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[54]	Title:	COMPOUNDS THAT ARE S1P MODULATING AGENTS AND/OR ATX MODULATING AGENTS		
[71]	Applicant(s):	BIOGEN MA INC		
[72]	Inventor(s):	GUCKIAN KEVIN KUMARAVEL GNANASAMBANDAM MA BIN MI SHA PENG HAIRUO SHAO ZHAOHUI SUN LIHONG TAVERAS ARTHUR XIN ZHILI ZHANG LEI		
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[51]	International Class 8:	A61K 31/54 20060101AFI20180528BHPH;		
[57]	Abstract:	Compounds of formula (I) can modulate the activity of one or more S1P receptors and/or the activity of autotaxin (ATX).		

N-($C_{1\text{-}4}$alkyl)carbamoyl, N,N-di-($C_{1\text{-}4}$alkyl)carbamoyl, $C_{1\text{-}4}$alkylamido, $C_{1\text{-}4}$alkylsulfonyl, $C_{1\text{-}4}$alkylsulfonamido, sulfamoyl, N-$C_{1\text{-}4}$alkylsulfamoyl, and N,N-($C_{1\text{-}4}$dialkyl)-sulfamoyl.

R^{17} and R^{18}, for each occurrence, can each independently be hydrogen, a halo, or a $C_{1\text{-}4}$haloalkyl.

R^c is hydrogen or a $C_{1\text{-}4}$alkyl.

i can be an integer from 0 to 6.

n can be an integer from 1 to 6.

m can be 0 or 1, provided that when m is 0, B comprises at least one nitrogen.

p can be 0 or an integer from 1 to 6.

q can be 0, 1, 2, 3, or 4.

The compound is not 2-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)octahydrocyclopenta[c]pyrrole- 3a-carboxylic acid or 6-phenoxy-2-(2-(4-phenylpiperidin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol.

In some embodiments, q is 1 and R^6 is t-butyl.

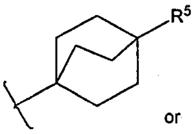
In some embodiments, q is 1 and R^6 is methyl, ethyl or isopropyl.

In some embodiments, R^6 is trifluoromethyl, difluoromethyl or monofluoromethyl.

In some embodiments, B can be selected from the group consisting of 9-azabicyclo[3.3.1]nonanyl, 8-azabicyclo[3.2.1]octanyl, decahydroisoquinolinyl, 2-azaspiro[3.3]heptanyl, bicyclo[3.2.1]octanyl, 5-azaspiro[2.3]hexanyl, 3-cyclohexylazetidinyl, bicyclo[2.2.1]heptanyl, adamantyl, 6-oxa-9-azaspiro[4.5]decanyl, 3-azabicyclo[3.3.1]nonanyl, 6-oxa-2-azaspiro[3.4]octanyl, 4-(1H-imidazol-4-yl)piperidinyl, octahydro-1H-pyrido[1,2-a]pyrazinyl, 2,3-dihydro-1H-indenyl, (1R,5S)-bicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.1]heptanyl, 1-(pyridin-4-yl)piperazinyl, 1-(pyridin-2-yl)piperazinyl, 1-(pyridin-3-yl)piperazinyl, 2-oxa-6-azaspiro[3.3]heptanyl, 4-(pyrimidin-2-yl)piperazin-1-yl, 3-azabicyclo[3.3.1]nonanyl, 4-(pyridin-2-yl)piperidin-1-yl, 4-phenylpiperazin-1-yl, 4-phenylpiperidin-1-yl, 4-(pyrazin-2-yl)piperazin-1-yl, 4-(pyridin-2-yl)-1,4-diazepan-1-yl, 4-(pyrimidin-2-yl)-1,4-diazepan-1-yl, 4-(pyrimidin-4-yl)piperazin-1-yl, 2,7-diazaspiro[3.5]nonanyl, 3-phenylazetidinyl, 2-oxa-7-azaspiro[3.5]nonanyl, 3-azabicyclo[3.1.0]hexanyl, 2,8-diazaspiro[4.5]decanyl, 3-oxa-9-azabicyclo[3.3.1]nonanyl, 7-azabicyclo[2.2.1]heptanyl, spiro[3.5]nonanyl, and tricyclo[2.2.1.02,6]heptanyl.

In some embodiments, B can be a bridged ring system.

In some embodiments, m can be 1, B can be a ring system represented by the following formula:



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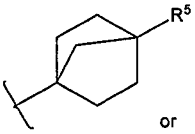

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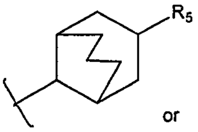

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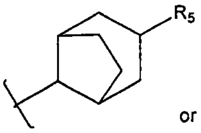

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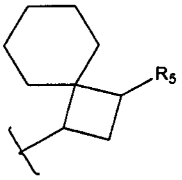
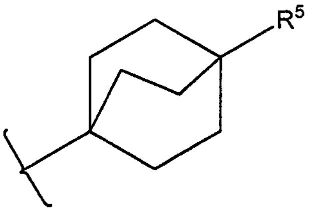


;

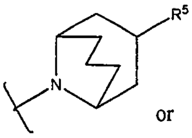
and R^5 can be CO_2H.

In some embodiments, B can be a bridged ring system represented by the following formula:



.

In some embodiments, m can be 0, B can be a ring system represented by the following formula:



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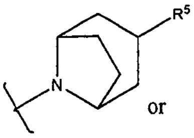

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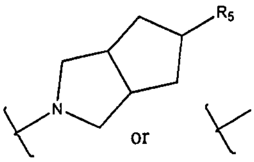

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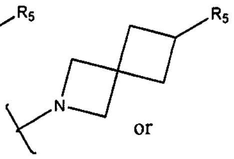

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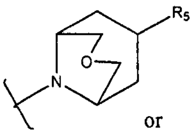

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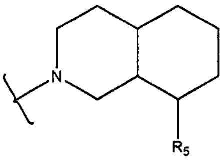

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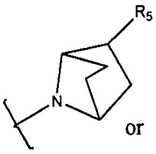

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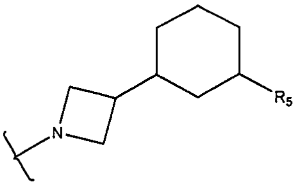
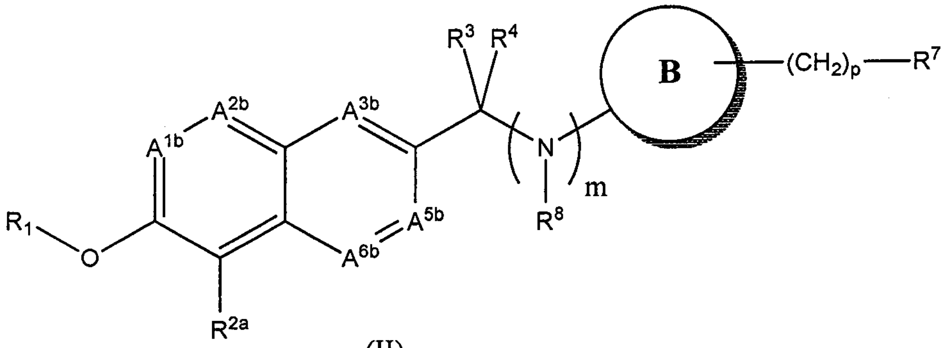


, wherein B is optionally further substituted by oxo, hydroxy, $-NH_2$, $-CONH_2$, or $-CO_2H$; and R^5 can be CO_2H.

In some embodiments, the compound can be represented by formula (II):



(II)

(II)

or a pharmaceutically acceptable salt thereof. In formula (II):

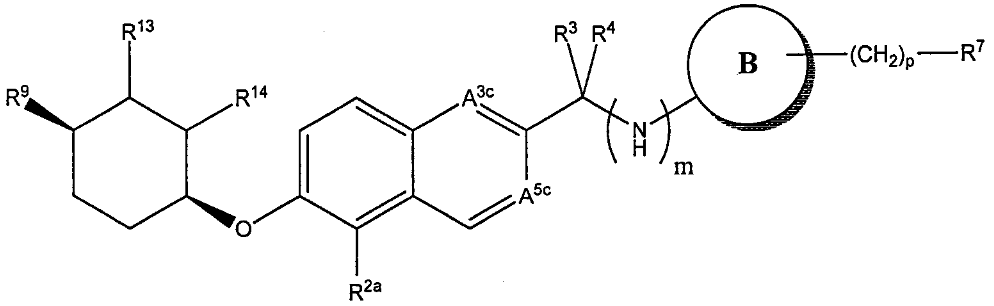
A^{1b}, A^{2b}, A^{3b}, A^{5b}, and A^{6b} can be CR^{2b} or N, wherein at least two of A^{1b}, A^{2b}, A^{3b}, A^{5b}, and A^{6b} are CR^{2b},

R^{2a} can be a halo, C_{1-6}haloalkyl or cyano, and

R^{2b}, for each occurrence, can be independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, cyano, carboxy, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-8}cycloalkyl, C_{3-8}halocycloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-8}cycloalkoxy, C_{3-8}halocycloalkoxy, C_{1-6}alkanoyl, amino, N-(C_{1-6}alkyl)amino, N,N-di-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyl, carbamoyl, N-(C_{1-6}alkyl)carbamoyl, N,N-di-(C_{1-6}alkyl)carbamoyl, C_{1-6}alkylamido, mercapto, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl , sulfamoyl, N-(C_{1-6}alkyl)sulfamoyl, N,N-di-(C_{1-6}alkyl)sulfamoyl, and C_{1-6}alkylsulfonamido.

In some embodiments, R^{2b}, for each occurrence, can be independently hydrogen or a halo.

In some embodiments, compound can be represented by formula (IIa):



(IIa)

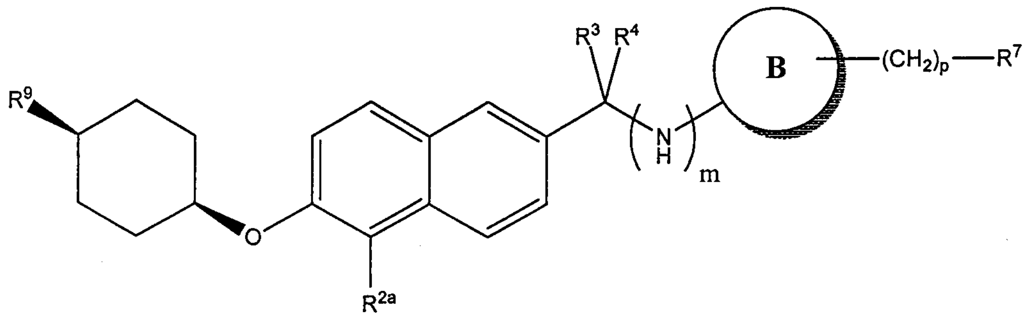
or a pharmaceutically acceptable salt thereof. In formula (IIa):

A^{3c} and A^{5c} can be N or CH, provided that only one of A^{3c} or A^{5c} is N,

R^9 can be a halo, an C_{1-6}alkyl, or a C_{1-6}haloalkyl, and

R^{13} and R^{14} can each independently be hydrogen or a C_{1-6}alkyl.

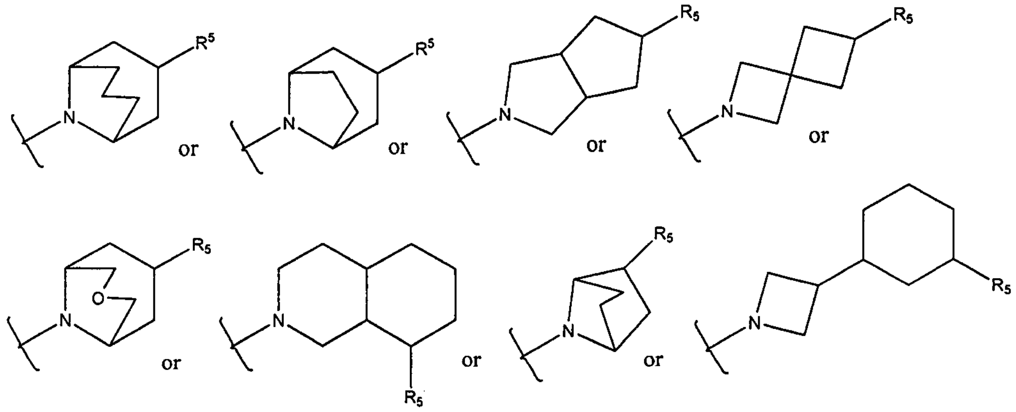
In some embodiments, the compound can be represented by formula (IIb):



(IIb)

or a pharmaceutically acceptable salt thereof.

In some embodiments, m can be 0, B can be a ring system represented by the following formula:



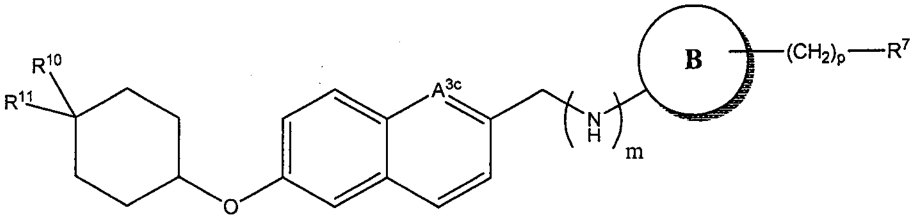
;

wherein B is optionally further substituted by oxo, hydroxy, $-NH_2$, $-CONH_2$, or $-CO_2H$; and R^5 can be CO_2H.

