq, J=14.2, 3.2 Hz, 1H), 2.18-2.03 (m, 1H), 1.86 (dt, J=14.3, 12.5 Hz, 1H), 1.29 (d, J=6.8 Hz, 3H).

Intermediate 123

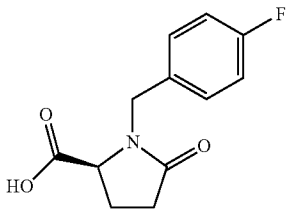
(2R,4r,6S)-2,6-dimethyltetrahydro-2H-thiopyran-4-carboxylic acid 1,1-dioxide



Following the procedures of Intermediate 122 Steps D and E, (2R,4r,6S)-4-((benzyloxy)methyl)-2,6-dimethyltetrahydro-2H-thiopyran 1,1-dioxide (isolated as a side product in Step C of the preparation of Intermediate 122) was converted into (2R,4r,6S)-2,6-dimethyltetrahydro-2H-thiopyran-4-carboxylic acid 1,1-dioxide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12-2.97 (m, 2H), 2.70 (tt, J=12.5, 3.1 Hz, 1H), 2.32 (d, J=11.9 Hz, 2H), 2.17-2.04 (m, 2H), 1.43 (d, J=6.6 Hz, 6H).

Intermediate 124

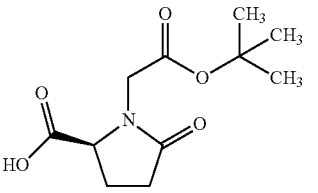
(S)-1-(4-fluorobenzyl)-5-oxopyrrolidine-2-carboxylic acid



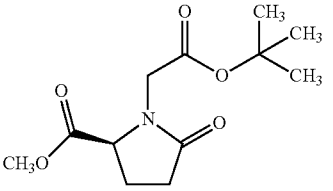
A suspension of NaH (60% in mineral oil; 0.336 g, 8.40 mmol) in THF (11 mL) was treated with (S)-ethyl 5-oxopyrrolidine-2-carboxylate (0.88 g, 5.60 mmol). The mixture was stirred at rt for 15 min, then 1-(bromomethyl)-4-fluorobenzene (0.837 mL, 6.72 mmol) was added and the mixture was stirred at rt overnight. The mixture was concentrated to give crude methyl (S)-1-(4-fluorobenzyl)-5-oxopyrrolidine-2-carboxylate, used without purification. This was dissolved in THF-MeOH-water (3:1:1, 112 mL) and treated with LiOH monohydrate (0.267 g, 11.16 mmol). The mixture was stirred at rt for 20 h, then was partially concentrated. The aqueous residue was diluted with water and washed twice with EtOAc. The aqueous phase was acidified with 1 M aqueous HCl to about pH 2, and then was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated to provide (S)-1-(4-fluorobenzyl)-5-oxopyrrolidine-2-carboxylic acid as a yellow syrup (0.54 g, 41% yield). LCMS m/z 238.3 $(M+H)^+$, HPLC t_R 0.92 min (method B). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (br. s., 1H), 7.28-7.21 (m, 2H), 7.19-7.11 (m, 2H), 4.79 (d, J=15.0 Hz, 1H), 3.97-3.89 (m, 2H), 2.41-2.20 (m, 3H), 1.98-1.91 (m, 1H).

Intermediate 125

(S)-1-(2-(tert-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid

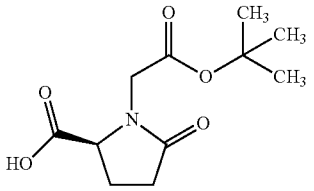


Step A: methyl (S)-1-(2-(tert-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate



A solution of (S)-methyl 5-oxopyrrolidine-2-carboxylate (2.50 g, 17.47 mmol) in dry MeCN (45 mL) under nitrogen was stirred on an ice-water bath and treated portionwise over 30 min with NaH (60% in mineral oil; 0.768 g, 19.21 mmol) portionwise. The resulting suspension was stirred on ice for 90 min, then was treated dropwise over 15 min with a solution of tert-butyl 2-bromoacetate (2.84 mL, 19.21 mmol) in MeCN (4 mL). The resulting suspension was warmed to rt and stirred for 3 h, then was concentrated under vacuum. The residue was partitioned between EtOAc and water, and the aqueous phase was extracted again with EtOAc. The combined organic phases were washed with saturated brine, dried over Na_2SO_4 and concentrated. The residue was twice stirred vigorously with hexane, followed by decantation of the hexane layer. The residue was concentrated under vacuum to give a pale tan viscous oil. The combined hexane washes, on nearly complete concentration, formed two phases. The upper phase was decanted, and the lower phase was rinsed with a small amount of hexane by decantation and dried under vacuum to provide a colorless oil. The two oils were combined and concentrated further under vacuum to provide methyl (S)-1-(2-(tert-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate (3.63 g, 78% yield). LCMS m/z 202 $(M+H—C_4H_8)^+$, 515 $(2M+H)^+$, HPLC t_R 0.73 min (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (d, J=17.8 Hz, 1H), 4.50-4.40 (m, 1H), 3.79 (s, 3H), 3.60 (d, J=18.0 Hz, 1H), 2.61-2.33 (m, 3H), 2.25-2.07 (m, 1H), 1.47 (s, 9H).

Step B: (S)-1-(2-(tert-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid



A solution of (S)-methyl 1-(2-(tert-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate (0.25 g, 0.972 mmol) in THF (3 mL) was stirred on an ice-water bath and treated with a solution of LiOH hydrate (0.043 g, 1.020 mmol) in water (3 mL). The solution was stirred for 60 min, then was treated with 1 M aqueous HCl (1.03 mL) and concentrated. The residue was partitioned between EtOAc and a small amount of water and the aqueous phase was extracted again with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated to provide (S)-1-(2-(tert-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylic acid as a light yellow-tan gum (220 mg, 89% yield). LCMS m/z 188 $(M+H—C_4H_8)^+$ and 509 $(2M+Na)^+$, HPLC t_R 0.65 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 4.53 (d, J=18.1 Hz, 1H), 4.52-4.42 (m, 1H), 3.70 (d, J=17.8 Hz, 1H), 2.67-2.41 (m, 3H), 2.33-2.17 (m, 1H), 1.48 (s, 9H).

The Intermediates in Table 7 were prepared using the same method or similar methods used to prepare Intermediates 124 and 125 by employing the appropriate starting materials.

TABLE 7

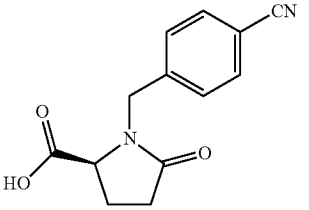
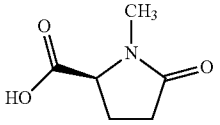
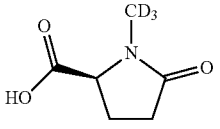
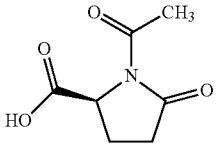
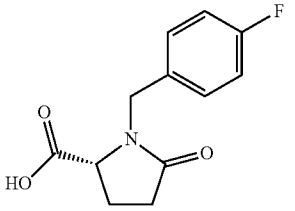
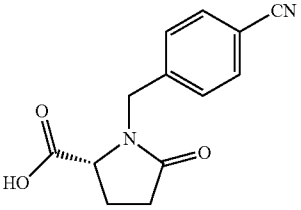
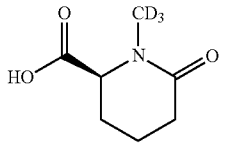
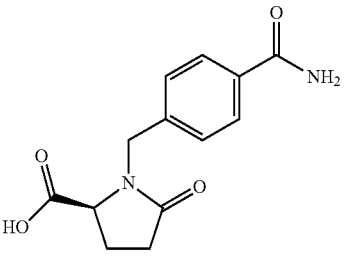
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
126		244.9 $(M+H)^+$	0.57	B
127		165.9 $(M+Na)^+$	0.40	B
128		169.0 $(M+Na)^+$	0.37	B
129		171.9 $(M+H)^+$	0.43	B

TABLE 7-continued

Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
130		237.9 $(M+H)^+$	0.63	B
131		244.9 $(M+H)^+$	0.57	B
132		161.1 $(M+H)^+$	0.40	B

Intermediate 133

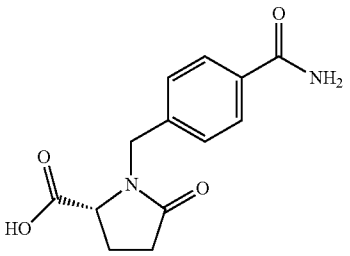
(S)-1-(4-carbamoylbenzyl)-5-oxopyrrolidine-2-carboxylic acid



A suspension of (S)-1-(4-cyanobenzyl)-5-oxopyrrolidine-2-carboxylic acid (Intermediate 126, 0.120 g, 0.491 mmol) in 85% aqueous H_2SO_4 (1.637 mL, 24.57 mmol) was heated at 60° C. After 100 min, the mixture was cooled to rt and poured onto ice and water. The resulting mixture was extracted with EtOAc, and the organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford (S)-1-(4-carbamoylbenzyl)-5-oxopyrrolidine-2-carboxylic acid as a yellow solid (46 mg, 46% yield). LCMS m/z 263.0 $(M+H)^+$, HPLC t_R 0.43 min (method B). ^1H NMR (400 MHz, DMSO-d_6): δ 13.01 (br. s., 1H), 7.93 (br. s., 1H), 7.83 (d, J=8.4 Hz, 2H), 7.31 (br. s., 1H), 7.27 (d, J=8.1 Hz, 2H), 4.87 (d, J=15.6 Hz, 1H), 4.01-3.92 (m, 2H), 2.33 (d, J=2.9 Hz, 3H), 1.98-1.93 (m, 1H).

Intermediate 134

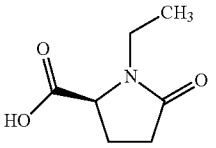
(R)-1-(4-carbamoylbenzyl)-5-oxopyrrolidine-2-carboxylic acid



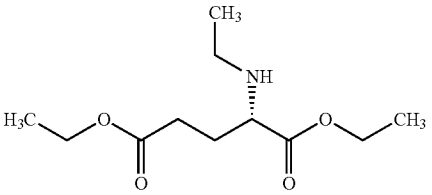
Following the procedure used to prepare Intermediate 133, (R)-1-(4-cyanobenzyl)-5-oxopyrrolidine-2-carboxylic acid (Intermediate 131) was converted into (R)-1-(4-carbamoylbenzyl)-5-oxopyrrolidine-2-carboxylic acid in 68% yield. LCMS m/z 262.9 $(M+H)^+$, HPLC t_R 0.44 min (method B).

Intermediate 135

(S)-1-ethyl-5-oxopyrrolidine-2-carboxylic acid

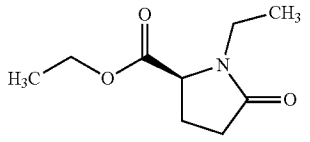


Step A: diethyl ethyl-L-glutamate



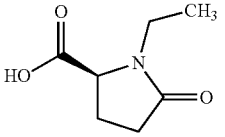
A mixture of (S)-diethyl 2-aminopentanedioate hydrochloride (1.5 g, 6.26 mmol) in THF (19 mL) and MeOH (10 mL) was treated with crushed KOH (0.410 g, 6.57 mmol) and stirred at rt for 10 min. The mixture was treated with a mixture of acetaldehyde (5 M in THF; 3.75 mL, 18.77 mmol) and acetic acid (0.394 mL, 6.88 mmol) in THF (2.4 mL). After 10 min, the reaction mixture was treated portionwise with sodium borohydride (0.474 g, 12.52 mmol). The mixture was stirred at rt for 18 h, then was concentrated. The residue was partitioned between EtOAc and 1.5 M aqueous K_2HPO_4. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford crude diethyl ethyl-L-glutamate as a yellow oil (1.39 g, 96% yield). LCMS m/z 232.2 $(M+H)^+$, HPLC t_R 0.53 min (method B).

Step B: ethyl (S)-1-ethyl-5-oxopyrrolidine-2-carboxylate



A solution of diethyl ethyl-L-glutamate (1.39 g, 6.01 mmol) in MeOH (12 mL) in a sealed vessel was heated at 140° C. for 15 min, then was heated via microwave irradiation for 15 min at 150° C. The mixture was cooled to rt, concentrated, and the residue was partitioned between EtOAc and 0.3 M aqueous HCl. The organic phase was washed sequentially with water and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to afford crude ethyl (S)-1-ethyl-5-oxopyrrolidine-2-carboxylate as a brown oil (0.39 g, 35% yield). LCMS m/z 186.1 $(M+H)^+$, HPLC t_R 0.61 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 4.28-4.18 (m, 3H), 3.76-3.64 (m, 1H), 3.11-2.99 (m, 1H), 2.58-2.46 (m, 1H), 2.42-2.26 (m, 2H), 2.14-2.03 (m, 1H), 1.30 (t, J=7.2 Hz, 3H), 1.14-1.10 (m, 3H).

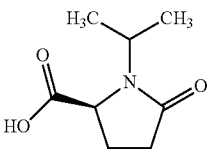
Step C: (S)-1-ethyl-5-oxopyrrolidine-2-carboxylic acid



A mixture of ethyl (S)-1-ethyl-5-oxopyrrolidine-2-carboxylate (0.39 g, 2.106 mmol) and LiOH monohydrate (0.166 g, 6.95 mmol) in THF (6 mL), MeOH (2 mL) and water (2 mL) was stirred at rt. After 16 h the mixture was concentrated, and the residue was partitioned between 1 M aqueous HCl and chloroform-isopropanol (93:7). The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated to afford (S)-1-ethyl-5-oxopyrrolidine-2-carboxylic acid as a brown syrup (0.357 g, quantitative yield), used without further purification. LCMS m/z 158.1 $(M+H)^+$, HPLC t_R 0.19 min (method B). ^1H NMR (400 MHz, $CDCl_3$): δ 4.93 (br. s, 1H), 4.27 (dd, J=9.0, 3.0 Hz, 1H), 3.85-3.65 (m, 1H), 3.09 (dq, J=14.1, 7.1 Hz, 1H), 2.67-2.50 (m, 1H), 2.49-2.29 (m, 2H), 2.25-2.12 (m, 1H), 1.14 (t, J=7.3 Hz, 3H).

Intermediate 136

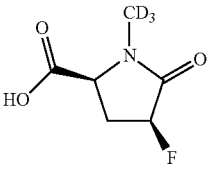
(S)-1-isopropyl-5-oxopyrrolidine-2-carboxylic acid



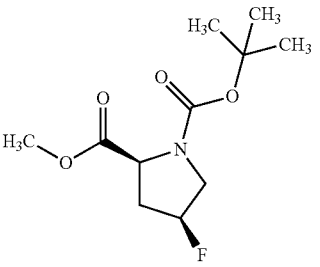
(S)-1-isopropyl-5-oxopyrrolidine-2-carboxylic acid was prepared by following the procedure used to prepare Intermediate 135, substituting acetone for acetaldehyde in Step A. LCMS m/z 172.1 $(M+H)^+$, HPLC t_R 0.19 min (method B).

Intermediate 137

(2S,4S)-4-fluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid

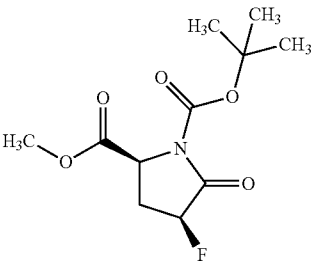


Step A: 1-(tert-butyl) 2-methyl (2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate



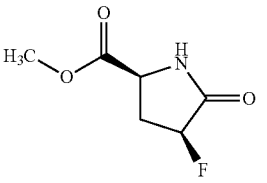
A solution of (2S,4S)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (10 g, 40.8 mmol) in DCM (204 mL) was cooled in an ice-water bath and treated slowly with DAST (6.46 mL, 48.9 mmol). The mixture was stirred at rt for 5.5 h, then was partitioned between water and additional DCM. The organic phase was washed with bine, dried over Na_2SO_4, filtered, and concentrated to afford 1-(tert-butyl) 2-methyl (2S,4S)-4-fluoropyrrolidine-1,2-dicarboxylate as a light yellow syrup (10.58 g, 94% yield, 90% estimated purity). LCMS m/z 270.2 $(M+Na)^+$, HPLC t_R 0.80 min (method B).

Step B: 1-(tert-butyl) 2-methyl (2S,4S)-4-fluoro-5-oxopyrrolidine-1,2-dicarboxylate



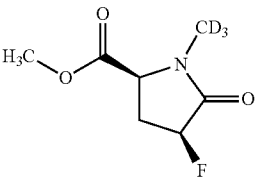
A solution of sodium periodate (44.6 g, 209 mmol) in water (435 ml) was treated with ruthenium(III) chloride hydrate (7.84 g, 34.8 mmol), forming a dark red solution. This was treated slowly with a solution of crude (2S,4S)-1-tert-butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate (9.55 g, 34.8 mmol) in EtOAc (145 mL). The mixture was stirred at rt for 17 h, then was treated with isopropanol (80 mL) and stirred at rt for 3 h. The mixture was filtered through Celite and the solids were washed with water and EtOAc. The combined filtrates were diluted with additional EtOAc and water. The organic phase was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with EtOAc-hexanes (10-50%), to provide 1-(tert-butyl) 2-methyl (2S,4S)-4-fluoro-5-oxopyrrolidine-1,2-dicarboxylate as a light yellow oil (67% yield). LCMS m/z 284.0 $(M+Na)^+$, HPLC t_R 0.76 min (method B). ^1H NMR (400 MHz, $CDCl_3$): δ 5.30-5.11 (m, 1H), 4.68 (dd, J=9.5, 2.0 Hz, 1H), 3.81 (s, 3H), 2.61-2.40 (m, 2H), 1.53 (s, 9H).

Step C: methyl (2S,4S)-4-fluoro-5-oxopyrrolidine-2-carboxylate



A solution of (2S,4S)-1-tert-butyl 2-methyl 4-fluoro-5-oxopyrrolidine-1,2-dicarboxylate (7.75 g, 25.8 mmol) in DCM (32 mL) was cooled in an ice-water bath and treated with TFA (12 mL). The mixture was stirred at rt for 2 h, then was concentrated and the residue partitioned between water and EtOAc. The organic phase was washed sequentially with 1.5 M aqueous K_2HPO_3 and brine, dried over Na_2SO_4, filtered, and concentrated. The aqueous phase was extracted with chloroform-isopropanol (3:1) to provide additional product. The two portions were combined to provide methyl (2S,4S)-4-fluoro-5-oxopyrrolidine-2-carboxylate as a dark yellow syrup (3.38 g, 81% yield). LCMS m/z 162.0 $(M+H)^+$, HPLC t_R 0.41 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (br. s., 1H), 5.23-5.03 (m, 1H), 4.47-4.34 (m, 1H), 3.82-3.78 (m, 3H), 2.69-2.58 (m, 2H).

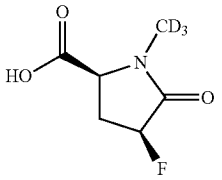
Step D: methyl (2S,4S)-4-fluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylate



A mixture of (2S,4S)-methyl 4-fluoro-5-oxopyrrolidine-2-carboxylate (0.48 g, 2.98 mmol) and Cs_2CO_3 (2.426 g, 7.45 mmol) in MeCN (16.55 mL) was treated with iodomethane-d_3 (0.927 mL, 14.89 mmol) and heated at 45° C. overnight in a sealed vial.

After 18 h, the mixture was cooled to rt, filtered and concentrated to afford methyl (2S,4S)-4-fluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylate as a light yellow solid (0.53 g, quantitative yield). LCMS m/z 179.1 $(M+H)^+$, HPLC t_R 0.46 min (method B).

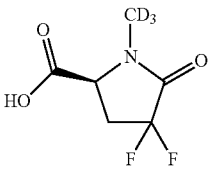
Step E: (2S,4S)-4-fluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid



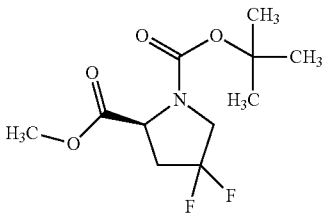
A mixture of methyl (2S,4S)-4-fluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylate (0.53 g, 2.97 mmol) and LiOH monohydrate (0.221 g, 9.22 mmol) in THF-MeOH-water (3:1:1) (29.7 mL) was stirred at rt for 18 h. The mixture was concentrated, the residue was treated with HCl (4 M in 1,4-dioxane, 2.380 mL, 9.52 mmol), and the mixture was concentrated again to dryness. The crude mixture containing (2S,4S)-4-fluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid was used without further purification. LCMS m/z 165.0 $(M+H)^+$, HPLC t_R 0.35 min (method B).

Intermediate 138

(S)-4,4-difluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid

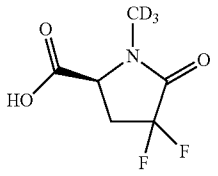


Step A: 1-(tert-butyl) 2-methyl (S)-4,4-difluoropyrrolidine-1,2-dicarboxylate



A solution of (S)-1-tert-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (5.02 g, 20.64 mmol) in DCM (83 mL) at −78° C. was treated dropwise with DAST (9.82 mL, 74.3 mmol). The mixture was stirred at this temperature for 15 min, then warmed to rt and stirred for 18 h. The mixture was cooled to 0° C., diluted with additional DCM and treated with ice and saturated aqueous $NaHCO_3$. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc-hexanes (10-20%), to provide 1-(tert-butyl) 2-methyl (S)-4,4-difluoropyrrolidine-1,2-dicarboxylate as a light yellow oil (4.48 g, 82% yield). LCMS m/z 288.1 $(M+Na)^+$, HPLC t_R 0.88 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 4.64-4.40 (m, 1H), 3.93-3.73 (m, 5H), 2.83-2.60 (m, 1H), 2.47 (qd, J=13.6, 5.3 Hz, 1H), 1.46 (d, J=18.5 Hz, 9H).

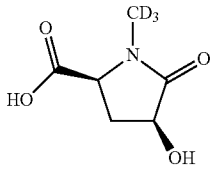
Step B: (S)-4,4-difluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid



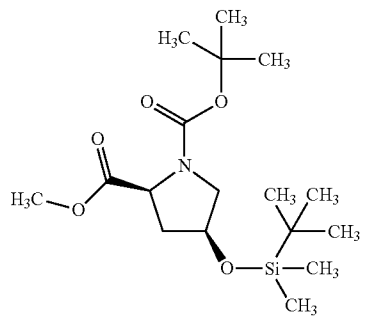
Following the procedures used in Steps B, C, D and E of the preparation of Intermediate 137, 1-(tert-butyl) 2-methyl (S)-4,4-difluoropyrrolidine-1,2-dicarboxylate was converted into (S)-4,4-difluoro-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid. LCMS m/z 182.9 $(M+H)^+$, HPLC t_R 0.41 min (method B).

Intermediate 139

(2S,4S)-4-hydroxy-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid



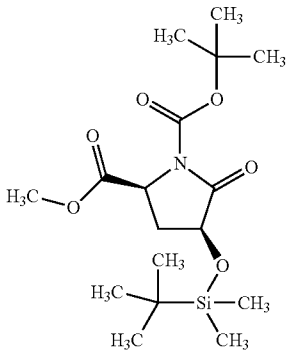
Step A: 1-(tert-butyl) 2-methyl (2S,4S)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate



A solution of (2S,4S)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (3.1 g, 12.64 mmol) in THF (56 mL), cooled in an ice-water bath, was treated slowly

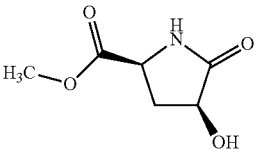
with a solution of tert-butylchlorodimethylsilane (2.286 g, 15.17 mmol) in THF (7.02 mL), then with Et_3N (2.82 mL, 20.22 mmol). The mixture was stirred at rt overnight. After 18 h, imidazole (1.721 g, 25.3 mmol) was added and the resulting thick suspension was stirred at rt overnight. Additional imidazole (0.42 g), tert-butylchlorodimethylsilane (1.1 g) and DMF (6 mL) were added and the mixture was heated at 45° C. for 6 h, then stirred at rt overnight. The mixture was concentrated and the residue was partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (80 g), eluting with EtOAc-hexanes (0-10%), to provide 1-(tert-butyl) 2-methyl (2S,4S)-4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate as a colorless oil (4.76 g, quantitative yield). LCMS m/z 382.2 $(M+Na)^+$, HPLC t_R 1.16 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 4.47-4.27 (m, 2H), 3.71 (s, 3H), 3.68-3.54 (m, 1H), 3.39-3.24 (m, 1H), 2.38-2.22 (m, 1H), 2.15-2.06 (m, 1H), 1.48 (s, 3H), 1.43 (s, 6H), 0.89-0.83 (m, 9H), 0.08-0.03 (m, 6H).).

Step B: 1-(tert-butyl) 2-methyl (2S,4S)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate



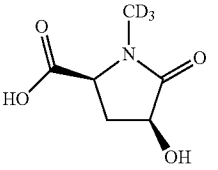
A solution of sodium periodate (7.08 g, 33.1 mmol) in water (126 mL) was treated with ruthenium(IV) oxide hydrate (0.400 g, 2.65 mmol) and stirred at rt for 5 min. This mixture was then treated with a solution of (2S,4S)-1-tert-butyl 2-methyl 4-((tert-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (4.76 g, 13.24 mmol) in EtOAc (63 mL) and stirred at rt. After 6 h, the mixture was diluted with EtOAc, filtered through Celite, and the solids were washed with water and EtOAc. The combined filtrates were partitioned between water and EtOAc. The organic phase was washed sequentially with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$ and brine, dried over Na_2SO_4, filtered and concentrated to afford 1-(tert-butyl) 2-methyl (2S,4S)-4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate as a colorless syrup (4.85 g, 98% yield). LCMS m/z 396.2 $(M+Na)^+$, HPLC t_R 1.08 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, J=7.8, 6.9 Hz, 1H), 4.29 (t, J=7.3 Hz, 1H), 3.77 (s, 3H), 2.57 (dt, J=13.0, 7.7 Hz, 1H), 2.00 (dt, J=13.0, 7.0 Hz, 1H), 1.51 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H).

Step C: methyl (2S,4S)-4-hydroxy-5-oxopyrrolidine-2-carboxylate



A solution of (2S,4S)-1-tert-butyl 2-methyl 4-((tert-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate (4.85 g, 12.98 mmol) in DCM (16 mL) was cooled in an ice-water bath and treated with TFA (3 mL). The mixture was warmed to rt, stirred for 2 h, and concentrated to provide methyl (2S,4S)-4-hydroxy-5-oxopyrrolidine-2-carboxylate as a yellow syrup in quantitative yield. LCMS m/z 159.9 $(M+H)^+$, HPLC t_R 0.38 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-6.70 (m, 1H), 4.47-4.36 (m, 2H), 4.26-4.16 (m, 1H), 3.81 (d, J=10.1 Hz, 3H), 2.96-2.70 (m, 1H), 2.21-2.08 (m, 1H).

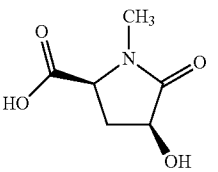
Step D: (2S,4S)-4-hydroxy-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid



Following the procedures used in Steps D and E of the preparation of Intermediate 137, methyl (2S,4S)-4-hydroxy-5-oxopyrrolidine-2-carboxylate was converted into (2S,4S)-4-hydroxy-1-(methyl-d_3)-5-oxopyrrolidine-2-carboxylic acid. LCMS m/z 163.0 $(M+H)^+$, HPLC t_R 0.31 min (method B).

Intermediate 140

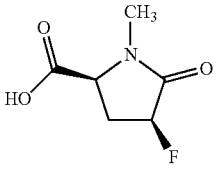
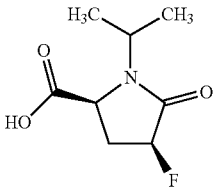
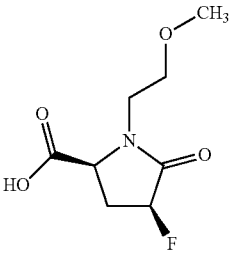
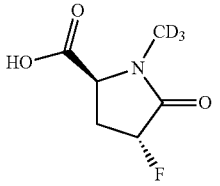
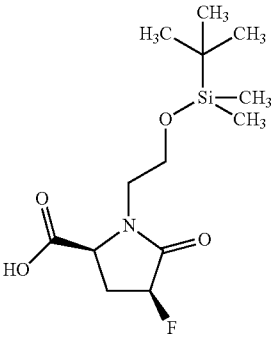
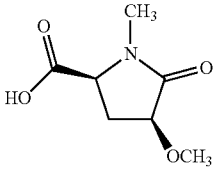
(2S,4S)-4-hydroxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid



(2S,4S)-4-hydroxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid was prepared using the procedures of Intermediate 139, substituting iodomethane for iodomethane-d_3. LCMS m/z 160.0 $(M+H)^+$, HPLC t_R 0.26 min (method B).

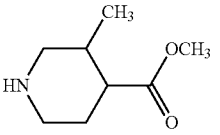
The Intermediates in Table 8 were prepared using the same methods or similar methods used to prepare Intermediates 137 through 140.

TABLE 8

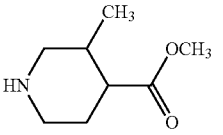
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
141		162.0 $(M + H)^+$	0.39	B
142		190.1 $(M + H)^+$	0.48	B
143		206.0 $(M + H)^+$	0.43	B
144		164.9 $(M + H)^+$	0.30	B
145		306.0 $(M + H)^+$	0.90	B
146		174.1 $(M + H)^+$	0.38	B

Intermediates 147 and 148

cis methyl 3-methylpiperidine-4-carboxylate



cis Peak 1

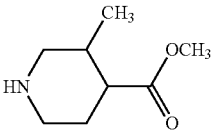


cis Peak 2

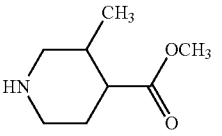
A solution of methyl 3-methylisonicotinate hydrochloride (2.63 g, 14 mmol) in acetic acid (25 mL) was treated with platinum(IV) oxide (0.20 g, 0.881 mmol) and stirred under a hydrogen atmosphere (50 psi) for 15 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was treated with 5% aqueous K_2CO_3 and extracted with DCM. The organic phase was dried and concentrated to give cis methyl 3-methylpiperidine-4-carboxylate, containing about 15% of the trans isomer, as an amber oil (1.4 g). The material was separated by chiral SFC using the following conditions: Column: Chiralpak® AD-H 50×250 mm, 5 m (Chiral Technologies Inc.); column temperature 35° C.; pressure 100 bars; mobile phase CO_2-MeOH (85:15) containing 0.1% NH_4OH; flow rate 250 mL/min; injection volume 1.5 mL. Peak 1 was eluted with t_R 5.5 min. Peak 2 was eluted with t_R 7.5 min. ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.07 (dt, J=12.5, 4.3 Hz, 1H), 2.91-2.72 (m, 2H), 2.67-2.51 (m, 2H), 2.10 (ddd, J=10.9, 7.3, 3.7 Hz, 1H), 1.79 (dtd, J=13.9, 10.3, 4.1 Hz, 1H), 1.68-1.54 (m, 1H), 1.43 (br. s., 1H), 0.94 (d, J=7.0 Hz, 3H).

Intermediates 149 and 150

trans methyl 3-methylpiperidine-4-carboxylate



trans Peak 1



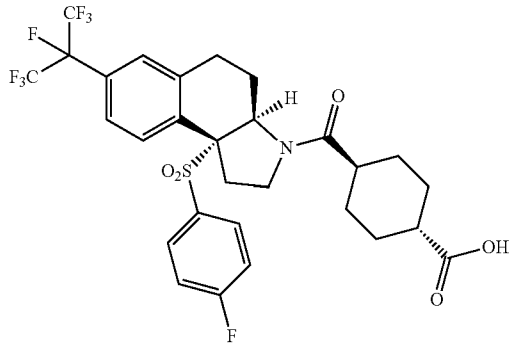
trans Peak 2

Anhydrous MeOH (25 mL) was treated portionwise with sodium (2.047 g, 89 mmol) and the mixture stirred until the metal was completely dissolved. This solution was treated with crude methyl 3-methylpiperidine-4-carboxylate (cis-trans mixture, about 85:15, prepared according to the procedure of Intermediates 147 and 148; 1.4 g, 8.91 mmol) and the solution was heated at reflux for 60 h. The solution was cooled to rt, neutralized with acetic acid and concentrated. The residue was treated with 2 M aqueous K_2CO_3 (100 mL) and extracted with DCM (3×75 mL). The combined organic phases were dried over Na_2SO_4 and concentrated give methyl 3-methylpiperidine-4-carboxylate (cis-trans mixture, about 10:90) as a pale amber oil. LCMS m/z 157.9 $(M+H)^+$, HPLC t_R 0.44 min (method B). This material was separated by chiral SFC using the following conditions: Column: Lux® Cellulose-4 30×250 mm, 5 m (Phenomenex Inc.); column temperature 35° C.; pressure 100 bars; mobile phase CO_2-MeOH (80:20); flow rate 180 mL/min; injection 85 mg

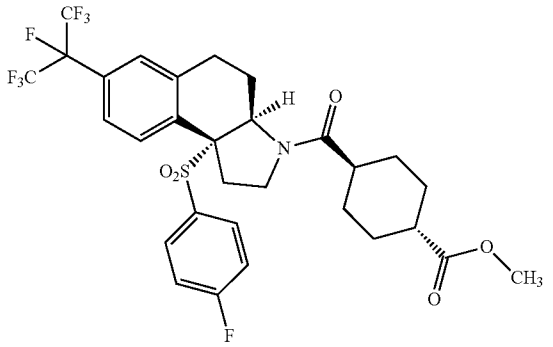
in 1 mL. Two enantiomers of trans methyl 3-methylpiperidine-4-carboxylate were obtained, both contaminated with cis methyl 3-methylpiperidine-4-carboxylate (about 9%). Peak 1 (colorless oil, 250 mg): ^{1}H NMR (400 MHz, MeOH-d_4) δ 3.69 (s, 3H), 3.05 (dt, J=12.7, 2.8 Hz, 1H), 2.98 (dd, J=12.8, 4.0 Hz, 1H), 2.56 (td, J=12.7, 2.9 Hz, 1H), 2.23 (dd, J=12.3, 11.4 Hz, 1H), 2.13 (ddd, J=12.1, 11.0, 3.7 Hz, 1H), 1.88-1.72 (m, 2H), 1.70-1.53 (m, 1H), 0.86 (d, J=6.6 Hz, 3H). Peak 2 (colorless oil, 350 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.07 (dt, J=12.5, 2.9 Hz, 1H), 3.00 (dd, J=12.5, 4.0 Hz, 1H), 2.55 (td, J=12.4, 2.9 Hz, 1H), 2.22 (dd, J=12.4, 11.1 Hz, 1H), 2.06 (ddd, J=11.9, 10.9, 3.7 Hz, 1H), 1.85-1.67 (m, 2H), 1.66-1.48 (m, 2H), 0.81 (d, J=6.4 Hz, 3H).

Example 1

(1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid

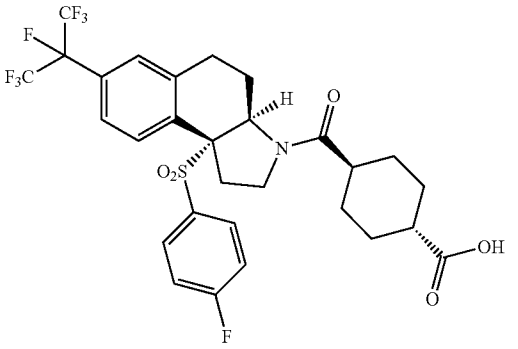


Step A: methyl (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate



A solution of ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 223 mg, 0.417 mmol), trans-4-(methoxycarbonyl)cyclohexanecarboxylic acid (0.140 g, 0.752 mmol) and DIPEA (0.358 mL, 2.052 mmol) in THF (4.2 mL) was treated with HATU (174 mg, 0.459 mmol). The mixture was stirred at rt for 2 h. Celite and EtOAc were added, and the mixture was concentrated to a dry powder, which was used to purify the material by column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 0-50%), to provide methyl (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-0.417 mmol), trans-4-(methoxycarbonyl)cyclohexane-1-carboxylate (246 mg, 88% yield). LCMS m/z 668.1 $(M+H)^+$, HPLC t_R 1.13 min (method B).

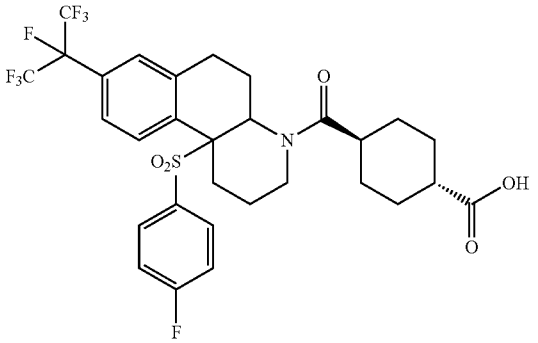
Step B: (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A solution of methyl (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate (246 mg, 0.368 mmol) in THF (2.5 mL) was treated with a solution of LiOH hydrate (35 mg, 1.474 mmol) in water (1.3 mL). The mixture was stirred for 3 h at rt, when LCMS showed partial conversion of the starting material. Additional LiOH hydrate (13 mg, 0.553 mmol) was added and the mixture was stirred for 2 h more. The mixture was treated with 1 M aqueous HCl and washed with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to provide the crude product (250 mg). The material was further purified by chiral SFC (column: Lux® Cellulose-4 4.6×250 mm 5 μm (Phenomenex Inc.); mobile phase: CO_2/MeOH (75:25); 35° C., 100 bar) to afford (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (140 mg, 58% yield). LCMS m/z 654.2 $(M+H)^+$, HPLC t_R 1.06 min (method B). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (br. s., 1H), 7.95-7.78 (m, 1H), 7.69-7.57 (m, 1H), 7.42-7.32 (m, 2H), 7.32-7.22 (m, 2H), 7.22-7.03 (m, 1H), 4.66 (dd, J=11.8, 5.0 Hz, 1H), 3.79-3.64 (m, 2H), 3.38 (ddd, J=14.4, 7.4, 3.7 Hz, 1H), 2.77-2.59 (m, 2H), 2.37-2.24 (m, 3H), 2.14 (d, J=13.0 Hz, 1H), 2.02-1.81 (m, 3H), 1.69 (d, J=3.7 Hz, 2H), 1.46-1.24 (m, 4H). ^{19}F NMR (376 MHz, DMSO-d_6) δ −104.9 (s, 1F), −77.3 (m, 1F), −77.0 (s, 6F).

Example 2

(1r,4r)-4-(10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-4-carbonyl)cyclohexane-1-carboxylic acid (homochiral)



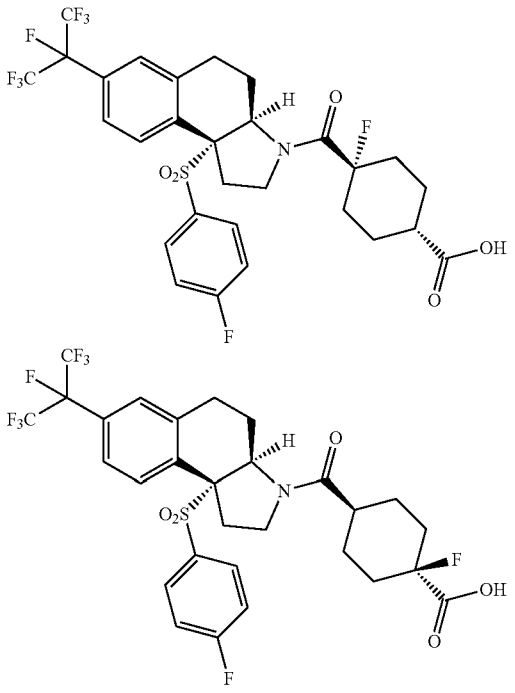
Homochiral from peak 2

A solution of trans-1,4-cyclohexanedicarboxylic acid monomethyl ester in DCM was treated with excess oxalyl chloride and catalytic DMF, and the mixture was stirred at rt for 1 h. The mixture was concentrated to provide (1r,4r)-methyl 4-(chlorocarbonyl)cyclohexanecarboxylate, which was used without further purification.

A solution of 10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (homochiral, from peak 2, Intermediate 61; 40 mg, 0.078 mmol), pyridine (0.5 mL) and DCM (1.5 mL) was cooled in an ice-water bath and treated with 4-dimethylaminopyridine (9.52 mg, 0.078 mmol), then was treated dropwise with a solution of crude (1r,4r)-methyl 4-(chlorocarbonyl)cyclohexanecarboxylate (47.8 mg, 0.234 mmol) in DCM (1 mL). The ice bath was removed and the mixture was stirred at rt overnight. The mixture was diluted with DCM (20 mL), washed sequentially with 1 M aqueous HCl, 1.5 M aqueous K_2HPO_4 and brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (2 mL) and MeOH (1 mL) and treated with a solution of lithium hydroxide monohydrate (65.4 mg, 1.558 mmol) in water (1 mL). The mixture was stirred at rt for 2.5 h, then was diluted with EtOAc (25 mL) and 1 M aqueous HCl (10 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method E, gradient 30-80% B, 25 min) to give homochiral (1r,4r)-4-(10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[ ]quinoline-4-carbonyl)cyclohexane-1-carboxylic acid (14 mg, 26% yield). LCMS m/z 668.1 $(M+H)^+$, HPLC t_R 2.29 min (method C).

Examples 3 and 4

(1S,4s)-4-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2, 3,3a, 4, 5, 9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid and (1S,4s)-1-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



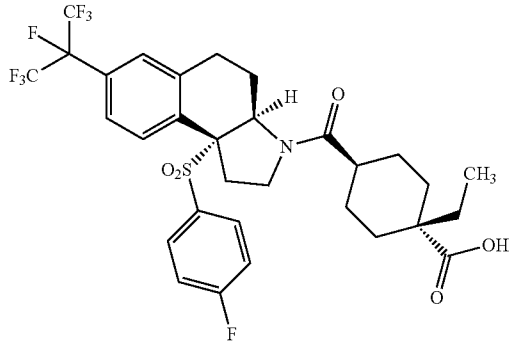
A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 100 mg, 0.187 mmol) in DMF (2 mL) was treated with a mixture of (1s,4s)-4-(tert-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid and (1s,4s)-4-(tert-butoxycarbonyl)-4-fluorocyclohexane-1-carboxylic acid (Intermediate 119; 92 mg, 0.373 mmol). PyBOP (146 mg, 0.280 mmol) and Et_3N (0.156 mL, 1.120 mmol) were added and the mixture was stirred at rt. When LCMS indicated that the reaction was complete, the mixture was concentrated and the residue was dissolved in DCM (1 mL) and treated with TFA (1 mL). After standing at rt for 1 h, the mixture was concentrated and the residue was purified by preparative HPLC (method E, gradient 20-75% B, 25 min). The major product isolated was (1S,4s)-4-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (32.7 mg, 26% yield). LCMS m/z 672.2 $(M+H)^+$, HPLC t_R 1.93 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.86 (d, J=8.3 Hz, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.42-7.18 (m, 5H), 4.98-4.85 (m, 0.25H), 4.78 (dd, J=11.9, 4.8 Hz, 0.75H), 4.03-2.59 (m, 5H), 2.44-1.16 (m, 13H), suggesting a 3:1 mixture of amide bond rotamers.

A second product isolated was (1S,4s)-1-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-

yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (6 mg, 5% yield). LCMS m/z 671.9 $(M+H)^+$, HPLC t_R 1.73 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.3 Hz, 1H), 7.44-7.34 (m, 2H), 7.33 (s, 1H), 7.25 (t, J=8.4 Hz, 2H), 4.65 (dd, J=11.6, 4.7 Hz, 1H), 3.82-2.59 (m, 7H), 2.41-1.13 (m, 11H).

Example 5

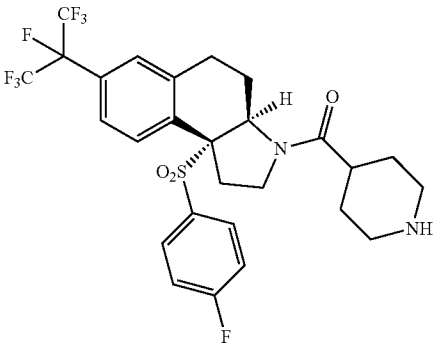
(1R,4r)-1-ethyl-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2, 3,3a, 4,5, 9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A solution of ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (Intermediate 32; 30 mg, 0.060 mmol) in DMF (0.8 mL) was treated with (1r,4r)-1-ethylcyclohexane-1,4-dicarboxylic acid (Intermediate 121; 24.06 mg, 0.120 mmol), DIPEA (31.5 μL, 0.180 mmol) and HATU (34.3 mg, 0.090 mmol). The mixture was stirred at rt for 1 h, then was purified by preparative HPLC (method E, gradient 40-80% B) to provide (1R,4r)-1-ethyl-4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (10 mg, 24% yield). LCMS m/z 682.4 $(M+H)^+$, HPLC t_R 2.28 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J=8.4 Hz, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.44-7.34 (m, 3H), 7.33-7.18 (m, 2H), 4.66 (dd, J=11.7, 4.7 Hz, 1H), 3.82-3.18 (m, 3H), 2.84-2.59 (m, 2H), 2.31 (br. s., 2H), 2.20-1.34 (m, 10H), 1.32-1.10 (m, 2H), 0.87-0.59 (m, 3H).

Example 6

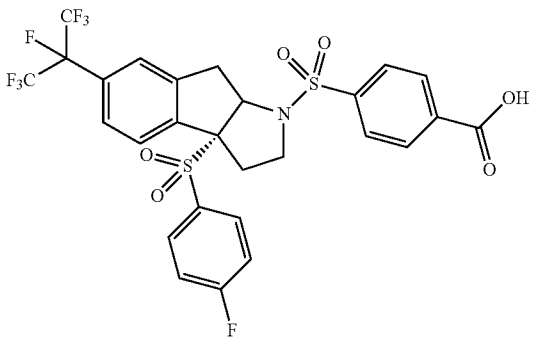
((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(piperidin-4-yl)methanone



A mixture of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (Intermediate 32; 120 mg, 0.240 mmol), 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (66.1 mg, 0.288 mmol) and N-methylmorpholine (0.079 mL, 0.721 mmol) in DMF (2 mL) was treated with HATU (110 mg, 0.288 mmol). The mixture was stirred overnight at rt, then was diluted with EtOAc and washed sequentially with 10% aqueous LiCl (twice) and brine. The combined aqueous phases were extracted with EtOAc, and the combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (12 g), eluting with EtOAc-hexanes (gradient from 0-80%), to provide crude tert-butyl 4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)piperidine-1-carboxylate. This material was dissolved in TFA (1 mL). After 1 h the mixture was concentrated, and the residue was dissolved in EtOAc and washed sequentially with 1.5 M aqueous K_2HPO_4 and brine. The combined aqueous phases were extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated to provide a tan solid (138 mg, 94% yield). A portion of this material (16 mg) was further purified by preparative HPLC (method E, gradient 30-70% B, 20 min) to provide ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(piperidin-4-yl) methanone (14.8 mg, 92% yield). LCMS m/z 611.1 $(M+H)^+$, HPLC t_R 1.82 min (method C).

Example 7

4-((3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-b]pyrrol-1(2H)-yl)sulfonyl)benzoic acid



Homochiral from peak 1

A solution of 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-b]pyrrole hydrochloride (homochiral, from peak 1, Intermediate 94; 30 mg, 0.057 mmol) and methyl 4-(chlorosulfonyl)benzoate (20.23 mg, 0.086 mmol) in DMF (0.5 mL) was treated with Et_3N (0.024 mL, 0.172 mmol) and stirred at rt. After 18 h, the mixture was diluted with EtOAc, washed sequentially with water, 5% aqueous LiCl and brine, and concentrated. The residue was dissolved in THF (2.5 mL) and ethanol (1.25 mL), treated with a solution of LiOH monohydrate (72.4 mg, 1.725 mmol) in water (1.25 mL), and stirred vigorously at rt. After 16.25 h, the mixture was treated slowly with HCl (4 M in 1,4-dioxane, 0.75 mL) and con-

centrated. The residue was purified by preparative HPLC (method E, gradient 30-70% B, 23 min), followed by re-purification by HPLC (method F, gradient 45-90% B, 20 min) to provide homochiral 4-((3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno [2,1-b]pyrrol-1(2H)-yl)sulfonyl)benzoic acid (16.6 mg, 45% yield). LCMS m/z 670.2 $(M+H)^+$, HPLC t_R 1.85 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 8.15 (d, J=8.1 Hz, 2H), 7.97 (d, J=8.2 Hz, 2H), 7.65 (q, J=8.2 Hz, 2H), 7.60 (s, 1H), 7.57 (dd, J=8.3, 5.0 Hz, 2H), 7.26 (t, J=8.5 Hz, 2H), 4.51 (d, J=6.1 Hz, 1H), 3.27 (d, J=18.2 Hz, 1H), 3.09-2.87 (m, 2H), 2.44 (d, J=12.8 Hz, 1H), 2.24-2.13 (m, 1H), one proton obscured by solvent peaks.

The Examples in Table 9 were prepared using procedures used to prepare Examples 1 through 7 or similar procedures, by reacting an appropriate amine intermediate with an appropriate acid, acid chloride, acid anhydride, sulfonyl chloride or sulfamyl chloride, followed by ester hydrolysis or other functional group deprotection as necessary.

TABLE 9

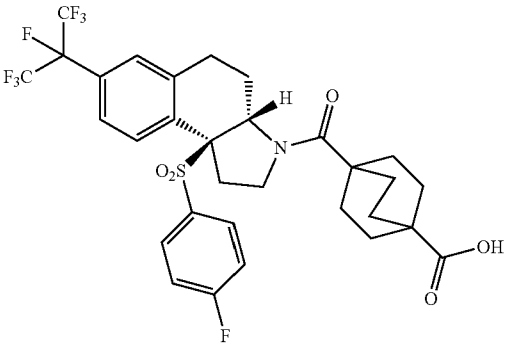
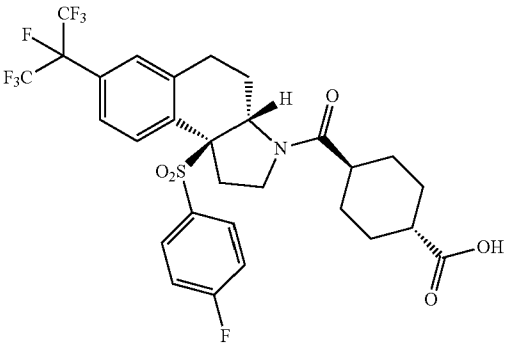
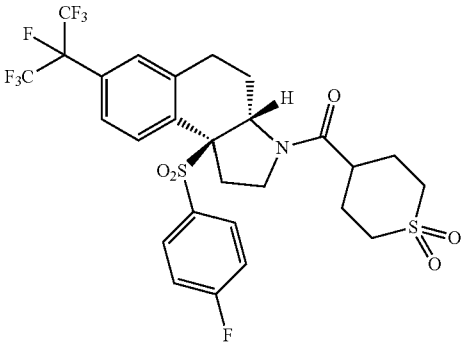
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
8		680.1 $(M + H)^+$	1.08	B
9		654.2 $(M + H)^+$	1.06	B
10		660.0 $(M + H)^+$	1.04	B

TABLE 9-continued

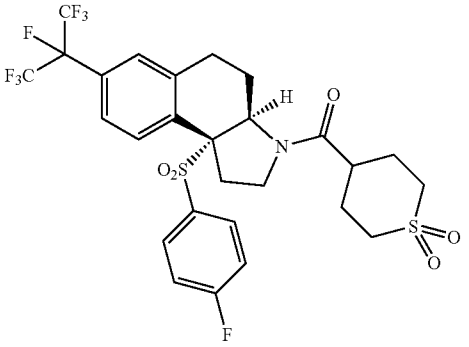
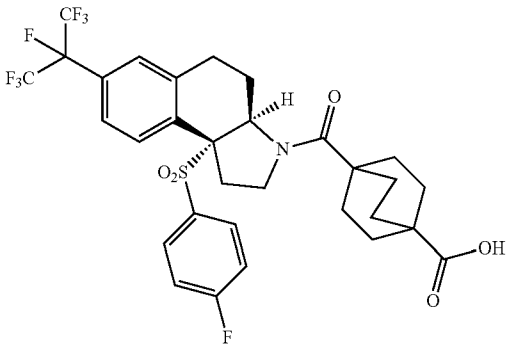
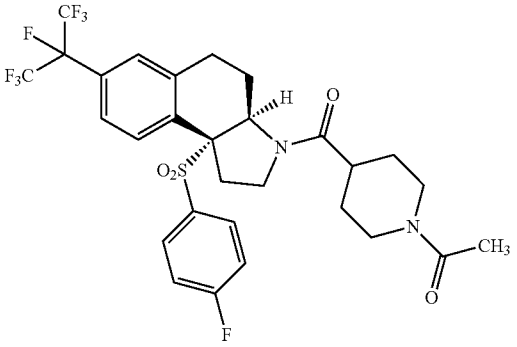
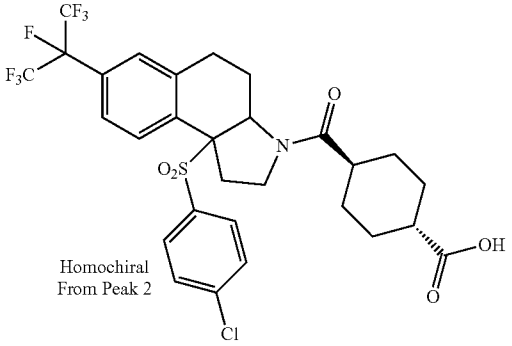
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
11		660.0 $(M + H)^+$	1.04	B
12		680.1 $(M + H)^+$	1.08	B
13		653.1 $(M + H)^+$	1.05	B
14	 Homochiral From Peak 2	670.0 $(M + H)^+$	1.08	B

TABLE 9-continued

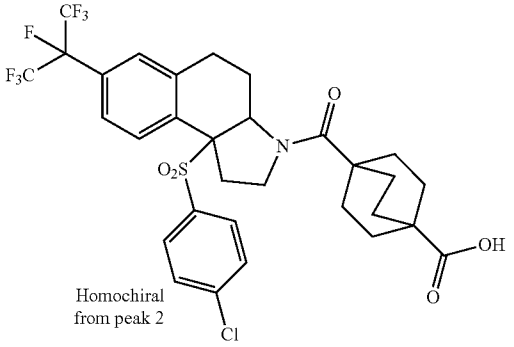
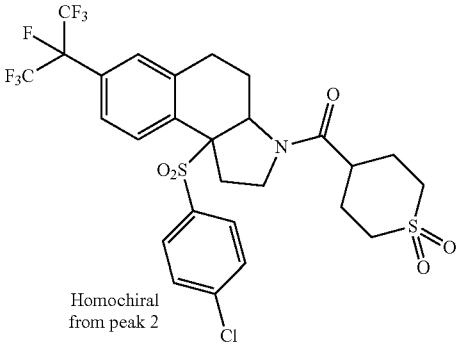
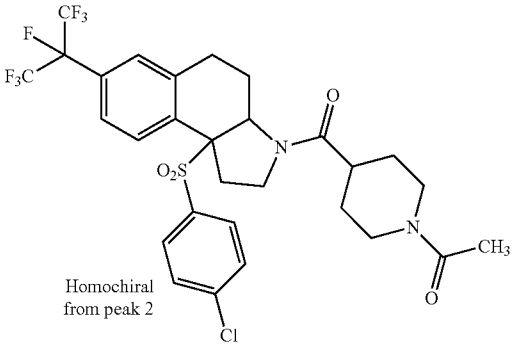
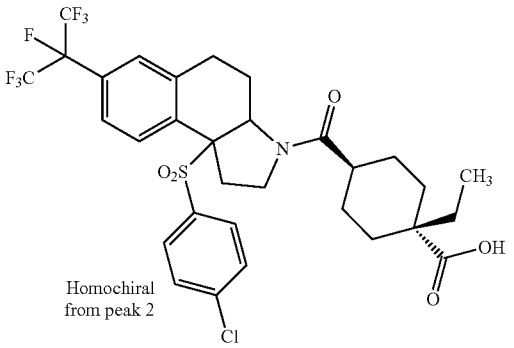
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
15		696.0 $(M + H)^+$	1.12	B
16		676.0 $(M + H)^+$	1.07	B
17		669.1 $(M + H)^+$	1.06	B
18		698.1 $(M + H)^+$	1.12	B

TABLE 9-continued

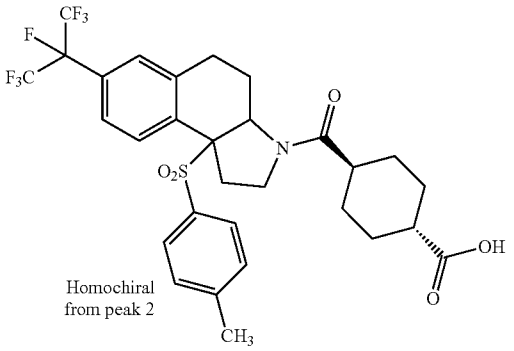
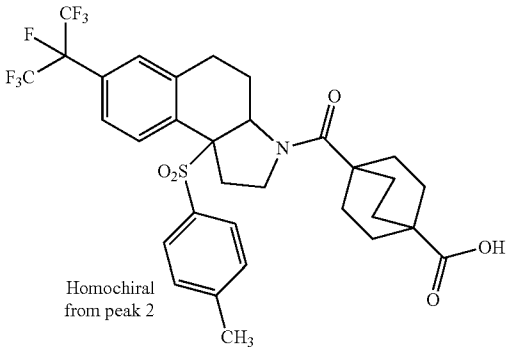
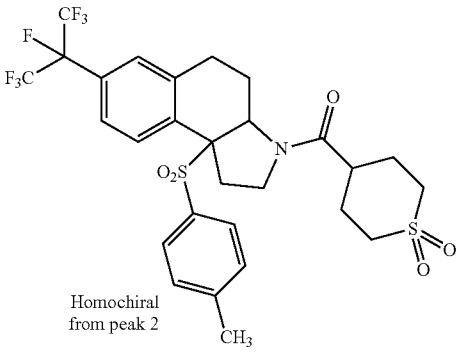
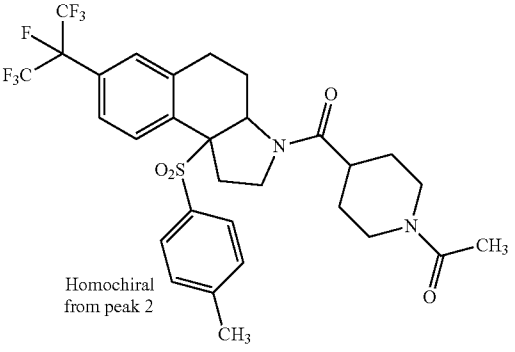
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
19		650.1 (M + H)+	1.07	B
20		676.1 (M + H)+	1.10	B
21		656.1 (M + H)+	1.05	B
22		649.2 (M + H)+	1.04	B

TABLE 9-continued

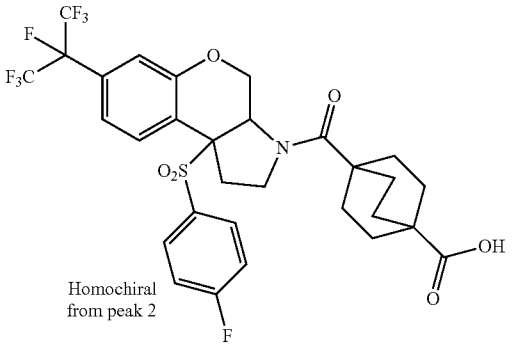
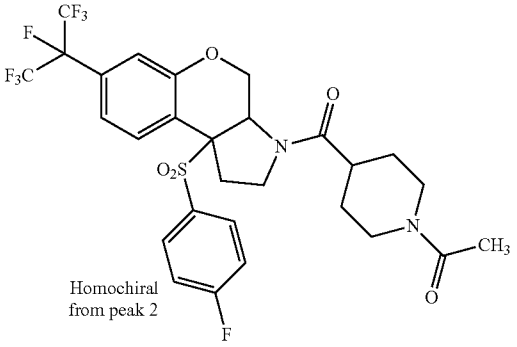
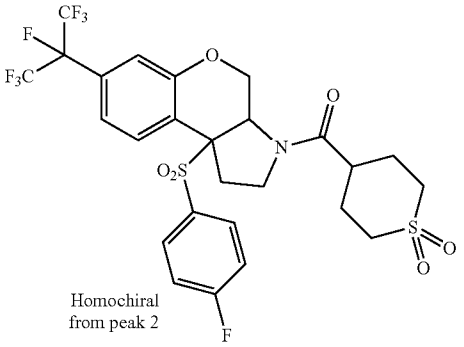
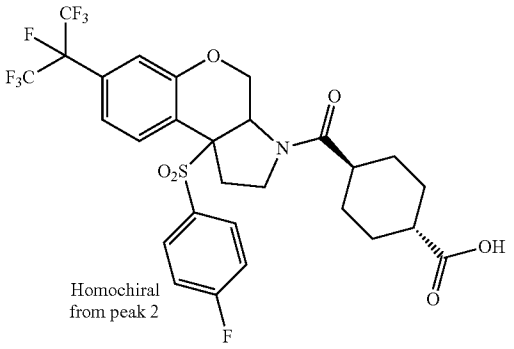
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
23		682.2 $(M + H)^+$	1.08	B
24		655.3 $(M + H)^+$	1.02	B
25		662.3 $(M + H)^+$	1.02	B
26		656.3 $(M + H)^+$	1.04	B

TABLE 9-continued

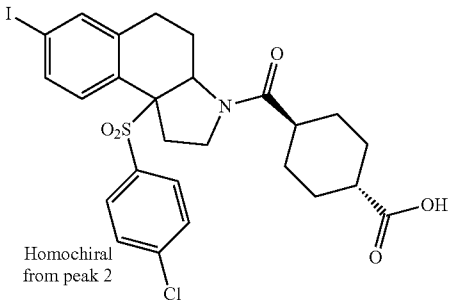
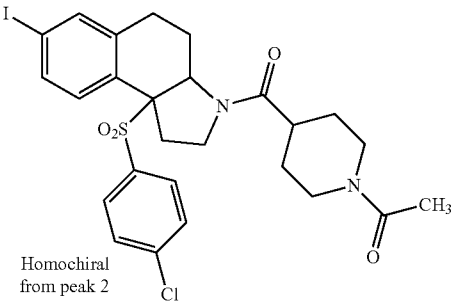
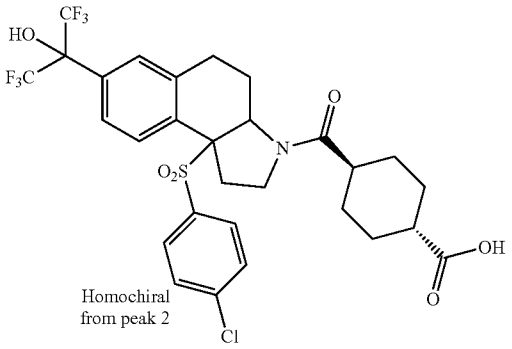
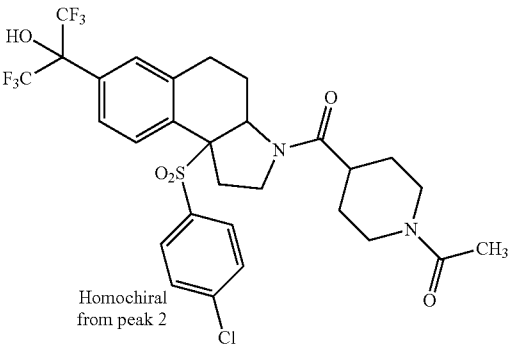
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
27		628.0 $(M + H)^+$	1.49	C
28		627.0 $(M + H)^+$	0.98	B
29		668.3 $(M + H)^+$	0.98	B
30		667.3 $(M + H)^+$	0.91	B

TABLE 9-continued

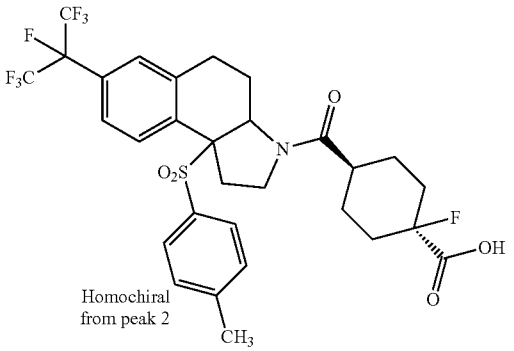
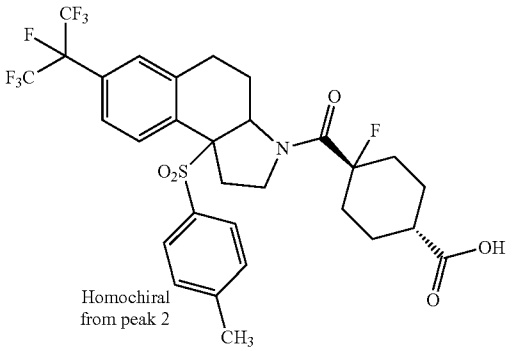
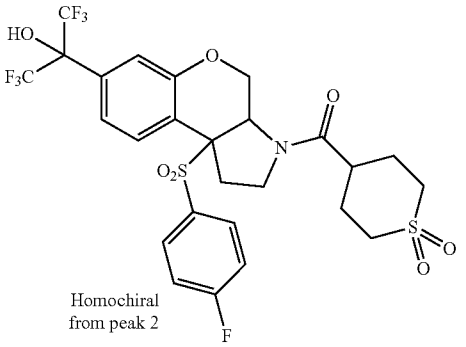
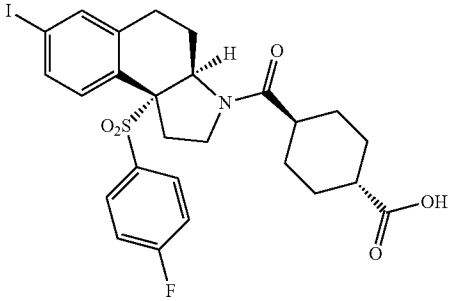
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
31		668.2 $(M + H)^+$	1.05	B
32		668.2 $(M + H)^+$	1.05	B
33		660.0 $(M + H)^+$	0.93	B
34		612.0 $(M + H)^+$	1.00	B

TABLE 9-continued

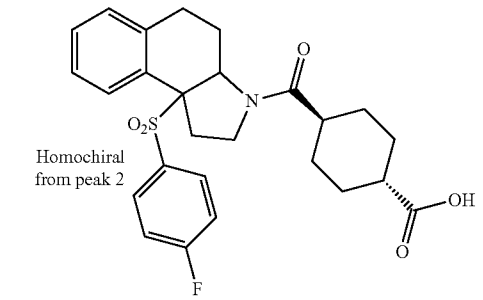
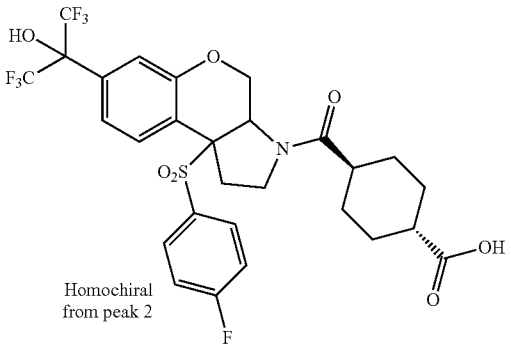
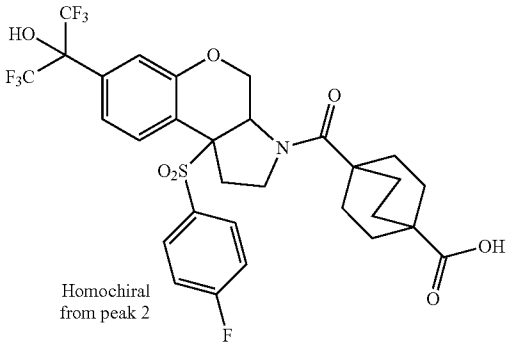
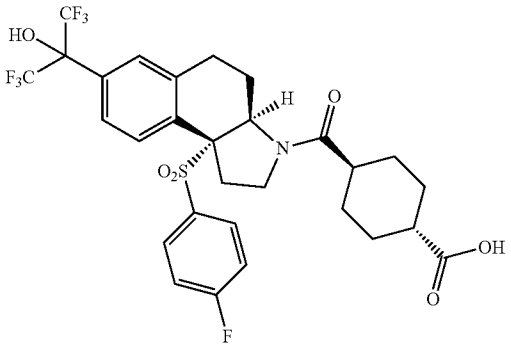
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
35		486.1 $(M + H)^+$	0.89	B
36		654.1 $(M + H)^+$	0.98	B
37		680.1 $(M + H)^+$	1.02	B
38		652.1 $(M + H)^+$	1.06	B

TABLE 9-continued

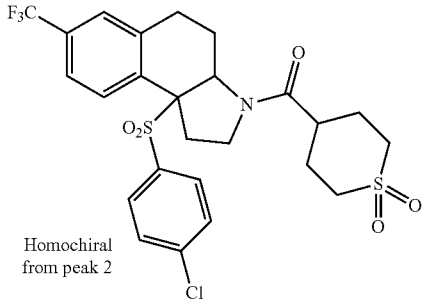
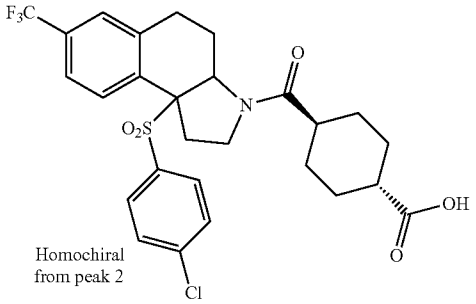
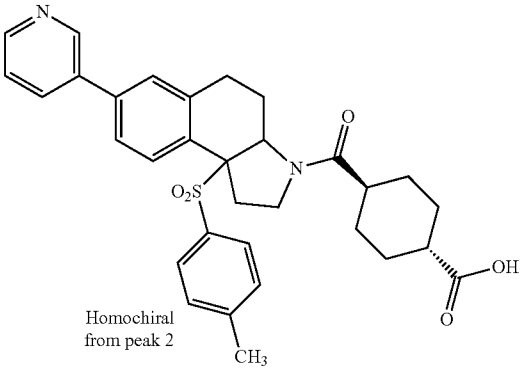
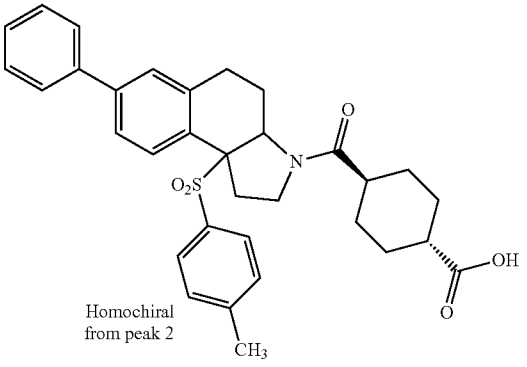
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
39	 Homochiral from peak 2	576.3 $(M + H)^+$	0.96	B
40	 Homochiral from peak 2	570.0 $(M + H)^+$	1.03	B
41	 Homochiral from peak 2	559.3 $(M + H)^+$	0.64	B
42	 Homochiral from peak 2	558.4 $(M + H)^+$	1.01	B

TABLE 9-continued

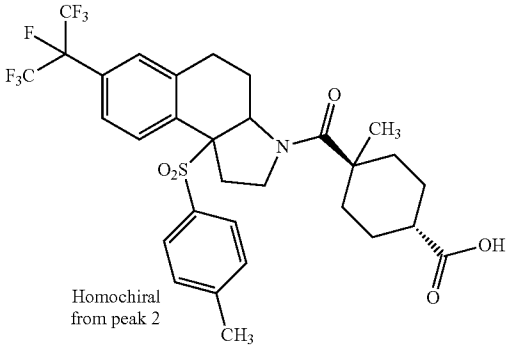
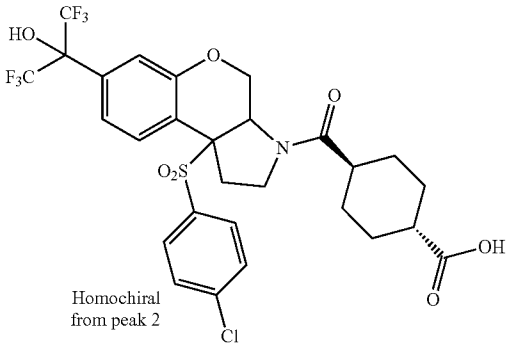
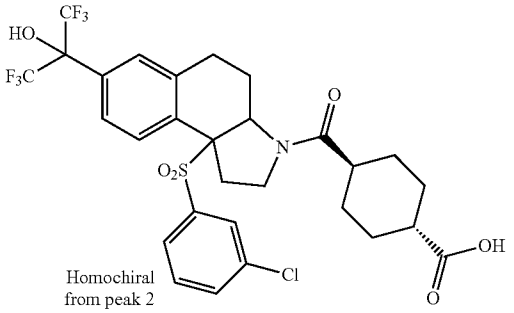
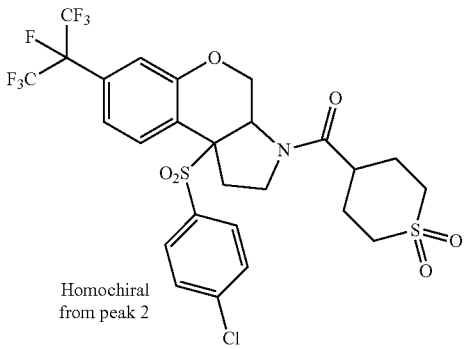
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
43	 Homochiral from peak 2	664.3 $(M + H)^+$	1.09	B
44	 Homochiral from peak 2	670.1 $(M + H)^+$	0.97	B
45	 Homochiral from peak 2	668.1 $(M + H)^+$	0.96	B
46	 Homochiral from peak 2	678.0 $(M + H)^+$	1.10	B

TABLE 9-continued

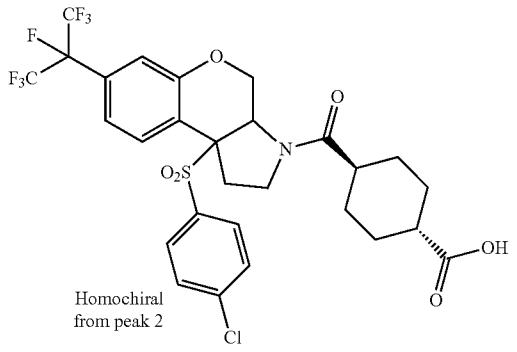
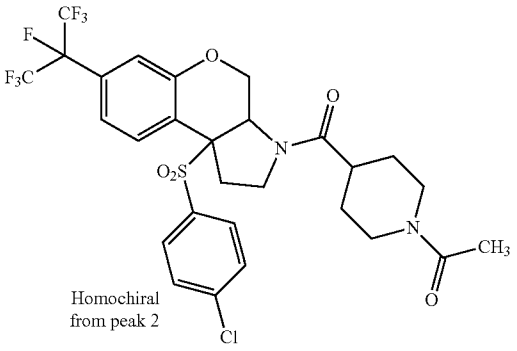
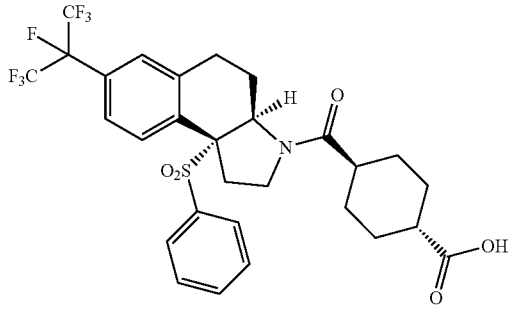
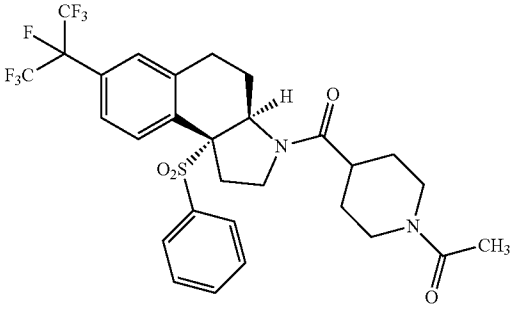
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
47	 Homochiral from peak 2	672.1 $(M + H)^+$	1.12	B
48	 Homochiral from peak 2	671.2 $(M + H)^+$	1.10	B
49		636.3 $(M + H)^+$	1.03	B
50		635.3 $(M + H)^+$	1.00	B

TABLE 9-continued

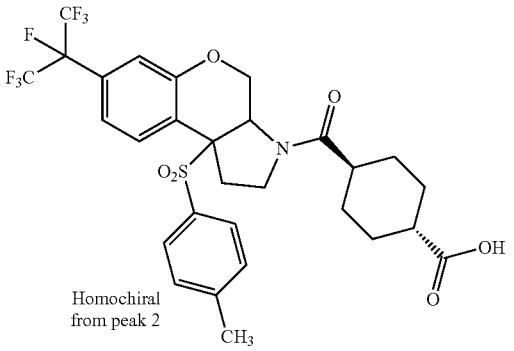
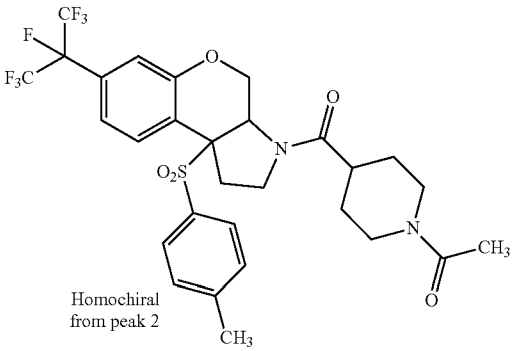
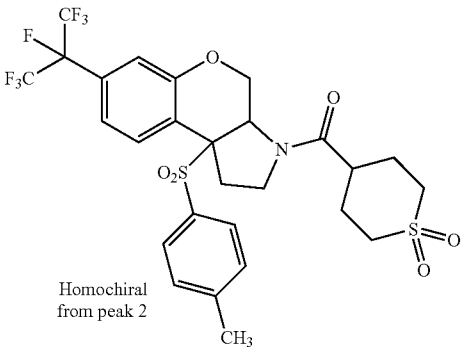
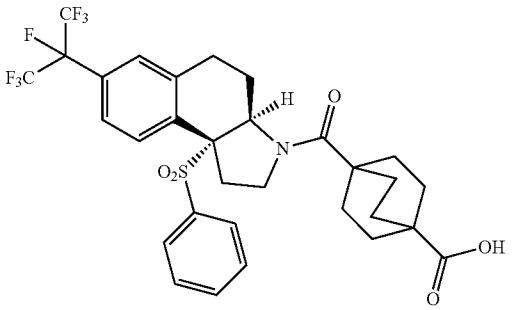
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
51	 Homochiral from peak 2	652.3 $(M + H)^+$	1.05	B
52	 Homochiral from peak 2	651.3 $(M + H)^+$	1.03	B
53	 Homochiral from peak 2	658.3 $(M + H)^+$	1.04	B
54		662.3 $(M + H)^+$	1.06	B

TABLE 9-continued

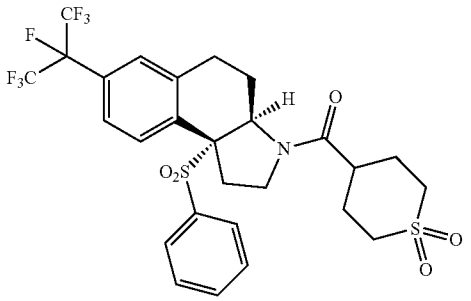
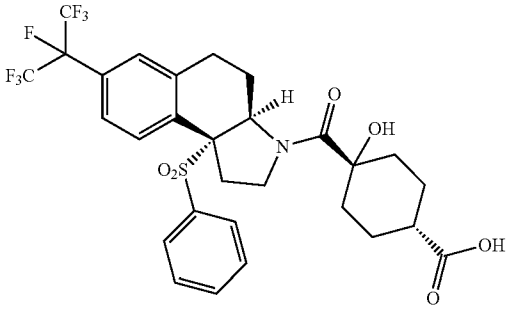
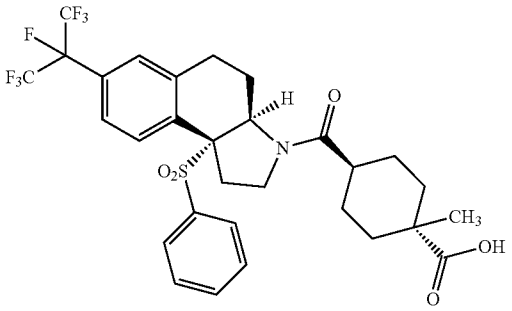
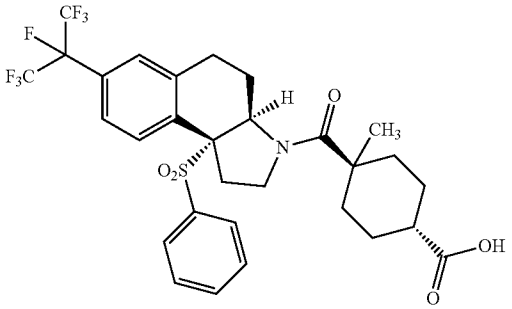
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
55		642.3 $(M + H)^+$	1.01	B
56		652.3 $(M + H)^+$	1.00	B
57		650.3 $(M + H)^+$	1.09	B
58		650.4 $(M + H)^+$	1.06	B

TABLE 9-continued

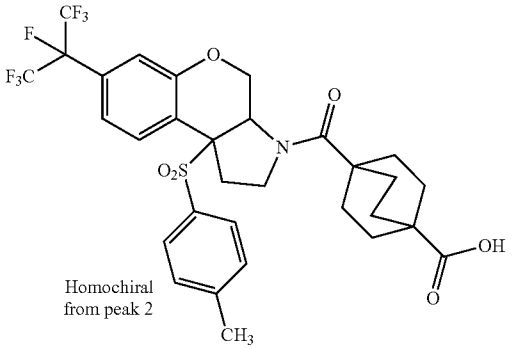
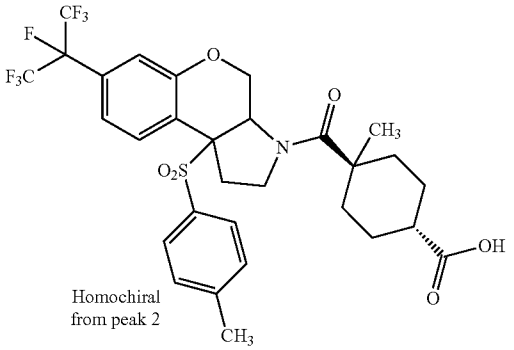
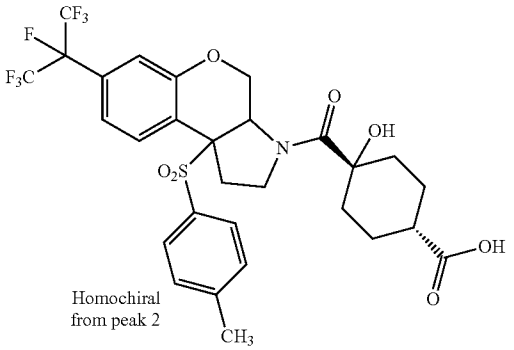
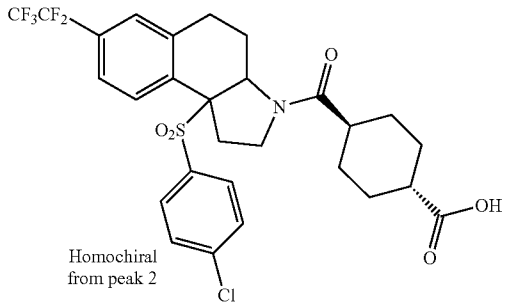
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
59	 Homochiral from peak 2	678.3 $(M + H)^+$	1.07	B
60	 Homochiral from peak 2	666.1 $(M + H)^+$	1.13	B
61	 Homochiral from peak 2	668.3 $(M + H)^+$	1.02	B
62	 Homochiral from peak 2	620.1 $(M + H)^+$	1.07	B

TABLE 9-continued

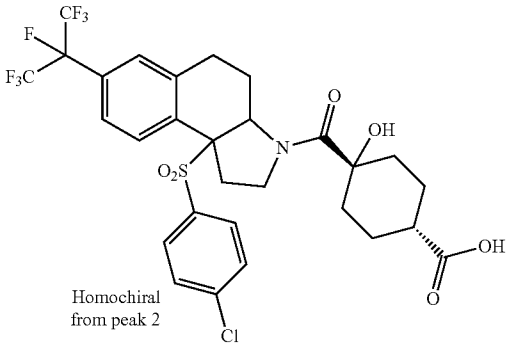
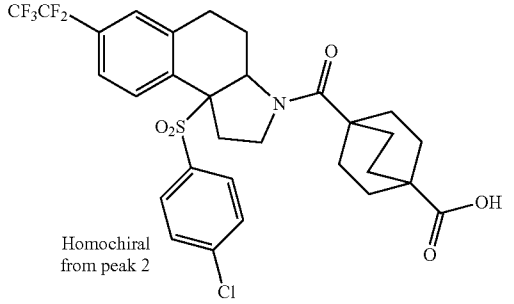
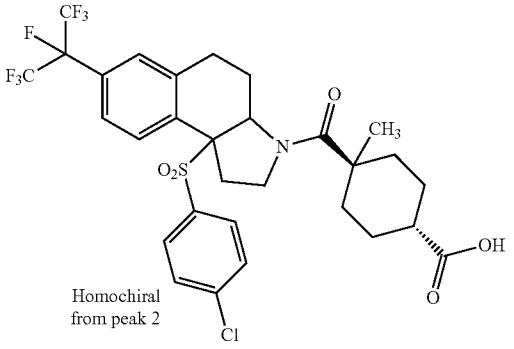
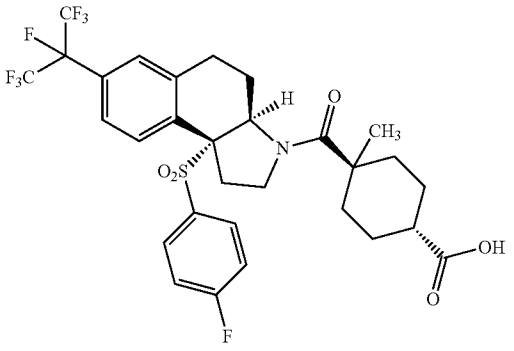
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
63		686.2 $(M + H)^+$	1.05	B
64		647.2 $(M + H)^+$	1.11	B
65		684.2 $(M + H)^+$	1.15	B
66		668.2 $(M + H)^+$	1.10	B

TABLE 9-continued

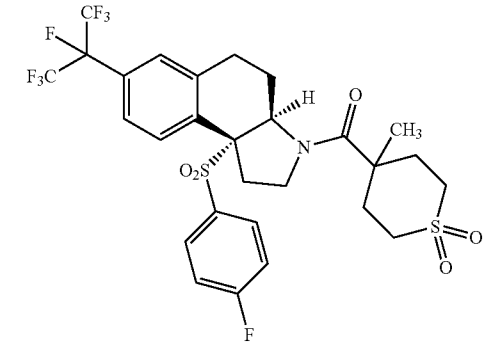
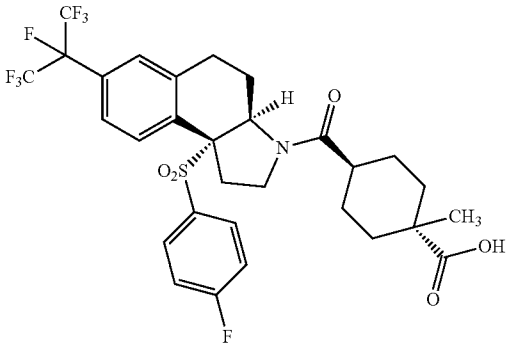
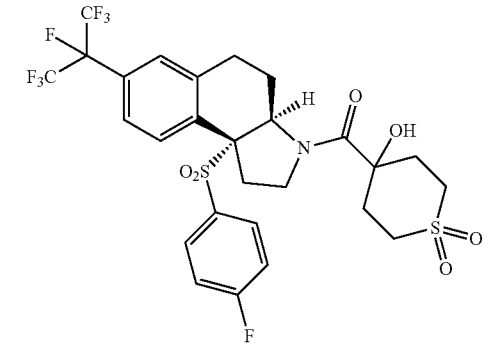
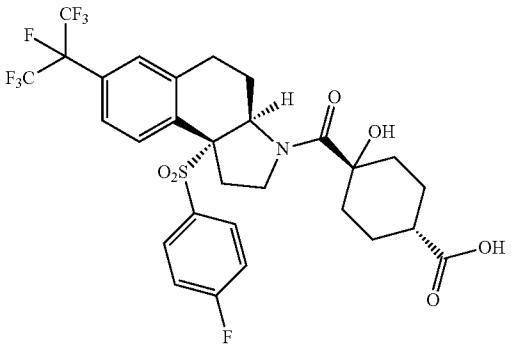
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
67		674.2 $(M + H)^+$	1.10	B
68		668.2 $(M + H)^+$	1.10	B
69		676.1 $(M + H)^+$	1.05	B
70		670.1 $(M + H)^+$	1.06	B

TABLE 9-continued

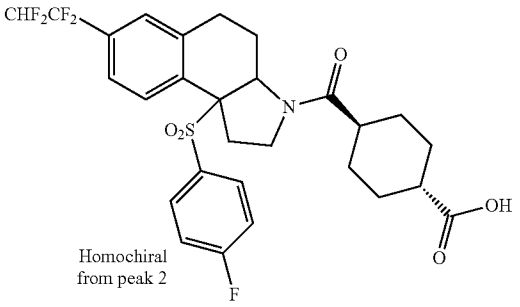
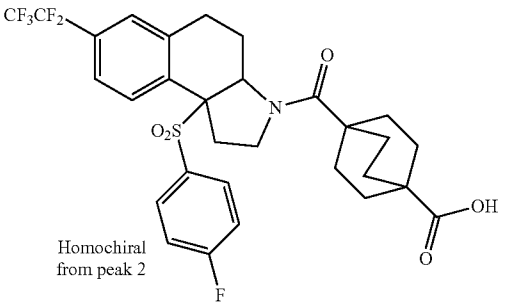
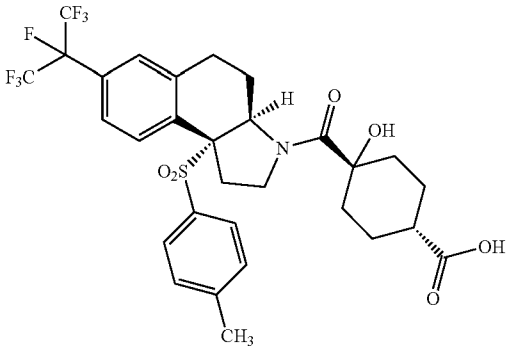
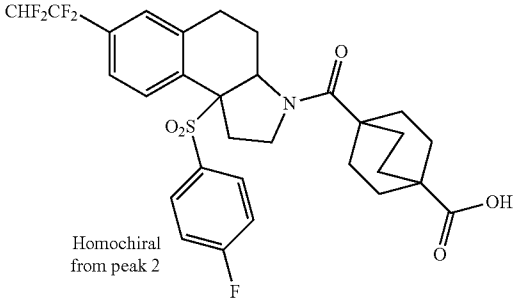
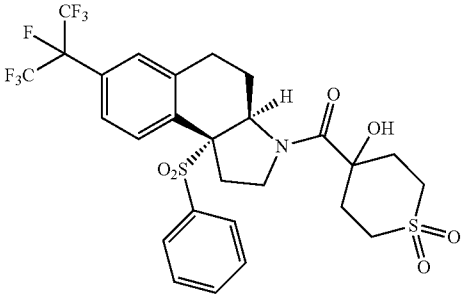
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
71	 Homochiral from peak 2	586.1 $(M + H)^+$	0.95	B
72	 Homochiral from peak 2	630.2 $(M + H)^+$	1.07	B
73		666.2 $(M + H)^+$	1.08	B
74	 Homochiral from peak 2	612.3 $(M + H)^+$	0.96	B
75		658.1 $(M + H)^+$	1.03	B

TABLE 9-continued

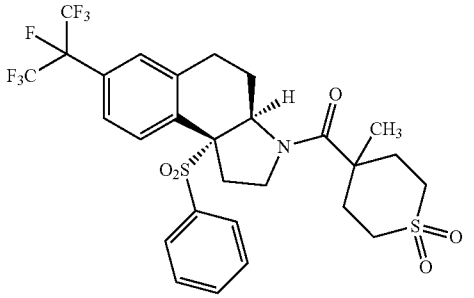
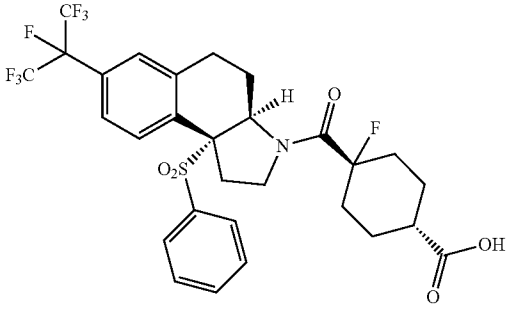
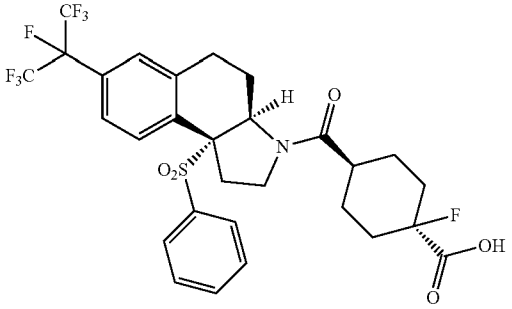
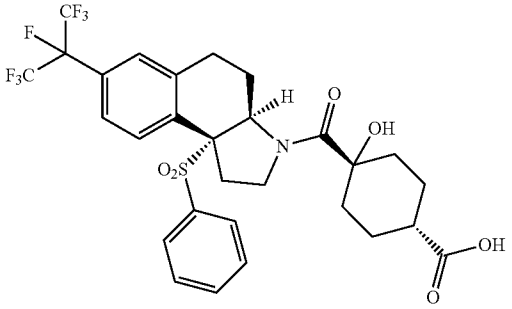
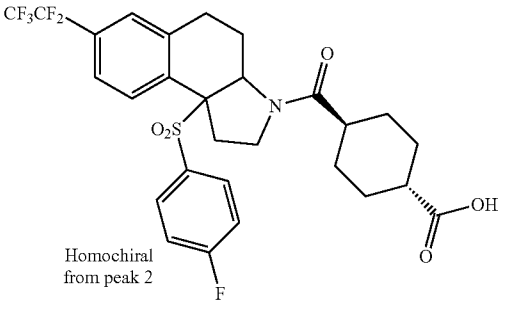
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
76		656.2 $(M + H)^+$	1.09	B
77		654.2 $(M + H)^+$	1.10	B
78		654.2 $(M + H)^+$	1.10	B
79		652.2 $(M + H)^+$	1.04	B
80	 Homochiral from peak 2	604.2 $(M + H)^+$	1.03	B

TABLE 9-continued

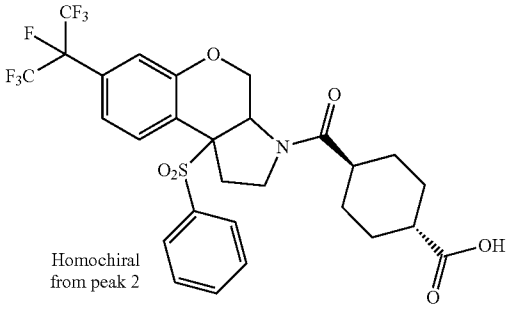
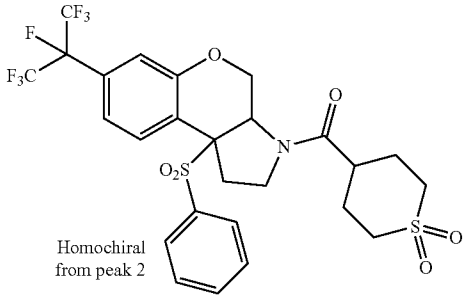
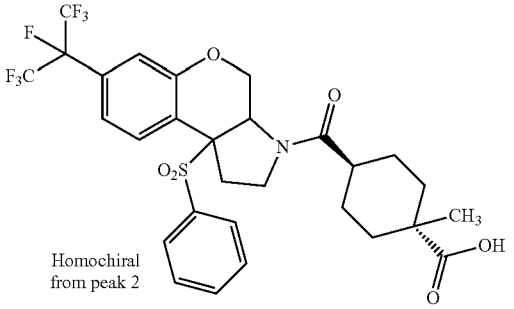
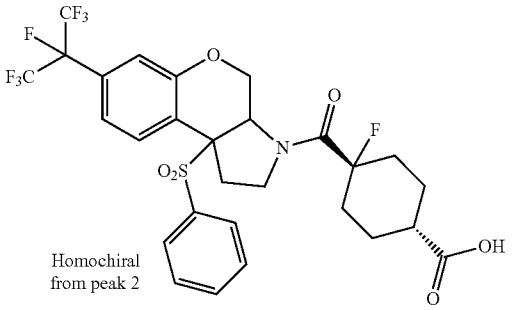
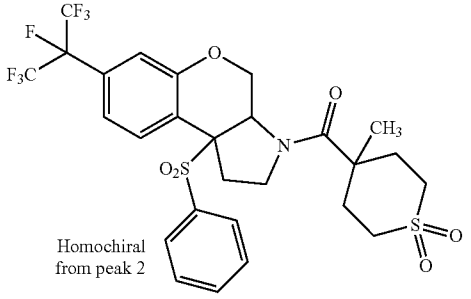
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
81	 Homochiral from peak 2	638.2 $(M + H)^+$	1.06	B
82	 Homochiral from peak 2	644.2 $(M + H)^+$	1.04	B
83	 Homochiral from peak 2	652.2 $(M + H)^+$	1.09	B
84	 Homochiral from peak 2	656.2 $(M + H)^+$	1.06	B
85	 Homochiral from peak 2	658.1 $(M + H)^+$	1.08	B

TABLE 9-continued

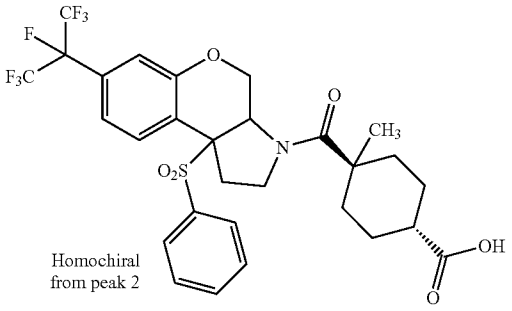
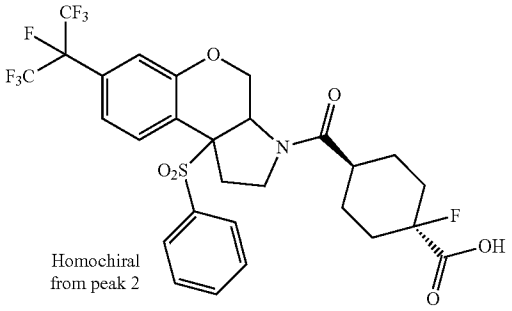
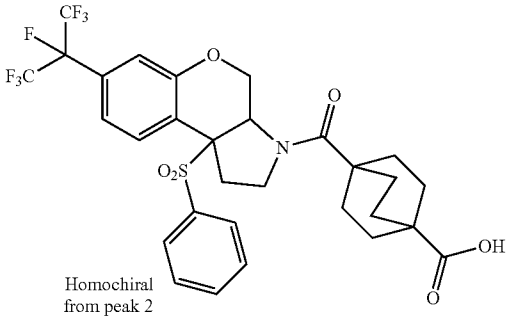
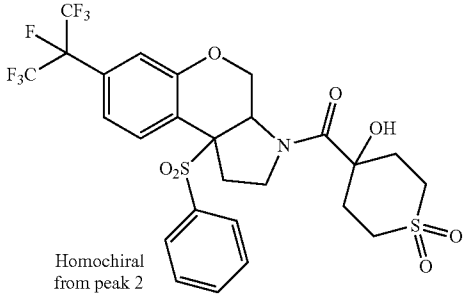
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
86	 Homochiral from peak 2	652.2 $(M + H)^+$	1.94	C
87	 Homochiral from peak 2	656.2 $(M + H)^+$	1.06	B
88	 Homochiral from peak 2	664.2 $(M + H)^+$	1.10	B
89	 Homochiral from peak 2	660.1 $(M + H)^+$	1.03	B

TABLE 9-continued

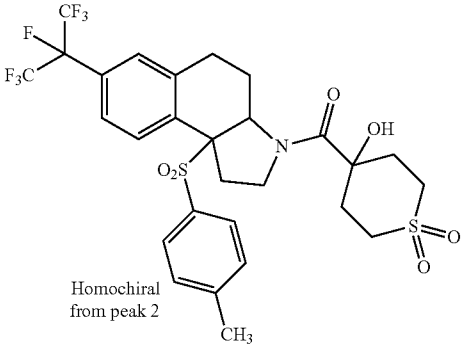
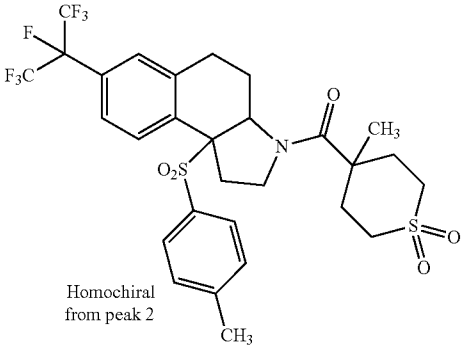
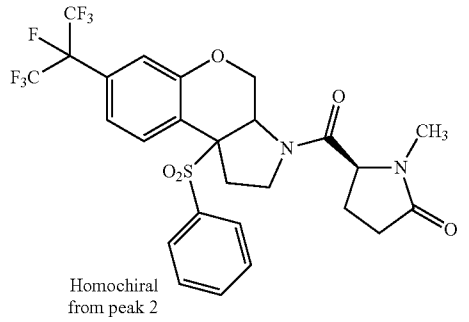
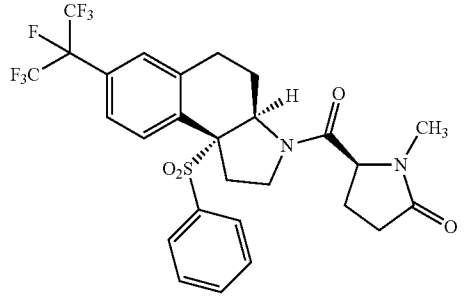
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
90		672.2 $(M + H)^+$	1.07	B
91		670.2 $(M + H)^+$	1.12	B
92		609.1 $(M + H)^+$	1.03	B
93		607.1 $(M + H)^+$	1.01	B

TABLE 9-continued

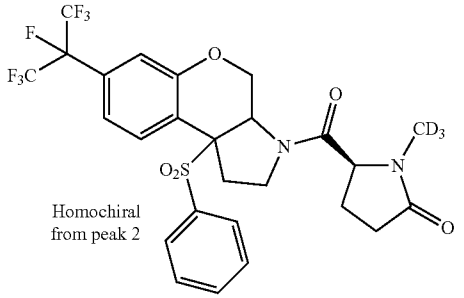
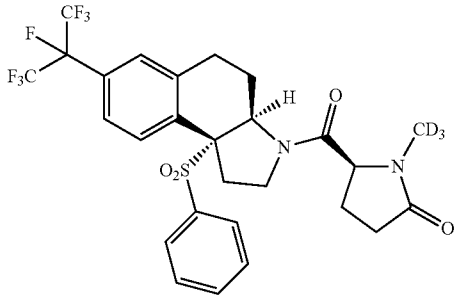
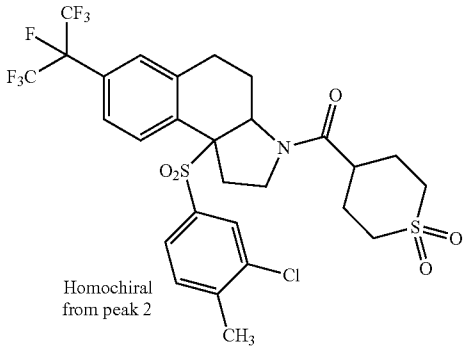
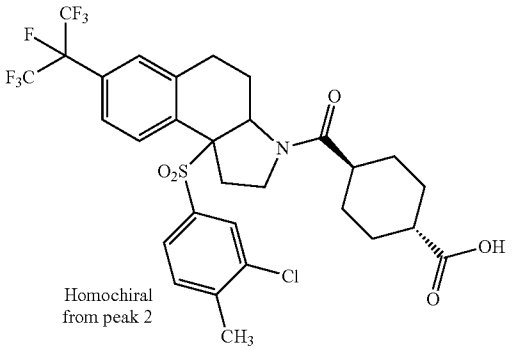
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
94	 Homochiral from peak 2	612.1 $(M + H)^+$	1.01	B
95		610.2 $(M + H)^+$	1.01	B
96	 Homochiral from peak 2	690.1 $(M + H)^+$	1.12	B
97	 Homochiral from peak 2	684.1 $(M + H)^+$	1.13	B

TABLE 9-continued

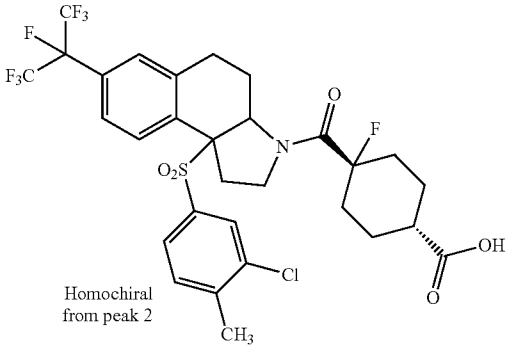
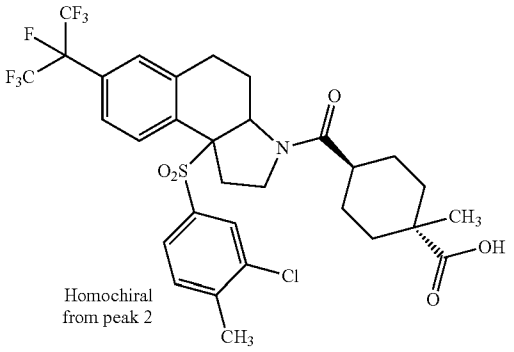
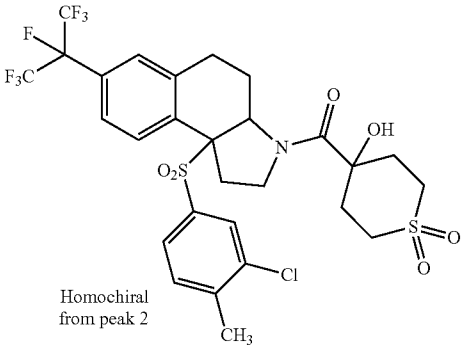
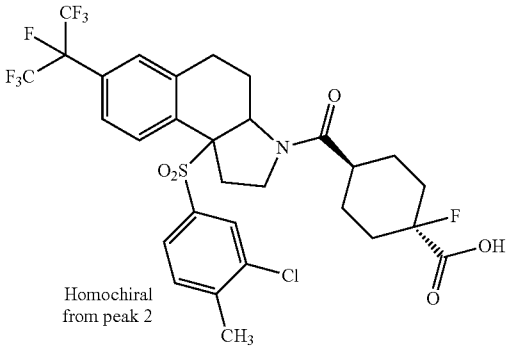
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
98	 Homochiral from peak 2	702.2 $(M + H)^+$	1.17	B
99	 Homochiral from peak 2	698.2 $(M + H)^+$	1.15	B
100	 Homochiral from peak 2	706.1 $(M + H)^+$	1.13	B
101	 Homochiral from peak 2	702.2 $(M + H)^+$	1.17	B

