

TRICYCLIC SULFONES AS ROR γ MODULATORS

FIELD OF THE INVENTION

This invention relates to modulators of the retinoid-related orphan receptor ROR γ 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, ROR α , ROR β , and ROR γ , 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 .

ROR γ is expressed in several tissues including the thymus, kidney, liver, and muscle. Two isoforms of ROR γ have been identified: ROR γ 1 and ROR γ 2 (also known, respectively, as ROR γ and ROR γ t). 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 ROR γ t is restricted to lymphoid cell types including CD4+CD8+ thymocytes, IL-17 producing T helper (Th17) cells, lymphoid tissue inducer (LTi) cells, and $\gamma\delta$ cells. ROR γ t is essential for the development of lymph nodes and Peyer's patches and for the normal differentiation of Th17, $\gamma\delta$, 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 ROR γ + 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. ROR γ directly regulates IL-17 transcription and disruption of ROR γ 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 ROR γ 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.

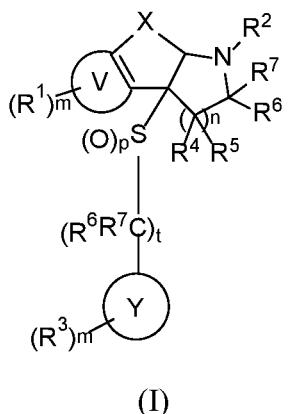
Each of the references in this Background section is hereby incorporated herein by reference in its entirety for all purposes.

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 ROR γ as targets in murine disease models, compounds capable of modulating ROR γ activity are

contemplated to provide a therapeutic benefit in the treatment of multiple immune and inflammatory disorders.

SUMMARY OF THE INVENTION

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



or pharmaceutically acceptable salts thereof, wherein all substituents are defined herein.

10 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.

15 In another aspect, the invention comprises methods for modulating ROR γ 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*.

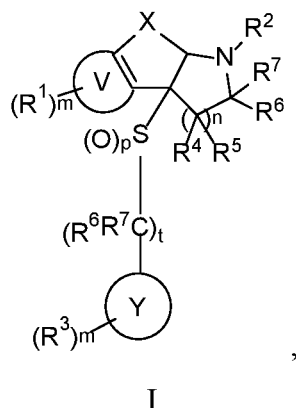
20 In another aspect, the invention comprises methods for treating a subject suffering from a disease or disorder modulated by ROR γ , the method comprising administering to a subject a therapeutically effective amount of a compound according to formula (I), stereoisomeric form, pharmaceutically acceptable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

25 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.

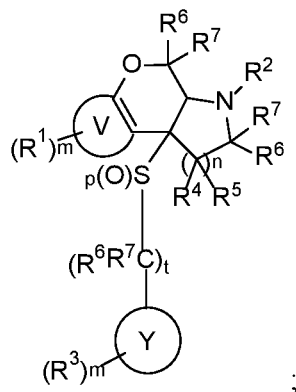
DETAILED DESCRIPTION OF THE INVENTION

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



or a stereoisomer or pharmaceutically acceptable salt thereof, wherein

X is $-\text{CR}^4\text{R}^5-$, $-(\text{CR}^4\text{R}^5)_2$, $-\text{OCR}^6\text{R}^7-$, $-\text{S}(\text{O})_p\text{CR}^6\text{R}^7-$ or $-\text{NR}^6\text{CR}^6\text{R}^7-$; wherein when
10 X is $-\text{OCR}^6\text{R}^7-$, $-\text{S}(\text{O})_p\text{CR}^6\text{R}^7-$ or $-\text{NR}^6\text{CR}^6\text{R}^7-$; the structure contemplated, for e.g. when
X is $-\text{OCR}^6\text{R}^7-$, would be



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

15 R^1 is, independently at each occurrence, selected from hydrogen, CD_3 , halo, OCF_3 , CN, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl-OH}$, -alkoxyalkoxy (e.g. $-\text{O-CH}_2\text{CH}_2\text{OCH}_3$), $\text{S}(\text{O})_p(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{S}(\text{O})_p(\text{C}_1-\text{C}_6)\text{alkyl-OH}$, -thioalkoxyalkoxy (e.g. $-\text{SCH}_2\text{CH}_2\text{OCH}_3$), $\text{NR}^{11}\text{R}^{11}$, $\text{C}_{1-6}\text{alkyl}$ substituted with 0-3 R^{1a} , $-(\text{CR}^{2e}\text{R}^{2f})\text{r}$ -3-14 membered carbocycle substituted with 0-3 R^{1a} and $-(\text{CR}^{2e}\text{R}^{2f})\text{r}$ -5-10 membered heterocycle comprising carbon
20 atoms, and 1-4 heteroatoms selected from N, O, and $\text{S}(\text{O})_p$ 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 ;

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 ;

5 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
10 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
15 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 ,
20 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
25 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
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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;

R⁴ and R⁵ are independently hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ haloalkyl, or

5 R⁴ and R⁵ together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R⁶ and R⁷ are independently hydrogen, C(=O)C₁₋₄ alkyl, C(=O)OC₁₋₄ alkyl, C₁₋₆ alkyl or C₁₋₆ haloalkyl; or

R⁶ and R⁷ taken together are =O;

10 R¹¹ is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3 R^f, CF₃, C₃₋₁₀ 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 R¹¹ and a second R¹¹, both attached to the same nitrogen atom, combine to
15 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, OCF₃, CF₃, CHF₂, CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -
20 (CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^f, C₁₋₆ haloalkyl, C₂₋₆ alkenyl substituted with 0-3 R^e, C₂₋₆ 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;

25 R^b is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3 R^d, C₁₋₆ haloalkyl, C₃₋₆ 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;

30 R^c is, independently at each occurrence, C₁₋₆ alkyl substituted with 0-3 R^f, -(CR^{2e}R^{2f})_r-C₃₋₆ 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

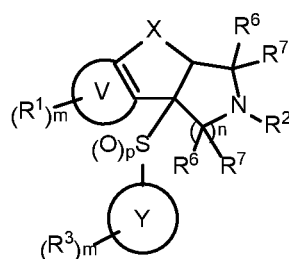
n is 0, 1 or 2;

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

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

t is 0 or 1.

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



(II)

or pharmaceutically acceptable salts thereof, wherein

R^1 is, independently at each occurrence, selected from halo, OCF_3 , CN, $-O(C_{1-6})$ alkyl, $-O(C_{1-6})$ alkyl-OH, -alkoxyalkoxy, S(O)_p(C_{1-6})alkyl, -S(O)_p(C_{1-6})alkyl-OH,

-thioalkoxyalkoxy (e.g. $-\text{SCH}_2\text{CH}_2\text{OCH}_3$), $\text{NR}^{11}\text{R}^{11}$, C_{1-6} alkyl substituted with 0-3 R^{1a} , $-(\text{CR}^{2e}\text{R}^{2f})_{r-3-14}$ membered carbocycle substituted with 0-3 R^{1a} and $-(\text{CR}^{2e}\text{R}^{2f})_{r-5-10}$ membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $\text{S}(\text{O})_p$ substituted with 0-3 R^{1a} ;

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

- R^2 is selected from hydrogen, $-(\text{CR}^{2e}\text{R}^{2f})_{r-1}\text{C}(\text{O})\text{R}^{2d}$, $-(\text{CR}^{2e}\text{R}^{2f})_{r-1}\text{C}(\text{O})\text{OR}^{2b}$, $-(\text{CR}^{2e}\text{R}^{2f})_{r-1}\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_{r-1}\text{S}(\text{O})_2\text{R}^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a} , C_{2-6} alkenyl substituted with 0-3 R^{2a} , $-(\text{CR}^{2e}\text{R}^{2f})_{r-3-10}$ membered carbocycle substituted with 0-4 R^a , and $-(\text{CR}^{2e}\text{R}^{2f})_{r-4-7}$ membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, and $\text{S}(\text{O})_p$ substituted with 0-3 R^a ;

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

- R^{2b} is, independently at each occurrence, hydrogen, CF_3 , $-(\text{CR}^{2e}\text{R}^{2f})_q\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{S}(\text{O})_p\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_{r-1}\text{C}(\text{O})\text{R}^{1d}$, $-(\text{CR}^{2e}\text{R}^{2f})_{r-1}\text{C}(\text{O})\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{OC}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_{r-1}\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{R}^{1c}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{OR}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{S}(\text{O})_2\text{R}^c$, 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, and $S(O)_p$ substituted with 0-2 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, and $S(O)_p$, substituted with 0-3 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 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, 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)NR¹¹R¹¹, -(CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, -
 (CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₁₋₆ 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
 5 substituted with 0-3 R^a;

R⁴ and R⁵ are independently hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ haloalkyl, or

R⁴ and R⁵ together with the carbon atom to which they are attached form a 3- to 6-
 membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R⁶ and R⁷ are independently hydrogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

10 R¹¹ is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3
 R^f, CF₃, C₃₋₁₀ 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, and S(O)_p substituted with 0-3 R^d;

or one R¹¹ and a second R¹¹, both attached to the same nitrogen atom, combine to
 15 form a heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, and
 S(O)_p substituted with 0-3 R^d;

R^a is, independently at each occurrence, hydrogen, =O, halo, OCF₃, CF₃, CHF₂,
 CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -
 20 (CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -
 NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^f, C₁₋₆ haloalkyl, C₂₋₆ alkenyl substituted
 with 0-3 R^a, C₂₋₆ alkynyl substituted with 0-3 R^a, -(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;

25 R^b is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3
 R^d, C₁₋₆ haloalkyl, C₃₋₆ 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, and S(O)_p
 substituted with 0-3 R^f, or -(CR^{2e}R^{2f})_r-6-10 membered carbocycle substituted with 0-3
 R^d;

30 R^c is, independently at each occurrence, C₁₋₆ alkyl substituted with 0-3 R^f, -
 (CR^{2e}R^{2f})_r-C₃₋₆ 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 , $-OR^e$, $-(CR^{2e}R^{2f})_r-C(O)R^c$, $-NR^eR^c$, $-NR^eC(O)OR^c$, $C(O)NR^eR^c$, $-NR^eC(O)R^c$, 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, and $S(O)_p$ substituted with 0-3 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 or $O(C_{1-6}$ alkyl);

or R^f is, independently at each occurrence, an optionally substituted $-(CR^{2e}R^{2f})_r$ -5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, 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);

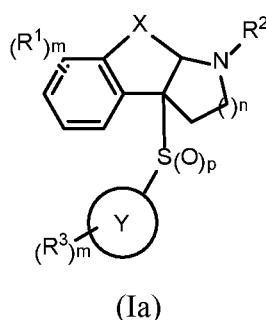
m is 0, 1, 2 or 3

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.

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



wherein

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

(CR^{2e}R^{2f})_qS(O)₂N R¹¹R¹¹, -(CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-2 R^a, C₁₋₆ 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)_n substituted with 0-4 R^a;

5 R^{2c} is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₃₋₁₀ cycloalkyl substituted with 0-3 R^a, C₆₋₁₀ 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;

10 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 ;

15 R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C₁₋₆ alkyl;

R³ is, independently at each occurrence, selected from hydrogen, halo, N₃, CN, -
(CR^{2c}R^{2f})r-OR^{3b}, -(CR^{2c}R^{2f})r-NR¹¹R¹¹, C₁₋₆ alkyl substituted with 0-3 R^{3a}, C₃₋₁₀
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 R³ 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 , $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-$
25 $C(O)OR^b$, $-(CR^{2e}R^{2f})_r-OC(O)R^b$, $-(CR^{2e}R^{2f})_r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})_r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, 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
30 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, CF₃, -(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, -

$(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C(O)NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C(O)R}^{1c}$, -
 $(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C(O)OR}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C(O)NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{S(O)}_2\text{NR}^{11}\text{R}^{11}$, -
 $(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{S(O)}_2\text{R}^c$, C_{1-6} alkyl substituted with 0-3 R^a , C_{1-6} haloalkyl, $-(\text{CR}^{2e}\text{R}^{2f})_r$ -3-14
 membered carbocycle substituted with 0-3 R^a , or $-(\text{CR}^{2e}\text{R}^{2f})_r$ -5-7 membered heterocycle
 5 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;

10 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 , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -phenyl substituted with 0-3
 R^d , or $-(\text{CR}^{2e}\text{R}^{2f})_r$ -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 ;

15 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, $=\text{O}$, halo, OCF_3 , CF_3 , CHF_2 ,
 CN , NO_2 , $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-S(O)}_p\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C(O)R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-}$
 20 C(O)OR^b , $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-OC(O)R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C(O)NR}^{11}\text{R}^{11}$, -
 $(\text{CR}^{2e}\text{R}^{2f})_r\text{-NR}^b\text{C(O)R}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-NR}^b\text{C(O)OR}^c$, $-\text{NR}^b\text{C(O)NR}^{11}\text{R}^{11}$, $-\text{S(O)}_p\text{NR}^{11}\text{R}^{11}$, -
 $\text{NR}^b\text{S(O)}_p\text{R}^c$, 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 , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -3-14 membered carbocycle,
 or $-(\text{CR}^{2e}\text{R}^{2f})_r$ -5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms
 25 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 , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -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 $-(\text{CR}^{2e}\text{R}^{2f})_r$ -6-10 membered carbocycle substituted with
 30 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,
5 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 ;

10 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), $N(C_{1-6} \text{ alkyl})_2$, $SO_2(C_{1-6} \text{ alkyl})$, CO_2H , $CO_2(C_{1-6} \text{ alkyl})$, OH, C_{3-6} cycloalkyl, CF_3 ;
15 $O(C_{1-6} \text{ alkyl})$; 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);

20 m is 0, 1, 2 or 3

n is 0, 1 or 2;

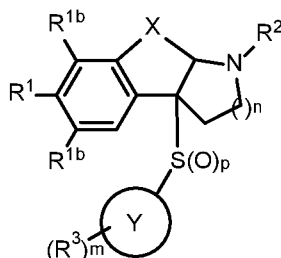
p and q are, independently at each occurrence, 0, 1, or 2; and

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

or a stereoisomer or pharmaceutically-acceptable salt thereof.

25

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



wherein

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

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

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

R^{1b} is, independently at each occurrence, hydrogen, CD_3 , halo, CF_3 , and $\text{C}_1\text{-C}_4$ alkyl;

20 R^2 is selected from hydrogen, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{R}^{2d}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{OR}^{2b}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{S}(\text{O})_2\text{R}^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a} , C_{2-6} alkenyl substituted with 0-3 R^{2a} , $-(\text{CR}^{2e}\text{R}^{2f})_{r-3-10}$ membered carbocycle substituted with 0-3 R^a , and $-(\text{CR}^{2e}\text{R}^{2f})_{r-4-7}$ membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from N, O, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_p$ substituted with 0-4 R^a ;

25 R^{2a} is, independently at each occurrence, hydrogen, $=\text{O}$, halo, OCF_3 , CN, NO_2 , $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{S}(\text{O})_p\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{OC}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{OC}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{OC}(\text{O})\text{OR}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{NR}^b\text{C}(\text{O})\text{R}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{NR}^b\text{C}(\text{O})\text{OR}^c$, $-\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-\text{S}(\text{O})_p\text{NR}^{11}\text{R}^{11}$, $-\text{NR}^b\text{S}(\text{O})_p\text{R}^c$, 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 , $-(\text{CR}^{2e}\text{R}^{2f})_{r-3-14}$ membered carbocycle substituted with 0-3 R^a , or $-(\text{CR}^{2e}\text{R}^{2f})_{r-4-7}$

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, CF₃, -(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,
 5 -(CR^{2e}R^{2f})_qOC(O)R^b, -(CR^{2e}R^{2f})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹,
 -(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)NR¹¹R¹¹, -
 (CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, -(CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-2 R^a, C₁₋₆
 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
 10 N, O, P(=O) and S(O)_p substituted with 0-4 R^a;

R^{2c} is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₃₋₁₀ cycloalkyl substituted with 0-3 R^a, C₆₋₁₀ 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;

15 R^{2d} is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-2 R^d, C₁₋₆ haloalkyl, C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C₃₋₁₀ 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
 20 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 C₁₋₆ alkyl;

R³ is, independently at each occurrence, selected from hydrogen, halo, N₃, CN, -(CR^{2e}R^{2f})_r-OR^{3b}, -(CR^{2e}R^{2f})_r-NR¹¹R¹¹, C₁₋₆ alkyl substituted with 0-3 R^{3a}, C₃₋₁₀ cycloalkyl substituted with 0-3 R^{3a}; and phenyl substituted with 0-3 R^{3a}, or 4-10
 25 membered heterocycle containing 1-4 heteroatoms selected from N, O, and S(O)_p, substituted with 0-3 R^{3a}, or two R³ 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, OCF₃, OCHF₂, CF₃, CHF₂, CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -
 30

(CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆ alkynyl substituted with 0-3 R^a, C₁₋₆ 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, CF₃, -(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})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(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)NR¹¹R¹¹, -(CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, -

(CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₁₋₆ 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;

R⁴ and R⁵ are independently hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ haloalkyl, or

R⁴ and R⁵ together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R⁶ and R⁷ are independently hydrogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

R¹¹ is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3 R^f, CF₃, C₃₋₁₀ 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 R¹¹ and a second R¹¹, 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, OCF₃, CF₃, CHF₂, CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^f, C₁₋₆ haloalkyl, C₂₋₆ alkenyl substituted with 0-3 R^e, C₂₋₆ alkynyl substituted with 0-3 R^e, -(CR^{2e}R^{2f})_r-3-14 membered carbocycle,

or $-(\text{CR}^{2e}\text{R}^{2f})_{r-5-7}$ 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, C₁₋₆ alkyl substituted with 0-3 R^d, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl substituted with 0-3 R^d, $-(\text{CR}^{2e}\text{R}^{2f})_{r-5-7}$ 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 $-(\text{CR}^{2e}\text{R}^{2f})_{r-6-10}$ membered carbocycle substituted with 0-3 R^d;

R^c is, independently at each occurrence, C₁₋₆ alkyl substituted with 0-3 R^f, $-(\text{CR}^{2e}\text{R}^{2f})_{r-3-6}$ cycloalkyl substituted with 0-3 R^f, or $-(\text{CR}^{2e}\text{R}^{2f})_{r-phenyl}$ substituted with 0-3 R^f;

R^d is, independently at each occurrence, hydrogen, =O, halo, OCF₃, CF₃, CN, NO₂, -OR^e, $-(\text{CR}^{2e}\text{R}^{2f})_{r-}\text{C}(\text{O})\text{R}^c$, -NR^eR^e, -NR^eC(O)OR^e, C(O)NR^eR^e, -NR^eC(O)R^e, CO₂H, CO₂R^c, -NR^eSO₂R^c, SO₂R^c, C₁₋₆ alkyl substituted with 0-3 R^f, C₃₋₆ cycloalkyl substituted with 0-3 R^f, $-(\text{CR}^{2e}\text{R}^{2f})_{r-phenyl}$ substituted with 0-3 R^f or $-(\text{CR}^{2e}\text{R}^{2f})_{r-5-7}$ 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, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, -5-7 membered heterocycle or $-(\text{CR}^{2e}\text{R}^{2f})_{r-phenyl}$ substituted with 0-3 R^f;

R^f is, independently at each occurrence, hydrogen, =O, halo, CN, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, SO₂(C₁₋₆ alkyl), CO₂H, CO₂(C₁₋₆ alkyl), OH, C₃₋₆ cycloalkyl, CF₃, O(C₁₋₆ alkyl); or an optionally substituted $-(\text{CR}^{2e}\text{R}^{2f})_{r-5-10}$ membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)_p, phenyl or C₃₋₆ cycloalkyl, each group optionally substituted with halo, CN, CF₃, C₁₋₆ alkyl or O(C₁₋₆ alkyl);

m is 0, 1, 2 or 3

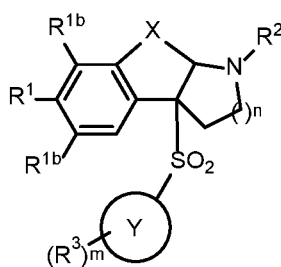
n is 0, 1 or 2;

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

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

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

R¹ is selected from halo, C₁₋₆ 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, CF₃, OCF₃, CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₁₋₆ haloalkyl, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆ 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, CD₃, halo, CF₃, and C₁-C₄ alkyl;

R² 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)NR¹¹R¹¹, -(CR^{2e}R^{2f})r-S(O)₂R^{2c}, C₁₋₆ alkyl substituted with 0-3 R^{2a}, C₂₋₆ 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)_n substituted with 0-4 R^a;

R^{2a} is, independently at each occurrence, hydrogen, =O, halo, OCF₃, CN, NO₂, - (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)NR¹¹R¹¹, -(CR^{2e}R^{2f})r-OC(O)OR^c, -(CR^{2e}R^{2f})r-

NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₁₋₆ haloalkyl, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆ 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, CF₃, -(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})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(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)NR¹¹R¹¹, -(CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, -(CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-2 R^a, C₁₋₆ 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, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₃₋₁₀ cycloalkyl substituted with 0-3 R^a, C₆₋₁₀ 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, C₁₋₆ alkyl substituted with 0-2 R^d, C₁₋₆ haloalkyl, C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C₃₋₁₀ 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 C₁₋₆ alkyl;

R³ is, independently at each occurrence, selected from hydrogen, halo, N₃, CN, -(CR^{2e}R^{2f})_r-OR^{3b}, -(CR^{2e}R^{2f})_r-NR¹¹R¹¹, C₁₋₆ alkyl substituted with 0-3 R^{3a}, C₃₋₁₀ 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 R³ 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, OCF₃, OCHF₂, CF₃, CHF₂, CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, - (CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆ alkynyl substituted with 0-3 R^a, C₁₋₆ 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, CF₃, -(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})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(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)NR¹¹R¹¹, -(CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, - (CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₁₋₆ 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;

R⁴ and R⁵ are independently hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ haloalkyl, or

R⁴ and R⁵ together with the carbon atom to which they are attached form a 3- to 6-membered spirocarbocyclyl ring or a spiroheterocyclyl ring;

R⁶ and R⁷ are independently hydrogen, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

R¹¹ is, independently at each occurrence, hydrogen, C₁₋₆ alkyl substituted with 0-3 R^f, CF₃, C₃₋₁₀ 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 R¹¹ and a second R¹¹, 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, OCF₃, CF₃, CHF₂, CN, NO₂, -(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, OCF₃, CF₃, CN, NO₂, $-OR^e$, $-(CR^{2e}R^{2f})_r-C(O)R^c$, $-NR^eR^e$, $-NR^eC(O)OR^c$, $C(O)NR^eR^e$, $-NR^eC(O)R^c$, CO₂H, CO₂R^c, $-NR^eSO_2R^c$, SO₂R^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, NH₂, NH(C_{1-6} alkyl), N(C_{1-6} alkyl)₂, SO₂(C_{1-6} alkyl), CO₂H, CO₂(C_{1-6} alkyl), OH, C_{3-6} cycloalkyl, CF₃, O(C_{1-6} alkyl), or

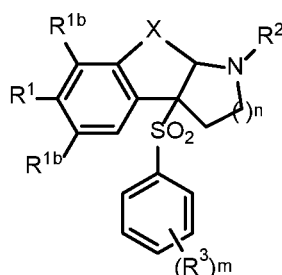
an optionally substituted $-(CR^{2e}R^{2f})_r$ -5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)_p, phenyl or C_{3-6} cycloalkyl, each group optionally substituted with halo, CN, CF₃, C_{1-6} alkyl or O(C_{1-6} alkyl);

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.

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



wherein

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

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

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

R^{1b} is, independently at each occurrence, hydrogen, CD_3 , halo, CF_3 , and $\text{C}_1\text{-C}_4$ alkyl;

25 R^2 is selected from hydrogen, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{R}^{2d}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{OR}^{2b}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r-\text{S}(\text{O})_2\text{R}^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a} , C_{2-6} alkenyl substituted with 0-3 R^{2a} , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -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, OCF₃, CN, NO₂, -
 (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, -
 5 (CR^{2e}R^{2f})_r-OC(O)R^b, -(CR^{2e}R^{2f})_r-OC(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-OC(O)OR^c, -(CR^{2e}R^{2f})_r-
 NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -
 NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₁₋₆
 haloalkyl, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆ 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
 10 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, CF₃, -(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})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹,
 15 -(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)NR¹¹R¹¹, -
 (CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, -(CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-2 R^a, C₁₋₆
 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, C₁₋₆ alkyl substituted with 0-3
 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₃₋₁₀ cycloalkyl substituted with 0-3 R^a, C₆₋₁₀ 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, C₁₋₆ alkyl substituted with 0-2
 25 R^d, C₁₋₆ haloalkyl, C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C₃₋₁₀ 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;

30 R^{2e} and R^{2f} are, independently at each occurrence, hydrogen, halogen or C₁₋₆ 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 ,
 5 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,
 10 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
 15 $S(O)_p$ 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 ;

20 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
 25 $S(O)_p$ 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 ;

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

an optionally substituted $-(\text{CR}^{2e}\text{R}^{2f})_r$ -5-10 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, P(=O) and S(O)_p, phenyl or C₃₋₆ cycloalkyl, each group optionally substituted with halo, CN, CF₃, C₁₋₆ alkyl or O(C₁₋₆ alkyl);

5 m is 0, 1, 2 or 3

n is 0, 1 or 2;

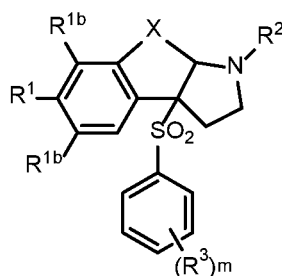
p and q are, independently at each occurrence, 0, 1, or 2; and

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

or a stereoisomer or pharmaceutically-acceptable salt thereof.

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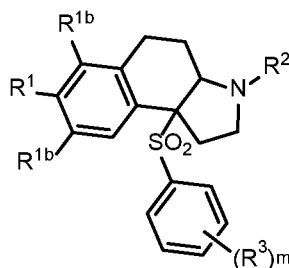
In a 6th aspect, the invention comprises compounds of the formula



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or a stereoisomer or pharmaceutically-acceptable salt thereof.

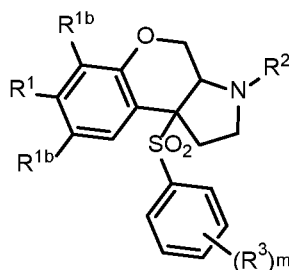
In a 7th aspect, the invention comprises compounds of the formula



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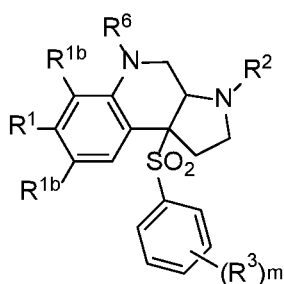
or a stereoisomer or pharmaceutically-acceptable salt thereof.

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



or a stereoisomer or pharmaceutically-acceptable salt thereof.

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



or a stereoisomer or pharmaceutically-acceptable salt thereof.

10

In a 10th aspect, the invention comprises compounds within any of the 7th, 8th or 9th 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

15 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 ;

20 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 ;

5 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 ;

10 R^3 is, independently at each occurrence, hydrogen, halo, N_3 , CN, OR^{3b} , $-NH_2$, $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, 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

20 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.

25 In an 11th 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 $-C(O)NR^{11}R^{11}$;

30 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, C₃₋₁₀ 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;

R³ is hydrogen, halo, cyclopropyl or C₁₋₆ alkyl;
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a 12th aspect, the invention comprises compounds within the 11th aspect,
wherein

R¹ is C₁₋₆ alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF₃, halo or C₁₋₆ alkyl substituted with 0-3 R^a;

R² is C₁₋₆ alkyl substituted with 0-3 R^{2a}, CO₂R^{2b}, -C(O)R^{2d} or -C(O)NR¹¹R¹¹;

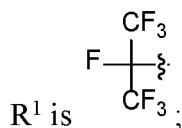
R^{2a} is hydrogen or C₁₋₆ alkyl substituted with 0-3 R^a;

R^{2b} is hydrogen, C₁₋₆ alkyl substituted with 0-2 R^a, C₃₋₆ 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, C₃₋₁₀ 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;

R³ is hydrogen, halo, cyclopropyl or C₁₋₆ alkyl;
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In a further aspect, the invention comprises compounds according to the 11th aspect, wherein



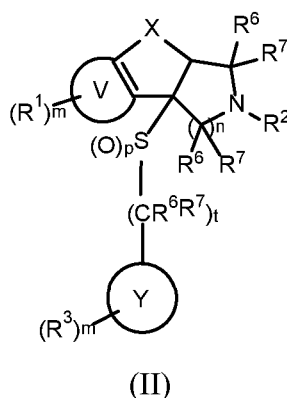
R² is -C(O)R^{2d};

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;

5 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:



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;

15 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 ;

20

25

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, OCF₃, CN, NO₂, $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})_r-OC(O)R^b$, $-(CR^{2e}R^{2f})_r-OC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-OC(O)OR^c$, $-(CR^{2e}R^{2f})_r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})_r-NR^bC(O)OR^c$, $NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, 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, CF₃, $-(CR^{2e}R^{2f})_qOR^b$, $-(CR^{2e}R^{2f})_qS(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^{1d}$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})_qOC(O)R^b$, $-(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, 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 C₁₋₆ alkyl;

R³ is, independently at each occurrence, selected from hydrogen, halo, N₃, CN, -
 5 (CR^{2e}R^{2f})_r-OR^{3b}, -(CR^{2e}R^{2f})_r-NR¹¹R¹¹, C₁₋₆ alkyl substituted with 0-3 R^{3a}, C₃₋₁₀
 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 R³ located on adjacent carbon atoms link to form a 5-7
 10 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, OCF₃, OCHF₂, CF₃,
 CHF₂, CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -
 15 (CR^{2e}R^{2f})_r-NR^bC(O)R^c, -(CR^{2e}R^{2f})_r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -
 NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆
 alkynyl substituted with 0-3 R^a, C₁₋₆ 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, CF₃, -(CR^{2e}R^{2f})_qOR^b, -
 20 (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})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(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)NR¹¹R¹¹, -(CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, -
 (CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₁₋₆ haloalkyl, -(CR^{2e}R^{2f})_r-3-14
 25 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;

R⁴ and R⁵ are independently hydrogen, halo, C₁₋₆ alkyl or C₁₋₆ haloalkyl, or

R⁴ and R⁵ together with the carbon atom to which they are attached form a 3- to 6-
 membered spirocarbocycl ring or a spiroheterocycl ring;

30 R⁶ and R⁷ are independently hydrogen, C₁₋₆ alkyl or C₁₋₆ 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 ;

5 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 0-3 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 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, $SO_2(C_{1-6} \text{ alkyl})$, CO_2H , $CO_2(C_{1-6} \text{ alkyl})$, OH, C_{3-6} cycloalkyl, CF_3 , $O(C_{1-6} \text{ alkyl})$, 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 $O(C_{1-6} \text{ alkyl})$;

m is 0, 1, 2 or 3

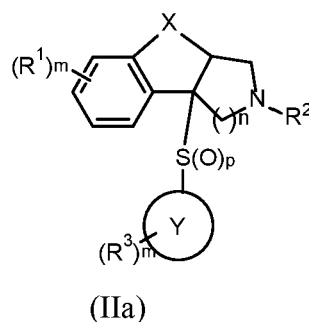
n is 1 or 2;

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



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, 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 , $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})_r-OC(O)R^b$, $-(CR^{2e}R^{2f})_r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r$ -

$\text{NR}^b\text{C}(\text{O})\text{R}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-NR}^b\text{C}(\text{O})\text{OR}^c$, $-\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-\text{S}(\text{O})_p\text{NR}^{11}\text{R}^{11}$, $-\text{NR}^b\text{S}(\text{O})_p\text{R}^c$, 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 , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -3-14 membered carbocycle substituted with 0-3 R^a , or $-(\text{CR}^{2e}\text{R}^{2f})_r$ -5-7 membered heterocycle comprising carbon atoms, and 1-4

5 heteroatoms selected from N, O, and $\text{S}(\text{O})_p$ substituted with 0-3 R^a ;

R^2 is selected from hydrogen, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{R}^{2d}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{OR}^{2b}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-S}(\text{O})_2\text{R}^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a} , C_{2-6} alkenyl substituted with 0-3 R^{2a} , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -3-10 membered carbocycle substituted with 0-3 R^a , and $-(\text{CR}^{2e}\text{R}^{2f})_r$ -4-7 membered heterocycle comprising carbon atoms, and 1-4

10 heteroatoms selected from N, O, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_p$ substituted with 0-4 R^a ;

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

20 R^{2b} is, independently at each occurrence, hydrogen, CF_3 , $-(\text{CR}^{2e}\text{R}^{2f})_q\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{S}(\text{O})_p\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{R}^{1d}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{OC}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{R}^{1c}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{OR}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{S}(\text{O})_2\text{R}^c$, C_{1-6} alkyl substituted with 0-2 R^a , C_{1-6} haloalkyl, $-(\text{CR}^{2e}\text{R}^{2f})_r$ -3-14 membered carbocycle substituted with 0-3 R^a , or $-(\text{CR}^{2e}\text{R}^{2f})_r$ -5-7 membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_p$ 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 $-(\text{CR}^{2e}\text{R}^{2f})_r$ -5-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_p$, 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

5 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} ;

10

R^{3a} is, independently at each occurrence, hydrogen, =O, halo, OCF₃, OCHF₂, CF₃, CHF₂, CN, NO₂, $-(CR^{2e}R^{2f})_r-OR^b$, $-(CR^{2e}R^{2f})_r-S(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^b$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})_r-OC(O)R^b$, $-(CR^{2e}R^{2f})_r-NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-NR^bC(O)R^c$, $-(CR^{2e}R^{2f})_r-NR^bC(O)OR^c$, $-NR^bC(O)NR^{11}R^{11}$, $-S(O)_pNR^{11}R^{11}$, $-NR^bS(O)_pR^c$, 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 ;

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R^{3b} is, independently at each occurrence, hydrogen, CF₃, $-(CR^{2e}R^{2f})_qOR^b$, $-(CR^{2e}R^{2f})_qS(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^{1d}$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})_qOC(O)R^b$, $-(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, 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

25

30 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);

10 m is 0, 1, 2 or 3

n is 1 or 2;

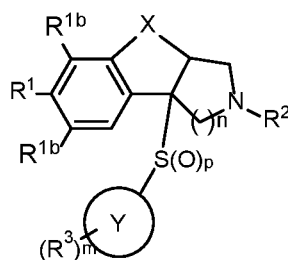
p and q are, independently at each occurrence, 0, 1, or 2; and

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

or a stereoisomer or pharmaceutically-acceptable salt thereof.

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In another aspect, the invention comprises compounds of the formula



20 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

25 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, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₃₋₁₀ cycloalkyl substituted with 0-3 R^a, C₆₋₁₀ 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, C₁₋₆ alkyl substituted with 0-2 R^d, C₁₋₆ haloalkyl, C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})r-C₃₋₁₀ 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 C₁₋₆ alkyl;

R³ is, independently at each occurrence, selected from hydrogen, halo, N₃, CN, -(CR^{2e}R^{2f})r-OR^{3b}, -(CR^{2e}R^{2f})r-NR¹¹R¹¹, C₁₋₆ alkyl substituted with 0-3 R^{3a}, C₃₋₁₀ 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 R³ 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, OCF₃, OCHF₂, CF₃, CHF₂, CN, NO₂, -(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-NR¹¹R¹¹, -(CR^{2e}R^{2f})r-C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})r-NR^bC(O)R^c, -(CR^{2e}R^{2f})r-NR^bC(O)OR^c, -NR^bC(O)NR¹¹R¹¹, -S(O)_pNR¹¹R¹¹, -NR^bS(O)_pR^c, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆ alkynyl substituted with 0-3 R^a, C₁₋₆ 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, CF₃, -(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})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})r-C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}, -

$(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{OR}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_q\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{11}$, -
 $(\text{CR}^{2e}\text{R}^{2f})_q\text{NR}^b\text{S}(\text{O})_2\text{R}^c$, C_{1-6} alkyl substituted with 0-3 R^a , C_{1-6} haloalkyl, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-3-14}$
 membered carbocycle substituted with 0-3 R^a , or $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-5-7}$ membered heterocycle
 comprising carbon atoms and 1-4 heteroatoms selected from N, O, and $\text{S}(\text{O})_p$ substituted
 5 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;

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

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

R^a is, independently at each occurrence, hydrogen, $=\text{O}$, halo, OCF_3 , CF_3 , CHF_2 ,
 CN , NO_2 , $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-S}(\text{O})_p\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-}$
 $\text{C}(\text{O})\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-OC}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-C}(\text{O})\text{NR}^{11}\text{R}^{11}$, -
 20 $(\text{CR}^{2e}\text{R}^{2f})_r\text{-NR}^b\text{C}(\text{O})\text{R}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-NR}^b\text{C}(\text{O})\text{OR}^c$, $-\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-\text{S}(\text{O})_p\text{NR}^{11}\text{R}^{11}$, -
 $\text{NR}^b\text{S}(\text{O})_p\text{R}^c$, 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 , $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-3-14}$ membered carbocycle,
 or $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-5-7}$ membered heterocycle comprising carbon atoms and 1-4 heteroatoms
 selected from N, O, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_p$ substituted with 0-4 R^f ;

25 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 , $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-5-7}$ membered
 heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, O, $\text{P}(=\text{O})$ and
 $\text{S}(\text{O})_p$ substituted with 0-4 R^f , or $-(\text{CR}^{2e}\text{R}^{2f})_r\text{-6-10}$ membered carbocycle substituted with
 0-3 R^d ;

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

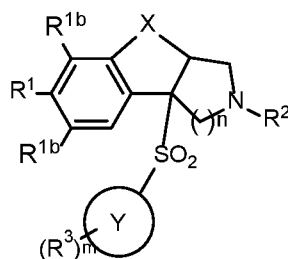
n is 1 or 2;

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

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

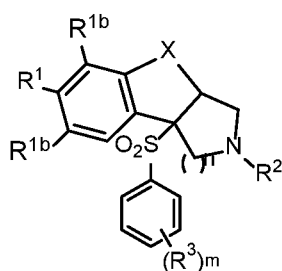
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

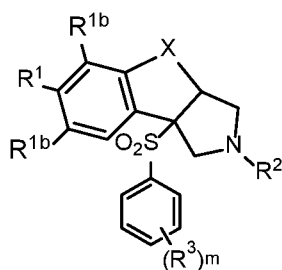
In another aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically acceptable salt thereof.

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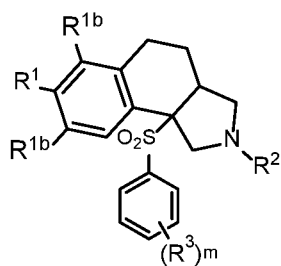
In another aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically acceptable salt thereof.

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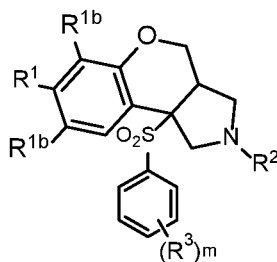
In another aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

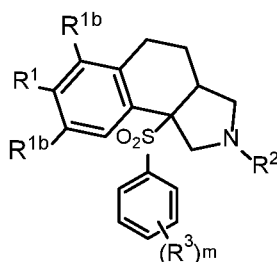
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In another aspect, the invention comprises compounds of the formula



or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



5

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

10 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

15 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 ;

20

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 ;

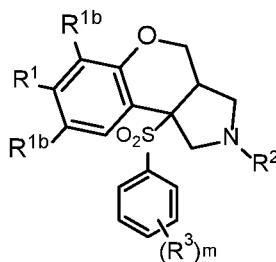
5 R^3 is, independently at each occurrence, hydrogen, halo, N_3 , CN, OR^{3b} , $-NH_2$, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl) $_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a} ;

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
15 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.

20 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} ;

25 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 ;

5 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 ;

10 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 ;

15 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 ;

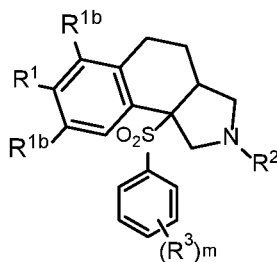
R^3 is, independently at each occurrence, hydrogen, halo, N_3 , CN, OR^{3b} , $-NH_2$, $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, C_{1-6} alkyl substituted with 0-3 R^{3a} or C_{3-10} cycloalkyl substituted with 0-3 R^{3a} ;

20 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 ;

30 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} ;

5 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 $-C(O)NR^{11}R^{11}$;

10 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 ;

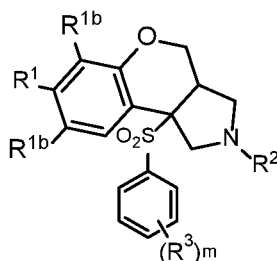
15 R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d , or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, $P(=O)$ and $S(O)_2$, substituted with 0-4 R^a ;

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

or a stereoisomer or pharmaceutically-acceptable salt thereof.

20

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 ;

5 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 $-C(O)NR^{11}R^{11}$;

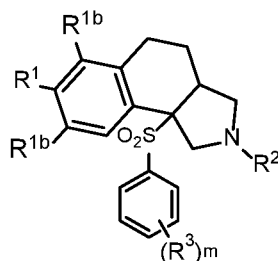
R^{2a} is hydrogen or C_{1-6} alkyl substituted with 0-3 R^a ;

10 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 ;

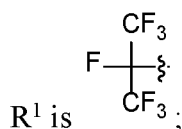
15 R^3 is hydrogen, halo or C_{1-6} alkyl;
or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



20

wherein



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

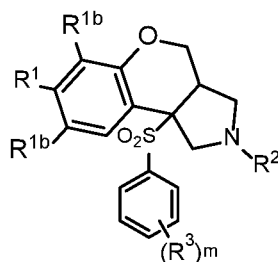
25 R^2 is $-C(O)R^{2d}$;

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 ;

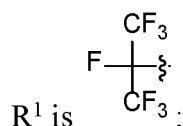
R^3 is F, Cl or methyl;

5 or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the invention comprises compounds of the formula



10 wherein



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

R^2 is $-C(O)R^{2d}$;

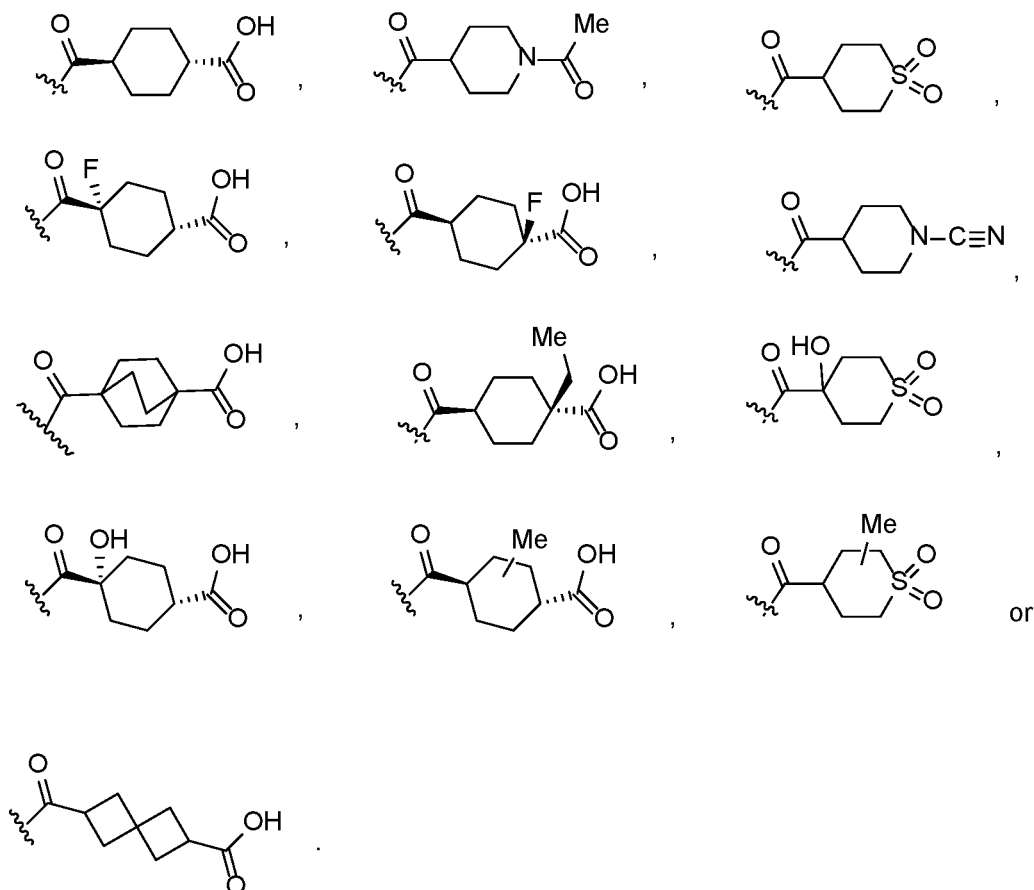
15 R^{2d} is, independently at each occurrence, C_{3-10} cycloalkyl substituted with 0-2 R^d , or a 4-10 membered heterocycle containing 1-4 heteroatoms selected from N, O, P(=O) and S(O)₂, substituted with 0-4 R^a ;

R^3 is F, Cl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

20

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:



According to different independent aspects, the present invention includes compounds of formula (I) or (II) wherein

5 $p=2$;

Y is a 6-membered aromatic ring, typically a phenyl;

X=-(CR⁴R⁵)₂-, -OCR⁶R⁷ or NR⁶CR⁶R⁷- wherein R⁴, R⁵, R⁶, R⁷ are defined above, or R⁴, R⁵, R⁶, R⁷ independently or together represent hydrogen.

10 In another aspect, the present invention includes compounds of formula (I) or (II)

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, wherein

R¹ is halo, phenyl substituted with 0-3 R^{1a}, or C₁₋₆ alkyl substituted with 0-3 R^{1a};

R^{1a} is, independently at each occurrence, hydrogen, CF₃, halo, C₁₋₆ alkyl

15 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 ;

5 R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-3 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, and $S(O)_p$ substituted with 0-3 R^a , or $-(CR^{2e}R^{2f})_r$ -phenyl substituted with 0-3 R^a ;

10 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, and $S(O)_p$, substituted with 0-3 R^a ;

15 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, and $S(O)_p$, substituted with 0-3 R^a ;

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

20 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 ;

30 or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the the present invention includes compounds of formula (I) or (II) , 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 0-3 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, and $S(O)_p$ substituted with 0-3 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, and $S(O)_2$, substituted with 0-3 R^a ;

R^3 is hydrogen, halo or C_{1-6} alkyl; or a stereoisomer or pharmaceutically-acceptable salt thereof.

In another aspect, the present invention includes compounds of formula (I) or (II) , wherein

R^1 is $\begin{array}{c} CF_3 \\ | \\ F-C- \\ | \\ CF_3 \end{array}$;

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, and $S(O)_2$, substituted with 0-3 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 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.

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

Another aspect of the invention is directed to the compounds, pharmaceutically acceptable salts thereof, tautomers or stereoisomers thereof and compositions according to the invention for use as a medicament.

10 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
15 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,
20 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,
25 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,
30 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
5 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
10 intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (*e.g.*, R³) 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 R³, then said group may optionally be substituted with up to two R³ groups and R³ at
15 each occurrence is selected independently from the definition of R³. 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
20 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
25 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
30 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, -CONH₂ 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, "C₁₋₁₀ alkyl" (or alkylene), is intended to include C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ alkyl groups. Additionally, for example, "C₁-C₆ 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, "C₂₋₆ alkenyl" (or alkenylene), is intended to include C₂, C₃, C₄, C₅, and C₆ 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, "C₂₋₆ alkynyl" (or

alkynylene), is intended to include C₂, C₃, C₄, C₅, and C₆ alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

One skilled in the field will understand that, when the designation "CO₂" is used

herein, this is intended to refer to the group $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—O—}$.

5 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(C₀₋₄)alkyl includes a substituted lower alkyl having at least one aryl
10 substituent and also includes an aryl directly bonded to another group, *i.e.*, aryl(C₀)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
15 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-C₁₋₆alkyl such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, *tert*-butoxy, pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-
20 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.

25 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
30 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

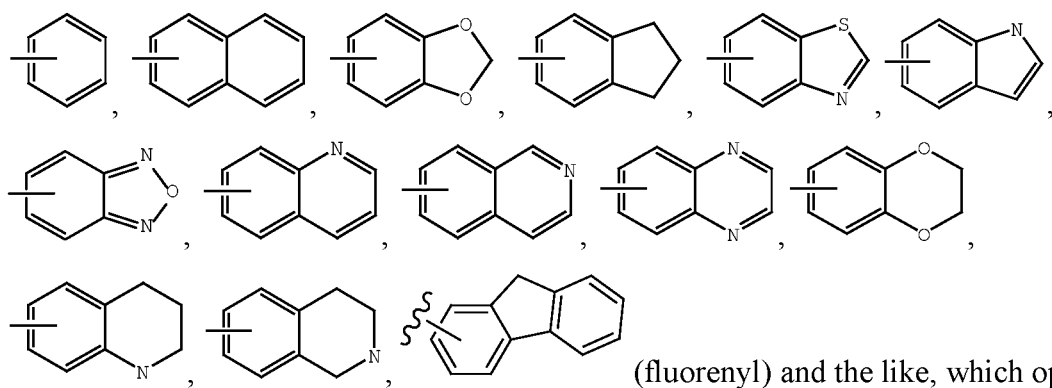
in the alkyl portion. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable
5 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
10 poly-cyclic ring systems. C₃₋₇ cycloalkyl is intended to include C₃, C₄, C₅, C₆, and C₇ cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, 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
15 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,
20 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
25 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.

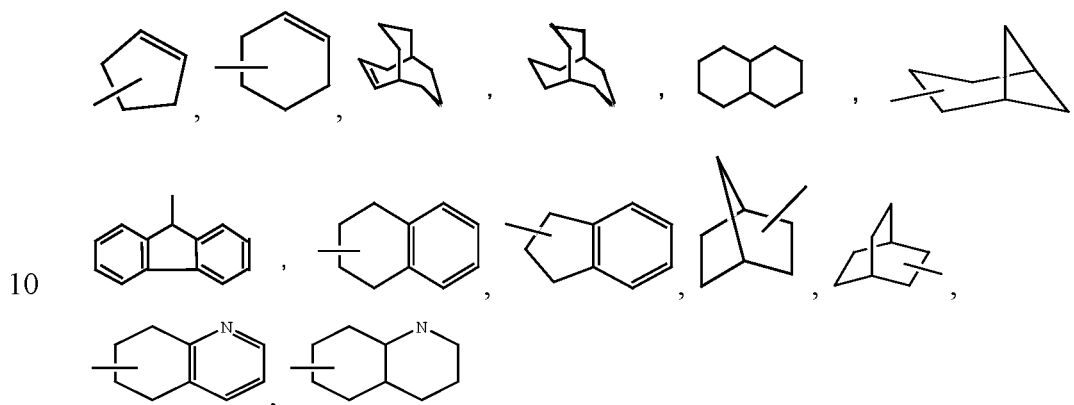
The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups
30 having 6 to 12 carbon atoms in the ring portion, such as phenyl, and naphthyl groups, each of which may be substituted.

Thus, examples of aryl groups include:



5 (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.

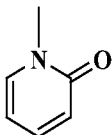
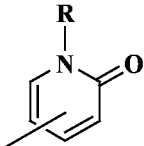
15 The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, di, and trifluoromethyl.

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

20 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 bicyclic 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 azetidiny, pyrrolidiny, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodiny, 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  and  ..

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 (O, 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).

5 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, 10 isoquinolinyl, benzimidazolyl, benzopyranyl, indoliziny, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxaliny, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl and the like.

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

15 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 20 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 25 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 30 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
5 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
10 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)
15 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
20 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,
25 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-
30 hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, 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-ephedrine, *N,N'*-dibenzylethylene-diamine, 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, pantoic, 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 C₁₋₆alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C₁₋₆alkanoyloxy-C₁₋₆alkyl, *e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C₁₋₆alkoxycarbonyloxy-C₁₋₆alkyl, *e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (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

5 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

10 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.

20 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

25 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

30

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.

5 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
10 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
15 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
20 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
25 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
30 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 µg/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
5 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 ROR γ receptors, relative to ROR γ receptors
10 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,
15 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 Jul;181(1):8-18; and A.M. Jetten, “Retinoid-related orphan receptors (RORs):
20 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,
25 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.,*
30 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., "ROR γ t drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation," *Nat.*

Immunol., 2011 Jun;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. Toussiot, "The IL23/Th17 pathway as a therapeutic target in chronic inflammatory diseases," *Inflamm. Allergy Drug Targets*, 2012 Apr;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., "ROR γ -expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F," *Gastroenterology*, 2009 Jan;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 ROR γ t under control of the CD2 promoter induces polyclonal plasmacytosis and autoantibody production in transgenic mice," *Eur. J. Immunol.*, 2012 Aug;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., "ROR γ t⁺ innate lymphocytes and $\gamma\delta$ 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 ROR γ t 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*

5 Oct;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*

10 Nov;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 Jul;18:1248-53,* which is hereby incorporated herein by reference in its
15 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
20 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
25 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.

30 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.

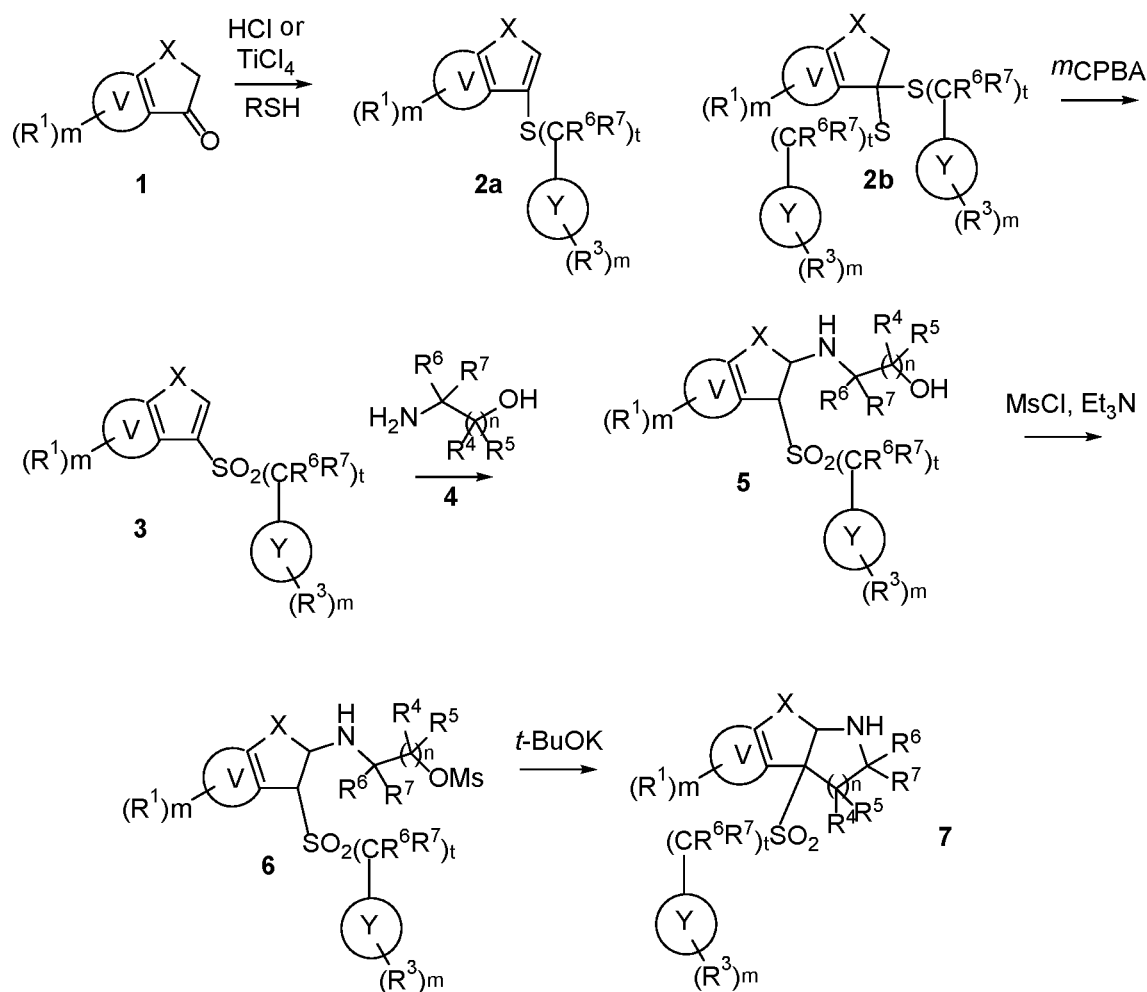
METHODS OF PREPARATION

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 TiCl₄ 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



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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

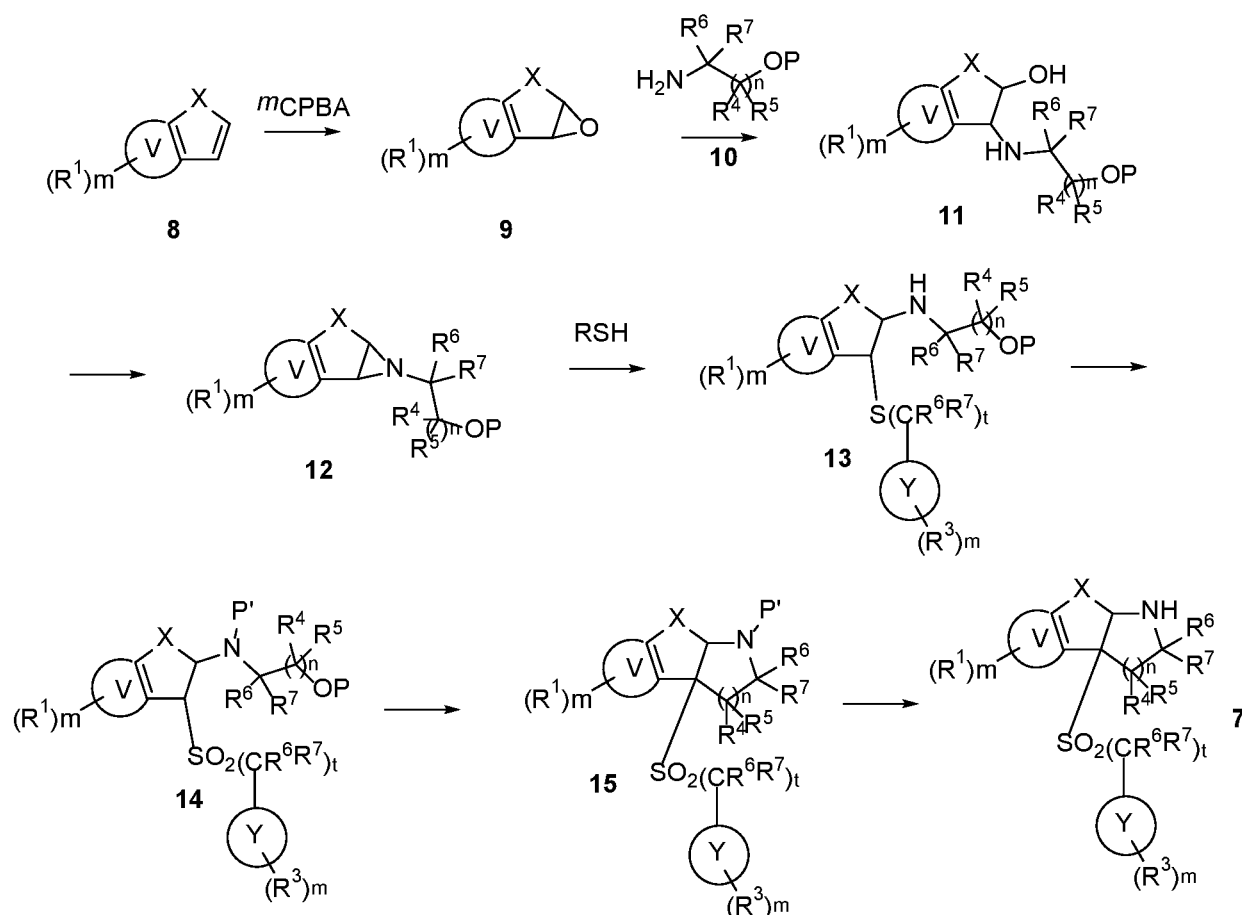
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acid, can provide the sulfone **14**. Selective removal of the alcohol protecting group, followed by conversion to the corresponding methanesulfonate and treatment with a base such as potassium *tert*-butoxide (as in Scheme 1) can provide **15**, which can be deprotected to provide the tricyclic amine **7**.

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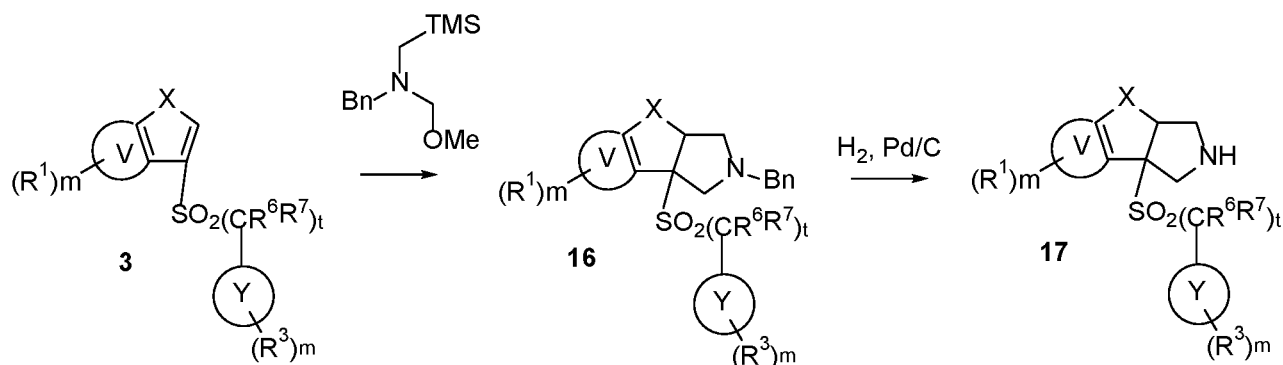
SCHEME 2



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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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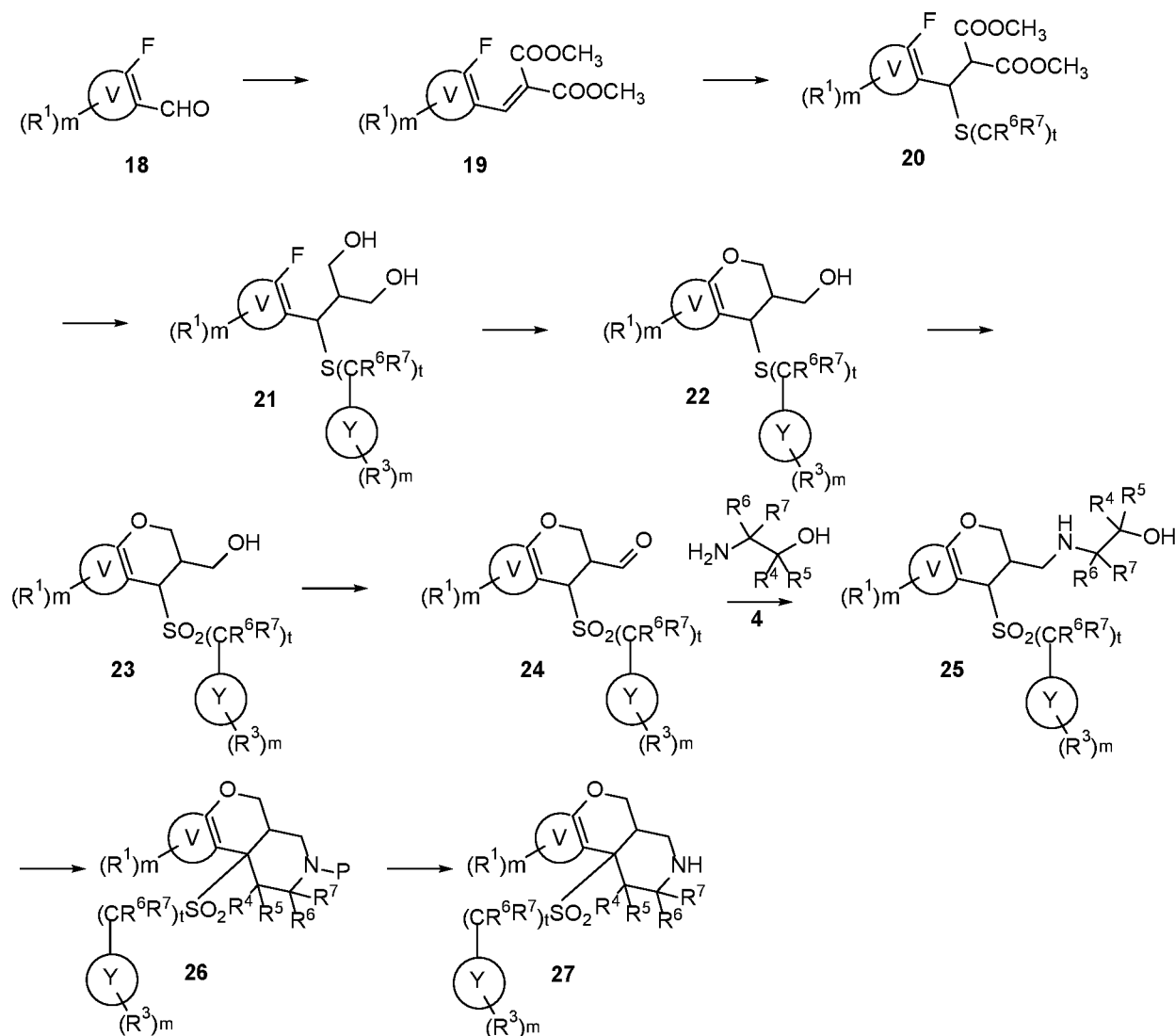
An approach to the synthesis of compounds of type **27** is shown in Scheme 4. An appropriate fluoro-substituted aldehyde **18** can be condensed with dimethyl malonate in the presence of an acid and base such as benzoic acid and piperidine to provide **19**. This compound can be reacted with an appropriate 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)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-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**.

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SCHEME 4



- 5 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
- 10 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.*

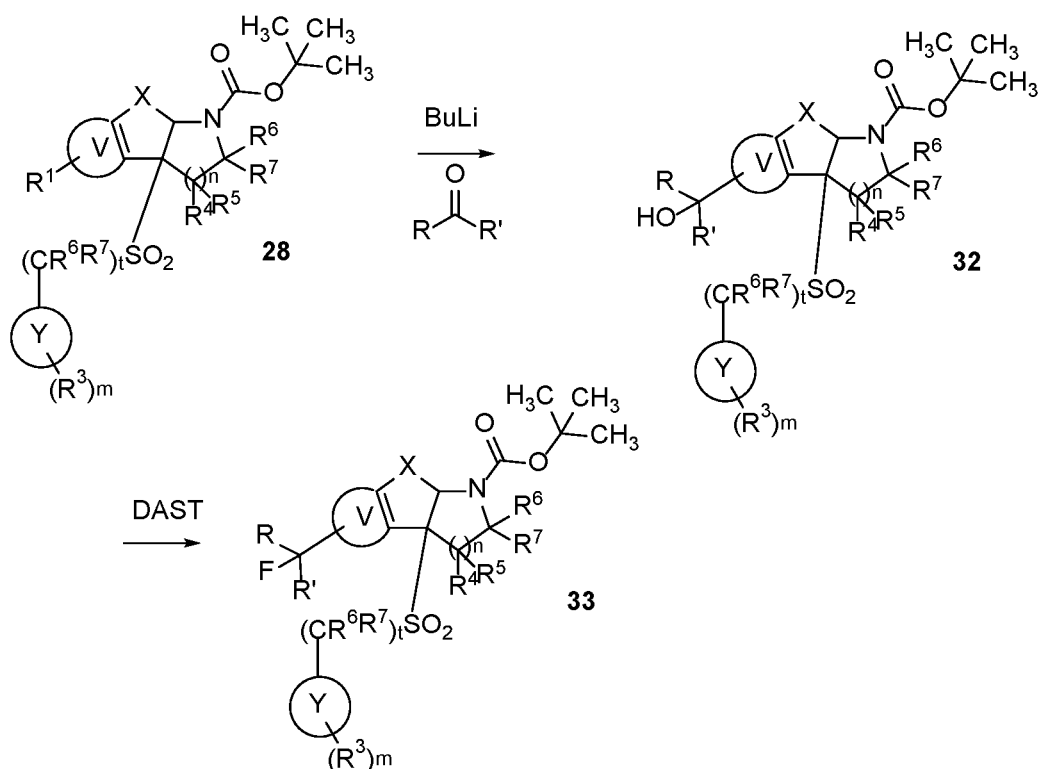
1999, 576, 147), to give **29** where R^{1'} can be aryl, heteroaryl or alkenyl (the latter of which can be further converted to the corresponding alkyl by catalytic reduction); (2) treatment with a zinc reagent such as zinc(II) cyanide or an alkyl- or cycloalkylzinc halide in the presence of a suitable 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 R¹ 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 R³ 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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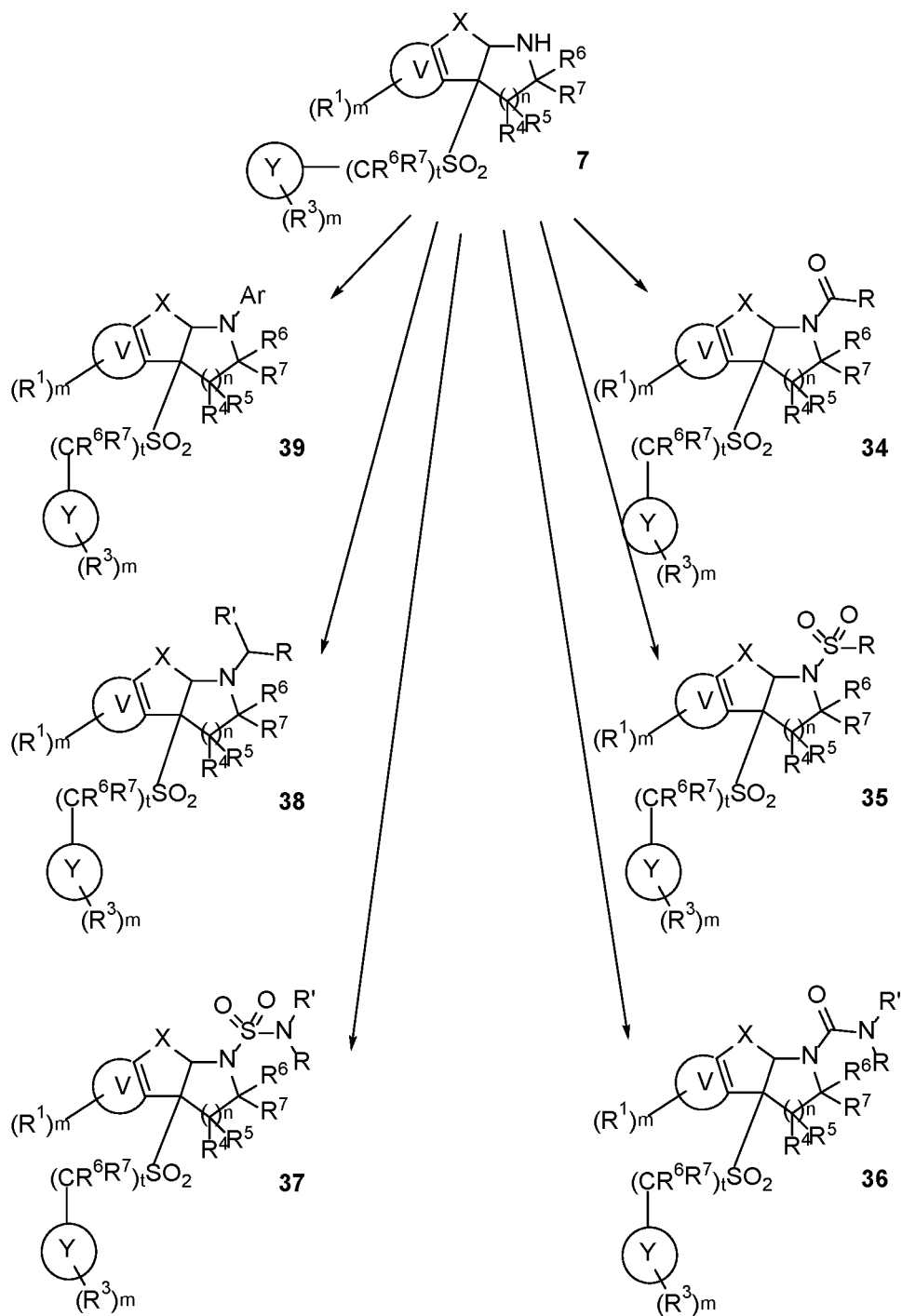
SCHEME 6



- 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 $\text{RC(=O)}_2\text{O}$ 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 $\text{RN(R')SO}_2\text{Cl}$ to provide a sulfamide **37**. An amine **7** can be treated with an appropriate substituted or unsubstituted alkyl halide, cycloalkyl halide, or arylalkyl halide
- 5 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
- 10 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 $\text{ArOS(=O)}_2\text{CF}_3$ 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,
- 15 2, 27; *Acc. Chem. Res.* 1998, 31, 805; *Angew. Chem. Int. Ed.* 2008, 47, 6338).

SCHEME 7

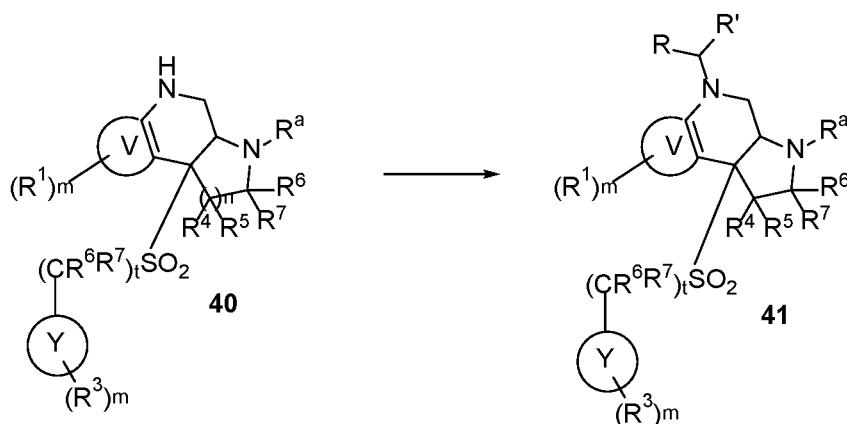


- A method for preparing certain compounds **41** is shown in Scheme 8. An amine
- 5 **40** can be treated with an aldehyde $RCHO$ or a ketone $RC(=O)R'$ in the presence of a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride to provide the alkylated amine **41**. Alternatively, an amine **40** can be treated with an alkyl chloride, alkyl bromide, alkyl iodide or other activated alkyl derivative 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.

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SCHEME 8



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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.

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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.

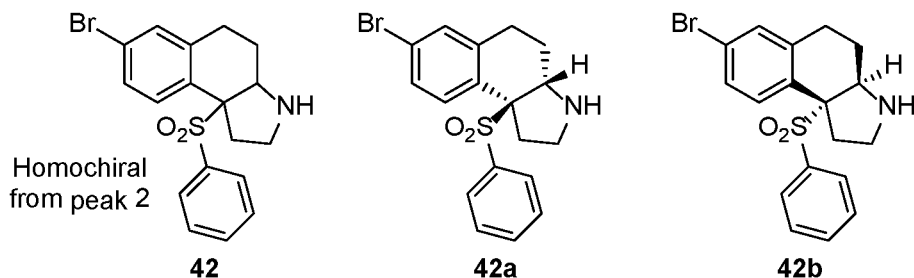
Examples

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.

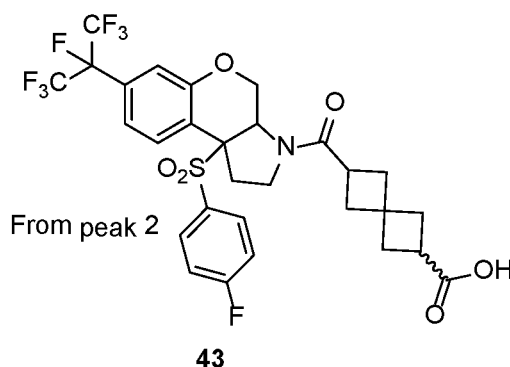
Heating of a reaction mixture via microwave irradiation was done in sealed vials using a Biotage® Initiator Microwave Synthesizer. Solvent removal was performed by concentration under reduced pressure. Column chromatography was generally performed using the flash chromatography technique (*J. Org. Chem.* 1978, 43, 2923), or with pre-packed 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.

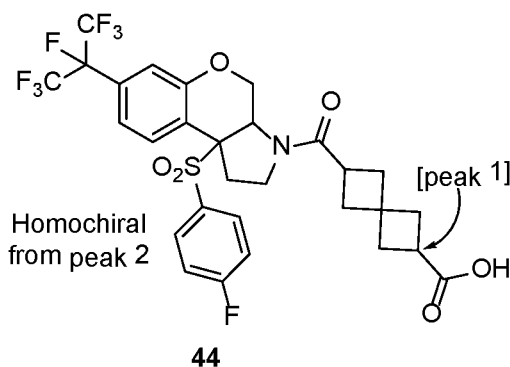
Many Intermediates and Examples are homochiral (entirely or mostly a single enantiomer), but in some cases the absolute configuration has not been proven. In those cases, a text notation to the left of the structure will indicate that the compound is homochiral, and indicates whether the compound was 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**.



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.



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**.



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:

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ABBREVIATION	NAME
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Boc	<i>tert</i> -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	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DMSO- <i>d</i> ₆	deuterated dimethyl sulfoxide
Et ₃ N	triethylamine
EtOAc	ethyl acetate
h	hours
HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
LCMS	liquid chromatography – mass spectrometry
MeCN	acetonitrile
MeOH	methanol
MeOH- <i>d</i> ₄	deuterated methanol
mCPBA	<i>meta</i> -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)

- 5 Column: Kinetex[®] XB-C₁₈ 3 x 75 mm, 2.6 μ 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 1mL/min; gradient 4.7 min.

Method B: (analytical)

- 10 Column: Acquity UPLC[®] BEH C₁₈ 2.1 x 50 mm, 1.7 μ 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)

- 15 Column: Acquity UPLC[®] BEH C₁₈ 2.1 x 50 mm, 1.7 μ 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; temperature: 50 °C; flow rate 1.0 mL/min; gradient: 0-100% B over 3 min, then 0.75 min isocratic at 100% B.

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Method D: (analytical)

- Column: Acquity UPLC[®] BEH C₁₈ 2.1 x 50 mm, 1.7 μ 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; temperature: 50 °C; flow rate 1.0 mL/min; gradient: 0-100% B over 3 min, then 0.75 min isocratic at 100% B.
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Method E: (preparative)

Column: XBridge™ C₁₈ 19 x 200 mm, 5 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; flow rate 20 mL/min; gradient: increasing B, then isocratic.

5 Method F: (preparative)

Column: XBridge™ C₁₈ 19 x 200 mm, 5 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; flow rate 20 mL/min; gradient: increasing B, then isocratic.

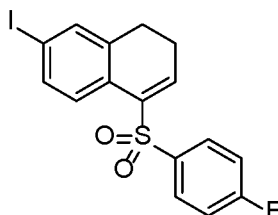
10 Method G: (preparative)

Column: Luna® C₁₈ 30 x 100 mm, 5 μm (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.

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Intermediate 1

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



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A solution of 6-iodo-3,4-dihydronaphthalen-1(2H)-one (13.3 g, 48.9 mmol) and TiCl₄ (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 Et₃N (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 x 250 mL). The combined organic layers were dried over Na₂SO₄, 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).

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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 ($\text{M}+\text{H}+\text{MeCN}$)⁺, 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).

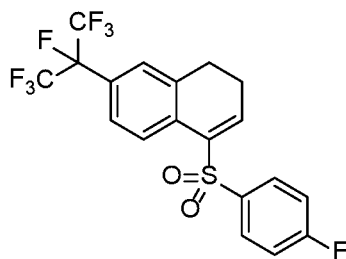
Alternative procedure:

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 x 125 mL), 0.5 M aqueous Na_2CO_3 (3 x 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 $\text{Na}_2\text{S}_2\text{O}_3$ (120 mL) for 5 min. The organic phase was separated, washed

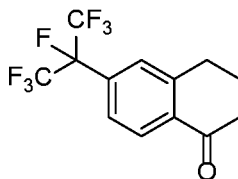
sequentially with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 120 mL), 10% aqueous Na_2CO_3 (3 x 200 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 0-20%) to give 4-((4-fluorophenyl)sulfonyl)-7-iodo-1,2-dihydronaphthalene (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

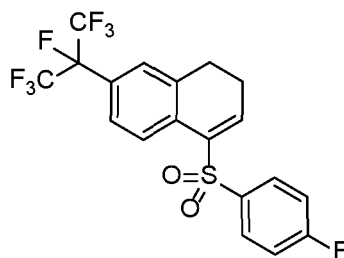


Activated copper was prepared by adding zinc dust (24.57 g, 376 mmol) portionwise with stirring to a solution of copper(II) sulfate (45.09 g, 283 mmol) in water (250 mL) over 10 min. The mixture was stirred 10 min longer, then the supernatant was decanted from the red precipitate. This was washed twice 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 Na₂SO₄ 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, CDCl₃) 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). ¹⁹F NMR (376 MHz, CDCl₃) δ -75.38 (d, *J*=7.2 Hz, 6F), -182.41 (septet, *J*=7.2 Hz, 1F).

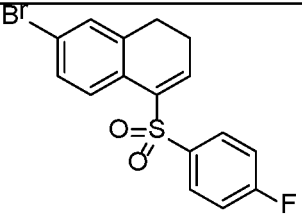
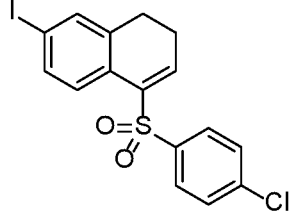
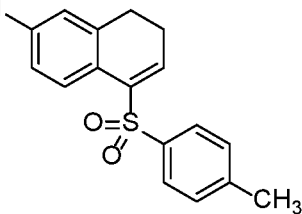
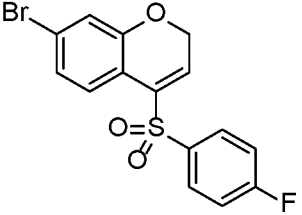
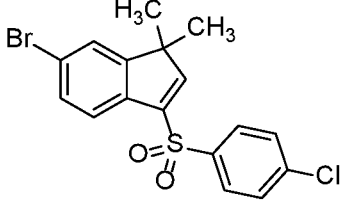
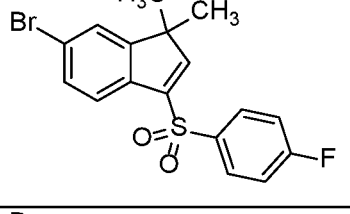
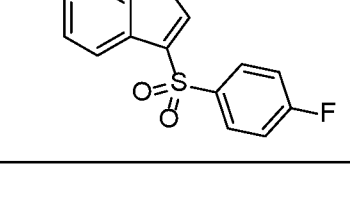
Step B: 4-(((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2-dihydronaphthalene

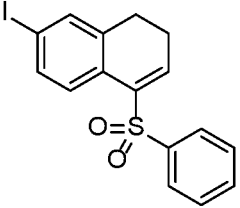
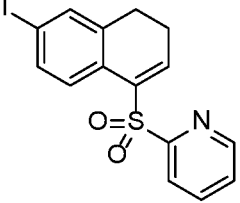
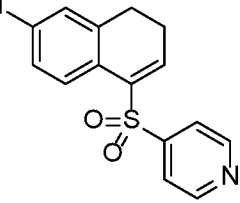
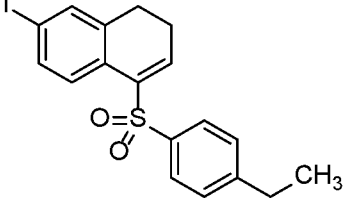
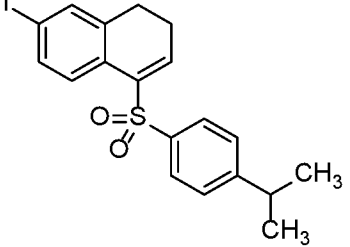
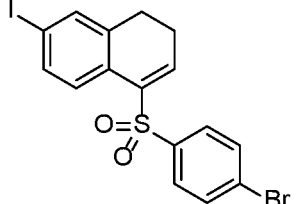
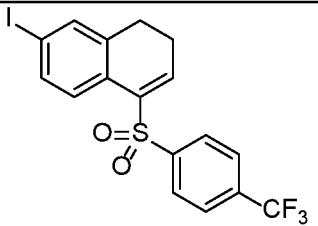


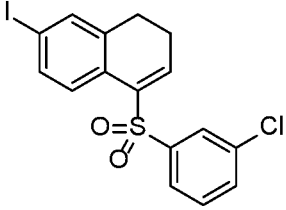
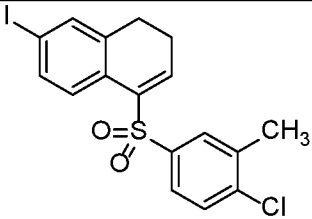
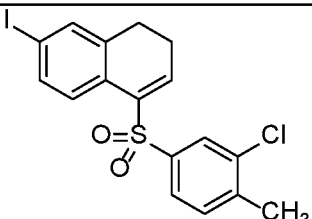
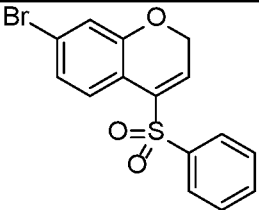
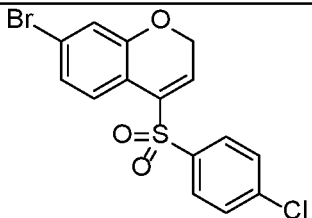
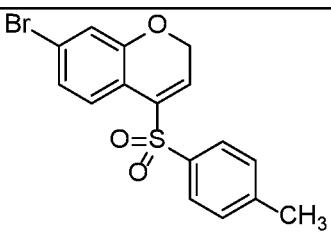
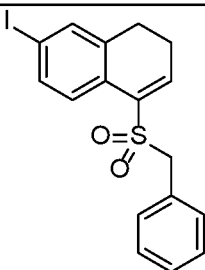
Following the alternative procedure used to prepare Intermediate 1, 6-(perfluoropropan-2-yl)-3,4-dihydronaphthalen-1(2H)-one was converted into 4-(((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2-dihydronaphthalene in quantitative yield, with minor impurities present, and was used without further purification. LCMS *m/z* 457.3 (M+H)⁺, HPLC *t_R* 1.12 min (method B). ¹H NMR (400 MHz, CDCl₃) 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).