In some embodiments, R^{2a} can be -Cl, $-CF_3$ or $-CHF_2$.

In some embodiments, R^9 can be methyl, ethyl, $-CF_3$ or *tert*-butyl.

In some embodiments, the compound can be represented by formula (III):



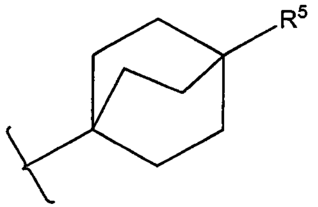
(III)

or a pharmaceutically acceptable salt thereof. In formula (III):

A^{3c} can be N or CH, and R^{10} and R^{11} can each independently be hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, tri-C_{1-6}alkylsilyl, or phenyl, wherein at least one of R^{10} or R^{11} is not hydrogen; or

R^{10} and R^{11} together with the carbon to which they are attached form a C_{3-8}spirocycloalkyl or 3- to 8-membered spiroheterocycloalkyl.

In some embodiments, m can be 1, B can be a bridged ring system represented by the following formula:



,

and R^5 can be CO_2H.

In some embodiments, X can be NH.

In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, is selected from the group consisting of:

4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino) bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((4,4-dimethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[2.5]octan-6-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[3.5]nonan-7-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[5.5]undecan-3-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-methylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-phenylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((4,4-dimethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[2.5]octan-6-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[3.5]nonan-7-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[4.5]decan-8-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[5.5]undecan-3-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate;

4-(((6-((cis-4-methylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-phenylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)-5-(trifluoromethyl)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

2-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperidin-4-yl)pyridine;

2-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperidin-4-yl)pyrimidine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-phenylpiperazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-3-yl)piperazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)-1,4-diazepane;

2-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)pyrimidine;

2-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)pyrazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-4-yl)piperazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyrimidin-2-yl)-1,4-diazepane;

4-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)pyrimidine;

4-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)-2-methylpyrimidine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-phenylpiperidine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

1-((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

1-((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

1-(pyridin-2-yl)-4-((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)piperazine;

1-((6-(heptyloxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

6-((cis-4-isopropylcyclohexyl)oxy)-2-((4-(pyridin-2-yl)piperazin-1-yl)methyl)quinoline;

3-(1-((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((4,4-dimethylcyclohexyl)oxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-(heptyloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((4,4-dimethylcyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((cis-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((cis-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

4-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

6-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-2-oxa-6-azaspiro[3.3]heptane;

3-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)(methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

8-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

3-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.1]nonane-9-carboxylic acid;

3-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.1]heptane-6-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.1]heptane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)amino)bicyclo[2.2.1]heptane-1-carboxylic acid;

4-((6-(trans-4-(Trimethylsilyl)cyclohexyloxy)naphthalen-2-yl)methylamino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(Trimethylsilyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-((6-(trans-4-tert-Butylcyclohexyloxy)naphthalen-2-yl)methylamino)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid;

4-((6-(trans-4-tert-Butylcyclohexyloxy)naphthalen-2-yl)methylamino)-1-(hydroxymethyl)bicyclo[2.2.2]octan-2-ol; and

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound can be selected from the group consisting of:

9-((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

3-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)methyl)amino)spiro[3.5]nonane-1-carboxylic acid;

3-(4-{[5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphtha-len-2-ylmethyl]-amino}-bicyclo[2.2.2]oct-1-yl)-propionic acid;

3-(4-(methyl((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)methyl)amino)bicyclo[2.2.2]octan-1-yl)propanoic acid;

9-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((R)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((S)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)ethyl)-9-azabicyclo[3.3.1]-nonane-3-carboxylic acid;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 1;

9-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 2;

8-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

COMPOUNDS THAT ARE S1P MODULATING AGENTS AND/OR ATX MODULATING AGENTS

TECHNICAL FIELD

This invention relates to compounds that are S1P modulating agents and/or ATX modulating agents, and methods of making and using such compounds.

BACKGROUND

Sphingosine 1-phosphate (S1P) is a lysophospholipid mediator that evokes a variety of cellular responses by stimulation of five members of the endothelial cell differentiation gene (EDG) receptor family. The EDG receptors are G-protein coupled receptors (GPCRs) and on stimulation propagate second messenger signals via activation of heterotrimeric G-protein alpha (G_α) subunits and beta-gamma ($G_{\beta\gamma}$) dimers. Ultimately, this S1P-driven signaling results in cell survival, increased cell migration and, often, mitogenesis. The recent development of agonists targeting S1P receptors has provided insight regarding the role of this signaling system in physiologic homeostasis. For example, the immunomodulating agent, FTY720 (2-amino-2-[2-(4-octylphenyl) ethyl] propane 1,3-diol), that following phosphorylation, is an agonist at 4 of 5 S1P receptors, revealed that affecting S1P receptor activity influences lymphocyte trafficking. Further, S1P type 1 receptor ($S1P_1$) antagonists cause leakage of the lung capillary endothelium, which suggests that S1P may be involved in maintaining the integrity of the endothelial barrier in some tissue beds. S1P type 4 receptors ($S1P_4$) are expressed mainly in leukocytes, and specifically $S1P_4$ mediates immunosuppressive effects of S1P by inhibiting proliferation and secretion of effector cytokines, while enhancing secretion of the suppressive cytokine IL-10. See, for example, Wang, W. et. al., (2005) *FASEB J.* 19(12): 1731-3, which is incorporated by reference in its entirety. S1P type 5 receptors ($S1P_5$) are exclusively expressed in oligodendrocytes and oligodendrocyte precursor cells (OPCs) and are vital for cell migration. Stimulation of $S1P_5$ inhibits OPC migration, which normally migrate considerable distances during brain development. See, for example, Novgorodov, A. et al., (2007) *FASEB J*, 21: 1503-1514, which is incorporated by reference in its entirety.

S1P has been demonstrated to induce many cellular processes, including those that result in platelet aggregation, cell proliferation, cell morphology, tumor-cell invasion, endothelial cell chemotaxis and angiogenesis. For these reasons, S1P receptors are good targets

9-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((4,4-difluorocyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((5-(difluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((6-(((trans,trans)-3,5-dimethylcyclohexyl)oxy)-5-(trifluoromethyl) naphthalene-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(2-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)acetyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(2-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-methylcyclohexyl)amino)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

2-(9-Azabicyclo[3.3.1]nonan-9-yl)-2-(6-((*cis*-4-methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)acetic acid;

9-((5-Chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-Chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

4-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)carbamoyl)bicyclo[2.2.2]octane-1-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-1-aminoindane-6-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-6-aminoindole-3-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-2-azabicyclo[1.2.3]octane-7-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-decahydroisoquinoline-5-carboxylic acid;

2-(2-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)acetyl)-2-azabicyclo[1.2.3]octane-7-carboxylic acid;

2-(2-(5-(difluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)acetyl)-2-azabicyclo[1.2.3]octane-7-carboxylic acid;

4-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)aminomethyl)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid;

7-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)-tricyclo[3.1.1.0]heptane-5-carboxylic acid;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)-naphthalene-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

3-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)-7,7-dimethylbicyclo[2.2.1]heptane-4-carboxylic acid;

8-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-aza-7-oxa-bicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-7-hydroxy-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 1;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 2;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

9-((6-((cis-4-trifluoromethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

methyl 2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-(7R,9aR)-octahydro-1H-pyrido[1,2-a]pyrazine-7-carboxylic acid;

3-(4-{[5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl]-amino}-bicyclo[2.2.2]oct-1-yl)-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-(7R,9aR)-octahydro-1H-pyrido[1,2-a]pyrazine-7-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-2-azaspiro[3.3]heptane-6-carboxylic acid;

N-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-amino-indane-5-carboxylic acid;

3-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-2-azaspiro[3.2]hexane-5-carboxylic acid;

N-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-decahydroisoquinoline-8-carboxylic acid;

3-((6-((cis-4-trifluoromethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.1]nonane-9-carboxylic acid;

N-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-4-aminobicyclo[2.2.1]heptane-1-carboxylic acid;

N-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-1-aminoadamantane-3-carboxylic acid;

3-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-3-azabicyclo[3.3.0]octane-7-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-((9S,9aR)-octahydro-1H-pyrido[1,2-a]pyrazin-9-yl)methanol;

8-((6-((4,4-difluorocyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

2-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-2-aza-6-oxaspiro[3.4]octane-7-carboxylic acid;

(1R,5S,7r)-3-((2-(4-(trifluoromethyl)cyclohexyloxy)-1-(trifluoromethyl)naphthalen-6-yl)methyl)-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-3-(azetidine-3-yl)-cyclohexane-1-carboxylic acid;

8-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

2-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-2-aza-5-oxaspiro[5.4]decane-8-carboxylic acid;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-8-aminobicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-8-aminobicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-1-amino-3,5-dimethyladamantane;

7-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-9-aminobicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-9-aza-7-oxabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-9-azabicyclo[3.3.1]nonane;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-7-hydroxy-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-7-oxo-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-((6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((*cis*-4-ethylcyclohexyl)oxy)-5-chloronaphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-Chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-Chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; and

8-((5-Chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

In another aspect, a pharmaceutical composition can include a pharmaceutically acceptable carrier or excipient and a compound, or a pharmaceutically acceptable salt thereof, according to any one of formulae (I), (IIa), (IIb) or (III).

In another aspect, a method of preventing, treating, or reducing symptoms of a condition mediated by S1P activity or ATX activity_in a mammal can include administering to said mammal an effective amount of a compound according to any one of formulae (I), (IIa), (IIb) or (III), or a pharmaceutically acceptable salt thereof.

In some embodiments, the condition can be selected from the group consisting of multiple sclerosis, an autoimmune disease, a chronic inflammatory disorder, asthma, an inflammatory neuropathy, arthritis, transplantation rejection, Crohn's disease, ulcerative colitis, lupus erythematosis, psoriasis, an ischemia-reperfusion injury, a solid tumor, a tumor metastasis, a disease associated with angiogenesis, a vascular disease, a pain condition, an acute viral disease, an inflammatory bowel condition, insulin-dependent diabetes, non-insulin dependent diabetes, a fibrosis of the lung, or a malignancy of the lung in a mammal.

In some embodiments, the condition can be multiple sclerosis.

In some embodiments, the condition can be rheumatoid arthritis.

In some embodiments, the method can include administering to the mammal an effective amount of one or more drugs selected from the group consisting of: a corticosteroid, a bronchodilator, an antiasthmatic, an antiinflammatory, an antirheumatic, an immunosuppressant, an antimetabolite, an immunomodulating agent, an antipsoriatic, and an antidiabetic.

In another aspect, a method of preventing, treating, or reducing chronic pain in a mammal can include comprising administering to said mammal an effective amount of a compound according to any one of any one of formulae (I), (IIa), (IIb) or (III), or a pharmaceutically acceptable salt thereof.

In some embodiments, the chronic pain can be inflammatory pain.

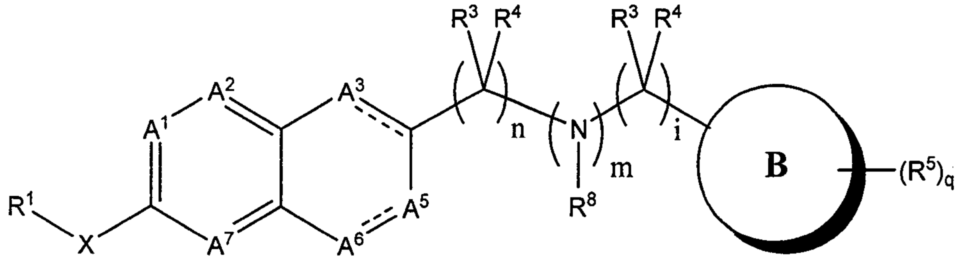
In some embodiments, the chronic pain can be neuropathic pain.

Other features or advantages will be apparent from the following detailed description of several embodiments, and also from the appended claims.

DETAILED DESCRIPTION

The disclosed compounds can be S1P modulating agents and/or ATX modulating agents. In other words, the disclosed compounds can have activity as receptor agonists or receptor antagonists at one or more S1P receptors, or as an ATX modulating agent. In particular, the compounds can be S1P4 antagonists, or ATX inhibitors. A given compound can be an S1P modulating agent with little or substantially no ATX activity; or can be an ATX modulating agent with little or substantially no S1P activity; or, in some cases, can simultaneously be an S1P modulating agent and an ATX modulating agent. Preferably, a given compound is either an S1P modulating agent with little or substantially no ATX activity; or is an ATX modulating agent with little or substantially no S1P activity.

A compound, or a pharmaceutically acceptable salt thereof, can be represented by formula (I):



(I)

In formula (I), X can be O, S(O)$_r$, NR^{12}, C(O) or CH$_2$, wherein r is 0, 1, or 2; A^1, A^2, and A^7 can each independently be CR^2 or N; A^3, A^5, and A^6 can each independently be CR^2, C(R^2)$_2$, N, or NR^{19}, wherein at least three of A^1, A^2, A^3, A^5, A^6, and A^7 are CR^2 or C(R^2)$_2$.

"------" can indicate a double or a single bond.

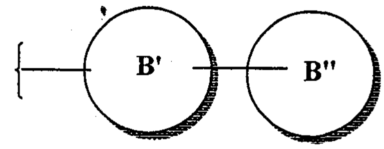
R^1 can be a C$_{6\text{-}20}$alkyl, a C$_{3\text{-}14}$carbocyclyl, a 3- to 15-membered heterocyclyl, a C$_{6\text{-}10}$aryl, or a five- to 14-membered heteroaryl, wherein R^1 may be optionally substituted with from one to six independently selected R^6.