TABLE 9-continued

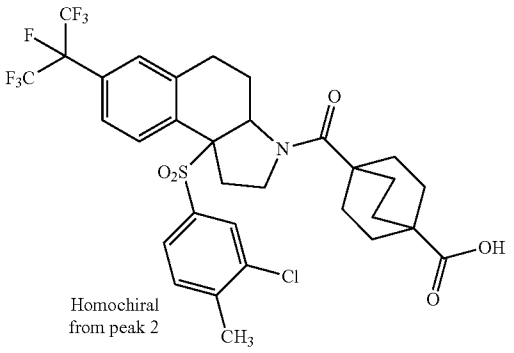
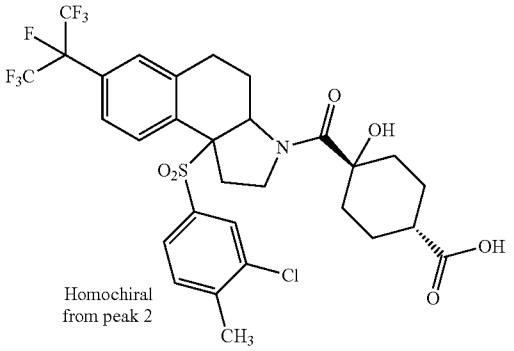
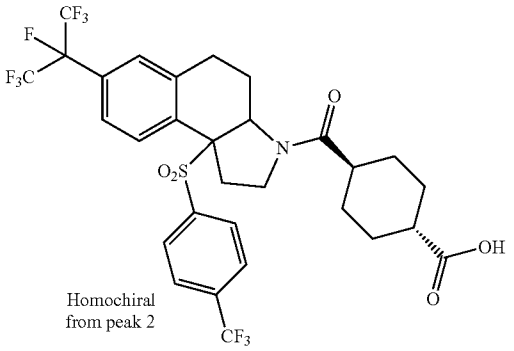
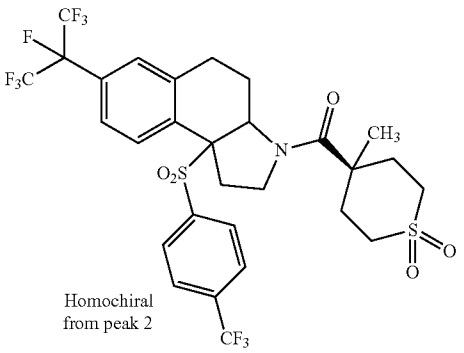
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
102	 Homochiral from peak 2	702.2 $(M + H)^+$	1.17	B
103	 Homochiral from peak 2	700.1 $(M + H)^+$	1.12	B
104	 Homochiral from peak 2	704.2 $(M + H)^+$	1.12	B
105	 Homochiral from peak 2	724.1 $(M + H)^+$	1.14	B

TABLE 9-continued

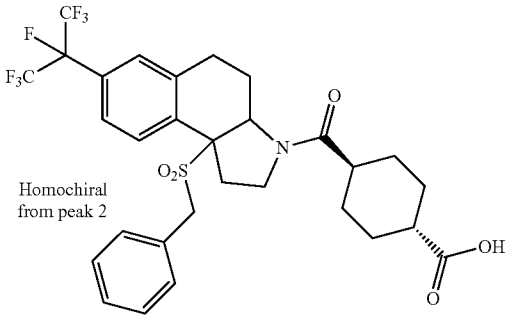
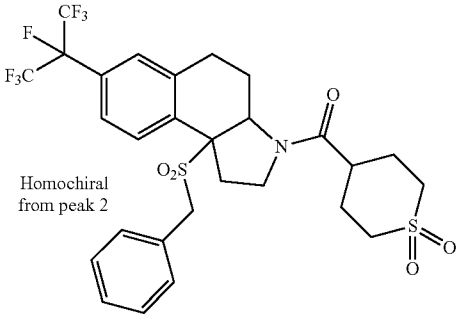
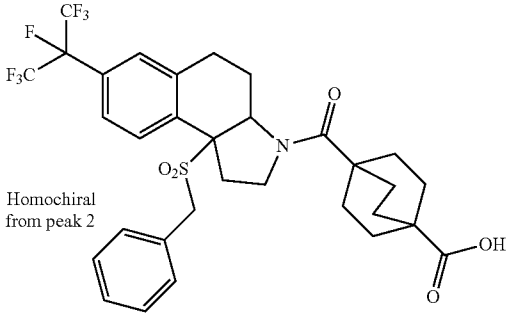
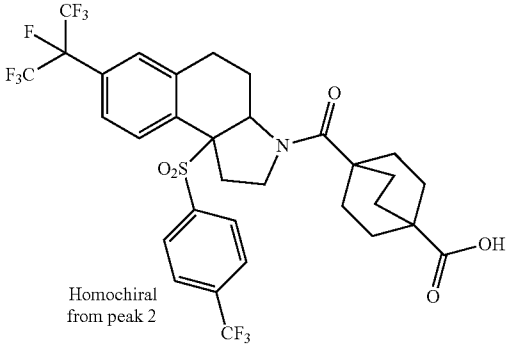
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
106		650.2 $(M + H)^+$	1.06	B
107		656.2 $(M + H)^+$	1.04	B
108		676.2 $(M + H)^+$	1.10	B
109		730.4 $(M + H)^+$	1.11	B

TABLE 9-continued

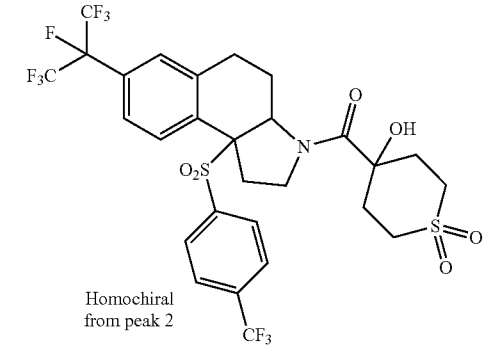
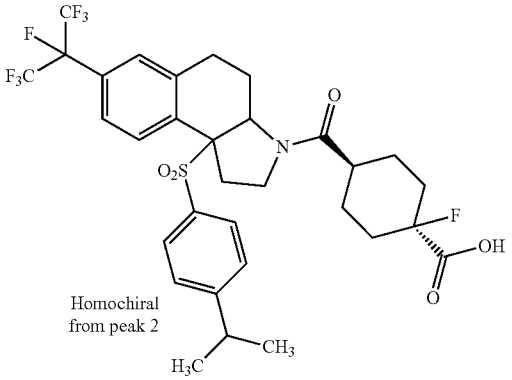
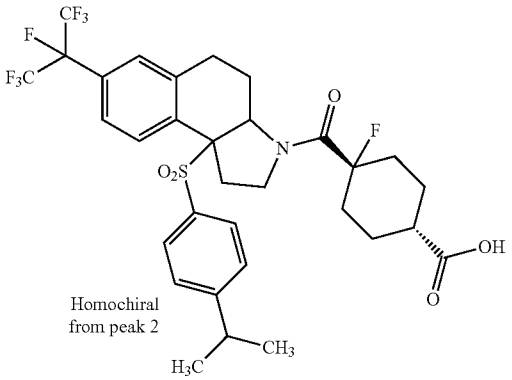
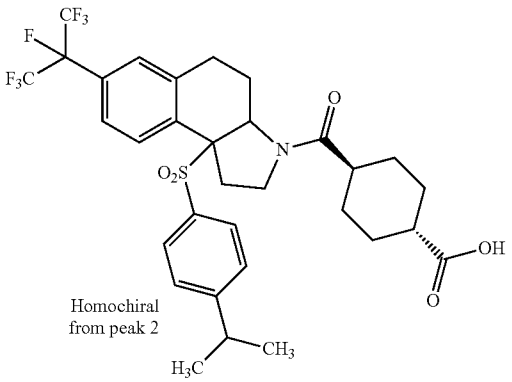
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
110		726.5 $(M + H)^+$	1.15	B
111		696.4 $(M + H)^+$	1.15	B
112		696.4 $(M + H)^+$	1.15	B
113		678.5 $(M + H)^+$	1.12	B

TABLE 9-continued

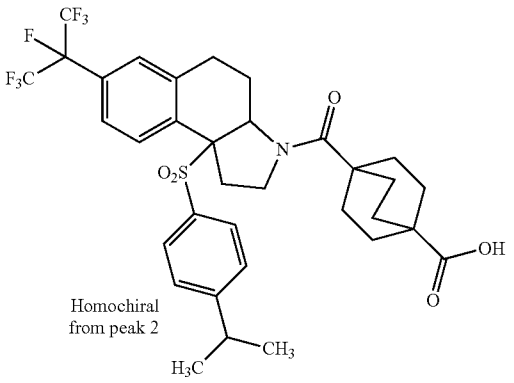
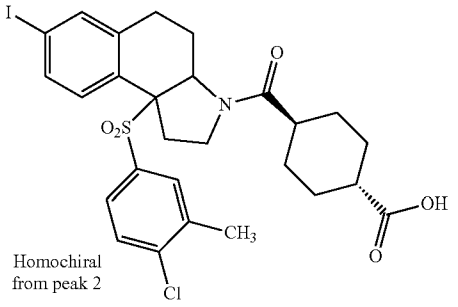
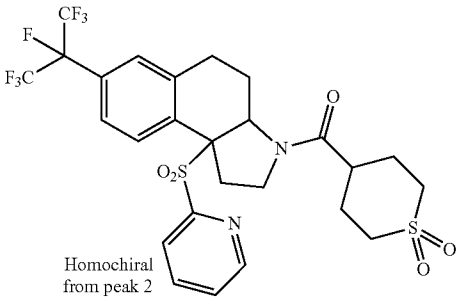
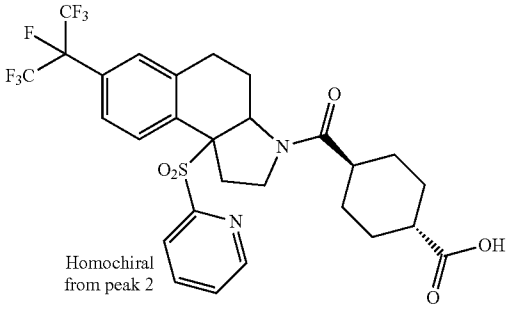
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
114		704.5 $(M + H)^+$	1.15	B
115		642.1 $(M + H)^+$	1.07	B
116		643.3 $(M + H)^+$	0.95	B
117		637.6 $(M + H)^+$	0.97	B

TABLE 9-continued

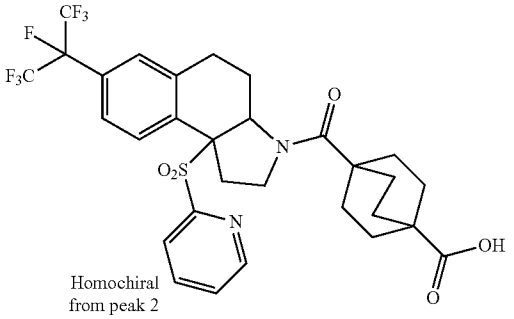
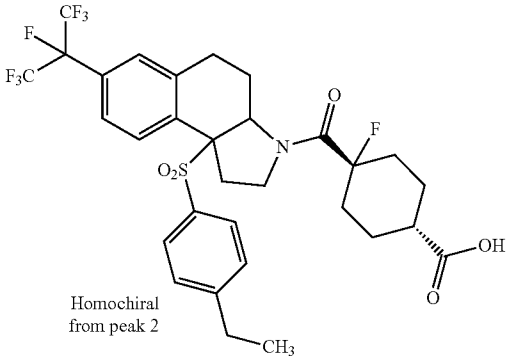
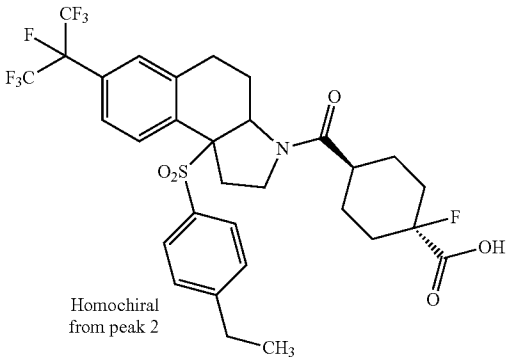
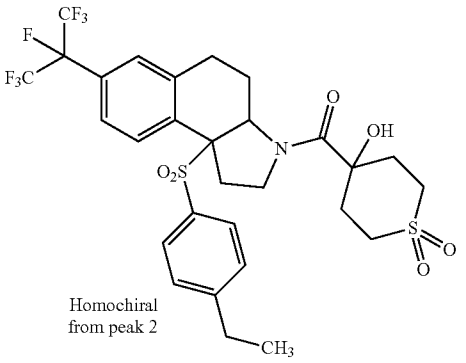
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
118	 Homochiral from peak 2	663.4 $(M + H)^+$	1.00	B
119	 Homochiral from peak 2	682.5 $(M + H)^+$	1.13	B
120	 Homochiral from peak 2	682.5 $(M + H)^+$	1.13	B
121	 Homochiral from peak 2	686.4 $(M + H)^+$	1.07	B

TABLE 9-continued

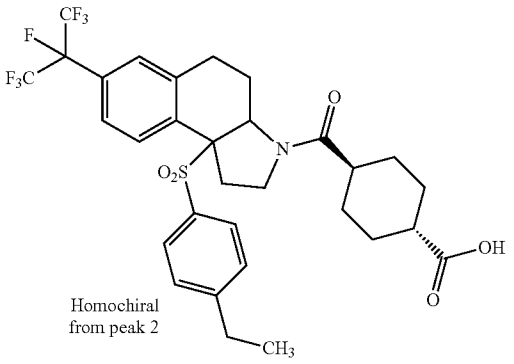
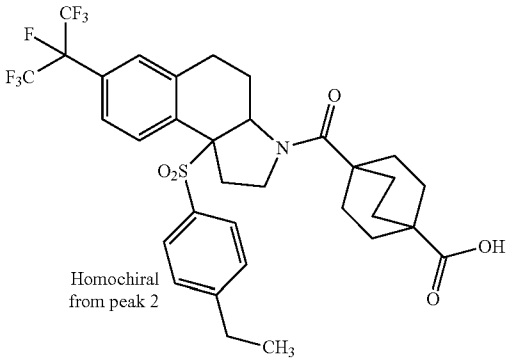
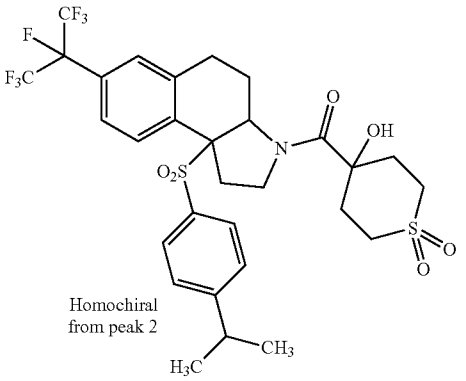
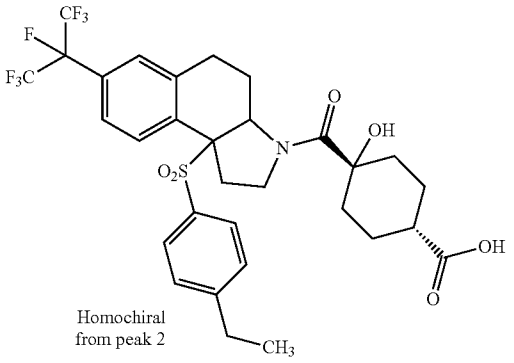
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
122		664.5 $(M + H)^+$	1.09	B
123		690.5 $(M + H)^+$	1.12	B
124		700.4 $(M + H)^+$	1.10	B
125		680.4 $(M + H)^+$	1.07	B

TABLE 9-continued

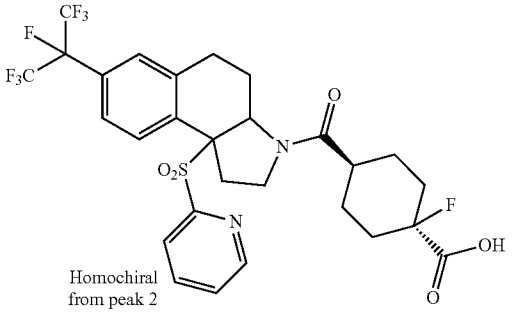
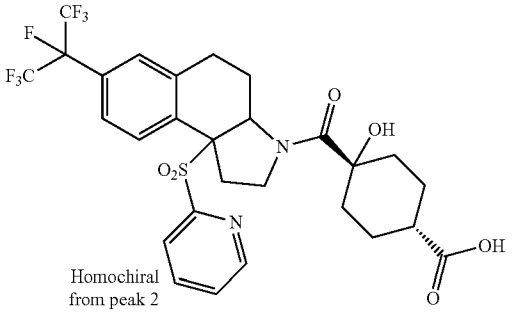
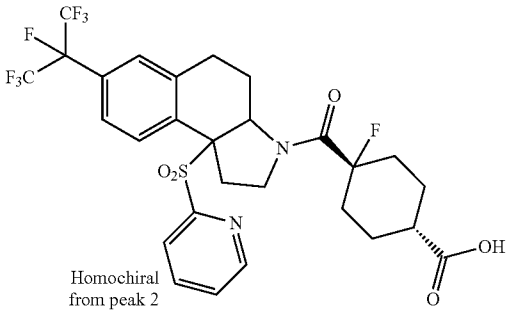
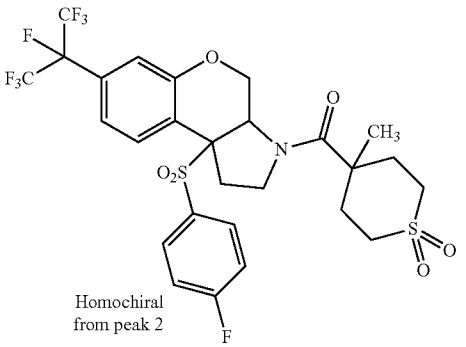
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
126	 Homochiral from peak 2	655.3 $(M + H)^+$	1.06	B
127	 Homochiral from peak 2	653.2 $(M + H)^+$	0.98	B
128	 Homochiral from peak 2	655.3 $(M + H)^+$	1.06	B
129	 Homochiral from peak 2	676.2 $(M + H)^+$	1.10	B

TABLE 9-continued

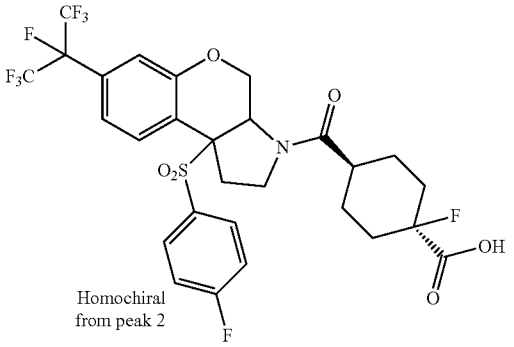
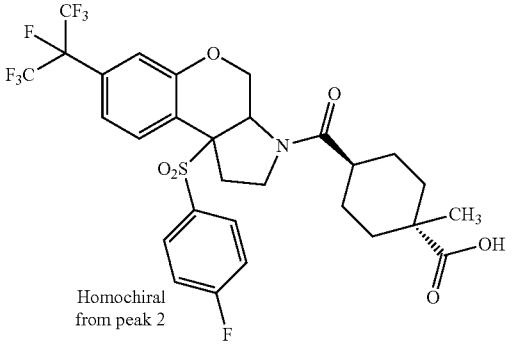
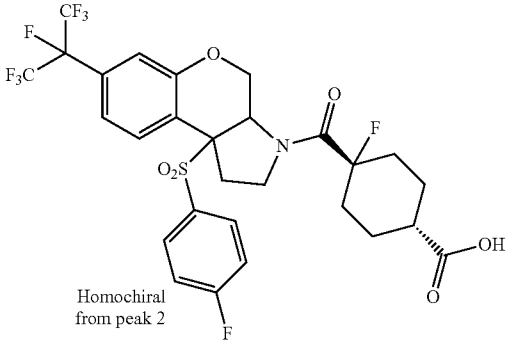
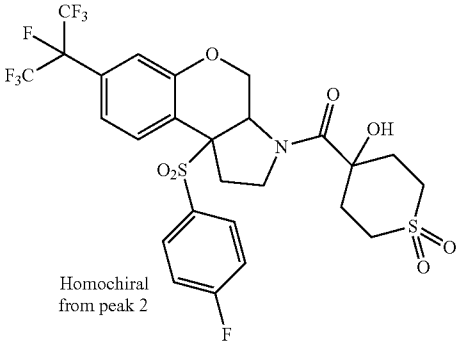
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
130		674.2 $(M + H)^+$	1.11	B
131		670.2 $(M + H)^+$	1.10	B
132		674.2 $(M + H)^+$	1.11	B
133		678.2 $(M + H)^+$	1.05	B

TABLE 9-continued

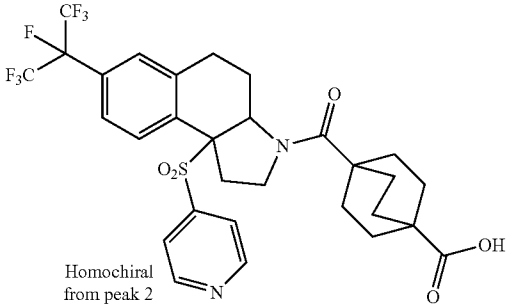
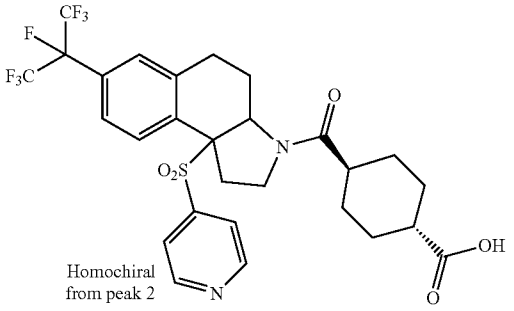
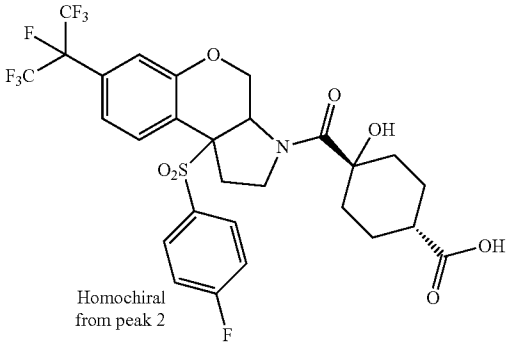
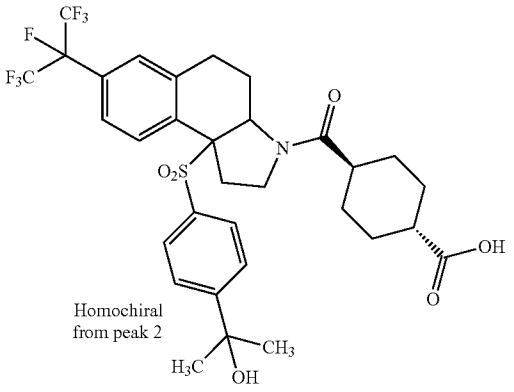
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
134		663.5 $(M + H)^+$	0.99	B
135		637.5 $(M + H)^+$	0.95	B
136		672.2 $(M + H)^+$	1.07	B
137		694.5 $(M + H)^+$	0.98	B

TABLE 9-continued

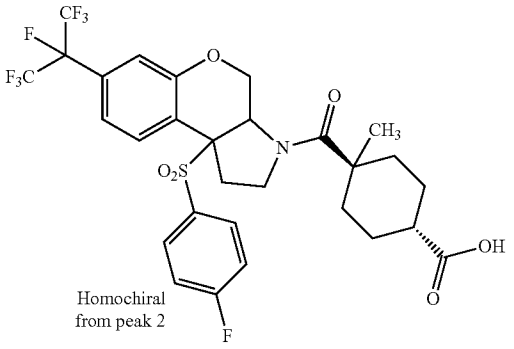
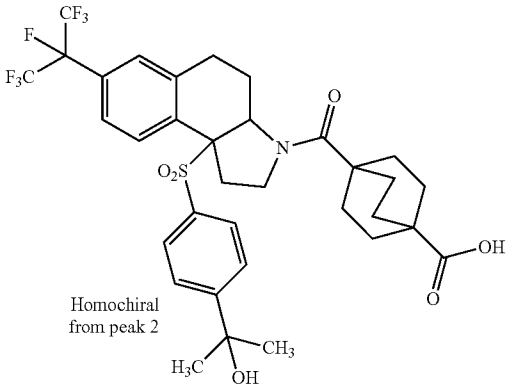
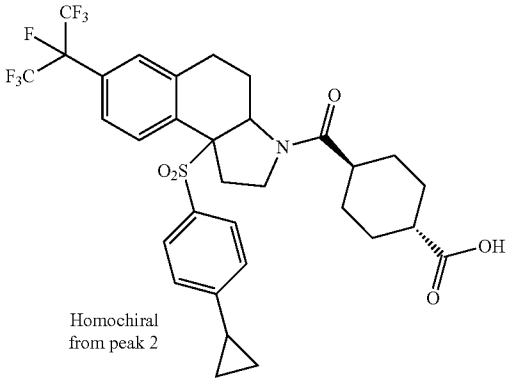
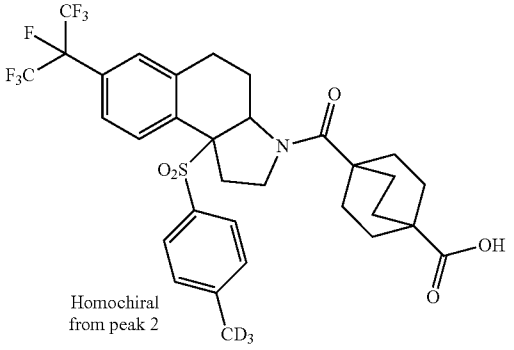
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
138	 Homochiral from peak 2	670.5 $(M + H)^+$	1.07	B
139	 Homochiral from peak 2	720.5 $(M + H)^+$	1.01	B
140	 Homochiral from peak 2	676.1 $(M + H)^+$	1.12	B
141	 Homochiral from peak 2	679.5 $(M + H)^+$	1.08	B

TABLE 9-continued

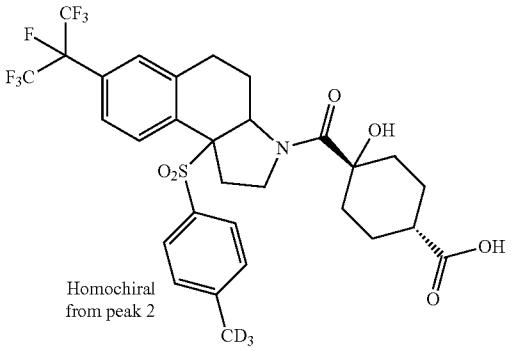
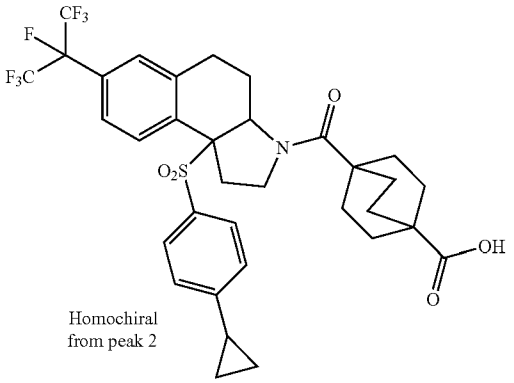
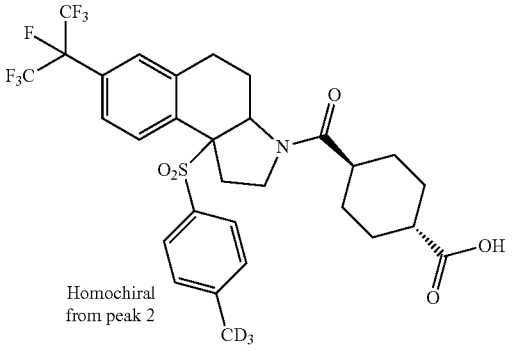
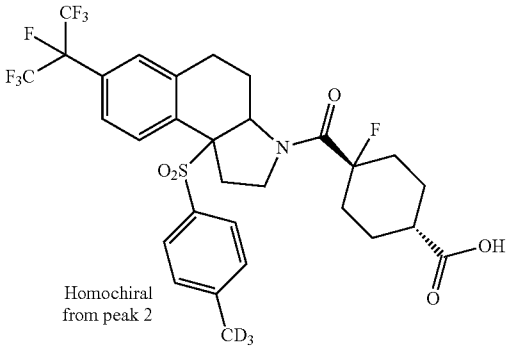
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
142		669.1 $(M + H)^+$	1.93	C
143		702.5 $(M + H)^+$	1.10	B
144		653.4 $(M + H)^+$	1.04	B
145		671.5 $(M + H)^+$	1.05	B

TABLE 9-continued

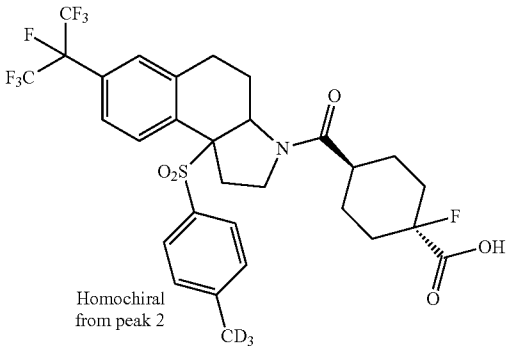
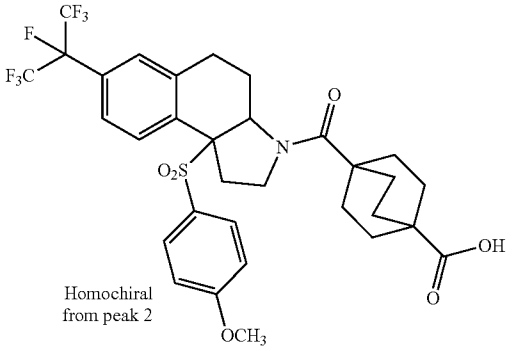
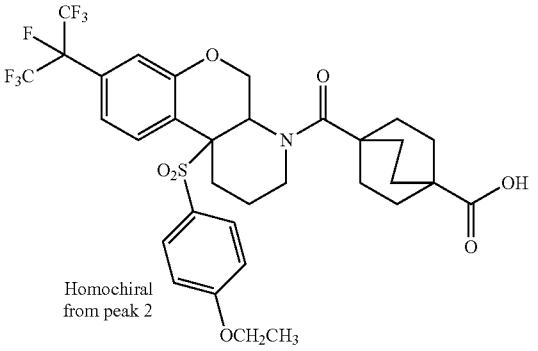
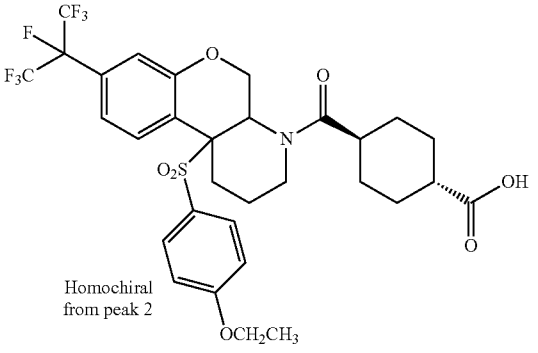
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
146		671.5 $(M + H)^+$	1.05	B
147		692.5 $(M + H)^+$	1.10	B
148		722.2 $(M + H)^+$	1.16	B
149		696.2 $(M + H)^+$	1.13	B

TABLE 9-continued

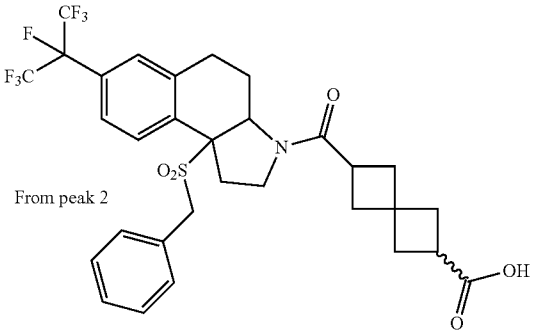
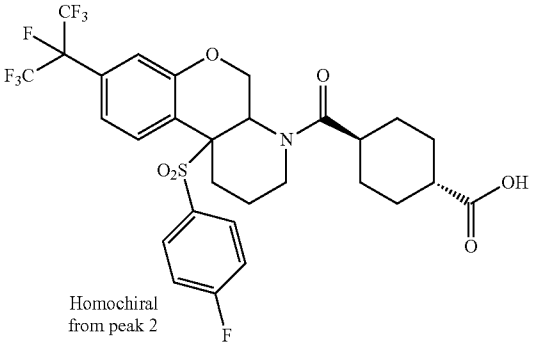
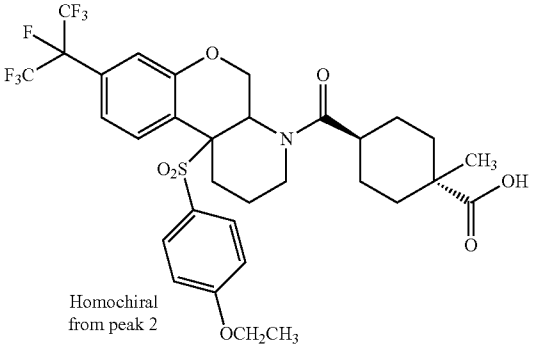
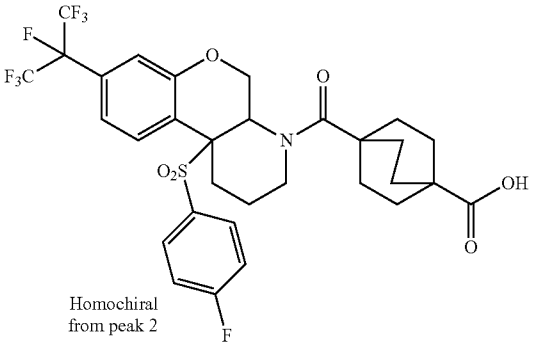
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
150		696.2 $(M + H)^+$	1.13	B
151		670.2 $(M + H)^+$	1.10	B
152		710.2 $(M + H)^+$	1.15	B
153		696.2 $(M + H)^+$	1.14	B

TABLE 9-continued

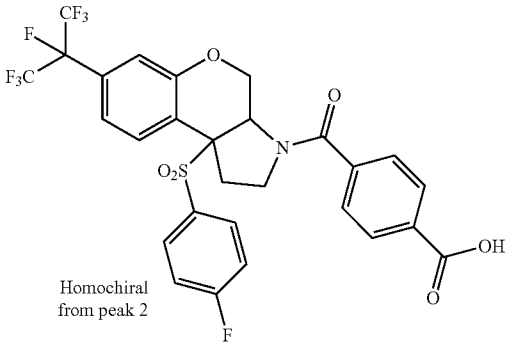
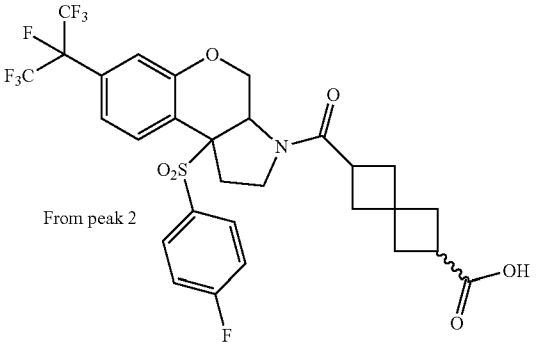
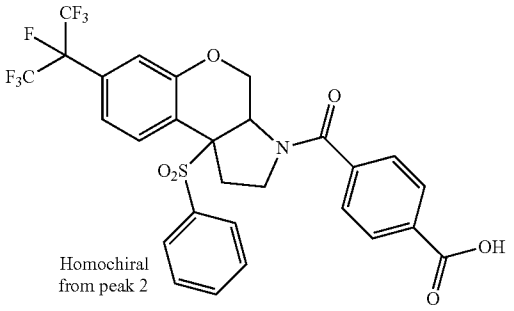
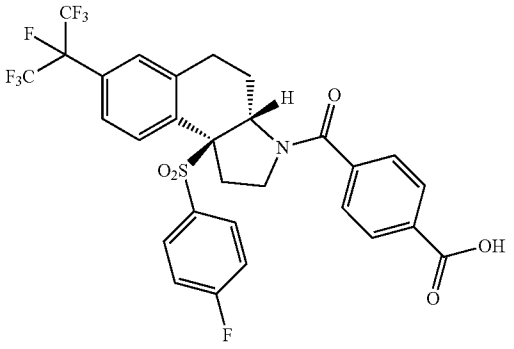
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
154	 Homochiral from peak 2	650.1 $(M + H)^+$	1.09	B
155	 From peak 2	668.1 $(M + H)^+$	1.10	B
156	 Homochiral from peak 2	632.1 $(M + H)^+$	1.08	B
157		648.1 $(M + H)^+$	1.09	B

TABLE 9-continued

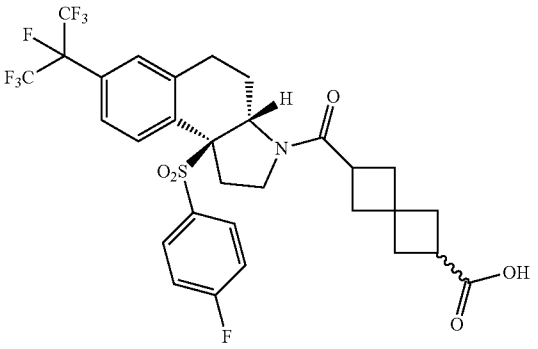
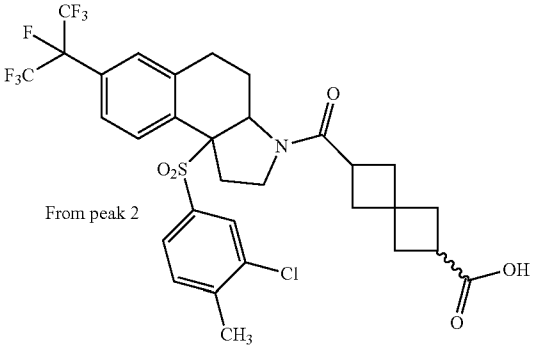
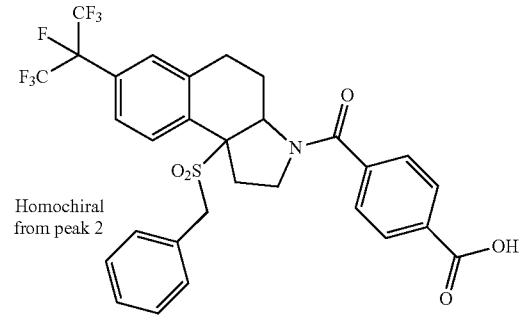
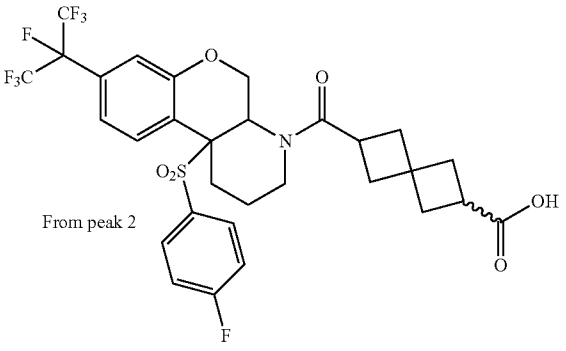
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
158		666.1 $(M + H)^+$	1.10	B
159	 From peak 2	696.2 $(M + H)^+$	1.16	B
160	 Homochiral from peak 2	650.1 $(M + H)^+$	1.09	B
161	 From peak 2	682.1 $(M + H)^+$	1.12	B

TABLE 9-continued

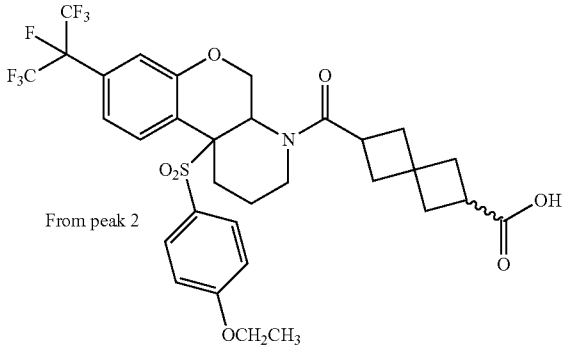
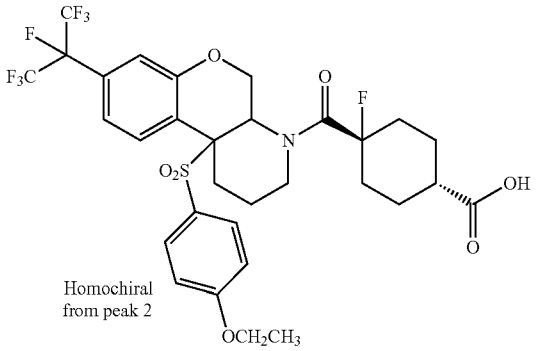
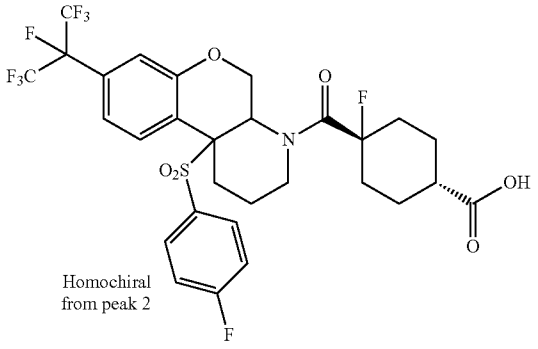
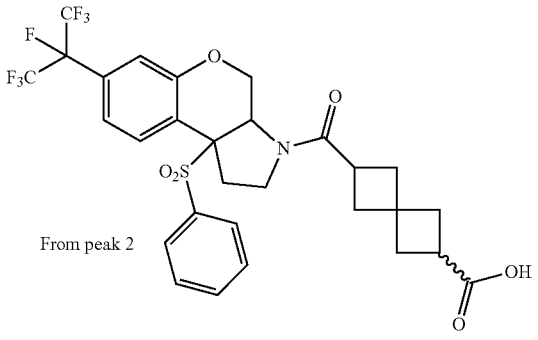
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
162	 From peak 2	708.2 $(M + H)^+$	1.14	B
163	 Homochiral from peak 2	714.2 $(M + H)^+$	1.17	B
164	 Homochiral from peak 2	688.2 $(M + H)^+$	1.14	B
165	 From peak 2	650.2 $(M + H)^+$	1.09	B

TABLE 9-continued

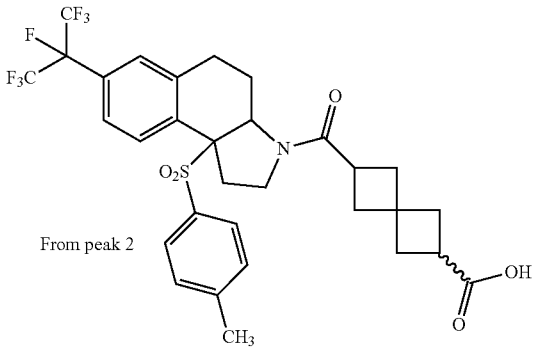
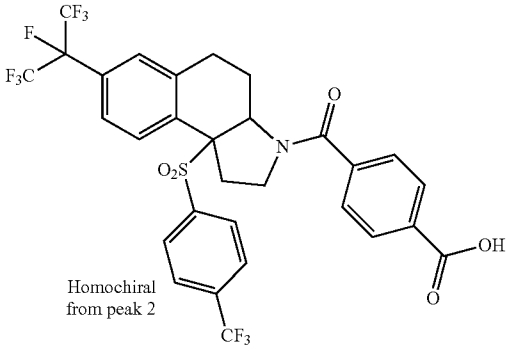
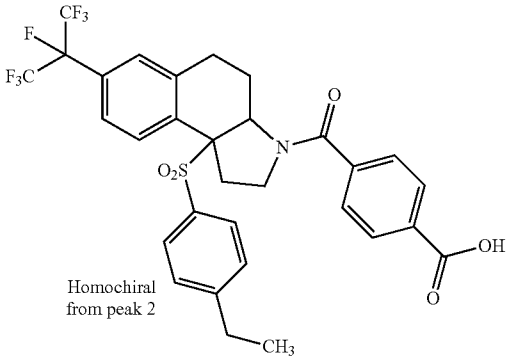
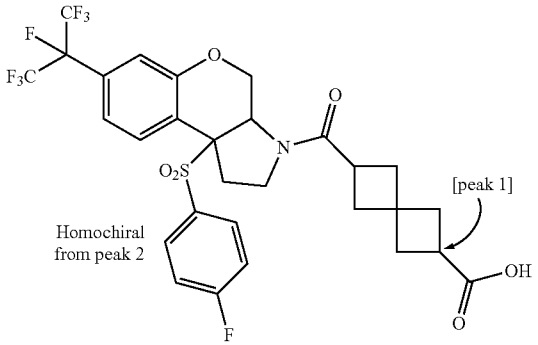
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
166		662.3 $(M + H)^+$	1.06	B
167		698.2 $(M + H)^+$	1.08	B
168		658.4 $(M + H)^+$	1.09	B
169		668.1 $(M + H)^+$	1.10	B

TABLE 9-continued

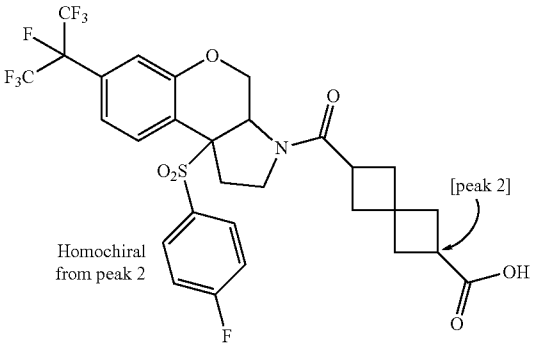
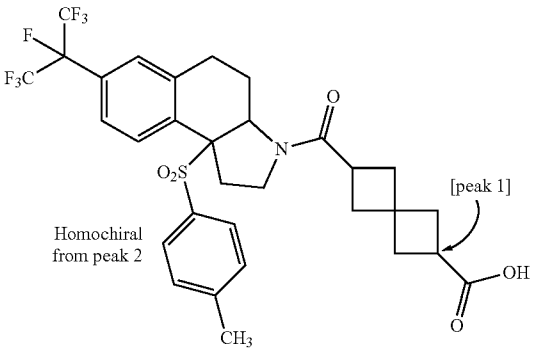
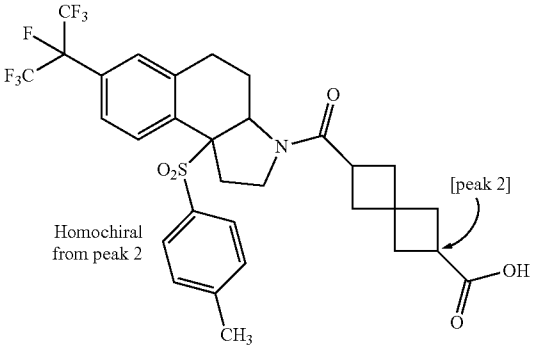
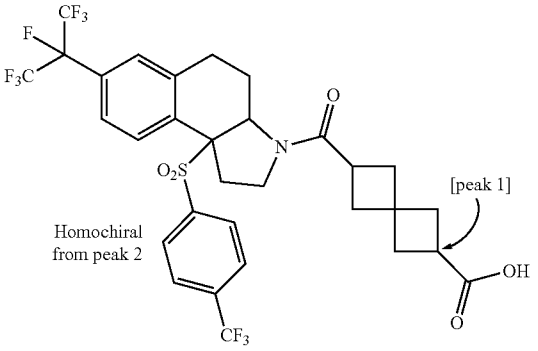
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
170		668.1 $(M + H)^+$	1.10	B
171		662.1 $(M + H)^+$	1.06	B
172		662.1 $(M + H)^+$	1.06	B
173		716.2 $(M + H)^+$	1.07	B

TABLE 9-continued

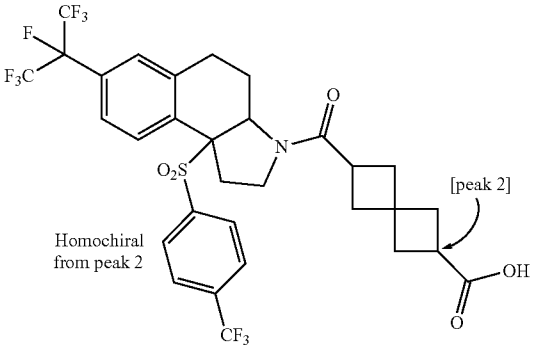
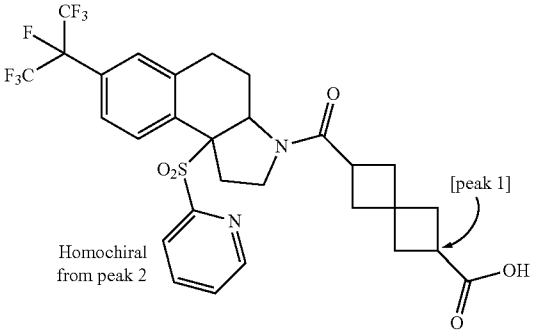
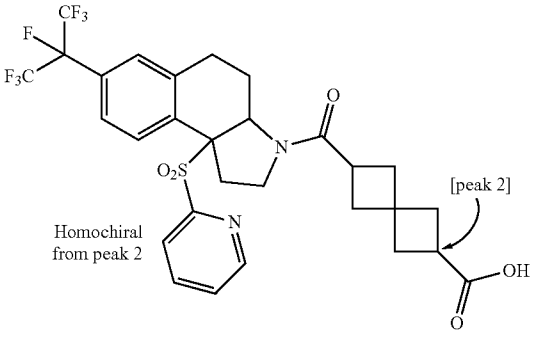
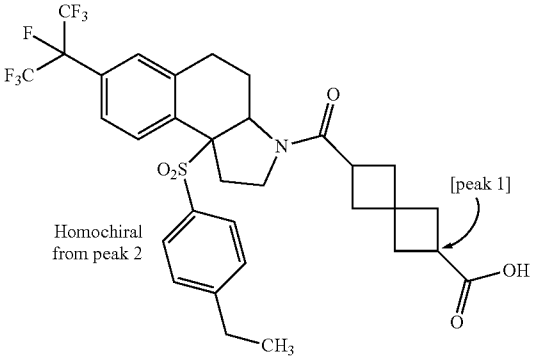
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
174		716.2 $(M + H)^+$	1.07	B
175		649.2 $(M + H)^+$	0.96	B
176		649.2 $(M + H)^+$	0.96	B
177		676.2 $(M + H)^+$	1.08	B

TABLE 9-continued

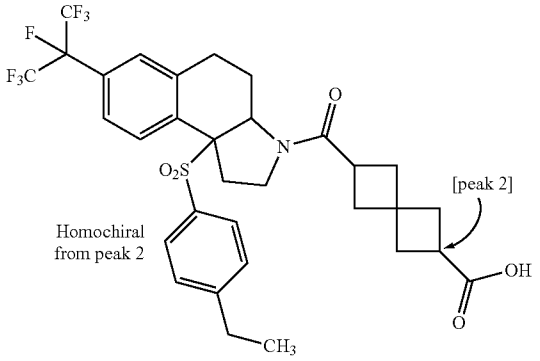
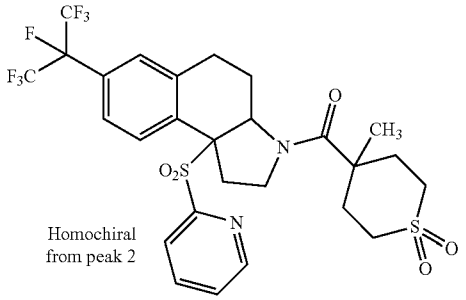
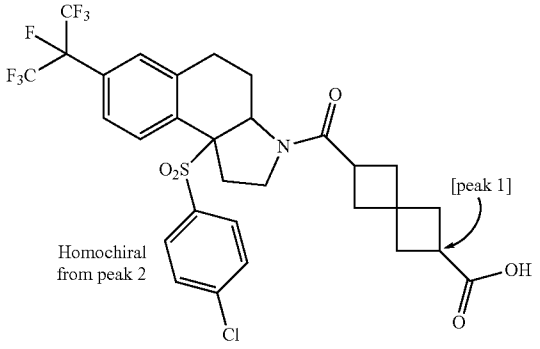
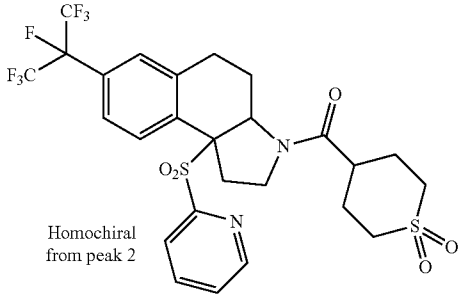
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
178		676.2 $(M + H)^+$	1.08	B
179		657.1 $(M + H)^+$	1.94	C
180		682.3 $(M + H)^+$	1.08	B
181		643.1 $(M + H)^+$	1.82	C

TABLE 9-continued

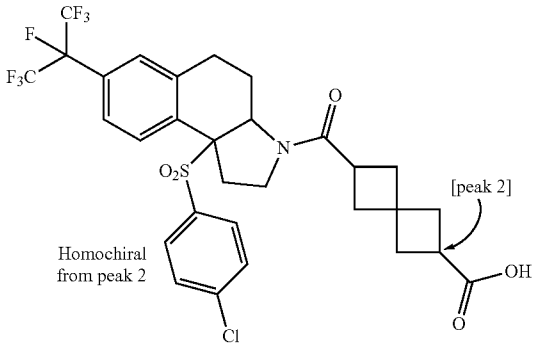
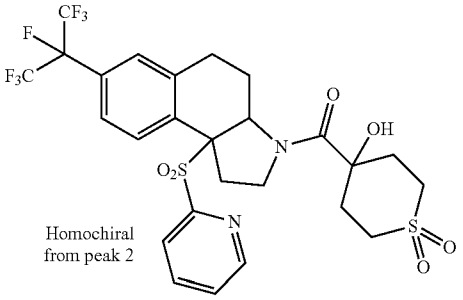
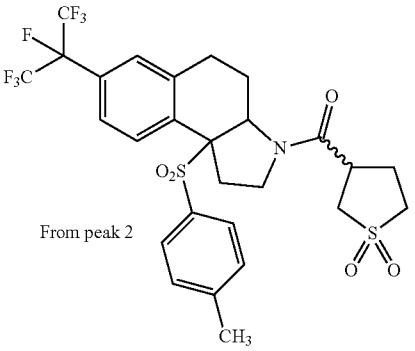
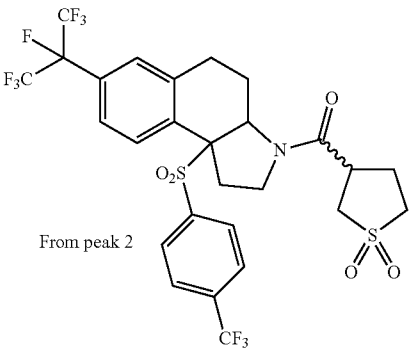
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
182		682.3 $(M + H)^+$	1.08	B
183		659.1 $(M + H)^+$	1.82	C
184		642.2 $(M + H)^+$	1.07	B
185		696.2 $(M + H)^+$	1.10	B

TABLE 9-continued

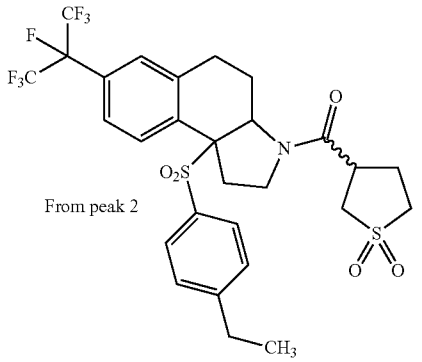
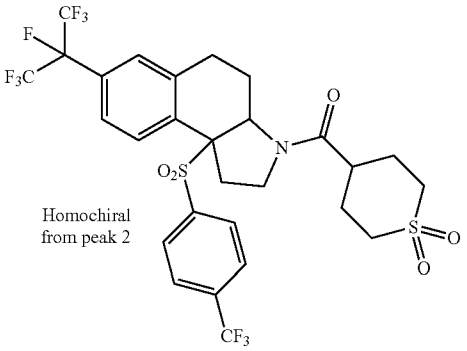
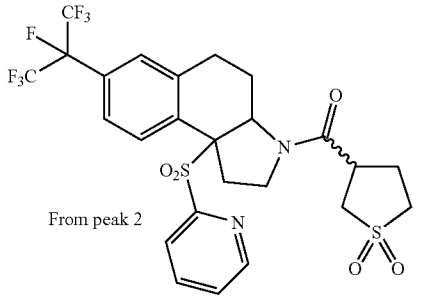
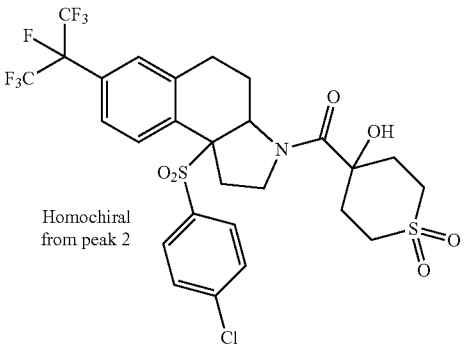
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
186	 From peak 2	656.2 $(M + H)^+$	1.11	B
187	 Homochiral from peak 2	710.2 $(M + H)^+$	1.09	B
188	 From peak 2	629.2 $(M + H)^+$	0.98	B
189	 Homochiral from peak 2	692.2 $(M + H)^+$	1.07	B

TABLE 9-continued

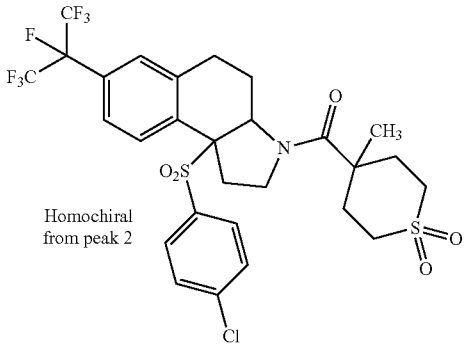
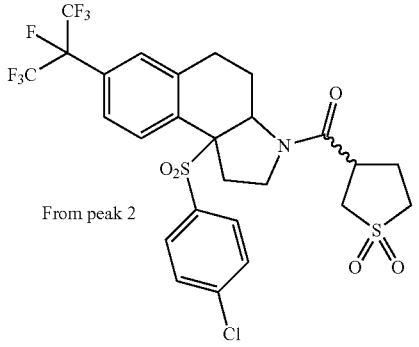
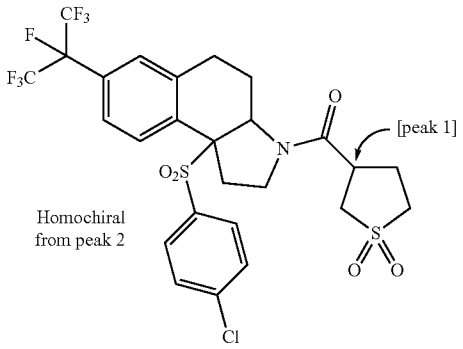
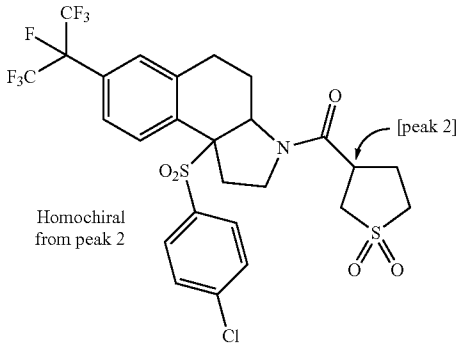
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
190		690.2 $(M + H)^+$	1.13	B
191		662.1 $(M + H)^+$	1.09	B
192		662.1 $(M + H)^+$	1.09	B
193		662.1 $(M + H)^+$	1.09	B

TABLE 9-continued

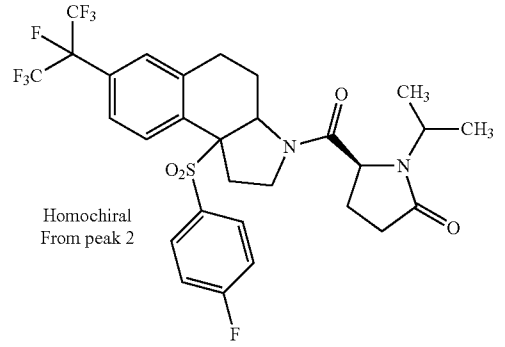
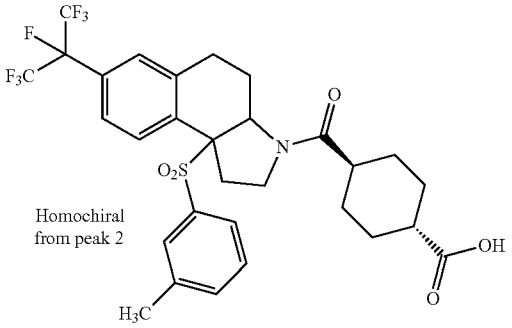
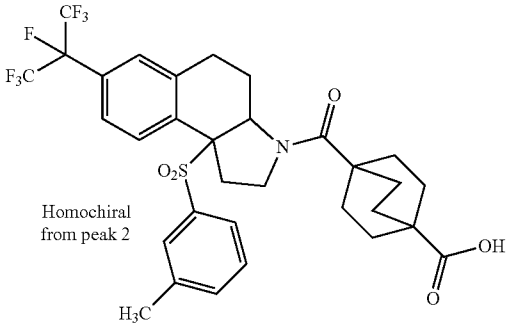
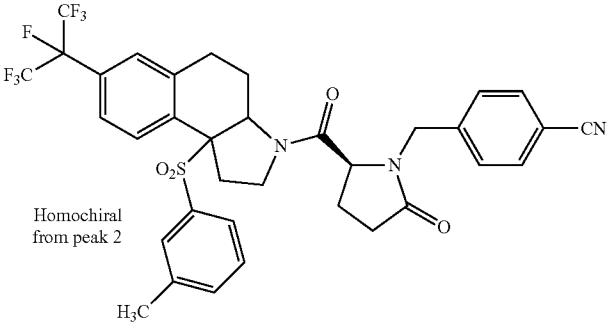
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
194	 Homochiral From peak 2	652.9 $(M + H)^+$	2.16	C
195	 Homochiral from peak 2	650.1 $(M + H)^+$	2.20	D
196	 Homochiral from peak 2	676.1 $(M + H)^+$	2.30	D
197	 Homochiral from peak 2	722.0 $(M + H)^+$	2.31	D

TABLE 9-continued

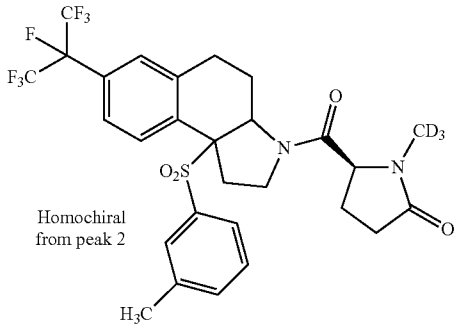
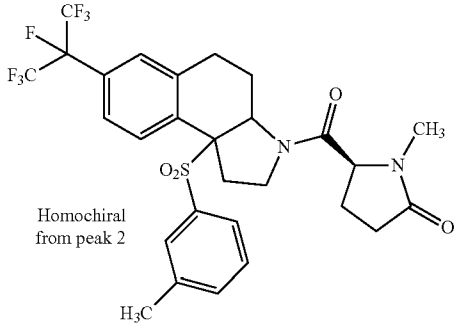
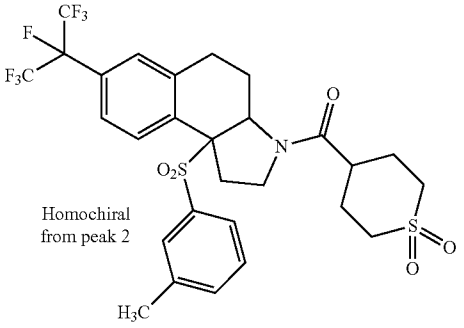
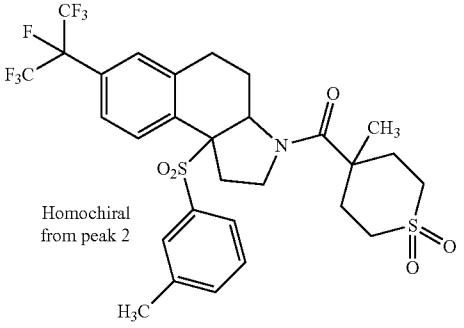
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
198		624.3 $(M + H)^+$	2.08	D
199		621.0 $(M + H)^+$	2.09	D
200		656.4 $(M + H)^+$	2.19	D
201		670.5 $(M + H)^+$	2.32	D

TABLE 9-continued

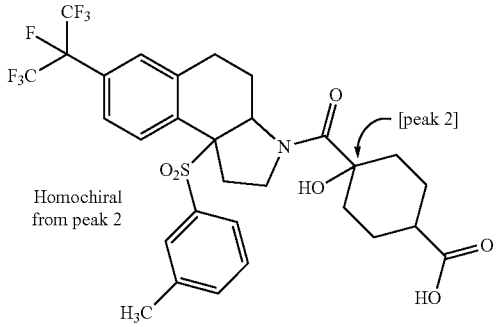
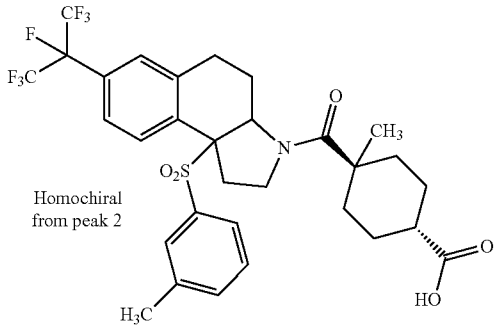
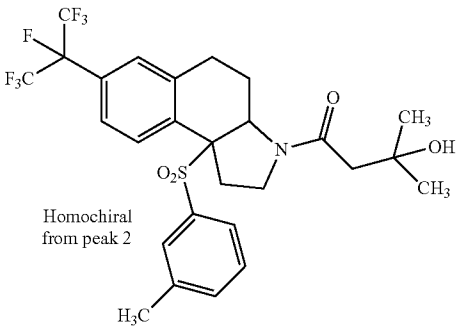
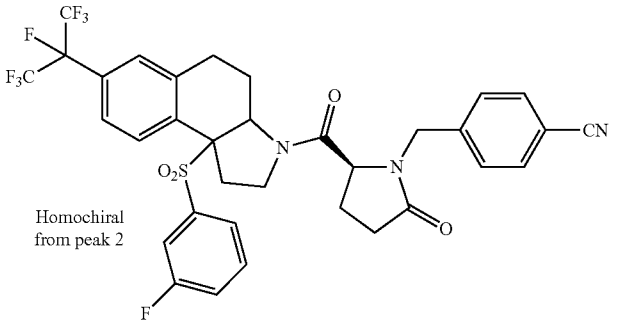
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
202		666.1 $(M + H)^+$	2.11	D
203		664.5 $(M + H)^+$	2.35	D
204		596.2 $(M + H)^+$	2.58	D
205		726.1 $(M + H)^+$	2.24	D

TABLE 9-continued

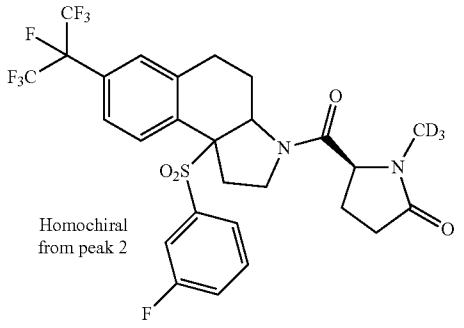
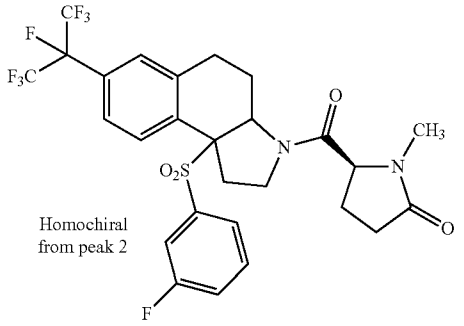
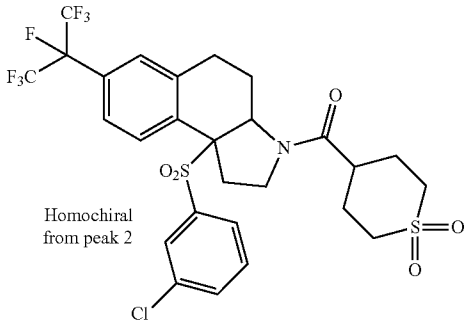
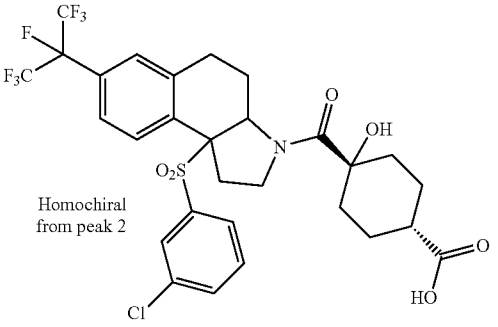
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
206		628.1 $(M + H)^+$	2.02	D
207		625.2 $(M + H)^+$	2.02	D
208		676.3 $(M + H)^+$	2.17	D
209		685.9 $(M + H)^+$	2.16	D

TABLE 9-continued

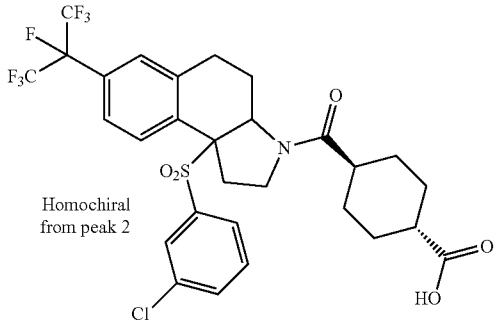
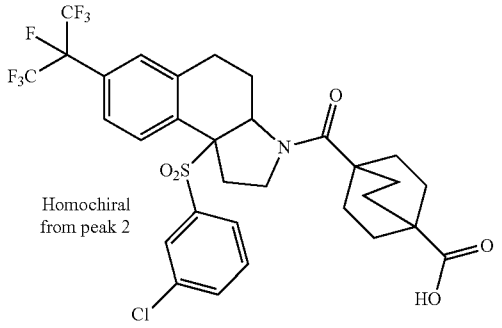
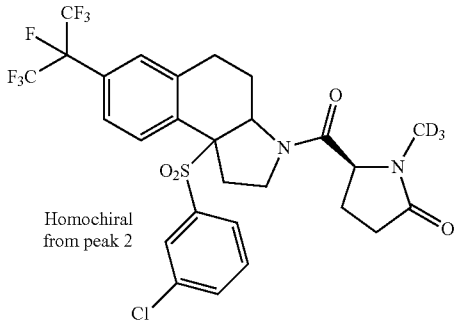
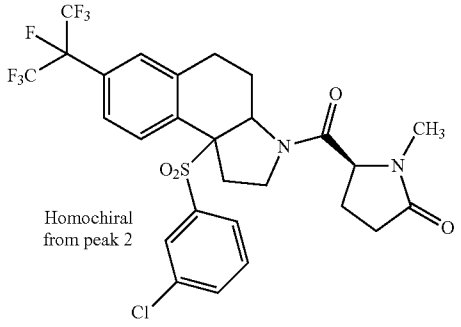
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
210		670.5 $(M + H)^+$	2.29	D
211		696.5 $(M + H)^+$	2.39	D
212		644.2 $(M + H)^+$	2.17	D
213		641.4 $(M + H)^+$	2.17	D

TABLE 9-continued

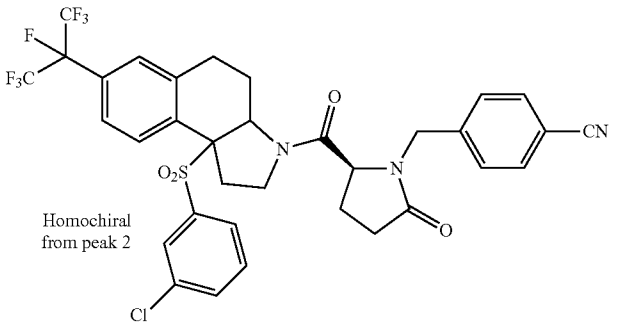
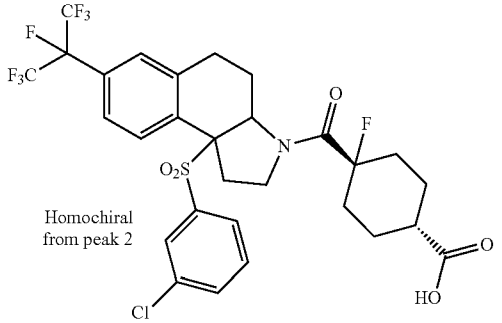
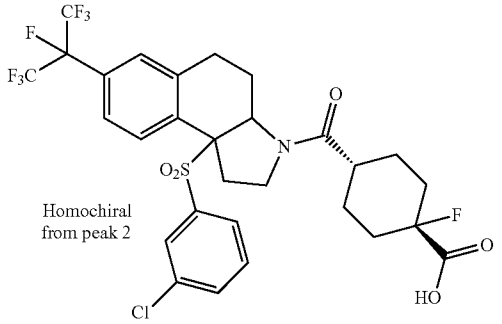
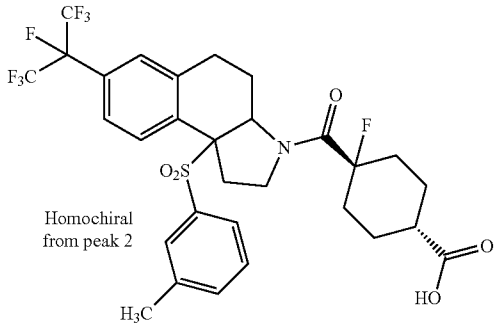
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
214		742.5 $(M + H)^+$	2.40	D
215		688.1 $(M + H)^+$	2.37	D
216		688.0 $(M + H)^+$	2.26	D
217		668.0 $(M + H)^+$	2.33	D

TABLE 9-continued

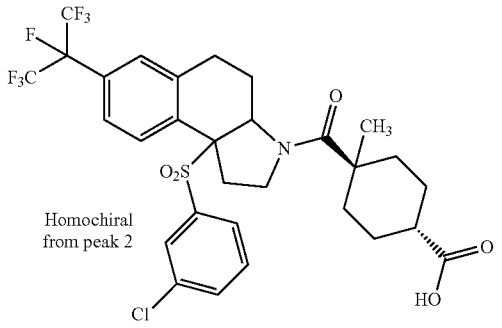
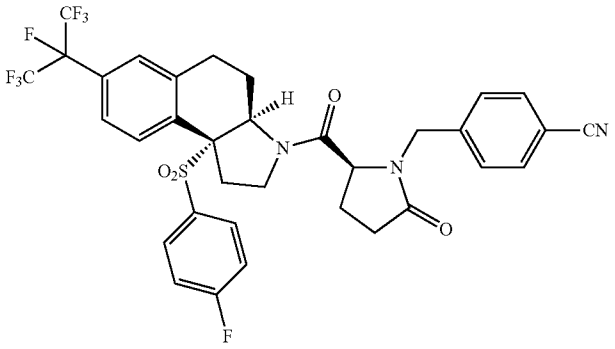
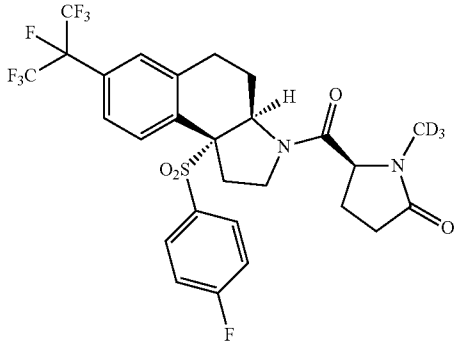
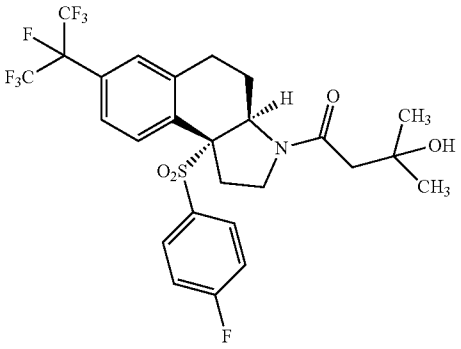
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
218		684.5 $(M + H)^+$	2.39	D
219		726.5 $(M + H)^+$	2.31	D
220		628.1 $(M + H)^+$	2.04	D
221		600.4 $(M + H)^+$	2.26	D

TABLE 9-continued

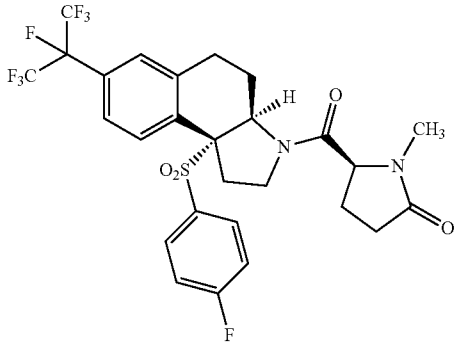
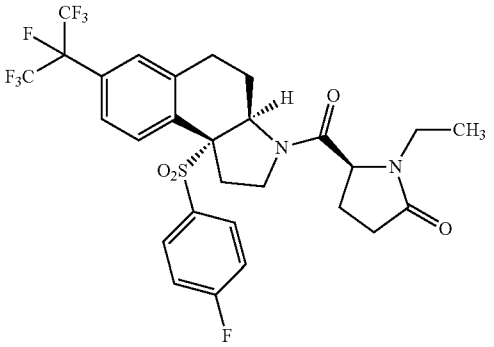
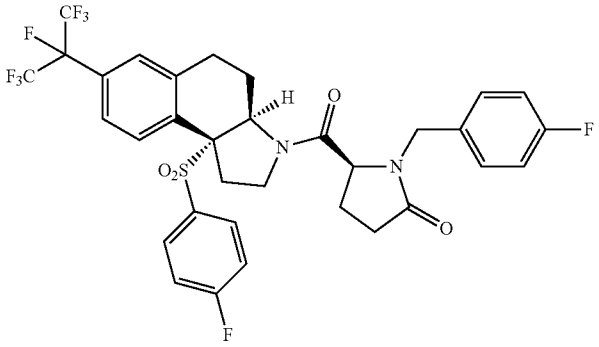
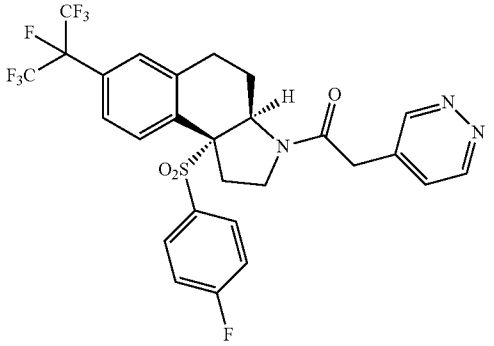
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
222		625.2 $(M + H)^+$	2.04	D
223		639.1 $(M + H)^+$	2.11	D
224		719.4 $(M + H)^+$	2.40	D
225		620.0 $(M + H)^+$	1.93	D

TABLE 9-continued

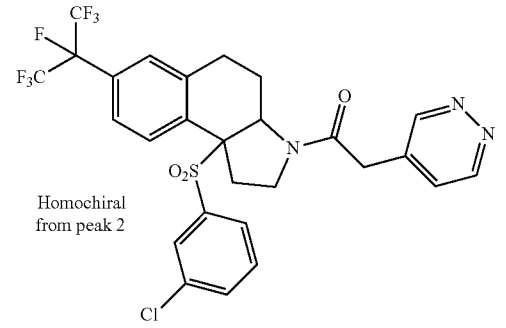
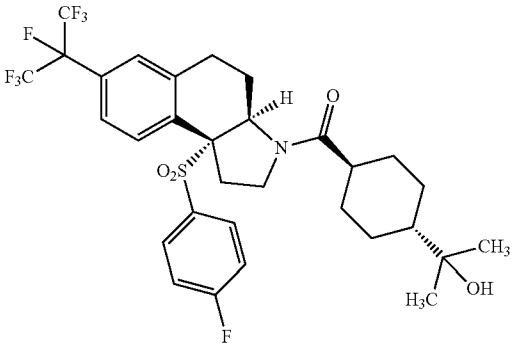
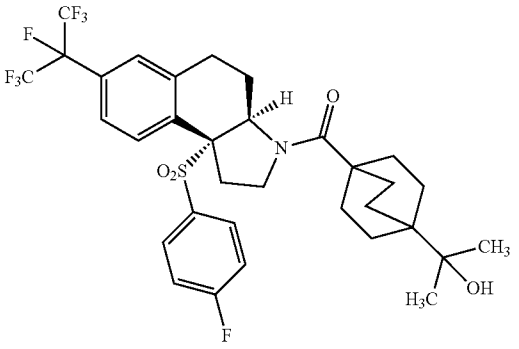
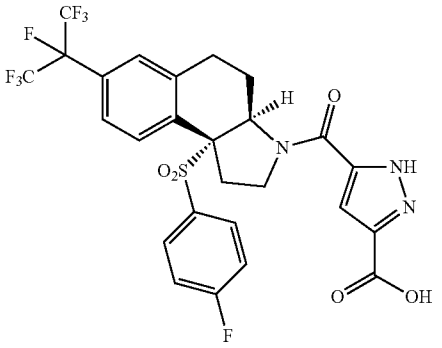
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
226	 Homochiral from peak 2	636.2 $(M + H)^+$	2.08	D
227		668.1 $(M + H)^+$	2.31	D
228		694.1 $(M + H)^+$	2.43	D
229		638.3 $(M + H)^+$	2.16	D

TABLE 9-continued

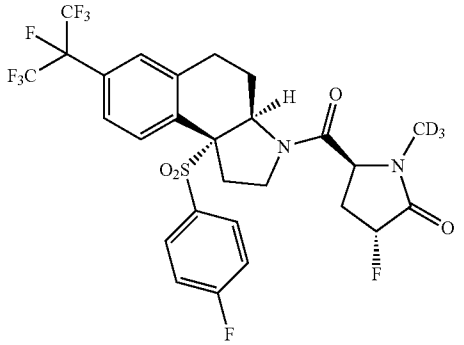
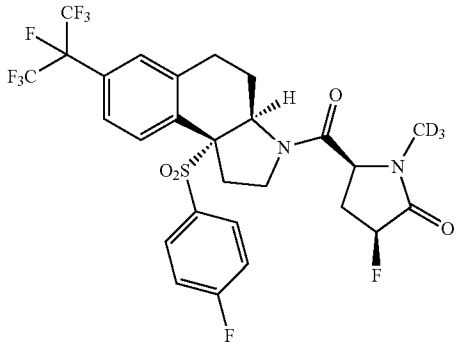
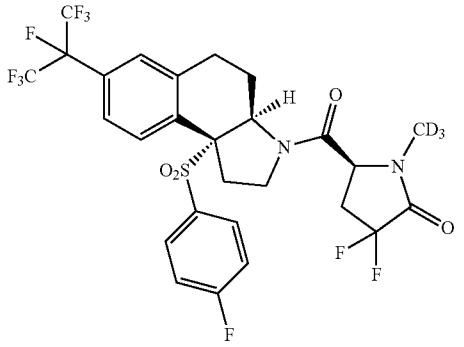
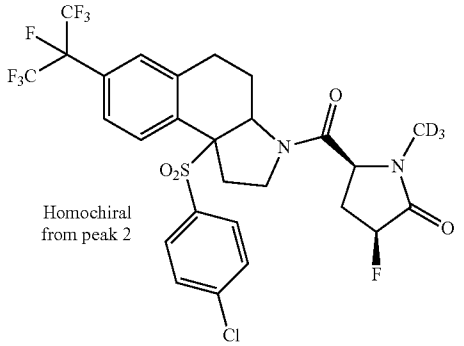
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
230		645.9 $(M + H)^+$	2.09	D
231		646.4 $(M + H)^+$	2.17	D
232		664.4 $(M + H)^+$	2.33	D
233	 Homochiral from peak 2	662.1 $(M + H)^+$	2.20	D

TABLE 9-continued

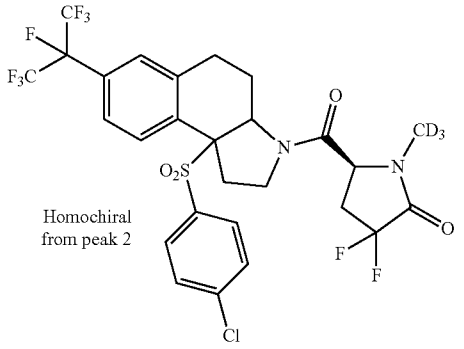
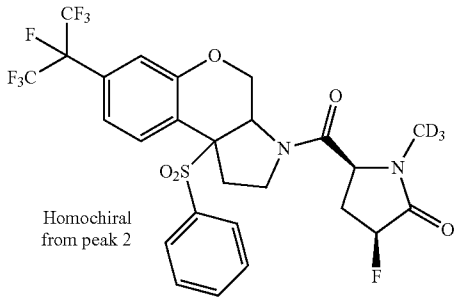
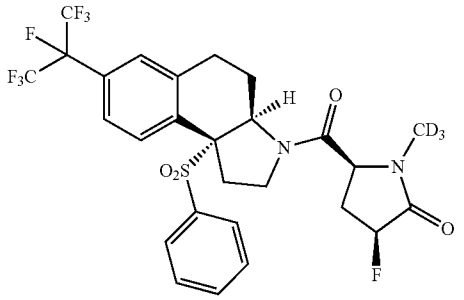
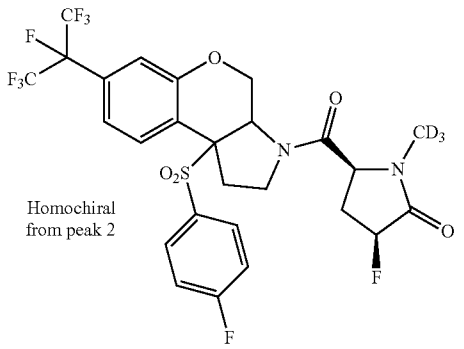
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
234	 Homochiral from peak 2	680.2 $(M + H)^+$	2.37	D
235	 Homochiral from peak 2	630.0 $(M + H)^+$	2.17	D
236		628.1 $(M + H)^+$	2.07	D
237	 Homochiral from peak 2	648.0 $(M + H)^+$	2.17	D

TABLE 9-continued

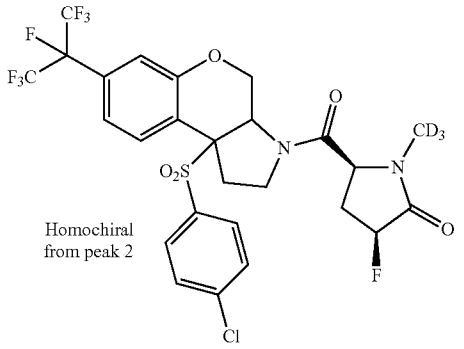
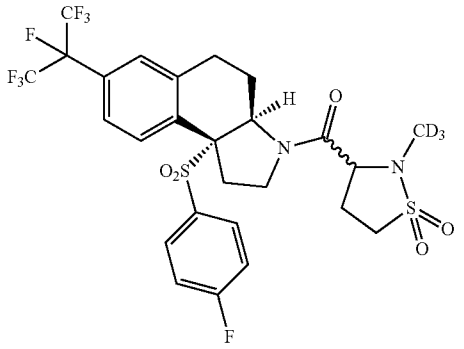
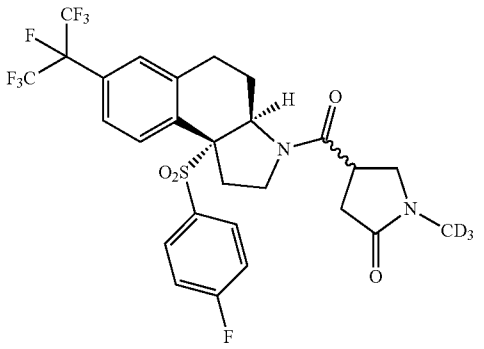
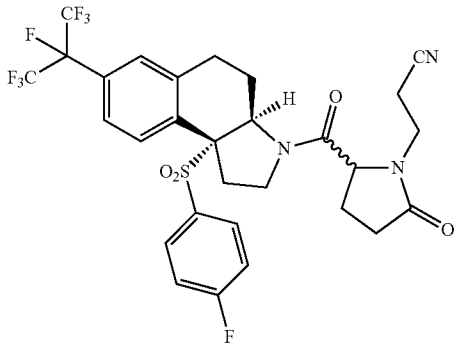
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
238	 Homochiral from peak 2	664.2 $(M + H)^+$	2.28	D
239		664.2 $(M + H)^+$	2.22	D
240		628.0 $(M + H)^+$	2.06	D
241		664.1 $(M + H)^+$	2.11	D

TABLE 9-continued

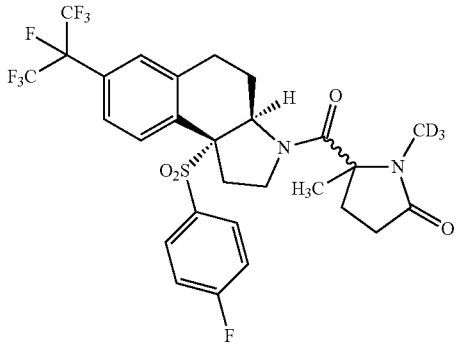
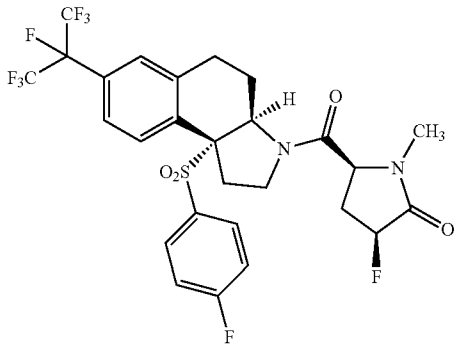
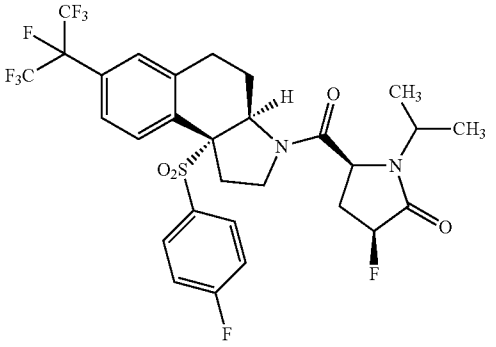
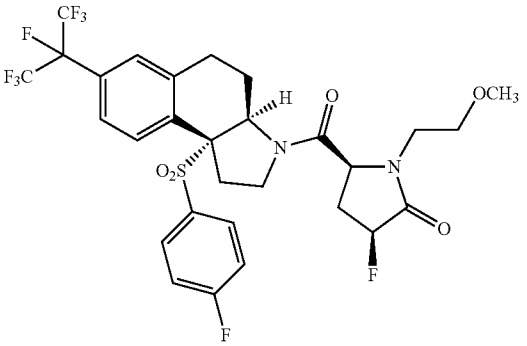
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
242		642.3 $(M + H)^+$	2.20	D
243		643.2 $(M + H)^+$	2.16	D
244		671.0 $(M + H)^+$	2.29	D
245		687.3 $(M + H)^+$	2.24	D

TABLE 9-continued

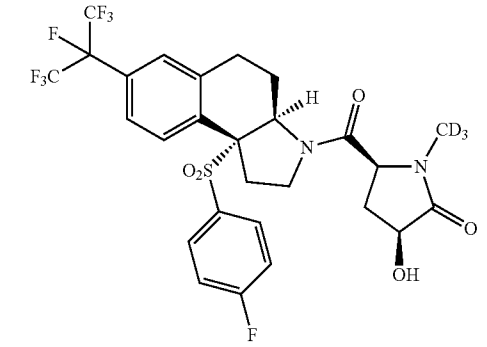
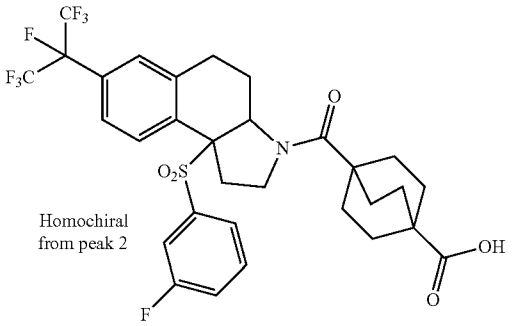
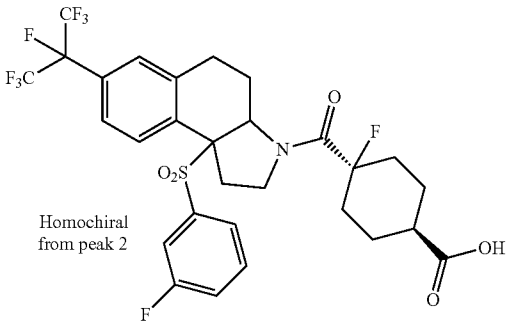
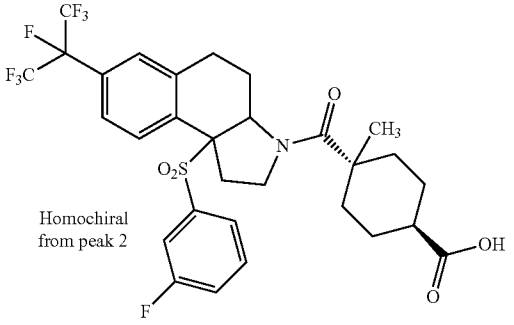
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
246		644.1 $(M + H)^+$	1.99	D
247	 Homochiral from peak 2	669.2 $(M + H)^+$	2.23	D
248	 Homochiral from peak 2	672.0 $(M + H)^+$	2.32	D
249	 Homochiral from peak 2	668.2 $(M + H)^+$	1.10	B

TABLE 9-continued

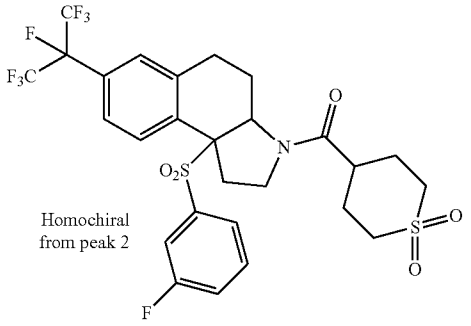
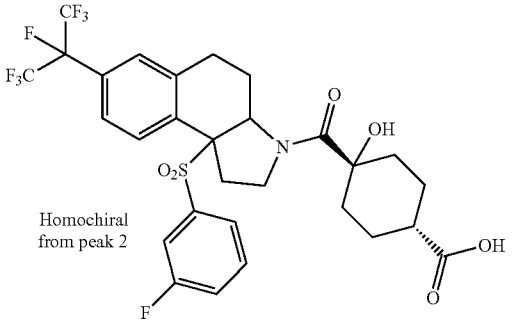
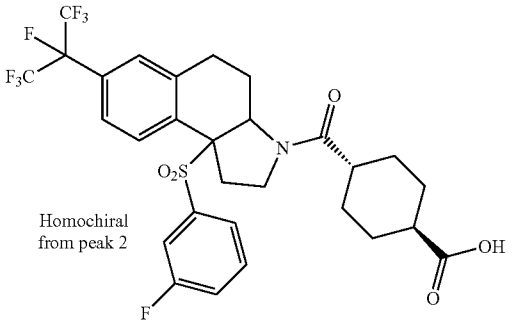
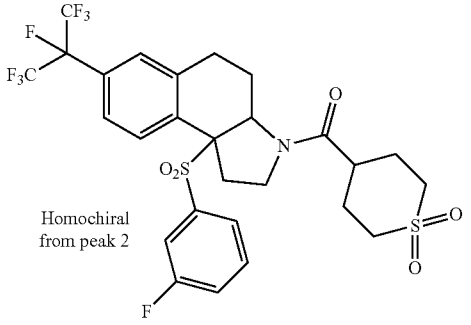
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
250		660.4 $(M + H)^+$	2.21	D
251		670.4 $(M + H)^+$	1.01	B
252		654.2 $(M + H)^+$	1.09	B
253		660.0 $(M + H)^+$	1.97	D

TABLE 9-continued

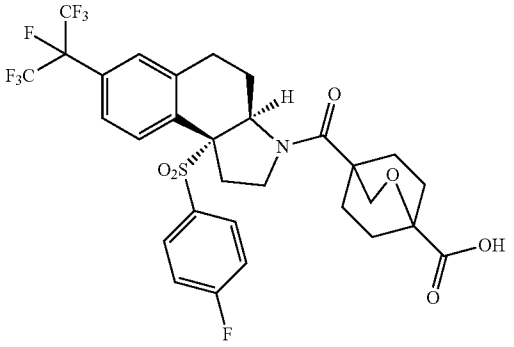
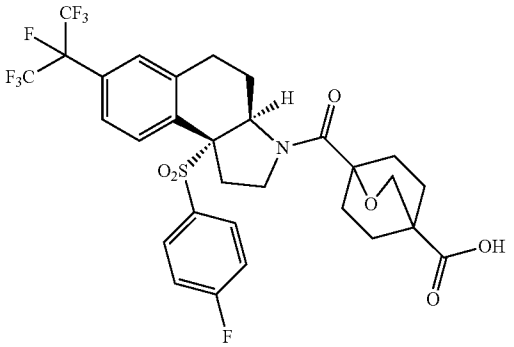
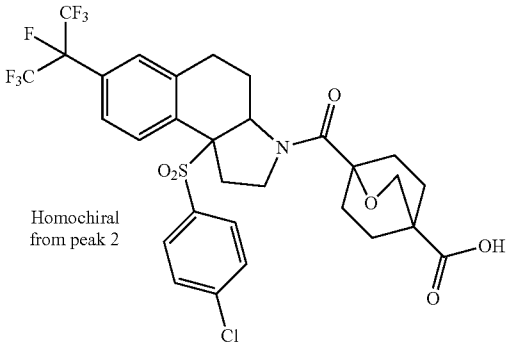
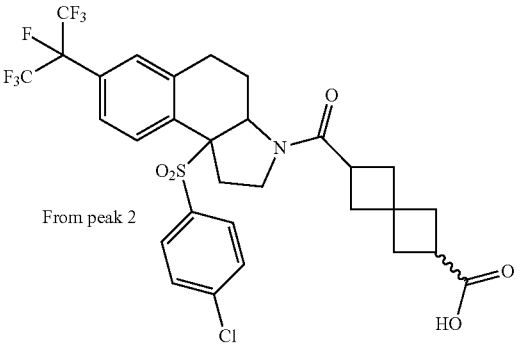
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
254		681.8 $(M + H)^+$	2.09	D
255		682.1 $(M + H)^+$	1.12	B
256	 Homochiral from peak 2	698.1 $(M + H)^+$	1.15	B
257	 From peak 2	682.2 $(M + H)^+$	2.40	D

TABLE 9-continued

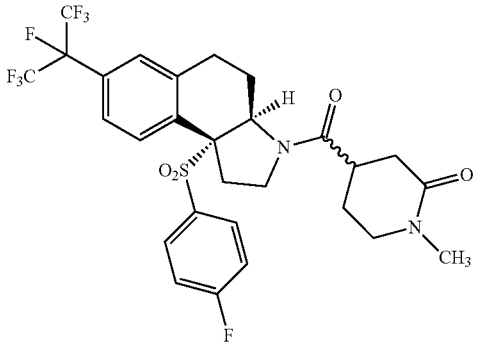
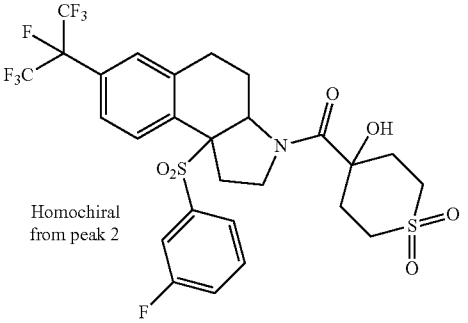
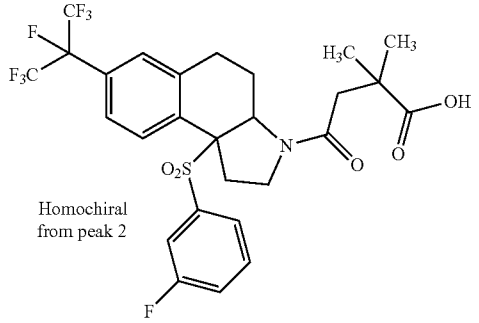
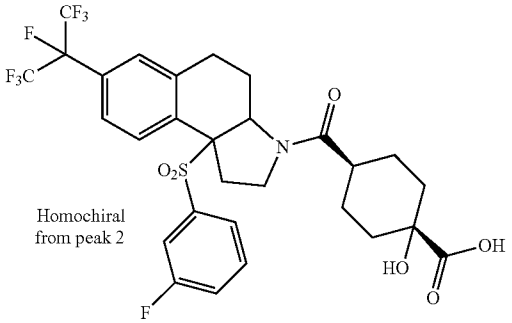
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
258		639.3 $(M + H)^+$	2.09	D
259		676.2 $(M + H)^+$	1.05	B
260		628.2 $(M + H)^+$	2.21	D
261		670.3 $(M + H)^+$	1.01	B

TABLE 9-continued

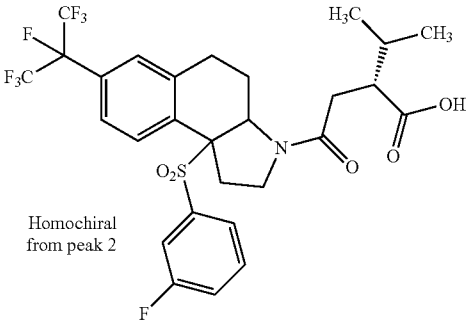
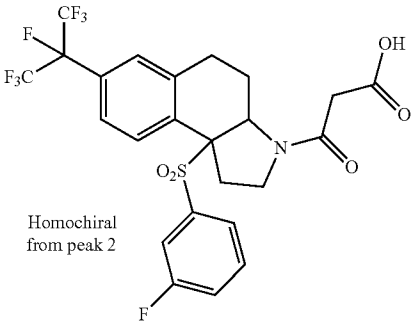
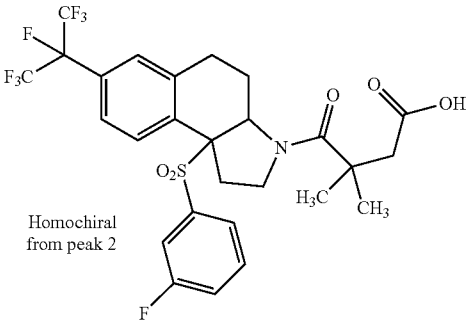
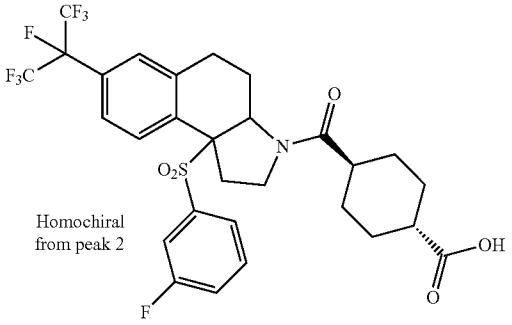
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
262		641.9 $(M + H)^+$	2.00	D
263		586.0 $(M + H)^+$	2.05	D
264		628.1 $(M + H)^+$	2.18	D
265		654.2 $(M + H)^+$	1.09	B

TABLE 9-continued

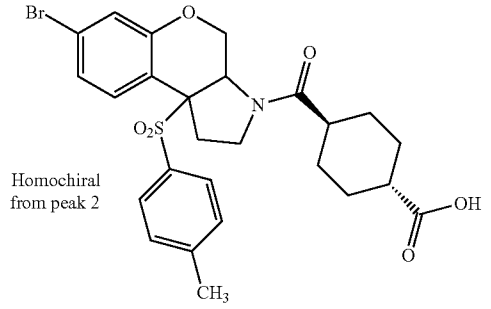
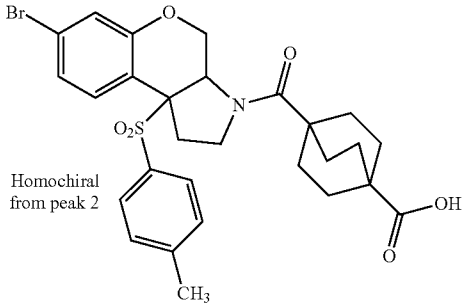
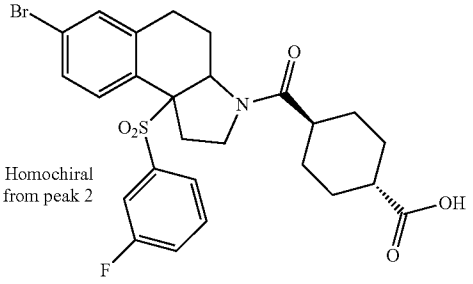
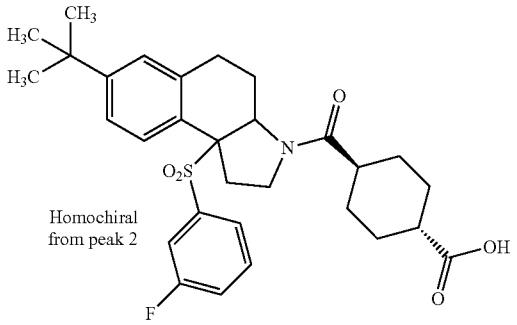
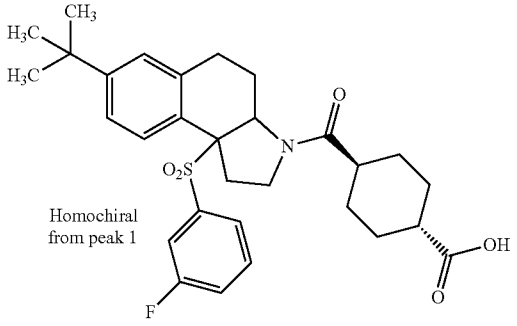
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
266		561.9 $(M + H)^+$	1.68	C
267		588.1 $(M + H)^+$	1.68	C
268		564.1 $(M + H)^+$	2.02	D
269		542.1 $(M + H)^+$	2.07	D
270		542.2 $(M + H)^+$	2.21	D