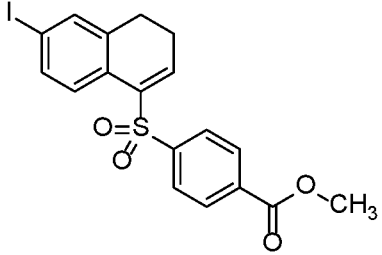
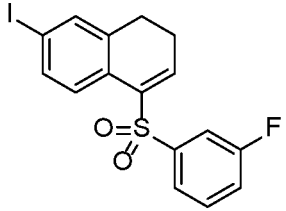
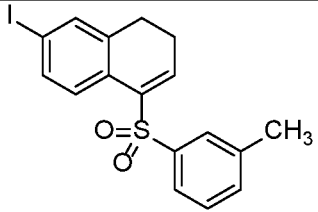
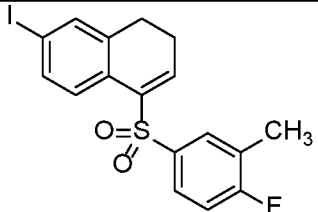
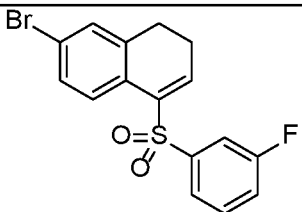
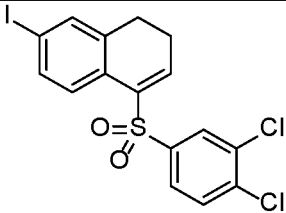
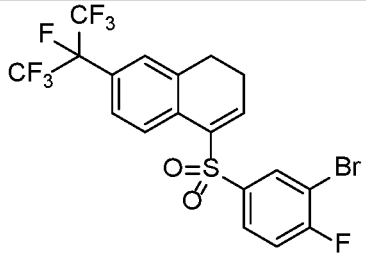
The Intermediates in Table 1 were prepared using the same methods or similar methods used to prepare Intermediates 1 and 2, by employing the appropriate ketone and substituted thiophenol.

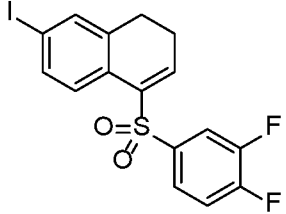
Table 1

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
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
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

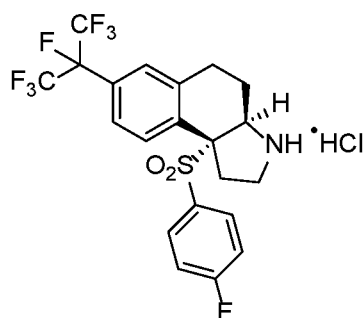
17		472.1 (M+H+MeCN) ⁺	1.13	B
18		486.0 (M+H+MeCN) ⁺	1.21	B
19		486.0 (M+H+MeCN) ⁺	1.21	B
20		350.9 (M+H) ⁺	1.06	B
21		447.9 (M+Na+MeCN) ⁺	1.10	B
22		365.0 (M+H) ⁺	1.06	B
23		452.0 (M+H+MeCN) ⁺	1.11	B

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
30		576.2 (M+H+MeCN) ⁺	1.16	B

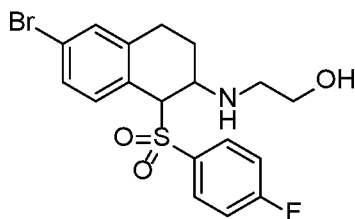
31		474.0 (M+H+MeCN) ⁺	1.09	B
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Intermediate 32

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



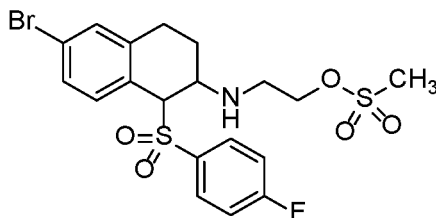
Step A: 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethan-1-ol



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 NaHCO₃, then twice with brine, dried over Na₂SO₄, 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-

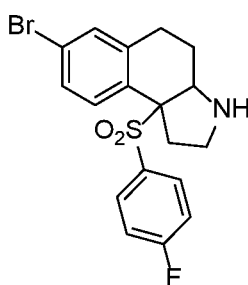
tetrahydronaphthalen-2-yl)amino)ethanol (2.8 g, 42% yield. LCMS m/z 427.8 (M+H)⁺, HPLC t_R 0.71 min (method B).

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 Et₃N (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 Na₂SO₄, 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



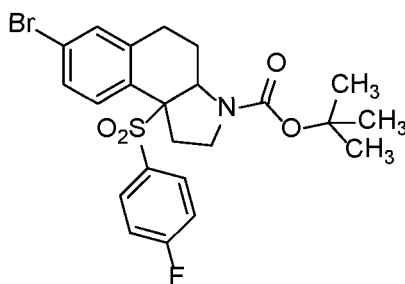
A solution of 2-((6-bromo-1-((4-fluorophenyl)sulfonyl)-1,2,3,4-tetrahydronaphthalen-2-yl)amino)ethyl methanesulfonate (2.9 g, 5.73 mmol) in THF (286 mL) was treated portionwise with potassium *tert*-butoxide ((3.21 g, 28.6 mmol) at rt, such that the temperature of the reaction mixture did not exceed 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 x 125 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated to provide crude 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-

benzo[*e*]indole (2.1 g), used without further purification. LCMS *m/z* 409.9 (M+H)⁺,

5 HPLC *t_R* 0.76 min (method B). ¹H NMR (400 MHz, CDCl₃) 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).

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



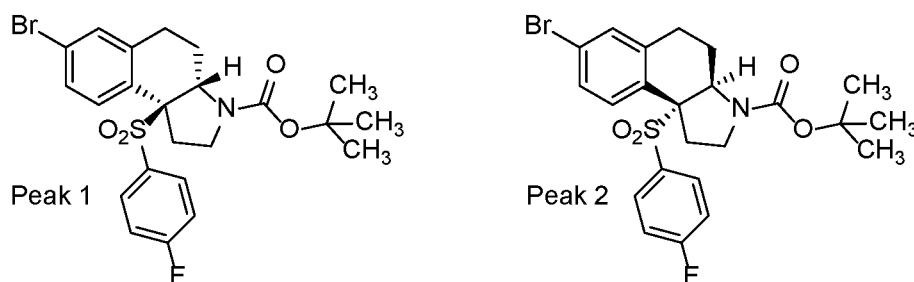
A solution of 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-

15 1*H*-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 Et₃N (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 Na₂SO₄, filtered and

20 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-3*H*-benzo[*e*]indole-3-carboxylate (1.6 g, 61% yield for 3 steps). LCMS *m/z* 453.9 (M+H-C₄H₈)⁺, HPLC *t_R* 1.15 min (method B). ¹H NMR (400 MHz, CDCl₃) 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),

25 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). ¹⁹F NMR (376 MHz) δ -102.6.

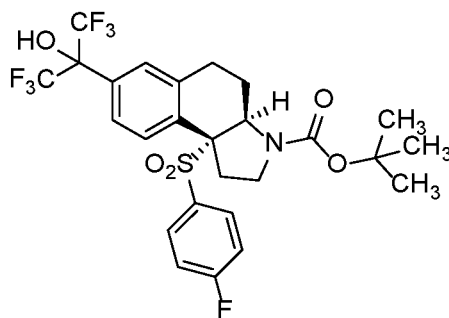
Step E: (3a*S*,9b*S*)-*tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate and (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-bromo-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate



5 A sample of *tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-bromo-3a,4,5,9b-tetrahydro-1*H*-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 x 250) mm, 5 μ m (Phenomenex Inc.); column temperature 24.9 $^{\circ}$ C; CO₂ flow rate: 2.10 mL/min; co-solvent: 30% of 0.2% diethylamine in MeOH, flow rate 0.9 mL/min; injection volume: 10
10 mL. Peak 1 ((3a*S*,9b*S*)-*tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate) was eluted with t_R 2.79 min. Peak 2 ((3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-bromo-3a,4,5,9b-tetrahydro-1*H*-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
15 from the anomalous dispersion signal using the FLACK method. Analytical data for Peak 2: LCMS m/z 453.9 (M+H-C₄H₈)⁺, HPLC t_R 1.15 min (method B); ¹H NMR (400 MHz, CDCl₃) 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). ¹⁹F NMR (376 MHz) δ -102.6.

20

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



tert-Butyllithium (3 M in heptane, 376 μ L, 0.940 mmol) was added dropwise to a stirred solution of (3*aR*,9*bR*)-*tert*-butyl 7-bromo-9*b*-((4-fluorophenyl)sulfonyl)-3*a*,4,5,9*b*-tetrahydro-1*H*-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 CF₃C(O)CF₃ (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 NH₄Cl (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 Na₂SO₄ 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 (3*aR*,9*bR*)-*tert*-butyl 9*b*-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3*a*,4,5,9*b*-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (200 mg, 71% yield, about 75% purity). LCMS *m/z* 541.8 (M+H-C₄H₈)⁺, HPLC *t_R* 1.08 min (method B). ¹H NMR (400 MHz, CDCl₃) 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). ¹⁹F NMR (376 MHz, CDCl₃) δ -102.5 (s, 1F), -75.5 (s, 6F).

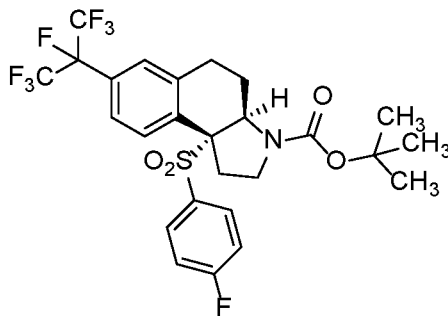
Alternative preparation of (3*aR*,9*bR*)-*tert*-butyl 9*b*-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3*a*,4,5,9*b*-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate

The same procedure was used, but starting with (3*aR*,9*bR*)-*tert*-butyl 9*b*-((4-fluorophenyl)sulfonyl)-7-iodo-3*a*,4,5,9*b*-tetrahydro-1*H*-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 (3*aR*,9*bR*)-*tert*-butyl 9*b*-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-

3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (0.7 g, 70% yield, about 80% purity).

Step G: (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-

5 3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate



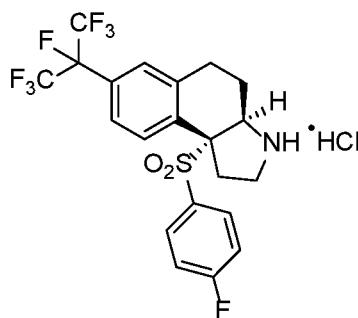
DAST (2.92 mL, 22.09 mmol) was added to a stirred solution of (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (1.1 g, 1.841 mmol) in 1,2-dichloroethane (18.41 mL) under N₂ at rt. The reaction 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 NaHCO₃. The aqueous phase was separated and extracted with EtOAc (100 mL). The combined organic phases were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 5-40%), to provide (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (800 mg, 72.5% yield). LCMS *m/z* 544.0 (M+H-C₄H₈)⁺, HPLC *t_R* 1.21 min (method B).

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

25 A mixture of activated copper (prepared as outlined in Step A of the preparation of Intermediate 2; 3.5g, 55 mmol) and (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-iodo-3a,4,5,9b-tetrahydro-1*H*-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 Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica, eluting with EtOAc-hexanes, to provide (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (3.6 g, 84% yield).

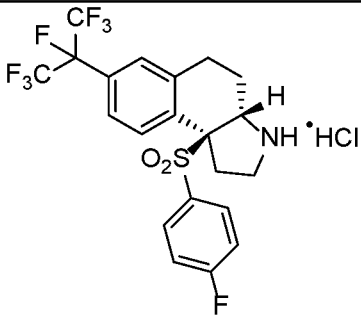
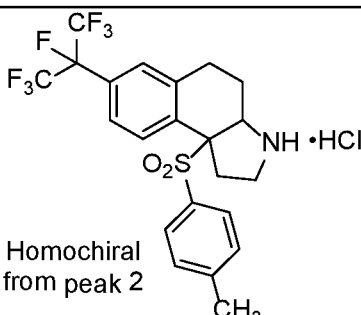
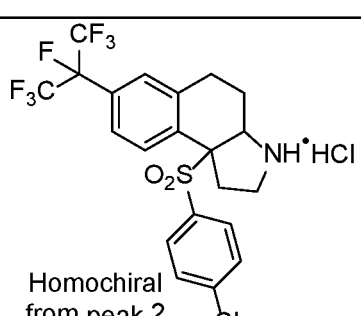
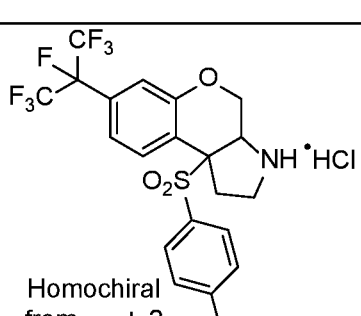
Step H: (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride

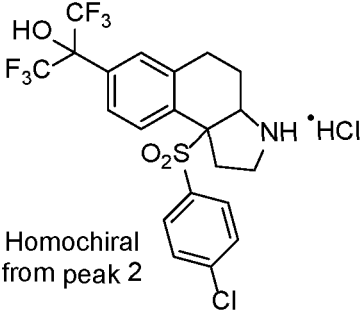
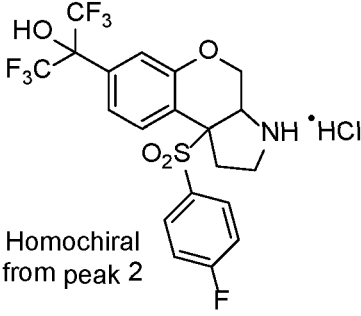
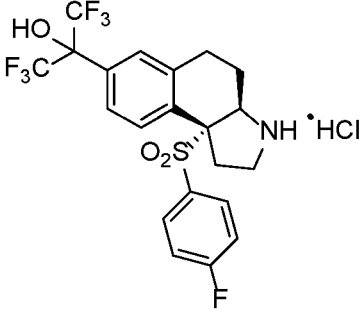
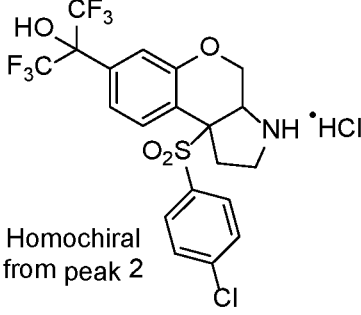
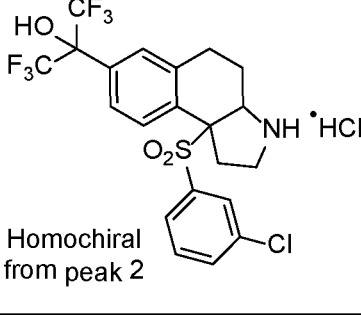


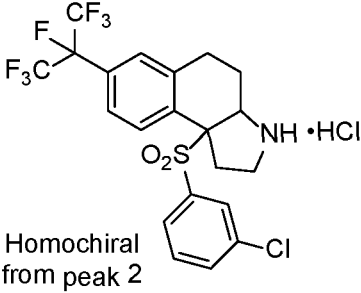
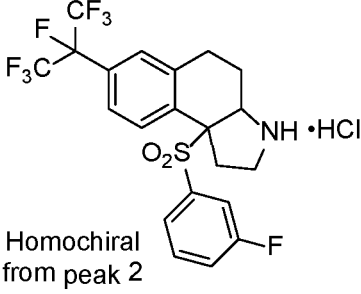
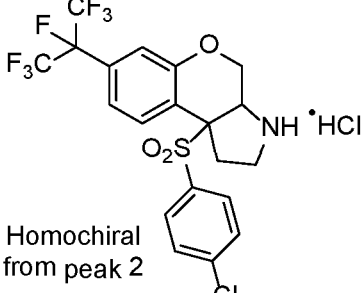
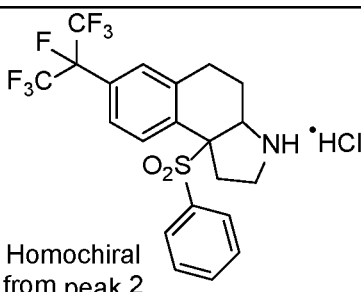
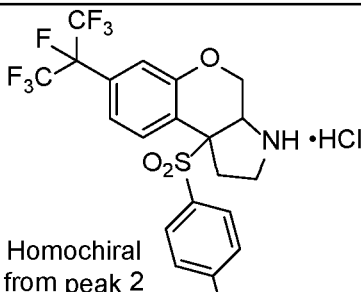
A solution of (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (250 mg, 0.417 mmol) in DCM (4.2 mL) was treated with HCl (4 M in 1,4-dioxane, 4.2 mL, 16.68 mmol). After 1 h at rt, the mixture was concentrated to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

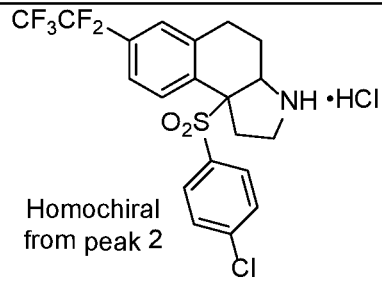
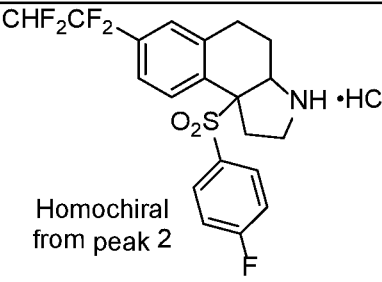
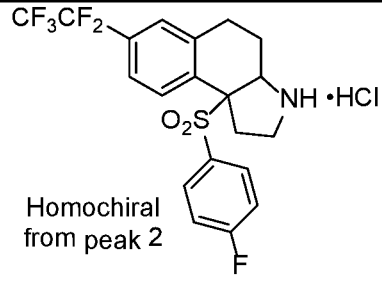
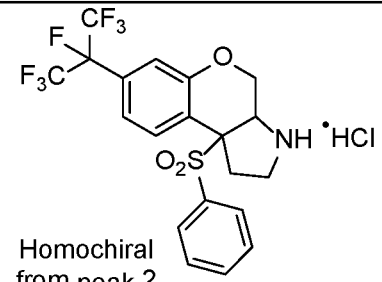
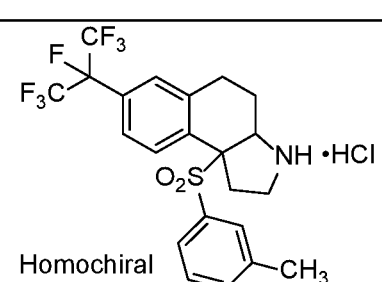
The Intermediates in Table 2 were prepared using procedures (or similar procedures) used in the preparation of Intermediate 32, starting from an appropriate vinylic sulfone, an appropriate aminocarbonyl, and other appropriate reagents. In the preparation of some of the Intermediates in Table 2, one or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

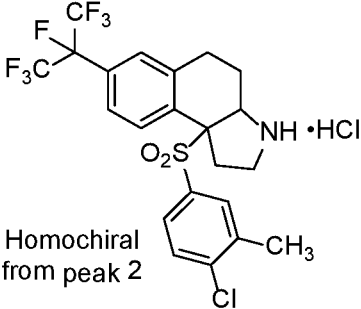
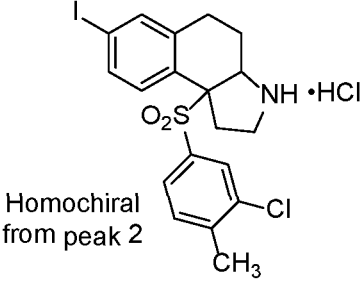
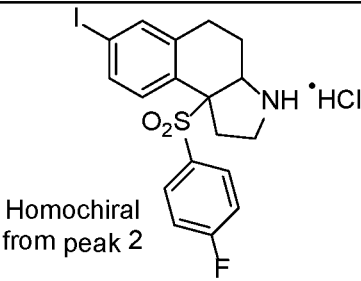
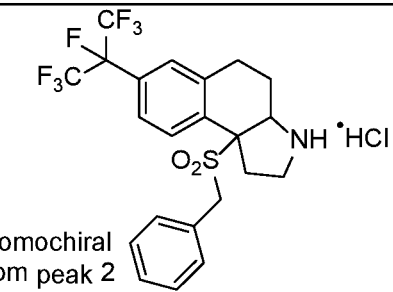
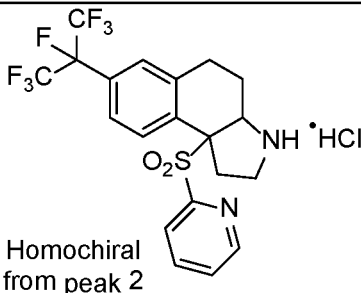
Table 2

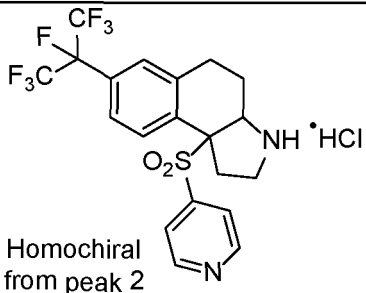
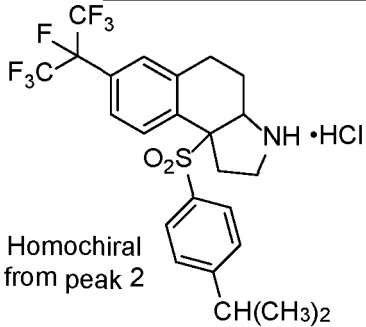
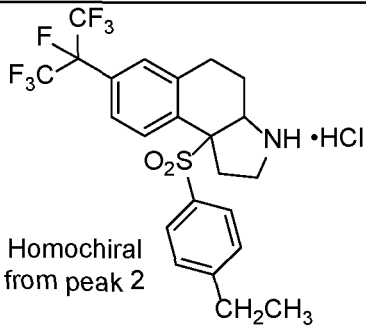
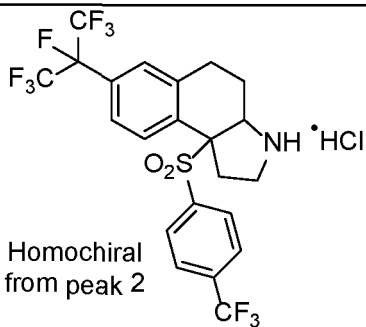
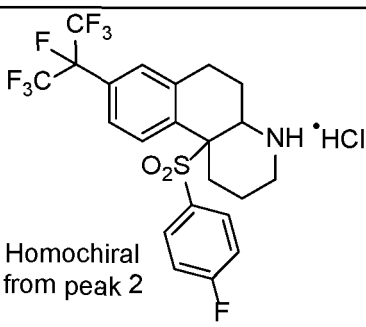
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
33		500.0 (M+H) ⁺	0.88	B
34	 Homochiral from peak 2	496.1 (M+H) ⁺	0.92	B
35	 Homochiral from peak 2	516.0 (M+H) ⁺	0.94	B
36	 Homochiral from peak 2	502.1 (M+H) ⁺	0.84	B

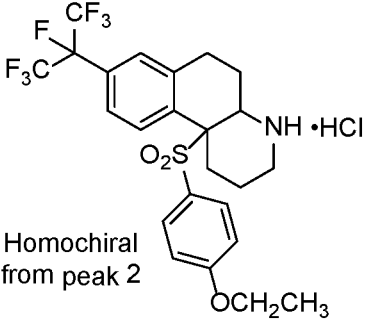
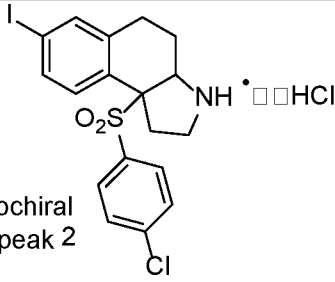
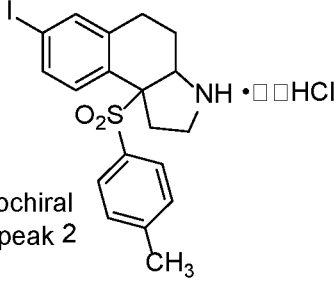
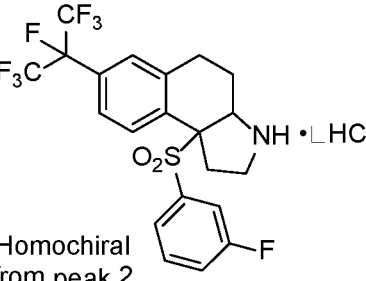
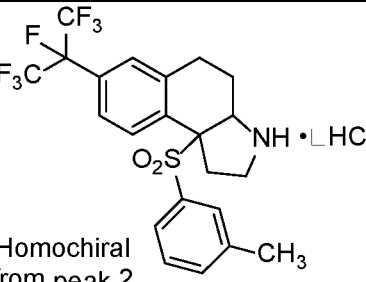
37	 Homochiral from peak 2	513.3 (M+H) ⁺	0.81	B
38	 Homochiral from peak 2	500.5 (M+H) ⁺	0.78	B
39		498.0 (M+H) ⁺	0.85	B
40	 Homochiral from peak 2	516.0 (M+H) ⁺	0.79	B
41	 Homochiral from peak 2	514.0 (M+H) ⁺	0.80	B

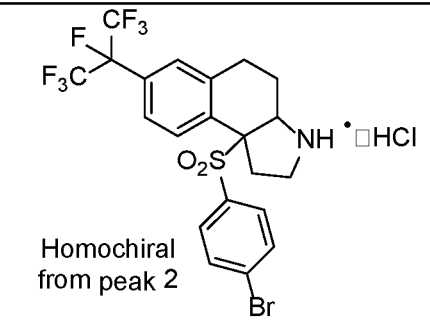
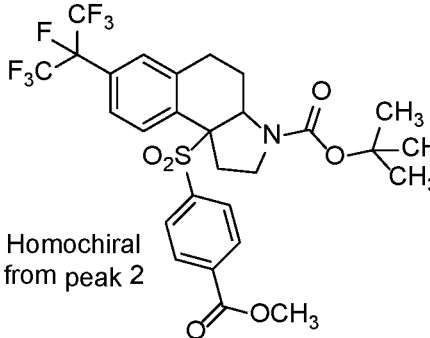
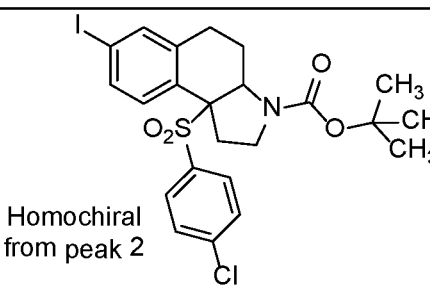
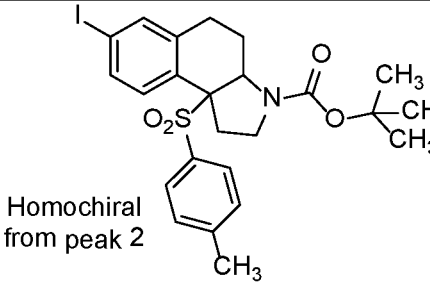
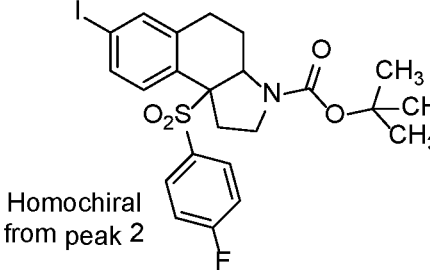
42	 Homochiral from peak 2	516.2 (M+H) ⁺	0.88	B
43	 Homochiral from peak 2	500.0 (M+H) ⁺	0.82	B
44	 Homochiral from peak 2	518.0 (M+H) ⁺	0.92	B
45	 Homochiral from peak 2	482.0 (M+H) ⁺	0.87	B
46	 Homochiral from peak 2	498.0 (M+H) ⁺	0.89	B

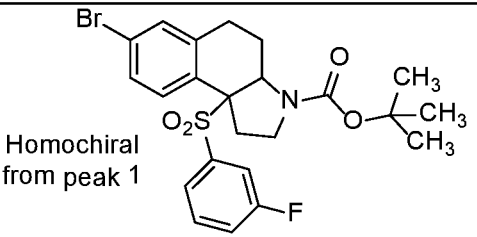
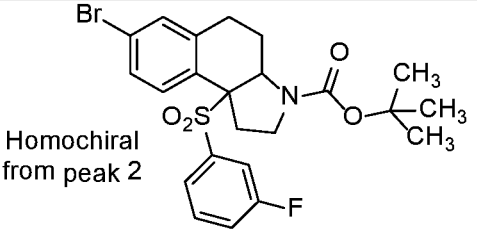
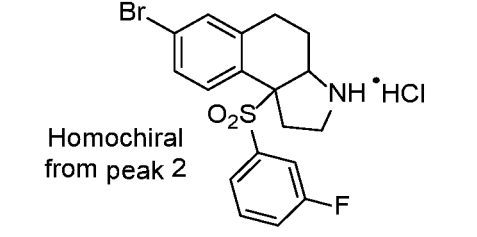
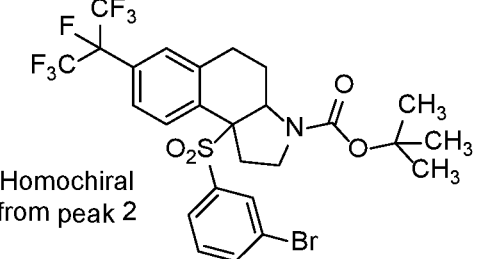
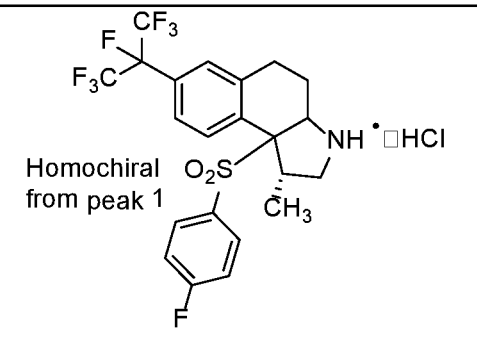
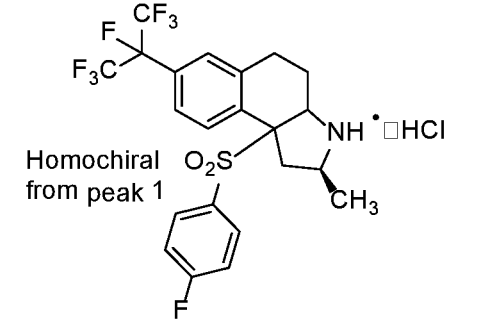
47	 Homochiral from peak 2	466.0 (M+H) ⁺	0.87	B
48	 Homochiral from peak 2	432.1 (M+H) ⁺	0.77	B
49	 Homochiral from peak 2	450.1 (M+H) ⁺	0.83	B
50	 Homochiral from peak 2	484.0 (M+H) ⁺	0.85	B
51	 Homochiral from peak 2	514.0 (M+H) ⁺	0.87	B

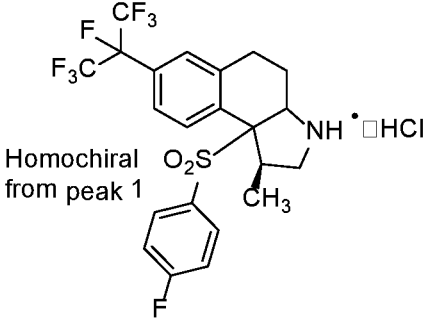
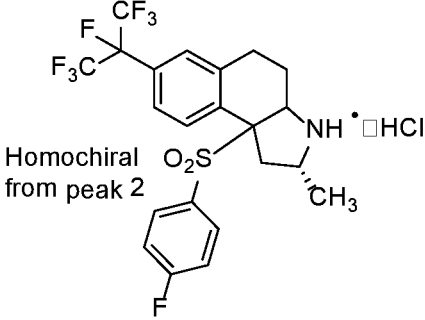
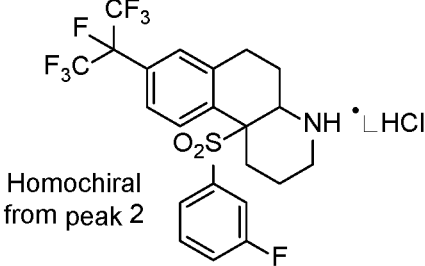
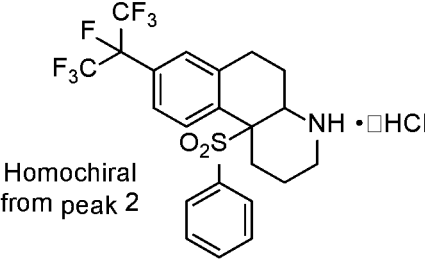
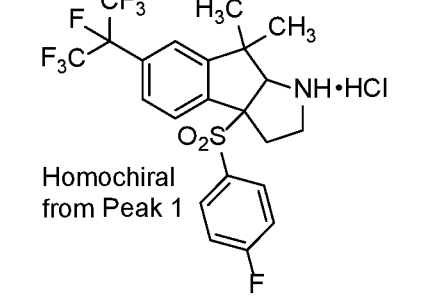
52	 Homochiral from peak 2	530.2 (M+H) ⁺	0.97	B
53	 Homochiral from peak 2	488.0 (M+H) ⁺	0.84	B
54	 Homochiral from peak 2	500.0 (M+H) ⁺	0.88	B
55	 Homochiral from peak 2	496.1 (M+H) ⁺	0.87	B
56	 Homochiral from peak 2	483.2 (M+H) ⁺	0.77	B

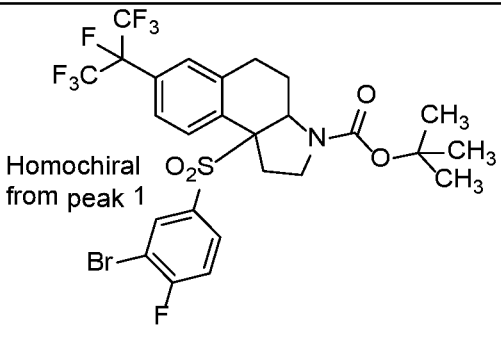
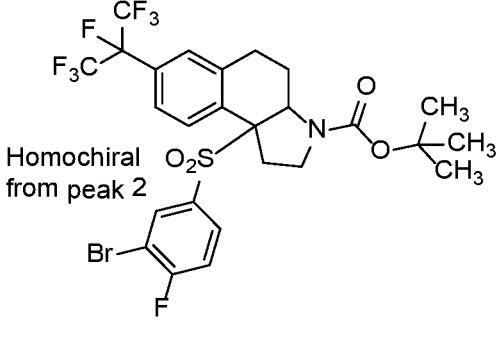
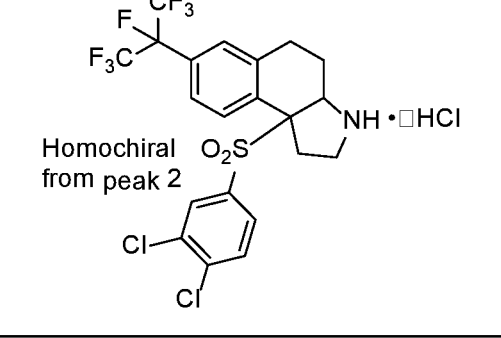
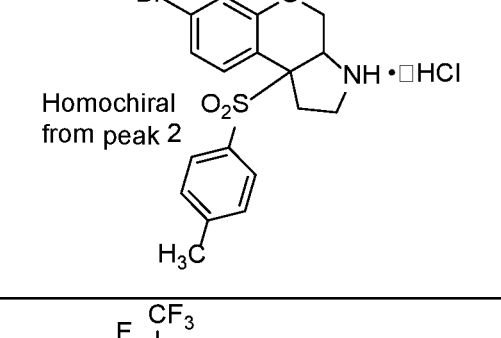
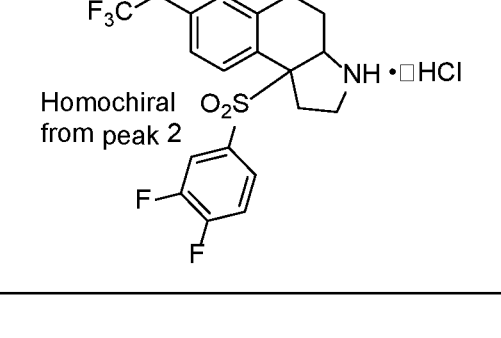
57	 Homochiral from peak 2	483.3 (M+H) ⁺	0.76	B
58	 Homochiral from peak 2	524.1 (M+H) ⁺	0.96	B
59	 Homochiral from peak 2	510.3 (M+H) ⁺	0.90	B
60	 Homochiral from peak 2	550.3 (M+H) ⁺	1.01	B
61	 Homochiral from peak 2	514.5 (M+H) ⁺	0.86	B

62	 Homochiral from peak 2	540.4 (M+H) ⁺	0.88	B
63	 Homochiral from peak 2	473.9 (M+H) ⁺	0.83	B
64	 Homochiral from peak 2	453.8 (M+H) ⁺	0.76	B
65	 Homochiral from peak 2	500.0 (M+H) ⁺	0.89	B
66	 Homochiral from peak 2	496.2 (M+H) ⁺	0.86	B

67	 Homochiral from peak 2	558.4 (M+H+MeCN) ⁺	1.22	B
68	 Homochiral from peak 2	584.4 (M+H-C ₄ H ₈) ⁺	1.17	B
69	 Homochiral from peak 2	517.8 (M+H-C ₄ H ₈) ⁺	1.22	B
70	 Homochiral from peak 2	497.7 (M+H-C ₄ H ₈) ⁺	1.18	B
71	 Homochiral from peak 2	501.8 (M+H-C ₄ H ₈) ⁺	2.45	C

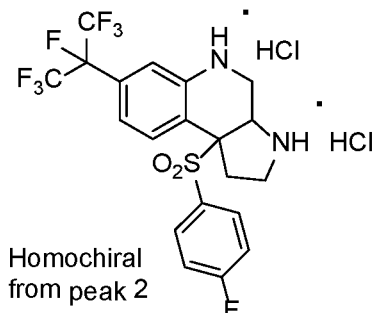
72	 Homochiral from peak 1	495.0 (M+H-C ₄ H ₈) ⁺	1.19	B
73	 Homochiral from peak 2	495.0 (M+H-C ₄ H ₈) ⁺	1.19	B
74	 Homochiral from peak 2	409.9 (M+H) ⁺	0.73	B
75	 Homochiral from peak 2	645.0 (M+H+MeCN -C ₄ H ₈) ⁺	1.27	B
76	 Homochiral from peak 1	514.1 (M+H) ⁺	0.90	B
77	 Homochiral from peak 1	514.0 (M+H) ⁺	0.88	B

78	 Homochiral from peak 1	514.1 (M+H) ⁺	0.90	B
79	 Homochiral from peak 2	514.0 (M+H) ⁺	0.89	B
80	 Homochiral from peak 2	514.1 (M+H) ⁺	0.92	B
81	 Homochiral from peak 2	496.1 (M+H) ⁺	0.89	B
82	 Homochiral from Peak 1	514.2 (M+H) ⁺	0.90	B

83	 Homochiral from peak 1	663.2 (M+H+MeCN -C ₄ H ₈) ⁺	1.22	B
84	 Homochiral from peak 2	663.2 (M+H+MeCN -C ₄ H ₈) ⁺	1.22	B
85	 Homochiral from peak 2	550.0 (M+H) ⁺	0.91	B
86	 Homochiral from peak 2	408.0 (M+H) ⁺	0.73	B
87	 Homochiral from peak 2	518.0 (M+H) ⁺	0.88	B

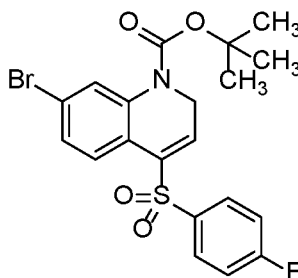
Intermediate 88

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



5

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



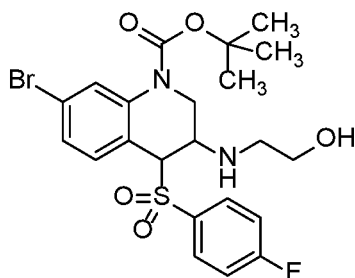
A solution of 7-bromo-2,3-dihydroquinolin-4(1H)-one (8 g, 35 mmol), 4-fluorobenzenethiol (7.9 mL, 74 mmol) and absolute ethanol (44 mL) was cooled with an ice-water bath. HCl gas was bubbled through the mixture until saturation was reached (as indicated by the formation of a white precipitate). The mixture 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 Na₂SO₄ 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 Na₂SO₄ and concentrated

to afford *tert*-butyl 7-bromo-4,4-bis((4-fluorophenyl)thio)-3,4-dihydroquinoline-1(2*H*)-carboxylate (20 g, 100% yield). HPLC t_R 1.37 min (method B).

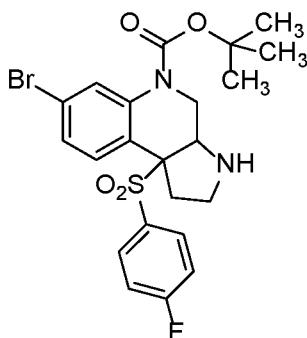
This material was dissolved in DCM (350 mL) and cooled with an ice-water bath. mCPBA (22 g, 172 mmol) was added and the mixture was stirred for 1 h. Additional
 5 mCPBA (22 g, 172 mmol) was added, and stirring was continued for 1 h more. The mixture was filtered to remove the insoluble material, and the filtrate was treated with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (120 mL) and stirred for 5 min. The organic phase was separated, washed sequentially with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2 x 120 mL), 10% aqueous Na_2CO_3 (3 x 200 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated to give crude *tert*-
 10 butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)quinoline-1(2*H*)-carboxylate (17 g) which was used without further purification. LCMS m/z 468.0 ($\text{M}+\text{H}+\text{MeCN}$)⁺, HPLC t_R 1.16 min (method B).

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



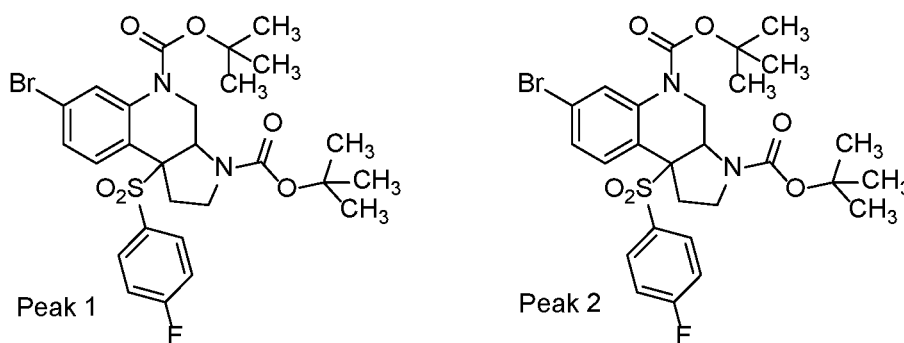
A solution of *tert*-butyl 7-bromo-4-((4-fluorophenyl)sulfonyl)quinoline-1(2*H*)-carboxylate (16.6 g, 35 mmol) in THF (700 mL) was stirred on an ice-water bath and treated with 2-aminoethanol (11 mL, 177 mmol). The mixture was stirred at about 5 °C
 20 for 30 min, then was concentrated. The resulting 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(2*H*)-carboxylate (19.5 g) which was used without further purification. LCMS m/z 529.0 ($\text{M}+\text{H}$)⁺, 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-5*H*-
 25 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(2*H*)-carboxylate (19 g, 35 mmol) in DCM (650 mL) was treated with MsCl (3.3 mL, 43 mmol), then with Et₃N (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 L). The organic phase was separated and washed 3 times with brine, dried over Na₂SO₄ and concentrated to give crude *tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4-tetrahydro-1*H*-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-3*H*-pyrrolo[2,3-*c*]quinoline-3,5(2*H*)-dicarboxylate, two homochiral enantiomers

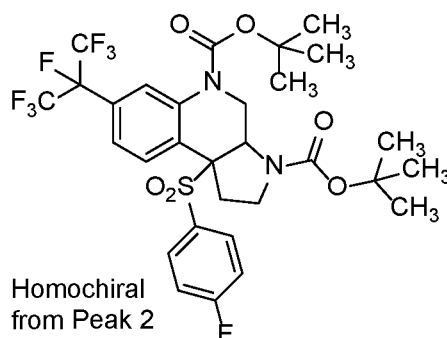


A solution of *tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*c*]quinoline-5-carboxylate (18 g, 35 mmol) in DCM (350 mL) was treated with di-*tert*-butyl dicarbonate (12 mL, 53 mmol) and diisopropylethylamine (18.5 mL, 106 mmol). The mixture was stirred at rt 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 Na₂SO₄ 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-3*H*-pyrrolo[2,3-*c*]quinoline-3,5(2*H*)-dicarboxylate (7.6 g, 35% overall yield from 7-bromo-2,3-dihydroquinolin-4(1*H*)-one).

This material was separated by chiral SFC using the following conditions: Column: Chiralcel® OD-H 50 × 250 mm, 5μm (Chiral Technologies Inc.); column temperature 35 °C; pressure 100 bars; mobile phase CO₂-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-CO₂C₄H₉-C₄H₉)⁺, HPLC *t*_R 1.22 min (method B).

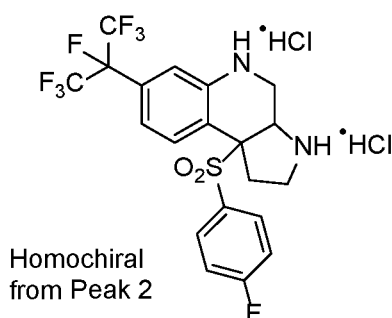
Step E: di-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,3a,4,9b-tetrahydro-3*H*-pyrrolo[2,3-*c*]quinoline-3,5(2*H*)-dicarboxylate (homochiral)



A sealable reaction vessel was charged with activated copper powder (prepared as outlined in Step A of the preparation of Intermediate 2; 3.5g, 55 mmol), homochiral di-*tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3a,4-dihydro-1*H*-pyrrolo[2,3-*c*]quinoline-3,5(2*H*)-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 Na₂SO₄ 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-1*H*-pyrrolo[2,3-

c]quinoline-3,5(2*H*)-dicarboxylate (712 mg, 22% yield) along with recovered starting material (1.1 g). LCMS *m/z* 545.0 (*M*+2*H*-CO₂C₄H₉-C₄H₉)⁺, HPLC *t_R* 1.27 min (method B).

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

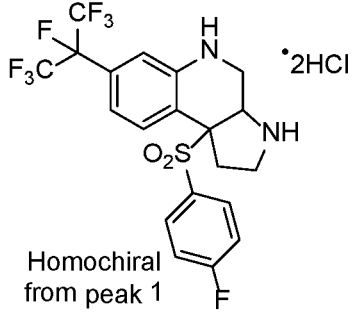
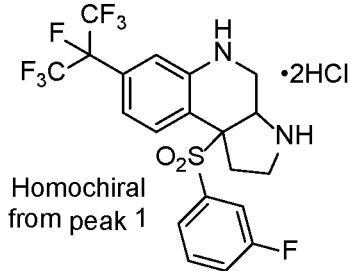
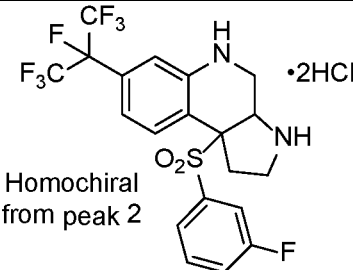
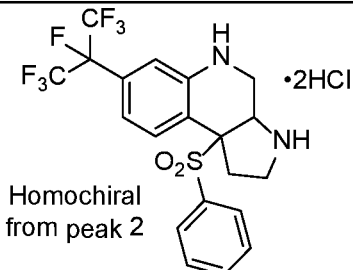
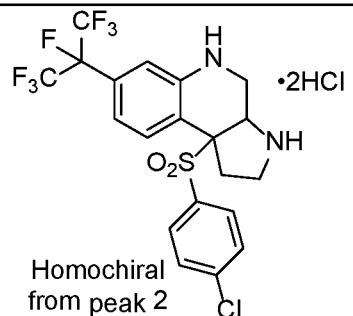


A solution of di-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4-dihydro-1*H*-pyrrolo[2,3-*c*]quinoline-3,5(2*H*)-dicarboxylate (from Peak 2; 358 mg, 0.511 mmol) in DCM (2.5 mL) was treated with HCl (4 M in 1,4-dioxane; 2.5 mL, 10 mmol). The mixture was allowed to stand at rt for 1 h, then was concentrated to provide 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -104.9 (s, 1F), -77.3 (m, 1F), -77.0 (s, 6F).

20 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.

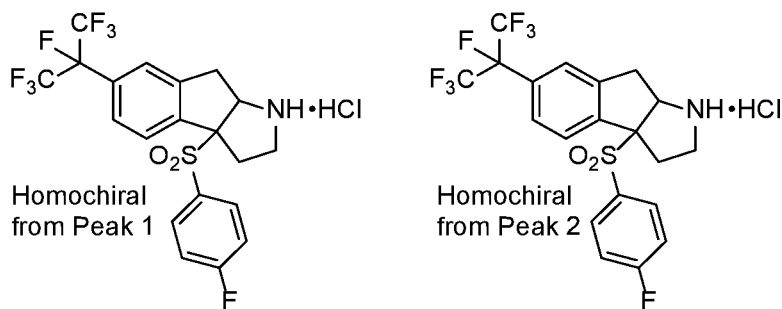
Table 3

Intermediate number	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
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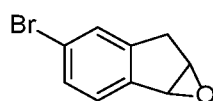
89	 Homochiral from peak 1	501.0 (M+H) ⁺	0.89	B
90	 Homochiral from peak 1	501.0 (M+H) ⁺	0.86	B
91	 Homochiral from peak 2	501.0 (M+H) ⁺	0.86	B
92	 Homochiral from peak 2	483.1 (M+H) ⁺	0.86	B
93	 Homochiral from peak 2	517.0 (M+H) ⁺	0.88	B

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)

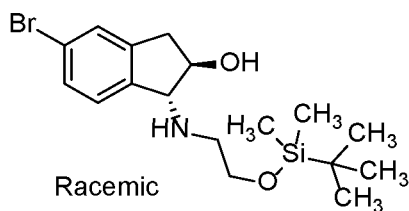


5 **Step A:** 4-bromo-1a,6a-dihydro-6*H*-indeno[1,2-*b*]oxirene



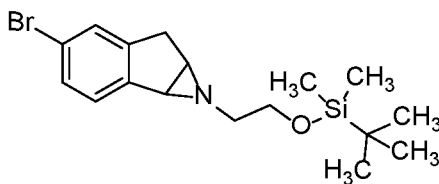
A solution of 6-bromo-1*H*-indene (prepared according to the procedure in US Pat. 7,678,798; 5.30 g, 27.2 mmol) in DCM (125 mL) was treated with NaHCO₃ (6.85 g, 82 mmol) and stirred vigorously on an ice-water bath. The mixture was treated portionwise over 20 min with mCPBA (9.38 g, 38.0 mmol). After 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 Na₂S₂O₃ (100 mL). Additional DCM (250 mL), 1.5 M aqueous K₂HPO₄ (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 K₂HPO₄, 10% aqueous Na₂S₂O₃, 1.5 M aqueous K₂HPO₄, water and brine, then dried over Na₂SO₄ 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-6*H*-indeno[1,2-*b*]oxirene as a white solid (4.324 g, 74%), contaminated with about 2% by weight of 5-bromo-1*H*-inden-2(3*H*)-one. ¹H NMR (400 MHz, CDCl₃) 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).

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



A solution of 4-bromo-1a,6a-dihydro-6*H*-indeno[1,2-*b*]oxirene (4.32 g, 20.06 mmol) in MeCN (90 mL) at rt was treated with LiClO₄ (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 Na₂SO₄ 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 (1*RS*,2*RS*)-5-bromo-1-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-2,3-dihydro-1*H*-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, CDCl₃) 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).

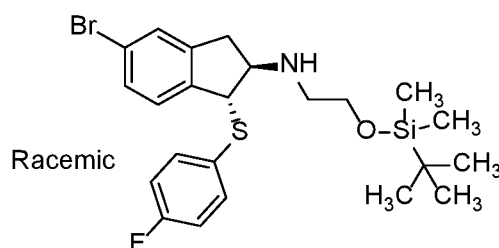
Step C: 4-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,1a,6,6a-tetrahydroindeno[1,2-*b*]azirine



A solution of racemic (1*RS*,2*RS*)-5-bromo-1-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-2,3-dihydro-1*H*-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

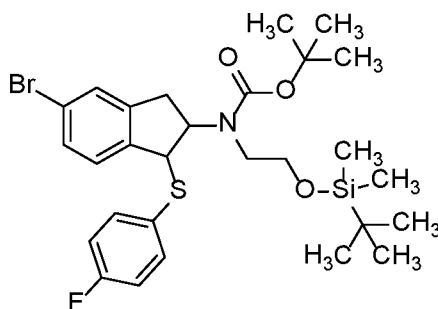
concentrated and the residue was purified by column chromatography on silica gel (330 g), eluting with EtOAc-hexanes (gradient from 0-25%) to provide 4-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,1a,6,6a-tetrahydroindeno[1,2-*b*]azirine as a light brown-yellow syrup (4.693 g, 83% yield). LCMS m/z 368.0 ($M+H$)⁺, HPLC t_R 0.91 min (method B). ¹H NMR (400 MHz, CDCl₃) 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: (1*RS*,2*RS*)-5-bromo-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-((4-fluorophenyl)thio)-2,3-dihydro-1*H*-inden-2-amine (racemic)



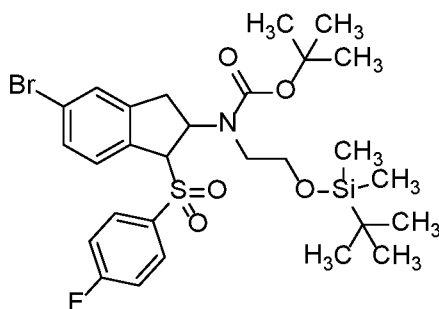
A solution of 4-bromo-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1,1a,6,6a-tetrahydroindeno[1,2-*b*]azirine (4.650 g, 12.62 mmol) in MeCN (60 mL) was treated rapidly dropwise with 4-fluorobenzenethiol (1.789 mL, 16.79 mmol) and the solution was stirred at rt. After 2 h, the mixture was concentrated 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 (1*RS*,2*RS*)-5-bromo-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-((4-fluorophenyl)thio)-2,3-dihydro-1*H*-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, CDCl₃) 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). ¹⁹F NMR (376 MHz, CDCl₃) δ -113.38 (tt, $J=8.3$, 5.4 Hz, 1F).

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



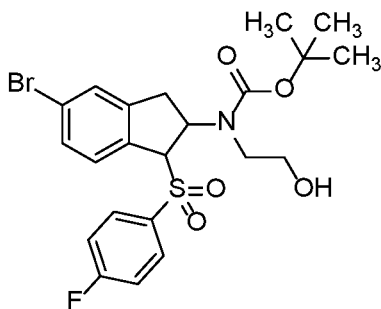
A solution of racemic (1*RS*,2*RS*)-5-bromo-N-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-((4-fluorophenyl)thio)-2,3-dihydro-1*H*-inden-2-amine (5.94 g, 11.96 mmol), Et₃N (2.168 mL, 15.55 mmol) and di-*tert*-butyl dicarbonate (3.61 mL, 15.55 mmol) in DCM (70 mL) was treated with 4-dimethylaminopyridine (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 Na₂SO₄ 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-1*H*-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-COOC₄H₉)⁺, HPLC *t_R* 1.09 min (method B). ¹H NMR (400 MHz, CDCl₃) 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-1*H*-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-COOC₄H₉)⁺, HPLC *t_R* 1.09 min (method B). ¹H NMR (400 MHz, CDCl₃) 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-1*H*-inden-2-yl)(2-((*tert*-butyldimethylsilyl)oxy)ethyl)carbamate



A solution of *tert*-butyl (5-bromo-1-((4-fluorophenyl)thio)-2,3-dihydro-1*H*-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 Na₂S₂O₃, 1.5 M aqueous K₂HPO₄ and brine, dried over Na₂SO₄ 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-1*H*-inden-2-yl)(2-((*tert*-butyldimethylsilyl)oxy)ethyl)carbamate as a white glassy solid (5.794g, 87% yield). LCMS *m/z* 528.2 (M+H-COOC₄H₉)⁺, 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).

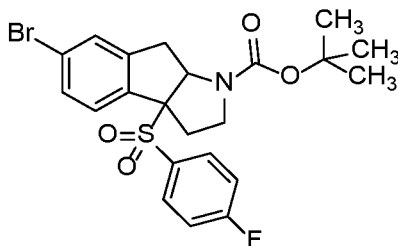
Step G: *tert*-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1*H*-inden-2-yl)(2-hydroxyethyl)carbamate



A solution of *tert*-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1*H*-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 NH₄Cl (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 Na₂SO₄ 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-1*H*-inden-2-yl)(2-hydroxyethyl)carbamate as a white glassy solid. (3.796 g, 80% yield). LCMS *m/z* 458.1 (M+H-C₄H₈)⁺, HPLC *t_R* 1.04 min (method B). ¹H NMR (400 MHz, CDCl₃) 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).

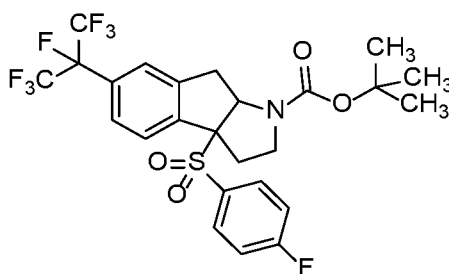
15 **Step H:** *tert*-butyl 6-bromo-3a-((4-fluorophenyl)sulfonyl)-3,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrole-1(2*H*)-carboxylate



A solution of *tert*-butyl (5-bromo-1-((4-fluorophenyl)sulfonyl)-2,3-dihydro-1*H*-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 Et₃N (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 NH₄Cl 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 Na₂SO₄ 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(2*H*)-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, CDCl₃) 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(2*H*)-carboxylate

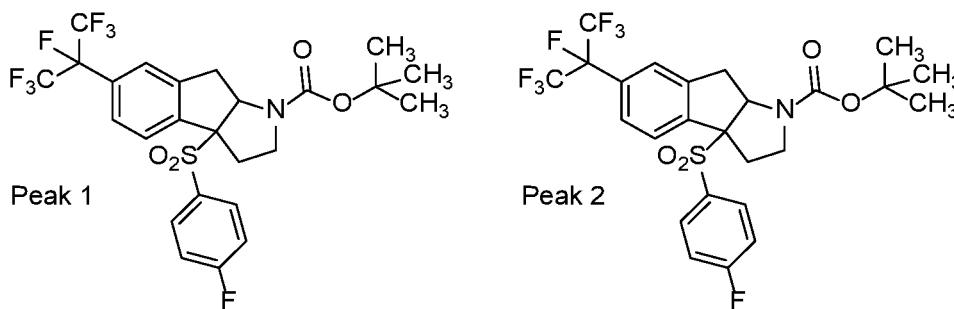


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A sealable reaction vessel was charged with activated copper powder (prepared as outlined in Step A of the preparation of Intermediate 2; 3.32 g, 52.2 mmol), *tert*-butyl 6-bromo-3a-((4-fluorophenyl)sulfonyl)-3,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrole-1(2*H*)-carboxylate (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 Na₂SO₄ 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(2*H*)-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, CDCl₃) 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). ¹⁹F NMR (376 MHz, CDCl₃) δ -75.40 - -75.76 (m, 6F), -101.67 (br. s., 1F), -181.88 (m, 1F).

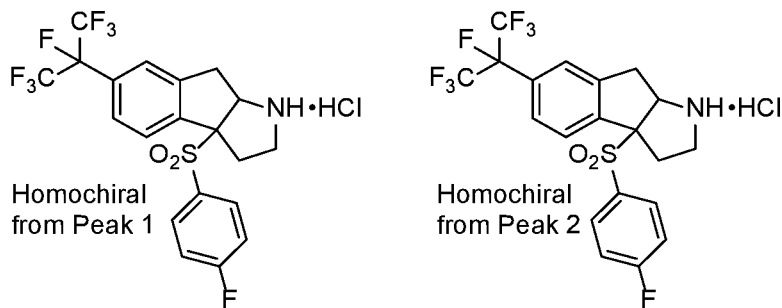
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Step J: *tert*-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrole-1(2*H*)-carboxylate (two homochiral enantiomers)



A sample of *tert*-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrole-1(2*H*)-carboxylate (2.95 g, 5.04 mmol) was separated by chiral SFC using the following conditions: Column: Chiralpak® IC (30 x 250) mm, 5µm (Chiral Technologies Inc.); column temperature 35 °C; pressure 100 bars; mobile phase CO₂-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)



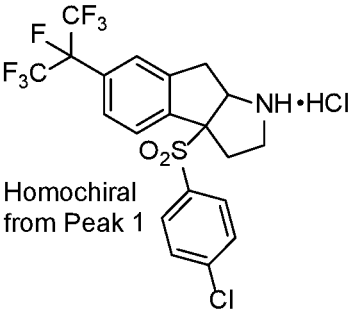
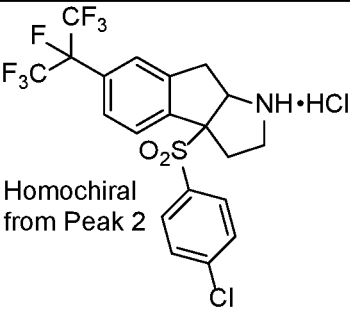
A solution of *tert*-butyl 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrole-1(2*H*)-carboxylate (single enantiomer, Peak 1 from Step J; 1.225 g, 2.092 mmol) in DCM (20 mL) was treated with HCl, 4 M in 1,4-dioxane (16 mL, 64.0 mmol) and allowed to stand 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, CDCl₃) 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(2*H*)-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.

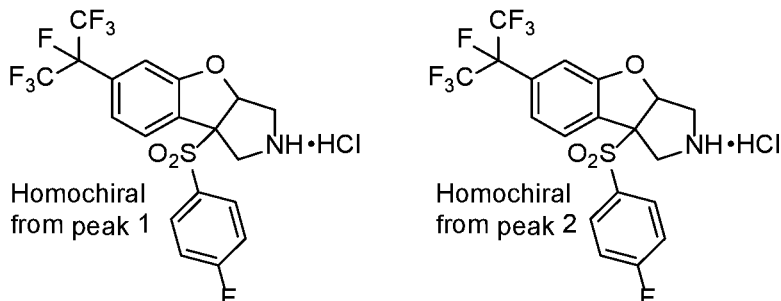
The Intermediates in Table 4 were prepared using the same or similar methods used in the preparation of Intermediates 94 and 95, by employing the appropriate thiol in Step D.

Table 4

Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
96	 Homochiral from Peak 1	502.0 ($\text{M}+\text{H}$) ⁺	0.88	B
97	 Homochiral from Peak 2	502.0 ($\text{M}+\text{H}$) ⁺	0.88	B

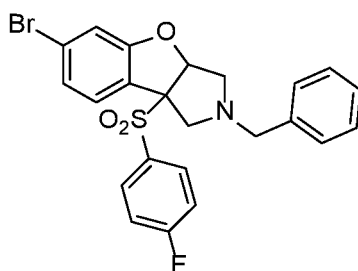
Intermediates 98 and 99

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



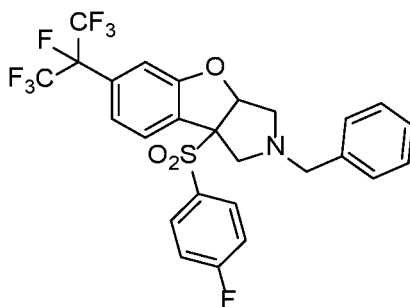
5

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



- 10 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
- 15 mixture was warmed to rt. After 2 h, the solution was diluted with DCM, washed with 1.5 M aqueous K₂HPO₄, dried over Na₂SO₄ 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
- 20 *m/z* 488.1 (M+H)⁺, HPLC *t_R* 1.04 min (method B). ¹H NMR (400 MHz, CDCl₃) 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).

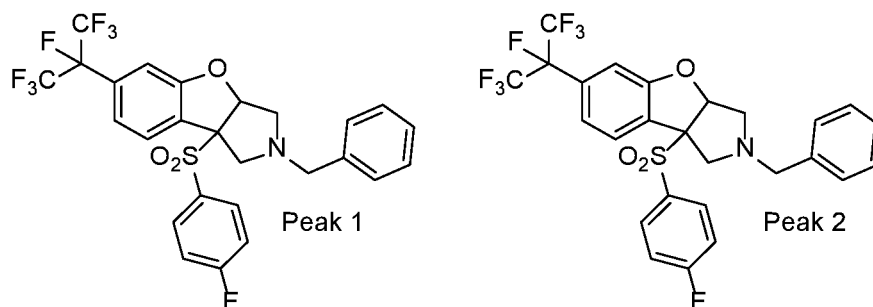
Step B: 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole



5 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
 10 t_R 1.16 min (method B). ¹H NMR (400 MHz, CDCl₃) 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). ¹⁹F NMR (376 MHz, CDCl₃) δ -75.63 (d, J =7.2 Hz, 6F), -101.83 (m, 1F), -181.37 (m, 1F).

15

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)

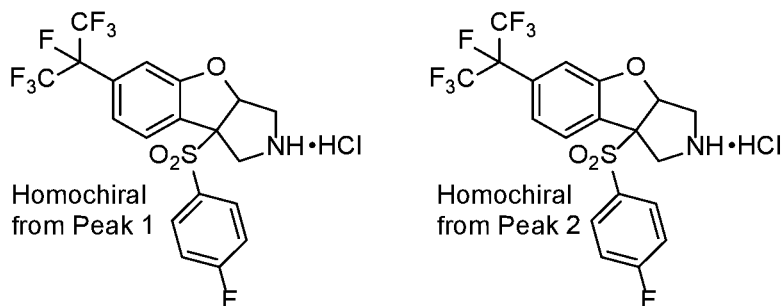


A sample of 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1H-benzofuro[2,3-c]pyrrole (640 mg, 1.109 mmol) was separated by
 20 chiral SFC using the following conditions: Column: Chiralcel[®] OD-H 50 x 250 mm, 5 μ m (Chiral Technologies Inc.); column temperature 35 °C; pressure 100 bars; mobile phase

CO₂-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.

5

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



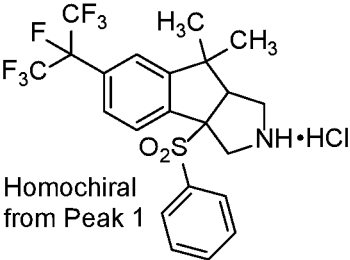
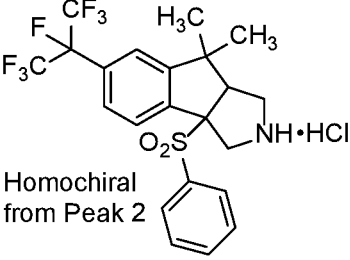
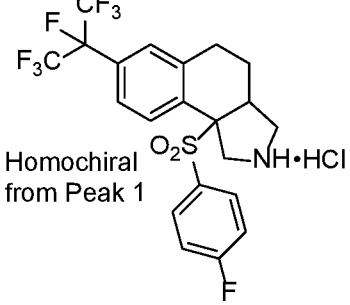
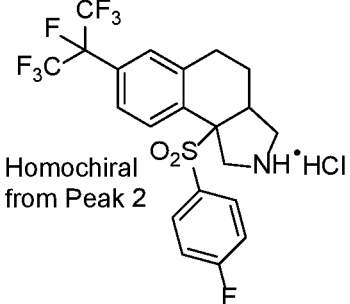
A solution of 2-benzyl-8b-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-2,3,3a,8b-tetrahydro-1*H*-benzofuro[2,3-*c*]pyrrole (single enantiomer, Peak 1 from Step C; 276 mg, 0.478 mmol) in MeOH (10 mL) was treated with 1.0 M aqueous HCl (0.574 mL, 0.574 mmol) and Pearlman's Catalyst (276 mg, 0.393 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-1*H*-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). ¹H 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-1*H*-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-1*H*-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.

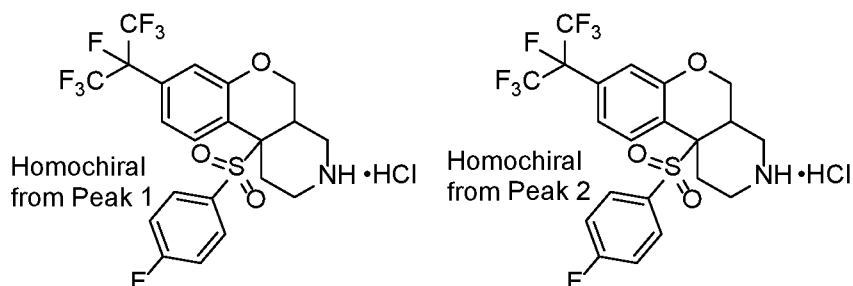
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Table 5

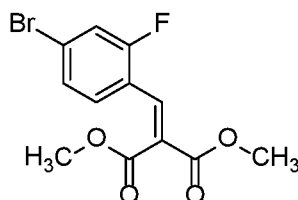
Intermediate number	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
100	 Homochiral from Peak 1	496.1 (M+H) ⁺	0.88	B
101	 Homochiral from Peak 2	496.1 (M+H) ⁺	0.88	B
102	 Homochiral from Peak 1	500.2 (M+H) ⁺	0.85	B
103	 Homochiral from Peak 2	500.3 (M+H) ⁺	0.85	B

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)

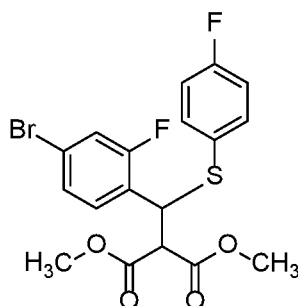


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Step A: dimethyl 2-(4-bromo-2-fluorobenzylidene)malonate

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 a 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).

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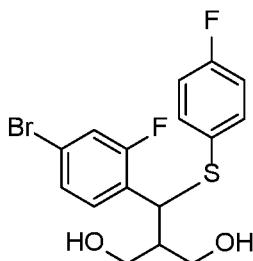
Step B: dimethyl 2-((4-bromo-2-fluorophenyl)((4-fluorophenyl)thio)methyl)malonate

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

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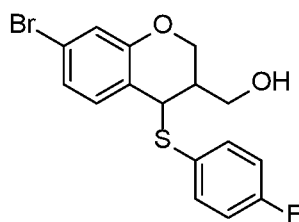
(238 mL) was heated at 60 °C for 4 h. The mixture was cooled to rt, filtered through Celite, and the solids were washed with EtOAc. The combined filtrates were concentrated and purified by column chromatography on silica gel (220 g), eluting with EtOAc-hexanes (5:95). A solid which formed in the effluent 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, CDCl₃) 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 K₂HPO₄ and brine, dried over Na₂SO₄, 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, CDCl₃) 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).

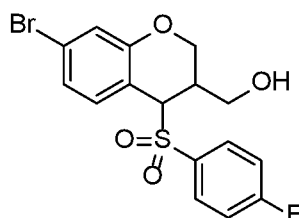
Step D: (7-bromo-4-((4-fluorophenyl)thio)chroman-3-yl)methanol



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.

- 5 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 Na₂SO₄, 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, CDCl₃) 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).

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

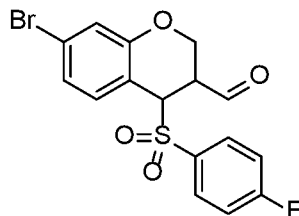


A solution of (7-bromo-4-((4-fluorophenyl)thio)chroman-3-yl)methanol (4.65 g, 12.59 mmol) in DCM (252 mL) was treated with mCPBA (6.77 g, 30.2 mmol) and stirred at rt. After 18 h, the mixture was diluted with DCM, washed sequentially with 10%

- 20 aqueous Na₂S₂O₃, saturated aqueous NaHCO₃ and 1.5 M aqueous K₂HPO₄. The organic phase was dried over Na₂SO₄ 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, CDCl₃) 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),
- 25

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



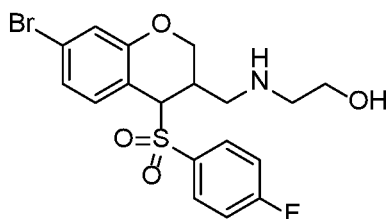
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A solution of (7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-yl)methanol (3.93 g, 9.79 mmol) in DCM (122 mL) was treated with 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (Dess-Martin periodinane; 4.15 g, 9.79 mmol) and stirred at rt.

10 After 2 h, the mixture was concentrated, and the residue was dissolved in EtOAc, washed sequentially with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$, 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).

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



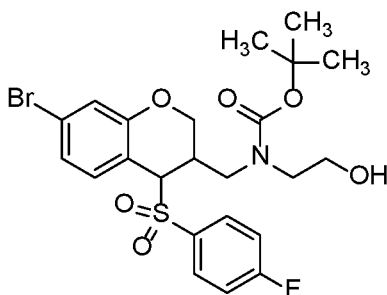
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A solution of 7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-carbaldehyde (3.97 g, 9.94 mmol) in 1,2-dichloroethane (301 mL) was treated with 2-aminoethanol (1.020 mL, 16.90 mmol), then with sodium triacetoxyborohydride (5.56 g, 26.3 mmol). The resulting 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, 25 dried over Na_2SO_4 and concentrated to afford 2-(((7-bromo-4-((4-

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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).

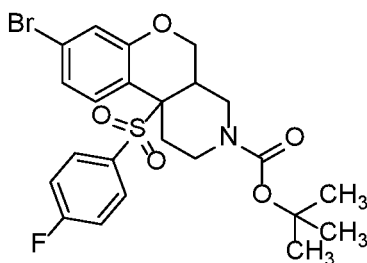
Step H: *tert*-butyl ((7-bromo-4-((4-fluorophenyl)sulfonyl)chroman-3-yl)methyl)(2-hydroxyethyl)carbamate



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 Et₃N (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 MgSO₄, 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, CDCl₃) 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).

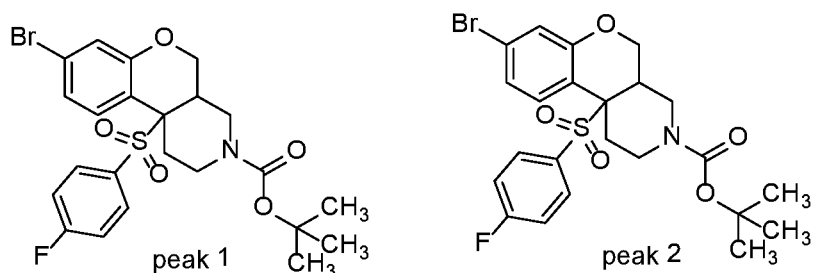
Step I: *tert*-butyl 8-bromo-10b-((4-fluorophenyl)sulfonyl)-1,4a,5,10b-tetrahydro-2H-chromeno[3,4-*c*]pyridine-3(4H)-carboxylate



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

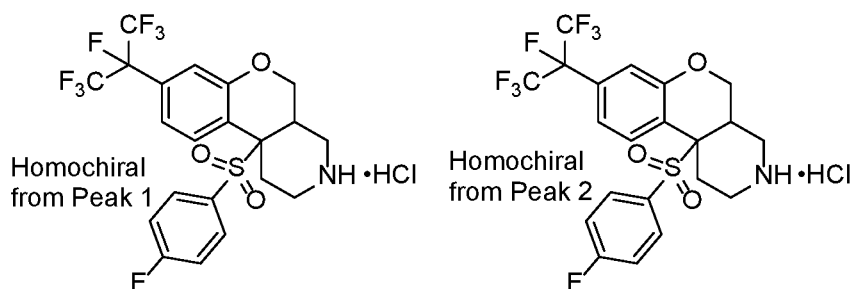
treated with MsCl (0.630 mL, 8.08 mmol), then with Et₃N (1.464 mL, 10.50 mmol). The mixture was stirred at rt for 1 h, then potassium *tert*-butoxide (4.08 g, 36.4 mmol) was added and stirring was continued for 2 h more. The mixture was treated with half-saturated brine and diluted with additional DCM. The organic phase was separated,
 5 washed with brine, dried over Na₂SO₄, 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-2*H*-chromeno[3,4-*c*]pyridine-3(4*H*)-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, CDCl₃) 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-2*H*-chromeno[3,4-*c*]pyridine-3(4*H*)-carboxylate (two homochiral enantiomers)



A sample of racemic *tert*-butyl 8-bromo-10b-((4-fluorophenyl)sulfonyl)-1,4a,5,10b-tetrahydro-2*H*-chromeno[3,4-*c*]pyridine-3(4*H*)-carboxylate (1.96 g) was separated by chiral SFC using the following conditions: Column: Lux[®] Cellulose-4 46 x 250 mm, 5 μm (Phenomenex Inc.); column temperature 30 °C; pressure 100 bars; mobile phase CO₂-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-2*H*-chromeno[3,4-*c*]pyridine hydrochloride (two homochiral enantiomers)

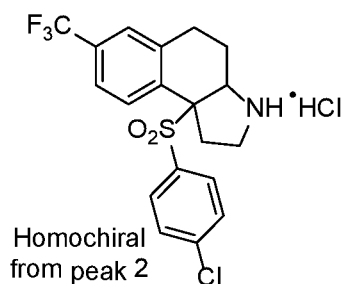


Following the procedures used in Steps I and K of the preparation of Intermediates 94 and 95, *tert*-butyl 8-bromo-10b-((4-fluorophenyl)sulfonyl)-1,4a,5,10b-tetrahydro-2*H*-chromeno[3,4-*c*]pyridine-3(4*H*)-carboxylate (homochiral, from Peak 1) was converted into one enantiomer of 10b-((4-fluorophenyl)sulfonyl)-8-(perfluoropropan-2-yl)-1,3,4,4a,5,10b-hexahydro-2*H*-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-2*H*-chromeno[3,4-*c*]pyridine-3(4*H*)-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-2*H*-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-1*H*-benzo[*e*]indole Hydrochloride



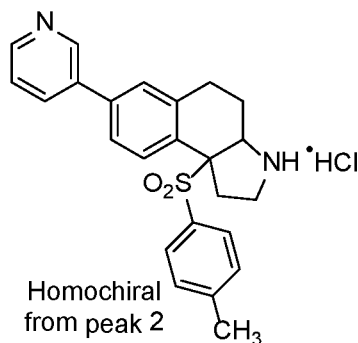
A mixture of *tert*-butyl 9b-((4-chlorophenyl)sulfonyl)-7-iodo-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (homochiral, from peak 2, Intermediate 69; 100 mg, 0.17 mmol), CuI (33 mg, 0.17 mmol) and KF (30 mg, 0.52 mmol) was placed in a sealed vial which was evacuated and filled with nitrogen 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 K₂HPO₄, 10% aqueous LiCl and brine, dried over Na₂SO₄ 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, 83mg, >100% yield). This material was used without further purification. LCMS *m/z* 416.0 (M+H)⁺, HPLC *t_R* 0.83 min (method B).

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Intermediate 107

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



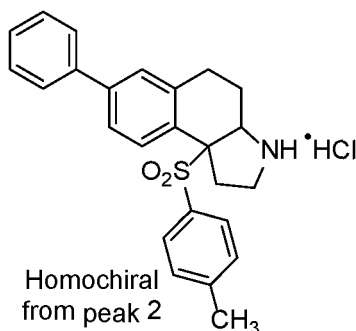
A mixture of *tert*-butyl 7-iodo-9b-tosyl-3a,4,5,9b-tetrahydro-1H-benzo[e]indole-3-carboxylate (homochiral, from peak 2, Intermediate 70; 50 mg, 0.090 mmol), chloro(2-dicyclohexyl-phosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (second generation Xphos precatalyst; 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 K₃PO₄ (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 Na₂SO₄ 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-1*H*-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).

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Intermediate 108

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

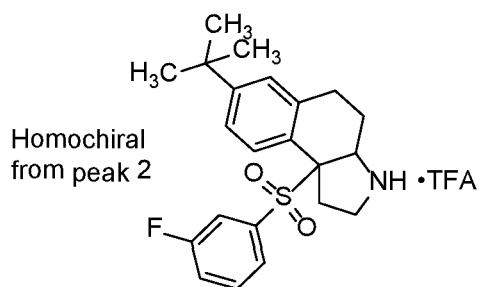


A solution of *tert*-butyl 7-iodo-9b-tosyl-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (homochiral, from peak 2, Intermediate 70; 20 mg, 0.036 mmol) in DMF (1 mL) was treated with 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (15 mg, 0.072 mmol), [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (2.6 mg, 3.6 μmol), and 2 M aqueous K₃PO₄ (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 Na₂SO₄ 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-1*H*-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).

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Intermediate 109

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

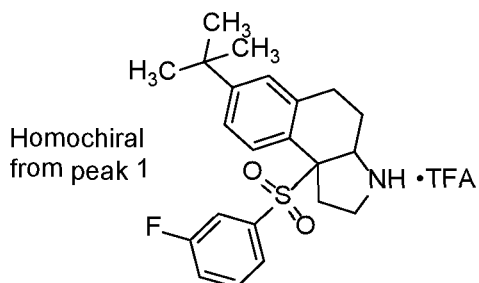


A mixture of *tert*-butyl 7-bromo-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (homochiral, from peak 2, Intermediate 73; 0.15 g, 0.294 mmol), THF (2.45 mL) and *tert*-butylzinc bromide (0.5 M in THF; 2.94 mL, 1.469 mmol) in a reaction vial was flushed with nitrogen.

Tetrakis(triphenylphosphine)palladium (3.04 mg, 2.94 μ mol) was added, and the vial was sealed and heated by microwave irradiation at 130 $^{\circ}$ C for 10 min. The cooled mixture was diluted with EtOAc (30 mL) and filtered. The filtrate was washed sequentially with water, saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ 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-1*H*-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-1*H*-benzo[*e*]indole trifluoroacetate



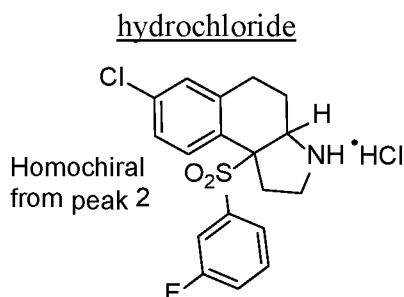
Following the procedure used to prepare Intermediate 109, *tert*-butyl 7-bromo-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate

(homochiral, from peak 1, Intermediate 72) was converted into crude 7-(*tert*-butyl)-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

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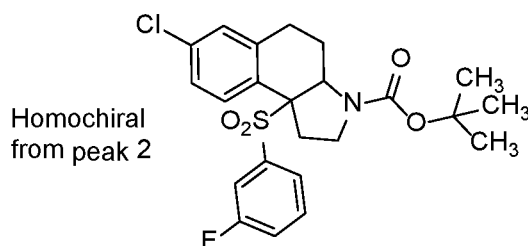
Intermediate 111

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



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



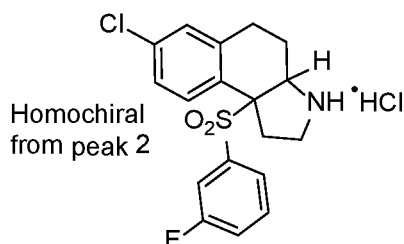
A mixture of copper(I) chloride (0.159 g, 1.607 mmol) and activated copper powder (prepared as outlined in Step A of the preparation of Intermediate 2; 0.102 g, 1.607 mmol) was placed in a sealable vial which was flushed with nitrogen. The mixture was treated with a solution of *tert*-butyl 7-bromo-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]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 x 50 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated to give *tert*-butyl 7-chloro-9b-((3-fluorophenyl)sulfonyl)-1,2,3a,4,5,9b-hexahydro-3*H*-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,

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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).

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

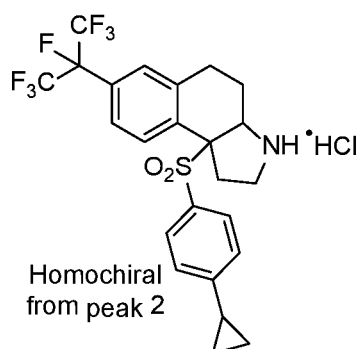


A mixture of *tert*-butyl 7-chloro-9b-((3-fluorophenyl)sulfonyl)-3a,4,5,9b-tetrahydro-1H-benzo[*e*]indole-3-carboxylate (65 mg, 0.139 mmol) and HCl (4 M in 1,4-dioxane; 2.0 mL, 8.00 mmol) was stirred at rt for 1.5 h. The mixture was concentrated to give 7-chloro-9b-((3-fluorophenyl)sulfonyl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[*e*]indole 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).

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Intermediate 112

9b-((4-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[*e*]indole Hydrochloride

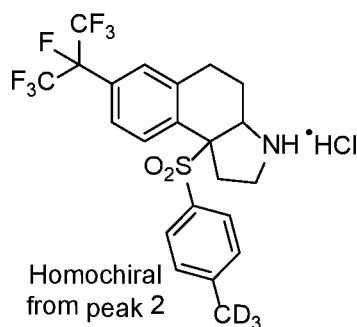


A solution of 9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[*e*]indole (homochiral, from peak 2, Intermediate 67; 100 mg, 0.15 mmol) and tetrakis(triphenylphosphine)palladium (8.8 mg, 7.6 μ mol) in

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 Na₂SO₄ 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-1*H*-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)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride

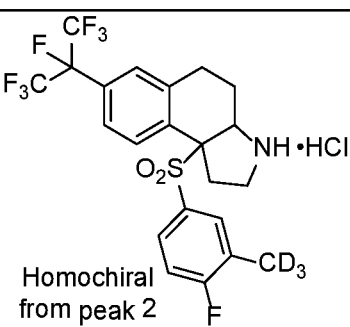
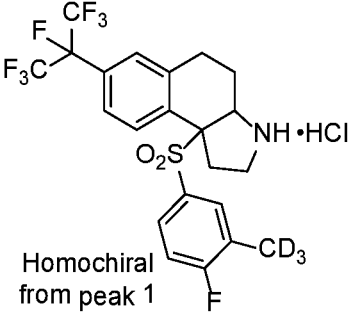


A solution of *tert*-butyl 9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (homochiral, from peak 2, Intermediate 67; 200 mg, 0.3 mmol) and iron(III) acetylacetonate (5.4 mg, 0.015 mmol) in THF (2 mL) was placed in a sealed tube which was 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 Na₂SO₄ 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-1*H*-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.