R^2, for each occurrence, can be independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, cyano, carboxy, C$_{1\text{-}6}$alkyl, C$_{1\text{-}6}$haloalkyl, C$_{3\text{-}8}$cycloalkyl,

C_{3-8}halocycloalkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-8}cycloalkoxy, C_{3-8}halocycloalkoxy, C_{1-6}alkanoyl, amino, N-(C_{1-6}alkyl)amino, N,N-di-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyl, C_{1-6}alkanoyloxy, carbamoyl, N-(C_{1-6}alkyl)carbamoyl, N,N-di-(C_{1-6}alkyl)carbamoyl, C_{1-6}alkylamido, mercapto, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl , sulfamoyl, N-(C_{1-6}alkyl)sulfamoyl, N,N-di-(C_{1-6}alkyl)sulfamoyl, and C_{1-6}alkylsulfonamido.

Each R^3 and each R^4 can each independently be hydrogen, a carboxy, C_{1-6}alkyl, or a C_{2-6}alkenyl; or R^3 and R^4 together with the carbon to which they are attached can be -C(=O)-, a C_{3-8}spirocycloalkyl, or a 3- to 8-membered spiroheterocycloalkyl.

B can be a fused ring system, a bridged ring system, a spiro ring system, or a combination thereof; or B can be a bicyclic ring system represented by the following formula:

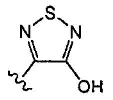


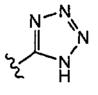
wherein B' and B" can each independently be selected from the group consisting of monocyclic C_{3-8}carbocyclyl, a monocyclic 3- to 8-membered heterocyclyl, phenyl, or a 5- to 6- membered heteroaryl, wherein the heterocyclyl and the heteroaryl comprises 1 to 3 heteroatoms independently selected from N, S, or O; provided that when B is a fused ring system it is not 1H-benzo[d][1,2,3]triazole.

R^5, for each occurrence, can independently be hydroxyl, halo, C_{1-6}alkyl, or $-(CR^{17}R^{18})_p-R^7$; or two R^5 on the same carbon atom may be =O.

R^6, for each occurrence, can be independently selected from the group consisting of halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, C_{3-8}cycloalkyl, C_{6-10}aryl, C_{1-6}alkoxy-C_{1-6}alkyl, and tri-(C_{1-6}alkyl)silyl; or two R^6 that are attached to the same carbon atom may form C_{3-8}spirocycloalkyl or 3- to 8-membered spiroheterocycloalkyl.

R^7 can be -OH, $-C(O)OR^{15}$, $-C(O)N(R^{16})_2$, $-C(O)N(R^{15})-S(O)_2R^{15}$, $-S(O)_2OR^{15}$, $-C(O)NHC(O)R^{15}$, -Si(O)OH, $-B(OH)_2$, $-N(R^{15})S(O)_2R^{15}$, $-S(O)_2N(R^{15})_2$, $-O-P(O)(OR^{15})_2$, $-P(O)(OR^{15})_2$, -CN, $-S(O)_2NHC(O)R^{15}$, $-C(O)NHS(O)_2R^{15}$, -C(O)NHOH, -C(O)NHCN, $-N(R^{20})_2$, or a heteroaryl or a heterocyclyl selected from the group consisting of formulae (a)-(i'):


(a)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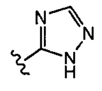
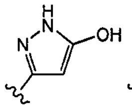

(c)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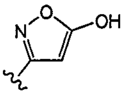
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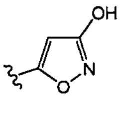
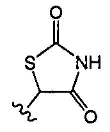
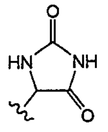
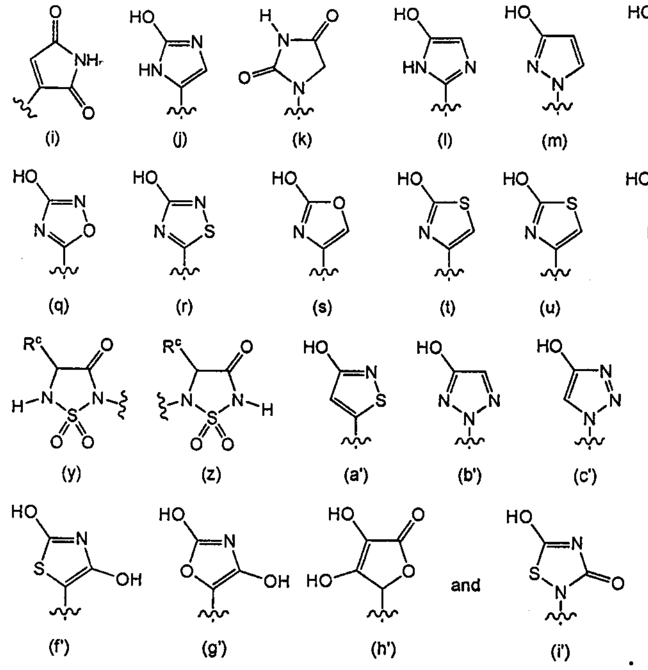

(f)


(g)


(h)



R^8, R^{12}, R^{19}, and R^{20} can each independently be hydrogen or a C_{1-6}alkyl.

R^{15} for each occurrence can be independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{6-10}aryl, a 5 to 14 membered heteroaryl, and a 3 to 15 membered heterocyclyl; wherein the heteroaryl or heterocyclyl can comprise from 1 to 10 heteroatoms independently selected from O, N, or S; and wherein R^{15} may be optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, C_{1-4}alkoxy, C_{1-4}alkyl, cyano, nitro, hydroxyl, amino, N-(C_{1-4}alkyl)amino, N,N-di-(C_{1-4}alkyl)amino, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylamido, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonamido, sulfamoyl, N-(C_{1-4}alkyl)sulfamoyl, and N,N-(C_{1-4}dialkyl)-sulfamoyl.

R^{16} can be R^{15}; or two R^{16} together with the nitrogen atom to which they are attached can form a 5 to 14 membered heteroaryl or a 3 to 15 membered heterocyclyl, wherein the heteroaryl or heterocyclyl can comprise from 1 to 10 heteroatoms independently selected from O, N, or S; and wherein the heteroaryl or heterocyclyl may be optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, C_{1-4}alkoxy, C_{1-4}alkyl, cyano, nitro, hydroxyl, amino, N-(C_{1-4}alkyl)amino, N,N-di-(C_{1-4}alkyl)amino, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylamido, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonamido, sulfamoyl, N-C_{1-4}alkylsulfamoyl, and N,N-(C_{1-4}dialkyl)-sulfamoyl.

R^{17} and R^{18}, for each occurrence, can each independently be hydrogen, a halo, or a C_{1-4}haloalkyl.

R^c is hydrogen or a C_{1-4}alkyl.

i can be an integer from 0 to 6.

n can be 0 or an integer from 1 to 6, provided that when n is 0, then m is 1, q is 0 and R^1 is a C_{3-14}carbocyclyl which is optionally substituted with from one to six R^6.

m can be 0 or 1, provided that when m is 0, B comprises at least one nitrogen.

p can be 0 or an integer from 1 to 6.

q can be 0, 1, 2, 3, or 4.

The compound of formula is not 2-((6-(trans-4-tert-butylcyclohexyloxy)-naphthalen-2-yl)methyl)octahydrocyclopenta[c]pyrrole- 3a-carboxylic acid or 6-phenoxy-2-(2-(4-phenylpiperidin-1-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol.

In some embodiments, B can be selected from the group consisting of 9-azabicyclo[3.3.1]nonanyl, 8-azabicyclo[3.2.1]octanyl, decahydroisoquinolinyl, 2-azaspiro[3.3]heptanyl, bicyclo[3.2.1]octanyl, 5-azaspiro[2.3]hexanyl, 3-cyclohexylazetidinyl, bicyclo[2.2.1]heptanyl, adamantyl, 6-oxa-9-azaspiro[4.5]decanyl, 3-azabicyclo[3.3.1]nonanyl, 6-oxa-2-azaspiro[3.4]octanyl, 4-(1H-imidazol-4-yl)piperidinyl, octahydro-1H-pyrido[1,2-a]pyrazinyl, 2,3-dihydro-1H-indenyl, (1R,5S)-bicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.1]heptanyl, 1-(pyridin-4-yl)piperazinyl, 1-(pyridin-2-yl)piperazinyl, 1-(pyridin-3-yl)piperazinyl, 2-oxa-6-azaspiro[3.3]heptanyl, 4-(pyrimidin-2-yl)piperazin-1-yl, 3-azabicyclo[3.3.1]nonanyl, 4-(pyridin-2-yl)piperidin-1-yl, 4-phenylpiperazin-1-yl, 4-phenylpiperidin-1-yl, 4-(pyrazin-2-yl)piperazin-1-yl, 4-(pyridin-2-yl)-1,4-diazepan-1-yl, 4-(pyrimidin-2-yl)-1,4-diazepan-1-yl, 4-(pyrimidin-4-yl)piperazin-1-yl, 2,7-diazaspiro[3.5]nonanyl, 3-phenylazetidinyl, 2-oxa-7-azaspiro[3.5]nonanyl, 3-azabicyclo[3.1.0]hexanyl, 2,8-diazaspiro[4.5]decanyl, 3-oxa-9-azabicyclo[3.3.1]nonanyl, 7-azabicyclo[2.2.1]heptanyl, spiro[3.5]nonanyl, and tricyclo[2.2.1.02,6]heptanyl.

B can be a bridged ring system.

In some embodiments, m can be 1; B can be a ring system represented by the following formula:

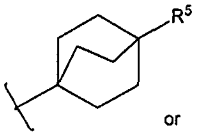
for therapeutic applications such as wound healing, tumor growth inhibition, and autoimmune diseases.

Sphingosine-1-phosphate signals cells in part via a set of G protein-coupled receptors named $S1P_1$, $S1P_2$, $S1P_3$, $S1P_4$, and $S1P_5$ (formerly EDG1, EDG5, EDG3, EDG6 and EDG8). The EDG receptors are G-protein coupled receptors (GPCRs) and on stimulation propagate second messenger signals via activation of heterotrimeric G-protein alpha (G_α) subunits and beta-gamma ($G_{\beta\gamma}$) dimers. These receptors share 50-55% amino acid sequence identity and cluster with three other receptors (LPA_1, LPA_2, and LPA_3 (formerly EDG2, EDG4 and EDG7) for the structurally related lysophosphatidic acid (LPA).

A conformational shift is induced in the G-Protein Coupled Receptor (GPCR) when the ligand binds to that receptor, causing GDP to be replaced by GTP on the α-subunit of the associated G-proteins and subsequent release of the G-proteins into the cytoplasm. The α-subunit then dissociates from the $\beta\gamma$-subunit and each subunit can then associate with effector proteins, which activate second messengers leading to a cellular response. Eventually the GTP on the G-proteins is hydrolyzed to GDP and the subunits of the G-proteins reassociate with each other and then with the receptor. Amplification plays a major role in the general GPCR pathway. The binding of one ligand to one receptor leads to the activation of many G-proteins, each capable of associating with many effector proteins leading to an amplified cellular response.

S1P receptors make good drug targets because individual receptors are both tissue and response specific. Tissue specificity of the S1P receptors is desirable because development of an agonist or antagonist selective for one receptor localizes the cellular response to tissues containing that receptor, limiting unwanted side effects. Response specificity of the S1P receptors is also of importance because it allows for the development of agonists or antagonists that initiate or suppress certain cellular responses without affecting other responses. For example, the response specificity of the S1P receptors could allow for an S1P mimetic that initiates platelet aggregation without affecting cell morphology.

Sphingosine-1-phosphate is formed as a metabolite of sphingosine in its reaction with sphingosine kinase and is stored in abundance in the aggregates of platelets where high levels of sphingosine kinase exist and sphingosine lyase is lacking. S1P is released during platelet aggregation, accumulates in serum, and is also found in malignant ascites. Reversible biodegradation of S1P most likely proceeds via hydrolysis by ectophosphohydrolases,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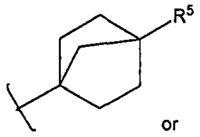
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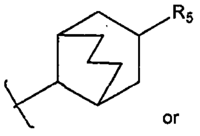
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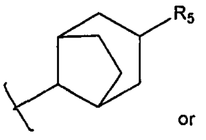
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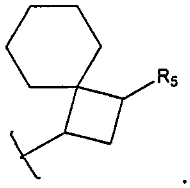
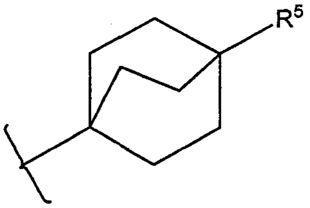

;

and R^5 can be CO_2H.