TABLE 9-continued

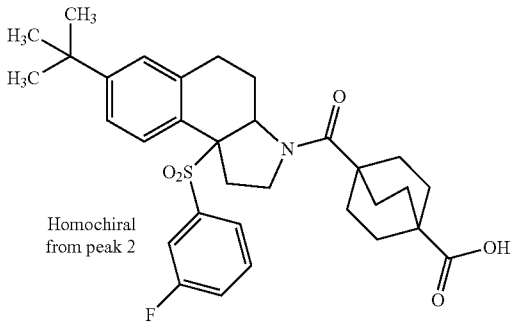
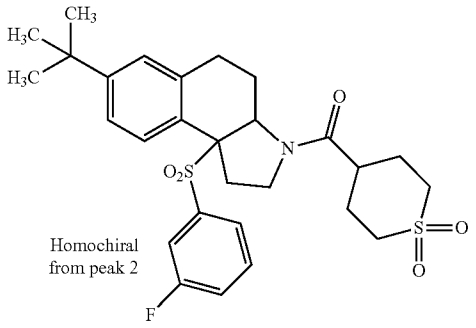
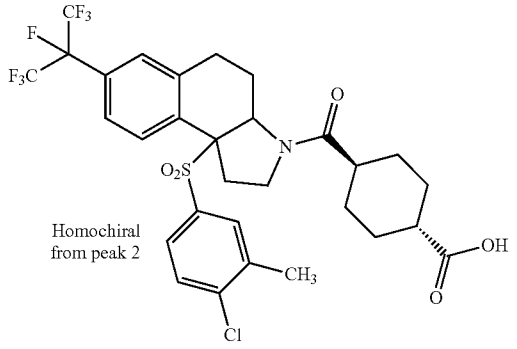
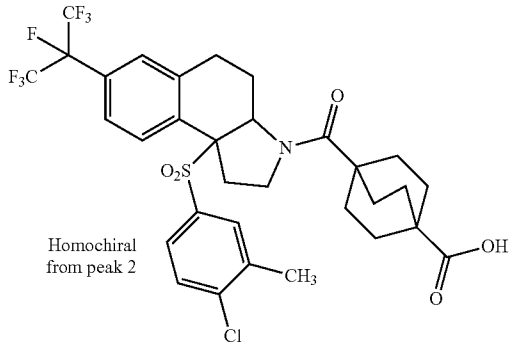
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
271		568.5 $(M + H)^+$	2.34	D
272		548.1 $(M + H)^+$	1.99	D
273		664.1 $(M + H)^+$	2.47	D
274		710.2 $(M + H)^+$	2.42	D

TABLE 9-continued

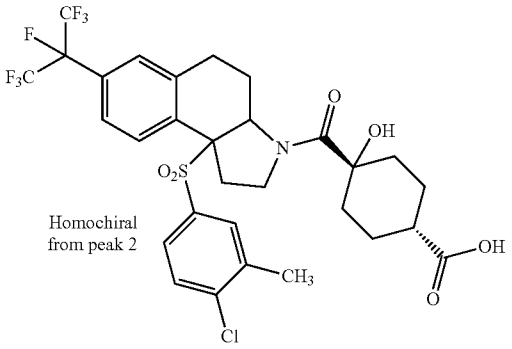
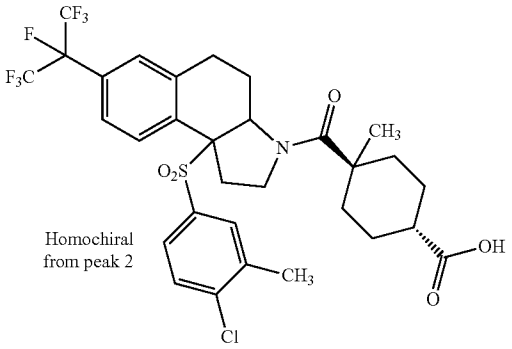
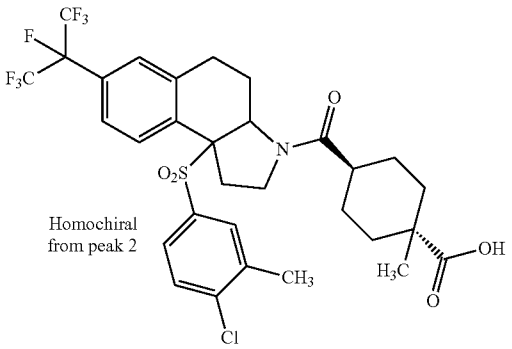
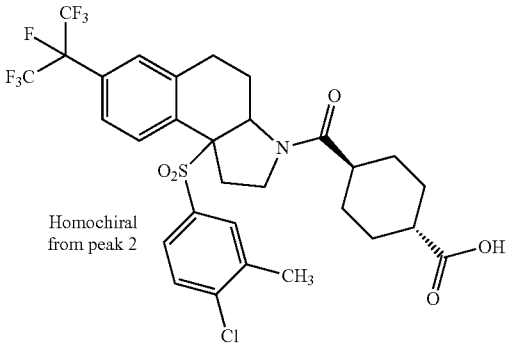
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
275		700.1 $(M + H)^+$	2.37	D
276		698.1 $(M + H)^+$	2.43	D
277		698.4 $(M + H)^+$	2.44	D
278		684.2 $(M + H)^+$	2.46	D

TABLE 9-continued

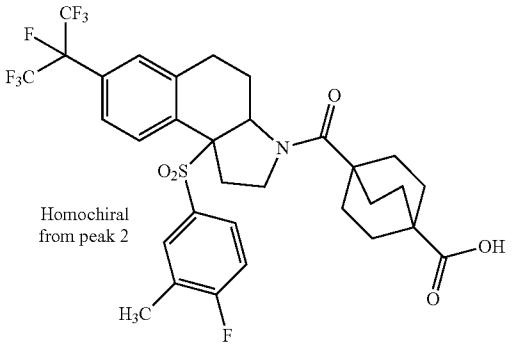
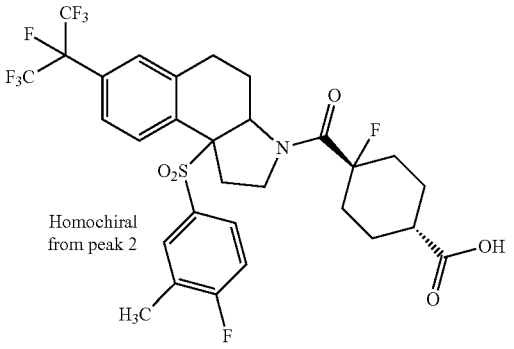
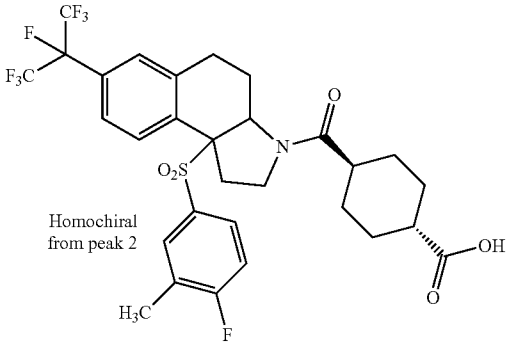
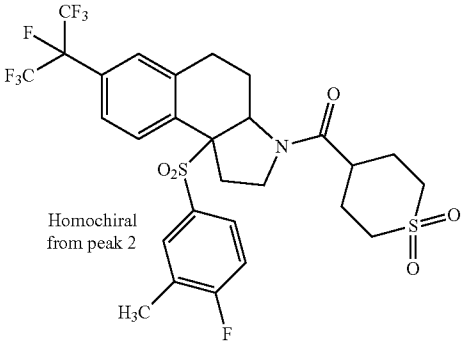
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
279		694.2 $(M + H)^+$	2.34	D
280		686.1 $(M + H)^+$	2.42	D
281		668.2 $(M + H)^+$	2.25	D
282		674.1 $(M + H)^+$	2.22	D

TABLE 9-continued

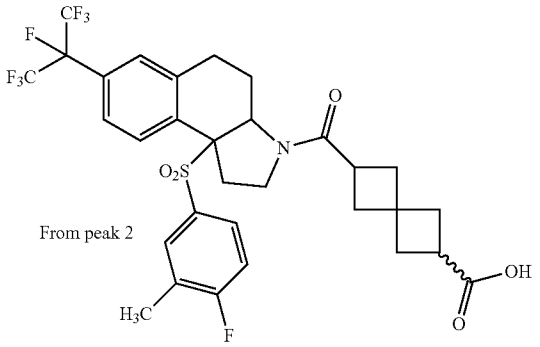
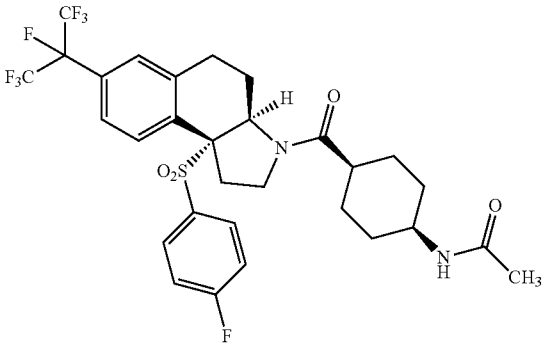
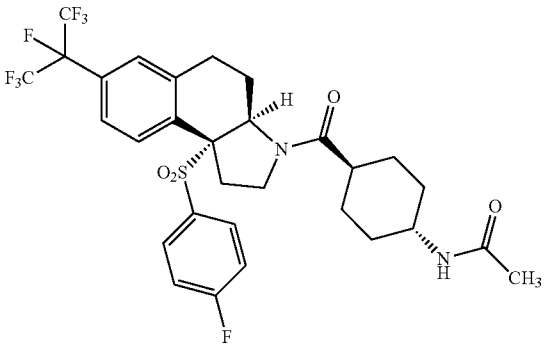
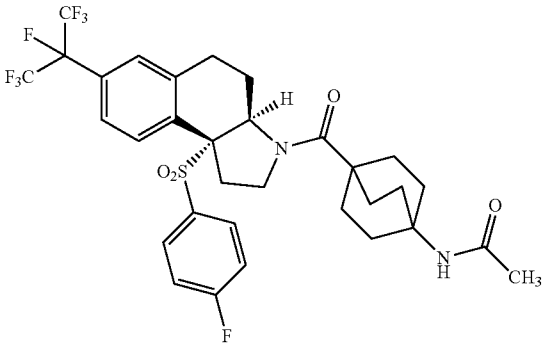
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
283	 From peak 2	680.0 $(M + H)^+$	2.28	D
284		667.0 $(M + H)^+$	2.15	D
285		693.2 $(M + H)^+$	2.23	D
286		667.0 $(M + H)^+$	2.14	D

TABLE 9-continued

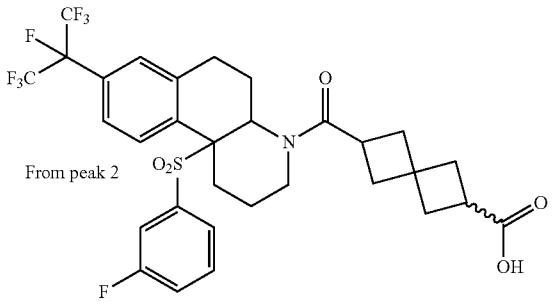
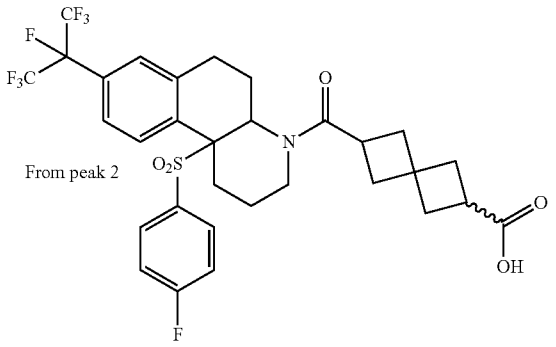
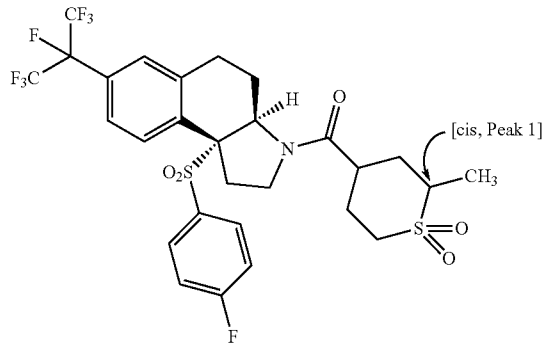
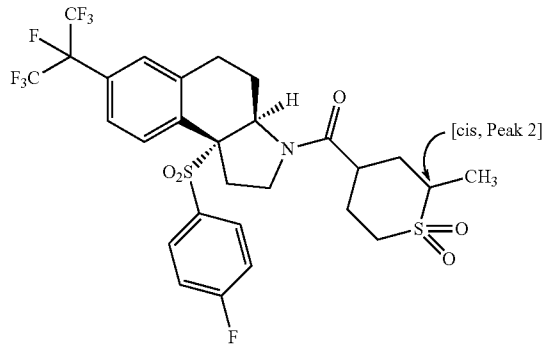
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
287		680.2 $(M + H)^+$	2.27	D
288		680.2 $(M + H)^+$	2.27	D
289		674.1 $(M + H)^+$	1.05	B
290		674.1 $(M + H)^+$	1.05	B

TABLE 9-continued

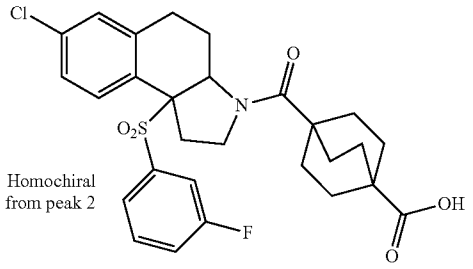
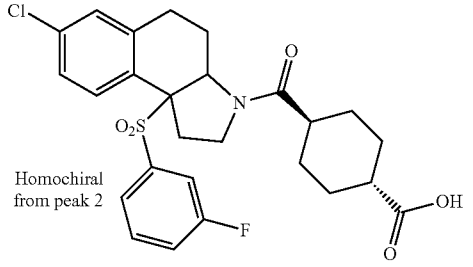
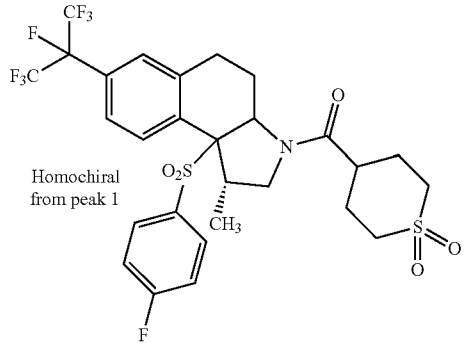
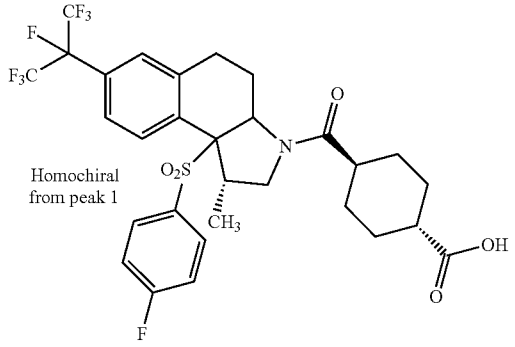
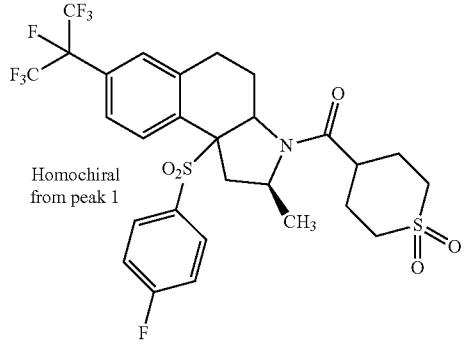
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
291	 Homochiral from peak 2	546.2 $(M + H)^+$	1.96	D
292	 Homochiral from peak 2	520.1 $(M + H)^+$	1.99	D
293	 Homochiral from peak 1	674.3 $(M + H)^+$	2.31	C
294	 Homochiral from peak 1	668.3 $(M + H)^+$	2.03	C
295	 Homochiral from peak 1	674.1 $(M + H)^+$	2.19	C

TABLE 9-continued

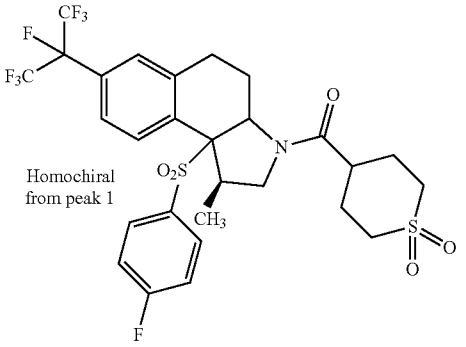
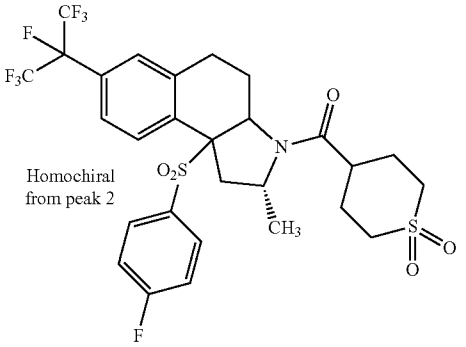
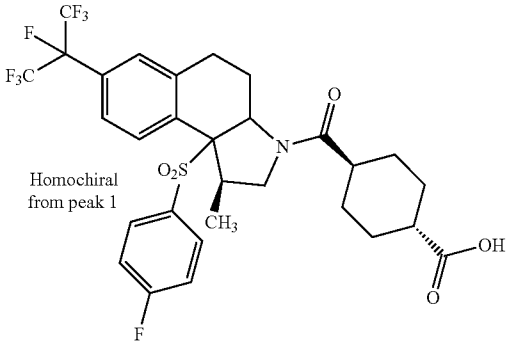
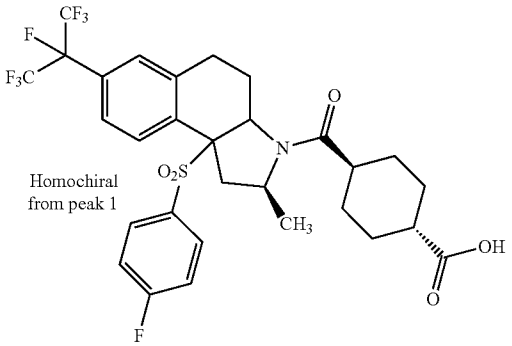
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
296		674.0 $(M + H)^+$	2.20	C
297		674.2 $(M + H)^+$	2.26	C
298		668.1 $(M + H)^+$	1.98	C
299		667.9 $(M + H)^+$	2.34	C

TABLE 9-continued

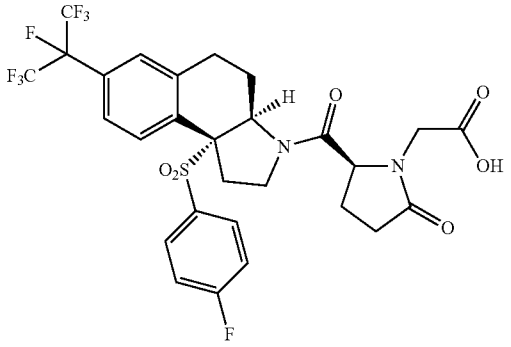
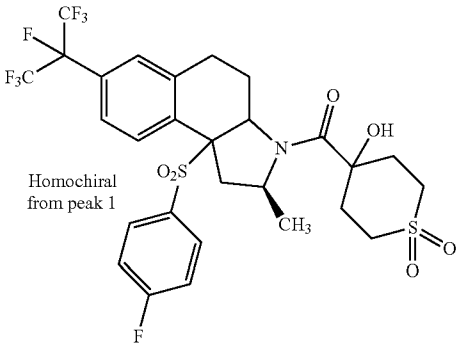
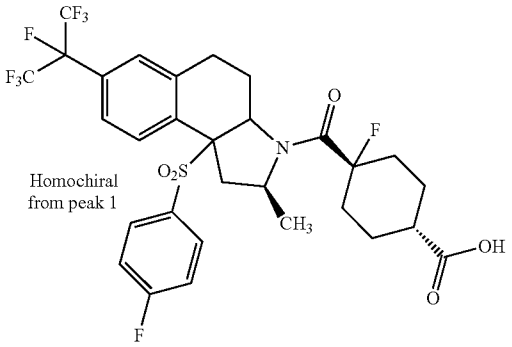
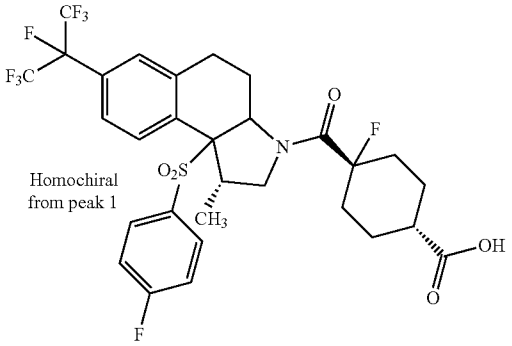
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
300		669.2 $(M + H)^+$	1.65	C
301		690.1 $(M + H)^+$	2.17	C
302		686.2 $(M + H)^+$	2.14	C
303		686.3 $(M + H)^+$	2.41	C

TABLE 9-continued

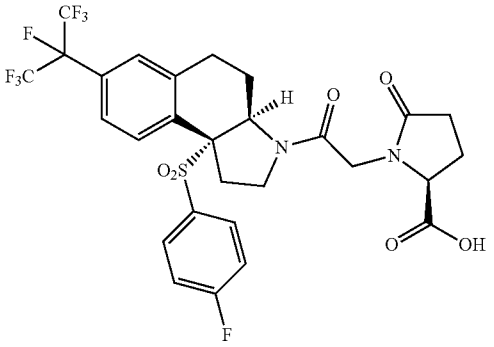
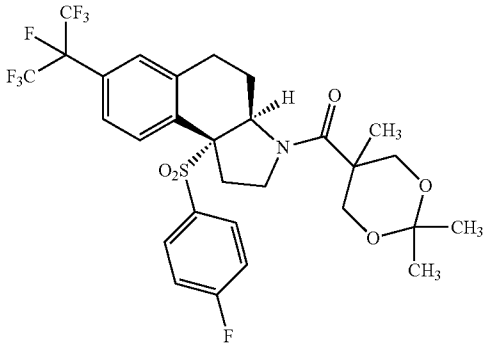
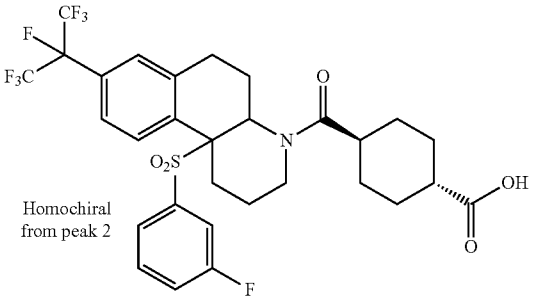
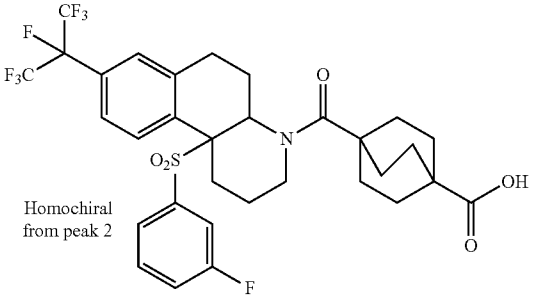
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
304		669.2 $(M + H)^+$	1.61	C
305		656.2 $(M + H)^+$	2.55	C
306	 Homochiral from peak 2	668.2 $(M + H)^+$	1.10	B
307	 Homochiral from peak 2	694.5 $(M + H)^+$	1.10	B

TABLE 9-continued

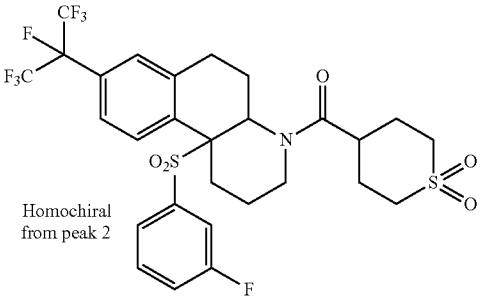
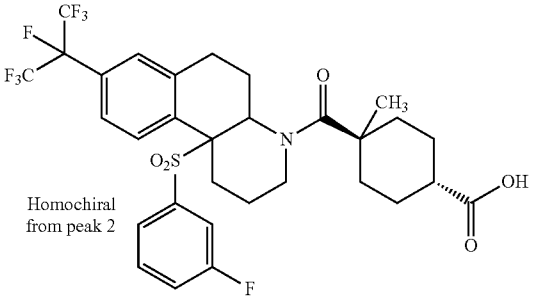
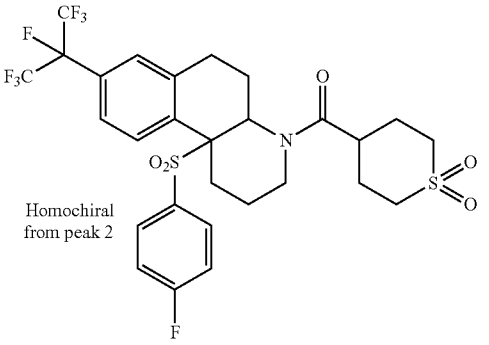
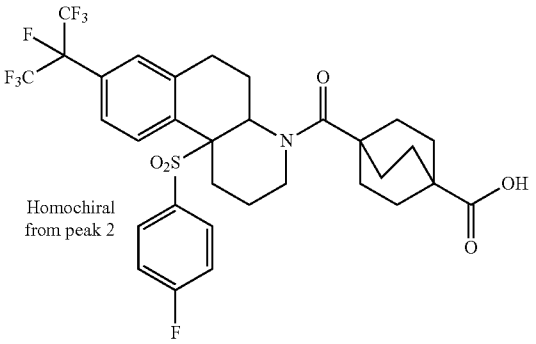
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
308		674.4 $(M + H)^+$	1.04	B
309		682.2 $(M + H)^+$	1.30	B
310		674.1 $(M + H)^+$	2.20	C
311		694.1 $(M + H)^+$	2.38	C

TABLE 9-continued

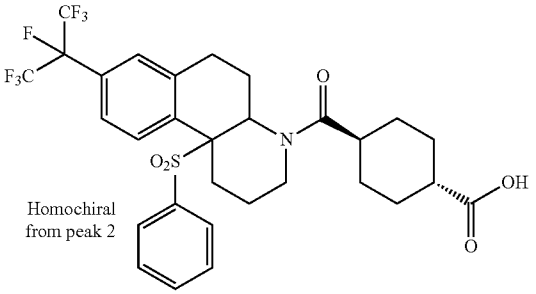
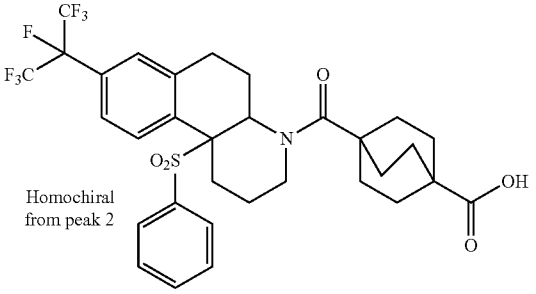
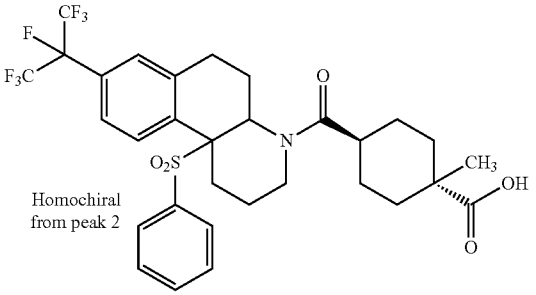
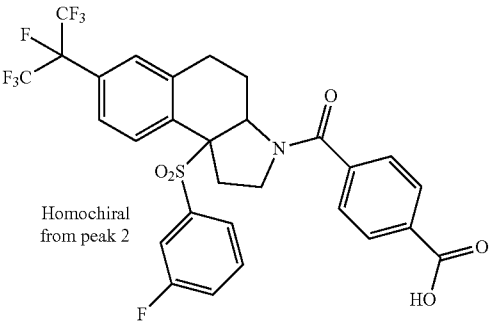
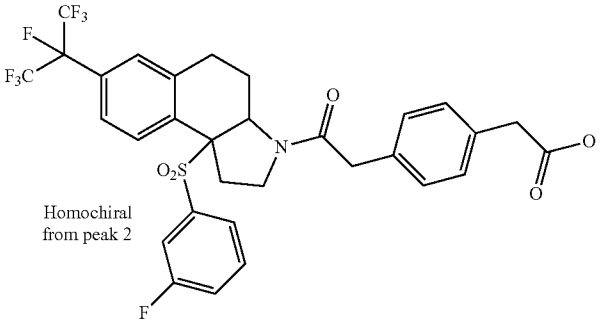
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
312		650.3 $(M + H)^+$	2.24	C
313		676.4 $(M + H)^+$	2.36	C
314		664.0 $(M + H)^+$	2.21	C
315		648.1 $(M + H)^+$	1.74	C
316		676.2 $(M + H)^+$	1.83	C

TABLE 9-continued

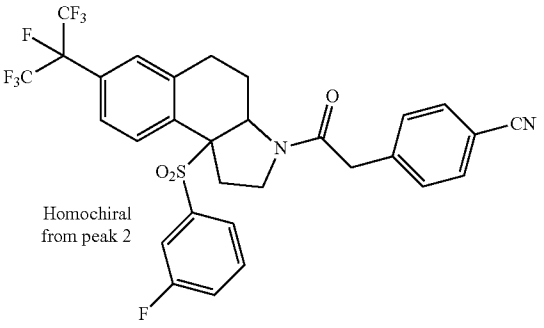
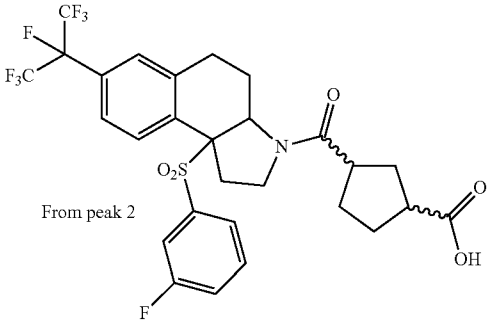
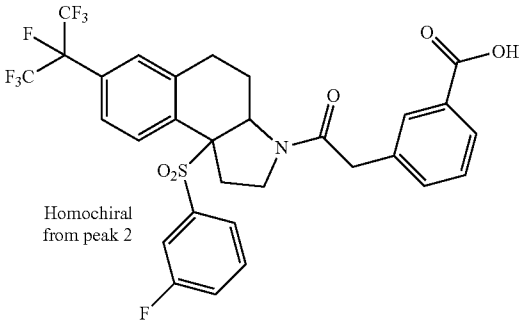
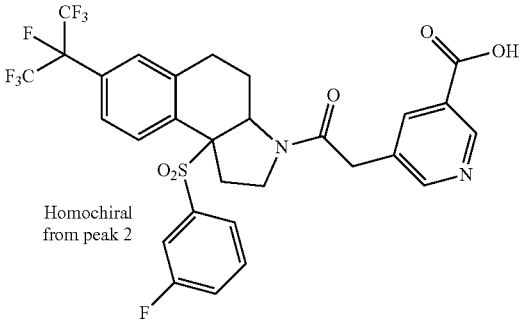
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
317		643.2 (M + H)+	2.34	C
318		640.1 (M + H)+	1.98	C
319		662.4 (M + H)+	1.81	C
320		663.4 (M + H)+	1.69	C

TABLE 9-continued

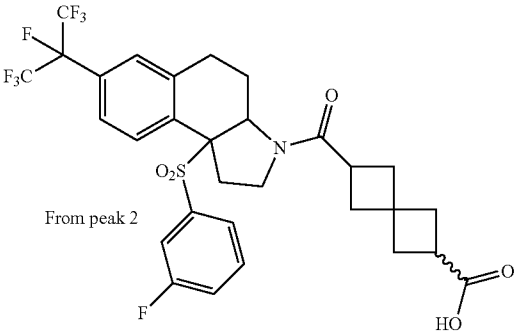
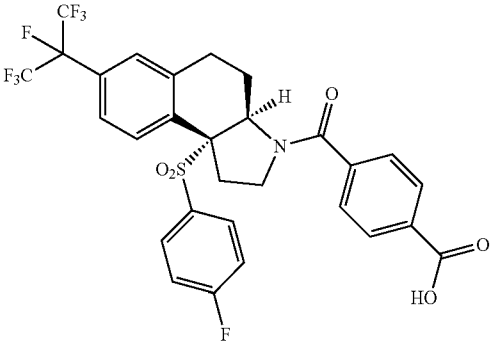
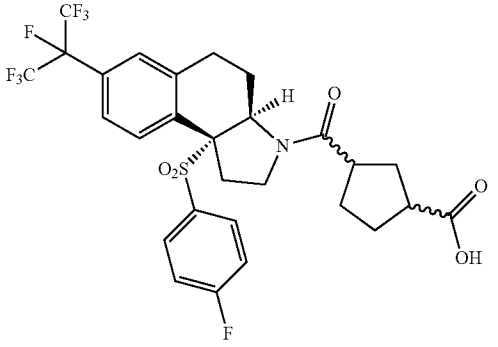
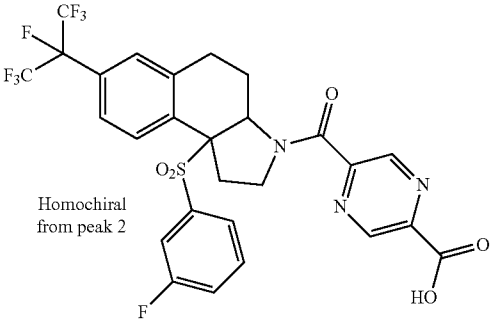
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
321	 From peak 2	666.2 $(M + H)^+$	2.04	C
322		648.1 $(M + H)^+$	2.19	D
323		640.1 $(M + H)^+$	1.84	C
324	 Homochiral from peak 2	650.1 $(M + H)^+$	2.07	D

TABLE 9-continued

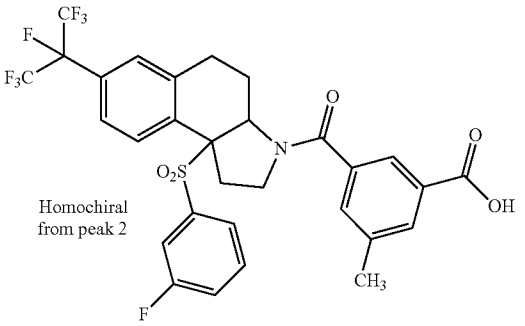
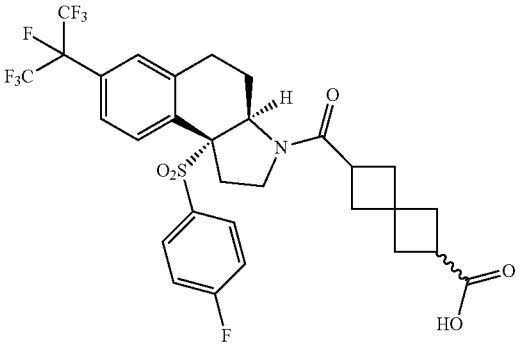
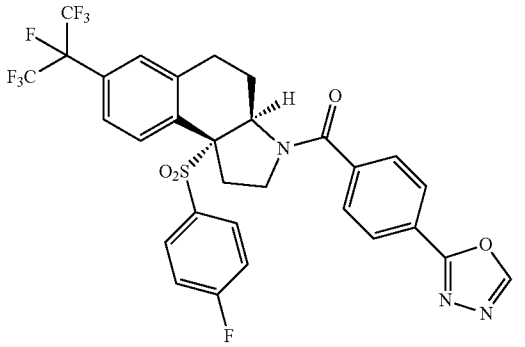
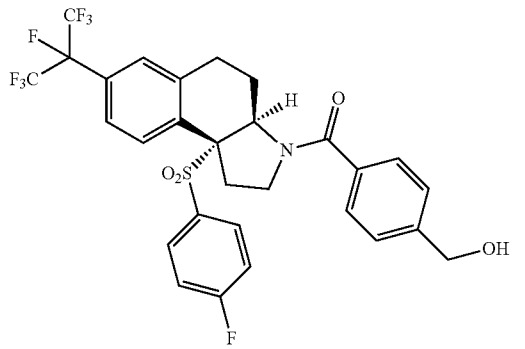
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
325	 Homochiral from peak 2	662.2 $(M + H)^+$	1.81	C
326		666.4 $(M + H)^+$	1.89	C
327		672.2 $(M + H)^+$	2.30	D
328		634.0 $(M + H)^+$	2.15	D

TABLE 9-continued

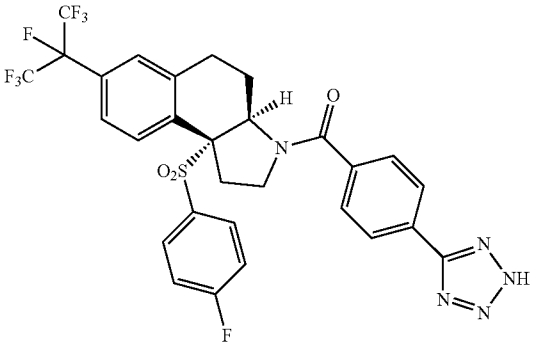
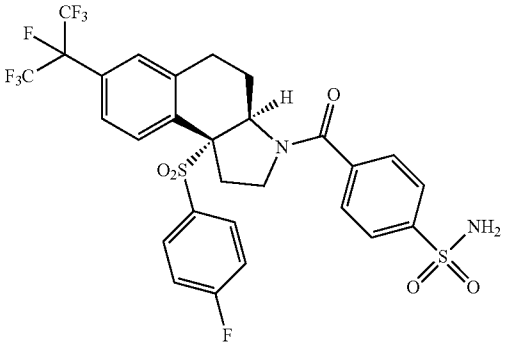
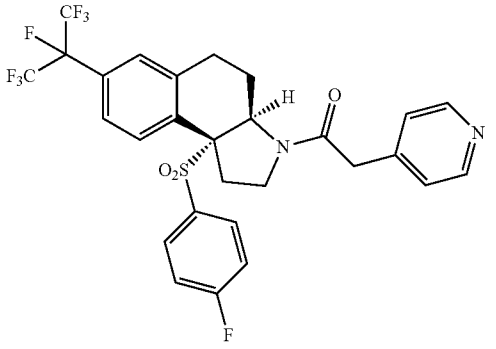
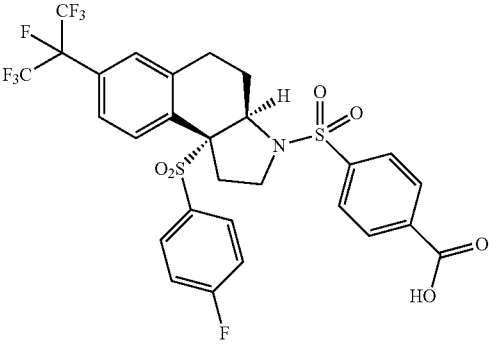
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
329		672.4 $(M + H)^+$	1.81	C
330		682.9 $(M + H)^+$	2.13	D
331		619.2 $(M + H)^+$	1.85	D
332		684.1 $(M + H)^+$	1.82	C

TABLE 9-continued

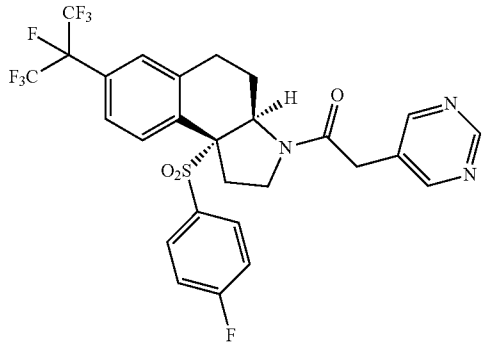
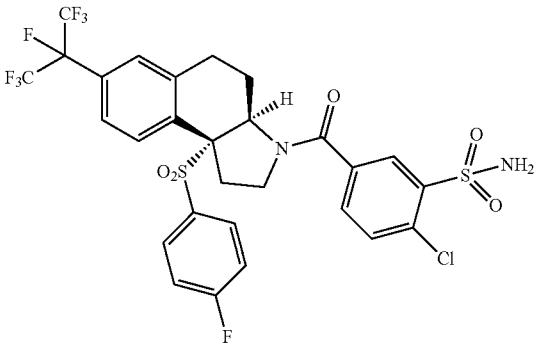
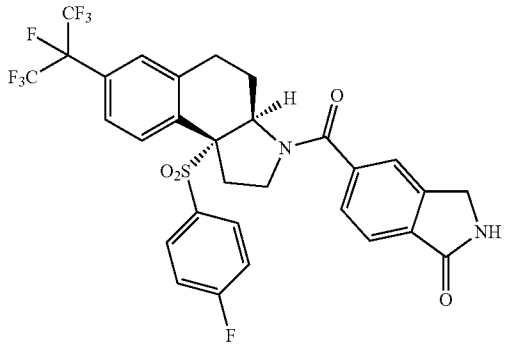
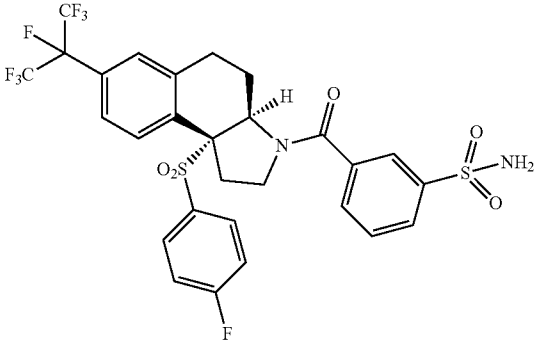
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
333		620.1 $(M + H)^+$	2.07	C
334		716.9 $(M + H)^+$	2.24	C
335		659.1 $(M + H)^+$	2.07	C
336		683.3 $(M + H)^+$	2.17	C

TABLE 9-continued

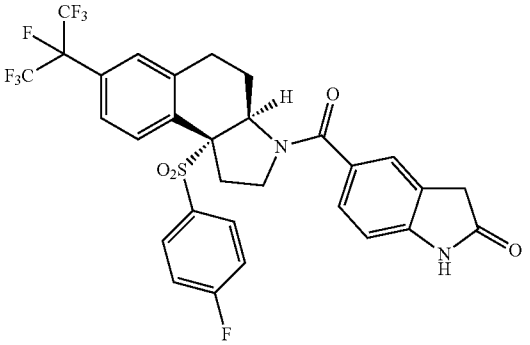
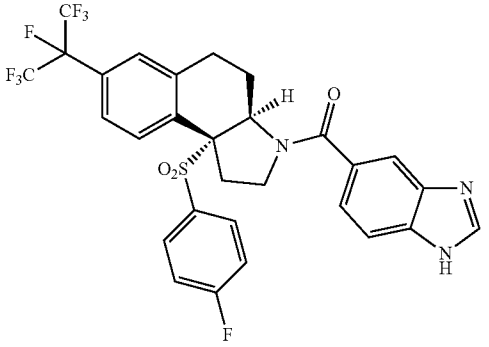
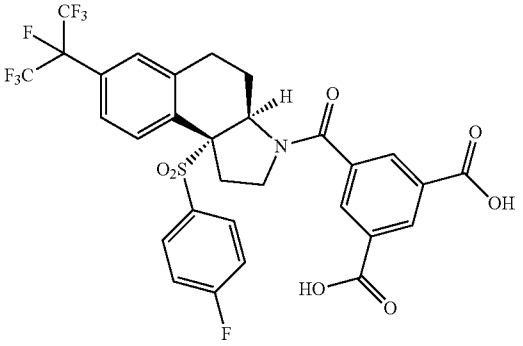
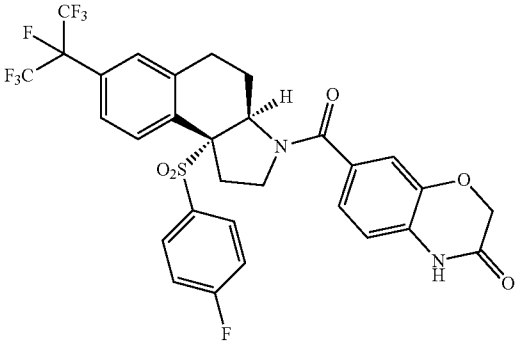
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
337		659.0 $(M + H)^+$	2.08	D
338		644.1 $(M + H)^+$	1.86	D
339		692.2 $(M + H)^+$	1.44	C
340		675.3 $(M + H)^+$	2.19	C

TABLE 9-continued

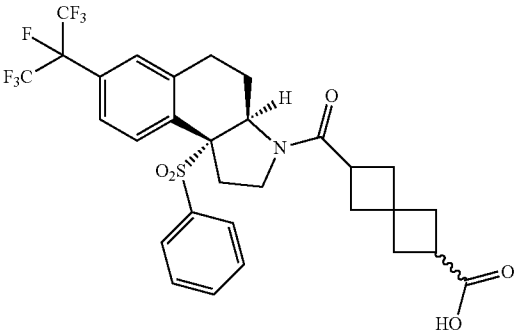
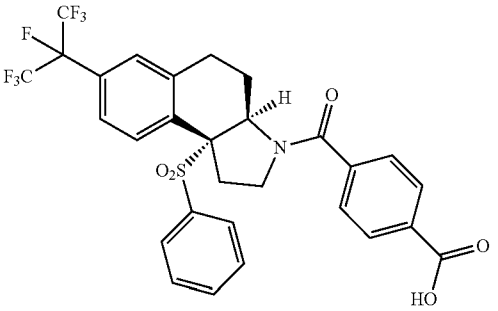
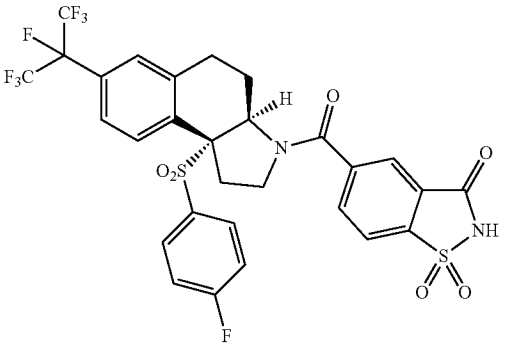
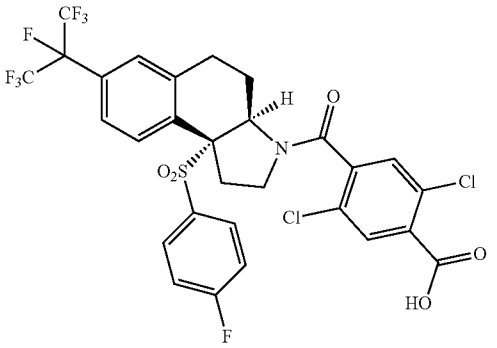
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
341		648.1 $(M + H)^+$	1.81	C
342		630.3 $(M + H)^+$	1.72	C
343		709.3 $(M + H)^+$	2.13	D
344		716.3 $(M + H)^+$	1.83	C

TABLE 9-continued

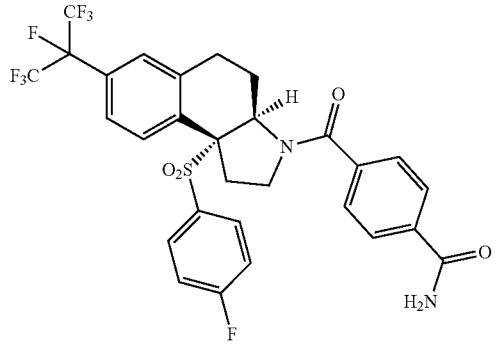
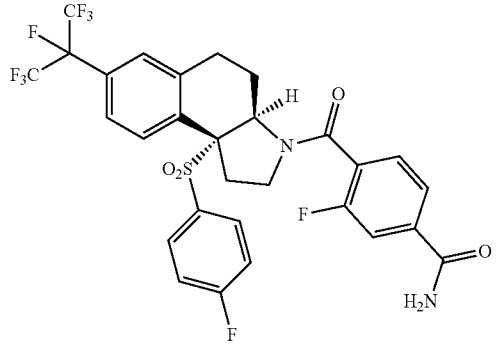
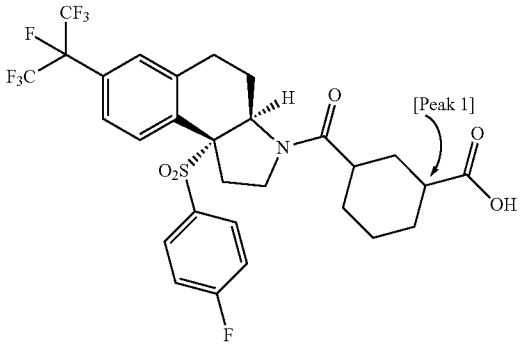
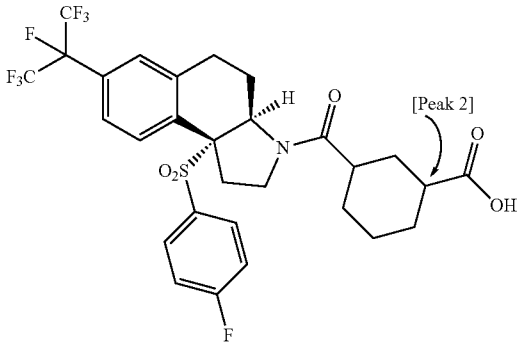
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
345		647.1 $(M + H)^+$	2.08	C
346		665.1 $(M + H)^+$	2.14	C
347		654.1 $(M + H)^+$	2.17	D
348		654.4 $(M + H)^+$	2.16	D

TABLE 9-continued

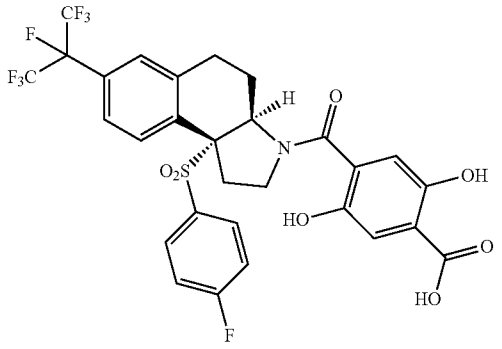
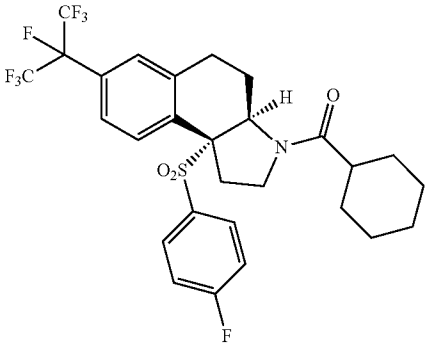
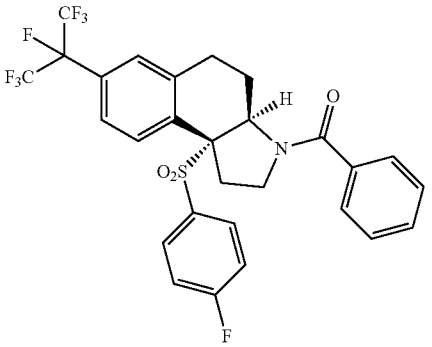
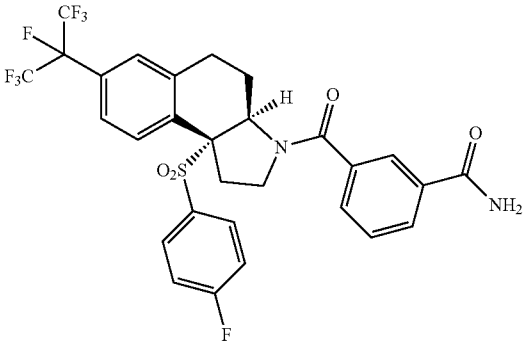
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
349		680.1 $(M + H)^+$	1.79	C
350		610.3 $(M + H)^+$	2.59	D
351		604.2 $(M + H)^+$	2.39	C
352		647.3 $(M + H)^+$	2.03	C

TABLE 9-continued

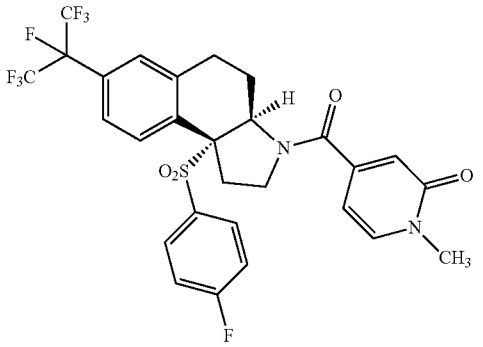
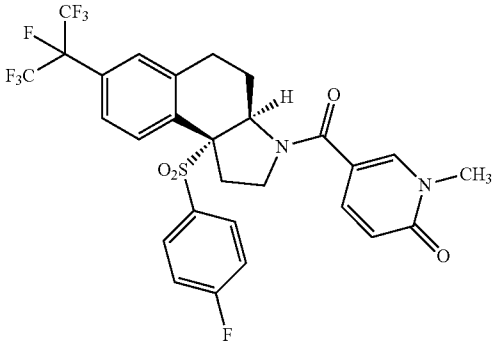
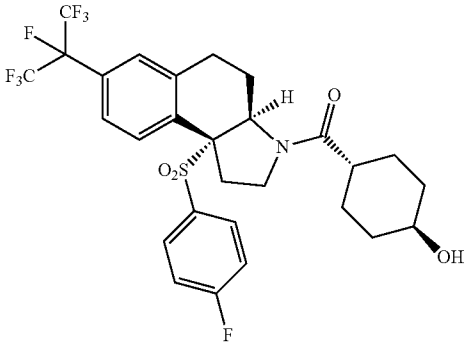
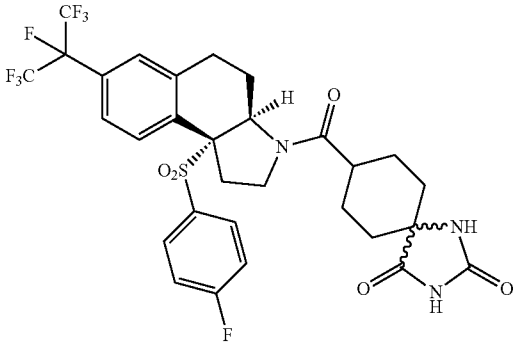
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
353		635.2 $(M + H)^+$	2.13	D
354		635.1 $(M + H)^+$	2.19	D
355		626.2 $(M + H)^+$	2.24	C
356		694.1 $(M + H)^+$	2.12	D

TABLE 9-continued

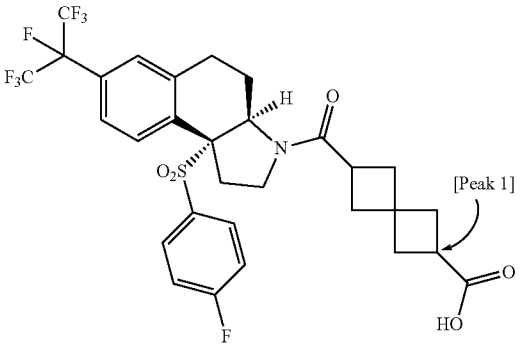
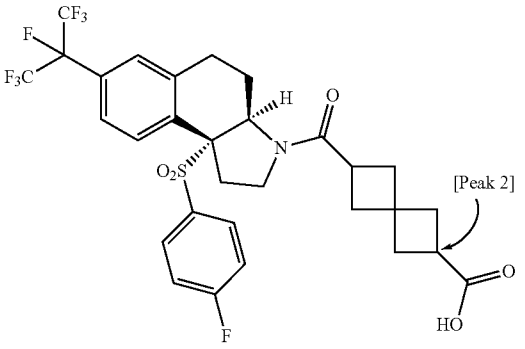
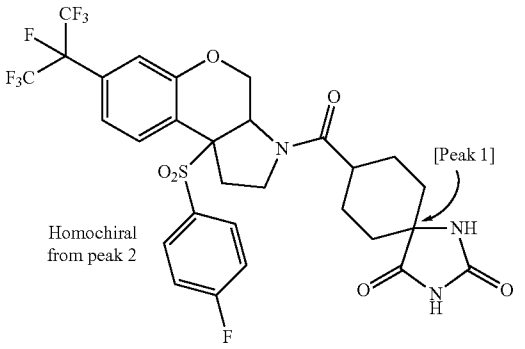
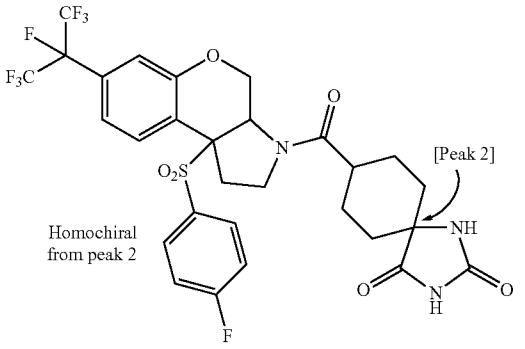
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
357		666.2 $(M + H)^+$	1.05	B
358		666.2 $(M + H)^+$	1.05	B
359		696.0 $(M + H)^+$	2.10	C
360		696.3 $(M + H)^+$	2.12	C

TABLE 9-continued

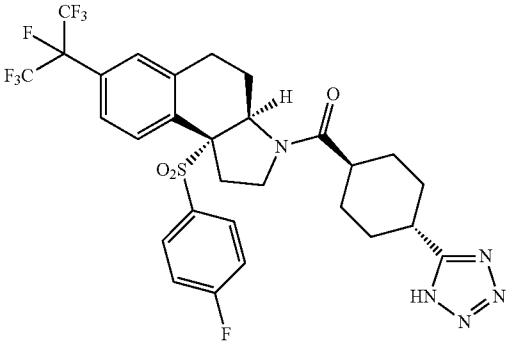
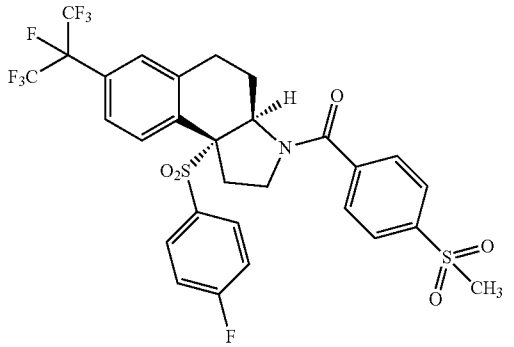
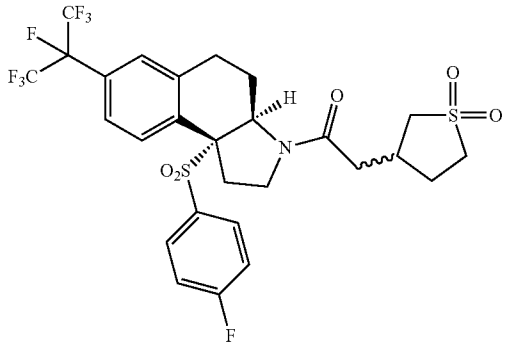
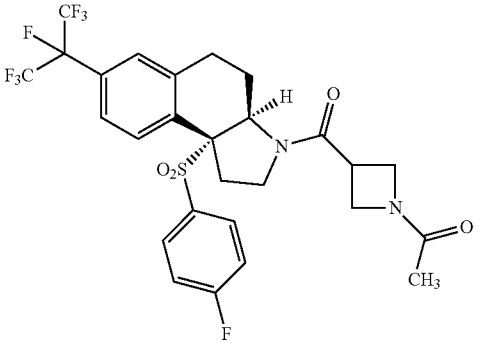
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
361		678.3 $(M + H)^+$	2.18	D
362		682.2 $(M + H)^+$	2.29	C
363		660.0 $(M + H)^+$	2.19	C
364		624.9 $(M + H)^+$	2.07	C

TABLE 9-continued

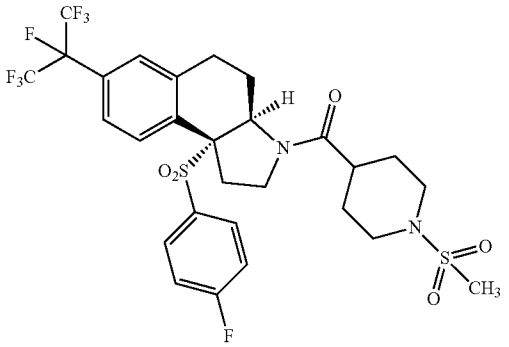
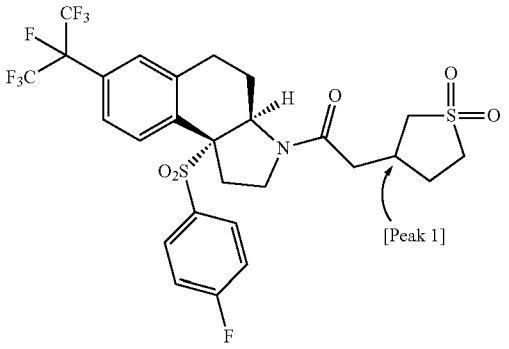
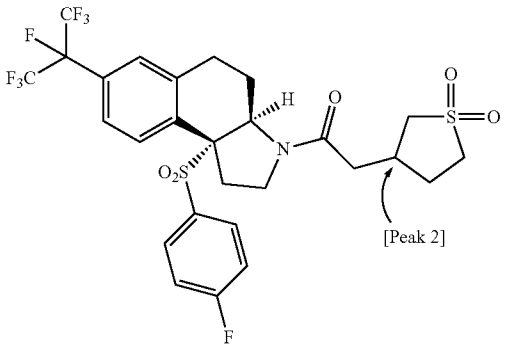
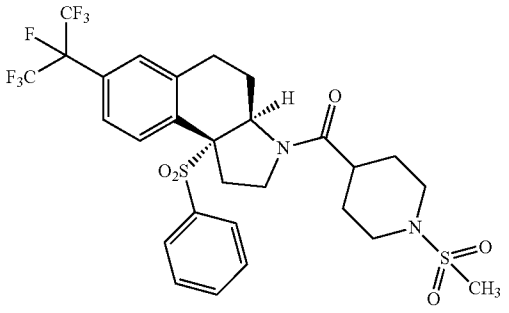
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
365		689.2 $(M + H)^+$	2.18	C
366		660.2 $(M + H)^+$	1.02	B
367		660.2 $(M + H)^+$	1.02	B
368		671.2 $(M + H)^+$	2.13	C

TABLE 9-continued

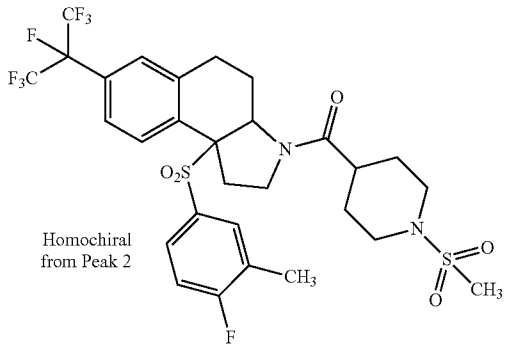
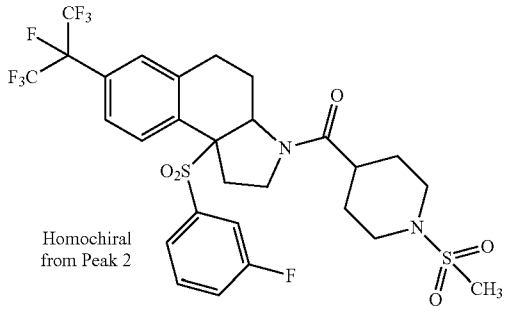
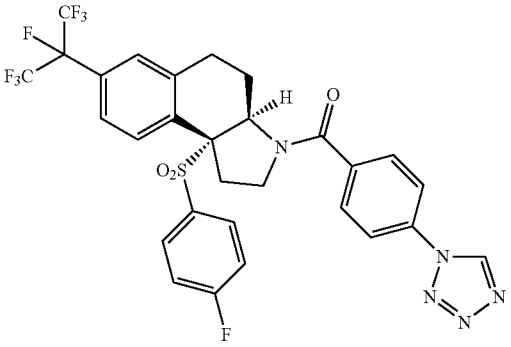
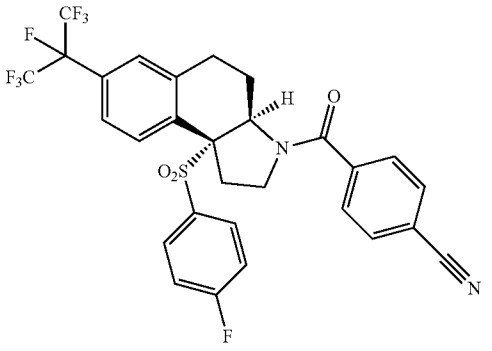
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
369	 Homochiral from Peak 2	703.2 $(M + H)^+$	2.26	D
370	 Homochiral from Peak 2	689.2 $(M + H)^+$	2.25	C
371		672.0 $(M + H)^+$	2.23	D
372		629.2 $(M + H)^+$	2.40	C

TABLE 9-continued

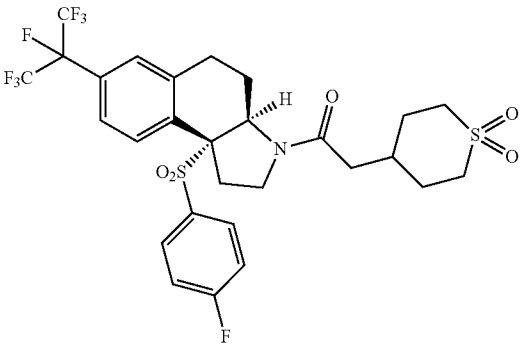
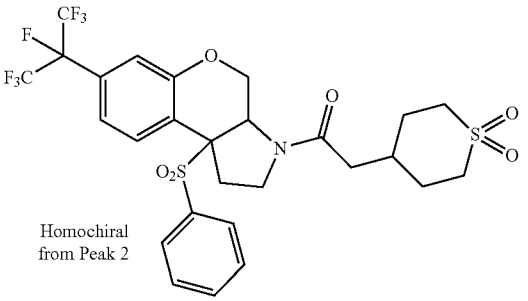
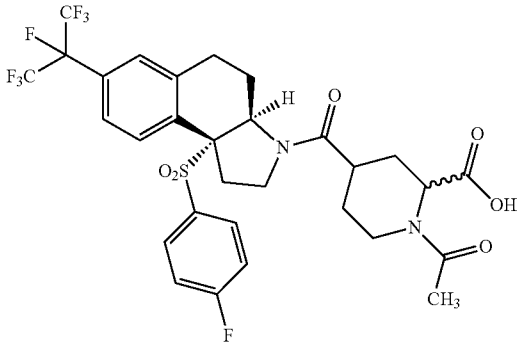
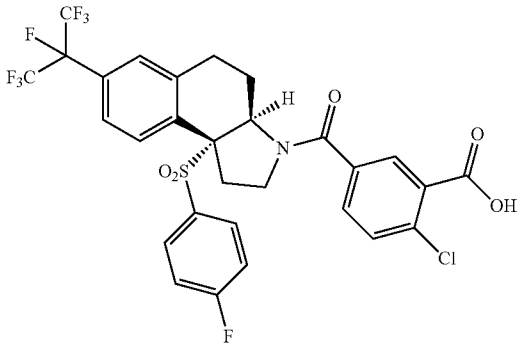
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
373		674.3 $(M + H)^+$	2.19	C
374	 Homochiral from Peak 2	658.0 $(M + H)^+$	2.14	D
375		697.2 $(M + H)^+$	1.71	C
376		682.2 $(M + H)^+$	2.34	D

TABLE 9-continued

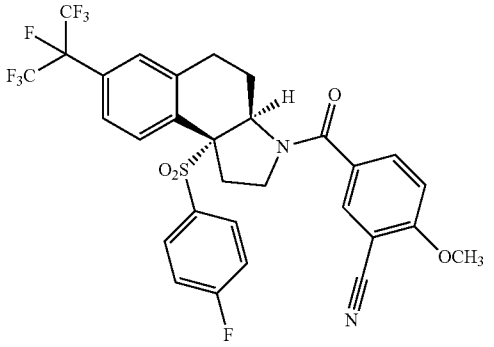
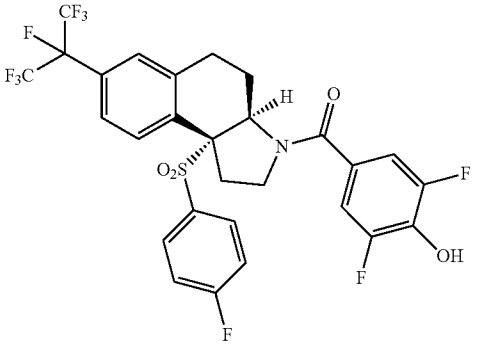
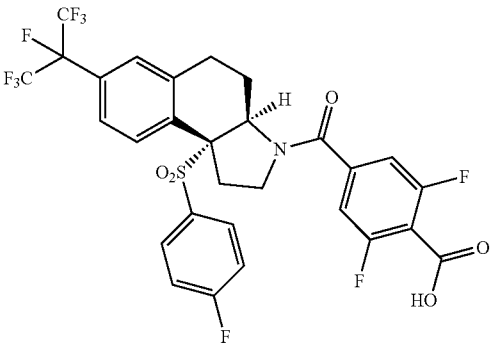
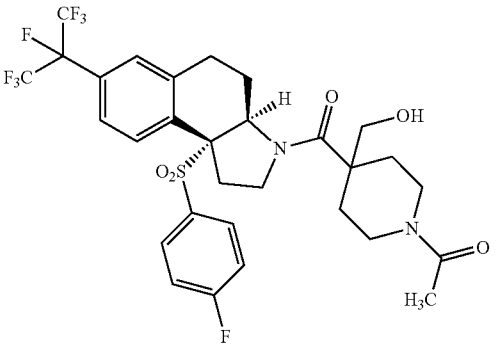
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
377		659.2 $(M + H)^+$	2.32	C
378		656.0 $(M + H)^+$	2.20	C
379		684.2 $(M + H)^+$	2.24	D
380		683.1 $(M + H)^+$	2.00	D

TABLE 9-continued

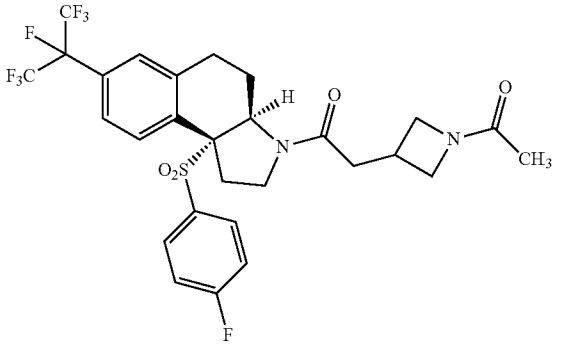
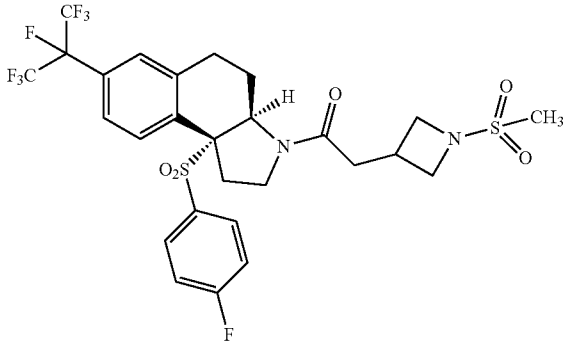
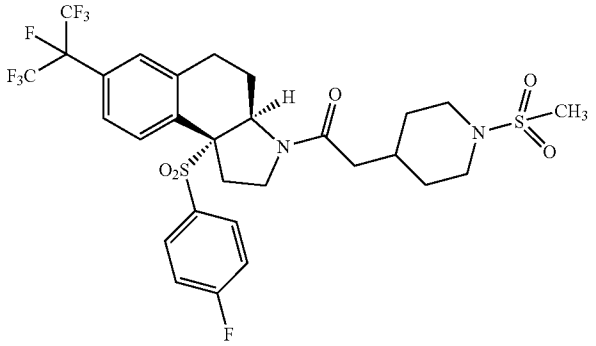
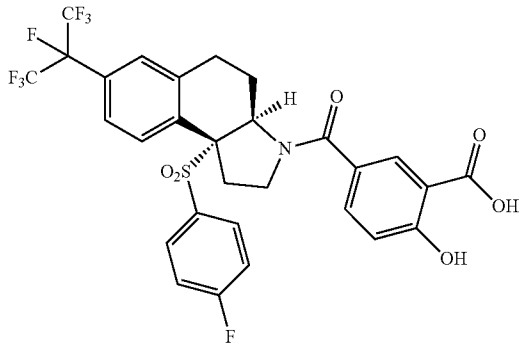
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
381		639.2 $(M + H)^+$	2.09	C
382		675.0 $(M + H)^+$	2.19	D
383		702.8 $(M + H)^+$	2.28	C
384		664.0 $(M + H)^+$	1.80	C

TABLE 9-continued

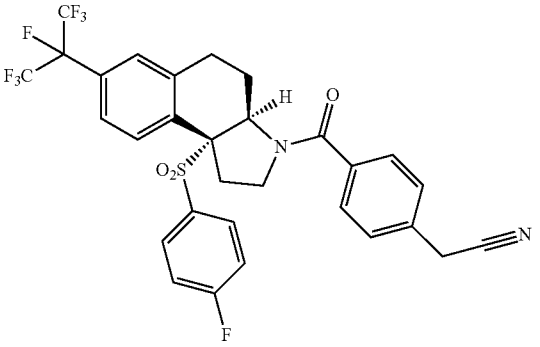
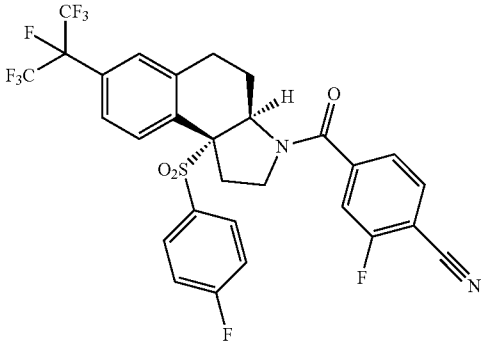
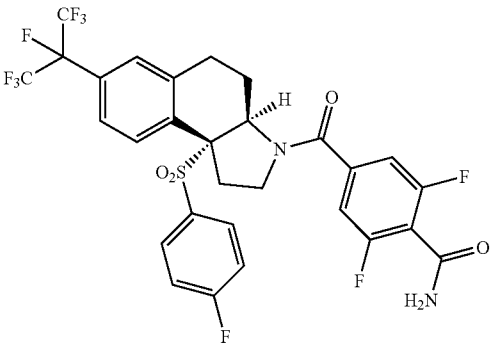
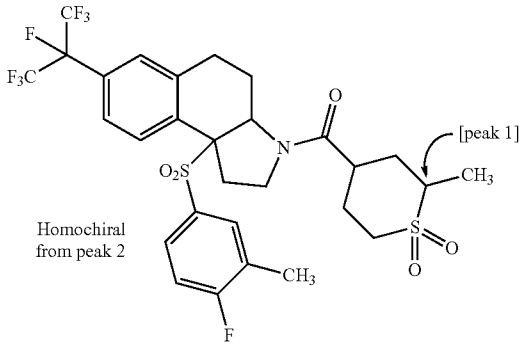
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
385		643.2 $(M + H)^+$	2.33	D
386		647.1 $(M + H)^+$	1.15	B
387		683.1 $(M + H)^+$	2.14	D
388		676.0 $(M + H)^+$	1.05	B

TABLE 9-continued

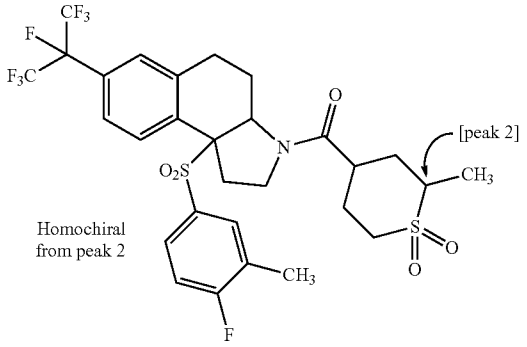
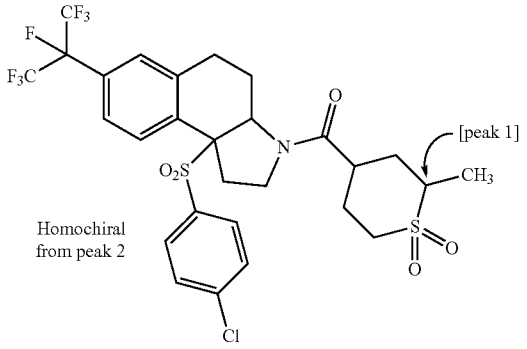
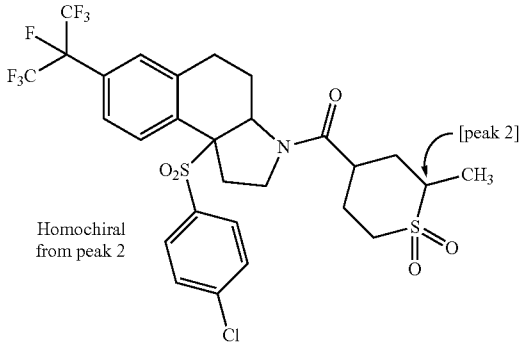
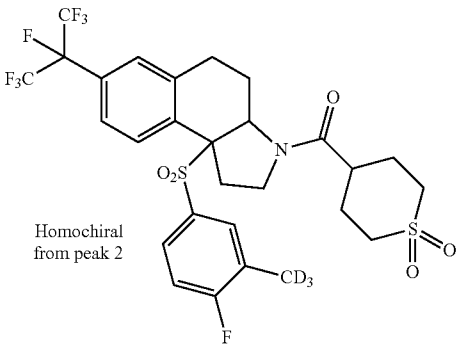
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
389		676.1 $(M + H)^+$	1.04	B
390		690.0 $(M + H)^+$	1.07	B
391		690.0 $(M + H)^+$	1.07	B
392		677.1 $(M + H)^+$	2.19	C

TABLE 9-continued

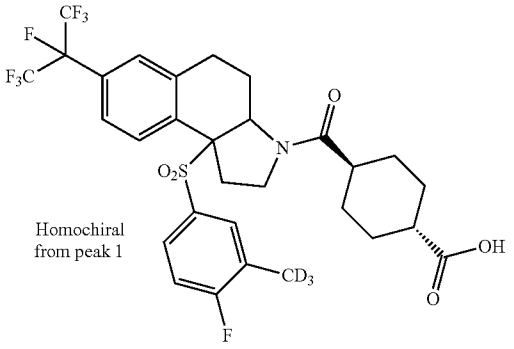
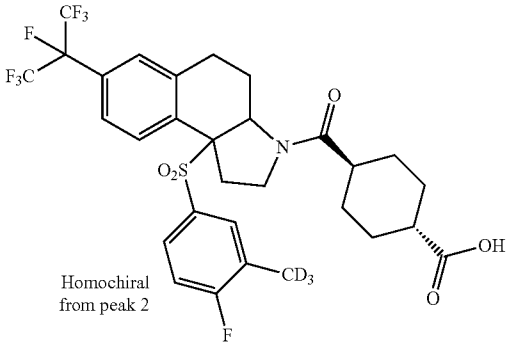
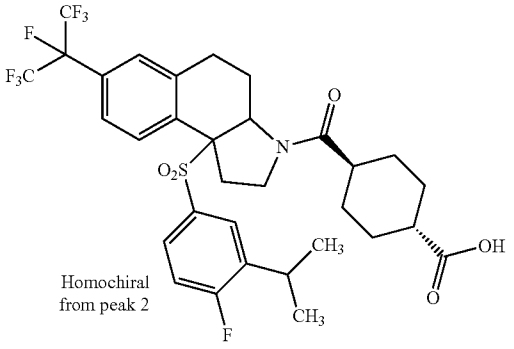
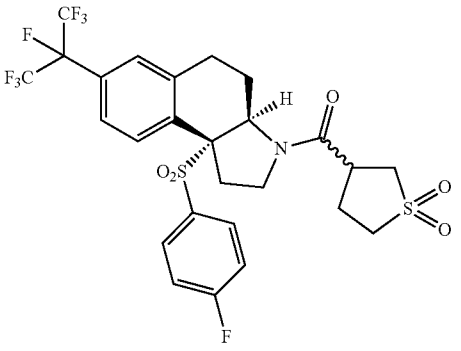
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
393		671.2 $(M + H)^+$	2.01	C
394		671.2 $(M + H)^+$	2.01	C
395		696.1 $(M + H)^+$	2.25	C
396		646.0 $(M + H)^+$	2.18	C

TABLE 9-continued

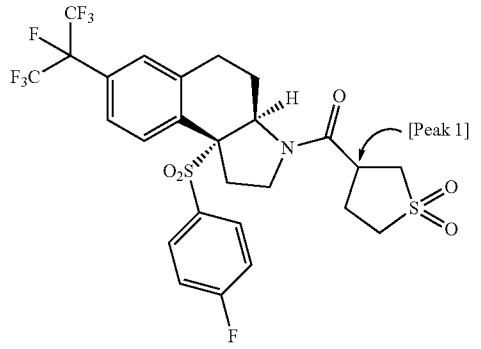
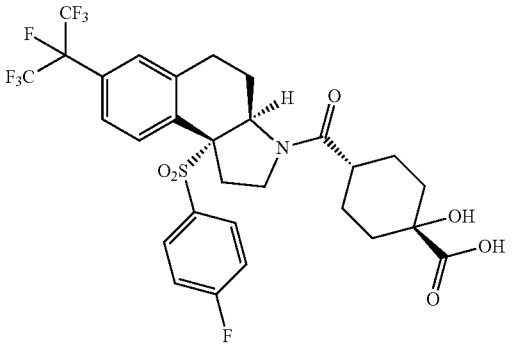
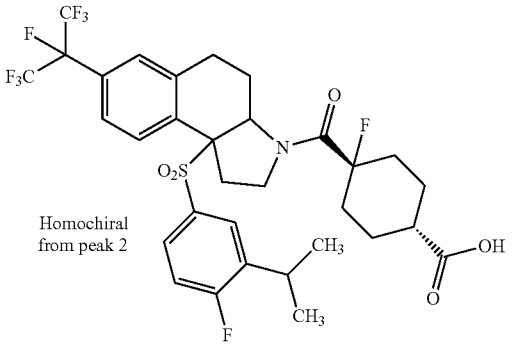
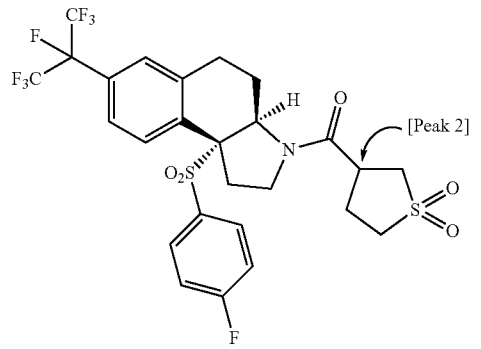
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
397		646.0 $(M + H)^+$	2.17	C
398		669.9 $(M + H)^+$	1.75	C
399		714.1 $(M + H)^+$	2.25	C
400		646.3 $(M + H)^+$	2.15	C

TABLE 9-continued

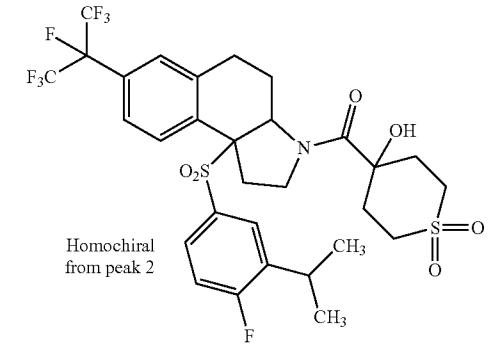
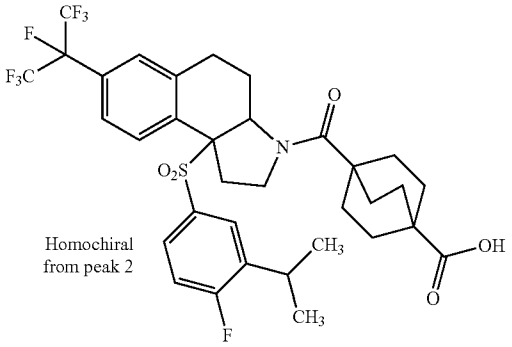
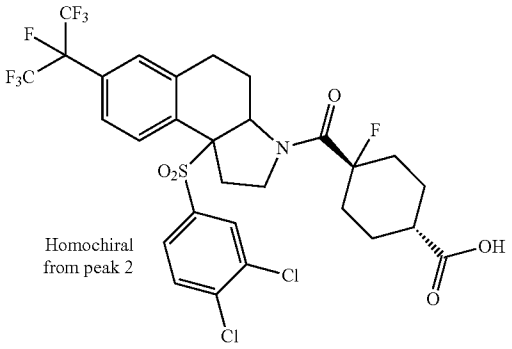
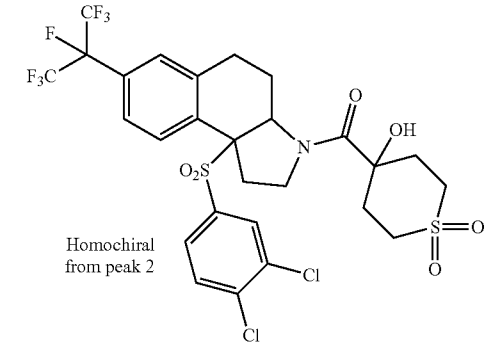
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
401		718.3 $(M + H)^+$	2.35	D
402		722.1 $(M + H)^+$	2.28	C
403		722.2 $(M + H)^+$	2.19	C
404		725.4 $(M + H)^+$	2.34	D

TABLE 9-continued

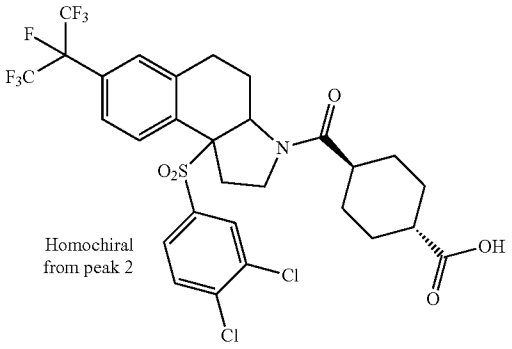
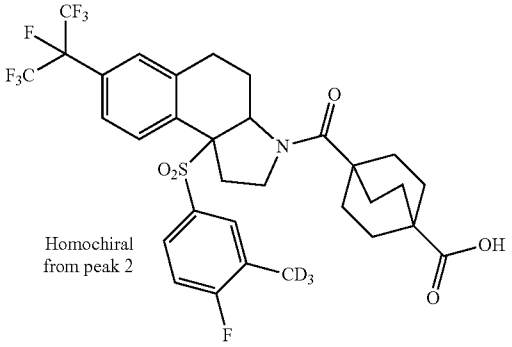
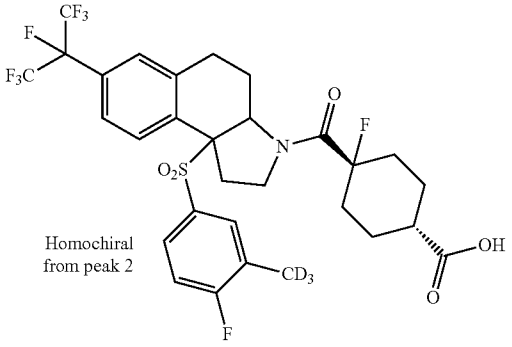
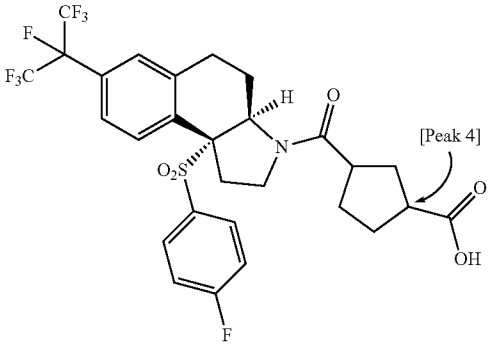
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
405		704.0 $(M + H)^+$	2.11	C
406		697.1 $(M + H)^+$	2.24	C
407		688.8 $(M + H)^+$	2.21	C
408		640.1 $(M + H)^+$	1.04	B

TABLE 9-continued

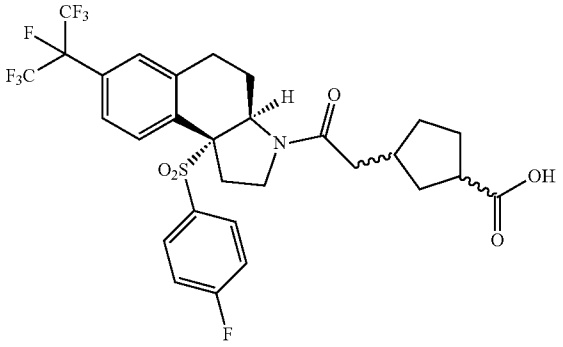
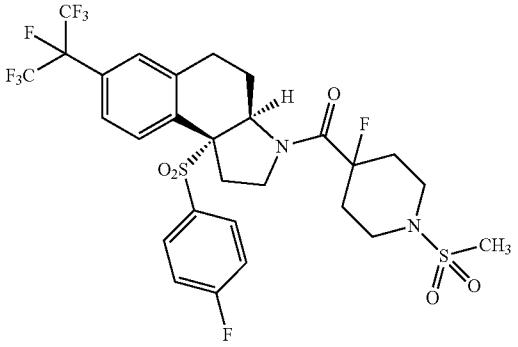
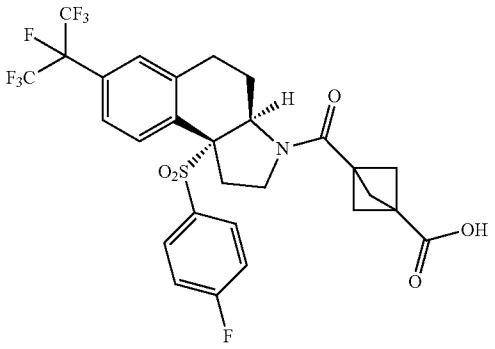
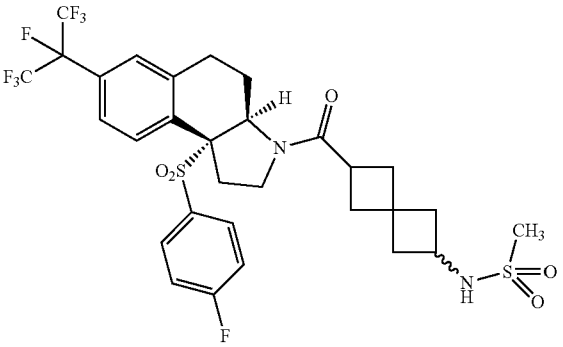
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
409		654.3 $(M + H)^+$	1.93	C
410		707.3 $(M + H)^+$	2.34	C
411		637.9 $(M + H)^+$	1.84	C
412		715.3 $(M + H)^+$	2.24	C

TABLE 9-continued

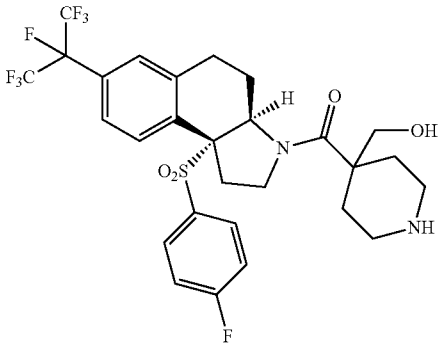
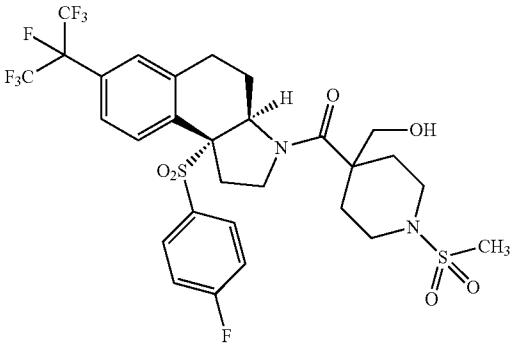
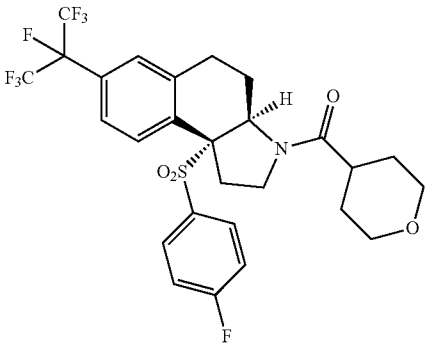
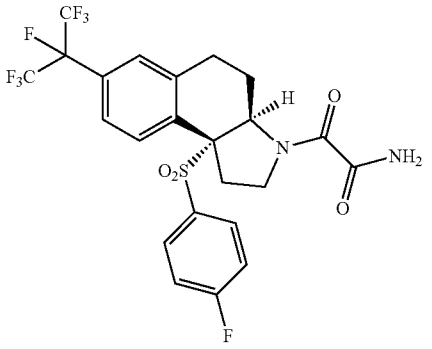
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
413		641.2 $(M + H)^+$	1.76	C
414		719.1 $(M + H)^+$	2.11	C
415		611.9 $(M + H)^+$	2.24	C
416		571.2 $(M + H)^+$	2.04	C

TABLE 9-continued

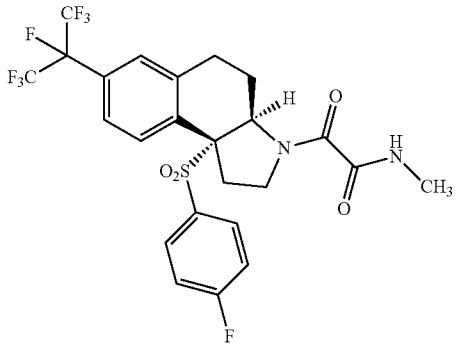
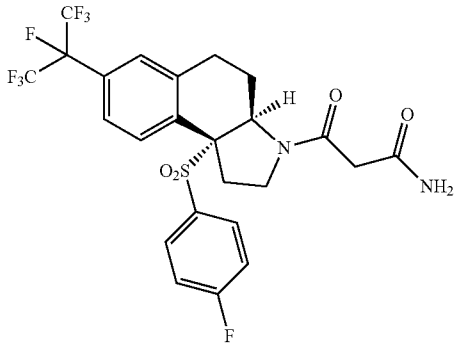
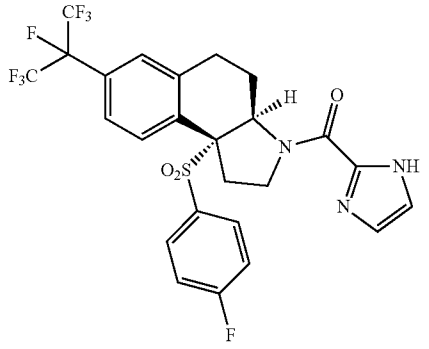
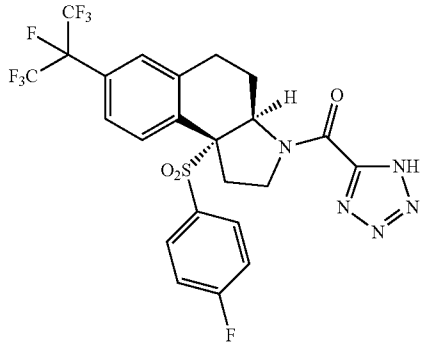
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
417		585.1 $(M + H)^+$	2.19	C
418		585.3 $(M + H)^+$	2.04	C
419		594.0 $(M + H)^+$	2.21	C
420		596.3 $(M + H)^+$	1.73	C

TABLE 9-continued

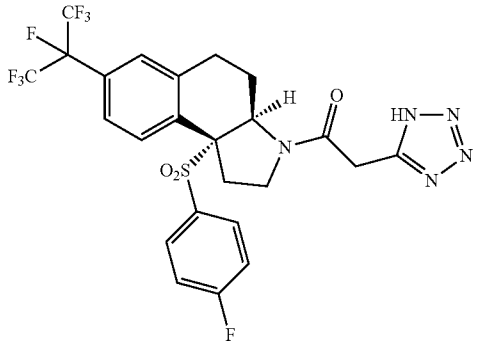
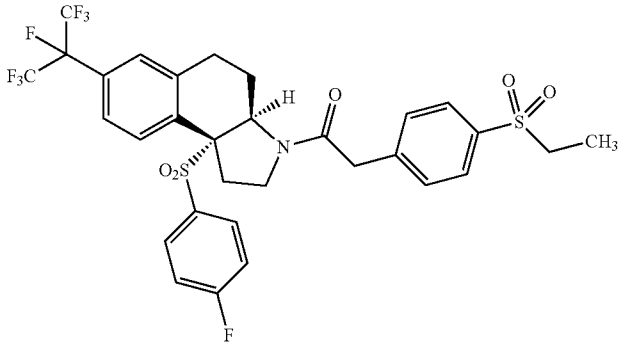
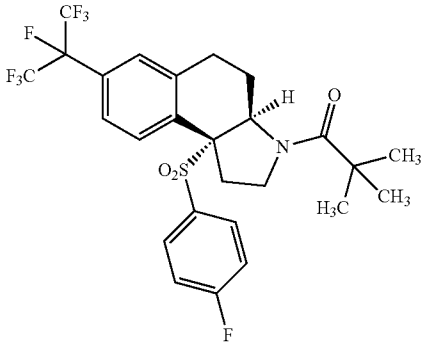
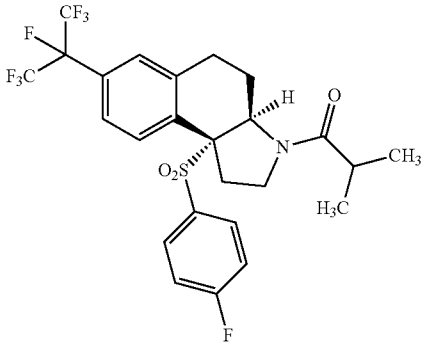
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
421		608.1 $(M + H)^+$	1.81	C
422		711.0 $(M + H)^+$	2.30	C
423		584.3 $(M + H)^+$	2.47	C
424		570.3 $(M + H)^+$	2.32	C

TABLE 9-continued

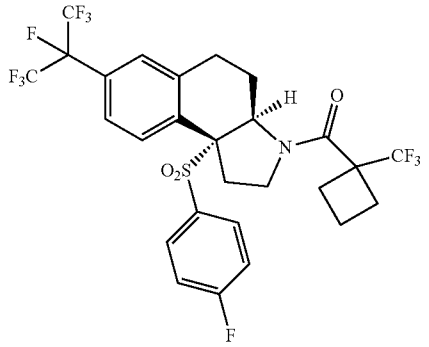
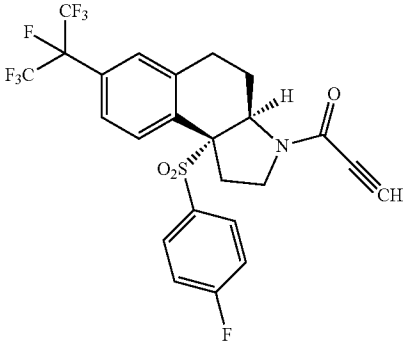
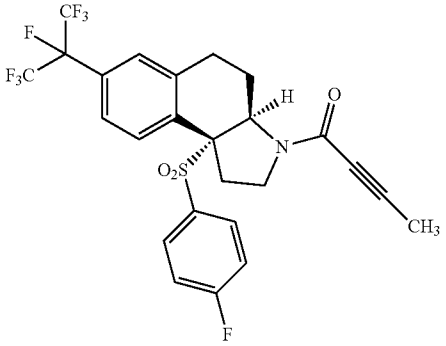
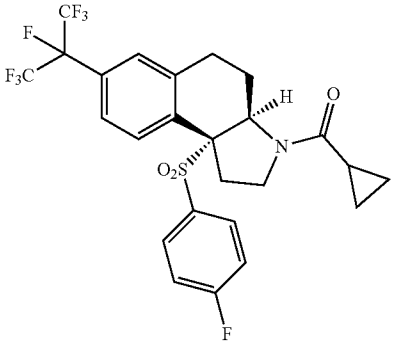
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
425		649.8 $(M + H)^+$	2.51	C
426		552.1 $(M + H)^+$	2.30	C
427		566.3 $(M + H)^+$	2.35	C
428		568.2 $(M + H)^+$	2.33	C

TABLE 9-continued

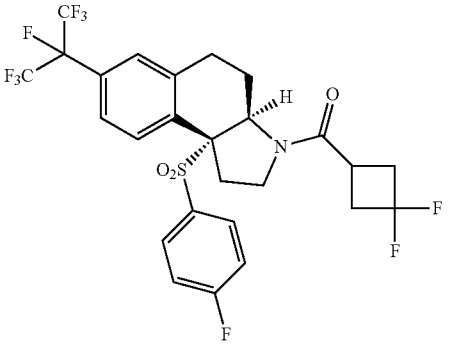
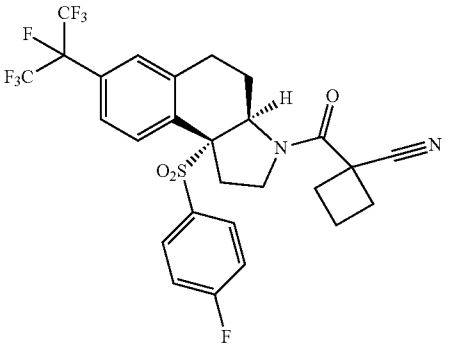
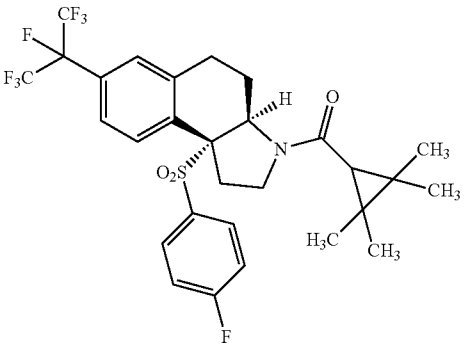
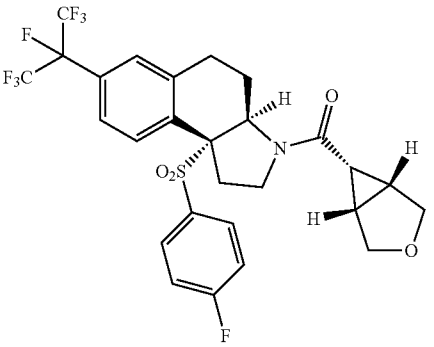
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
429		618.2 $(M + H)^+$	2.46	C
430		607.3 $(M + H)^+$	2.48	C
431		624.4 $(M + H)^+$	2.77	C
432		610.2 $(M + H)^+$	2.21	C

TABLE 9-continued

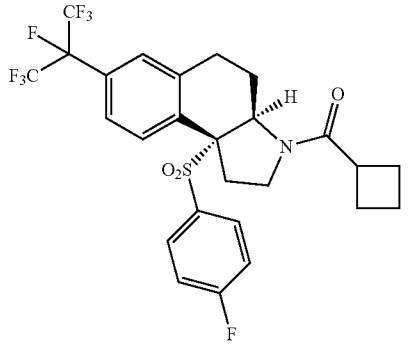
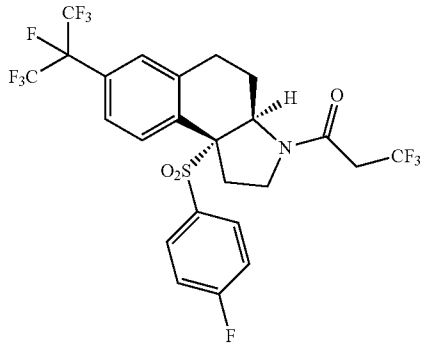
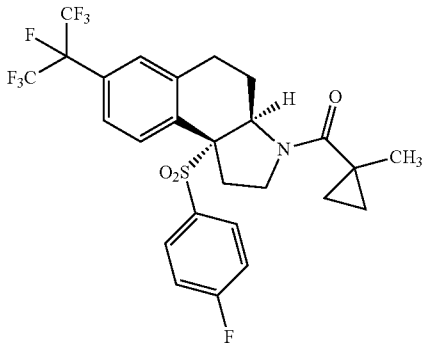
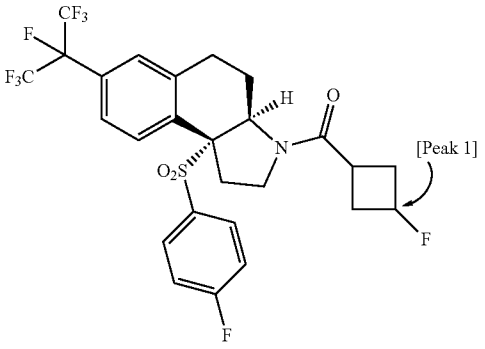
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
433		582.3 $(M + H)^+$	2.46	C
434		610.3 $(M + H)^+$	2.43	C
435		582.1 $(M + H)^+$	2.46	C
436		600.4 $(M + H)^+$	2.30	C

TABLE 9-continued

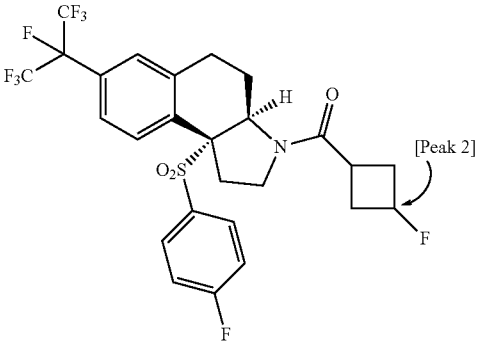
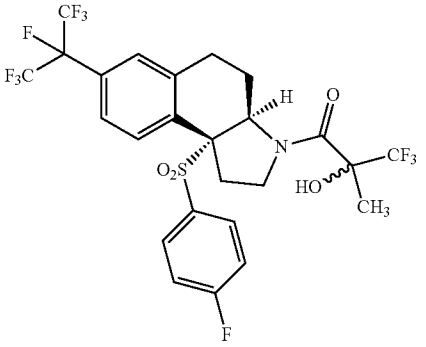
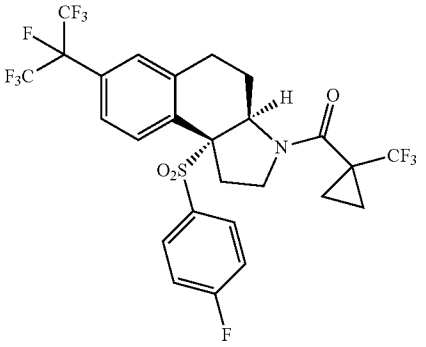
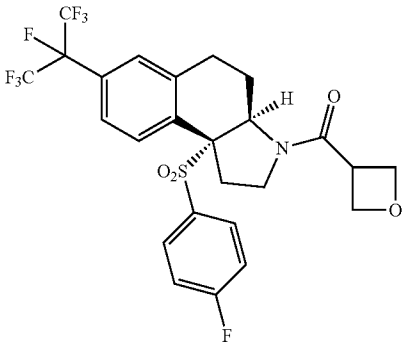
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
437		600.1 $(M + H)^+$	2.34	C
438		638.9 $(M + H)^+$	2.45	C
439		636.0 $(M + H)^+$	2.56	C
440		584.1 $(M + H)^+$	2.24	C