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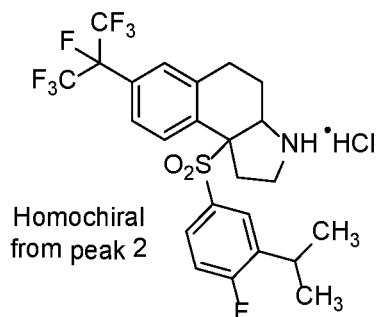
Table 6

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
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

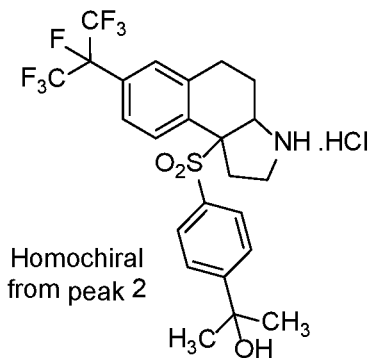
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A mixture of *tert*-butyl 9b-((3-bromo-4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (homochiral, from peak 2, Intermediate 84; 113 mg, 0.167 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (28.0 mg, 0.167 mmol) and 2 M aqueous K₃PO₄ (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 K₂HPO₄ 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-1*H*-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-9b*H*-benzo[*e*]indol-9b-yl)sulfonyl)phenyl)propan-2-ol hydrochloride



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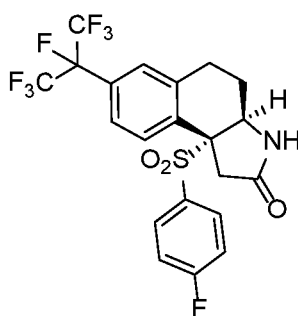
A solution of *tert*-butyl 9b-((4-(methoxycarbonyl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (homochiral, from peak 2, Intermediate 68; 150 mg, 0.24 mmol) in THF (5 mL) was cooled in a dry ice-acetone bath and treated dropwise with methyllithium (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 NH₄Cl. The phases were separated and the aqueous

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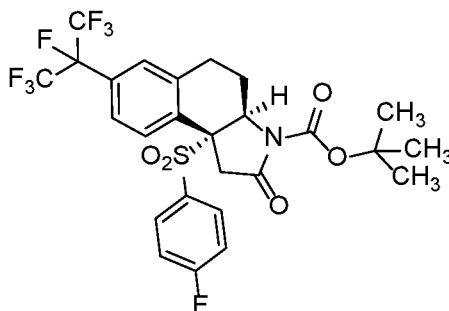
phase was extracted twice with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. The residue was treated with 4 M HCl in 1,4-dioxane (0.5 mL) and allowed to stand at rt for 1 h. The mixture was concentrated, affording crude 2-(4-((7-(perfluoropropan-2-yl)-1,2,3,3a,4,5-hexahydro-9bH-
 5 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

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



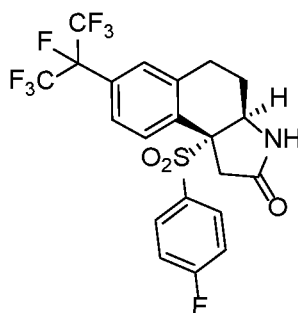
Step A: *tert*-butyl (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-2-oxo-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indole-3-carboxylate



A solution of (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-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
 20 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 Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (40 g), eluting with EtOAc-hexanes (gradient from 0-30%), to give (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-2-oxo-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate as a white glassy solid (0.50 g, 70% yield). LCMS *m/z* 599.0 (M+H+MeCN-C₄H₉)⁺, HPLC *t_R* 1.16 min (method B).

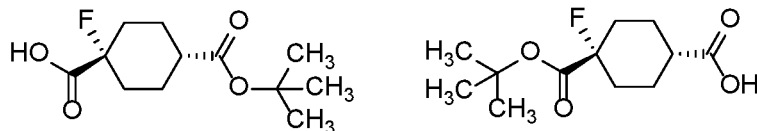
10 **Step B:** (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,3,3a,4,5,9b-hexahydro-2*H*-benzo[*e*]indol-2-one



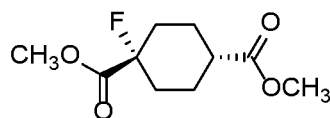
A solution of (3a*R*,9b*R*)-*tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-2-oxo-7-(perfluoropropan-2-yl)-3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (0.47 g, 0.766 mmol) in EtOAc (2 mL) was treated with HCl (2 M in diethyl ether; 1.915 mL, 3.83 mmol) and the mixture was stirred at rt for 15 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 K₂HPO₄ (20 mL) and extracted with DCM (2 x 20 mL). The combined organic phases were dried over Na₂SO₄ and concentrated to give (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,3,3a,4,5,9b-hexahydro-2*H*-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, CDCl₃) 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 (1*s*,4*s*)-4-(*tert*-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid and (1*s*,4*s*)-4-(*tert*-butoxycarbonyl)-4-fluorocyclohexane-1-carboxylic acid

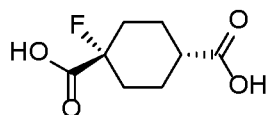


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Step A: dimethyl (1*s*,4*s*)-1-fluorocyclohexane-1,4-dicarboxylate

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 (1*r*,4*r*)-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 NH₄Cl (20 mL), the mixture was diluted with EtOAc (300 mL), washed sequentially with water (30 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated. The residue was purified by column chromatography, eluting with EtOAc-hexanes (gradient from 0-10%), to give dimethyl (1*s*,4*s*)-1-fluorocyclohexane-1,4-dicarboxylate as the second peak from the column (330 mg, 16% yield, minor isomer). ¹H NMR (400 MHz, CDCl₃) δ 3.76 (s, 3H), 3.66 (s, 3H), 2.44 - 2.29 (m, 1H), 2.26 - 1.73 (m, 8H).

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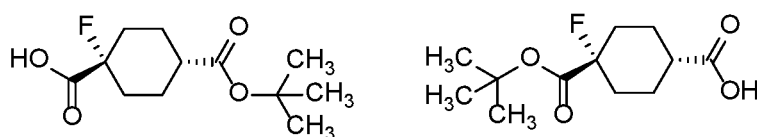
Step B: (1*s*,4*s*)-1-fluorocyclohexane-1,4-dicarboxylic acid

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A mixture of dimethyl (1*s*,4*s*)-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 (MgSO₄), filtered and concentrated to give (1*s*,4*s*)-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).

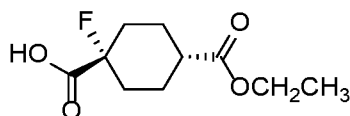
Step C: mixture of (1*s*,4*s*)-4-(*tert*-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid and (1*s*,4*s*)-4-(*tert*-butoxycarbonyl)-4-fluorocyclohexane-1-carboxylic acid



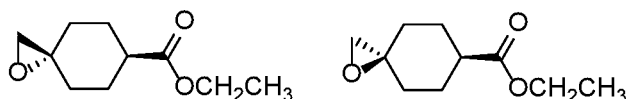
4-Dimethylaminopyridine (9.6 mg, 0.079 mmol) was added to a solution of (1*s*,4*s*)-1-fluorocyclohexane-1,4-dicarboxylic acid (50 mg, 0.263 mmol) and di-*tert*-butyl dicarbonate (73 μL, 0.316 mmol) in *tert*-butanol (2 mL). After stirring at rt for 15 h, the mixture was treated with EtOAc (60 mL), washed sequentially with 0.2 M aqueous HCl (5 mL), water (5 mL) and brine (5 mL), dried (MgSO₄), filtered and concentrated to give crude (1*s*,4*s*)-4-(*tert*-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid (55 mg), contaminated with (1*s*,4*s*)-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

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

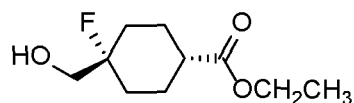


Step A: mixture of ethyl (3*r*,6*r*)-1-oxaspiro[2.5]octane-6-carboxylate and ethyl (3*s*,6*s*)-1-oxaspiro[2.5]octane-6-carboxylate



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 x 50 mL). The combined organic phases were dried over Na₂SO₄ 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 (3*r*,6*r*)-1-oxaspiro[2.5]octane-6-carboxylate and ethyl (3*s*,6*s*)-1-oxaspiro[2.5]octane-6-carboxylate (3.8 g, 66% yield). ¹H NMR (400 MHz, CDCl₃) 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).

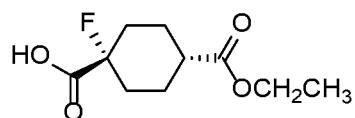
Step B: ethyl (1*s*,4*s*)-4-fluoro-4-(hydroxymethyl)cyclohexane-1-carboxylate



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 (3*r*,6*r*)-1-oxaspiro[2.5]octane-6-carboxylate and ethyl (3*s*,6*s*)-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 NH₄OH (25 mL) and DCM (25 mL). The mixture was adjusted to pH 8 using concentrated aqueous NH₄OH and extracted with DCM (2 x 50 mL). The combined organic phases were washed sequentially with 1 M aqueous HCl (50 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (24 g), eluting with EtOAc-hexanes (gradient from 0-30%), to give (1*s*,4*s*)-ethyl 4-fluoro-4-(hydroxymethyl)cyclohexanecarboxylate as a solid (390 mg, 35% yield). ¹H NMR (400 MHz, CDCl₃) 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). (1*r*,4*r*)-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).

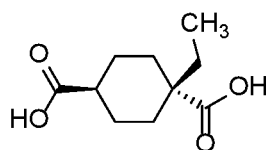
5 **Step C: (1*s*,4*s*)-4-(ethoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid**



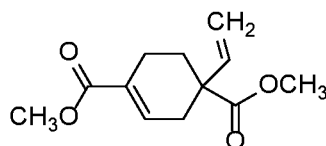
A solution of (1*s*,4*s*)-ethyl 4-fluoro-4-(hydroxymethyl)cyclohexanecarboxylate (0.76 g, 3.72 mmol) in MeCN (8 mL) and tetrachloromethane (8.00 mL) was treated with a solution of periodic acid (3.48 g, 15.26 mmol) in water (12.00 mL), then with
 10 ruthenium(III) chloride hydrate (0.034 g, 0.149 mmol). 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 x 20 mL). The combined organic phases were washed with brine (2 x 30 mL), dried over Na_2SO_4 and concentrated to give crude (1*s*,4*s*)-4-(ethoxycarbonyl)-
 15 1-fluorocyclohexanecarboxylic acid as a solid (0.74g, 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

20 **(1*r*,4*r*)-1-ethylcyclohexane-1,4-dicarboxylic acid**



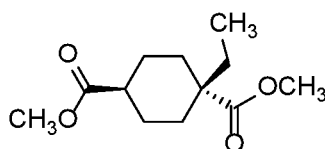
Step A: dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate



25 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

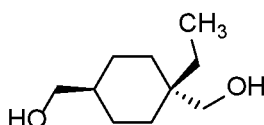
reach rt and stirring was continued for 12 h. The mixture was treated with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with 1.5 M aqueous HCl (2 x 50 mL) followed by 50 mL saturated brine, dried over Na₂SO₄, filtered and concentrated to provide a pale yellow 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, CDCl₃) 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 (1*r*,4*r*)-1-ethylcyclohexane-1,4-dicarboxylate



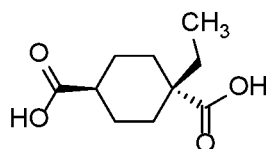
A solution of dimethyl 4-vinylcyclohex-1-ene-1,4-dicarboxylate (1 g, 4.46 mmol) in DCM (100 mL) was treated with iridium(I) hexafluorophosphate (1,5-cyclooctadiene)-(pyridine)-(tricyclohexylphosphine) (Crabtree's catalyst; 72 mg, 0.089 mmol). The solution was stirred under a hydrogen atmosphere (balloon 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 x 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 (1*r*,4*r*)-1-ethylcyclohexane-1,4-dicarboxylate (1 g, 98% yield) as colorless liquid. ¹H NMR (300 MHz, CDCl₃) 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: ((1*r*,4*r*)-1-ethylcyclohexane-1,4-diyl)dimethanol



A solution of dimethyl (1*r*,4*r*)-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
5 by TLC (silica gel, 10% EtOAc in hexanes). After complete conversion, the mixture was cooled to 0 °C and slowly treated with saturated aqueous NH₄Cl (about 5 mL). The mixture was further diluted with additional saturated aqueous NH₄Cl (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄ and concentrated to yield ((1*r*,4*r*)-1-ethylcyclohexane-1,4-
10 diyl)dimethanol as a colorless liquid (150 mg, 99% yield). ¹H NMR (300 MHz, CDCl₃) 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).

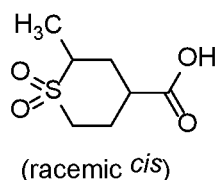
Step D: (1*r*,4*r*)-1-ethylcyclohexane-1,4-dicarboxylic acid



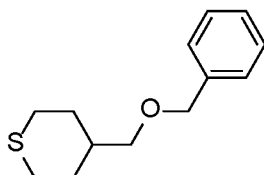
A solution of ((1*r*,4*r*)-1-ethylcyclohexane-1,4-diyl)dimethanol (150 mg, 0.871 mmol) in acetone (15 mL) at 0 °C was slowly treated with freshly prepared aqueous chromic acid [prepared by adding H₂SO₄ (0.278 mL, 5.22 mmol) to a cold solution of sodium dichromate dihydrate (1.04 g, 3.48 mmol) in water (5 mL) at 0 °C with stirring for
20 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 x 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 Na₂SO₄ and concentrated to give (1*r*,4*r*)-1-ethylcyclohexane-1,4-dicarboxylic acid as a
25 white solid (117 mg, 67% yield). ¹H 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

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

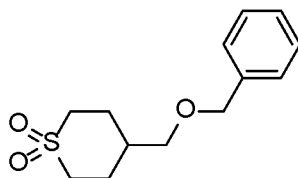


Step A: 4-((benzyloxy)methyl)tetrahydro-2H-thiopyran



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 NH₄Cl (20 mL), diluted with water (50 mL) and extracted with EtOAc (75 mL). The organic phase was washed sequentially with 10% aqueous LiCl (3 x 30 mL) and brine (30 mL), dried over Na₂SO₄ 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). ¹H NMR (400 MHz, CDCl₃) 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).

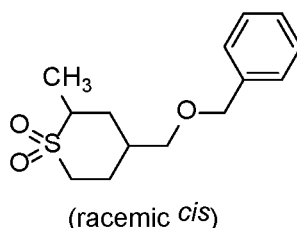
Step B: 4-((benzyloxy)methyl)tetrahydro-2H-thiopyran 1,1-dioxide



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 Na₂S₂O₃ (120 mL). The organic phase was separated and washed with 10% aqueous K₂CO₃ (2 x 150 mL), dried over Na₂SO₄ 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-2*H*-thiopyran 1,1-dioxide as a white solid (4.9 g, 91% yield). ¹H NMR (400 MHz, CDCl₃) 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).

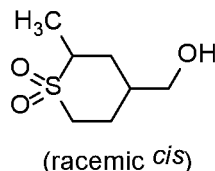
Step C: (2*RS*,4*RS*)-4-((benzyloxy)methyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide



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-2*H*-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 NH₄Cl (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine, dried over Na₂SO₄ 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-2*H*-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). ¹H NMR (400 MHz, CDCl₃) 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 (2*R*,4*r*,6*S*)-4-((benzyloxy)methyl)-2,6-dimethyltetrahydro-2*H*-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: (2*RS*,4*RS*)-4-(hydroxymethyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide

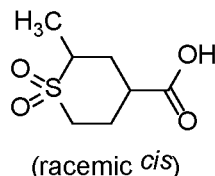


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A solution of (2*RS*,4*RS*)-4-((benzyloxy)methyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (0.45 g, 1.677 mmol) in MeOH (2 mL) and ethanol (10 mL) was treated with palladium on carbon (160 mg, 0.075 mmol) and stirred under a hydrogen atmosphere (balloon pressure) for 1.5 h. The mixture was filtered to remove the catalyst and the filtrate was concentrated to give (2*RS*,4*RS*)-4-(hydroxymethyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide as a white solid (280 mg, 94% yield). ¹H NMR (400 MHz, CDCl₃) 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).

10

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



15

A solution of (2*RS*,4*RS*)-4-(hydroxymethyl)-2-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (0.275 g, 1.543 mmol) in MeCN (0.9 mL) and CCl₄ (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 Na₂SO₄ and concentrated. The residue was treated with EtOAc (125 mL) and MeOH (10 mL), filtered (Acrodisc syringe filter, 25 mm, 0.45 μm) and concentrated to give (2*RS*,4*RS*)-2-methyltetrahydro-2*H*-

20

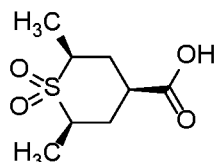
25

thiopyran-4-carboxylic acid 1,1-dioxide as a gray solid (165 mg, 56% yield), used without further purification. ^1H NMR (400 MHz, $\text{MeOH-}d_4$) 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).

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Intermediate 123

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

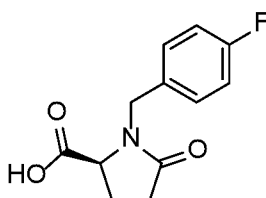


Following the procedures of Intermediate 122 Steps D and E, (2*R*,4*r*,6*S*)-4-((benzyloxy)methyl)-2,6-dimethyltetrahydro-2*H*-thiopyran 1,1-dioxide (isolated as a side product in Step C of the preparation of Intermediate 122) was converted into (2*R*,4*r*,6*S*)-2,6-dimethyltetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide. ^1H 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).

15

Intermediate 124

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



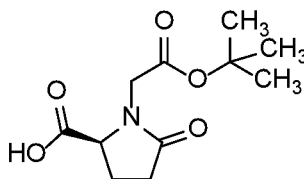
A suspension of NaH (60% in mineral oil; 0.336 g, 8.40 mmol) in THF (11 mL) was treated with (*S*)-ethyl 5-oxopyrrolidine-2-carboxylate (0.88 g, 5.60 mmol). The mixture was stirred at rt for 15 min, then 1-(bromomethyl)-4-fluorobenzene (0.837 mL, 6.72 mmol) was added and the mixture was stirred at rt 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

25

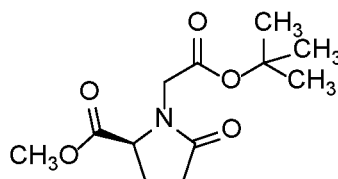
about pH 2, and then was extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄ and concentrated to provide (*S*)-1-(4-fluorobenzyl)-5-oxopyrrolidine-2-carboxylic acid as a yellow syrup (0.54 g, 41% yield). LCMS *m/z* 238.3 (M+H)⁺, HPLC *t_R* 0.92 min (method B). ¹H NMR (400 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



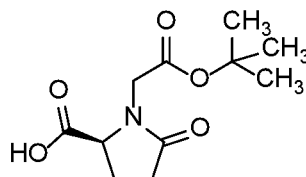
Step A: methyl (*S*)-1-(2-(*tert*-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate



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 Na₂SO₄ 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). ¹H NMR (400 MHz, CDCl₃) 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

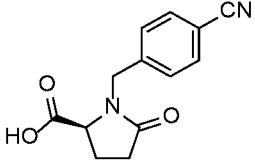
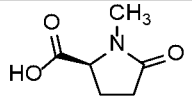
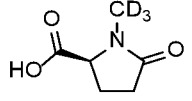
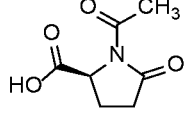
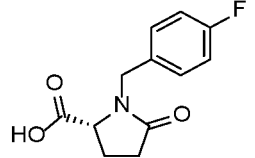
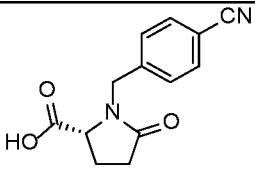
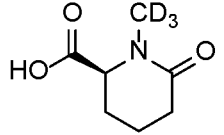


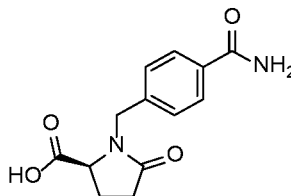
A solution of (*S*)-methyl 1-(2-(*tert*-butoxy)-2-oxoethyl)-5-oxopyrrolidine-2-carboxylate (0.25 g, 0.972 mmol) in THF (3 mL) was stirred on an ice-water bath and treated with a solution of LiOH hydrate (0.043 g, 1.020 mmol) in water (3 mL). The solution was stirred for 60 min, then was treated with 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 Na₂SO₄ 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, CDCl₃) 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
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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
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**

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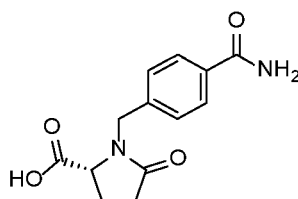
A suspension of (*S*)-1-(4-cyanobenzyl)-5-oxopyrrolidine-2-carboxylic acid (Intermediate 126, 0.120 g, 0.491 mmol) in 85% aqueous H₂SO₄ (1.637 mL, 24.57 mmol) was heated at 60 °C. After 100 min, the mixture was cooled to rt and poured onto ice and water. The resulting mixture was extracted with EtOAc, and the organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to afford (*S*)-1-(4-

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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

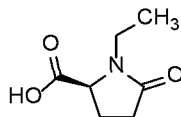
(R)-1-(4-carbamoylbenzyl)-5-oxopyrrolidine-2-carboxylic acid



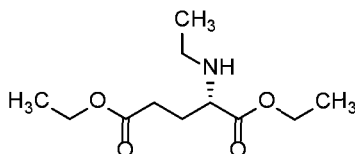
Following the procedure used to prepare Intermediate 133, (*R*)-1-(4-cyanobenzyl)-5-oxopyrrolidine-2-carboxylic acid (Intermediate 131) was converted into (*R*)-1-(4-carbamoylbenzyl)-5-oxopyrrolidine-2-carboxylic acid in 68% yield. LCMS m/z 262.9 (M+H)⁺, HPLC t_R 0.44 min (method B).

Intermediate 135

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



Step A: diethyl ethyl-L-glutamate

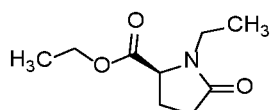


A mixture of (*S*)-diethyl 2-aminopentanedioate hydrochloride (1.5 g, 6.26 mmol) in THF (19 mL) and MeOH (10 mL) was treated with crushed KOH (0.410 g, 6.57 mmol) and stirred at rt for 10 min. The mixture was treated with a mixture of acetaldehyde (5 M in THF; 3.75 mL, 18.77 mmol) and acetic acid (0.394 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 K₂HPO₄. The organic phase was washed with brine, dried over Na₂SO₄, 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).

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



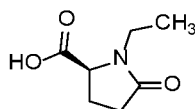
A solution of diethyl ethyl-L-glutamate (1.39 g, 6.01 mmol) in MeOH (12 mL) in a sealed vessel was heated at 140 °C for 15 min, then was heated via microwave irradiation for 15 min at 150 °C. The mixture was cooled to rt, concentrated, and the residue was partitioned between EtOAc and 0.3 M aqueous HCl. The organic phase was washed sequentially with water and saturated aqueous NaHCO₃, dried over Na₂SO₄, filtered, and concentrated to afford crude ethyl (*S*)-1-ethyl-5-oxopyrrolidine-2-carboxylate as a brown oil (0.39g, 35% yield). LCMS *m/z* 186.1 (M+H)⁺, HPLC *t_R* 0.61 min (method B). ¹H NMR (400 MHz, CDCl₃) 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).

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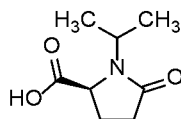
Step C: (*S*)-1-ethyl-5-oxopyrrolidine-2-carboxylic acid



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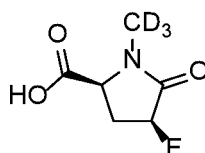
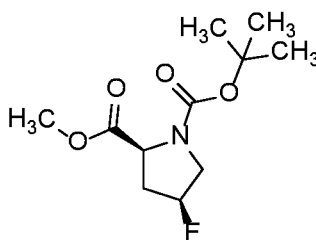
A mixture of ethyl (*S*)-1-ethyl-5-oxopyrrolidine-2-carboxylate (0.39 g, 2.106 mmol) and LiOH monohydrate (0.166 g, 6.95 mmol) in THF (6 mL), MeOH (2 mL) and water (2 mL) was stirred at rt. After 16 h the mixture was concentrated, and the residue was partitioned between 1 M aqueous HCl and chloroform-isopropanol (93:7). The organic phase was washed with brine, dried over Na₂SO₄, 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, CDCl₃): 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

- 5 (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).

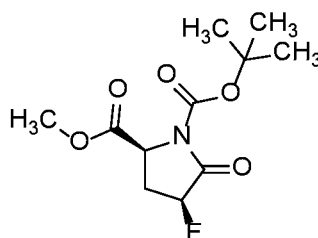
Intermediate 137

- 10 (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

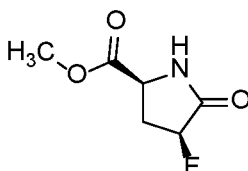
- 15 A solution of (2S,4S)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (10 g, 40.8 mmol) in DCM (204 mL) was cooled in an ice-water bath and treated slowly with DAST (6.46 mL, 48.9 mmol). The mixture was stirred at rt for 5.5 h, then was partitioned between water and additional DCM. The organic phase was washed with brine, dried over Na₂SO₄, 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).
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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 (2*S*,4*S*)-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 Na₂SO₄, 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 (2*S*,4*S*)-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, CDCl₃): 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).

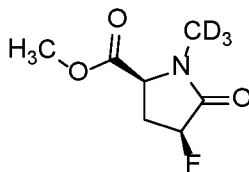
Step C: methyl (2*S*,4*S*)-4-fluoro-5-oxopyrrolidine-2-carboxylate



A solution of (2*S*,4*S*)-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 K₂HPO₃ and brine, dried over Na₂SO₄, 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 (2*S*,4*S*)-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, CDCl₃) 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 (2*S*,4*S*)-4-fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylate

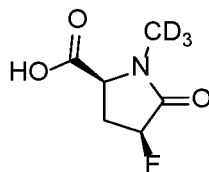


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A mixture of (2*S*,4*S*)-methyl 4-fluoro-5-oxopyrrolidine-2-carboxylate (0.48 g, 2.98 mmol) and Cs₂CO₃ (2.426 g, 7.45 mmol) in MeCN (16.55 mL) was treated with iodomethane-*d*₃ (0.927 mL, 14.89 mmol) and heated at 45 °C overnight in a sealed vial. After 18 h, the mixture was cooled to rt, filtered and concentrated to afford methyl

10 (2*S*,4*S*)-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: (2*S*,4*S*)-4-fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid



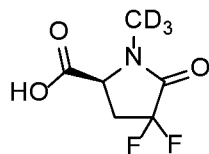
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A mixture of methyl (2*S*,4*S*)-4-fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylate (0.53 g, 2.97 mmol) and LiOH monohydrate (0.221 g, 9.22 mmol) in THF-MeOH-water (3:1:1) (29.7 mL) was stirred at rt for 18 h. The mixture was concentrated, the 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 (2*S*,4*S*)-4-

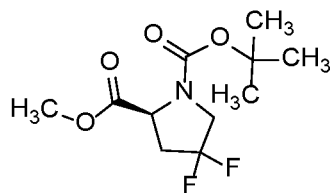
20 fluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid was used without further purification. LCMS *m/z* 165.0 (M+H)⁺, HPLC *t_R* 0.35 min (method B).

Intermediate 138

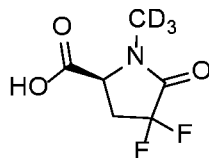
(*S*)-4,4-difluoro-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid



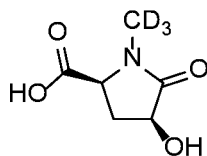
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Step A: 1-(*tert*-butyl) 2-methyl (*S*)-4,4-difluoropyrrolidine-1,2-dicarboxylate

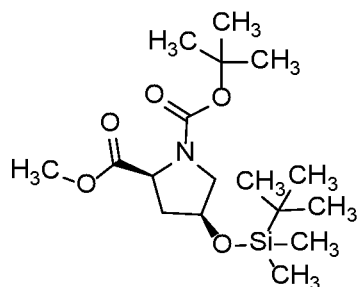
A solution of (*S*)-1-*tert*-butyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate (5.02 g, 20.64 mmol) in DCM (83 mL) at -78 °C was treated dropwise with DAST (9.82 mL, 74.3 mmol). The mixture was stirred at this temperature for 15 min, then warmed to rt and stirred for 18 h. The mixture was cooled to 0 °C, diluted with additional DCM and treated with ice and saturated aqueous NaHCO₃. The organic phase was separated, washed with brine, dried over Na₂SO₄, 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, CDCl₃) 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(2*S*,4*S*)-4-hydroxy-1-(methyl-*d*₃)-5-oxopyrrolidine-2-carboxylic acid

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



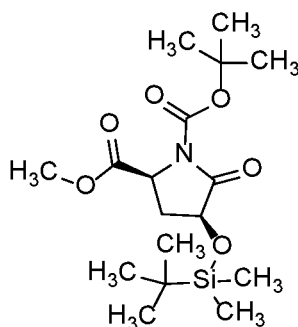
5 A solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (3.1 g, 12.64 mmol) in THF (56 mL), cooled in an ice-water bath, was treated slowly with a solution of *tert*-butylchlorodimethylsilane (2.286 g, 15.17 mmol) in THF (7.02 mL), then with Et₃N (2.82 mL, 20.22 mmol). 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

10 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 Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel (80

15 g), eluting with EtOAc-hexanes (0-10%), to provide 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-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, CDCl₃) 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).

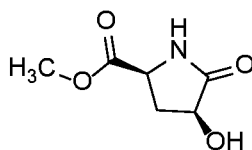
20 (m, 9H), 0.08 - 0.03 (m, 6H).

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

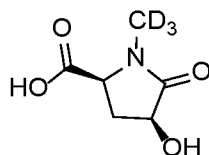


A solution of sodium periodate (7.08 g, 33.1 mmol) in water (126 mL) was treated with ruthenium(IV) oxide hydrate (0.400 g, 2.65 mmol) and stirred at rt for 5 min. This mixture was then treated with a solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (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 NaHCO₃, 10% aqueous Na₂S₂O₃ and brine, dried over Na₂SO₄, filtered and concentrated to afford 1-((*tert*-butyl) 2-methyl (2*S*,4*S*)-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, CDCl₃) 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 (2*S*,4*S*)-4-hydroxy-5-oxopyrrolidine-2-carboxylate



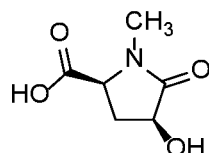
A solution of (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-((*tert*-butyldimethylsilyl)oxy)-5-oxopyrrolidine-1,2-dicarboxylate (4.85 g, 12.98 mmol) in DCM (16 mL) was cooled in an ice-water bath and treated with TFA (3 mL). The mixture was warmed to rt, stirred for 2 h, and concentrated to provide methyl (2*S*,4*S*)-4-hydroxy-5-oxopyrrolidine-2-carboxylate 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, CDCl₃) 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: (2*S*,4*S*)-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 (2*S*,4*S*)-4-hydroxy-5-oxopyrrolidine-2-carboxylate was converted into (2*S*,4*S*)-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

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

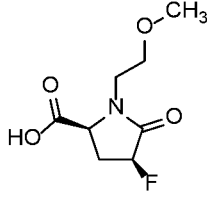
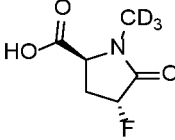
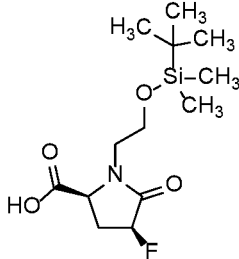
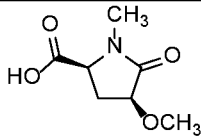


(2*S*,4*S*)-4-hydroxy-1-methyl-5-oxopyrrolidine-2-carboxylic acid was prepared using the procedures of Intermediate 139, substituting iodomethane for iodomethane-*d*₃. LCMS *m/z* 160.0 (M+H)⁺, HPLC *t*_R 0.26 min (method B).

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

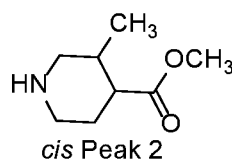
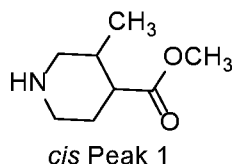
Table 8

Intermediate number	Structure	LCMS <i>m/z</i> observed	HPLC <i>t</i> _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



5

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 K₂CO₃ 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, 5μm (Chiral Technologies Inc.); column temperature 35 °C; pressure 100 bars; mobile phase CO₂-MeOH (85:15) containing 0.1% NH₄OH; flow rate 250 mL/min; injection volume 1.5 mL. Peak 1 was eluted with *t*_R 5.5

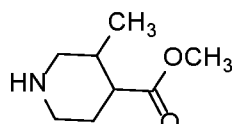
15

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).

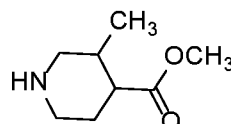
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Intermediates 149 and 150

trans methyl 3-methylpiperidine-4-carboxylate



trans Peak 1

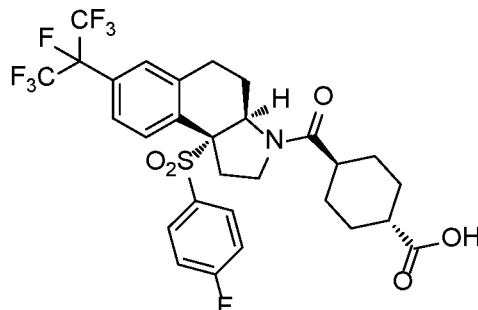


trans Peak 2

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 x 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 ($\text{M}+\text{H}$) $^+$, HPLC t_R 0.44 min (method B). This material was separated by chiral SFC using the following conditions: Column: Lux[®] Cellulose-4 30 x 250 mm, 5 μm (Phenomenex Inc.); column temperature 35 $^\circ\text{C}$; 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): ^1H NMR (400 MHz, $\text{MeOH}-d_4$) 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): ^1H 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).

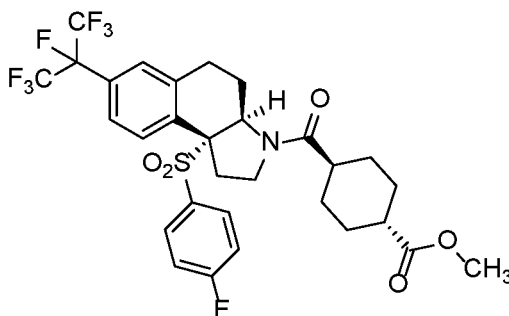
Example 1

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



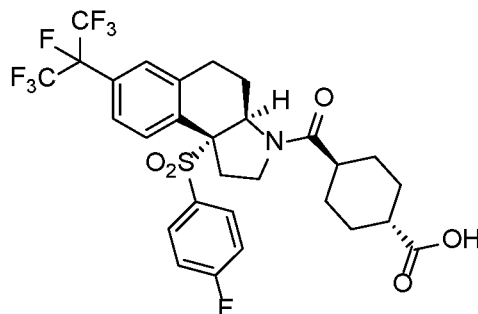
5

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



- 10 A solution of ((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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
- 15 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 (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylate (246 mg, 88% yield). LCMS *m/z* 668.1 (M+H)⁺,
- 20 HPLC *t_R* 1.13 min (method B).

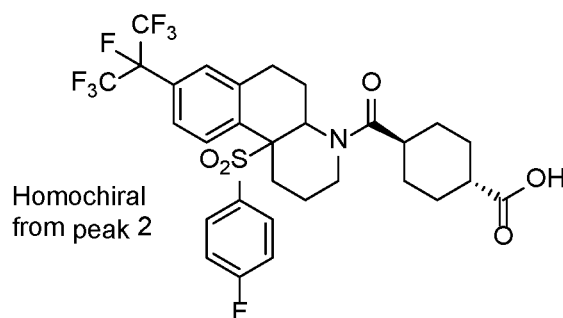
Step B: (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A solution of methyl (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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 x 20 mL). The combined organic layers were dried over Na₂SO₄, 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: CO₂/MeOH (75:25); 35 °C, 100 bar) to afford (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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). ¹H 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). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -104.9 (s, 1F), -77.3 (m, 1F), -77.0 (s, 6F).

Example 2

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



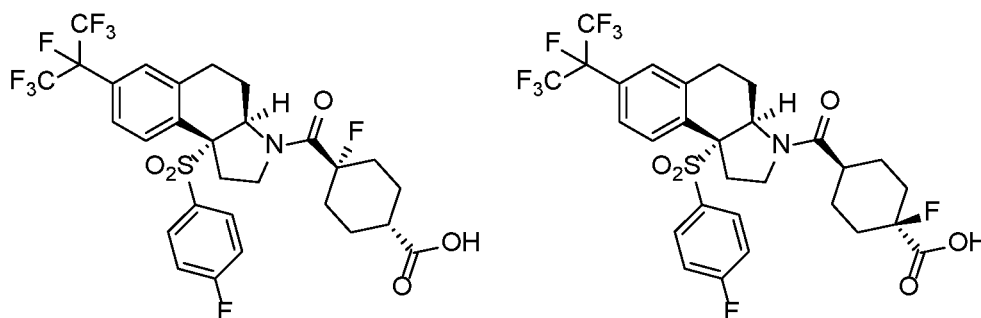
A solution of trans-1,4-cyclohexanedicarboxylic acid monomethyl ester in DCM was treated with excess oxalyl chloride and catalytic DMF, and the mixture was stirred at
 5 rt for 1 h. The mixture was concentrated to provide (1*r*,4*r*)-methyl 4-(chlorocarbonyl)cyclohexanecarboxylate, which was used without 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-
 10 water bath and treated with 4-dimethylaminopyridine (9.52 mg, 0.078 mmol), then was treated dropwise with a solution of crude (1*r*,4*r*)-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 K₂HPO₄
 15 and brine, dried over Na₂SO₄ 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 Na₂SO₄ and concentrated. The residue was
 20 purified by preparative HPLC (method E, gradient 30-80% B, 25 min) to give homochiral (1*r*,4*r*)-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 (14 mg, 26% yield). LCMS *m/z* 668.1 (M+H)⁺, HPLC *t_R* 2.29 min (method C).

Examples 3 and 4

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

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



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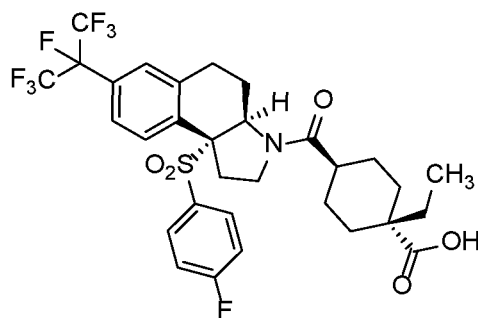
A solution of (3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32; 100 mg, 0.187 mmol) in DMF (2 mL) was treated with a mixture of (1*S*,4*s*)-4-(*tert*-butoxycarbonyl)-1-fluorocyclohexane-1-carboxylic acid and (1*S*,4*s*)-4-(*tert*-butoxycarbonyl)-4-fluorocyclohexane-1-carboxylic acid (Intermediate 119; 92 mg, 0.373 mmol). PyBOP (146 mg, 0.280 mmol) and Et₃N (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 (1*S*,4*s*)-4-fluoro-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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 (1*S*,4*s*)-1-fluoro-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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

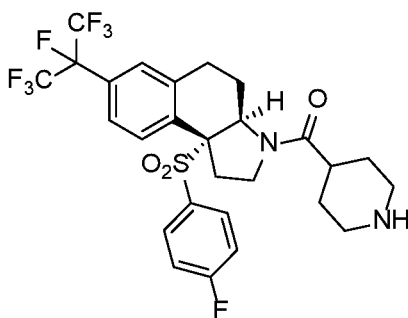
5 (1*R*,4*r*)-1-ethyl-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A solution of ((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-
 10 2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole (Intermediate 32; 30 mg, 0.060 mmol) in
 DMF (0.8 mL) was treated with (1*r*,4*r*)-1-ethylcyclohexane-1,4-dicarboxylic acid
 (Intermediate 121; 24.06 mg, 0.120 mmol), DIPEA (31.5 μ L, 0.180 mmol) and HATU
 (34.3 mg, 0.090 mmol). The mixture was stirred at rt for 1h, then was purified by
 preparative HPLC (method E, gradient 40-80% B) to provide (1*R*,4*r*)-1-ethyl-4-
 15 ((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-
 hexahydro-1*H*-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),
 20 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

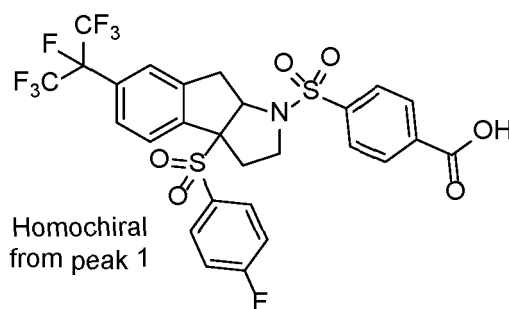
((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-
 hexahydro-3*H*-benzo[*e*]indol-3-yl)(piperidin-4-yl)methanone



A mixture of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 MgSO₄ 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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 K₂HPO₄ and brine. The combined aqueous phases were extracted with EtOAc, and the combined organic phases were dried over Na₂SO₄ 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 ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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

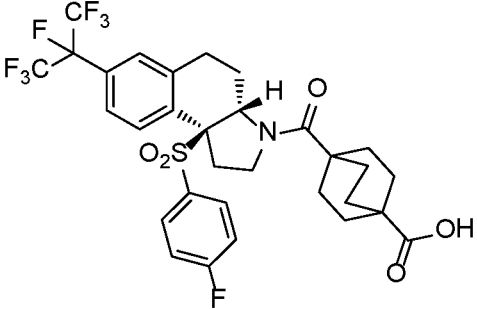
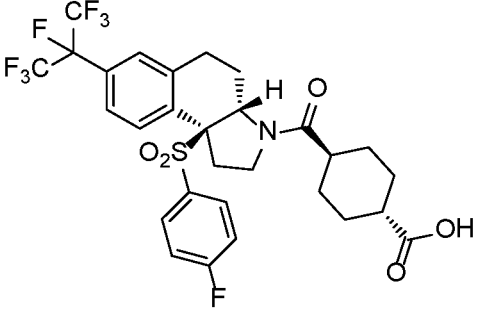
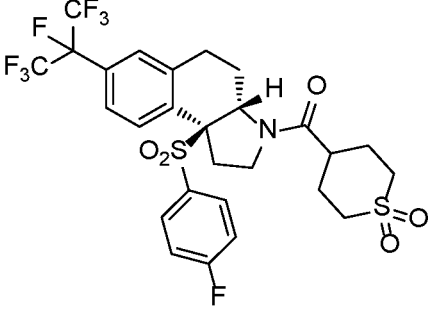
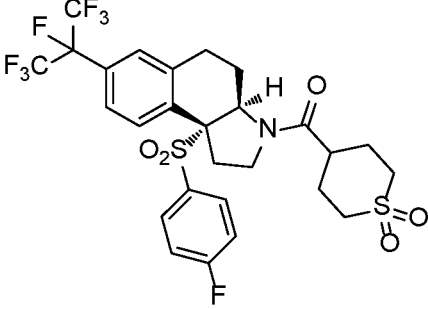
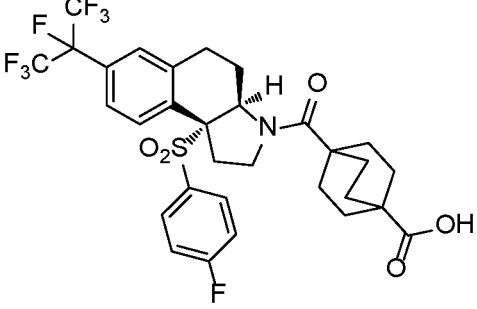
4-((3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-3,3a,8,8a-tetrahydroindeno[2,1-*b*]pyrrol-1(2*H*)-yl)sulfonyl)benzoic acid



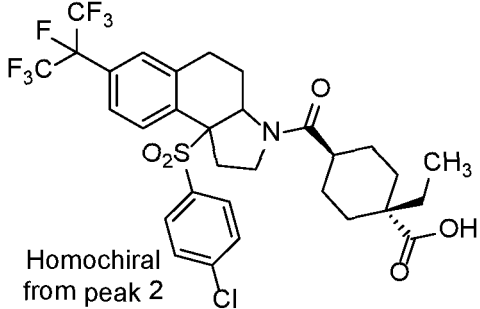
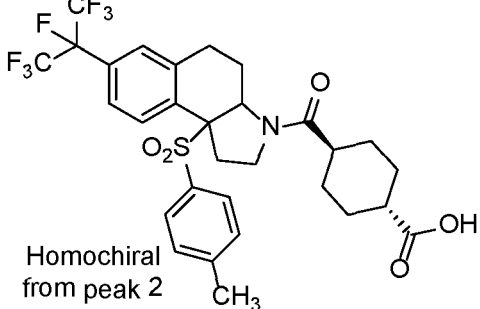
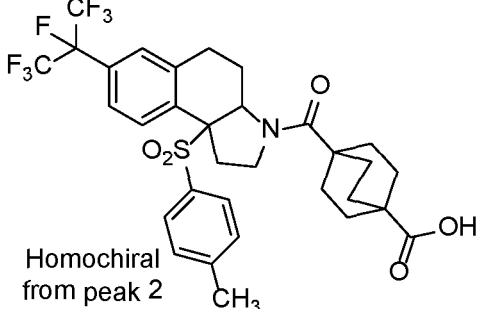
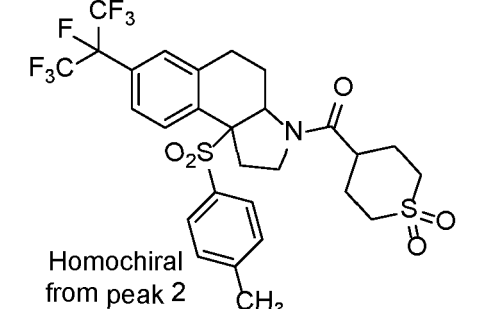
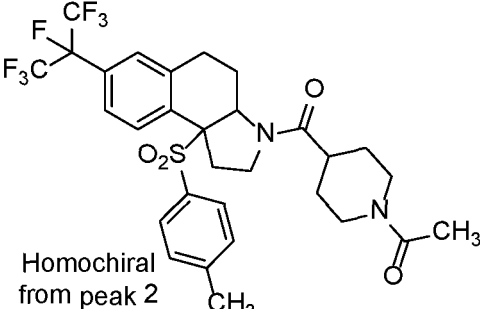
A solution of 3a-((4-fluorophenyl)sulfonyl)-6-(perfluoropropan-2-yl)-1,2,3,3a,8,8a-hexahydroindeno[2,1-*b*]pyrrole hydrochloride (homochiral, from peak 1, Intermediate 94; 30 mg, 0.057 mmol) and methyl 4-(chlorosulfonyl)benzoate (20.23 mg, 0.086 mmol) in DMF (0.5 mL) was treated with Et₃N (0.024 mL, 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 concentrated. 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(2*H*)-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.

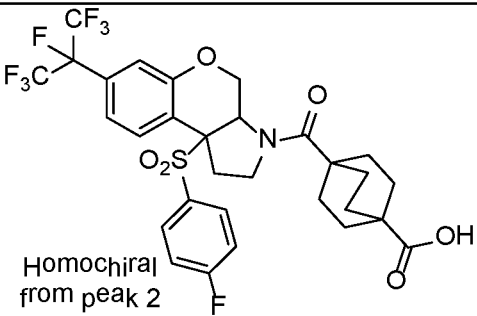
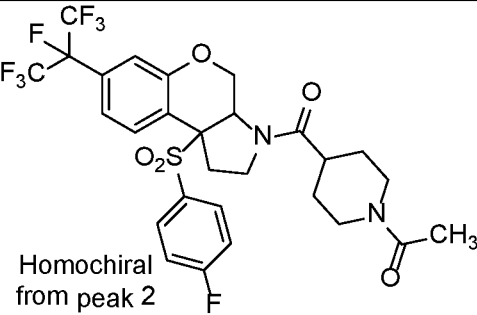
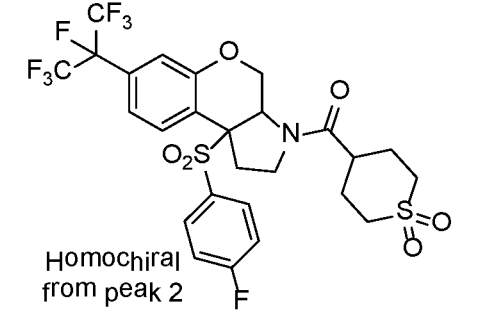
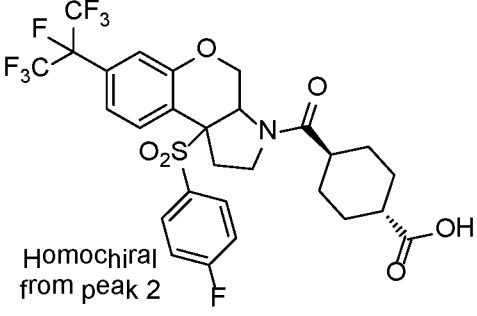
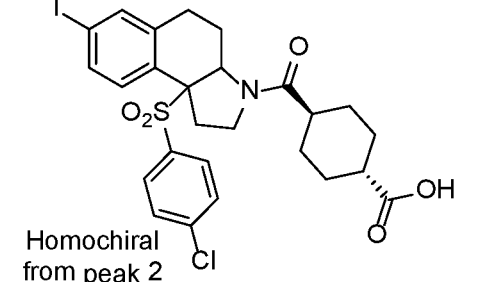
The Examples in Table 9 were prepared using procedures used to prepare Examples 1 through 7 or similar procedures, by reacting an appropriate amine intermediate with an appropriate acid, acid chloride, acid anhydride, sulfonyl chloride or sulfamyl chloride, followed by ester hydrolysis or other functional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

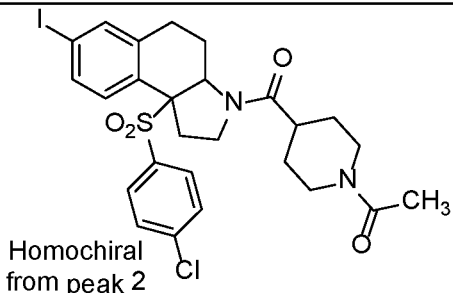
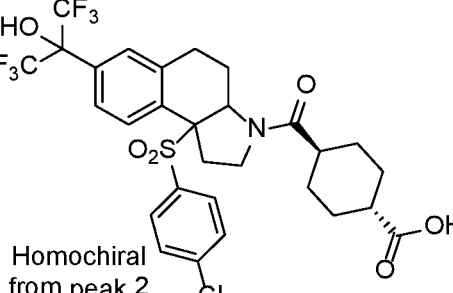
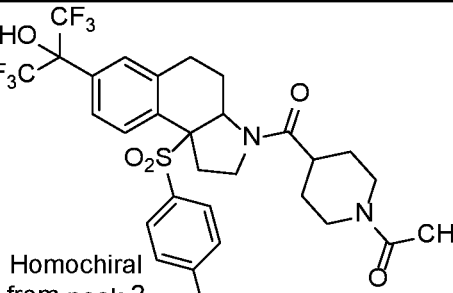
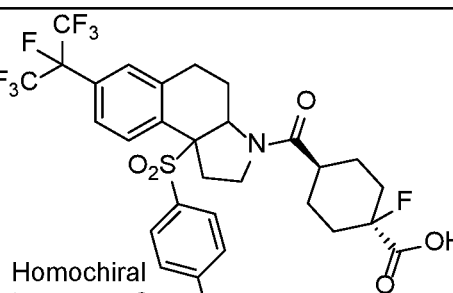
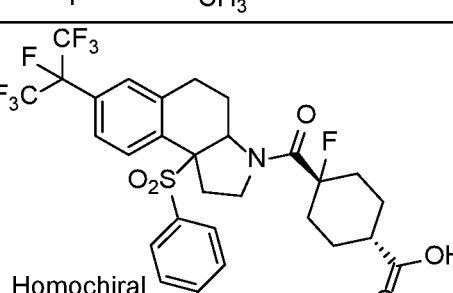
Table 9

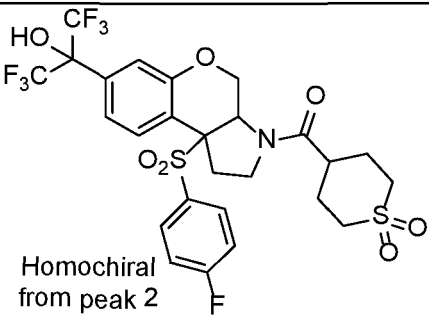
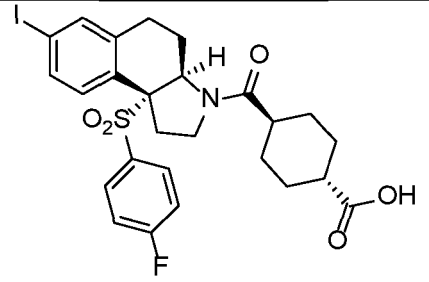
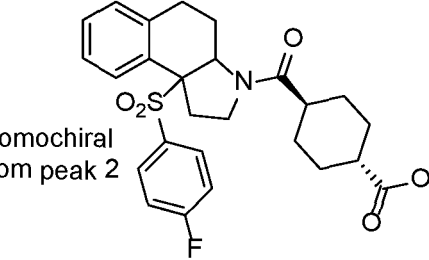
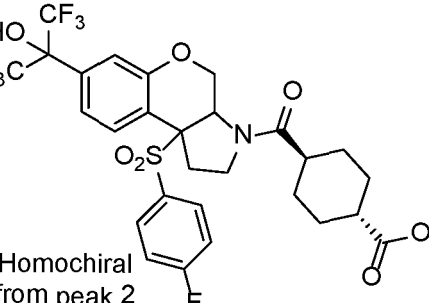
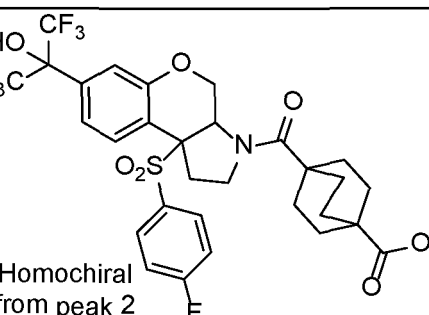
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
8		680.1 (M+H) ⁺	1.08	B
9		654.2 (M+H) ⁺	1.06	B
10		660.0 (M+H) ⁺	1.04	B
11		660.0 (M+H) ⁺	1.04	B
12		680.1 (M+H) ⁺	1.08	B

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
13		653.1 (M+H) ⁺	1.05	B
14	Homochiral From peak 2	670.0 (M+H) ⁺	1.08	B
15	Homochiral from peak 2	696.0 (M+H) ⁺	1.12	B
16	Homochiral from peak 2	676.0 (M+H) ⁺	1.07	B
17	Homochiral from peak 2	669.1 (M+H) ⁺	1.06	B

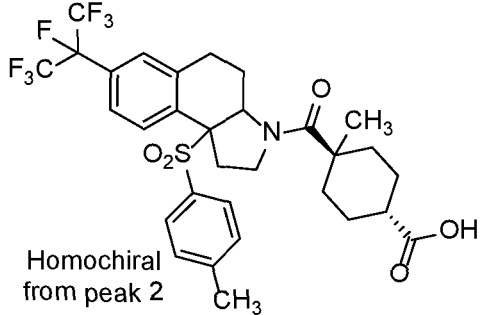
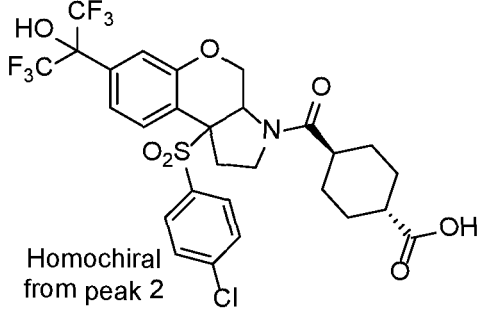
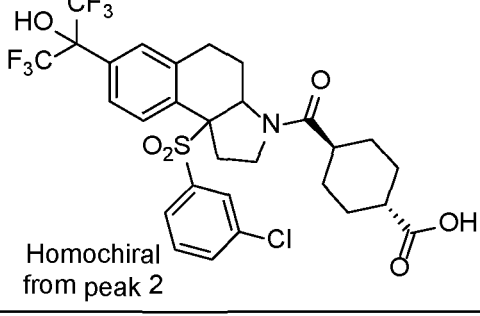
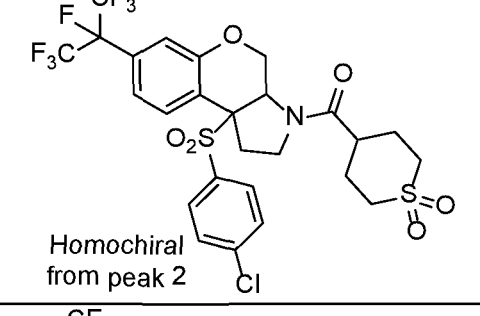
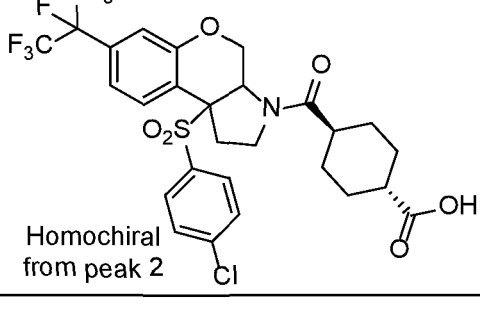
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
18	 Homochiral from peak 2	698.1 (M+H) ⁺	1.12	B
19	 Homochiral from peak 2	650.1 (M+H) ⁺	1.07	B
20	 Homochiral from peak 2	676.1 (M+H) ⁺	1.10	B
21	 Homochiral from peak 2	656.1 (M+H) ⁺	1.05	B
22	 Homochiral from peak 2	649.2 (M+H) ⁺	1.04	B

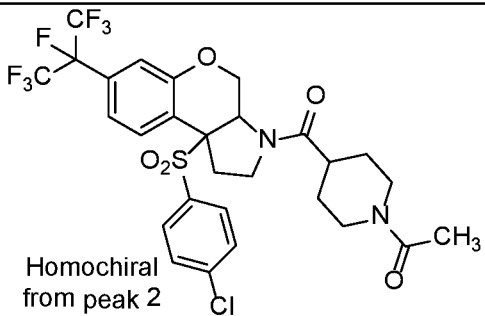
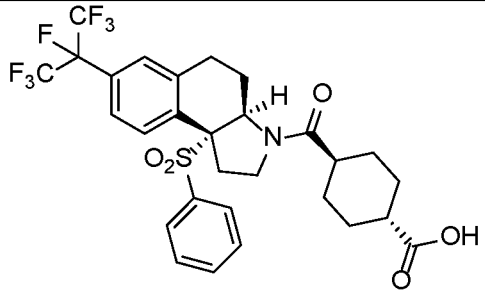
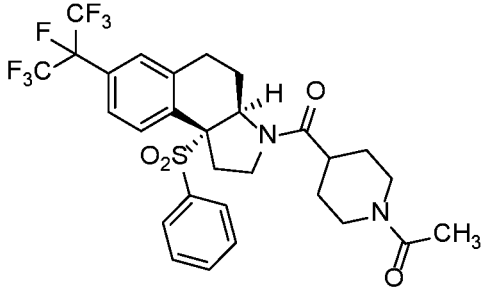
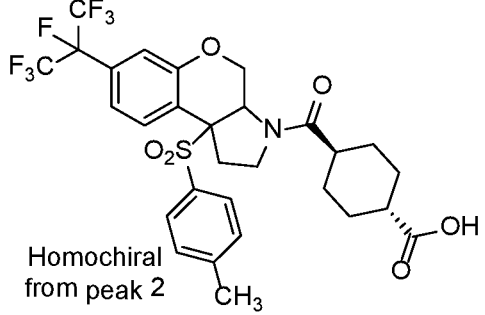
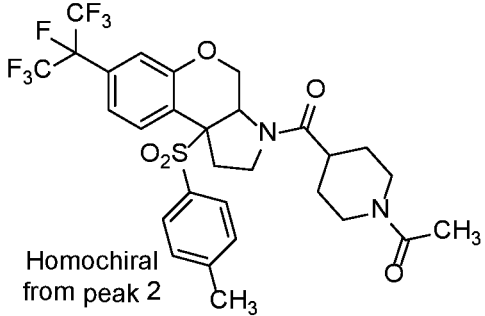
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
23	 Homochiral from peak 2	682.2 (M+H) ⁺	1.08	B
24	 Homochiral from peak 2	655.3 (M+H) ⁺	1.02	B
25	 Homochiral from peak 2	662.3 (M+H) ⁺	1.02	B
26	 Homochiral from peak 2	656.3 (M+H) ⁺	1.04	B
27	 Homochiral from peak 2	628.0 (M+H) ⁺	1.49	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
28	 Homochiral from peak 2	627.0 (M+H) ⁺	0.98	B
29	 Homochiral from peak 2	668.3 (M+H) ⁺	0.98	B
30	 Homochiral from peak 2	667.3 (M+H) ⁺	0.91	B
31	 Homochiral from peak 2	668.2 (M+H) ⁺	1.05	B
32	 Homochiral from peak 2	668.2 (M+H) ⁺	1.05	B

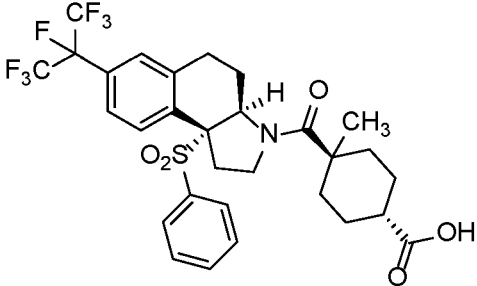
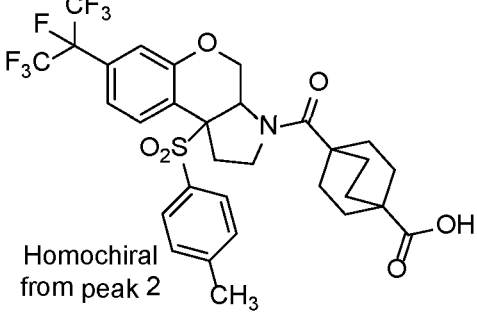
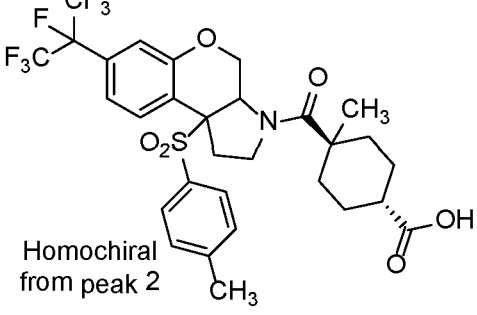
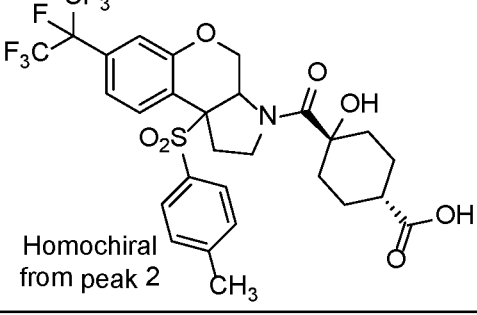
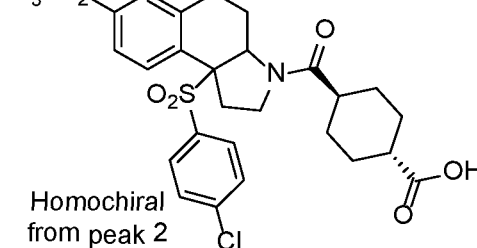
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
33	 Homochiral from peak 2	660.0 (M+H) ⁺	0.93	B
34	 Homochiral from peak 2	612.0 (M+H) ⁺	1.00	B
35	 Homochiral from peak 2	486.1 (M+H) ⁺	0.89	B
36	 Homochiral from peak 2	654.1 (M+H) ⁺	0.98	B
37	 Homochiral from peak 2	680.1 (M+H) ⁺	1.02	B

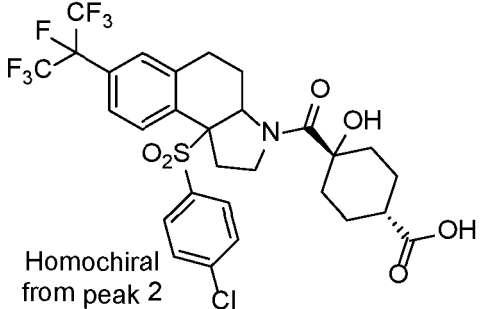
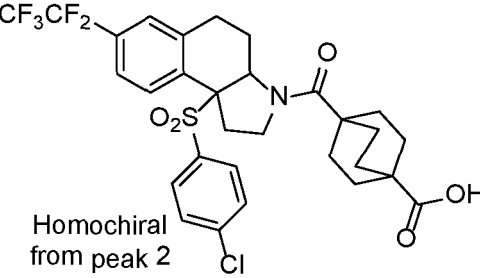
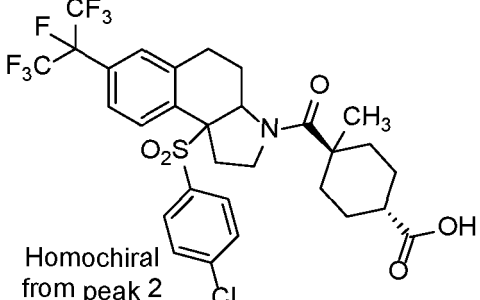
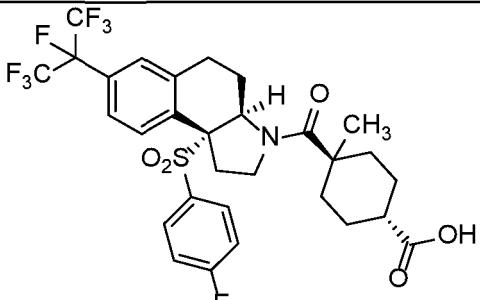
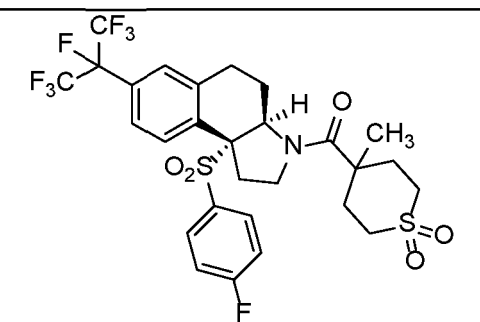
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
38		652.1 (M+H) ⁺	1.06	B
39	Homochiral from peak 2	576.3 (M+H) ⁺	0.96	B
40	Homochiral from peak 2	570.0 (M+H) ⁺	1.03	B
41	Homochiral from peak 2	559.3 (M+H) ⁺	0.64	B
42	Homochiral from peak 2	558.4 (M+H) ⁺	1.01	B

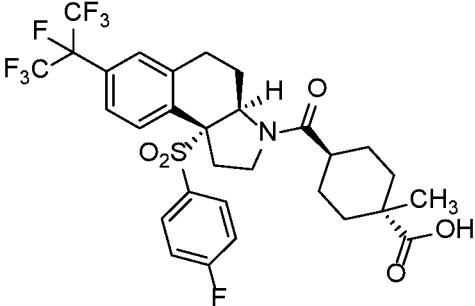
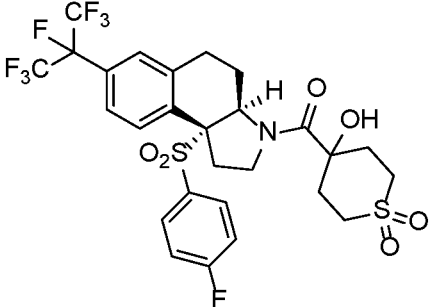
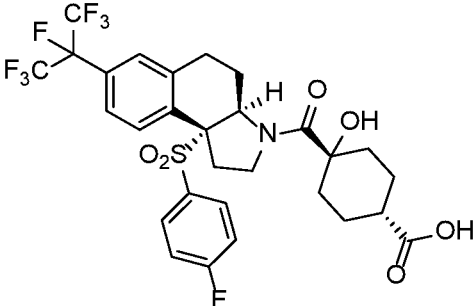
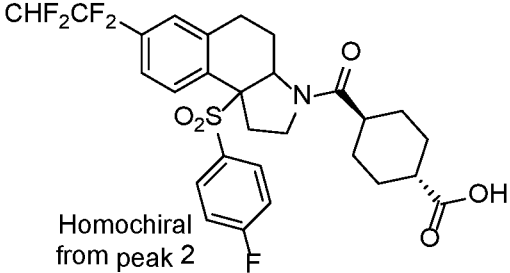
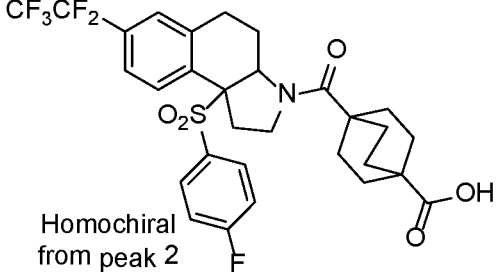
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
43	 Homochiral from peak 2	664.3 (M+H) ⁺	1.09	B
44	 Homochiral from peak 2	670.1 (M+H) ⁺	0.97	B
45	 Homochiral from peak 2	668.1 (M+H) ⁺	0.96	B
46	 Homochiral from peak 2	678.0 (M+H) ⁺	1.10	B
47	 Homochiral from peak 2	672.1 (M+H) ⁺	1.12	B

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
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
51	 Homochiral from peak 2	652.3 (M+H) ⁺	1.05	B
52	 Homochiral from peak 2	651.3 (M+H) ⁺	1.03	B

Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
53	Homochiral from peak 2	658.3 (M+H) ⁺	1.04	B
54		662.3 (M+H) ⁺	1.06	B
55		642.3 (M+H) ⁺	1.01	B
56		652.3 (M+H) ⁺	1.00	B
57		650.3 (M+H) ⁺	1.09	B

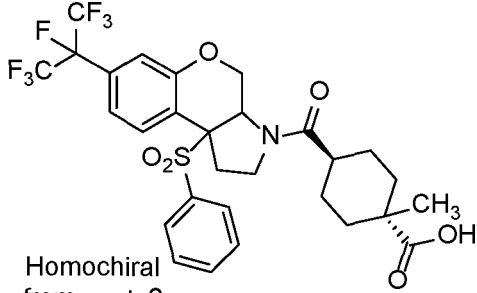
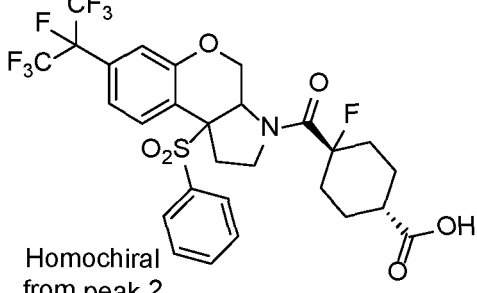
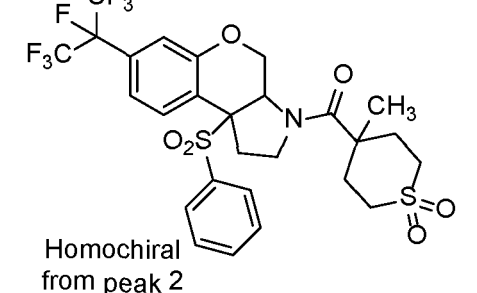
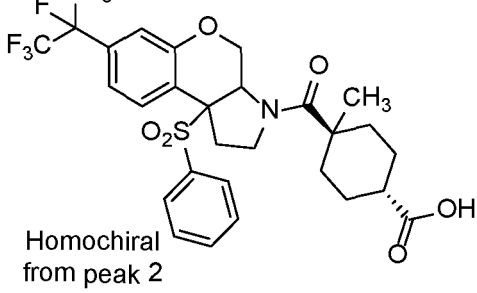
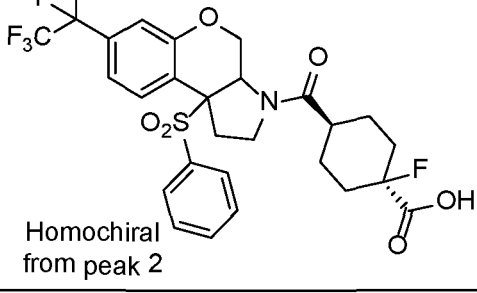
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
58		650.4 (M+H) ⁺	1.06	B
59	 Homochiral from peak 2	678.3 (M+H) ⁺	1.07	B
60	 Homochiral from peak 2	666.1 (M+H) ⁺	1.13	B
61	 Homochiral from peak 2	668.3 (M+H) ⁺	1.02	B
62	 Homochiral from peak 2	620.1 (M+H) ⁺	1.07	B

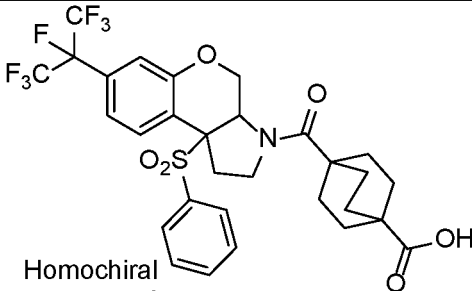
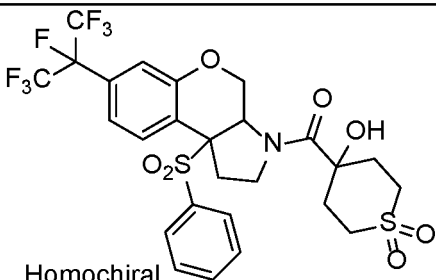
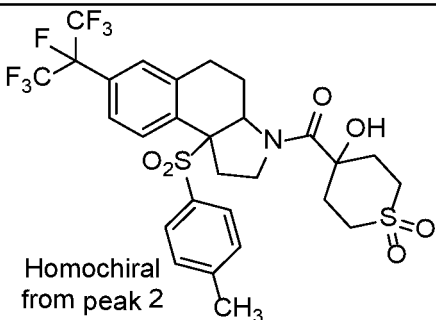
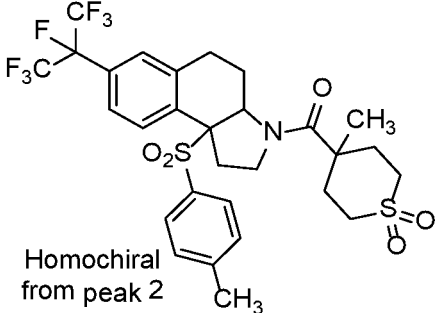
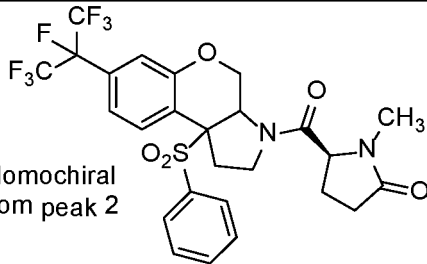
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
63	 Homochiral from peak 2	686.2 (M+H) ⁺	1.05	B
64	 Homochiral from peak 2	647.2 (M+H) ⁺	1.11	B
65	 Homochiral from peak 2	684.2 (M+H) ⁺	1.15	B
66		668.2 (M+H) ⁺	1.10	B
67		674.2 (M+H) ⁺	1.10	B

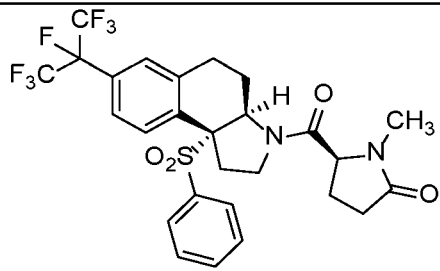
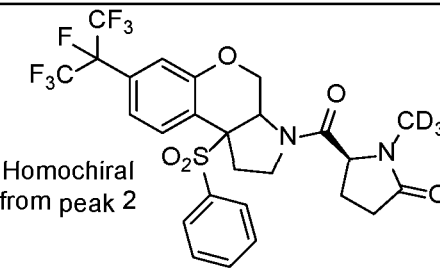
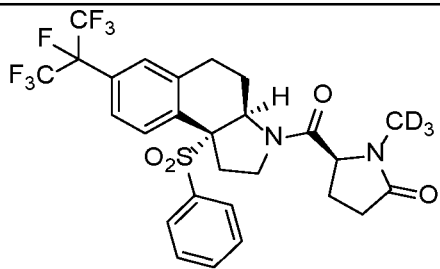
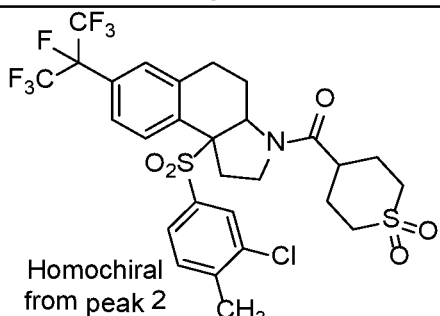
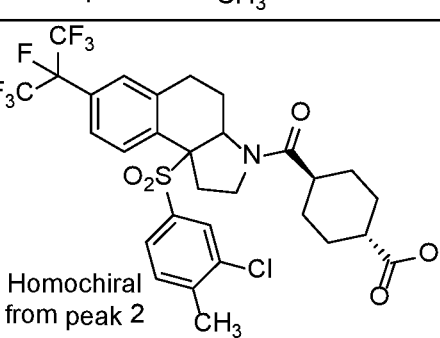
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
68		668.2 (M+H) ⁺	1.10	B
69		676.1 (M+H) ⁺	1.05	B
70		670.1 (M+H) ⁺	1.06	B
71	 Homochiral from peak 2	586.1 (M+H) ⁺	0.95	B
72	 Homochiral from peak 2	630.2 (M+H) ⁺	1.07	B

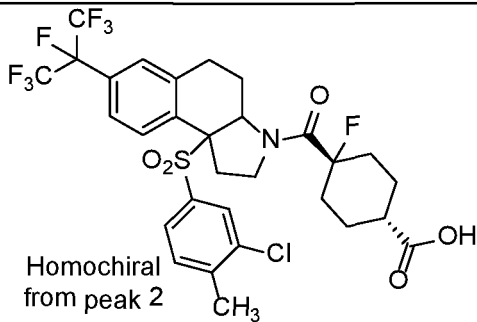
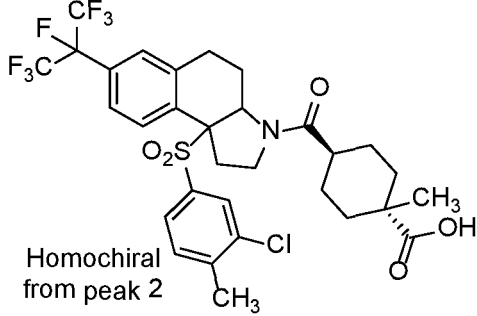
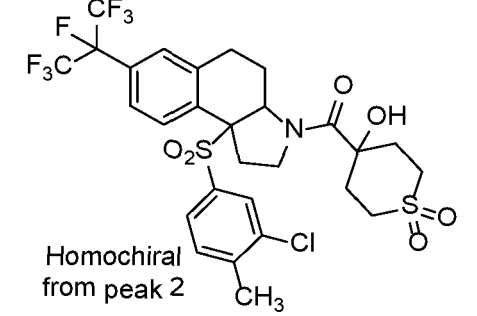
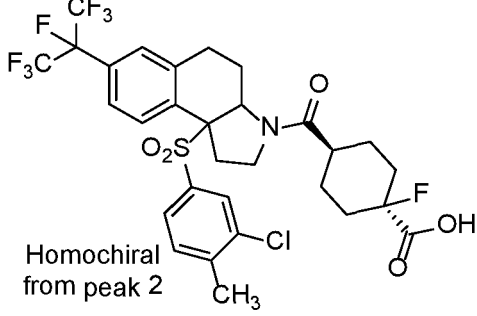
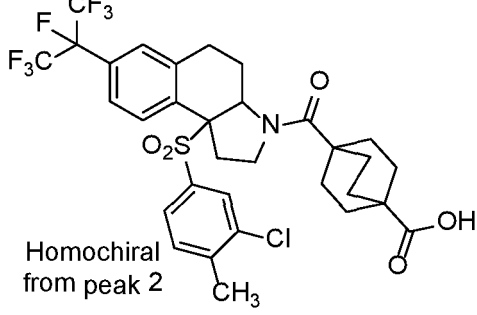
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
73		666.2 (M+H) ⁺	1.08	B
74	Homochiral from peak 2	612.3 (M+H) ⁺	0.96	B
75		658.1 (M+H) ⁺	1.03	B
76		656.2 (M+H) ⁺	1.09	B
77		654.2 (M+H) ⁺	1.10	B

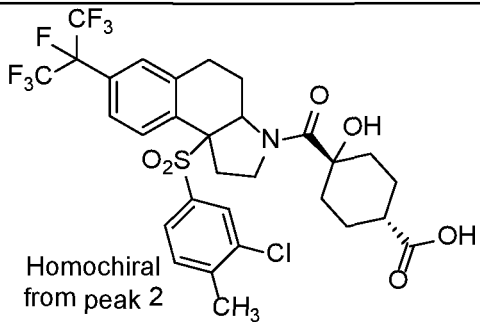
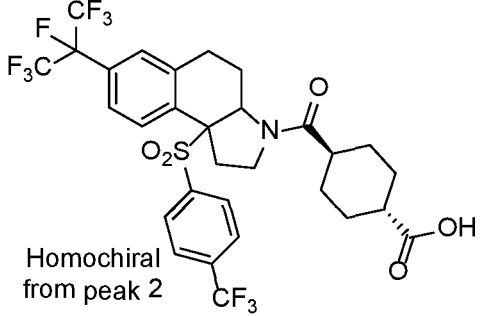
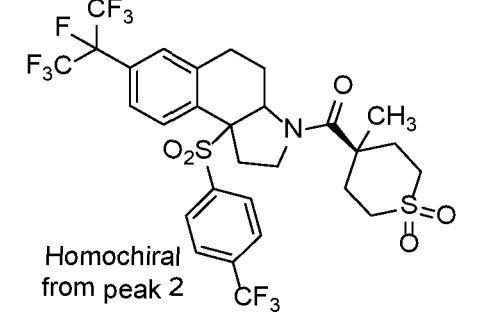
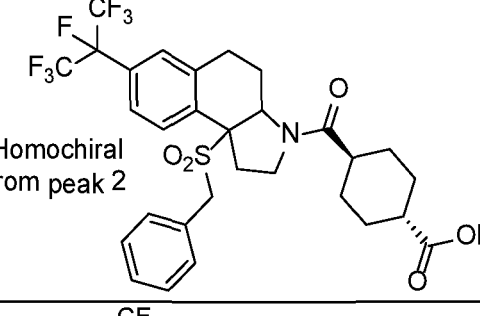
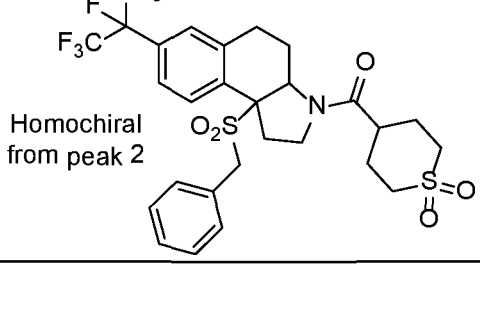
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
78		654.2 (M+H) ⁺	1.10	B
79		652.2 (M+H) ⁺	1.04	B
80		604.2 (M+H) ⁺	1.03	B
81		638.2 (M+H) ⁺	1.06	B
82		644.2 (M+H) ⁺	1.04	B

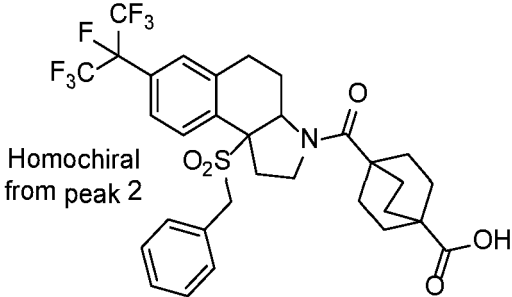
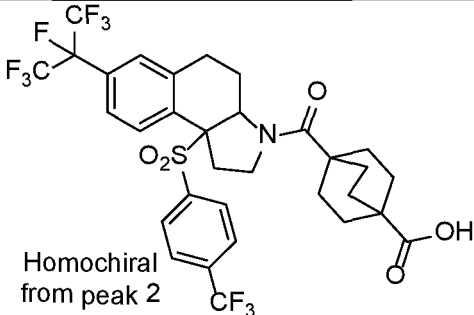
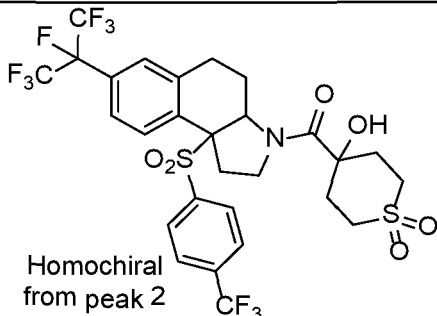
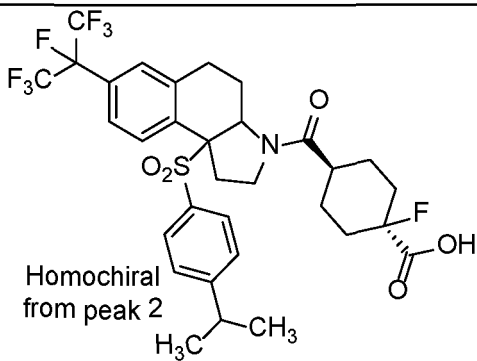
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
83	 Homochiral from peak 2	652.2 (M+H) ⁺	1.09	B
84	 Homochiral from peak 2	656.2 (M+H) ⁺	1.06	B
85	 Homochiral from peak 2	658.1 (M+H) ⁺	1.08	B
86	 Homochiral from peak 2	652.2 (M+H) ⁺	1.94	C
87	 Homochiral from peak 2	656.2 (M+H) ⁺	1.06	B