B can be a bridged ring system represented by the following formula: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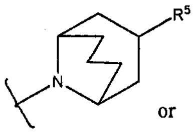
In some embodiments, m can be 0; B can be a ring system represented by the following formula: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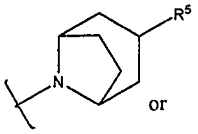
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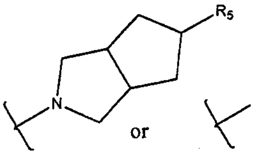
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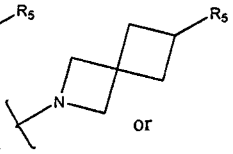
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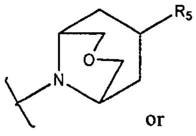
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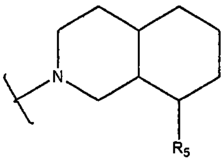
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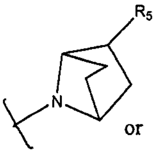
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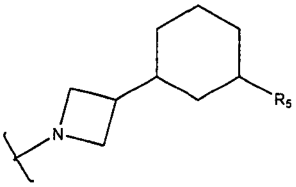
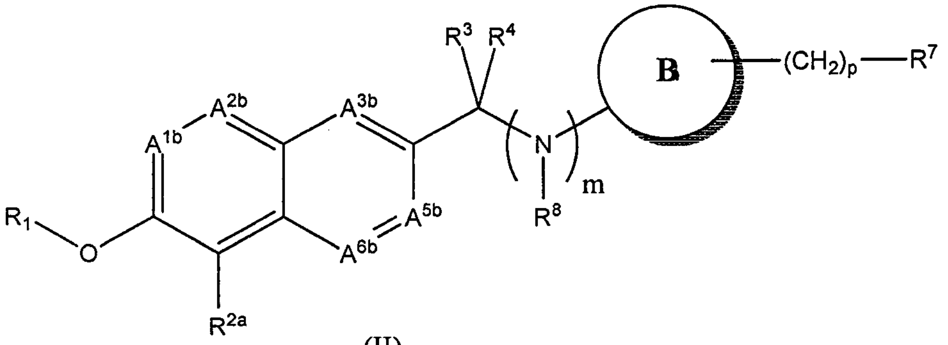

wherein B is optionally further substituted by oxo, hydroxy, $-NH_2$, $-CONH_2$, or $-CO_2H$; and R^5 can be CO_2H.

B can be a bridged ring system selected from 9-aza-bicyclo[3.3.1]nonane substituted with R^5 at the 3-position; and 8-aza-bicyclo[3.2.1]octane substituted with R^5 at the 3-position.

In some embodiments, the compound of formula (I), or a pharmaceutically acceptable salt thereof, can be represented by formula (II):



(II)

(II)

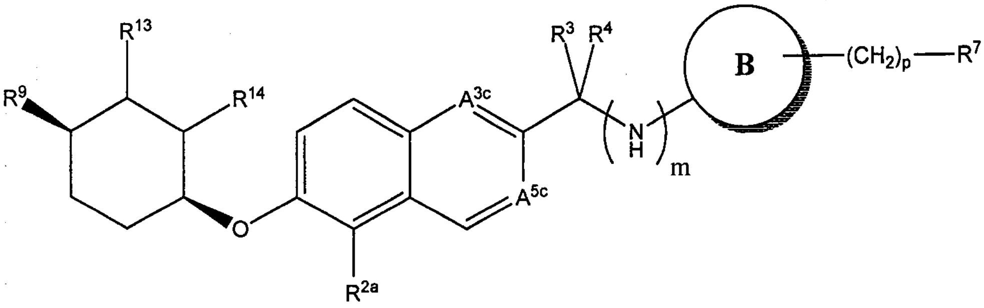
In formula (II), A^{1b}, A^{2b}, A^{3b}, A^{5b}, and A^{6b} can be CR^{2b} or N, wherein at least two of A^{1b}, A^{2b}, A^{3b}, A^{5b}, and A^{6b} can be CR^{2b}.

R^{2a} can be a halo, $C_{1\text{-}6}$haloalkyl or cyano.

R^{2b}, for each occurrence, can be independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, cyano, carboxy, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}8}$cycloalkyl, $C_{3\text{-}8}$halocycloalkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$haloalkoxy, $C_{3\text{-}8}$cycloalkoxy, $C_{3\text{-}8}$halocycloalkoxy, $C_{1\text{-}6}$alkanoyl, amino, N-($C_{1\text{-}6}$alkyl)amino, N,N-di-($C_{1\text{-}6}$alkyl)amino, $C_{1\text{-}6}$alkoxycarbonyl, carbamoyl, N-($C_{1\text{-}6}$alkyl)carbamoyl, N,N-di-($C_{1\text{-}6}$alkyl)carbamoyl, $C_{1\text{-}6}$alkylamido, mercapto, $C_{1\text{-}6}$alkylthio, $C_{1\text{-}6}$alkylsulfonyl , sulfamoyl, N-($C_{1\text{-}6}$alkyl)sulfamoyl, N,N-di-($C_{1\text{-}6}$alkyl)sulfamoyl, and $C_{1\text{-}6}$alkylsulfonamido.

In some embodiments of formula (II), R^{2b}, for each occurrence, can independently be hydrogen or a halo.

In some embodiments, the compound of formula (I), or a pharmaceutically acceptable salt thereof, can be represented by formula (IIa):



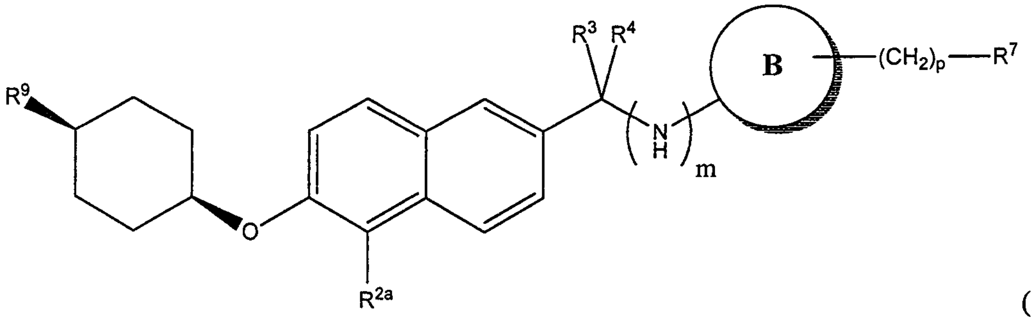
(IIa)

In formula (IIa), A^{3c} and A^{5c} can be N or CH, provided that only one of A^{3c} or A^{5c} is N.

R^9 can be a halo, an $C_{1\text{-}6}$alkyl, or a $C_{1\text{-}6}$haloalkyl.

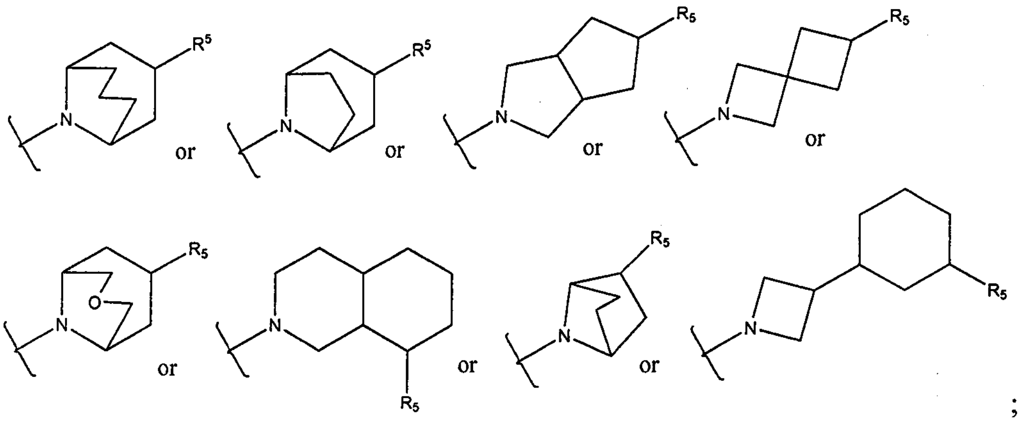
R^{13} and R^{14} can each independently be hydrogen or a $C_{1\text{-}6}$alkyl.

In some embodiments, the compound of formula (I), or a pharmaceutically acceptable salt thereof, can be represented by formula (IIb):



(IIb).

In some embodiments, for a compound of formula (II), (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, m can be 0; B can be a ring system represented by the following formula:



;

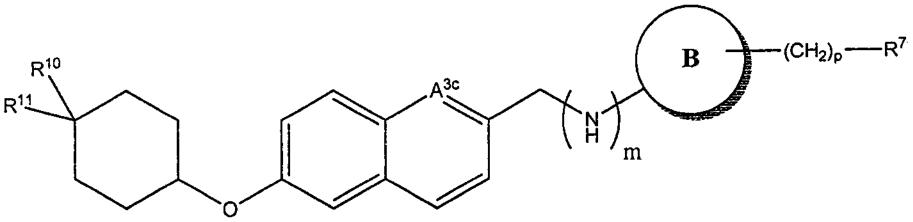
wherein B is optionally further substituted by oxo, hydroxy, $-NH_2$, $-CONH_2$, or $-CO_2H$; and R^5 can be CO_2H.

In some embodiments, for a compound of formula (II), (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, B can be a bridged ring system selected from 9-aza-bicyclo[3.3.1]nonane substituted with R^5 at the 3-position; and 8-aza-bicyclo[3.2.1]octane substituted with R^5 at the 3-position.

In some embodiments, for a compound of formula (II), (IIa), or (IIb), or a pharmaceutically acceptable salt thereof, R^{2a} can be -Cl, $-CF_3$ or $-CHF_2$.

In some embodiments, for a compound of formula (IIb), or a pharmaceutically acceptable salt thereof, R^9 can be methyl, ethyl, $-CF_3$ or *tert*-butyl.

In some embodiments, the compound of formula (I), or a pharmaceutically acceptable salt thereof, can be represented by formula (III):

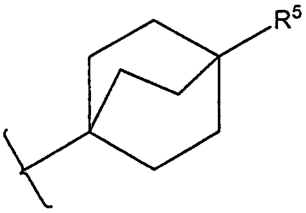


(III)

In formula (III), A^{3c} can be N or CH.

R^{10} and R^{11} can each independently be hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, tri-C_{1-6}alkylsilyl, or phenyl, wherein at least one of R^{10} or R^{11} is not hydrogen; or R^{10} and R^{11} together with the carbon to which they are attached can form a C_{3-8}spirocycloalkyl or 3- to 8-membered spiroheterocycloalkyl.

In some embodiments, for a compound of formula (III), or a pharmaceutically acceptable salt thereof, m can be 1; B can be a bridged ring system represented by the following formula:



; and R^5 can be CO_2H.

A compound can be selected from the group consisting of:

4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino) bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((4,4-dimethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[2.5]octan-6-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[3.5]nonan-7-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[5.5]undecan-3-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-methylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-phenylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((4,4-dimethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[2.5]octan-6-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[3.5]nonan-7-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[4.5]decan-8-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[5.5]undecan-3-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate;

4-(((6-((cis-4-methylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-phenylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)-5-(trifluoromethyl)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

2-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperidin-4-yl)pyridine;

2-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperidin-4-yl)pyrimidine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-phenylpiperazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-3-yl)piperazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)-1,4-diazepane;

2-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)pyrimidine;

2-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)pyrazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-4-yl)piperazine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyrimidin-2-yl)-1,4-diazepane;

4-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)pyrimidine;

4-(4-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)piperazin-1-yl)-2-methylpyrimidine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-phenylpiperidine;

1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

1-((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

1-((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

1-(pyridin-2-yl)-4-((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)piperazine;

1-((6-(heptyloxy)naphthalen-2-yl)methyl)-4-(pyridin-2-yl)piperazine;

6-((cis-4-isopropylcyclohexyl)oxy)-2-((4-(pyridin-2-yl)piperazin-1-yl)methyl)quinoline;

3-(1-((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((4,4-dimethylcyclohexyl)oxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-(heptyloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((4,4-dimethylcyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((cis-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

3-(1-((6-((cis-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

4-(1-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;

6-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-2-oxa-6-azaspiro[3.3]heptane;

3-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)(methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

8-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

3-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.1]nonane-9-carboxylic acid;

3-((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.1]heptane-6-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.1]heptane-1-carboxylic acid;

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)amino)bicyclo[2.2.1]heptane-1-carboxylic acid;

4-((6-(trans-4-(Trimethylsilyl)cyclohexyloxy)naphthalen-2-yl)methylamino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-((cis-4-(Trimethylsilyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-((6-(trans-4-tert-Butylcyclohexyloxy)naphthalen-2-yl)methylamino)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid;

4-((6-(trans-4-tert-Butylcyclohexyloxy)naphthalen-2-yl)methylamino)-1-(hydroxymethyl)bicyclo[2.2.2]octan-2-ol; and

4-(((6-((trans-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

A compound can be selected from the group consisting of:

9-((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

3-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)methyl)amino)spiro[3.5]nonane-1-carboxylic acid;

3-(4-{[5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphtha-len-2-ylmethyl]-amino}-bicyclo[2.2.2]oct-1-yl)-propionic acid;

3-(4-(methyl((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)methyl)amino)bicyclo[2.2.2]octan-1-yl)propanoic acid;

9-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((R)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((S)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)ethyl)-9-azabicyclo[3.3.1]-nonane-3-carboxylic acid;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 1;

9-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 2;

8-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((4,4-difluorocyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((5-(difluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((6-(((trans,trans)-3,5-dimethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(2-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)acetyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(2-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-methylcyclohexyl)amino)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

2-(9-Azabicyclo[3.3.1]nonan-9-yl)-2-(6-((*cis*-4-methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)acetic acid;

9-((5-Chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

specifically the sphingosine-1-phosphate phosphohydrolases. Irreversible degradation of S1P is catalyzed by S1P lyase yielding ethanolamine phosphate and hexadecenal.