TABLE 9-continued

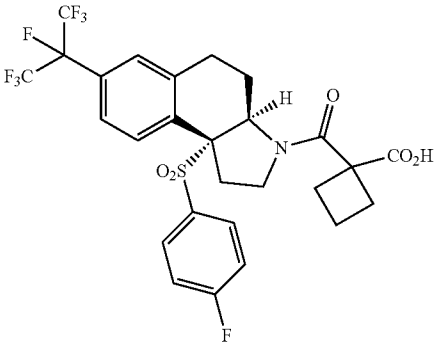
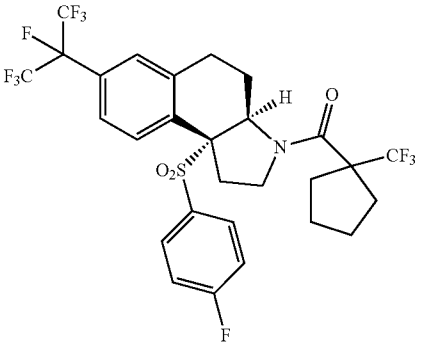
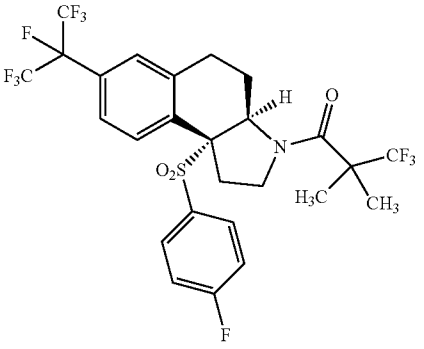
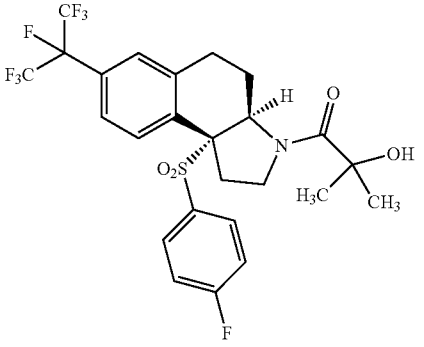
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
441		626.3 $(M + H)^+$	1.77	C
442		664.1 $(M + H)^+$	2.74	C
443		638.2 $(M + H)^+$	2.62	C
444		586.2 $(M + H)^+$	2.25	C

TABLE 9-continued

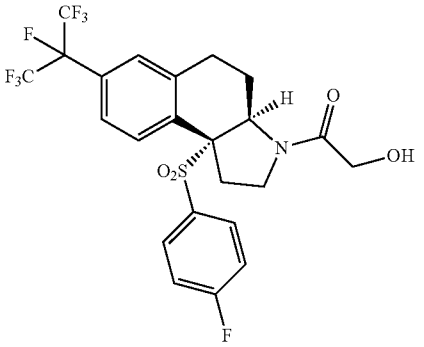
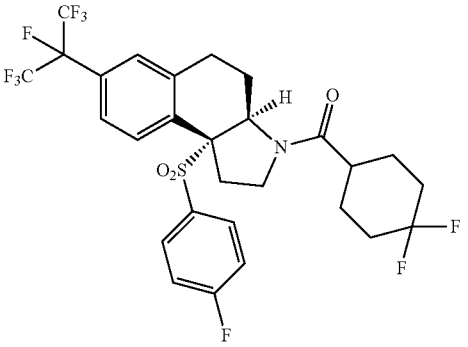
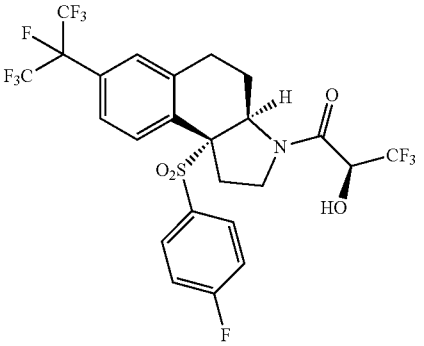
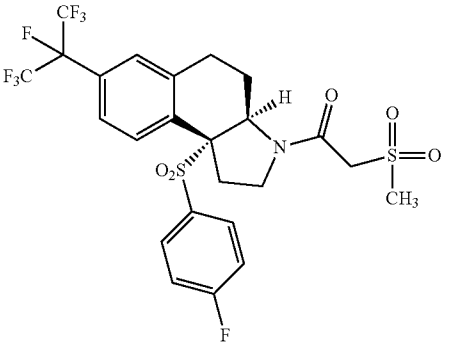
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
445		558.0 $(M + H)^+$	2.11	C
446		646.3 $(M + H)^+$	2.50	C
447		626.1 $(M + H)^+$	2.19	C
448		620.1 $(M + H)^+$	2.12	C

TABLE 9-continued

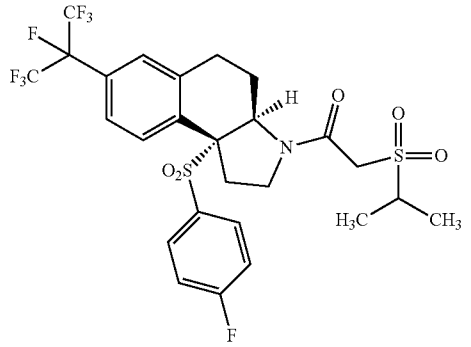
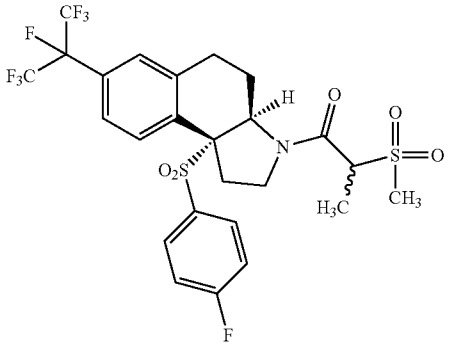
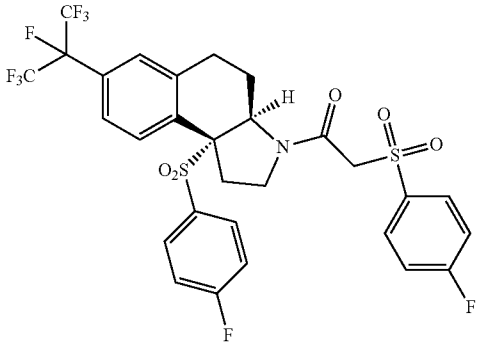
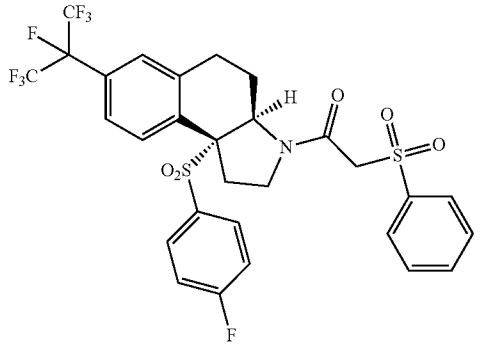
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
449		648.1 $(M + H)^+$	2.24	C
450		634.2 $(M + H)^+$	2.18	C
451		700.0 $(M + H)^+$	2.38	C
452		682.2 $(M + H)^+$	2.42	C

TABLE 9-continued

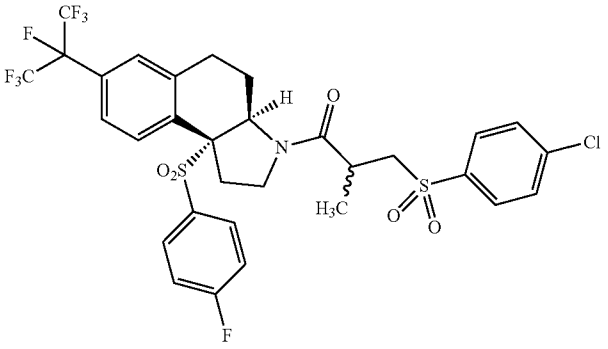
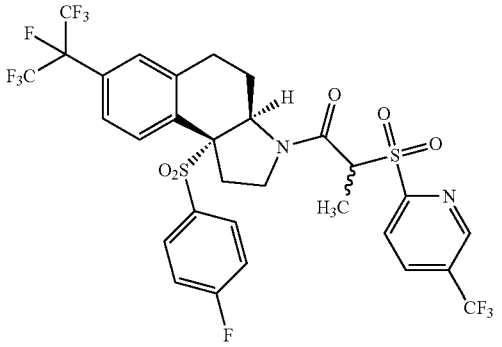
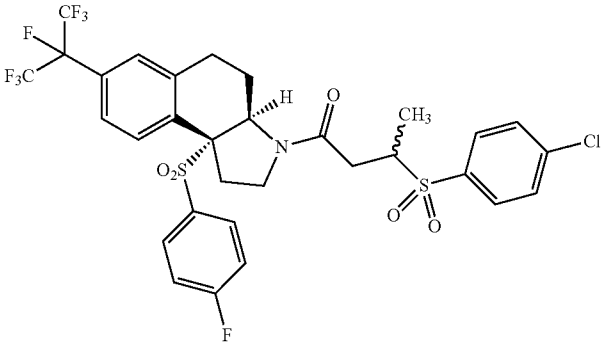
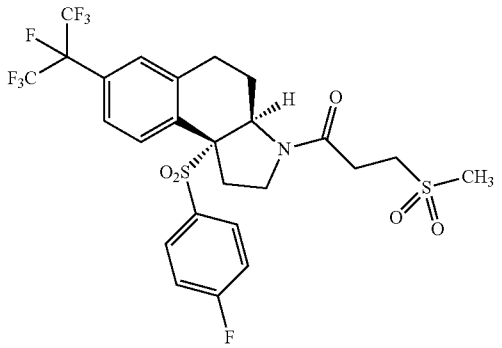
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
453		745.1 $(M + H)^+$	2.55	C
454		765.9 $(M + H)^+$	2.51	C
455		744.1 $(M + H)^+$	2.57	C
456		633.8 $(M + H)^+$	2.13	C

TABLE 9-continued

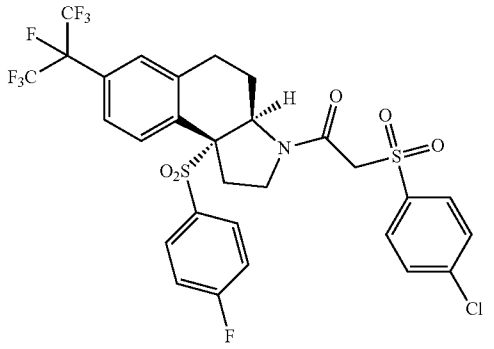
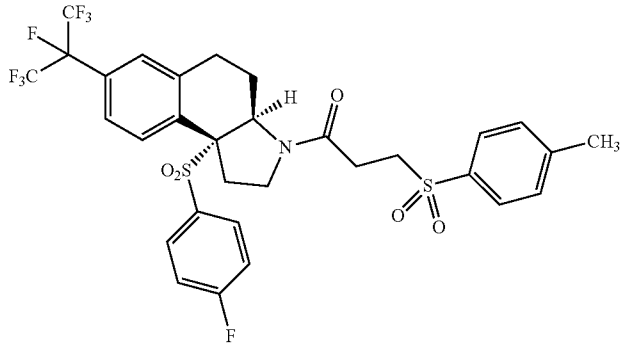
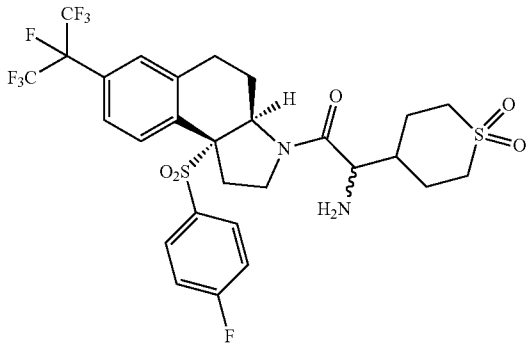
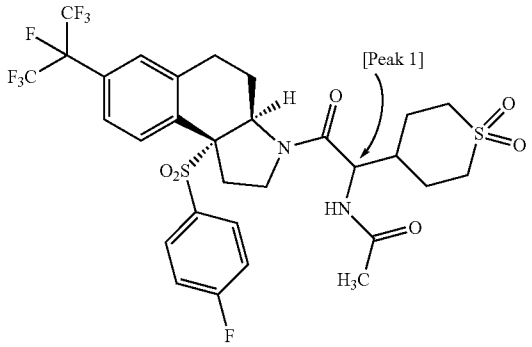
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
457		716.2 $(M + H)^+$	2.51	C
458		710.2 $(M + H)^+$	2.49	C
459		689.1 $(M + H)^+$	1.94	C
460		731.0 $(M + H)^+$	2.00	C

TABLE 9-continued

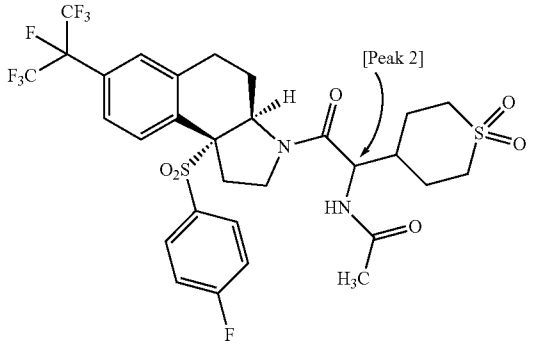
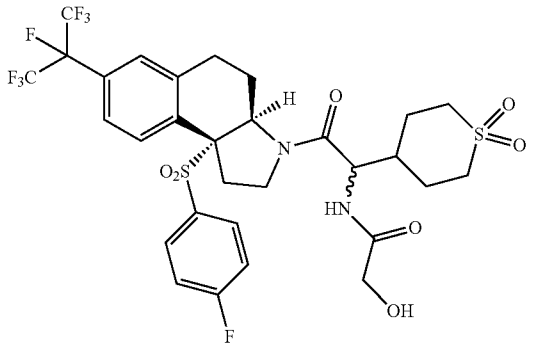
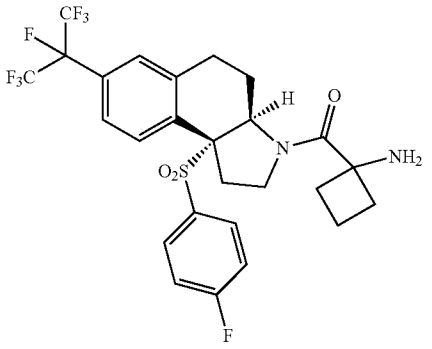
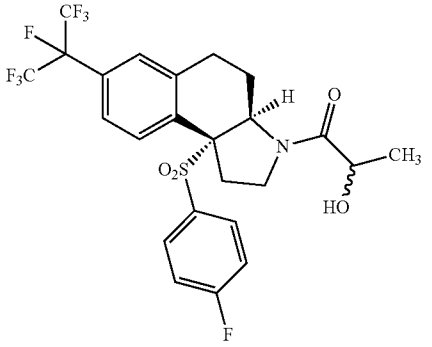
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
461		731.2 $(M + H)^+$	2.07	C
462		747.0 $(M + H)^+$	1.91	C
463		597.2 $(M + H)^+$	2.15	C
464		572.0 $(M + H)^+$	2.16	C

TABLE 9-continued

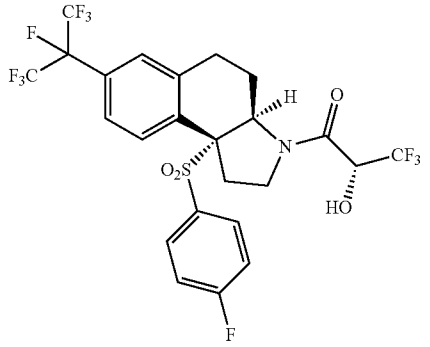
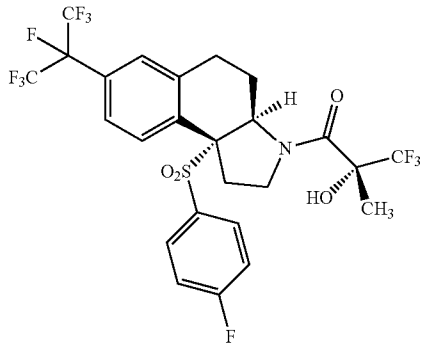
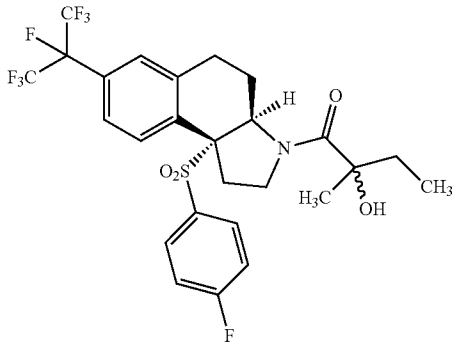
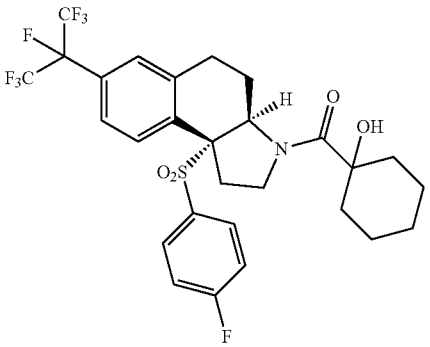
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
465		626.1 $(M + H)^+$	2.38	C
466		640.0 $(M + H)^+$	2.40	C
467		600.2 $(M + H)^+$	2.30	C
468		625.9 $(M + H)^+$	2.47	C

TABLE 9-continued

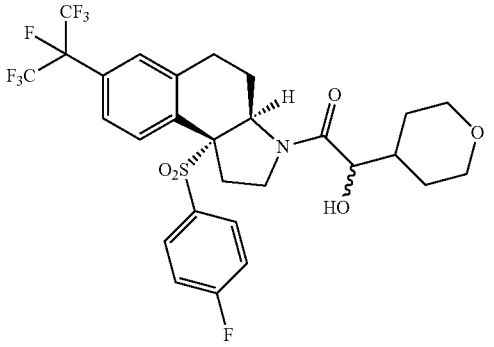
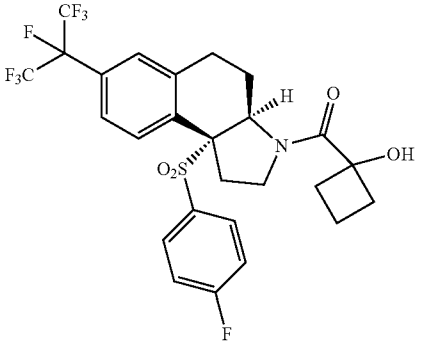
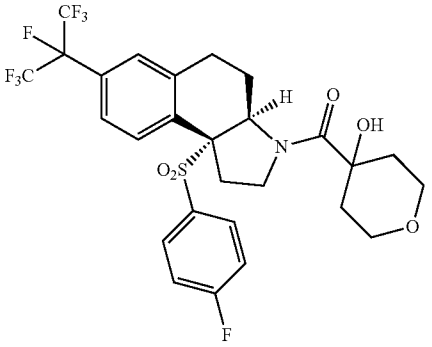
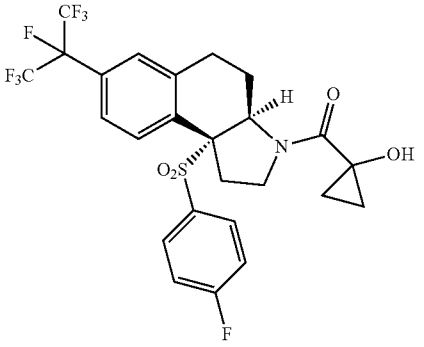
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
469		642.2 $(M + H)^+$	2.18	C
470		598.0 $(M + H)^+$	2.28	C
471		628.2 $(M + H)^+$	2.17	C
472		584.1 $(M + H)^+$	2.20	C

TABLE 9-continued

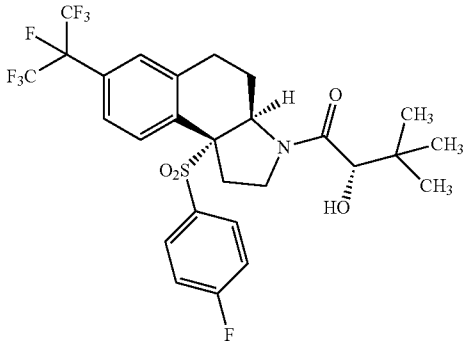
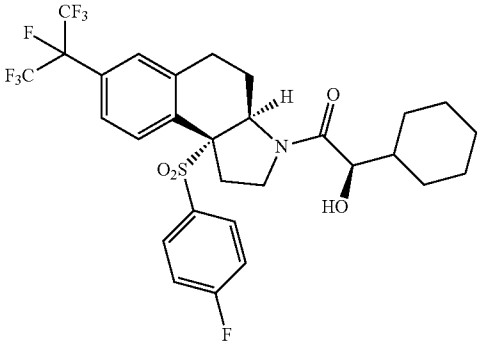
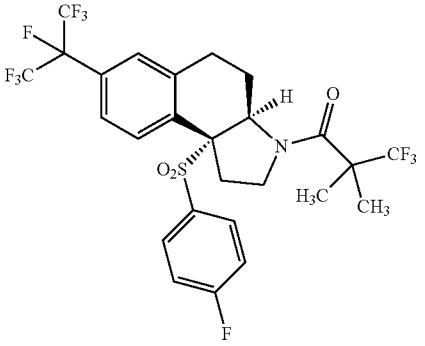
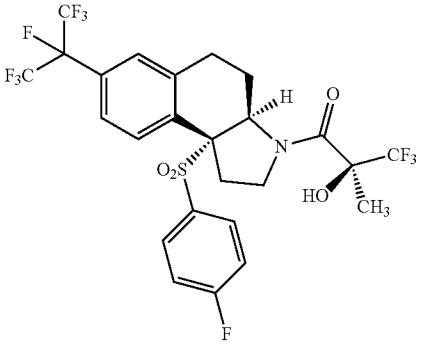
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
473		613.9 $(M + H)^+$	2.50	C
474		640.0 $(M + H)^+$	2.53	C
475		638.1 $(M + H)^+$	2.55	C
476		640.2 $(M + H)^+$	2.36	C

TABLE 9-continued

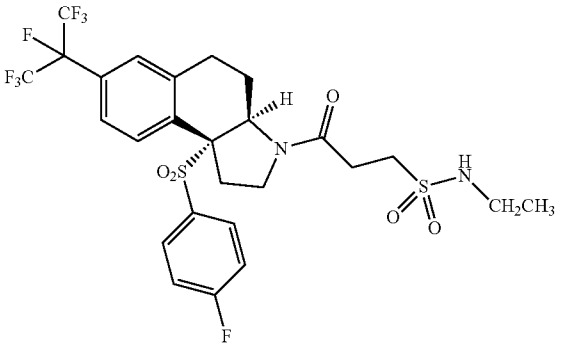
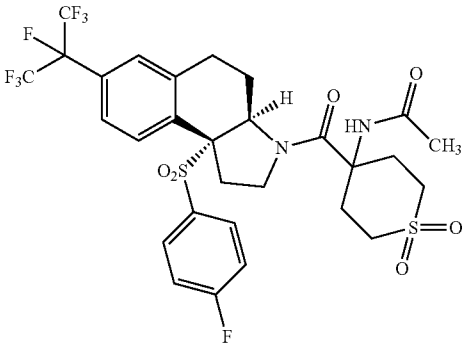
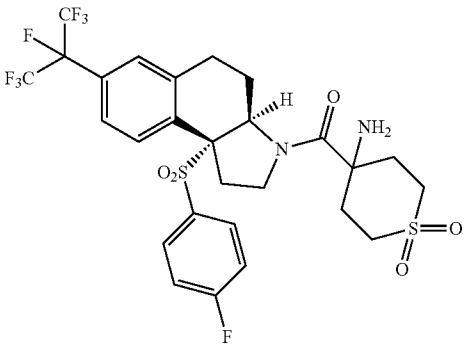
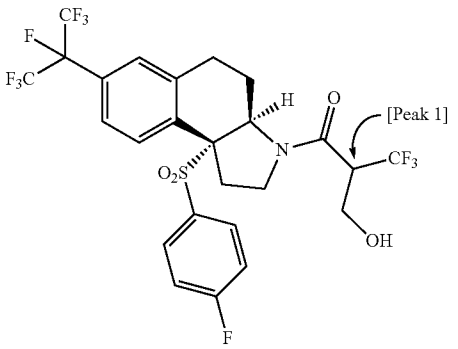
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
477		663.0 $(M + H)^+$	2.19	C
478		717.0 $(M + H)^+$	2.00	C
479		675.2 $(M + H)^+$	2.09	C
480		640.1 $(M + H)^+$	1.84	C

TABLE 9-continued

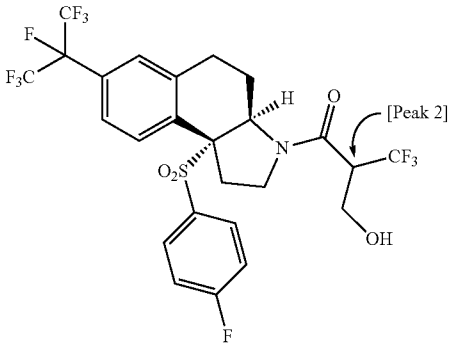
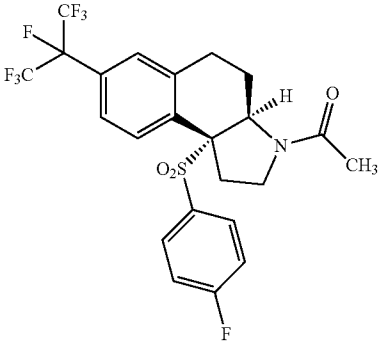
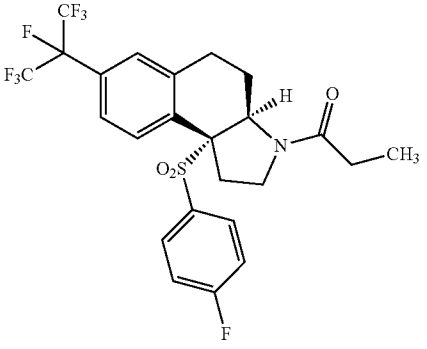
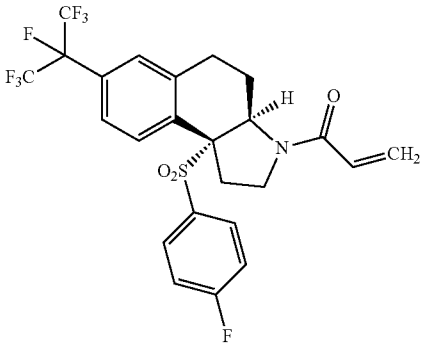
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
481		640.0 $(M + H)^+$	1.89	C
482		541.9 $(M + H)^+$	2.11	C
483		556.3 $(M + H)^+$	2.23	C
484		554.1 $(M + H)^+$	2.20	C

TABLE 9-continued

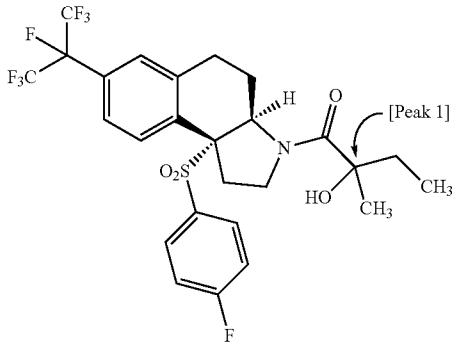
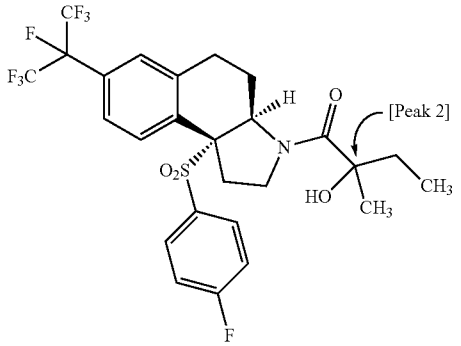
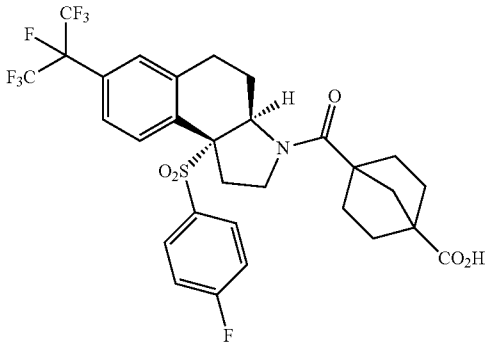
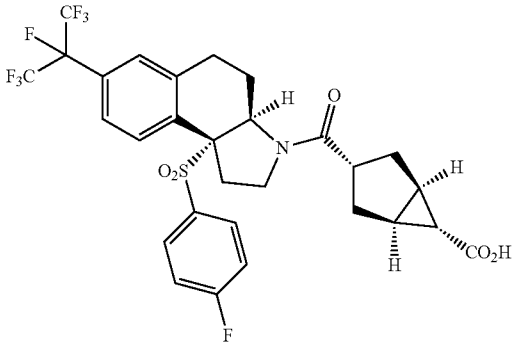
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
485		600.1 $(M + H)^+$	2.37	C
486		600.1 $(M + H)^+$	2.35	C
487		666.1 $(M + H)^+$	1.85	C
488		652.2 $(M + H)^+$	1.88	C

TABLE 9-continued

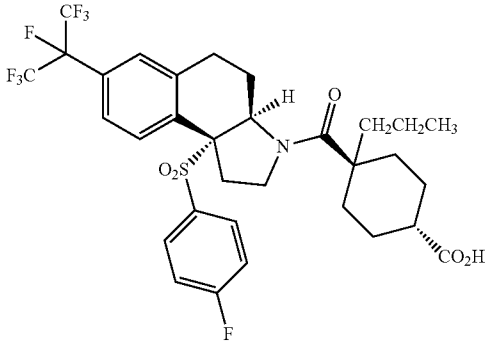
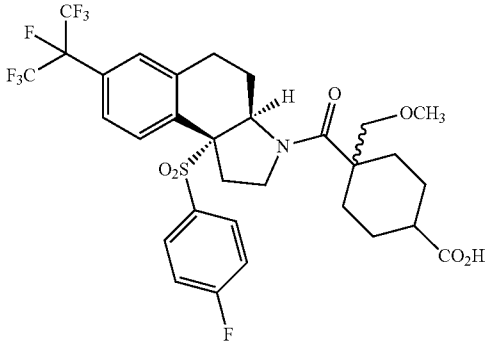
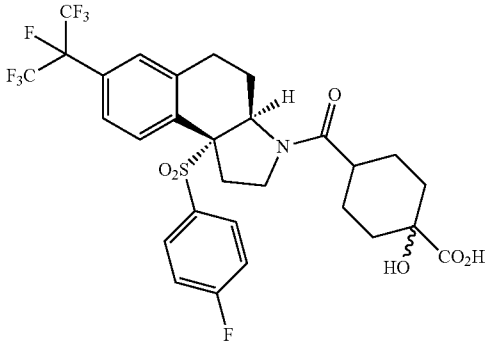
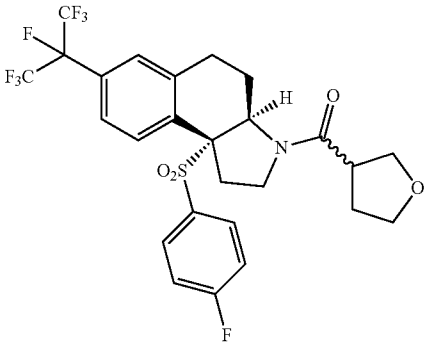
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
489		696.0 $(M + H)^+$	2.14	C
490		698.0 $(M + H)^+$	2.22	D
491		670.2 $(M + H)^+$	2.04, 2.07	D
492		598.1 $(M + H)^+$	2.20	C

TABLE 9-continued

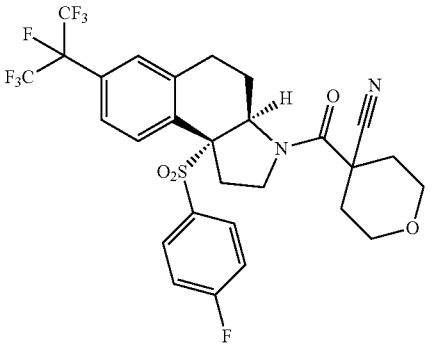
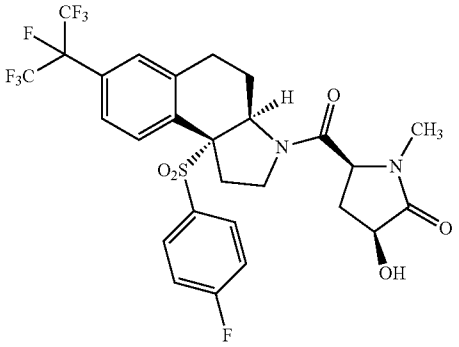
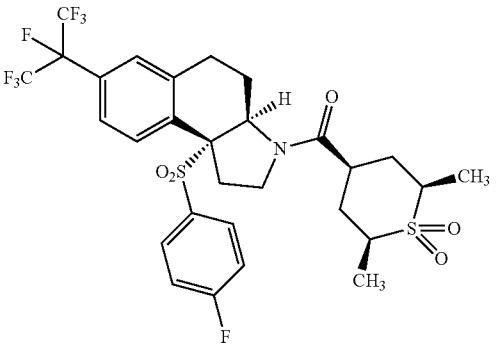
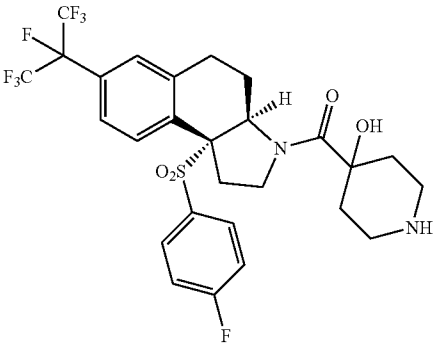
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
493		637.2 $(M + H)^+$	2.36	C
494		641.3 $(M + H)^+$	2.02	C
495		688.2 $(M + H)^+$	2.25	C
496		627.2 $(M + H)^+$	1.80	C

TABLE 9-continued

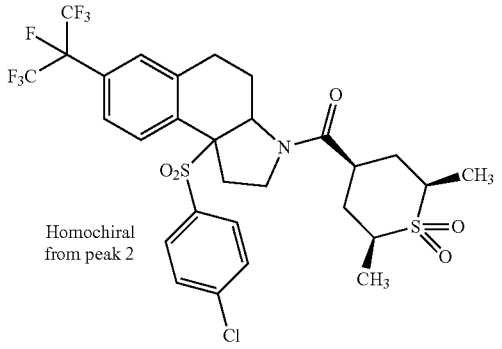
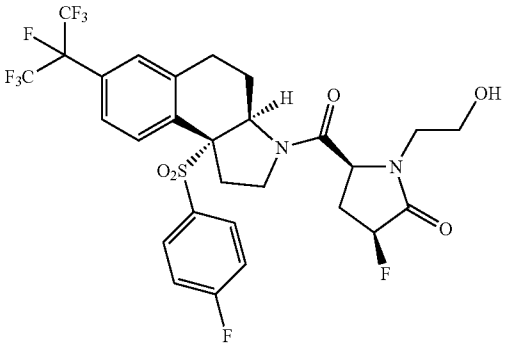
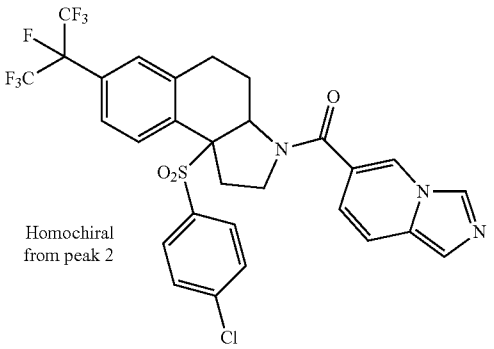
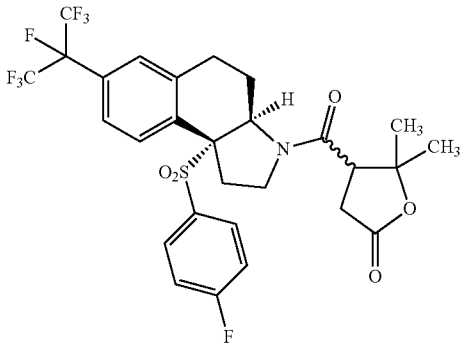
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
497	 Homochiral from peak 2	704.1 $(M + H)^+$	2.32	C
498		673.2 $(M + H)^+$	2.09	C
499	 Homochiral from peak 2	660.2 $(M + H)^+$	2.31	C
500		640.2 $(M + H)^+$	2.26 2.29	C

TABLE 9-continued

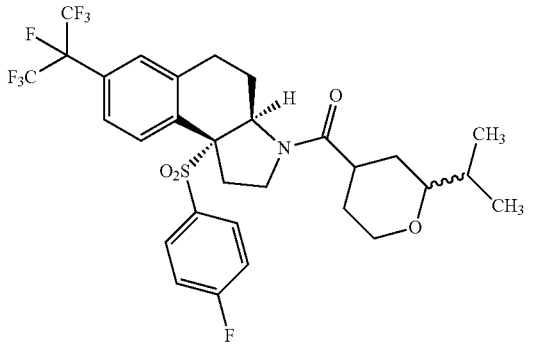
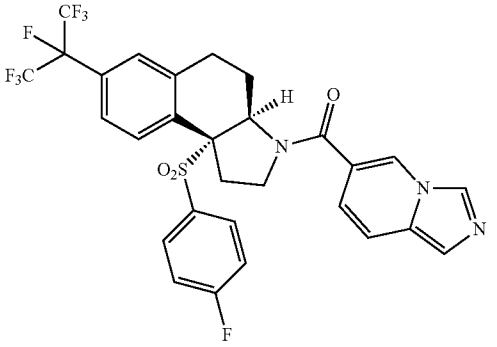
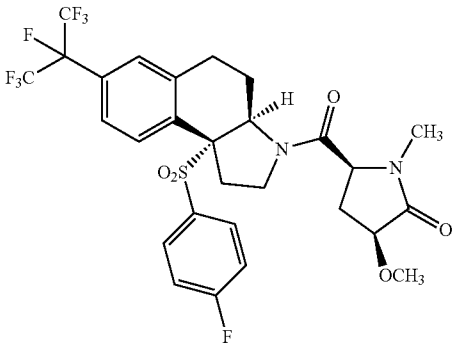
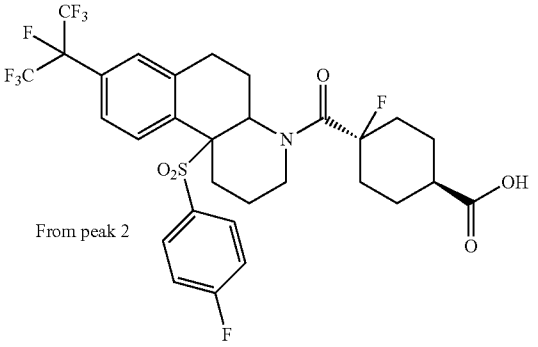
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
501		654.3 $(M + H)^+$ 2.54 2.56		C
502		644.2 $(M + H)^+$	2.21	C
503		654.9 $(M + H)^+$	2.16	C
504	 From peak 2	686.2 $(M + H)^+$	2.03	C

TABLE 9-continued

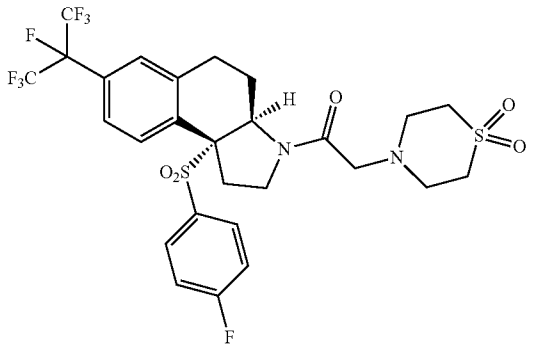
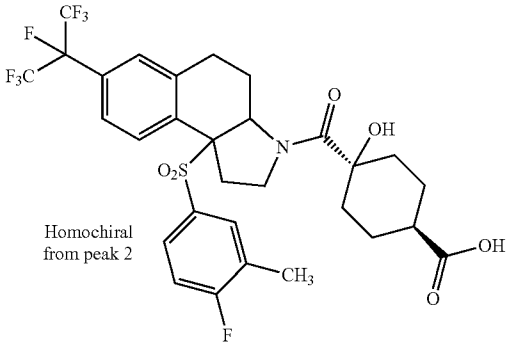
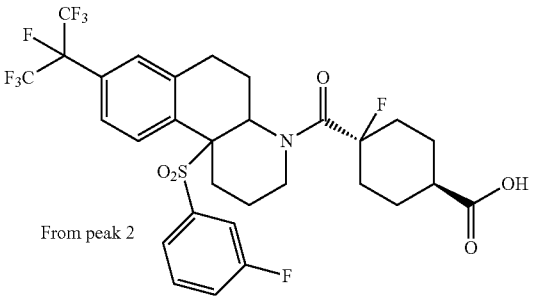
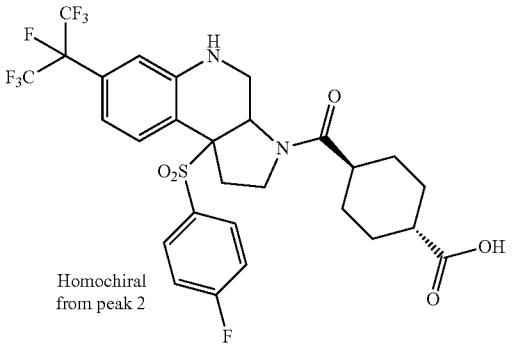
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
505		675.1 $(M + H)^+$	2.18	C
506	 Homochiral from peak 2	684.2 $(M + H)^+$	1.90	C
507	 From peak 2	686.3 $(M + H)^+$	2.01	C
508	 Homochiral from peak 2	655.2 $(M + H)^+$	1.04	B

TABLE 9-continued

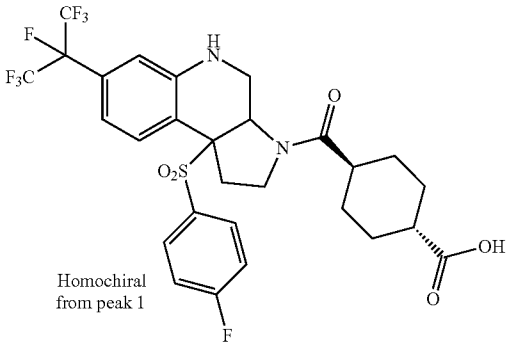
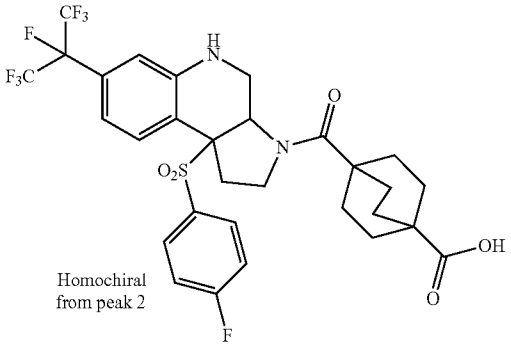
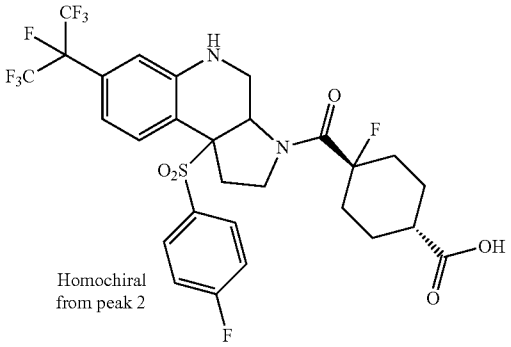
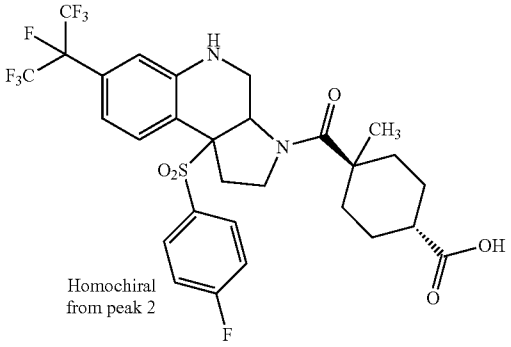
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
509	 Homochiral from peak 1	655.2 $(M + H)^+$	1.04	B
510	 Homochiral from peak 2	681.1 $(M + H)^+$	1.93	C
511	 Homochiral from peak 2	673.2 $(M + H)^+$	1.09	B
512	 Homochiral from peak 2	669.2 $(M + H)^+$	1.98	C

TABLE 9-continued

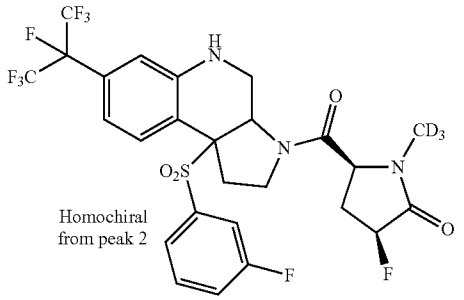
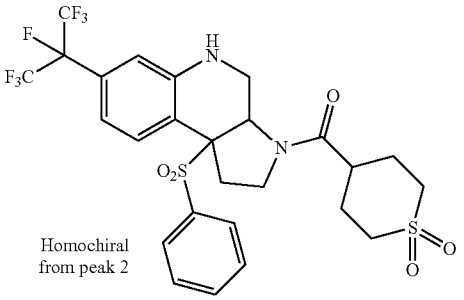
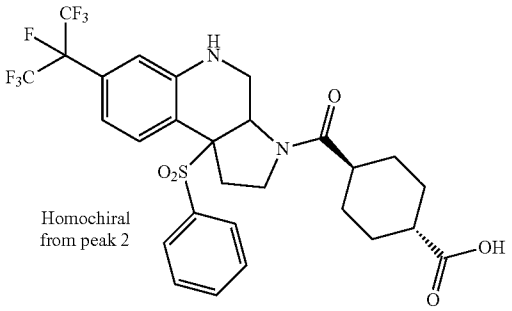
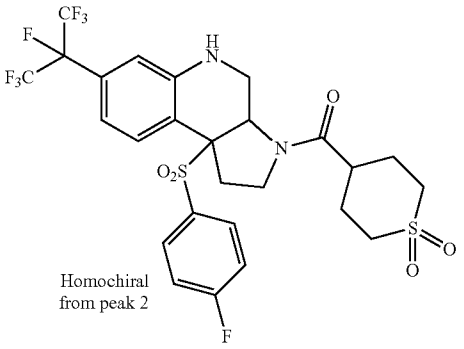
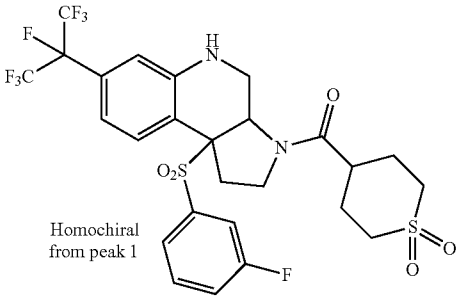
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
513	 Homochiral from peak 2	647.1 $(M + H)^+$	1.05	B
514	 Homochiral from peak 2	643.1 $(M + H)^+$	0.99	B
515	 Homochiral from peak 2	637.1 $(M + H)^+$	1.02	B
516	 Homochiral from peak 2	661.1 $(M + H)^+$	1.01	B
517	 Homochiral from peak 1	661.1 $(M + H)^+$	1.01	B

TABLE 9-continued

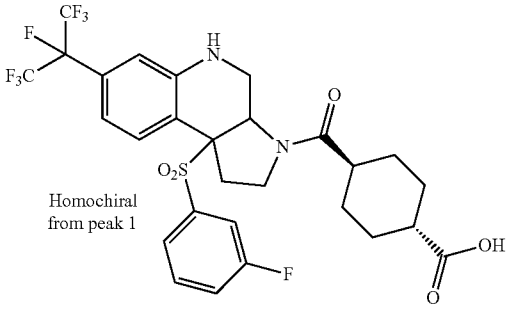
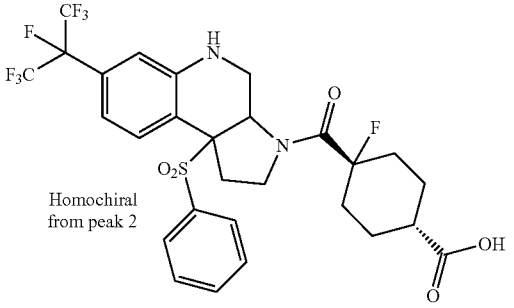
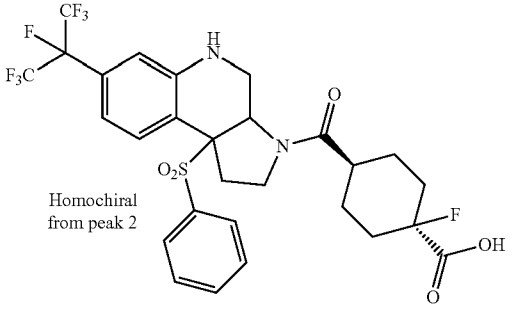
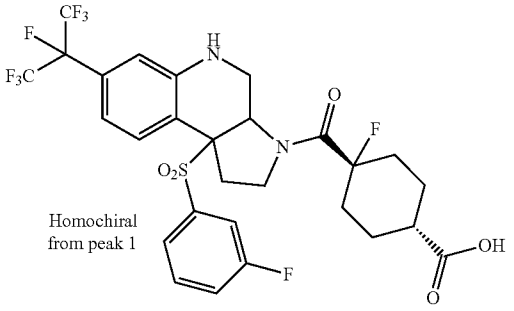
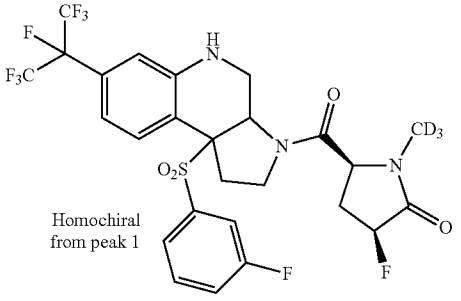
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
518	 Homochiral from peak 1	655.3 $(M + H)^+$	1.00	B
519	 Homochiral from peak 2	655.3 $(M + H)^+$	0.99	B
520	 Homochiral from peak 2	655.3 $(M + H)^+$	0.99	B
521	 Homochiral from peak 1	673.2 $(M + H)^+$	1.03	B
522	 Homochiral from peak 1	647.1 $(M + H)^+$	1.01	B

TABLE 9-continued

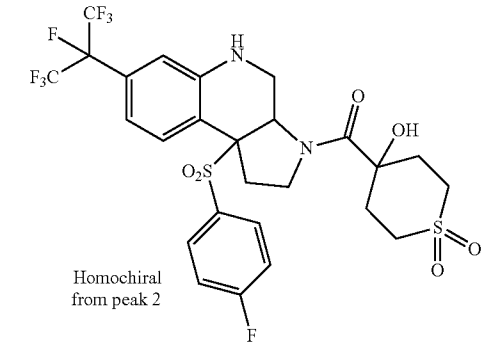
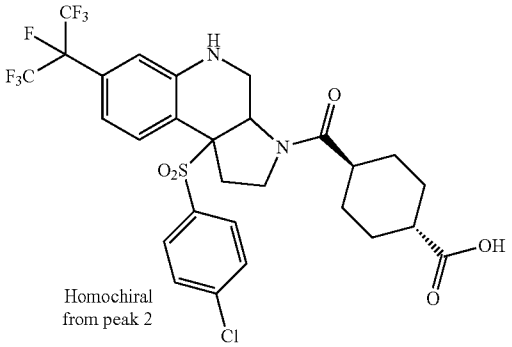
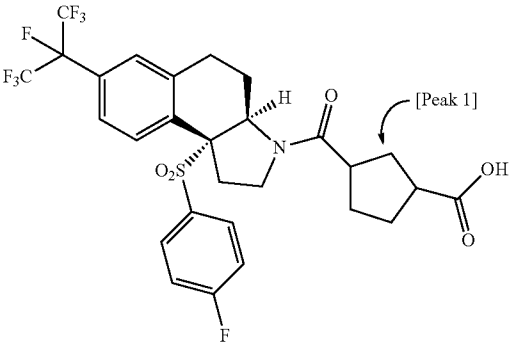
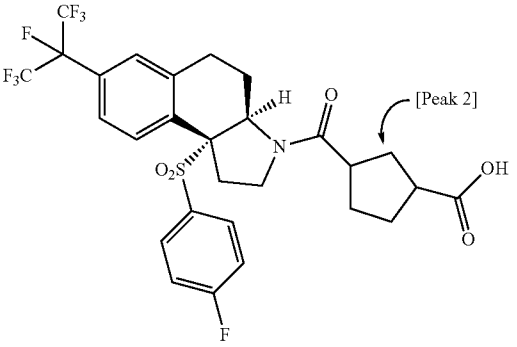
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
523	 Homochiral from peak 2	677.2 $(M + H)^+$	2.02	D
524	 Homochiral from peak 2	671.2 $(M + H)^+$	1.92	C
525	 [Peak 1]	654.2 $(M + H)^+$	1.05	B
526	 [Peak 2]	654.2 $(M + H)^+$	1.04	B

TABLE 9-continued

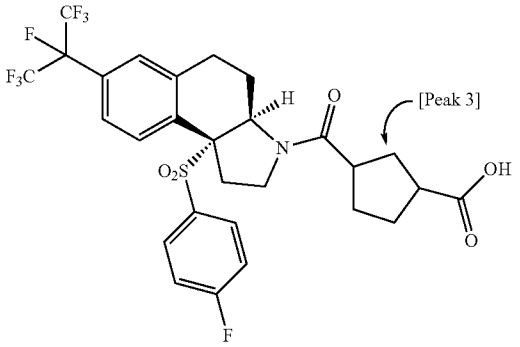
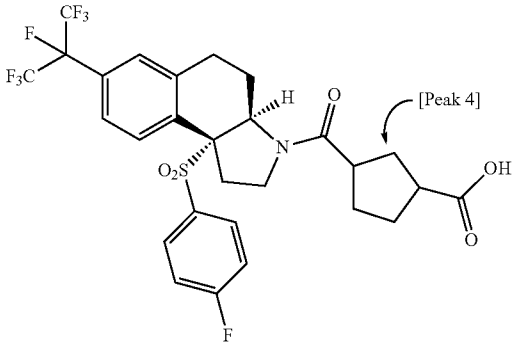
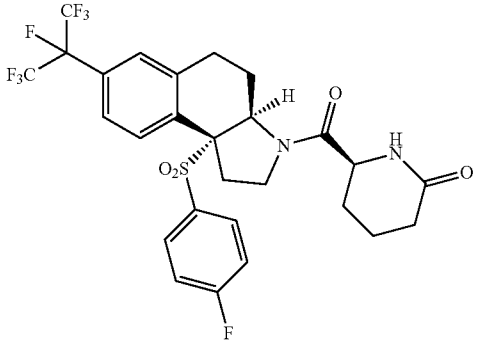
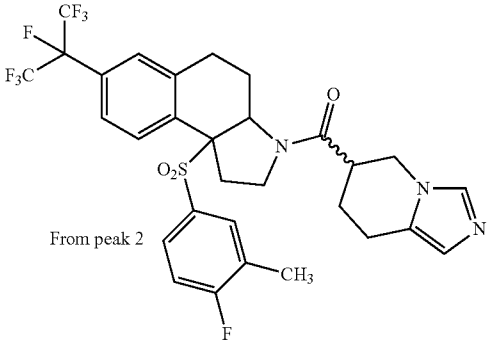
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
527		654.2 $(M + H)^+$	1.04	B
528		654.2 $(M + H)^+$	1.04	B
529		625.1 $(M + H)^+$	2.03	C
530		661.9 $(M + H)^+$	2.20	C

TABLE 9-continued

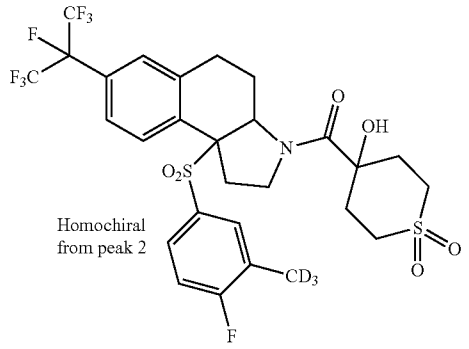
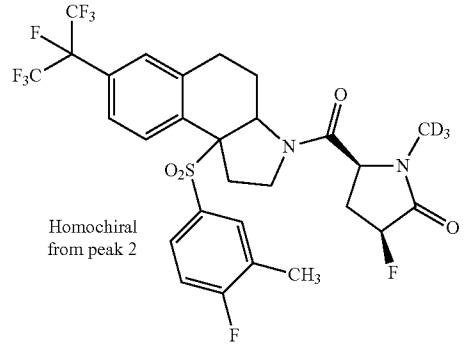
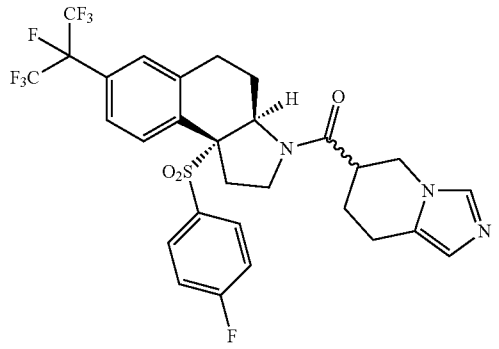
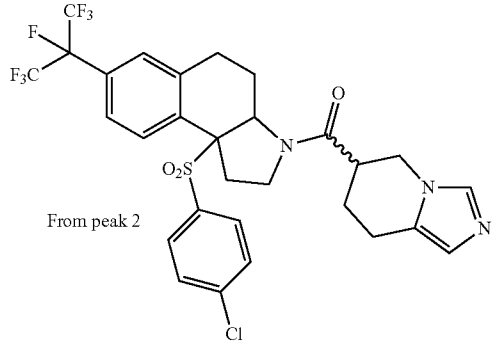
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
531	 Homochiral from peak 2	693.2 $(M + H)^+$	2.26	C
532	 Homochiral from peak 2	660.0 $(M + H)^+$	2.28	C
533		648.2 $(M + H)^+$	2.09	C
534	 From peak 2	664.1 $(M + H)^+$	2.20	C

TABLE 9-continued

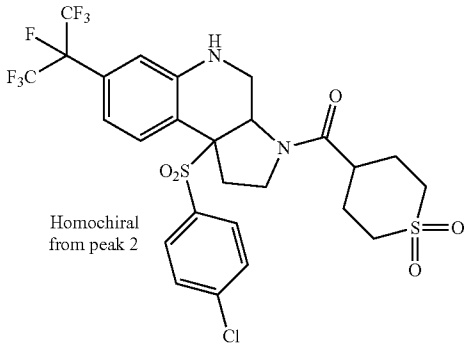
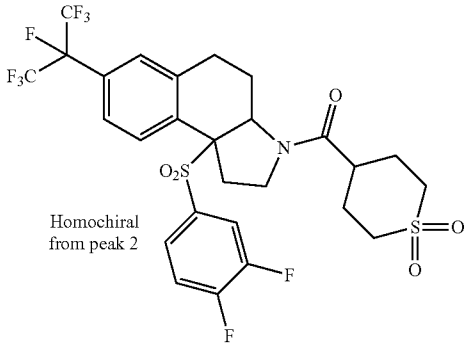
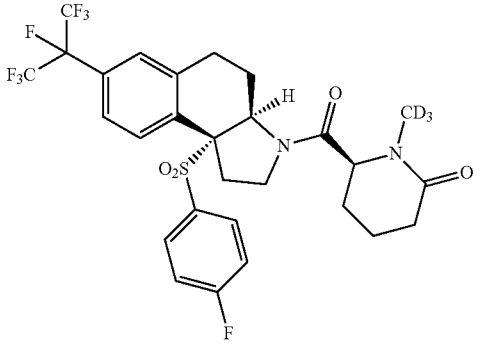
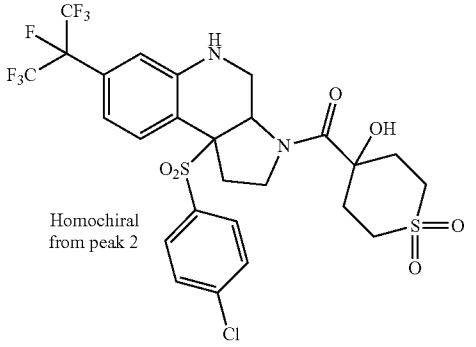
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
535		677.1 $(M + H)^+$	2.18	C
536		677.9 $(M + H)^+$	2.20	C
537		642.1 $(M + H)^+$	2.10	C
538		693.3 $(M + H)^+$	2.16	C

TABLE 9-continued

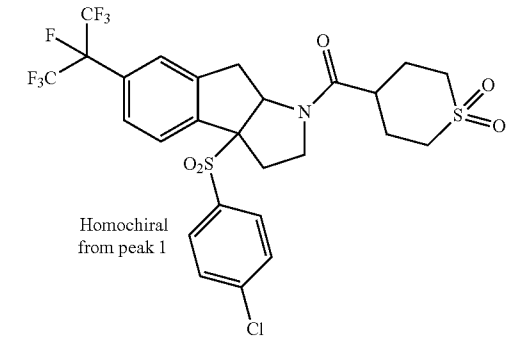
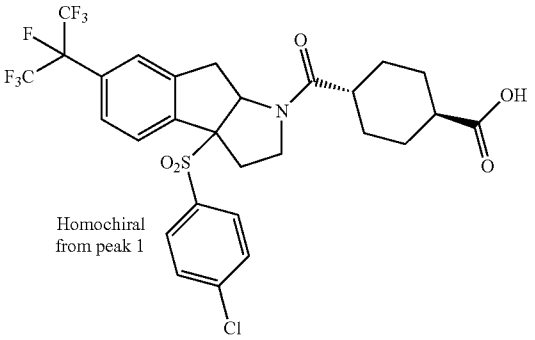
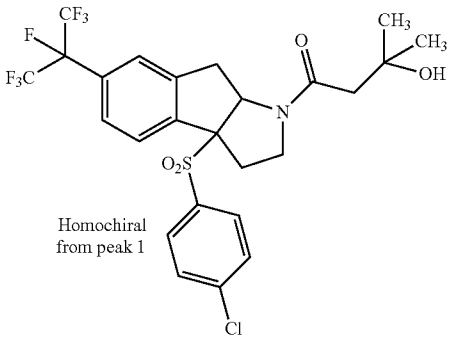
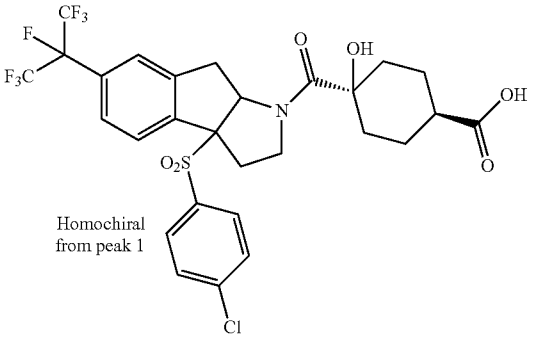
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
539		662.1 $(M + H)^+$	1.06	B
540		656.1 $(M + H)^+$	1.08	B
541		602.2 $(M + H)^+$	1.11	B
542		672.1 $(M + H)^+$	1.06	B

TABLE 9-continued

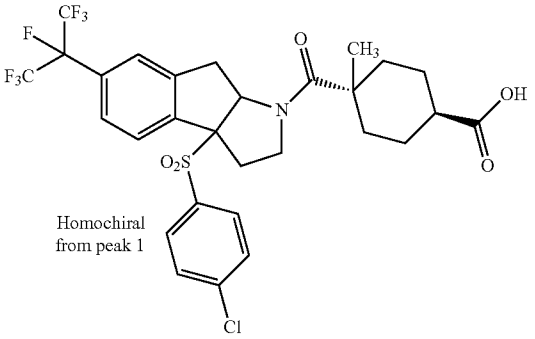
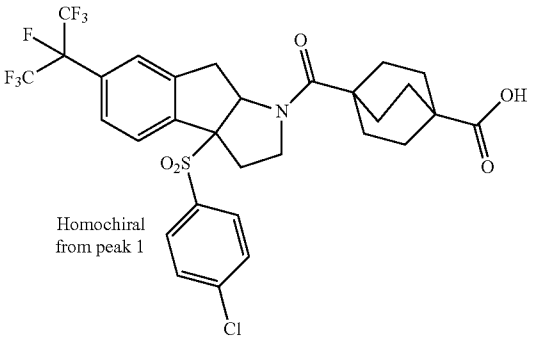
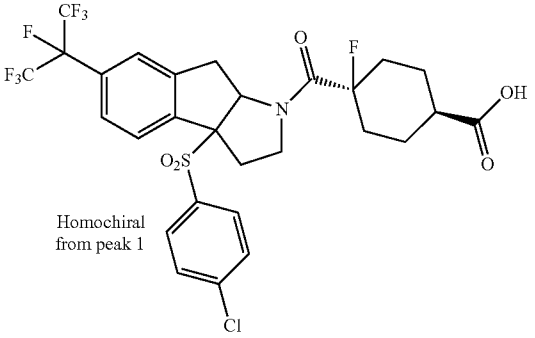
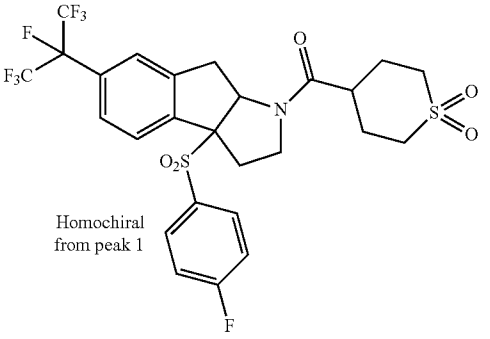
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
543		670.1 $(M + H)^+$	1.12	B
544		682.2 $(M + H)^+$	2.02	C
545		673.9 $(M + H)^+$	1.95	C
546		646.3 $(M + H)^+$	2.03	C

TABLE 9-continued

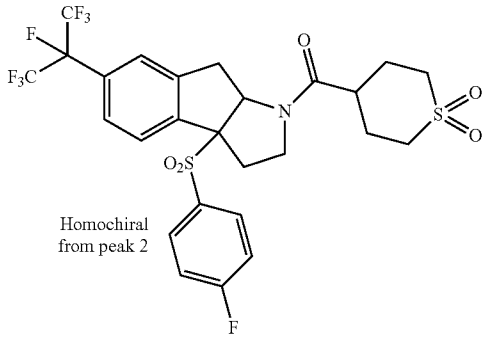
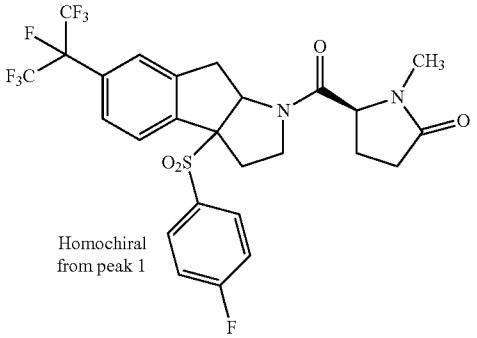
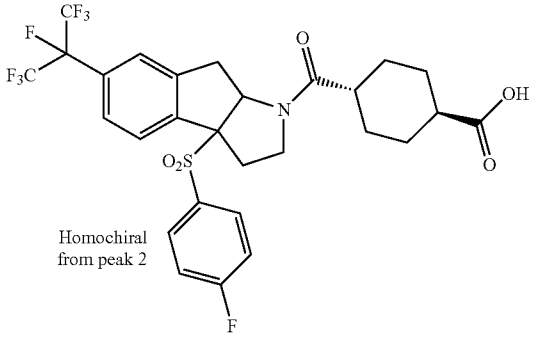
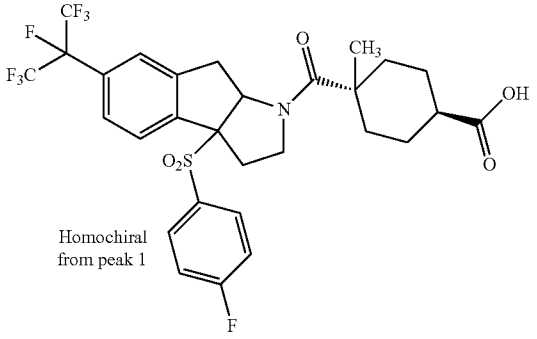
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
547		646.4 $(M + H)^+$	2.04	C
548		610.8 $(M + H)^+$	1.93	C
549		640.4 $(M + H)^+$	1.81	C
550		653.9 $(M + H)^+$	2.08	C

TABLE 9-continued

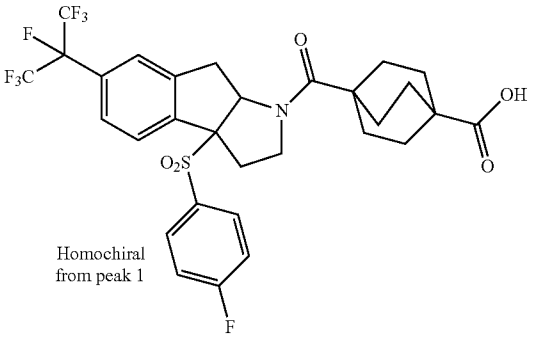
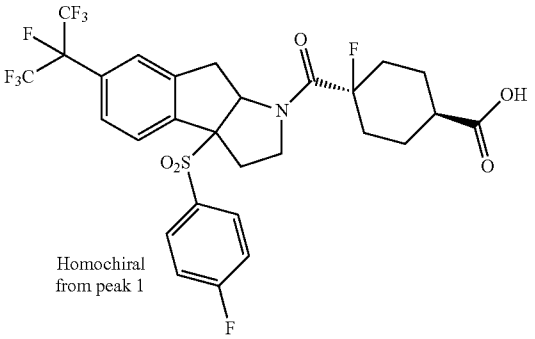
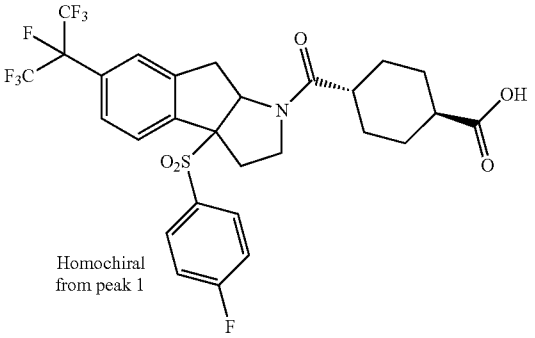
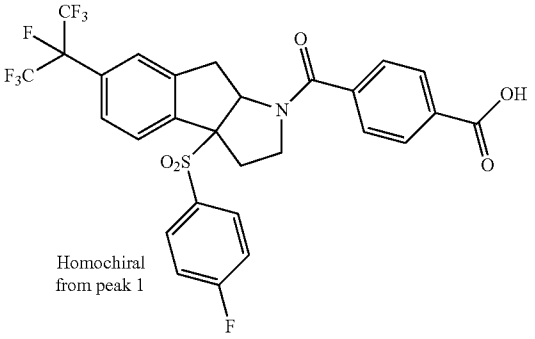
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
551	 Homochiral from peak 1	666.4 $(M + H)^+$	1.93	C
552	 Homochiral from peak 1	658.2 $(M + H)^+$	1.84	C
553	 Homochiral from peak 1	640.0 $(M + H)^+$	1.79	C
554	 Homochiral from peak 1	634.4 $(M + H)^+$	1.70	C

TABLE 9-continued

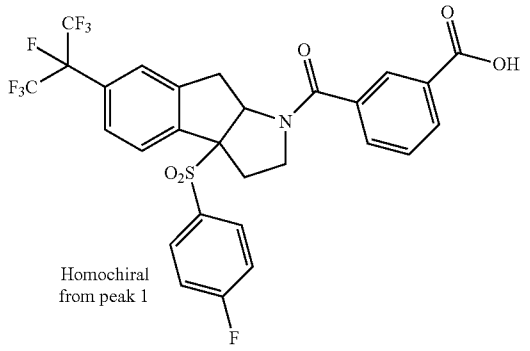
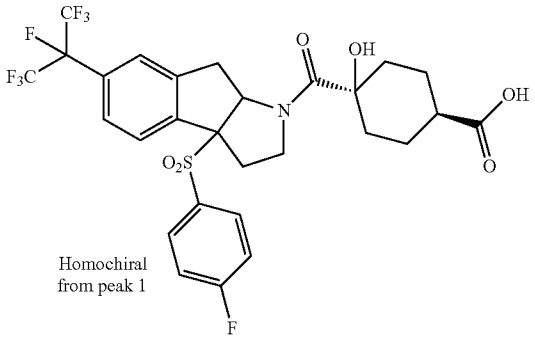
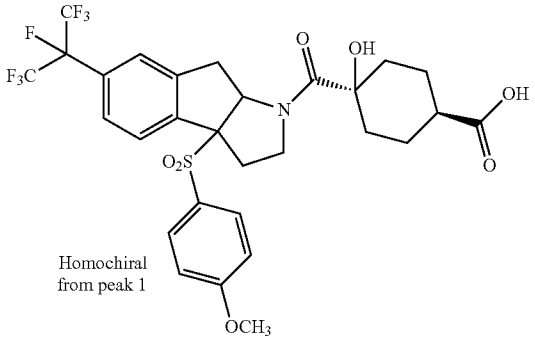
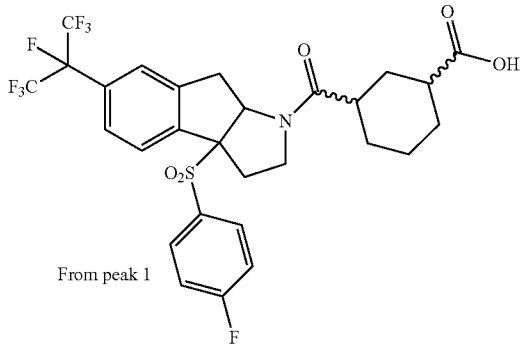
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
555	 Homochiral from peak 1	634.3 $(M + H)^+$	1.71	C
556	 Homochiral from peak 1	655.8 $(M + H)^+$	1.71	C
557	 Homochiral from peak 1	668.0 $(M + H)^+$	1.68	C
558	 From peak 1	640.2 $(M + H)^+$	1.08	B

TABLE 9-continued

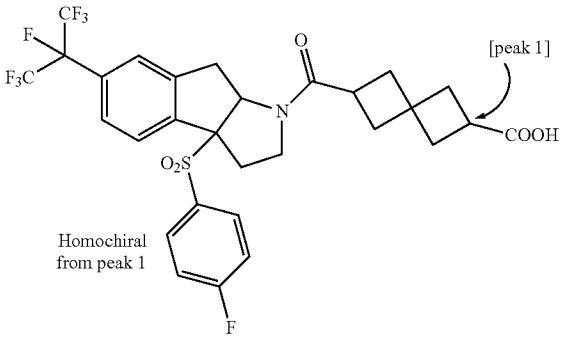
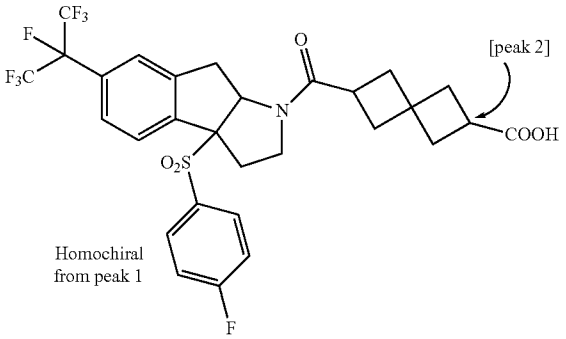
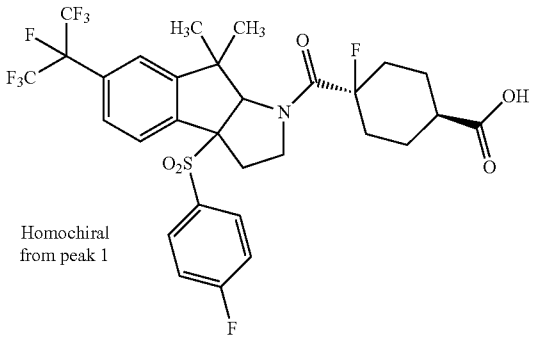
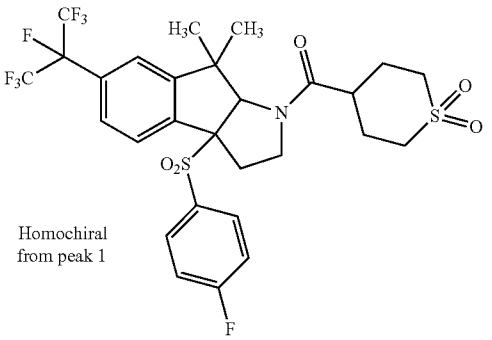
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
559		652.1 $(M + H)^+$	1.07	B
560		652.1 $(M + H)^+$	1.08	B
561		686.4 $(M + H)^+$	1.93	C
562		674.3 $(M + H)^+$	2.16	C

TABLE 9-continued

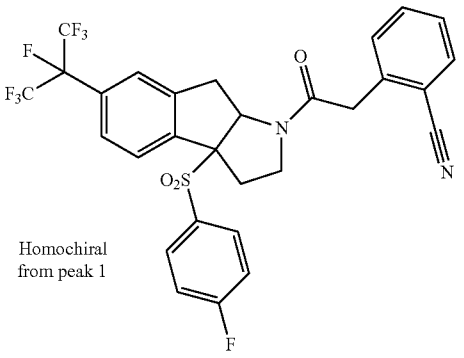
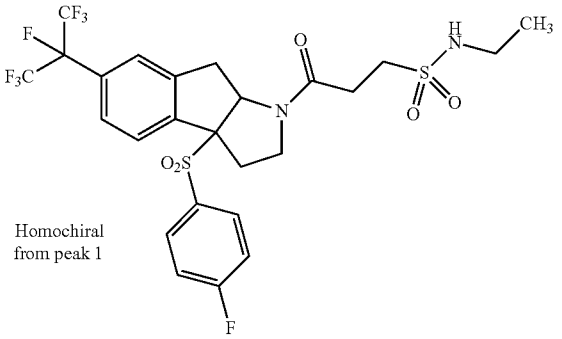
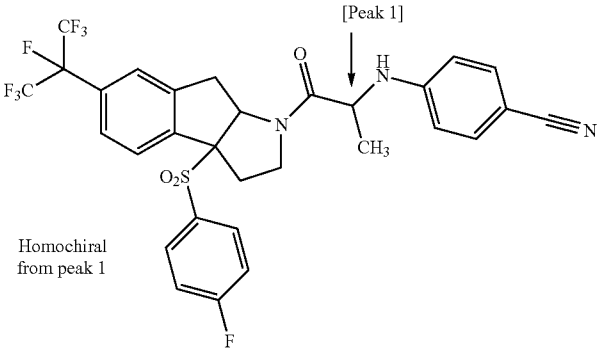
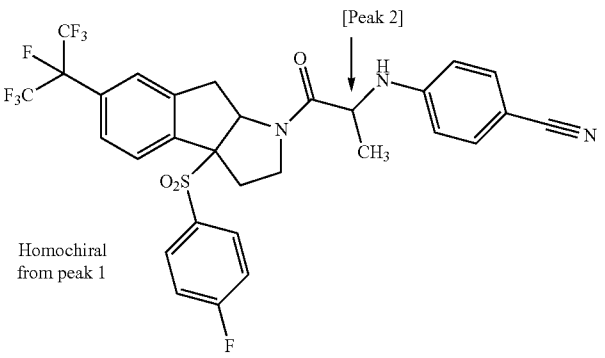
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
563	 Homochiral from peak 1	629.0 $(M + H)^+$	2.34	C
564	 Homochiral from peak 1	649.2 $(M + H)^+$	2.10	C
565	 [Peak 1] Homochiral from peak 1	658.2 $(M + H)^+$	2.26	C
566	 [Peak 2] Homochiral from peak 1	658.0 $(M + H)^+$	2.30	C

TABLE 9-continued

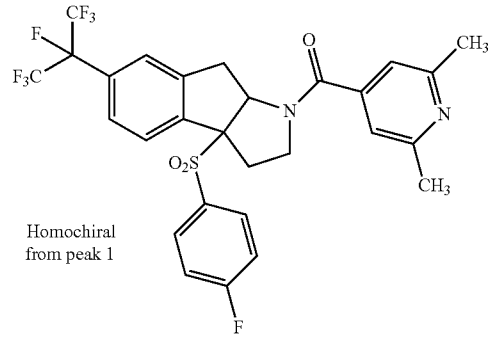
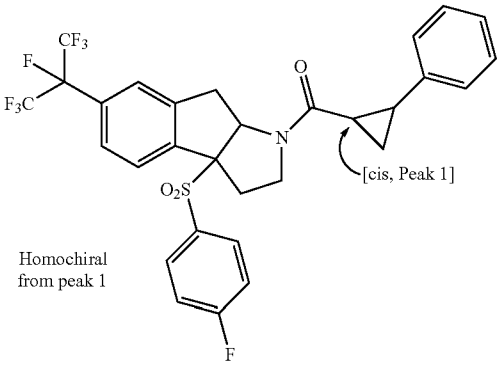
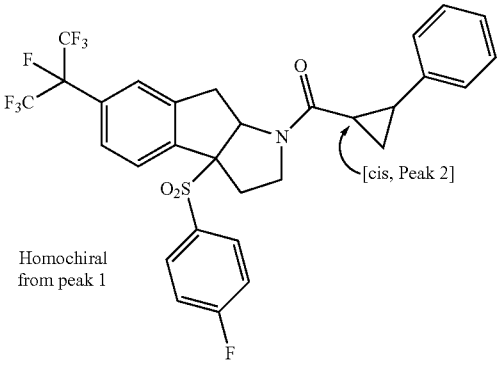
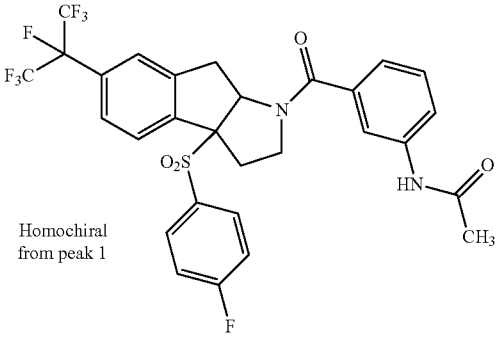
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
567	 Homochiral from peak 1	621.1 $(M + H)^+$	2.05	C
568	 Homochiral from peak 1	630.1 $(M + H)^+$	2.51	C
569	 Homochiral from peak 1	630.2 $(M + H)^+$	2.60	C
570	 Homochiral from peak 1	647.4 $(M + H)^+$	2.22	C

TABLE 9-continued

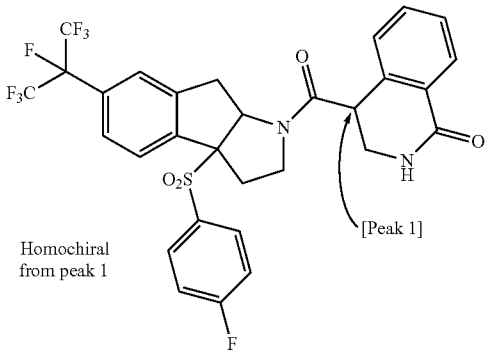
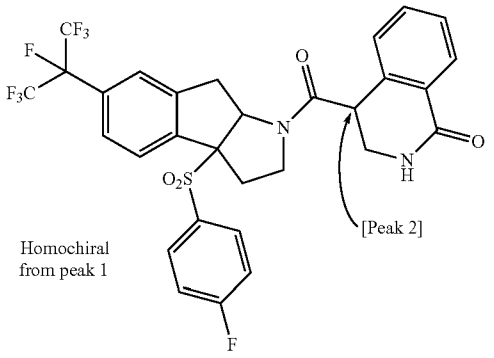
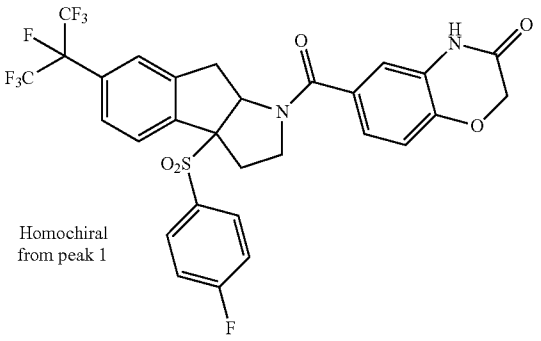
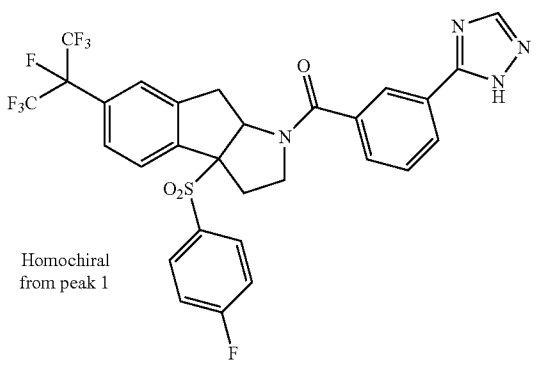
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
571		659.1 $(M + H)^+$	2.21	C
572		659.4 $(M + H)^+$	2.27	C
573		661.1 $(M + H)^+$	2.26	C
574		657.1 $(M + H)^+$	2.14	C

TABLE 9-continued

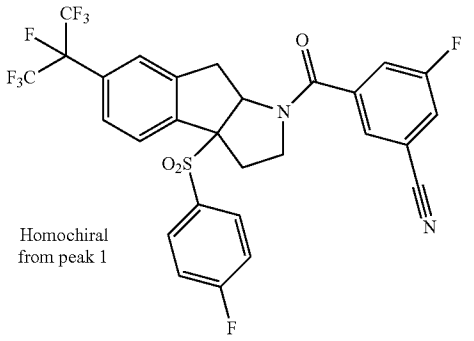
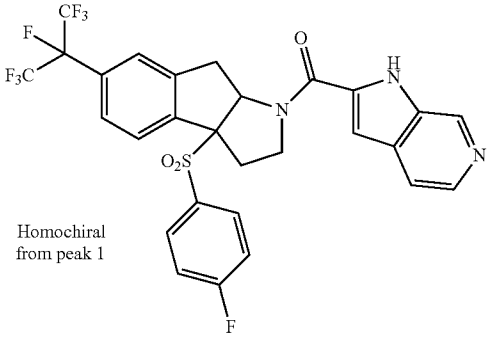
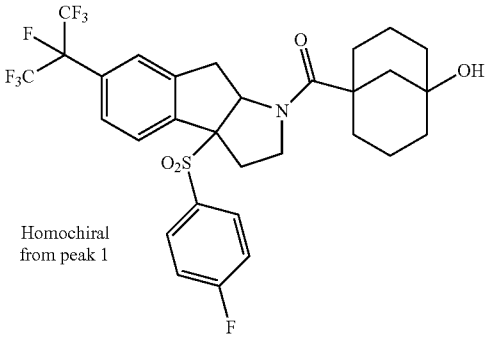
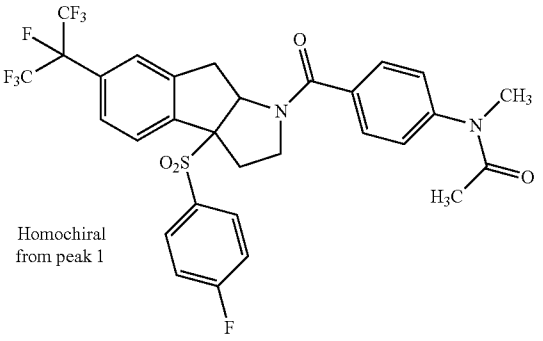
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
575	 Homochiral from peak 1	632.9 $(M + H)^+$	2.26	C
576	 Homochiral from peak 1	630.0 $(M + H)^+$	2.13	C
577	 Homochiral from peak 1	651.9 $(M + H)^+$	2.37	C
578	 Homochiral from peak 1	661.1 $(M + H)^+$	2.22	C

TABLE 9-continued

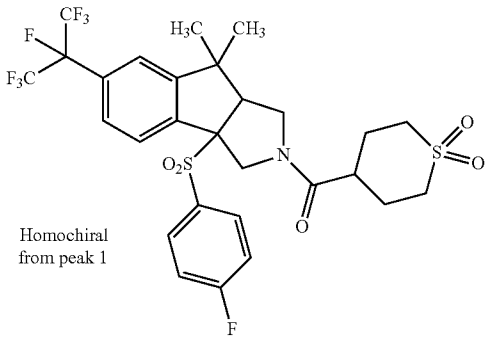
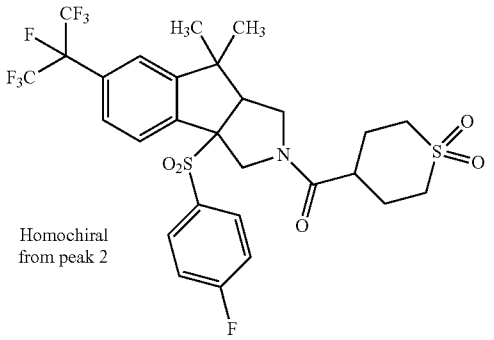
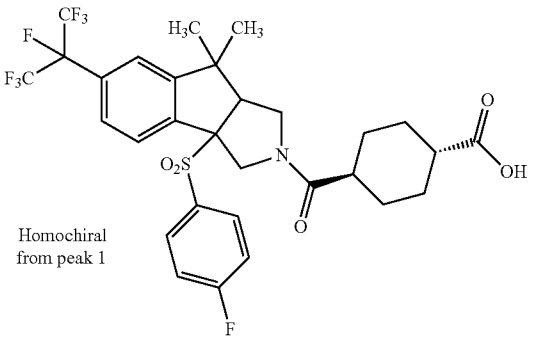
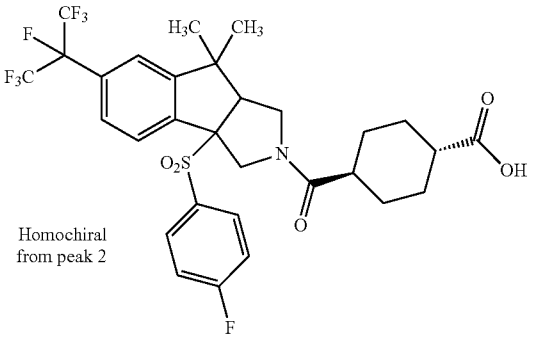
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
579	 Homochiral from peak 1	656.1 $(M + H)^+$	2.07	C
580	 Homochiral from peak 2	656.1 $(M + H)^+$	2.07	C
581	 Homochiral from peak 1	650.1 $(M + H)^+$	1.80	C
582	 Homochiral from peak 2	650.1 $(M + H)^+$	1.81	C

TABLE 9-continued

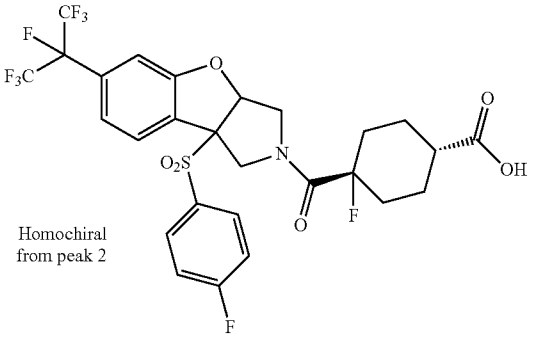
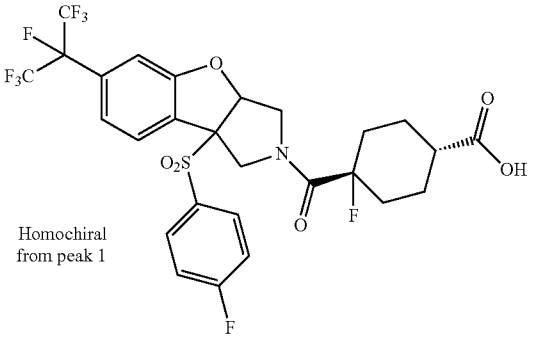
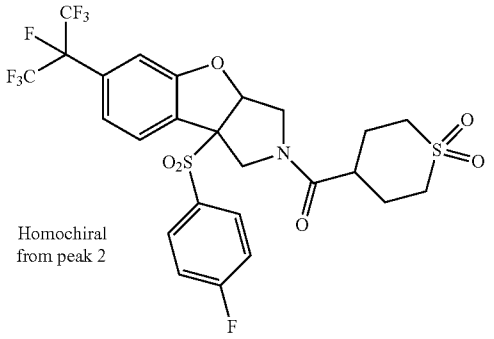
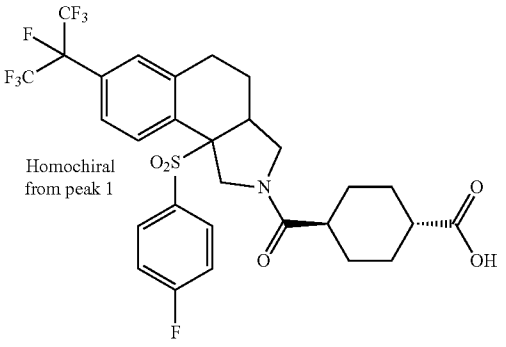
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
583	 Homochiral from peak 2	660.1 $(M + H)^+$	1.89	C
584	 Homochiral from peak 1	660.1 $(M + H)^+$	1.84	C
585	 Homochiral from peak 2	648.0 $(M + H)^+$	1.99	C
586	 Homochiral from peak 1	654.5 $(M + H)^+$	1.02	B

TABLE 9-continued

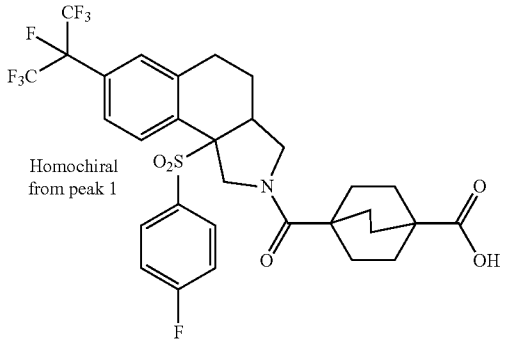
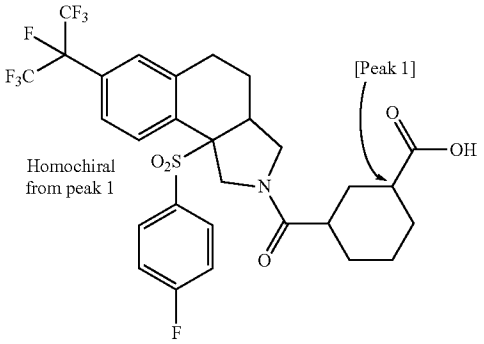
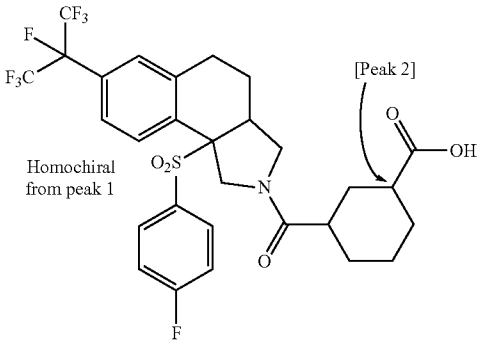
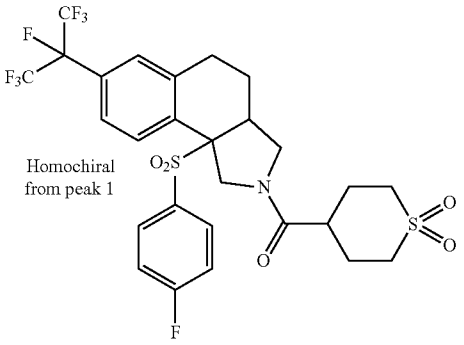
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
587		680.4 $(M + H)^+$	1.04	B
588		654.1 $(M + H)^+$	2.181	D
589		654.2 $(M + H)^+$	2.158	D
590		660.0 $(M + H)^+$	2.094	D

TABLE 9-continued

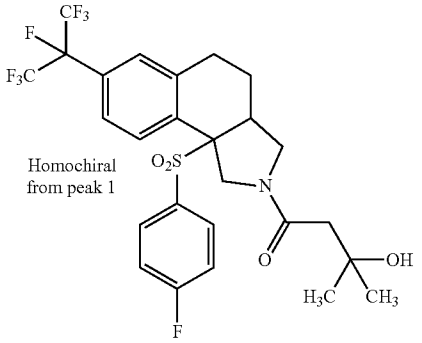
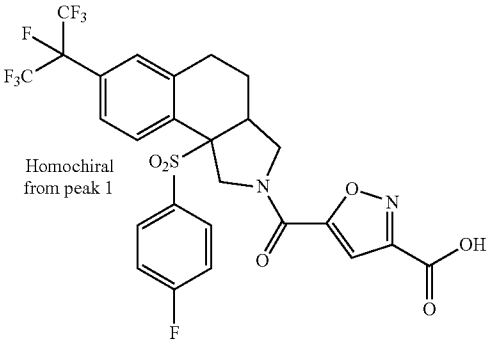
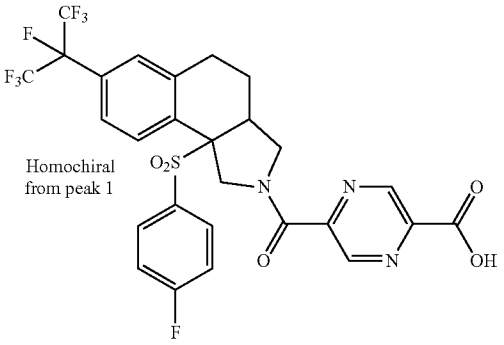
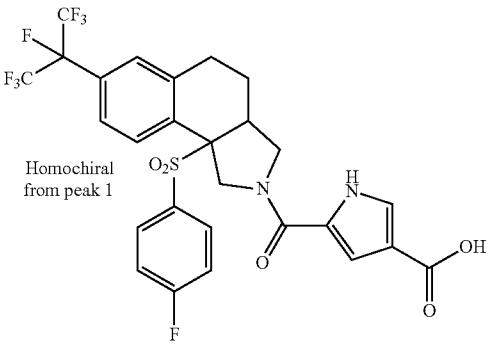
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
591		599.8 $(M + H)^+$	2.205	D
592		638.9 $(M + H)^+$	2.163	D
593		650.2 $(M + H)^+$	2.239	D
594		637.2 $(M + H)^+$	1.983	D

TABLE 9-continued

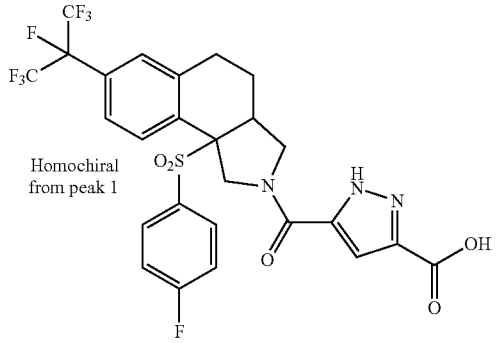
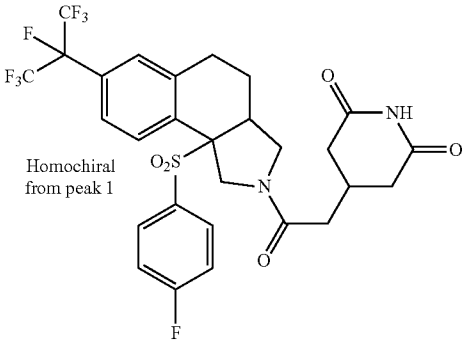
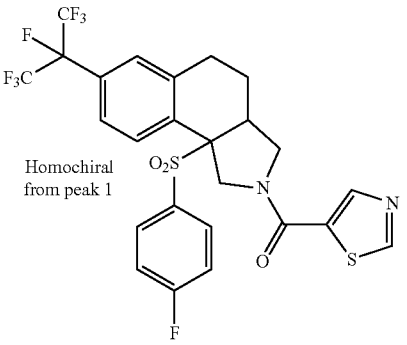
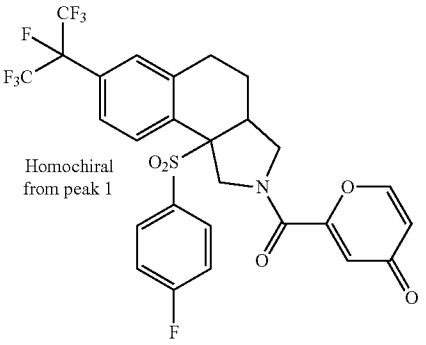
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
595		637.8 $(M + H)^+$	2.003	D
596		653.4 $(M + H)^+$	2.03	C
597		611.3 $(M + H)^+$	2.19	C
598		622.3 $(M + H)^+$	2.11	C

TABLE 9-continued

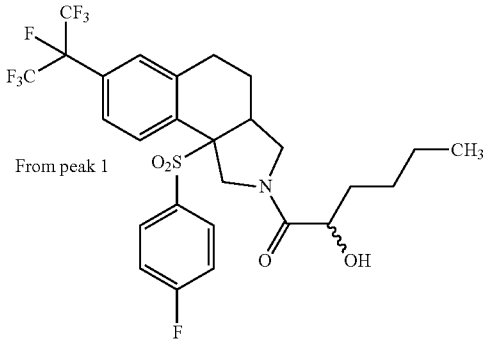
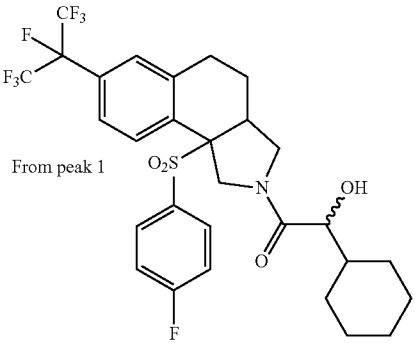
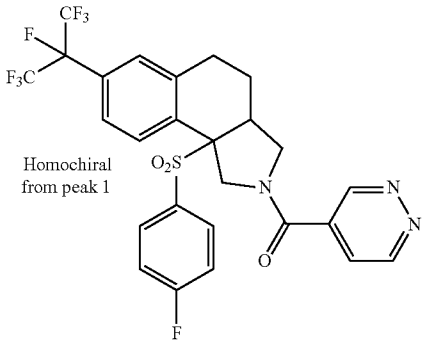
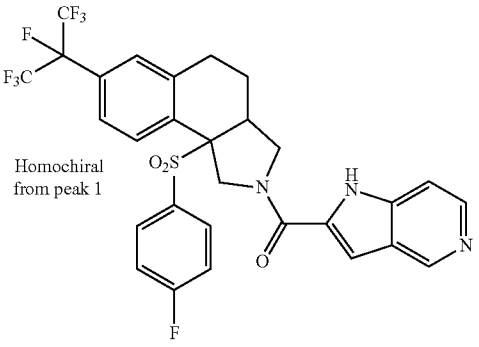
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
599	 From peak 1	614.4 $(M + H)^+$	2.38	C
600	 From peak 1	640.4 $(M + H)^+$	2.5	C
601	 Homochiral from peak 1	606.3 $(M + H)^+$	2.05	D
602	 Homochiral from peak 1	644.4 $(M + H)^+$	2.11	C

TABLE 9-continued

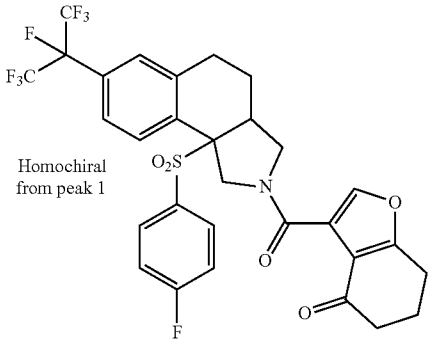
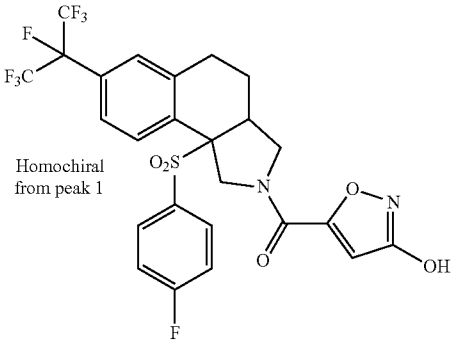
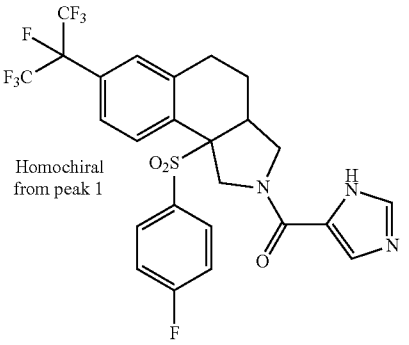
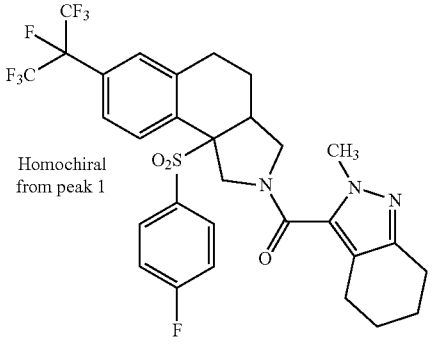
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
603	 Homochiral from peak 1	662.4 $(M + H)^+$	2.26	C
604	 Homochiral from peak 1	611.3 $(M + H)^+$	1.81	C
605	 Homochiral from peak 1	594 $(M + H)^+$	1.95	C
606	 Homochiral from peak 1	662.4 $(M + H)^+$	2.43	C