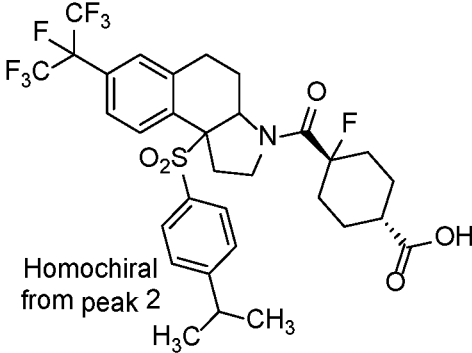
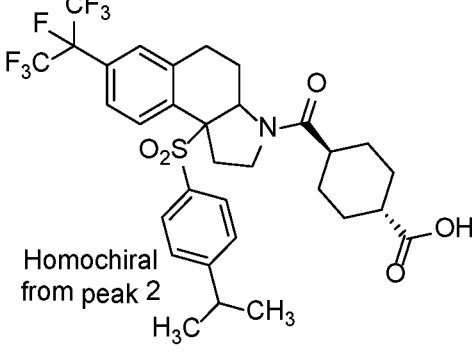
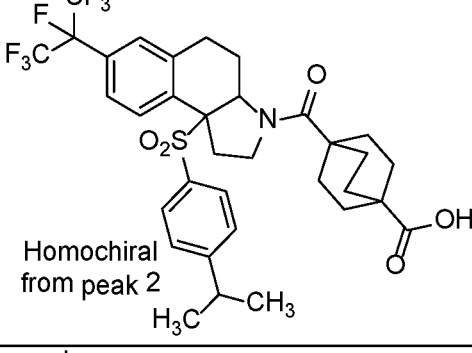
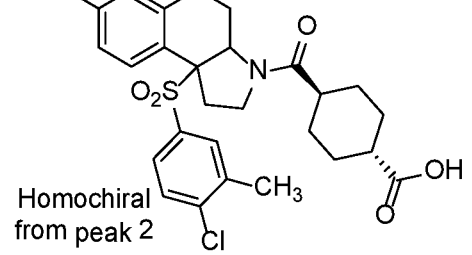
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
88	 Homochiral from peak 2	664.2 (M+H) ⁺	1.10	B
89	 Homochiral from peak 2	660.1 (M+H) ⁺	1.03	B
90	 Homochiral from peak 2	672.2 (M+H) ⁺	1.07	B
91	 Homochiral from peak 2	670.2 (M+H) ⁺	1.12	B
92	 Homochiral from peak 2	609.1 (M+H) ⁺	1.03	B

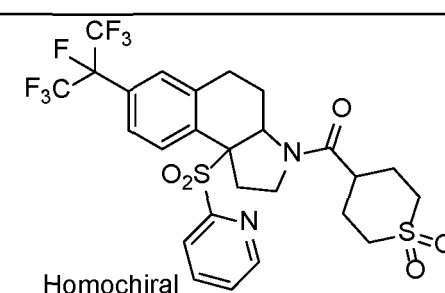
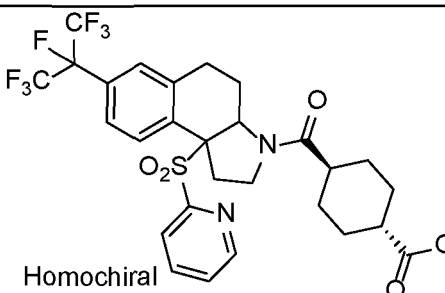
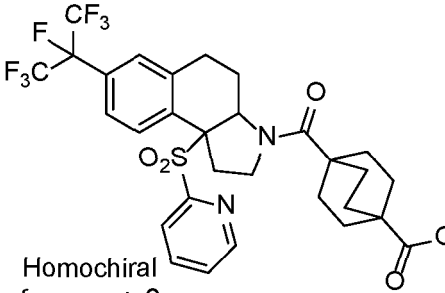
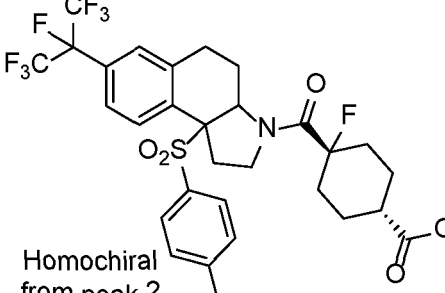
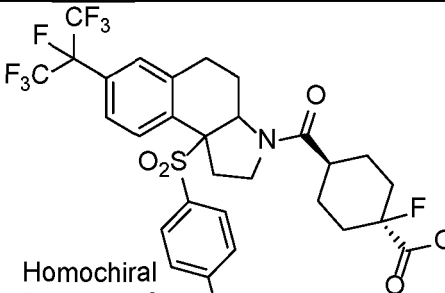
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
93		607.1 (M+H) ⁺	1.01	B
94	 Homochiral from peak 2	612.1 (M+H) ⁺	1.01	B
95		610.2 (M+H) ⁺	1.01	B
96	 Homochiral from peak 2	690.1 (M+H) ⁺	1.12	B
97	 Homochiral from peak 2	684.1 (M+H) ⁺	1.13	B

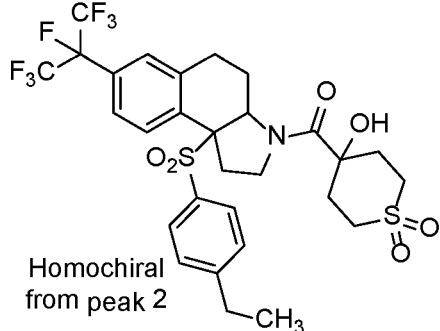
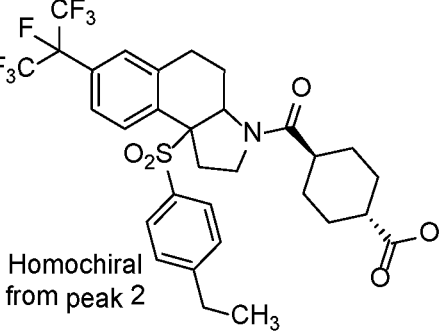
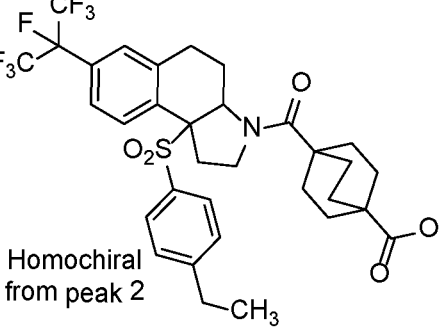
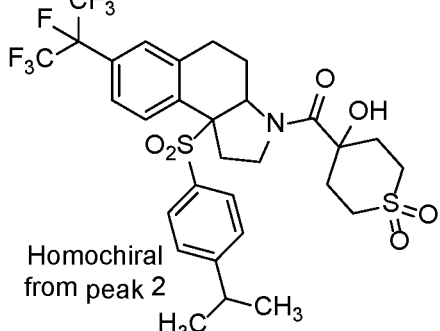
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
98	 Homochiral from peak 2	702.2 (M+H) ⁺	1.17	B
99	 Homochiral from peak 2	698.2 (M+H) ⁺	1.15	B
100	 Homochiral from peak 2	706.1 (M+H) ⁺	1.13	B
101	 Homochiral from peak 2	702.2 (M+H) ⁺	1.17	B
102	 Homochiral from peak 2	702.2 (M+H) ⁺	1.17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

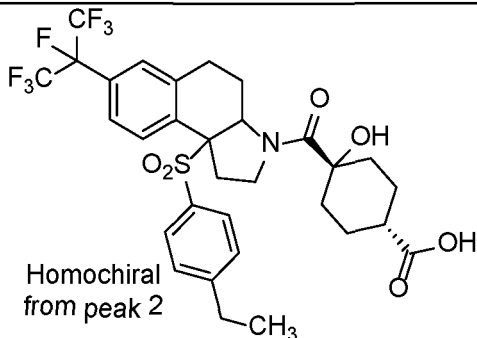
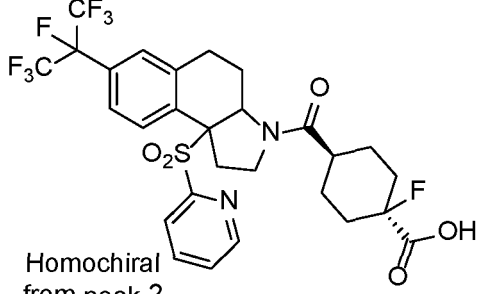
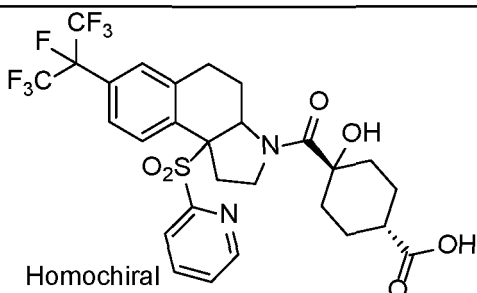
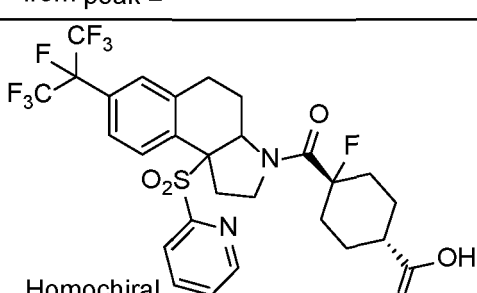
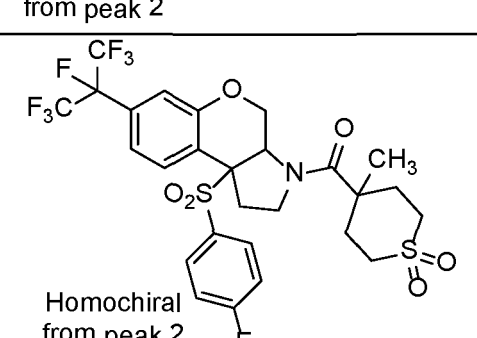
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
103	 Homochiral from peak 2	700.1 (M+H) ⁺	1.12	B
104	 Homochiral from peak 2	704.2 (M+H) ⁺	1.12	B
105	 Homochiral from peak 2	724.1 (M+H) ⁺	1.14	B
106	 Homochiral from peak 2	650.2 (M+H) ⁺	1.06	B
107	 Homochiral from peak 2	656.2 (M+H) ⁺	1.04	B

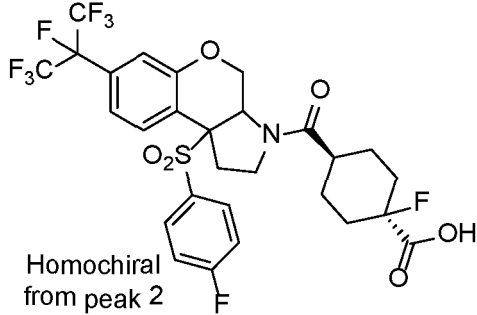
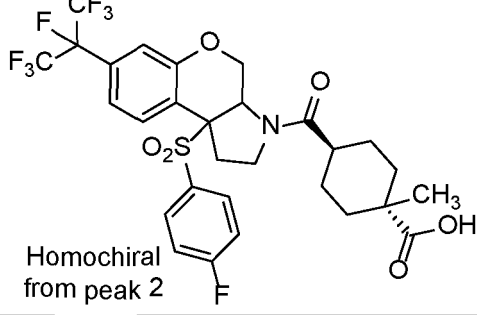
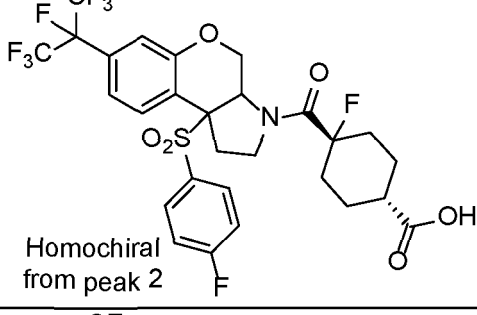
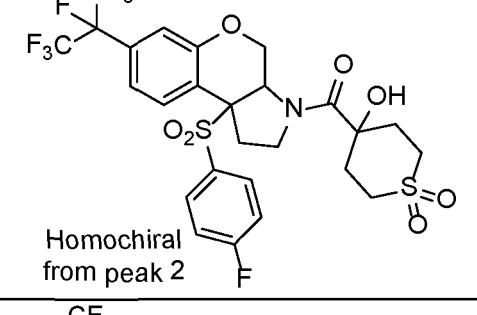
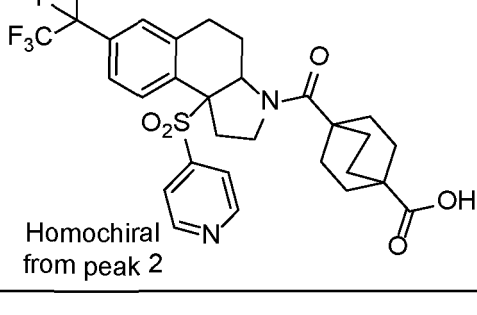
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
108	 Homochiral from peak 2	676.2 (M+H) ⁺	1.10	B
109	 Homochiral from peak 2	730.4 (M+H) ⁺	1.11	B
110	 Homochiral from peak 2	726.5 (M+H) ⁺	1.15	B
111	 Homochiral from peak 2	696.4 (M+H) ⁺	1.15	B

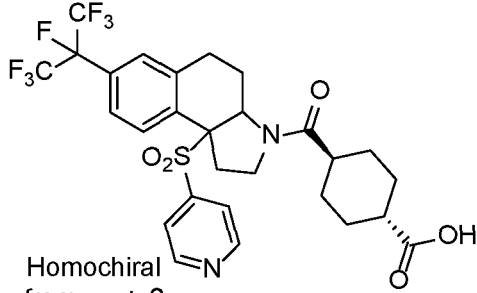
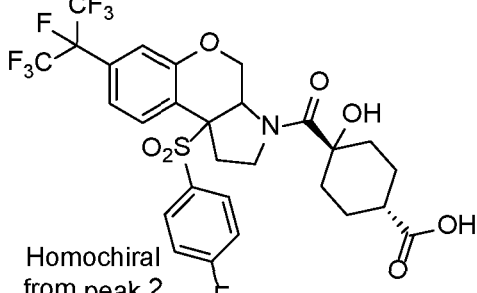
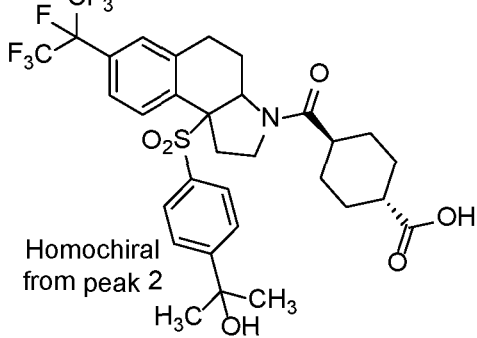
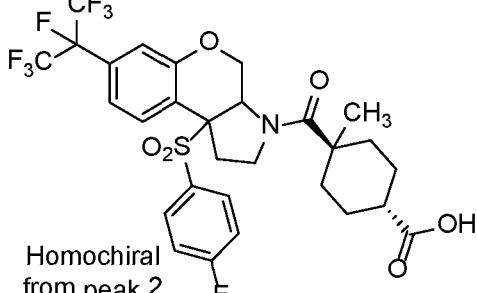
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
112	 Homochiral from peak 2	696.4 (M+H) ⁺	1.15	B
113	 Homochiral from peak 2	678.5 (M+H) ⁺	1.12	B
114	 Homochiral from peak 2	704.5 (M+H) ⁺	1.15	B
115	 Homochiral from peak 2	642.1 (M+H) ⁺	1.07	B

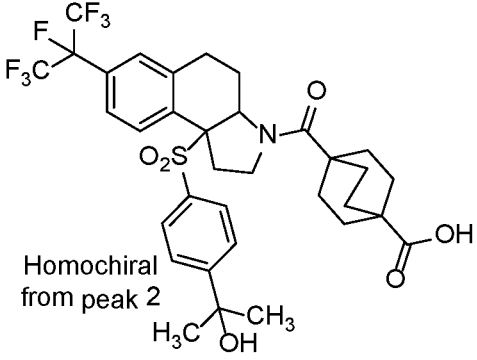
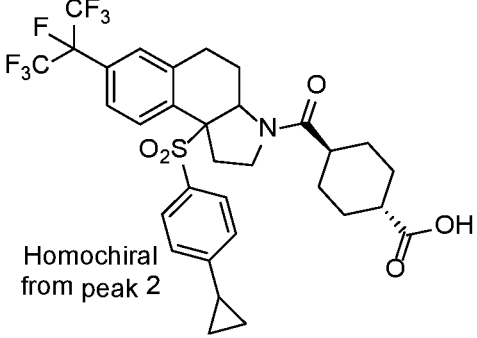
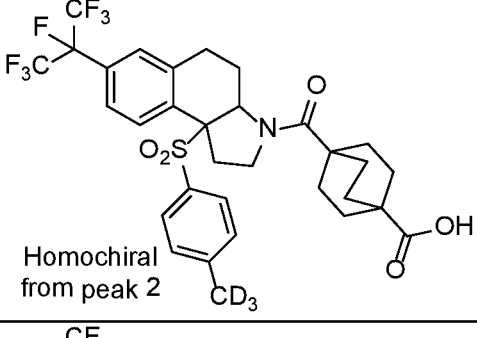
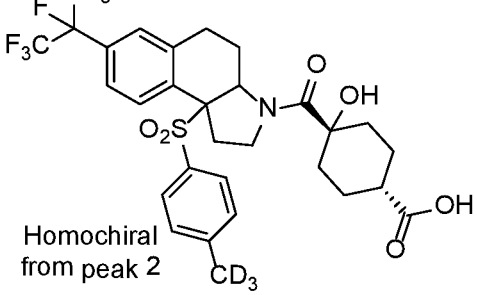
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
116	 Homochiral from peak 2	643.3 (M+H) ⁺	0.95	B
117	 Homochiral from peak 2	637.6 (M+H) ⁺	0.97	B
118	 Homochiral from peak 2	663.4 (M+H) ⁺	1.00	B
119	 Homochiral from peak 2	682.5 (M+H) ⁺	1.13	B
120	 Homochiral from peak 2	682.5 (M+H) ⁺	1.13	B

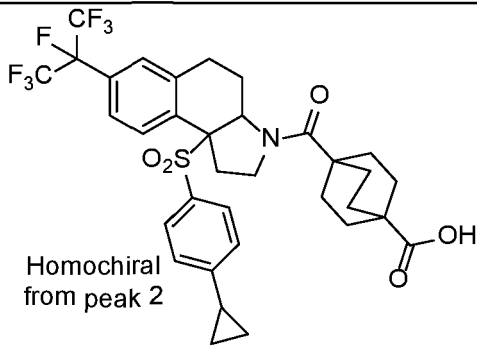
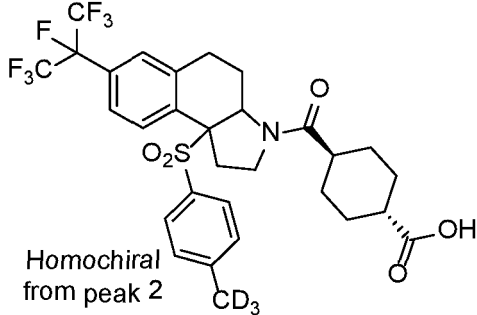
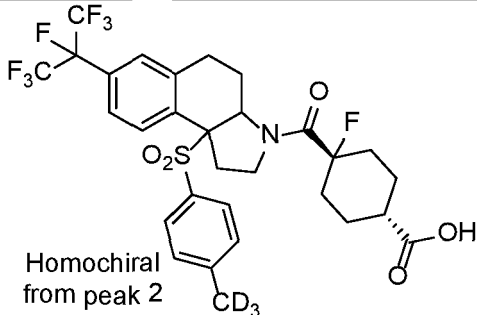
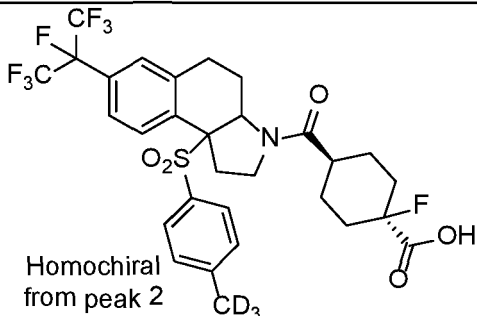
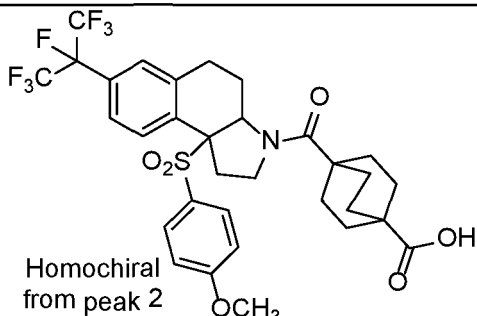
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
121	 Homochiral from peak 2	686.4 (M+H) ⁺	1.07	B
122	 Homochiral from peak 2	664.5 (M+H) ⁺	1.09	B
123	 Homochiral from peak 2	690.5 (M+H) ⁺	1.12	B
124	 Homochiral from peak 2	700.4 (M+H) ⁺	1.10	B

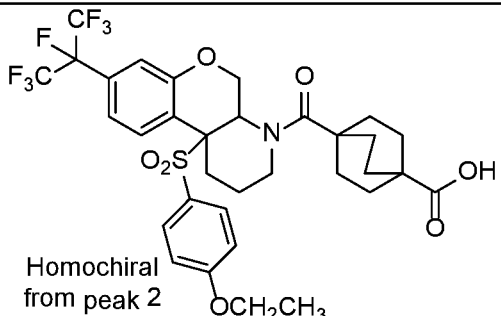
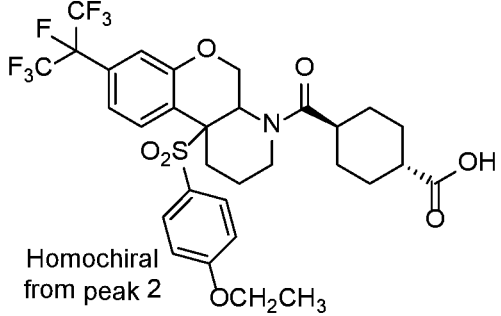
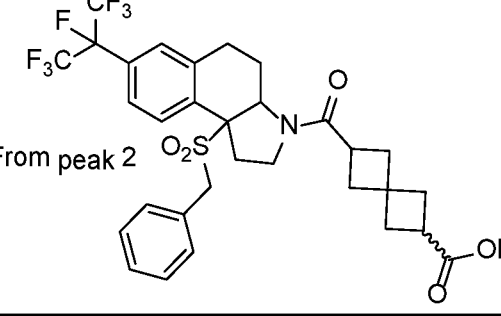
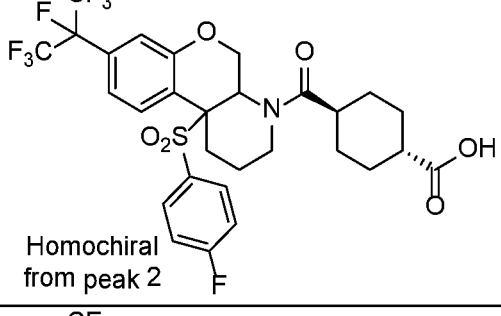
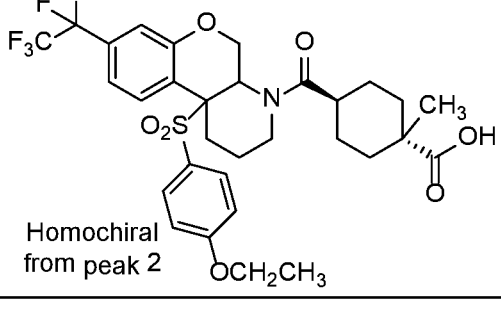
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
125	 Homochiral from peak 2	680.4 (M+H) ⁺	1.07	B
126	 Homochiral from peak 2	655.3 (M+H) ⁺	1.06	B
127	 Homochiral from peak 2	653.2 (M+H) ⁺	0.98	B
128	 Homochiral from peak 2	655.3 (M+H) ⁺	1.06	B
129	 Homochiral from peak 2	676.2 (M+H) ⁺	1.10	B

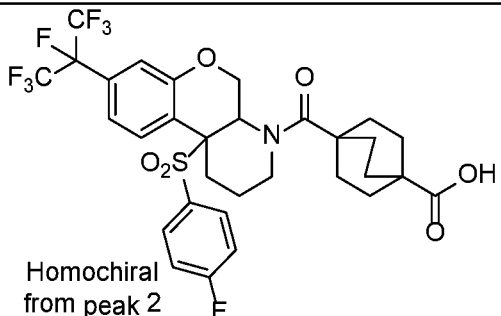
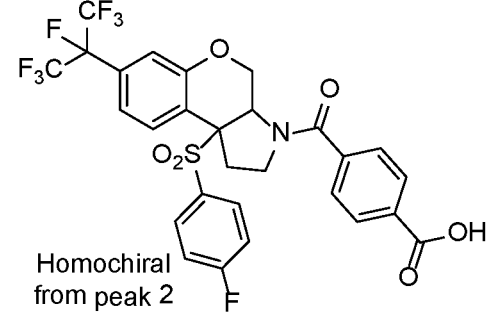
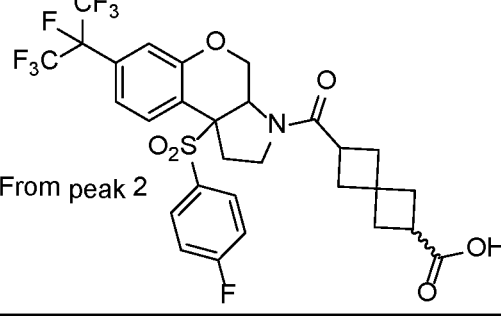
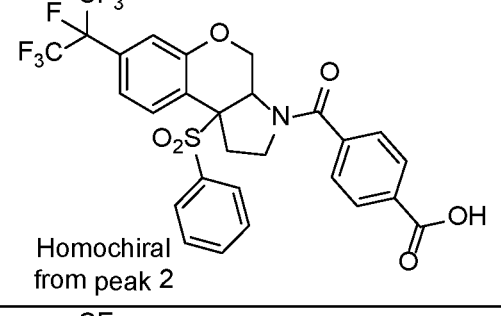
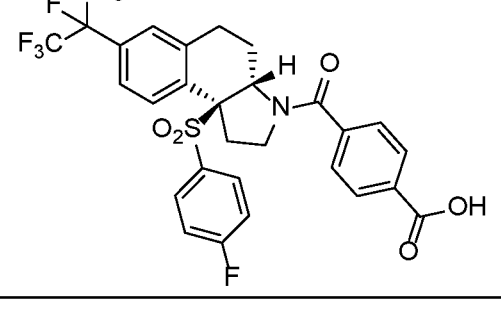
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
130	 Homochiral from peak 2	674.2 (M+H) ⁺	1.11	B
131	 Homochiral from peak 2	670.2 (M+H) ⁺	1.10	B
132	 Homochiral from peak 2	674.2 (M+H) ⁺	1.11	B
133	 Homochiral from peak 2	678.2 (M+H) ⁺	1.05	B
134	 Homochiral from peak 2	663.5 (M+H) ⁺	0.99	B

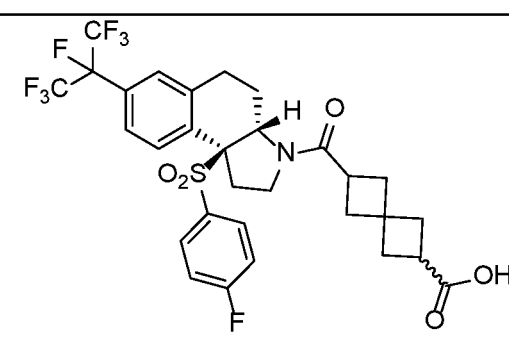
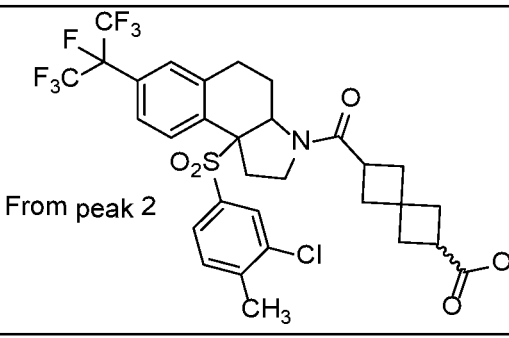
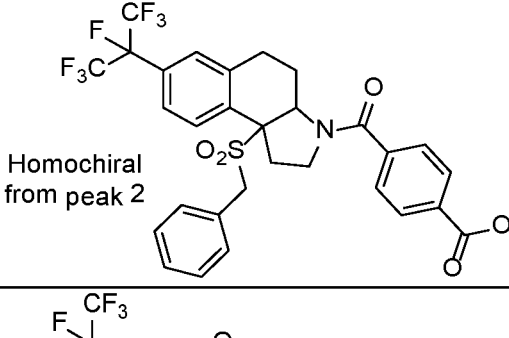
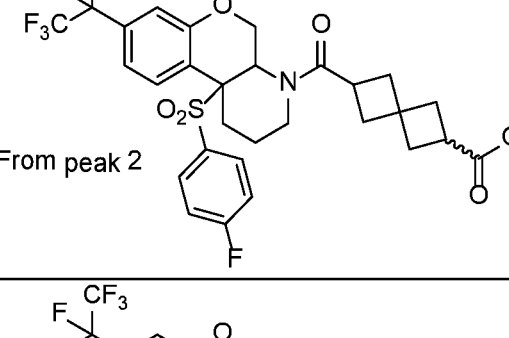
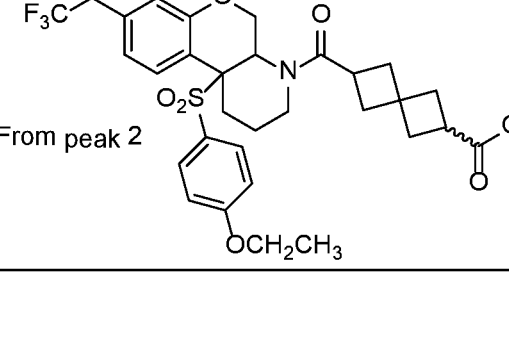
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC metho d
135	 Homochiral from peak 2	637.5 (M+H) ⁺	0.95	B
136	 Homochiral from peak 2	672.2 (M+H) ⁺	1.07	B
137	 Homochiral from peak 2	694.5 (M+H) ⁺	0.98	B
138	 Homochiral from peak 2	670.5 (M+H) ⁺	1.07	B

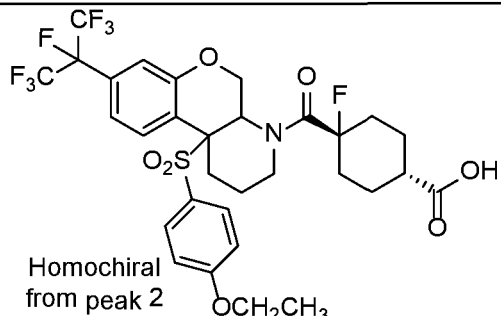
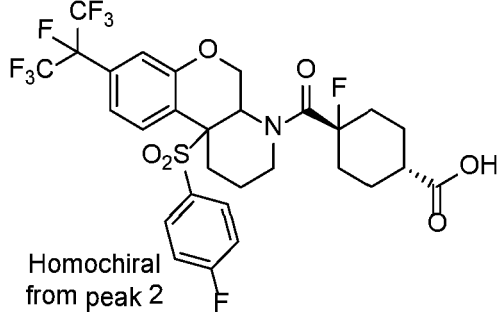
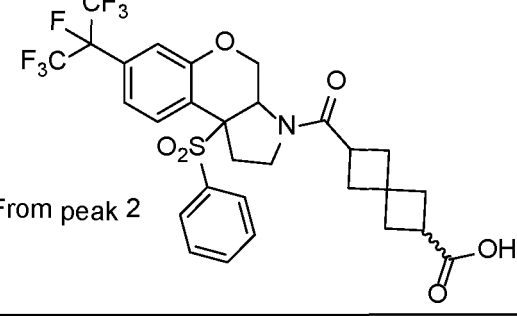
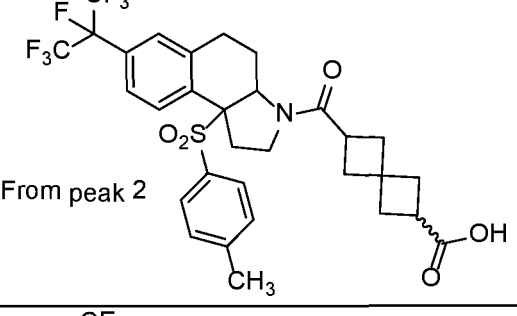
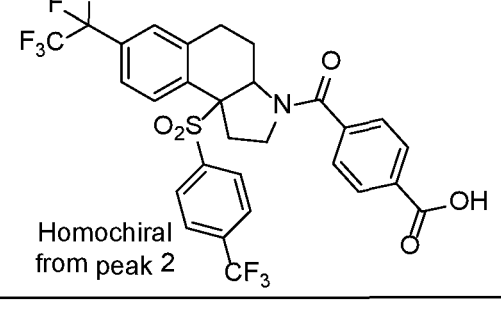
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
139	 Homochiral from peak 2	720.5 (M+H) ⁺	1.01	B
140	 Homochiral from peak 2	676.1 (M+H) ⁺	1.12	B
141	 Homochiral from peak 2	679.5 (M+H) ⁺	1.08	B
142	 Homochiral from peak 2	669.1 (M+H) ⁺	1.93	C

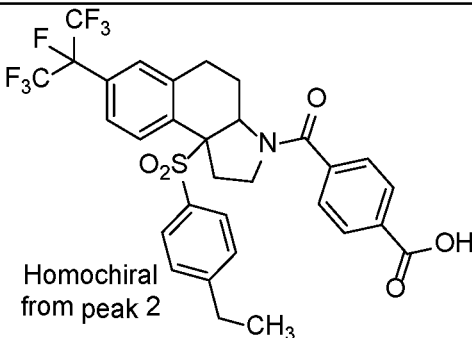
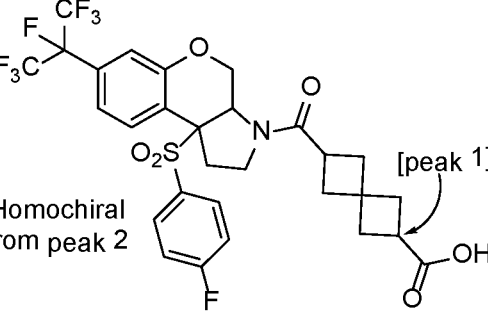
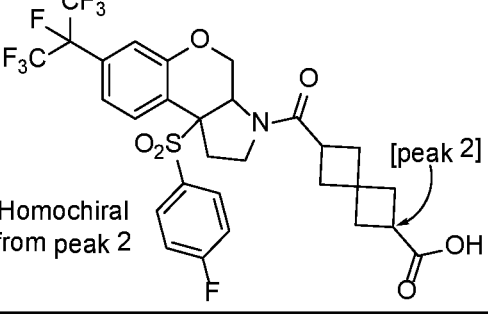
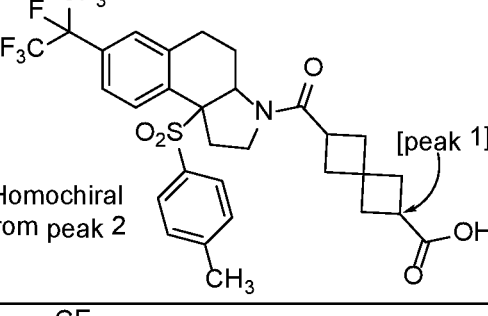
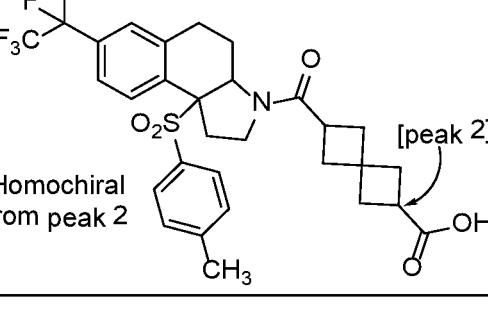
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
143	 Homochiral from peak 2	702.5 (M+H) ⁺	1.10	B
144	 Homochiral from peak 2	653.4 (M+H) ⁺	1.04	B
145	 Homochiral from peak 2	671.5 (M+H) ⁺	1.05	B
146	 Homochiral from peak 2	671.5 (M+H) ⁺	1.05	B
147	 Homochiral from peak 2	692.5 (M+H) ⁺	1.10	B

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
148	 Homochiral from peak 2	722.2 (M+H) ⁺	1.16	B
149	 Homochiral from peak 2	696.2 (M+H) ⁺	1.13	B
150	 From peak 2	696.2 (M+H) ⁺	1.13	B
151	 Homochiral from peak 2	670.2 (M+H) ⁺	1.10	B
152	 Homochiral from peak 2	710.2 (M+H) ⁺	1.15	B

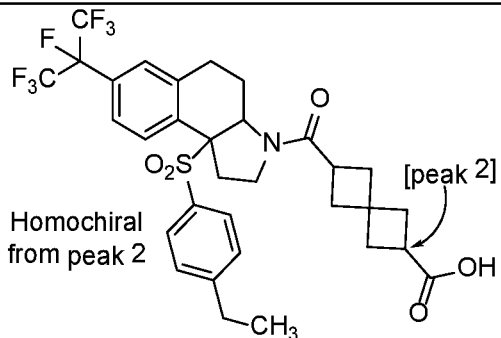
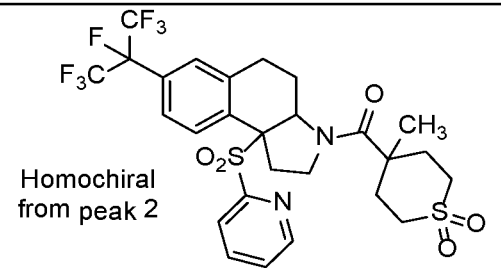
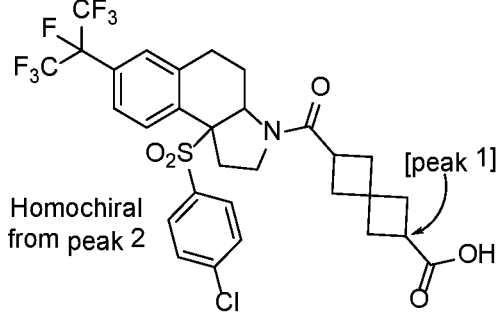
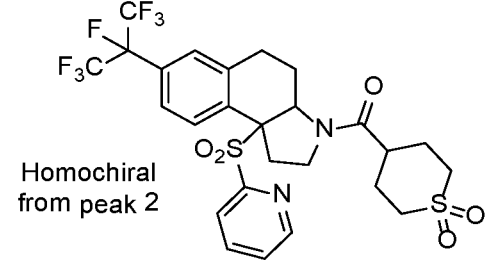
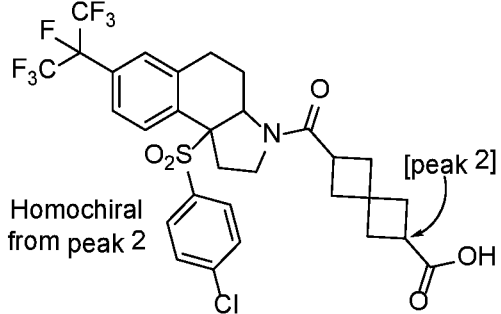
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
153	 Homochiral from peak 2	696.2 (M+H) ⁺	1.14	B
154	 Homochiral from peak 2	650.1 (M+H) ⁺	1.09	B
155	 From peak 2	668.1 (M+H) ⁺	1.10	B
156	 Homochiral from peak 2	632.1 (M+H) ⁺	1.08	B
157		648.1 (M+H) ⁺	1.09	B

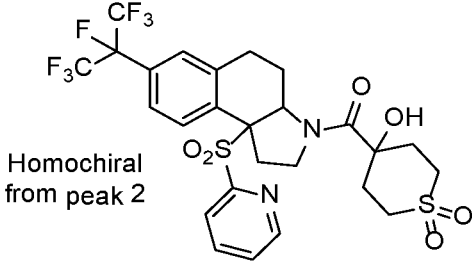
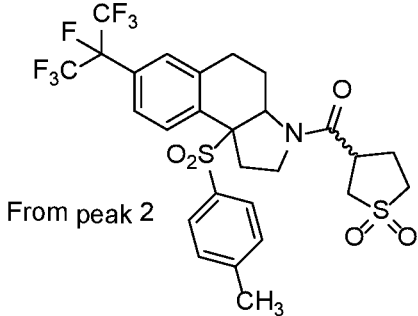
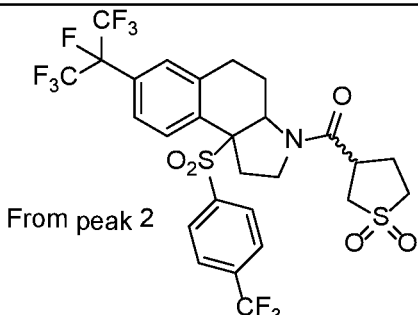
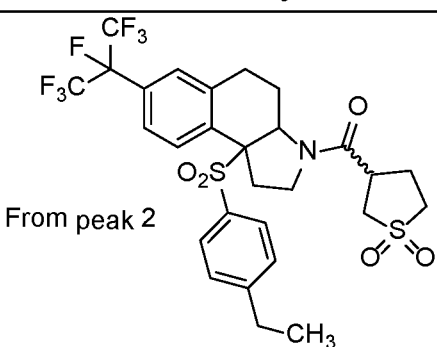
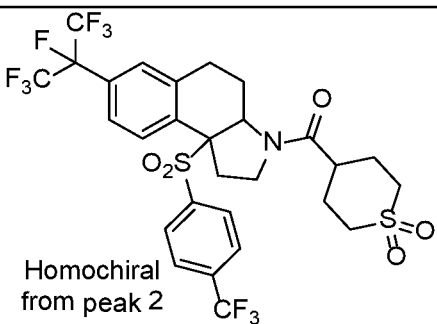
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
158		666.1 (M+H) ⁺	1.10	B
159	From peak 2 	696.2 (M+H) ⁺	1.16	B
160	Homochiral from peak 2 	650.1 (M+H) ⁺	1.09	B
161	From peak 2 	682.1 (M+H) ⁺	1.12	B
162	From peak 2 	708.2 (M+H) ⁺	1.14	B

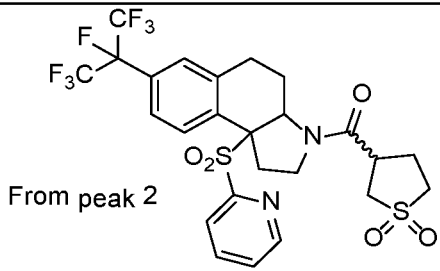
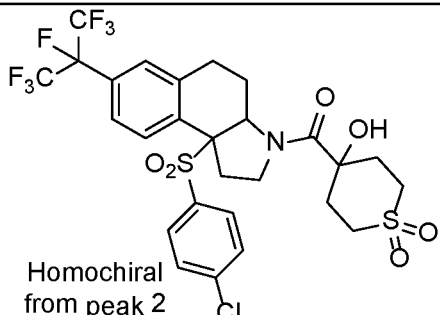
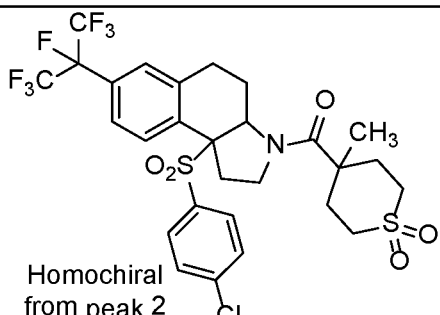
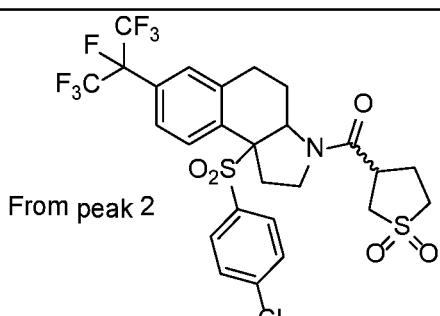
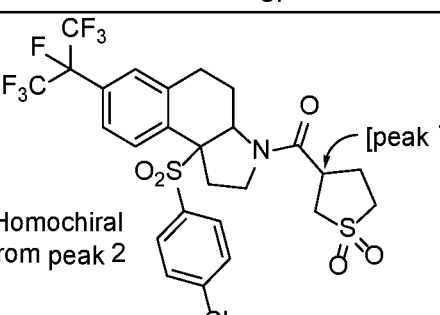
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
163	 Homochiral from peak 2	714.2 (M+H) ⁺	1.17	B
164	 Homochiral from peak 2	688.2 (M+H) ⁺	1.14	B
165	 From peak 2	650.2 (M+H) ⁺	1.09	B
166	 From peak 2	662.3 (M+H) ⁺	1.06	B
167	 Homochiral from peak 2	698.2 (M+H) ⁺	1.08	B

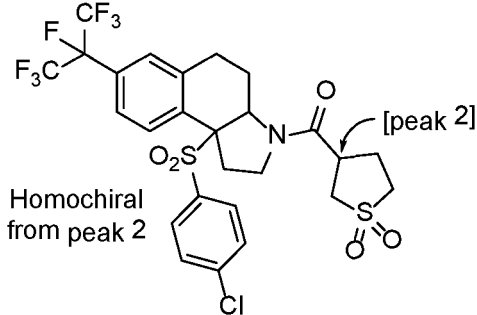
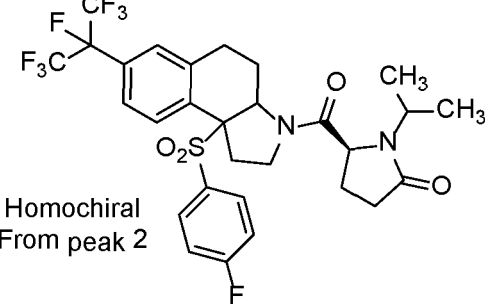
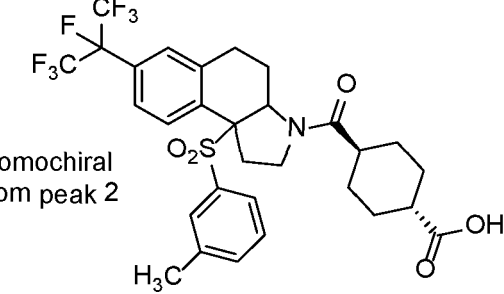
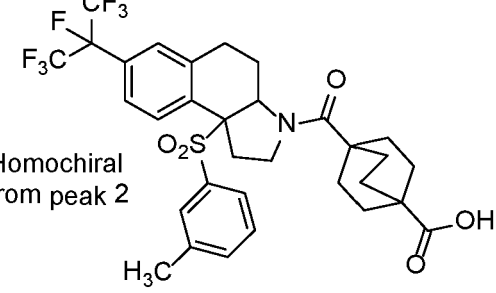
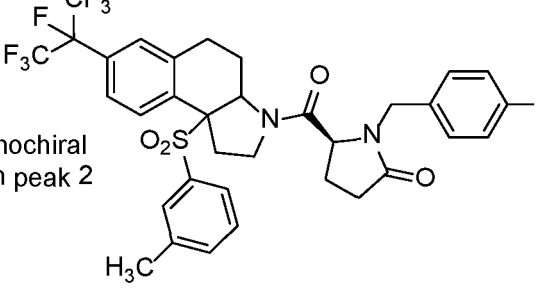
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
168	 Homochiral from peak 2	658.4 (M+H) ⁺	1.09	B
169	 Homochiral from peak 2 [peak 1]	668.1 (M+H) ⁺	1.10	B
170	 Homochiral from peak 2 [peak 2]	668.1 (M+H) ⁺	1.10	B
171	 Homochiral from peak 2 [peak 1]	662.1 (M+H) ⁺	1.06	B
172	 Homochiral from peak 2 [peak 2]	662.1 (M+H) ⁺	1.06	B

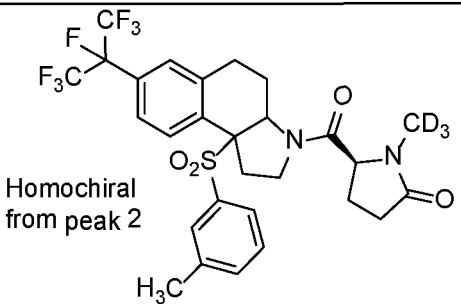
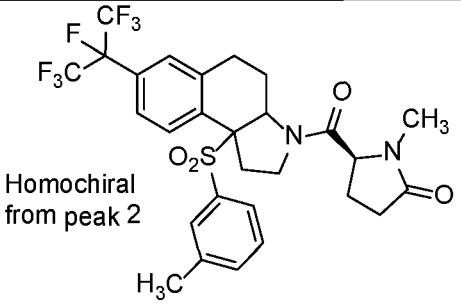
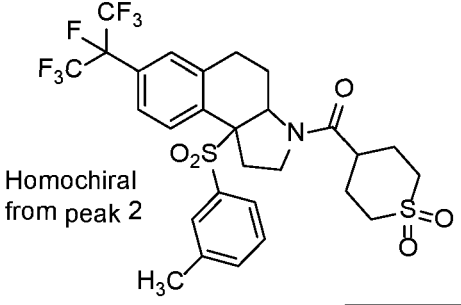
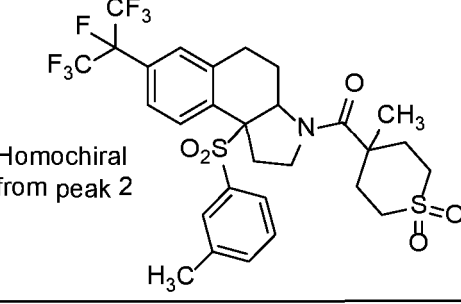
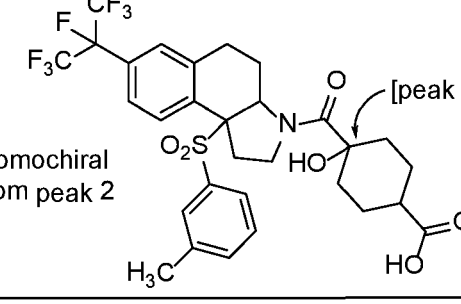
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
173	Homochiral from peak 2 [peak 1]	716.2 (M+H) ⁺	1.07	B
174	Homochiral from peak 2 [peak 2]	716.2 (M+H) ⁺	1.07	B
175	Homochiral from peak 2 [peak 1]	649.2 (M+H) ⁺	0.96	B
176	Homochiral from peak 2 [peak 2]	649.2 (M+H) ⁺	0.96	B
177	Homochiral from peak 2 [peak 1]	676.2 (M+H) ⁺	1.08	B

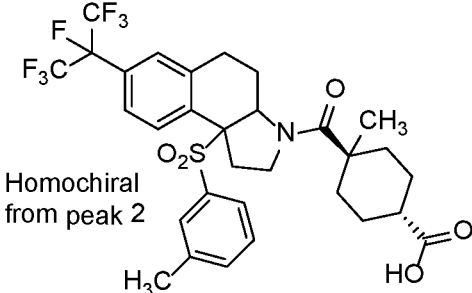
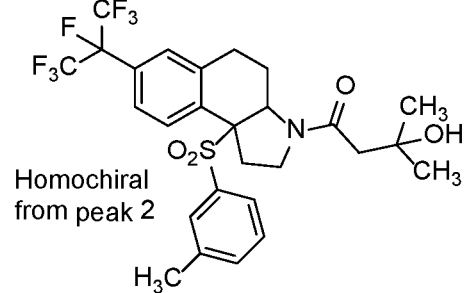
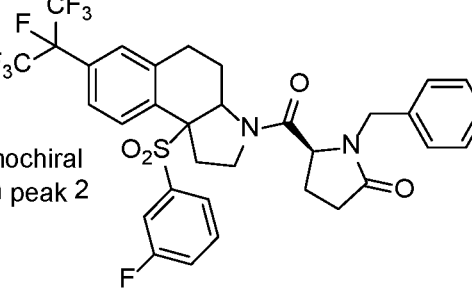
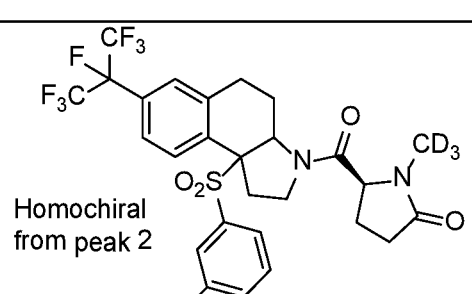
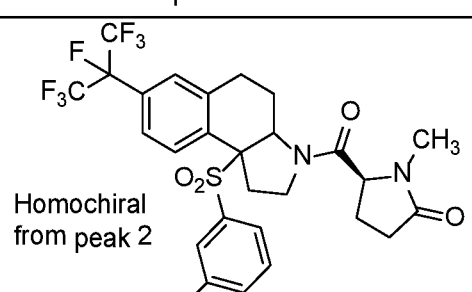
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
178	 Homochiral from peak 2	676.2 (M+H) ⁺	1.08	B
179	 Homochiral from peak 2	657.1 (M+H) ⁺	1.94	C
180	 Homochiral from peak 2	682.3 (M+H) ⁺	1.08	B
181	 Homochiral from peak 2	643.1 (M+H) ⁺	1.82	C
182	 Homochiral from peak 2	682.3 (M+H) ⁺	1.08	B

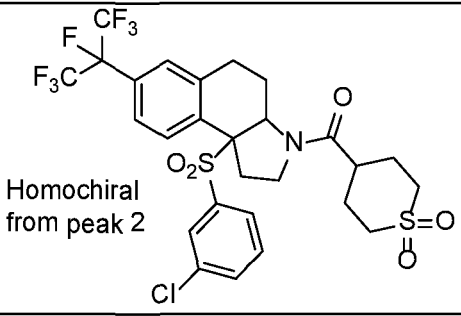
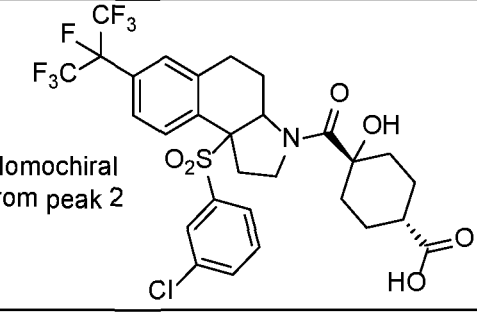
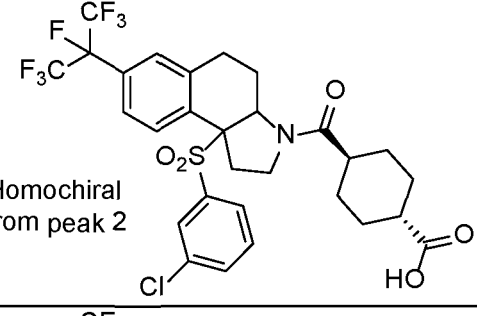
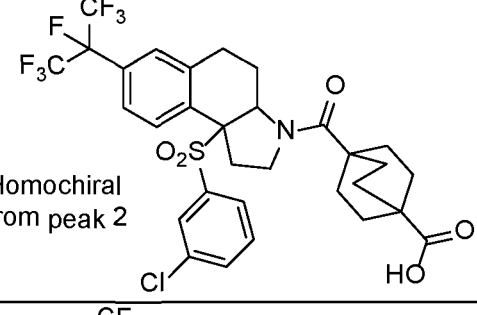
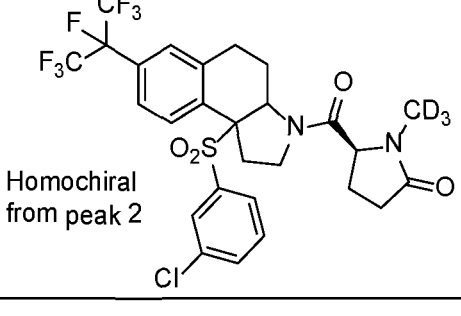
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
183	 Homochiral from peak 2	659.1 (M+H) ⁺	1.82	C
184	 From peak 2	642.2 (M+H) ⁺	1.07	B
185	 From peak 2	696.2 (M+H) ⁺	1.10	B
186	 From peak 2	656.2 (M+H) ⁺	1.11	B
187	 Homochiral from peak 2	710.2 (M+H) ⁺	1.09	B

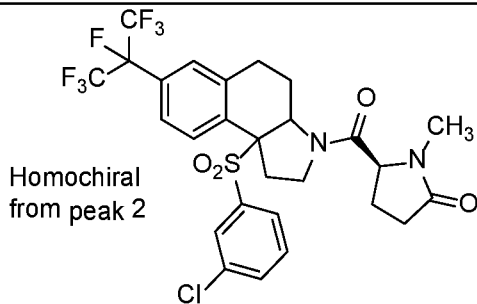
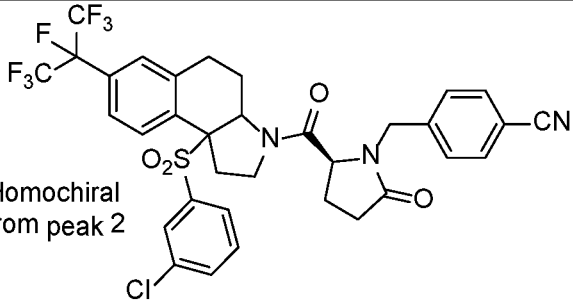
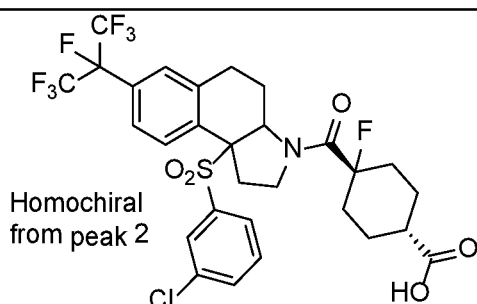
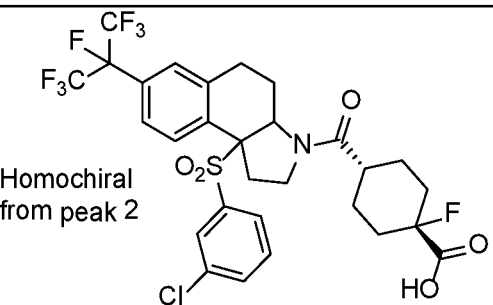
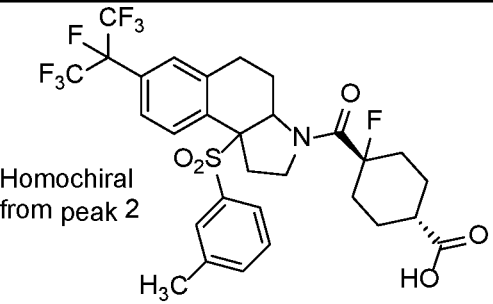
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
188	 From peak 2	629.2 (M+H) ⁺	0.98	B
189	 Homochiral from peak 2	692.2 (M+H) ⁺	1.07	B
190	 Homochiral from peak 2	690.2 (M+H) ⁺	1.13	B
191	 From peak 2	662.1 (M+H) ⁺	1.09	B
192	 Homochiral from peak 2	662.1 (M+H) ⁺	1.09	B

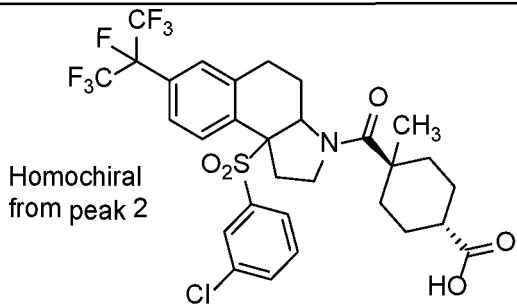
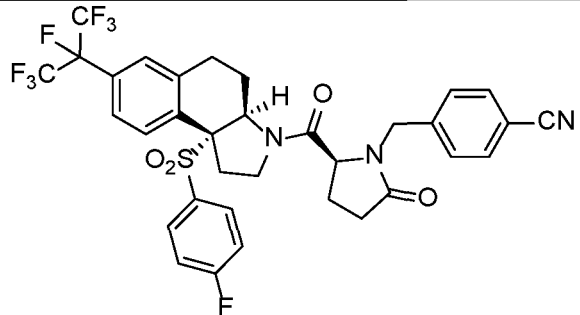
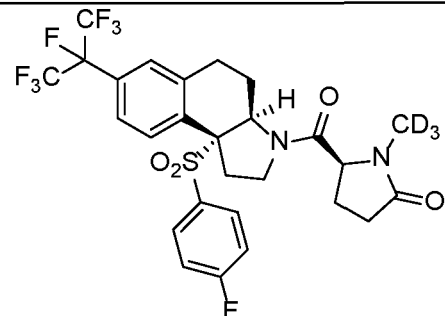
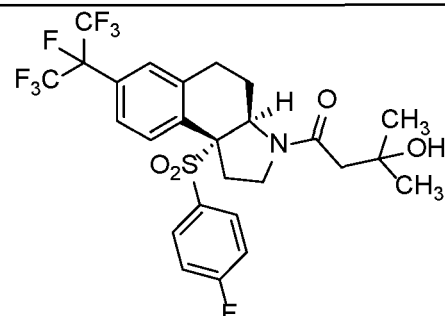
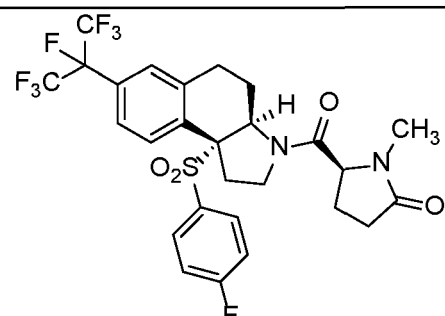
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
193	 Homochiral from peak 2	662.1 (M+H) ⁺	1.09	B
194	 Homochiral From peak 2	652.9 (M+H) ⁺	2.16	C
195	 Homochiral from peak 2	650.1 (M+H) ⁺	2.20	D
196	 Homochiral from peak 2	676.1 (M+H) ⁺	2.30	D
197	 Homochiral from peak 2	722.0 (M+H) ⁺	2.31	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
198	 Homochiral from peak 2	624.3 (M+H) ⁺	2.08	D
199	 Homochiral from peak 2	621.0 (M+H) ⁺	2.09	D
200	 Homochiral from peak 2	656.4 (M+H) ⁺	2.19	D
201	 Homochiral from peak 2	670.5 (M+H) ⁺	2.32	D
202	 Homochiral from peak 2	666.1 (M+H) ⁺	2.11	D

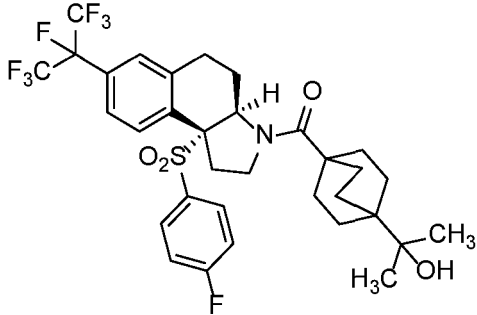
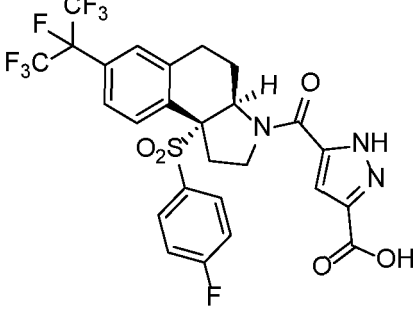
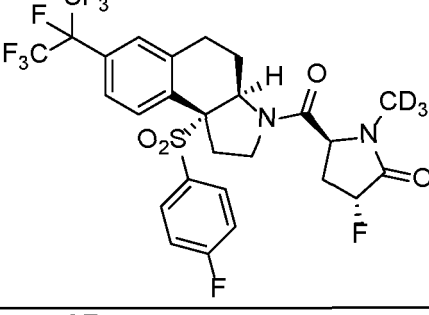
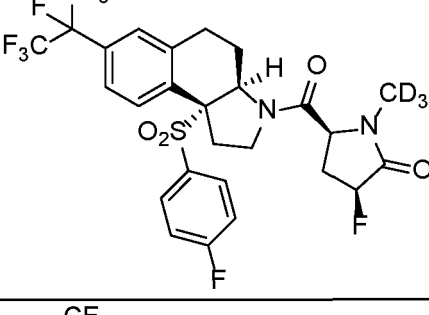
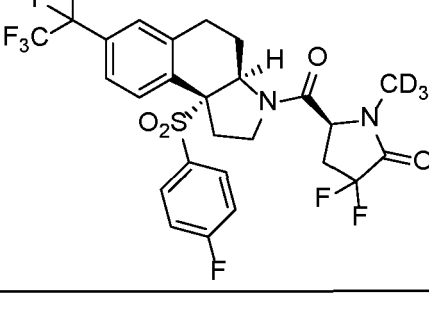
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
203	 Homochiral from peak 2	664.5 (M+H) ⁺	2.35	D
204	 Homochiral from peak 2	596.2 (M+H) ⁺	2.58	D
205	 Homochiral from peak 2	726.1 (M+H) ⁺	2.24	D
206	 Homochiral from peak 2	628.1 (M+H) ⁺	2.02	D
207	 Homochiral from peak 2	625.2 (M+H) ⁺	2.02	D

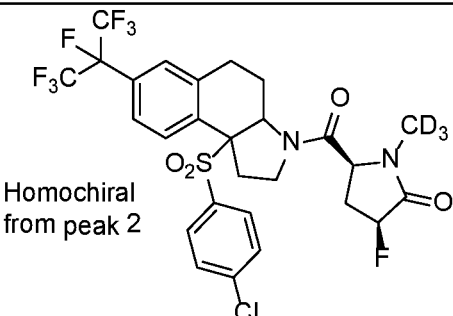
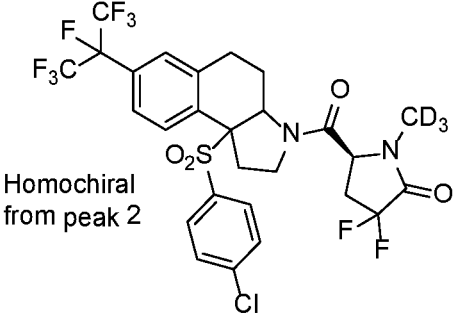
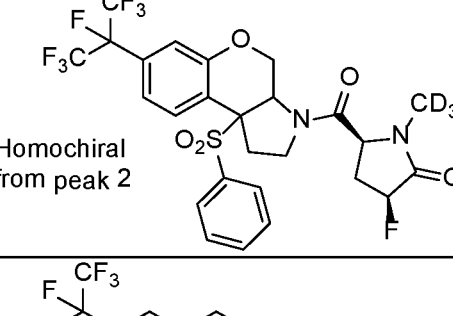
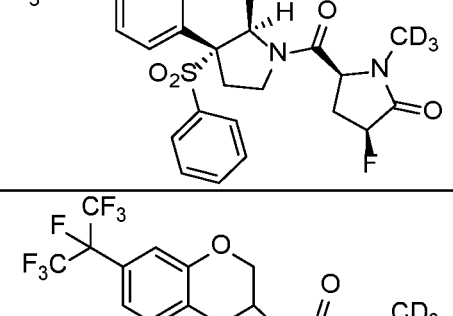
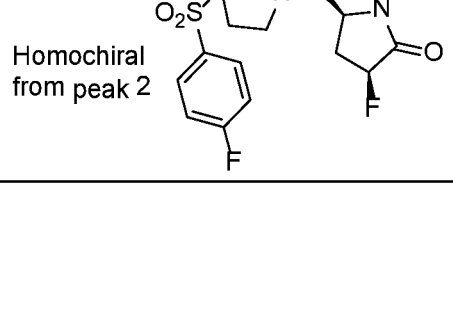
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
208	 Homochiral from peak 2	676.3 (M+H) ⁺	2.17	D
209	 Homochiral from peak 2	685.9 (M+H) ⁺	2.16	D
210	 Homochiral from peak 2	670.5 (M+H) ⁺	2.29	D
211	 Homochiral from peak 2	696.5 (M+H) ⁺	2.39	D
212	 Homochiral from peak 2	644.2 (M+H) ⁺	2.17	D

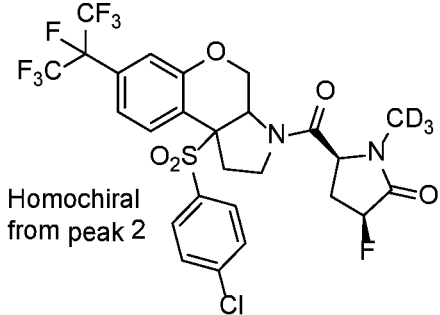
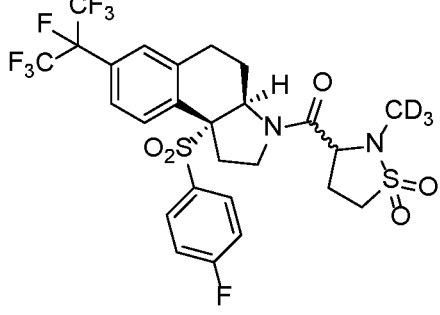
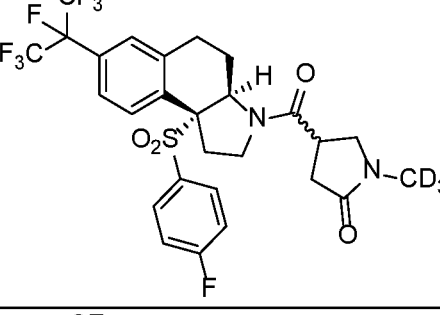
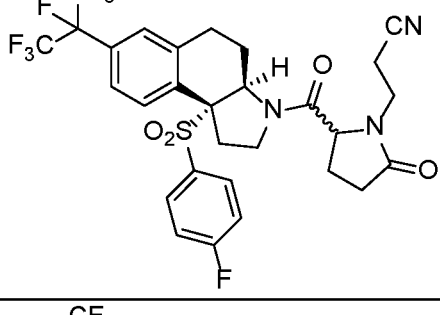
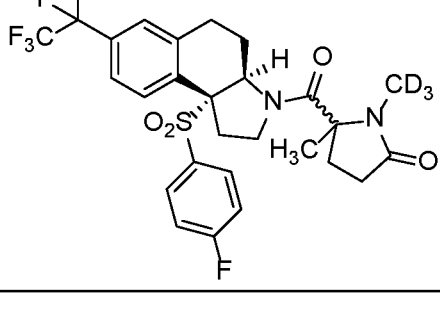
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
213	 Homochiral from peak 2	641.4 (M+H) ⁺	2.17	D
214	 Homochiral from peak 2	742.5 (M+H) ⁺	2.40	D
215	 Homochiral from peak 2	688.1 (M+H) ⁺	2.37	D
216	 Homochiral from peak 2	688.0 (M+H) ⁺	2.26	D
217	 Homochiral from peak 2	668.0 (M+H) ⁺	2.33	D

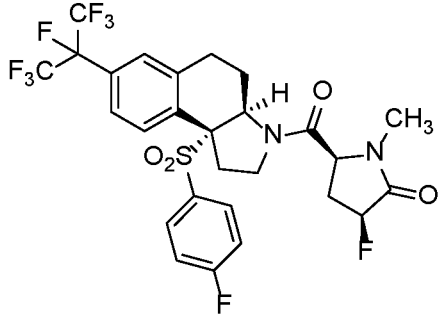
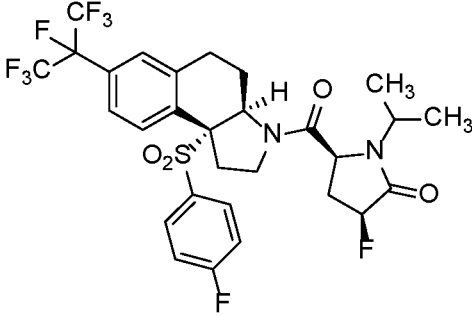
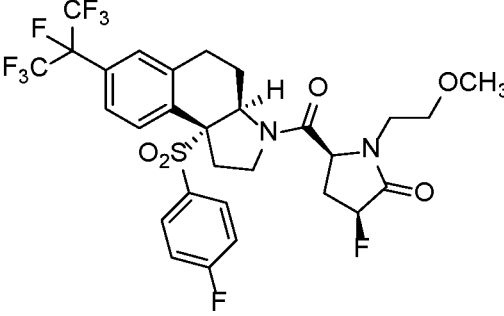
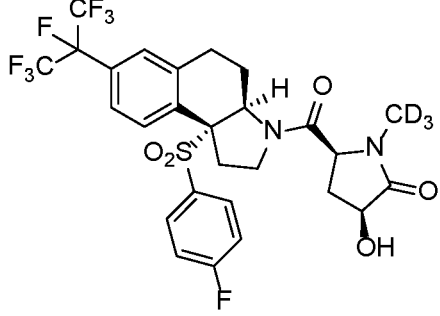
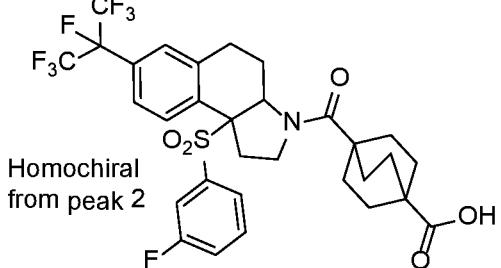
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
218	 Homochiral from peak 2	684.5 (M+H) ⁺	2.39	D
219		726.5 (M+H) ⁺	2.31	D
220		628.1 (M+H) ⁺	2.04	D
221		600.4 (M+H) ⁺	2.26	D
222		625.2 (M+H) ⁺	2.04	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
223		639.1 (M+H) ⁺	2.11	D
224		719.4 (M+H) ⁺	2.40	D
225		620.0 (M+H) ⁺	1.93	D
226		636.2 (M+H) ⁺	2.08	D
227		668.1 (M+H) ⁺	2.31	D

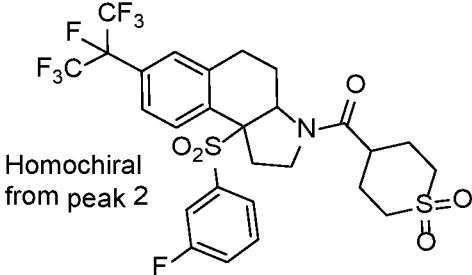
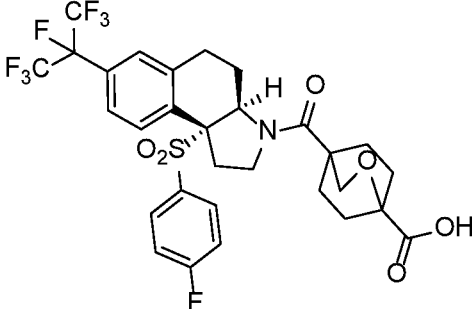
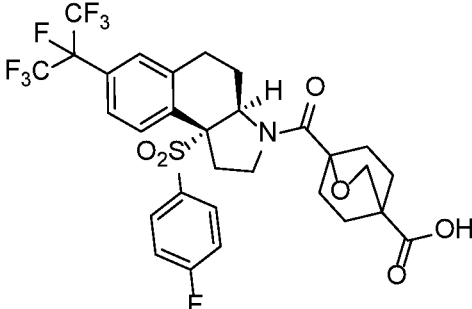
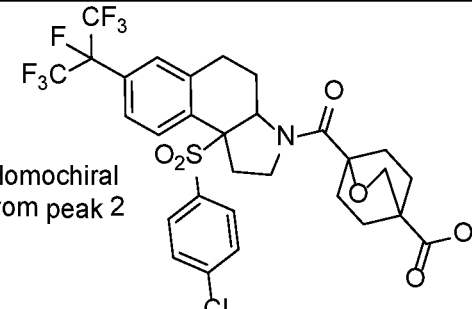
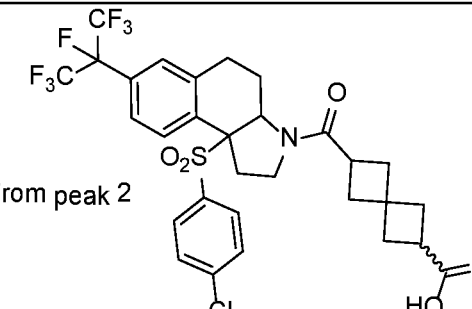
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
228		694.1 (M+H) ⁺	2.43	D
229		638.3 (M+H) ⁺	2.16	D
230		645.9 (M+H) ⁺	2.09	D
231		646.4 (M+H) ⁺	2.17	D
232		664.4 (M+H) ⁺	2.33	D

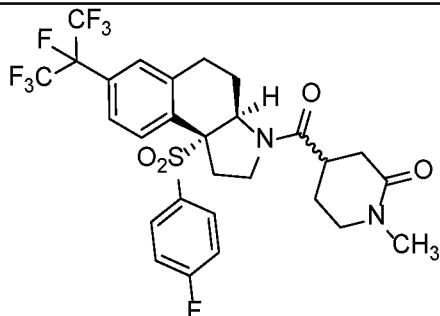
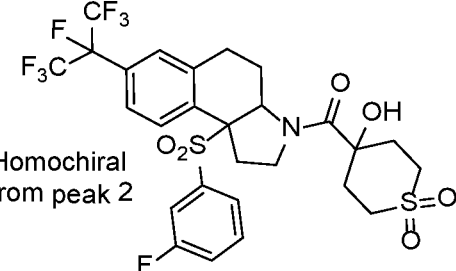
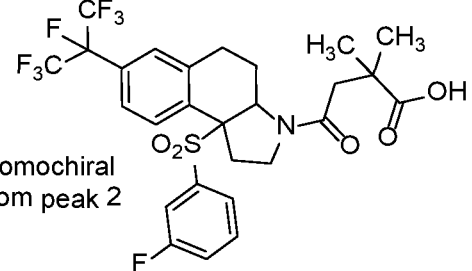
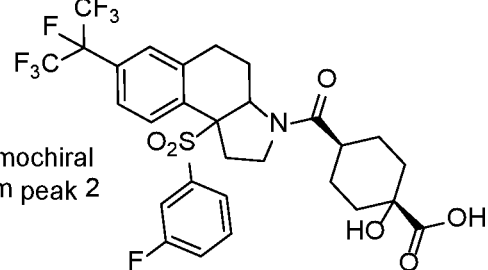
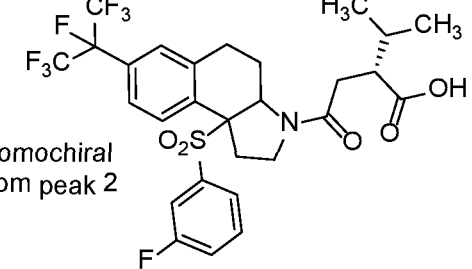
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
233	 Homochiral from peak 2	662.1 (M+H) ⁺	2.20	D
234	 Homochiral from peak 2	680.2 (M+H) ⁺	2.37	D
235	 Homochiral from peak 2	630.0 (M+H) ⁺	2.17	D
236	 Homochiral from peak 2	628.1 (M+H) ⁺	2.07	D
237	 Homochiral from peak 2	648.0 (M+H) ⁺	2.17	D

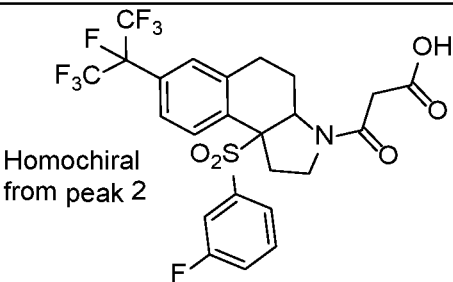
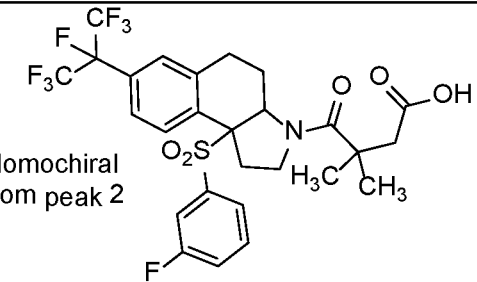
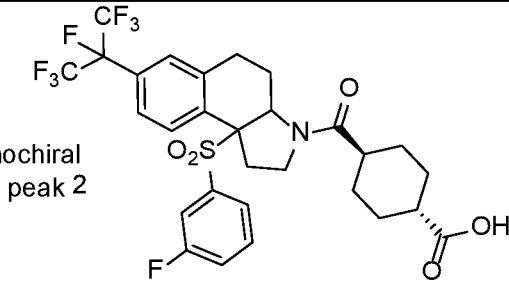
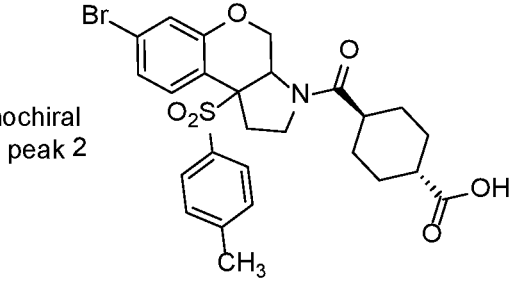
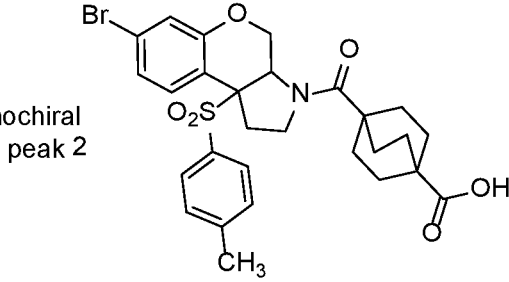
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
238	 Homochiral from peak 2	664.2 (M+H) ⁺	2.28	D
239		664.2 (M+H) ⁺	2.22	D
240		628.0 (M+H) ⁺	2.06	D
241		664.1 (M+H) ⁺	2.11	D
242		642.3 (M+H) ⁺	2.20	D

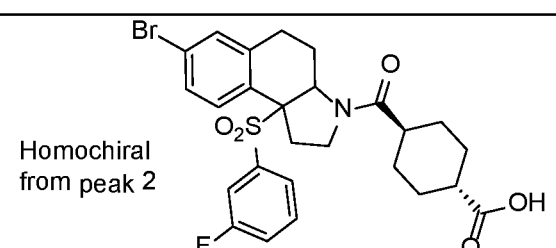
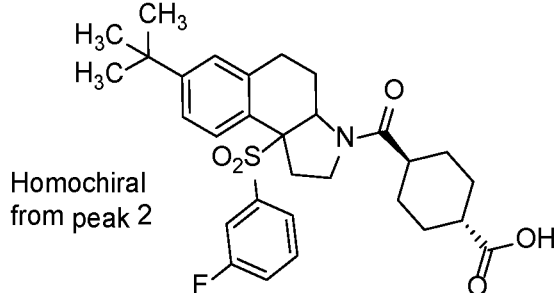
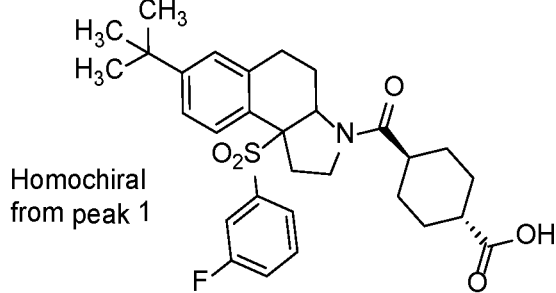
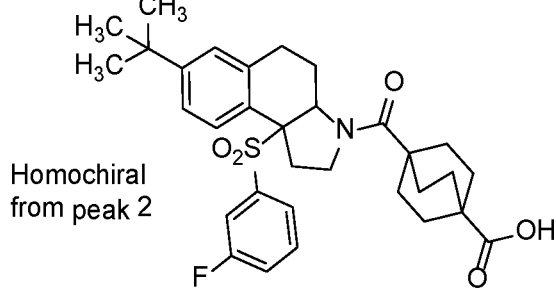
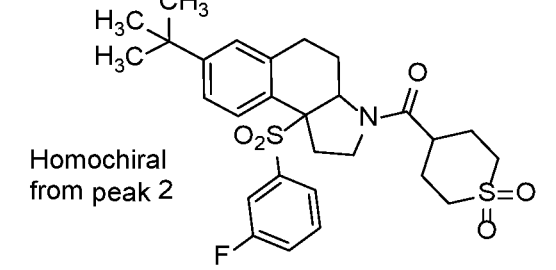
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
243		643.2 (M+H) ⁺	2.16	D
244		671.0 (M+H) ⁺	2.29	D
245		687.3 (M+H) ⁺	2.24	D
246		644.1 (M+H) ⁺	1.99	D
247	 Homochiral from peak 2	669.2 (M+H) ⁺	2.23	D

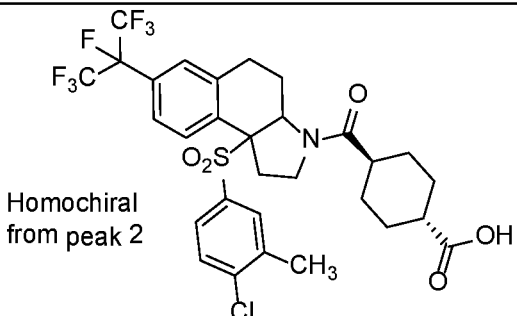
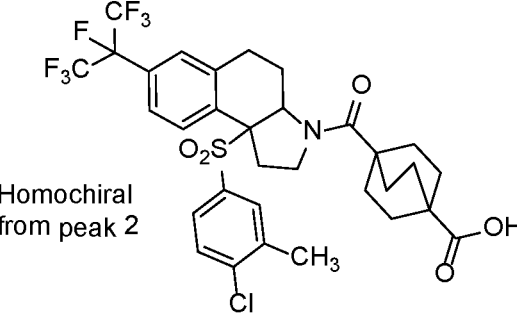
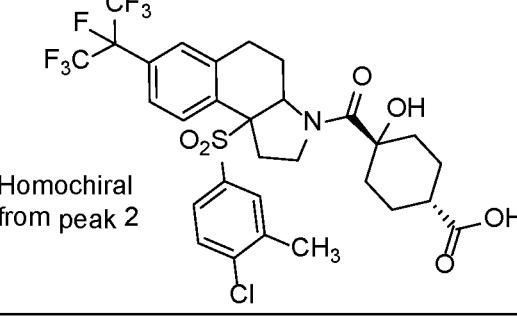
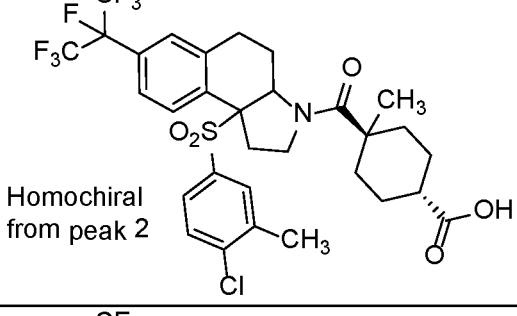
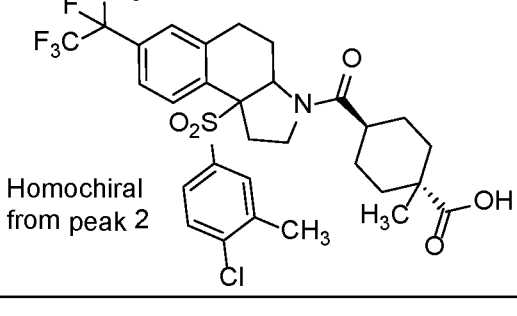
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248	Homochiral from peak 2	672.0 (M+H) ⁺	2.32	D
249	Homochiral from peak 2	668.2 (M+H) ⁺	1.10	B
250	Homochiral from peak 2	660.4 (M+H) ⁺	2.21	D
251	Homochiral from peak 2	670.4 (M+H) ⁺	1.01	B
252	Homochiral from peak 2	654.2 (M+H) ⁺	1.09	B