Autotaxin (ATX, ENPP2) is a secreted glycoprotein widely present in biological fluids, including blood, cancer ascites, synovial, pleural and cerebrospinal fluids, originally isolated from the supernatant of melanoma cells as an autocrine motility stimulation factor (Stracke, M.L., et al. Identification, purification, and partial sequence analysis of autotaxin, a novel motility- stimulating protein. J Biol Chem 267, 2524-2529 (1992), which is incorporated by reference in its entirety). ATX is encoded by a single gene on human chromosome 8 (mouse chromosome 15) whose transcription, regulated by diverse transcription factors (Hoxal3, NFAT-1 and v-jun), results in four alternatively spliced isoforms (α, β, γ, and δ). See, for example, Giganti, A., et al Murine and Human Autotaxin alpha, beta, and gamma Isoforms: Gene organization, tissue distribution and biochemical characterization. J Biol Chem 283, 7776-7789 (2008); and van Meeteren, L.A. & Moolenaar, W.H. Regulation and biological activities of the autotaxin-LPA axis. Prog Lipid Res 46, 145- 160 (2007); Hashimoto, et al, "Identification and Biochemical Charaterization of a Novel Autotaxin Isoform, ATXδ," J. of Biochemistry Advance Access (October 11, 2011); each of which is incorporated by reference in its entirety.

ATX is synthesized as a prepro-enzyme, secreted into the extracellular space after the proteolytic removal of its N-terminal signal peptide (Jansen, S., el al Proteolytic maturation and activatio of autotaxin (NPP2), a secreted metastasis-enhancing lysophospho lipase D. J Cell Sci 118, 3081-3089 (2005), which is incorporated by reference in its entirety). ATX is a member of the ectonucleotide pyrophosphatase/phosphodiesterase family of ectoenzymes (E-NPP) that hydrolyze phosphodiesterase (PDE) bonds of various nucleotides and derivatives (Stefan, C, Jansen, S. & Bollen, M. NPP-type ectophosphodiesterases: unity in diversity. Trends Biochem Sci 30, 542-550 (2005), which is incorporated by reference in its entirety). The enzymatic activity of ATX was enigmatic, until it was shown to be identical to lysophospholipase D (lysoPLD) (Umezu-Goto, M., et al. Autotaxin has lysophospholipase D activity leading to tumor cell growth and motility by lysophosphatidic acid production. J Cell Biol 158, 227-233 (2002), which is incorporated by reference in its entirety), which is widely present in biological fluids. Since ATX is a constitutively active enzyme, the biological outcome of ATX action will largely depend on its expression levels and the local availability of its substrates. The major lysophospholipid substrate for ATX, lysophosphatidylcholine (LPC), is secreted by the liver and is abundantly present in plasma (at about 100 μM) as a predominantly albumin bound form (Croset, M., Brossard, N., Polette, A. & Lagarde, M.

9-((5-Chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

4-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)carbamoyl)bicyclo[2.2.2]octane-1-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-1-aminoindane-6-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-6-aminoindole-3-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-2-azabicyclo[1.2.3]octane-7-carboxylic acid;

N-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-ylcarbonyl)-decahydroisoquinoline-5-carboxylic acid;

2-(2-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)acetyl)-2-azabicyclo[1.2.3]octane-7-carboxylic acid;

2-(2-(5-(difluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalene-2-yl)acetyl)-2-azabicyclo[1.2.3]octane-7-carboxylic acid;

4-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)aminomethyl)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid;

7-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)-tricyclo[3.1.1.0]heptane-5-carboxylic acid;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)-naphthalene-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

3-(((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)-7,7-dimethylbicyclo[2.2.1]heptane-4-carboxylic acid;

8-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-aza-7-oxa-bicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-7-hydroxy-9-aza-bicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(6-((*cis*-4-Methylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 1;

9-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid, enantiomer 2;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(5-(difluoromethyl)-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

9-((6-((cis-4-trifluoromethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

methyl 2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-(7R,9aR)-octahydro-1H-pyrido[1,2-a]pyrazine-7-carboxylic acid;

3-(4-{[5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl]-amino}-bicyclo[2.2.2]oct-1-yl)-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-(7R,9aR)-octahydro-1H-pyrido[1,2-a]pyrazine-7-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-2-azaspiro[3.3]heptane-6-carboxylic acid;

N-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-amino-indane-5-carboxylic acid;

3-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-2-azaspiro[3.2]hexane-5-carboxylic acid;

N-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-decahydroisoquinoline-8-carboxylic acid;

3-((6-((cis-4-trifluoromethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.1]nonane-9-carboxylic acid;

N-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-4-aminobicyclo[2.2.1]heptane-1-carboxylic acid;

N-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-1-aminoadamantane-3-carboxylic acid;

3-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-3-azabicyclo[3.3.0]octane-7-carboxylic acid;

2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-((9S,9aR)-octahydro-1H-pyrido[1,2-a]pyrazin-9-yl)methanol;

8-((6-((4,4-difluorocyclohexyl)oxy)-5-(trifluoromethyl)naphthalene-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

2-(5-trifluoromethyl-6-(4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-2-aza-6-oxaspiro[3.4]octane-7-carboxylic acid;

(1R,5S,7r)-3-((2-(4-(trifluoromethyl)cyclohexyloxy)-1-(trifluoromethyl)naphthalen-6-yl)methyl)-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-3-(azetidine-3-yl)-cyclohexane-1-carboxylic acid;

8-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)quinolin-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

2-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-2-aza-5-oxaspiro[5.4]decane-8-carboxylic acid;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-8-aminobicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-8-aminobicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-1-amino-3,5-dimethyladamantane;

7-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-7-azabicyclo[2.2.1]heptane-2-carboxylic acid;

N-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-9-aminobicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-9-aza-7-oxabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-9-azabicyclo[3.3.1]nonane;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-7-hydroxy-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethyl-cyclohexyloxy)-naphthalen-2-ylmethyl)-7-oxo-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-((6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 1;

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid, enantiomer 2;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-trifluoromethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((*cis*-4-ethylcyclohexyl)oxy)-5-chloronaphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-Chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-Chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; and

8-((5-Chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

The term “fused ring system,” as used herein, is a ring system that has two or three rings (preferably two rings) independently selected from carbocyclyl, heterocyclyl, aryl or heteroaryl rings that share one side. A fused ring system may have from 4-15 ring members, preferably from 5-10 ring members. Examples of fused ring systems include octahydroisoquinolin-2(1H)-yl, 2,3-dihydro-1H-indenyl, octahydro-1H-pyrido[1,2-a]pyrazinyl, and decahydroisoquinolinyl).

The term “bridged ring system,” as used herein, is a ring system that has a carbocyclyl or heterocyclyl ring wherein two non-adjacent atoms of the ring are connected (bridged) by one or more (preferably from one to three) atoms selected from C, N, O, or S. A bridged ring system can have more than one bridge within the ring system (e.g., adamantyl). A bridged ring system may have from 6-10 ring members, preferably from 7-10 ring members. Examples of bridged ring systems include adamantyl, 9-azabicyclo[3.3.1]nonan-9-yl, 8-azabicyclo[3.2.1]octanyl, bicyclo[2.2.2]octanyl, 3-azabicyclo[3.1.1]heptanyl, bicyclo[2.2.1]heptanyl, (1R,5S)-bicyclo[3.2.1]octanyl, 3-azabicyclo[3.3.1]nonanyl, and bicyclo[2.2.1]heptanyl. More preferably, the bridged ring system is selected from the group consisting of 9-azabicyclo[3.3.1]nonan-9-yl, 8-azabicyclo[3.2.1]octanyl, and bicyclo[2.2.2]octanyl.

The term “spiro ring system,” as used herein, is a ring system that has two rings each of which are independently selected from a carbocyclyl or a heterocyclyl, wherein the two ring structures having one atom in common. Spiro ring systems have from 5 to 14 ring members. Example of spiro ring systems include 2-azaspiro[3.3]heptanyl, spiropentanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,7-diazaspiro[3.5]nonanyl, 2-oxa-7-azaspiro[3.5]nonanyl, 6-oxa-9-azaspiro[4.5]decanyl, 6-oxa-2-azaspiro[3.4]octanyl, 5-azaspiro[2.3]hexanyl and 2,8-diazaspiro[4.5]decanyl.

As used herein, the term "alkyl" refers to a fully saturated branched or unbranched hydrocarbon moiety. Preferably the alkyl comprises 1 to 20 carbon atoms, more preferably 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In some embodiments, an alkyl comprises from 6 to 20 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, or n-decyl.

"Alkylene" refers to a divalent alkyl group. Examples of alkylene groups include methylene, ethylene, propylene, n-butylene, and the like. The alkylene is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the carbon chain.

As used herein, the term "haloalkyl" refers to an alkyl, as defined herein, that is substituted by one or more halo groups as defined herein. Preferably the haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl including perhaloalkyl. A monohaloalkyl can have one iodo, bromo, chloro or fluoro substituent. Dihaloalkyl and polyhaloalkyl groups can be substituted with two or more of the same halo atoms or a combination of different halo groups. Non-limiting examples of haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. A perhaloalkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms. Preferred haloalkyl groups are trifluoromethyl and difluoromethyl.

"Halogen" or "halo" may be fluoro, chloro, bromo or iodo.

As used herein, the term "alkoxy" refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Preferably, alkoxy groups have about 1-6 carbon atoms, more preferably about 1-4 carbon atoms.

As used herein, the term "haloalkoxy" refers to haloalkyl-O-, wherein haloalkyl is defined herein above. Representative example of haloalkoxy groups are trifluoromethoxy, difluoromethoxy, and 1,2-dichloroethoxy. Preferably, haloalkoxy groups have about 1-6 carbon atoms, more preferably about 1-4 carbon atoms.

As used herein, the term "alkylthio" refers to alkyl-S-, wherein alkyl is defined herein above.

As used herein, the term "carbocyclyl" refers to saturated or partially unsaturated (but not aromatic) monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-14 carbon atoms, preferably 3-9, or more preferably 3-8 carbon atoms. Carbocyclyls include fused or bridged ring systems. The term “carbocyclyl” encompasses cycloalkyl groups. The term “cycloalkyl” refers to completely saturated monocyclic, bicyclic or tricyclic hydrocarbon groups of 3-12 carbon atoms, preferably 3-9, or more preferably 3-8 carbon atoms. Exemplary monocyclic carbocyclyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl or cyclohexenyl. Exemplary bicyclic carbocyclyl groups include bornyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, or bicyclo[2.2.2]octyl. Exemplary tricyclic carbocyclyl groups include adamantyl.

As used herein, the term "halocycloalkyl" refers to a cycloalkyl, as defined herein, that is substituted by one or more halo groups as defined herein. Preferably the halocycloalkyl can be monohalocycloalkyl, dihalocycloalkyl or polyhalocycloalkyl including perhalocycloalkyl. A monohalocycloalkyl can have one iodo, bromo, chloro or fluoro substituent. Dihalocycloalkyl and polyhalocycloalkyl groups can be substituted with two or more of the same halo atoms or a combination of different halo groups.

As used herein, the term "cycloalkoxy" refers to cycloalkyl-O-, wherein cycloalkyl is defined herein above.

As used herein, the term "halocycloalkoxy" refers to halocycloalkyl-O-, wherein halocycloalkyl is defined herein above.

The term “spirocycloalkyl” as used herein, is a cycloalkyl that has one ring atom in common with the group to which it is attached. Spirocycloalkyl groups may have from 3 to 14 ring members. In a preferred embodiment, the spirocycloalkyl has from 3 to 8 ring carbon atoms and is monocyclic.

The term "aryl" refers to monocyclic, bicyclic or tricyclic aromatic hydrocarbon groups having from 6 to 14 carbon atoms in the ring portion. In one embodiment, the term aryl refers to monocyclic and bicyclic aromatic hydrocarbon groups having from 6 to 10 carbon atoms. Representative examples of aryl groups include phenyl, naphthyl, fluorenyl, and anthracenyl.

The term "aryl" also refers to a bicyclic or tricyclic group in which at least one ring is aromatic and is fused to one or two non-aromatic hydrocarbon ring(s). Nonlimiting examples include tetrahydronaphthalene, dihydronaphthalenyl and indanyl.

As used herein, the term "heterocyclyl" refers to a saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic ring system which has from 3- to 15-ring members at least one of which is a heteroatom, and up to 10 of which may be heteroatoms, wherein the heteroatoms are independently selected from O, S and N, and wherein N and S can be optionally oxidized to various oxidation states. In one embodiment, a heterocyclyl is a 3-8-membered monocyclic. In another embodiment, a heterocyclyl is a 6-12-membered bicyclic. In yet another embodiment, a heterocyclycyl is a 10-15-membered tricyclic ring system. The heterocyclyl group can be attached at a heteroatom or a carbon atom. Heterocyclyls include fused or bridged ring systems. The term “heterocyclyl” encompasses heterocycloalkyl groups. The term “heterocycloalkyl” refers to completely saturated monocyclic, bicyclic or tricyclic heterocyclyl comprising 3-15 ring members, at least one of which is a heteroatom, and up to 10 of which may be heteroatoms, wherein the heteroatoms are independently selected from O, S and N, and wherein N and S can be optionally oxidized to various oxidation states. Examples of heterocyclyls include dihydrofuranyl, [1,3]dioxolane, 1,4-dioxane, 1,4-dithiane, piperazinyl, 1,3-dioxolane, imidazolidinyl, imidazolinyl, pyrrolidine, dihydropyran, oxathiolane, dithiolane, I,3-dioxane, 1,3-dithianyl, oxathianyl, thiomorpholinyl, oxiranyl, aziridinyl, oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, azepinyl, oxapinyl, oxazepinyl and diazepinyl.