TABLE 9-continued

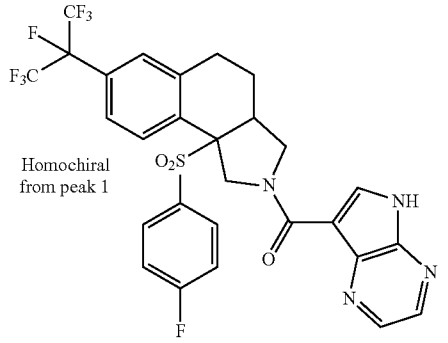
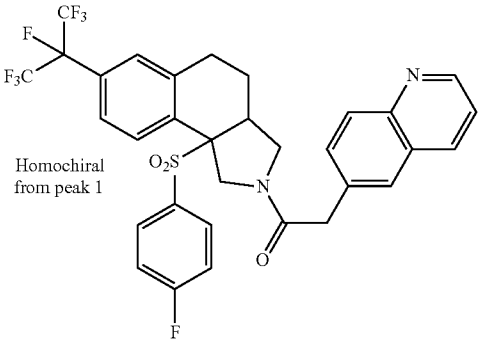
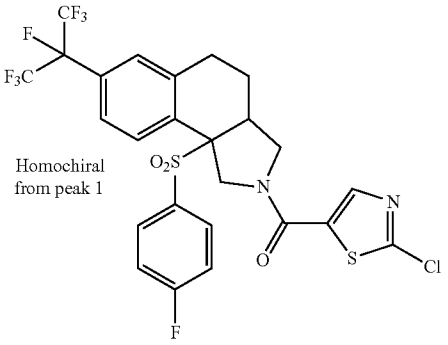
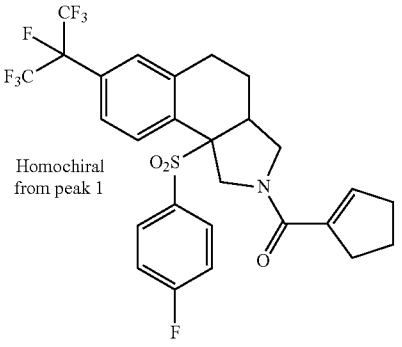
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
607		645.4 $(M + H)^+$	2.08	C
608		669.1 $(M + H)^+$	2.2	C
609		645.3 $(M + H)^+$	2.42	C
610		593.8 $(M + H)^+$	2.33	D

TABLE 9-continued

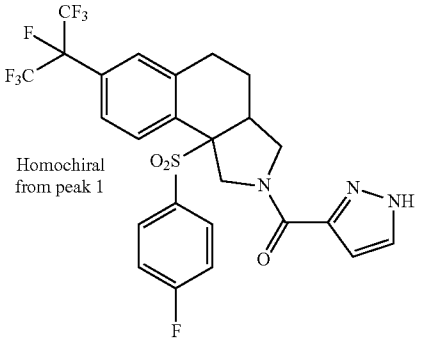
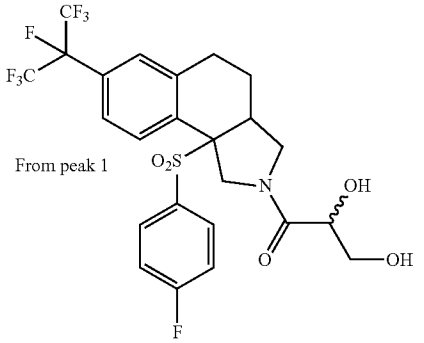
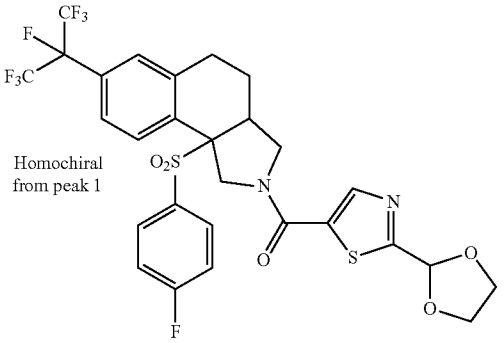
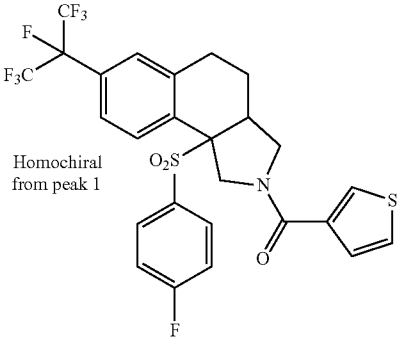
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
611	 Homochiral from peak 1	594.0	2.05	D
612	 From peak 1	587.8 $(M + H)^+$	1.88	C
613	 Homochiral from peak 1	682.8 $(M + H)^+$	2.22	C
614	 Homochiral from peak 1	609.9 $(M + H)^+$	2.27	D

TABLE 9-continued

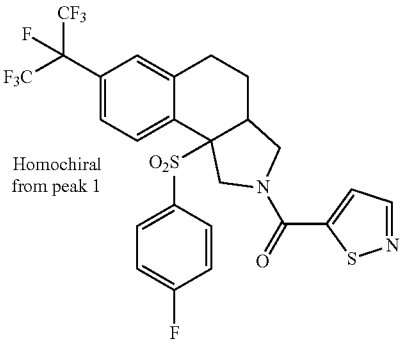
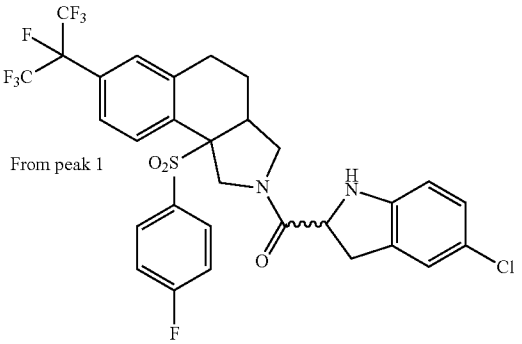
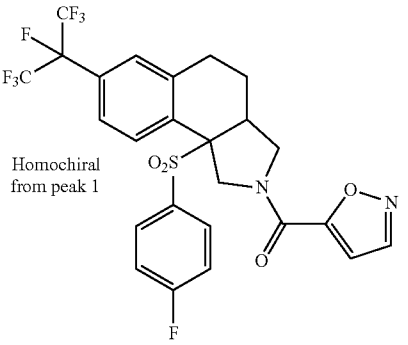
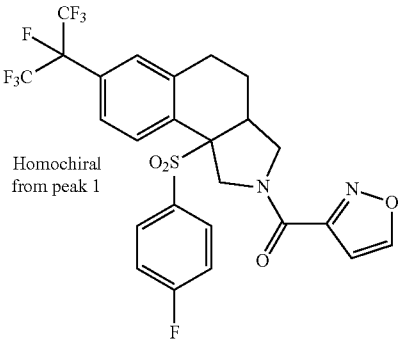
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
615	 Homochiral from peak 1	610.9 $(M + H)^+$	2.24	C
616	 From peak 1	679.1 $(M + H)^+$	2.45	C
617	 Homochiral from peak 1	594.9 $(M + H)^+$	2.2	C
618	 Homochiral from peak 1	595.1 $(M + H)^+$	2.24	D

TABLE 9-continued

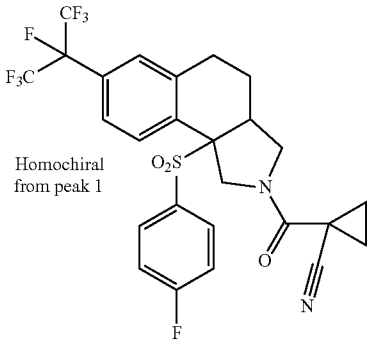
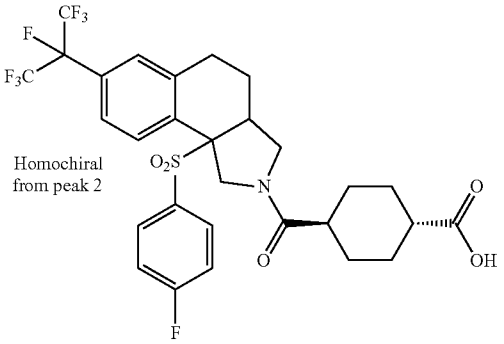
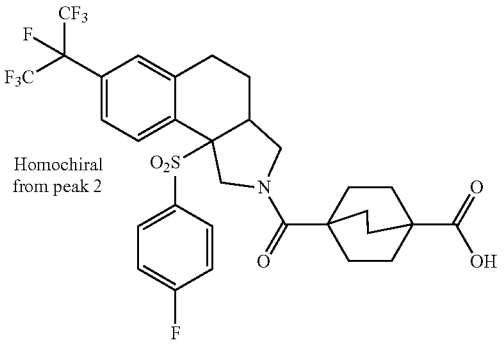
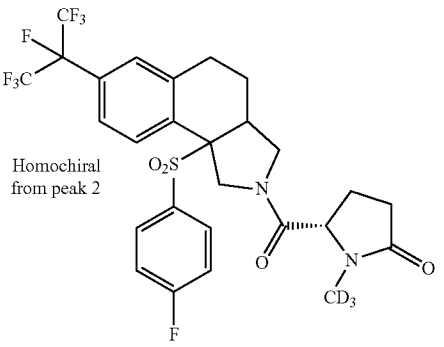
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
619		593.0 $(M + H)^+$	2.26	C
620		654.4 $(M + H)^+$	2.170	D
621		680.4 $(M + H)^+$	2.26	D
622		628.1 $(M + H)^+$	2.053	D

TABLE 9-continued

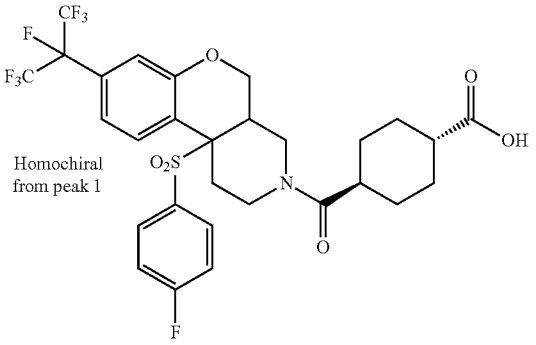
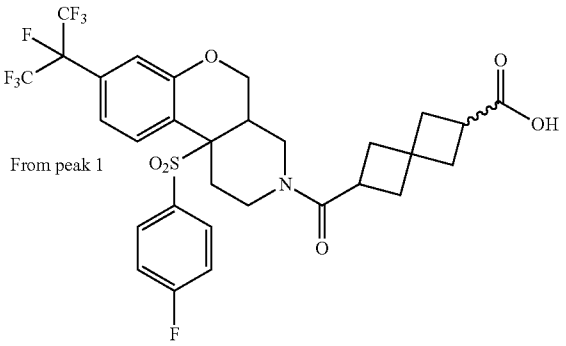
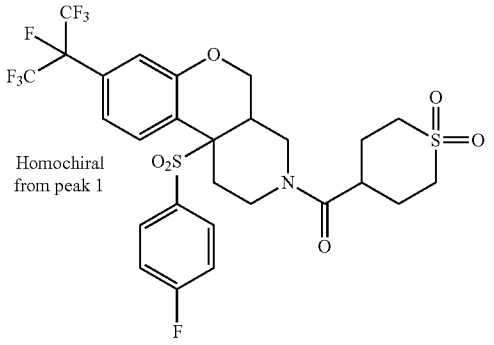
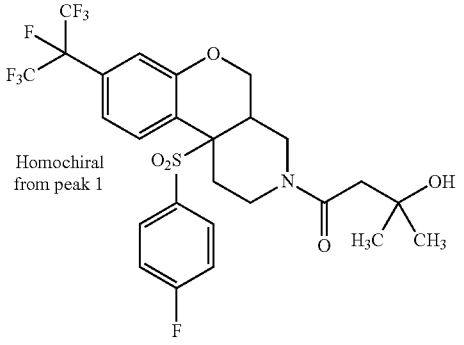
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
623		670.3 $(M + H)^+$	1.01	B
624		682.3 $(M + H)^+$	1.02	B
625		676.2 $(M + H)^+$	0.99	B
626		616.2 $(M + H)^+$	1.03	B

TABLE 9-continued

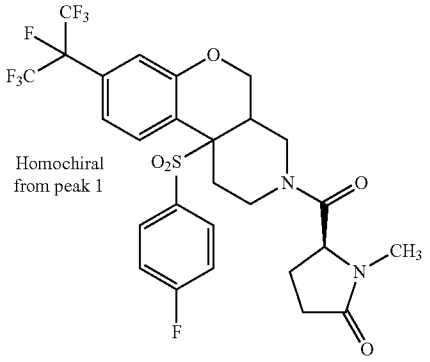
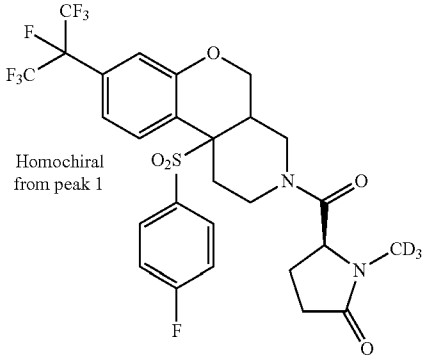
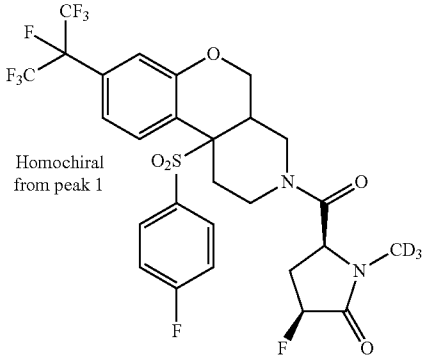
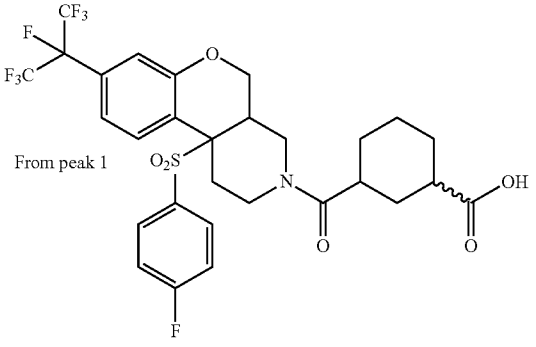
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
627	 Homochiral from peak 1	641.2 $(M + H)^+$	0.97	B
628	 Homochiral from peak 1	644.2 $(M + H)^+$	0.98	B
629	 Homochiral from peak 1	662.2 $(M + H)^+$	1.00	B
630	 From peak 1	670.3 $(M + H)^+$	1.03	B

TABLE 9-continued

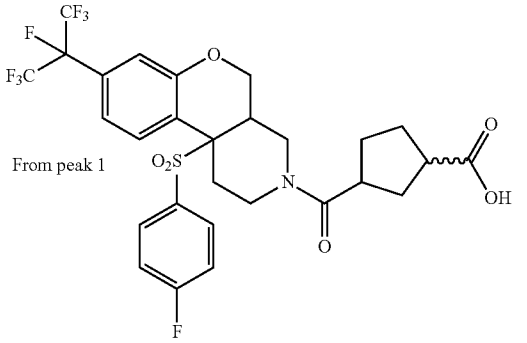
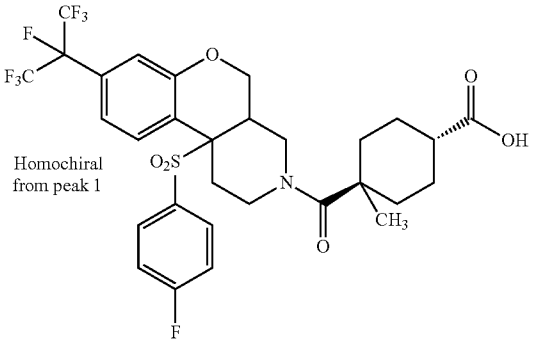
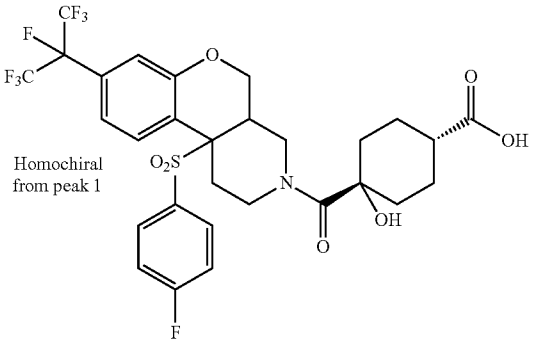
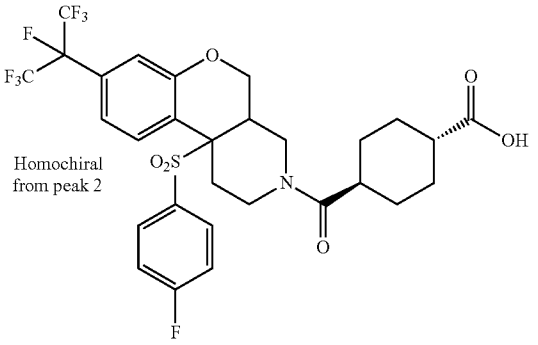
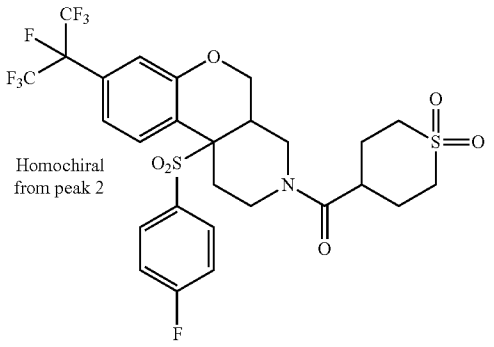
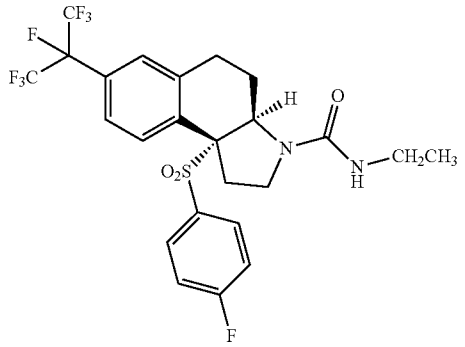
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
631	 From peak 1	656.3 $(M + H)^+$	1.01	B
632	 Homochiral from peak 1	683.9 $(M + H)^+$	1.04	B
633	 Homochiral from peak 1	686.2 $(M + H)^+$	1.00	B
634	 Homochiral from peak 2	670.3 $(M + H)^+$	1.01	B

TABLE 9-continued

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
635	 Homochiral from peak 2	676.3 $(M + H)^+$	1.00	B

Example 636

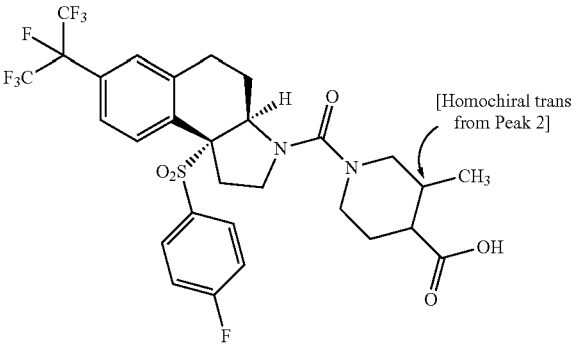
(3aR,9bR)—N-ethyl-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carboxamide



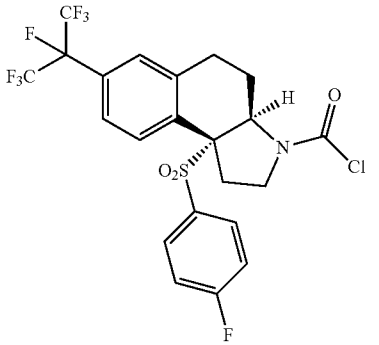
A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) in DMF (1 mL) was treated with DIPEA (0.020 mL, 0.112 mmol) and ethyl isocyanate (4.43 μL, 0.056 mmol). The mixture was stirred at rt for 2 h, then was treated with water (0.1 mL, 5.55 mmol) and purified by preparative HPLC (method E, gradient 40-80% B, 20 min) to afford (3aR,9bR)—N-ethyl-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carboxamide (11.2 mg, 67% yield). LCMS m/z 571.3 $(M+H)^+$, HPLC t_R 2.26 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, J=8.4 Hz, 1H), 7.60 (d, J=8.4 Hz, 1H), 7.46-7.37 (m, 2H), 7.32 (br. s., 1H), 7.23 (t, J=8.5 Hz, 2H), 6.28 (br. s., 1H), 4.55 (dd, J=11.7, 4.7 Hz, 1H), 3.42-3.35 (m, 1H), 3.33-3.27 (m, 1H), 3.27-3.20 (m, 1H), 3.09-2.98 (m, 2H), 2.67-2.56 (m, 1H), 2.29 (d, J=9.0 Hz, 1H), 1.96 (t, J=14.5 Hz, 1H), 1.26-1.14 (m, 2H), 1.00 (t, J=7.1 Hz, 3H).

Example 637

1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylpiperidine-4-carboxylic acid



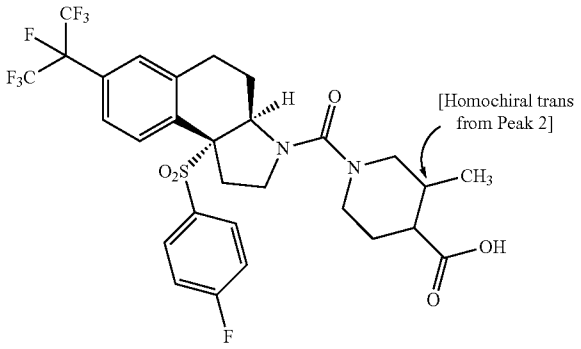
Step A: (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carbonyl chloride



A solution of triphosgene (143 mg, 0.481 mmol) in DCM (5 mL) was placed under nitrogen and cooled to −78° C. The mixture was treated with pyridine (0.162 mL, 2.002 mmol),

stirred for 5 min, and then warmed to rt. After 10 min, a solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 200 mg, 0.400 mmol) and pyridine (0.081 mL, 1.001 mmol) in DCM (2 mL) was added dropwise to the mixture, which then stirred at rt overnight. The mixture was partitioned between DCM (25 mL) and 1 M aqueous HCl (15 mL). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated to give (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carbonyl chloride as an orange solid (180 mg, 80% yield) which was used without further purification.

Step B: 1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylpiperidine-4-carboxylic acid



A solution of crude (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carbonyl chloride (40 mg, 0.071 mmol) and DIPEA (0.037 mL, 0.214 mmol) in DMF (1.2 mL) was treated with trans methyl 3-methylpiperidine-4-carboxylate (homochiral, from peak 2, Intermediate 150; 22.38 mg, 0.142 mmol) and the mixture was stirred at rt. After 2 h, the mixture was diluted with EtOAc (10 mL), washed sequentially with 1 M aqueous HCl, 10% aqueous LiCl and brine, dried over Na_2SO_4 and concentrated to give crude methyl 1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylpiperidine-4-carboxylate. LCMS m/z 683.2 $(M+H)^+$, HPLC t_R 1.16 min (method B). This material was dissolved in THF (2 mL) and treated with a solution of LiOH monohydrate (59.7 mg, 1.424 mmol) in water (1 mL). The mixture was heated at 55° C. for 5 h, cooled to rt and partitioned between EtOAc (10 mL) and 1 M aqueous HCl (5 mL). The organic phase was washed with brine, dried and concentrated. The residue was purified by HPLC (method E, gradient 35-65%) to provide 1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylpiperidine-4-carboxylic acid (10 mg, 21% yield). LCMS m/z 669.2 $(M+H)^+$, HPLC t_R 2.23 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, J=8.5 Hz, 1H), 7.62 (d, J=8.2 Hz, 1H), 7.46-7.36 (m, 3H), 7.35-7.26 (m, 2H), 4.76 (dd, J=8.9, 4.5 Hz, 1H), 3.72-3.28 (m, 2H), 3.13-3.00 (m, 1H), 2.70-2.47 (m, 5H), 2.40 (t, J=12.3 Hz, 1H), 2.16-1.95 (m, 2H), 1.93-1.70 (m, 2H), 1.64-1.37 (m, 3H), 0.83 (d, J=6.3 Hz, 3H).

The Examples in Table 10 were prepared using procedures used to prepare Example 637 or similar procedures by using appropriate amine starting materials, followed by ester hydrolysis or other protecting group removal if appropriate.

TABLE 10

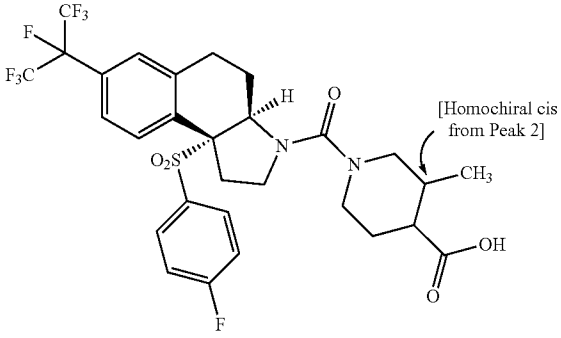
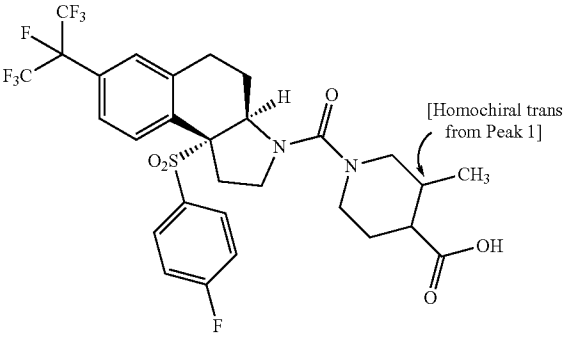
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
638		668.9 $(M+H)^+$	2.22	D
639		669.5 $(M+H)^+$	2.22	D

TABLE 10-continued

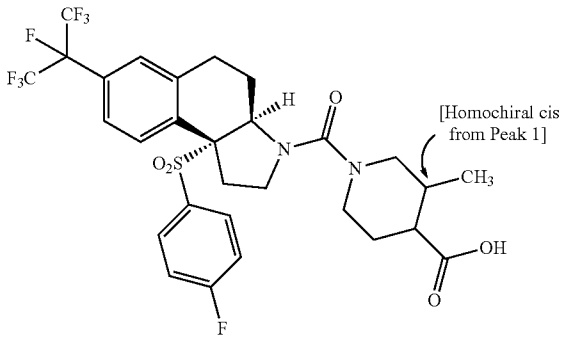
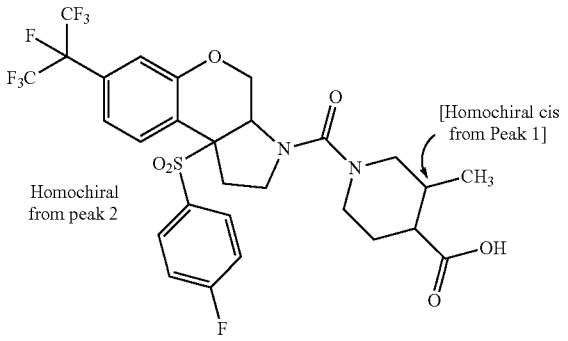
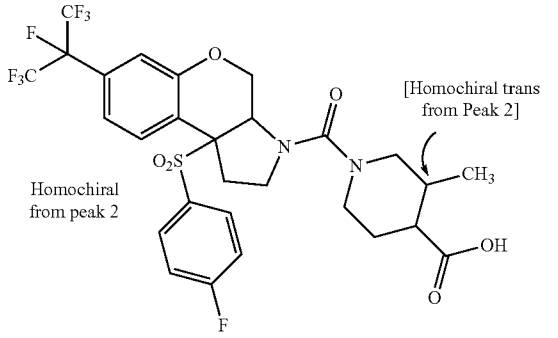
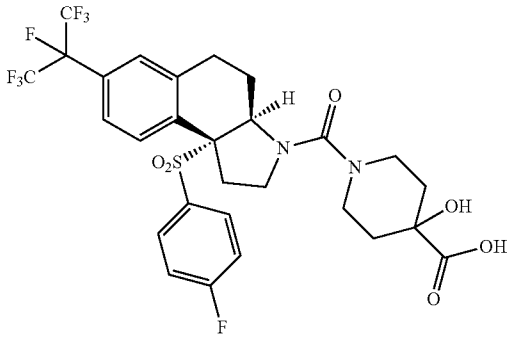
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
640		669.2 (M + H)+	2.23	D
641		671.0 (M + H)+	1.80	C
642		671.4 (M + H)+	1.79	C
643		671.1 (M + H)+	1.99	D

TABLE 10-continued

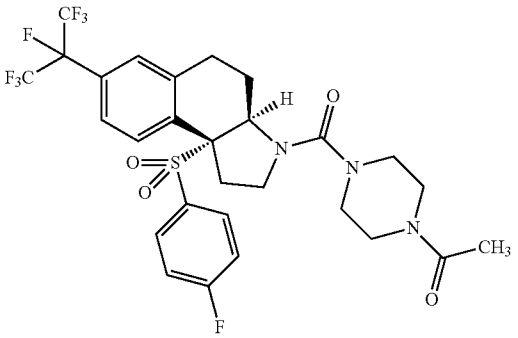
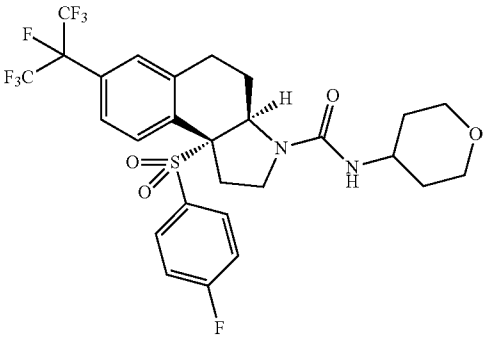
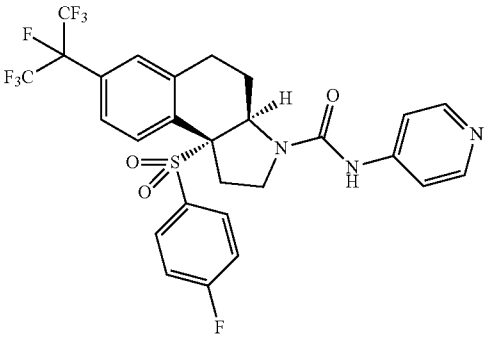
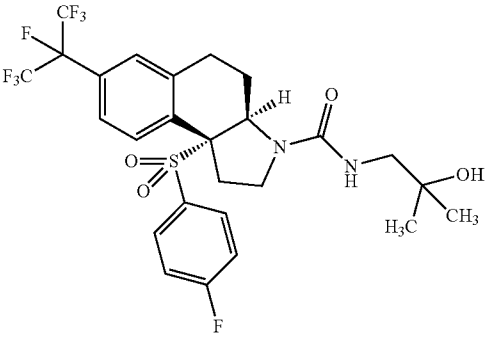
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
644		654.4 $(M + H)^+$	2.12	D
645		627.4 $(M + H)^+$	2.17	D
646		620.3 $(M + H)^+$	1.97	D
647		615.4 $(M + H)^+$	2.12	D

TABLE 10-continued

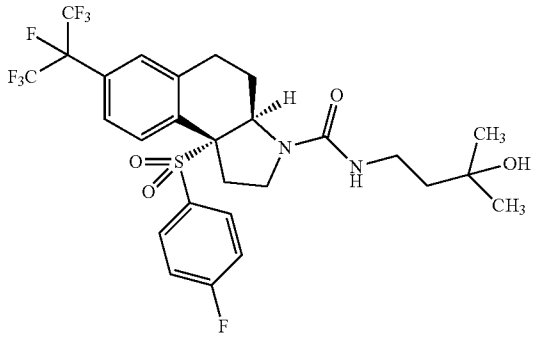
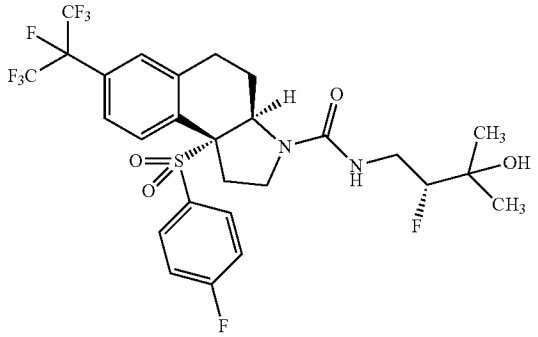
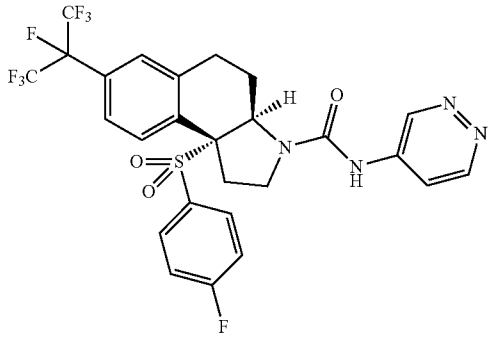
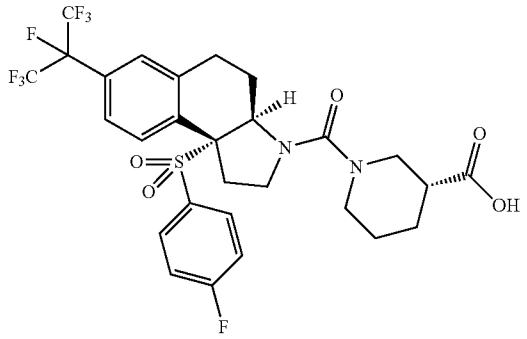
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
648		629.4 $(M + H)^+$	2.15	D
649		647.4 $(M + H)^+$	2.17	D
650		621.2 $(M + H)^+$	2.03	D
651		656.2 $(M + H)^+$	2.21	D

TABLE 10-continued

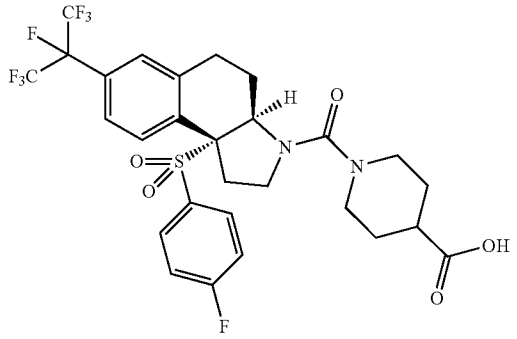
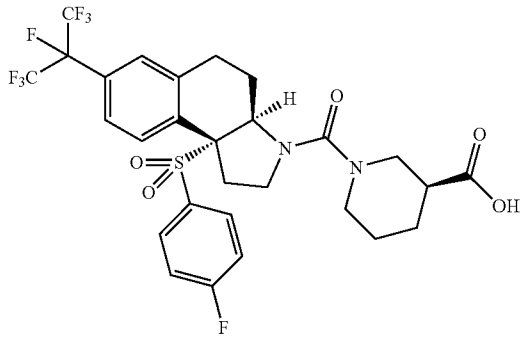
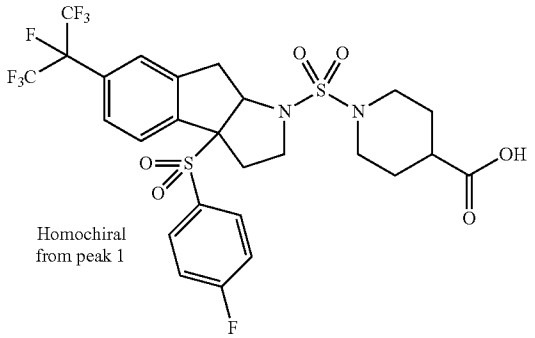
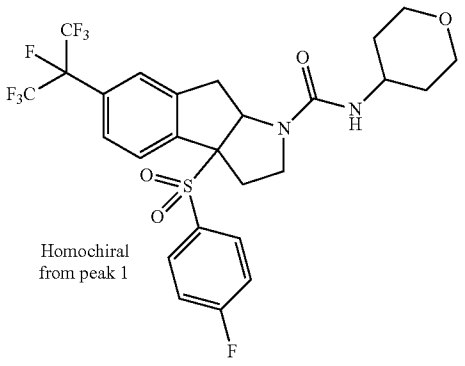
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
652		655.0 $(M + H)^+$	2.13	D
653		655.4 $(M + H)^+$	2.22	D
654	 Homochiral from peak 1	677.3 $(M + H)^+$	1.82	C
655	 Homochiral from peak 1	613.2 $(M + H)^+$	2.12	C

TABLE 10-continued

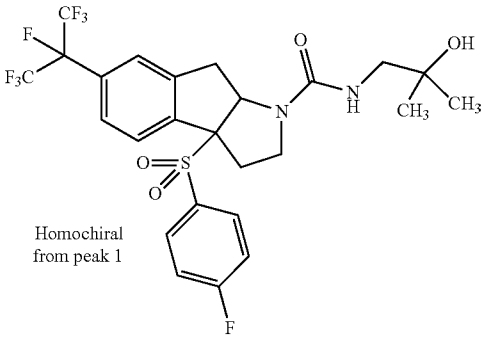
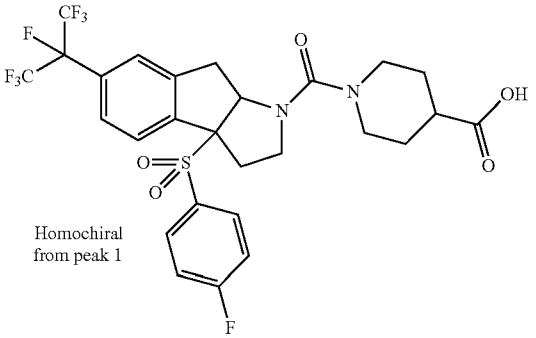
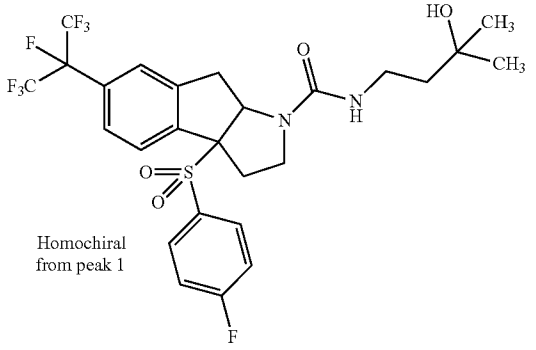
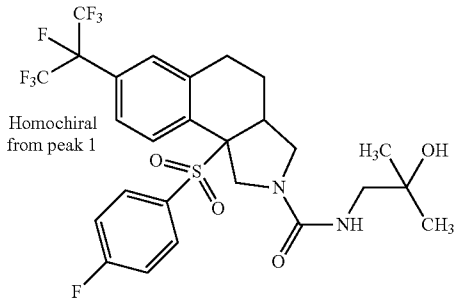
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
656		601.2 $(M + H)^+$	2.06	C
657		641.1 $(M + H)^+$	1.76	C
658		615.2 $(M + H)^+$	2.09	C
659		615.4 $(M + H)^+$	2.14	D

TABLE 10-continued

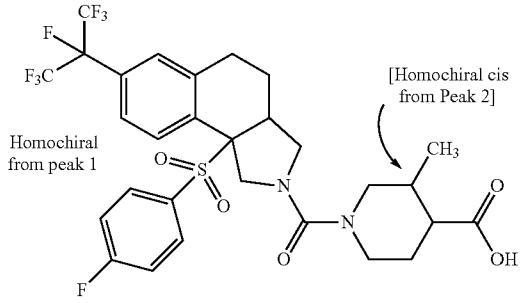
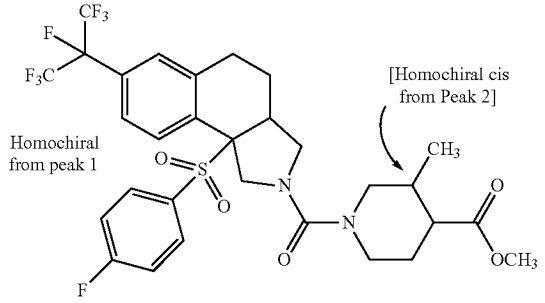
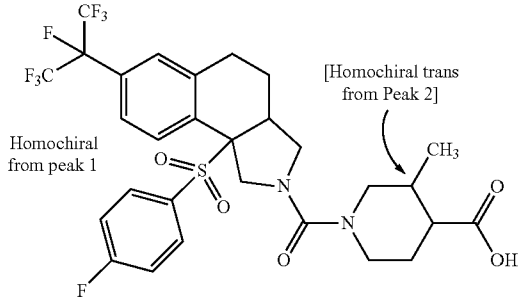
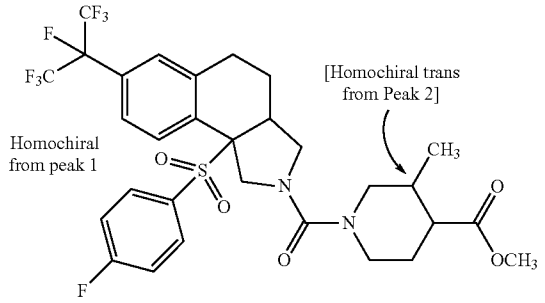
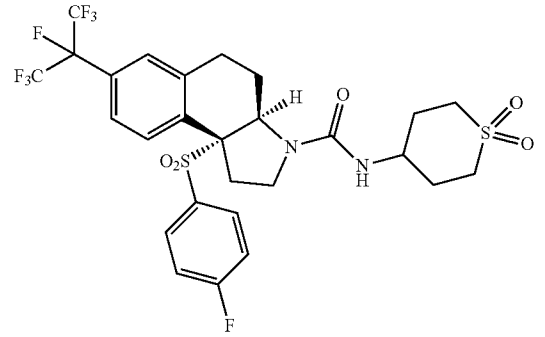
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
660		669.4 $(M + H)^+$	2.23	D
661		683.4 $(M + H)^+$	2.48	D
662		669.4 $(M + H)^+$	2.25	D
663		683.3 $(M + H)^+$	2.50	D
664		675.2 $(M + H)^+$	2.06	C

TABLE 10-continued

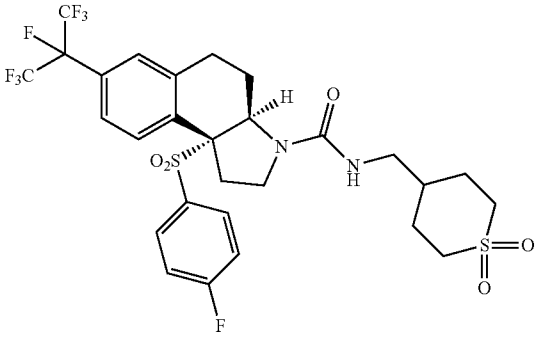
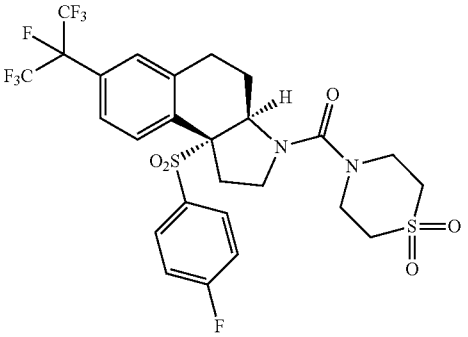
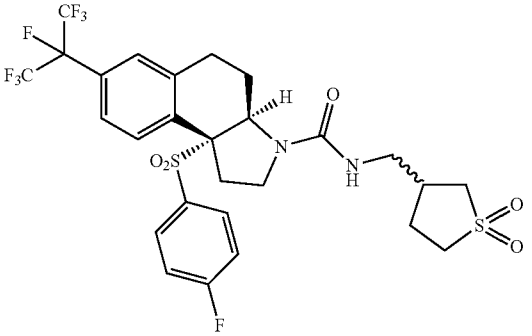
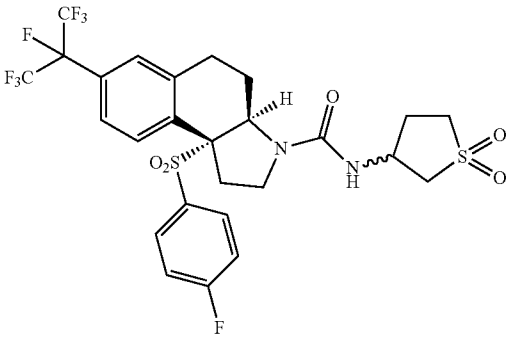
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
665		689.1 $(M + H)^+$	2.04	C
666		661.1 $(M + H)^+$	2.13	C
667		675.0 $(M + H)^+$	2.06	C
668		661.2 $(M + H)^+$	2.09	C

TABLE 10-continued

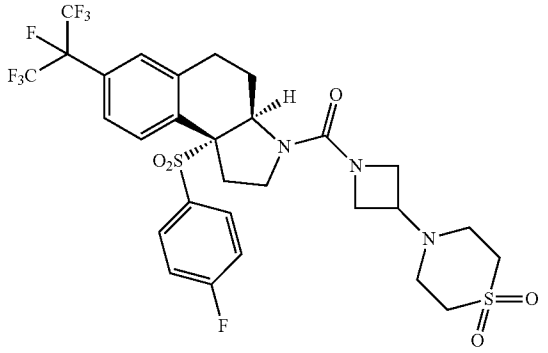
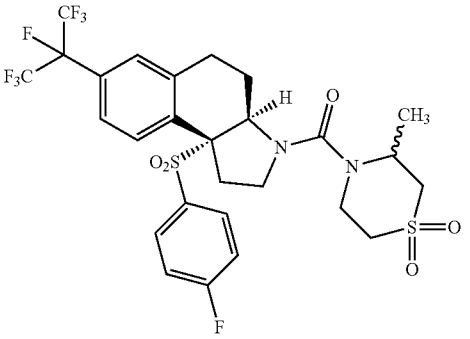
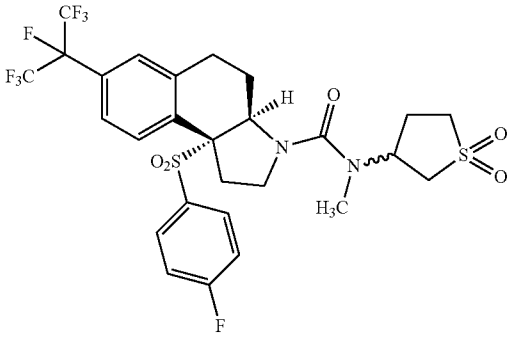
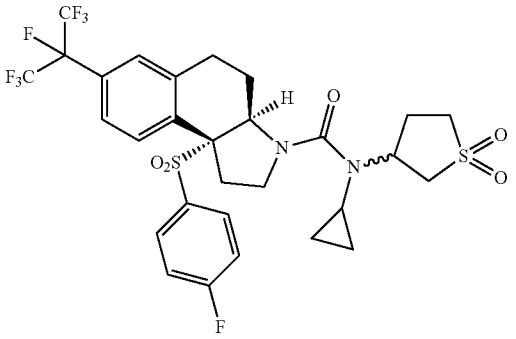
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
669		716.0 $(M + H)^+$	2.06	C
670		675.1 $(M + H)^+$	2.25	C
671		675.2 $(M + H)^+$	2.23	C
672		701.0 $(M + H)^+$	2.35	C

TABLE 10-continued

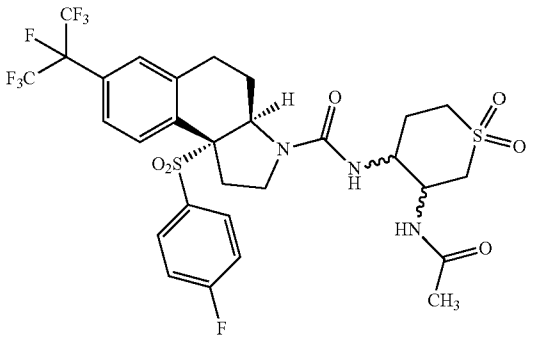
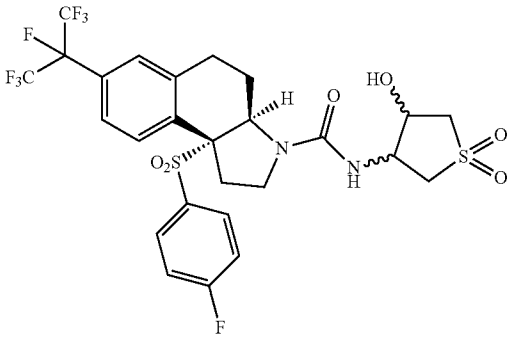
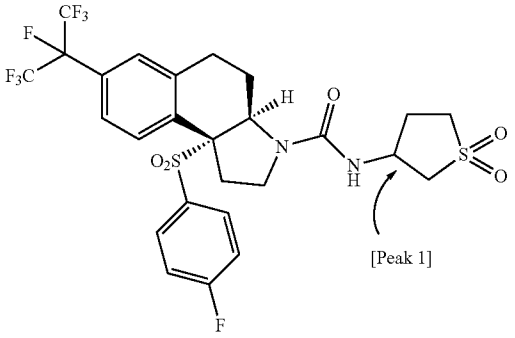
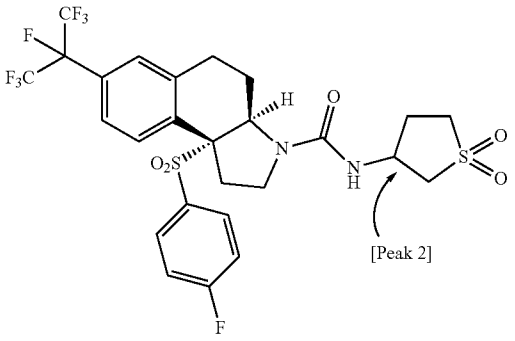
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
673		732.3 $(M + H)^+$	2.07	C
674		677.3 $(M + H)^+$ 1.99 2.01		C
675	 [Peak 1]	661.1 $(M + H)^+$	2.11	C
676	 [Peak 2]	660.8 $(M + H)^+$	2.11	C

TABLE 10-continued

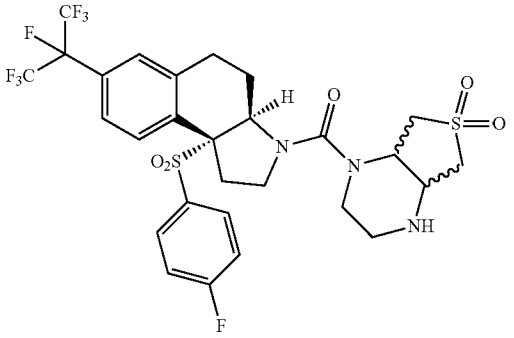
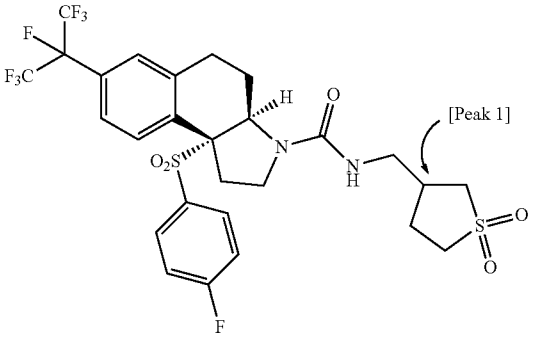
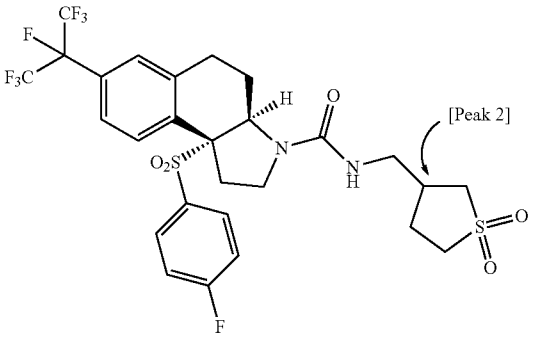
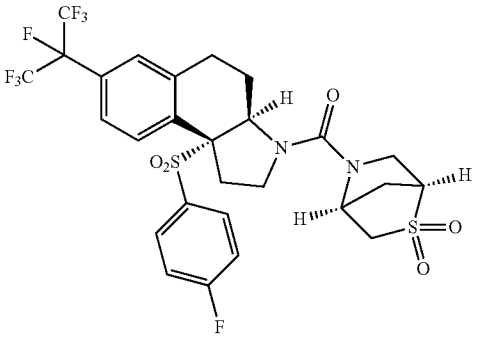
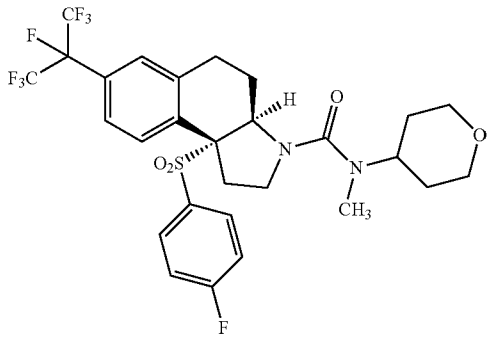
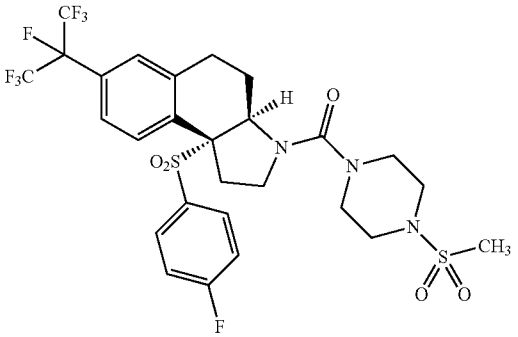
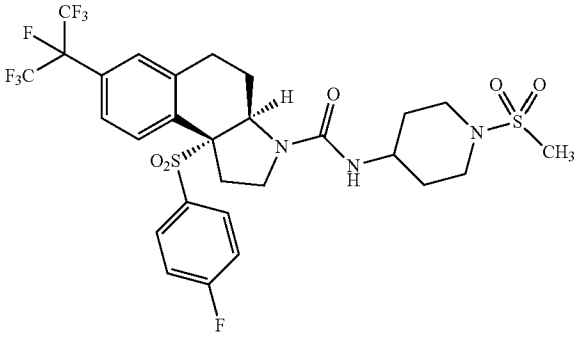
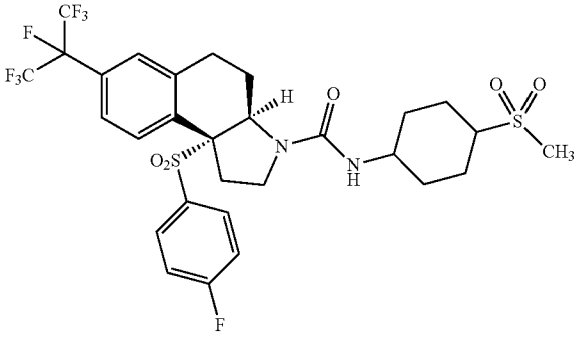
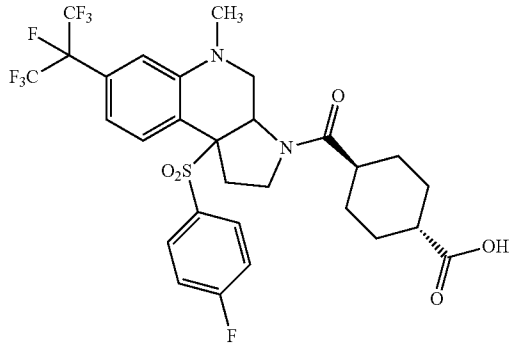
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
677		702.0 $(M + H)^+$	1.81	D
678		675.1 $(M + H)^+$	2.11	C
679		675.1 $(M + H)^+$	2.11	C
680		672.9 $(M + H)^+$	2.15	C

TABLE 10-continued

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
681		641.2 $(M + H)^+$	2.31	C
682		690.2 $(M + H)^+$	2.21	C
683		703.9 $(M + H)^+$	2.18	C
684		689.1 $(M + H)^+$	2.14	C

Example 685

(1r,4r)-4-(9b-((4-fluorophenyl)sulfonyl)-5-methyl-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline-3-carbonyl)cyclohexane-1-carboxylic acid



Homochiral from peak 2

A solution of homochiral (1r,4r)-4-(9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline-3-carbonyl)cyclohexanecarboxylic acid (Example 509; 50 mg, 0.076 mmol) in MeOH (764 μL) was treated with 37% aqueous formaldehyde (62 mg, 0.76 mmol), acetic acid (87 μL, 1.5 mmol) and sodium cyanoborohydride (48 mg, 0.76 mmol), and stirred at rt for 1 h. The mixture was diluted with EtOAc and washed with 1 M aqueous HCl. The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by chiral SFC using the following conditions: Column: Lux® Cellulose-4 46×250 mm, 5 μm (Phenomenex Inc.); column temperature 35° C.; pressure 100 bars; mobile phase CO_2-MeOH (75:25). This provided (1r,4r)-4-(9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline-3-carbonyl) cyclohexanecarboxylic acid (32 mg, 62% yield). LCMS m/z 669.2 $(M+H)^+$, HPLC t_R 1.09 min (method B). ^1H NMR (400 MHz, MeOH-d_4) δ 7.86 (d, J=8.4 Hz, 1H), 7.43-7.35 (m, 2H), 7.13-6.96 (m, 3H), 6.77 (s, 1H), 4.76 (dd, J=10.3, 5.5 Hz, 1H), 4.01-3.88 (m, 1H), 3.86-3.75 (m, 1H), 3.68-3.48 (m, 2H), 3.15 (s, 3H), 2.83-2.70 (m, 1H), 2.66-2.50 (m, 2H), 2.42-2.26 (m, 1H), 2.18-1.94 (m, 3H), 1.94-1.83 (m, 1H), 1.64-1.44 (m, 4H). ^{19}F NMR (376 MHz, MeOH-d_4) δ −104.9 (s, 1F), −77.3 (m, 1F), −77.0 (s, 6F).

The Examples in Table 11 were prepared using procedures used to prepare Example 685 or similar procedures, by using an appropriate amine starting material with an appropriate carbonyl compound.

TABLE 11

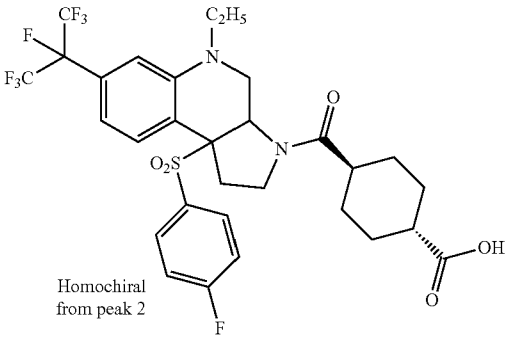
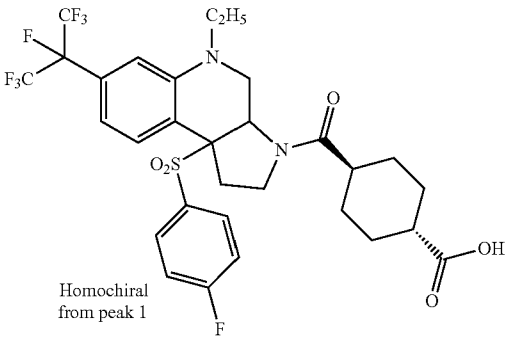
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
686	 Homochiral from peak 2	683.2 $(M + H)^+$	1.13	B
687	 Homochiral from peak 1	683.2 $(M + H)^+$	1.13	B

TABLE 11-continued

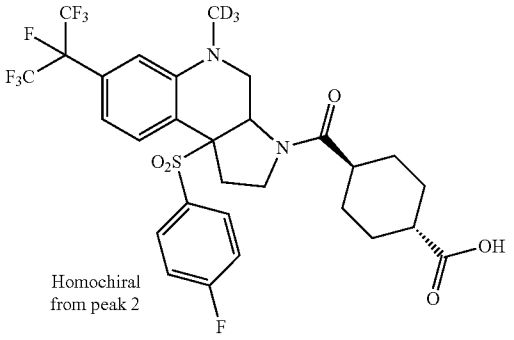
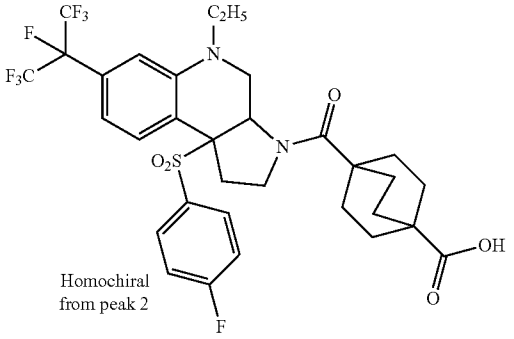
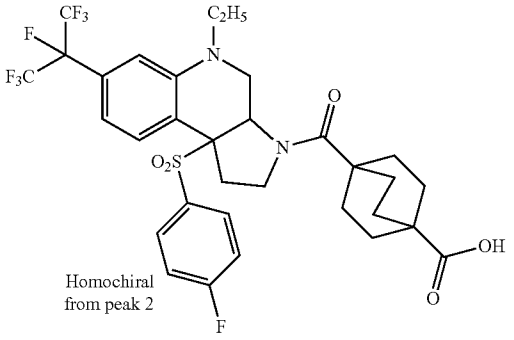
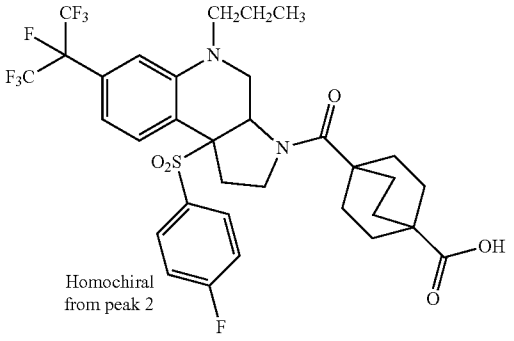
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
688		672.2 $(M + H)^+$	1.10	B
689		695.5 $(M + H)^+$	1.14	B
690		709.5 $(M + H)^+$	1.17	B
691		723.2 $(M + H)^+$	2.29	C

TABLE 11-continued

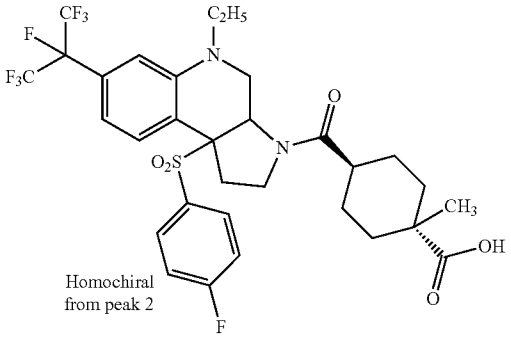
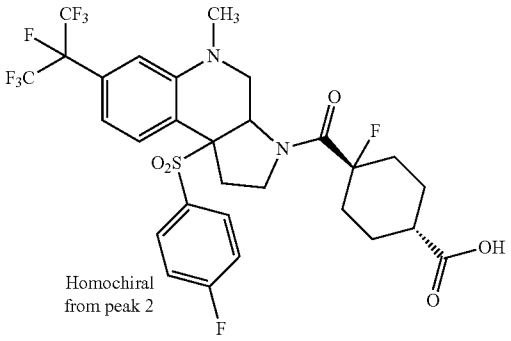
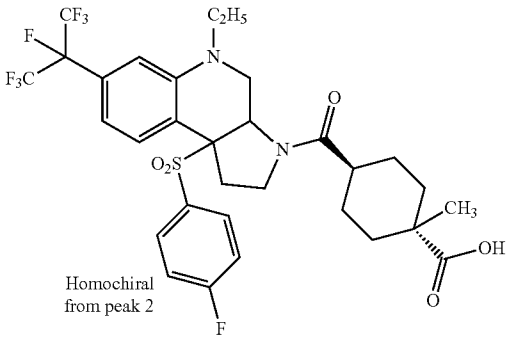
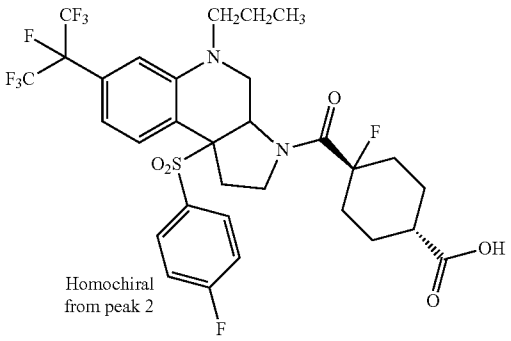
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
692		697.3 $(M + H)^+$	1.16	B
693		687.1 $(M + H)^+$	1.14	B
694		683.2 $(M + H)^+$	1.12	B
695		715.2 $(M + H)^+$	1.19	B

TABLE 11-continued

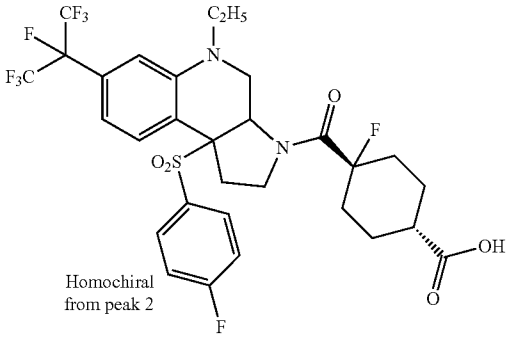
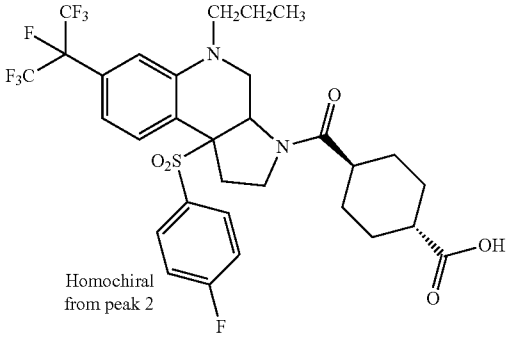
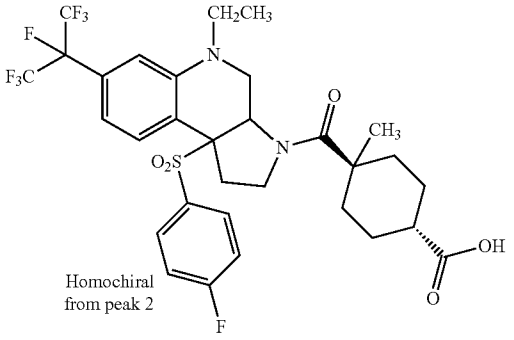
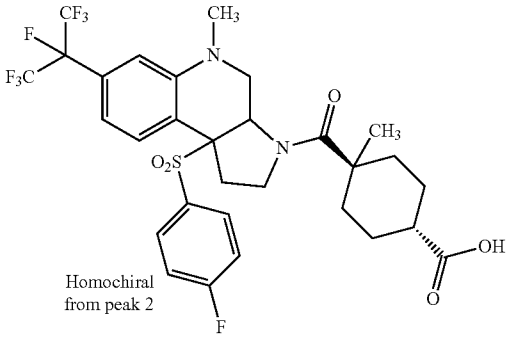
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
696			1.17	B
697		697.1 $(M + H)^+$	1.17	B
698		697.2 $(M + H)^+$	1.17	B
699		683.1 $(M + H)^+$	1.14	B

TABLE 11-continued

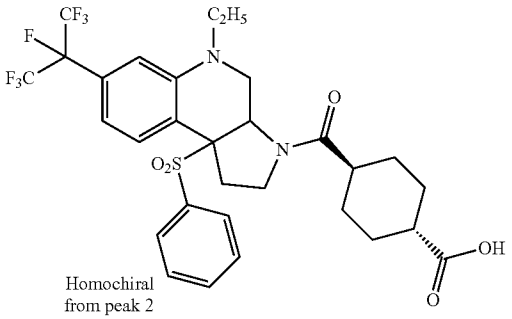
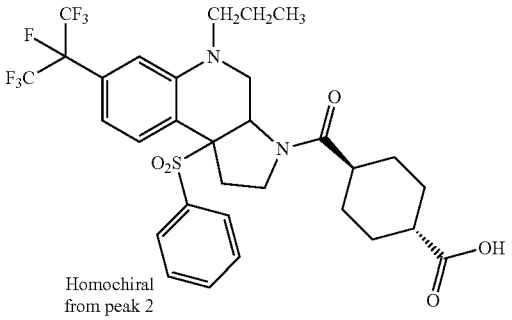
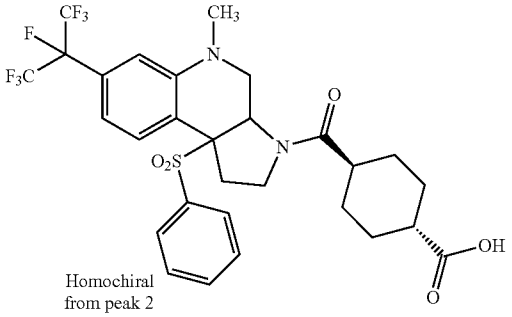
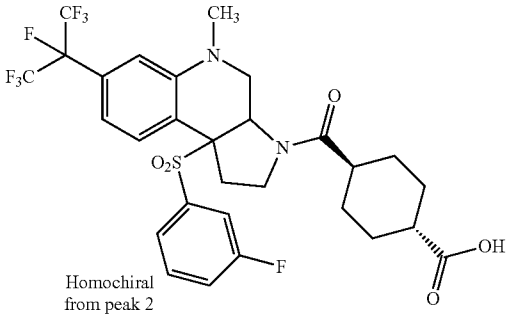
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
700	 Homochiral from peak 2	665.2 $(M + H)^+$	1.07	B
701	 Homochiral from peak 2	679.5 $(M + H)^+$	1.10	B
702	 Homochiral from peak 2	651.1 $(M + H)^+$	1.04	B
703	 Homochiral from peak 2	669.2 $(M + H)^+$	1.08	B

TABLE 11-continued

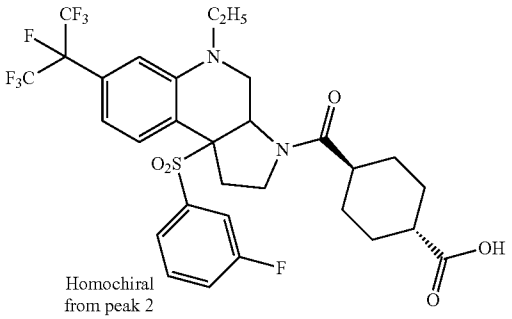
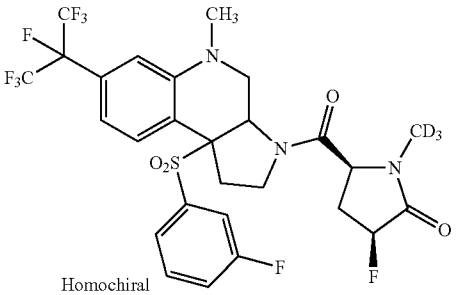
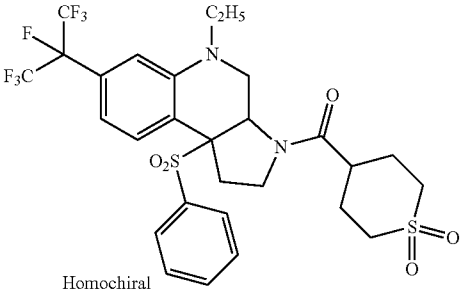
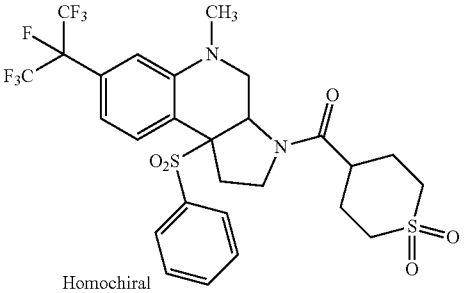
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
704	 Homochiral from peak 2	683.2 $(M + H)^+$	1.11	B
705	 Homochiral from peak 2	661.2 $(M + H)^+$	1.08	B
706	 Homochiral from peak 2	671.1 $(M + H)^+$	1.08	B
707	 Homochiral from peak 2	657.1 $(M + H)^+$	1.05	B

TABLE 11-continued

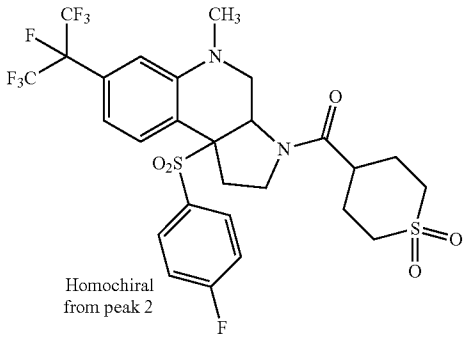
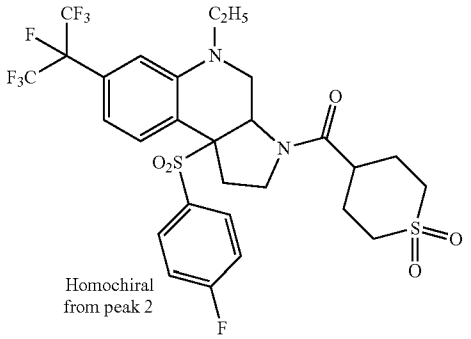
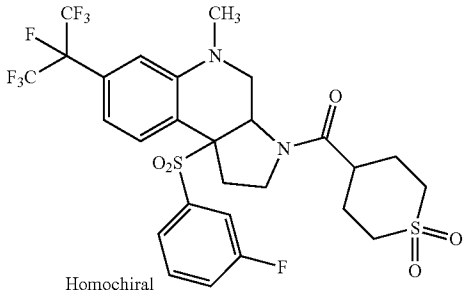
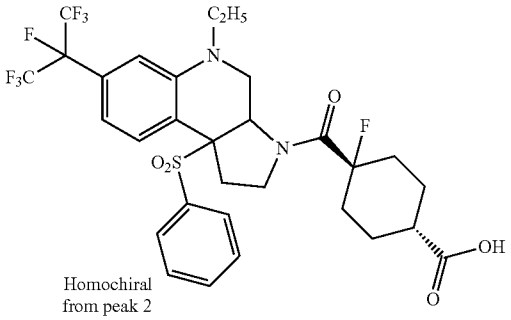
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
708	 Homochiral from peak 2	675.1 $(M + H)^+$	1.06	B
709	 Homochiral from peak 2	689.1 $(M + H)^+$	1.09	B
710	 Homochiral from peak 1	675.1 $(M + H)^+$	1.95	C
711	 Homochiral from peak 2	683.2 $(M + H)^+$	2.21	C

TABLE 11-continued

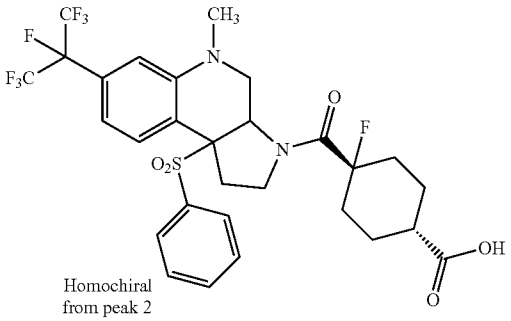
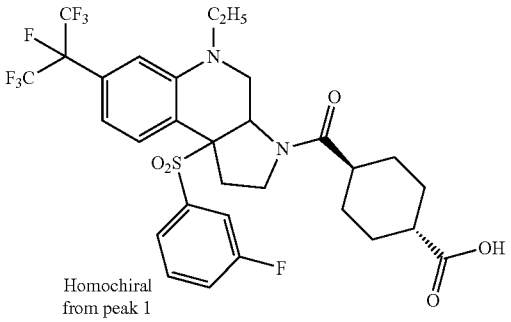
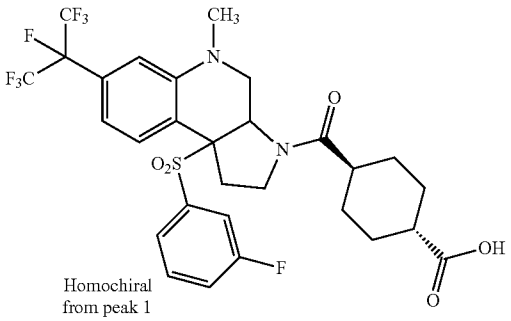
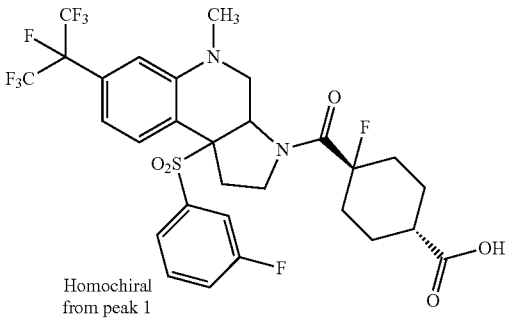
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
712	 Homochiral from peak 2	669.2 $(M + H)^+$	2.29	C
713	 Homochiral from peak 1	683.5 $(M + H)^+$	1.10	B
714	 Homochiral from peak 1	669.4 $(M + H)^+$	1.10	B
715	 Homochiral from peak 1	687.1 $(M + H)^+$	1.07	B

TABLE 11-continued

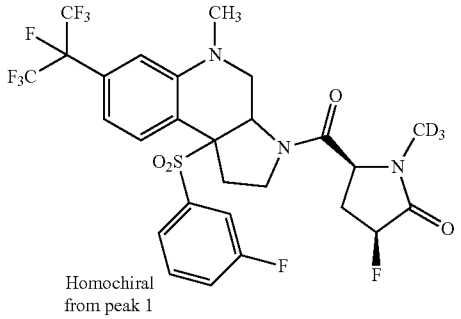
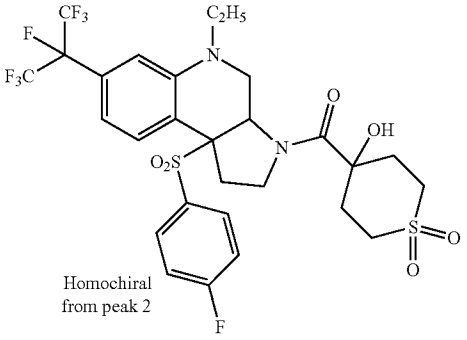
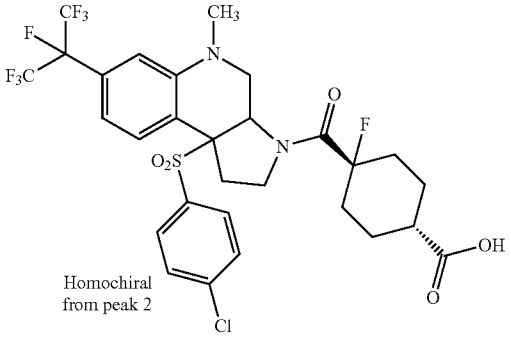
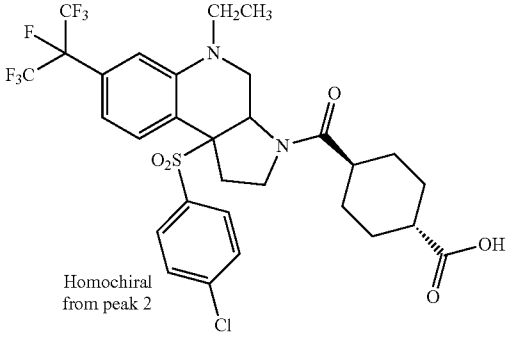
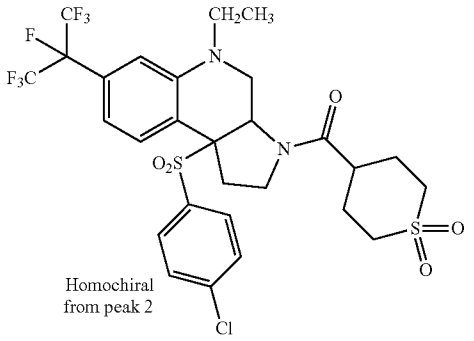
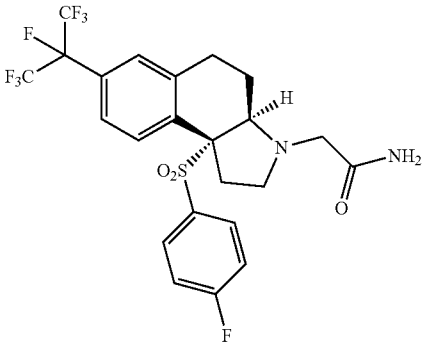
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
716	 Homochiral from peak 1	661.1 $(M + H)^+$	1.05	B
717	 Homochiral from peak 2	691.2 $(M + H)^+$	2.15	C
718	 Homochiral from peak 2	685.2 $(M + H)^+$	2.03	C
719	 Homochiral from peak 2	699.1 $(M + H)^+$	2.15	C

TABLE 11-continued

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
720	 Homochiral from peak 2	705.0 $(M + H)^+$	2.39	C

Example 721

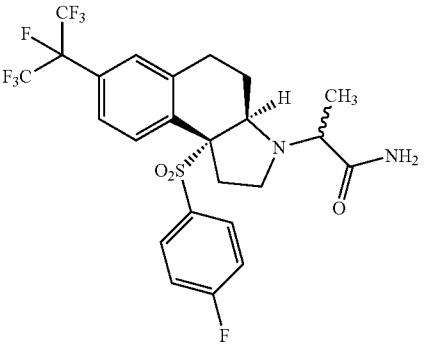
2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetamide



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) in DCM (2 mL) was treated with 2-bromoacetamide (15.5 mg, 0.112 mmol). DIPEA (0.049 mL, 0.28 mmol) was added and the mixture was stirred at rt for 24 h. The mixture was concentrated and the residue was purified by preparative HPLC (method E, gradient 35-100% B, 15 min) to afford 2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetamide (10.8 mg, 69% yield). LCMS m/z 557.0 $(M+H)^+$, HPLC t_R 2.06 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.51 (s, 2H), 7.37-7.27 (m, 4H), 7.26-7.19 (m, 2H), 7.11 (br. s., 1H), 3.70-3.62 (m, 0.5H), 3.60-3.50 (m, 1H), 3.41 (d, J=16.1 Hz, 0.5H), 3.13-3.02 (m, 2H), 2.96 (d, J=16.2 Hz, 1H), 2.71-2.64 (m, 1H), 2.60 (d, J=16.2 Hz, 1H), 2.42-2.32 (m, 1H), 2.10 (d, J=7.3 Hz, 1H), 1.90 (t, J=13.2 Hz, 1H), 1.34-1.23 (m, 1H).

Example 722

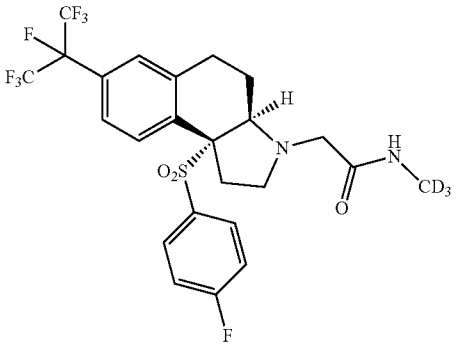
(RS)-2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)propanamide



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) in DMF (1.5 mL) was treated with racemic 2-bromopropanamide (17 mg, 0.112 mmol). DIPEA (0.049 mL, 0.28 mmol) was added and the mixture was heated at 60° C. for 16 h. The mixture was cooled to rt and purified by preparative HPLC (method E, gradient 45-90% B, 22 min) to afford (RS)-2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)propanamide (9.5 mg, 58% yield). LCMS m/z 570.8 $(M+H)^+$, HPLC t_R 2.13 and 2.15 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.59-7.37 (m, 3H), 7.37-7.13 (m, 4H), 7.06 (br. s., 1H), 6.95 (br. s., 1H), 3.51-3.42 (m, 0.5H), 3.38-3.29 (m, 0.5H), 3.18-3.00 (m, 1.5H), 2.99-2.86 (m, 2.5H), 2.76 (s, 0.5H), 2.58 (br. s., 0.5H), 2.41-2.33 (m, 0.5H), 2.31-2.23 (m, 0.5H), 2.22-2.15 (m, 0.5H), 2.12-2.03 (m, 0.5H), 1.92-1.73 (m, 1.5H), 1.30-1.22 (m, 0.5H), 1.20 (d, J=6.9 Hz, 1.5H), 1.14 (d, J=6.8 Hz, 1.5H).

Example 723

2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)-N-(methyl-d_3)acetamide



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 21.1 mg, 0.037 mmol) in DMF (1 mL) was treated with methyl 2-bromoacetate (0.012 mL, 0.123 mmol). DIPEA (0.049 mL, 0.28 mmol) was added and the mixture was stirred at rt for 2 h. The mixture was treated with brine (1 mL) and extracted with EtOAc (10 mL). The organic extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (2 mL) and treated with a solution of LiOH monohydrate (13.29 mg, 0.555 mmol) in water (0.5 mL). MeOH (0.3 mL) was added to afford a clear solution and the mixture was stirred at rt for 2 h. The mixture was concentrated and diluted with EtOAc (5 mL) and 1 M aqueous HCl (5 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (2 mL) and treated with HATU (56.3 mg, 0.148 mmol), DIPEA and methan-d_3-amine hydrochloride (10.44 mg, 0.148 mmol). The mixture was stirred at rt for 16 h. The mixture was purified by preparative HPLC (method F, gradient 45-90% B, 20 min) to afford 2-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)-N-(methyl-d_3) acetamide (8.1 mg, 37% yield). LCMS m/z 574.3 $(M+H)^+$, HPLC t_R 2.19 min (method C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.56-7.44 (m, 2H), 7.39-7.29 (m, 3H), 7.28-7.16 (m, 2H), 3.68 (dd, J=9.4, 6.1 Hz, 1H), 3.41 (br. s., 1H), 3.10 (dd, J=13.5, 5.3 Hz, 1H), 3.06-2.99 (m, 1H), 2.97 (s, 1H), 2.71-2.57 (m, 2H), 2.44-2.32 (m, 1H), 2.08 (dd, J=12.5, 5.2 Hz, 1H), 1.91 (t, J=13.5 Hz, 1H), 1.38-1.24 (m, 1H).

The Examples in Table 12 were prepared using the procedures used to prepare Examples 721 through 723, or similar procedures, by using the appropriate alkyl bromide or alkyl chloride, followed by ester hydrolysis or other protecting group removal if required.

TABLE 12

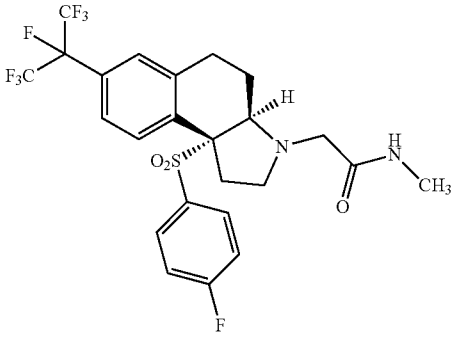
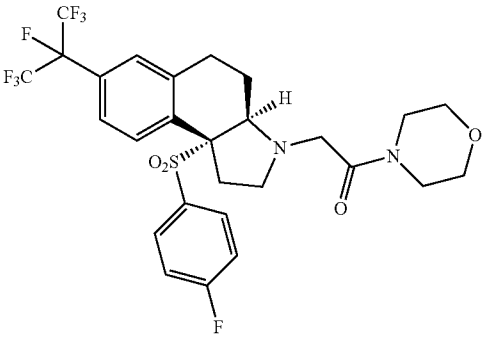
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
724		570.8 $(M + H)^+$	2.14	C
725		627.0 $(M + H)^+$	2.19	C

TABLE 12-continued

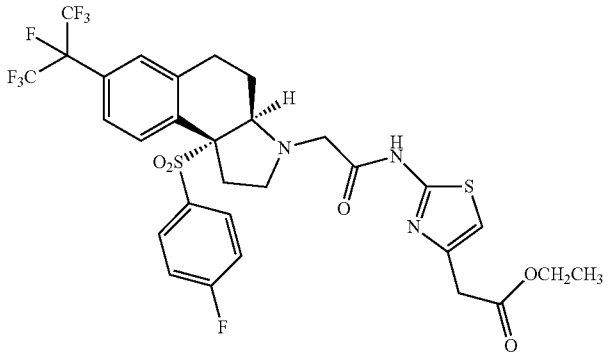
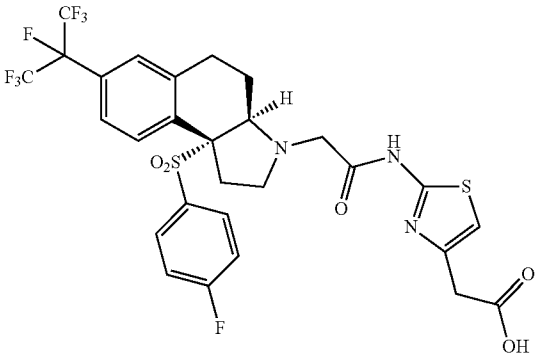
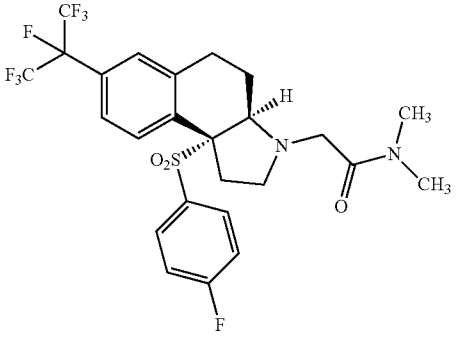
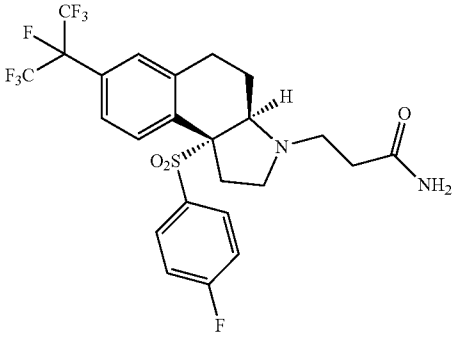
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
726		726.0 $(M + H)^+$	2.46	C
727		698.4 $(M + H)^+$	1.83	C
728		548.8 $(M + H)^+$	2.22	C
729		571.0 $(M + H)^+$	2.01	C

TABLE 12-continued

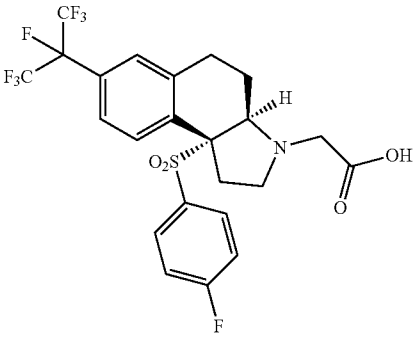
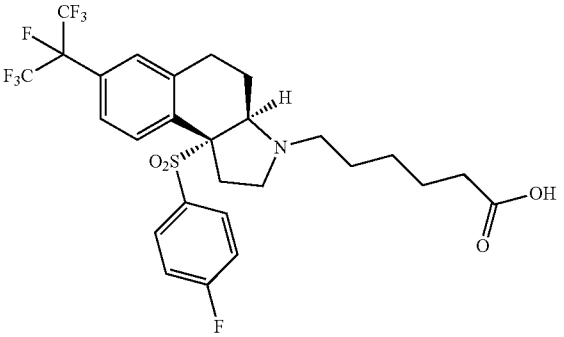
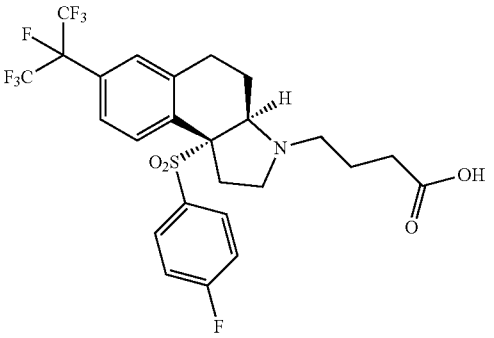
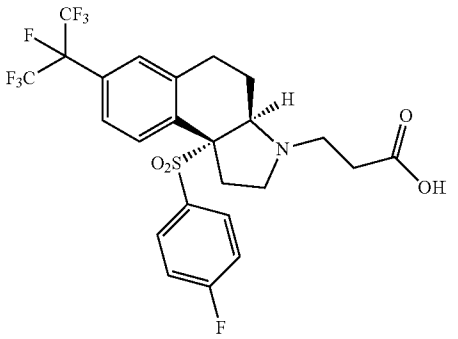
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
730		558.2 $(M + H)^+$	1.72	C
731		614.1 $(M + H)^+$	2.14	C
732		586.3 $(M + H)^+$	1.86	C
733		572.0 $(M + H)^+$	1.81	C

TABLE 12-continued

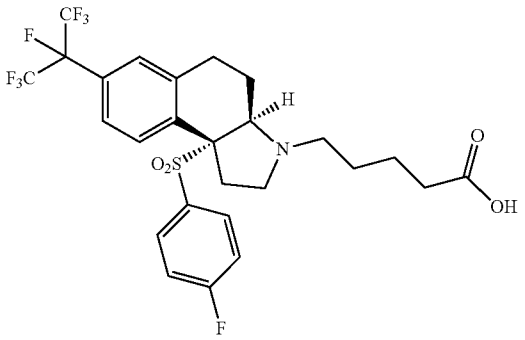
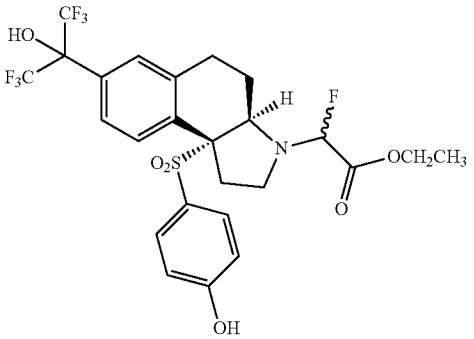
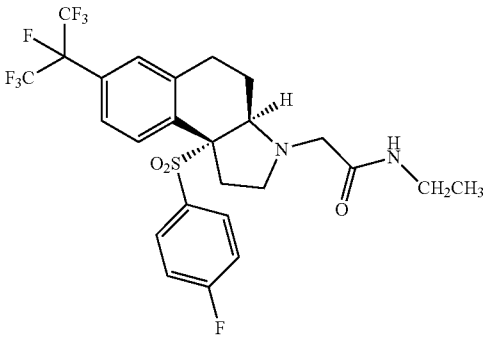
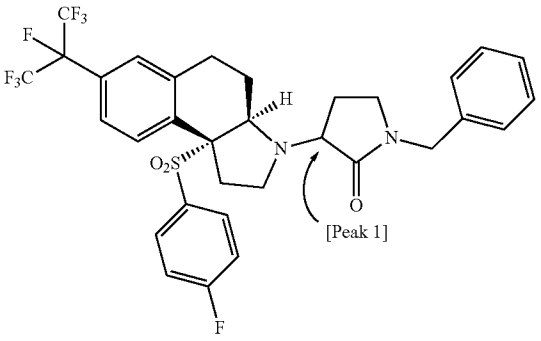
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
734		599.9 $(M + H)^+$	1.96	C
735		600.4 $(M + H)^+$	2.37	C
736		585.3 $(M + H)^+$	2.29	C
737		673.5 $(M + H)^+$	2.57	C

TABLE 12-continued

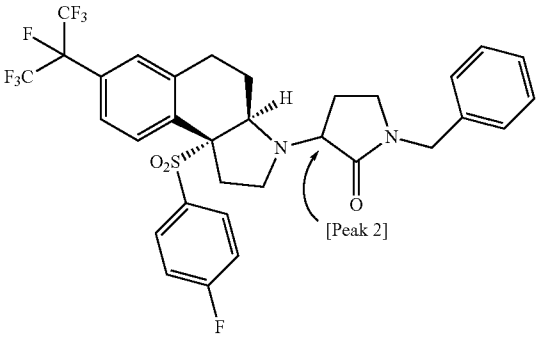
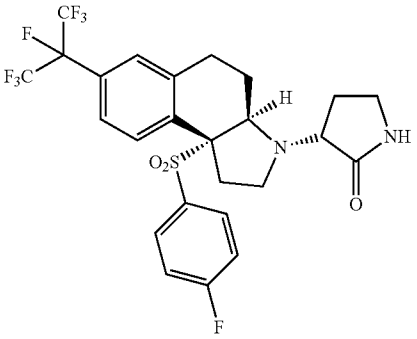
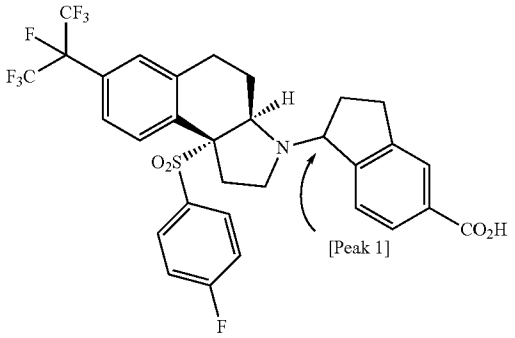
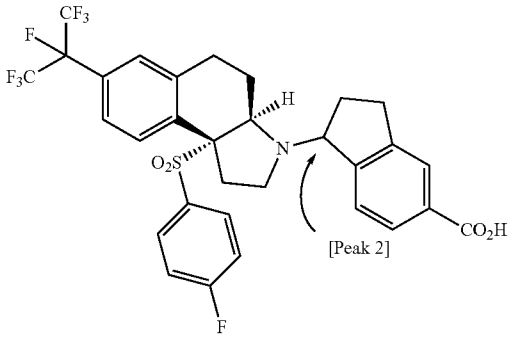
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
738		673.4 $(M + H)^+$	2.51	C
739		583.0 $(M + H)^+$	2.06	C
740		660.3 $(M + H)^+$	2.24	C
741		660.0 $(M + H)^+$	2.21	C

TABLE 12-continued

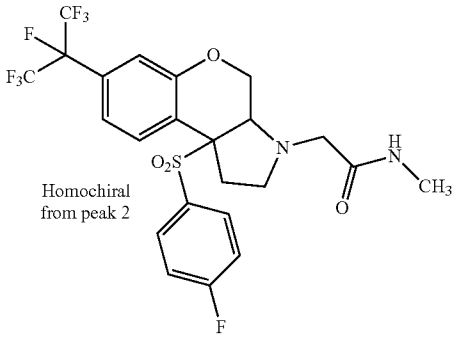
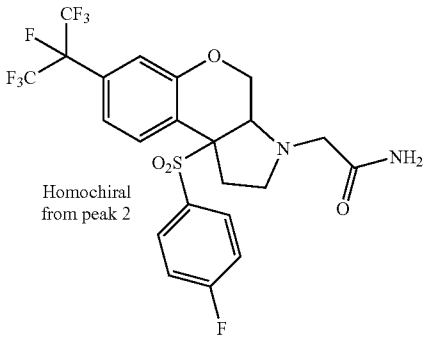
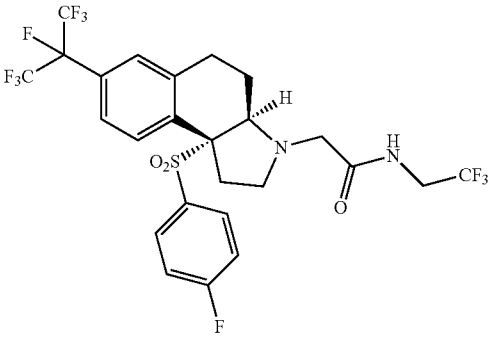
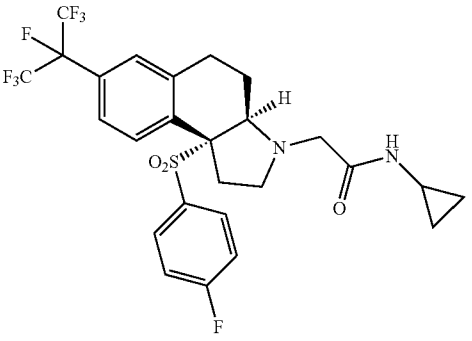
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
742	 Homochiral from peak 2	572.8 $(M + H)^+$	2.07	C
743	 Homochiral from peak 2	558.9 $(M + H)^+$	1.99	C
744		639.4 $(M + H)^+$	2.40	C
745		597.3 $(M + H)^+$	2.31	C

TABLE 12-continued

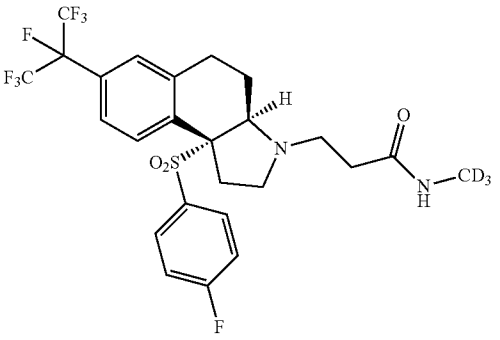
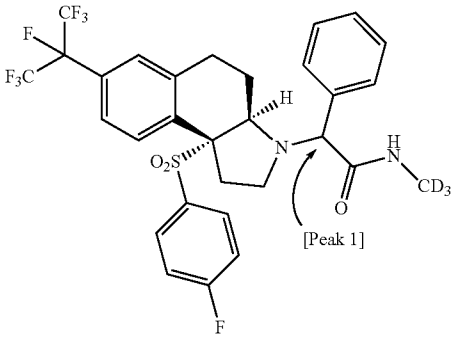
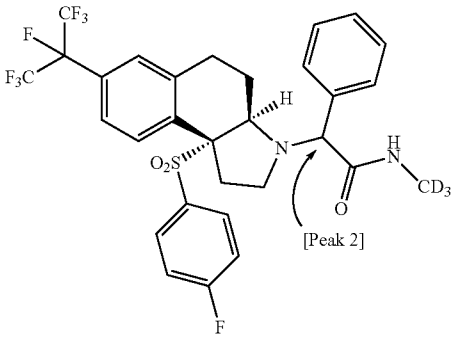
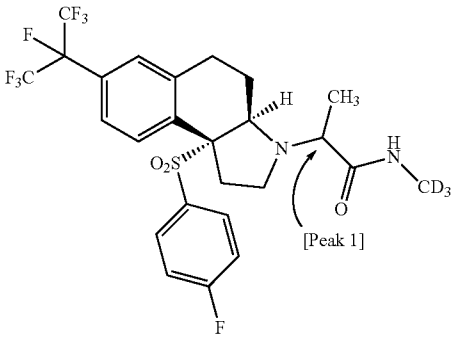
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
746		588.4 $(M + H)^+$	2.12	C
747		650.4 $(M + H)^+$	2.38	C
748		650.4 $(M + H)^+$	2.44	C
749		587.9 $(M + H)^+$	2.22	C

TABLE 12-continued

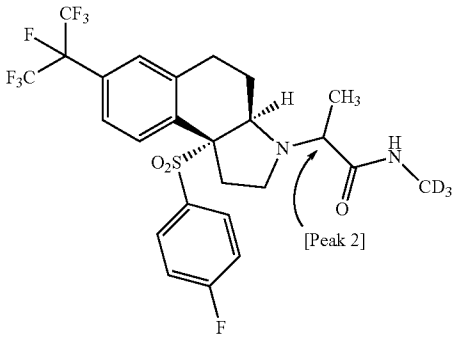
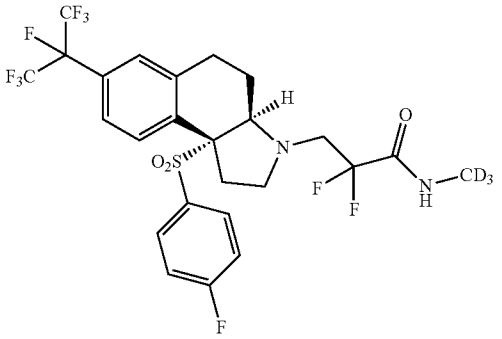
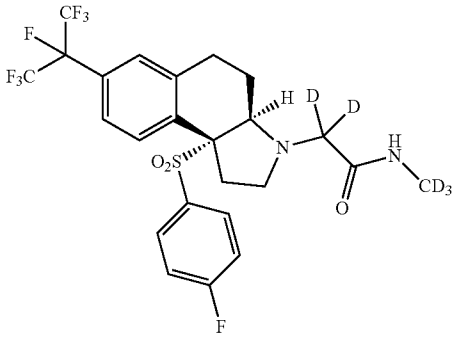
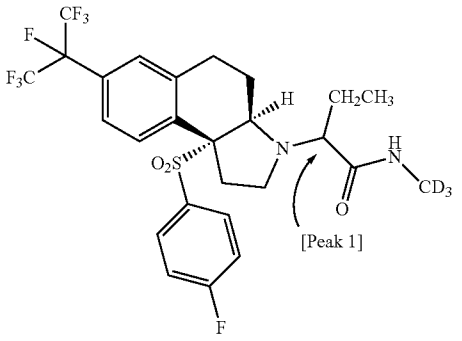
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
750		588.2 $(M + H)^+$	2.24	C
751		623.8 $(M + H)^+$	2.31	C
752		576.3 $(M + H)^+$	2.19	C
753		602.1 $(M + H)^+$	2.26	C

TABLE 12-continued

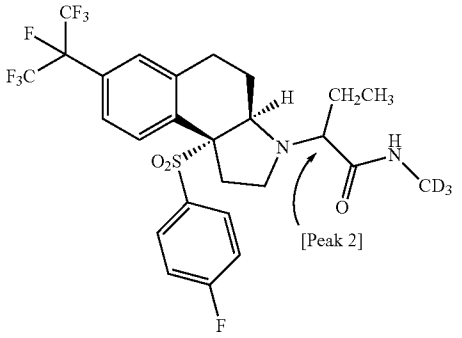
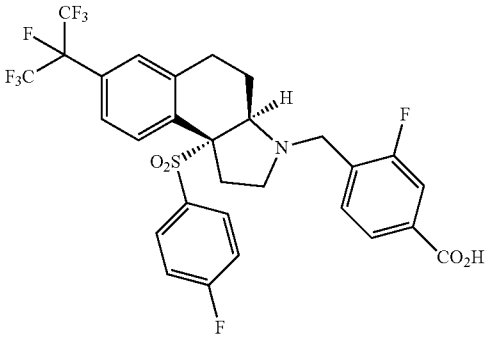
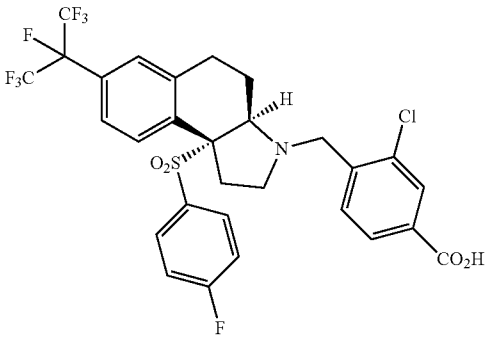
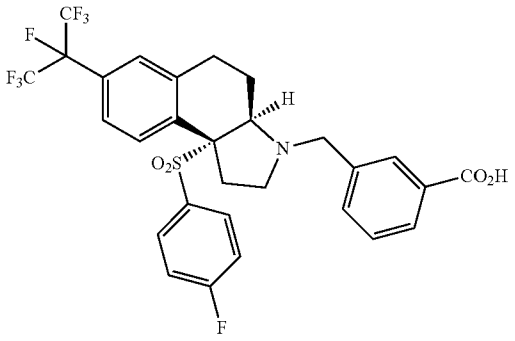
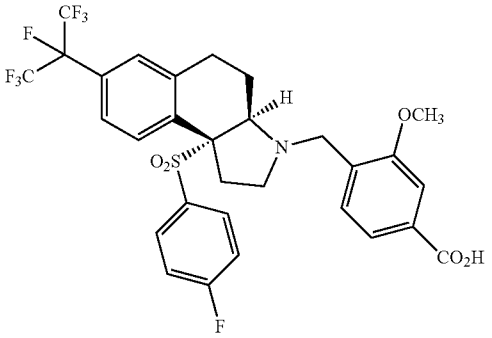
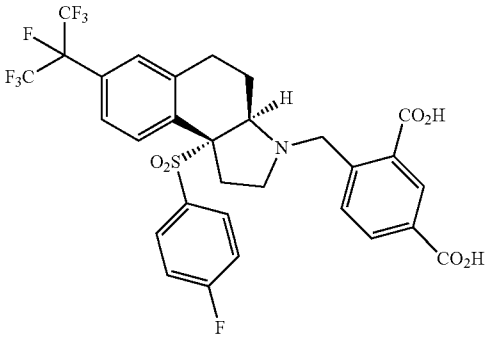
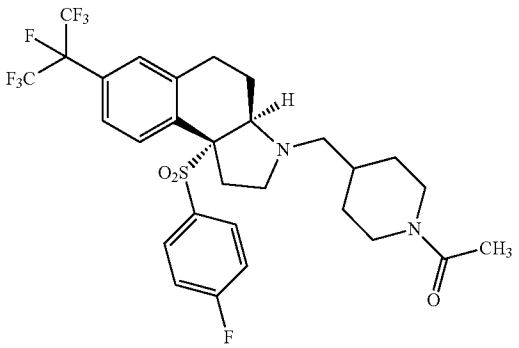
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
754		602.0 $(M + H)^+$	2.32	C
755		652.3 $(M + H)^+$	2.02	C
756		668.3 $(M + H)^+$	2.10	C
757		634.1 $(M + H)^+$	2.09	C

TABLE 12-continued

Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
758		664.2 $(M + H)^+$	2.07	C
759		678.0 $(M + H)^+$	1.67	C

Example 760

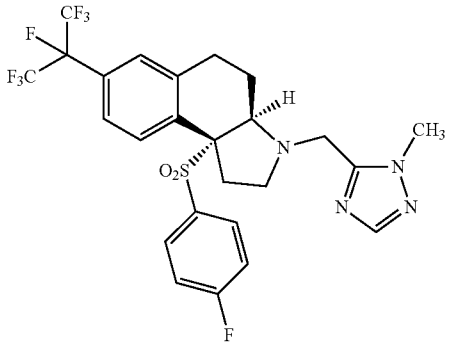
1-(4-(((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methyl)piperidin-1-yl)ethan-1-one



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 20 mg, 0.037 mmol) in 1,2-dichloroethane (2 mL) was treated with tert-butyl 4-formylpiperidine-1-carboxylate (19.9 mg, 0.093 mmol). DIPEA (0.02 mL, 0.112 mmol) was added and the mixture was stirred at rt for 30 min. The mixture was then treated with sodium triacetoxyborohydride (27.7 mg, 0.131 mmole). After 16 h, the mixture was concentrated. The residue was taken up in EtOAc (10 mL) and washed with 1 M aqueous NaOH (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in DCM (3 mL) and TFA (0.5 mL) and the mixture was stirred at rt for 20 min. The mixture was concentrated, and the residue was dissolved in DCM (2 mL) and treated with Et_3N (0.049 mL, 0.35 mmol) followed by a solution of acetyl chloride (7.11 μL, 0.100 mmol) in DCM (0.5 mL). The mixture was stirred at rt for 1.5 h, then was treated with MeOH (0.5 mL). The mixture was stirred at rt for 5 min and concentrated. The residue was purified by preparative HPLC (method F, gradient 30-70% B, 20 min) to afford 1-(4-(((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methyl)piperidin-1-yl)ethan-1-one (13.8 mg, 86% yield). LCMS m/z 639.1 $(M+H)^+$, HPLC t_R 2.37 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.52 (d, J=8.3 Hz, 1H), 7.46-7.31 (m, 4H), 7.31-7.21 (m, 3H), 7.16 (s, 1H), 7.06 (s, 1H), 4.35 (t, J=12.6 Hz, 1H), 3.81 (br. s., 1H), 3.54-3.36 (m, 1H), 3.33-3.21 (m, 1H), 3.13-2.95 (m, 2H), 2.77 (d, J=15.7 Hz, 1H), 2.60-2.53 (m, 3H), 2.06 (br. s., 1H), 1.98 (d, J=2.2 Hz, 3H), 1.95-1.67 (m, 3H), 1.56 (d, J=11.5 Hz, 1H), 1.25-0.92 (m, 2H).