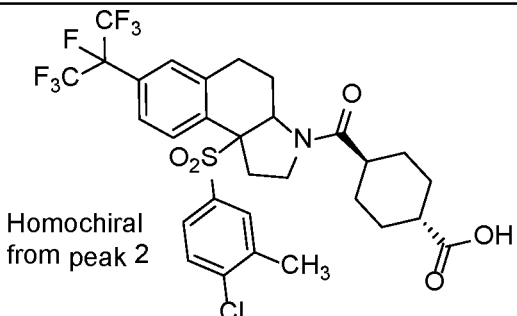
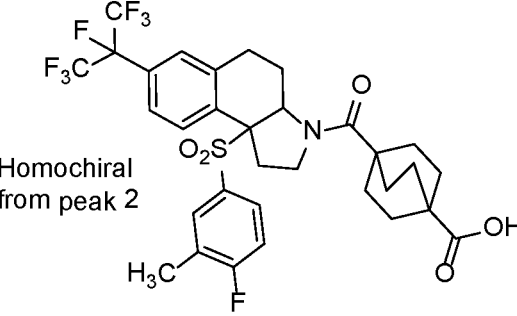
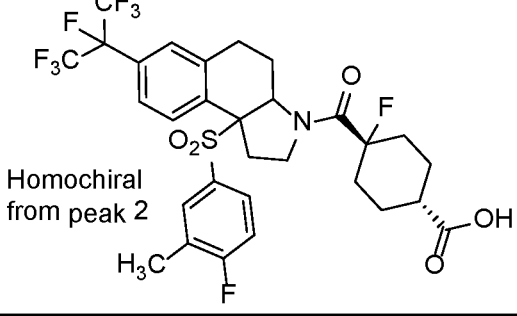
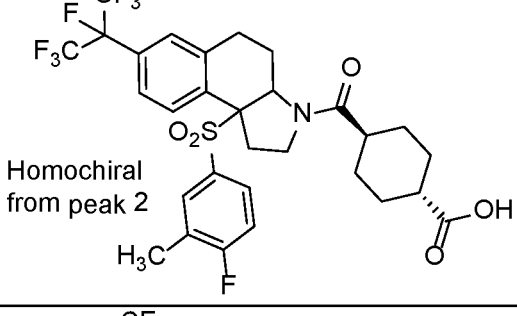
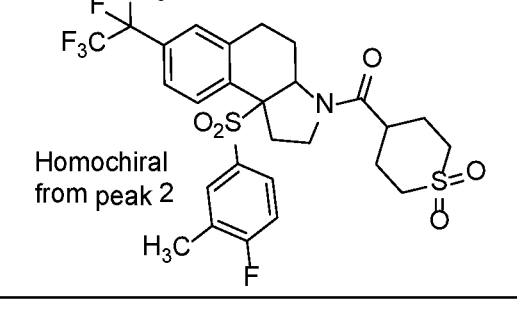
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
253	 Homochiral from peak 2	660.0 (M+H) ⁺	1.97	D
254		681.8 (M+H) ⁺	2.09	D
255		682.1 (M+H) ⁺	1.12	B
256	 Homochiral from peak 2	698.1 (M+H) ⁺	1.15	B
257	 From peak 2	682.2 (M+H) ⁺	2.40	D

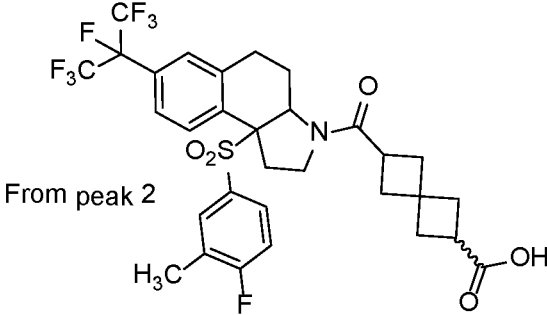
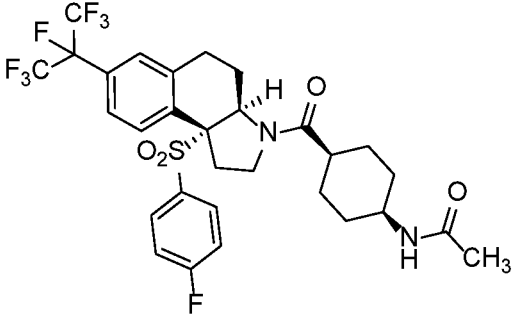
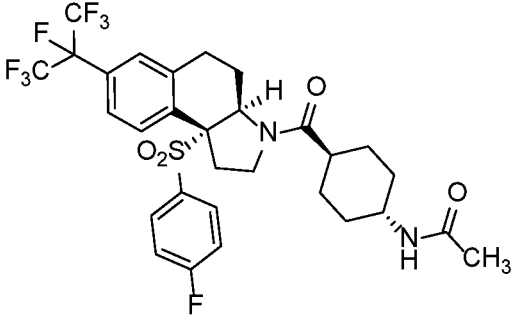
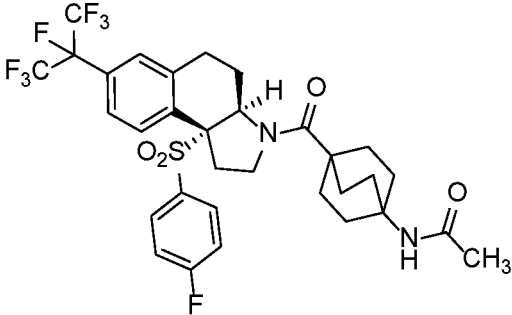
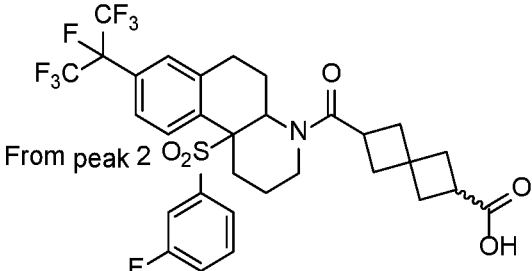
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
258		639.3 (M+H) ⁺	2.09	D
259	 Homochiral from peak 2	676.2 (M+H) ⁺	1.05	B
260	 Homochiral from peak 2	628.2 (M+H) ⁺	2.21	D
261	 Homochiral from peak 2	670.3 (M+H) ⁺	1.01	B
262	 Homochiral from peak 2	641.9 (M+H) ⁺	2.00	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
263	 Homochiral from peak 2	586.0 (M+H) ⁺	2.05	D
264	 Homochiral from peak 2	628.1 (M+H) ⁺	2.18	D
265	 Homochiral from peak 2	654.2 (M+H) ⁺	1.09	B
266	 Homochiral from peak 2	561.9 (M+H) ⁺	1.68	C
267	 Homochiral from peak 2	588.1 (M+H) ⁺	1.68	C

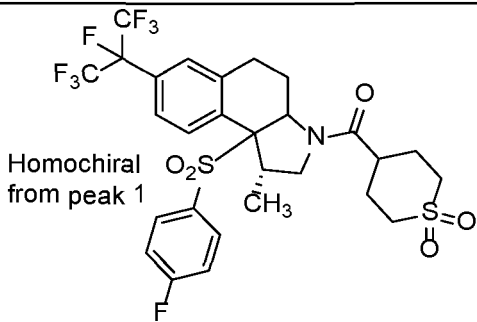
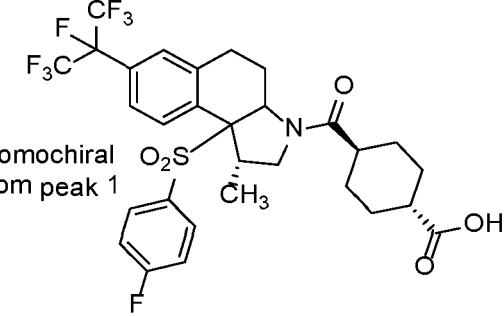
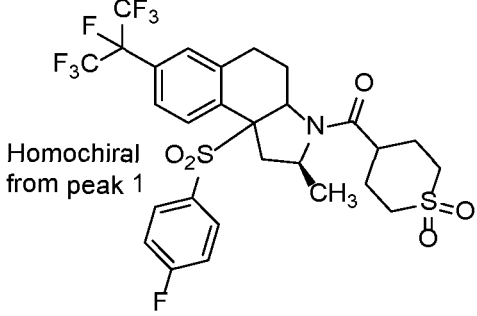
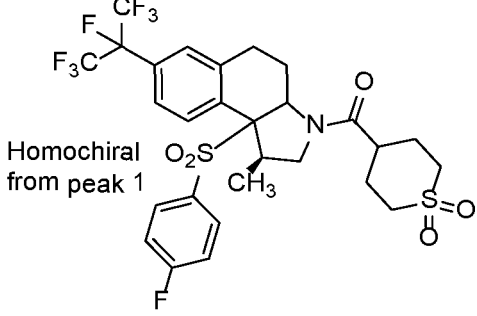
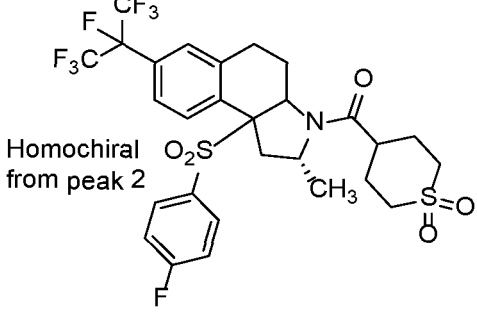
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268	Homochiral from peak 2 	564.1 (M+H) ⁺	2.02	D
269	Homochiral from peak 2 	542.1 (M+H) ⁺	2.07	D
270	Homochiral from peak 1 	542.2 (M+H) ⁺	2.21	D
271	Homochiral from peak 2 	568.5 (M+H) ⁺	2.34	D
272	Homochiral from peak 2 	548.1 (M+H) ⁺	1.99	D

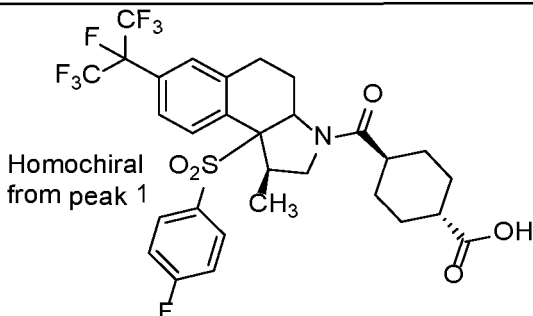
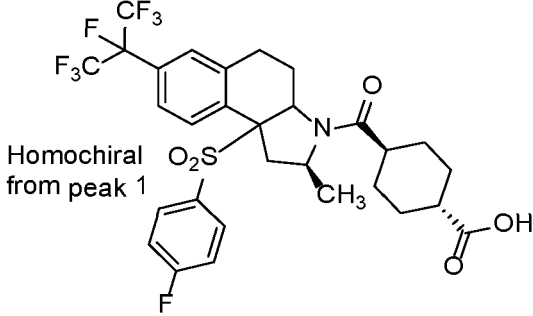
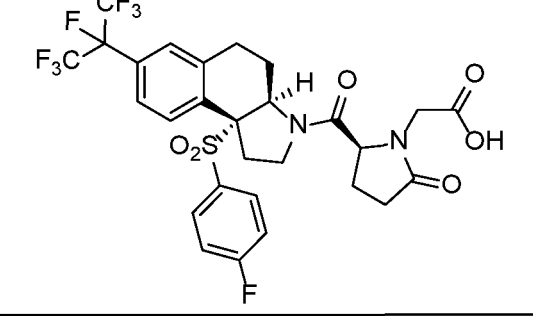
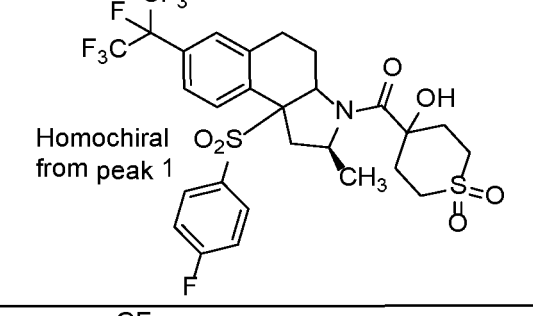
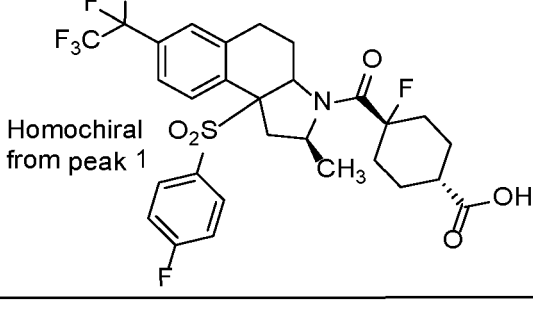
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
273	 Homochiral from peak 2	664.1 (M+H) ⁺	2.47	D
274	 Homochiral from peak 2	710.2 (M+H) ⁺	2.42	D
275	 Homochiral from peak 2	700.1 (M+H) ⁺	2.37	D
276	 Homochiral from peak 2	698.1 (M+H) ⁺	2.43	D
277	 Homochiral from peak 2	698.4 (M+H) ⁺	2.44	D

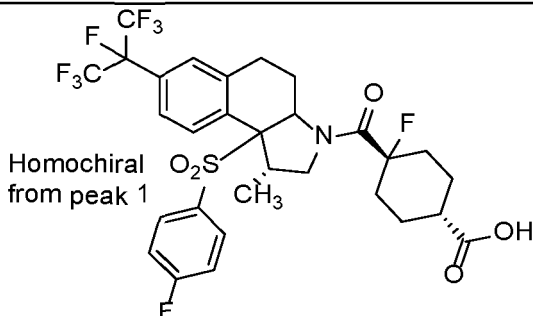
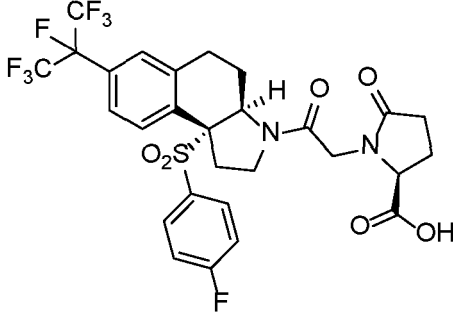
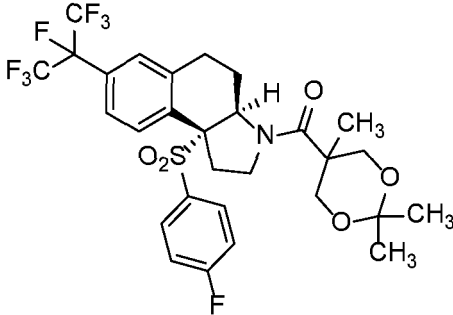
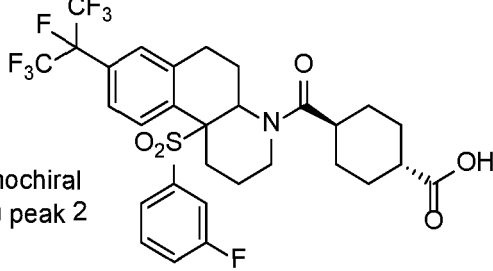
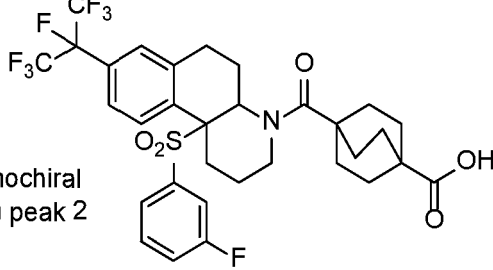
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
278	 Homochiral from peak 2	684.2 (M+H) ⁺	2.46	D
279	 Homochiral from peak 2	694.2 (M+H) ⁺	2.34	D
280	 Homochiral from peak 2	686.1 (M+H) ⁺	2.42	D
281	 Homochiral from peak 2	668.2 (M+H) ⁺	2.25	D
282	 Homochiral from peak 2	674.1 (M+H) ⁺	2.22	D

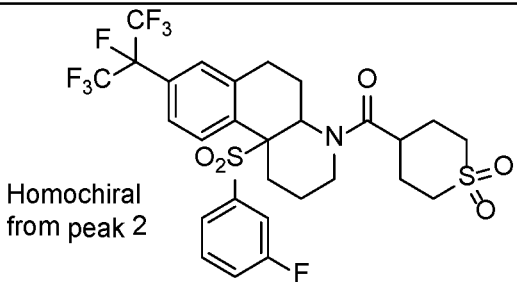
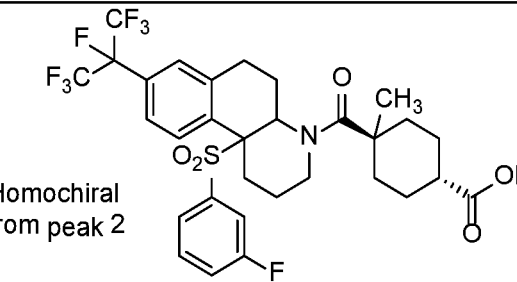
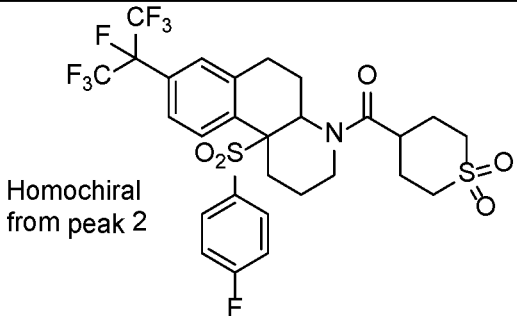
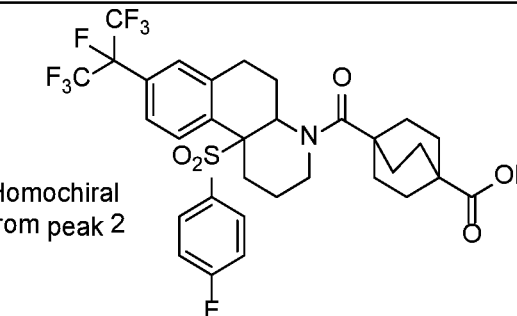
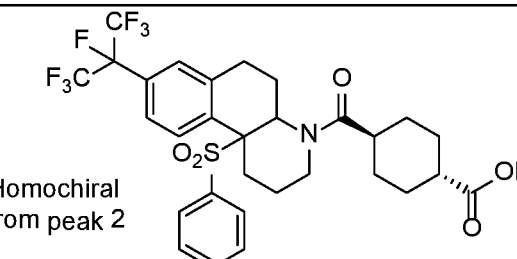
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
283	 From peak 2	680.0 (M+H) ⁺	2.28	D
284		667.0 (M+H) ⁺	2.15	D
285		693.2 (M+H) ⁺	2.23	D
286		667.0 (M+H) ⁺	2.14	D
287	 From peak 2	680.2 (M+H) ⁺	2.27	D

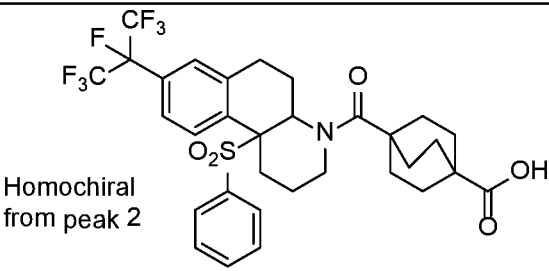
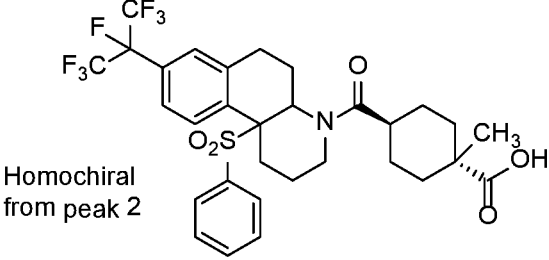
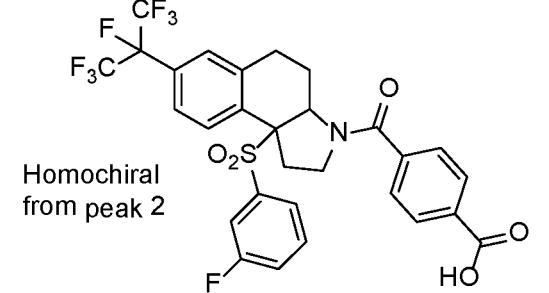
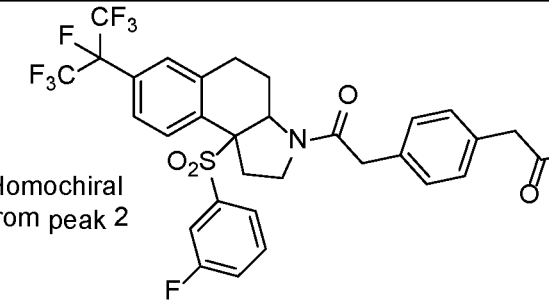
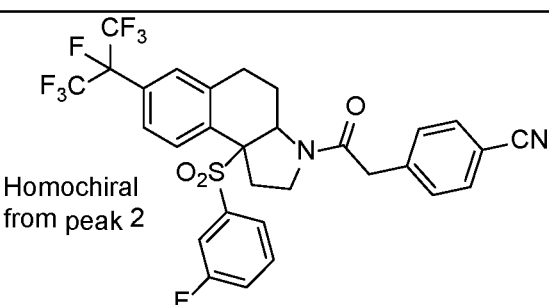
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
288	From peak 2	680.2 (M+H) ⁺	2.27	D
289	[cis, Peak 1]	674.1 (M+H) ⁺	1.05	B
290	[cis, Peak 2]	674.1 (M+H) ⁺	1.05	B
291	Homochiral from peak 2	546.2 (M+H) ⁺	1.96	D
292	Homochiral from peak 2	520.1 (M+H) ⁺	1.99	D

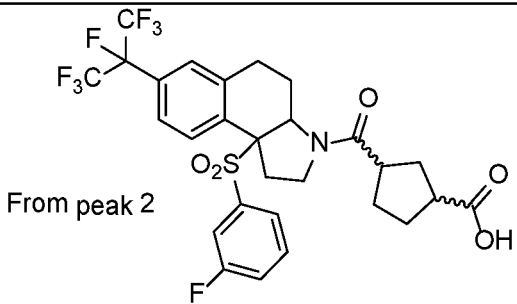
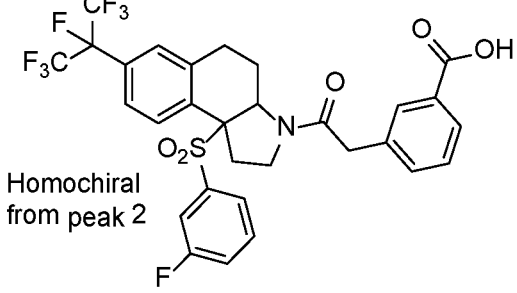
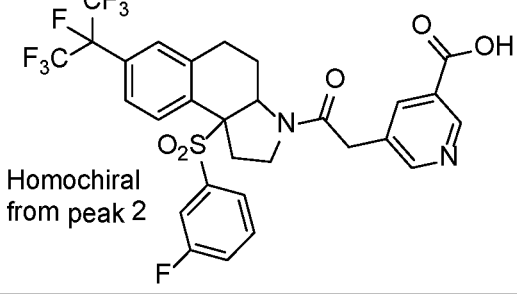
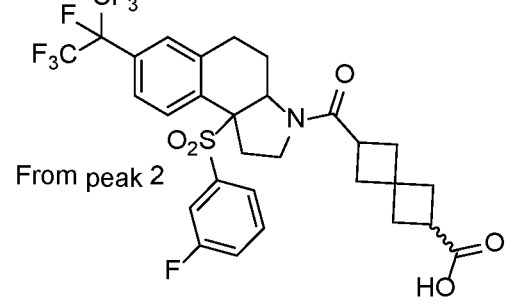
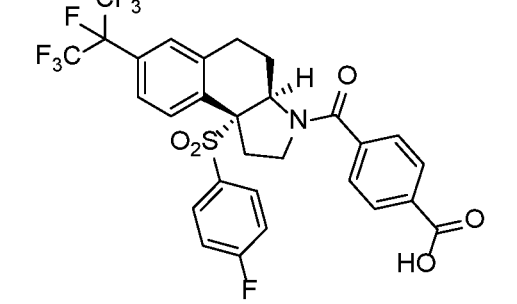
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
293	 Homochiral from peak 1	674.3 (M+H) ⁺	2.31	C
294	 Homochiral from peak 1	668.3 (M+H) ⁺	2.03	C
295	 Homochiral from peak 1	674.1 (M+H) ⁺	2.19	C
296	 Homochiral from peak 1	674.0 (M+H) ⁺	2.20	C
297	 Homochiral from peak 2	674.2 (M+H) ⁺	2.26	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
298	 Homochiral from peak 1	668.1 (M+H) ⁺	1.98	C
299	 Homochiral from peak 1	667.9 (M+H) ⁺	2.34	C
300		669.2 (M+H) ⁺	1.65	C
301	 Homochiral from peak 1	690.1 (M+H) ⁺	2.17	C
302	 Homochiral from peak 1	686.2 (M+H) ⁺	2.14	C

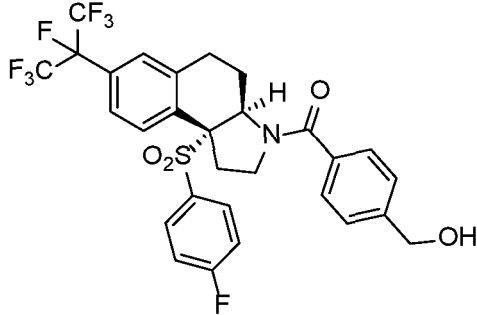
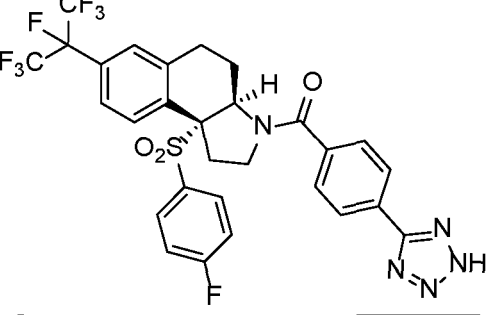
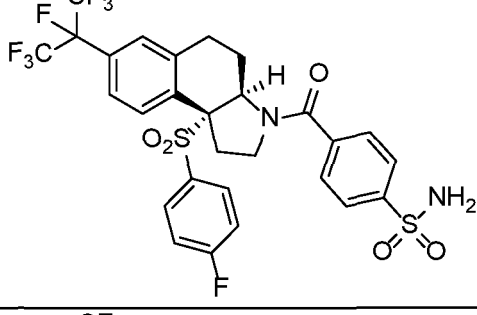
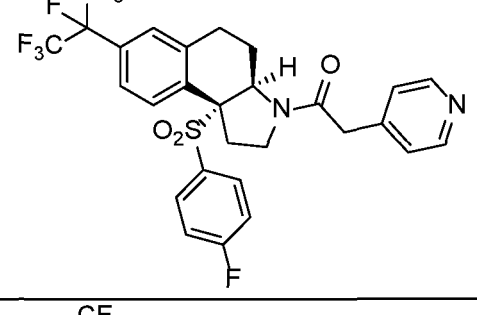
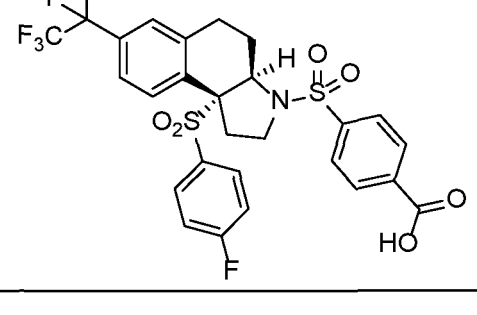
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
303	 Homochiral from peak 1	686.3 (M+H) ⁺	2.41	C
304		669.2 (M+H) ⁺	1.61	C
305		656.2 (M+H) ⁺	2.55	C
306	 Homochiral from peak 2	668.2 (M+H) ⁺	1.10	B
307	 Homochiral from peak 2	694.5 (M+H) ⁺	1.10	B

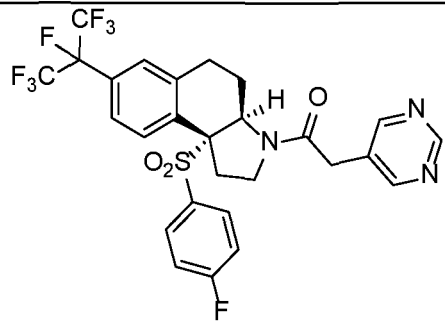
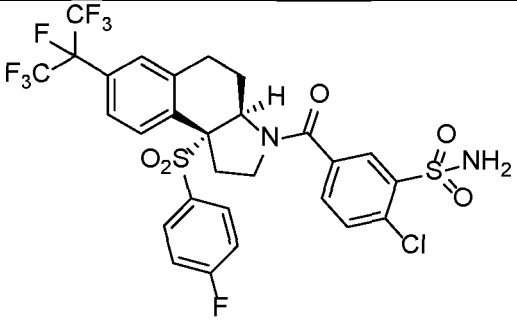
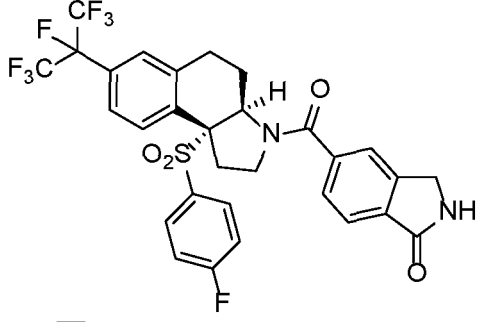
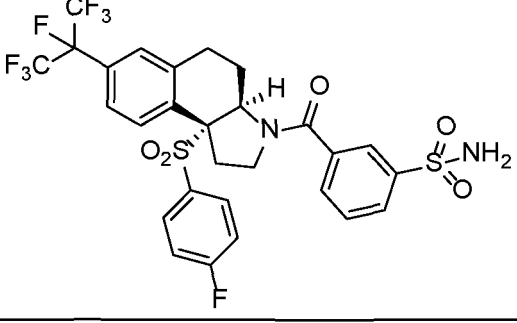
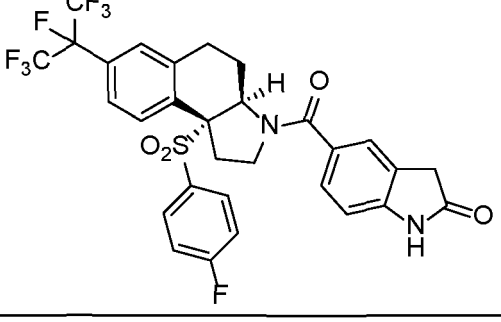
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
308	 Homochiral from peak 2	674.4 (M+H) ⁺	1.04	B
309	 Homochiral from peak 2	682.2 (M+H) ⁺	1.30	B
310	 Homochiral from peak 2	674.1 (M+H) ⁺	2.20	C
311	 Homochiral from peak 2	694.1 (M+H) ⁺	2.38	C
312	 Homochiral from peak 2	650.3 (M+H) ⁺	2.24	C

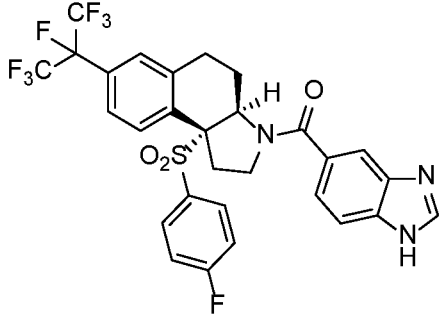
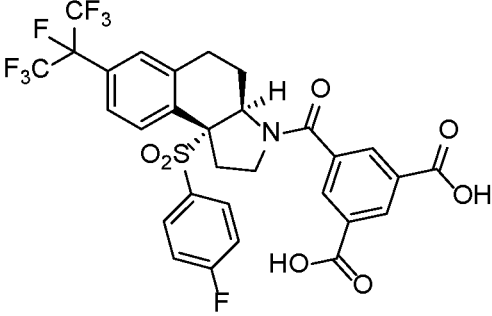
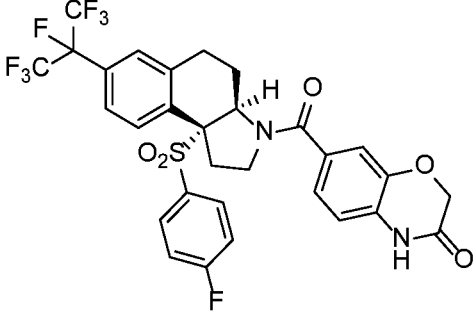
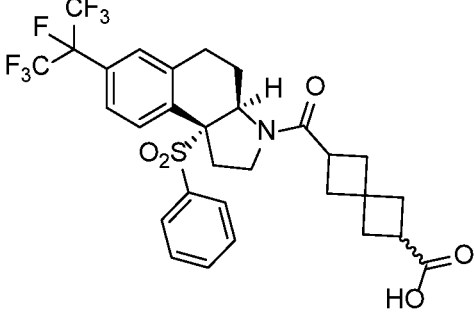
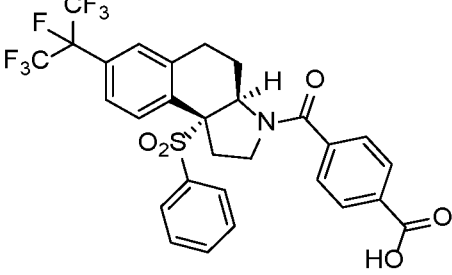
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
313	 Homochiral from peak 2	676.4 (M+H) ⁺	2.36	C
314	 Homochiral from peak 2	664.0 (M+H) ⁺	2.21	C
315	 Homochiral from peak 2	648.1 (M+H) ⁺	1.74	C
316	 Homochiral from peak 2	676.2 (M+H) ⁺	1.83	C
317	 Homochiral from peak 2	643.2 (M+H) ⁺	2.34	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
318	 From peak 2	640.1 (M+H) ⁺	1.98	C
319	 Homochiral from peak 2	662.4 (M+H) ⁺	1.81	C
320	 Homochiral from peak 2	663.4 (M+H) ⁺	1.69	C
321	 From peak 2	666.2 (M+H) ⁺	2.04	C
322	 From peak 2	648.1 (M+H) ⁺	2.19	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
323		640.1 (M+H) ⁺	1.84	C
324	Homochiral from peak 2	650.1 (M+H) ⁺	2.07	D
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

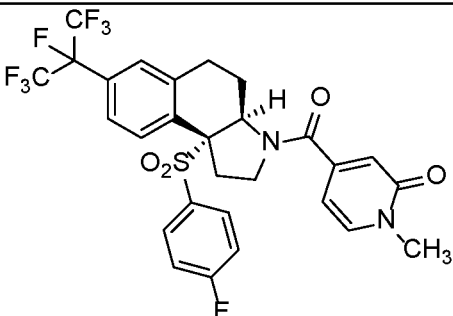
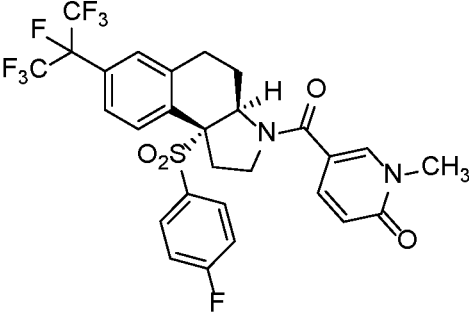
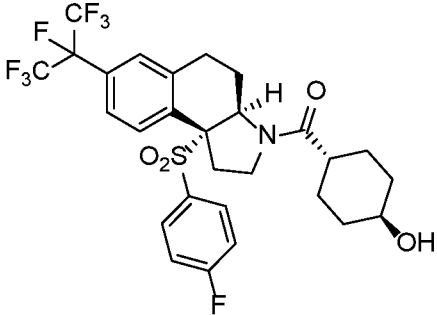
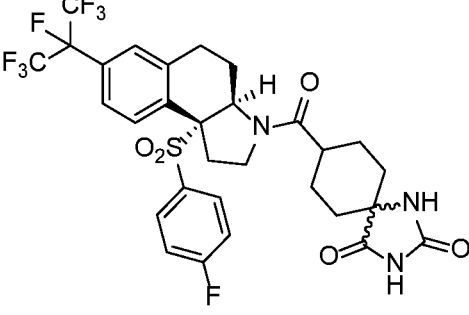
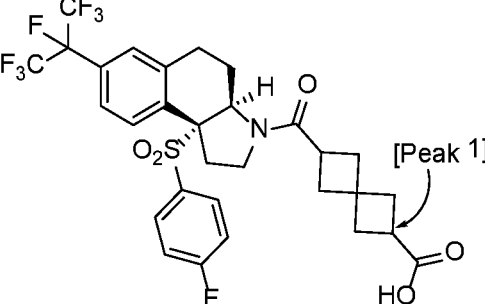
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
328		634.0 (M+H) ⁺	2.15	D
329		672.4 (M+H) ⁺	1.81	C
330		682.9 (M+H) ⁺	2.13	D
331		619.2 (M+H) ⁺	1.85	D
332		684.1 (M+H) ⁺	1.82	C

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
337		659.0 (M+H) ⁺	2.08	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
338		644.1 (M+H) ⁺	1.86	D
339		692.2 (M+H) ⁺	1.44	C
340		675.3 (M+H) ⁺	2.19	C
341		648.1 (M+H) ⁺	1.81	C
342		630.3 (M+H) ⁺	1.72	C

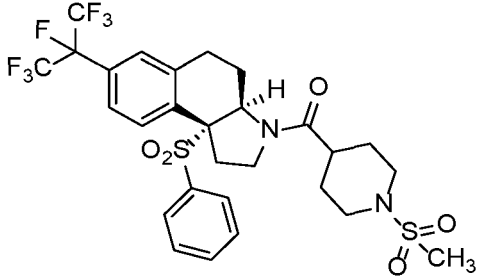
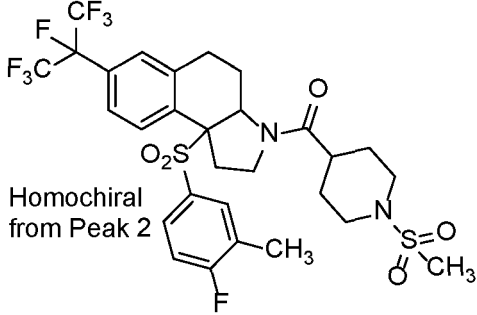
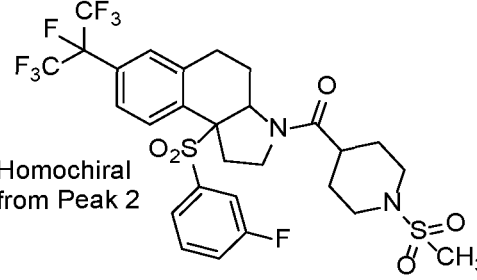
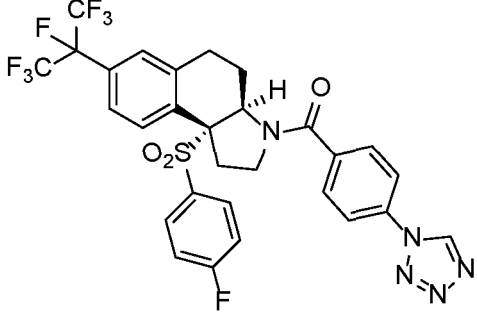
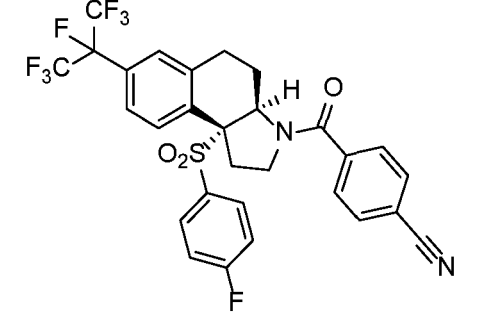
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
343		709.3 (M+H) ⁺	2.13	D
344		716.3 (M+H) ⁺	1.83	C
345		647.1 (M+H) ⁺	2.08	C
346		665.1 (M+H) ⁺	2.14	C
347		654.1 (M+H) ⁺	2.17	D

Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
348		654.4 (M+H) ⁺	2.16	D
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

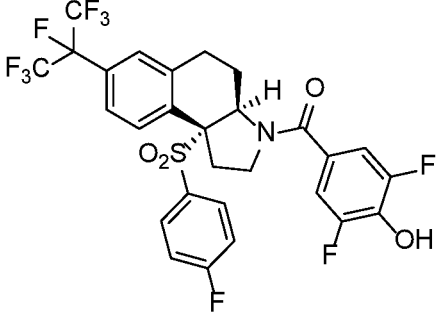
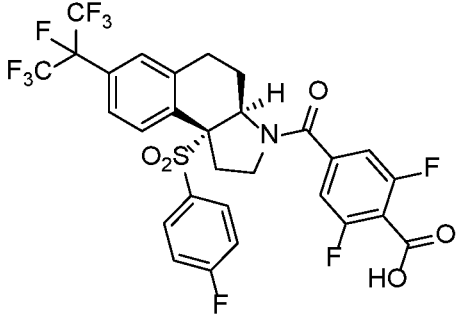
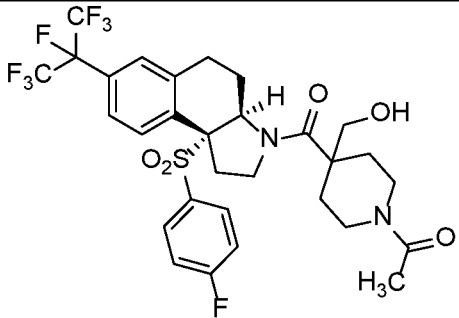
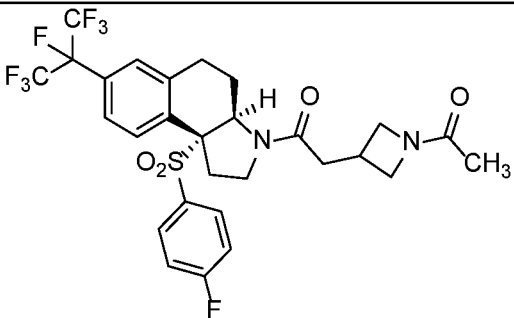
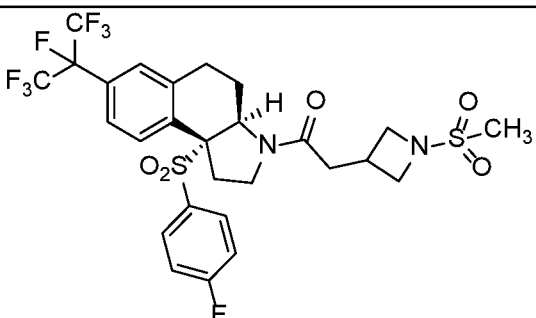
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353		635.2 (M+H) ⁺	2.13	D
354		635.1 (M+H) ⁺	2.19	D
355		626.2 (M+H) ⁺	2.24	C
356		694.1 (M+H) ⁺	2.12	D
357		666.2 (M+H) ⁺	1.05	B

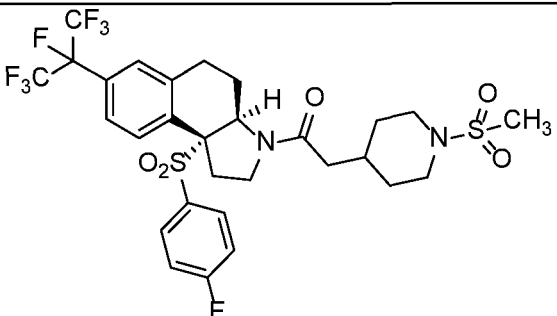
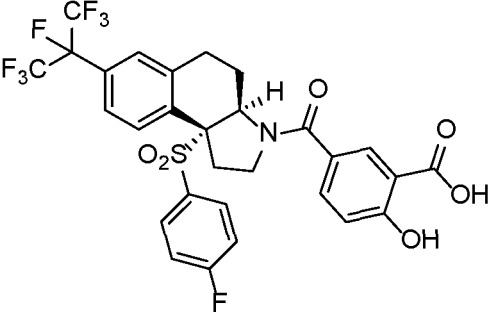
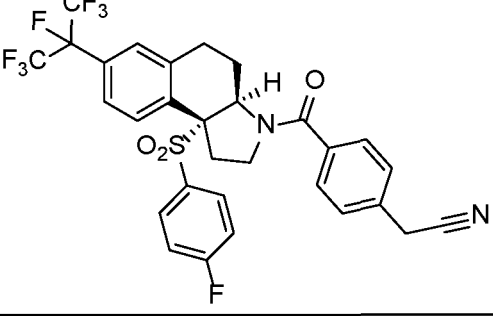
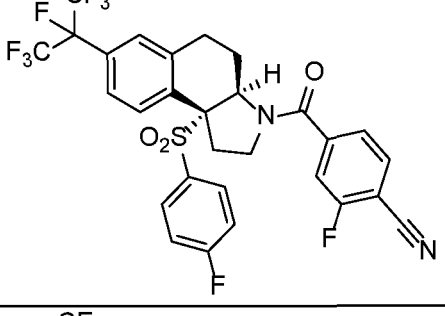
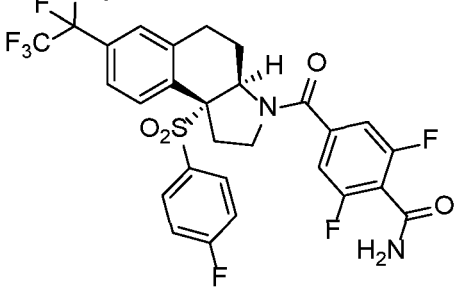
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
358		666.2 (M+H) ⁺	1.05	B
359		696.0 (M+H) ⁺	2.10	C
360		696.3 (M+H) ⁺	2.12	C
361		678.3 (M+H) ⁺	2.18	D
362		682.2 (M+H) ⁺	2.29	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
363		660.0 (M+H) ⁺	2.19	C
364		624.9 (M+H) ⁺	2.07	C
365		689.2 (M+H) ⁺	2.18	C
366		660.2 (M+H) ⁺	1.02	B
367		660.2 (M+H) ⁺	1.02	B

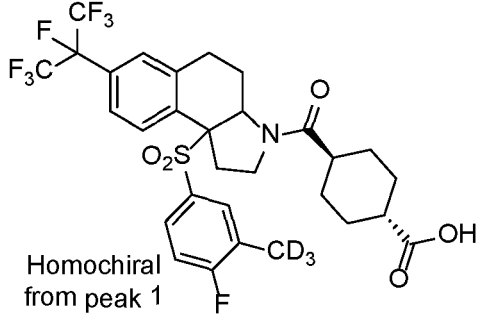
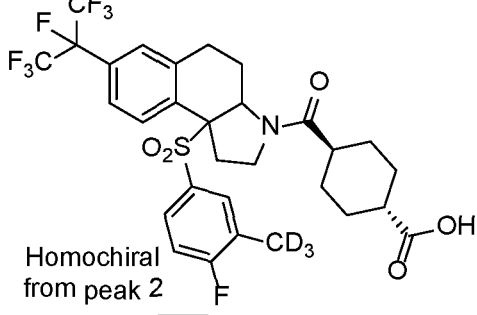
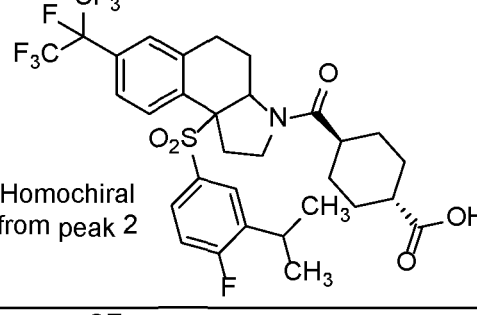
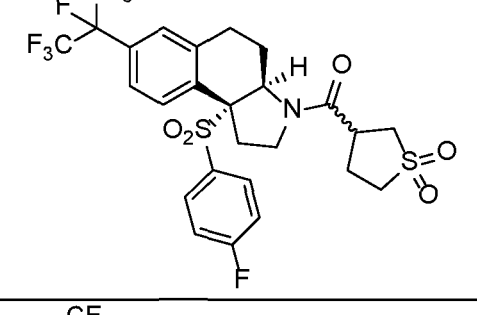
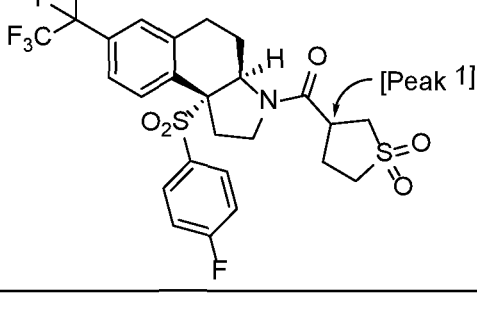
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
368		671.2 (M+H) ⁺	2.13	C
369	 Homochiral from Peak 2	703.2 (M+H) ⁺	2.26	D
370	 Homochiral from Peak 2	689.2 (M+H) ⁺	2.25	C
371		672.0 (M+H) ⁺	2.23	D
372		629.2 (M+H) ⁺	2.40	C

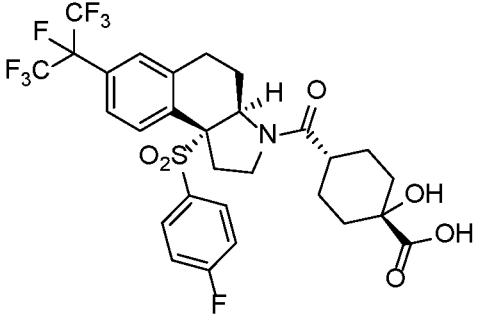
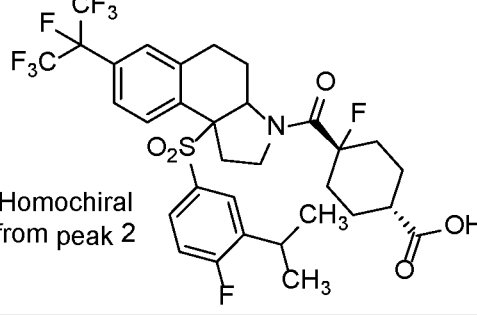
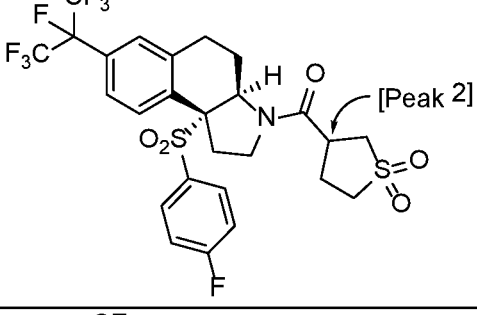
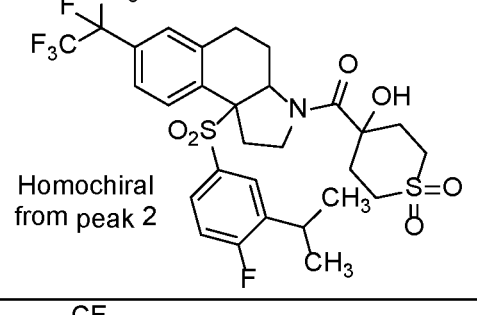
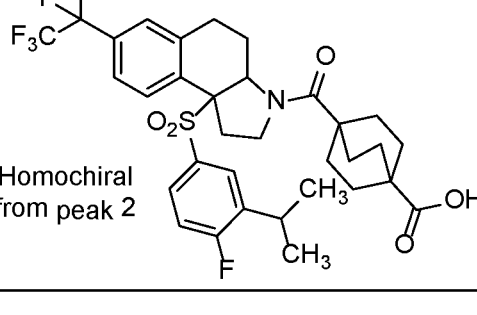
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
373		674.3 (M+H) ⁺	2.19	C
374	Homochiral from Peak 2	658.0 (M+H) ⁺	2.14	D
375		697.2 (M+H) ⁺	1.71	C
376		682.2 (M+H) ⁺	2.34	D
377		659.2 (M+H) ⁺	2.32	C

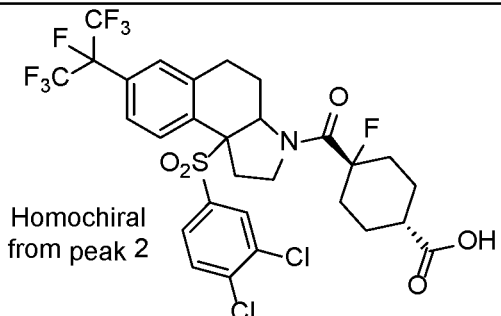
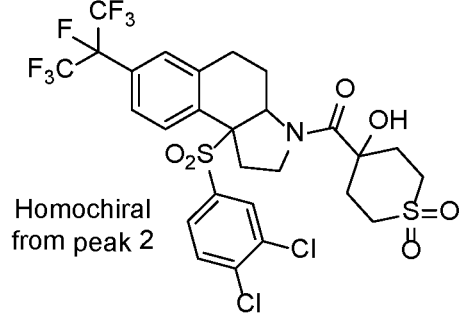
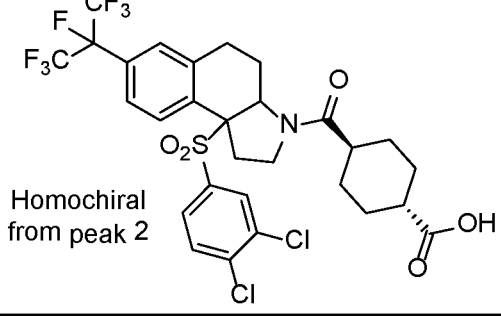
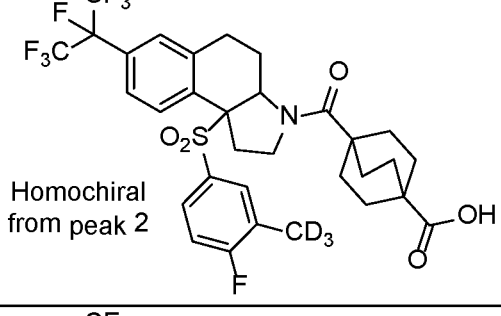
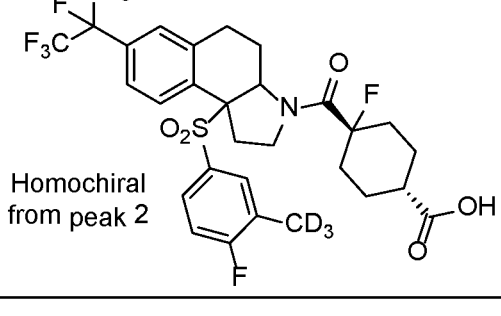
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
378		656.0 (M+H) ⁺	2.20	C
379		684.2 (M+H) ⁺	2.24	D
380		683.1 (M+H) ⁺	2.00	D
381		639.2 (M+H) ⁺	2.09	C
382		675.0 (M+H) ⁺	2.19	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
383		702.8 (M+H) ⁺	2.28	C
384		664.0 (M+H) ⁺	1.80	C
385		643.2 (M+H) ⁺	2.33	D
386		647.1 (M+H) ⁺	1.15	B
387		683.1 (M+H) ⁺	2.14	D

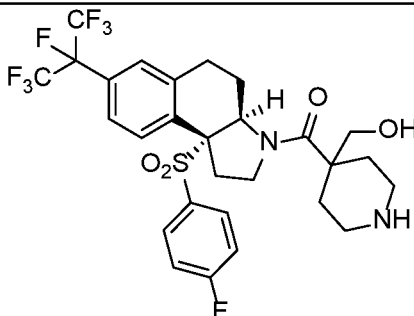
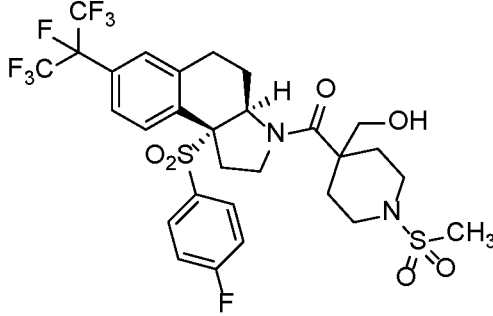
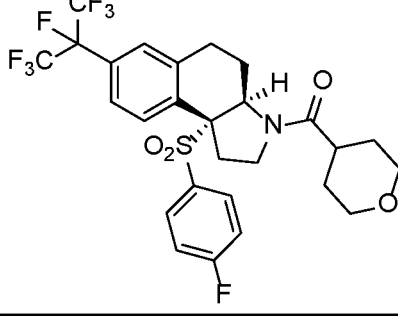
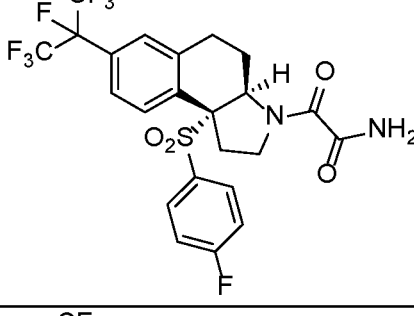
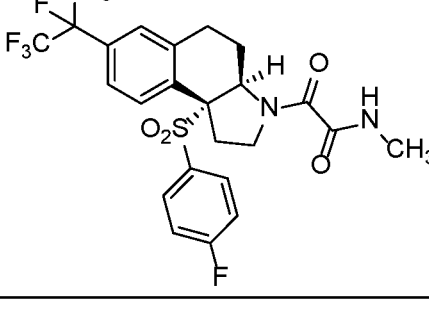
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
388	Homochiral from peak 2 [peak 1]	676.0 (M+H) ⁺	1.05	B
389	Homochiral from peak 2 [peak 2]	676.1 (M+H) ⁺	1.04	B
390	Homochiral from peak 2 [peak 1]	690.0 (M+H) ⁺	1.07	B
391	Homochiral from peak 2 [peak 2]	690.0 (M+H) ⁺	1.07	B
392	Homochiral from peak 2	677.1 (M+H) ⁺	2.19	C

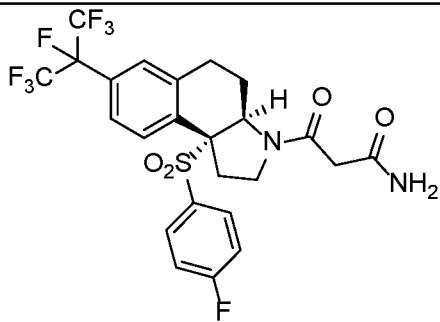
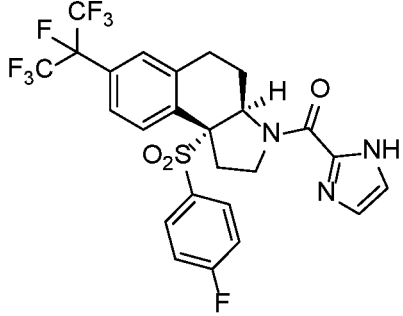
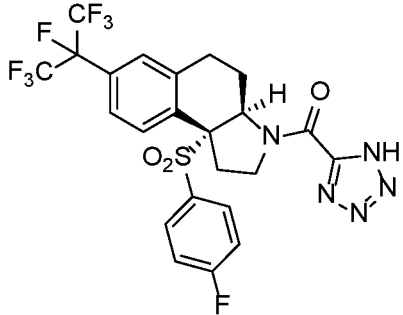
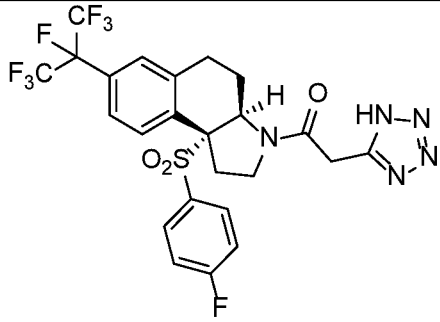
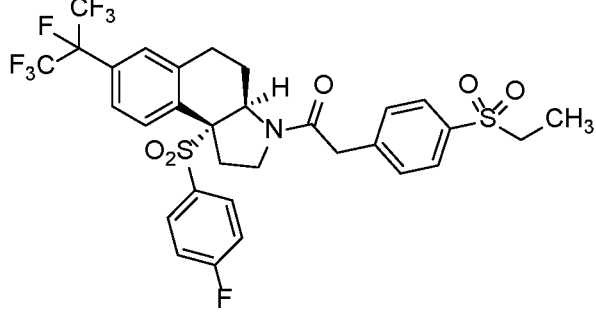
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393	 Homochiral from peak 1	671.2 (M+H) ⁺	2.01	C
394	 Homochiral from peak 2	671.2 (M+H) ⁺	2.01	C
395	 Homochiral from peak 2	696.1 (M+H) ⁺	2.25	C
396		646.0 (M+H) ⁺	2.18	C
397	 [Peak 1]	646.0 (M+H) ⁺	2.17	C

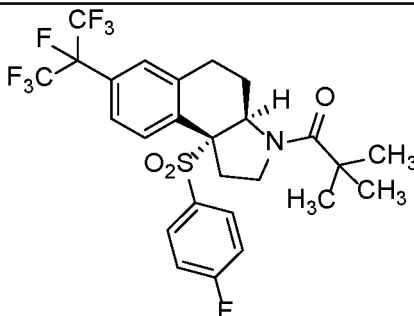
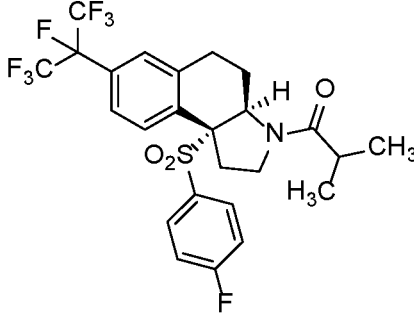
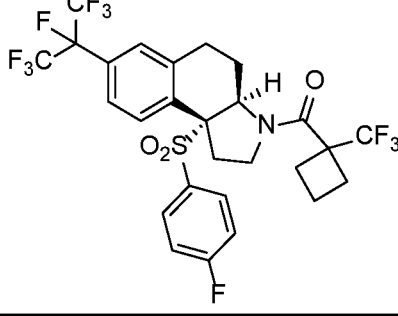
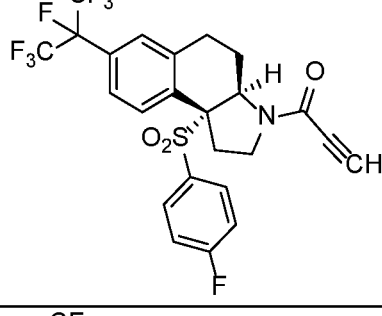
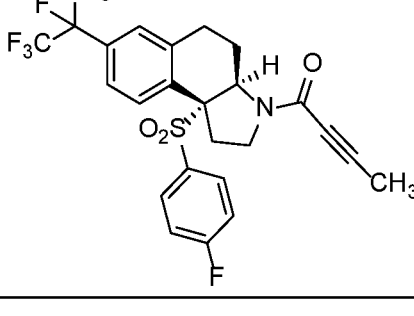
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
398		669.9 (M+H) ⁺	1.75	C
399	 Homochiral from peak 2	714.1 (M+H) ⁺	2.25	C
400	 [Peak 2]	646.3 (M+H) ⁺	2.15	C
401	 Homochiral from peak 2	718.3 (M+H) ⁺	2.35	D
402	 Homochiral from peak 2	722.1 (M+H) ⁺	2.28	C

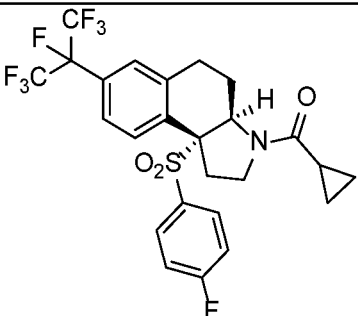
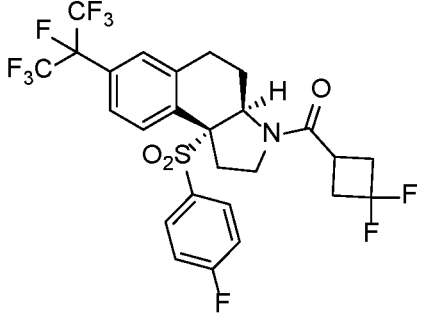
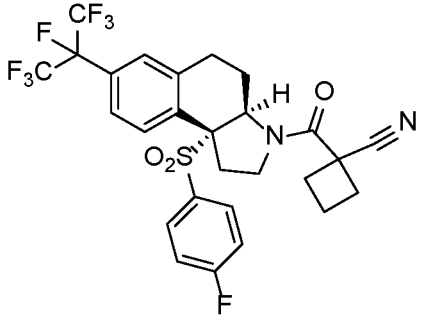
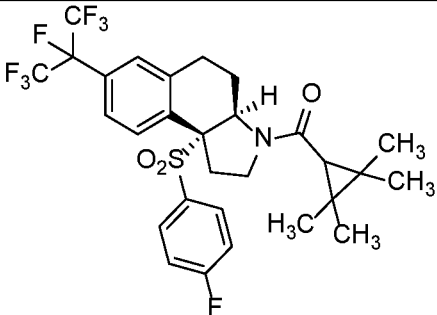
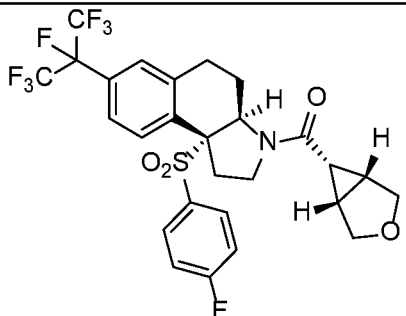
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
403	 Homochiral from peak 2	722.2 (M+H) ⁺	2.19	C
404	 Homochiral from peak 2	725.4 (M-H) ⁻	2.34	D
405	 Homochiral from peak 2	704.0 (M+H) ⁺	2.11	C
406	 Homochiral from peak 2	697.1 (M+H) ⁺	2.24	C
407	 Homochiral from peak 2	688.8 (M+H) ⁺	2.21	C

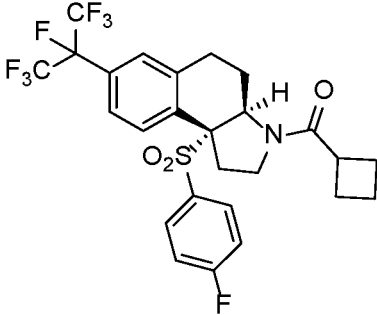
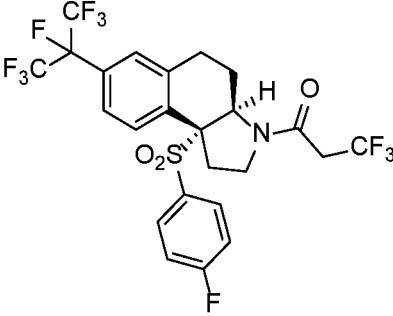
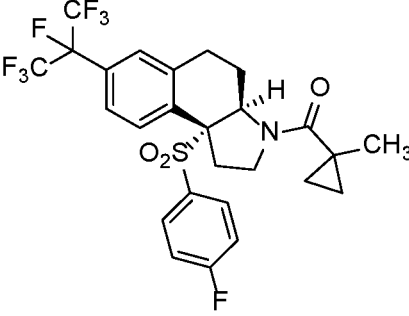
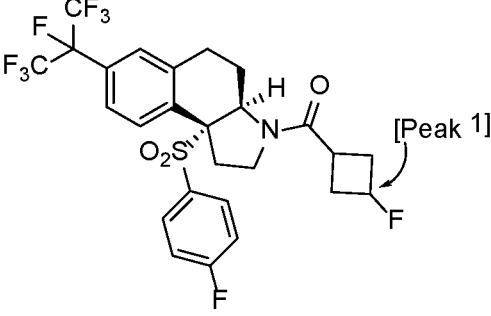
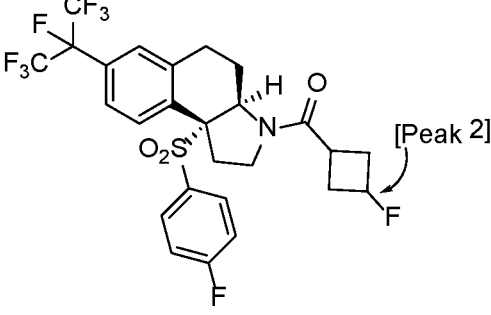
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
408		640.1 (M+H) ⁺	1.04	B
409		654.3 (M+H) ⁺	1.93	C
410		707.3 (M+H) ⁺	2.34	C
411		637.9 (M+H) ⁺	1.84	C
412		715.3 (M+H) ⁺	2.24	C

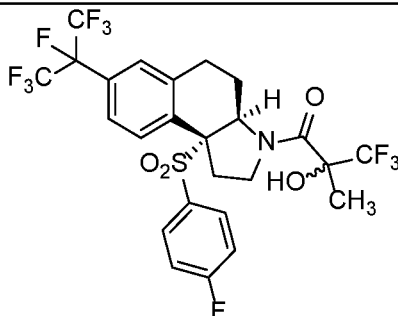
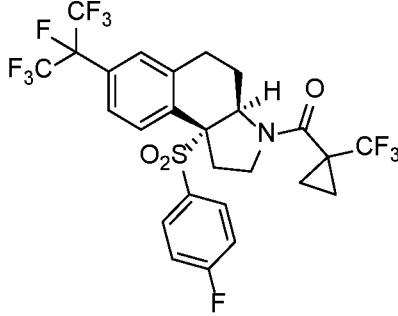
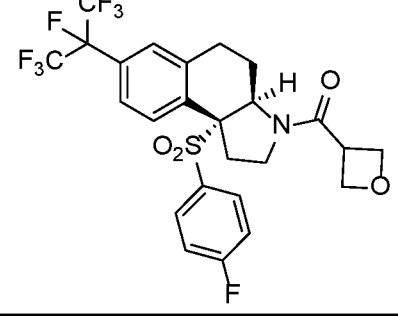
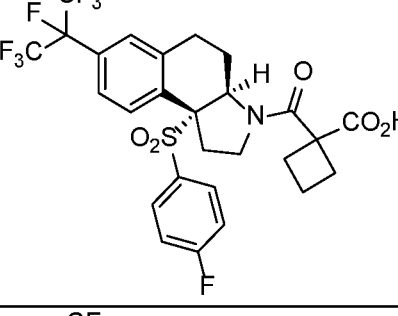
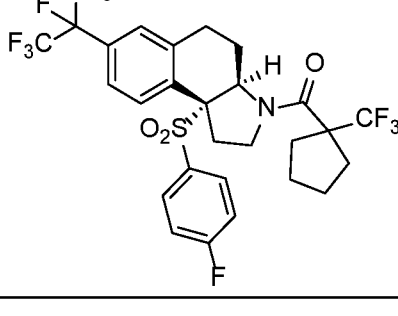
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
413		641.2 (M+H) ⁺	1.76	C
414		719.1 (M+H) ⁺	2.11	C
415		611.9 (M+H) ⁺	2.24	C
416		571.2 (M+H) ⁺	2.04	C
417		585.1 (M+H) ⁺	2.19	C

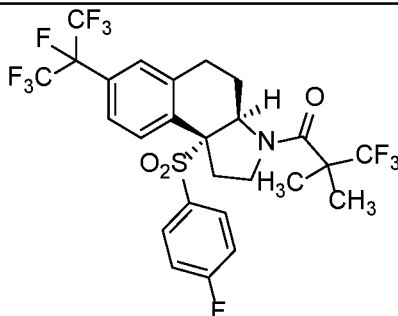
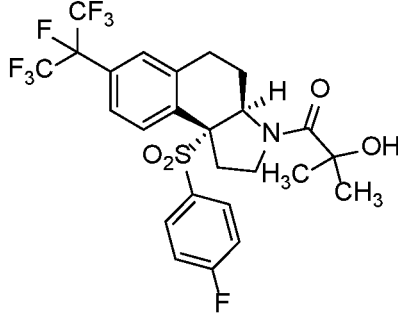
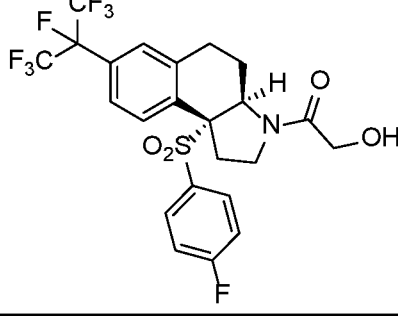
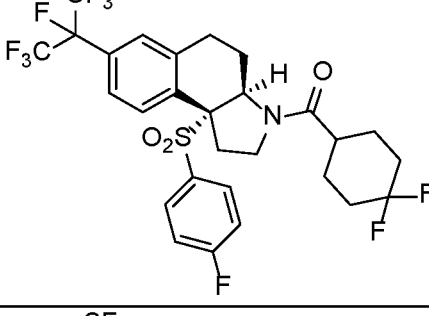
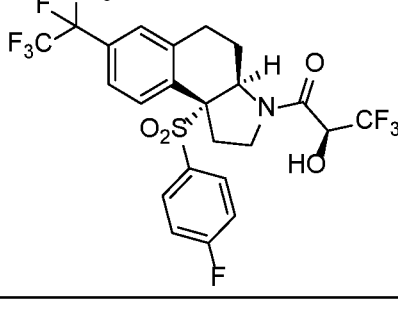
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
418		585.3 (M+H) ⁺	2.04	C
419		594.0 (M+H) ⁺	2.21	C
420		596.3 (M+H) ⁺	1.73	C
421		608.1 (M+H) ⁺	1.81	C
422		711.0 (M+H) ⁺	2.30	C

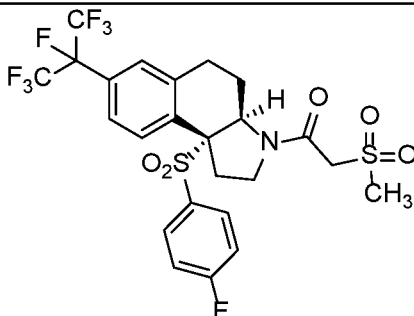
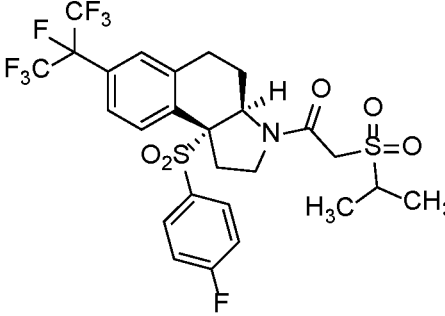
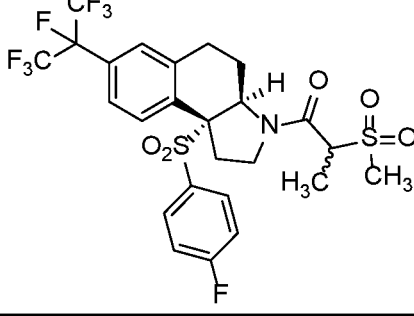
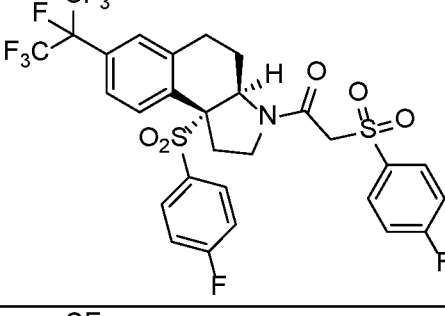
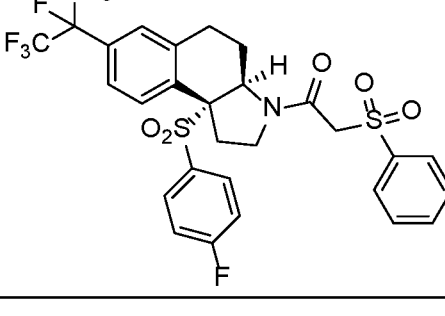
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
423		584.3 (M+H) ⁺	2.47	C
424		570.3 (M+H) ⁺	2.32	C
425		649.8 (M+H) ⁺	2.51	C
426		552.1 (M+H) ⁺	2.30	C
427		566.3 (M+H) ⁺	2.35	C

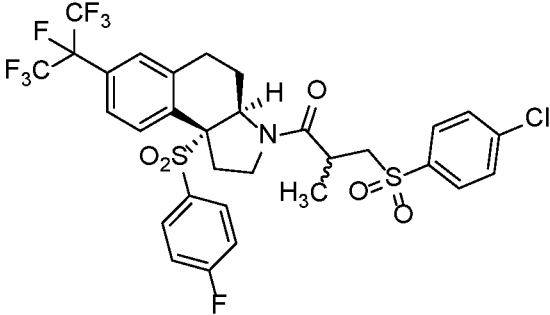
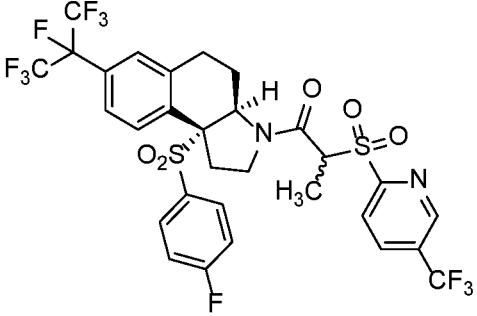
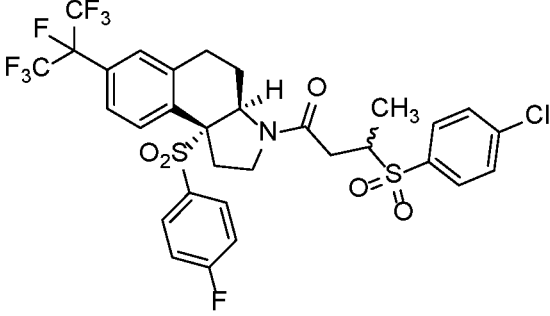
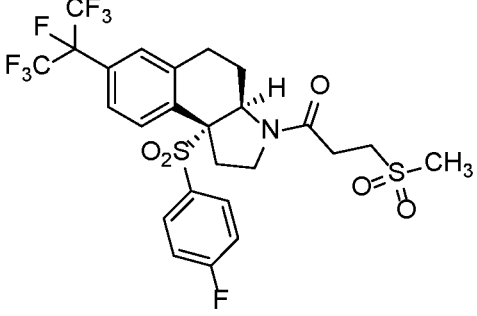
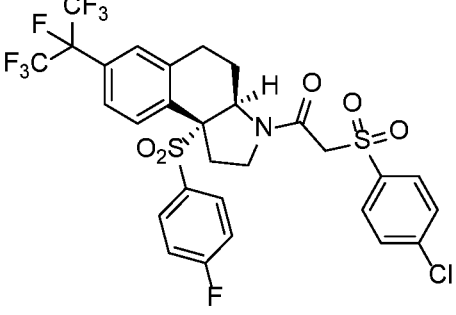
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
428		568.2 (M+H) ⁺	2.33	C
429		618.2 (M+H) ⁺	2.46	C
430		607.3 (M+H) ⁺	2.48	C
431		624.4 (M+H) ⁺	2.77	C
432		610.2 (M+H) ⁺	2.21	C

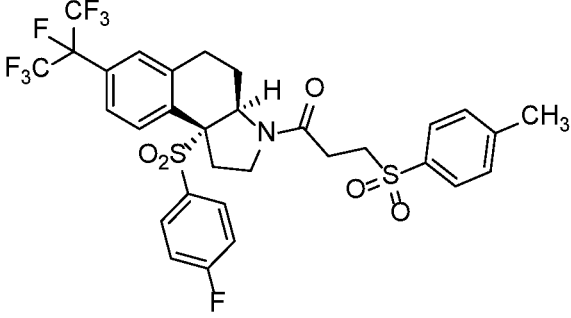
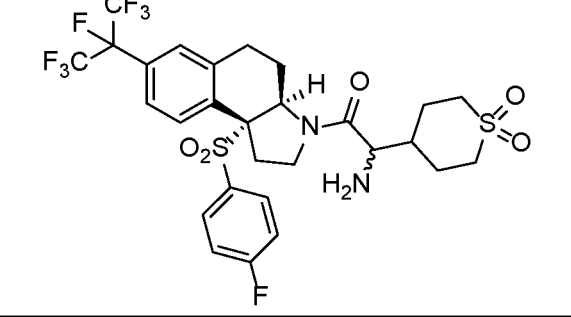
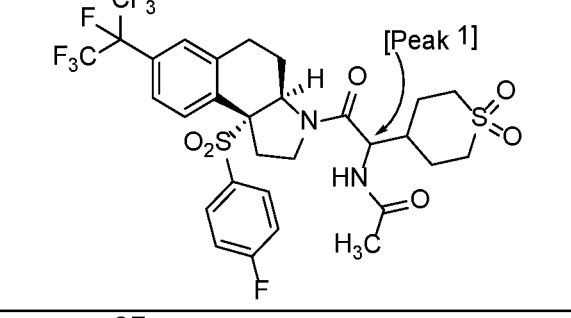
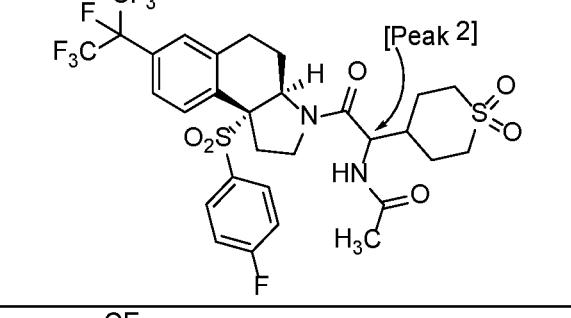
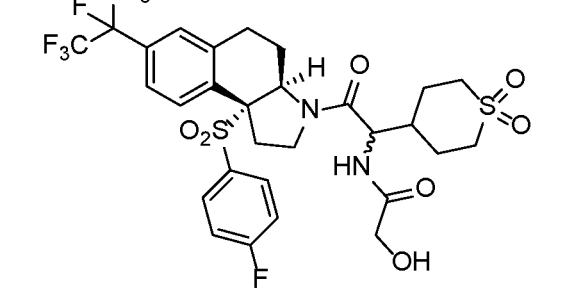
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
433		582.3 (M+H) ⁺	2.46	C
434		610.3 (M+H) ⁺	2.43	C
435		582.1 (M+H) ⁺	2.46	C
436		600.4 (M+H) ⁺	2.30	C
437		600.1 (M+H) ⁺	2.34	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
438		638.9 (M+H) ⁺	2.45	C
439		636.0 (M+H) ⁺	2.56	C
440		584.1 (M+H) ⁺	2.24	C
441		626.3 (M+H) ⁺	1.77	C
442		664.1 (M+H) ⁺	2.74	C

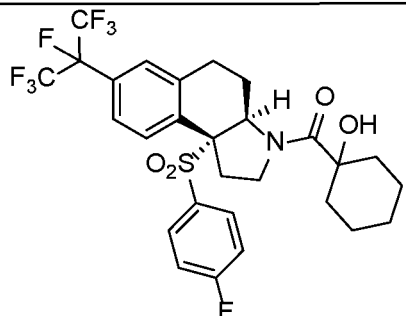
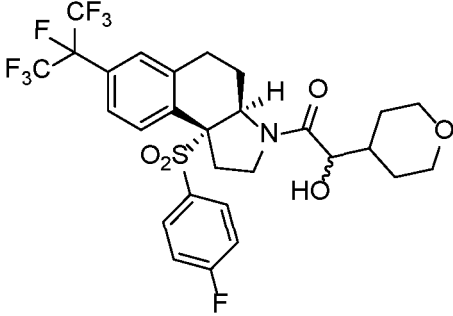
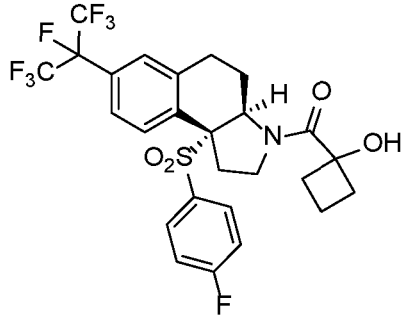
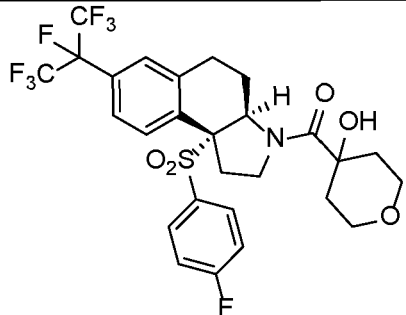
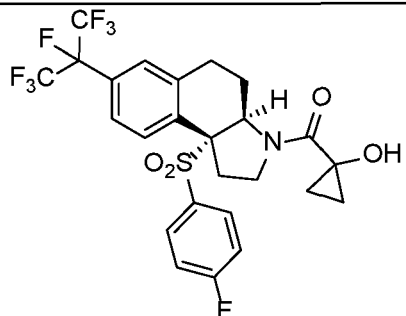
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
443		638.2 (M+H) ⁺	2.62	C
444		586.2 (M+H) ⁺	2.25	C
445		558.0 (M+H) ⁺	2.11	C
446		646.3 (M+H) ⁺	2.50	C
447		626.1 (M+H) ⁺	2.19	C

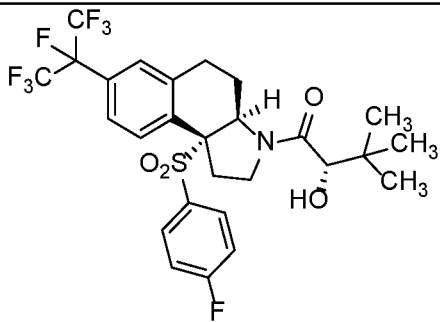
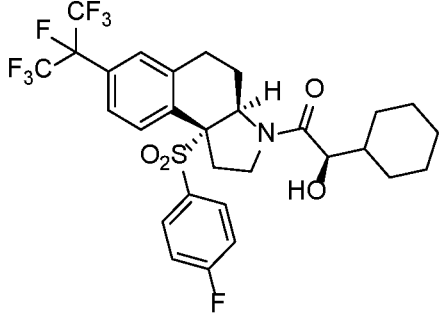
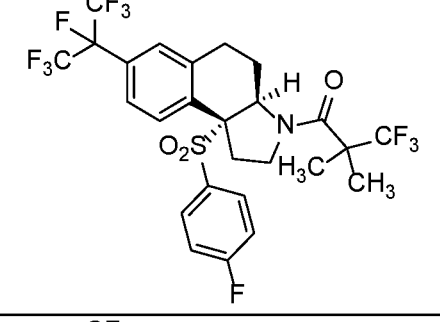
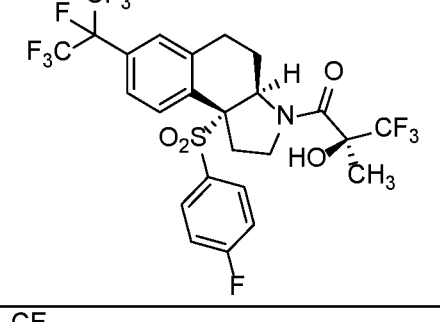
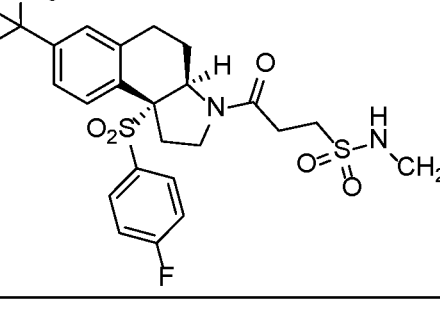
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
448		620.1 (M+H) ⁺	2.12	C
449		648.1 (M+H) ⁺	2.24	C
450		634.2 (M+H) ⁺	2.18	C
451		700.0 (M+H) ⁺	2.38	C
452		682.2 (M+H) ⁺	2.42	C