The term “spiroheterocycloalkyl” as used herein, is a heterocycloalkyl that has one ring atom in common with the group to which it is attached. Spiroheterocycloalkyl groups may have from 3 to 15 ring members. In a preferred embodiment, the spiroheterocycloalkyl has from 3 to 8 ring atoms selected from carbon, nitrogen, sulfur and oxygen and is monocyclic.

As used herein, the term "heteroaryl" refers to a 5-14 membered monocyclic-, bicyclic-, or tricyclic-ring system, having 1 to 10 heteroatoms independently selected from N, O or S, wherein N and S can be optionally oxidized to various oxidation states, and wherein at least one ring in the ring system is aromatic. In one embodiment, the heteroaryl is monocyclic and has 5 or 6 ring members. Examples of monocyclic heteroaryl groups include pyridyl, thienyl, furanyl, pyrrolyl, pyrazolyl, imidazoyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl and tetrazolyl. In another embodiment, the heteroaryl is bicyclic and has from 8 to 10 ring members. Examples of bicyclic heteroaryl groups include indolyl, benzofuranyl, quinolyl, isoquinolyl indazolyl, indolinyl, isoindolyl, indolizinyl, benzamidazolyl, quinolinyl, 5,6,7,8-tetrahydroquinoline and 6,7-dihydro-5H-pyrrolo[3,2-d]pyrimidine.

An amino is a group having the formula NH_2-. The term N-alkylamino is an amino group in which one of the hydrogen atoms is replaced with an alkyl group. The term N,N-dialkylamino is an amino group in which each hydrogen atoms is replaced with an alkyl group which may be the same or different.

The term “alkanoyl” refers to alkyl-C(O)- wherein the alkyl is defined as above.

The term “alkoxycarbonyl” refers to alkoxy-C(O)-, wherein the alkoxy group is defined as above.

The term “alkanoyloxy” refers to alkyl-C(O)O-, wherein the alkyl is defined as above.

A carbamoyl is a group having the formula $NH_2C(O)$-. The term N-alkylcarbamoyl is a carbamoyl group in which one of the hydrogen atoms is replaced with an alkyl group. The term N,N-dialkylcarbamoyl is a carbamoyl group in which each hydrogen atoms is replaced with an alkyl group which may be the same or different.

The term “alkylamido” refers to a group having the formula alkyl-C(O)-NH-. As used herein, the term "alkylsulfonyl" refers to a group having the formula alkyl-SO_2-.

A sulfamoyl is a group having the formula $NH_2S(O)_2$-. The term N-alkylsulfamoyl is a sulfamoyl group in which one of the hydrogen atoms is replaced with an alkyl group. The term N,N-dialkylsulfamoyl is a sulfamoyl group in which each hydrogen atoms is replaced with an alkyl group which may be the same or different.

The term “alkylsulfonamido” refers to a group having the formula alkyl-$S(O)_2$-NH-.

The term “trialkylsilyl” refers to $(alkyl)_3$-Si-, wherein each of the alkyl groups may be the same or different .

The number of carbon atoms in a group is specified herein by the prefix “C_{x-xx}”, wherein x and xx are integers. For example, "C_{1-4}alkyl" is an alkyl group which has from 1 to 4 carbon atoms; C_{1-6}alkoxy is an alkoxy group having from 1 to 6 carbon atoms; C_{6-10}aryl is an aryl group which has from 6 to 10 carbon atoms; C_{1-4}haloalkyl is a haloalkyl group which has from 1 to 4 carbon atoms; and N,N-di-C_{1-6}alkylamino is a N,N-dialkylamino group in which the nitrogen is substituted with two alkyl groups each of which is independently from 1 to 6 carbon atoms.

The phrase “compound of the invention,” as used herein, refers to compounds represented by formulae (I), (II), (IIa), (IIb), and (III), and any of the specific examples disclosed herein.

The disclosed compounds can contain one or more asymmetric centers in the molecule. In accordance with the present disclosure any structure that does not designate the stereochemistry is to be understood as embracing all the various optical isomers (e.g., diastereomers and enantiomers) in pure or substantially pure form, as well as mixtures thereof (such as a racemic mixture, or an enantiomerically enriched mixture). It is well known in the art how to prepare such optically active forms (for example, resolution of the racemic form by recrystallization techniques, synthesis from optically-active starting materials, by chiral synthesis, or chromatographic separation using a chiral stationary phase). The compounds can be isotopically-labeled compounds, for example, compounds including various isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, or chlorine. The disclosed compounds may exist in tautomeric forms and mixtures and separate individual tautomers are contemplated. In addition, some compounds may exhibit polymorphism.

By way of clarity, compounds of the invention included all isotopes of the atoms present in formulae (I), (II), (IIa), (IIb), and (III) and any of the examples or embodiments disclosed herein. For example, H (or hydrogen) represents any isotopic form of hydrogen including ^{1}H, ^{2}H (D), and ^{3}H (T); C represents any isotopic form of carbon including ^{12}C, ^{13}C, and ^{14}C; O represents any isotopic form of oxygen including ^{16}O, ^{17}O and ^{18}O; N represents any isotopic form of nitrogen including ^{13}N, ^{14}N and ^{15}N; P represents any isotopic form of phosphorous including ^{31}P and ^{32}P; S represents any isotopic form of sulfur including ^{32}S and ^{35}S; F represents any isotopic form of fluorine including ^{19}F and ^{18}F; Cl represents any isotopic form of chlorine including ^{35}Cl, ^{37}Cl and ^{36}Cl; and the like. In a preferred embodiment, compounds represented by formulae (I)-(III) and any of the examples or embodiments disclosed herein comprises isotopes of the atoms therein in their naturally occurring abundance. However, in certain instances, it is desirable to enrich one or more atom in a particular isotope which would normally be present in less abundance. For example, ^{1}H would normally be present in greater than 99.98% abundance; however, a compound of the invention can be enriched in ^{2}H or ^{3}H at one or more positions where H is present. In particular embodiments of the compounds of formulae (I)-(III), when, for example, hydrogen is enriched in the deuterium isotope, the symbol "D" may be used to represent the enrichment in

Characterization of plasma unsaturated lysophosphatidylcholines in human and rat Biochem J 345 Pt 1, 61-67 (2000), which is incorporated by reference in its entirety). LPC is also detected in tumor-cell conditioned media (Umezu-Goto, M., et al.), presumably as a constituent of shed microvesicles. ATX, through its lysoPLD activity converts LPC to lysophosphatidic acid (LPA).

LPC is an important inflammatory mediator with recognized effects in multiple cell types and pathophysiological processes. It is a major component of oxidized low density lipoprotein (oxLDL) and it can exist in several other forms including free, micellar, bound to hydrophobic proteins such as albumin and incorporated in plasma membranes. It is produced by the hydrolysis of phosphatidylcholine (PC) by PLA2 with concurrent release of arachidonic acid and in turn of other pro-inflammatory mediators (prostaglandins and leukotrienes). Moreover, LPC externalization constitutes a chemotactic signal to phagocytic cells, while interaction with its receptors can also stimulate lymphocytic responses. LPC has been shown to have therapeutic effects in experimental sepsis, possibly by suppressing endotoxin-induced HMGB1 release from macrophages/monocytes.

LPA, the product of ATX action on LPC, is a bioactive phospholipid with diverse functions in almost every mammalian cell line (Moolenaar, W.H., van Meeteren, L.A. & Giepmans, B.N. The ins and outs of lysophosphatidic acid signaling. Bioessays 28, 870-881 (2004), which is incorporated by reference in its entirety). LPA is a major constituent of serum bound tightly to albumin, gelsolin and possibly other as yet unidentified proteins. See, e.g., Goetzl, E.J., et al Gelsolin binding and. cellular presentation of lysophosphatidic acid. J Biol Chem 275, 14573-14578 (2000); and Tigyi, G. & Miledi, R, Lysophosphatidates bound to serum albumin activate membrane currents in Xenopus oocytes and neurite retraction in PC12 pheochromocytoma cells. J Biol Chem 267, 21360-21367 (1992); each of which is incorporated by reference in its entirety.

LPA is also found in other biofluids, such as saliva and follicular fluid, and has been implicated in a wide array of functions, such as wound heeling, tumor invasion and metastasis, neurogenesis, myelination, astrocytes outgrowth and neurite retraction. The long list of LPA functions was also explained with the discovery that it signals through G-protein coupled receptors (GPCRs), via classical second messenger pathways. Five mammalian cell-surface LPA receptors have been identified so far. The best known are LPA1-3 (namely Edg-2, Edg-4 and Edg7) which are all members of the so-called 'endothelial differentiation gene' (EDG) family of GPCRs (Contos, J.J., Ishii, I. & Chun, J. Lysophosphatidic acid receptors. Mol Pharmacol 58, 1188-1196 (2000), which is incorporated by reference in its entirety). LPA deuterium. In one embodiment, when a compound of the invention is enriched in a radioactive isotope, for example ^{3}H and ^{14}C, they may be useful in drug and/or substrate tissue distribution assays. It is to be understood that the invention encompasses all such isotopic forms which modulate S1P and/or ATX activity.

Exemplary compounds represented by formula (I) which may be useful as S1P modulating agents and/or ATX modulating agents include:

4-(((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-ethylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-tert-butylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[3.5]nonan-7-yl-oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)methylamino)bicyclo[2.2.2]octane-1-carboxylic acid;

2-((2-(trans-4-tert-butylcyclohexyloxy)naphthalen-6-yl)methyl)-octahydro-1*H*-pyrido[1,2-*a*]pyrazine-7-carboxylic acid;

4-(((5-trifluoromethyl-6-(trans-4-tert-butylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((5-trifluoromethyl-6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-methylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cyclohexyl)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[5.5]undecan-3-yl-oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-methylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-isopropylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-

1-carboxylic acid;

4-(((6-(trans-4-methylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(heptyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)amino)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-phenylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-ethylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-isopropylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(4,4-dimethylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-ethylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-isopropylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)amino)-2-hydroxybicyclo[2.2.2]octane-1-acetic acid;

4-(((6-(4,4-dimethylcyclohexyloxy)napthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-(1,1-dimethylpropyl)cyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[3.5]nonan-7-yl-oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[5.5]undecan-3-yl-oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-isopropylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-(1,1-dimethylpropyl)cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-trifluoromethylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-ethylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[4.5]decan-8-yl-oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-phenylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-phenylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-phenylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-methylcyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-(trimethylsilyl)cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(cis-4-(trimethylsilyl)cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(trans-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[3.5]nonan-7-yl-oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[2.5]octan-6-yl-oxy)napthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-(((6-(spiro[2.5]octan-6-yl-oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid;

4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyridine-2-yl)piperazine;

4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyridine-4-yl)piperazine;

4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-phenylpiperazine;

4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyrimidine-2-yl)piperazine; 1-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-4-phenylpiperidine;

4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyrimidine-2-yl)piperazine;

4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyrazine-2-yl)piperazine;

4-((6-(cis-4-ethylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyridine-2-yl)piperazine;
4-((6-(spiro[4.5]decan-8-yl-oxy)naphthalen-2-yl)methyl)-1-(pyridine-2-yl)piperazine;
4-((6-(heptyloxy)naphthalen-2-yl)methyl)-1-(pyridine-2-yl)piperazine;
4-((6-(cis-4-isopropylcyclohexyloxy)quinolin-2-yl)methyl)-1-(pyridine-2-yl)piperazine;
4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyridine-2-yl)-1,4-diazepane;
1-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-4-(pyrimidine-2-yl)piperidine;
4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyrimidine-2-yl)-1,4-diazepane;
4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyrimidine-4-yl)piperazine; 4-((6-(cis-4-isopropylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyridine-2-yl)piperazine;
1-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-4-(pyridine-2-yl)piperidine;
4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(pyridine-3-yl)piperazine;
4-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-1-(2-methylpyrimidine-4-yl) piperazine;
3-(1-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
3-(1-((6-(4,4-dimethylcyclohexyloxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid; 3-(1-((6-(heptyloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
4-(1-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
3-(1-((6-(cis-2-ethylcyclohexyloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
3-(1-((6-(cis-2-isopropylcyclohexyloxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
3-(1-((6-(cis-2-ethylcyclohexyloxy)quinolin-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
3-(1-((6-(cis-2-isopropylcyclohexyloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
3-(1-((6-(4,4-dimethylcyclohexyloxy)napthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxylic acid;
3-(1-((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)azetidin-3-yl)cyclohexanecarboxyl

ic acid; 2-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-2-aza-6-oxaspiro[3.3]heptane; 7-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-2,7-diazaspiro[3.5]nonane; 2-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-6-hydroxy-2-azaspiro[3.3]heptane; 1-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-3-phenylazetidine; 2-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-2,7-diazaspiro[3.5]nonane; 1-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-3,3-di(hydroxymethyl)azetidine; 7-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-2-oxa-7-azaspiro[3.5]nonane; 8-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-3-oxo-2-aza-8-azaspiro[4.5]decane; 4-(((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.1]heptane-1-carboxylic acid; 4-(((5-trifluoromethyl-6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.1]heptane-1-carboxylic acid; 3-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.1]heptane-6-carboxylic acid; 3-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.1]nonane-9-carboxylic acid; 3-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid; 8-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; or 9-((6-(trans-4-tert-butylcyclohexyloxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid.