Example 761

(3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-3-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.030 mmol) in DMF (1 mL) was treated with 1-methyl-1H-1,2,4-triazole-5-carbaldehyde (16.68 mg, 0.150 mmol) and Et_3N (6.1 μL, 0.044 mmol). Sodium triacetoxyborohydride (63.7 mg, 0.300 mmole) was added and the mixture was stirred at rt for 3 h. The mixture was treated with water (0.1 mL, 5.55 mmol) and purified by preparative HPLC (method E, gradient 45-90% B, 22 min) to afford (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-3-((1-methyl-1H-1,2,4-triazol-5-yl)methyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (12.0 mg, 67% yield). LCMS m/z 594.9 $(M+H)^+$, HPLC t_R 2.17 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.54-7.43 (m, 2H), 7.35-7.27 (m, 3H), 7.27-7.18 (m, 2H), 4.15 (d, J=14.1 Hz, 1H), 3.85 (d, J=14.1 Hz, 1H), 3.79 (s, 2H), 3.10 (dd, J=14.0, 5.3 Hz, 1H), 2.88 (t, J=7.7 Hz, 1H), 2.77-2.69 (m, 1H), 2.59-2.53 (m, 1H), 2.36-2.23 (m, 1H), 2.10-1.97 (m, 1H), 1.87 (t, J=13.2 Hz, 1H), 1.28-1.13 (m, 3H).

The Examples in Table 13 were prepared using the procedures used to prepare Examples 760 and 761 using the appropriate carbonyl compound, followed by ester hydrolysis or other protecting group removal if required.

TABLE 13

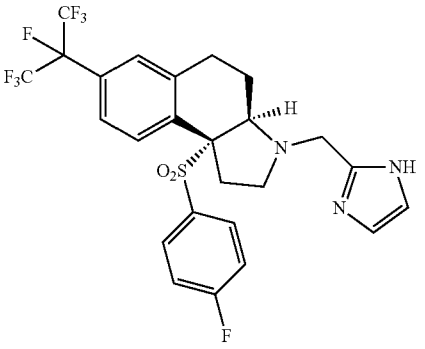
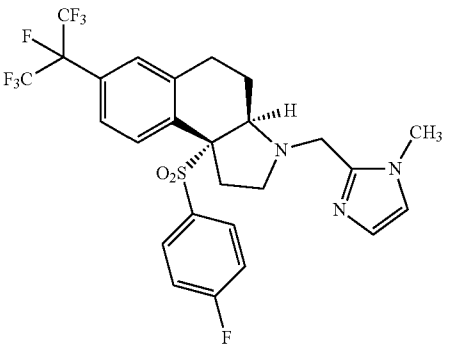
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
762		579.8 $(M + H)^+$	2.03	C
763		593.9 $(M + H)^+$	2.24	C

TABLE 13-continued

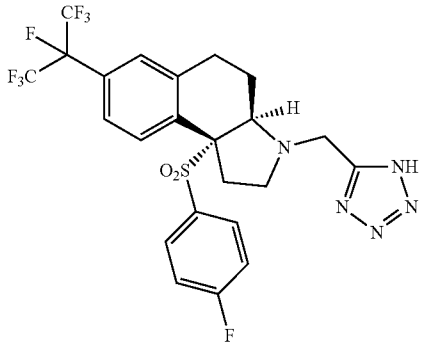
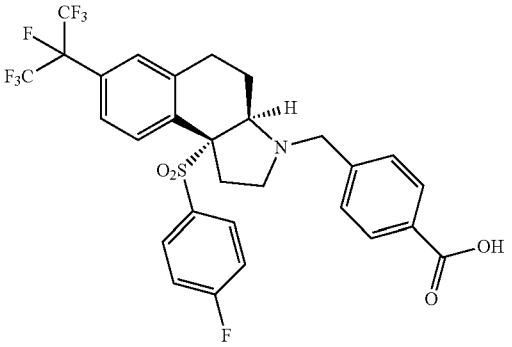
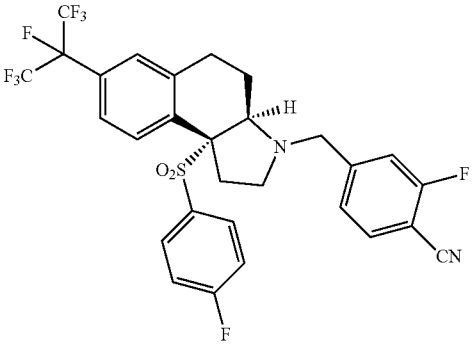
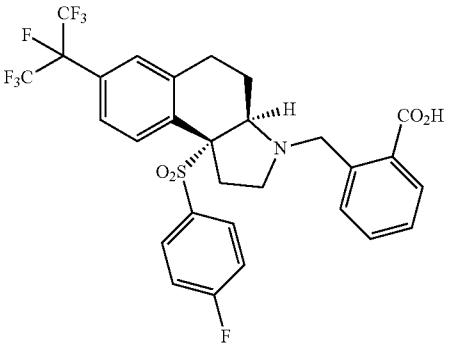
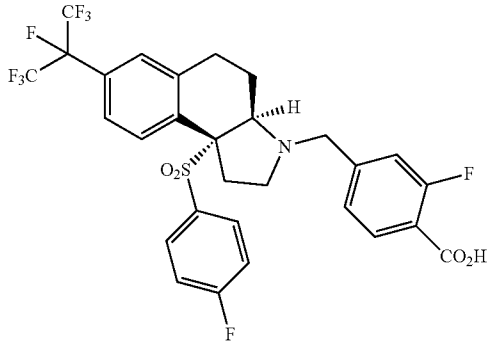
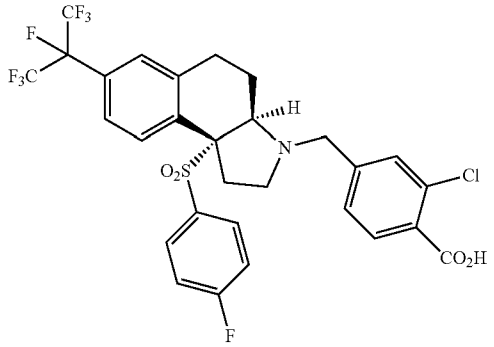
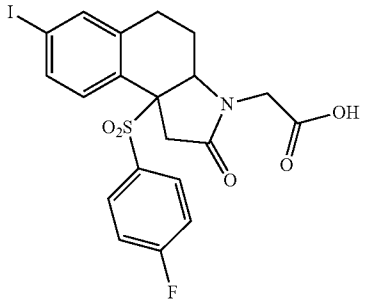
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
764		582.3 $(M + H)^+$	1.68	C
765		634.2 $(M + H)^+$	1.94	C
766		633.0 $(M + H)^+$	2.68	C
767		634.2 $(M + H)^+$	2.06	C

TABLE 13-continued

Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
768		652.0 $(M + H)^+$	2.02	C
769		668.1 $(M + H)^+$	1.94	C

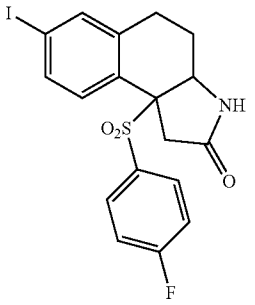
Example 770

9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetic acid



Homochiral from peak 2

Step A: 9b-((4-fluorophenyl)sulfonyl)-7-iodo-1,3,3a,4,5,9b-hexahydro-2H-benzo[e]indol-2-one

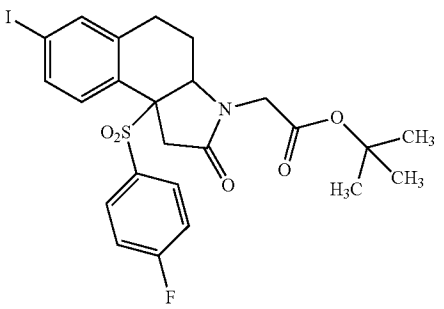


Homochiral from peak 2

Following the procedures used to prepare Intermediate 118, homochiral tert-butyl 9b-((4-fluorophenyl)sulfonyl)-7-iodo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carboxylate (Intermediate 71) was converted into homochiral 9b-((4-fluorophenyl)sulfonyl)-7-iodo-1,3,3a,4,5,9b-hexa-

hydro-2H-benzo[e]indol-2-one in 59% yield. LCMS m/z 513.0 (M+H+MeCN)$^+$, HPLC t_R 0.91 min (method B). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.62 (m, 1H), 7.50-7.42 (m, 2H), 7.41 (s, 1H), 7.18 (d, J=8.4 Hz, 1H), 7.12 (dd, J=8.9, 8.3 Hz, 2H), 4.44-4.32 (m, 1H), 3.69 (d, J=18.5 Hz, 1H), 2.89 (d, J=18.3 Hz, 1H), 2.49 (dt, J=16.2, 3.8 Hz, 1H), 2.21-2.07 (m, 1H), 1.95-1.80 (m, 1H), 1.50-1.33 (m, 1H).

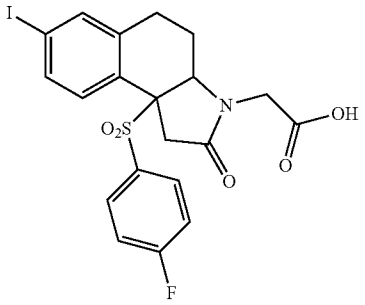
Step B: tert-butyl 2-(9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetate



Homochiral from peak 2

A solution of homochiral 9b-((4-fluorophenyl)sulfonyl)-7-iodo-3,3a,4,5-tetrahydro-1H-benzo[e]indol-2-one (0.07 g, 0.149 mmol) in THF (1 mL) was cooled to −78° C. and treated with potassium bis(trimethylsilyl)amide (1 M; 0.149 mL, 0.149 mmol), stirred for 20 min, then treated with tert-butyl bromoacetate (0.066 mL, 0.446 mmol). After 30 min, the mixture was allowed to warm to rt over 1 h and treated with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc, and the organic phase was dried and concentrated. The residue was purified by column chromatography on silica gel to give crude homochiral tert-butyl 2-(9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetate (0.11 g) which was used in the next step without further purification. LCMS m/z 530.0 (M+H—C_4H_8)$^+$, HPLC t_R 1.09 min (method B).

Step C: 2-(9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl) acetic acid

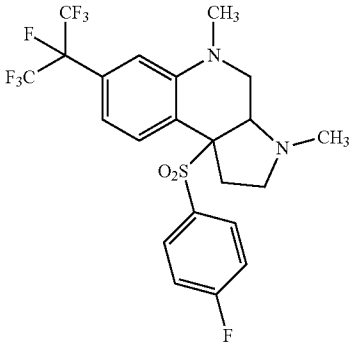


Homochiral from peak 2

A solution of crude homochiral tert-butyl 2-(9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetate (0.11 g, 0.188 mmol) in DCM (0.1 mL) was treated with 85% phosphoric acid (0.103 mL, 1.503 mmol) and stirred at rt for 48 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL). The organic phase was washed sequentially with water (3×15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method E, gradient 10-50% B) to give homochiral 2-(9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetic acid (51 mg, 51% yield). LCMS m/z 528.1 (M−H)$^-$, HPLC t_R 1.34 min (method C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.67 (d, J=8.2 Hz, 1H), 7.60 (dd, J=8.4, 5.0 Hz, 2H), 7.52 (s, 1H), 7.41 (t, J=8.5 Hz, 2H), 7.18 (d, J=8.2 Hz, 1H), 4.39 (dd, J=11.3, 5.2 Hz, 1H), 3.98-3.68 (m, 2H), 3.05 (d, J=18.6 Hz, 1H), 2.50 (br. s., 2H), 2.17 (dd, J=8.5, 4.0 Hz, 1H), 1.87 (t, J=13.7 Hz, 1H), 1.43-1.15 (m, 1H).

Example 771

9b-((4-fluorophenyl)sulfonyl)-3,5-dimethyl-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline

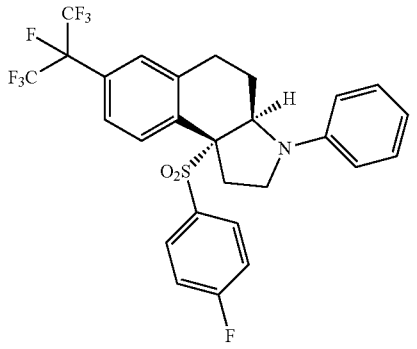


Homochiral from peak 2

A solution of 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline dihydrochloride (homochiral, from peak 2, Intermediate 88; 20 mg, 0.040 mmol) in MeOH (200 μL) was treated with acetic acid (114 μL, 1.998 mmol), 37% aqueous formaldehyde (29.8 μL, 0.400 mmol) and sodium cyanoborohydride (25.1 mg, 0.400 mmol). The mixture was stirred at rt for 1 h, then was diluted with EtOAc, washed with 1 M aqueous NaOH, dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method E, gradient 50-100% B, 25 min) to provide 9b-((4-fluorophenyl)sulfonyl)-3,5-dimethyl-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline (5.6 mg, 27% yield). LCMS m/z 528.8 (M+H)$^+$, HPLC t_R 2.3 min (method C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.47 (d, J=8.2 Hz, 1H), 7.38-7.30 (m, 2H), 7.20 (t, J=8.7 Hz, 2H), 6.97 (d, J=8.2 Hz, 1H), 6.49 (s, 1H), 3.52 (br. s., 1H), 3.28 (dd, J=12.2, 5.4 Hz, 1H), 3.07 (dd, J=13.8, 6.9 Hz, 1H), 3.00 (t, J=7.8 Hz, 1H), 2.76 (dd, J=12.1, 7.0 Hz, 1H), 2.60-2.52 (s+m, 4H), 2.43-2.19 (s+m, 4H).

Example 772

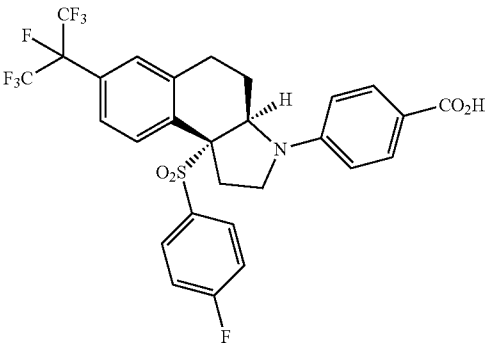
(3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3-phenyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) and bromobenzene (8.79 mg, 0.056 mmol) in 1,4-dioxane (1 mL) was bubbled with nitrogen for 2 min. Palladium(II) acetate (1.26 mg, 5.60 μmol), BINAP (5.23 mg, 8.40 μmol) and Cs_2CO_3 (54.7 mg, 0.168 mmol) were added, and the mixture was heated at 90° C. under a nitrogen atmosphere for 16 h. The mixture was cooled to rt, diluted with EtOAc (5 mL) and washed with brine (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC (method F, gradient 45-100% B, 25 min) to afford (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3-phenyl-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (3.6 mg, 22% yield). LCMS m/z 575.9 $(M+H)^+$, HPLC t_R 2.69 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J=8.3 Hz, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.46 (dd, J=8.2, 5.1 Hz, 2H), 7.36 (s, 1H), 7.19 (t, J=7.7 Hz, 2H), 7.12 (t, J=8.6 Hz, 2H), 6.75-6.61 (m, 2H), 4.45 (dd, J=11.7, 4.7 Hz, 1H), 3.52 (s, 1H), 3.39 (br. s., 1H), 3.27-3.13 (m, 1H), 2.76-2.65 (m, 3H), 2.40 (d, J=8.8 Hz, 1H), 2.23 (t, J=14.3 Hz, 1H), 1.23 (d, J=12.0 Hz, 1H).

Example 773

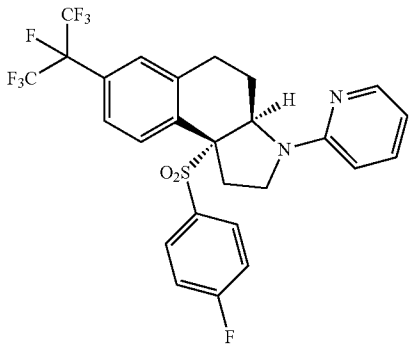
4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)benzoic acid



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 20 mg, 0.037 mmol) and tert-butyl 4-bromobenzoate (19.19 mg, 0.075 mmol) in 1,4-dioxane (2 mL) was bubbled with nitrogen for 2 min. Palladium(II) acetate (1.676 mg, 7.46 μmol), BINAP (6.97 mg, 8.40 μmol) and Cs_2CO_3 (73.0 mg, 0.224 mmol) were added, and the mixture was heated at 90° C. under a nitrogen atmosphere for 16 h. The mixture was cooled to rt, diluted with EtOAc (10 mL) and washed with brine (10 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in DCM (2 mL) and treated with TFA (1 mL). The mixture was stirred at rt for 4 h, concentrated, and the residue was purified by preparative HPLC (method E, gradient 45-90% B, 19 min) to afford 4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)benzoic acid (17.4 mg, 70% yield). LCMS m/z 618.0 $(M-H)^-$, HPLC t_R 2.14 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, J=8.4 Hz, 1H), 7.77 (d, J=8.4 Hz, 2H), 7.63 (d, J=8.3 Hz, 1H), 7.57-7.47 (m, 2H), 7.39 (s, 1H), 7.13 (t, J=8.5 Hz, 2H), 6.71 (d, J=8.4 Hz, 2H), 4.55 (dd, J=11.7, 4.4 Hz, 1H), 3.16 (s, 3H), 2.81-2.67 (m, 3H), 2.43-2.26 (m, 2H), 1.29 (d, J=11.8 Hz, 1H).

Example 774

(3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3-(pyridin-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) and bromopyridine (13.27 mg, 0.084 mmol) in 1,4-dioxane (2 mL) was bubbled with nitrogen for 2 min. Palladium(II) acetate (1.26 mg, 5.60 μmol), Xantphos (4.05 mg, 7.00 μmol) and sodium tert-butoxide (16.14 mg, 0.168 mmol) were added, and the mixture was heated at 90° C. under nitrogen for 16 h. The mixture was cooled to rt, diluted with EtOAc (5 mL) and washed with brine (5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC (method E, gradient 30-70% B, 20 min) to afford (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3-(pyridin-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (11.2 mg, 65% yield). LCMS m/z 577.3 $(M+H)^+$, HPLC t_R 2.64 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ

8.13 (d, J=4.8 Hz, 1H), 7.90 (d, J=8.4 Hz, 1H), 7.74 (br. s., 1H), 7.65 (d, J=8.5 Hz, 1H), 7.50-7.41 (m, 2H), 7.38 (s, 1H), 7.21-7.11 (m, 2H), 6.83 (d, J=5.9 Hz, 2H), 4.83 (dd, J=11.7, 4.6 Hz, 1H), 3.74-3.64 (m, 1H), 2.86-2.70 (m, 3H), 2.54 (s, 2H), 2.19 (t, J=15.2 Hz, 1H), 1.34 (d, J=12.6 Hz, 1H).

The Examples in Table 14 were prepared using the procedures used to prepare Examples 772 through 774 or similar procedures, using an appropriate aryl bromide or iodide followed by ester hydrolysis or other protecting group removal if required.

TABLE 14

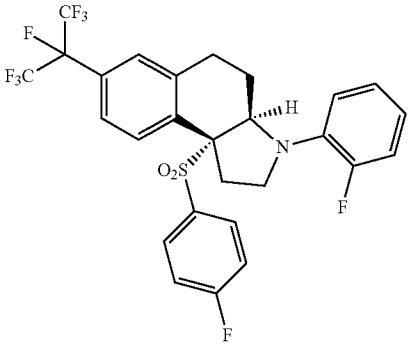
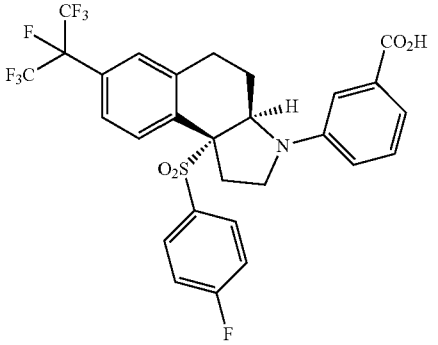
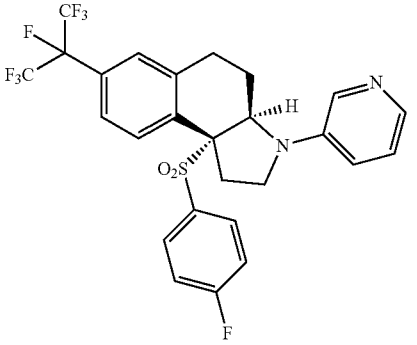
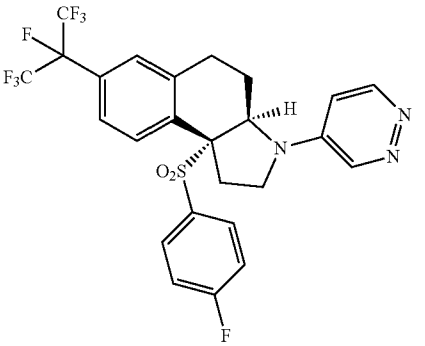
Ex. #r	Structure	LCMS m/z observed	HPLC t_R (min.)	HPLC method
775		594.0 $(M + H)^+$	2.85	C
776		620.3 $(M + H)^+$	1.97	C
777		577.2 $(M + H)^+$	2.35	C
778		578.2 $(M + H)^+$	2.10	C

TABLE 14-continued

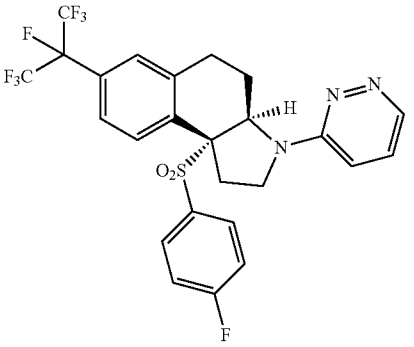
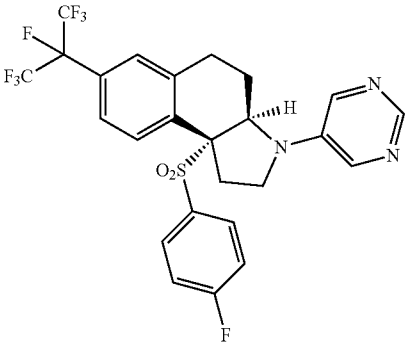
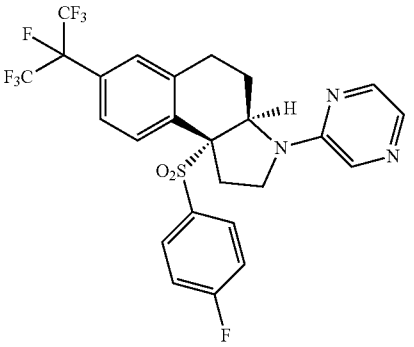
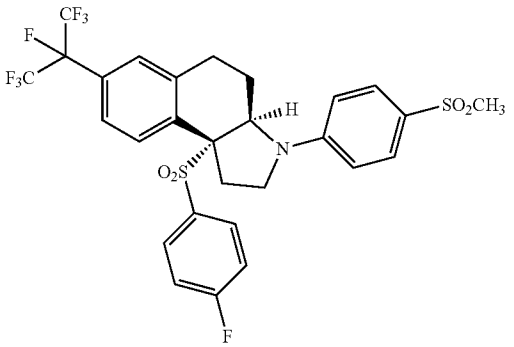
Ex. #r	Structure	LCMS m/z observed	HPLC t_R (min.)	HPLC method
779		578.0 $(M + H)^+$	2.22	C
780		578.1 $(M + H)^+$	2.22	C
781		578.0 $(M + H)^+$	2.40	C
782		654.1 $(M + H)^+$	2.39	C

TABLE 14-continued

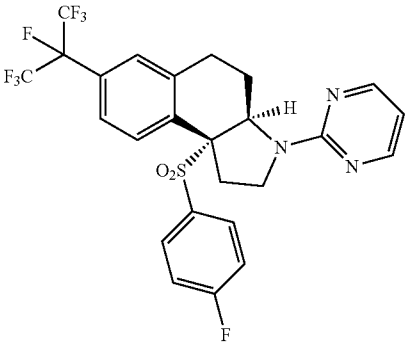
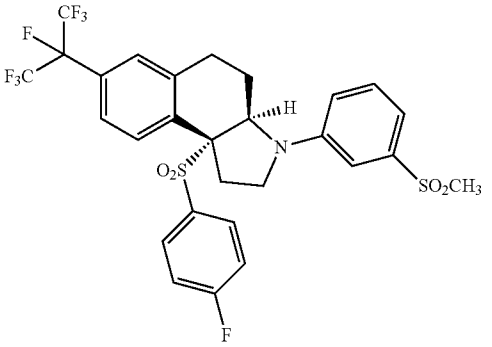
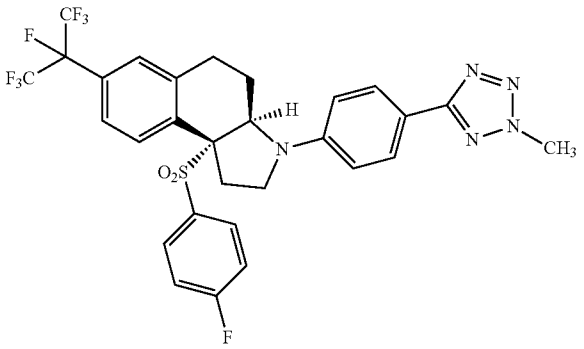
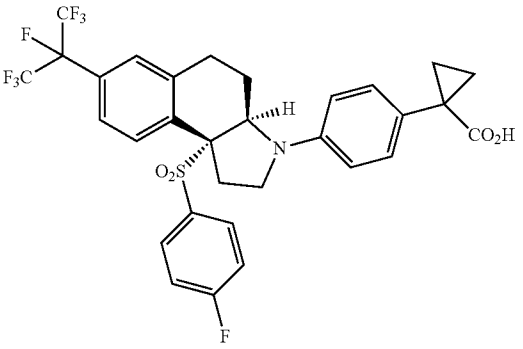
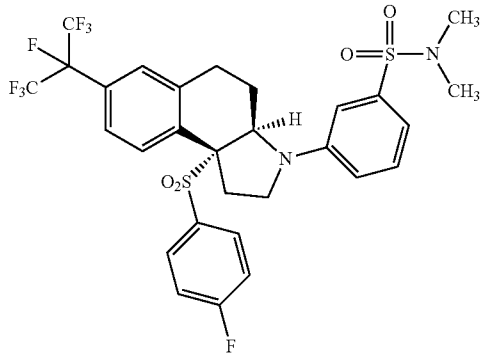
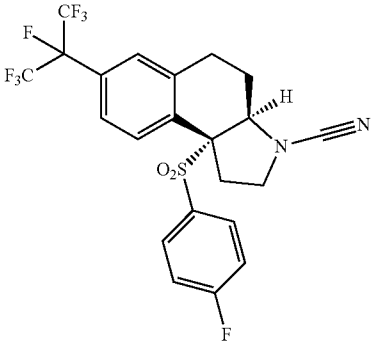
Ex. #r	Structure	LCMS m/z observed	HPLC t_R (min.)	HPLC method
783		577.9 $(M + H)^+$	2.44	C
784		654.3 $(M + H)^+$	2.41	C
785		658.0 $(M + H)^+$	2.57	C
786		660.4 $(M + H)^+$	2.28	C

TABLE 14-continued

Ex. #r	Structure	LCMS m/z observed	HPLC t_R (min.)	HPLC method
787		683.3 $(M + H)^+$	2.51	C

Example 788

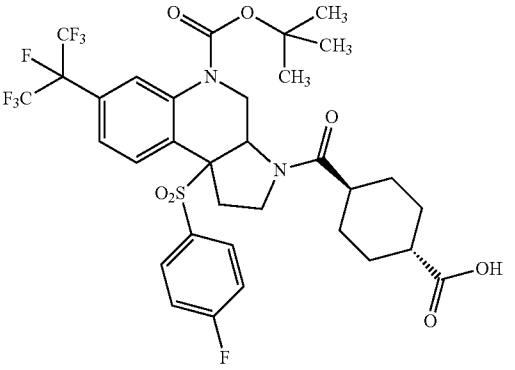
(3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carbonitrile



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) in DMF (1 mL) was treated with Cs_2CO_3 (48.9 mg, 0.150 mmol) and cyanogen bromide (9.54 mg, 0.09 mmol). The mixture was stirred at rt for 2 h, treated with water (0.1 mL, 5.55 mmol) and purified by preparative HPLC (method E, gradient 40-80% B, 20 min) to afford (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indole-3-carbonitrile (10.6 mg, 67% yield). LCMS m/z 525.3 $(M+H)^+$, HPLC t_R 2.35 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, J=8.5 Hz, 1H), 7.61 (d, J=8.2 Hz, 1H), 7.47-7.38 (m, 2H), 7.32 (s, 1H), 7.22 (t, J=8.7 Hz, 2H), 4.55 (dd, J=10.8, 5.3 Hz, 1H), 3.65-3.55 (m, 2H), 3.38 (d, J=9.2 Hz, 1H), 3.28 (dt, J=14.0, 5.0 Hz, 1H), 2.71-2.56 (m, 1H), 2.24-2.15 (m, 1H), 1.89 (t, J=13.1 Hz, 1H), 1.54-1.38 (m, 1H).

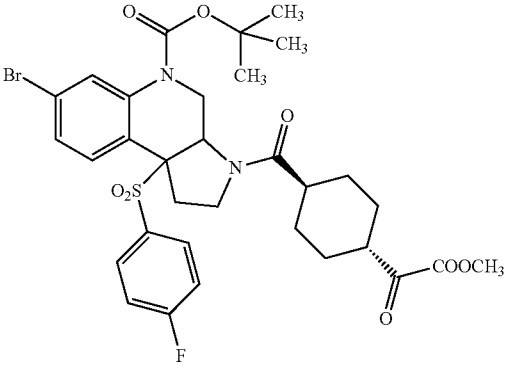
Example 789

(1r,4r)-4-(5-(tert-butoxycarbonyl)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline-3-carbonyl)cyclohexane-1-carboxylic acid



Homochiral from peak 1

Step A: tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3-((1r,4r)-4-(2-methoxy-2-oxoacetyl)cyclohexane-1-carbonyl)-1,2,3,3a,4,9b-hexahydro-5H-pyrrolo[2,3-c]quinoline-5-carboxylate

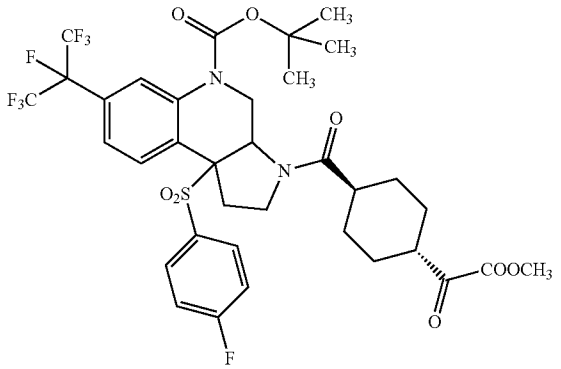


Homochiral from peak 1

A solution of tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-c]quinoline-5(9bH)-carboxylate (the product from Intermediate 88 Step C; 4.09 g, 8 mmol) in DCM (80 mL) was treated with (1r,4r)-4-(methoxycarbonyl)cyclohexanecarboxylic acid (2.234 g, 12.00 mmol), DIPEA (4.19 ml, 24.00 mmol) and HATU (4.56 g, 12.00 mmol). The mixture was stirred at rt for 1 h. The mixture was concentrated and purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to provide tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3-((1r,4r)-4-(methoxycarbonyl)cyclohexanecarbonyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-c]quinoline-5(9bH)-carboxylate. LCMS m/z 623.4 $(M+H—C_4H_8)^+$, HPLC t_R 1.15 min (method B).

This material was separated by chiral SFC using the following conditions: Column: Lux® Cellulose-4 50×250 mm, 5 μm (Phenomenex Inc.); column temperature 35° C.; pressure 100 bars; mobile phase CO_2-MeOH (80:20); flow rate 300 mL/min. Peak 1 was eluted with t_R 6.6 min. Peak 2 was eluted with t_R 8.2 min.

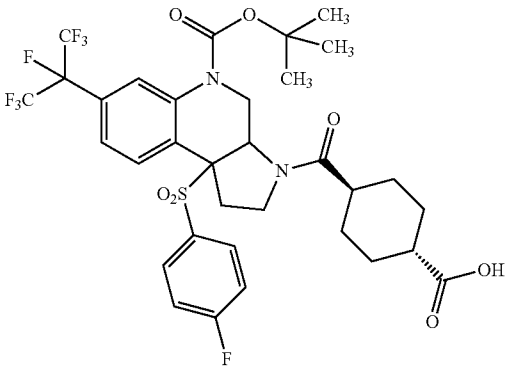
Step B: tert-butyl 9b-((4-fluorophenyl)sulfonyl)-3-((1r,4r)-4-(2-methoxy-2-oxoacetyl)cyclohexane-1-carbonyl)-7-(perfluoropropan-2-yl)-1,2,3,3a,4,9b-hexahydro-5H-pyrrolo[2,3-c]quinoline-5-carboxylate



Homochiral from peak 1

Following the procedure of Intermediate 2 Step A, tert-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3-((1r,4r)-4-(methoxycarbonyl)cyclohexanecarbonyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-c]quinoline-5(9bH)-carboxylate (1 g, 1.471 mmol) was converted into tert-butyl 9b-((4-fluorophenyl)sulfonyl)-3-((1r,4r)-4-(methoxycarbonyl)cyclohexanecarbonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-c]quinoline-5(9bH)-carboxylate (0.35 g, 31% yield). LCMS m/z 713.5 $(M+H—C_4H_8)^+$, HPLC t_R 1.18 min (method B).

Step C: (1r,4r)-4-(5-(tert-butoxycarbonyl)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline-3-carbonyl)cyclohexane-1-carboxylic acid

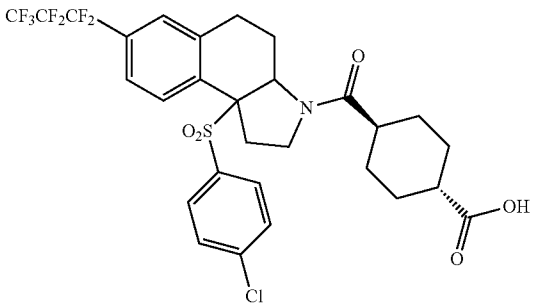


Homochiral from peak 1

A solution of tert-butyl 9b-((4-fluorophenyl)sulfonyl)-3-((1r,4r)-4-(methoxycarbonyl)cyclohexanecarbonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4-tetrahydro-1H-pyrrolo[2,3-c]quinoline-5(9bH)-carboxylate (25 mg, 0.033 mmol) in 1,4-dioxane (325 L) was treated with a solution of LiOH hydrate (7.79 mg, 0.325 mmol) in water (58.6 μL, 3.25 mmol). After 2 h at rt, the mixture was diluted with DMF and purified by preparative HPLC (method E, gradient 40-100% B, 20 min) to provide (1r,4r)-4-(5-(tert-butoxycarbonyl)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-pyrrolo[2,3-c]quinoline-3-carbonyl)cyclohexane-1-carboxylic acid (7.6 mg, 31% yield). LCMS m/z 755.3 $(M+H)^+$, HPLC t_R 1.15 min (method B). ^1H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, J=8.2 Hz, 1H), 7.55 (d, J=8.8 Hz, 2H), 7.20 (d, J=8.9 Hz, 4H), 4.66 (dd, J=12.3, 5.3 Hz, 1H), 4.55 (dd, J=11.0, 5.5 Hz, 1H), 3.81-3.67 (m, 1H), 2.82-2.70 (m, 1H), 2.63 (t, J=11.8 Hz, 1H), 2.41 (br. s., 1H), 2.20 (br. s., 1H), 1.92 (d, J=14.0 Hz, 2H), 1.83-1.64 (m, 2H), 1.51-1.35 (m, 6H), 1.32 (s, 9H).

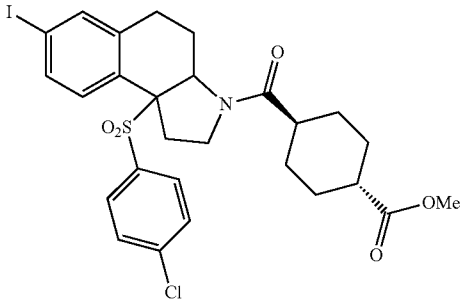
Example 790

(1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



Homochiral from peak 2

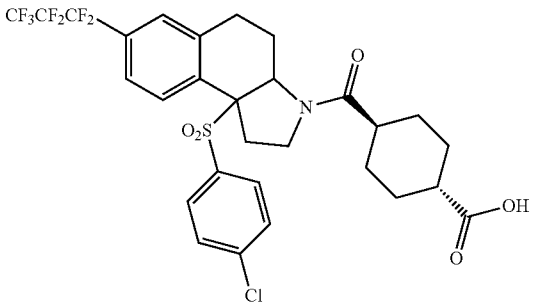
Step A: methyl (1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate



Homochiral from peak 2

A solution of crude 9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 63, prepared from 0.25 g of homochiral tert-butyl 9b-((4-chlorophenyl)sulfonyl)-7-iodo-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate) in THF (1 mL) was treated with (1r,4r)-4-(methoxycarbonyl)cyclohexanecarboxylic acid (0.097 g, 0.523 mmol), PyBOP (0.272 g, 0.523 mmol) and Et_3N (0.304 mL, 2.178 mmol). The mixture was stirred at rt for 1 h, then was diluted with EtOAc, washed sequentially with 1.5 M aqueous K_2HPO_4, water and brine and concentrated to provide crude methyl (1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate as a light yellow solid (430 mg, >100% yield) which was used without further purification. LCMS m/z 642.0 $(M+H)^+$, HPLC t_R 1.14 min (method B).

Step B: (1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid

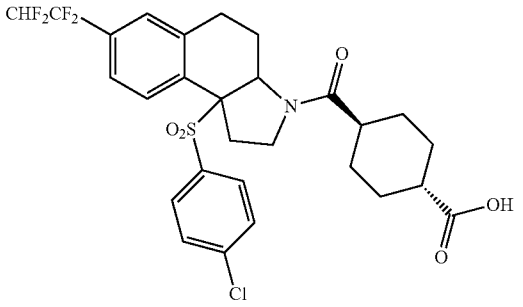


Homochiral from peak 2

A sample of wet activated copper (prepared according to the procedure in Step A of Intermediate 2; 150 mg) was washed by decantation twice with MeOH, then twice with dry DMF. This was combined with (1r,4r)-methyl 4-(-9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexanecarboxylate (30 mg, 0.047 mmol) and DMF (1 mL). The mixture was sonicated for 1 min, treated with 1,1,1,2,2,3,3-heptafluoro-3-iodopropane (69.1 mg, 0.237 mmol), and heated at 120° C. After 7 h, the mixture was cooled to rt, filtered and concentrated. The residue was dissolved in THF (1 mL) and treated with a solution of LiOH hydrate (22.38 mg, 0.935 mmol) in water (0.2 mL) and the mixture was heated at 60° C. After 1 h, the mixture was cooled to rt, acidified with 1 M aqueous HCl, concentrated, diluted with DMF and purified by preparative HPLC (method E, gradient 30-80% B, 20 min) to provide (1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (14.4 mg, 46% yield). LCMS m/z 670.3 $(M+H)^+$, HPLC t_R 1.07 min (method B).

Example 791

(1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(1,1,2,2-tetrafluoroethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid

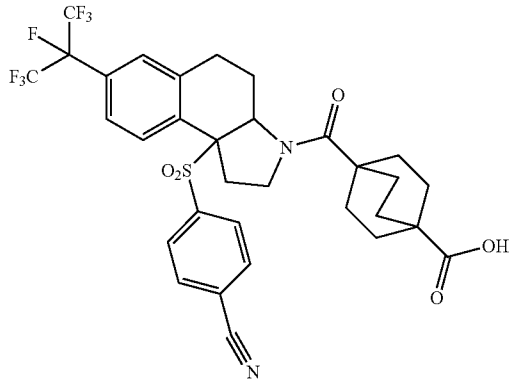


Homochiral from peak 2

Following the procedure used to prepare Example 790 but substituting 1,1,2,2-tetrafluoro-1-iodoethane for 1,1,1,2,2,3,3-heptafluoro-3-iodopropane in Step B, (1r,4r)-methyl 4-(-9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl) cyclohexanecarboxylate (30 mg, 0.047 mmol) was converted to (1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(1,1,2,2-tetrafluoroethyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (8.8 mg, 31% yield). LCMS m/z 602.1 $(M+H)^+$, HPLC t_R 0.99 min (method B).

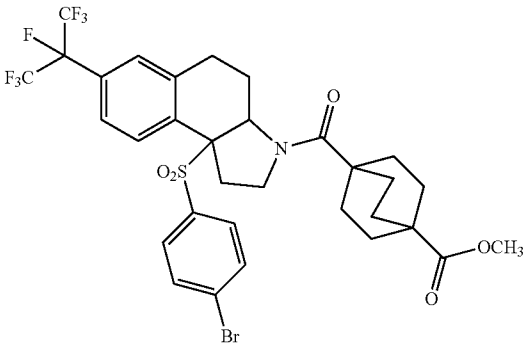
Example 792

4-(9b-((4-cyanophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylic acid



Homochiral from peak 2

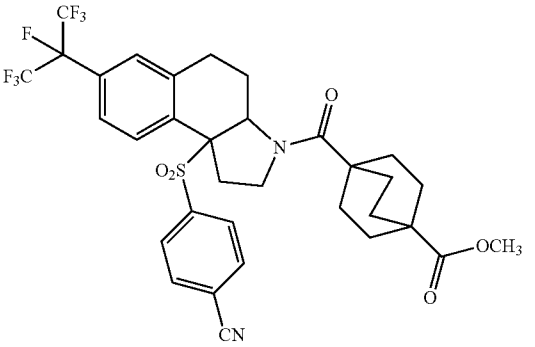
Step A: methyl 4-(9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate



Homochiral from peak 2

A solution of crude 9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (homochiral, from peak 2, Intermediate 67, prepared from 120 mg of tert-butyl 9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate) in THF (2 mL) was treated with 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (77 mg, 0.363 mmol), PyBOP (113 mg, 0.218 mmol) and DIPEA (0.063 mL, 0.363 mmol). The mixture was heated at 80° C. for 3 h, then was cooled to rt, diluted with EtOAc, washed sequentially with 1.5 M aqueous K_2HPO_4, water and brine, dried and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 0-60%), to provide methyl 4-(9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate (120 mg, 88%). LCMS m/z 754.5 $(M+H)^+$, HPLC t_R 1.18 min (method B).

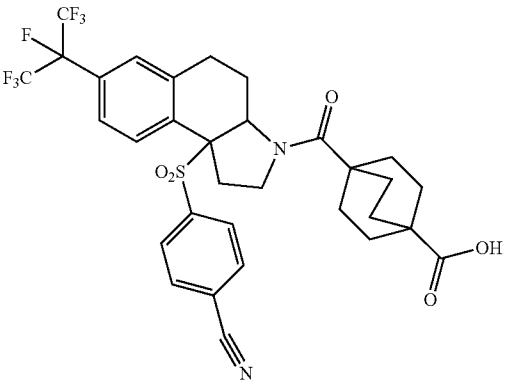
Step B: methyl 4-(9b-((4-cyanophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate



Homochiral from peak 2

A mixture of methyl 4-(9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate (20 mg, 0.027 mmol), zinc cyanide (3 mg, 0.027 mmol) and tetrakis(triphenylphosphine)palladium (3 mg, 2.7 μmol) in DMF (1 mL) was subjected to three evacuate-fill cycles with nitrogen. The mixture was heated at 120° C. for 30 min, then was cooled to rt. The mixture was partitioned between EtOAc and brine, and the organic phase was dried over Na_2SO_4 and concentrated to provide crude methyl 4-(9b-((4-cyanophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate which was used without further purification. LCMS m/z 701.2 $(M+H)^+$, HPLC t_R 1.17 min (method B).

Step C: 4-(9b-((4-cyanophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylic acid

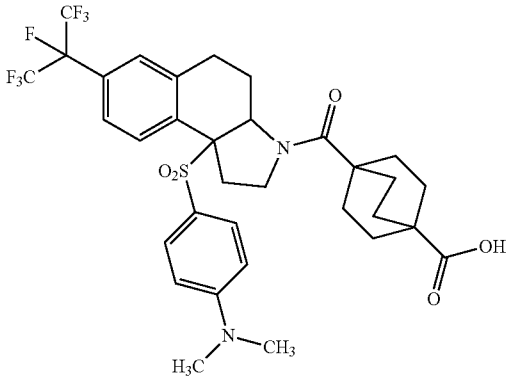


Homochiral from peak 2

A solution of the crude methyl 4-(9b-((4-cyanophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate (from Step B) in THF (1 mL) and water (0.1 mL) was treated with LiOH hydrate (6.35 mg, 0.265 mmol) and heated at 50° C. overnight. The mixture was cooled to rt, acidified with 1 M aqueous HCl, and extracted with EtOAc. The organic phase was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method E, gradient 30-70% B, 20 min) to provide 4-(9b-((4-cyanophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (3.1 mg, 17% yield). LCMS m/z 687.2 $(M+H)^+$, HPLC t_R 1.98 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.91 (d, J=8.2 Hz, 2H), 7.87 (d, J=8.5 Hz, 1H), 7.63 (d, J=8.3 Hz, 1H), 7.49 (d, J=8.2 Hz, 2H), 7.35 (s, 1H), 4.85 (dd, J=11.5, 4.8 Hz, 1H), 4.00-3.86 (m, 1H), 3.71 (br. s., 1H), 3.35 (br. s., 1H), 2.76-2.59 (m, 2H), 2.21 (d, J=8.8 Hz, 1H), 1.95 (t, J=14.6 Hz, 1H), 1.79-1.51 (m, 12H), 1.30-1.12 (m, 1H).

Example 793

4-(9b-((4-(dimethylamino)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylic acid

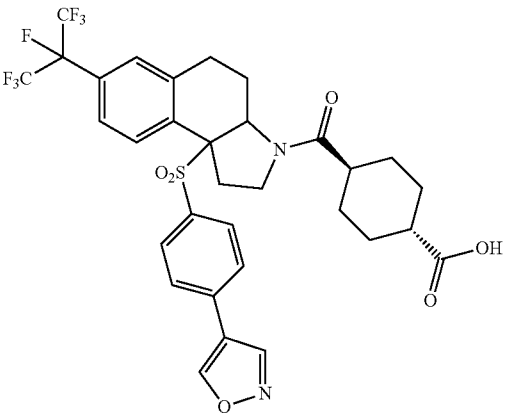


Homochiral from peak 2

A mixture of homochiral methyl 4-(9b-((4-bromophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate (Example 792 Step A; 20 mg, 0.027 mmol), BINAP (8 mg, 0.013 mmol), sodium tert-butoxide (5 mg, 0.053 mmol) and tris(dibenzylideneacetone)dipalladium (4.9 mg, 5.3 μmol) in toluene (1 mL) was subjected to three evacuate-fill cycles with nitrogen. Dimethylamine (0.066 mL, 0.13 mmol) was added and the mixture was heated in a sealed vessel at 100° C. for 2 h. The mixture was cooled to rt and partitioned between EtOAc and brine. The organic phase was dried over Na_2SO_4 and concentrated, and the residue was purified by preparative HPLC (method E, gradient 30-80% B, 20 min) to provide 4-(9b-((4-(dimethylamino)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylic acid (1.9 mg, 10% yield). LCMS m/z 705.2 $(M+H)^+$, HPLC t_R 2.31 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J=8.5 Hz, 1H), 7.61 (d, J=8.3 Hz, 1H), 7.32 (br. s., 1H), 6.98 (d, J=8.0 Hz, 2H), 6.52 (d, J=8.7 Hz, 2H), 4.78 (dd, J=11.1, 4.8 Hz, 1H), 3.98-3.80 (m, 1H), 3.64 (br. s., 1H), 3.21 (br. s., 1H), 2.96 (s, 6H), 2.66-2.56 (m, 2H), 2.22 (m, 1H), 1.86 (t, J=13.7 Hz, 1H), 1.79-1.49 (m, 12H), 1.14 (m, 1H).

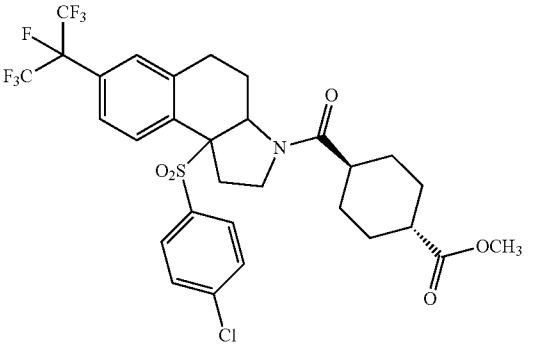
Example 794

(1r,4r)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



Homochiral from peak 2

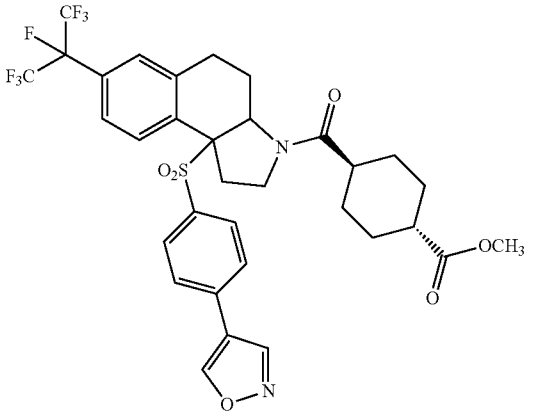
Step A: methyl (1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexanecarboxylate



Homochiral from peak 2

Following the procedure of Example 790 Step A, 9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (homochiral, from peak 2, Intermediate 35) was converted into methyl (1r,4r)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexanecarboxylate, which was used without further purification. LCMS m/z 684.3 $(M+H)^+$, HPLC t_R 1.13 (method B).

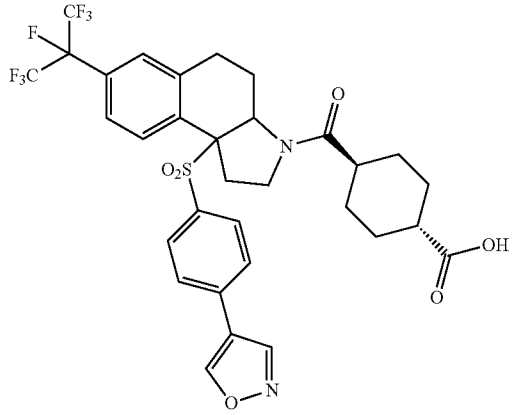
Step B: methyl (1r,4r)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate



Homochiral from peak 2

A mixture of (1r,4r)-methyl 4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexanecarboxylate (40 mg, 0.058 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (23 mg, 0.12 mmol) and K_3PO_4 (0.088 mL, 0.18 mmol) in DMF (1 mL) was subjected to three evacuate-fill cycles with nitrogen. Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (second generation Xphos precatalyst; 2.3 mg, 2.9 μmol) was added and the mixture was again subjected to three evacuate-fill cycles with nitrogen. The mixture was heated at 110° C. for 3 h, then was cooled to rt and diluted with EtOAc. The solution was washed sequentially with 10% aqueous LiCl, water and brine, dried over Na_2SO_4 and to provide crude methyl (1r,4r)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate which was used without further purification. LCMS m/z 717.4 $(M+H)^+$, HPLC t_R 1.02 min (method B).

Step C: (1r,4r)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid

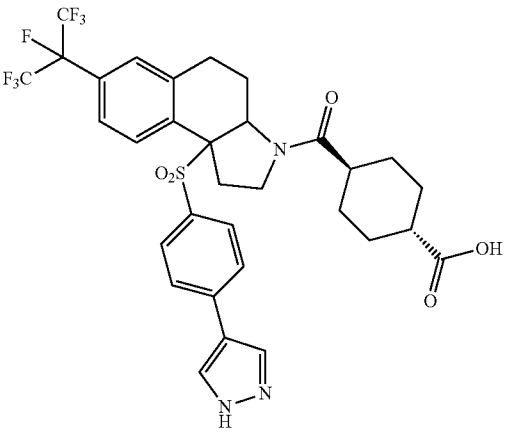


Homochiral from peak 2

A solution of crude methyl (1r,4r)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate (from Step B) in THF (1 mL) and water (0.2 mL) was treated with LiOH (14.0 mg, 0.585 mmol) and stirred at rt overnight. The mixture was acidified with 1 M aqueous HCl, and extracted twice with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method E, gradient 15-55% B, 20 min), then purified again by preparative HPLC (method E, gradient 20-45% B, 25 min) to provide (1r,4r)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (2 mg, 4.6% yield). LCMS m/z 703.3 $(M+H)^+$, HPLC t_R 0.95 min (method B).

Example 795

(1r,4r)-4-(9b-((4-(1H-pyrazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid

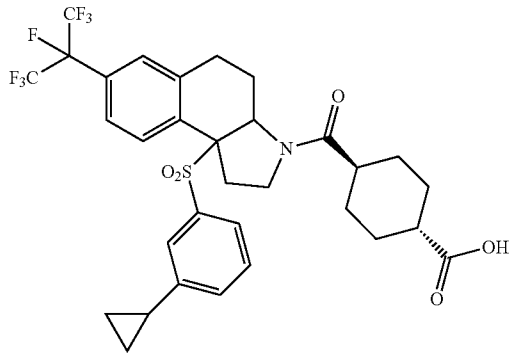


Homochiral from peak 2

Following the procedures used to prepare Example 794, but substituting tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate in place of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole in Step B, 9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (homochiral, from peak 2, Intermediate 35) was converted into (1r,4r)-4-(9b-((4-(1H-pyrazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid after deprotection with TFA. LCMS m/z 702.4 $(M+H)^+$, HPLC t_R 1.55 min (analytical HPLC condition C).

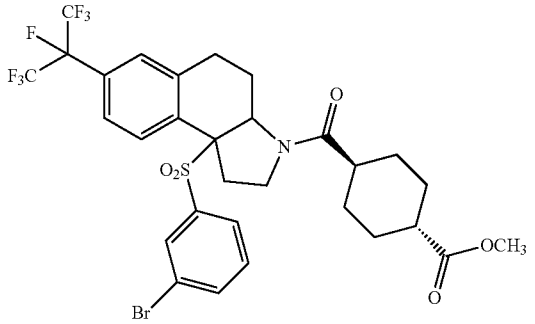
Example 796

(1r,4r)-4-(9b-((3-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



Homochiral from peak 2

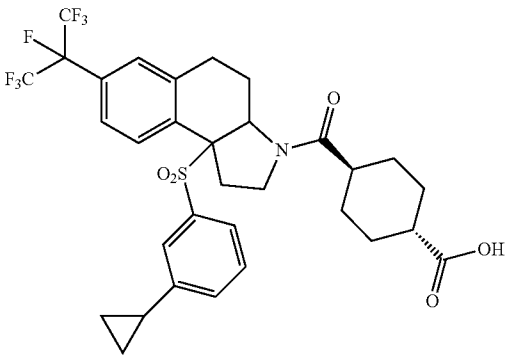
Step A: methyl (1r,4r)-4-(9b-((3-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate



Homochiral from peak 2

A solution of tert-butyl 9b-((3-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 75; 0.35 g, 0.530 mmol) in DCM (10 mL) was treated with TFA (6 mL, 78 mmol) and the mixture was stirred at rt for 1 h, then was concentrated. The residue was dissolved in DCM (50 mL) and the solution was washed with 1.5 M aqueous K_2HPO_4 (50 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved in DCM (10 mL) and treated with DIPEA (0.294 mL, 1.681 mmol) and a solution of trans-methyl 4-(chlorocarbonyl)cyclohexane-1-carboxylate in DCM (2 mL), prepared from treatment of trans-1,4-cyclohexanedicarboxylic acid monomethyl ester (0.099 g, 0.530 mmol) with excess oxalyl chloride and a catalytic amount of DMF in DCM. The mixture was stirred at rt for 1.5 h, diluted with DCM (50 mL), washed with 1 M aqueous HCl and 1.5 M aqueous K_2HPO_4, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give methyl (1r,4r)-4-(9b-((3-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate as a yellow solid (365 mg, 95% yield). LCMS m/z 728.1 $(M+H)^+$, HPLC t_R 1.18 min (method B).

Step B: (1r,4r)-4-(9b-((3-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid

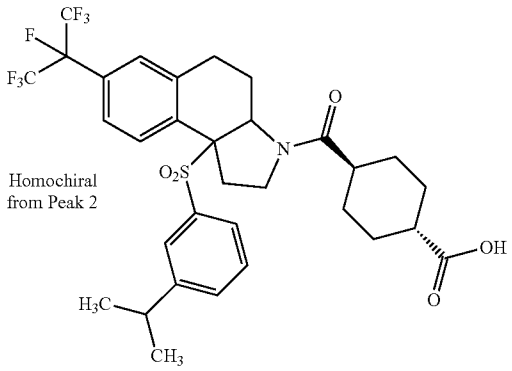
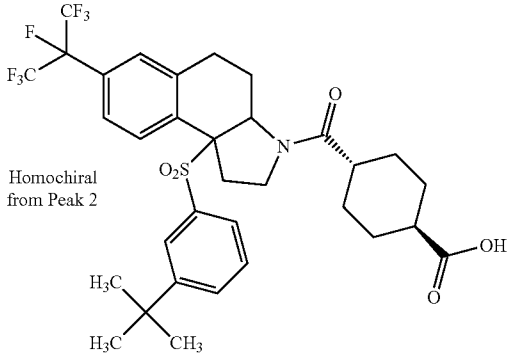


Homochiral from peak 2

A mixture of methyl (1r,4r)-4-(9b-((3-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylate (0.05 g, 0.069 mmol) and cyclopropylzinc bromide (0.5 M in THF; 0.138 mL, 0.069 mmol) in THF (0.572 ml) in a sealable vial was flushed with nitrogen and treated with tetrakis(triphenylphosphine)palladium (0.793 mg, 0.686 μmol). The vial was sealed and heated by microwave irradiation at 130° C. for 15 min. The cooled mixture was diluted with EtOAc (15 mL) and washed sequentially with 1 M aqueous HCl and brine. The organic phase was dried and concentrated, and the residue was treated with THF (3 mL), MeOH (1 mL) and a solution of LiOH monohydrate (0.058 g, 1.373 mmol) in water (1 mL) for 3 h. The mixture was diluted with EtOAc (8 mL), washed sequentially with 1 M aqueous HCl (6 mL) and brine (6 mL), dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method E, gradient 30-90% B, 20 min, followed by method F, gradient 45-90% F, 20 min) to provide (1r,4r)-4-(9b-((3-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (13 mg, 26% yield). LCMS m/z 676.1 $(M+H)^+$, HPLC t_R 2.01 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.91-7.81 (m, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.43-7.25 (m, 3H), 7.16 (d, J=7.3 Hz, 1H), 6.83 (s, 1H), 4.65 (dd, J=11.7, 4.8 Hz, 1H), 3.80-3.08 (m, 2H), 2.63 (d, J=12.3 Hz, 3H), 2.40-1.09 (m, 14H), 0.93 (d, J=6.6 Hz, 2H), 0.67-0.38 (m, 2H).

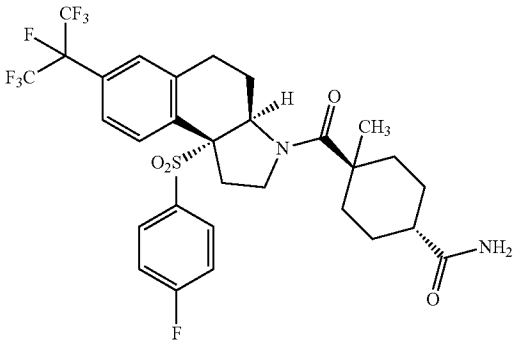
The Examples in Table 15 were prepared using procedures used to prepare Example 796, using the appropriate organozinc reagent in place of cyclopropylzinc bromide.

TABLE 15

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
797		678.5 $(M + H)^+$	2.42	D
798		692.3 $(M + H)^+$	2.43	D

Example 799

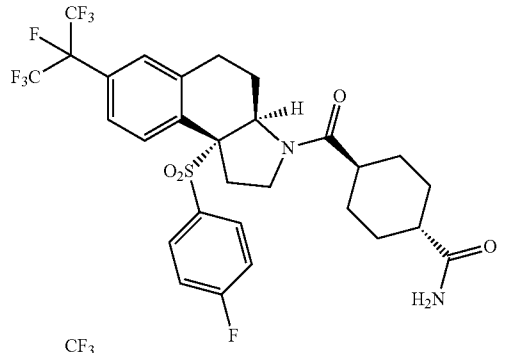
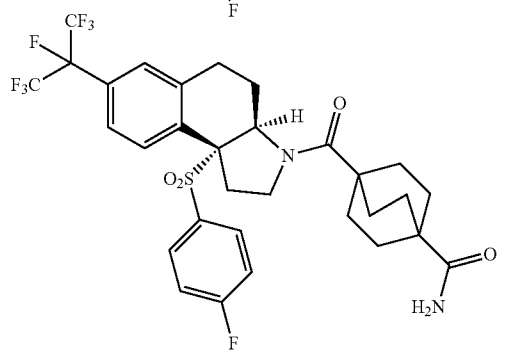
(1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-4-methylcyclohexanecarboxamide



A solution of (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-4-methylcyclohexanecarboxylic acid (Example 66; 33 mg, 0.049 mmol) in DMF (1 mL) was treated with BOP (32.8 mg, 0.074 mmol) and stirred at rt for 10 min. The mixture was then treated with aqueous NH_4OH (0.5 mL, 12.84 mmol). After 30 min, the mixture was diluted with EtOAc and washed sequentially with 10% aqueous LiCl (twice) and brine. The combined aqueous layers were extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method F, gradient 40-80% B, 19 min) to afford (1R,4r)-4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-4-methylcyclohexanecarboxamide (10.3 mg, 31% yield). LCMS m/z 667.2 $(M+H)^+$, t_R 2.22 min (method D). ^1H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J=8.5 Hz, 1H), 7.63 (d, J=8.5 Hz, 1H), 7.35-7.30 (m, 3H), 7.28-7.23 (m, 2H), 7.19 (d, J=11.3 Hz, 1H), 6.67 (br. s., 1H), 4.88 (dd, J=11.6, 4.9 Hz, 1H), 4.00-3.92 (m, 1H), 3.74-3.67 (m, 1H), 2.72-2.62 (m, 2H), 2.23 (dt, J=7.8, 3.7 Hz, 1H), 2.08-2.00 (m, 1H), 1.90-1.81 (m, 1H), 1.71-1.51 (m, 9H), 1.28-1.19 (m, 1H), 1.13 (s, 3H).

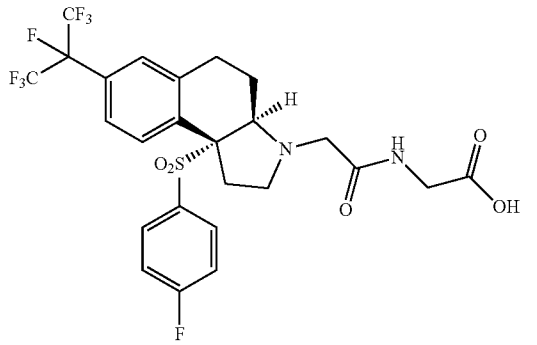
The Examples in Table 16 were prepared using procedures used to prepare Example 799, using the appropriate acid as starting material.

TABLE 16

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
800		653.4 $(M + H)^+$	1.99	C
801		679.2 $(M + H)^+$	2.08	C

Example 802

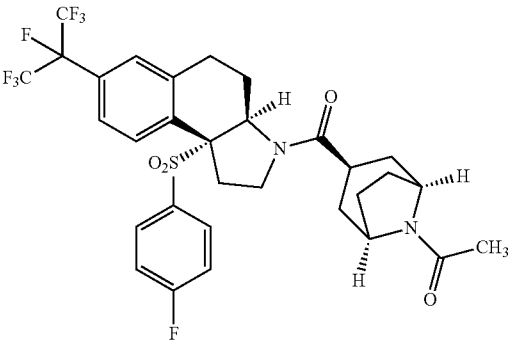
(2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetyl)glycine



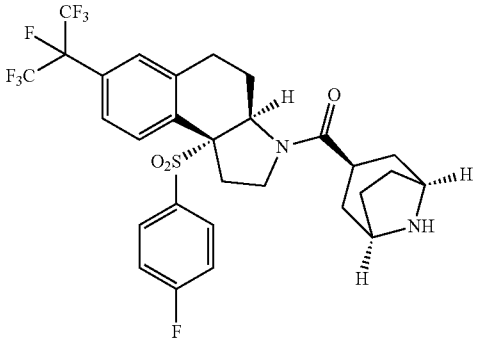
A solution of 2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)acetic acid (Example 730, as the TFA salt; 75 mg, 0.112 mmol) in DMF (1 mL) was treated with 1-hydroxybenzotriazole (25.7 mg, 0.168 mmol), N-(3-dimethylaminopropyl)-N-ethylcarbodiimide (32.1 mg, 0.168 mmol), and tert-butyl 2-aminoacetate hydrochloride (28.1 mg, 0.168 mmol). The mixture was stirred overnight, then was diluted with EtOAc and brine. The organic layer was separated and washed sequentially with brine (3×) and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give crude tert-butyl (2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetyl)glycinate (110 mg, >100% yield), used without purification. LCMS m/z 671.3 $(M+H)^+$, HPLC t_R 0.98 min (method B). A portion of this material (40 mg) was dissolved in DCM (1 mL), treated with TFA (2 mL) and stirred at rt. After 4 h, the solution was concentrated and the residue was purified by preparative HPLC (method E, gradient 17-57% B, 25 min) to provide (2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetyl)glycine (2.9 mg, 7% yield). LCMS m/z 615.1 $(M+H)^+$, t_R 1.72 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 8.06 (br. s., 1H), 7.52 (s, 2H), 7.40-7.30 (m, 3H), 7.30-7.20 (m, 2H), 3.83-3.62 (m, 2H), 3.23-3.09 (m, 2H), 3.03 (d, J=16.2 Hz, 1H), 2.75-2.58 (m, 2H), 2.45-2.30 (m, 1H), 2.12 (br. s., 1H), 2.00-1.85 (m, 1H), 1.41-1.25 (m, 1H), 2 protons obscured by solvent peak.

Example 803

1-((1R,3s,5S)-3-((3aR,9bR)-9b-((4-fluorophenyl)sulfon)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-8-azabicyclo[3.2.1]octan-8-yl)ethan-1-one

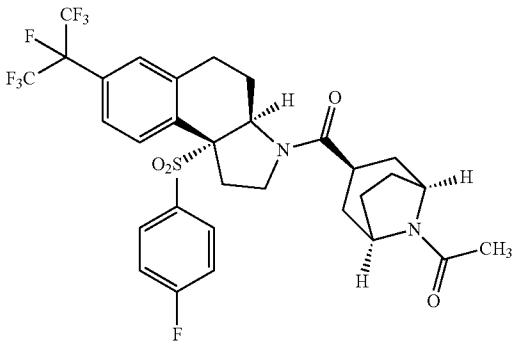


Step A: ((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone



A mixture of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (Intermediate 32; 80 mg, 0.160 mmol), (1R,3s,5S)-8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid (40.9 mg, 0.160 mmol), DIPEA (0.084 mL, 0.481 mmol) and DMF (2 mL) was treated with 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (50% in DMF; 0.150 mL, 0.240 mmol) and stirred at rt for 30 min. The mixture was diluted with EtOAc (20 mL), washed sequentially with 1 M aqueous HCl and brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in DCM (2 mL), treated with TFA (1 mL) and the mixture was stirred at rt for 1 h. The mixture was concentrated and the residue was dissolved in DCM (20 mL), washed with 1.5 M aqueous K_2HPO_4 (2×10 mL), dried over Na_2SO_4 and concentrated to give crude ((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone, used without further purification. LCMS m/z 637.2 $(M+H)^+$, HPLC t_R 0.96 min (method B).

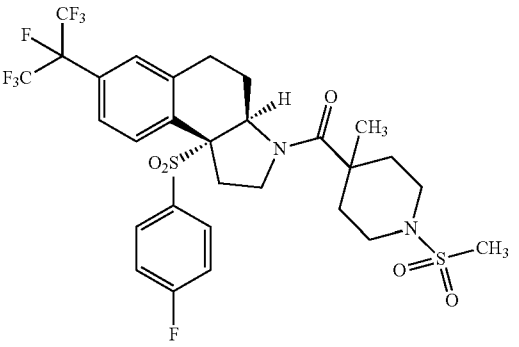
Step B: 1-((1R,3s,5S)-3-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-8-azabicyclo[3,2,1]octan-8-yl)ethan-1-one



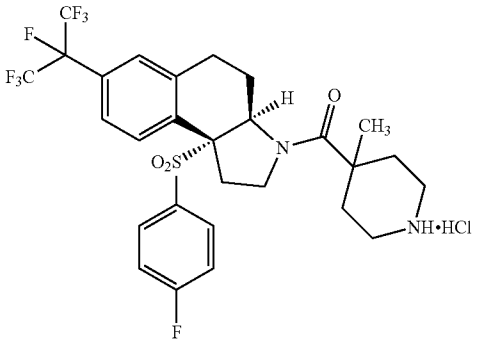
A solution of crude ((1R,3s,55S)-8-azabicyclo[3.2.1]octan-3-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone (50 mg, 0.079 mmol) in DCM (1 mL) and pyridine (0.5 mL) was treated dropwise with acetyl chloride (1 M in DCM; 0.314 mL, 0.314 mmol) and the mixture was stirred at rt for 30 min. The mixture was diluted with DCM (15 mL), washed sequentially with 1 M aqueous HCl (2×10 mL) and brine (10 mL), dried and concentrated. The residue was purified by preparative HPLC (method E, gradient 40-80% B, 25 min, then method F, gradient 47-72% B, 25 min) to provide 1-((1R,3s,5S)-3-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-8-azabicyclo[3.2.1]octan-8-yl)ethan-1-one (17 mg, 32% yield). LCMS m/z 679.2 $(M+H)^+$, HPLC t_R 2.11 (method D).

Example 804

((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(4-methyl-1-(methylsulfonyl)piperidin-4-yl)methanone



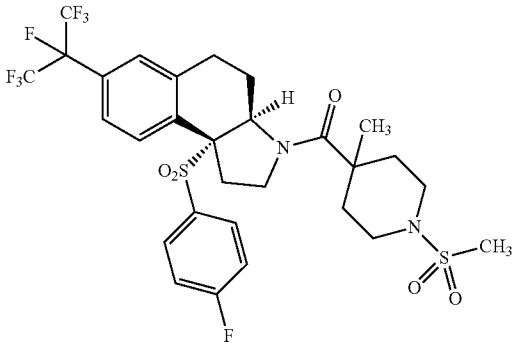
Step A: ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(4-methylpiperidin-4-yl)methanone hydrochloride



A mixture of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 25 mg, 0.047 mmol), 1-(tert-butoxycarbonyl)-4-methylpiperidine-4-carboxylic acid (13.62 mg, 0.056 mmol) and DIPEA (0.024 mL, 0.140 mmol) in DMF (1 mL) was treated with HATU (21.29 mg, 0.056 mmol) and stirred at rt for 5 h. The mixture was diluted with EtOAc and washed sequentially with 10%

aqueous LiCl (twice) and brine. The combined aqueous phases were extracted with EtOAc, and the combined organic phases were dried over $MgSO_4$ and concentrated. The residue was dissolved in HCl (4 M in 1,4-dioxane; 1 mL, 4.00 mmol) and stirred at rt overnight. The solution was concentrated to provide crude ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(4-methylpiperidin-4-yl) methanone hydrochloride (31.1 mg), used without further purification. LCMS m/z 625.1 $(M+H)^+$, HPLC t_R 0.91 min (method B).

Step B: ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(4-methyl-1-(methylsulfonyl) piperidin-4-yl)methanone



A solution of crude ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e] indol-3-yl)(4-methylpiperidin-4-yl)methanone hydrochloride (31.1 mg, 0.047 mmol) and Et_3N (0.033 mL, 0.235 mmol) in DCM (1 mL) was treated at rt with MsCl (7.33 μL, 0.094 mmol) and stirred overnight at rt. The mixture was concentrated and the residue was purified by preparative HPLC (method E, gradient 45-100%, 19 min) to provide ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)(4-methyl-1-(methylsulfonyl)piperidin-4-yl)methanone (10.1 mg, 31% yield). LCMS m/z 703.0 $(M+H)^+$, HPLC t_R 2.33 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.33-7.28 (m, 3H), 7.26-7.21 (m, 2H), 4.90 (dd, J=11.5, 5.0 Hz, 1H), 3.98-3.90 (m, 1H), 3.38-3.31 (m, 1H), 3.30-3.24 (m, 2H), 3.02-2.93 (m, 1H), 2.88-2.81 (m, 1H), 2.80 (s, 3H), 2.73-2.64 (m, 2H), 2.62 (br. s., 1H), 2.25 (dd, J=8.2, 4.3 Hz, 1H), 2.18-2.11 (m, 2H), 1.87-1.78 (m, 1H), 1.55-1.44 (m, 2H), 1.30-1.20 (m, 1H), 1.15 (s, 3H).

The Examples in Table 17 were prepared using procedures used to prepare Examples 803 and 804 or similar procedures, using the appropriate amine and acid starting materials and appropriate acyl chloride, sulfonyl chloride or other reagent as appropriate.

TABLE 17

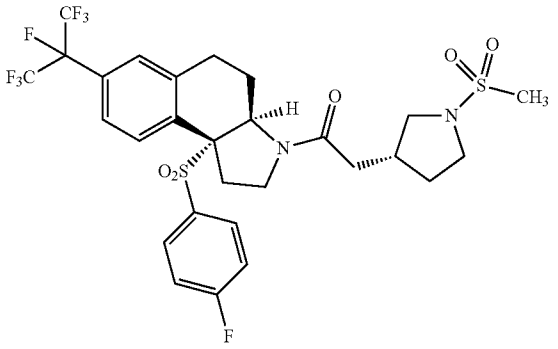
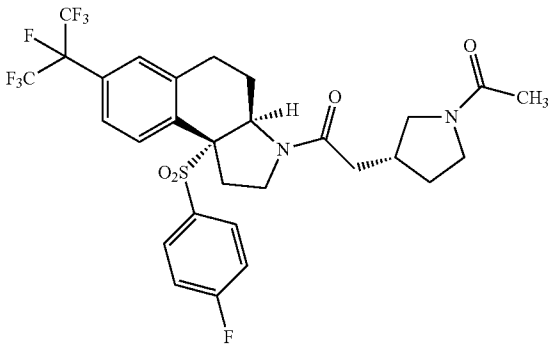
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
805		688.9 $(M+H)^+$	2.22	C
806		653.0 $(M+H)^+$	2.05	C

TABLE 17-continued

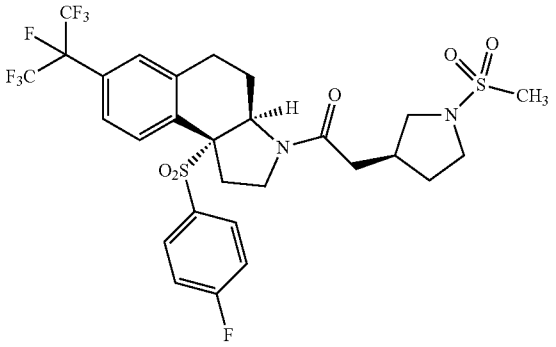
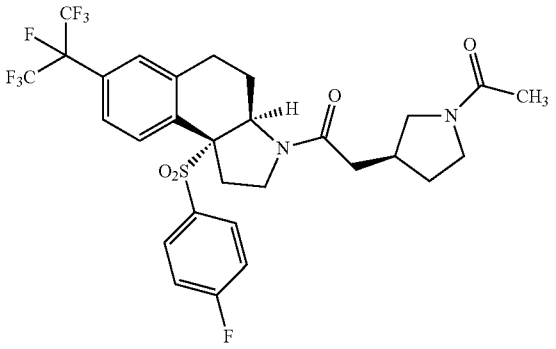
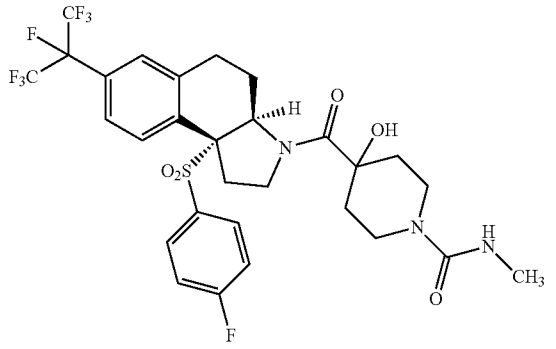
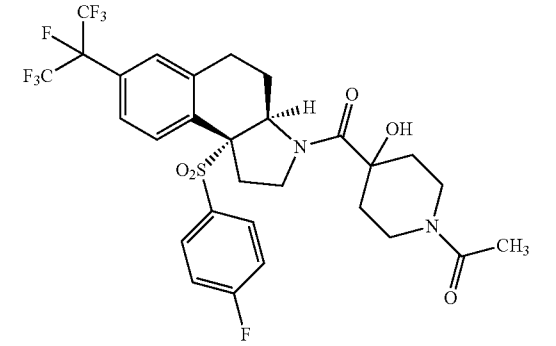
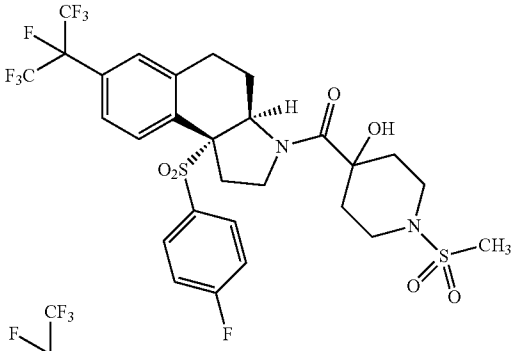
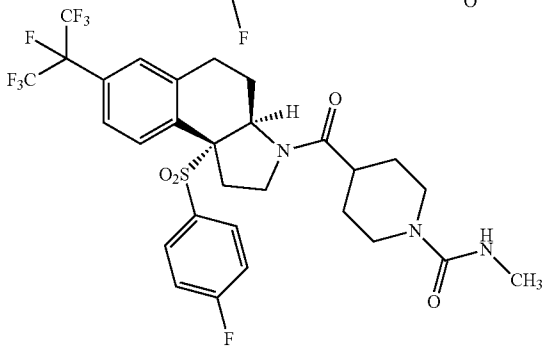
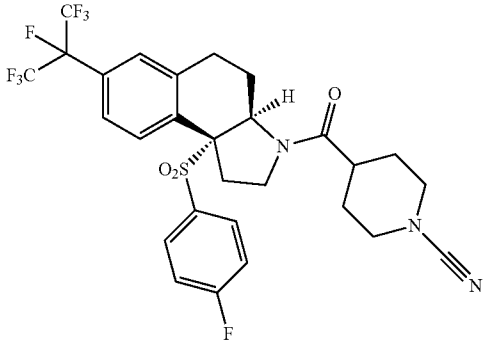
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
807		689.3 $(M + H)^+$	2.18	C
808		652.9 $(M + H)^+$	2.09	C
809		684.2 $(M + H)^+$	2.03	C
810		669.0 $(M + H)^+$	2.03	C

TABLE 17-continued

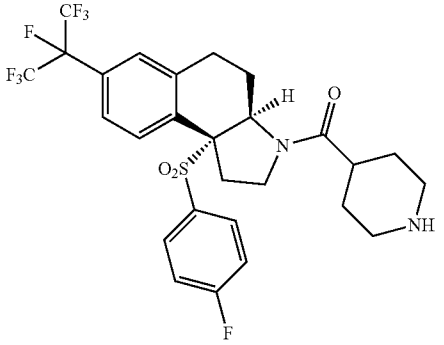
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
811		705.0 $(M + H)^+$	2.15	C
812		667.9 $(M + H)^+$	2.11	C

Example 813

4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)piperidine-1-carbonitrile



Step A: ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(piperidin-4-yl)methanone



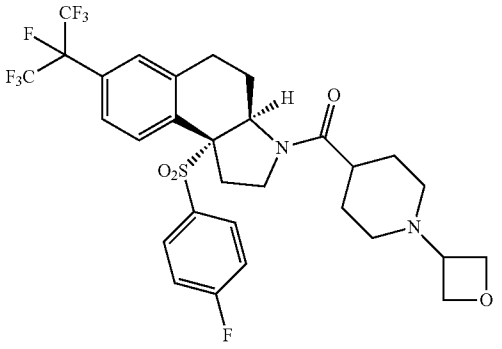
A solution of ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 30 mg, 0.060 mmol) in DCM (0.6 mL) was treated with 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (27.5 mg, 0.120 mmol), DIPEA (31.5 μL, 0.180 mmol) and HATU (34.3 mg, 0.090 mmol). The mixture was stirred at rt for 1 h. The mixture was then treated with TFA (1 mL) and the mixture was stirred for 1 h more, then was concentrated. The residue was dissolved in EtOAc, washed twice with 1 M aqueous NaOH, dried over Na_2SO_4 and concentrated. to provide crude ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(piperidin-4-yl)methanone trifluoroacetate, used without purification. LCMS m/z 611.1 $(M+H)^+$, HPLC t_R 0.91 min (method B).

Step B: 4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)piperidine-1-carbonitrile

The crude ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(piperidin-4-yl)methanone from step A was dissolved in DCM (2 mL) and treated with Et_3N (0.033 mL, 0.240 mmol) and cyanogen bromide (12.73 mg, 0.120 mmol). After 1 h at rt, the mixture was concentrated and the residue was purified by preparative HPLC (method E, gradient 40-85% B, 25 min) to give 4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)piperidine-1-carbonitrile (9.6 mg, 25% yield). LCMS m/z 636.0 $(M+H)^+$, HPLC t_R 1.06 min (method B).

Example 814

((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(1-(oxetan-3-yl)piperidin-4-yl)methanone



Crude ((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(piperidin-4-yl)methanone (Example 813 Step A; prepared from 40 mg of Intermediate 32) was dissolved in anhydrous MeOH (2 mL), treated with 3-oxetanone (28.9 mg, 0.400 mmol) and stirred at rt for 1 h. The mixture was then treated with sodium cyanoborohydride (20.13 mg, 0.320 mmol) and stirred at rt for 1 h. The mixture was treated with 1 M aqueous HCl (5 mL) and concentrated. The residue was partitioned between EtOAc (20 mL) and 1.5 M aqueous K_2HPO_4 (15 mL) and the organic phase was washed with brine and concentrated. The residue was purified by preparative HPLC (method E, gradient 40-80% B, 20 min) to give ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(1-(oxetan-3-yl)piperidin-4-yl)methanone (7.5 mg, 13% yield). LCMS m/z 666.9 $(M+H)^+$, HPLC t_R 1.82 min (method D).

The Examples in Table 18 were prepared using procedures used to prepare Example 814 or similar procedures.

TABLE 18

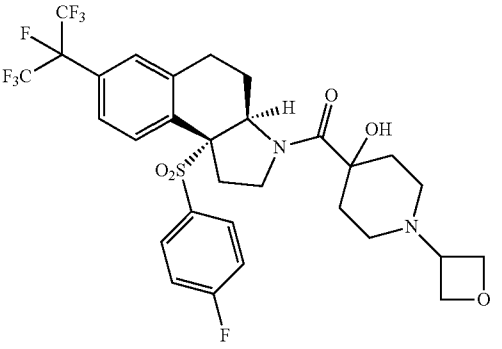
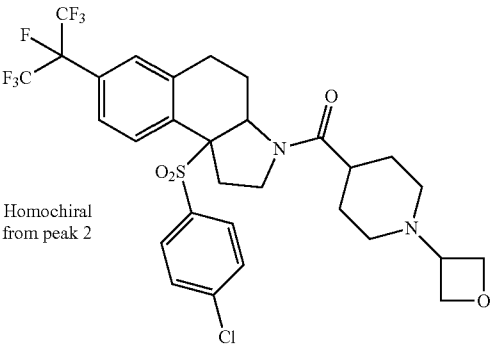
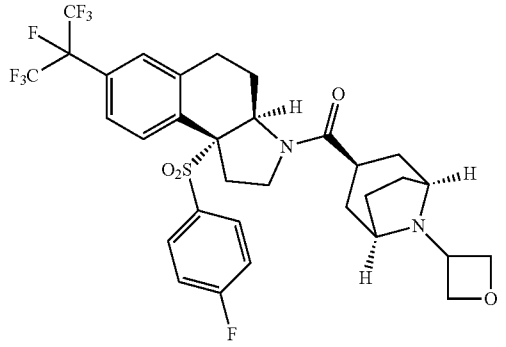
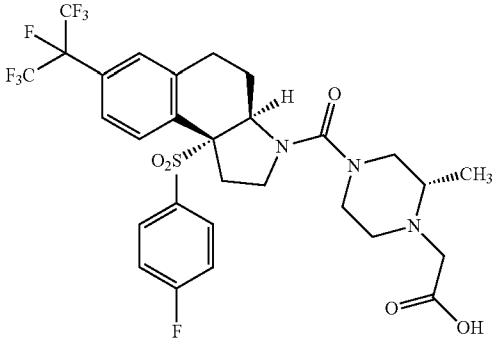
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
815		683.3 $(M + H)^+$	1.77	D
816	 Homochiral from peak 2	683.3 $(M + H)^+$	2.06	D

TABLE 18-continued

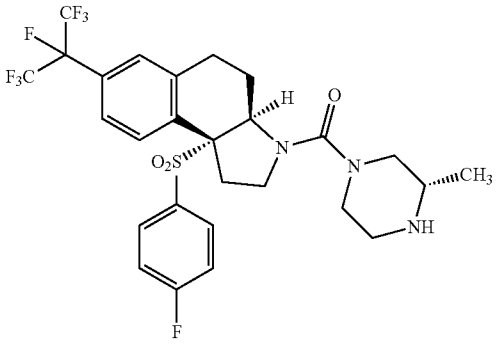
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
817		693.4 $(M + H)^+$	1.90	D

Example 818

2-((S)-4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylpiperazin-1-yl)acetic acid

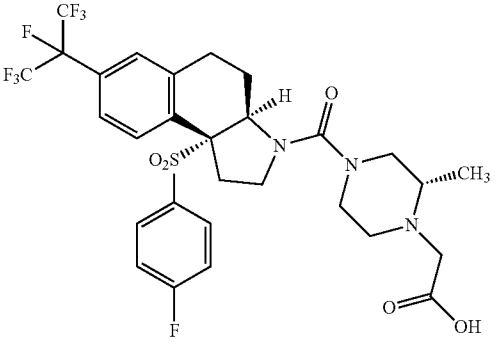


Step A: ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((S)-3-methylpiperazin-1-yl) methanone



A solution of (3aR,9bR)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 0.05 g, 0.100 mmol) and triphosgene (0.012 g, 0.039 mmol) in DCM (1 mL) was treated at rt with DIPEA (0.087 mL, 0.501 mmol). After stirring for 30 min, the mixture was treated with tert-butyl (S)-2-methylpiperazine-1-carboxylate (0.020 g, 0.100 mmol) and stirred overnight at rt. The mixture was diluted with DCM and washed sequentially with saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were extracted with DCM, and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was dissolved in DCM (1 mL) and treated with TFA (0.5 mL, 6.49 mmol). After stirring for 2 h, the mixture was concentrated. The residue was dissolved in EtOAc and washed sequentially with 1.5 M aqueous K_2HPO_4 and brine, dried over $MgSO_4$ and concentrated to provide crude ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((S)-3-methylpiperazin-1-yl)methanone (0.06 g), used without further purification. LCMS m/z 626.2 $(M+H)^+$, t_R 0.92 min (method B).

Step B: 2-((S)-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylpiperazin-1-yl)acetic acid

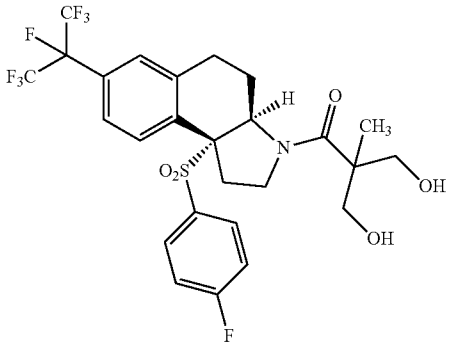


A mixture of crude ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((S)-3-methylpiperazin-1-yl)methanone (0.06 g, 0.096 mmol), Cs_2CO_3 (0.078 g, 0.240 mmol) and tert-butyl bromoacetate (0.022 mL, 0.144 mmol) in

DMF (0.75 mL) was heated at 60° C. After 6 h, the mixture was cooled to rt, diluted with EtOAc and washed sequentially with 10% aqueous LiCl (2×) and brine. The combined aqueous layers were extracted with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in DCM (1.5 mL), treated with TFA (0.75 mL, 9.73 mmol) and stirred at rt. After 4 h, the mixture was concentrated, and the residue was purified by preparative HPLC (method E, gradient 30-70% B, 20 min) to provide 2-((S)-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylpiperazin-1-yl)acetic acid (23.6 mg, 36% yield). LCMS m/z 684.1 $(M+H)^+$, t_R 1.84 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, J=8.4 Hz, 1H), 7.63-7.53 (m, 3H), 7.34 (br. s., 1H), 7.30 (d, J=6.8 Hz, 1H), 6.72 (d, J=7.3 Hz, 1H), 4.80 (dd, J=8.8, 4.5 Hz, 1H), 4.08-3.99 (m, 1H), 3.87-3.79 (m, 1H), 3.58 (d, J=14.7 Hz, 1H), 3.14-3.06 (m, 2H), 3.03-2.93 (m, 2H), 2.66-2.53 (m, 4H), 1.96-1.86 (m, 2H), 1.76-1.68 (m, 2H), 1.50-1.41 (m, 2H), 1.14 (d, J=5.9 Hz, 3H).

Example 819

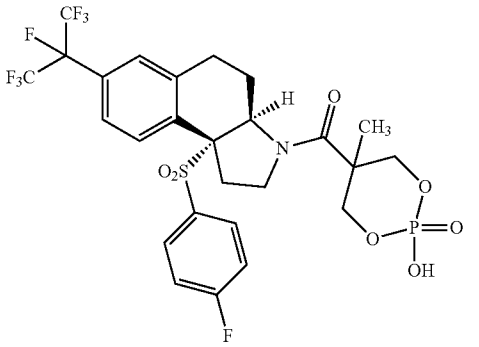
1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one



A solution of ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)(2,2,5-trimethyl-1,3-dioxan-5-yl)methanone (Example 305; 76 mg, 0.087 mmol) in MeOH (5 mL) was treated with p-toluenesulfonic acid hydrate (1.654 mg, 8.69 μmol) and stirred at rt. After 60 min, the mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to provide a tan glassy solid (64 mg, >100% yield, about 80% purity). A sample of this material (12 mg) was purified by preparative HPLC (method E, gradient 40-80% B, 20 min) to provide 1-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one (6.2 mg, 11% yield). LCMS m/z 616.1 $(M+H)^+$, HPLC t_R 2.00 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J=8.5 Hz, 1H), 7.63 (d, J=8.4 Hz, 1H), 7.39-7.30 (m, 3H), 7.29-7.19 (m, 2H), 4.82 (dd, J=11.1, 4.8 Hz, 1H), 4.65 (t, J=5.3 Hz, 1H), 4.55 (br. s., 1H), 4.10-3.95 (m, 1H), 3.58-3.23 (m, 2H), 2.76-2.59 (m, 2H), 2.51 (br. s., 4H), 2.30-2.15 (m, 1H), 1.88 (t, J=14.2 Hz, 1H), 1.34-1.17 (m, 1H), 1.01 (s, 3H).

Example 820

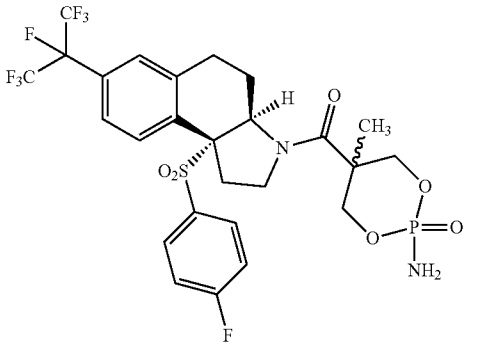
((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(2-hydroxy-5-methyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)methanone



A solution of phosphorus oxychloride (7.33 μL, 0.079 mmol) in pyridine (0.5 mL) was stirred on an ice-water bath and treated in portions over 50 min with a solution of crude 1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one (Example 819; 55 mg, 0.071 mmol) in pyridine (0.5 mL). The mixture was warmed to rt and stirred for 35 min. The solution was then added dropwise to a stirred solution of $NaHCO_3$ (26.4 mg, 0.315 mmol) in water (1 mL), causing gas evolution. After stirring for 60 min, the mixture was concentrated and the residue was purified by preparative HPLC (method E, gradient 20-60% B, 20 min) to provide ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(2-hydroxy-5-methyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)methanone (28.4 mg, 59% yield). LCMS m/z 677.9 $(M+H)^+$, 676.3 $(M-H)^-$, HPLC t_R 1.73 min (method C). ^1H NMR (600 MHz, DMSO-d_6) δ 7.87 (d, J=8.5 Hz, 1H), 7.62 (d, J=8.3 Hz, 1H), 7.34-7.27 (m, 3H), 7.27-7.19 (m, 2H), 4.83 (dd, J=11.5, 5.0 Hz, 1H), 4.38-4.24 (m, 2H), 4.03-3.27 (m, 4H), 2.77-2.59 (m, 2H), 2.26-2.15 (m, 1H), 1.83 (t, J=13.9 Hz, 1H), 1.33-1.23 (m, 1H), 1.21 (s, 3H); one proton presumably hidden by solvent peak.

Example 821

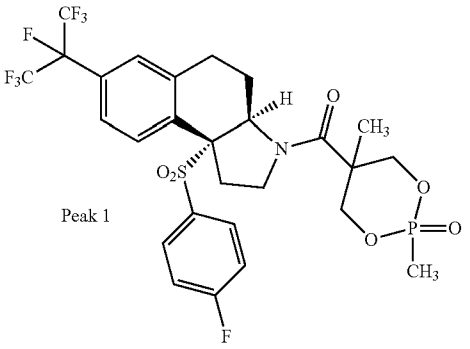
(2-amino-5-methyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone

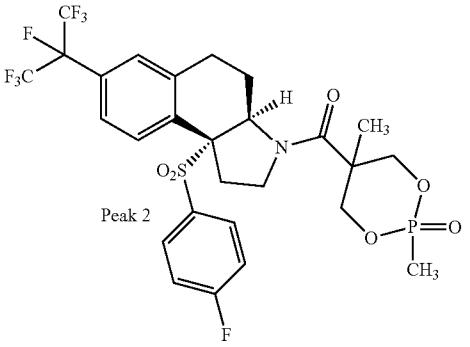


Following the procedure of Example 820 but quenching the reaction mixture into aqueous ammonia instead of aqueous $NaHCO_3$, 1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one (Example 819) was converted into (2-amino-5-methyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone as a mixture of isomers in 13% yield. LCMS m/z 677.4 (M+H)+, HPLC t_R 2.02 min (method C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (d, J=8.0 Hz, 1H), 7.64 (d, J=8.1 Hz, 1H), 7.34 (br. s., 1H), 7.32-7.18 (m, 4H), 5.07-4.77 (m, 2H), 4.62-4.40 (m, 2H), 4.25-4.02 (m, 2H), 4.03-3.86 (m, 1H), 3.76 (br. s., 1H), 3.38 (br. s., 1H), 2.82-2.60 (m, 2H), 2.22 (m, 1H), 1.92-1.67 (m, 1H), 1.43-1.18 (m, 3H).

Examples 822 and 823

(2,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone (two homochiral isomers)





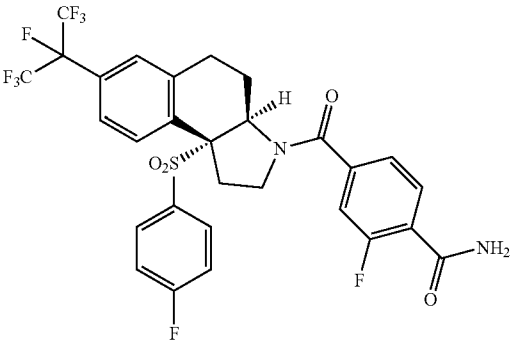
Following the procedure of Example 820 but using methylphosphonic dichloride in place of phosphorus oxychloride, 1-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one (Example 819) was converted into two isomers of (2,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone, which were separated by preparative HPLC (method E, gradient 40-80%, 19 min).

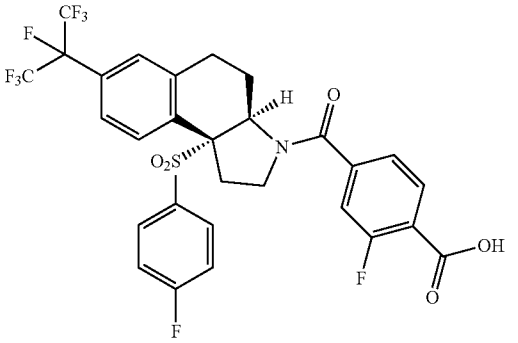
Peak 1 (11% yield): LCMS m/z 676.0 (M+H)$^+$, HPLC t_R 2.12 min (method C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, J=8.5 Hz, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.34 (br. s., 1H), 7.31-7.21 (m, 4H), 4.85 (dd, J=11.5, 4.8 Hz, 1H), 4.58 (t, J=10.1 Hz, 1H), 4.51 (t, J=10.0 Hz, 1H), 4.36-4.18 (m, 2H), 4.04-3.93 (m, 1H), 3.77 (br. s., 1H), 3.42-3.11 (m, 1H), 2.82-2.70 (m, 1H), 2.67 (d, J=16.6 Hz, 1H), 2.21 (d, J=8.1 Hz, 1H), 1.83 (t, J=13.7 Hz, 1H), 1.54 (d, J=17.1 Hz, 3H), 1.32 (s+m, 4H).

Peak 2 (18% yield): LCMS m/z 676.1 (M+H)$^+$, HPLC t_R 2.23 min (method C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96-7.85 (m, 1H), 7.65 (d, J=7.6 Hz, 1H), 7.39-7.21 (m, 5H), 5.00-4.77 (m, 1H), 4.73-4.51 (m, 2H), 4.24 (dd, J=12.2, 7.3 Hz, 1H), 4.10 (dd, J=10.8, 6.4 Hz, 1H), 3.97 (q, J=8.2 Hz, 1H), 3.85-3.44 (m, 2H), 2.86-2.72 (m, 1H), 2.72-2.61 (m, 2H), 2.18 (d, J=8.1 Hz, 1H), 1.97-1.76 (m, 1H), 1.60 (d, J=16.9 Hz, 3H), 1.45-1.20 (m, 1H), 1.13 (s, 3H).

Examples 824 and 825

2-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)benzamide and 2-fluoro-4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)benzoic acid





A solution of crude 2-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)benzonitrile (Example 386, prepared from 70 mg of Intermediate 32) in acetic acid (3.2 mL, 55.9 mmol) was treated with concentrated aqueous HCl (0.8 mL, 26.3 mmol) and heated at 70° C. for 7 h. The mixture was cooled to rt and concentrated, and the residue was purified by preparative HPLC to provide 2-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)benzamide (Example 824; 8 mg, 9% yield). LCMS m/z 665.1 (M+H)$^+$, t_R 1.06 min (method B). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.98 (d, J=8.8 Hz, 1H),

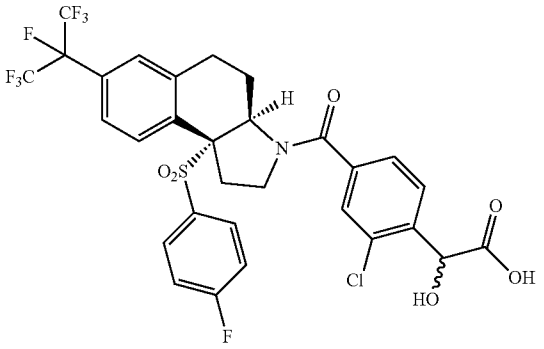
7.91 (d, J=7.9 Hz, 1H), 7.63 (d, J=8.4 Hz, 1H), 7.47-7.40 (m, 3H), 7.38 (s, 1H), 7.33 (s, 1H), 7.14 (d, J=8.8 Hz, 2H), 5.10 (dd, J=11.7, 5.1 Hz, 1H), 3.84-3.75 (m, 1H), 3.72-3.64 (m, 1H), 3.53-3.44 (m, 1H), 2.75-2.66 (m, 2H), 2.52-2.45 (m, 1H), 2.11-2.02 (m, 1H), 1.63-1.50 (m, 1H).

Also isolated was 2-fluoro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)benzoic acid (Example 825; 11.1 mg, 12% yield). LCMS m/z 666.3 $(M+H)^+$, t_R 1.05 min (method B). ^1H NMR (400 MHz, MeOH-d_4) δ 8.05 (dd, J=7.9, 3.1 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.65-7.61 (m, 1H), 7.47-7.32 (m, 5H), 7.16-7.11 (m, 2H), 5.10 (dd, J=11.9, 5.3 Hz, 1H), 3.82-3.75 (m, 1H), 3.72-3.64 (m, 1H), 3.52-3.44 (m, 1H), 2.75-2.66 (m, 2H), 2.52-2.45 (m, 1H), 2.10-2.04 (m, 1H), 1.62-1.53 (m, 1H).

Also isolated was recovered starting material (Example 386; 9.5 mg, 11% yield).

Example 826

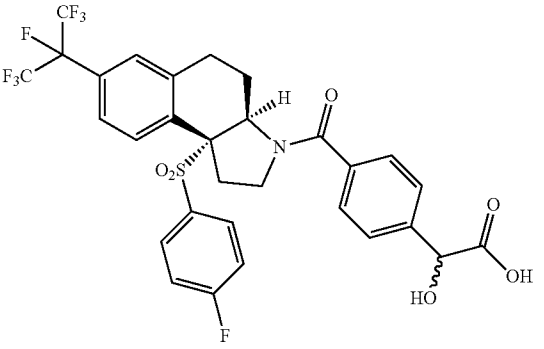
(RS)-2-(2-chloro-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-v)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)phenyl)-2-hydroxyacetic acid



A solution of 2-chloro-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)benzaldehyde (prepared by the procedure of Example 1 Step A, from Intermediate 32 and 3-chloro-4-formylbenzoic acid; 53.3 mg, 0.08 mmol) and cyanotrimethylsilane (0.054 mL, 0.400 mmol) in DCM (1.5 mL) was stirred on an ice-water bath and treated with titanium(IV) isopropoxide (0.234 mL, 0.800 mmol). The mixture was stirred for 5 h, then was treated with cyanotrimethylsilane (0.054 mL, 0.400 mmol) and titanium(IV) isopropoxide (0.234 mL, 0.800 mmol). After stirring overnight at rt, the mixture was treated with 1 N aqueous HCl and diluted with DCM and filtered, dried over $MgSO_4$ and concentrated. The residue was treated with acetic acid (1.6 mL, 27.9 mmol) and concentrated aqueous HCl (0.4 mL, 13.16 mmol) and stirred at 70° C. for 2.5 h. The mixture was cooled to rt, diluted with EtOAc and washed sequentially with water and brine. The combined aqueous layers were extracted with additional EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC (method E, gradient 45-90% B, 20 min) to afford (RS)-2-(2-chloro-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)phenyl)-2-hydroxyacetic acid (15.4 mg, 25% yield). LCMS m/z 712.1 $(M+H)^+$, t_R 1.80 min (Method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.85 (d, J=8.5 Hz, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.51 (d, J=7.3 Hz, 1H), 7.46 (br. s., 2H), 7.40-7.37 (m, 3H), 7.30 (t, J=8.2 Hz, 2H), 5.22 (br. s., 1H), 4.95 (dd, J=11.2, 4.8 Hz, 1H), 3.63-3.57 (m, 1H), 3.40-3.35 (m, 1H), 3.33-3.26 (m, 1H), 2.79-2.71 (m, 1H), 2.69-2.61 (m, 1H), 2.31-2.25 (m, 1H), 2.11-2.02 (m, 1H), 1.55-1.45 (m, 1H).