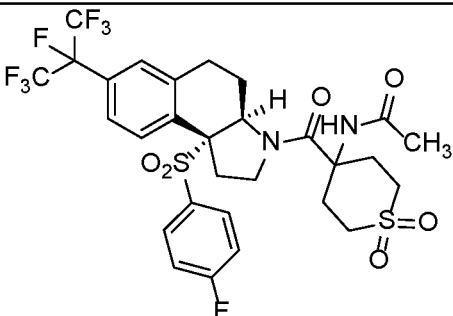
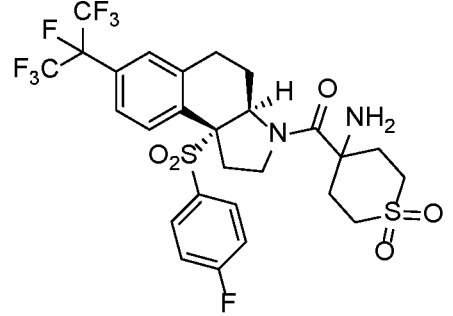
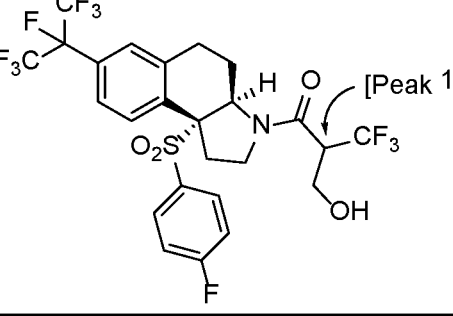
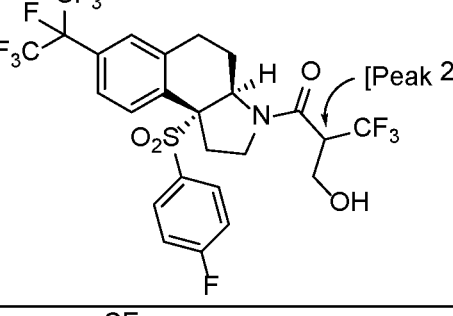
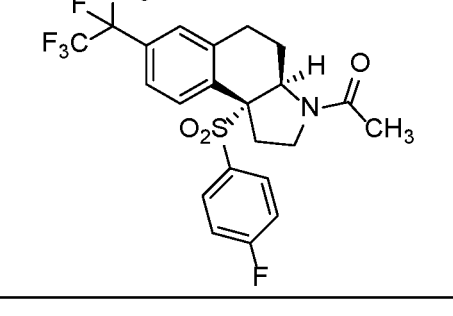
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
453		745.1 (M+H) ⁺	2.55	C
454		765.9 (M+H) ⁺	2.51	C
455		744.1 (M+H) ⁺	2.57	C
456		633.8 (M+H) ⁺	2.13	C
457		716.2 (M+H) ⁺	2.51	C

Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
458		710.2 (M+H) ⁺	2.49	C
459		689.1 (M+H) ⁺	1.94	C
460		731.0 (M+H) ⁺	2.00	C
461		731.2 (M+H) ⁺	2.07	C
462		747.0 (M+H) ⁺	1.91	C

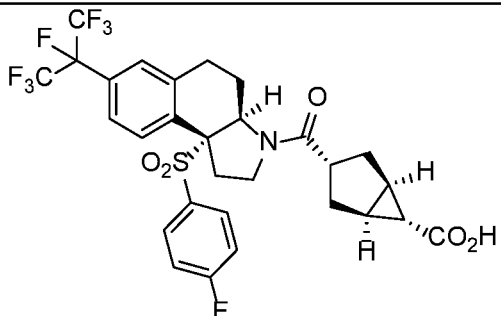
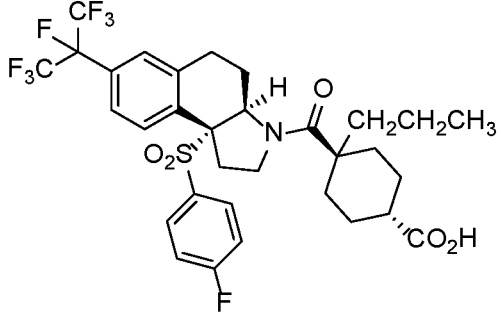
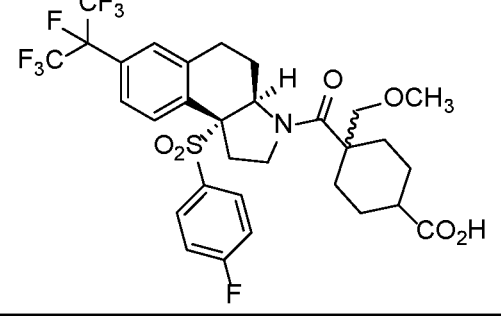
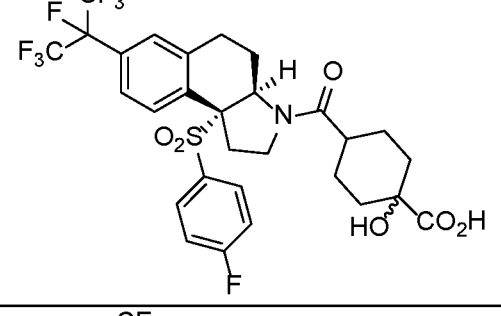
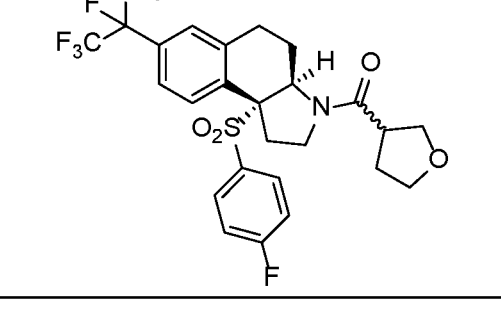
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
463		597.2 (M+H) ⁺	2.15	C
464		572.0 (M+H) ⁺	2.16	C
465		626.1 (M+H) ⁺	2.38	C
466		640.0 (M+H) ⁺	2.40	C
467		600.2 (M+H) ⁺	2.30	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
468		625.9 (M+H) ⁺	2.47	C
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

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
477		663.0 (M+H) ⁺	2.19	C

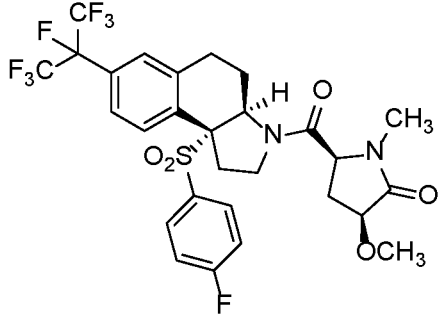
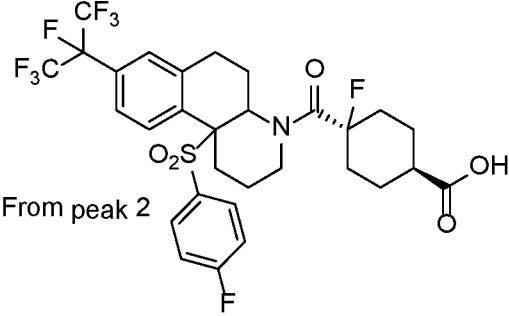
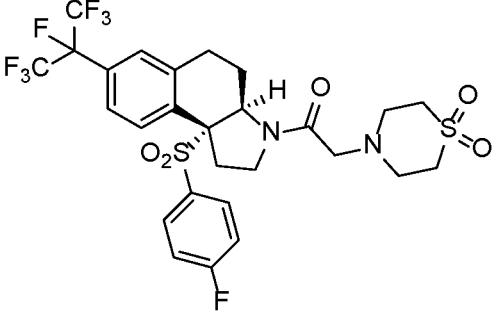
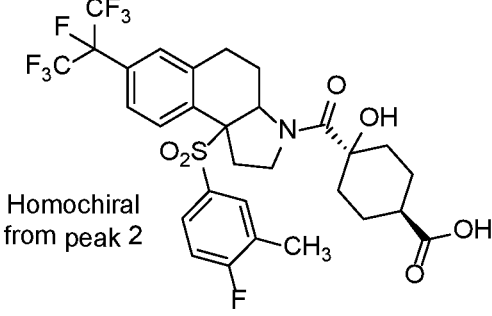
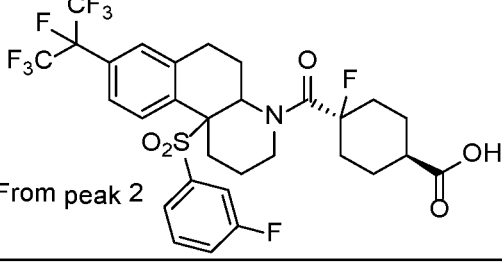
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
478		717.0 (M+H) ⁺	2.00	C
479		675.2 (M+H) ⁺	2.09	C
480		640.1 (M+H) ⁺	1.84	C
481		640.0 (M+H) ⁺	1.89	C
482		541.9 (M+H) ⁺	2.11	C

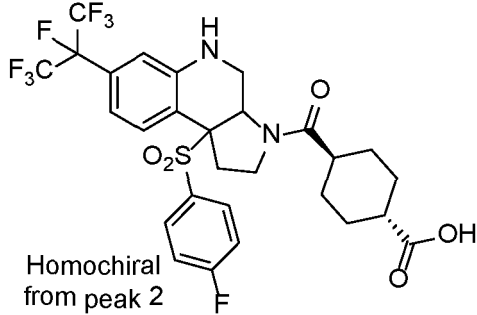
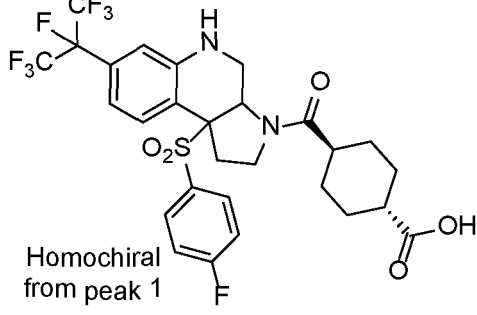
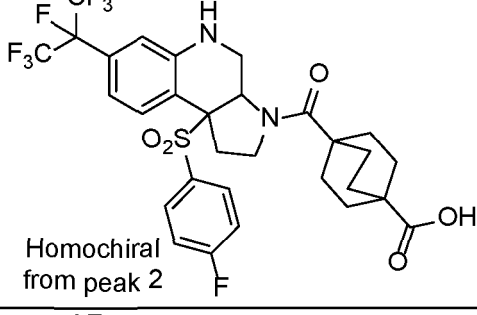
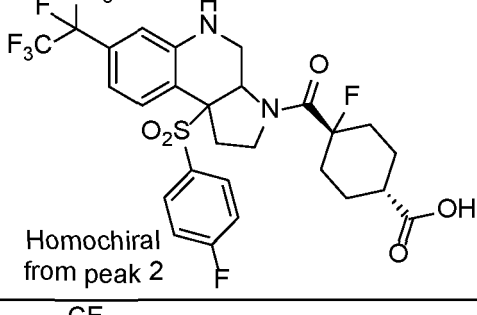
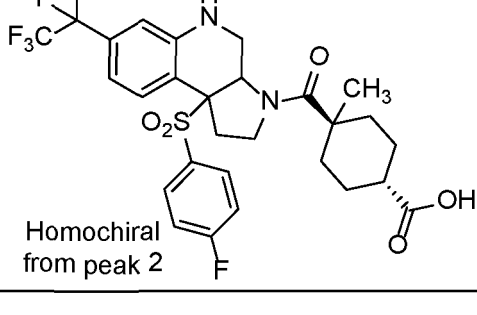
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
483		556.3 (M+H) ⁺	2.23	C
484		554.1 (M+H) ⁺	2.20	C
485		600.1 (M+H) ⁺	2.37	C
486		600.1 (M+H) ⁺	2.35	C
487		666.1 (M+H) ⁺	1.85	C

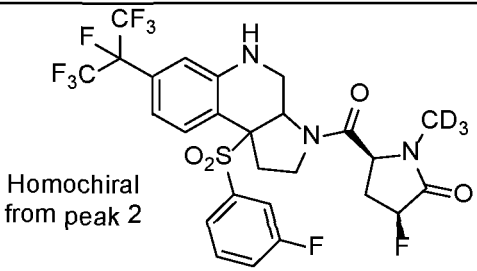
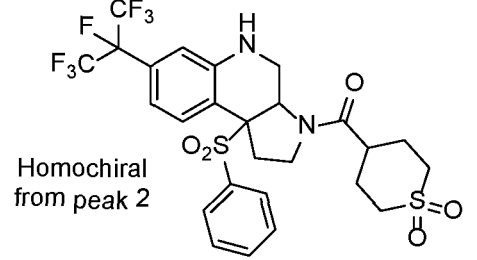
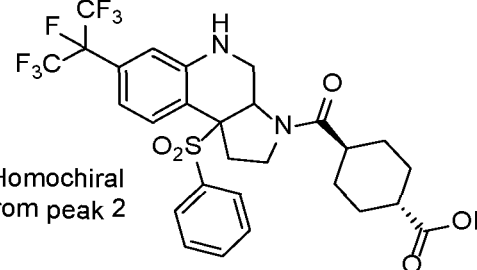
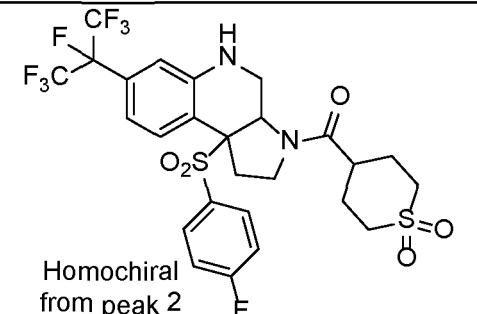
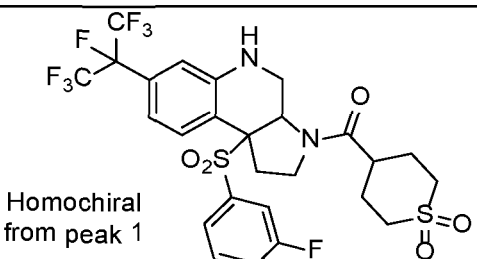
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
488		652.2 (M+H) ⁺	1.88	C
489		696.0 (M+H) ⁺	2.14	C
490		698.0 (M+H) ⁺	2.22	D
491		670.2 (M+H) ⁺	2.04, 2.07	D
492		598.1 (M+H) ⁺	2.20	C

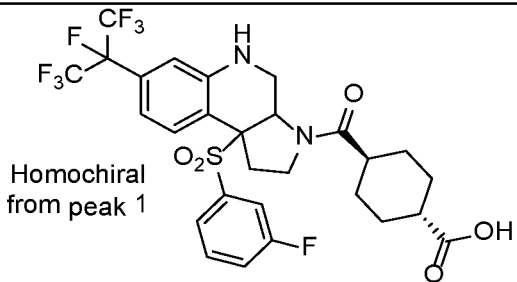
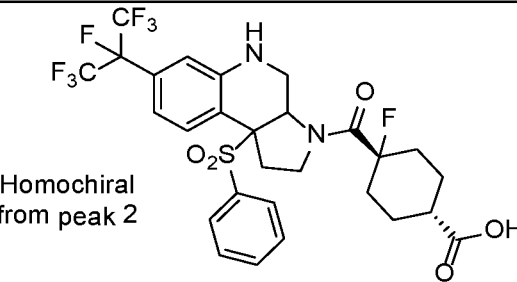
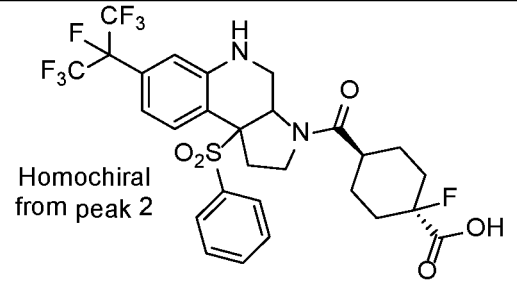
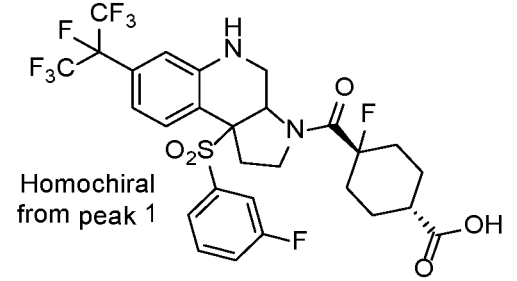
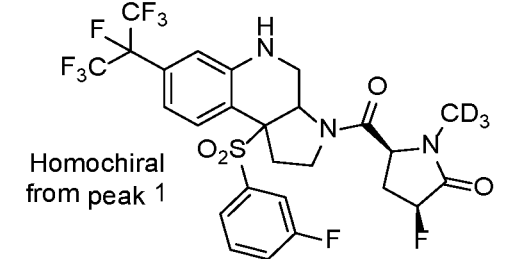
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
493		637.2 (M+H) ⁺	2.36	C
494		641.3 (M+H) ⁺	2.02	C
495		688.2 (M+H) ⁺	2.25	C
496		627.2 (M+H) ⁺	1.80	C
497	Homochiral from peak 2	704.1 (M+H) ⁺	2.32	C

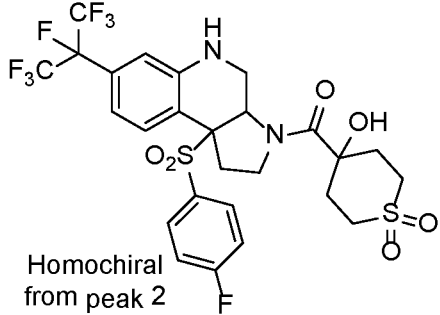
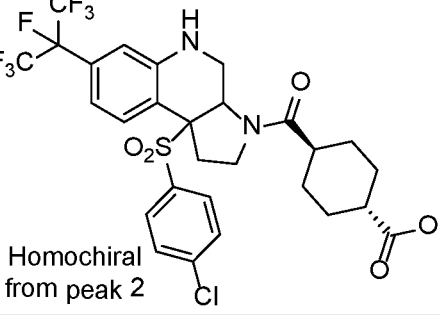
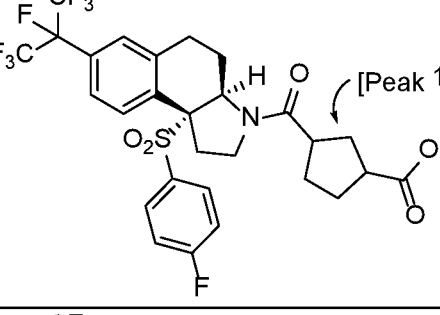
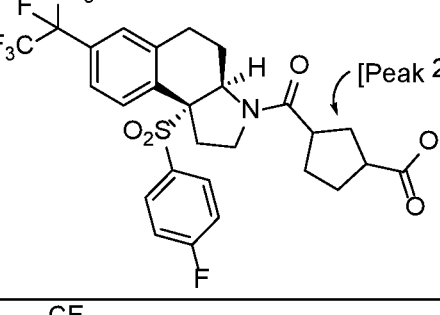
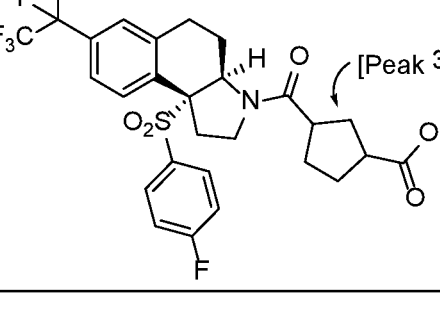
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
498		673.2 (M+H) ⁺	2.09	C
499	Homochiral from peak 2	660.2 (M+H) ⁺	2.31	C
500		640.2 (M+H) ⁺	2.26 2.29	C
501		654.3 (M+H) ⁺	2.54 2.56	C
502		644.2 (M+H) ⁺	2.21	C

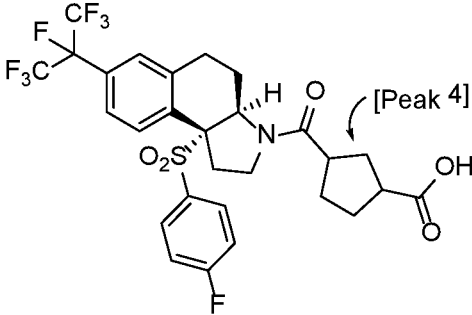
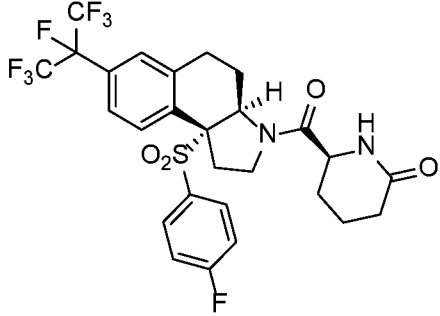
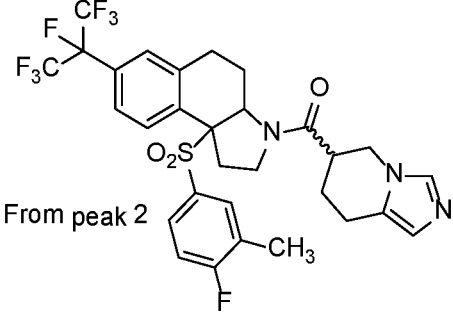
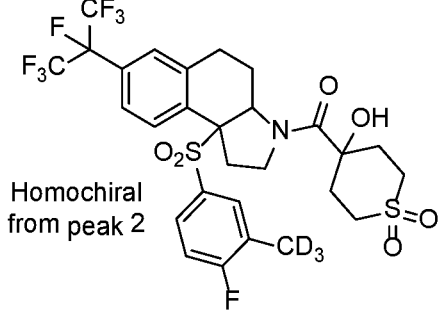
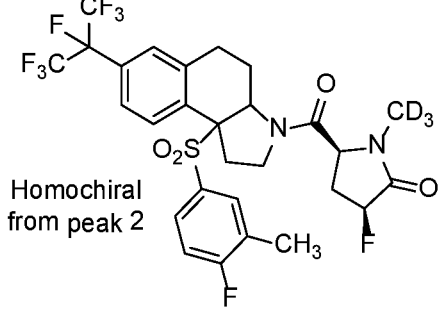
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
503		654.9 (M+H) ⁺	2.16	C
504	 From peak 2	686.2 (M+H) ⁺	2.03	C
505		675.1 (M+H) ⁺	2.18	C
506	 Homochiral from peak 2	684.2 (M+H) ⁺	1.90	C
507	 From peak 2	686.3 (M+H) ⁺	2.01	C

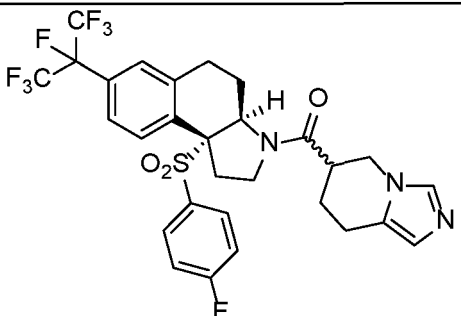
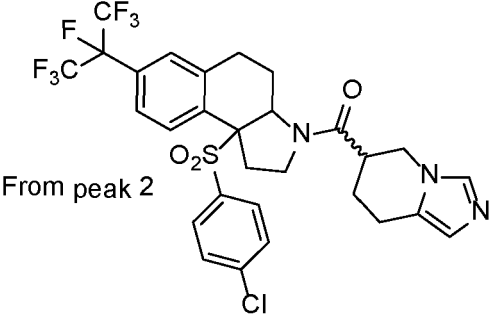
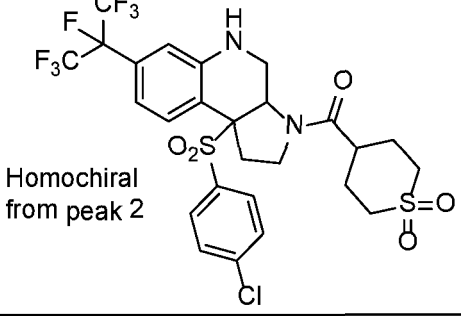
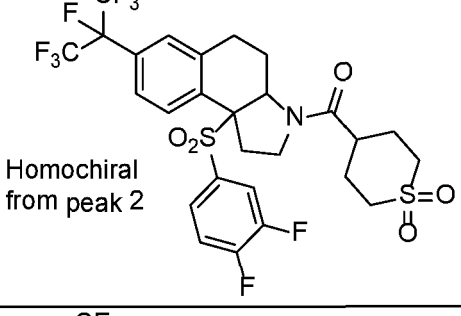
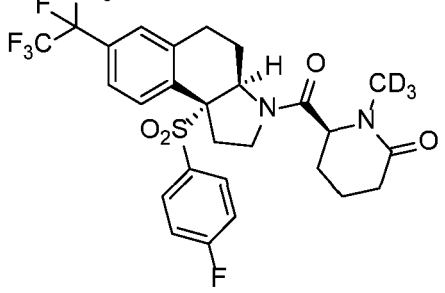
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
508	 Homochiral from peak 2	655.2 (M+H) ⁺	1.04	B
509	 Homochiral from peak 1	655.2 (M+H) ⁺	1.04	B
510	 Homochiral from peak 2	681.1 (M+H) ⁺	1.93	C
511	 Homochiral from peak 2	673.2 (M+H) ⁺	1.09	B
512	 Homochiral from peak 2	669.2 (M+H) ⁺	1.98	C

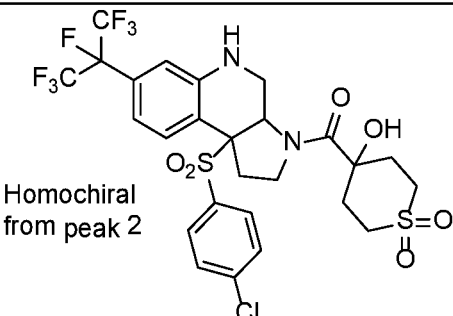
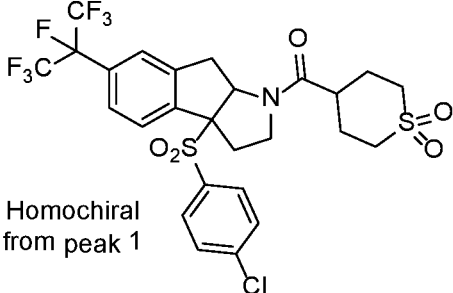
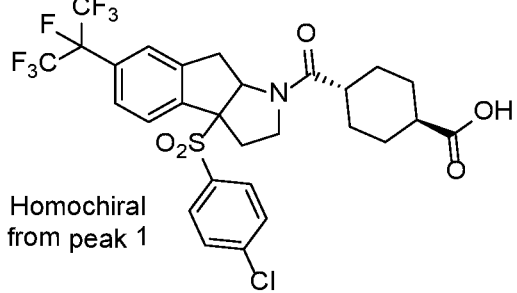
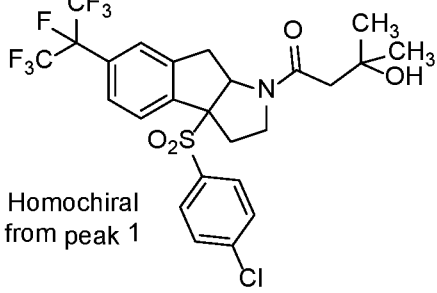
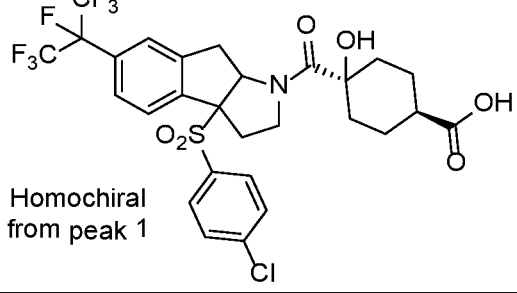
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
513	 Homochiral from peak 2	647.1 (M+H) ⁺	1.05	B
514	 Homochiral from peak 2	643.1 (M+H) ⁺	0.99	B
515	 Homochiral from peak 2	637.1 (M+H) ⁺	1.02	B
516	 Homochiral from peak 2	661.1 (M+H) ⁺	1.01	B
517	 Homochiral from peak 1	661.1 (M+H) ⁺	1.01	B

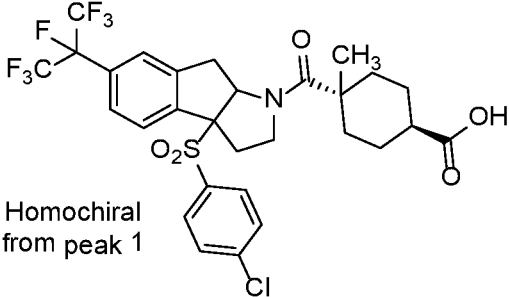
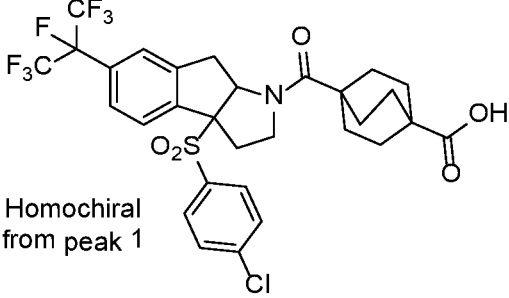
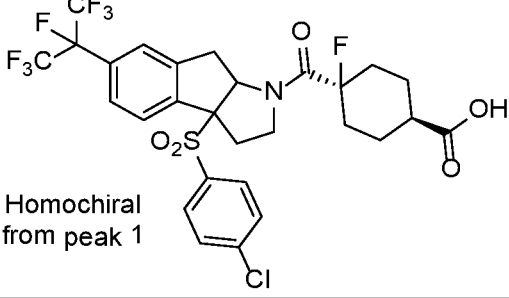
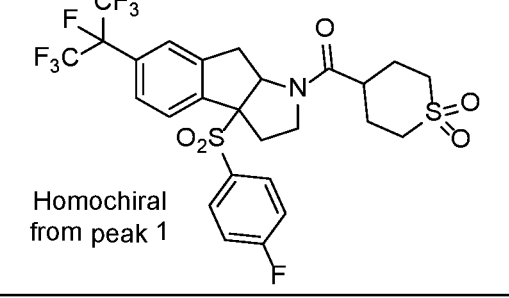
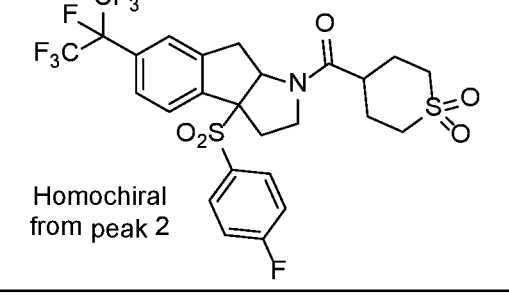
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
518	 Homochiral from peak 1	655.3 (M+H) ⁺	1.00	B
519	 Homochiral from peak 2	655.3 (M+H) ⁺	0.99	B
520	 Homochiral from peak 2	655.3 (M+H) ⁺	0.99	B
521	 Homochiral from peak 1	673.2 (M+H) ⁺	1.03	B
522	 Homochiral from peak 1	647.1 (M+H) ⁺	1.01	B

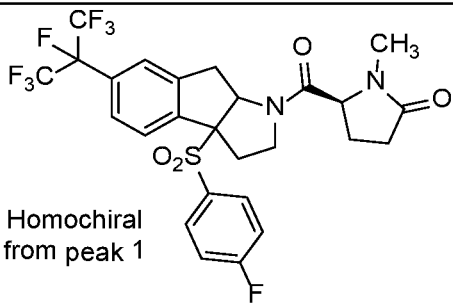
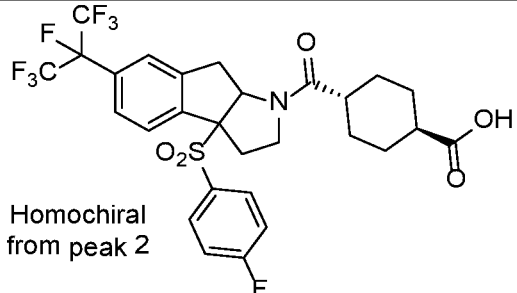
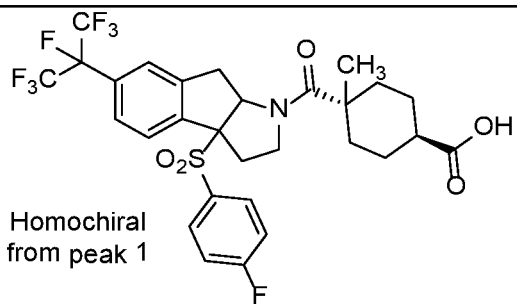
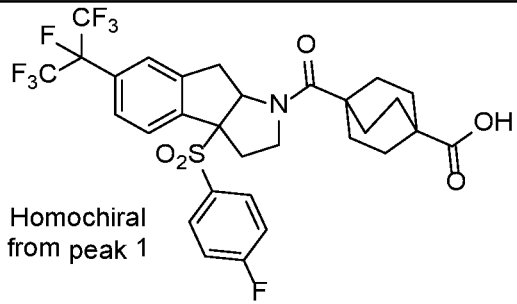
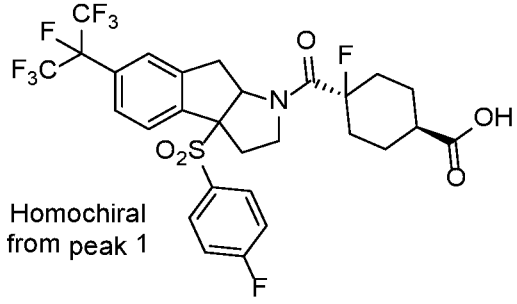
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
523	 Homochiral from peak 2	677.2 (M+H) ⁺	2.02	D
524	 Homochiral from peak 2	671.2 (M+H) ⁺	1.92	C
525	 [Peak 1]	654.2 (M+H) ⁺	1.05	B
526	 [Peak 2]	654.2 (M+H) ⁺	1.04	B
527	 [Peak 3]	654.2 (M+H) ⁺	1.04	B

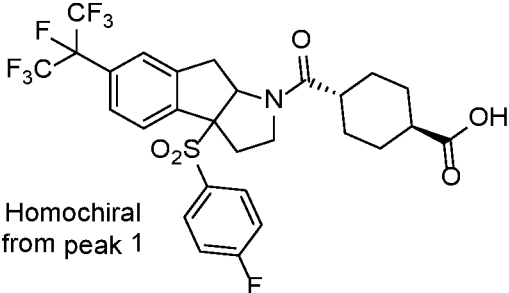
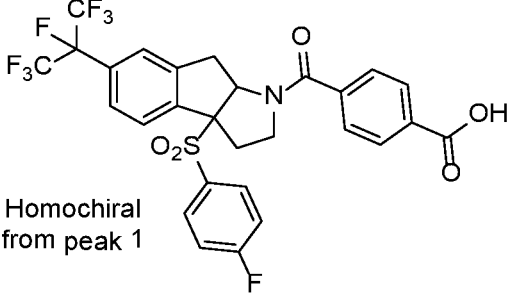
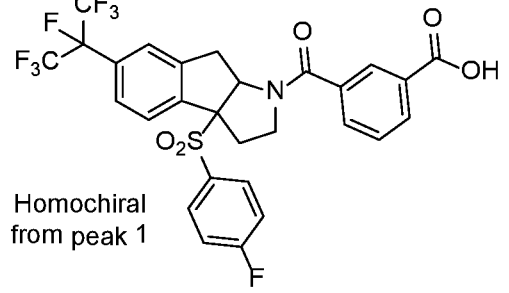
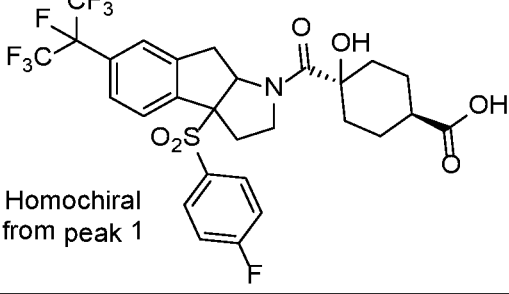
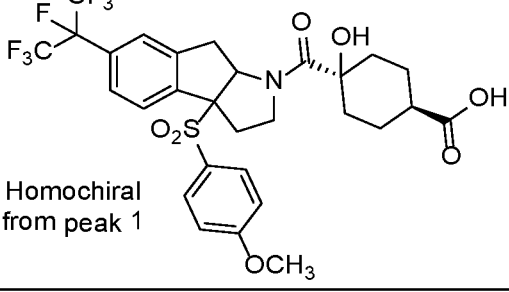
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
528		654.2 (M+H) ⁺	1.04	B
529		625.1 (M+H) ⁺	2.03	C
530		661.9 (M+H) ⁺	2.20	C
531		693.2 (M+H) ⁺	2.26	C
532		660.0 (M+H) ⁺	2.28	C

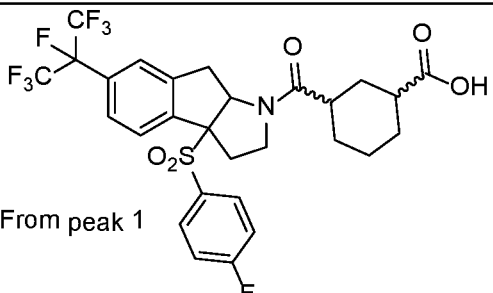
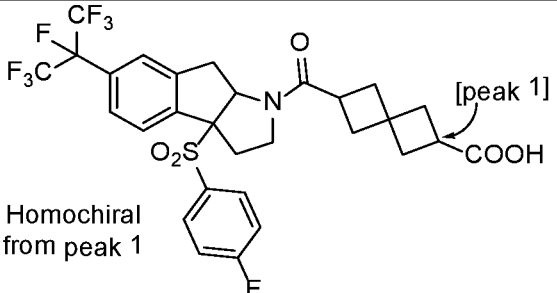
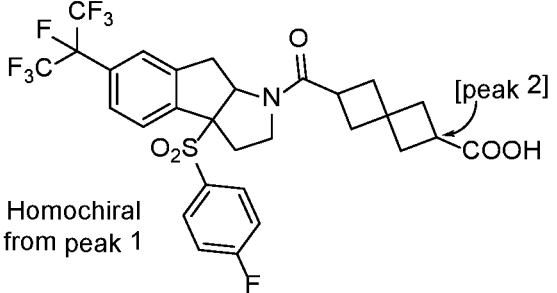
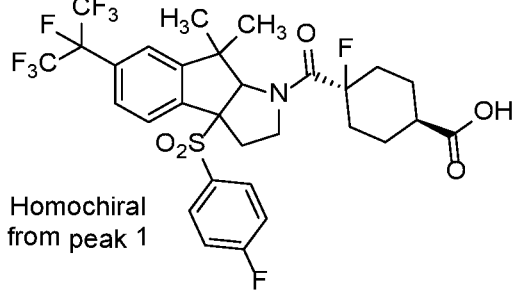
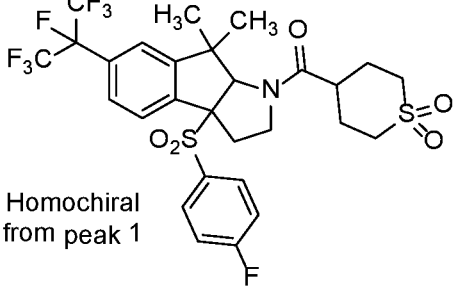
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
533		648.2 (M+H) ⁺	2.09	C
534	From peak 2 	664.1 (M+H) ⁺	2.20	C
535	Homochiral from peak 2 	677.1 (M+H) ⁺	2.18	C
536	Homochiral from peak 2 	677.9 (M+H) ⁺	2.20	C
537		642.1 (M+H) ⁺	2.10	C

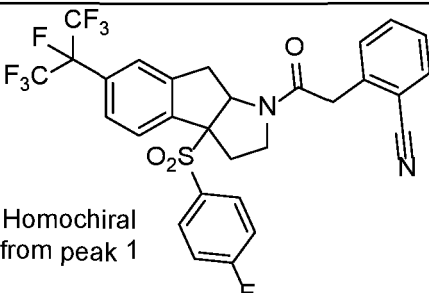
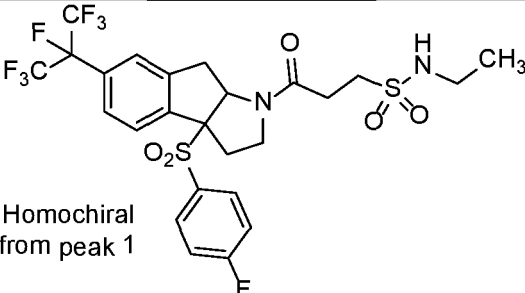
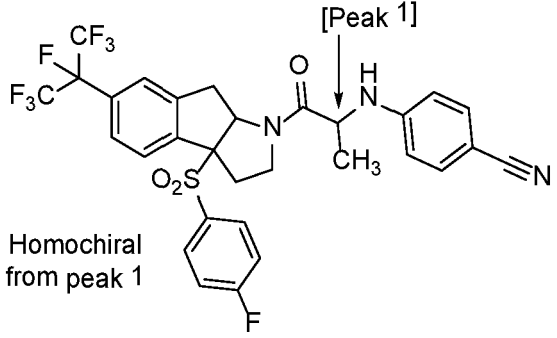
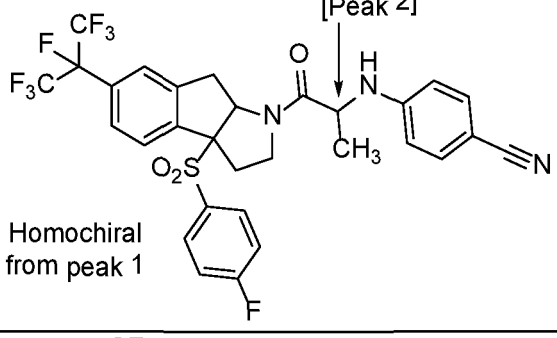
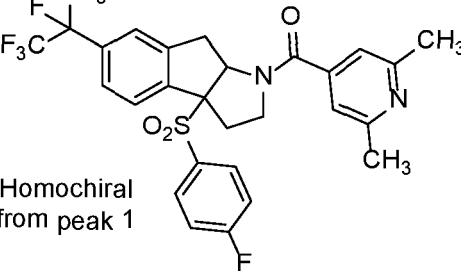
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
538	 Homochiral from peak 2	693.3 (M+H) ⁺	2.16	C
539	 Homochiral from peak 1	662.1 (M+H) ⁺	1.06	B
540	 Homochiral from peak 1	656.1 (M+H) ⁺	1.08	B
541	 Homochiral from peak 1	602.2 (M+H) ⁺	1.11	B
542	 Homochiral from peak 1	672.1 (M+H) ⁺	1.06	B

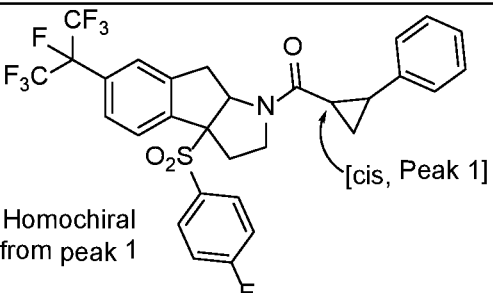
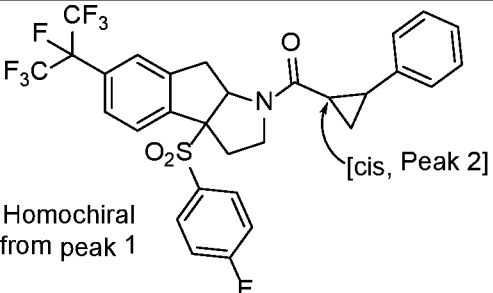
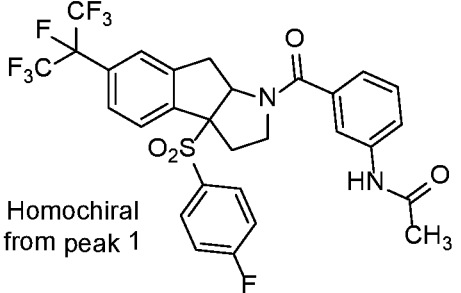
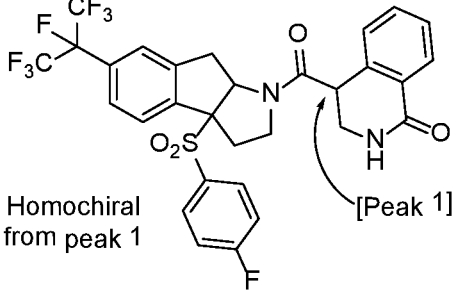
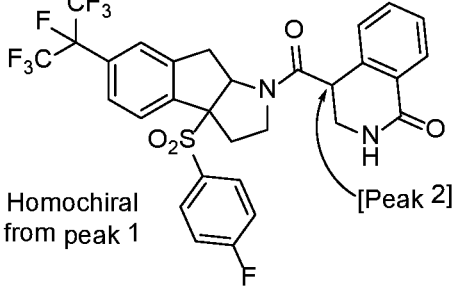
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
543	 Homochiral from peak 1	670.1 (M+H) ⁺	1.12	B
544	 Homochiral from peak 1	682.2 (M+H) ⁺	2.02	C
545	 Homochiral from peak 1	673.9 (M+H) ⁺	1.95	C
546	 Homochiral from peak 1	646.3 (M+H) ⁺	2.03	C
547	 Homochiral from peak 2	646.4 (M+H) ⁺	2.04	C

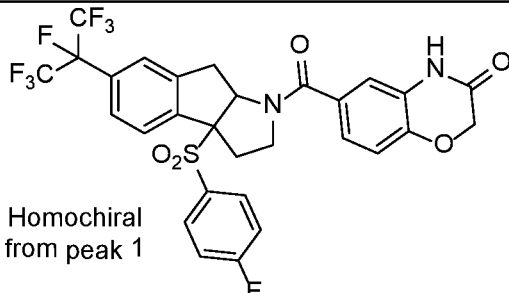
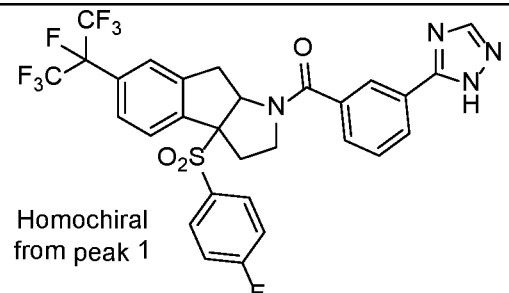
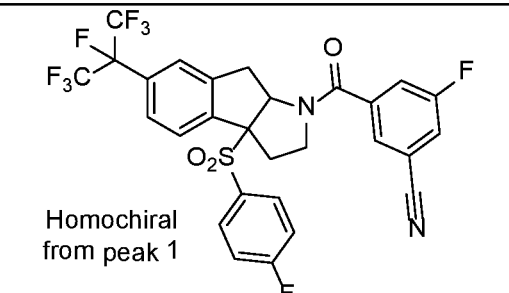
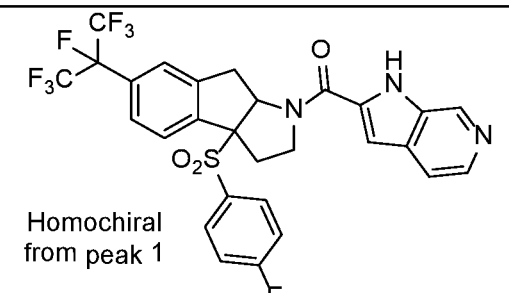
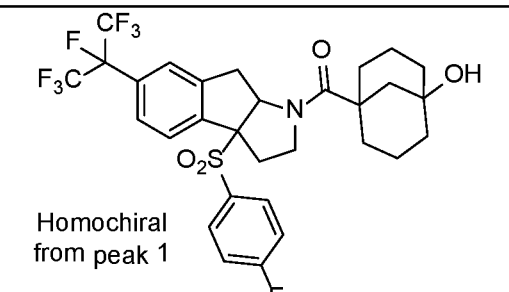
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
548	 Homochiral from peak 1	610.8 (M+H) ⁺	1.93	C
549	 Homochiral from peak 2	640.4 (M+H) ⁺	1.81	C
550	 Homochiral from peak 1	653.9 (M+H) ⁺	2.08	C
551	 Homochiral from peak 1	666.4 (M+H) ⁺	1.93	C
552	 Homochiral from peak 1	658.2 (M+H) ⁺	1.84	C

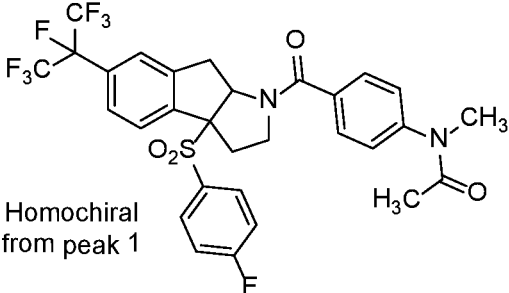
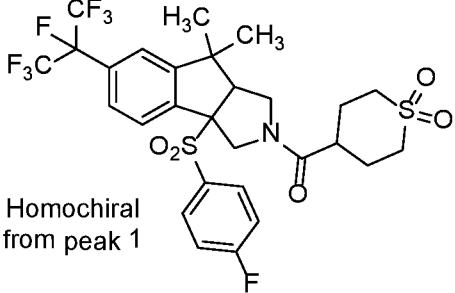
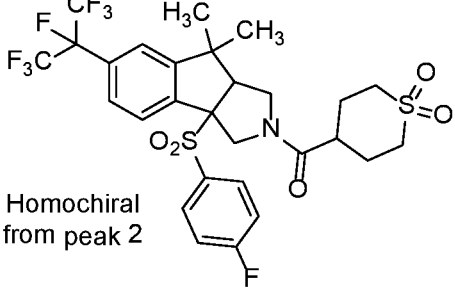
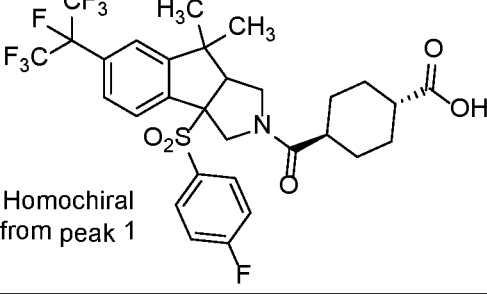
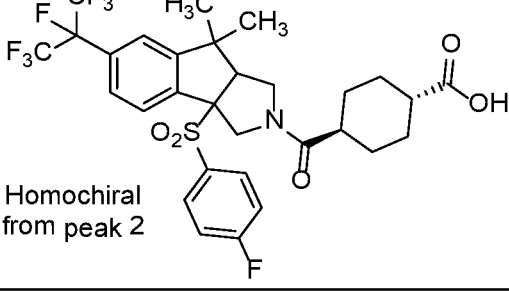
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
553	 Homochiral from peak 1	640.0 (M+H) ⁺	1.79	C
554	 Homochiral from peak 1	634.4 (M+H) ⁺	1.70	C
555	 Homochiral from peak 1	634.3 (M+H) ⁺	1.71	C
556	 Homochiral from peak 1	655.8 (M+H) ⁺	1.71	C
557	 Homochiral from peak 1	668.0 (M+H) ⁺	1.68	C

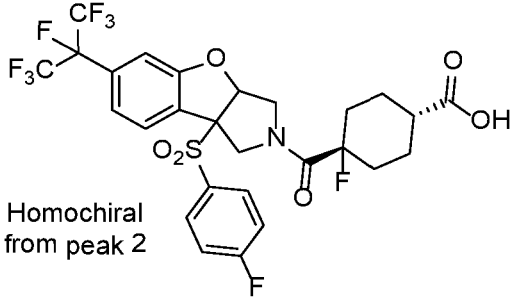
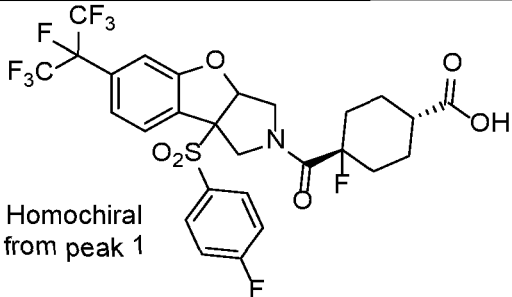
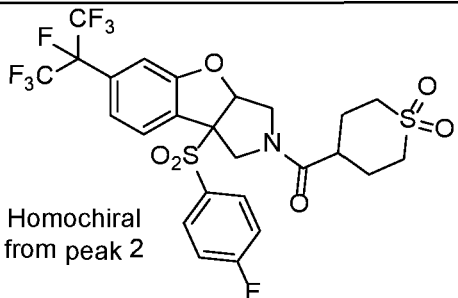
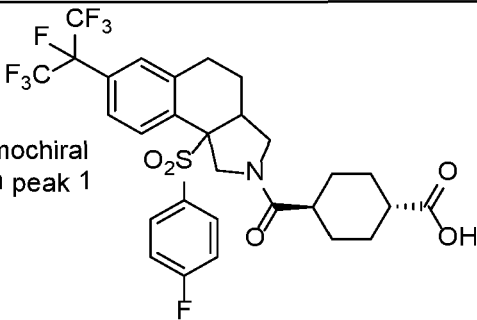
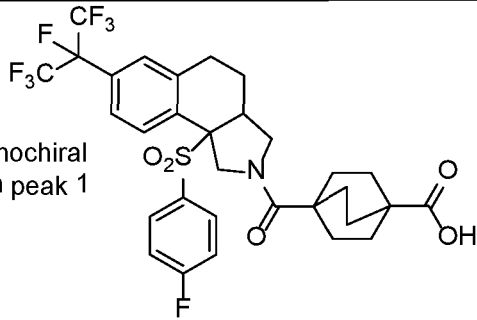
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
558	 From peak 1	640.2 (M+H) ⁺	1.08	B
559	 Homochiral from peak 1	652.1 (M+H) ⁺	1.07	B
560	 Homochiral from peak 1	652.1 (M+H) ⁺	1.08	B
561	 Homochiral from peak 1	686.4 (M+H) ⁺	1.93	C
562	 Homochiral from peak 1	674.3 (M+H) ⁺	2.16	C

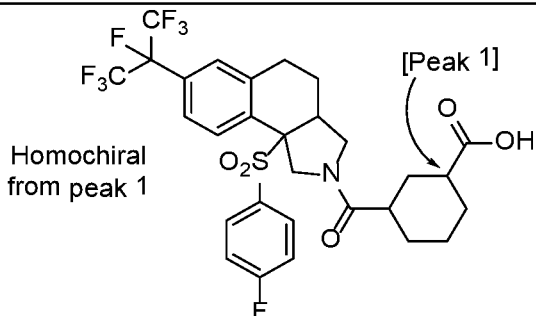
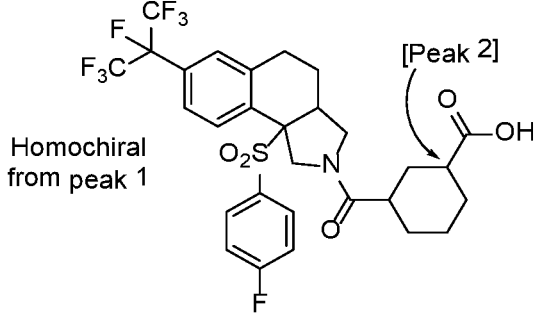
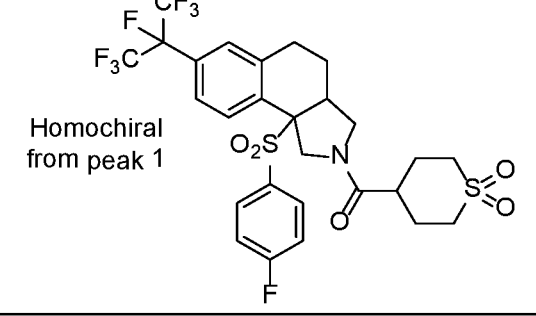
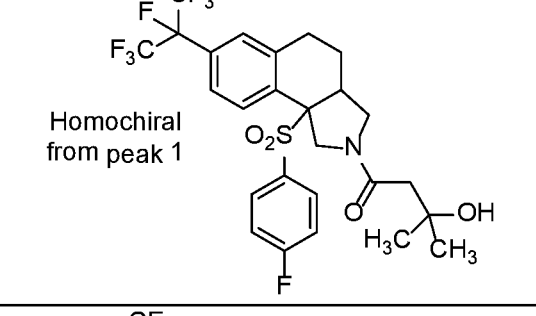
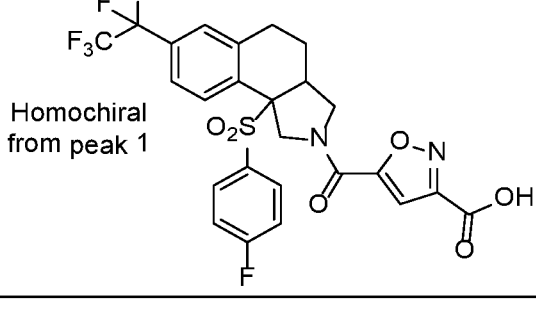
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
563	 Homochiral from peak 1	629.0 (M+H) ⁺	2.34	C
564	 Homochiral from peak 1	649.2 (M+H) ⁺	2.10	C
565	 Homochiral from peak 1	658.2 (M+H) ⁺	2.26	C
566	 Homochiral from peak 1	658.0 (M+H) ⁺	2.30	C
567	 Homochiral from peak 1	621.1 (M+H) ⁺	2.05	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
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
571	 Homochiral from peak 1	659.1 (M+H) ⁺	2.21	C
572	 Homochiral from peak 1	659.4 (M+H) ⁺	2.27	C

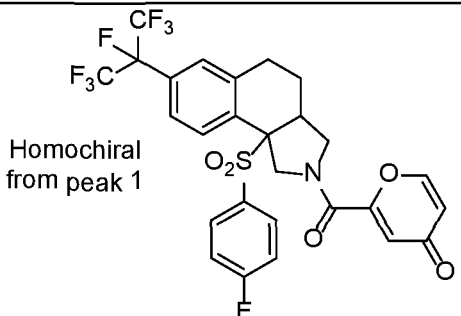
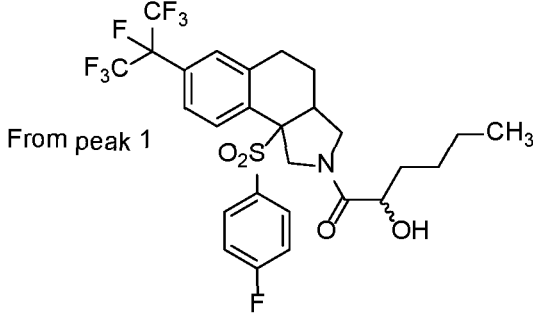
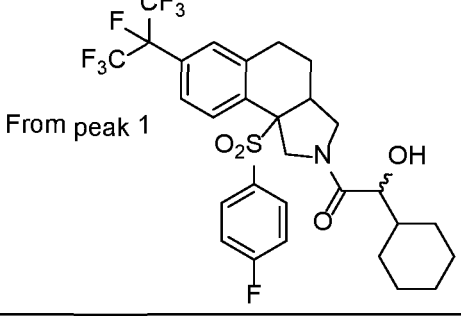
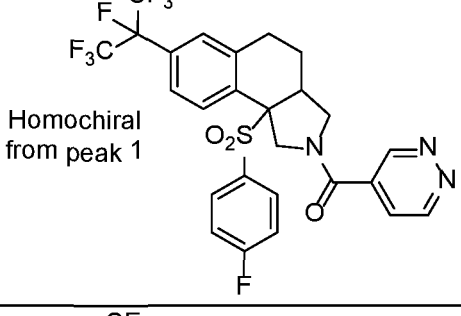
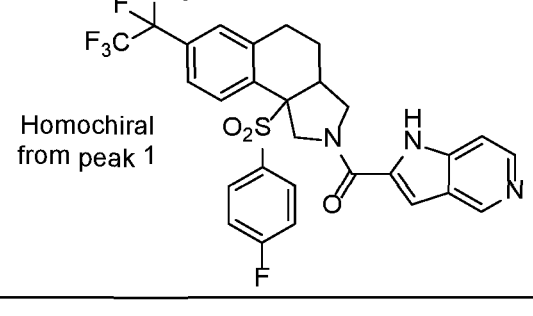
Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
573	 Homochiral from peak 1	661.1 (M+H) ⁺	2.26	C
574	 Homochiral from peak 1	657.1 (M+H) ⁺	2.14	C
575	 Homochiral from peak 1	632.9 (M+H) ⁺	2.26	C
576	 Homochiral from peak 1	630.0 (M+H) ⁺	2.13	C
577	 Homochiral from peak 1	651.9 (M+H) ⁺	2.37	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
578	 Homochiral from peak 1	661.1 (M+H) ⁺	2.22	C
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

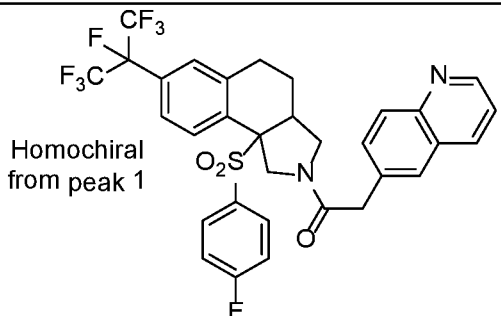
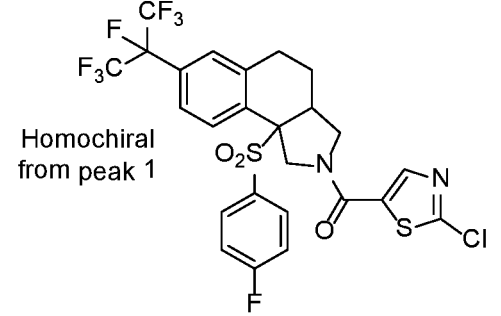
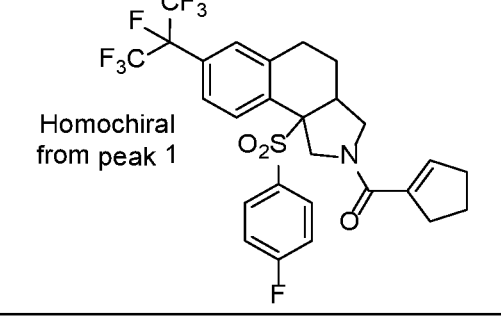
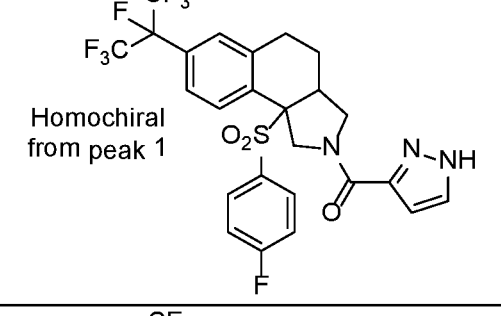
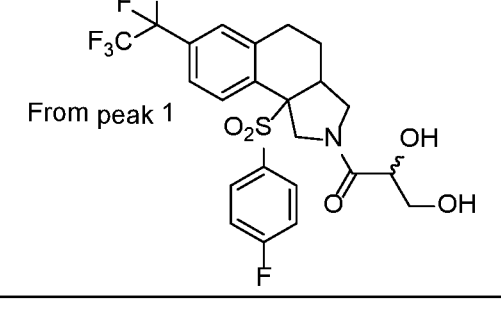
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
583	 Homochiral from peak 2	660.1 (M+H) ⁺	1.89	C
584	 Homochiral from peak 1	660.1 (M+H) ⁺	1.84	C
585	 Homochiral from peak 2	648.0 (M+H) ⁺	1.99	C
586	 Homochiral from peak 1	654.5 (M+H) ⁺	1.02	B
587	 Homochiral from peak 1	680.4 (M+H) ⁺	1.04	B

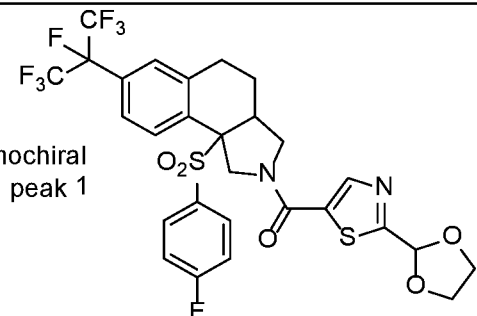
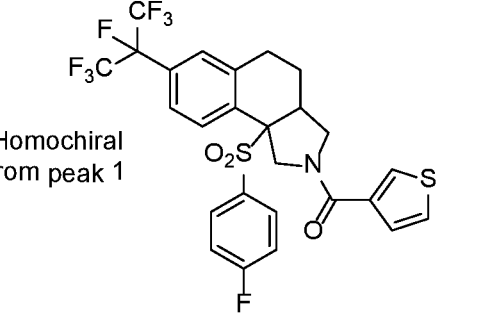
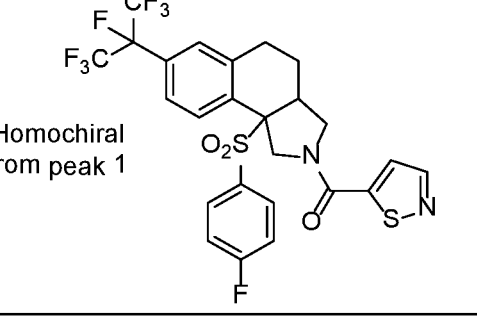
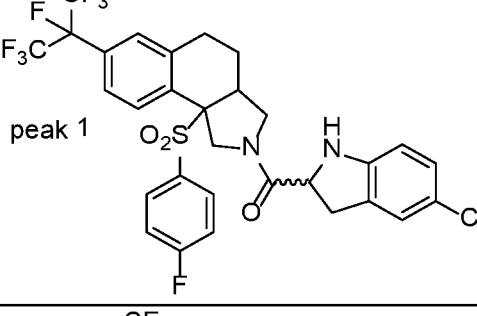
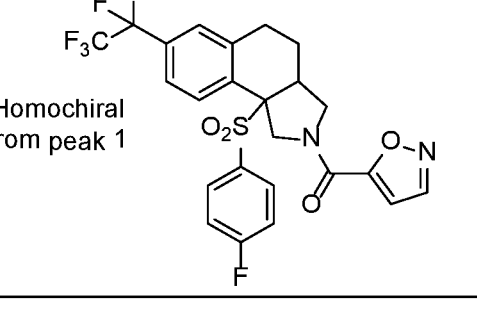
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
588	Homochiral from peak 1 	654.1 (M+H) ⁺	2.181	D
589	Homochiral from peak 1 	654.2 (M+H) ⁺	2.158	D
590	Homochiral from peak 1 	660.0 (M+H) ⁺	2.094	D
591	Homochiral from peak 1 	599.8 (M+H) ⁺	2.205	D
592	Homochiral from peak 1 	638.9 (M+H) ⁺	2.163	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
593	Homochiral from peak 1	650.2 (M+H) ⁺	2.239	D
594	Homochiral from peak 1	637.2 (M+H) ⁺	1.983	D
595	Homochiral from peak 1	637.8 (M+H) ⁺	2.003	D
596	Homochiral from peak 1	653.4 (M+H) ⁺	2.03	C
597	Homochiral from peak 1	611.3 (M+H) ⁺	2.19	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
598	Homochiral from peak 1 	622.3 (M+H) ⁺	2.11	C
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

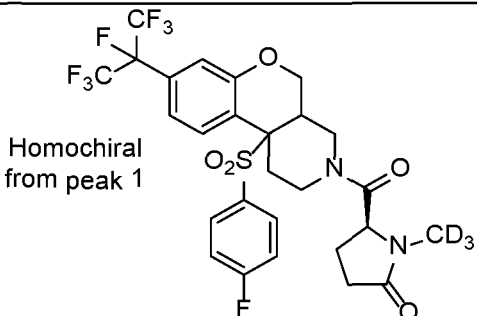
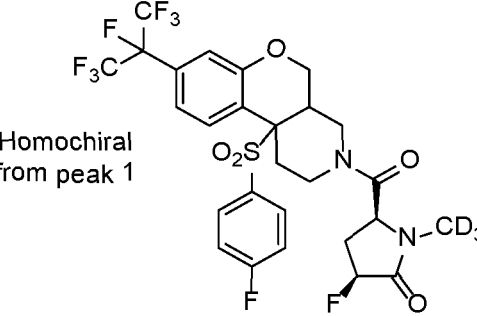
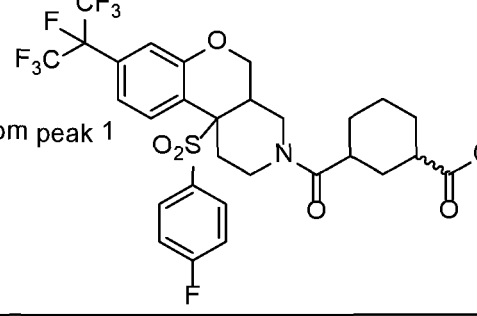
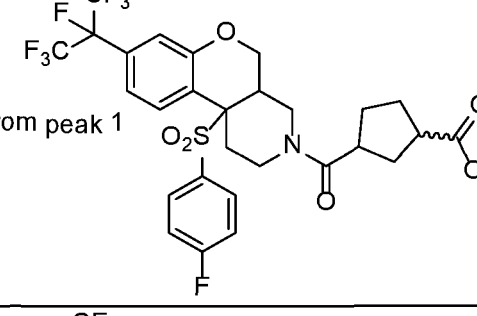
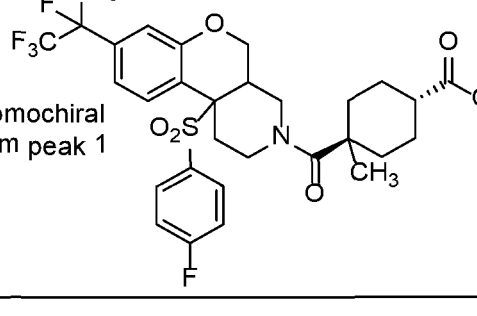
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
603	Homochiral from peak 1	662.4 (M+H) ⁺	2.26	C
604	Homochiral from peak 1	611.3 (M+H) ⁺	1.81	C
605	Homochiral from peak 1	594 (M+H) ⁺	1.95	C
606	Homochiral from peak 1	662.4 (M+H) ⁺	2.43	C
607	Homochiral from peak 1	645.4 (M+H) ⁺	2.08	C

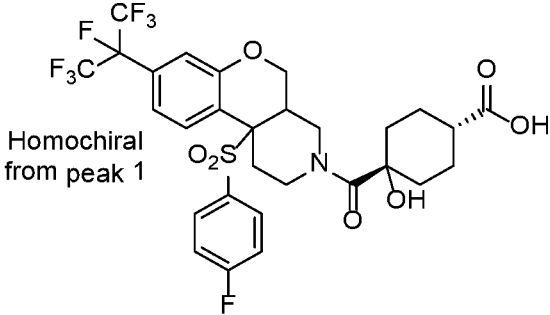
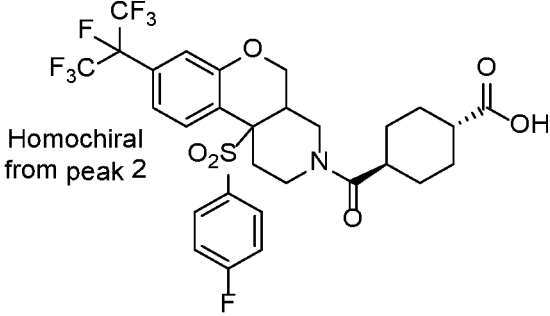
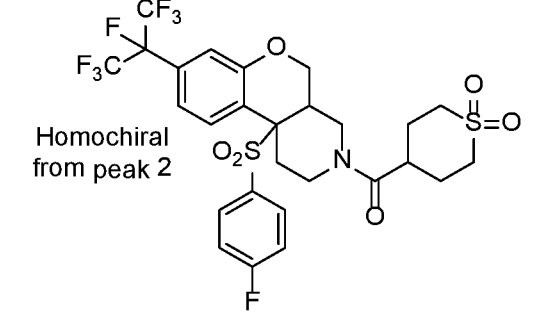
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
608	Homochiral from peak 1 	669.1 (M+H) ⁺	2.2	C
609	Homochiral from peak 1 	645.3 (M+H) ⁺	2.42	C
610	Homochiral from peak 1 	593.8 (M+H) ⁺	2.33	D
611	Homochiral from peak 1 	594.0	2.05	D
612	From peak 1 	587.8 (M+H) ⁺	1.88	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
613	Homochiral from peak 1 	682.8 (M+H) ⁺	2.22	C
614	Homochiral from peak 1 	609.9 (M+H) ⁺	2.27	D
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

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
618	Homochiral from peak 1	595.1 (M+H) ⁺	2.24	D
619	Homochiral from peak 1	593.0 (M+H) ⁺	2.26	C
620	Homochiral from peak 2	654.4 (M+H) ⁺	2.170	D
621	Homochiral from peak 2	680.4 (M+H) ⁺	2.26	D
622	Homochiral from peak 2	628.1 (M+H) ⁺	2.053	D

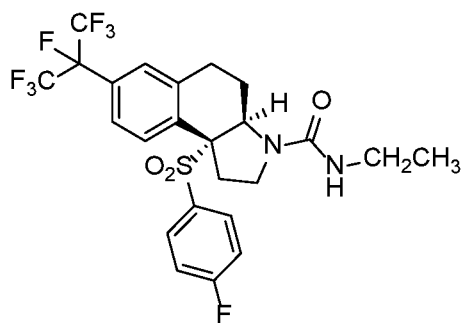
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
623	Homochiral from peak 1	670.3 (M+H) ⁺	1.01	B
624	From peak 1	682.3 (M+H) ⁺	1.02	B
625	Homochiral from peak 1	676.2 (M+H) ⁺	0.99	B
626	Homochiral from peak 1	616.2 (M+H) ⁺	1.03	B
627	Homochiral from peak 1	641.2 (M+H) ⁺	0.97	B

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
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
631	From peak 1 	656.3 (M+H) ⁺	1.01	B
632	Homochiral from peak 1 	683.9 (M+H) ⁺	1.04	B

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
633	 Homochiral from peak 1	686.2 (M+H) ⁺	1.00	B
634	 Homochiral from peak 2	670.3 (M+H) ⁺	1.01	B
635	 Homochiral from peak 2	676.3 (M+H) ⁺	1.00	B

Example 636

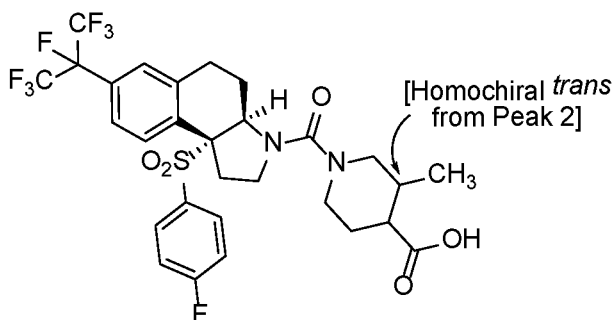
(3a*R*,9b*R*)-*N*-ethyl-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indole-3-carboxamide



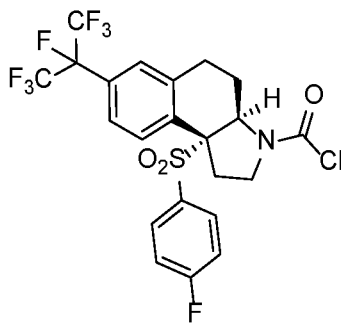
A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) in DMF (1 mL) was treated with DIPEA (0.020 mL, 0.112 mmol) and ethyl isocyanate (4.43 μ L, 0.056 mmol). The mixture was 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 (3a*R*,9b*R*)-*N*-ethyl-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylpiperidine-4-carboxylic acid

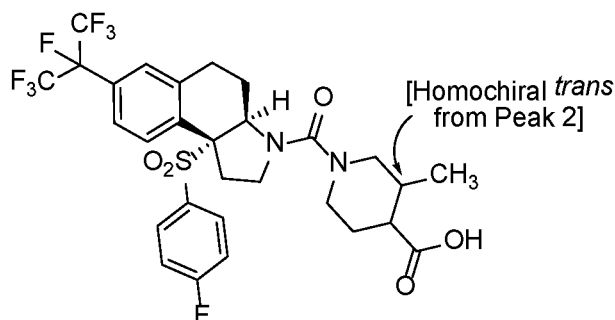


Step A: (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indole-3-carbonyl chloride



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 (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 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 Na₂SO₄ and concentrated to give (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indole-3-carbonyl chloride as an orange solid (180 mg, 80 % yield) which was used without further purification.

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



A solution of crude (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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 Na₂SO₄ and concentrated to give crude methyl 1-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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

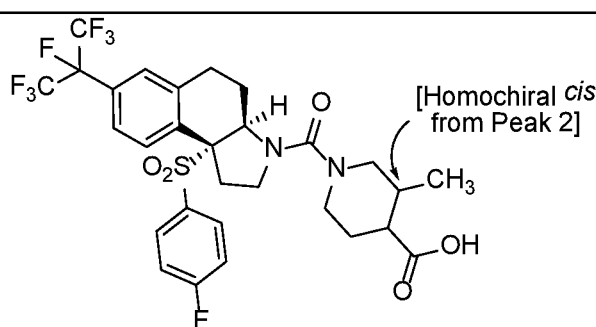
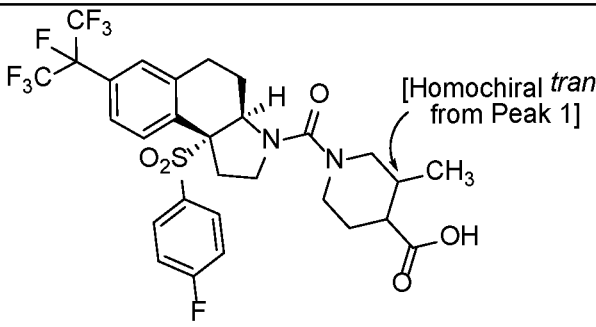
5 1-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylpiperidine-4-carboxylic acid (10 mg, 21% yield). LCMS m/z 669.2 ($M+H$)⁺, HPLC t_R 2.23 min (method C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.87 (d, $J=8.5$ Hz, 1H), 7.62 (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,

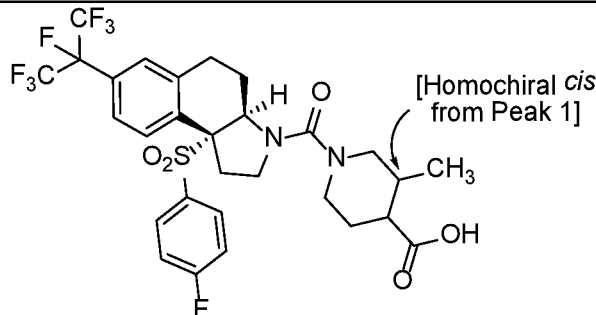
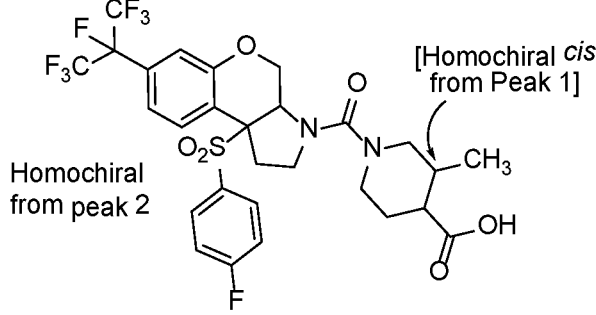
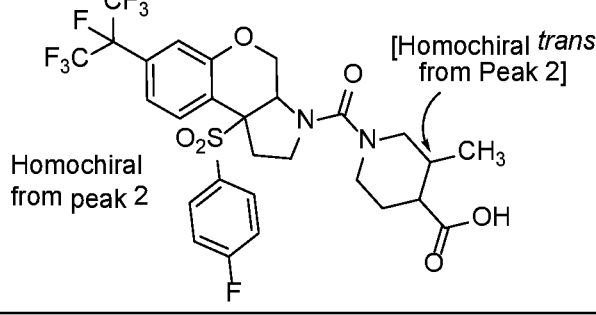
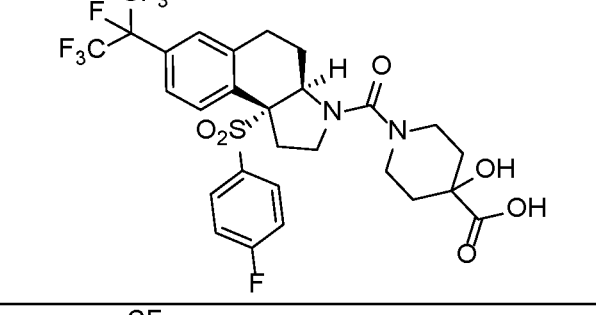
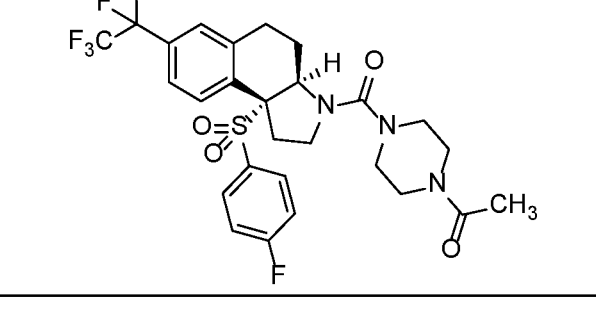
10 1H), 2.70 - 2.47 (m, 5H), 2.40 (t, $J=12.3$ Hz, 1H), 2.16 - 1.95 (m, 2H), 1.93 - 1.70 (m, 2H), 1.64 - 1.37 (m, 3H), 0.83 (d, $J=6.3$ Hz, 3H).

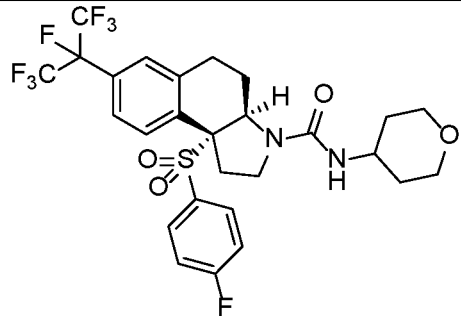
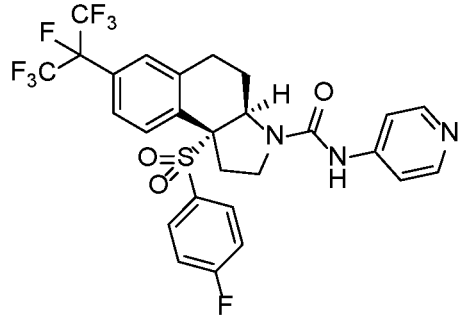
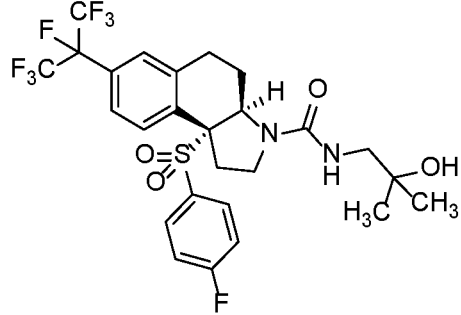
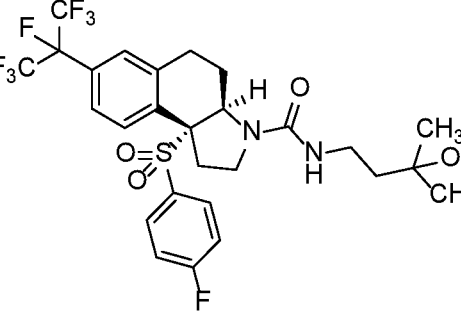
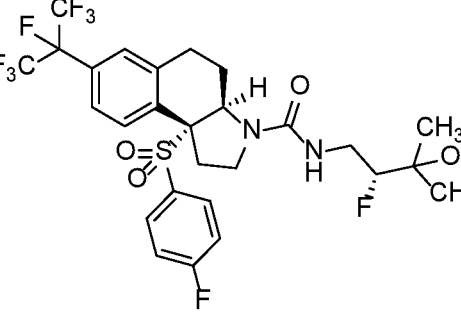
The Examples in Table 10 were prepared using procedures used to prepare Example 637 or similar procedures by using appropriate amine starting materials,

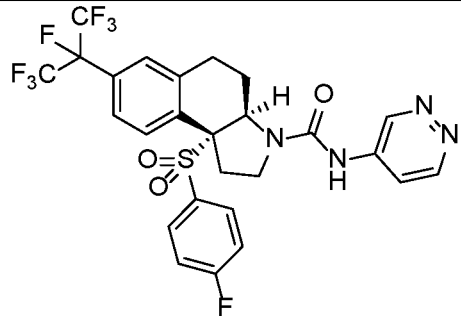
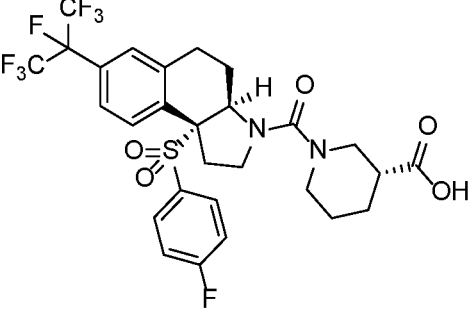
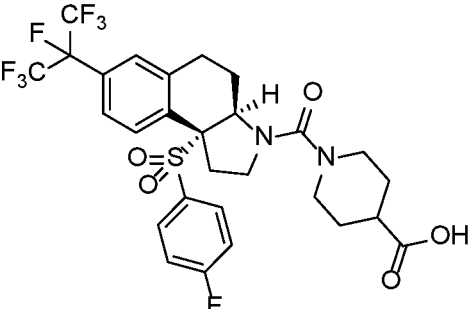
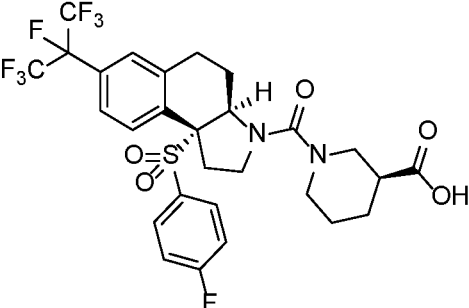
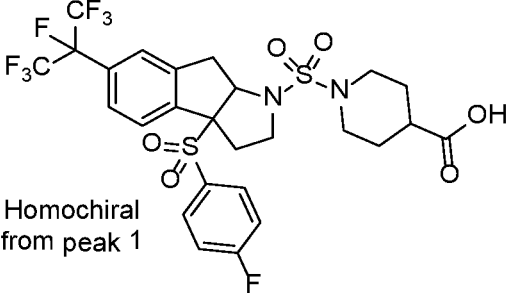
15 followed by ester hydrolysis or other protecting group removal if appropriate.