Additional exemplary compounds represented by formula (I) which may be useful as ATX modulating agents and/or S1P modulating agents include: 8-((5-difluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-(2-(5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)acetyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 9-(2-(5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)acetyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

2-(5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-oyl)decahydroisoquinolin-8-carboxylic acid;

9-(5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-oyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(5-trifluoromethyl-6-(cis-4-methylcyclohexyloxy)naphthalen-2-oyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(2-(5-trifluoromethyl-6-(trans-(cis-3,5-dimethyl)cyclohexyloxy)naphthalen-2-yl)acetyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-oyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalene-2-yl)methyl)amino)bicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-trifluoromethyl-6-(cis-4-methylcyclohexyloxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(5-trifluoromethyl-6-(cis-4-methylcyclohexyloxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

1-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalene-2-yl)methyl)4-imidazol-4-yl-piperidine;

8-((5-trifluoromethyl-6-(cis-4-methylcyclohexyloxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((5-trifluoromethyl-6-(cis-4-methylcyclohexyloxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

7-((5-trifluoromethyl-6-(cis-4-methylcyclohexyloxy)naphthalen-2-yl)methyl)-7-aza-10-oxaspiro[4.5]decane-3-carboxylic acid;

9-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)quinolin-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)quinolin-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

3-(1-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)azetidine-3-yl)cyclohexane-1-carboxylic acid;

3-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.1]nonane-7-carboxylic acid;

2-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-2-aza-6-oxaspiro[3.4]octane-7-carboxylic acid;

8-((5-trifluoromethyl-6-(4,4-difluorocyclohexyloxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-((5-trifluoromethyl-6-(4,4-difluorocyclohexyloxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
3-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.0]octane-7-carboxylic acid;
3-(1-(((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalene-2-yl)methyl)methylamino)bicyclo[2.2.2]octan-4-yl)propionic acid;
3-(((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalene-2-yl)methyl)amino)adamantyl-1-carboxylic acid;
1-(((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalene-2-yl)methyl)amino)bicyclo[2.2.1]heptane-4-carboxylic acid;
3-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.3.1]nonane-9-carboxylic acid;
2-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)decahydroisoquinolin-8-carboxylic acid;
5-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-5-azaspiro[2.3]hexane-1-carboxylic acid;
9-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid;
3-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-3-azabicyclo[3.1.0]hexane-6-carboxylic acid;
1-(5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-oyl)amino-2,3-dihydroindene-6-carboxylic acid;
3-(1-(((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octan-4-yl)propionic acid;
2-((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalen-2-yl)methyl)-2-azaspiro[3.3]heptane-6-carboxylic acid;
(7R,9aR)-2-((2-(trans-4-(trifluoromethyl)cyclohexyloxy)-1-(trifluoromethyl)naphthalen-6-yl)methyl)-octahydro-1H-pyrido[1,2-a]pyrazine-7-carboxylic acid;
1-(((5-trifluoromethyl-6-(cis-4-trifluoromethylcyclohexyloxy)naphthalene-2-yl)methyl)amino)bicyclo[2.2.2]octane-4-carboxylic acid; methyl

(7R,9aR)-2-((2-(trans-4-(trifluoromethyl)cyclohexyloxy)-1-(trifluoromethyl)naphthalen-6-yl) methyl)-octahydro-1H-pyrido[1,2-a]pyrazine-7-carboxylate;
8-(5-chloro-6-((cis-4-(trifluoromethyl) cyclohexyl)oxy)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(1-(5-cyano-6-((cis-4-methylcyclohexyl)oxy) naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-((5-cyano-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-(1-(5-cyano-6-((cis-4-methylcyclohexyl)oxy) naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)amino)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
2-((trans-4-(tert-butyl)cyclohexyl)amino) quinazoline-6-carboxylic acid;
9-(2-((trans-4-(tert-butyl)cyclohexyl)amino) quinazoline-6-carbonyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-((3-((cis-4-methylcyclohexyl)amino)isoquinolin-7-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-((4-chloro-3-((cis-4-methylcyclohexyl) amino)isoquinolin-7-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(3-((trans-4-(tert-butyl)cyclohexyl) amino)isoquinoline-7-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-((8-chloro-7-((cis-4-ethylcyclohexyl)oxy) isoquinolin-3-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-((8-bromo-7-((cis-4-ethylcyclohexyl)oxy) isoquinolin-3-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-((8-(trifluoromethyl)-7-((cis-4-(trifluoromethyl) cyclohexyl)oxy)isoquinolin-3-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-((6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)quinolin-2-yl)amino)bicyclo[3.3.1]nonane-3-carboxylic acid;
9-((5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-((5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-(1-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl) oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(5-cyano-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-cyano-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoro-methyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-cyano-6-((cis-4-methylcyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(5-cyano-6-((cis-4-methylcyclohexyl)oxy)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-(1-(5-cyano-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-(1-(5-cyano-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 9-(1-(5-cyano-6-(((1s,4s)-4-(trifluoromethyl)cyclohexyl) oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-((5-cyano-6-((cis-4-(trifluoromethyl)cyclohexyl) oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl) amino)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; methyl 8-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)amino)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylate;
8-((r)-1-(6-((cis-4-methylcyclohexyl)oxy)-5-(trifluoromethyl) naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-((s)-1-(6-((cis-4-methylcyclohexyl)oxy)-5-(trifluoromethyl) naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(1-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy) naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(1-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl) oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-(1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]non

receptors can couple to at least three distinct G proteins (G_q, G_i and $G_{12/13}$), which, in turn, feed into multiple effector systems. LPA activates G_q and thereby stimulates phospholipase C (PLC), with subsequent phosphatidylinositol - bisphosphate hydrolysis and generation of multiple second messengers leading to protein kinase C activation and changes in cytosolic calcium. LPA also activates G_i, which leads to at least three distinct signaling routes: inhibition of adenylyl cyclase with inhibition of cyclic AMP accumulation; stimulation of the mitogenic RAS-MAPK (mitogen-activated protein kinase) cascade; and activation of phosphatidylinositol 3-kinase (PI3K), leading to activation of the guanosine diphosphate/guanosine triphosphate (GDP/GTP) exchange factor TIAM1 and the downstream RAC GTPase, as well as to activation of the AKT/PKB antiapoptotic pathway. Finally, LPA activates $G_{12/13}$, leading to activation of the small GTPase RhoA, which drives cytoskeletal contraction and cell rounding. So, LPA not only signals via classic second messengers such as calcium, diacylglycerol and cAMP, but it also activates RAS- and RHO-family GTPases, the master switches that control cell proliferation, migration and morphogenesis.

LPA signaling through the RhoA-Rho kinase pathway mediates neurite retraction and inhibition of axon growth. Interfering with LPA signaling has been shown to promote axonal regeneration and functional recovery after CNS injury or cerebral ischemia. (See Broggini, et al., *Molecular Biology of the Cell* (2010), *21*:521-537.) It has been reported that addition of LPA to dorsal root fibers in *ex vivo* culture causes demyelination, whereas LPC fails to cause significant demyelination of nerve fibers in *ex vivo* cultures without further addition of recombinant ATX to the culture which when added caused significant demyelination at equivalent levels to LPA presumable due to conversion of LPC to LPA through the enzymatic activity of ATX. Moreover, injury induced demyelination was attenuated by about 50% in atx$^{+/-}$ mice (Nagai, *et al.*, *Molecular Pain* (2010), *6*:78).

A number of diseases or disorders involve demyelination of the central or peripheral nervous system which can occur for a number of reasons such as immune dysfunction as in multiple sclerosis, encephalomyelitis, Guillain-Barre Syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), transverse myelitis, and optic neuritis; demyelination due to injury such as spinal cord injury, traumatic brain injury, stroke, acute ischemic optic neuropathy, or other ischemia, cerebral palsy, neuropathy (e.g. neuropathy due to diabetes, chronic renal failure, hypothyroidism, liver failure, or compression of the nerve (e.g. in Bell's palsy)), post radiation injury, and central pontine myelolysis (CPM); inherited conditions such as Charcot-Marie-Tooth disease (CMT), Sjogren-Larsson syndrome, Refsum disease, Krabbe disease, Canavan disease, Alexander disease, Friedreich's ataxia, Pelizaeus–Merzbacher ane-3-carboxylic acid; 9-((R)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 9-((S)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 9-((R)-1-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 9-((S)-1-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-((R)-1-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((S)-1-(5-chloro-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; methyl 9-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)amino)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylate; methyl 9-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)amino)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylate; 8-((R)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((S)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 9-((R)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 9-((S)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-((R)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((S)-1-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; methyl 8-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)amino)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylate; 8-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)amino)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 9-(2-((cis-4-(tert-butyl)cyclohexyl)amino)quinazoline-6-carbonyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-((3-((trans-4-methylcyclohexyl)amino)

isoquinolin-7-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(2-((cis-4-(tert-butyl)cyclohexyl)amino)quinazoline-6-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(2-((trans-4-methylcyclohexyl)amino)quinazoline-6-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-((3-((trans-4-methylcyclohexyl)amino)isoquinolin-7-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-((4-chloro-3-((trans-4-methylcyclohexyl)amino)isoquinolin-7-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(3-(((1s,4s)-4-methylcyclohexyl)amino)isoquinoline-7-carbonyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-(3-((cis-4-methylcyclohexyl)amino)isoquinoline-7-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(2-((trans-4-(tert-butyl)cyclohexyl)amino)quinazoline-6-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(3-((trans-4-methylcyclohexyl)amino)isoquinoline-7-carbonyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-(3-((trans-4-methylcyclohexyl)amino)isoquinoline-7-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-(2-((trans-4-methylcyclohexyl)amino)quinazoline-6-carbonyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-(2-((cis-4-methylcyclohexyl)amino)quinazoline-6-carbonyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
9-((4-chloro-3-((trans-4-methylcyclohexyl)amino)isoquinolin-7-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-(3-((cis-4-(tert-butyl)cyclohexyl)amino)isoquinoline-7-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-(2-((cis-4-methylcyclohexyl)amino)quinazoline-6-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
8-((3-((cis-4-methylcyclohexyl)amino)isoquinolin-7-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;
9-((4-chloro-3-((cis-4-methylcyclohexyl)amino)isoquinolin-7-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;
8-(3-((cis-4-(tert-butyl)cyclohexyl)amino)-4-chloroisoquinoline-7-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(3-((trans-4-(tert-butyl)cyclohexyl)amino)-4-chloroisoquinoline-7-carbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 9-((8-bromo-7-((cis-4-(trifluoromethyl)cyclohexyl)oxy)isoquinolin-3-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-((8-bromo-7-((cis-4-(trifluoromethyl)cyclohexyl)oxy)isoquinolin-3-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((8-bromo-7-((cis-4-ethylcyclohexyl)oxy)isoquinolin-3-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((8-chloro-7-((cis-4-ethylcyclohexyl)oxy)isoquinolin-3-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((6-((cis 4-ethylcyclohexyl)oxy)quinolin-2-yl)amino)bicyclo[3.2.1]octane-3-carboxylic acid; 9-((8-bromo-7-((cis-4-methylcyclohexyl)oxy)isoquinolin-3-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-((6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)quinolin-2-yl)amino)bicyclo[3.2.1]octane-3-carboxylic acid; 9-((5-chloro-6-((cis-4-ethylcyclohexyl)oxy)quinolin-2-yl)amino)bicyclo[3.3.1]nonane-3-carboxylic acid; (1R,3S,5S)-9-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3,7-dicarboxylic acid; 9-(1R,3S,5S,7s)-2-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-2-azaadamantane-5-carboxylic acid; 9-(1R,3R,5S)-7-amino-9-((5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 9-((6-(bicyclo[3.1.0]hexan-3-yloxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid; 8-((6-(bicyclo[3.1.0]hexan-3-yloxy)-5-(trifluoromethyl)naphthalen-2-yl)methyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((R)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane3 -carboxylic acid; 8-((S)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3- -carboxylic acid; 8-((R)-1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid; 8-((S)-1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((R)-1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((S)-1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-((R)-1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl) naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-((S)-1-(6-((cis-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl) naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-((R)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((S)-1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((R)-1-(6-(((1s,4S)-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl) naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((S)-1-(6-(((1s,4R)-4-ethylcyclohexyl)oxy)-5-(trifluoromethyl) naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

4-(2-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)oxy)naphthalen-2-yl)propyl)-2H-tetrazol-5-yl)piperidine;

9-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carbonitrile; or

8-(1-(5-(trifluoromethyl)-6-((cis-4-(trifluoromethyl) cyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carbonitrile.

Compounds of the invention can modulate the activity of S1P receptors. A compound of the invention can have S1P receptor agonist or antagonist activity. The compound can be selective for the S1P4 receptor. The compound can be a selective S1P4 antagonist. Being selective can mean that the compound binds to the receptor (or relatively small group of related molecules or proteins) in a complex mixture, or in other words, when exposed to a variety of closely related receptor types, the compound can bind preferentially to just one of the receptor types.

The compound can have a greater affinity for the S1P4 receptor, by at by at least 100-fold, by at least 50-fold, by at least 10-fold, by at least 5-fold or by at least 2-fold, than for S1P1 receptor, S1P2 receptor, S1P3 receptor, or S1P5 receptor.