Example 827

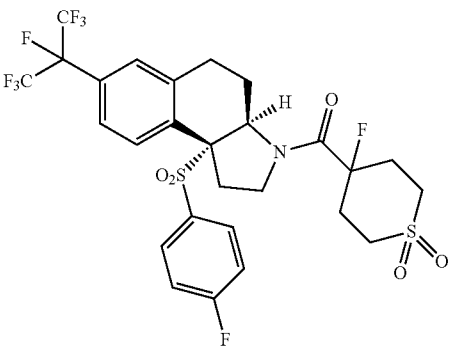
(RS)-2-(4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)phenyl)-2-hydroxyacetic acid



(RS)-2-(4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo [e]indole-3-carbonyl)phenyl)-2-hydroxyacetic acid was prepared by the procedure of Example 826 but substituting 4-formylbenzoic acid for 3-chloro-4-formylbenzoic acid in the preparation of the starting material. LCMS m/z 678.1 $(M+H)^+$, t_R 1.74 min (Method C).

Example 828

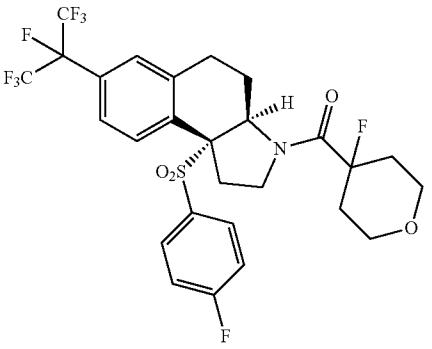
(4-fluoro-1,1-dioxidotetrahydro-2H-thiopyran-4-yl) ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone



A solution of ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)(4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl) methanone (Example 69; 20 mg, 0.030 mmol) in DCM (1 mL) was treated with DAST (0.020 mL, 0.148 mmol) and stirred at rt. After 75 min the mixture was treated with saturated aqueous $NaHCO_3$ (1.5 mL) and the layers were separated. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (method E, gradient 40-90% B, 20 min) to provide (4-fluoro-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)methanone (8.8 mg, 44% yield). LCMS m/z 678.1 $(M+H)^+$, HPLC t_R 2.31 (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.93-7.85 (m, 1H), 7.65 (d, J=8.2 Hz, 1H), 7.40-7.30 (m, 3H), 7.27 (t, J=8.5 Hz, 2H), 4.81 (dd, J=11.7, 4.7 Hz, 1H), 3.96 (d, J=4.6 Hz, 1H), 3.92-3.77 (m, 1H), 3.61-3.11 (m, 4H), 2.87-2.31 (m, 7H), 2.29-2.13 (m, 1H), 1.92 (t, J=13.9 Hz, 1H), 1.47-1.30 (m, 1H).

Example 829

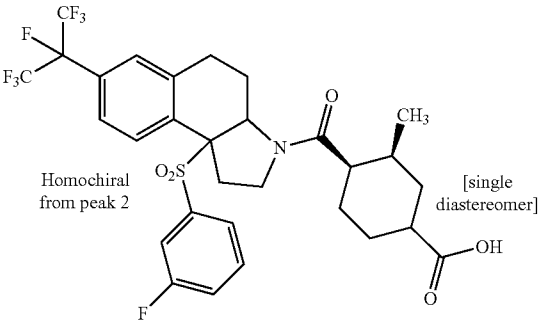
((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(4-fluorotetrahydro-2H-pyran-4-yl)methanone



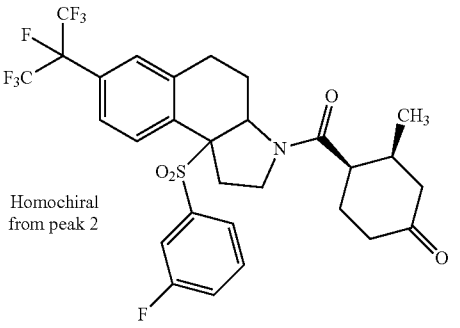
Following the procedure of Example 828, ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(4-hydroxytetrahydro-2H-pyran-4-yl)methanone (Example 471; 12.5 mg, 0.020 mmol) was converted into ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)(4-fluorotetrahydro-2H-pyran-4-yl)methanone (6.9 mg, 55% yield). LCMS m/z 630.2 $(M+H)^+$, HPLC t_R 2.43 min (method C). ^1H NMR (500 MHz, DMSO-d_6) δ 7.93-7.82 (m, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.42-7.17 (m, 5H), 5.53-4.51 (m, 2H), 4.09-3.06 (m, 5H), 2.86-2.57 (m, 4H), 2.35-1.20 (m, 6H).

Example 830

(3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid

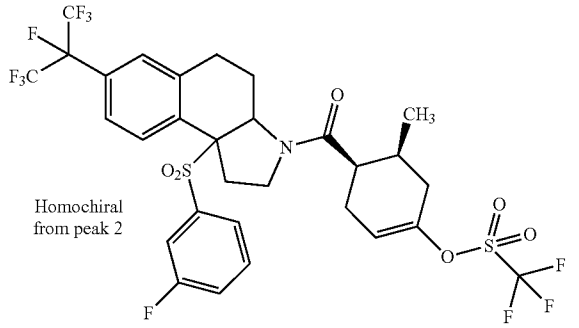


Step A: (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one



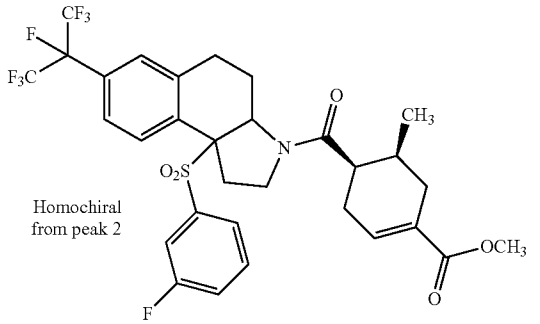
A solution of 9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (homochiral, from peak 2, Intermediate 43; 100 mg, 0.2 mmol) in DMF (1.5 mL) was treated with (1R,2S)-2-methyl-4-oxocyclohexanecarboxylic acid (*Tetrahedron* 1994, 50, 11743; 40.7 mg, 0.26 mmol), HATU (99 mg, 0.26 mmol), and 4-methylmorpholine (0.066 mL, 0.601 mmol). The mixture was stirred at rt overnight, then was diluted with EtOAc and saturated brine. The organic phase was separated and washed sequentially with brine (3×), 1 M aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give crude (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one (105 mg, 82% yield). LCMS m/z 638.3 $(M+H)^+$, HPLC t_R 1.08 min (method B).

Step B: (4R,5S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate



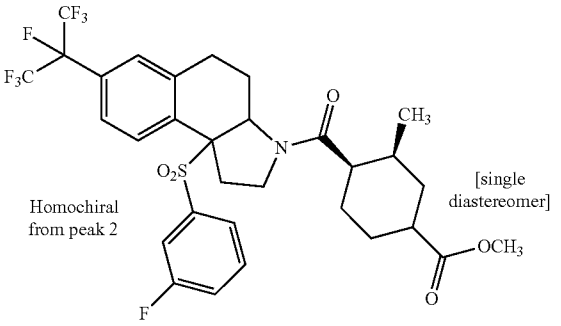
A solution of (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexanone (100 mg, 0.157 mmol) in THF (2 mL) at −78° C. was treated with 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl) methanesulfonamide (61.6 mg, 0.173 mmol). Potassium bis(trimethylsilyl)amide (1 M in THF; 0.2 mL, 0.2 mmol) was then added dropwise at −78° C. After stirring for 30 min, the mixture was warmed to rt, stirred for 1.5 h, then was treated with water. The mixture was extracted with EtOAc, and the organic phase was washed with brine, dried over $MgSO_4$ and concentrated to provide crude (4R,5S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (82 mg, 68% yield). LCMS m/z 770.4 $(M+H)^+$, HPLC t_R 1.21 min (method B).

Step C: methyl (4R,5S)-4-(9b-((3-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-ene-1-carboxylate



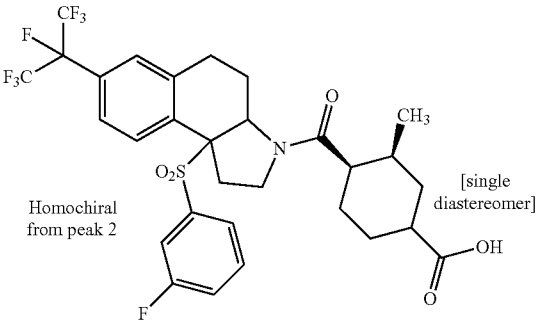
A solution of (4R,5S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (80 mg, 0.104 mmol) in DMF (1 mL) and MeOH (1 mL) was treated with palladium(II) acetate (2.3 mg, 10.39 mol), 1,1'-bis(diphenylphosphino) ferrocene (5.76 mg, 10.39 μmol), and tri-n-butylamine (0.075 mL, 0.312 mmol). Carbon monoxide was bubbled through the mixture for 10 min. The mixture was then heated at 80° C. under a carbon monoxide atmosphere (balloon pressure) for 2 h. After cooling to rt, the mixture was diluted with EtOAc and water. The organic phase was separated, washed with brine (3×), dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC (method G, gradient 20-100% B, 10 min) to give methyl (4R,5S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-ene-1-carboxylate (70.2 mg, 99% yield). LCMS m/z 680.2 $(M+H)^+$, HPLC t_R 1.14 min (method B).

Step D: methyl (3S,4R)-4-(9b-((3-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate



A solution of (4R,5S)-methyl 4-((3aR,9bR)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-5-methylcyclohex-1-enecarboxylate (35 mg, 0.051 mmol) in DCM (1.5 mL) was treated with iridium(I) hexafluorophosphate (1,5-cyclooctadiene)-(pyridine)-(tricyclohexylphosphine) (Crabtree's catalyst; 12.4 mg, 0.015 mmol) and the mixture was stirred at rt overnight under a hydrogen atmosphere (balloon pressure). The mixture was filtered and the filtrate was concentrated to give a single diastereomer of crude methyl (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate (36.9 mg, quantitative yield). LCMS m/z 682.5 $(M+H)^+$, HPLC t_R 1.14 min (method B).

Step E: (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid

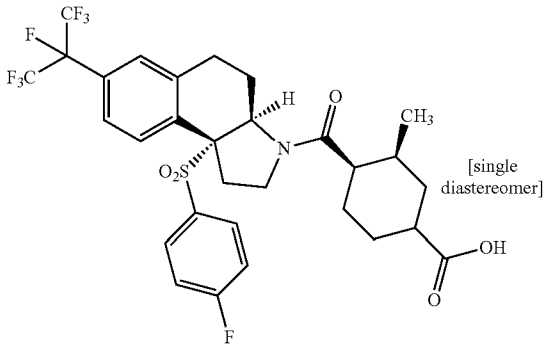


A solution of methyl (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-

1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate (36 mg, 0.053 mmol) in THF (1.5 mL) and MeOH (0.2 mL) was treated with 1 M aqueous LiOH (0.211 mL, 0.211 mmol). The mixture was stirred overnight at rt, then was purified by preparative HPLC (method G, gradient 20-100% B, 10 min) to give a single diastereomer of (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid (9 mg, 26% yield). LCMS m/z 668.4 $(M+H)^+$, HPLC t_R 1.06 min (method B). ^1H NMR (400 MHz, MeOH-d_4) δ 8.00 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.8 Hz, 1H), 7.50-7.34 (m, 2H), 7.30-7.18 (m, 2H), 6.81 (dd, J=8.1, 2.0 Hz, 1H), 4.87 (s, 1H), 4.12-3.98 (m, 1H), 3.89 (td, J=9.9, 3.1 Hz, 1H), 3.56 (ddd, J=14.7, 8.1, 2.5 Hz, 1H), 3.40-3.34 (m, 1H), 2.79-2.65 (m, 2H), 2.63-2.52 (m, 2H), 2.50-2.42 (m, 2H), 2.03 (d, J=9.0 Hz, 1H), 1.99-1.85 (m, 3H), 1.84-1.72 (m, 1H), 1.65-1.43 (m, 2H), 1.39-1.22 (m, 1H), 1.10 (d, J=7.0 Hz, 3H).

Example 831

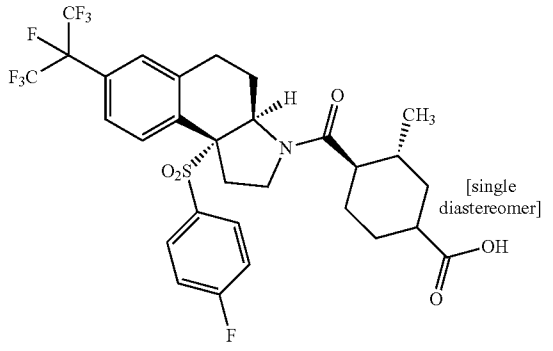
(3S,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid



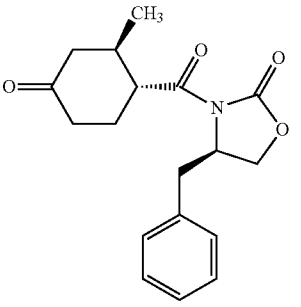
Following the procedures of Example 830, (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32) was converted into a single diastereomer of (3S,4R)-4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid. LCMS m/z 668.2 $(M+H)^+$, HPLC t_R 2.01 min (method C).

Example 832

(3R,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid

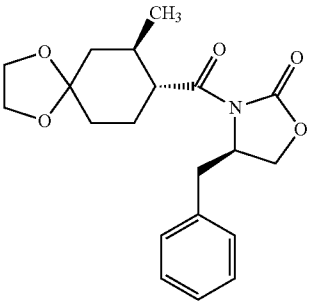


Step A. (R)-4-benzyl-3-((1R,2R)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one



A solution of (R,E)-4-benzyl-3-(but-2-enoyl)oxazolidin-2-one (8.0 g, 32.6 mmol) in DCM (40 mL) at −78° C. was treated with diethylaluminum chloride (1 M in hexane, 48.9 mL, 48.9 mmol). After 10 min, (buta-1,3-dien-2-yloxy) trimethylsilane (20.1 mL, 114 mmol) in DCM (5 mL) was added dropwise at −78° C. The solution was warmed to rt and stirred overnight. A mixture of THF (4 mL) and 6 M aqueous HCl (4 mL) was added, and the mixture was stirred for 30 min. Celite and EtOAc was added, and the mixture was filtered. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give (R)-4-benzyl-3-((1R,2R)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one (1.2 g, 12% yield). LCMS m/z 316.2 $(M+H)^+$, HPLC t_R 0.87 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 3H), 7.24-7.19 (m, 2H), 4.74 (ddt, J=9.3, 7.4, 3.2 Hz, 1H), 4.32-4.20 (m, 2H), 3.79 (td, J=10.7, 3.4 Hz, 1H), 3.26 (dd, J=13.4, 3.3 Hz, 1H), 2.82 (dd, J=13.4, 9.5 Hz, 1H), 2.54-2.44 (m, 3H), 2.42-2.27 (m, 2H), 2.16 (dd, J=14.0, 12.7 Hz, 1H), 1.90-1.76 (m, 1H), 1.02 (d, J=6.4 Hz, 3H).

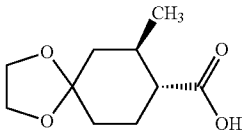
Step B. (R)-4-benzyl-3-((7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one



A solution of (R)-4-benzyl-3-((1R,2R)-2-methyl-4-oxocyclohexanecarbonyl)oxazolidin-2-one (1.0 g, 3.17 mmol) was dissolved in DCM (10 mL) and cooled to 0° C. The mixture was treated with 2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane (0.974 mL, 3.96 mmol), stirred for 5 min, then treated with trimethylsilyl trifluoromethanesulfonate (0.059 mL, 0.317 mmol). The mixture was warmed to rt and stirred overnight. Et_3N (0.075 mL, 0.539 mmol) was added, followed by saturated aqueous $NaHCO_3$. The mixture was extracted with DCM, and the organic phase was dried over

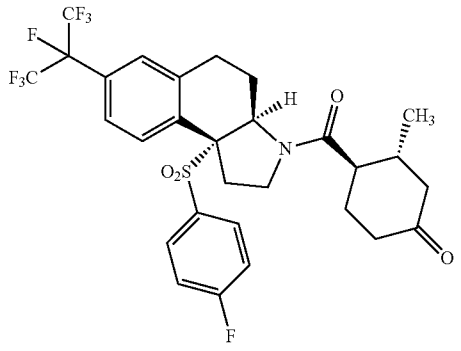
$MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give (R)-4-benzyl-3-((7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one (750 mg, 66% yield). LCMS m/z 360.3 $(M+H)^+$, HPLC t_R 0.94 min (method B).

Step C. (7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid



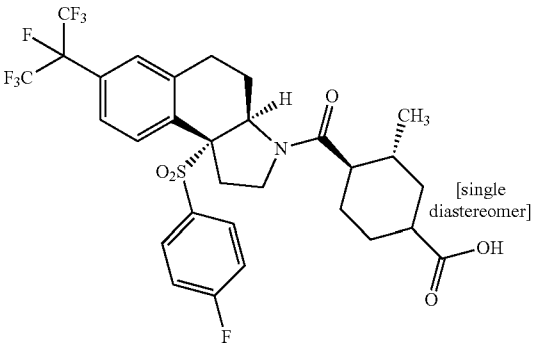
A solution of (R)-4-benzyl-3-((7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one (750 mg, 2.087 mmol) in THF (15 mL) was cooled to 0° C. and treated with 33% aqueous hydrogen peroxide (0.853 mL, 8.35 mmol). After 5 min, 1 M aqueous LiOH (4.17 mL, 4.17 mmol) was added and the mixture was stirred for 2 h. Saturated aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$ were added, followed by water. The mixture was partially concentrated, and the aqueous residue was extracted with DCM (3×). The aqueous phase was acidified with 6 M aqueous HCl and extracted with EtOAc. This organic phase was dried over $MgSO_4$, filtered and concentrated to give crude (7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (290 mg, 69% yield), used without further purification. LCMS m/z 201.1 (M+H)+, HPLC t_R 0.60 min (method B).

Step D. (3R,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one



A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole (Intermediate 32; 100 mg, 0.200 mmol) in DMF (1.5 mL) was treated with (7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid (40 mg, 0.200 mmol), HATU (76 mg, 0.200 mmol), and 4-methylmorpholine (0.066 mL, 0.599 mmol). The mixture was stirred overnight, then diluted with EtOAc and saturated brine. The organic phase was removed, and washed sequentially with brine (3×), 1 M aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to give a mixture of ((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((7R,8R)-7-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanone (LCMS m/z 682.3 $(M+H)^+$, HPLC t_R 1.11 min) and (3R,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one (LCMS m/z 638.3 (M+H)+, HPLC t_R 1.07 min, method B). The material was dissolved in THF (2 mL), treated with 6 M aqueous HCl (1 mL) and stirred at rt overnight. The mixture was extracted with EtOAc, and the organic phase was washed sequentially with brine (3×), 1 M aqueous HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give (3R,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexanone (48 mg, 38% yield). LCMS m/z 638.3 $(M+H)^+$, t_R 1.06 min (method B).

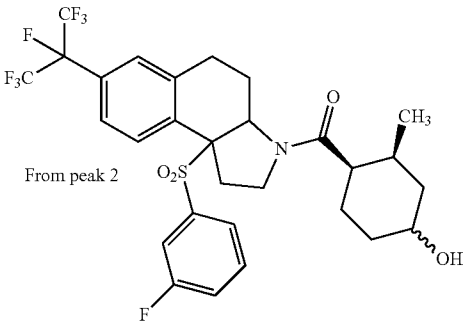
Step E: (3R,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid



Following the procedures of Example 830 Steps B-E, (3R,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexanone was converted into a single diastereomer of (3R,4R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid. LCMS m/z 668.3 $(M+H)^+$, HPLC t_R 1.05 min (method B).

Example 833

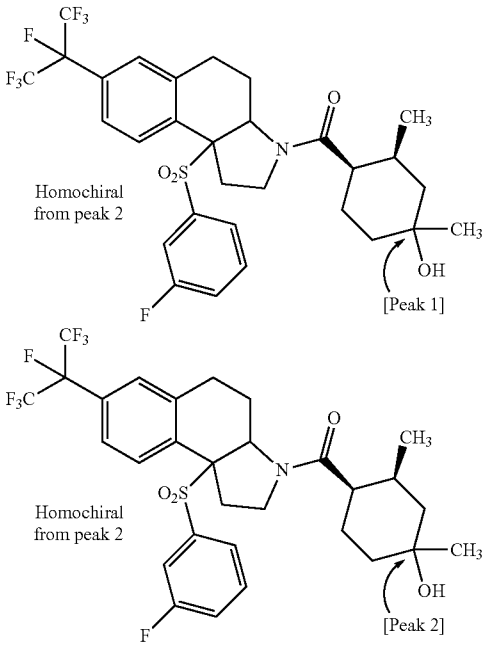
(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((1R,2S)-4-hydroxy-2-methylcyclohexyl)methanone



A solution of homochiral (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one (Example 830 Step A; 30 mg, 0.047 mmol) in MeOH (1.5 mL) was treated with $NaBH_4$ (1.78 mg, 0.047 mmol). The mixture was stirred overnight at rt, then was filtered and purified by preparative HPLC (method G, gradient 20-100% B, 10 min) to give (9b-((3-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((1R,2S)-4-hydroxy-2-methylcyclohexyl)methanone as a mixture of diastereomers (9.1 mg, 29% yield). LCMS m/z 640.4 $(M+H)^+$, HPLC t_R 1.07 min (method B). ^1H NMR (400 MHz, MeOH-d_4) δ 7.98 (d, J=8.4 Hz, 1H), 7.61 (d, J=8.1 Hz, 1H), 7.39-7.33 (m, 2H), 7.25 (s, 1H), 7.07 (t, J=8.7 Hz, 2H), 4.04-3.95 (m, 1H), 3.80 (td, J=9.7, 2.5 Hz, 1H), 3.65-3.50 (m, 2H), 2.82-2.76 (m, 1H), 2.69 (dt, J=14.7, 9.6 Hz, 1H), 2.61-2.54 (m, 1H), 2.51-2.44 (m, 1H), 2.16-2.04 (m, 1H), 1.92-1.79 (m, 3H), 1.73-1.64 (m, 4H), 1.26 (dd, J=13.1, 2.8 Hz, 1H), 1.13 (d, J=7.0 Hz, 3H), 1.02 (dd, J=10.6, 6.8 Hz, 1H).

Examples 834 and 835

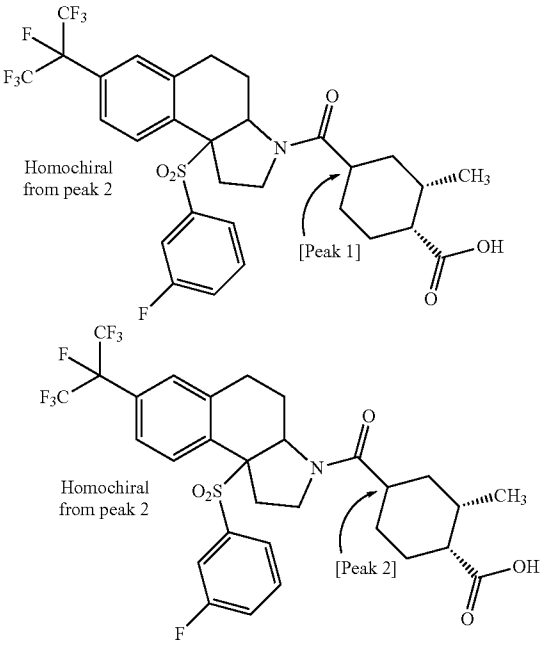
(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((1R,2S)-4-hydroxy-2,4-dimethylcyclohexyl) methanone (2 single diastereomers)



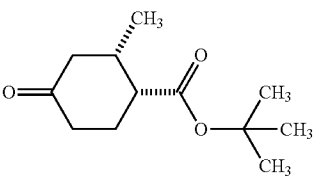
A solution of homochiral (3S,4R)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-3-methylcyclohexan-1-one (Example 830 Step A; 30 mg, 0.047 mmol) in THF (1 mL) was cooled to 0° C. and treated with methylmagnesium bromide (3 M in diethyl ether; 0.024 mL, 0.071 mmol). The mixture was warmed to rt over 1 h, then was treated with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with brine (3×), dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC (method E, gradient 40-100% B, 20 min, then method E, gradient 55-80% B, 25 min) to provide two separated diastereomers of (9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)((1R,2S)-4-hydroxy-2,4-dimethylcyclohexyl)methanone. Peak 1 (Example 834, 3.3 mg, 11% yield) LCMS m/z 654.5 $(M+H)^+$, HPLC t_R 2.36 min (method D). Peak 2 (Example 835, 2.0 mg, 6% yield) LCMS m/z 654.4 $(M+H)^+$, HPLC t_R 2.37 min (method D).

Examples 836 and 837

(1R,2S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



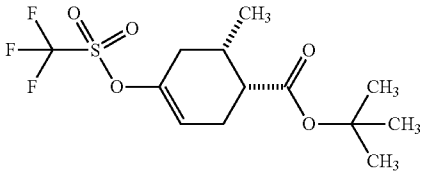
Step A: tert-butyl (1R,2S)-2-methyl-4-oxocyclohexane-1-carboxylate



A solution of (1R,2S)-2-methyl-4-oxocyclohexanecarboxylic acid (*Tetrahedron* 1994, 50, 11743; 150 mg, 0.96 mmol) in tert-butanol (2.5 mL) and THF (2.5 mL) was treated with (E)-tert-butyl N,N'-diisopropylcarbamimidate (385 mg, 1.921 mmol). The mixture was stirred overnight at rt, filtered and concentrated. The residue was taken up in diethyl ether, filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 0-10%), to

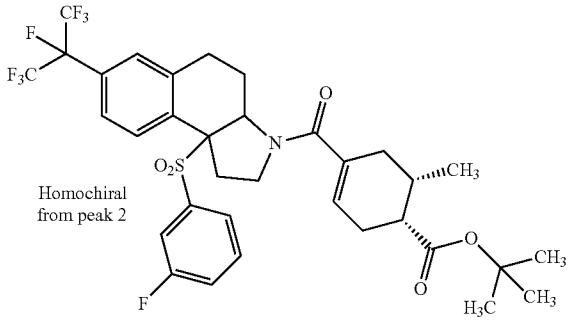
give tert-butyl (1R,2S)-2-methyl-4-oxocyclohexane-1-carboxylate (62 mg, 30% yield). LCMS m/z 157.1 $(M+H-C_4H_8)^+$, HPLC t_R 0.9 min (Method B).

Step B: tert-butyl (1R,6S)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate



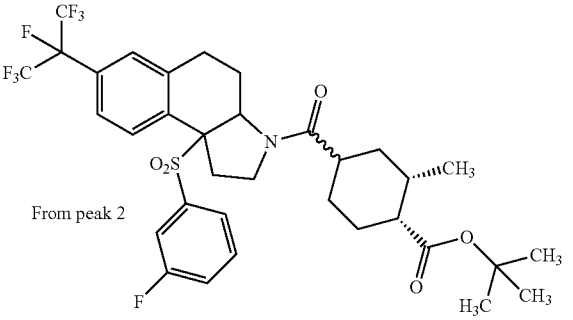
Following the procedure of Example 830 Step B, tert-butyl (1R,2S)-2-methyl-4-oxocyclohexane-1-carboxylate was converted into tert-butyl (1R,6S)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate in 99% yield. LCMS m/z 367.1 $(M+Na)^+$, HPLC t_R 1.15 min (method B).

Step C: tert-butyl (1R,6S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carboxylate



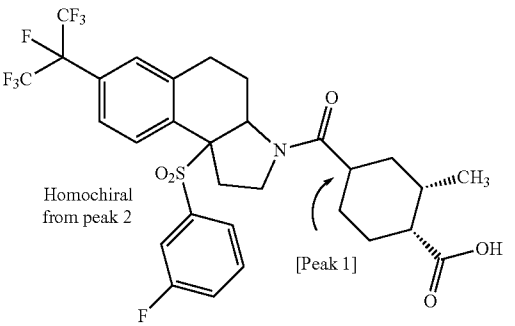
A solution of (1R,6S)-tert-butyl 6-methyl-4-(((trifluoromethyl)sulfonyl)oxy) cyclohex-3-enecarboxylate (80 mg, 0.232 mmol) in DMF (1.5 mL) was treated with 9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (homochiral, from peak 2, Intermediate 43; 116 mg, 0.232 mmol) and tri-n-butylamine (0.17 mL, 0.697 mmol). Carbon monoxide was bubbled through this solution for 5 min. Bis(triphenylphosphine)palladium(II) chloride (8.15 mg, 0.012 mmol) was added and the mixture was again bubbled with carbon monoxide for 5 min. The mixture was heated at 98° C. under an atmosphere of carbon monoxide (balloon pressure) for 2 h. After cooling to rt, the mixture was diluted with water and extracted with EtOAc. The organic phase was washed with brine (3×), dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give homochiral tert-butyl (1R,6S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carboxylate (63 mg, 38% yield). LCMS m/z 722.5 $(M+H)^+$, HPLC t_R 1.21 min (method B).

Step D: tert-butyl (1R,2S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate (mixture of diastereomers)

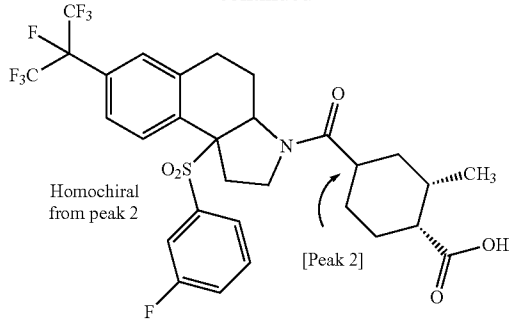


A solution of tert-butyl (1R,6S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carboxylate (30 mg, 0.042 mmol) in DCM (1.5 mL) was treated with iridium(I) hexafluorophosphate (1,5-cyclooctadiene)-(pyridine)-(tricyclohexylphosphine) (Crabtree's catalyst; 8 mg, 9.94 μmol) and stirred at rt overnight under a hydrogen atmosphere (balloon pressure). The mixture was filtered and concentrated to provide tert-butyl (1R,2S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate as a mixture of diastereomers (25 mg, 83% yield). LCMS m/z 724.6 $(M+H)^+$, HPLC t_R 1.23 min (method B).

Step E: (1R,2S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



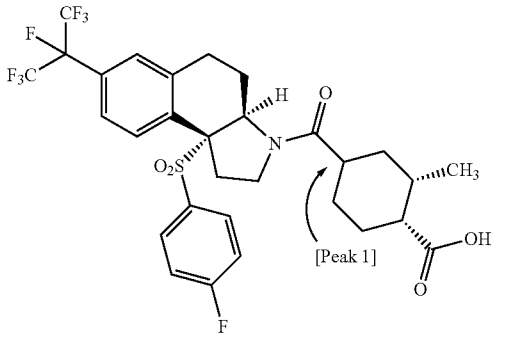
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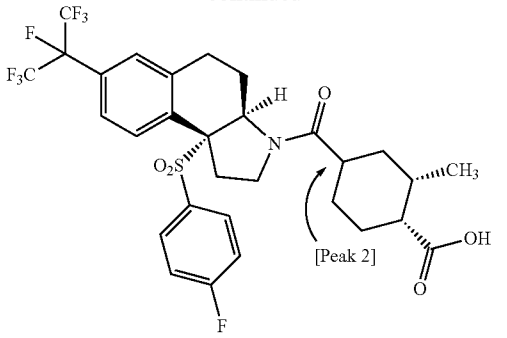
A solution of tert-butyl (1R,2S)-4-(9b-((3-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate (25 mg, 0.035 mmol) in DCM (1 mL) was treated with TFA (3 mL) and stirred at rt for 30 min. The mixture was concentrated and the residue was purified by preparative HPLC (method G, gradient 20-100% B, 10 min) to provide two homochiral diastereomers of (1R,2S)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid. Peak 1 (Example 836; t_R 9.3 min, 9.5 mg, 39% yield). LCMS m/z 668.4 $(M+H)^+$, HPLC t_R 1.06 min (method B). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.00 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.49-7.37 (m, 2H), 7.30-7.25 (m, 2H), 6.89 (dt, J=8.1, 1.9 Hz, 1H), 4.81-4.77 (m, 1H), 3.90 (dd, J=10.2, 5.4 Hz, 2H), 3.58 (dt, J=14.9, 5.2 Hz, 1H), 2.79-2.67 (m, 2H), 2.64-2.49 (m, 3H), 2.48-2.40 (m, 1H), 2.00-1.87 (m, 1H), 1.86-1.66 (m, 5H), 1.59-1.47 (m, 1H), 1.31 (qd, J=12.7, 3.2 Hz, 1H), 1.02 (d, J=7.0 Hz, 3H). Peak 2 (Example 837; t_R 9.9 min, 6 mg, 25% yield). LCMS m/z 668.3 $(M+H)^+$, HPLC t_R 1.08 min (method B). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.00 (d, J=8.4 Hz, 1H), 7.63 (d, J=8.6 Hz, 1H), 7.48-7.36 (m, 2H), 7.31-7.25 (m, 2H), 6.87 (dt, J=8.2, 2.0 Hz, 1H), 4.80-4.78 (m, 1H), 4.01-3.82 (m, 2H), 3.57 (ddd, J=14.9, 8.0, 3.1 Hz, 1H), 2.72 (dt, J=14.8, 9.5 Hz, 1H), 2.65-2.51 (m, 4H), 2.49-2.39 (m, 1H), 2.17-2.08 (m, 1H), 2.02-1.64 (m, 5H), 1.52 (d, J=13.0 Hz, 1H), 1.37-1.23 (m, 1H), 1.07 (d, J=6.8 Hz, 3H).

Examples 838 and 839

(1R,2S)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2.3.3a,4.5.9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



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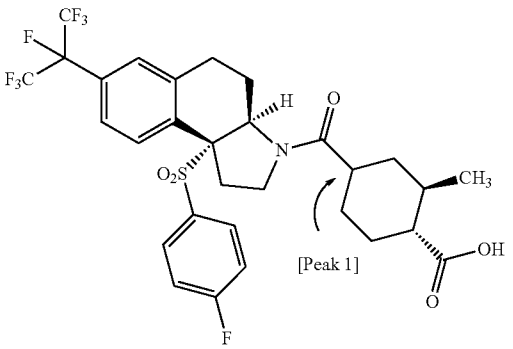


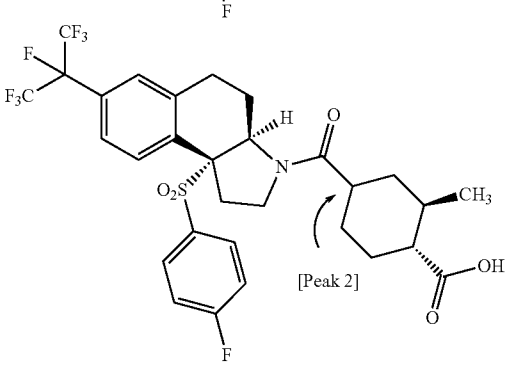
The two homochiral diastereomers of (1R,2S)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid were prepared using the procedures of Examples 836 and 837, using Intermediate 32 in place of Intermediate 43

in Step C. Peak 1 (Example 838) LCMS m/z 668.1 $(M+H)^+$, HPLC t_R 1.99 min (method D). Peak 2 (Example 839) LCMS m/z 668.2 $(M+H)^+$, HPLC t_R 2.27 min (method D).

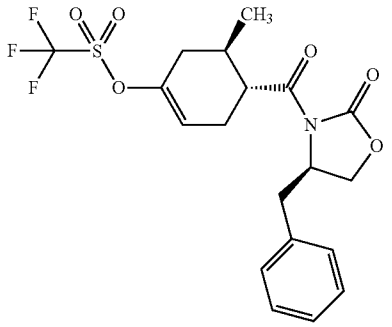
Examples 840 and 841

(1R,2R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



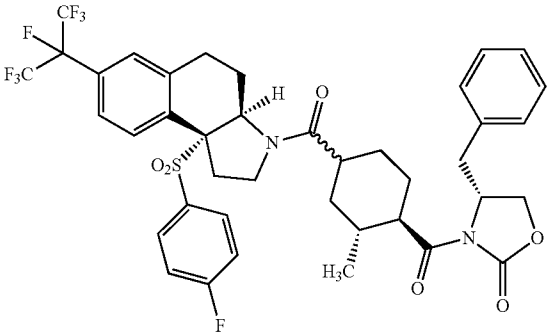


Step A. (4R,5R)-4-((R)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate



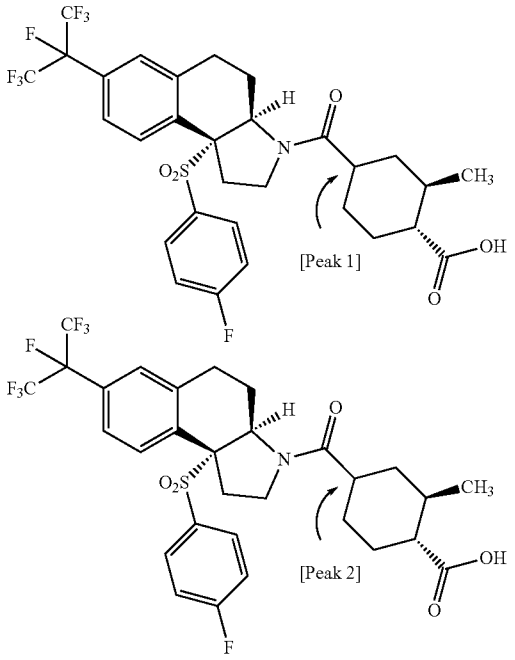
Using the procedure of Example 830 Step B, (R)-4-benzyl-3-((1R,2R)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one (Example 832 Step A) was converted into crude (4R,5R)-4-((R)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate in 75% yield. This material was used without purification.

Step B: (4R)-4-benzyl-3-((1R,2R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one



Using the procedures of Examples 836 and 837, Steps C and D, (4R,5R)-4-((R)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and Intermediate 32 were converted into (4R)-4-benzyl-3-((1R,2R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one as a mixture of two diastereomers in 27% yield. LCMS m/z 827.7 $(M+H)^+$, HPLC t_R 1.17 min (method B).

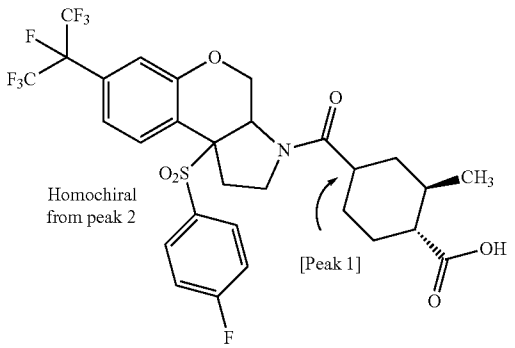
Step C: (1R,2R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



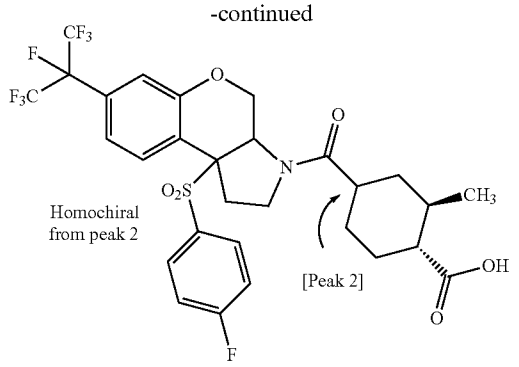
Using the procedure of Example 832 Step C, followed by preparative HPLC separation, the mixture of diastereomers of (4R)-4-benzyl-3-((1R,2R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one was converted into the two homochiral diastereomers of (1R,2R)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid. Peak 1 (Example 840; 28% yield) LCMS m/z 668.5 $(M+H)^+$, HPLC t_R 1.05 min (method B). Peak 2 (Example 841; 8% yield) LCMS m/z 668.5 $(M+H)^+$, HPLC t_R 1.08 min (method B).

Examples 842 and 843

(1R,2R)-4-(9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-b]pyrrole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



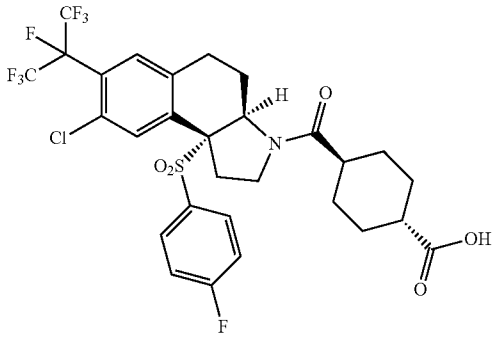
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Two homochiral diastereomers of (1R,2R)-4-(9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-b]pyrrole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid were prepared using the procedures of Examples 840 and 841 but using Intermediate 38 instead of Intermediate 32 in Step B. Peak 1 (Example 842) LCMS m/z 670.0 $(M+H)^+$, HPLC t_R 2.01 min (method C). Peak 2 (Example 843) LCMS m/z 670.1 $(M+H)^+$, HPLC t_R 2.14 min (method C).

Example 844

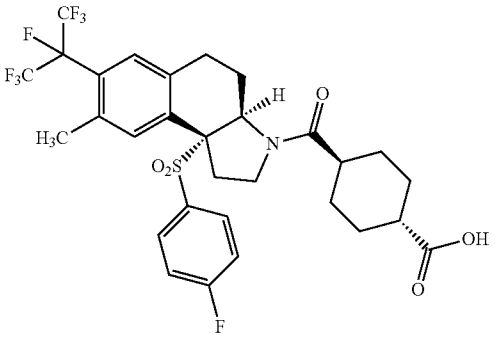
(1R,4r)-4-((3aR,9bR)-8-chloro-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



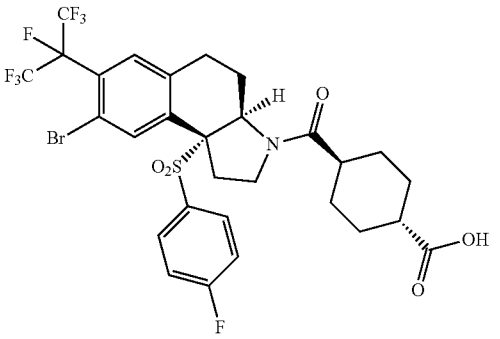
A solution of (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (Example 1; 124 mg, 0.190 mmol) in concentrated sulfuric acid (1 mL) was treated with N-chlorosuccinimide (50.7 mg, 0.379 mmol). The mixture was stirred at rt overnight, then was heated at 50° C. for 7 h. The mixture was cooled to −78° C. and treated dropwise with water. The mixture was warmed to rt and extracted with EtOAc. The organic phase was washed sequentially with water and brine, dried and concentrated. The residue was purified by preparative HPLC (method F, gradient 45-90% B, 27 min) to provide (1R,4r)-4-((3aR,9bR)-8-chloro-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (6.5 mg, 5% yield). LCMS m/z 688.0 $(M+H)^+$, HPLC t_R 2.04 min (method C).

Example 845

(1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-8-methyl-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



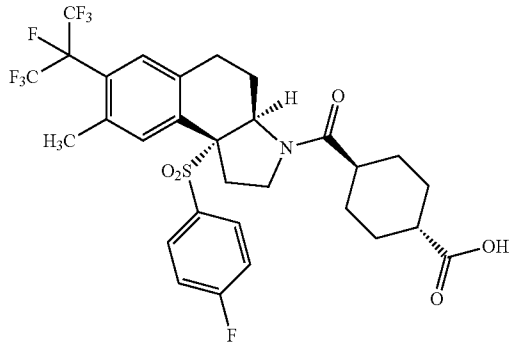
Step A: (1R,4r)-4-((3aR,9bR)-8-bromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A solution of N-bromosuccinimide (40.8 mg, 0.230 mmol) in concentrated sulfuric acid (1 mL) was stirred for 10 min at rt, then was treated with (1R,4r)-4-((3 aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (Example 1; 100 mg, 0.153 mmol). The mixture was stirred at rt overnight, then was cooled to −78° C. and treated dropwise with water. The mixture was warmed to rt and extracted three times with EtOAc. The combined organic phases were washed sequentially with water and brine, dried and concentrated. The residue was purified by column chromatography on silica gel (12 g), eluting with MeOH-DCM (gradient from 0-10%), to provide (1R,4r)-4-((3aR,9bR)-8-bromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (22 mg, 20% yield), contaminated with starting material. LCMS m/z 732.0 $(M+H)^+$, HPLC t_R 1.07 min (method B). ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.40-7.31 (m, 2H), 7.10 (br. s., 1H), 7.04-6.96 (m, 2H), 4.77 (dd, J=12.1, 4.8 Hz, 1H), 4.10-4.01 (m, 1H), 3.93-3.80 (m,

1H), 3.66-3.56 (m, 1H), 2.65-2.39 (m, 6H), 2.28-2.06 (m, 2H), 1.98-1.45 (m, 6H), 1.26-1.11 (m, 1H).

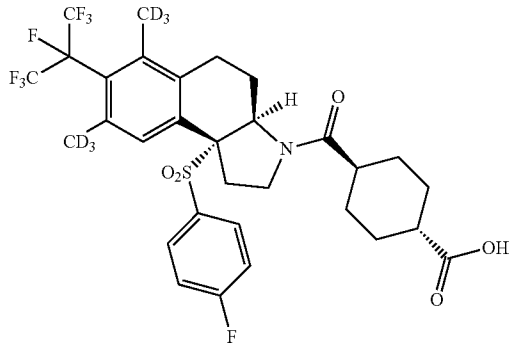
Step B: (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-8-methyl-7-(perfluoropropan-2-yl)-2,3,3a, 4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl) cyclohexane-1-carboxylic acid



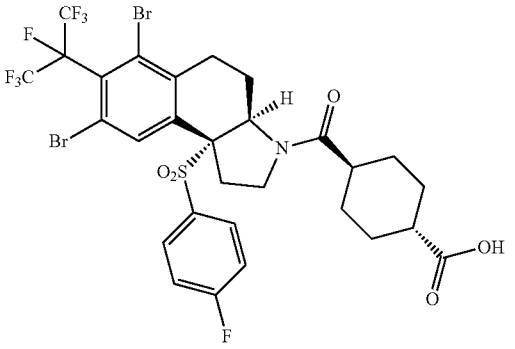
A solution of the impure (1R,4r)-4-((3aR,9bR)-8-bromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid from Step A (22 mg, 0.030 mmol) and iron(III) acetylacetonate (2.121 mg, 6.01 μmol) in THF (1 mL) was subjected to 3 evacuate-fill cycles with nitrogen. Methylmagnesium bromide (3 M in diethyl ether; 0.015 mL, 0.045 mmol) was added dropwise. The mixture was stirred at rt for 30 min, then was diluted with EtOAc, washed sequentially with 0.5 M aqueous HCl, water and brine, and dried and concentrated. The residue was purified by preparative HPLC to provide (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-8-methyl-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (3.6 mg, 18% yield). LCMS m/z 668.0 $(M+H)^+$, HPLC t_R 1.96 min (method C).

Example 846

(1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-6,8-dimethyl(d_6)-7-(perfluoropropan-2-yl)-2,3, 3a4.5.9b-hexahydro-1H-benzo[e]indole-3-carbonyl) cyclohexane-1-carboxylic acid

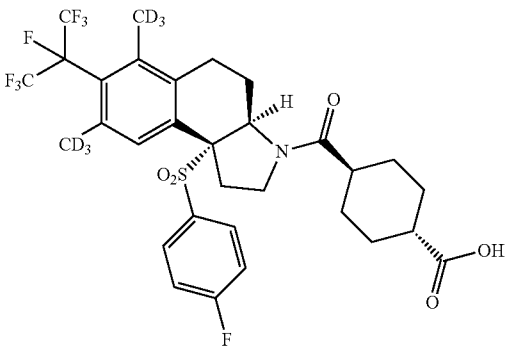


Step A: (1R,4r)-4-((3aR,9bR)-6,8-dibromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3, 3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl) cyclohexane-1-carboxylic acid



A mixture of (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (Example 1; 120 mg, 0.184 mmol) and N-bromosuccinimide (98 mg, 0.551 mmol) was dissolved in concentrated sulfuric acid (1 mL). The mixture was stirred at rt overnight, then was cooled to −78° C. and treated dropwise with water. The mixture was warmed to rt and extracted with EtOAc. The organic phase was washed sequentially with water (twice) and brine, dried and concentrated. The residue was purified by column chromatography on silica gel (12 g), eluting with EtOAc-hexanes (gradient from 0-100%), to provide (1R,4r)-4-((3aR,9bR)-6,8-dibromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (64 mg, 43% yield). LCMS m/z 809.9 $(M+H)^+$, HPLC t_R 1.11 min (method B).

Step B: (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl) sulfonyl)-6,8-dimethyl(d_6)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A solution of (1R,4r)-4-((3aR,9bR)-8-bromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (32 mg, 0.039 mmol) and iron(III) acetylacetonate (2.79 mg, 7.89 μmol) in THF (1 mL) was

subjected to 3 evacuate-fill cycles with nitrogen. Methyl(d_3) magnesium bromide (1 M in diethyl ether; 0.118 mL, 0.118 mmol) was added dropwise. The mixture was stirred at rt for 30 min, then was diluted with EtOAc, washed sequentially with 0.5 M aqueous HCl, water and brine, and dried and concentrated. The residue was purified by preparative HPLC (method F, gradient 45-90% B, 27 min) to provide (1R,4r)-4-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-6,8-dimethyl (d_6)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)cyclohexane-1-carboxylic acid (9 mg, 17% yield). LCMS m/z 688.0 $(M+H)^+$, HPLC t_R 2.04 min (method C).

Additional examples prepared according to the procedures used to prepare Examples 1-846 or similar procedures are shown in Table 19.

TABLE 19

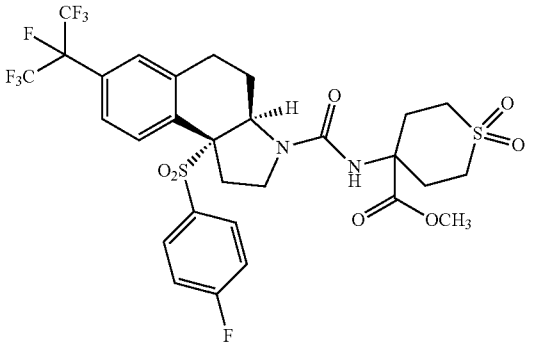
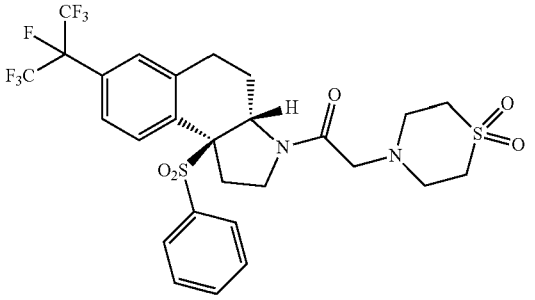
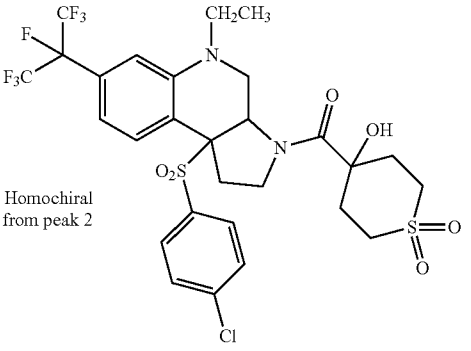
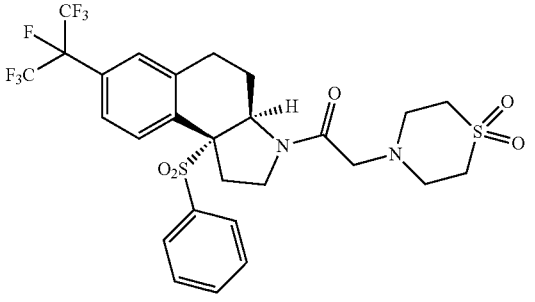
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
847		733.1 $(M + H)^+$	2.14	C
848		657.1 $(M + H)^+$	2.07	C
849	 Homochiral from peak 2	720.8 $(M + H)^+$	2.39	C
850		656.9 $(M + H)^+$	2.07	C

TABLE 19-continued

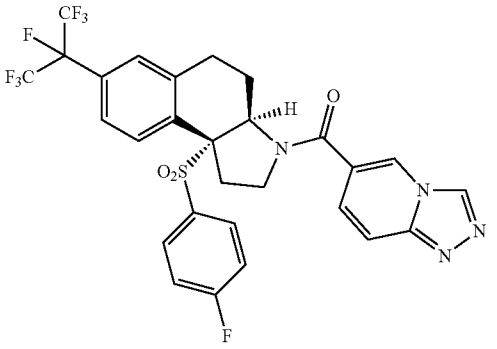
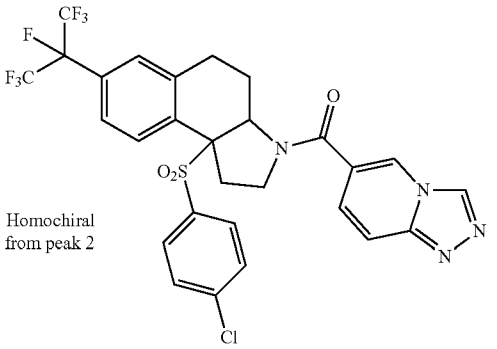
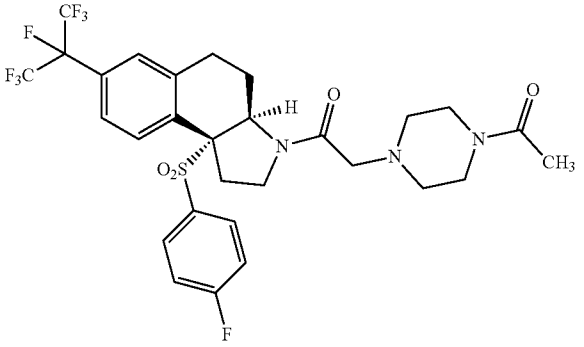
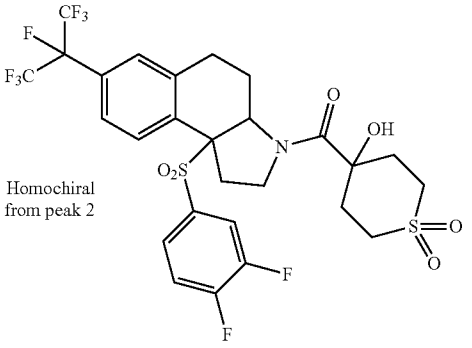
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
851		645.3 $(M + H)^+$	0.97	B
852	 Homochiral from peak 2	661.1 $(M + H)^+$	1.00	B
853		668.3 $(M + H)^+$	0.85	B
854	 Homochiral from peak 2	693.3 $(M + H)^+$	2.17	C

TABLE 19-continued

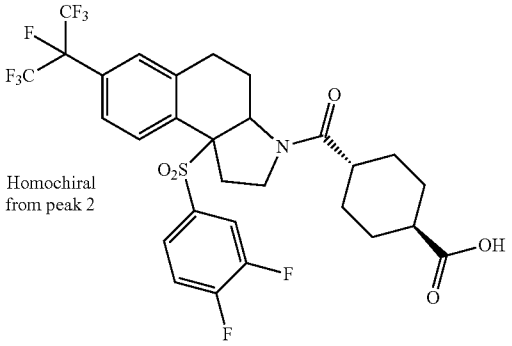
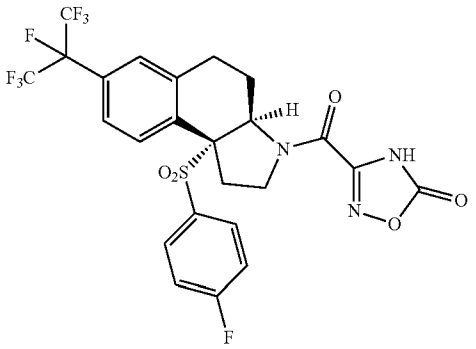
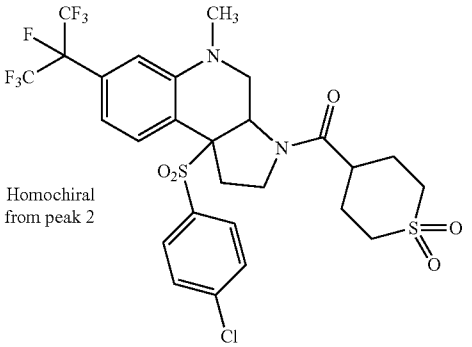
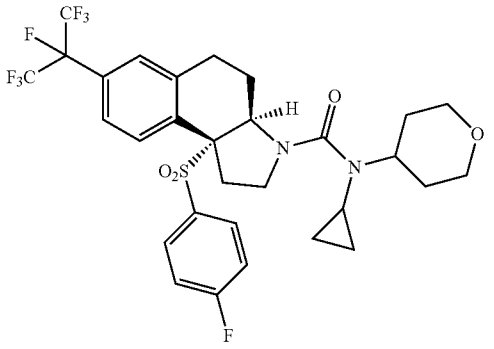
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
855	 Homochiral from peak 2	672.1 $(M + H)^+$	2.02	C
856		612.1 $(M + H)^+$	2.26	D
857	 Homochiral from peak 2	691.1 $(M + H)^+$	2.31	C
858		667.0 $(M + H)^+$	2.42	C

TABLE 19-continued

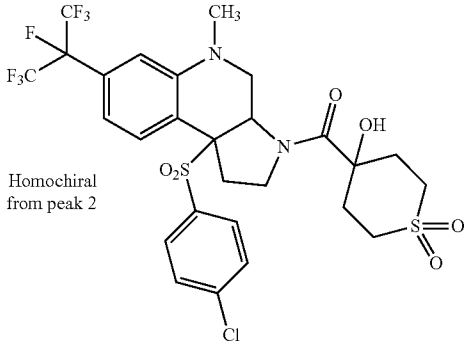
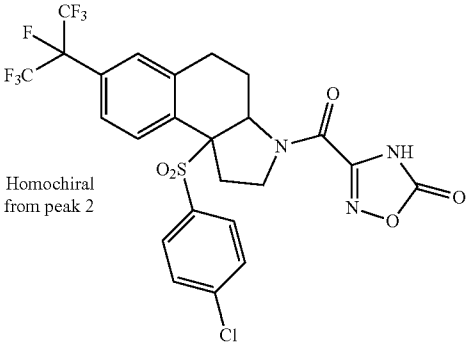
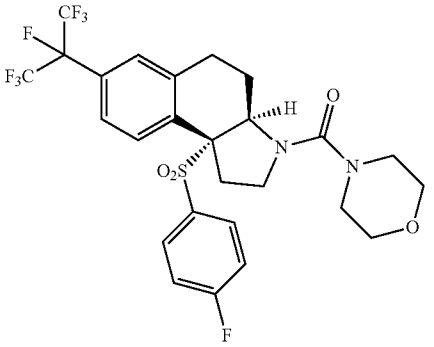
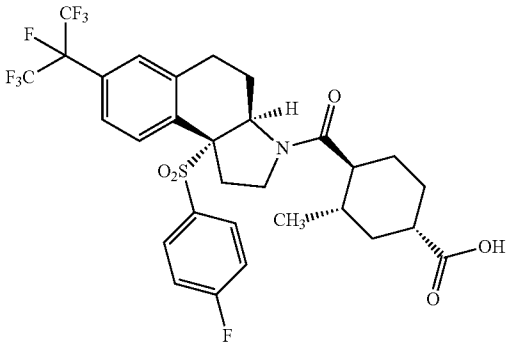
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
859	 Homochiral from peak 2	707.0 $(M + H)^+$	2.29	C
860	 Homochiral from peak 2	628.1 $(M + H)^+$	1.88	C
861		612.8 $(M + H)^+$	2.25	C
862		668.2 $(M + H)^+$	1.94	C

TABLE 19-continued

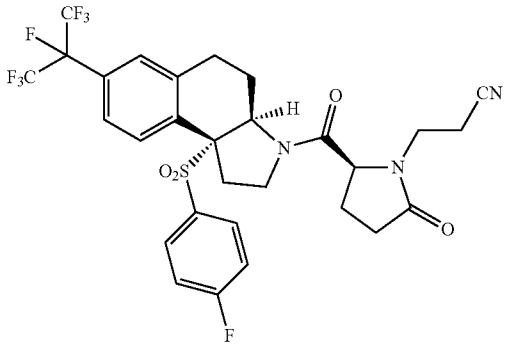
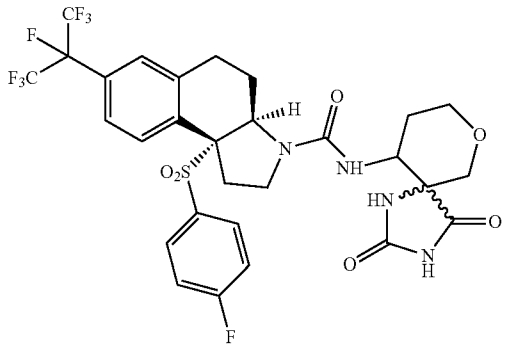
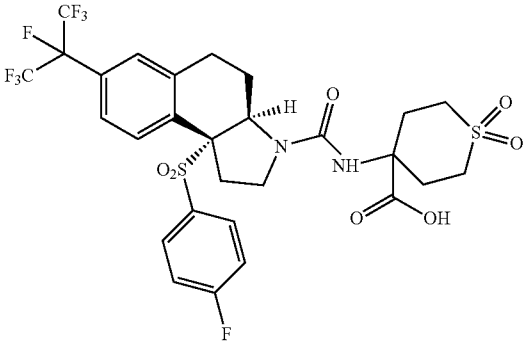
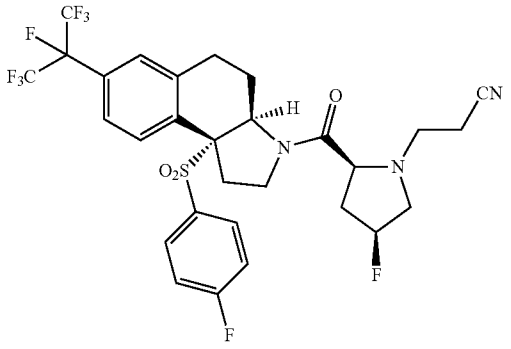
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
863		663.9 $(M + H)^+$	2.14	C
864		711.3 $(M + H)^+$	1.92	C
865		719.3 $(M + H)^+$	1.68	C
866		667.9 $(M + H)^+$	2.29	C

TABLE 19-continued

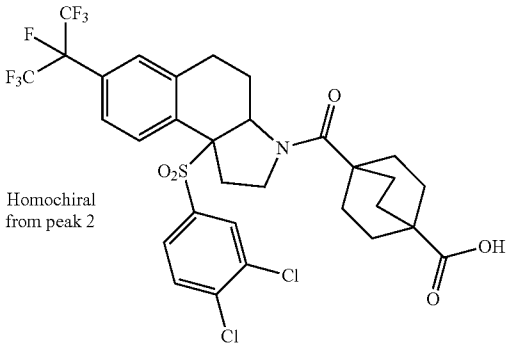
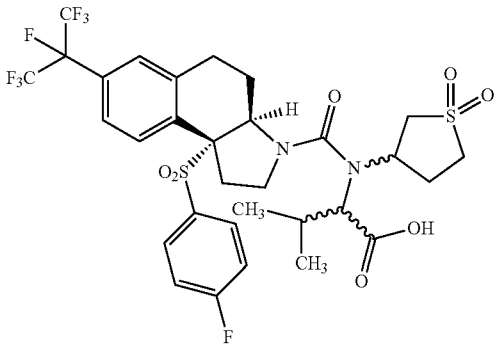
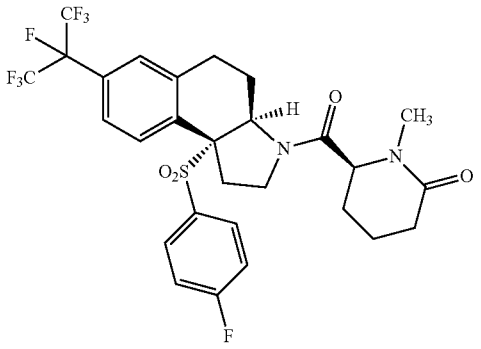
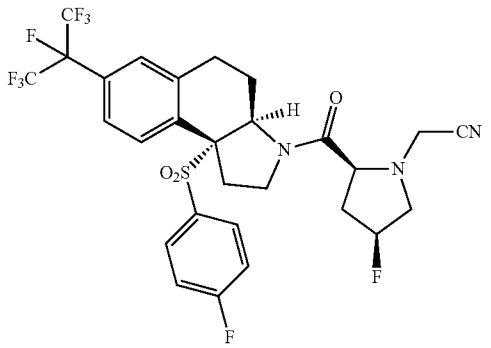
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
867	 Homochiral from peak 2	730.1 $(M + H)^+$	2.23	C
868		761.0 $(M + H)^+$	1.93	C
869		639.2 $(M + H)^+$	2.18	C
870		654.1 $(M + H)^+$	2.27	C

TABLE 19-continued

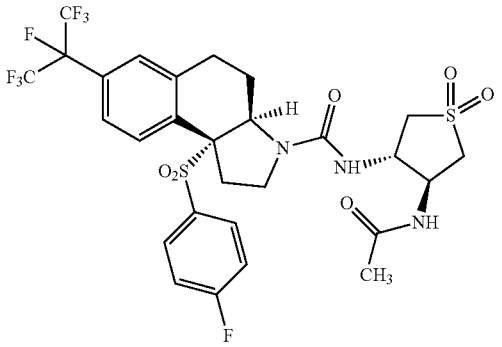
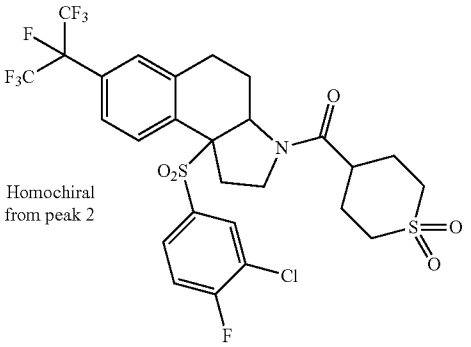
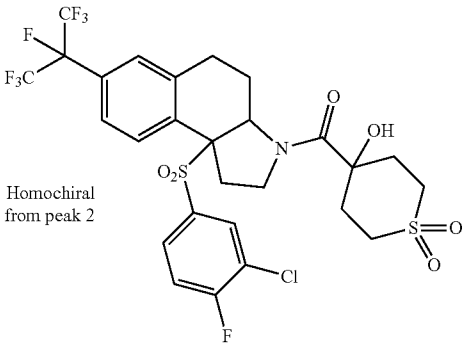
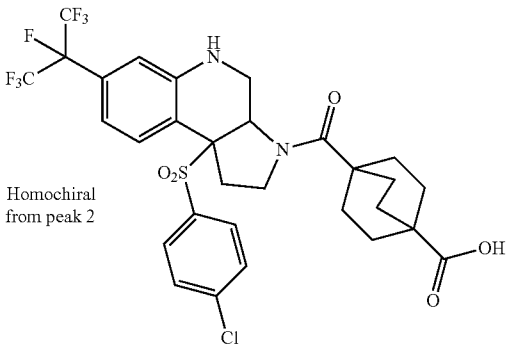
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
871		718.1 $(M + H)^+$	2.01	C
872	 Homochiral from peak 2	694.1 $(M + H)^+$	2.29	C
873	 Homochiral from peak 2	710.1 $(M + H)^+$	2.26	C
874	 Homochiral from peak 2	697.0 $(M + H)^+$	2.28	D

TABLE 19-continued

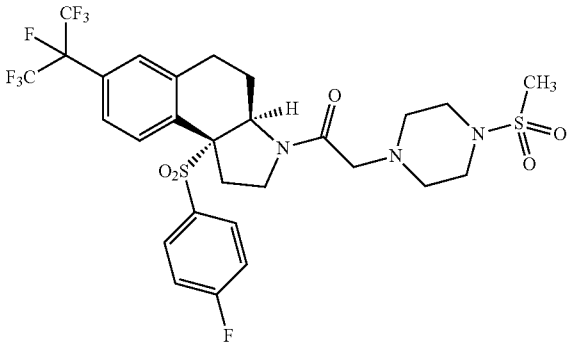
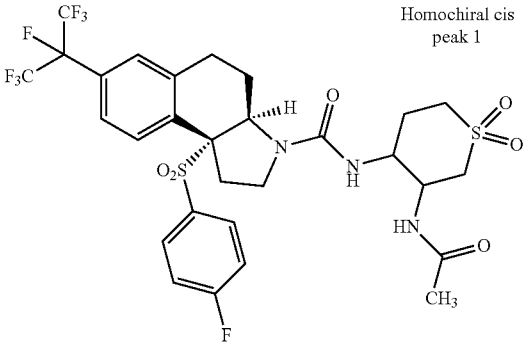
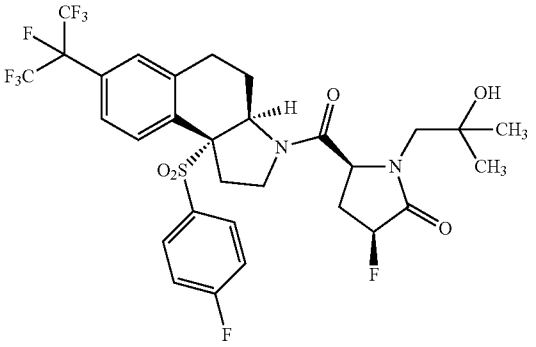
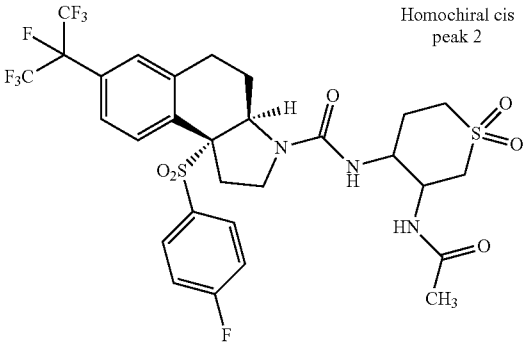
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
875		704.1 $(M + H)^+$	2.17	C
876	Homochiral cis peak 1 	732.2 $(M + H)^+$	2.00	C
877		701.1 $(M + H)^+$	2.20	C
878	Homochiral cis peak 2 	732.1 $(M + H)^+$	1.99	C

TABLE 19-continued

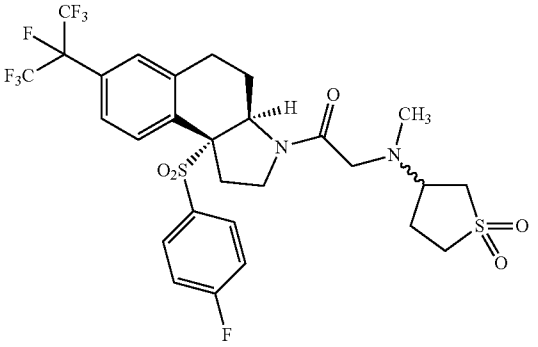
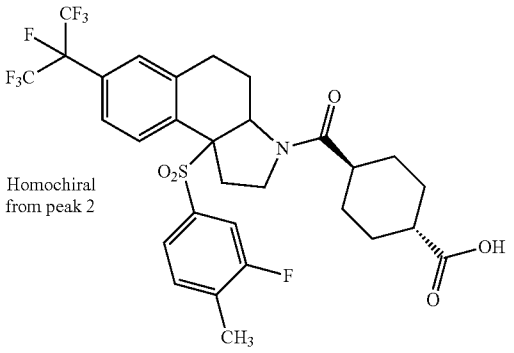
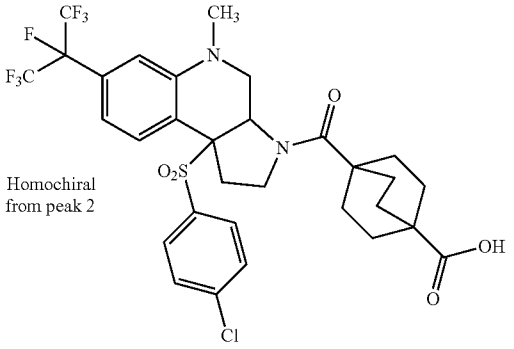
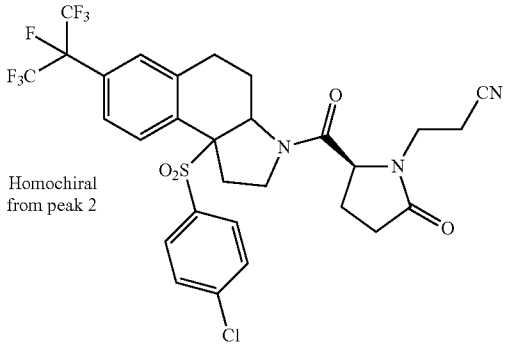
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
879		689.1 $(M + H)^+$	0.88	B
880	 Homochiral from peak 2	668.1 $(M + H)^+$	2.07	C
881	 Homochiral from peak 2	711.2	2.17	C
882	 Homochiral from peak 2	680.0	2.28	C

TABLE 19-continued

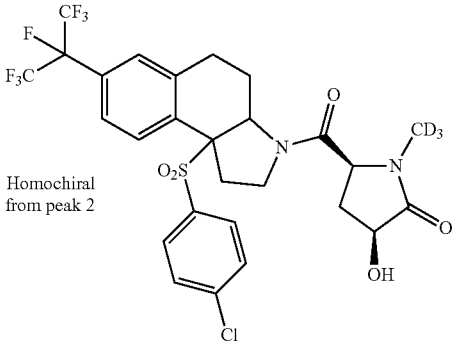
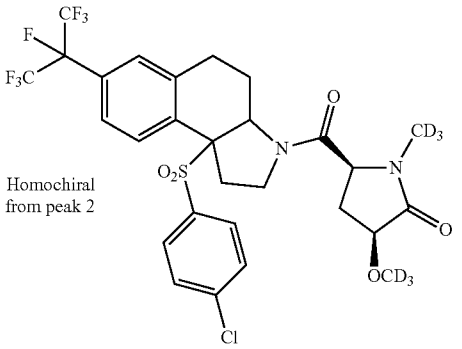
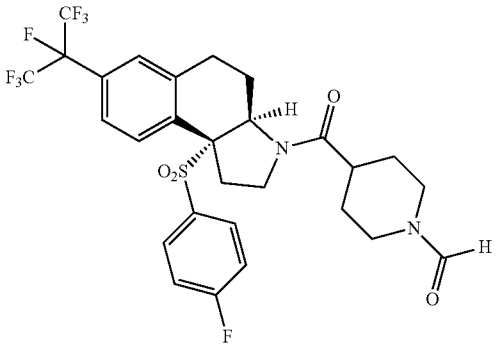
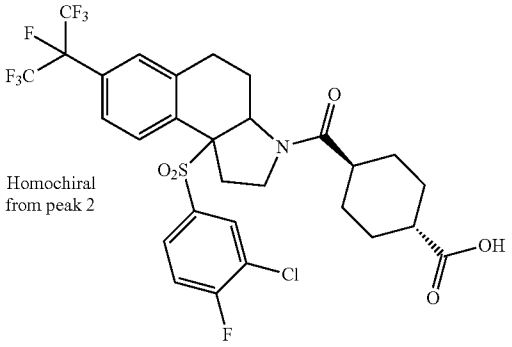
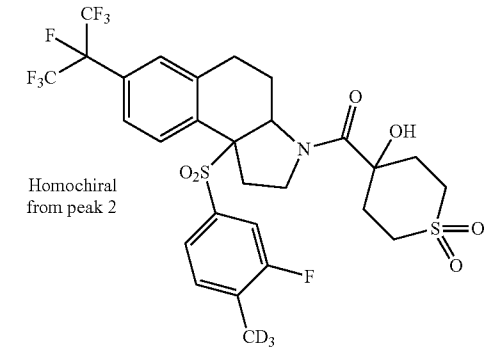
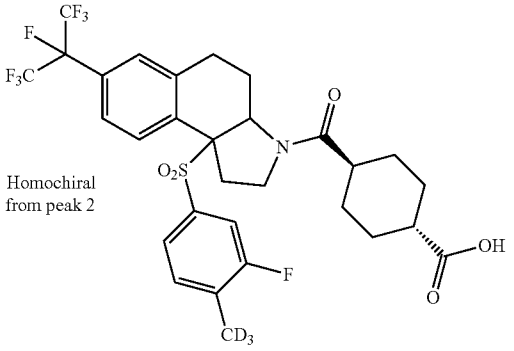
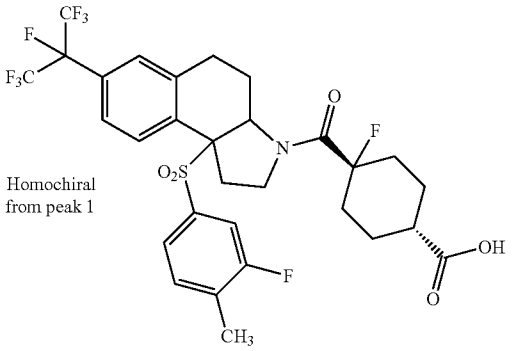
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
883	 Homochiral from peak 2	660.2	2.11	C
884	 Homochiral from peak 2	677.1	2.65	C
885		639.2	2.08	C
886	 Homochiral from peak 2	688.1	1.97	C

TABLE 19-continued

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
887	 Homochiral from peak 2	693.1	2.19	C
888	 Homochiral from peak 2	671.2	2.02	C
889	 Homochiral from peak 1	686.2	2.05	C

General RORγ SPA Binding Assay

The binding of potential ligands to RORγ is measured by competition with [^{3}H]25-hydroxycholesterol (Perkin Elmer NET674250UC) using a scintillation proximity assay (SPA). The ligand binding domain of human RORγ (A262-S507) with an N-terminal His tag is expressed in *E. coli* and purified using nickel affinity chromatography. 15 μg/well RORγ (A262-S507) is incubated with test compound at varying concentrations in 3-fold serial dilution, with final concentrations ranging from 16.6 μM to 0.28 nM, for 10 min at rt in PBS buffer (Invitrogen #14190-144) containing 0.5% fatty acid free BSA (Gemini Bio-Products, Cat. #700-107P) and 0.1% glycerol (Sigma Cat#G5516). 10 nM of [^{3}H] 25-hydroxycholesterol is then added, and the reaction is incubated for 10 min. 10 mg/mL of Copper-His Tag-PVT beads (Perkin Elmer cat # RPNQ0095) are added, and the mixture is incubated for 60 min. The reaction is read on a TopCount Microplate scintillation plate reader (Perkin Elmer). The competition data of the test compound over a range of concentrations was plotted as percentage inhibition of radioligand specifically bound in the absence of test compound (percent of total signal). After correcting for non-specific binding, IC_{50} values were determined. The IC_{50} value is defined as the concentration of test compound needed to reduce [^{3}H] 25-hydroxycholesterol specific binding by 50% and is calculated using the four parameter logistic equation to fit the normalized data.

IC_{50} values for compounds of the invention in the RORγ binding assay are provided below.

Ex. No.	RORγ Binding IC_{50}, μM
1	0.070
2	0.089
3	0.065
4	0.107
5	0.240
6	0.257

-continued

Ex. No.	RORγ Binding IC_{50}, μM
7	1.033
8	4.277
9	5.354
10	8.688
11	0.107
12	0.118
13	0.144
14	0.062
15	0.185
16	0.142
17	0.184
18	0.189
19	0.095
20	0.173
21	0.244
22	0.137
23	0.088
24	0.132
25	0.152
26	0.100
27	0.078
28	0.155
29	0.330
31	0.081
32	0.199
33	0.290
34	0.075
35	0.549
36	0.218
37	2.437
38	5.608
39	0.024
40	0.062
41	0.336
42	0.186
43	0.421
44	0.138
45	0.138
46	0.111
47	0.130
48	0.030
49	0.059
50	0.053
51	0.085
52	0.073
53	0.121
54	0.060
55	0.060
56	0.183
57	0.049
58	0.085
59	0.103
60	0.071
61	0.454
62	0.033
63	0.021
65	0.058
66	0.054
67	0.024
68	0.023
69	0.036
70	0.068
71	0.031
72	0.028
73	0.078
74	0.018
75	0.043
76	0.045
77	0.033
78	0.042
79	0.033
80	0.019
81	0.046
82	0.067
83	0.039
84	0.033
85	0.016

-continued

Ex. No.	RORγ Binding IC_{50}, μM
86	0.041
87	0.039
88	0.056
89	0.079
90	0.076
91	0.028
92	0.062
93	0.071
94	0.020
95	0.050
96	0.118
97	0.146
98	0.133
99	0.084
100	0.175
101	0.163
102	0.124
103	0.108
104	0.263
105	0.230
106	0.055
107	0.051
108	0.050
109	0.074
110	0.093
111	0.058
112	0.090
113	0.118
114	0.073
115	0.026
116	0.026
117	0.056
118	0.071
119	0.058
120	0.083
121	0.051
122	0.127
123	0.043
124	0.188
125	0.052
126	0.109
127	0.044
128	0.082
129	0.042
130	0.094
131	0.079
132	0.097
133	0.076
134	0.048
135	0.110
136	0.044
137	0.671
138	0.065
139	0.347
140	0.061
141	0.096
142	0.050
143	0.129
144	0.066
145	0.074
146	0.064
147	0.250
148	0.442
149	0.265
150	0.011
151	0.056
152	1.631
153	0.056
154	0.058
155	0.040
156	0.193
157	3.562
158	6.188
159	0.082
160	0.196
161	0.049
162	1.130

-continued

Ex. No.	RORγ Binding IC_{50}, μM
163	0.113
164	0.231
165	0.031
166	0.043
167	0.656
168	0.184
169	0.140
170	0.068
171	0.256
172	0.185
173	0.147
174	0.060
175	0.077
176	0.070
177	0.099
178	0.079
179	0.132
180	0.035
181	0.121
182	0.072
183	0.037
184	0.031
185	0.021
186	0.042
187	0.043
188	0.063
189	0.041
190	0.020
191	0.009
192	0.021
193	0.021
194	0.162
195	0.049
196	0.043
197	0.040
198	0.045
199	0.041
200	0.143
201	0.141
202	0.204
203	0.068
204	0.079
205	0.136
206	0.059
207	0.054
208	0.038
209	0.123
210	0.024
211	0.022
212	0.022
213	0.097
214	0.064
215	0.092
216	0.111
217	0.095
218	0.216
219	0.135
220	0.031
221	0.027
222	0.030
223	0.058
224	0.129
225	0.114
226	0.145
227	0.137
228	0.464
229	0.056
230	0.175
231	0.068
232	0.174
233	0.045
234	0.283
235	0.053
236	0.039
237	0.042
238	0.071
239	0.014

-continued

Ex. No.	RORγ Binding IC_{50}, μM
240	0.013
241	0.036
242	0.025
243	0.064
244	0.112
245	0.054
246	0.046
247	0.040
248	0.034
249	0.068
250	0.046
251	0.054
252	0.048
253	3.556
254	0.084
255	0.024
256	0.324
257	0.124
258	0.012
259	0.075
260	0.075
261	0.115
262	0.069
263	0.648
264	0.016
265	3.098
266	1.652
267	0.182
268	0.108
269	0.044
270	3.430
271	0.050
272	0.042
273	0.064
274	0.179
275	0.150
276	0.166
277	0.068
278	5.561
279	0.042
280	0.052
281	0.032
282	0.055
283	0.033
284	0.051
285	0.046
286	0.088
287	0.040
288	0.022
289	0.042
290	0.053
291	0.237
292	0.134
293	0.160
294	0.125
295	0.205
296	0.055
297	0.043
298	0.049
299	0.047
300	0.019
301	0.089
302	0.154
303	0.038
304	0.075
305	0.066
306	0.031
307	0.035
308	0.026
309	0.056
310	0.184
311	0.037
312	0.068
313	0.032
314	0.099
315	0.097
316	0.103

-continued

Ex. No.	RORγ Binding IC_{50}, μM
317	0.336
318	0.111
319	0.078
320	0.333
321	0.081
322	0.074
323	0.125
324	0.128
325	0.152
326	0.128
327	0.082
328	0.054
329	0.062
330	0.115
331	0.054
332	0.121
333	0.088
334	0.041
335	0.140
336	0.119
337	0.186
338	0.239
339	0.197
340	0.037
341	0.044
342	0.119
343	0.106
344	0.010
345	0.022
346	0.078
347	0.005
348	0.034
349	0.601
350	0.240
351	0.085
352	0.096
353	0.953
354	0.230
355	0.285
356	0.266
357	0.104
358	0.136
359	0.130
360	0.077
361	0.046
362	0.047
363	0.012
364	0.020
365	0.035
366	0.035
367	0.062
368	0.024
369	0.035
370	0.035
371	0.109
372	0.161
373	0.055
374	0.058
375	0.060
376	0.255
377	0.628
378	0.072
379	0.055
380	0.036
381	0.089
382	0.038
383	0.032
384	0.150
385	0.780
386	0.215
387	0.025
388	0.024
389	0.050
390	0.027
391	0.013
392	0.056
393	4.411

-continued

Ex. No.	RORγ Binding IC_{50}, μM
394	0.060
395	0.058
396	0.029
397	0.090
398	0.040
399	0.048
400	0.087
401	0.134
402	0.638
403	0.046
404	0.034
405	0.012
406	0.031
407	0.021
408	0.073
409	0.143
410	0.047
411	0.016
412	0.034
413	0.015
414	0.020
415	0.014
416	0.135
417	0.178
418	0.128
419	1.106
420	0.732
421	0.164
422	0.087
423	0.046
424	0.084
425	0.055
426	0.956
427	0.272
428	0.050
429	0.173
430	0.077
431	0.044
432	0.052
433	0.063
434	0.086
435	0.188
436	0.049
437	0.051
438	0.073
439	0.214
440	0.072
441	0.159
442	0.145
443	0.048
444	0.045
445	0.070
446	0.143
447	0.014
448	0.026
449	0.030
450	0.032
451	0.177
452	0.153
453	0.443
454	0.718
455	0.083
456	0.027
457	0.076
458	0.101
459	0.064
460	0.030
461	0.068
462	0.059
463	0.037
464	0.023
465	0.053
466	0.028
467	0.050
468	0.022
469	0.021
470	0.025

-continued

Ex. No.	RORγ Binding IC_{50}, μM
471	0.030
472	0.025
473	0.017
474	0.026
475	0.019
476	0.023
477	0.018
478	0.028
479	0.035
482	0.085
483	0.092
484	0.098
485	0.036
486	0.051
487	0.283
488	0.145
489	0.438
490	0.195
491	0.121
492	0.052
493	0.103
494	0.023
495	0.064
496	0.077
497	0.064
498	0.042
499	0.026
500	0.053
501	0.037
502	0.020
503	0.083
504	0.057
505	0.088
506	0.223
507	0.135
508	2.830
509	0.255
510	0.079
511	0.041
512	0.022
513	6.561
514	0.181
515	0.056
516	0.015
517	0.017
518	0.047
519	0.041
520	0.057
521	0.026
522	0.018
523	0.045
524	0.071
525	0.319
526	0.098
527	0.398
528	0.225
529	0.199
530	0.195
531	3.665
532	0.300
533	0.229
534	0.171
535	0.255
536	0.126
537	0.242
538	0.493
539	0.197
540	0.251
541	0.093
542	0.074
543	0.029
544	0.714
545	0.056
546	0.105
547	9.193
548	0.336
549	7.576

-continued

Ex. No.	RORγ Binding IC_{50}, μM
550	0.178
551	0.166
552	0.042
553	0.076
554	0.168
555	0.595
556	0.086
557	0.128
558	7.982
559	1.006
560	0.082
561	0.110
562	0.224
563	1.935
564	0.275
565	0.123
566	0.643
567	0.444
568	0.489
569	0.047
570	0.596
571	1.352
572	5.920
573	1.393
574	0.384
575	0.416
576	0.273
577	0.011
578	4.563
579	0.108
580	1.518
581	0.098
582	6.891
583	2.798
584	13.826
585	8.537
586	0.079
587	0.158
588	0.894
589	0.771
590	0.064
591	0.202
592	0.145
593	0.130
594	0.245
595	0.825
596	0.120
597	0.333
598	0.166
599	0.311
600	0.197
601	0.231
602	0.100
603	0.267
604	0.319
605	0.397
606	0.244
607	0.342
608	0.286
609	0.117
610	0.185
611	0.610
612	0.360
613	0.660
614	0.190
615	0.125
616	1.364
617	0.192
618	0.392
619	0.271
620	0.493
621	0.308
622	4.508
623	6.586
624	1.754
625	0.425
626	0.897

-continued

Ex. No.	RORγ Binding IC_{50}, μM
627	1.450
628	0.744
629	3.545
630	6.753
631	1.701
632	5.779
633	0.249
634	5.967
635	4.957
636	0.171
637	0.092
638	0.070
639	0.023
640	0.051
641	0.083
642	0.156
643	0.161
644	0.034
645	0.022
646	0.030
647	0.037
648	0.031
649	0.032
650	0.086
651	0.278
652	0.115
653	0.064
654	4.676
655	1.175
656	1.380
657	0.038
658	1.269
659	0.340
660	0.174
661	0.010
662	0.546
663	1.613
664	0.023
665	0.015
666	0.048
667	0.017
668	0.047
669	0.039
670	0.024
671	0.032
672	0.065
673	0.039
674	0.051
675	0.057
676	0.048
677	0.079
678	0.105
679	0.231
680	0.151
681	0.193
682	0.159
683	0.210
684	0.243
685	0.028
686	0.064
687	7.301
688	0.057
689	0.040
690	0.044
691	0.143
692	0.004
693	0.625
694	0.217
695	0.225
696	0.218
697	0.068
698	0.117
699	0.020
700	0.276
701	0.100
702	0.051
703	1.883

-continued

Ex. No.	RORγ Binding IC_{50}, μM
704	2.125
705	1.470
706	0.161
707	0.043
708	0.015
709	0.031
710	0.030
711	0.026
712	0.027
713	0.048
714	0.082
715	0.030
716	0.030
717	0.070
718	0.076
719	0.295
720	0.428
721	0.052
722	0.073
723	0.136
724	0.142
725	0.095
726	0.114
727	0.077
728	0.077
729	0.052
730	0.082
731	0.119
732	0.044
733	0.332
734	0.131
735	0.103
736	0.078
737	0.368
738	0.139
739	0.196
740	0.561
741	0.284
742	0.064
743	0.084
744	0.084
745	0.150
746	0.147
747	0.300
748	0.542
749	0.138
750	0.099
751	0.070
752	0.072
753	0.034
754	0.075
755	0.170
756	0.054
757	0.048
758	0.087
759	0.107
760	0.119
761	0.112
762	0.309
763	0.109
764	0.687
765	0.208
766	1.348
767	0.091
768	0.291
769	0.117
770	9.197
771	0.157
772	0.609
773	1.801
774	0.679
775	0.534
776	1.490
777	0.493
778	0.171
779	0.283
780	0.097

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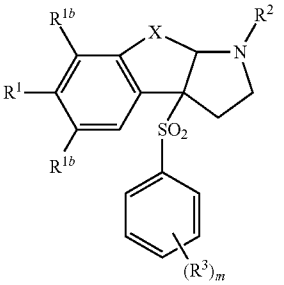
Ex. No.	RORγ Binding IC_{50}, μM
781	0.913
782	0.148
783	0.507
784	0.154
785	3.199
786	1.441
787	4.311
788	0.098
789	1.866
790	0.041
791	0.078
792	0.186
793	0.398
794	0.566
795	2.382
796	0.100
797	0.136
798	0.167
799	0.151
800	0.612
801	0.023
802	0.045
803	0.073
804	0.088
805	0.088
806	0.145
807	0.283
808	0.107
809	0.025
810	0.050
811	0.023
812	0.195
813	0.115
814	0.125
815	0.018
816	0.105
817	0.601
818	0.848
819	0.029
820	0.047
821	0.018
822	0.049
823	0.039
824	0.142
825	0.489
826	1.086
827	0.078
828	0.008
829	0.047
830	0.032
831	0.093
832	0.209
833	0.074
834	0.172
835	0.083
836	0.013
837	0.056
838	0.075
839	0.416
840	0.082
841	0.215
842	0.053
843	0.092
844	0.097
845	0.205
846	0.057
847	0.099
848	3.306
849	0.616
850	0.274
851	0.357
852	0.317
853	0.176
854	0.110
855	0.092
856	4.434
857	0.229

-continued

Ex. No.	RORγ Binding IC_{50}, μM
858	0.305
859	0.114
860	6.301
861	0.296
862	0.158
863	0.079
864	0.131
865	0.086
866	0.547
867	0.318
868	0.278
869	0.292
870	0.162
871	0.215
872	0.226
873	0.193
874	0.423
875	0.169
876	0.158
877	0.300
878	0.172
879	0.256
880	0.382
881	0.191
882	0.135
883	0.201
884	0.477
885	0.167

What is claimed is:

1. A compound of the formula



wherein

X is —CR^4R^5—, —$(CR^4R^5)_2$, —OCR^6R^7—, —$S(O)_pCR^6R^7$— or —$NR^6CR^6R^7$—;

R^1 is halo, C_{1-6} alkyl substituted with 0-3 R^{1a}, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})_r$—OR^b, —$(CR^{2e}R^{2f})_r$—$S(O)_pR^b$, —$(CR^{2e}R^{2f})_r$—$C(O)R^b$, —$(CR^{2e}R^{2f})_r$—$C(O)OR^b$, —$(CR^{2e}R^{2f})$r-$OC(O)R^b$, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_r$—$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})_r$-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, —$(CR^{2e}R^{2f})$r-C(O)R^{2d}, —$(CR^{2e}R^{2f})$r-C(O)OR^2b, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$S(O)_2R^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, —$(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)R^b, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})$r-OC(O)R^b, —$(CR^{2e}R^{2f})$r-OC(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-OC(O)OR^c, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a,

R^{2b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})$qOR^b, —$(CR^{2e}R^{2f})_q$S(O)pR^b, —$(CR^{2e}R^{2f})$r-C(O)R^{1d}, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})_q$OC(O)R^b, —$(CR^{2e}R^{2f})_q$$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})_q$$NR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})_q$$NR^bC(O)OR^c$, —$(CR^{2e}R^{2f})_q$$NR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})qS(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})qNR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-2 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a,

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-2 R^d, C_{1-6} haloalkyl, C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C_{3-10} cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a —$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a,

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C_{1-6} alkyl;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, —$(CR^{2e}R^{2f})$r-OR^{3b}, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, C_{1-6} alkyl substituted with 0-3 R^{3a}, C_{3-10} cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from the group consisting of N, O and S(O)p, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)R^b, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})$r-OC(O)R^b, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, —$(CR^{2e}R^{2f})$qOR^b, —$(CR^{2e}R^{2f})$q$S(O)pR^b$, —$(CR^{2e}R^{2f})$r-C(O)R^{1d}, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})$qOC(O)R^b, —$(CR^{2e}R^{2f})$q$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$q$NR^bC(O)R^{1c}$, —$(CR^{2e}R^{2f})$q$NR^bC(O)OR^c$, —$(CR^{2e}R^{2f})$q$NR^bC(O)NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$q$S(O)_2NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$q$NR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and S(O)p substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^d, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, —$(CR^{2e}R^{2f})$r-OR^b, —$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, —$(CR^{2e}R^{2f})$r-C(O)R^b, —$(CR^{2e}R^{2f})$r-C(O)OR^b, —$(CR^{2e}R^{2f})$r-OC(O)R^b, —$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-C(O)$NR^{11}R^{11}$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, —$(CR^{2e}R^{2f})$r-$NR^bC(O)$

OR^c—$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^f, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^e, C_{2-6} alkynyl substituted with 0-3 R^e, —$(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, C_{3-6} cycloalkyl substituted with 0-3 R^d, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f, or —$(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C_{1-6} alkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-C_{3-6} cycloalkyl substituted with 0-3 R^f, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, —OR^e, —$(CR^{2e}R^{2f})$r-C(O)R^c, —NR^eR^e, —$NR^eC(O)OR^c$, C(O)NR^eR^e, —$NR^eC(O)R^c$, CO_2H, CO_2R^c, —$NR^eSO_2R^c$, SO_2R^c, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, hydrogen, C(O)NR^fR^f, C_{1-6} alkyl, C_{3-6} cycloalkyl, -5-7 membered heterocycle or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $SO_2(C_{1-6}$ alkyl), CO_2H, $CO_2(C_{1-6}$ alkyl), OH, C_{3-6} cycloalkyl, CF_3, $O(C_{1-6}$ alkyl), or

an optionally substituted —$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, phenyl or C_{3-6} cycloalkyl, each group optionally substituted with halo, CN, CF_3, C_{1-6} alkyl or $O(C_{1-6}$ alkyl);

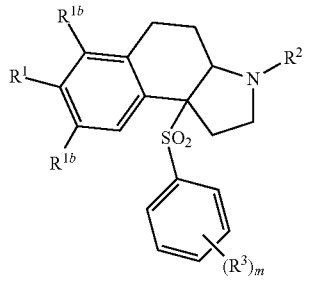
m is 0, 1,2 or 3

p and q are, independently at each occurrence, 0, 1, or 2; and

r is 0, 1, 2, 3, or 4,

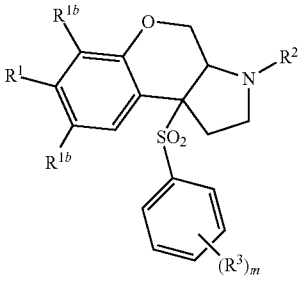
or a stereoisomer or pharmaceutically-acceptable salt thereof.

2. The compound according to claim **1** of the formula



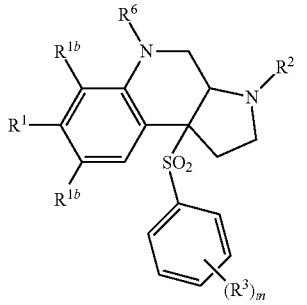
or a stereoisomer or pharmaceutically-acceptable salt thereof.

3. The compound according to claim **1** of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

4. The compound according to claim **1** of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

5. The compound according to claim **2** wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-OR^b, and —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a,

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, —$C(O)R^{2d}$, —C(O)$NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a,

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, —$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or —$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or —$(CR^{2e}R^{2f})$r-5-10-membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, C(O)$NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a 4-10

membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, $—NH_2$, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $—(CR^{2e}R^{2f})$r-OR^b, $—(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $—(CR^{2e}R^{2f})$r-$C(O)R^b$, $—(CR^{2e}R^{2f})$r-$C(O)OR^b$, $—(CR^{2e}R^{2f})$r-$OC(O)R^b$, $—(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)R$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

6. The compound according to claim **3** wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})$r-OR^b, and $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, $—C(O)R^{2d}$, $—C(O)NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-10-membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})_r$-phenyl substituted with 0-2 R^a, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, $—NH_2$, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $—(CR^{2e}R^{2f})$r-OR^b, $—(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $—(CR^{2e}R^{2f})$r-$C(O)R^b$, $—(CR^{2e}R^{2f})$r-$C(O)OR^b$, $—(CR^{2e}R^{2f})$r-$OC(O)R^b$, $—(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)R$, $—(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, $—(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or $—(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

7. The compound according to claim **5** wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, $—C(O)R^{2d}$ or $—C(O)NR^{11}R^{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is hydrogen, halo, cyclopropyl or C_{1-6} alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

8. The compound according to claim **6** wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, $—C(O)R^{2d}$ or $—C(O)NR_{11}R_{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

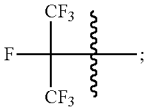
R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a, C_{3-6} cycloalkyl substituted with 0-3 R^a, $—(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or $—(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is hydrogen, halo, cyclopropyl or C_{1-6} alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

9. The compound according to claim 7 wherein R^1 is



R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

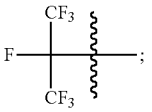
R^2 is —C(O)R^{2d};

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(═O) and $S(O)_2$, substituted with 0-4 R^a;

R^3 is F, Cl, cyclopropyl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

10. The compound according to claim 8 wherein R^1 is



R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

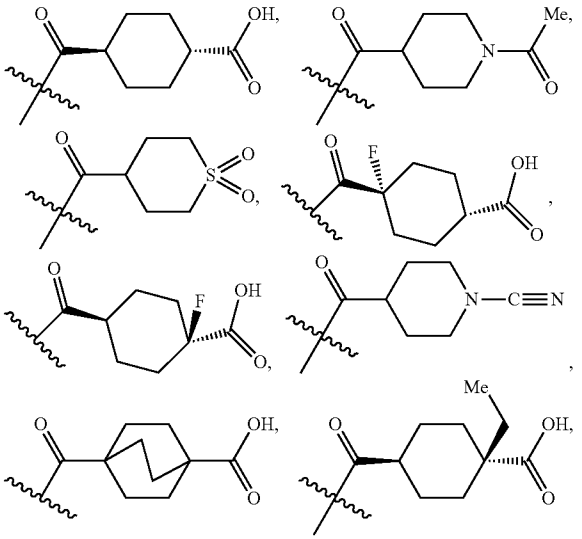
R^2 is —C(O)R^{2d};

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(═O) and $S(O)_2$, substituted with 0-4 R^a;

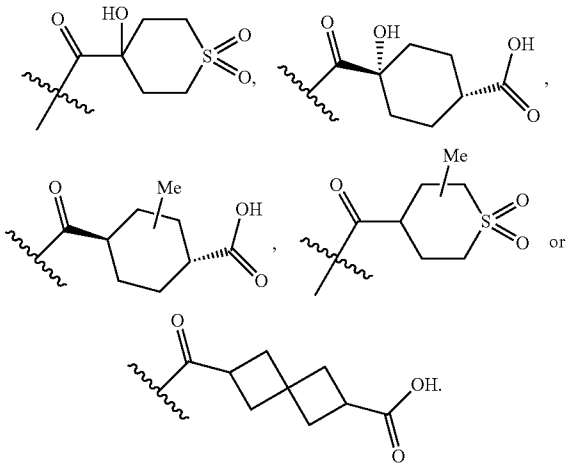
R^3 is F, Cl, cyclopropyl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

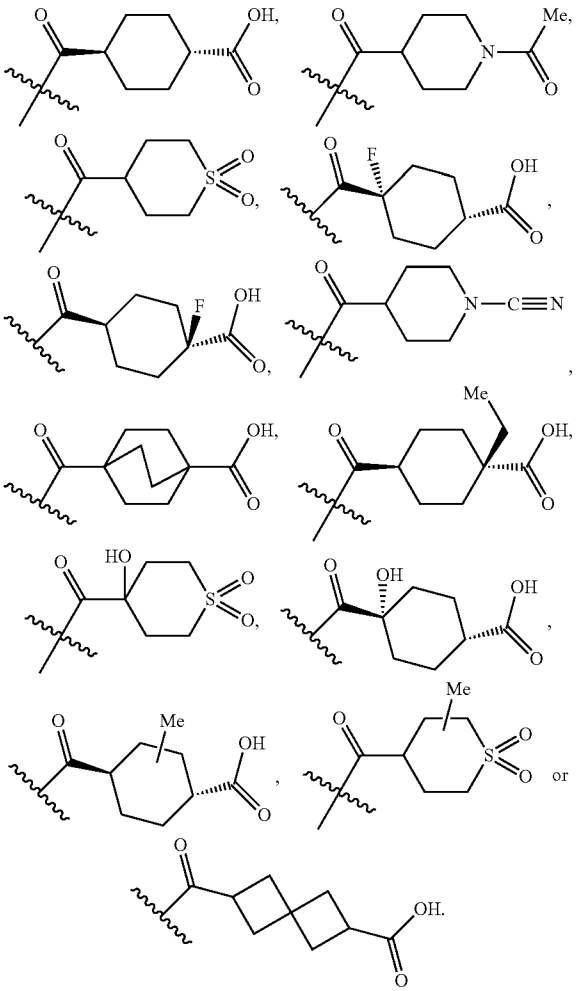
11. The compound according to claim 9 wherein R^2 is



-continued

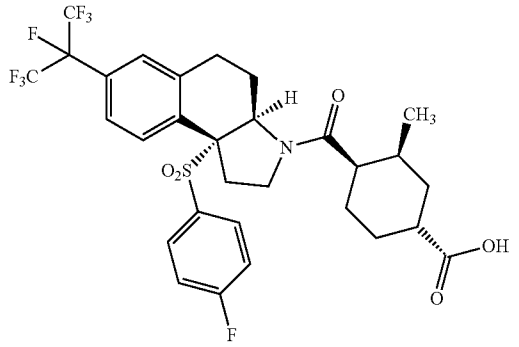


12. The compound according to claim 10 wherein R^2 is



13. A pharmaceutical composition comprising one or more compounds according to claim 1 and a pharmaceutically acceptable carrier or diluent.

14. A compound having the formula



[single diastereomer]

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

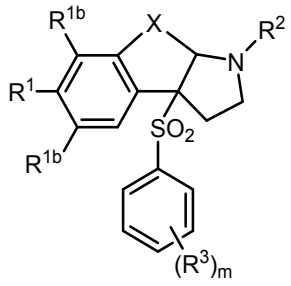
15. A pharmaceutical composition comprising the compound of claim **14** and a pharmaceutically acceptable carrier.