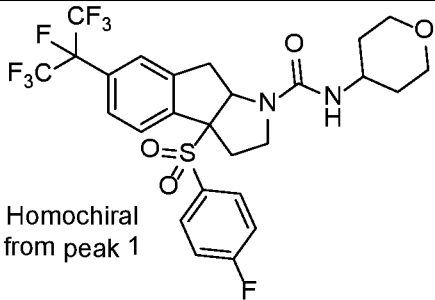
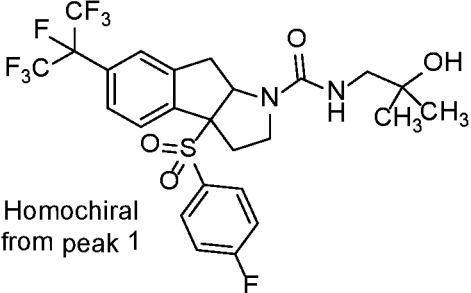
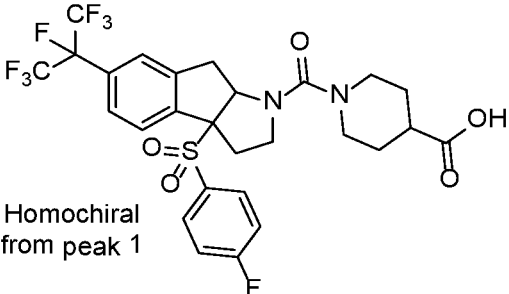
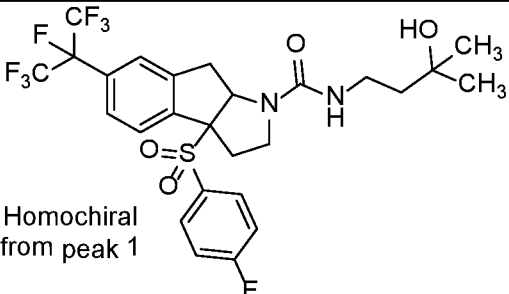
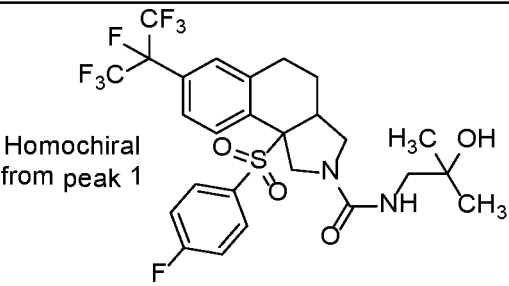
Table 10

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

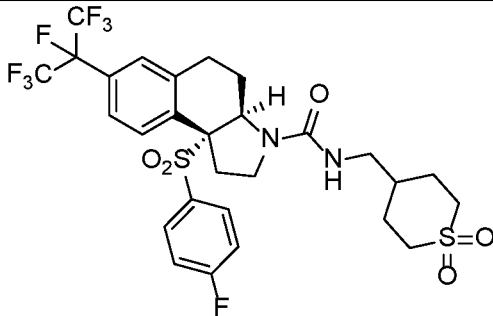
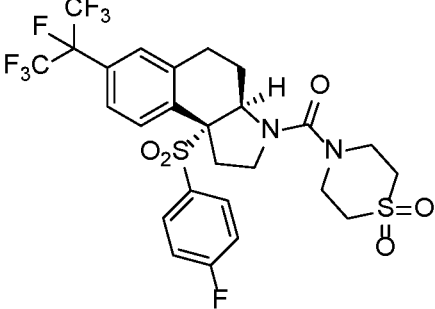
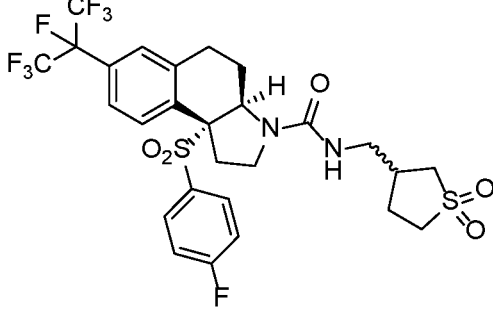
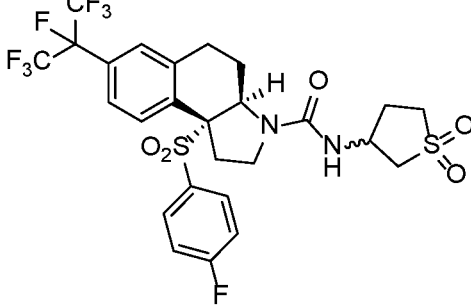
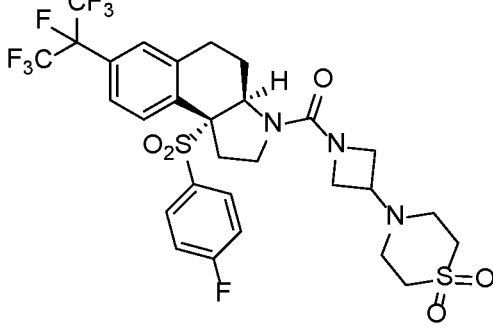
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
640	 [Homochiral <i>cis</i> from Peak 1]	669.2 (M+H) ⁺	2.23	D
641	 [Homochiral <i>cis</i> from Peak 1] Homochiral from peak 2	671.0 (M+H) ⁺	1.80	C
642	 [Homochiral <i>trans</i> from Peak 2] Homochiral from peak 2	671.4 (M+H) ⁺	1.79	C
643	 [Homochiral <i>trans</i> from Peak 2]	671.1 (M+H) ⁺	1.99	D
644	 [Homochiral <i>trans</i> from Peak 2]	654.4 (M+H) ⁺	2.12	D

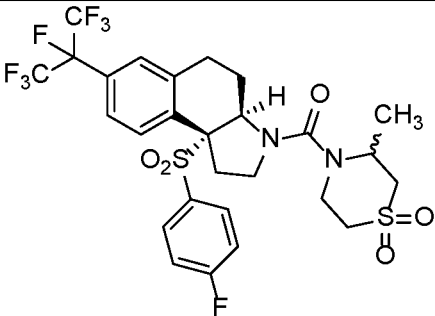
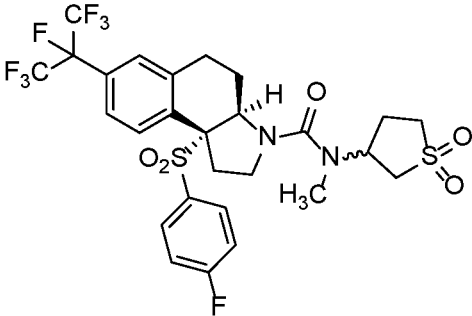
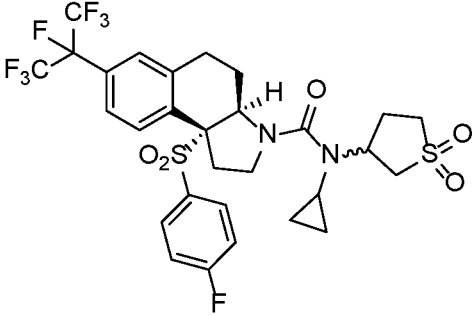
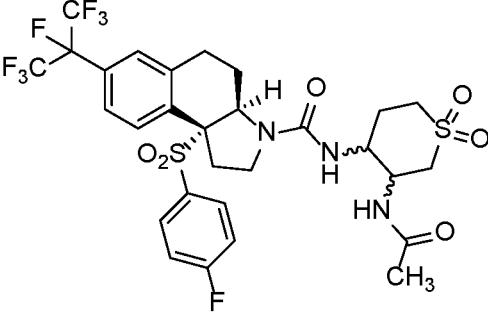
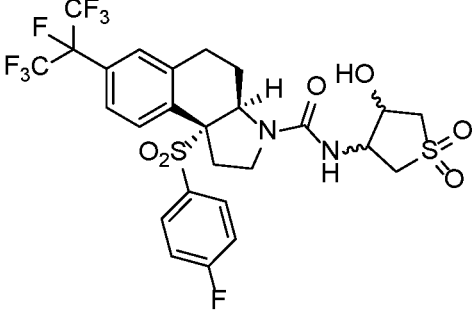
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
645		627.4 (M+H) ⁺	2.17	D
646		620.3 (M+H) ⁺	1.97	D
647		615.4 (M+H) ⁺	2.12	D
648		629.4 (M+H) ⁺	2.15	D
649		647.4 (M+H) ⁺	2.17	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
650		621.2 (M+H) ⁺	2.03	D
651		656.2 (M+H) ⁺	2.21	D
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

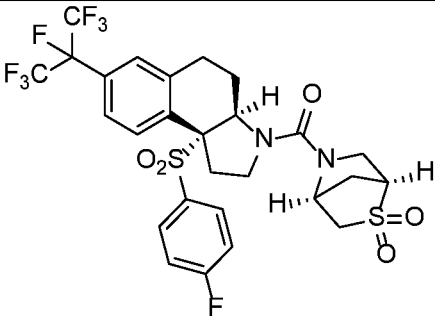
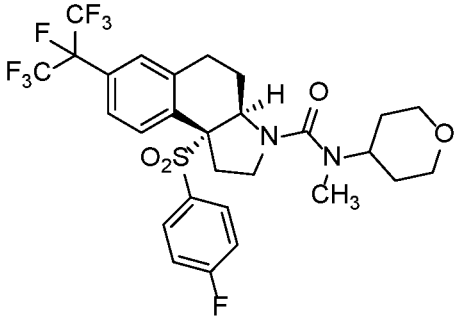
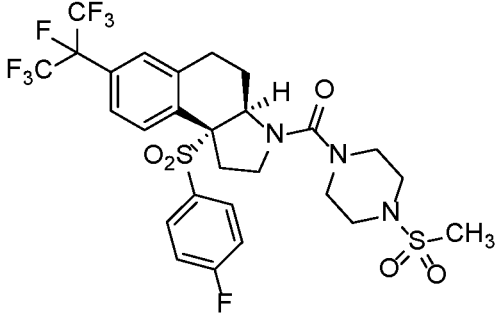
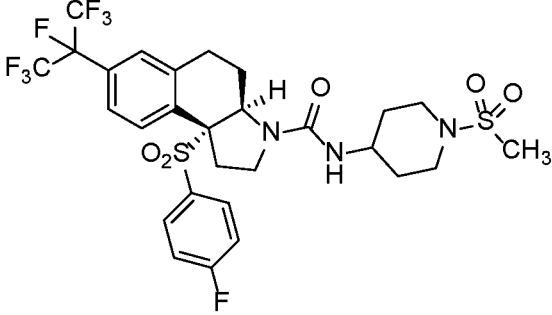
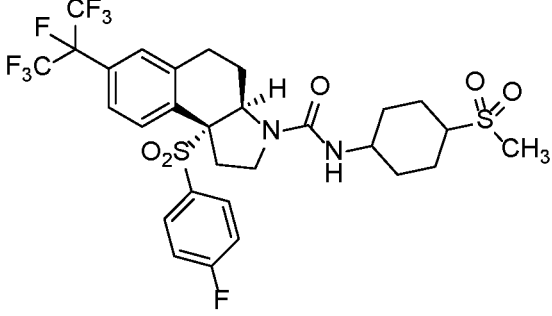
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
655	 Homochiral from peak 1	613.2 (M+H) ⁺	2.12	C
656	 Homochiral from peak 1	601.2 (M+H) ⁺	2.06	C
657	 Homochiral from peak 1	641.1 (M+H) ⁺	1.76	C
658	 Homochiral from peak 1	615.2 (M+H) ⁺	2.09	C
659	 Homochiral from peak 1	615.4 (M+H) ⁺	2.14	D

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
660	Homochiral from peak 1 [Homochiral <i>cis</i> from Peak 2] CH₃	669.4 (M+H) ⁺	2.23	D
661	Homochiral from peak 1 [Homochiral <i>cis</i> from Peak 2] CH₃	683.4 (M+H) ⁺	2.48	D
662	Homochiral from peak 1 [Homochiral <i>trans</i> from Peak 2] CH₃	669.4 (M+H) ⁺	2.25	D
663	Homochiral from peak 1 [Homochiral <i>trans</i> from Peak 2] CH₃	683.3 (M+H) ⁺	2.50	D
664	CH₃	675.2 (M+H) ⁺	2.06	C

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
669		716.0 (M+H) ⁺	2.06	C

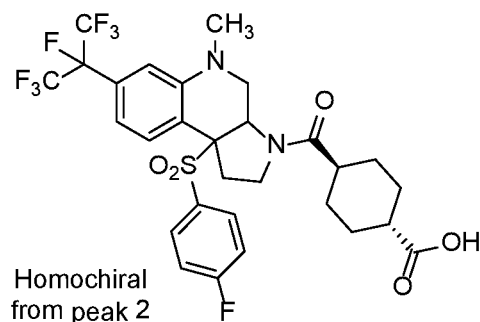
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
670		675.1 (M+H) ⁺	2.25	C
671		675.2 (M+H) ⁺	2.23	C
672		701.0 (M+H) ⁺	2.35	C
673		732.3 (M+H) ⁺	2.07	C
674		677.3 (M+H) ⁺	1.99 2.01	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
675		661.1 (M+H) ⁺	2.11	C
676		660.8 (M+H) ⁺	2.11	C
677		702.0 (M+H) ⁺	1.81	D
678		675.1 (M+H) ⁺	2.11	C
679		675.1 (M+H) ⁺	2.11	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
680		672.9 (M+H) ⁺	2.15	C
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

(1*r*,4*r*)-4-(9b-((4-fluorophenyl)sulfonyl)-5-methyl-7-(perfluoropropan-2-yl)-
2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*c*]quinoline-3-carbonyl)cyclohexane-1-
carboxylic acid

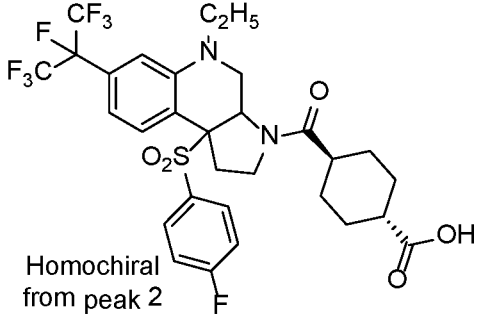
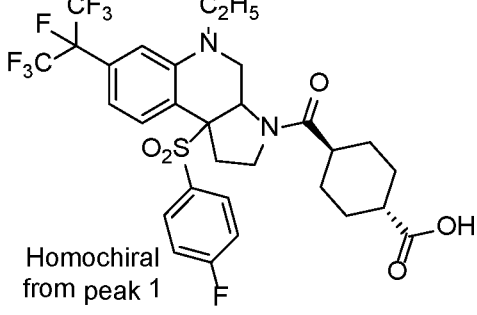
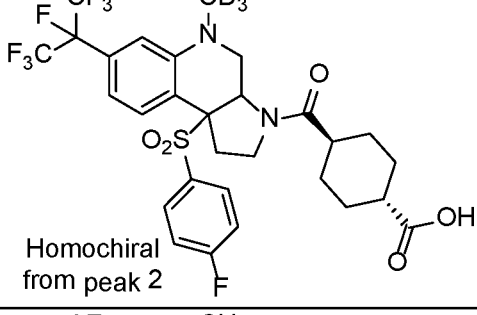
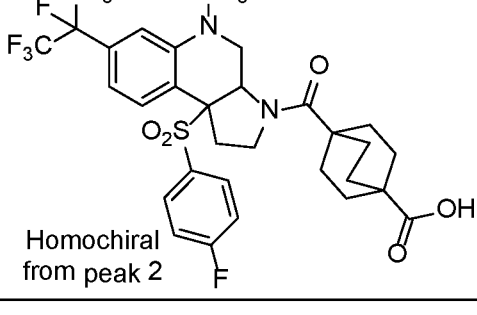


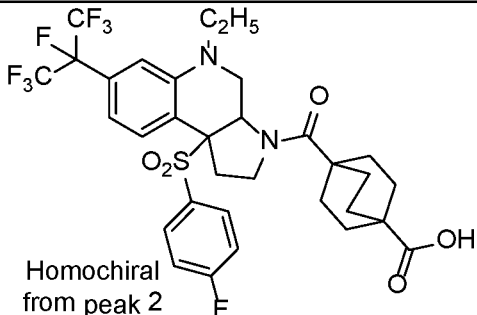
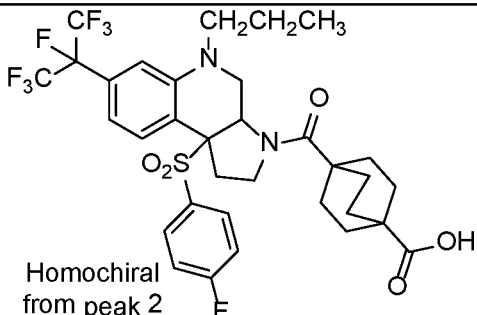
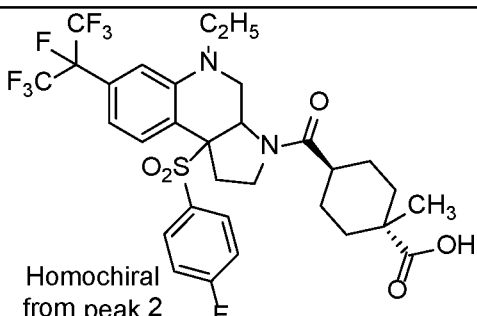
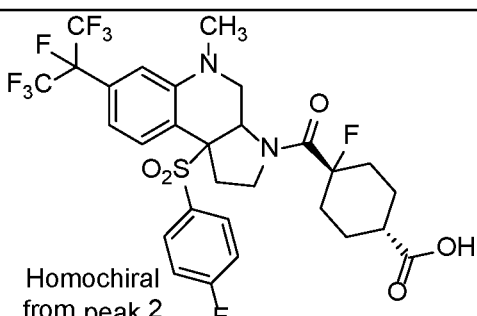
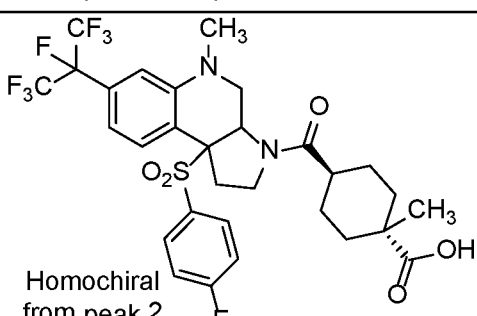
A solution of homochiral (1*r*,4*r*)-4-(9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*c*]quinoline-3-carbonyl)cyclohexanecarboxylic acid (Example 509; 50 mg, 0.076 mmol) in MeOH (764
 10 μ L) was treated with 37% aqueous formaldehyde (62 mg, 0.76 mmol), acetic acid (87 μ L, 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 Na₂SO₄ and concentrated. The residue was purified by chiral SFC using the following conditions: Column: Lux[®] Cellulose-4 46 $\times$ 250 mm, 5 μ m
 15 (Phenomenex Inc.); column temperature 35 $^{\circ}$ C; pressure 100 bars; mobile phase CO₂-MeOH (75:25). This provided (1*r*,4*r*)-4-(9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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),
 20 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). ¹⁹F 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.

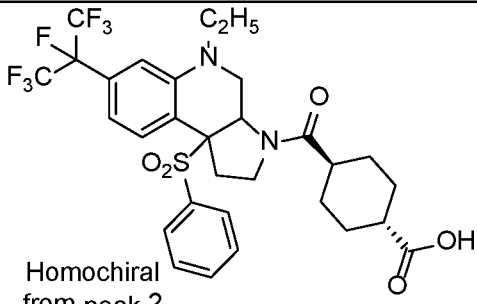
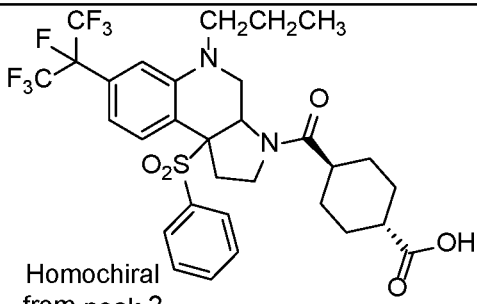
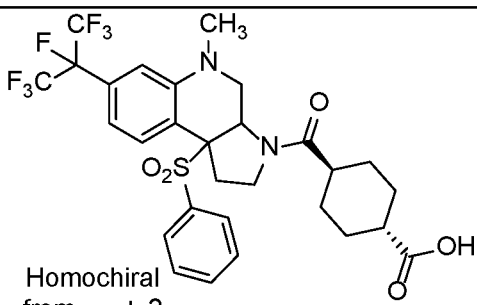
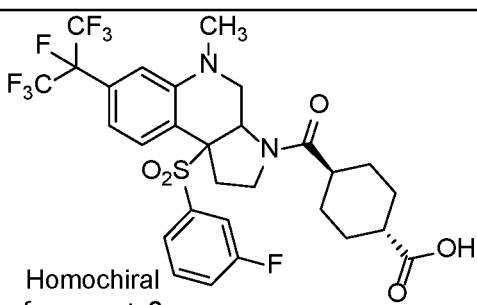
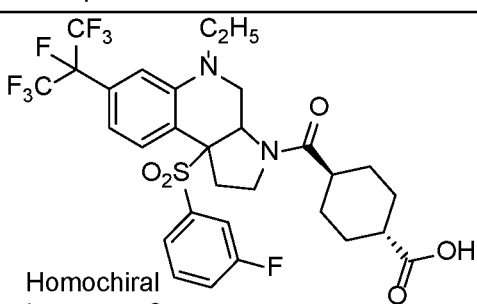
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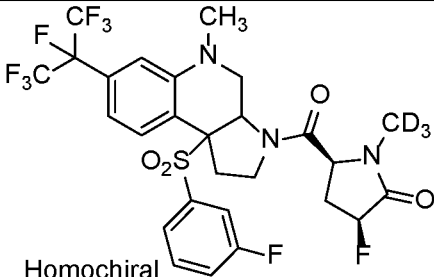
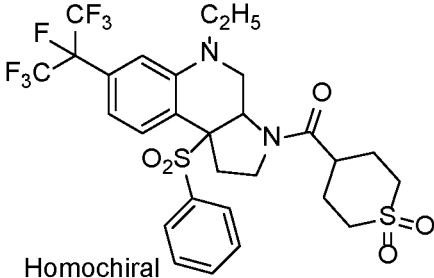
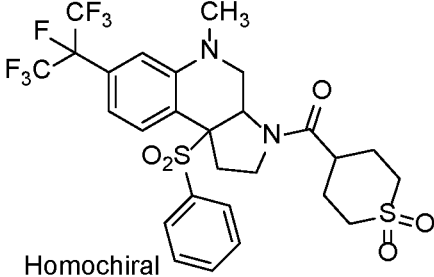
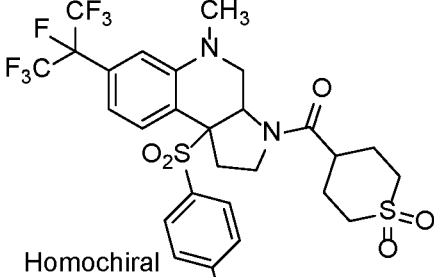
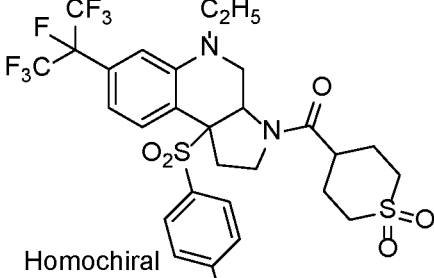
Table 11

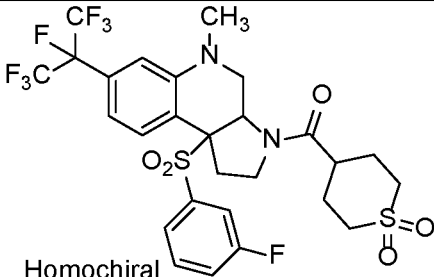
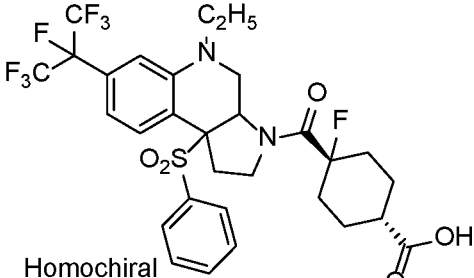
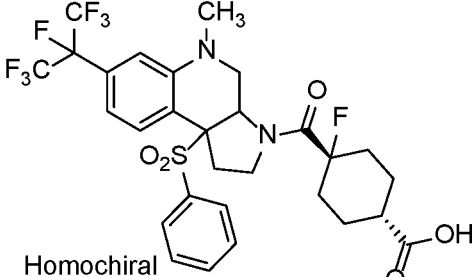
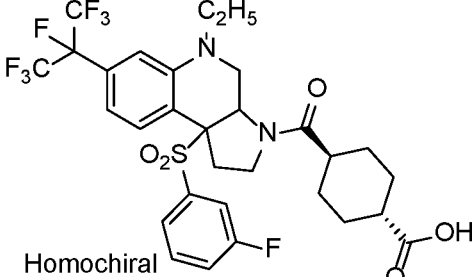
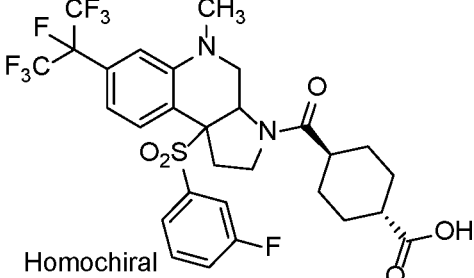
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
686	 Homochiral from peak 2	683.2 (M+H) ⁺	1.13	B
687	 Homochiral from peak 1	683.2 (M+H) ⁺	1.13	B
688	 Homochiral from peak 2	672.2 (M+H) ⁺	1.10	B
689	 Homochiral from peak 2	695.5 (M+H) ⁺	1.14	B

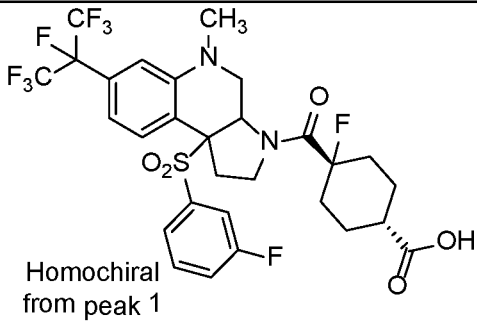
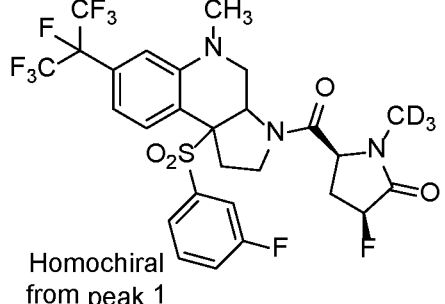
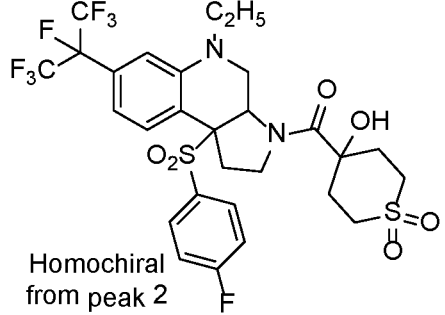
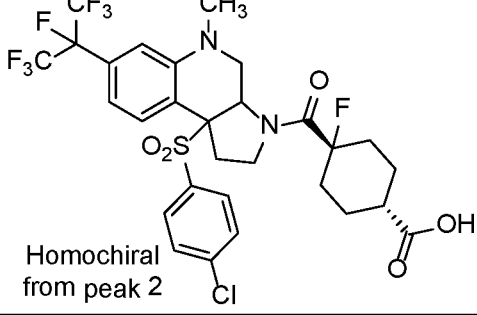
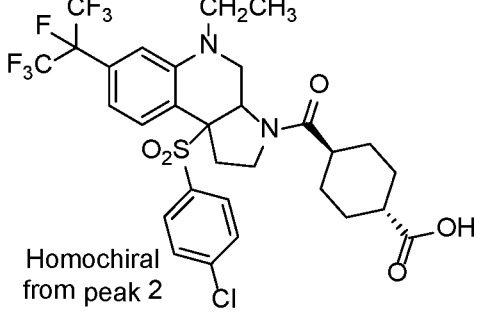
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
690	 Homochiral from peak 2	709.5 (M+H) ⁺	1.17	B
691	 Homochiral from peak 2	723.2 (M+H) ⁺	2.29	C
692	 Homochiral from peak 2	697.3 (M+H) ⁺	1.16	B
693	 Homochiral from peak 2	687.1 (M+H) ⁺	1.14	B
694	 Homochiral from peak 2	683.2 (M+H) ⁺	1.12	B

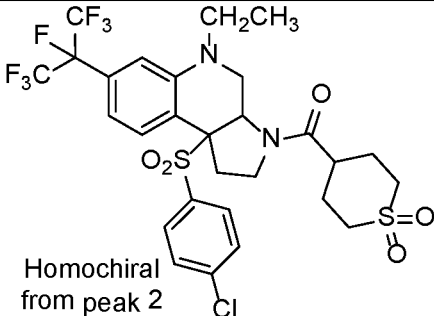
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
695	Homochiral from peak 2	715.2 (M+H) ⁺	1.19	B
696	Homochiral from peak 2		1.17	B
697	Homochiral from peak 2	697.1 (M+H) ⁺	1.17	B
698	Homochiral from peak 2	697.2 (M+H) ⁺	1.17	B
699	Homochiral from peak 2	683.1 (M+H) ⁺	1.14	B

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
704	 Homochiral from peak 2	683.2 (M+H) ⁺	1.11	B

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
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
708	 Homochiral from peak 2	675.1 (M+H) ⁺	1.06	B
709	 Homochiral from peak 2	689.1 (M+H) ⁺	1.09	B

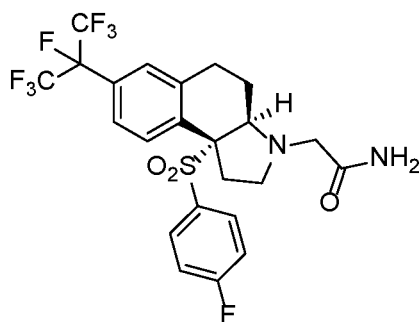
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
710	 Homochiral from peak 1	675.1 (M+H) ⁺	1.95	C
711	 Homochiral from peak 2	683.2 (M+H) ⁺	2.21	C
712	 Homochiral from peak 2	669.2 (M+H) ⁺	2.29	C
713	 Homochiral from peak 1	683.5 (M+H) ⁺	1.10	B
714	 Homochiral from peak 1	669.4 (M+H) ⁺	1.10	B

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
715	 Homochiral from peak 1	687.1 (M+H) ⁺	1.07	B
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

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

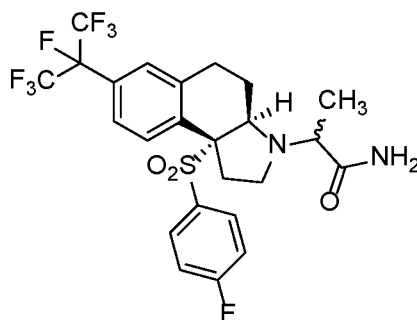
2-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)acetamide



A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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

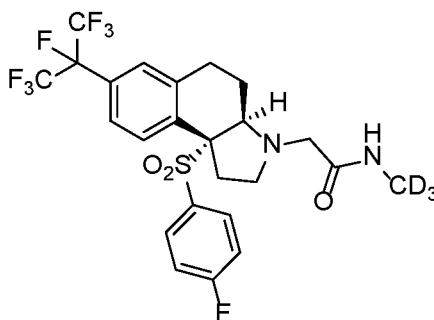
(*RS*)-2-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)propanamide



5 A solution of (3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-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

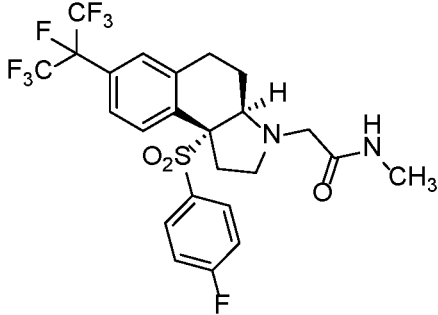
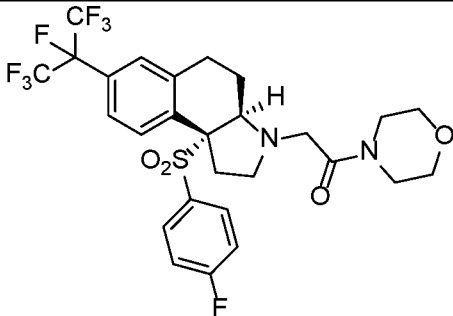
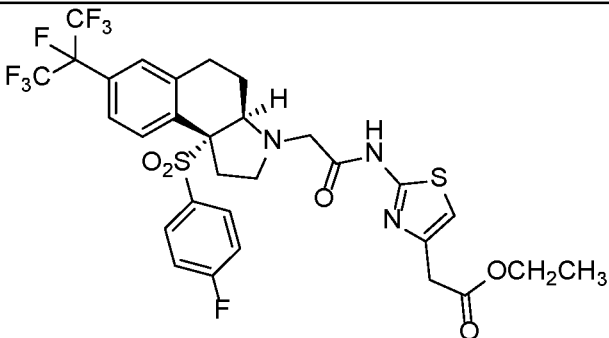
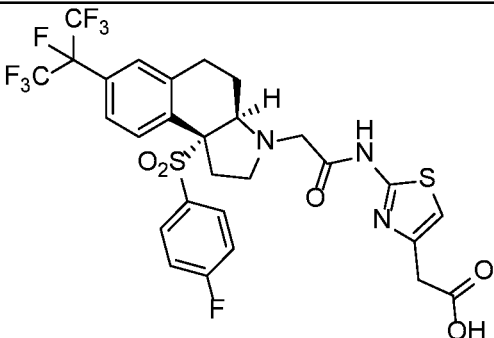
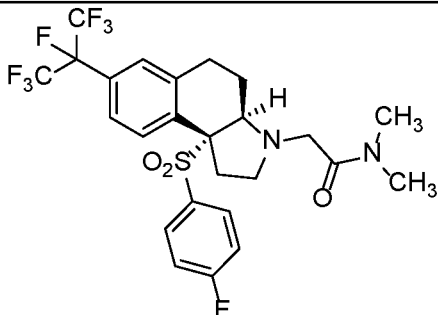
20 2-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)-*N*-(methyl-*d*₃)acetamide



A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 Na₂SO₄ 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 Na₂SO₄ 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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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). ¹H 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
726		726.0 (M+H) ⁺	2.46	C
727		698.4 (M+H) ⁺	1.83	C
728		548.8 (M+H) ⁺	2.22	C

Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
729		571.0 (M+H) ⁺	2.01	C
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

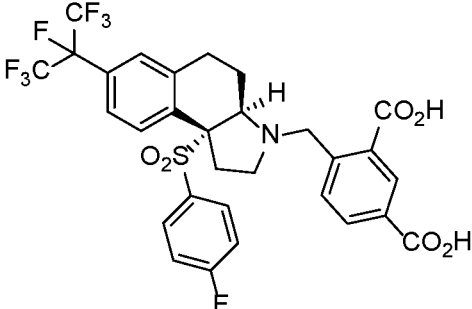
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
734		599.9 (M+H) ⁺	1.96	C
735		600.4 (M+H) ⁺	2.37	C
736		585.3 (M+H) ⁺	2.29	C
737		673.5 (M+H) ⁺	2.57	C
738		673.4 (M+H) ⁺	2.51	C

Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
739		583.0 (M+H) ⁺	2.06	C
740		660.3 (M+H) ⁺	2.24	C
741		660.0 (M+H) ⁺	2.21	C
742		572.8 (M+H) ⁺	2.07	C
743		558.9 (M+H) ⁺	1.99	C

Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
744		639.4 (M+H) ⁺	2.40	C
745		597.3 (M+H) ⁺	2.31	C
746		588.4 (M+H) ⁺	2.12	C
747		650.4 (M+H) ⁺	2.38	C
748		650.4 (M+H) ⁺	2.44	C

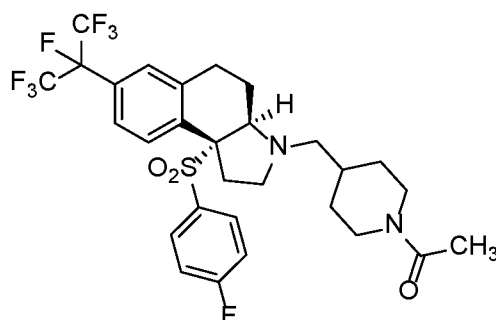
Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
749		587.9 (M+H) ⁺	2.22	C
750		588.2 (M+H) ⁺	2.24	C
751		623.8 (M+H) ⁺	2.31	C
752		576.3 (M+H) ⁺	2.19	C
753		602.1 (M+H) ⁺	2.26	C

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
758		664.2 (M+H) ⁺	2.07	C

Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
759		678.0 (M+H) ⁺	1.67	C

Example 760

1-(4-(((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)methyl)piperidin-1-yl)ethan-1-one

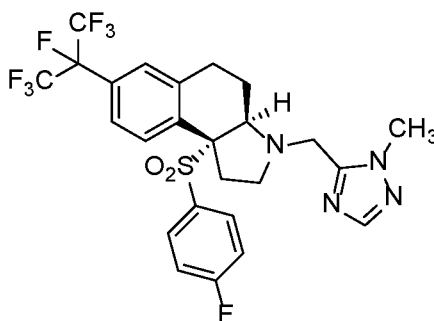


A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32; 20 mg, 0.037 mmol) in 1,2-dichloroethane (2 mL) was treated with *tert*-butyl 4-formylpiperidine-1-carboxylate (19.9 mg, 0.093 mmol). DIPEA (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 Na₂SO₄, 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 Et₃N (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-(((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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

(3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-3-((1-methyl-1*H*-1,2,4-triazol-5-yl)methyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole

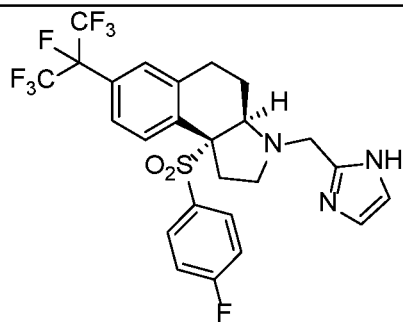
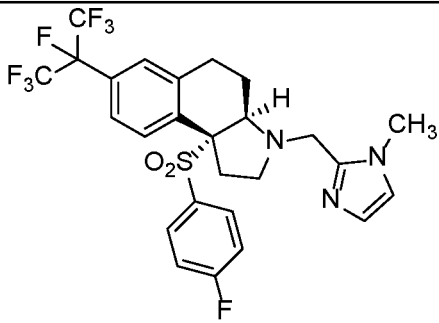
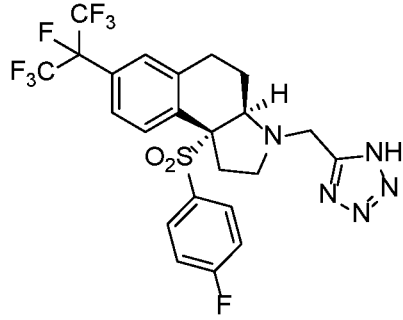


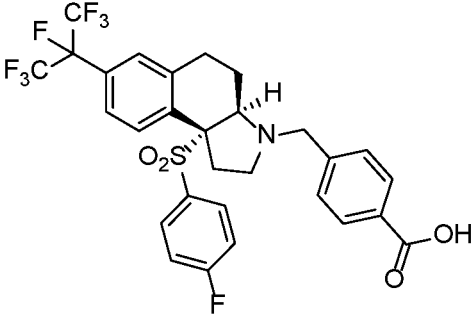
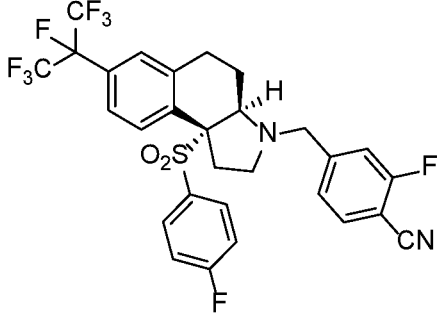
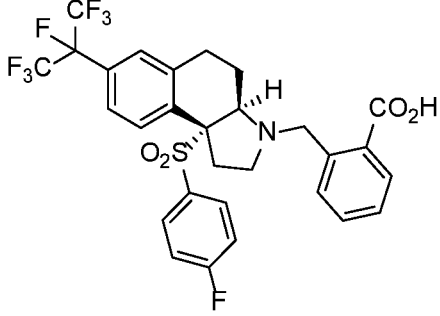
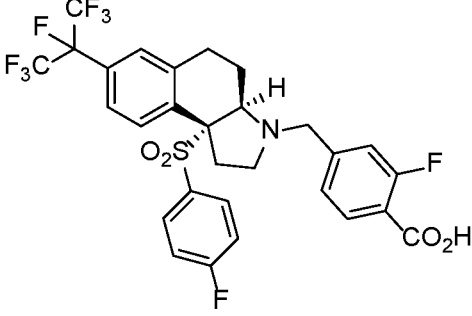
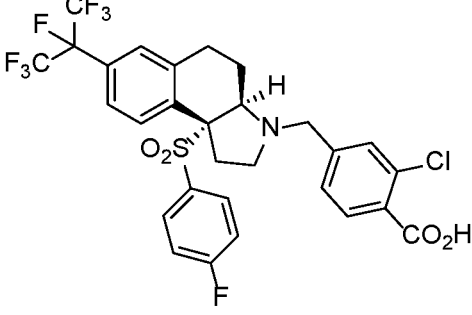
A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32; 15 mg, 0.030 mmol) in DMF (1 mL) was treated with 1-methyl-1*H*-1,2,4-triazole-5-carbaldehyde (16.68 mg, 0.150 mmol) and Et₃N (6.1 μL, 0.044 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 (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-3-((1-methyl-1*H*-1,2,4-triazol-5-yl)methyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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
- 5 Examples 760 and 761 using the appropriate carbonyl compound, followed by ester hydrolysis or other protecting group removal if required.

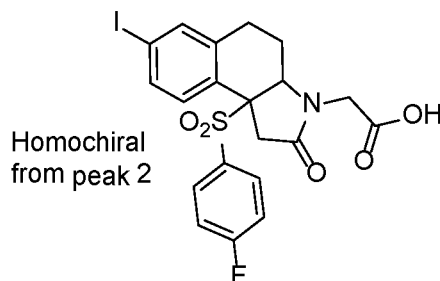
Table 13

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
764		582.3 (M+H) ⁺	1.68	C

Ex. #	Structure	MS observed	HPLC ret. time (min.)	HPLC method
765		634.2 (M+H) ⁺	1.94	C
766		633.0 (M+H) ⁺	2.68	C
767		634.2 (M+H) ⁺	2.06	C
768		652.0 (M+H) ⁺	2.02	C
769		668.1 (M+H) ⁺	1.94	C

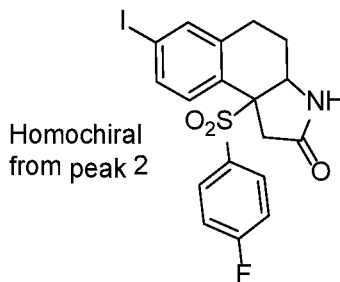
Example 770

9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetic acid



5

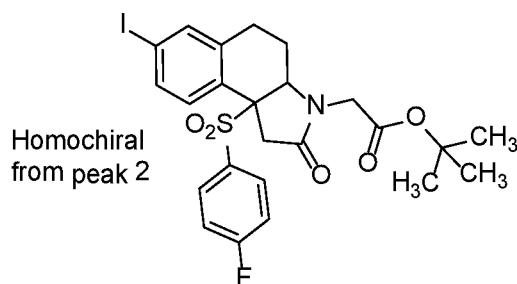
Step A: 9b-((4-fluorophenyl)sulfonyl)-7-iodo-1,3,3a,4,5,9b-hexahydro-2H-benzo[e]indol-2-one



10 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-hexahydro-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). ¹H NMR (400

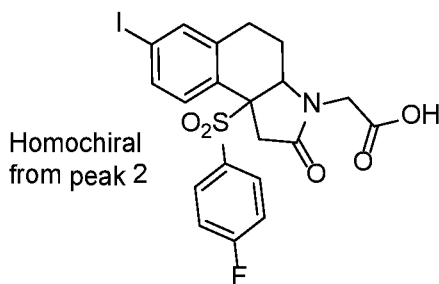
15 MHz, CDCl₃) δ 7.67 - 7.62 (m, 1H), 7.50 - 7.42 (m, 2H), 7.41 (s, 1H), 7.18 (d, $J=8.4$ Hz, 1H), 7.12 (dd, $J=8.9, 8.3$ Hz, 2H), 4.44 - 4.32 (m, 1H), 3.69 (d, $J=18.5$ Hz, 1H), 2.89 (d, $J=18.3$ Hz, 1H), 2.49 (dt, $J=16.2, 3.8$ Hz, 1H), 2.21 - 2.07 (m, 1H), 1.95 - 1.80 (m, 1H), 1.50 - 1.33 (m, 1H).

20 **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



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 NH₄Cl. 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-C₄H₈)⁺, 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

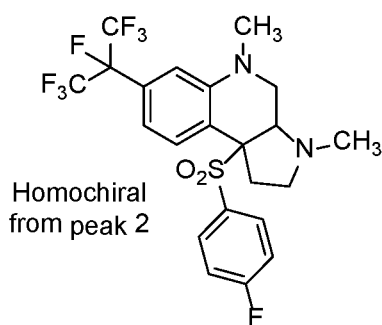


A solution of crude homochiral *tert*-butyl 2-(9b-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3H-benzo[e]indol-3-yl)acetate (0.11 g, 0.188 mmol) in DCM (0.1 mL) was treated with 85% phosphoric acid (0.103 mL, 1.503 mmol) and stirred at rt for 48 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL). The organic phase was washed sequentially with water (3 x 15 mL) and brine (15 mL), dried over Na₂SO₄ and concentrated. The residue was purified by

preparative HPLC (method E, gradient 10-50% B) to give homochiral 2-((4-fluorophenyl)sulfonyl)-7-iodo-2-oxo-1,2,3a,4,5,9b-hexahydro-3*H*-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). ¹H 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

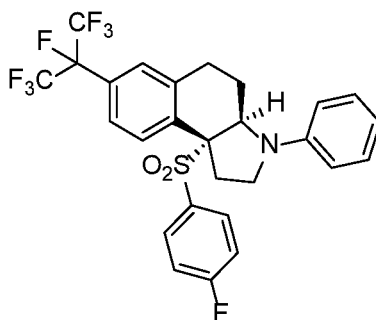
10 9b-((4-fluorophenyl)sulfonyl)-3,5-dimethyl-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*c*]quinoline



A solution of 9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*c*]quinoline dihydrochloride (homochiral, from peak 2, Intermediate 88; 20 mg, 0.040 mmol) in MeOH (200 μ L) was treated with acetic acid (114 μ L, 1.998 mmol), 37% aqueous formaldehyde (29.8 μ L, 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 Na₂SO₄ 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-1*H*-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). ¹H 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

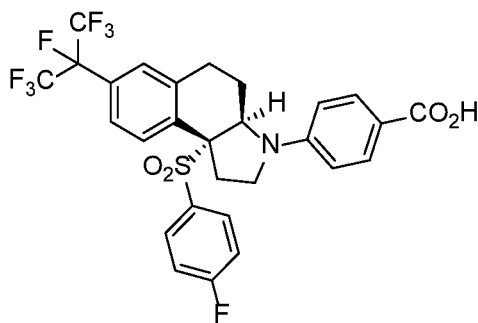
(3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole



5 A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 μ mol), BINAP (5.23 mg, 8.40 μ mol) and Cs₂CO₃ (54.7 mg, 0.168 mmol) were added, and the mixture
10 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 Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC (method F, gradient 45-100% B, 25 min) to afford (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole (3.6 mg, 22% yield). LCMS *m/z* 575.9 (M+H)⁺, HPLC *t_R* 2.69 min
15 (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),
20 1.23 (d, *J*=12.0 Hz, 1H).

Example 773

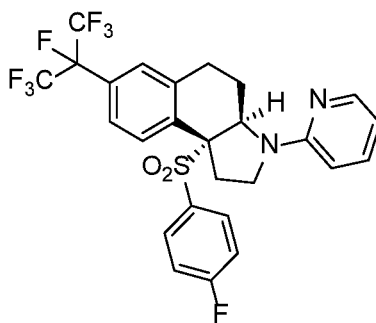
4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)benzoic acid



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 μ mol), BINAP (6.97 mg, 8.40 μ mol) and Cs₂CO₃ (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 Na₂SO₄, 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

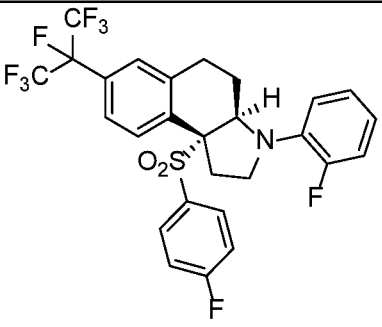
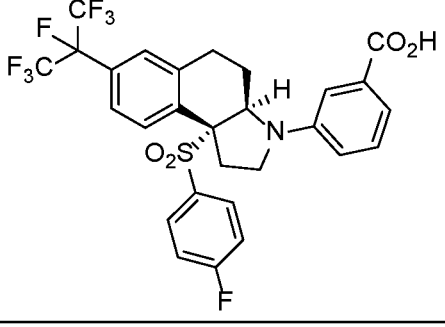
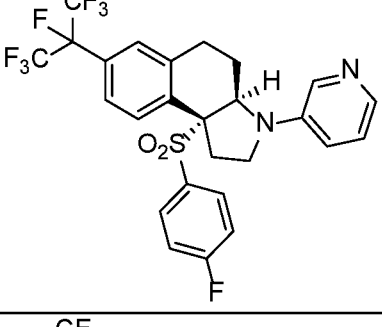
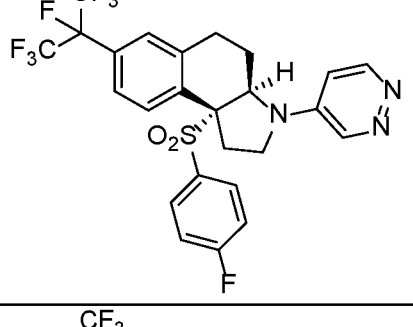
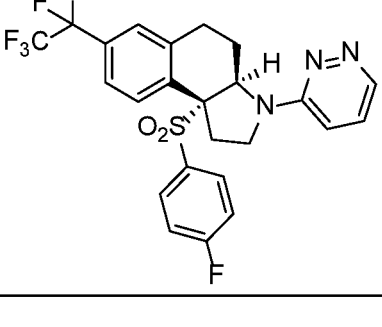
(3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-3-(pyridin-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole

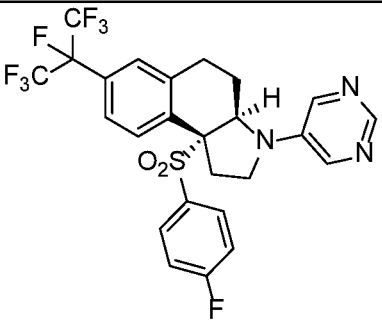
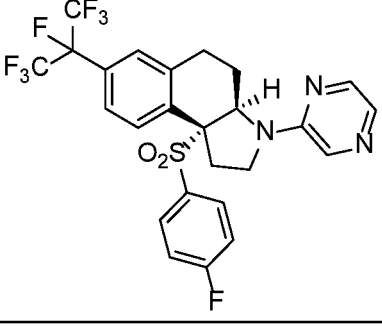
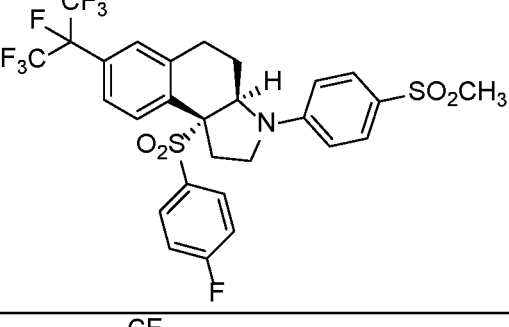
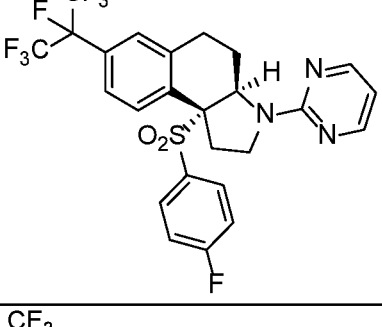
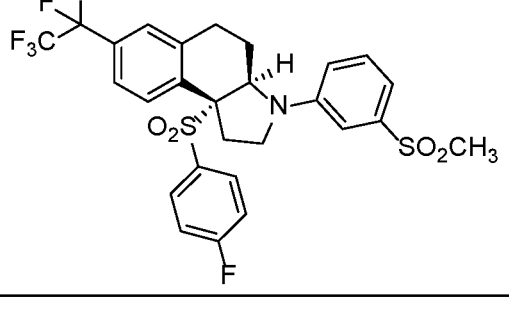


A solution of (3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole hydrochloride (Intermediate 32; 15 mg, 0.028 mmol) and bromopyridine (13.27 mg, 0.084 mmol) in 1,4-dioxane (2 mL) was
 5 bubbled with nitrogen for 2 min. Palladium(II) acetate (1.26 mg, 5.60 μ mol), Xantphos (4.05 mg, 7.00 μ mol) 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 Na₂SO₄, filtered and concentrated. The residue was purified by preparative HPLC
 10 (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),
 15 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
 20 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
779		578.0 (M+H) ⁺	2.22	C

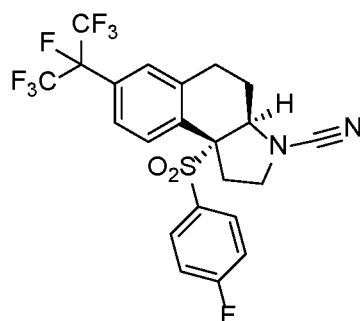
Ex. #r	Structure	LCMS m/z observed	HPLC t_R (min.)	HPLC method
780		578.1 (M+H) ⁺	2.22	C
781		578.0 (M+H) ⁺	2.40	C
782		654.1 (M+H) ⁺	2.39	C
783		577.9 (M+H) ⁺	2.44	C
784		654.3 (M+H) ⁺	2.41	C

Ex. #r	Structure	LCMS m/z observed	HPLC t_R (min.)	HPLC method
785		658.0 (M+H) ⁺	2.57	C
786		660.4 (M+H) ⁺	2.28	C
787		683.3 (M+H) ⁺	2.51	C

Example 788

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

5



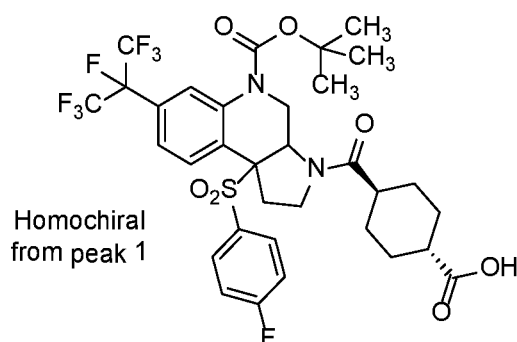
A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32; 15 mg,

0.028 mmol) in DMF (1 mL) was treated with Cs₂CO₃ (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 (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-

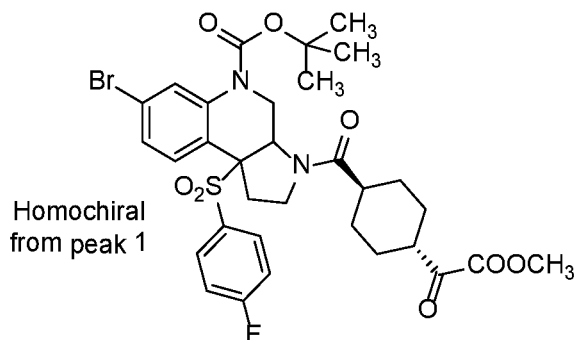
- 5 (perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indole-3-carbonitrile (10.6 mg, 67% yield). LCMS *m/z* 525.3 (M+H)⁺, HPLC *t_R* 2.35 min (method C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.75 (d, *J*=8.5 Hz, 1H), 7.61 (d, *J*=8.2 Hz, 1H), 7.47 - 7.38 (m, 2H), 7.32 (s, 1H), 7.22 (t, *J*=8.7 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

- 15 (1*r*,4*r*)-4-(5-(*tert*-butoxycarbonyl)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*c*]quinoline-3-carbonyl)cyclohexane-1-carboxylic acid



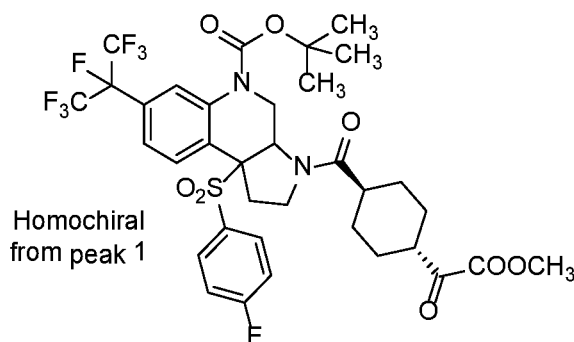
- 20 Step A: *tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3-((1*r*,4*r*)-4-(2-methoxy-2-oxoacetyl)cyclohexane-1-carbonyl)-1,2,3,3a,4,9b-hexahydro-5*H*-pyrrolo[2,3-*c*]quinoline-5-carboxylate



A solution of *tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*c*]quinoline-5(9*bH*)-carboxylate (the product from Intermediate 88 Step C; 4.09 g, 8 mmol) in DCM (80 mL) was treated with (1*r*,4*r*)-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-((1*r*,4*r*)-4-(methoxycarbonyl)cyclohexanecarbonyl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*c*]quinoline-5(9*bH*)-carboxylate. LCMS *m/z* 623.4 (M+H-C₄H₈)⁺, HPLC *t_R* 1.15 min (method B).

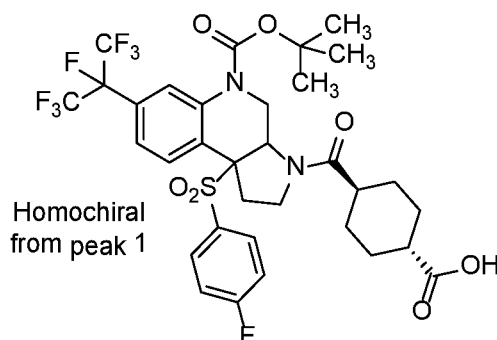
This material was separated by chiral SFC using the following conditions: Column: Lux[®] Cellulose-4 50 × 250 mm, 5 μm (Phenomenex Inc.); column temperature 35 °C; pressure 100 bars; mobile phase CO₂-MeOH (80:20); flow rate 300 mL/min. Peak 1 was eluted with *t_R* 6.6 min. Peak 2 was eluted with *t_R* 8.2 min.

Step B: *tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-3-((1*r*,4*r*)-4-(2-methoxy-2-oxoacetyl)cyclohexane-1-carbonyl)-7-(perfluoropropan-2-yl)-1,2,3,3a,4,9b-hexahydro-5*H*-pyrrolo[2,3-*c*]quinoline-5-carboxylate



Following the procedure of Intermediate 2 Step A, *tert*-butyl 7-bromo-9b-((4-fluorophenyl)sulfonyl)-3-((1*r*,4*r*)-4-(methoxycarbonyl)cyclohexanecarbonyl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*c*]quinoline-5(9*bH*)-carboxylate (1 g, 1.471 mmol) was converted into *tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-3-((1*r*,4*r*)-4-(methoxycarbonyl)cyclohexanecarbonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*c*]quinoline-5(9*bH*)-carboxylate (0.35 g, 31% yield). LCMS *m/z* 713.5 (M+H-C₄H₈)⁺, HPLC *t_R* 1.18 min (method B).

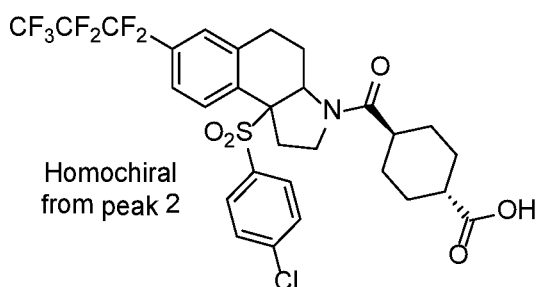
Step C: (1*r*,4*r*)-4-(5-(*tert*-butoxycarbonyl)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2,3-*c*]quinoline-3-carbonyl)cyclohexane-1-carboxylic acid



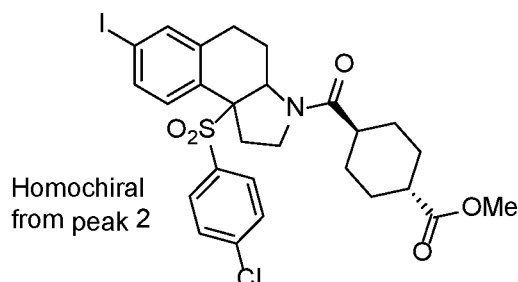
- 5 A solution of *tert*-butyl 9b-((4-fluorophenyl)sulfonyl)-3-((1*r*,4*r*)-4-(methoxycarbonyl)cyclohexanecarbonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*c*]quinoline-5(9*bH*)-carboxylate (25 mg, 0.033 mmol) in 1,4-dioxane (325 μ L) was treated with a solution of LiOH hydrate (7.79 mg, 0.325 mmol) in water (58.6 μ L, 3.25 mmol). After 2 h at rt, the mixture was diluted with DMF and purified by
- 10 preparative HPLC (method E, gradient 40-100% B, 20 min) to provide (1*r*,4*r*)-4-(5-(*tert*-butoxycarbonyl)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).
- 15

Example 790

- 20 (1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid

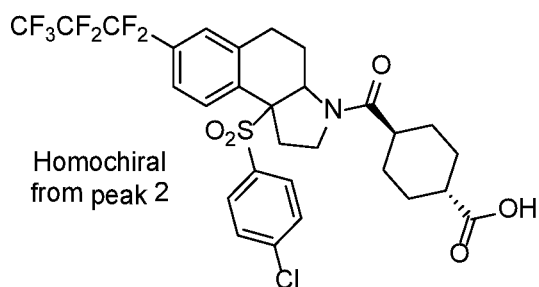


Step A: methyl (1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylate



5 A solution of crude 9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1*H*-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-1*H*-benzo[*e*]indole-3-carboxylate) in THF (1 mL) was treated with (1*r*,4*r*)-4-(methoxycarbonyl)cyclohexanecarboxylic acid (0.097 g, 0.523 mmol), PyBOP (0.272 g, 0.523 mmol) and Et₃N (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 K₂HPO₄, water and brine and concentrated to provide crude methyl (1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1*H*-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: (1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



20

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 (1*r*,4*r*)-methyl 4-(9b-((4-chlorophenyl)sulfonyl)-7-

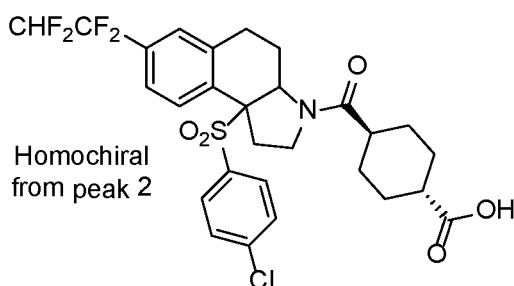
iodo-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexanecarboxylate (30 mg, 0.047 mmol) and DMF (1 mL). The mixture was sonicated for 1 min, treated with 1,1,1,2,2,3,3-heptafluoro-3-iodopropane (69.1 mg, 0.237 mmol), and heated at 120 °C. After 7 h, the mixture was cooled to rt, filtered and concentrated. The residue was

5 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 (1*r*,4*r*)-

10 4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-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

(1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(1,1,2,2-tetrafluoroethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid

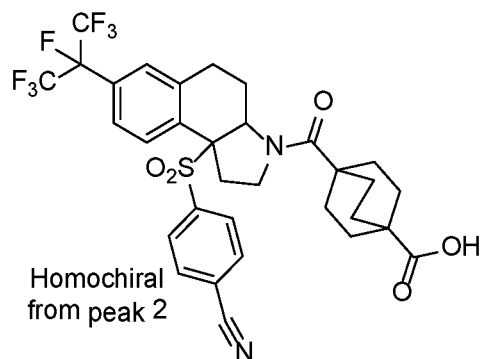


Following the procedure used to prepare Example 790 but substituting 1,1,2,2-tetrafluoro-1-iodoethane for 1,1,1,2,2,3,3-heptafluoro-3-iodopropane in Step B, (1*r*,4*r*)-methyl 4-(9b-((4-chlorophenyl)sulfonyl)-7-iodo-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexanecarboxylate (30 mg, 0.047 mmol) was converted

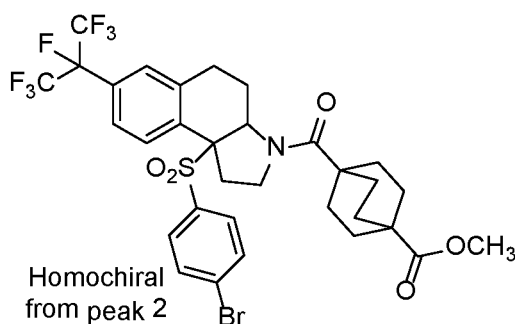
20 to (1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(1,1,2,2-tetrafluoroethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid (8.8 mg, 31% yield). LCMS m/z 602.1 (M+H)⁺, HPLC t_R 0.99 min (method B).

Example 792

4-(9b-((4-cyanophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylic acid



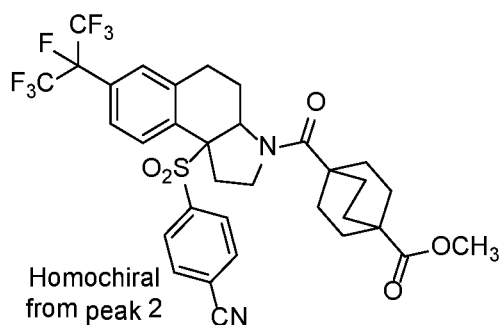
Step A: methyl 4-(9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate



5

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 K₂HPO₄, 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).

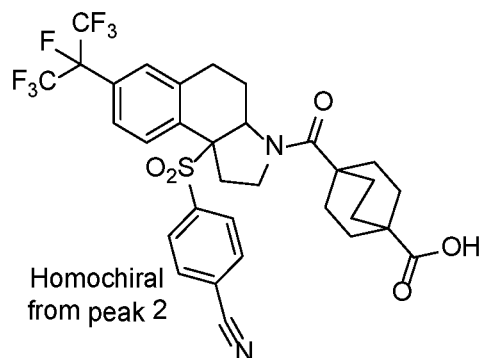
Step B: methyl 4-(9b-((4-cyanophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1H-benzo[e]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate



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

- 5 tetrakis(triphenylphosphine)palladium (3 mg, 2.7 μ mol) 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 Na₂SO₄ 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
- 10 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



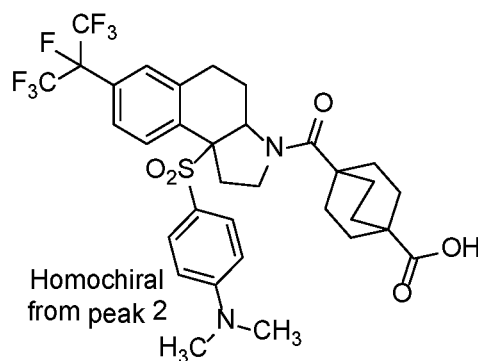
15

- 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
- 20 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 Na₂SO₄ 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-1*H*-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-1*H*-benzo[*e*]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylic acid



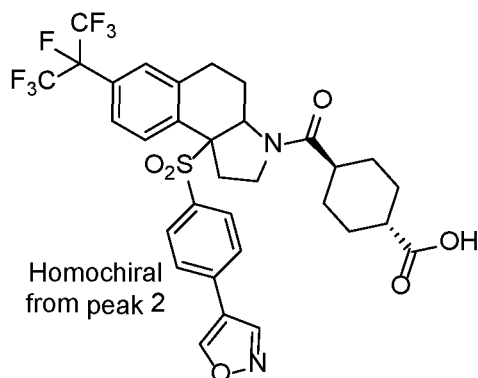
A mixture of homochiral methyl 4-(9b-((4-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)bicyclo[2.2.2]octane-1-carboxylate (Example 792 Step A; 20 mg, 0.027 mmol), BINAP (8 mg, 0.013 mmol), sodium *tert*-butoxide (5 mg, 0.053 mmol) and tris(dibenzylideneacetone)dipalladium (4.9 mg, 5.3 μ mol) 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 Na₂SO₄ 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-1*H*-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).

5

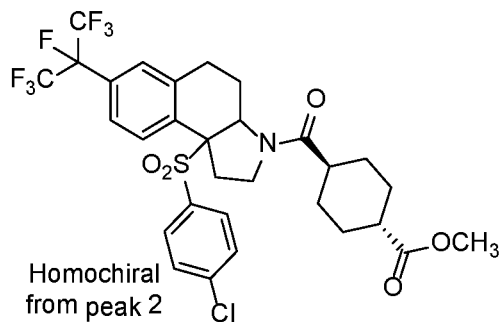
Example 794

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



10

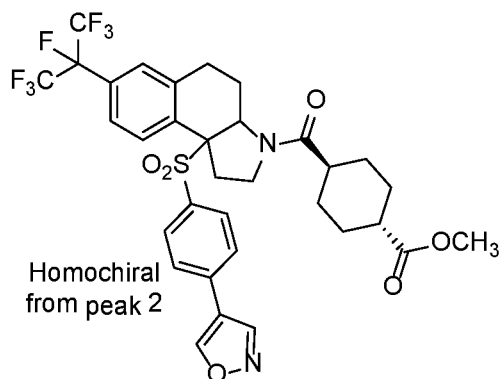
Step A: methyl (1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexanecarboxylate



Following the procedure of Example 790 Step A, 9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride (homochiral, from peak 2, Intermediate 35) was converted into methyl (1*r*,4*r*)-4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

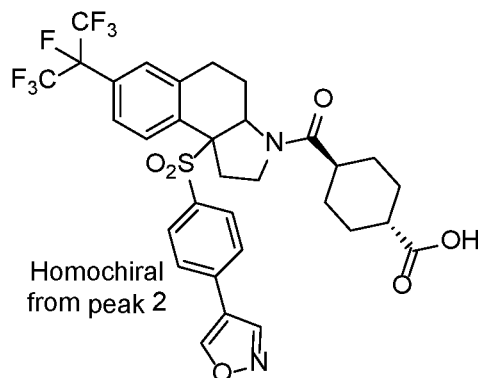
20

Step B: methyl (1*r*,4*r*)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylate



A mixture of (1*r*,4*r*)-methyl 4-(9b-((4-chlorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 K₃PO₄ (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 Na₂SO₄ and to provide crude methyl (1*r*,4*r*)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

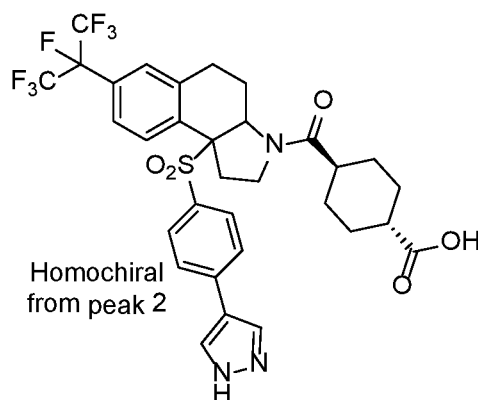
Step C: (1*r*,4*r*)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A solution of crude methyl (1*r*,4*r*)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 Na₂SO₄ 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 (1*r*,4*r*)-4-(9b-((4-(isoxazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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

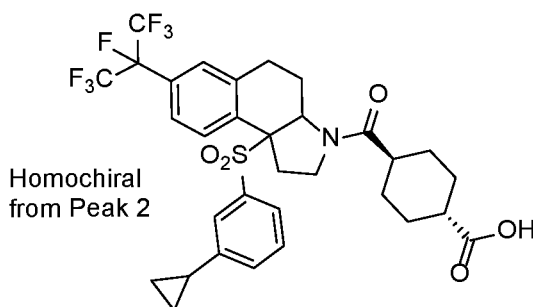
(1*r*,4*r*)-4-(9b-((4-(1*H*-pyrazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



Following the procedures used to prepare Example 794, but substituting *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-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-1*H*-benzo[*e*]indole hydrochloride (homochiral, from peak 2, Intermediate 35) was converted into (1*r*,4*r*)-4-(9b-((4-(1*H*-pyrazol-4-yl)phenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

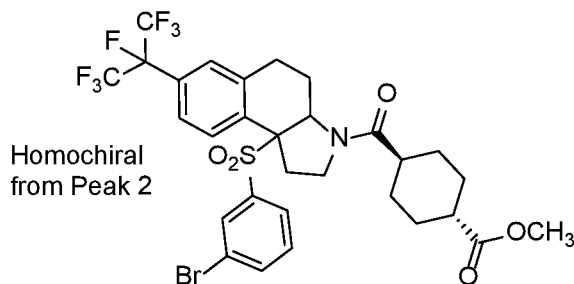
Example 796

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



5

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

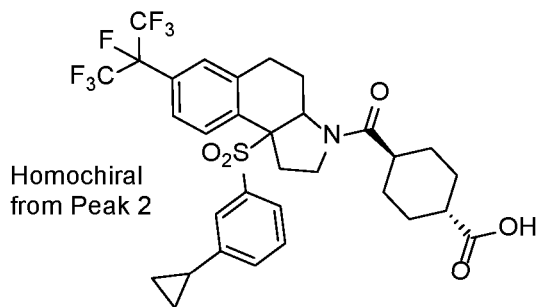


A solution of *tert*-butyl 9b-((3-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-
 3a,4,5,9b-tetrahydro-1*H*-benzo[*e*]indole-3-carboxylate (homochiral, from peak 2,
 Intermediate 75; 0.35 g, 0.530 mmol) in DCM (10 mL) was treated with TFA (6 mL, 78
 mmol) and the mixture was stirred at rt for 1 h, then was concentrated. The residue was
 dissolved in DCM (50 mL) and the solution was washed with 1.5 M aqueous K₂HPO₄ (50
 mL), dried over Na₂SO₄ 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 K₂HPO₄, dried over Na₂SO₄ and concentrated. The residue was purified by
 column chromatography on silica gel to give methyl (1*r*,4*r*)-4-(9b-((3-
 bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-

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: (1*r*,4*r*)-4-(9b-((3-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-

5 2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



A mixture of methyl (1*r*,4*r*)-4-(9b-((3-bromophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 μ mol). 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 Na₂SO₄ 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 (1*r*,4*r*)-4-(9b-((3-cyclopropylphenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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.

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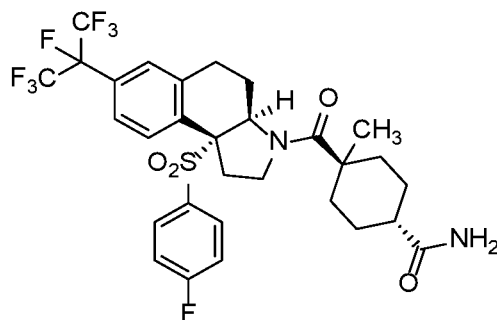
Table 15

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
797	Homochiral from Peak 2	678.5 (M+H) ⁺	2.42	D
798	Homochiral from Peak 2	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

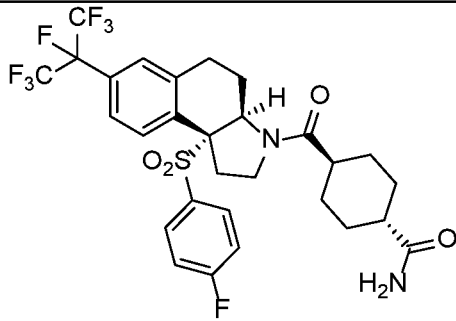
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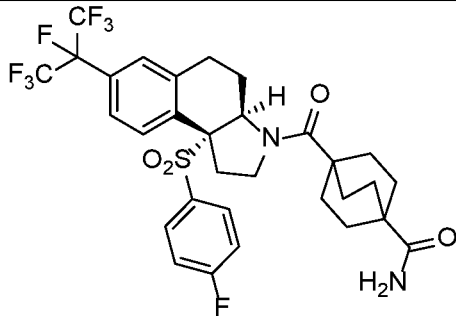


A solution of (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-4-methylcyclohexanecarboxylic acid (Example 66; 33 mg, 0.049 mmol) in DMF (1 mL) was treated with BOP (32.8 mg, 0.074 mmol) and stirred at rt for 10 min. The mixture was then treated with aqueous NH₄OH (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 Na₂SO₄ and concentrated. The residue was purified by preparative HPLC (method F, gradient 40-80% B, 19 min) to afford (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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 (500MHz, 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.

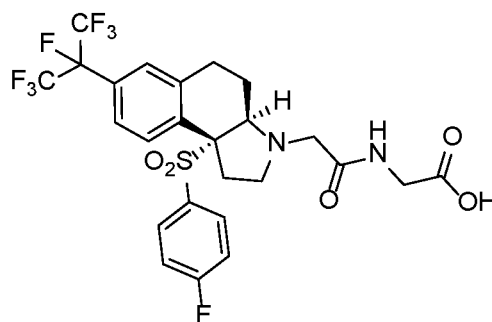
Table 16

Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
800		653.4 (M+H) ⁺	1.99	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
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

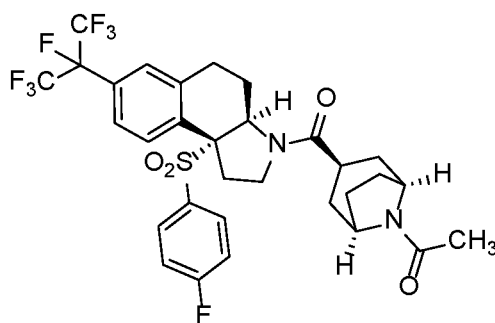


A solution of 2-((3aR,9bR)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1H-benzo[e]indol-3-yl)acetic acid (Example 730, as the TFA salt; 75 mg, 0.112 mmol) in DMF (1 mL) was treated with 1-hydroxybenzotriazole (25.7 mg, 0.168 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (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 (3x) and saturated aqueous NaHCO₃, dried over MgSO₄, 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,

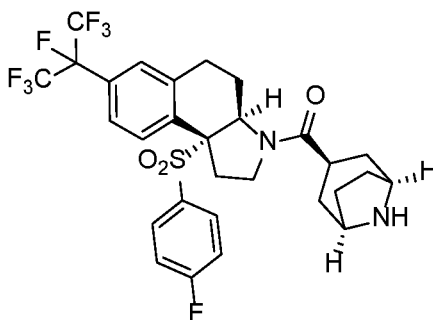
the solution was concentrated and the residue was purified by preparative HPLC (method E, gradient 17-57% B, 25 min) to provide (2-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)acetyl)glycine (2.9 mg, 7% yield). LCMS m/z 615.1 ($M+H$)⁺, 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-((1*R*,3*s*,5*S*)-3-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-8-azabicyclo[3.2.1]octan-8-yl)ethan-1-one



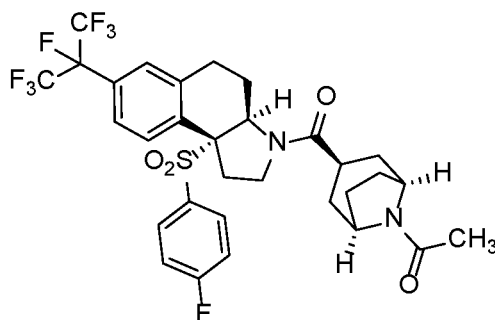
Step A: ((1*R*,3*s*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl)((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)methanone



A mixture of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole (Intermediate 32; 80 mg, 0.160 mmol), (1*R*,3*s*,5*S*)-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 Na₂SO₄ 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 K₂HPO₄ (2 x 10 mL), dried over Na₂SO₄ and concentrated to give crude ((1*R*,3*s*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl)((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-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).

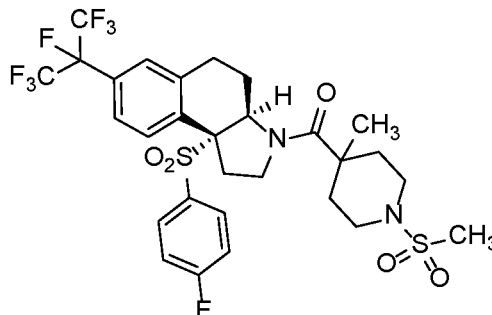
Step B: 1-((1*R*,3*s*,5*S*)-3-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-8-azabicyclo[3.2.1]octan-8-yl)ethan-1-one



A solution of crude ((1*R*,3*s*,5*S*)-8-azabicyclo[3.2.1]octan-3-yl)((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-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 x 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-((1*R*,3*s*,5*S*)-3-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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).

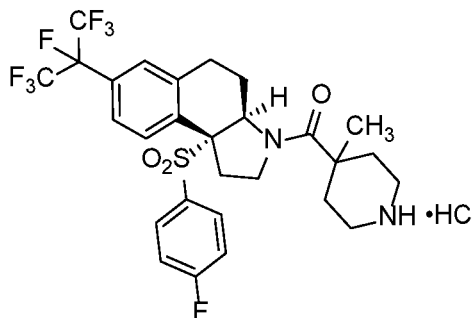
Example 804

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



5

Step A: ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(4-methylpiperidin-4-yl)methanone hydrochloride



10

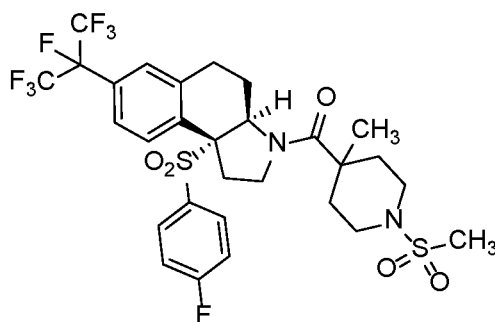
A mixture of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32; 25 mg, 0.047 mmol), 1-(*tert*-butoxycarbonyl)-4-methylpiperidine-4-carboxylic acid (13.62 mg, 0.056 mmol) and DIPEA (0.024 mL, 0.140 mmol) in 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 MgSO₄ 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 ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(4-methylpiperidin-4-yl)methanone hydrochloride

20

(31.1 mg), used without further purification. LCMS m/z 625.1 (M+H)⁺, HPLC t_R 0.91 min (method B).

Step B: ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-

5 1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(4-methyl-1-(methylsulfonyl)piperidin-4-yl)methanone



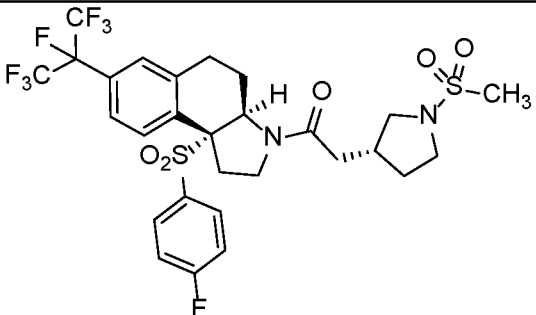
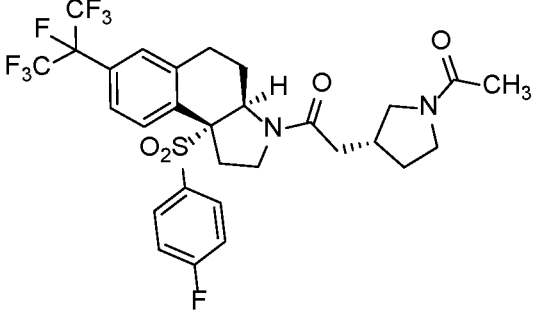
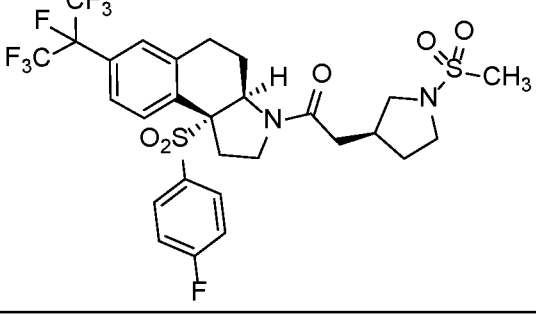
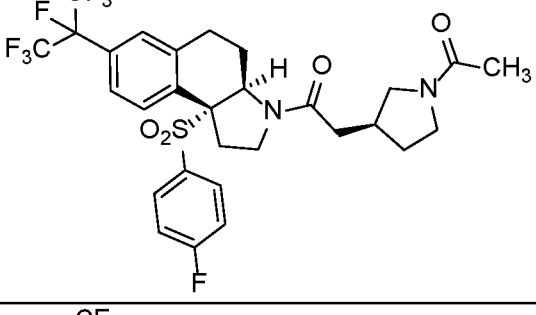
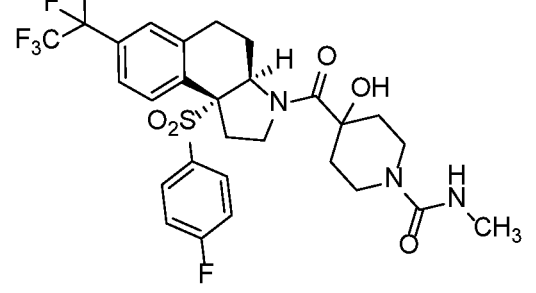
A solution of crude ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-benzo[*e*]indol-3-yl)(4-methylpiperidin-4-yl)methanone

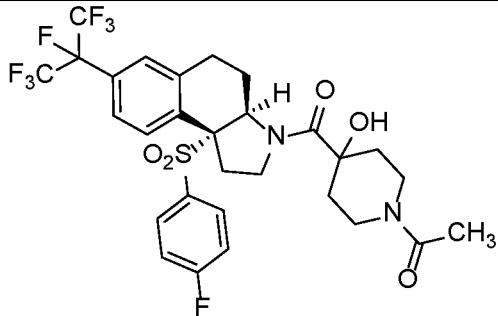
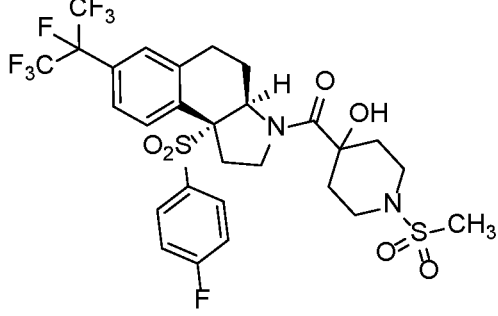
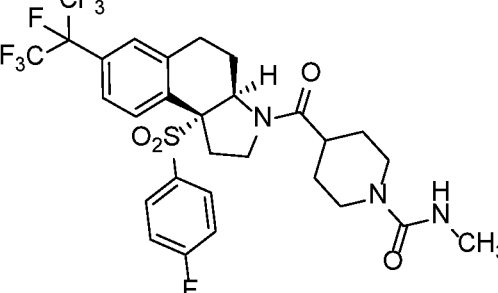
10 hydrochloride (31.1 mg, 0.047 mmol) and Et₃N (0.033 mL, 0.235 mmol) in DCM (1 mL) was treated at rt with MsCl (7.33 μL, 0.094 mmol) and stirred overnight at rt. The mixture was concentrated and the residue was purified by preparative HPLC (method E, gradient 45-100%, 19 min) to provide ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-benzo[*e*]indol-3-yl)(4-methyl-1-

15 (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
20 (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
25 starting materials and appropriate acyl chloride, sulfonyl chloride or other reagent as appropriate.