* * * * *

Allowed Claims:

Claim 1-5 (Canceled)

6. (Previously presented) A compound of the formula



wherein

X is $-CR^4R^5-$, $-(CR^4R^5)_2$, $-OCR^6R^7-$, $-S(O)_pCR^6R^7-$ or $-NR^6CR^6R^7-$;

R^1 is halo, C_{1-6} alkyl substituted with 0-3 R^{1a}, $-(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^{1a} or $-(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^{1a}**;**

R^{1a} is, independently at each occurrence, hydrogen, =O, halo, CF_3, OCF_3, CN, NO_2, $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})$r-$OC(O)R^b$, $-(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $-(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, $-(CR^{2e}R^{2f})_r$-3-14 membered carbocycle substituted with 0-3 R^a, or $-(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, $-(CR^{2e}R^{2f})$r-$C(O)R^{2d}$, $-(CR^{2e}R^{2f})$r-$C(O)OR^{2b}$, $-(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})$r-$S(O)_2R^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a}, C_{2-6} alkenyl substituted with 0-3 R^{2a}, $-(CR^{2e}R^{2f})$r-3-10 membered carbocycle substituted with 0-3 R^a, or $-(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CN, NO_2, -$(CR^{2e}R^{2f})$r-OR^b, -$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, -$(CR^{2e}R^{2f})$r-$C(O)R^b$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})$r-$OC(O)R^b$, -$(CR^{2e}R^{2f})$r-$OC(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$OC(O)OR^c$, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, -$NR^bC(O)NR^{11}R^{11}$, -$S(O)_pNR^{11}R^{11}$, -$NR^bS(O)_pR^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^a, $C_{1\text{-}6}$ haloalkyl, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^a, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^a, -$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or -$(CR^{2e}R^{2f})$r-4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2b} is, independently at each occurrence, hydrogen, CF_3, -$(CR^{2e}R^{2f})_qOR^b$, -$(CR^{2e}R^{2f})_qS(O)pR^b$, -$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})_qOC(O)R^b$, -$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)N\ R^{11}R^{11}$, -$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, -$(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, -$(CR^{2e}R^{2f})_qNR^bC(O)N\ R^{11}R^{11}$, -$(CR^{2e}R^{2f})qS(O)_2N\ R^{11}R^{11}$, -$(CR^{2e}R^{2f})qNR^bS(O)_2R^c$, $C_{1\text{-}6}$ alkyl substituted with 0-2 R^a, $C_{1\text{-}6}$ haloalkyl, -$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^a, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^a, $C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^a, $C_{6\text{-}10}$ aryl substituted with 0-3 R^a, or -$(CR^{2e}R^{2f})$r-5-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-2 R^d, $C_{1\text{-}6}$ haloalkyl, $C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^d, where the cycloalkyl ring may be fused, bridged or spirocyclic, -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-2 R^a, or a -$(CR^{2e}R^{2f})$r-4-10 membered heterocycle where the heterocycle may be fused, bridged or spirocyclic, containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or $C_{1\text{-}6}$ alkyl;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, -$(CR^{2e}R^{2f})$r-OR^{3b}, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^{3a}, $C_{3\text{-}10}$ cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10 membered heterocycle containing 1-4 heteroatoms

selected from the group consisting of N, O, and $S(O)_p$, substituted with 0-3 R^{3a}, or two R^3 located on adjacent carbon atoms link to form a 5-7 membered carbocycle or a 5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatom selected from the group consisting of N, O and S(O)p, both optionally substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, $-(CR^{2e}R^{2f})r$-3-14 membered carbocycle substituted with 0-3 R^a, or $-(CR^{2e}R^{2f})r$-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^{3b} is, independently at each occurrence, hydrogen, CF_3, $-(CR^{2e}R^{2f})qOR^b$, $-(CR^{2e}R^{2f})qS(O)pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^{1d}$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})qOC(O)R^b$, $-(CR^{2e}R^{2f})qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})qNR^bC(O)N\ R^{11}R^{11}$, $-(CR^{2e}R^{2f})qS(O)_2N\ R^{11}R^{11}$, $-(CR^{2e}R^{2f})qNR^bS(O)_2R^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{1-6} haloalkyl, $-(CR^{2e}R^{2f})r$-3-14 membered carbocycle substituted with 0-3 R^a, or $-(CR^{2e}R^{2f})r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a;

R^4 and R^5 are independently hydrogen, halo, C_{1-6} alkyl or C_{1-6} haloalkyl, or

R^4 and R^5 together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R^6 and R^7 are independently hydrogen, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{11} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^f, CF_3, C_{3-10} cycloalkyl substituted with 0-3 R^f, $-(CR^{2e}R^{2f})r$-phenyl substituted with 0-3 R^d, or $-(CR^{2e}R^{2f})r$-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

or one R^{11} and a second R^{11}, both attached to the same nitrogen atom, combine to form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, -$(CR^{2e}R^{2f})$r-OR^b, -$(CR^{2e}R^{2f})$r-S(O)pR^b, -$(CR^{2e}R^{2f})$r-$C(O)R^b$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})$r-$OC(O)R^b$, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, -$NR^bC(O)NR^{11}R^{11}$, -$S(O)_pNR^{11}R^{11}$, -$NR^bS(O)_pR^c$, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $C_{1\text{-}6}$ haloalkyl, $C_{2\text{-}6}$ alkenyl substituted with 0-3 R^e, $C_{2\text{-}6}$ alkynyl substituted with 0-3 R^e, -$(CR^{2e}R^{2f})$r-3-14 membered carbocycle, or -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^b is, independently at each occurrence, hydrogen, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^d, $C_{1\text{-}6}$ haloalkyl, $C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^d, -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f ,or -$(CR^{2e}R^{2f})$r-6-10 membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, -$(CR^{2e}R^{2f})$r-$C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^f, or -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF_3, CF_3, CN, NO_2, -OR^e, -$(CR^{2e}R^{2f})$r-$C(O)R^c$, -NR^eR^e, -$NR^eC(O)OR^c$,$C(O)NR^eR^e$, -$NR^eC(O)R^c$, CO_2H, CO_2R^c, -$NR^eSO_2R^c$, SO_2R^c, $C_{1\text{-}6}$ alkyl substituted with 0-3 R^f, $C_{3\text{-}6}$ cycloalkyl substituted with 0-3 R^f, -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f or -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^f;

R^e is, independently at each occurrence, hydrogen, $C(O)NR^fR^f$, $C_{1\text{-}6}$ alkyl, $C_{3\text{-}6}$ cycloalkyl, -5-7 membered heterocycle or -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH_2, $NH(C_{1\text{-}6}$ alkyl), $N(C_{1\text{-}6}$ alkyl$)_2$, $SO_2(C_{1\text{-}6}$ alkyl), CO_2H, $CO_2(C_{1\text{-}6}$ alkyl), OH, $C_{3\text{-}6}$ cycloalkyl, CF_3, $O(C_{1\text{-}6}$ alkyl), or

an optionally substituted -$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, phenyl or $C_{3\text{-}6}$ cycloalkyl, each group optionally substituted with halo, CN, CF_3, $C_{1\text{-}6}$ alkyl or $O(C_{1\text{-}6}$ alkyl);

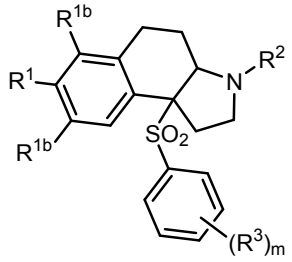
m is 0, 1, 2 or 3

p and q are, independently at each occurrence, 0, 1, or 2; and

r is 0, 1, 2, 3, or 4,

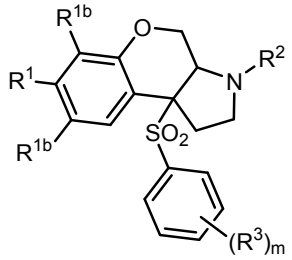
or a stereoisomer or pharmaceutically-acceptable salt thereof.

7. (Previously presented) The compound according to claim 6 of the formula



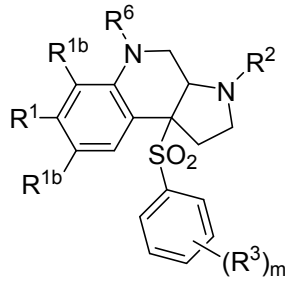
or a stereoisomer or pharmaceutically-acceptable salt thereof.

8. (Previously presented) The compound according to claim 6 of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

9. (Previously presented) The compound according to claim 6 of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

10. (Previously presented) The compound according to claim 7 wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, -$(CR^{2e}R^{2f})$r-OR^b, and -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a,

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, -$C(O)R^{2d}$, -$C(O)NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a,

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a , C_{3-6} cycloalkyl substituted with 0-3 R^a, -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or -$(CR^{2e}R^{2f})$r- 5-10-membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})_r$-phenyl substituted with 0-2 R^a, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a ;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, -NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, -$(CR^{2e}R^{2f})$r-OR^b, -$(CR^{2e}R^{2f})$r-S(O)pR^b, -$(CR^{2e}R^{2f})$r-$C(O)R^b$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})$r-$OC(O)R^b$, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, -$NR^bC(O)NR^{11}R^{11}$, -$S(O)_pNR^{11}R^{11}$, -$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, -$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or -$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

11. (Previously presented) The compound according to claim 8 wherein

R^1 is halo, phenyl substituted with 0-3 R^{1a}, or C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo, C_{1-6} alkyl substituted with 0-3 R^a, -$(CR^{2e}R^{2f})$r-OR^b, and -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is hydrogen, SO_2R^{2c}, C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, -$C(O)R^{2d}$, -$C(O)NR^{11}R^{11}$; or a 5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a , C_{3-6} cycloalkyl substituted with 0-3 R^a, -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{3-10} cycloalkyl substituted with 0-3 R^a, C_{6-10} aryl substituted with 0-3 R^a, or -$(CR^{2e}R^{2f})$r- 5-10-membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a;

R^{2d} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^d, C_{1-6} haloalkyl, $C(O)NR^{11}R^{11}$, C_{3-10} cycloalkyl substituted with 0-2 R^d, $(CR^{2e}R^{2f})_r$-phenyl substituted with 0-2 R^a, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$, substituted with 0-4 R^a ;

R^3 is, independently at each occurrence, hydrogen, halo, N_3, CN, OR^{3b}, -NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl$)_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a};

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, -$(CR^{2e}R^{2f})$r-OR^b, -$(CR^{2e}R^{2f})$r-S(O)pR^b, -$(CR^{2e}R^{2f})$r-$C(O)R^b$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})$r-$OC(O)R^b$, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, -

$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, -$NR^bC(O)NR^{11}R^{11}$, -$S(O)_pNR^{11}R^{11}$, -$NR^bS(O)_pR^c$, C_{1-6} alkyl substituted with 0-3 R^a, C_{2-6} alkenyl substituted with 0-3 R^a, C_{2-6} alkynyl substituted with 0-3 R^a, C_{1-6} haloalkyl, -$(CR^{2e}R^{2f})$r-3-14 membered carbocycle substituted with 0-3 R^a, or -$(CR^{2e}R^{2f})$r-5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, and $S(O)_p$ substituted with 0-3 R^a; and

R^{3b} is, independently at each occurrence, hydrogen, C_{1-6} alkyl substituted with 0-3 R^a or phenyl substituted with 0-3 R^a;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

12. (Previously presented) The compound according to claim 10 wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, -$C(O)R^{2d}$ or -$C(O)NR^{11}R^{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a , C_{3-6} cycloalkyl substituted with 0-3 R^a, -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a ;

R^3 is hydrogen, halo, cyclopropyl or C_{1-6} alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

13. (Previously presented) The compound according to claim 11 wherein

R^1 is C_{1-6} alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF_3, halo or C_{1-6} alkyl substituted with 0-3 R^a;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is C_{1-6} alkyl substituted with 0-3 R^{2a}, CO_2R^{2b}, -$C(O)R^{2d}$ or -$C(O)NR^{11}R^{11}$;

R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a , C_{3-6} cycloalkyl substituted with 0-3 R^a, -$(CR^{2e}R^{2f})$r-5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_p$ substituted with 0-4 R^a, or -$(CR^{2e}R^{2f})$r-phenyl substituted with 0-3 R^a;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a ;

R^3 is hydrogen, halo, cyclopropyl or C_{1-6} alkyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

14. (Previously presented) The compound according to claim 12 wherein

R^1 is  ;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

R^2 is -$C(O)R^{2d}$;

R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a ;

R^3 is F, Cl, cyclopropyl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

15. (Previously presented) The compound according to claim 13 wherein

R^1 is  ;

R^{1b} is, independently at each occurrence, hydrogen, CD_3, halo, CF_3, and C_1-C_4 alkyl;

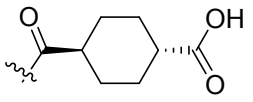
R^2 is -$C(O)R^{2d}$;

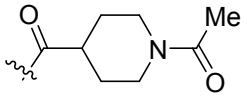
R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d, or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from the group consisting of N, O, P(=O) and $S(O)_2$, substituted with 0-4 R^a ;

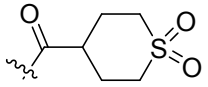
R^3 is F, Cl, cyclopropyl or methyl;

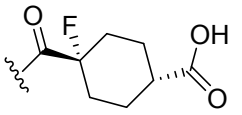
or a stereoisomer or pharmaceutically-acceptable salt thereof.

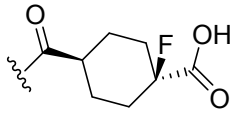
16. (Previously presented) The compound according to claim 14 wherein R^2 is

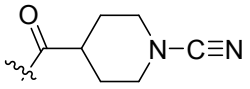


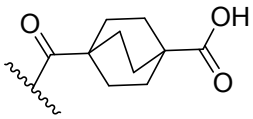
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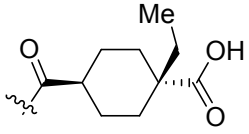
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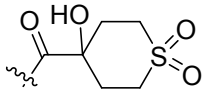
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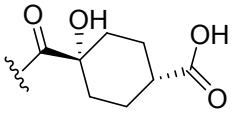
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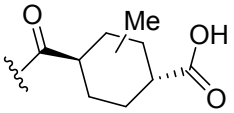
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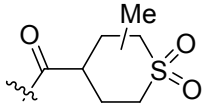
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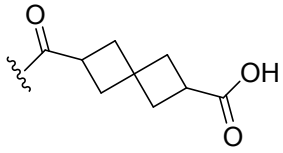
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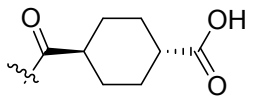
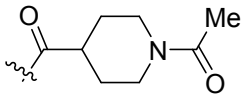
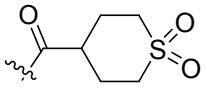
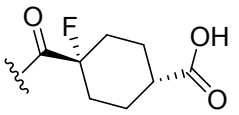
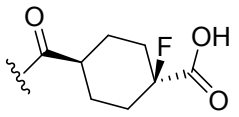
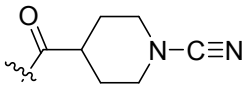
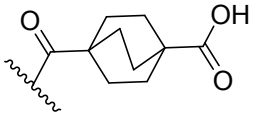
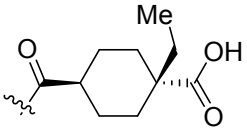
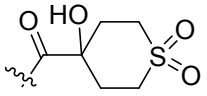
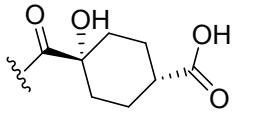
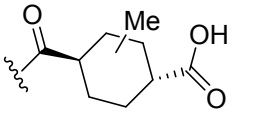
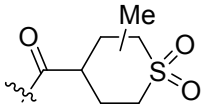
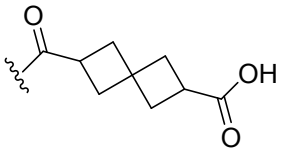
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17. (Previously presented) The compound according to claim 15 wherein R^2 is

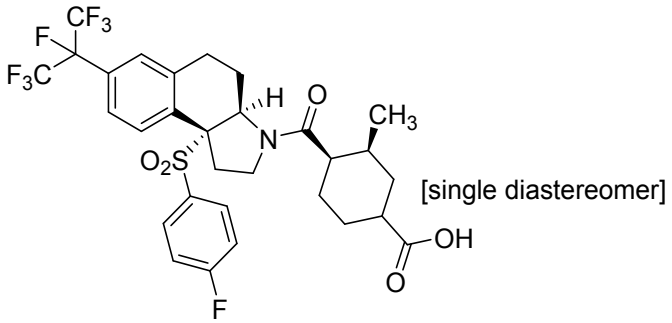

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or

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18. (Previously presented) A pharmaceutical composition comprising one or more compounds according to claim 6 and a pharmaceutically acceptable carrier or diluent.

19. (Canceled)

20. (Canceled)

21. (New) A compound having the formula


[single diastereomer]

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

22. (New) A pharmaceutical composition comprising the compound of claim 21 and a pharmaceutically acceptable carrier.

Notificación de Aprobación	**Solicitud No.** 15/148,209	**Solicitante(s)** DUAN ET AL.	
	Examinador PANCHAM BAKSHI	**Unidad Tecnica** 1671	**Estado de AIA (Primer inventor en presentar)** Sí

-**La FECHA DE ENVÍO de este comunicado aparece en la portada con la dirección correspondiente—**
Todas las reivindicaciones son aprobadas, EL JUICIO SOBRE LOS MÉRITOS ESTÁ (O PERMANECE) CERRADO en esta solicitud. Si no se incluye aquí (o es previamente enviado por correo), una Notificación de Concesión (PTOL-85), u otra comunicación apropiada se enviará por correo a su debido tiempo. ESTA NOTIFICACIÓN DE CONCESIÓN NO ES UNA AUTORIZACIÓN DE DERECHOS DE PATENTE. Esta solicitud está sujeta al retiro de la emisión a la iniciativa de la Oficina o sobre la petición del solicitante. Véase 37 CFR 1.313 y MPEP 1308.

1. [X] Esta comunicación es en respuesta a la contestación con fecha 04/11/2017.
[ ] Una(s) declaración(es)/ declaración(es) jurada(s) bajo **37 CFR 1.130(b)** fue/fueron registrados en____.

2. [ ] Una elección fue hecha por el solicitante en respuesta a un requisito de restricción establecido durante la entrevista en_____; el requisito de restricción y la elección han sido incorporados en esta acción.

3. [X] La(s) reivindicación(es) concedida(s) es/son 6-18. Como resultado de la(s) reivindición(es) concedida(s), usted puede ser elegible para beneficiarse del programa **Tramite Acelerado de Patentes** en una oficina de propiedad intelectual participante para la solicitud correspondiente. Para obtener más información, consulte http://www.uspto.gov/patents/init_events/pph/index.js o envíe una petición a PPHfeedback@uspto.gov.

4. [ ] Se reconoce una reivindicación de prioridad extranjera bajo 35 U.S.C. § 119 (a) - (d) o (f).

Copias certificadas:

a) [ ] Todas b) [ ] Algunas *c) [ ] Ninguna de las:

1. [ ] Copias certificadas de los documentos de prioridad han sido recibidas.

2. [ ] Copias certificadas de los documentos prioridad han sido recibidas en la Solicitud No.____.

3. [ ] Copias de las copias certificadas de los documentos de prioridad han sido recibidas en esta fase nacional de la solicitud desde la Oficina Internacional (Regla PCT 17.2.(a))

* Copias certificadas no recibidas: ____.

El Solicitante tiene TRES MESES DESDE LA "FECHA DE ENVÍO" de esta comunicación para presentar una respuesta que cumpla con los requisitos indicados a continuación. El incumplimiento fuera del tiempo resultará en el ABANDONO de esta solicitud. **ESTE PERIODO DE TRES MESES NO ES EXTENDIBLE.**

5. [ ] DIBUJOS CORREGIDOS (como "hojas de repuesto") deben ser presentados.

[ ] Incluir cambios requeridos por la Enmienda / Comentario adjunto del Examinador o en la acción de la Oficina del Documento No. / Fecha de envío____.

Los signos de identificación tales como el número de solicitud (véase 37 CFR 1.84 (c)) deberían ser escritos en los dibujos en la parte delantera (no en la parte posterior) de cada hoja. Las hojas de repuesto deberían estar etiquetadas como tales en la cabecera de acuerdo con 37 CFR 1.121 (d).

6. [ ] DEPÓSITO DE y/o INFORMACIÓN acerca del depósito de MATERIAL BIOLÓGICO debe ser presentada. Tenga en cuenta el comentario adjunto del Examinador respecto al REQUISITO PARA EL DEPÓSITO DE MATERIAL BIOLÓGICO.

Archivo(s) adjunto(s)

1. ☐ Notificación de Referencias Citadas (PTO-892)
2. ☐ Declaraciones de Divulgación de Información (PTO / SB / 08), Documento No. / Fecha de envío
3. ☐ Comentario del examinador con respecto al Requerimiento
4. ☐ Resumen de la Entrevista (PTO-413), Documento No. / Fecha de envío _____.
5. ☒ Enmienda / Comentario del Examinador
6. ☒ Declaración de las razones de concesión del Examinador
7. ☐ Otro _____.

/ PANCHAM BAKSHI Examinador primario, Unidad de Arte 1671	06/01/2017

Solicitud / Número de Control: 15/148,209

Unidad de Arte: 1671

ACCIÓN DETALLADA

La presente solicitud, presentada a partir o después del 16 de marzo de 2013, está siendo examinada bajo el primer inventor para registrar las disposiciones de la AIA.

Se reconoce las observaciones y modificaciones del solicitante en la respuesta presentada el 11/04/2017.

Estado de la Solicitud

Las reivindicaciones 6-18 han sido modificadas y las reivindicaciones 1-5 han sido canceladas por la modificación de fecha 11/04/2017. En consecuencia, las reivindicaciones 6-20 están pendientes, de las cuales las reivindicaciones 19 y 20 se retiran debido a restricciones anteriores y elección **sin estar de acuerdo**.

Objeciones Retiradas

Las objeciones realizadas bajo 35USC § 112 (b) en acción oficial con fecha 02/01/2017 se retiran por la presente en vista de la cancelación de las reivindicaciones 1 a 5 por parte del Solicitante y la modificación a la recivindicación 10 con respecto al formato Markush. Además, las objeciones realizadas bajo 35USC § 102 en acción oficial con fecha 01/02/2017 se retiran por la presente en vista de la cancelación por parte del Solicitante de las reivindicaciones 1 y 2 de la modificación de la reivindicación 18 que no está prevista en la técnica anterior. Además, se retiran las objeciones realizados bajo 35USC § 103 en acción oficial con fecha 01/02/2017 en vista de la cancelación por parte del Solicitante de las reivindicaciones 1-5 modificación de las reclamaciones 6-18 y los comentarios del solicitante que se consideran persuasivos.

Modificaciones del Examinador

Una modificación del examinador a la solicitud aparece a continuación. Si los cambios y/o adiciones son inaceptables para el solicitante, se puede presentar una modificación según lo dispuesto por 37 CFR 1.312. Para garantizar el examen de dicha modificación, DEBE presentarse a más tardar en el momento del pago de la tasa de emisión.

Solicitud / Número de Control: 15/148,209

Unidad de Arte: 1671

La solicitud se ha modificado como sigue:

En las reivindicaciones

Las reivindicaciones 19 y 20 han sido canceladas.

Contestación

La **elección del requisito de especie (A) para el Grupo I,** como se establece en la Acción oficial enviada el 14/10/2016, ha sido reconsiderada y **se retira por la presente**.

En vista del retiro del **requisito de elección de especies** mencionado anteriormente, se informa al solicitante que si una reivindicación presentada en una solicitud de continuación o divisional es anticipada por, o incluye todas las limitaciones de, una reivindicación que es concedida en la presente solicitud, tal reivindicación puede estar sujeta a objeciones de doble patentamiento provisionales estatutarias y/o no estatuarias sobre las reivindicaciones de la presente solicitud.

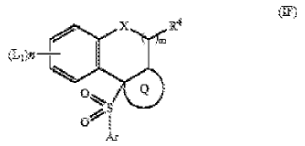
Razones para la Concesión

Las observaciones del solicitante y la modificación presentada el 11/04/2017, se han considerado completamente y se encuentran persuasivas.

La siguiente es una declaración de razones del examinador para la concesión:

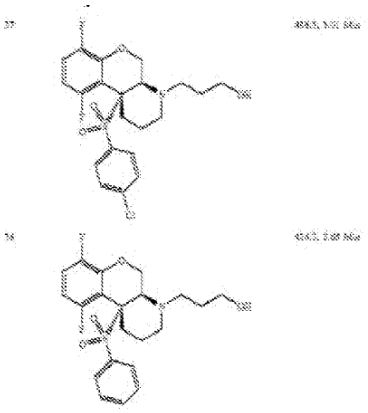
El compuesto del solicitante de fórmula como en las presentes reivindicaciones es nuevo y no es obvio sobre la técnica anterior de registro. Ninguna de las técnicas anteriores de registro divulga o enseña el compuesto del solicitante de fórmula como en las reivindicaciones actuales. La técnica anterior más cercana, Asberom (US 20070197581 Al) enseña un compuesto de fórmula:

30. The compound of claim 1 having the formula (IF):



(IF)

y especies:



que son diferentes con respecto al tamaño del anillo heterocíclico Q de las presentes reivindicaciones. Además, entre cientos de compuestos descritos por la técnica anterior citada, el anillo Q tiene 6 miembros en todos los compuestos y, por lo tanto, es diferente del anillo de pirrolidina de las reivindicaciones presentes. Además, la técnica anterior citada no sugerirá ni motivará a un experto en la materia a seleccionar un compuesto con anillo de pirrolidina como en las reivindicaciones de la presente invención.

Por lo tanto, las reivindicaciones 6-18 son concedidas.

Conclusión

Las reivindicaciones 6-18 son concedidas

Industria y Comercio SUPERINTENDENCIA	Espacio reservado para el adhesivo de radicación

DIRECCIÓN DE NUEVAS CREACIONES

Procedimiento acelerado de exámenes de patente (pph)

1	**NÚMERO DE SOLICITUD ANTE LA SIC**	NC2017/0012545
2	**OFICINA DE PRIMERA PRESENTACIÓN (OPP)**	**US**
3	**NÚMERO(S) DE SOLICITUD O PUBLICACIÓN DE LA(S) SOLICITUD(ES) (OPP):**	1. US 9,815,859
4	☐ **REPRESENTANTE LEGAL** ☒ **APODERADO**	

APELLIDOS	NOMBRES	IDENTIFICACIÓN
CONCHA	JUAN PABLO	C.C . 80.416.654 T.P . 80.677

DIRECCIÓN	Av. 82 No. 10-62 Piso 5	No. TELÉFONO	6341500
CIUDAD	Bogotá	CORREO ELECTRÓNICO	Juan.concha@bakermckenzie.com
PAÍS	Colombia	No. RADICACIÓN O PROTOCOLO DE PODER GENERAL	

5 CONDICIONES PARA ACCEDER A ESTE PROCESO:

5.1. DATOS DE PRIORIDAD ☒ SI ☐ NO

(33) PAÍS DE ORIGEN	CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. Estados Unidos de América	US	62/158,178	07/05/2015

5.2. DATOS SOLICITUD INTERNACIONAL PCT ☒ SI ☐ NO

Solicitud Internacional No.	PCT/US2016/031118	**Fecha**	06/05/2016
Publicación Internacional No.	WO/2016/179460	**Fecha**	10/11/2016

El solicitante presenta una copia de la(s) reivindicación(es) patentable(s) u otorgable(s) de la solicitud de la Oficina de Primera Presentación que profirió el examen de patentabilidad, junto con una traducción al castellano. ☒ SI ☐ NO

REQUISITOS PARA EL RECONOCIMIENTO DE LOS RESULTADOS DE EXÁMENES DE PATENTABILIDAD EFECTUADOS A SOLICITUDES EXTRANJERAS

Para que la Superintendencia de Industria y Comercio pueda reconocer los resultados de exámenes de patentabilidad producidos por otras Oficinas de Propiedad Industrial se debe cumplir con las siguientes condiciones:

(a) Al momento de solicitar el examen de patentabilidad, si el solicitante pide que se reconozcan exámenes de patentabilidad de otras oficinas extranjeras, deberá aportar junto con el pago de la tasa correspondiente, los siguientes anexos:

(i) Copia de las resoluciones, fallos o decisiones que han sido relevantes para la determinación de la patentabilidad de la(s) solicitud(es) en la Oficina que haya proferido el examen de patentabilidad que contienen reivindicaciones patentables u otorgables que son la base de la petición, y si es del caso, su traducción al castellano. ☒ SI ☐ NO

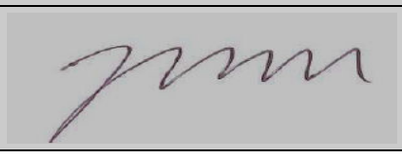
(ii) Copia de todas las reivindicaciones determinadas como patentables u otorgables en la Oficina que profirió el examen de patentabilidad y, si es del caso, su traducción al castellano. ☒ SI ☐ NO

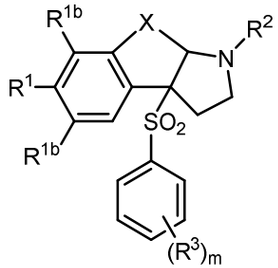
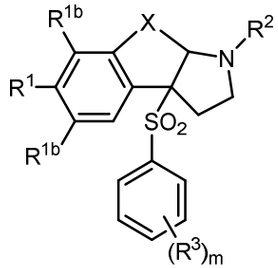
(iii) Copia de los antecedentes, información o documentos citados por el examinador de la Oficina de Primera Presentación del examen de patentabilidad, en las resoluciones, fallos o decisiones correspondientes, incluyendo la literatura no patente. Los documentos de patente deberán presentarse siempre y cuando no estén disponibles para la Superintendencia de Industria y Comercio mediante el simple acceso a bases de datos gratuitas. ☐ SI ☒ NO

(iv) Una tabla de correspondencias de las reivindicaciones que han sido determinadas como patentables u otorgables en la solicitud de la Oficina que haya proferido el examen de patentabilidad. ☒ SI

7 FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)



6	TABLA DE CORRESPONDENCIA DE REIVINDICACIONES		
	Reivindicaciones otorgadas en la patente US 9,815,859	**Reivindicaciones en la solicitud en Colombia NC2017/0012545**	Explicación sobre la suficiente correspondencia ó Comentarios que explican la correspondencia
	1. Un compuesto de la Fórmula  en donde X es $-CR^4R^5-$, $-(CR^4R^5)_2$, $-OCR^6R^7-$, $-S(O)_pCR^6R^7-$ o $-NR^6CR^6R^7-$; R^1 es halo, alquilo C_{1-6} sustituido con 0-3 R^{1a}, $-(CR^{2e}R^{2f})r-$carbociclo de 3-14 elementos sustituido con 0-3 R^{1a} o $-(CR^{2e}R^{2f})r-$heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados	1. Un compuesto de la Fórmula  en donde X es $-CR^4R^5-$, $-(CR^4R^5)_2$, $-OCR^6R^7-$, $-S(O)_pCR^6R^7-$ o $-NR^6CR^6R^7-$; R^1 es halo, alquilo C_{1-6} sustituido con 0-3 R^{1a}, $-(CR^{2e}R^{2f})r-$carbociclo de 3-14 elementos sustituido con 0-3 R^{1a} o $-(CR^{2e}R^{2f})r-$heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados	Corresponden totalmente.

de N, O y $S(O)_p$, sustituido con 0-3 R^{1a};	de N, O y $S(O)_p$, sustituido con 0-3 R^{1a};	
R^{1a} es, independientemente en cada caso, hidrógeno, =O, halo, CF_3, OCF_3, CN, NO_2, $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a , o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos que comprende átomos de carbono, y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;	R^{1a} es, independientemente en cada caso, hidrógeno, =O, halo, CF_3, OCF_3, CN, NO_2, $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a , o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos que comprende átomos de carbono, y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;	
R^{1b} es, independientemente de cada caso, hidrógeno, CD_3, halo, CF_3 y	R^{1b} es, independientemente de cada caso, hidrógeno, CD_3, halo, CF_3 y	

alquilo C_{1-4};	alquilo C_{1-4};	
R^2 es hidrógeno, $-(CR^{2e}R^{2f})r-C(O)R^{2d}$, $-(CR^{2e}R^{2f})r-C(O)OR^{2b}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-S(O)2R^{2c}$, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, $-(CR^{2e}R^{2f})r-$carbociclo de 3-10 elementos sustituido con 0-3 R^a , o $-(CR^{2e}R^{2f})r-$heterociclo de 4-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;	R^2 es hidrógeno, $-(CR^{2e}R^{2f})r-C(O)R^{2d}$, $-(CR^{2e}R^{2f})r-C(O)OR^{2b}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-S(O)2R^{2c}$, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, $-(CR^{2e}R^{2f})r-$carbociclo de 3-10 elementos sustituido con 0-3 R^a , o $-(CR^{2e}R^{2f})r-$heterociclo de 4-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;	
R^{2a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-OC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-OC(O)OR^c$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-$	R^{2a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-OC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-OC(O)OR^c$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-$	

$S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 4-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;	$S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 4-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;	
R^{2b} es, independientemente en cada caso, hidrógeno, CF_3, $-(CR^{2e}R^{2f})_qOR^b$, $-(CR^{2e}R^{2f})_qS(O)pR^b$, $-(CR^{2e}R^{2f})r$-$C(O)R^{1d}$, $-(CR^{2e}R^{2f})r$-$C(O)OR^b$, $-(CR^{2e}R^{2f})_qOC(O)R^b$, $-(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})r$-$C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $-CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-	R^{2b} es, independientemente en cada caso, hidrógeno, CF_3, $-(CR^{2e}R^{2f})_qOR^b$, $-(CR^{2e}R^{2f})_qS(O)pR^b$, $-(CR^{2e}R^{2f})r$-$C(O)R^{1d}$, $-(CR^{2e}R^{2f})r$-$C(O)OR^b$, $-(CR^{2e}R^{2f})_qOC(O)R^b$, $-(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})r$-$C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $-CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-	

carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2d} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r$-cicloalquilo C_{3-10} sustituido con 0-3 R^d, en donde el anillo de cicloalquilo puede ser fusionado, en	carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2d} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r$-cicloalquilo C_{3-10} sustituido con 0-3 R^d, en donde el anillo de cicloalquilo puede ser fusionado, en	

puente o espirocíclico, -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-2 R^a o un -$(CR^{2e}R^{2f})$r-heterociclo de 4-10 elementos, en donde el heterociclo puede ser fusionado, en puente o espirocíclico, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2e} y R^{2f} son, independientemente en cada caso, hidrógeno, halógeno o alquilo C_{1-6}; R^3 se selecciona, independientemente en cada caso, de hidrógeno, halo, N_3, CN, -$(CR^{2e}R^{2f})$r-OR^{3b}, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, alquilo C_{1-6} sustituido con 0-3 R^{3a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{3a}; y fenilo sustituido con 0-3 R^{3a} o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O y $S(O)_p$, sustituido con 0-3 R^{3a} , o dos R^3	puente o espirocíclico, -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-2 R^a o un -$(CR^{2e}R^{2f})$r-heterociclo de 4-10 elementos, en donde el heterociclo puede ser fusionado, en puente o espirocíclico, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2e} y R^{2f} son, independientemente en cada caso, hidrógeno, halógeno o alquilo C_{1-6}; R^3 se selecciona, independientemente en cada caso, de hidrógeno, halo, N_3, CN, -$(CR^{2e}R^{2f})$r-OR^{3b}, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, alquilo C_{1-6} sustituido con 0-3 R^{3a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{3a}; y fenilo sustituido con 0-3 R^{3a} o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O y $S(O)_p$, sustituido con 0-3 R^{3a} , o dos R^3 ubicados	

ubicados en un enlace de átomos de carbono adyacentes para formar un carbociclo de 5-7 elementos o un heterociclo de 5-7 elementos, que comprenden átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, ambos opcionalmente sustituidos con 0-3 R^{3a};	en un enlace de átomos de carbono adyacentes para formar un carbociclo de 5-7 elementos o un heterociclo de 5-7 elementos, que comprenden átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, ambos opcionalmente sustituidos con 0-3 R^{3a};	
R^{3a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o -	R^{3a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o -	

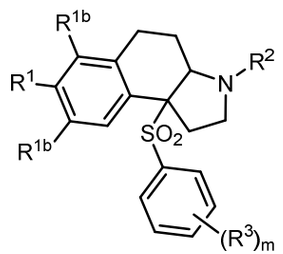
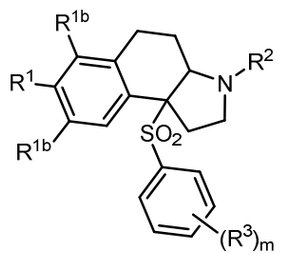
$(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;	$(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;	
R^{3b} es, independientemente en cada caso, hidrógeno, CF_3, $-(CR^{2e}R^{2f})_qOR^b$, $-(CR^{2e}R^{2f})_qS(O)_pR^b$, $-(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, $-(CR^{2e}R^{2f})$r-$C(O)OR^b$, $-(CR^{2e}R^{2f})_qOC(O)R^b$, $-(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})_qNR^bC(O)N$ $R^{11}R^{11}$, $-(CR^{2e}R^{2f})_qS(O)_2N$ $R^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;	R^{3b} es, independientemente en cada caso, hidrógeno, CF_3, $-(CR^{2e}R^{2f})_qOR^b$, $-(CR^{2e}R^{2f})_qS(O)_pR^b$, $-(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, $-(CR^{2e}R^{2f})$r-$C(O)OR^b$, $-(CR^{2e}R^{2f})_qOC(O)R^b$, $-(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})_qNR^bC(O)N$ $R^{11}R^{11}$, $-(CR^{2e}R^{2f})_qS(O)_2N$ $R^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;	
R^4 y R^5 son independientemente	R^4 y R^5 son independientemente	

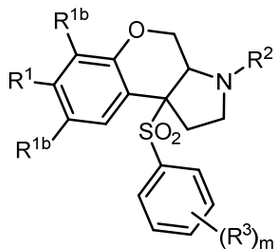
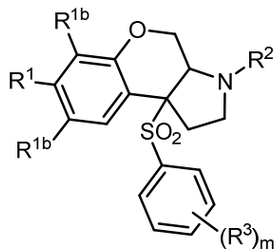
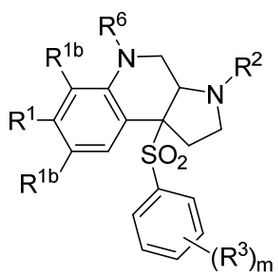
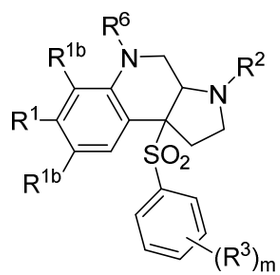
hidrógeno, halo, alquilo C_{1-6} o haloalquilo C_{1-6}, o R^4 y R^5, junto con el átomo de carbono al que están unidos, forman un anillo espirocarbociclilo de 3 a 6 elementos o un anillo espiroheterociclilo; R^6 y R^7 son independientemente hidrógeno, alquilo C_{1-6} o haloalquilo C_{1-6}; R^{11} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^f, CF_3, cicloalquilo C_{3-10} sustituido con 0-3 R^f, $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^d o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprenden átomos de carbono y 1-4 heteroátomos seleccionados N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^d; o un R^{11} y un segundo R^{11}, ambos unidos al mismo átomo de nitrógeno, se combinan para formar un heterociclo, que	hidrógeno, halo, alquilo C_{1-6} o haloalquilo C_{1-6}, o R^4 y R^5, junto con el átomo de carbono al que están unidos, forman un anillo espirocarbociclilo de 3 a 6 elementos o un anillo espiroheterociclilo; R^6 y R^7 son independientemente hidrógeno, alquilo C_{1-6} o haloalquilo C_{1-6}; R^{11} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^f, CF_3, cicloalquilo C_{3-10} sustituido con 0-3 R^f, $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^d o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprenden átomos de carbono y 1-4 heteroátomos seleccionados N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^d; o un R^{11} y un segundo R^{11}, ambos unidos al mismo átomo de nitrógeno, se combinan para formar un heterociclo, que	

comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^d; R^a es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^f, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^e, alquinilo C_{2-6} sustituido con 0-3 R^e, $-(CR^{2e}R^{2f})r-$carbociclo de 3-14 elementos o $-(CR^{2e}R^{2f})r-$heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f; R^b es, independientemente en cada	comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^d; R^a es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^f, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^e, alquinilo C_{2-6} sustituido con 0-3 R^e, $-(CR^{2e}R^{2f})r-$carbociclo de 3-14 elementos o $-(CR^{2e}R^{2f})r-$heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f; R^b es, independientemente en cada	

caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-3 R^d, $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f o $-(CR^{2e}R^{2f})r$-carbociclo de 6-10 elementos sustituido con 0-3 R^d; R^c es, independientemente en cada caso, alquilo C_{1-6} sustituido con 0-3 R^f, $-(CR^{2e}R^{2f})r$-cicloalquilo C_{3-6} sustituido con 0-3 R^f o $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^f; R^d es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CR^{2e}R^{2f})r-C(O)R^c$, $-NR^eR^e$, $-NR^eC(O)OR^c$,$C(O)NR^eR^e$, $-NR^eC(O)R^c$, CO_2H, CO_2R^c, $-NR^eSO_2R^c$, SO_2R^c, alquilo C_{1-6} sustituido con 0-3 R^f, cicloalquilo C_{3-6}	caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-3 R^d, $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f o $-(CR^{2e}R^{2f})r$-carbociclo de 6-10 elementos sustituido con 0-3 R^d; R^c es, independientemente en cada caso, alquilo C_{1-6} sustituido con 0-3 R^f, $-(CR^{2e}R^{2f})r$-cicloalquilo C_{3-6} sustituido con 0-3 R^f o $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^f; R^d es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CF_3, CN, NO_2, $-OR^e$, $-(CR^{2e}R^{2f})r-C(O)R^c$, $-NR^eR^e$, $-NR^eC(O)OR^c$,$C(O)NR^eR^e$, $-NR^eC(O)R^c$, CO_2H, CO_2R^c, $-NR^eSO_2R^c$, SO_2R^c, alquilo C_{1-6} sustituido con 0-3 R^f, cicloalquilo C_{3-6}	

sustituido con 0-3 R^f, $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^f o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f; R^e se selecciona, independientemente en cada caso, de hidrógeno, $C(O)NR^fR^f$, alquilo C_{1-6}, cicloalquilo C_{3-6}, -heterociclo de 5-7 elementos o $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^f; R^f es, independientemente en cada caso, hidrógeno, =O, halo, CN, NH_2, NH(alquilo C_1-$_6$), N(alquilo C_1-$_6)_2$, SO_2(alquilo C_1-$_6$), CO_2H, CO_2(alquilo C_1-$_6$), OH, cicloalquilo C_{3-6}, CF_3; O(alquilo C_1-$_6$); o un $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos opcionalmente sustituido, que	sustituido con 0-3 R^f, $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^f o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f; R^e se selecciona, independientemente en cada caso, de hidrógeno, $C(O)NR^fR^f$, alquilo C_{1-6}, cicloalquilo C_{3-6}, -heterociclo de 5-7 elementos o $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^f; R^f es, independientemente en cada caso, hidrógeno, =O, halo, CN, NH_2, NH(alquilo C_1-$_6$), N(alquilo C_1-$_6)_2$, SO_2(alquilo C_1-$_6$), CO_2H, CO_2(alquilo C_1-$_6$), OH, cicloalquilo C_{3-6}, CF_3; O(alquilo C_1-$_6$); o un $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos opcionalmente sustituido, que	

comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, fenilo o cicloalquilo C_{3-6}, cada grupo opcionalmente sustituido con halo, CN, CF_3, C_{1-6} alquilo o O(alquilo C_1-$_6$); m es 0, 1, 2 o 3 p y q son, independientemente de cada caso, 0, 1 o 2; y r es 0, 1, 2, 3 o 4, o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, fenilo o cicloalquilo C_{3-6}, cada grupo opcionalmente sustituido con halo, CN, CF_3, C_{1-6} alquilo o O(alquilo C_1-$_6$); m es 0, 1, 2 o 3 p y q son, independientemente de cada caso, 0, 1 o 2; y r es 0, 1, 2, 3 o 4, o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	
2. El compuesto de conformidad con la reivindicación 1, de la Fórmula 	2. El compuesto de conformidad con la reivindicación 1, de la Fórmula 	Corresponden totalmente.

o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	
3. El compuesto de conformidad con la reivindicación 1, de la Fórmula  o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	3. El compuesto de conformidad con la reivindicación 1, de la Fórmula  o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	Corresponden totalmente.
4. El compuesto de conformidad con la reivindicación 1, de la Fórmula 	4. El compuesto de conformidad con la reivindicación 1, de la Fórmula 	Corresponden totalmente.

o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	
5. El compuesto de conformidad con la reivindicación 2, en donde R^1 es halo, fenilo sustituido con 0-3 R^{1a}, o alquilo C_{1-6} sustituido con 0-3 R^{1a}; R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, alquilo C_{1-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r-OR^b$, y $-(CR^{2e}R^{2f})_r$-fenilo sustituido con 0-3 R^a, R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4}; R^2 es hidrógeno, SO_2R^{2c}, alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$; o un heterociclo de 5-7 miembros que comprende	5. El compuesto de conformidad con la reivindicación 2, en donde R^1 es halo, fenilo sustituido con 0-3 R^{1a}, o alquilo C_{1-6} sustituido con 0-3 R^{1a}; R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, alquilo C_{1-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r-OR^b$, y $-(CR^{2e}R^{2f})_r$-fenilo sustituido con 0-3 R^a, R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4}; R^2 es hidrógeno, SO_2R^{2c}, alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$; o un heterociclo de 5-7 miembros que comprende átomos de carbono, y 1-4 heteroátomos	Corresponden totalmente.

átomos de carbono, y 1-4 heteroátomos seleccionado del grupo que consiste de N, O, P(=O) y S(O)p substituido con 0-4 R^a, R^{2a} es hidrógeno o alquilo C_{1-6} sustituido con 0-3 R^a; R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^a; R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10}	seleccionado del grupo que consiste de N, O, P(=O) y S(O)p substituido con 0-4 R^a, R^{2a} es hidrógeno o alquilo C_{1-6} sustituido con 0-3 R^a; R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^a; R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a, o $-(CR^{2e}R^{2f})$r-	

sustituido con 0-3 R^a, o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2d} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, cicloalquilo C_{3-10} sustituido con 0-2 R^d, $(CR^{2e}R^{2f})_r$-fenilo sustituido con 0-2 R^a, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^3 es, independientemente en cada caso, hidrógeno, halo, N_3, CN, OR^{3b}, $-NH_2$, NH(alquilo C_{1-6}), N (alquilo $C_{1-6})_2$,alquilo C_{1-6} sustituido con 0-3 R^{3a} o cicloalquilo C_{3-10} sustituido con 0-3 R^{3a}; R^{3a} es, independientemente en	heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2d} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, cicloalquilo C_{3-10} sustituido con 0-2 R^d, $(CR^{2e}R^{2f})_r$-fenilo sustituido con 0-2 R^a, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^3 es, independientemente en cada caso, hidrógeno, halo, N_3, CN, OR^{3b}, $-NH_2$, NH(alquilo C_{1-6}), N (alquilo $C_{1-6})_2$,alquilo C_{1-6} sustituido con 0-3 R^{3a} o cicloalquilo C_{3-10} sustituido con 0-3 R^{3a}; R^{3a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3,	

cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;y R^{3b} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, o fenilo sustituido con 0-3 R^a ;	$OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;y R^{3b} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, o fenilo sustituido con 0-3 R^a ; o un estereoisómero o una sal	

o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	del mismo farmacéuticamente aceptable.	
6. El compuesto de conformidad con la reivindicación 3, en donde R^1 es halo, fenilo sustituido con 0-3 R^{1a}, o alquilo C_{1-6} sustituido con 0-3 R^{1a}; R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, alquilo C_{1-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r-OR^b$, y $(CR^{2e}R^{2f})_r$ fenilo sustituido con 0-3 R^a; R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4}; R^2 se selecciona de hidrógeno, SO_2R^{2c}, alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$; o un heterociclo de 5-7 miembros que comprende átomos de carbono, y 1-4 heteroátomos	6. El compuesto de conformidad con la reivindicación 3, en donde R^1 es halo, fenilo sustituido con 0-3 R^{1a}, o alquilo C_{1-6} sustituido con 0-3 R^{1a}; R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, alquilo C_{1-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r-OR^b$, y $(CR^{2e}R^{2f})_r$ fenilo sustituido con 0-3 R^a; R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4}; R^2 se selecciona de hidrógeno, SO_2R^{2c}, alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$; o un heterociclo de 5-7 miembros que comprende átomos de carbono, y 1-4 heteroátomos	Corresponden totalmente.

seleccionado del grupo que consiste de N, O, P(=O) y S(O)p substituido con 0-4 R^a,	seleccionado del grupo que consiste de N, O, P(=O) y S(O)p substituido con 0-4 R^a,	
R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a;	R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a;	
R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r-$heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})r-$fenilo sustituido con 0-3 R^a;	R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r-$heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})r-$fenilo sustituido con 0-3 R^a;	
R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r-$heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados de	R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r-$heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados de	

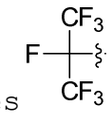
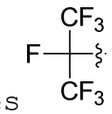
N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2d} es, independientemente de cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, cicloalquilo C_{3-10} sustituido con 0-2 R^d, $(CR^{2e}R^{2f})$r-fenilo sustituido con 0-2 R^a o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^3 se selecciona, independientemente en cada caso, de hidrógeno, halo, N_3, CN, OR^{3b}, $-NH_2$, NH(alquilo C_{1-6}), N (alquilo $C_{1-6})_2$,alquilo C_{1-6} sustituido con 0-3 R^{3a} o cicloalquilo C_{3-10} sustituido con 0-3 R^{3a}; R^{3a} es independientemente en cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})$r-OR^b, $-(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $-(CR^{2e}R^{2f})$r-$C(O)R^b$, -	N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^{2d} es, independientemente de cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, cicloalquilo C_{3-10} sustituido con 0-2 R^d, $(CR^{2e}R^{2f})$r-fenilo sustituido con 0-2 R^a o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a; R^3 se selecciona, independientemente en cada caso, de hidrógeno, halo, N_3, CN, OR^{3b}, $-NH_2$, NH(alquilo C_{1-6}), N (alquilo $C_{1-6})_2$,alquilo C_{1-6} sustituido con 0-3 R^{3a} o cicloalquilo C_{3-10} sustituido con 0-3 R^{3a}; R^{3a} es independientemente en cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})$r-OR^b, $-(CR^{2e}R^{2f})$r-$S(O)_pR^b$, $-(CR^{2e}R^{2f})$r-$C(O)R^b$, -	

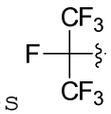
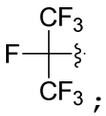
$(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a; y R^{3b} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a o fenilo sustituido con 0-3 R^a; o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	$(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a; y R^{3b} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a o fenilo sustituido con 0-3 R^a; o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	

7. El compuesto de conformidad con la reivindicación 5, en donde R^1 es alquilo C_{1-6} sustituido con 0-3 R^{1a}, R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, o alquilo C_{1-6} sustituido con 0-3 R^a; R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4}; R^2 es alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$; R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a; R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r-$ heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O)	7. El compuesto de conformidad con la reivindicación 5, en donde R^1 es alquilo C_{1-6} sustituido con 0-3 R^{1a}, R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, o alquilo C_{1-6} sustituido con 0-3 R^a; R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4}; R^2 es alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$; R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a; R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r-$ heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O)	Corresponden totalmente.

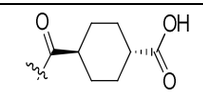
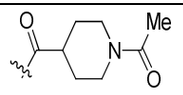
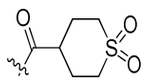
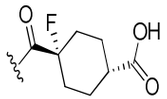
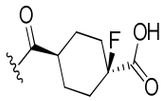
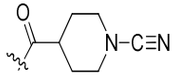
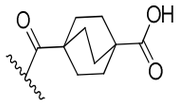
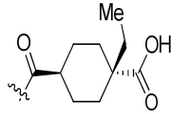
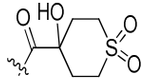
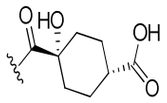
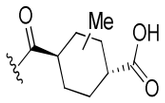
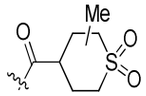
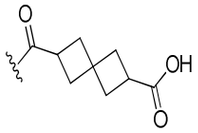
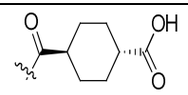
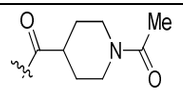
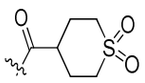
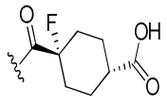
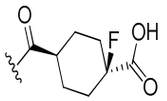
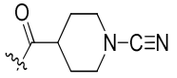
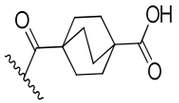
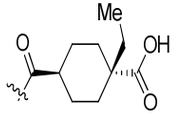
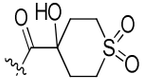
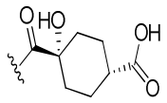
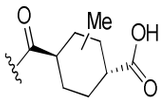
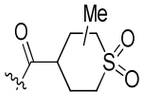
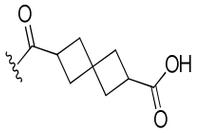
y $S(O)_p$, sustituido con 0-4 R^a, o -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^a; R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a; R^3 es hidrógeno, halo, ciclopropilo o alquilo C_{1-6}; o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	y $S(O)_p$, sustituido con 0-4 R^a, o -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^a; R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a; R^3 es hidrógeno, halo, ciclopropilo o alquilo C_{1-6}; o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	
8. El compuesto de conformidad con la reivindicación 6, en donde R^1 es alquilo C_{1-6} sustituido con 0-3 R^{1a}, R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, o alquilo C_{1-6} sustituido con 0-3 R^a; R^{1b} es, independientemente en	8. El compuesto de conformidad con la reivindicación 6, en donde R^1 es alquilo C_{1-6} sustituido con 0-3 R^{1a}, R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, o alquilo C_{1-6} sustituido con 0-3 R^a; R^{1b} es, independientemente en	Corresponden totalmente.

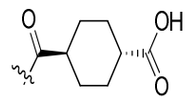
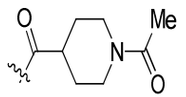
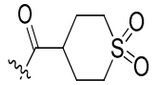
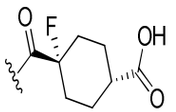
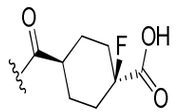
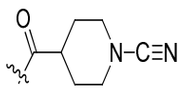
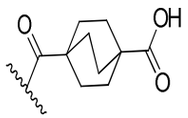
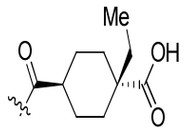
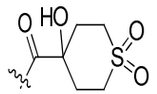
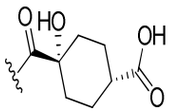
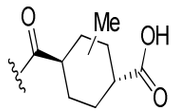
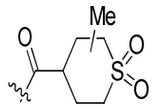
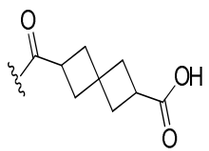
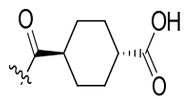
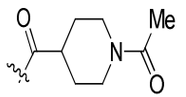
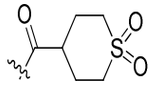
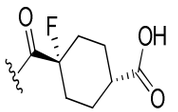
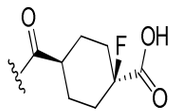
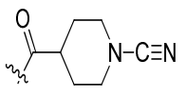
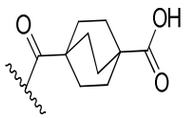
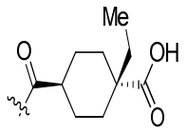
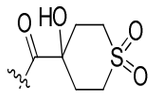
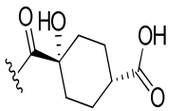
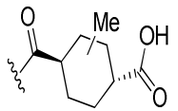
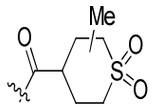
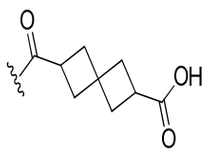
cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4};	cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4};	
R^2 es alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, o $-C(O)NR^{11}R^{11}$;	R^2 es alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, o $-C(O)NR^{11}R^{11}$;	
R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a;	R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a;	
R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r-$ heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})r-$fenilo sustituido con 0-3 R^a;	R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r-$ heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})r-$fenilo sustituido con 0-3 R^a;	
R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_2$,	R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_2$, sustituido con 0-4	

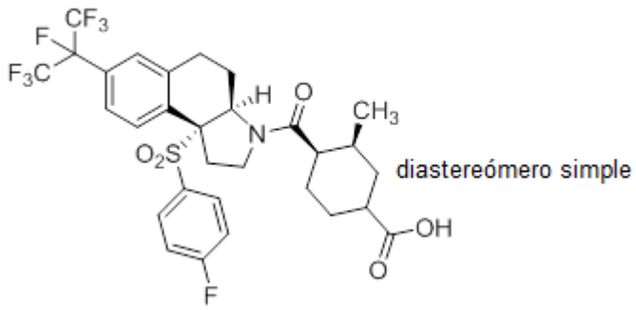
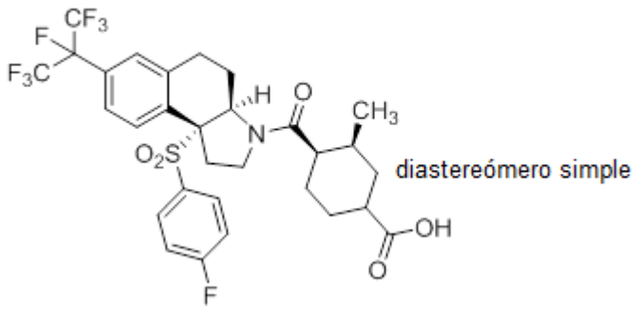
sustituido con 0-4 R^a; R^3 es hidrógeno, halo, ciclopropilo o alquilo C_{1-6}; o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	R^a; R^3 es hidrógeno, halo, ciclopropilo o alquilo C_{1-6}; o un estereoisómero o una sal del mismo farmacéuticamente aceptable.	
9. El compuesto de conformidad con la reivindicación 7 en donde  R^1 es ; R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_1-C_4; R^2 es $-C(O)R^{2d}$; R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de	9. El compuesto de conformidad con la reivindicación 7 en donde  R^1 es ; R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_1-C_4; R^2 es $-C(O)R^{2d}$; R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de	Corresponden totalmente.

N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a;	N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a;	
R^3 es F, Cl, ciclopropilo o metilo;	R^3 es F, Cl, ciclopropilo o metilo;	
o un estereoisómero o una sal de estos farmacéuticamente aceptable.	o un estereoisómero o una sal de estos farmacéuticamente aceptable.	
10. El compuesto de conformidad con la reivindicación 8, en donde  R^1 es ;	10. El compuesto de conformidad con la reivindicación 8, en donde  R^1 es ;	Corresponden totalmente.
R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_1-C_4;	R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_1-C_4;	
R^2 es $-C(O)R^{2d}$;	R^2 es $-C(O)R^{2d}$;	
R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de	R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de	

N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a; R^3 es F, Cl, ciclopropilo o metilo; o un estereoisómero o una sal de estos farmacéuticamente aceptable.	N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a; R^3 es F, Cl, ciclopropilo o metilo; o un estereoisómero o una sal de estos farmacéuticamente aceptable.	
11. El compuesto de conformidad con la reivindicación 9, en donde R^2 es	11. El compuesto de conformidad con la reivindicación 9, en donde R^2 es	Corresponden totalmente.

 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  o  .	 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  o  .	
12. El compuesto de conformidad con la reivindicación 10, en donde R^2 es	12. El compuesto de conformidad con la reivindicación 10, en donde R^2 es	Corresponden totalmente.

 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  o  .	 ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  o  .	
13. Una composición farmacéutica que comprende uno o más compuestos de acuerdo con la reivindicación 1 y portador o diluyente farmacéuticamente aceptable.	13. Una composición farmacéutica que comprende uno o más compuestos de acuerdo con la reivindicación 1 y portador o diluyente farmacéuticamente aceptable.	Corresponden totalmente.

14. Un compuesto que tiene la formula  o una sal de estos farmacéuticamente aceptable, un tautómero o un estereoisómero del mismo.	14. Un compuesto que tiene la formula  o una sal de estos farmacéuticamente aceptable, un tautómero o un estereoisómero del mismo.	Corresponden totalmente.
15. Una composición farmacéutica que comprende el compuesto de la reivindicación 14 y un portador farmacéuticamente aceptable.	15. Una composición farmacéutica que comprende el compuesto de la reivindicación 14 y un portador farmacéuticamente aceptable.	Corresponden totalmente.

Notificación de Aprobación	**Solicitud No.** 15/148,209	**Solicitante(s)** DUAN ET AL.	
	Examinador PANCHAM BAKSHI	**Unidad Tecnica** 1671	**Estado de AIA (Primer inventor en presentar)** Sí

-**La FECHA DE ENVÍO de este comunicado aparece en la portada con la dirección correspondiente—**

Todas las reivindicaciones son aprobadas, EL JUICIO SOBRE LOS MÉRITOS ESTÁ (O PERMANECE) CERRADO en esta solicitud. Si no se incluye aquí (o es previamente enviado por correo), una Notificación de Concesión (PTOL-85), u otra comunicación apropiada se enviará por correo a su debido tiempo. ESTA NOTIFICACIÓN DE CONCESIÓN NO ES UNA AUTORIZACIÓN DE DERECHOS DE PATENTE. Esta solicitud está sujeta al retiro de la emisión a la iniciativa de la Oficina o sobre la petición del solicitante. Véase 37 CFR 1.313 y MPEP 1308.

1. [X] Esta comunicación es en respuesta a la contestación con fecha 08/29/2017.
   [ ] Una(s) declaración(es)/ declaración(es) jurada(s) bajo **37 CFR 1.130(b)** fue/fueron registrados en____.

2. [ ] Una elección fue hecha por el solicitante en respuesta a un requisito de restricción establecido durante la entrevista en_____; el requisito de restricción y la elección han sido incorporados en esta acción.

3. [X] La(s) reivindicación(es) concedida(s) es/son 6-18 y 21-22. Como resultado de la(s) reivindición(es) concedida(s), usted puede ser elegible para beneficiarse del programa **Tramite Acelerado de Patentes** en una oficina de propiedad intelectual participante para la solicitud correspondiente. Para obtener más información, consulte http://www.uspto.gov/patents/init_events/pph/index.js o envíe una petición a PPHfeedback@uspto.gov.

4. [ ] Se reconoce una reivindicación de prioridad extranjera bajo 35 U.S.C. § 119 (a) - (d) o (f).

Copias certificadas:

a) [ ] Todas b) [ ] Algunas *c) [ ] Ninguna de las:

1. [ ] Copias certificadas de los documentos de prioridad han sido recibidas.
2. [ ] Copias certificadas de los documentos prioridad han sido recibidas en la Solicitud No.____.
3. [ ] Copias de las copias certificadas de los documentos de prioridad han sido recibidas en esta fase nacional de la solicitud desde la Oficina Internacional (Regla PCT 17.2.(a))

* Copias certificadas no recibidas: ____.

El Solicitante tiene TRES MESES DESDE LA "FECHA DE ENVÍO" de esta comunicación para presentar una respuesta que cumpla con los requisitos indicados a continuación. El incumplimiento fuera del tiempo resultará en el ABANDONO de esta solicitud. **ESTE PERIODO DE TRES MESES NO ES EXTENDIBLE.**

5. [ ] DIBUJOS CORREGIDOS (como "hojas de repuesto") deben ser presentados.

[ ] Incluir cambios requeridos por la Enmienda / Comentario adjunto del Examinador o en la acción de la Oficina del Documento No. / Fecha de envío____.

Los signos de identificación tales como el número de solicitud (véase 37 CFR 1.84 (c)) deberían ser escritos en los dibujos en la parte delantera (no en la parte posterior) de cada hoja. Las hojas de repuesto deberían estar etiquetadas como tales en la cabecera de acuerdo con 37 CFR 1.121 (d).

6. [ ] DEPÓSITO DE y/o INFORMACIÓN acerca del depósito de MATERIAL BIOLÓGICO debe ser presentada. Tenga en cuenta el comentario adjunto del Examinador respecto al REQUISITO PARA EL DEPÓSITO DE MATERIAL BIOLÓGICO.

Archivo(s) adjunto(s) 1. ☐ Notificación de Referencias Citadas (PTO-892) 2. ☐ Declaraciones de Divulgación de Información (PTO / SB / 08), Documento No. / Fecha de envío 3. ☐ Comentario del examinador con respecto al Requerimiento 4. ☐ Resumen de la Entrevista (PTO-413), Documento No. / Fecha de envío _____.	5. ☐ Enmienda / Comentario del Examinador 6. ☐ Declaración de las razones de concesión del Examinador 7. ☐ Otro _____.
/ PANCHAM BAKSHI Examinador primario, Unidad de Arte 1671	10/06/2017

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23914 7590 06/13/2017

HENRY HADAD
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER
BAKSHI, PANCHAM

ART UNIT	PAPER NUMBER
1671	

DATE MAILED: 06/13/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,209	05/06/2016	Jingwu Duan	12493-US-NP	9419

TITLE OF INVENTION: TRICYCLIC SULFONES AS RORγ MODULATORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/13/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23914 7590 06/13/2017
HENRY HADAD
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,209	05/06/2016	Jingwu Duan	12493-US-NP	9419

TITLE OF INVENTION: TRICYCLIC SULFONES AS RORγ MODULATORS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/13/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
BAKSHI, PANCHAM	1671	514-110000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,209	05/06/2016	Jingwu Duan	12493-US-NP	9419

23914 7590 06/13/2017

HENRY HADAD
BRISTOL-MYERS SQUIBB COMPANY
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P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
BAKSHI, PANCHAM	

ART UNIT	PAPER NUMBER
1671	

DATE MAILED: 06/13/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/148,209	Applicant(s) DUAN ET AL.	
	Examiner PANCHAM BAKSHI	Art Unit 1671	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *04/11/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *6-18*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/PANCHAM BAKSHI/ Primary Examiner, Art Unit 1671	06/01/2017

DETAILED ACTION

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's Remarks and amendment, in the reply filed on 04/11/2017 is acknowledged.

Status of the Application

Claims 6-18 have been amended and claims 1-5 have been canceled by the amendment dated 04/11/2017. Accordingly, Claims **6-20** are pending, of which claims **19 and 20** are withdrawn because of earlier restriction and election **without traverse**.

Withdrawn Rejections

The rejections made under 35USC § 112 (b) in office action dated 02/01/2017 is hereby withdrawn in view of Applicant's canceling of claims 1-5 and amendment of claim 10 with respect to Markush format. Further, the rejections made under 35USC § 102 in office action dated 02/01/2017 is hereby withdrawn in view of Applicant's canceling of claims 1 and 2 amendment of claim 18 which is not anticipated by the prior art of record. Further, the rejections made under 35USC § 103 in office action dated 02/01/2017 is hereby withdrawn in view of Applicant's canceling of claims 1-5 amendment of claims 6-18 and applicant's remarks which are found persuasive.

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

In the Claims

Claims 19 and 20 have been canceled.

Rejoinder

The **election of species requirement (A) for Group I**, as set forth in the Office action mailed on 10/14/2016, has been reconsidered and **is hereby withdrawn.**

In view of the above noted withdrawal of **the election of species requirement**, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

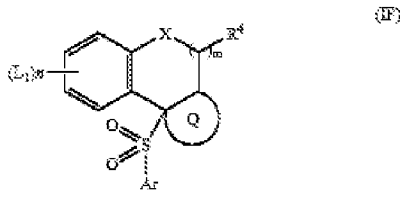
Reasons for Allowance

Applicant's Remarks and amendment filed on 04/11/2017, has been fully considered and is found persuasive.

The following is an Examiner's statement of reasons for allowance:

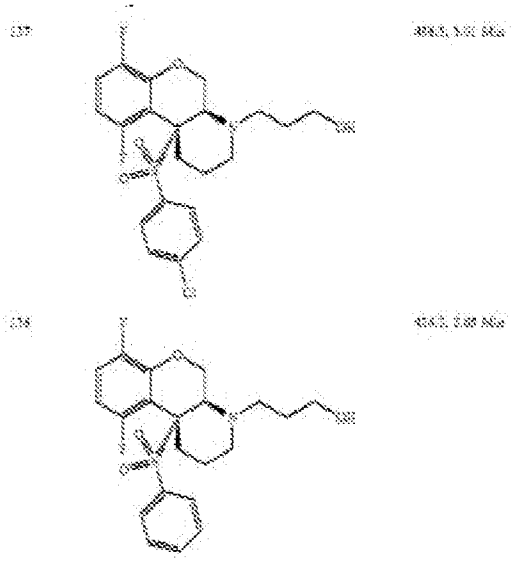
Applicant's compound of formula as in the instant claims is novel and unobvious over the prior art of record. None of the prior art of record disclose or teach applicant's compound of formula as in the instant claims. The closest prior art, **Asberom (US 20070197581 A1)** teaches compound of formula:

30. The compound of claim 1 having the formula (IF):



(IF)

and species:



which are different with respect to size of the heterocyclic ring Q of the instant claims. Further, among hundreds of compounds disclosed by the cited prior art, Q ring is 6 membered in all of the compounds and thus different from pyrrolidine ring of the instant claims. Further**,** the cited prior art would not suggest nor motivate to a person of ordinary skill in the art to select compound with pyrrolidine ring as in the instant claims.

Therefore, claims **6-18** are allowed.

Conclusion

Claims **6-18** are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PANCHAM BAKSHI whose telephone number is (571)270-3463. The examiner can normally be reached on Monday through Thursday 8-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SAJJADI FEREYDOUN can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

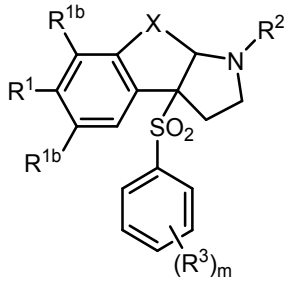
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PANCHAM BAKSHI/
Primary Examiner, Art Unit 1671

Reivindicaciones otorgables

Reivindiaciones 1-5 (Eliminadas)

6. Un compuesto de la Fórmula



en donde

X es $-CR^4R^5-$, $-(CR^4R^5)_2$, $-OCR^6R^7-$, $-S(O)_pCR^6R^7-$ o $-NR^6CR^6R^7-$;

R^1 es halo, alquilo C_{1-6} sustituido con 0-3 R^{1a}, $-(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^{1a} o $-(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^{1a};

R^{1a} es, independientemente en cada caso, hidrógeno, =O, halo, CF_3, OCF_3, CN, NO_2, $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})$r-

$OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r$-carbociclo de 3-14 elementos sustituido con 0-3 R^a , o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos que comprende átomos de carbono, y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;

R^{1b} es, independientemente de cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4};

R^2 es hidrógeno, $-(CR^{2e}R^{2f})r-C(O)R^{2d}$, $-(CR^{2e}R^{2f})r-C(O)OR^{2b}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-S(O)2R^{2c}$, alquilo C_{1-6} sustituido con 0-3 R^{2a}, alquenilo C_{2-6} sustituido con 0-3 R^{2a}, $-(CR^{2e}R^{2f})r$-carbociclo de 3-10 elementos sustituido con 0-3 R^a , o $-(CR^{2e}R^{2f})r$-heterociclo de 4-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^{2a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-OC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-OC(O)OR^c$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, alquenilo C_{2-6}

sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, -$(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^a o -$(CR^{2e}R^{2f})$r-heterociclo de 4-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^{2b} es, independientemente en cada caso, hidrógeno, CF_3, -$(CR^{2e}R^{2f})_qOR^b$, -$(CR^{2e}R^{2f})_qS(O)pR^b$, -$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})_qOC(O)R^b$, -$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, -$(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, -$(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, -$CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, alquilo C_{1-6} sustituido con 0-2 R^a, haloalquilo C_{1-6}, -$(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^a o -$(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a o -$(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^{2d} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-cicloalquilo C_{3-10} sustituido con 0-3 R^d, en donde el anillo de cicloalquilo puede ser fusionado,

en puente o espirocíclico, -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-2 R^a o un -$(CR^{2e}R^{2f})$r-heterociclo de 4-10 elementos, en donde el heterociclo puede ser fusionado, en puente o espirocíclico, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^{2e} y R^{2f} son, independientemente en cada caso, hidrógeno, halógeno o alquilo C_{1-6};

R^3 se selecciona, independientemente en cada caso, de hidrógeno, halo, N_3, CN, -$(CR^{2e}R^{2f})$r-OR^{3b}, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, alquilo C_{1-6} sustituido con 0-3 R^{3a}, cicloalquilo C_{3-10} sustituido con 0-3 R^{3a}; y fenilo sustituido con 0-3 R^{3a} o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O y $S(O)_p$, sustituido con 0-3 R^{3a} , o dos R^3 ubicados en un enlace de átomos de carbono adyacentes para formar un carbociclo de 5-7 elementos o un heterociclo de 5-7 elementos, que comprenden átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, ambos opcionalmente sustituidos con 0-3 R^{3a};

R^{3a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, -$(CR^{2e}R^{2f})$r-OR^b, -$(CR^{2e}R^{2f})$r-$S(O)_pR^b$, -$(CR^{2e}R^{2f})$r-$C(O)R^b$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})$r-$OC(O)R^b$, -$(CR^{2e}R^{2f})$r-$NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)R^c$, -$(CR^{2e}R^{2f})$r-$NR^bC(O)OR^c$, -$NR^bC(O)NR^{11}R^{11}$, -$S(O)_pNR^{11}R^{11}$, -$NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido

con 0-3 R^a, haloalquilo C_{1-6}, -$(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^a o -$(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;

R^{3b} es, independientemente en cada caso, hidrógeno, CF_3, -$(CR^{2e}R^{2f})_qOR^b$, -$(CR^{2e}R^{2f})_qS(O)_pR^b$, -$(CR^{2e}R^{2f})$r-$C(O)R^{1d}$, -$(CR^{2e}R^{2f})$r-$C(O)OR^b$, -$(CR^{2e}R^{2f})_qOC(O)R^b$, -$(CR^{2e}R^{2f})_qNR^{11}R^{11}$, -$(CR^{2e}R^{2f})$r-$C(O)NR^{11}R^{11}$, -$(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, -$(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, -$(CR^{2e}R^{2f})_qNR^bC(O)N$ $R^{11}R^{11}$, -$(CR^{2e}R^{2f})_qS(O)_2N$ $R^{11}R^{11}$, -$(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, alquilo C_{1-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, -$(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^a o -$(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;

R^4 y R^5 son independientemente hidrógeno, halo, alquilo C_{1-6} o haloalquilo C_{1-6}, o

R^4 y R^5, junto con el átomo de carbono al que están unidos, forman un anillo espirocarbociclilo de 3 a 6 elementos o un anillo espiroheterociclilo;

R^6 y R^7 son independientemente hidrógeno, alquilo C_{1-6} o haloalquilo C_{1-6};

R^{11} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^f, CF_3, cicloalquilo C_{3-10} sustituido con 0-3 R^f, -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^d

o $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprenden átomos de carbono y 1-4 heteroátomos seleccionados N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^d;

o un R^{11} y un segundo R^{11}, ambos unidos al mismo átomo de nitrógeno, se combinan para formar un heterociclo, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^d;

R^a es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^f, haloalquilo C_{1-6}, alquenilo C_{2-6} sustituido con 0-3 R^e, alquinilo C_{2-6} sustituido con 0-3 R^e, $-(CR^{2e}R^{2f})r-$carbociclo de 3-14 elementos o $-(CR^{2e}R^{2f})r-$heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f;

R^b es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, cicloalquilo C_{3-6} sustituido con 0-3 R^d, $-(CR^{2e}R^{2f})r-$heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f o $-(CR^{2e}R^{2f})r-$carbociclo de 6-10 elementos sustituido con 0-3 R^d;

R^c es, independientemente en cada caso, alquilo C_{1-6} sustituido con 0-3 R^f, -$(CR^{2e}R^{2f})$r-cicloalquilo C_{3-6} sustituido con 0-3 R^f o -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^f;

R^d es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, CF_3, CN, NO_2, -OR^e, -$(CR^{2e}R^{2f})$r-$C(O)R^c$, -NR^eR^e, -$NR^eC(O)OR^c$,$C(O)NR^eR^e$, -$NR^eC(O)R^c$, CO_2H, CO_2R^c, -$NR^eSO_2R^c$, SO_2R^c, alquilo C_{1-6} sustituido con 0-3 R^f, cicloalquilo C_{3-6} sustituido con 0-3 R^f, -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^f o -$(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^f;

R^e se selecciona, independientemente en cada caso, de hidrógeno, $C(O)NR^fR^f$, alquilo C_{1-6}, cicloalquilo C_{3-6}, -heterociclo de 5-7 elementos o -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^f;

R^f es, independientemente en cada caso, hidrógeno, =O, halo, CN, NH_2, NH(alquilo C_1-$_6$), N(alquilo C_1-$_6$)$_2$, SO_2(alquilo C_1-$_6$), CO_2H, CO_2(alquilo C_1-$_6$), OH, cicloalquilo C_{3-6}, CF_3; O(alquilo C_1-$_6$); o

un -$(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos opcionalmente sustituido, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, fenilo o cicloalquilo C_{3-6}, cada grupo opcionalmente sustituido con halo, CN, CF_3, C_{1-6} alquilo o O(alquilo C_1-$_6$);

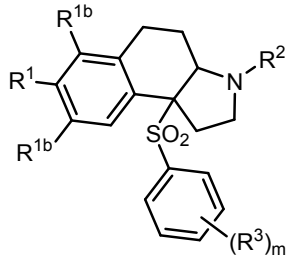
m es 0, 1, 2 o 3

p y q son, independientemente de cada caso, 0, 1 o 2; y

r es 0, 1, 2, 3 o 4,

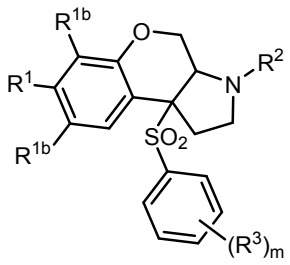
o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

7. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 6, de la Fórmula



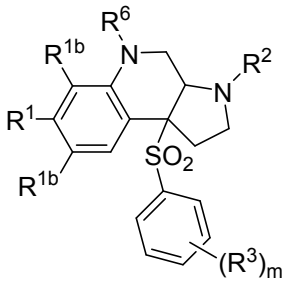
o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

8. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 6, de la Fórmula



o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

9. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 6, de la Fórmula



o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

10 (Presentada anteriormente) El compuesto de conformidad con la reivindicación 7, en donde

R^1 es halo, fenilo sustituido con 0-3 R^{1a}, o alquilo C_{1-6} sustituido con 0-3 R^{1a};

R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, alquilo C_{1-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})_r-OR^b$, y $-(CR^{2e}R^{2f})_r$-fenilo sustituido con 0-3 R^a,

R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4};

R^2 es hidrógeno, SO_2R^{2c}, alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$; o un heterociclo de 5-7 miembros que comprende átomos de carbono, y 1-4 heteroátomos seleccionado del grupo que consiste de N, O, P(=O) y S(O)p substituido con 0-4 R^a,

R^{2a} es hidrógeno o alquilo C_{1-6} sustituido con 0-3 R^a;

R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a,

$-(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^a;

R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a, o $-(CR^{2e}R^{2f})r$-heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^{2d} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, cicloalquilo C_{3-10} sustituido con 0-2 R^d, $(CR^{2e}R^{2f})_r$-fenilo sustituido con 0-2 R^a, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^3 es, independientemente en cada caso, hidrógeno, halo, N_3, CN, OR^{3b}, $-NH_2$, NH(alquilo C_{1-6}), N (alquilo $C_{1-6})_2$,alquilo C_{1-6} sustituido con 0-3 R^{3a} o cicloalquilo C_{3-10} sustituido con 0-3 R^{3a};

R^{3a} es, independientemente en cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido

con 0-3 R^a, haloalquilo C_{1-6}, -$(CR^{2e}R^{2f})$r-carbociclo de 3-14 elementos sustituido con 0-3 R^a o -$(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a;y

R^{3b} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, o fenilo sustituido con 0-3 R^a ;

o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

11. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 8, en donde

R^1 es halo, fenilo sustituido con 0-3 R^{1a}, o alquilo C_{1-6} sustituido con 0-3 R^{1a};

R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, alquilo C_{1-6} sustituido con 0-3 R^a, -$(CR^{2e}R^{2f})_r$-OR^b, y $(CR^{2e}R^{2f})_r$ fenilo sustituido con 0-3 R^a;

R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4};

R^2 se selecciona de hidrógeno, SO_2R^{2c}, alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, -$C(O)R^{2d}$, -$C(O)NR^{11}R^{11}$; o un heterociclo de 5-7 miembros que comprende átomos de carbono, y 1-4 heteroátomos seleccionado del grupo que consiste de N, O, P(=O) y S(O)p substituido con 0-4 R^a,

R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a;

R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, -$(CR^{2e}R^{2f})$r-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o -$(CR^{2e}R^{2f})$r-fenilo sustituido con 0-3 R^a;

R^{2c} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, cicloalquilo C_{3-10} sustituido con 0-3 R^a, arilo C_{6-10} sustituido con 0-3 R^a o -$(CR^{2e}R^{2f})$r-heterociclo de 5-10 elementos, que contiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^{2d} es, independientemente de cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^d, haloalquilo C_{1-6}, $C(O)NR^{11}R^{11}$, cicloalquilo C_{3-10} sustituido con 0-2 R^d, $(CR^{2e}R^{2f})$r-fenilo sustituido con 0-2 R^a o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a;

R^3 se selecciona, independientemente en cada caso, de hidrógeno, halo, N_3, CN, OR^{3b}, -NH_2, NH(alquilo C_{1-6}), N(alquilo C_{1-6})$_2$,alquilo C_{1-6} sustituido con 0-3 R^{3a} o cicloalquilo C_{3-10} sustituido con 0-3 R^{3a};

R^{3a} es independientemente en cada caso, hidrógeno, =O, halo, OCF_3, $OCHF_2$, CF_3, CHF_2, CN, NO_2, $-(CR^{2e}R^{2f})r-OR^b$, $-(CR^{2e}R^{2f})r-S(O)_pR^b$, $-(CR^{2e}R^{2f})r-C(O)R^b$, $-(CR^{2e}R^{2f})r-C(O)OR^b$, $-(CR^{2e}R^{2f})r-OC(O)R^b$, $-(CR^{2e}R^{2f})r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, alquilo C_{1-6} sustituido con 0-3 R^a, alquenilo C_{2-6} sustituido con 0-3 R^a, alquinilo C_{2-6} sustituido con 0-3 R^a, haloalquilo C_{1-6}, $-(CR^{2e}R^{2f})r-$carbociclo de 3-14 elementos sustituido con 0-3 R^a o $-(CR^{2e}R^{2f})r-$heterociclo de 5-10 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O y $S(O)_p$, sustituido con 0-3 R^a; y

R^{3b} es, independientemente en cada caso, hidrógeno, alquilo C_{1-6} sustituido con 0-3 R^a o fenilo sustituido con 0-3 R^a;

o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

12. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 10, en donde

R^1 es alquilo C_{1-6} sustituido con 0-3 R^{1a},

R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, o alquilo C_{1-6} sustituido con 0-3 R^a;

R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4};

R^2 es alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b}, $-C(O)R^{2d}$, $-C(O)NR^{11}R^{11}$;

R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a;

R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^a;

R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a;

R^3 es hidrógeno, halo, ciclopropilo o alquilo C_{1-6};

o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

13. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 6, en donde

R^1 es alquilo C_{1-6} sustituido con 0-3 R^{1a},

R^{1a} es, independientemente en cada caso, hidrógeno, CF_3, halo, o alquilo C_{1-6} sustituido con 0-3 R^a;

R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_{1-4};

R^2 es alquilo C_{1-6} substituted con 0-3 R^{2a}, CO_2R^{2b},

$-C(O)R^{2d}$, o $-C(O)NR^{11}R^{11}$;

R^{2a} es hidrógeno, o alquilo C_{1-6} sustituido con 0-3 R^a;

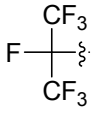
R^{2b} es hidrógeno, alquilo C_{1-6} sustituido con 0-2 R^a, cicloalquilo C_{3-6} sustituido con 0-3 R^a, $-(CR^{2e}R^{2f})r$-heterociclo de 5-7 elementos, que comprende átomos de carbono y 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_p$, sustituido con 0-4 R^a, o $-(CR^{2e}R^{2f})r$-fenilo sustituido con 0-3 R^a;

R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d, o un heterociclo de 4-10 elementos, que tiene 1-4 heteroátomos seleccionados de N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a;

R^3 es hidrógeno, halo, ciclopropilo o alquilo C_{1-6};

o un estereoisómero o una sal del mismo farmacéuticamente aceptable.

14. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 12 en donde

R^1 es  ;

R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_1-C_4;

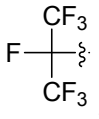
R^2 es $-C(O)R^{2d}$;

R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a;

R^3 es F, Cl, ciclopropilo o metilo;

o un estereoisómero o una sal de estos farmacéuticamente aceptable.

15. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 13, en donde

R^1 es  ;

R^{1b} es, independientemente en cada caso, hidrógeno, CD_3, halo, CF_3 y alquilo C_1-C_4;

R^2 es $-C(O)R^{2d}$;

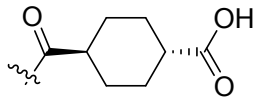
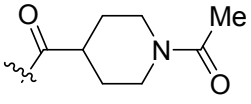
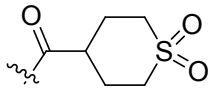
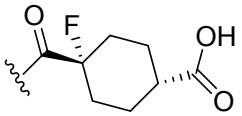
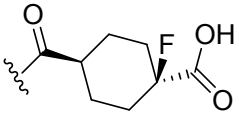
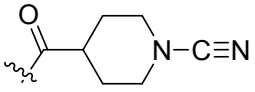
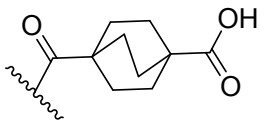
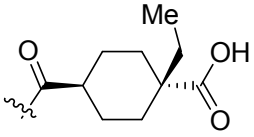
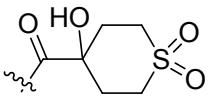
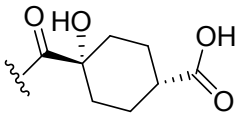
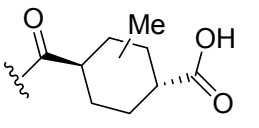
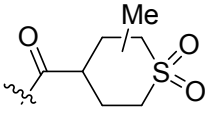
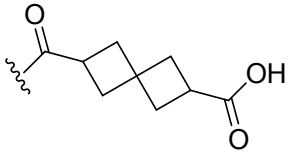
R^{2d} es, independientemente en cada caso, cicloalquilo C_{3-10} sustituido con 0-2 R^d o un heterociclo de 4-10 elementos, que contiene 1-4 heteroátomos seleccionados del grupo que consiste de N, O, P(=O) y $S(O)_2$, sustituido con 0-4 R^a;

R^3 es F, Cl, ciclopropilo o metilo;

o un estereoisómero o una sal de estos farmacéuticamente aceptable.

16. (Presentada anteriormente) El compuesto de conformidad con la reivindicación 14, en donde

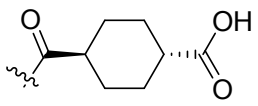
R^2 es

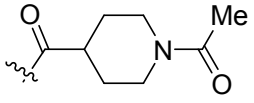

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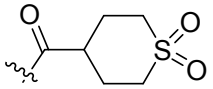
17. (Presentada anteriormente) El compuesto de

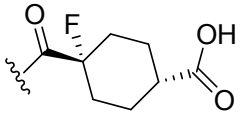
conformidad con la reivindicación 15, en donde

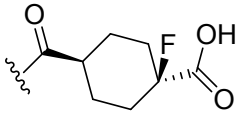
R^2 es

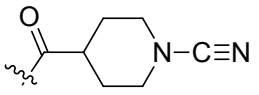


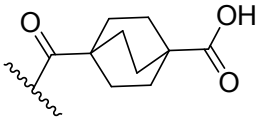
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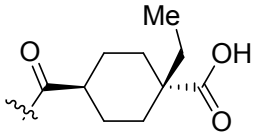
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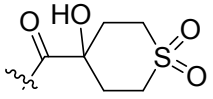
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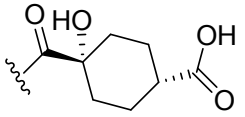
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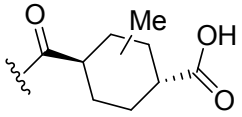
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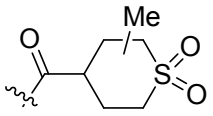
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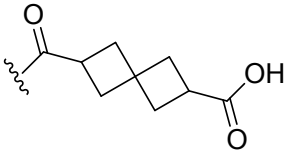
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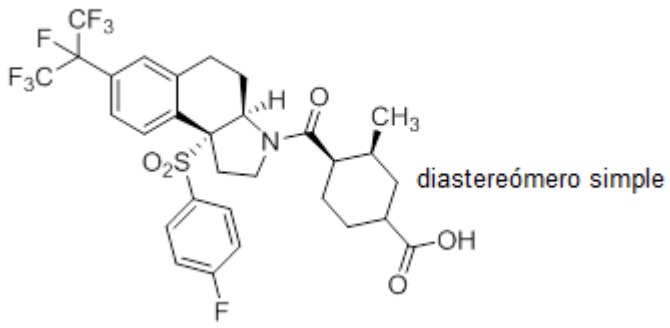
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18. (Presentada anteriormente) Una composición farmacéutica que comprende uno o más compuestos de acuerdo con la reivindicación 6 y portador o diluyente farmacéuticamente aceptable.

19. (Eliminada)

20. (Eliminada)

21. (Nueva) Un compuesto que tiene la formula



o una sal de estos farmacéuticamente aceptable, un tautómero o un estereoisómero del mismo.

22. (Nueva) Una composición farmacéutica que comprende el compuesto de la reivindicación 21 y un portador

farmacéuticamente aceptable.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,209	05/06/2016	Jingwu Duan	12493-US-NP	9419

23914 7590 02/01/2017

HENRY HADAD
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
BAKSHI, PANCHAM	

ART UNIT	PAPER NUMBER
1671	

NOTIFICATION DATE	DELIVERY MODE
02/01/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@bms.com
wendy.torres@bms.com
bms_pair@firsttofile.com

Office Action Summary	Application No. 15/148,209	Applicant(s) DUAN ET AL.	
	Examiner PANCHAM BAKSHI	Art Unit 1671	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/05/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-20* is/are pending in the application.

5a) Of the above claim(s) *9,11,13,15,17,19 and 20* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-8,10,12,14 and 18* is/are rejected.

8)☒ Claim(s) *16* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *08/11/2016; 08/31/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

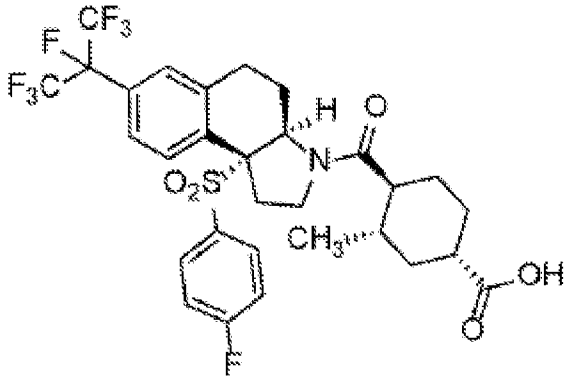
The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Status of the Application

Claims **1-20** are pending.

Election/Restrictions

Applicant's election **without traverse** of Group I, claims **1-18,** directed to a compound and a composition comprising the same**,** and the species:



in the reply filed on 12/05/2016 is acknowledged. The election was made without traverse.

Since the elected species reads on claims **1-7, 10, 12, 14, 16 and 18, these claims** are under current examination. The claims are examined on the extend they read on the elected species.

The elected species is found free of prior art and the search was extended to species encompassed by compound of formula (I) and Claim 8 is rejoined.

Claims 9, 11, 13, 15, 17 and **19-20** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims **1-8, 10, 12, 14, 16 and 18** are under current examination.

Claim Objections

Claim **1** is objected to as it is an independent claim and should start with "A".

Appropriate correction is required.

Claim **2-8, 10, 12, 14 and 16** are objected to as these are dependent claims and should start with "The".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

> The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims **1-5 and 10** are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 1-5 and 10 are indefinite as these claims at several occasions recites phrase "selected from", which renders the claim indefinite. For instance, claim 1, after structural formula (I), line 4. This is because the claims are in improper Markush or alternative format. Applicant is suggested to amend the claims by reciting either "selected from a group consisting of" or replace "selected from" with "is" or "are".

Appropriate correction required.

Claim Rejections - 35 USC § 102

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

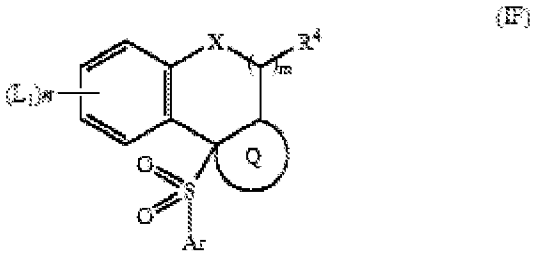
A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

Claims 1, 2 and 18 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by **Asberom** (US 2007/0197581 A1).

Asberom discloses compound of formula:

30. The compound of claim 1 having the formula (IF):



(IF)

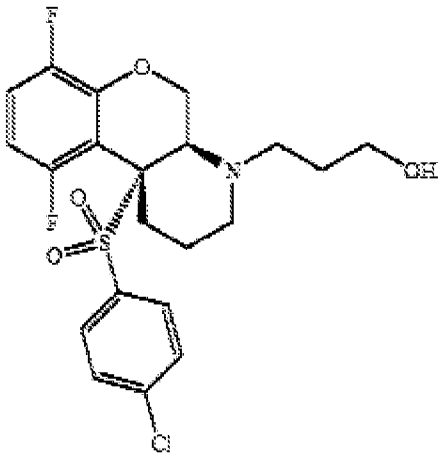
wherein X is –C(R1)2, -O-, -S-, etc.;

Q is substituted or unsubstituted hetercycloalkyl ring or substituted or unsubstituted cycloalkyl ring, wherein substituent L3 is selected from H, C1-C6 alkyl etc;

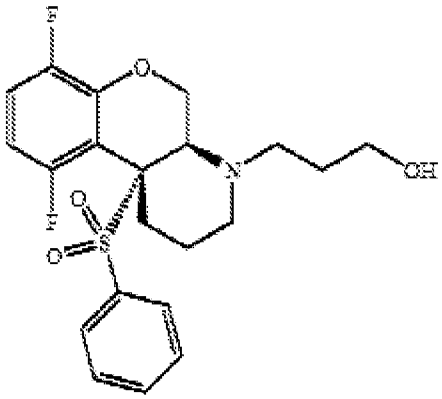
L1 is halogen, alkyl, haloalkyl etc;

Ar is a phenyl ring substituted with one or more L1 substituents (claim 1, 30) (overlaps with genus of the instant claims). The cited prior art further discloses several species and composition comprising the same which reads on the instant claims (Claims 1, 30 and 170). For instance,

137 458.3, 3.01 Min



138 424.2, 2.65 Min



(page 106, table 3) reads on the instant claims 1, 2 and 18 when X =OCR6R7; R6=R7=H; R1=halo; n=2; Y=phenyl; R2=C1-C6 alkyl substituted with 1 R2a; R2a=(CR2eR2f)rORb; r=0; Rb=H; R3=halogen or hydrogen and m=0 or 1; p=2. Since the cited prior art reads on the instant claims 1, 2 and 18, these claims are anticipated.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the

statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

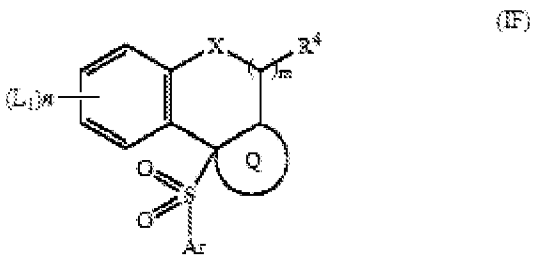
effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 1-8, 10, 12, 14 and 18 are rejected under 35 U.S.C. 103 as being unpatentable over **Asberom** (US 2007/0197581 A1).

Determining the scope and contents of the prior art

Asberom teaches compound of formula:

30. The compound of claim 1 having the formula (IF):



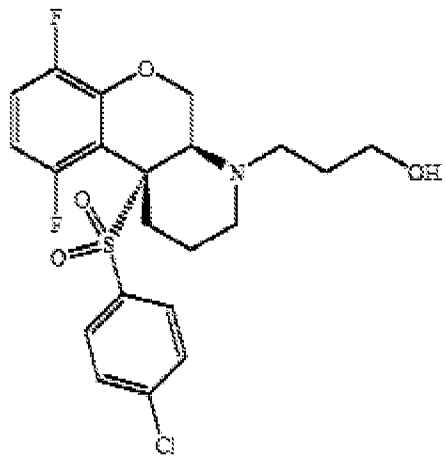
(IF)

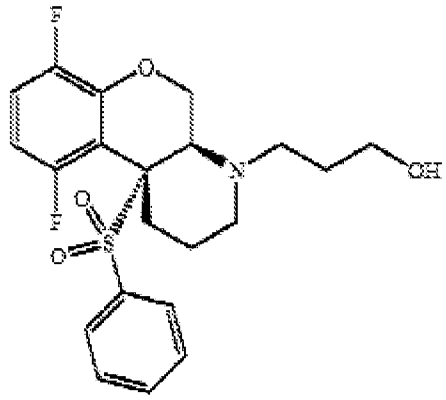
wherein X is –C(R1)2, -O-, -S-, etc.;

Q is substituted or unsubstituted hetercycloalkyl ring or substituted or unsubstituted cycloalkyl ring, wherein substituent L3 is selected from H, C1-C6 alkyl;

L1 is halogen, alkyl, haloalkyl etc;

Ar is a phenyl ring substituted with one or more L1 substituents (claim 1, 30) (overlaps with genus of the instant claims). The cited prior art further discloses several species and composition comprising the same which reads on the instant claims (Claims 1, 30 and 170). For instance,

137  458.3, 3.01 Min

138  424.2, 2.65 Min

(page 106, table 3) meets limitations of the instant claims 1, 2 and 18 when X =OCR6R7; R6=R7=H; R1=halo; n=2; Y=phenyl; R2=C1-C6 alkyl substituted with 1 R2a; R2a=(CR2eR2f)rORb; r=0; Rb=H; R3=halogen or hydrogen and m=0 or 1; p=2.

Ascertaining the differences between the prior art and the claims at issue

Asberom teaches genus of compounds which overlaps in scope with the instant claims. Further, the cited prior art teaches several species which are encompassed by the genus of the instant claims 1 and 2. However, species taught by the cited prior art with regard to instant

claims 3-8, 10, 12 and 14 differs with respect to as being positional isomer with respect to position of R1, R1a, R1b and/or size of the heterocyclic ring Q.

Resolving the level of ordinary skill in the pertinent art

With regard to the above difference of scope- Since examples of species or subgenus taught by the cited prior art are structurally similar to that claimed, it would have been obvious to a person of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *Deuel,* 51 F.3d at 1558, 34 USPQ2d at 1214. "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

In addition, Compounds which are position isomers (in instant application tert-butyl as elected species vs. sec-butyl in the cited prior art) (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In reWilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers *prima facie* obvious).

Thus with the guidance provided by **Asberom**, it would have been *prima facie* obvious to a person of ordinary skill in the art to make chemically similar compounds and arrive at the instant invention. This is because the person of ordinary skill would reasonably expect that the compounds chemically similar to the compounds taught by **Asberom** will function in similar manner.

Considering objective evidence present in the application indicating obviousness or nonobviousness

To establish a prima facie case of obviousness, three basic criteria must be met: (1) the prior art reference must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (3) there must be a reasonable expectation of success; and (MPEP § 2143).

In this case, **Asberom** teaches genus of compounds which overlaps in scope with the instant claims. Further, the cited prior art teaches several species which are encompassed by the genus of the instant claims 1 and 2.

In KSR International Vo. V. Teleflex Inc., 82 USPQ2d (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (Id. At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (Id. At 1395). See MPEP 2143 - Examples of Basic Requirements of a Prima Facie Case of Obviousness [R-9].

In this case at least prong (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success would apply.

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103."KSR, 550 U.S. at ___, 82 USPQ2d at 1397. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. Further, there is a reasonable expectation that the compounds chemically similar to the compounds taught by **Asberom** will function in similar manner.

Therefore, it would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention by taking the advantage of the teaching of the above cited references and to make the instantly claimed compounds with a reasonable expectation of success.

Allowable subject Matter

Elected species and claim 16, present allowable subject matter over the prior art on record.

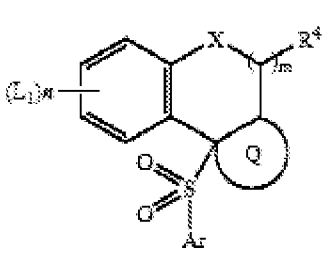
Reasons for Allowance

The following is an Examiner's statement of reasons for indicating allowable subject matter:

Applicant's elected species and compounds of formula (I) with R2 as in the instant claim 16 are novel and unobvious over the prior art of record. None of the prior art of record disclose

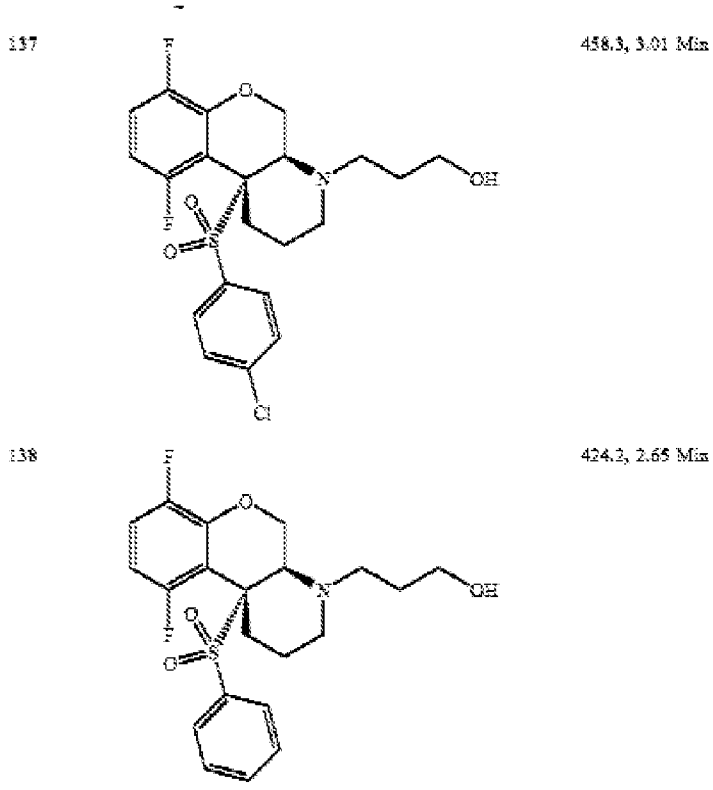
or teach applicant's elected species and compounds of formula (I) with R2 as in the instant claim 16. The closest prior art, **Asberom (US 20070197581 A1)** teaches compound of formula:

30. The compound of claim 1 having the formula (IF):



(IF)

and species:



137 458.3, 3.01 Min

138 424.2, 2.65 Min

which are different with respect to R2 group substitution on heterocyclic ring Q of the cited prior art. Further, the cited prior art would not suggest nor motivate to a person of ordinary skill in the art to make elected species or compound of formula (I) with R2 as in the instant claim 16.

Objection

Claim **16 is** objected to as being dependent upon a rejected base claim **1**, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PANCHAM BAKSHI whose telephone number is (571)270-3463. The examiner can normally be reached on Monday through Thursday 8-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SAJJADI FEREYDOUN can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PANCHAM BAKSHI/
Primary Examiner, Art Unit 1671

Notice of Allowability	Application No. 15/148,209	Applicant(s) DUAN ET AL.	
	Examiner PANCHAM BAKSHI	Art Unit 1671	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *04/11/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *6-18*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/PANCHAM BAKSHI/ Primary Examiner, Art Unit 1671	06/01/2017

DETAILED ACTION

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's Remarks and amendment, in the reply filed on 04/11/2017 is acknowledged.

Status of the Application

Claims 6-18 have been amended and claims 1-5 have been canceled by the amendment dated 04/11/2017. Accordingly, Claims **6-20** are pending, of which claims **19 and 20** are withdrawn because of earlier restriction and election **without traverse**.

Withdrawn Rejections

The rejections made under 35USC § 112 (b) in office action dated 02/01/2017 is hereby withdrawn in view of Applicant's canceling of claims 1-5 and amendment of claim 10 with respect to Markush format. Further, the rejections made under 35USC § 102 in office action dated 02/01/2017 is hereby withdrawn in view of Applicant's canceling of claims 1 and 2 amendment of claim 18 which is not anticipated by the prior art of record. Further, the rejections made under 35USC § 103 in office action dated 02/01/2017 is hereby withdrawn in view of Applicant's canceling of claims 1-5 amendment of claims 6-18 and applicant's remarks which are found persuasive.

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

In the Claims

Claims 19 and 20 have been canceled.

Rejoinder

The **election of species requirement (A) for Group I**, as set forth in the Office action mailed on 10/14/2016, has been reconsidered and **is hereby withdrawn.**

In view of the above noted withdrawal of **the election of species requirement**, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

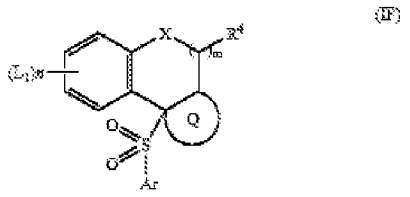
Reasons for Allowance

Applicant's Remarks and amendment filed on 04/11/2017, has been fully considered and is found persuasive.

The following is an Examiner's statement of reasons for allowance:

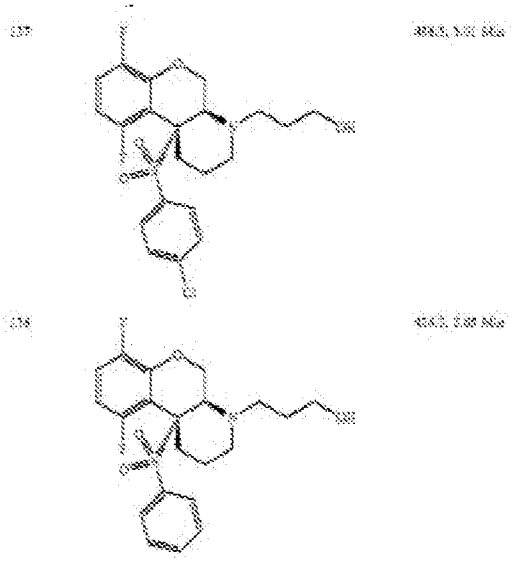
Applicant's compound of formula as in the instant claims is novel and unobvious over the prior art of record. None of the prior art of record disclose or teach applicant's compound of formula as in the instant claims. The closest prior art, **Asberom (US 20070197581 A1)** teaches compound of formula:

30. The compound of claim 1 having the formula (IF):



(IF)

and species:



which are different with respect to size of the heterocyclic ring Q of the instant claims. Further, among hundreds of compounds disclosed by the cited prior art, Q ring is 6 membered in all of the compounds and thus different from pyrrolidine ring of the instant claims. Further**,** the cited prior art would not suggest nor motivate to a person of ordinary skill in the art to select compound with pyrrolidine ring as in the instant claims.

Therefore, claims **6-18** are allowed.

Conclusion

Claims **6-18** are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PANCHAM BAKSHI whose telephone number is (571)270-3463. The examiner can normally be reached on Monday through Thursday 8-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SAJJADI FEREYDOUN can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PANCHAM BAKSHI/
Primary Examiner, Art Unit 1671