Table 17

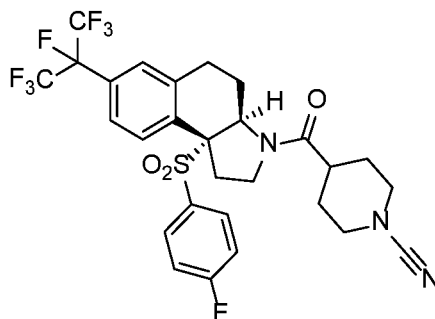
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
805		688.9 (M+H) ⁺	2.22	C
806		653.0 (M+H) ⁺	2.05	C
807		689.3 (M+H) ⁺	2.18	C
808		652.9 (M+H) ⁺	2.09	C
809		684.2 (M+H) ⁺	2.03	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
810		669.0 (M+H) ⁺	2.03	C
811		705.0 (M+H) ⁺	2.15	C
812		667.9 (M+H) ⁺	2.11	C

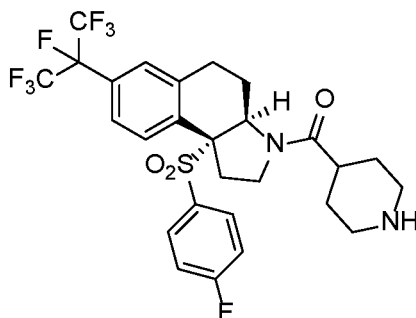
Example 813

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

5



Step A: ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(piperidin-4-yl)methanone



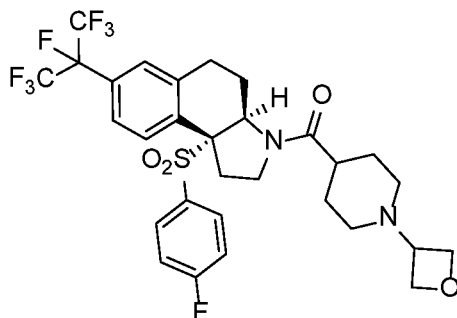
A solution of ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32; 30 mg, 0.060 mmol) in DCM (0.6 mL) was treated with 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (27.5 mg, 0.120 mmol), DIPEA (31.5 μ L, 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 Na₂SO₄ and concentrated. to provide crude ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)piperidine-1-carbonitrile

The crude ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(piperidin-4-yl)methanone from step A was dissolved in DCM (2 mL) and treated with Et₃N (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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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

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



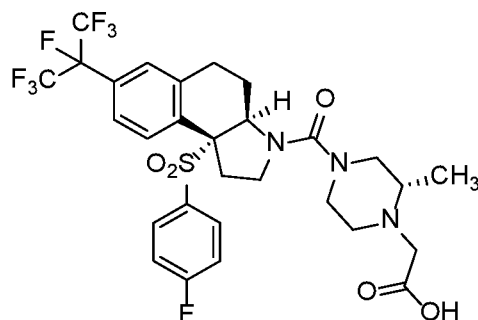
Crude ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-
 5 1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(piperidin-4-yl)methanone (Example 813
 Step A; prepared from 40 mg of Intermediate 32) was dissolved in anhydrous MeOH (2
 mL), treated with 3-oxetanone (28.9 mg, 0.400 mmol) 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
 10 concentrated. The residue was partitioned between EtOAc (20 mL) and 1.5 M aqueous
 K₂HPO₄ (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
 ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-
 hexahydro-3*H*-benzo[*e*]indol-3-yl)(1-(oxetan-3-yl)piperidin-4-yl)methanone (7.5 mg,
 15 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.

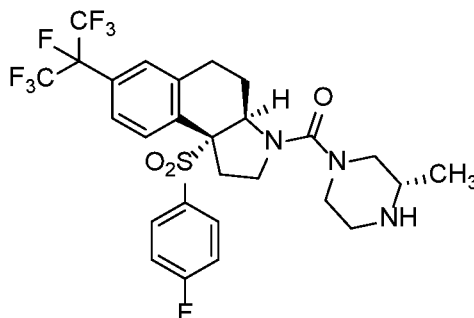
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
815		683.3 (M+H) ⁺	1.77	D
816		683.3 (M+H) ⁺	2.06	D
817		693.4 (M+H) ⁺	1.90	D

Example 818

2-((*S*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-
 5 2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylpiperazin-1-yl)acetic
acid

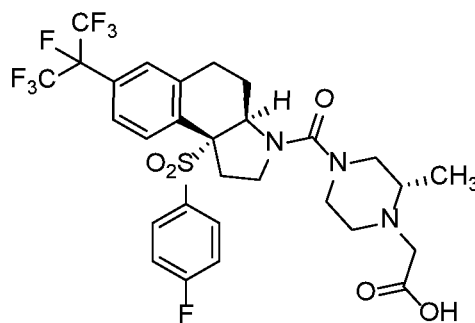


Step A: ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)((*S*)-3-methylpiperazin-1-yl)methanone



A solution of (3a*R*,9b*R*)-9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-
 5 2,3,3a,4,5,9b-hexahydro-1*H*-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
 10 saturated aqueous NaHCO₃ and brine. The combined aqueous layers were extracted with
 DCM, and the combined organic layers were dried over MgSO₄ 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 K₂HPO₄ and brine, dried over MgSO₄ and
 15 concentrated to provide crude ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-
 (perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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).

20 **Step B:** 2-((*S*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-
 2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylpiperazin-1-yl)acetic
 acid



A mixture of crude ((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)((*S*)-3-methylpiperazin-1-yl)methanone (0.06 g, 0.096 mmol), Cs₂CO₃ (0.078 g, 0.240 mmol) and *tert*-butyl

5 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 (2x) and brine. The combined aqueous layers were extracted with EtOAc, and the combined organic layers were dried over Na₂SO₄ and concentrated. The residue

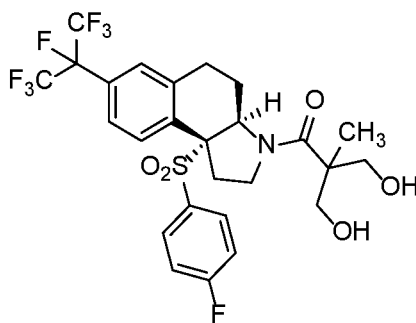
10 After 4 h, the mixture was concentrated, and the residue was purified by preparative HPLC (method E, gradient 30-70% B, 20 min) to provide 2-((*S*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylpiperazin-1-yl)acetic acid (23.6 mg, 36% yield).

LCMS *m/z* 684.1 (M+H)⁺, *t_R* 1.84 min (method C). ¹H NMR (500MHz, 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).

20

Example 819

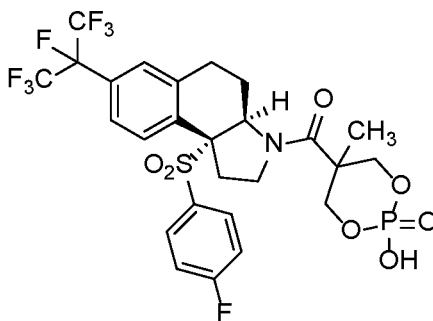
1-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one



A solution of ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-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 μ mol) and stirred at rt. After 60 min, the mixture was concentrated and the residue was dissolved in EtOAc, washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ 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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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

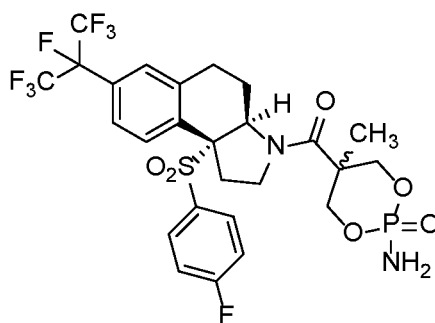
1-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(2-hydroxy-5-methyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)methanone



A solution of phosphorus oxychloride (7.33 μ L, 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-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-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 NaHCO₃ (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 ((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-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)((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)methanone

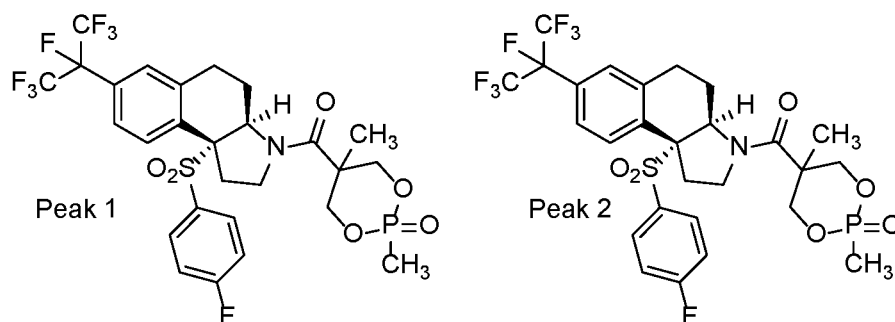


Following the procedure of Example 820 but quenching the reaction mixture into aqueous ammonia instead of aqueous NaHCO₃, 1-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-benzo[*e*]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one (Example 819) was converted into (2-amino-5-methyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)((3*aR*,9*bR*)-9*b*-((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). ¹H 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)((3a*R*,9b*R*)-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)



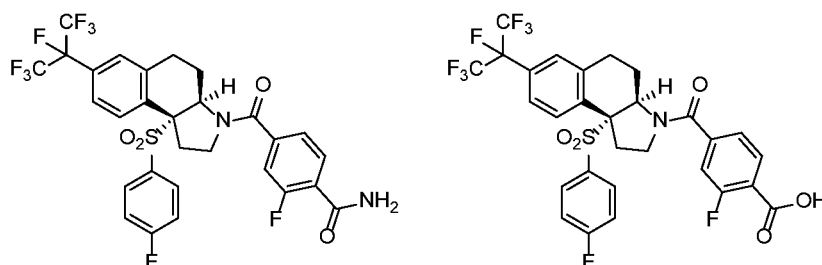
Following the procedure of Example 820 but using methylphosphonic dichloride in place of phosphorus oxychloride, 1-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-benzo[e]indol-3-yl)-3-hydroxy-2-(hydroxymethyl)-2-methylpropan-1-one (Example 819) was converted into two isomers of (2,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-5-yl)((3a*R*,9b*R*)-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). ¹H 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). ¹H 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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)benzamide and 2-fluoro-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)benzoic acid



A solution of crude 2-fluoro-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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). ¹H 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).

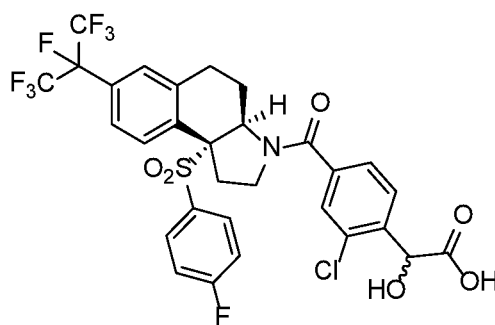
Also isolated was 2-fluoro-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)benzoic

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

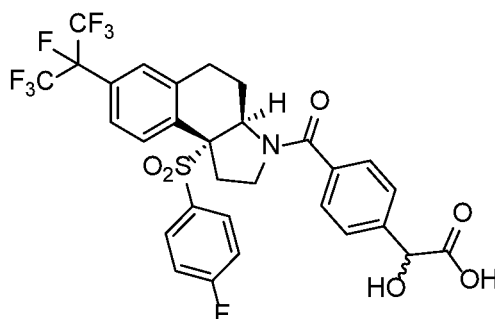


A solution of 2-chloro-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)benzaldehyde (prepared by the procedure of Example 1 Step A, from Intermediate 32 and 3-chloro-4-formylbenzoic acid; 53.3 mg, 0.08 mmol) and cyanotrimethylsilane (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 MgSO₄ 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 MgSO₄, 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-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-

2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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),
 5 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

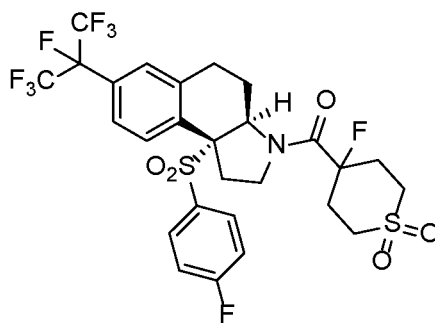
10 (*RS*)-2-(4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)phenyl)-2-hydroxyacetic acid



(*RS*)-2-(4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)phenyl)-2-hydroxyacetic acid
 15 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

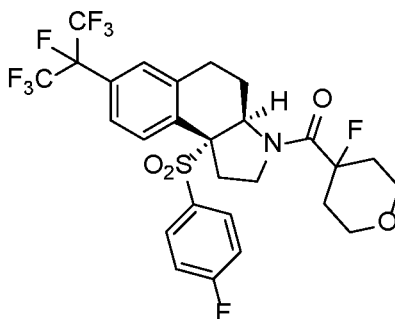
20 (4-fluoro-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)methanone



A solution of ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-4,5-dihydro-1*H*-benzo[*e*]indol-3-yl)(4-hydroxy-1,1-dioxidotetrahydro-2*H*-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 NaHCO₃ (1.5 mL) and the layers were separated. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified by preparative HPLC (method E, gradient 40-90% B, 20 min) to provide (4-fluoro-1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-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

((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)(4-fluorotetrahydro-2*H*-pyran-4-yl)methanone



20

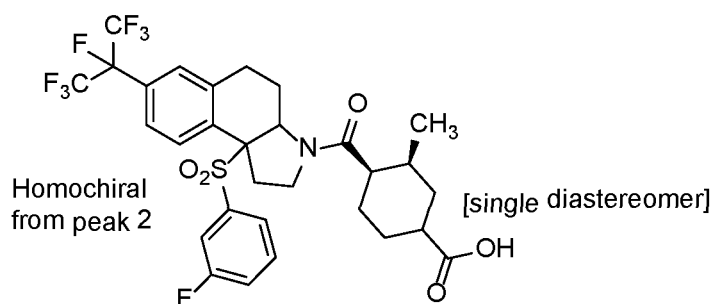
Following the procedure of Example 828, ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-

benzo[*e*]indol-3-yl)(4-hydroxytetrahydro-2*H*-pyran-4-yl)methanone (Example 471; 12.5 mg, 0.020 mmol) was converted into ((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)(4-fluorotetrahydro-2*H*-pyran-4-yl)methanone (6.9 mg, 55% yield). LCMS *m/z* 630.2

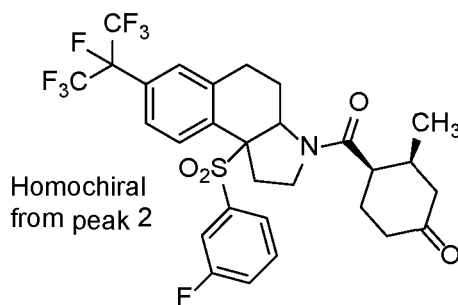
- 5 (M+H)⁺, HPLC *t_R* 2.43 min (method C). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.93 - 7.82 (m, 1H), 7.65 (d, *J*=8.0 Hz, 1H), 7.42 - 7.17 (m, 5H), 5.53 - 4.51 (m, 2H), 4.09 - 3.06 (m, 5H), 2.86 - 2.57 (m, 4H), 2.35 - 1.20 (m, 6H).

Example 830

- 10 (3*S*,4*R*)-4-(9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid



- 15 Step A: (3*S*,4*R*)-4-(9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexan-1-one

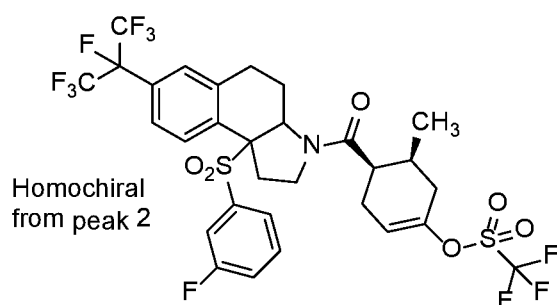


- A solution of 9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole hydrochloride (homochiral, from peak 2, Intermediate 43; 100 mg, 0.2 mmol) in DMF (1.5 mL) was treated with (1*R*,2*S*)-2-methyl-4-oxocyclohexanecarboxylic acid (*Tetrahedron* 1994, 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 (3x), 1 M aqueous

HCl and saturated aqueous NaHCO₃, dried over MgSO₄, filtered and concentrated to give crude (3*S*,4*R*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

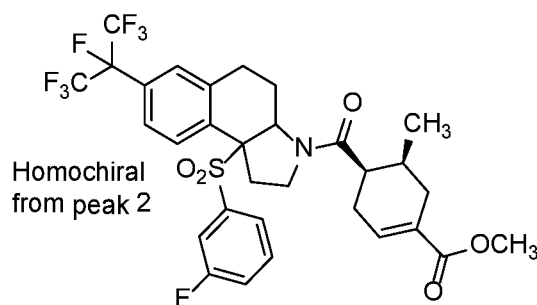
5

Step B: (4*R*,5*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate



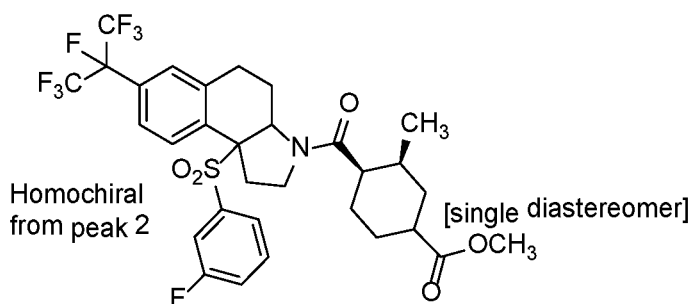
10 A solution of (3*S*,4*R*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexanone (100 mg, 0.157 mmol) in THF (2 mL) at -78 °C was treated with 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (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
15 °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 MgSO₄ and concentrated to provide crude (4*R*,5*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (82
20 mg, 68% yield). LCMS *m/z* 770.4 (M+H)⁺, HPLC *t_R* 1.21 min (method B).

Step C: methyl (4*R*,5*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-5-methylcyclohex-1-ene-1-carboxylate



A solution of (4*R*,5*S*)-4-(9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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
 5 treated with palladium(II) acetate (2.3 mg, 10.39 μ mol), 1,1'-bis(diphenylphosphino)ferrocene (5.76 mg, 10.39 μ mol), 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
 10 phase was separated, washed with brine (3x), dried over MgSO₄, filtered and concentrated. The residue was purified by preparative HPLC (method G, gradient 20-100% B, 10 min) to give methyl (4*R*,5*S*)-4-(9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-5-methylcyclohex-1-ene-1-carboxylate (70.2 mg, 99% yield). LCMS *m/z* 680.2 (M+H)⁺,
 15 HPLC *t_R* 1.14 min (method B).

Step D: methyl (3*S*,4*R*)-4-(9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate

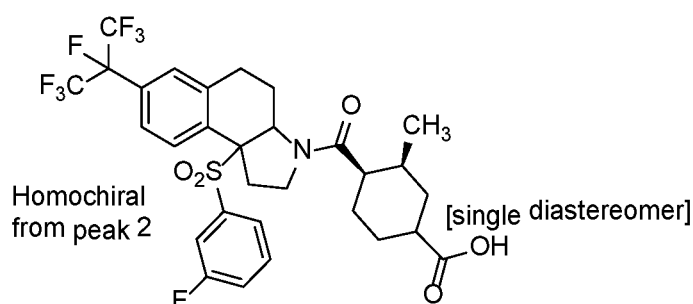


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A solution of (4*R*,5*S*)-methyl 4-((3*aR*,9*bR*)-9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-5-methylcyclohex-1-enecarboxylate (35 mg, 0.051 mmol) in DCM (1.5 mL) was treated

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
 (3*S*,4*R*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-
 5 hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylate (36.9 mg,
 hexahydro-1*H*-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).

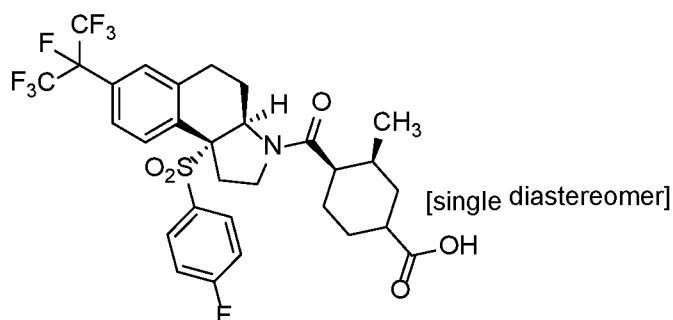
Step E: (3*S*,4*R*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-
 10 hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid



A solution of methyl (3*S*,4*R*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-
 (perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-
 methylcyclohexane-1-carboxylate (36 mg, 0.053 mmol) in THF (1.5 mL) and MeOH (0.2
 15 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 (3*S*,4*R*)-4-(9b-((3-
 fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-
 benzo[*e*]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid (9 mg, 26% yield).
 20 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
 25 - 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

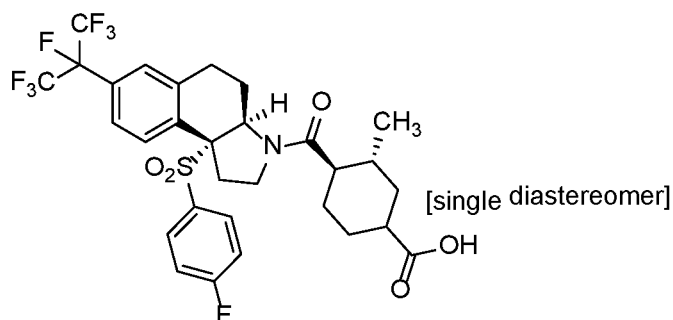
(3*S*,4*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid



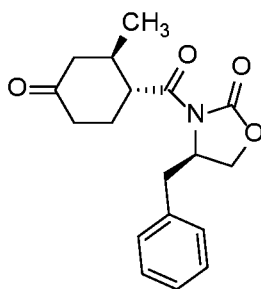
- 5 Following the procedures of Example 830, (3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole hydrochloride (Intermediate 32) was converted into a single diastereomer of (3*S*,4*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*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

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

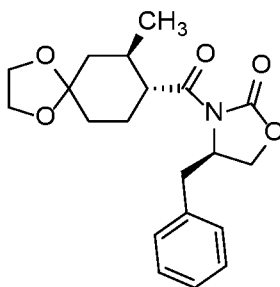


Step A. (*R*)-4-benzyl-3-((1*R*,2*R*)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one



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 MgSO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give (*R*)-4-benzyl-3-((1*R*,2*R*)-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, CDCl₃) 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).

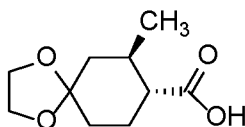
Step B. (*R*)-4-benzyl-3-((7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one



A solution of (*R*)-4-benzyl-3-((1*R*,2*R*)-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-dioxo-2,7-disila-octane (0.974 mL, 3.96 mmol), stirred for 5 min, then treated with trimethylsilyl

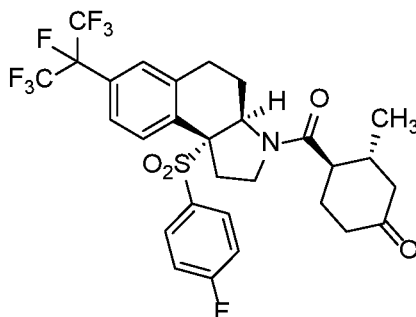
trifluoromethanesulfonate (0.059 mL, 0.317 mmol). The mixture was warmed to rt and stirred overnight. Et₃N (0.075 mL, 0.539 mmol) was added, followed by saturated aqueous NaHCO₃. The mixture was extracted with DCM, and the organic phase was dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give (*R*)-4-benzyl-3-((7*R*,8*R*)-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. (7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylic acid



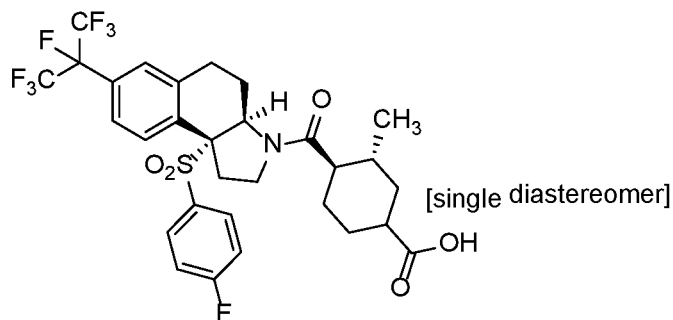
A solution of (*R*)-4-benzyl-3-((7*R*,8*R*)-7-methyl-1,4-dioxaspiro[4.5]decane-8-carbonyl)oxazolidin-2-one (750 mg, 2.087 mmol) in THF (15 mL) was cooled to 0 °C and treated with 33% aqueous hydrogen peroxide (0.853 mL, 8.35 mmol). After 5 min, 1 M aqueous LiOH (4.17 mL, 4.17 mmol) was added and the mixture was stirred for 2 h. Saturated aqueous Na₂SO₃ and saturated aqueous NaHCO₃ were added, followed by water. The mixture was partially concentrated, and the aqueous residue was extracted with DCM (3x). The aqueous phase was acidified with 6 M aqueous HCl and extracted with EtOAc. This organic phase was dried over MgSO₄, filtered and concentrated to give crude (7*R*,8*R*)-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. (3*R*,4*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexan-1-one



A solution of (3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole (Intermediate 32; 100 mg, 0.200 mmol) in DMF (1.5 mL) was treated with (7*R*,8*R*)-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 (3x), 1 M aqueous HCl and saturated aqueous NaHCO₃, dried over MgSO₄, filtered, and concentrated to give a mixture of ((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3a,4,5,9b-hexahydro-3*H*-benzo[*e*]indol-3-yl)((7*R*,8*R*)-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 (3*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 (3x), 1 M aqueous HCl and saturated aqueous NaHCO₃, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give (3*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

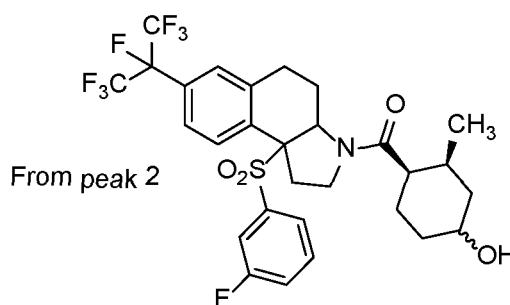
Step E: (3*R*,4*R*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexane-1-carboxylic acid



Following the procedures of Example 830 Steps B-E, (3*R*,4*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexanone was converted into a single diastereomer of (3*R*,4*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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

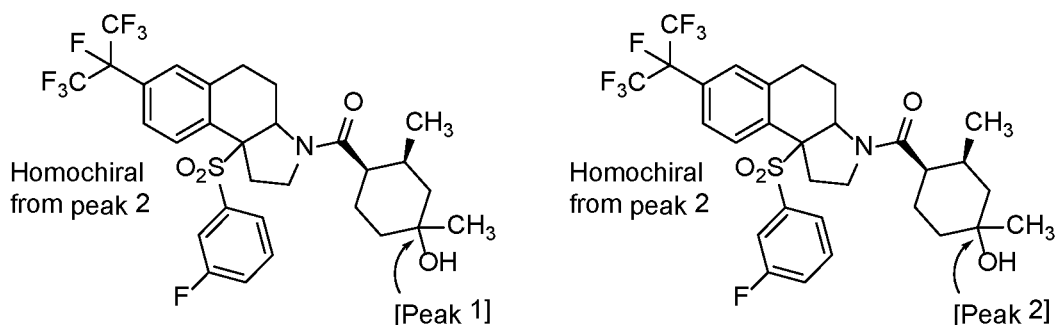
(9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)((1*R*,2*S*)-4-hydroxy-2-methylcyclohexyl)methanone



A solution of homochiral (3*S*,4*R*)-4-(9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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 NaBH₄ (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 (9*b*-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3*a*,4,5,9*b*-hexahydro-3*H*-benzo[*e*]indol-3-yl)((1*R*,2*S*)-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)

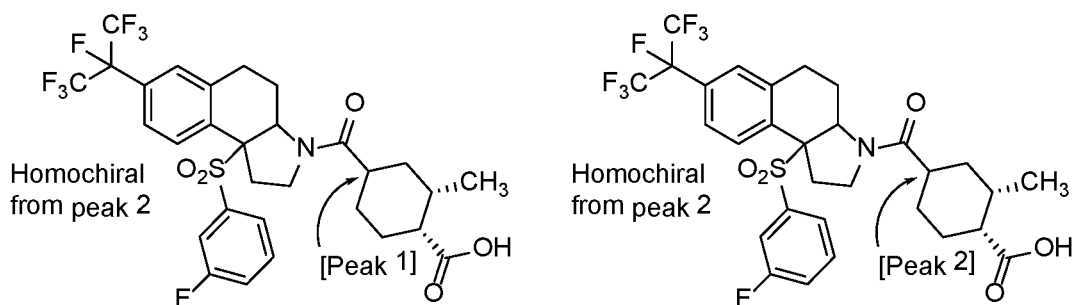


- 5 A solution of homochiral (3*S*,4*R*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-3-methylcyclohexan-1-one (Example 830 Step A; 30 mg, 0.047 mmol) in THF (1 mL) was cooled to 0 °C and treated with methylmagnesium bromide (3 M in diethyl ether; 0.024 mL, 0.071 mmol). The mixture was warmed to rt over 1 h, then was treated with saturated
- 10 aqueous NaHCO₃ and extracted with EtOAc. The organic phase was washed with brine (3x), dried over MgSO₄, 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-3*H*-
- 15 benzo[*e*]indol-3-yl)((1*R*,2*S*)-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).

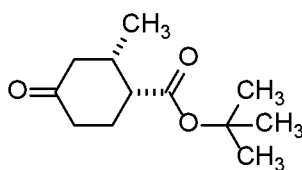
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Examples 836 and 837

(1*R*,2*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)

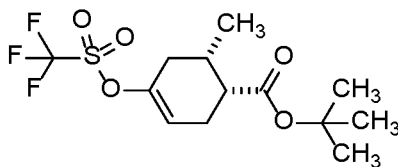


Step A: *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate



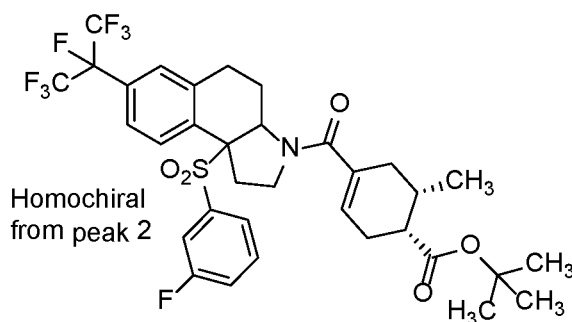
5 A solution of (1*R*,2*S*)-2-methyl-4-oxocyclohexanecarboxylic acid (*Tetrahedron* 1994, 50, 11743; 150 mg, 0.96 mmol) in *tert*-butanol (2.5 mL) and THF (2.5 mL) was treated with (*E*)-*tert*-butyl *N,N*-diisopropylcarbamimidate (385 mg, 1.921 mmol). The mixture was stirred overnight at rt, filtered and concentrated. The residue was taken up in diethyl ether, filtered, and the filtrate was concentrated. The residue was purified by
10 column chromatography on silica gel, eluting with EtOAc-hexanes (gradient from 0-10%), to give *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate (62 mg, 30% yield). LCMS *m/z* 157.1 (*M*+*H*-C₄H₈)⁺, HPLC *t_R* 0.9 min (Method B).

15 **Step B:** *tert*-butyl (1*R*,6*S*)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate



Following the procedure of Example 830 Step B, *tert*-butyl (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylate was converted into *tert*-butyl (1*R*,6*S*)-6-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-ene-1-carboxylate in 99% yield. LCMS *m/z*
20 367.1 (*M*+*Na*)⁺, HPLC *t_R* 1.15 min (method B).

Step C: *tert*-butyl (1*R*,6*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-6-methylcyclohex-3-ene-1-carboxylate

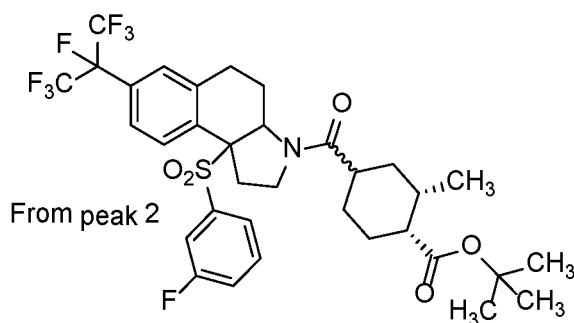


5

A solution of (1*R*,6*S*)-*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-1*H*-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 (3x), dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with EtOAc-hexanes, to give homochiral *tert*-butyl (1*R*,6*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

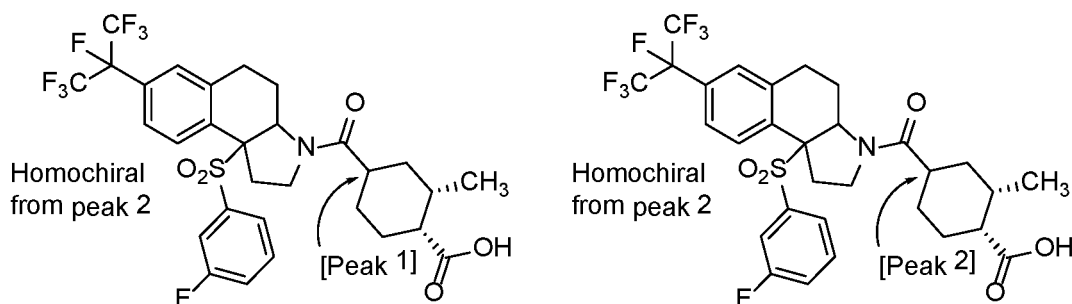
20

Step D: *tert*-butyl (1*R*,2*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate (mixture of diastereomers)



A solution of *tert*-butyl (1*R*,6*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 μ mol) and stirred at rt overnight under a hydrogen atmosphere (balloon pressure). The mixture was filtered and concentrated to provide *tert*-butyl (1*R*,2*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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: (1*R*,2*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)

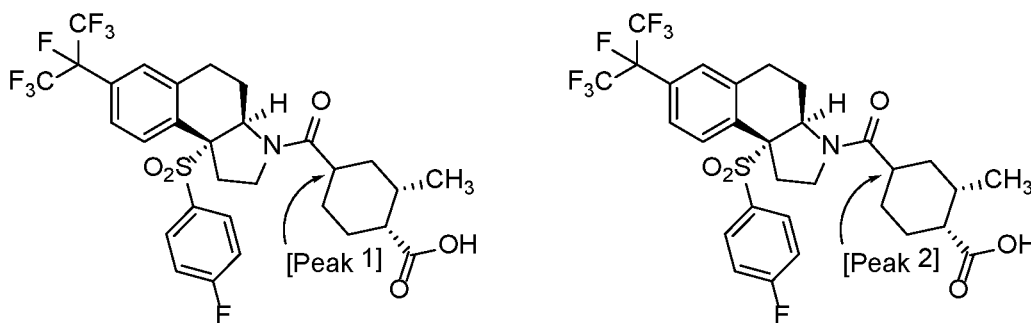


A solution of *tert*-butyl (1*R*,2*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylate (25 mg, 0.035 mmol) in DCM (1mL) was treated with TFA (3 mL) and stirred at rt for 30 min. The mixture was concentrated and the residue was purified by preparative HPLC (method G, gradient 20-100% B, 10 min) to provide two homochiral diastereomers of (1*R*,2*S*)-4-(9b-((3-fluorophenyl)sulfonyl)-7-

(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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). ¹H 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). ¹H 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

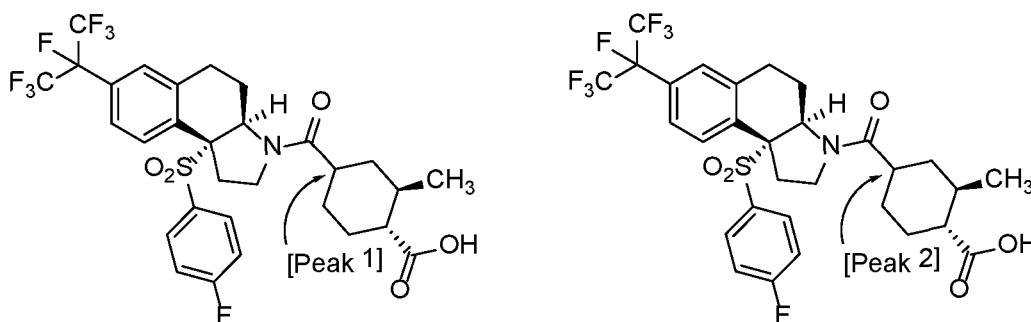
(1*R*,2*S*)-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



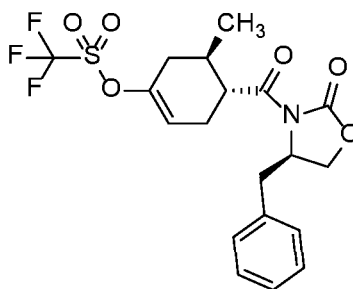
The two homochiral diastereomers of (1*R*,2*S*)-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid were prepared using the procedures of Examples 836 and 837, using Intermediate 32 in 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

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

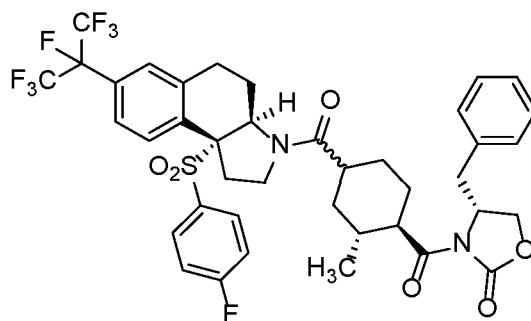


Step A. (4*R*,5*R*)-4-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate



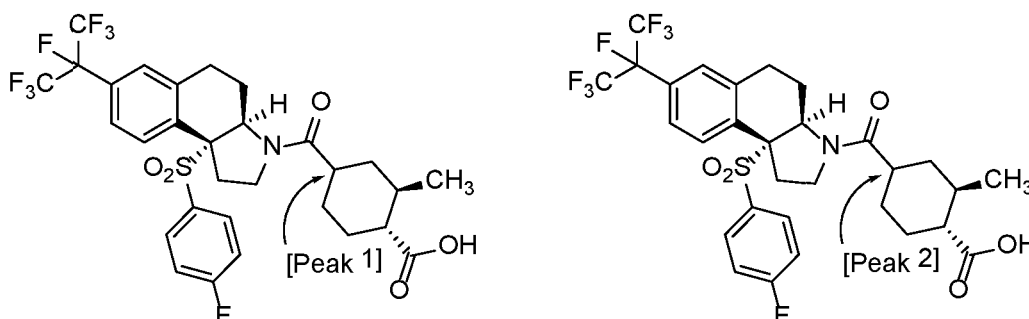
10 Using the procedure of Example 830 Step B, (*R*)-4-benzyl-3-((1*R*,2*R*)-2-methyl-4-oxocyclohexane-1-carbonyl)oxazolidin-2-one (Example 832 Step A) was converted into crude (4*R*,5*R*)-4-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate in 75% yield. This material was used without purification.

15 **Step B:** (4*R*)-4-benzyl-3-((1*R*,2*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one



Using the procedures of Examples 836 and 837, Steps C and D, (4*R*,5*R*)-4-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-5-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and Intermediate 32 were converted into (4*R*)-4-benzyl-3-((1*R*,2*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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: (1*R*,2*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid (2 single diastereomers)



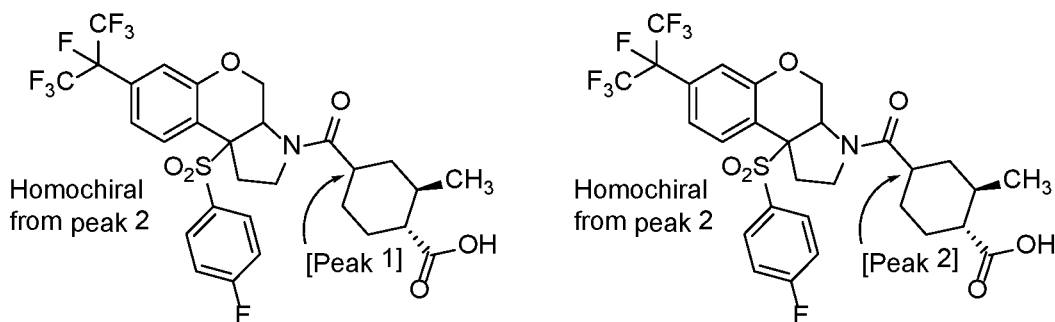
Using the procedure of Example 832 Step C, followed by preparative HPLC separation, the mixture of diastereomers of (4*R*)-4-benzyl-3-((1*R*,2*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)-2-methylcyclohexane-1-carbonyl)oxazolidin-2-one was converted into the two homochiral diastereomers of (1*R*,2*R*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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

(1*R*,2*R*)-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

5

(2 single diastereomers)



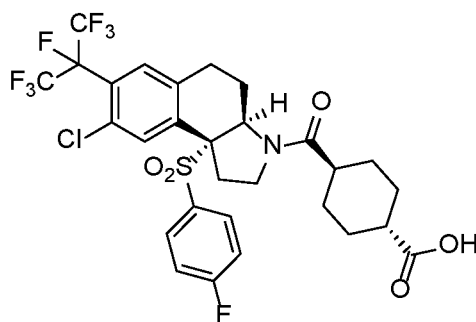
Two homochiral diastereomers of (1*R*,2*R*)-4-(9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-1,2,3,3a,4,9b-hexahydrochromeno[3,4-*b*]pyrrole-3-carbonyl)-2-methylcyclohexane-1-carboxylic acid were prepared using the procedures of Examples 840 and 841 but using Intermediate 38 instead of Intermediate 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).

10

Example 844

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(1*R*,4*r*)-4-((3a*R*,9b*R*)-8-chloro-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



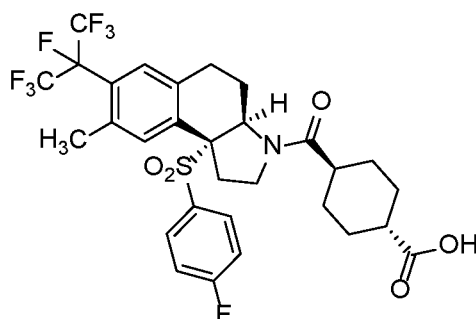
A solution of (1*R*,4*r*)-4-((3a*R*,9b*R*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid (Example 1; 124 mg, 0.190 mmol) in concentrated sulfuric acid (1 mL) was treated with *N*-chlorosuccinimide (50.7 mg, 0.379 mmol). The mixture was stirred at rt overnight, then was heated at 50 °C for 7 h. The

20

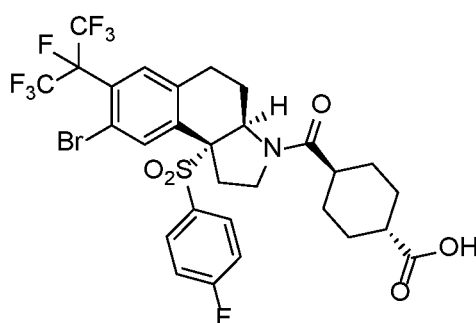
mixture was cooled to -78 °C and treated dropwise with water. The mixture was warmed to rt and extracted with EtOAc. The organic phase was washed sequentially with water and brine, dried and concentrated. The residue was purified by preparative HPLC (method F, gradient 45-90% B, 27 min) to provide (1*R*,4*r*)-4-((3*aR*,9*bR*)-8-chloro-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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

(1*R*,4*r*)-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-8-methyl-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



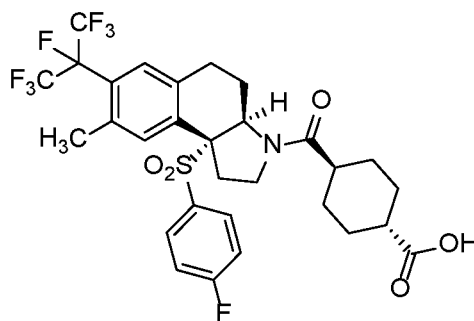
Step A: (1*R*,4*r*)-4-((3*aR*,9*bR*)-8-bromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



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 (1*R*,4*r*)-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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 (1*R*,4*r*)-4-
 5 ((3*aR*,9*bR*)-8-bromo-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-
 2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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, CDCl₃) 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
 10 (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: (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-8-methyl-7-
 (perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-
 15 carbonyl)cyclohexane-1-carboxylic acid

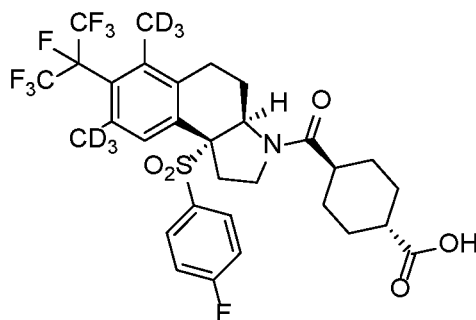


A solution of the impure (1*R*,4*r*)-4-((3*aR*,9*bR*)-8-bromo-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-
 benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid from Step A (22 mg, 0.030
 20 mmol) and iron(III) acetylacetonate (2.121 mg, 6.01 μmol) in 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
 25 provide (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-8-methyl-7-
 (perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-

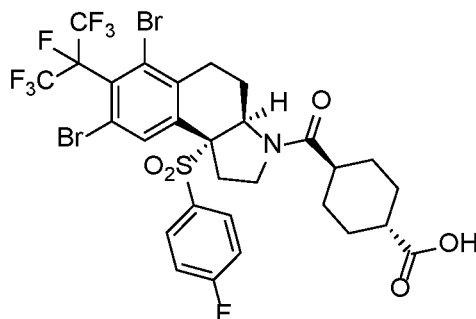
carbonyl)cyclohexane-1-carboxylic acid (3.6 mg, 18% yield). LCMS m/z 668.0 (M+H)⁺, HPLC t_R 1.96 min (method C).

Example 846

- 5 (1*R*,4*r*)-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-6,8-dimethyl(*d*₆)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



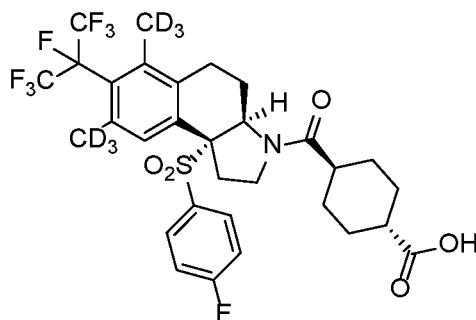
- 10 **Step A:** (1*R*,4*r*)-4-((3*aR*,9*bR*)-6,8-dibromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid



- A mixture of (1*R*,4*r*)-4-((3*aR*,9*bR*)-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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 (1*R*,4*r*)-4-((3*aR*,9*bR*)-

6,8-dibromo-9b-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3a,4,5,9b-hexahydro-1*H*-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).

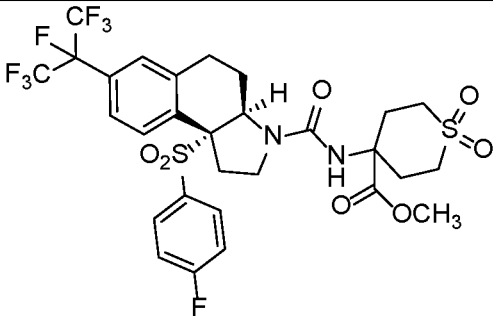
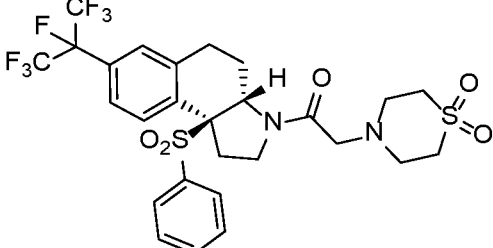
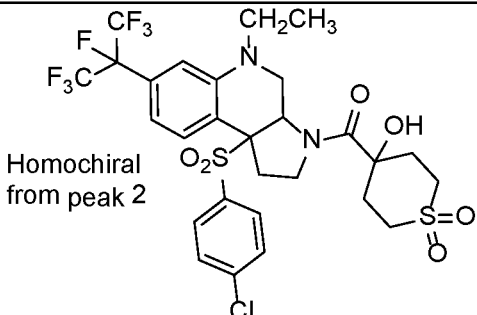
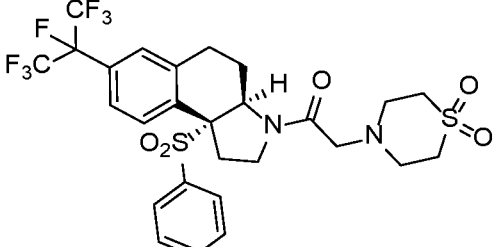
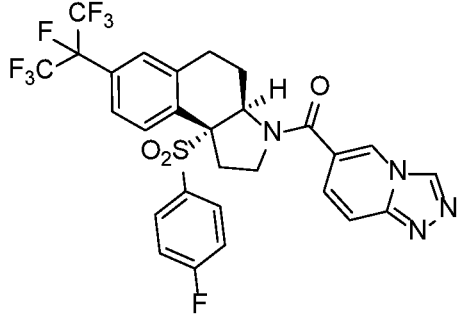
5 **Step B:** (1*R*,4*r*)-4-(((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-6,8-dimethyl(*d*₆)-7-
(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-
carbonyl)cyclohexane-1-carboxylic acid

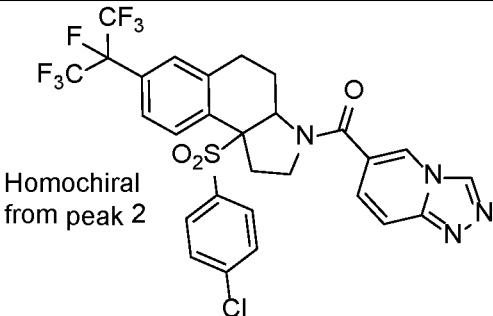
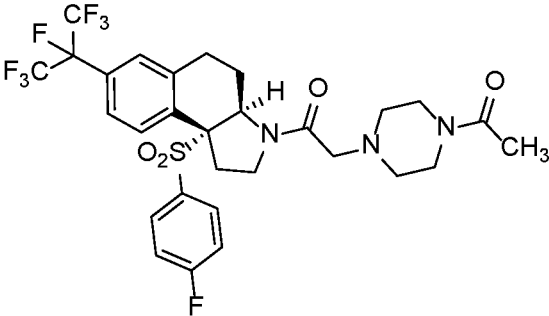
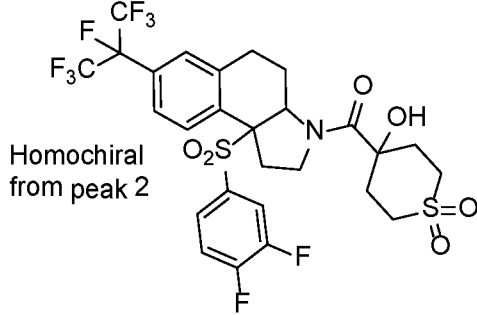
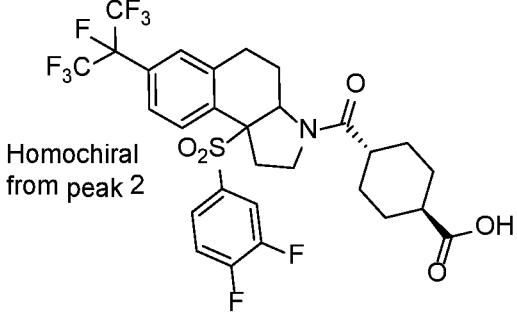
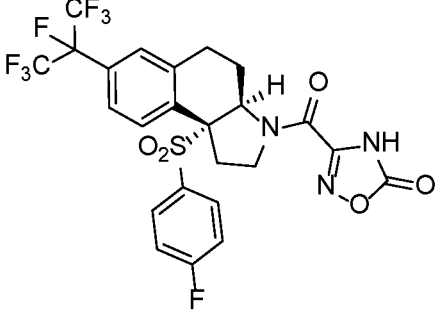


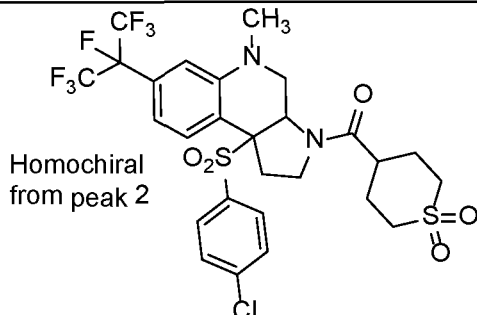
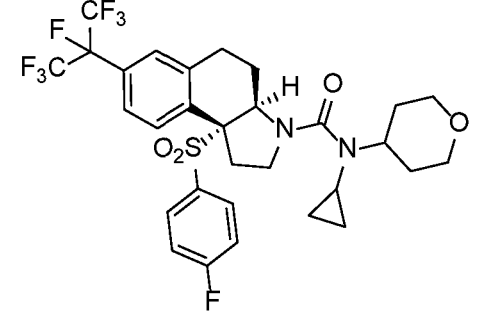
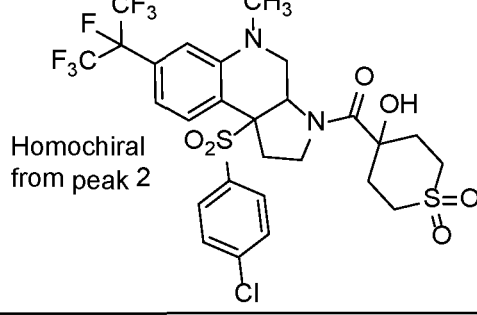
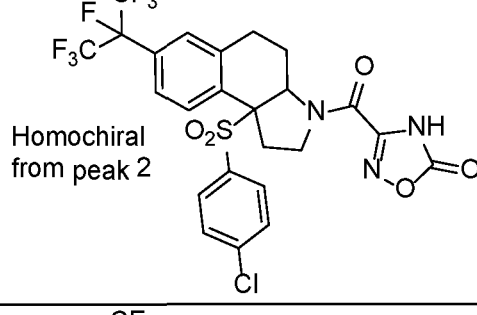
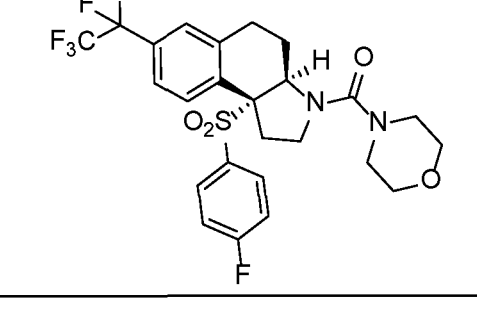
A solution of (1*R*,4*r*)-4-((3*aR*,9*bR*)-8-bromo-9*b*-((4-fluorophenyl)sulfonyl)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-benzo[*e*]indole-3-carbonyl)cyclohexane-1-carboxylic acid (32 mg, 0.039 mmol) and iron(III) acetylacetonate (2.79 mg, 7.89 μ mol) in THF (1 mL) was subjected to 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 (1*R*,4*r*)-4-((3*aR*,9*bR*)-9*b*-((4-fluorophenyl)sulfonyl)-6,8-dimethyl(*d*₆)-7-(perfluoropropan-2-yl)-2,3,3*a*,4,5,9*b*-hexahydro-1*H*-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).

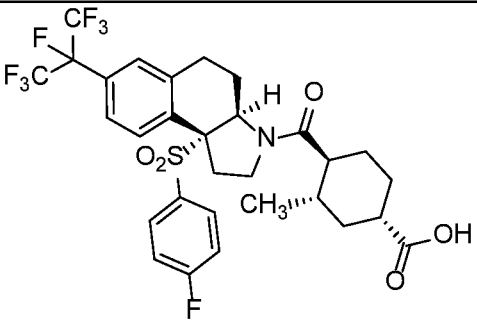
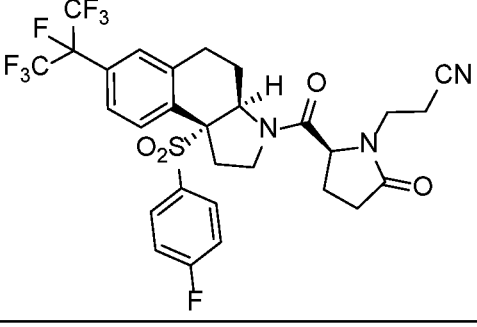
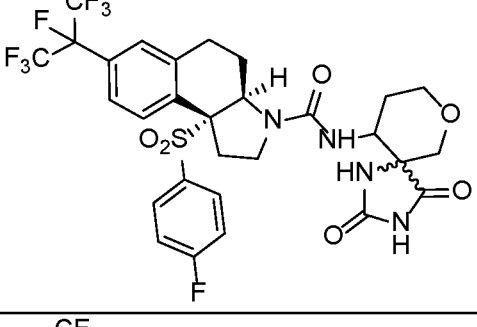
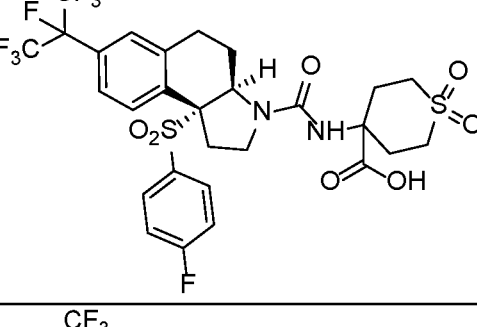
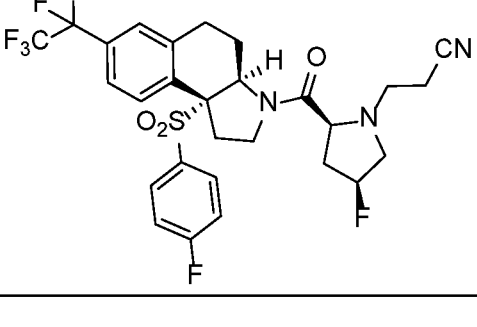
Additional examples prepared according to the procedures used to prepare Examples 1-846 or similar procedures are shown in Table 19.

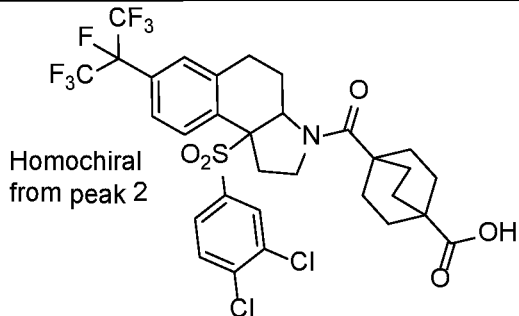
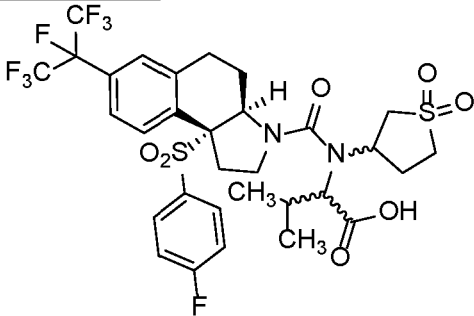
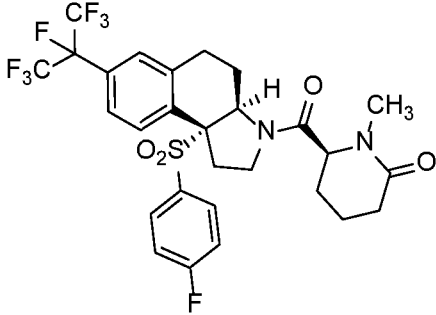
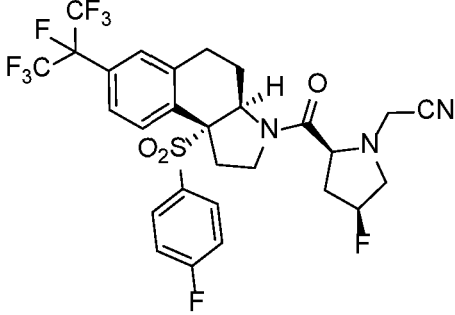
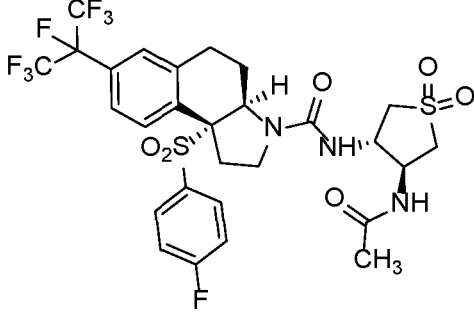
Table 19

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
851		645.3 (M+H) ⁺	0.97	B

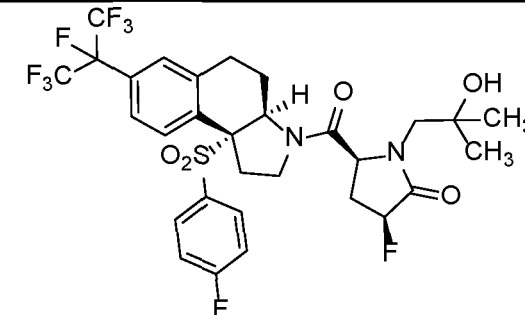
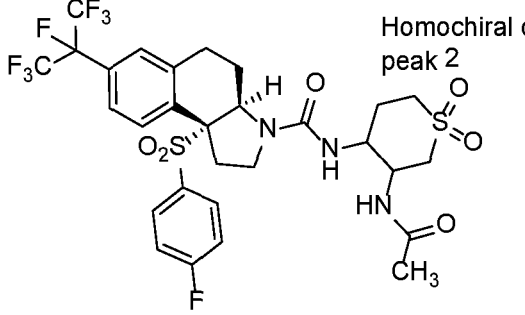
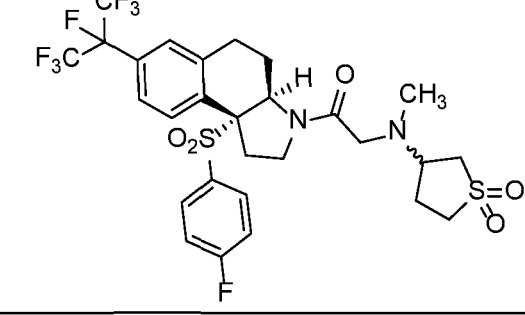
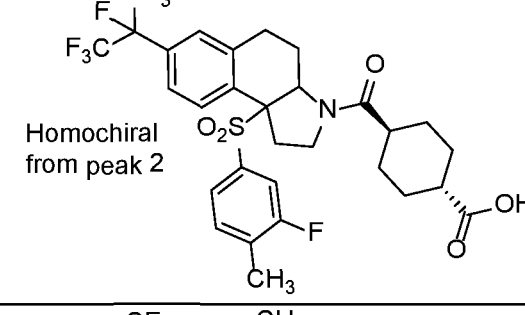
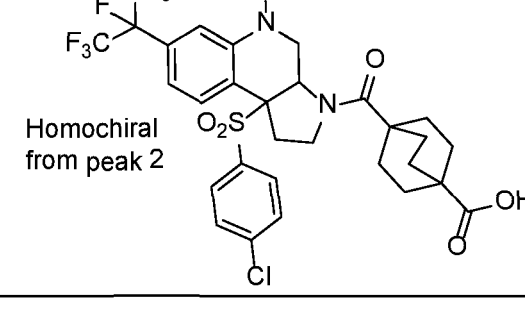
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
852	 Homochiral from peak 2	661.1 (M+H) ⁺	1.00	B
853		668.3 (M+H) ⁺	0.85	B
854	 Homochiral from peak 2	693.3 (M+H) ⁺	2.17	C
855	 Homochiral from peak 2	672.1 (M+H) ⁺	2.02	C
856		612.1 (M+H) ⁺	2.26	D

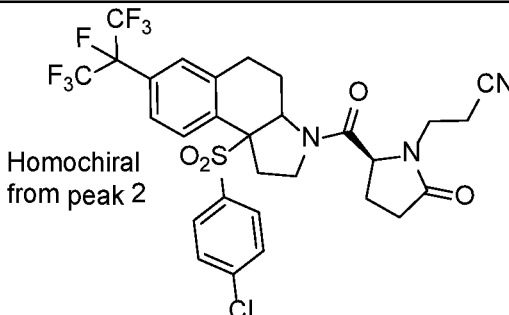
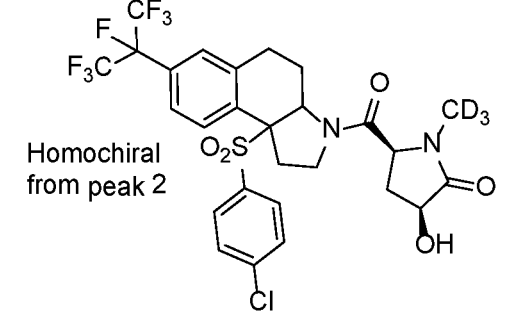
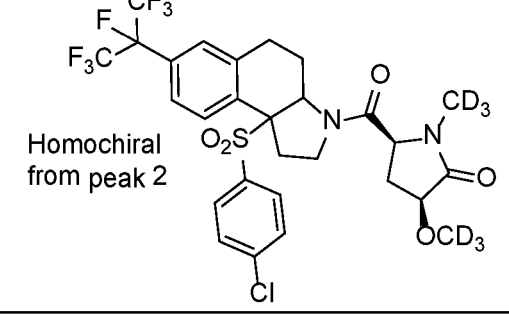
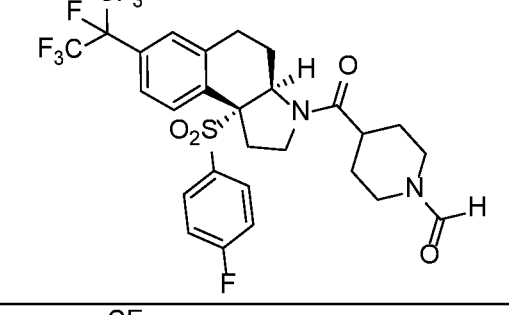
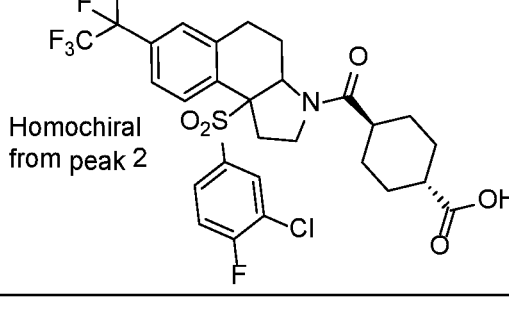
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
857	 Homochiral from peak 2	691.1 (M+H) ⁺	2.31	C
858		667.0 (M+H) ⁺	2.42	C
859	 Homochiral from peak 2	707.0 (M+H) ⁺	2.29	C
860	 Homochiral from peak 2	628.1 (M+H) ⁺	1.88	C
861		612.8 (M+H) ⁺	2.25	C

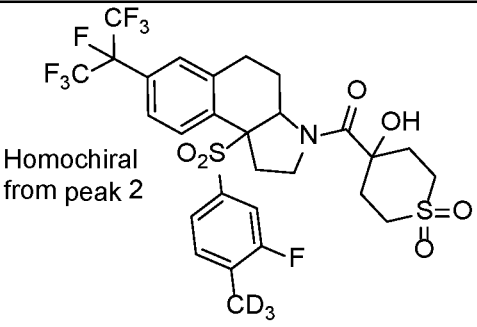
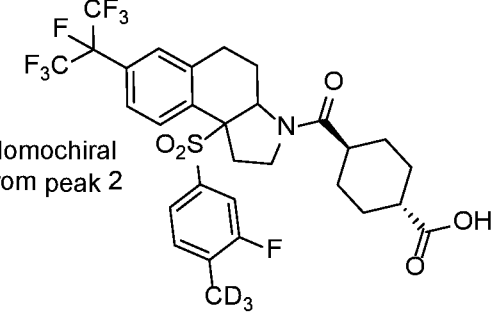
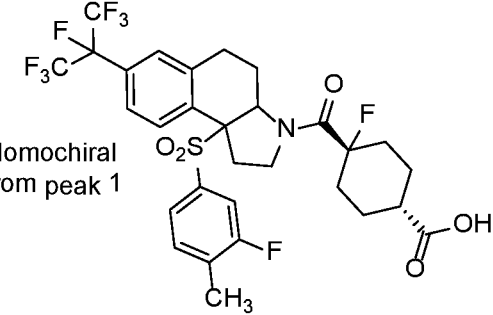
Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
862		668.2 (M+H) ⁺	1.94	C
863		663.9 (M+H) ⁺	2.14	C
864		711.3 (M+H) ⁺	1.92	C
865		719.3 (M+H) ⁺	1.68	C
866		667.9 (M+H) ⁺	2.29	C

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
871		718.1 (M+H) ⁺	2.01	C

Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (min)	HPLC method
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
875		704.1 (M+H) ⁺	2.17	C
876	Homochiral cis peak 1	732.2 (M+H) ⁺	2.00	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
877		701.1 (M+H) ⁺	2.20	C
878		732.1 (M+H) ⁺	1.99	C
879		689.1 (M+H) ⁺	0.88	B
880		668.1 (M+H) ⁺	2.07	C
881		711.2	2.17	C

Ex. #	Structure	LCMS m/z observed	HPLC t_R (min)	HPLC method
882	 Homochiral from peak 2	680.0	2.28	C
883	 Homochiral from peak 2	660.2	2.11	C
884	 Homochiral from peak 2	677.1	2.65	C
885	 Homochiral from peak 2	639.2	2.08	C
886	 Homochiral from peak 2	688.1	1.97	C

Ex. #	Structure	LCMS <i>m/z</i> observed	HPLC <i>t_R</i> (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 ROR γ SPA binding assay

The binding of potential ligands to ROR γ is measured by competition with [^3H] 25-hydroxycholesterol (Perkin Elmer NET674250UC) using a scintillation proximity assay (SPA). The ligand binding domain of human ROR γ (A262-S507) with an N-terminal His tag is expressed in *E. coli* and purified using nickel affinity chromatography. 15 μg /well ROR γ (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). 10nM of [^3H] 25-hydroxycholesterol is then added, and the reaction is incubated for 10min. 10mg/mL of Copper-His Tag-PVT beads (Perkin Elmer cat # RPNQ0095) are

added, and the mixture is incubated for 60min. 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).

- 5 After correcting for non-specific binding, IC₅₀ values were determined. The IC₅₀ value is defined as the concentration of test compound needed to reduce [³H] 25-hydroxycholesterol specific binding by 50% and is calculated using the four parameter logistic equation to fit the normalized data.

10 IC₅₀ values for compounds of the invention in the ROR γ binding assay are provided below.

Ex. No.	ROR γ Binding IC ₅₀ , μ M
1	0.070
2	0.089
3	0.065
4	0.107
5	0.240
6	0.257
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
781	0.913
782	0.148
783	0.507
784	0.154
785	3.199
786	1.441
787	4.311
788	0.098

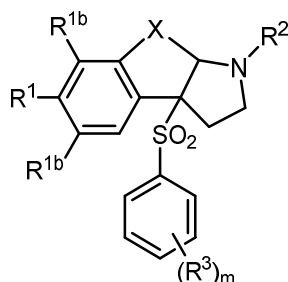
Ex. No.	ROR γ Binding IC ₅₀ , μ M
789	1.866
790	0.041
791	0.078
792	0.186
793	0.398
794	0.566
795	2.382
796	0.100
797	0.136
798	0.167
799	0.151
800	0.612
801	0.023
802	0.045
803	0.073
804	0.088
805	0.088
806	0.145
807	0.283
808	0.107
809	0.025
810	0.050
811	0.023
812	0.195
813	0.115
814	0.125
815	0.018
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

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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
858	0.305
859	0.114
860	6.301
861	0.296
862	0.158
863	0.079
864	0.131

Ex. No.	ROR γ Binding IC ₅₀ , μ M
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

Claims

1. A compound of the formula



wherein

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

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

R^{1a} is, independently at each occurrence, hydrogen, $=\text{O}$, halo, CF_3 , OCF_3 , CN, NO_2 , $-(\text{CR}^{2e}\text{R}^{2f})_r$ - OR^b , $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{S}(\text{O})_p\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{OC}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{NR}^b\text{C}(\text{O})\text{R}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{NR}^b\text{C}(\text{O})\text{OR}^c$, $-\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-\text{S}(\text{O})_p\text{NR}^{11}\text{R}^{11}$, $-\text{NR}^b\text{S}(\text{O})_p\text{R}^c$, 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 , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -3-14 membered carbocycle substituted with 0-3 R^a , or $-(\text{CR}^{2e}\text{R}^{2f})_r$ -5-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, and $\text{S}(\text{O})_p$ 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, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{R}^{2d}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{OR}^{2b}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{S}(\text{O})_2\text{R}^{2c}$, C_{1-6} alkyl substituted with 0-3 R^{2a} , C_{2-6} alkenyl substituted with 0-3 R^{2a} , $-(\text{CR}^{2e}\text{R}^{2f})_r$ -3-10 membered carbocycle substituted with 0-3 R^a , or $-(\text{CR}^{2e}\text{R}^{2f})_r$ -4-7 membered heterocycle comprising carbon atoms, and 1-4 heteroatoms selected from the group consisting of N, O, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_p$ substituted with 0-4 R^a ;

R^{2a} is, independently at each occurrence, hydrogen, $=\text{O}$, halo, OCF_3 , CN, NO_2 , $-(\text{CR}^{2e}\text{R}^{2f})_r$ - OR^b , $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{S}(\text{O})_p\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{OR}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{OC}(\text{O})\text{R}^b$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{OC}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{OC}(\text{O})\text{OR}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{NR}^b\text{C}(\text{O})\text{R}^c$, $-(\text{CR}^{2e}\text{R}^{2f})_r$ - $\text{NR}^b\text{C}(\text{O})\text{OR}^c$, $-\text{NR}^b\text{C}(\text{O})\text{NR}^{11}\text{R}^{11}$, $-\text{S}(\text{O})_p\text{NR}^{11}\text{R}^{11}$, $-\text{NR}^b\text{S}(\text{O})_p\text{R}^c$, C_{1-6} alkyl substituted with 0-3 R^a , C_{1-6}

haloalkyl, C₂₋₆ alkenyl substituted with 0-3 R^a, C₂₋₆ 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, CF₃, -(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})_qNR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C(O)NR¹¹R¹¹, -(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)NR¹¹R¹¹, -(CR^{2e}R^{2f})_qS(O)₂NR¹¹R¹¹, -(CR^{2e}R^{2f})_qNR^bS(O)₂R^c, C₁₋₆ alkyl substituted with 0-2 R^a, C₁₋₆ 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, C₁₋₆ alkyl substituted with 0-3 R^a, C₂₋₆ alkenyl substituted with 0-3 R^a, C₃₋₁₀ cycloalkyl substituted with 0-3 R^a, C₆₋₁₀ 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, C₁₋₆ alkyl substituted with 0-2 R^d, C₁₋₆ haloalkyl, C(O)NR¹¹R¹¹, -(CR^{2e}R^{2f})_r-C₃₋₁₀ 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 C₁₋₆ alkyl;

R³ is, independently at each occurrence, hydrogen, halo, N₃, CN, -(CR^{2e}R^{2f})_r-OR^{3b}, -(CR^{2e}R^{2f})_r-NR¹¹R¹¹, C₁₋₆ alkyl substituted with 0-3 R^{3a}, C₃₋₁₀ 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 R³ 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 , $-(CR^{2e}R^{2f})_qOR^b$, $-(CR^{2e}R^{2f})_qS(O)_pR^b$, $-(CR^{2e}R^{2f})_r-C(O)R^{1d}$, $-(CR^{2e}R^{2f})_r-C(O)OR^b$, $-(CR^{2e}R^{2f})_qOC(O)R^b$, $-(CR^{2e}R^{2f})_qNR^{11}R^{11}$, $-(CR^{2e}R^{2f})_r-C(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bC(O)R^{1c}$, $-(CR^{2e}R^{2f})_qNR^bC(O)OR^c$, $-(CR^{2e}R^{2f})_qNR^bC(O)NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qS(O)_2NR^{11}R^{11}$, $-(CR^{2e}R^{2f})_qNR^bS(O)_2R^c$, 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 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, C₁₋₆ alkyl substituted with 0-3 R^d , C₁₋₆ haloalkyl, C₃₋₆ 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, C₁₋₆ alkyl substituted with 0-3 R^f , $-(CR^{2e}R^{2f})_r$ -C₃₋₆ 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, OCF₃, CF₃, CN, NO₂, -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, CO₂H, CO₂R^c, -NR^eSO₂R^c, SO₂R^c, C₁₋₆ alkyl substituted with 0-3 R^f , C₃₋₆ 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, C₁₋₆ alkyl, C₃₋₆ 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, NH₂, NH(C₁₋₆ alkyl), N(C₁₋₆ alkyl)₂, SO₂(C₁₋₆ alkyl), CO₂H, CO₂(C₁₋₆ alkyl), OH, C₃₋₆ cycloalkyl, CF₃, O(C₁₋₆ 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 C₃₋₆ cycloalkyl, each group optionally substituted with halo, CN, CF₃, C₁₋₆ alkyl or O(C₁₋₆ alkyl);

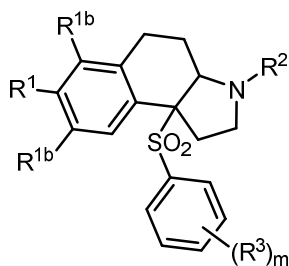
m is 0, 1, 2 or 3

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

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

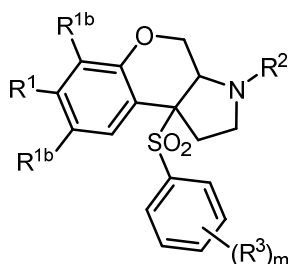
or a stereoisomer or pharmaceutically-acceptable salt thereof.

2. The compound according to claim 1 of the formula



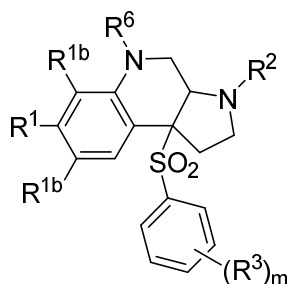
or a stereoisomer or pharmaceutically-acceptable salt thereof.

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} , $-NH_2$, $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, 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.

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_{1-4} 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} , $-NH_2$, $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, 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.

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 ;

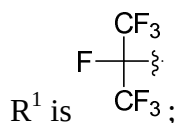
R^{2b} is hydrogen, C_{1-6} alkyl substituted with 0-2 R^a , C_{3-6} cycloalkyl substituted with 0-3 R^a , $-(CR^{2e}R^{2f})_{r-5-7}$ membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from the group consisting of N, O, $P(=O)$ and $S(O)_p$ substituted with 0-4 R^a , or $-(CR^{2e}R^{2f})_{r-phenyl}$ 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^{1b} is, independently at each occurrence, hydrogen, CD_3 , halo, CF_3 , and $\text{C}_1\text{-C}_4$ alkyl;

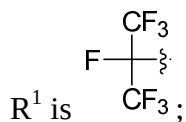
R^2 is $-\text{C}(\text{O})\text{R}^{2d}$;

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, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_2$, 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^{1b} is, independently at each occurrence, hydrogen, CD_3 , halo, CF_3 , and $\text{C}_1\text{-C}_4$ alkyl;

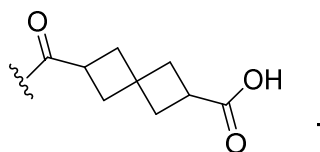
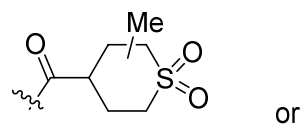
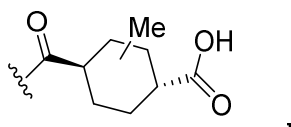
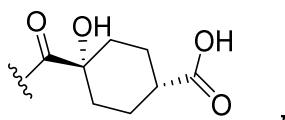
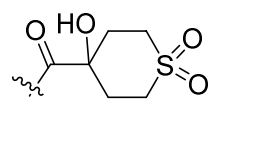
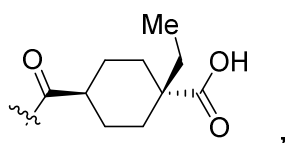
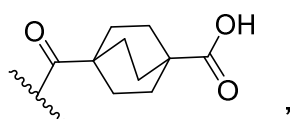
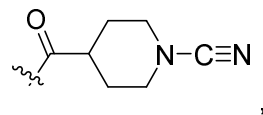
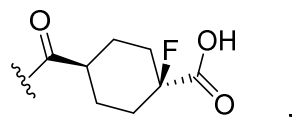
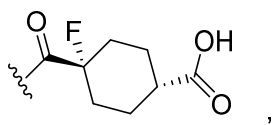
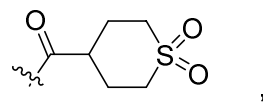
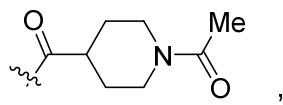
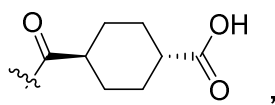
R^2 is $-\text{C}(\text{O})\text{R}^{2d}$;

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, $\text{P}(=\text{O})$ and $\text{S}(\text{O})_2$, substituted with 0-4 R^a ;

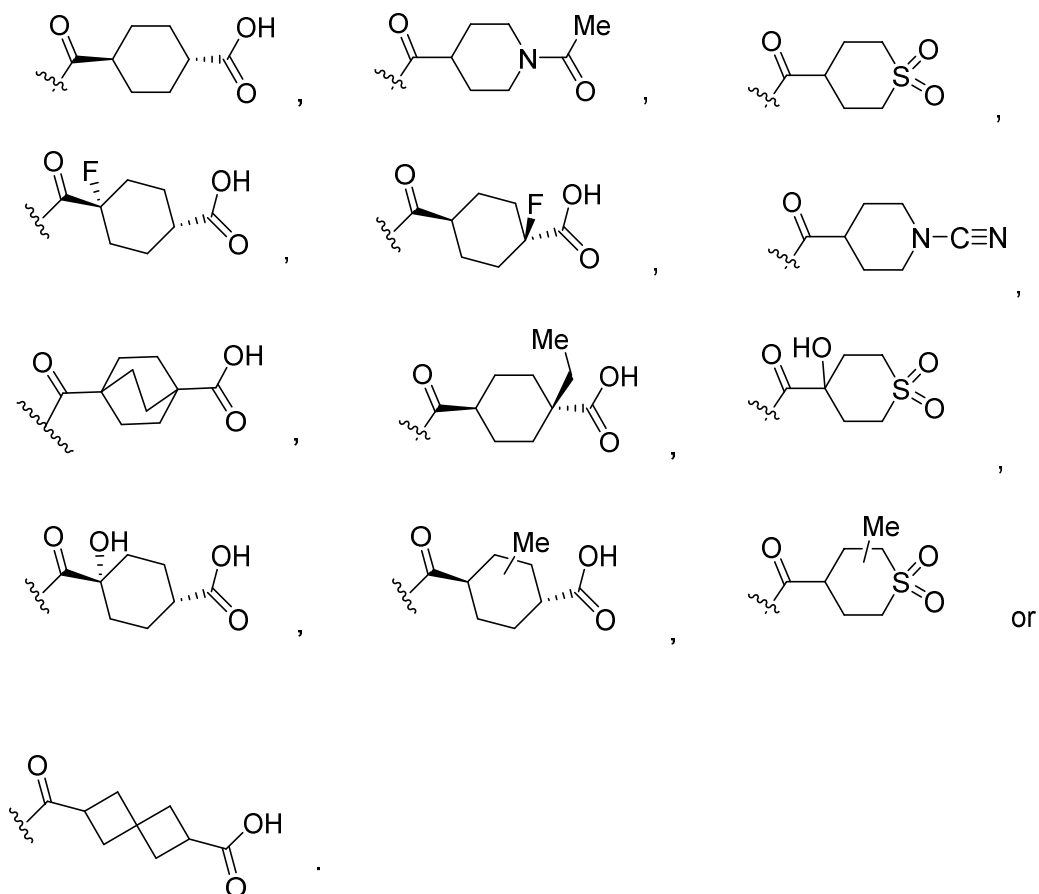
R^3 is F, Cl, cyclopropyl or methyl;

or a stereoisomer or pharmaceutically-acceptable salt thereof.

11. The compound according to claim 9 wherein R^2 is

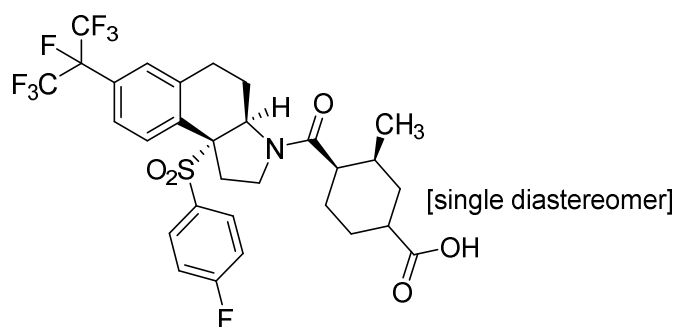


12. The compound according to claim 10 wherein R^2 is



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



or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

15. A pharmaceutical composition comprising the compound of claim 14 and a pharmaceutically acceptable carrier.