An inhibitor of S1P4 mediated activity can block S1P interaction with an S1P4 receptor. For example, the inhibitor can be an antagonist of an S1P4 receptor. An antagonist can be a molecule that has affinity for the receptor but does not induce activity or a specific activity from the receptor. The antagonist can bind with an S1P4 receptor with an IC_{50} value of less than 1 μM, less than 750 nM, less than 500 nM, less than 250 nM or less than 100 nM. The antagonist can bind with an S1P4 receptor with an IC_{50} value in a range between 1 nM and 1 μM, between 1 nM and 500 nM, between 10 nM and 250 nM, between 25 nm and 100 nM, or between 50 nM and 100 nM.

The compounds can also promote oligodendrocyte progenitor cell differentiation. The compounds can promote myelination or remyelination.

An "S1P modulating agent" refers a compound or composition that is capable of inducing a detectable change in S1P receptor activity in vivo or in vitro (e.g., at least 10% increase or decrease in S1P activity as measured by a given assay such as the assays described in the examples and known in the art. "S1P receptor," refers to all of the S1P receptor subtypes (for example, the S1P receptors S1P1, S1P2, S1P3, S1P4, or S1P5), unless the specific subtype is indicated. It is well known in the art how to determine S1P agonist or antagonist activity using the standard tests described herein, or using other similar tests which are well known in the art. In some cases, depending on the cell type and conditions used, an S1P modulating agent can have agonist or antagonist activity, even at the same receptor subtype.

The biological effects of an S1P modulating agent vary depending on whether the compound has S1P receptor agonist or antagonist activity. Potential uses of an S1P modulating agent include, but are not limited to, prevention or treatment of a pathological condition or symptom in a mammal. For example, the condition can include asthma, an inflammatory neuropathies, arthritis, lupus erythematosis, psoriasis, an ischemia reperfusion injury, a solid tumor, a tumor metastasis, a disease associated with angiogenesis, a vascular disease, a pain condition, an acute viral disease, or insulin-dependent diabetes, and non-insulin dependent diabetes. The condition can alter lymphocyte trafficking as a method of treatment for neuropathic pain, inflammation-induced pain (e.g., where prostaglandins are involved) or treatment of autoimmune pathologies such as uveitis, type I diabetes, rheumatoid arthritis, chronic inflammatory disorders, inflammatory bowel diseases (e.g., Crohn's disease and ulcerative colitis), multiple sclerosis, and in drug-eluting stents. Additional uses can include treatment of brain degenerative diseases, heart diseases, cancers, or hepatitis C. See, for example, WO 2005/085295, WO 2004/010987, WO 03/097028, and WO 2006/072562, each of which is incorporated by reference in its entirety. A class of S1P receptor agonists are described in provisional U.S. Application no. 60/956,111, filed August 15, 2007, and PCT/US2008/073378, filed August 15, 2008, each of which is incorporated by reference in its entirety. See also provisional U.S. Application no. 61/231,539, filed August 5, 2009, and PCT/US2010/44607, filed August 5, 2010, each of which is incorporated by reference in its entirety. See also provisional U.S. Application no. 61/440,254, filed February 7, 2011, and PCT/US2012/23799 filed February 6, 2012, each of which is incorporated by reference in its entirety.

Additional potential uses of an S1P modulating agent include, but are not limited to, prevention or treatment of a pathological condition or symptom in a mammal. For example, the condition can include inhibited cell migration of oligodendrocyte precursor cells (OPCs).

Potential uses of an S1P receptor antagonist, and S1P4 receptor type selective antagonists particularly, include, but are not limited to, prevention or treatment of a pathological condition or symptom in a mammal.

LPA has been shown to be involved in lymphocyte trafficking and helps promote entry of lymphocytes into secondary lymphoid organs (see Kanda, et al., Nat. Immunology (2008), 9:415-423). Therefore, the disclosed compounds are expected to be useful for altering lymphocyte trafficking as a method for prolonging allograft survival, for example transplantation including solid organ transplants, treatment of graft vs. host disease, bone marrow transplantation, and the like.

An "ATX modulating agent" refers a compound or composition that is capable of inducing a detectable change in ATX activity in vivo or in vitro (e.g., at least 10% increase or decrease in ATX activity as measured by a given assay such as the assays described in the examples and known in the art. A compound of the invention be an ATX modulating agent, i.e., it can modulate the activity of ATX. For example, a compound of the invention can be an ATX inhibitor. The compound can be a selective ATX modulating agent. Being selective can mean that the compound binds to ATX preferentially when exposed to a variety of potential binding partners. The compound can have a greater affinity for the ATX, by at by at least 100-fold, by at least 50-fold, by at least 10-fold, by at least 5-fold or by at least 2-fold, than for other binding partners. Affinity can be measured, for example, as a dissociation constant (K_d), as an inhibition constant (such as IC_{50}), or another measure; provided that affinity is measured in a consistent fashion between ATX and the other binding partners it is compared to.

An inhibitor of ATX mediated activity can block interaction of ATX with its native substrate(s), such as LPC. For example, the inhibitor can show an IC_{50} value of less than 1 μM, less than 750 nM, less than 500 nM, less than 250 nM, less than 100 nM, less than 50 nM, less than 25 nM, or less than 10 nM, when measured in a FRET-based assay using FS-3 substrate (see, e.g., Ferguson, C.G., et al., Org Lett. 2006 May 11; 8(10): 2023–2026, which is incorporated by reference in its entirety).

Some substrates and inhibititors of ATX are described in WO 2011/151461, which is incorporated by reference in its entirety.

Potential uses of an ATX modulating agent include, but are not limited to, prevention or treatment of a pathological condition or symptom in a mammal. The pathological disorder can be an inflammatory disorder, an autoimmune disorder, a fibrosis of the lung, or a malignancy of the lung. Prevention or treatment of the pathological condition or symptom can include administering to the mammal an effective amount of an ATX modulating agent, e.g., an ATX inhibitor, to prevent, treat or reduce symptoms of the inflammatory disorder, autoimmune disorder, the fibrosis of the lung, or the malignancy of the lung. In one embodiment, the inflammatory disorder is rheumatoid arthritis (RA). In another embodiment, the autoimmune disorder is multiple sclerosis (MS). A particular example of lung fibrosis is an interstitial lung disease, for instance, pulmonary fibrosis. See, for example, WO 2011/151461, which is incorporated by reference in its entirety.

In some embodiments, an ATX inhibitor of the present invention can be used to treat or prevent a demyelinating disease or disorder. Demyelinating diseases or disorders include multiple sclerosis, Guillain-Barre Syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), transverse myelitis, and optic neuritis, spinal cord injury, stroke or other ischemia, cerebral palsy, Charcot-Marie-Tooth disease (CMT), Sjogren-Larsson syndrome, Refsum disease, Krabbe disease, Canavan disease, Alexander disease, nerve damage due to pernicious anemia, progressive multifocal leukoencephalopathy (PML), Lyme disease, tabes dorsalis due to untreated syphilis, demyelination due to exposure to an organophosphates, demyelination due to vitamin B12 deficiency or copper deficiency.

In addition, disclosed compounds can be useful as antagonists of the cannabinoid CB_1 receptor. CB_1 antagonism is associated with a decrease in body weight and an improvement in blood lipid profiles. The CB_1 antagonism could be in concert with S1P receptor activity, or be independent of activity at any S1P receptor.

In addition, disclosed compounds can be useful for inhibition of group IVA cytosolic PLA_2 ($cPLA_2$). $cPLA_2$ catalyzes the release of eicosanoic acids (e.g., arachidonic acid). The eicosanoic acids are transformed to pro-inflammatory eicosanoids such as prostaglandins and leukotrienes. Thus, disclosed compounds may be useful as anti-inflammatory agents. This inhibition could be in concert with S1P receptor activity, or be independent of activity at any S1P receptor.

In addition, disclosed compounds may be useful for inhibition of the multiple substrate lipid kinase (MuLK). MuLK is highly expressed in many human tumor cells and thus its inhibition might slow the growth or spread of tumors.

Neurological Disorders

MS can begin with a relapsing-remitting pattern of neurologic involvement, which then can progress to a chronic phase with increasing neurological damage. MS can be associated with the destruction of myelin, oligodendrocytes or axons localized to chronic lesions. The demyelination observed in MS may not always permanent and remyelination has been documented in early stages of the disease. Remyelination of neurons can require oligodendrocytes.

The distal tip of an extending axon or neurite can include a specialized region, known as the growth cone. Growth cones can sense the local environment and can guide axonal growth toward a neuron's target cell. Growth cones can respond to environmental cues, for example, surface adhesiveness, growth factors, neurotransmitters and electric fields. The growth cones can advance at a rate of one to two millimeters per day. The growth cone can explore the area ahead of it and on either side, by means of elongations classified as lamellipodia and filopodia. When an elongation contacts an unfavorable surface, it can withdraw. When an elongation contacts a favorable growth surface, it can continue to extend and guides the growth cone in that direction. When the growth cone reaches an appropriate target cell a synaptic connection can be created.

Nerve cell function can be influenced by contact between neurons and other cells in their immediate environment (Rutishauser, et al., 1988, *Physiol. Rev.* 68:819, which is incorporated by reference in its entirety). These cells can include specialized glial cells, oligodendrocytes in the central nervous system (CNS), and Schwann cells in the peripheral nervous system (PNS), which can sheathe the neuronal axon with myelin (Lemke, 1992, in *An Introduction to Molecular Neurobiology*, Z. Hall, Ed., p. 281, Sinauer, each of which is incorporated by reference in its entirety). LPA causes the collapse of the neuron growth cone and tends to inhibit or reverse the morphological differentiation of many neuronal cell lines (see Gendaszewska-Darmach, Acta Biochimica Polonica (2008), 55(2):227-240). Since ATX activity is involved in the generation of LPA, inhibitors of ATX should increase the ability of the nervous system to make synaptic connections. Thus, ATX inhibitors may be useful in treating neurodegenerative disorders such as Alzheimer’s disease, Huntington’s disease, Parkinson’s disease (including Parkinson’s dementia), Lewy Body Dementia, amylotrophic lateral sclerosis (ALS), Friedreich's ataxia, spinal muscular atrophy.

CNS neurons can have the inherent potential to regenerate after injury, but they can be inhibited from doing so by inhibitory proteins present in myelin (Brittis et al., 2001, *Neuron* 30:11-14; Jones et al., 2002, *J. Neurosci.* 22:2792-2803; Grimpe et al., 2002, *J. Neurosci.*:22:3144-3160, each of which is incorporated by reference in its entirety).

Several myelin inhibitory proteins found on oligodendrocytes have been characterized. Known examples of myelin inhibitory proteins can include NogoA (Chen et al., Nature, 2000, 403, 434-439; Grandpre et al., *Nature* 2000, 403, 439-444, each of which is incorporated by reference in its entirety), myelin associated glycoprotein (MAG) (McKerracher et al., 1994, *Neuron* 13:805-811; Mukhopadhyay et al., 1994, *Neuron* 13:757-767, each of which is incorporated by reference in its entirety) or oligodendrocyte glycoprotein (OM-gp), Mikol et al., 1988, *J. Cell. Biol.*106:1273-1279, each of which is incorporated by reference in its entirety). Each of these proteins can be a ligand for the neuronal Nogo receptor-1 (NgR1 (Wang et al., *Nature* 2002, 417, 941-944; Grandpre et al., *Nature* 2000, 403, 439-444; Chen et al., *Nature*, 2000, 403, 434-439; Domeniconi et al., *Neuron* 2002, published online June 28, 2002, each of which is incorporated by reference in its entirety).

Nogo receptor-1 (NgR1) is a GPI-anchored membrane protein that contains 8 leucine rich repeats (Fournier et al., 2001, *Nature* 409:341-346, which is incorporated by reference in its entirety). Upon interaction with inhibitory proteins (e.g., NogoA, MAG and OM-gp), the NgR1 complex can transduce signals that lead to growth cone collapse and inhibition of neurite outgrowth.

There is a need for molecules and methods for inhibiting NgR1-mediated growth cone collapse and the resulting inhibition of neurite outgrowth. Additionally, there is a need for molecules which increase neuronal survival and axon regeneration, particularly for the treatment of disease, disorders or injuries that involve axonal injury, neuronal or oligodendrocyte cell death, demyelination or dymyelination or generally relate to the nervous system.

Such diseases, disorders or injuries can include, but are not limited to, multiple sclerosis (MS), progressive multifocal leukoencephalopathy (PML), encephalomyelitis (EPL), central pontine myelolysis (CPM), adrenoleukodystrophy, Alexander's disease, Pelizaeus Merzbacher disease (PMZ), Globoid cell Leucodystrophy (Krabbe's disease) and Wallerian Degeneration, optic neuritis, transverse myelitis, amylotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, Parkinson's disease, spinal cord injury, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, stroke, acute ischemic optic neuropathy, vitamin E deficiency, isolated vitamin E deficiency syndrome, AR, Bassen-Kornzweig syndrome, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, trigeminal neuralgia, or Bell's palsy. Among these diseases, MS may the most widespread, affecting approximately 2.5 million people worldwide.

Various disease-modifying treatments may be available for MS, including the use of corticosteroids and immunomodulating agents such as interferon beta or Tysabri®. In addition, because of the central role of oligodendrocytes and myelination in MS, there have been efforts to develop therapies to increase oligodendrocyte numbers or enhance myelination. See, e.g., Cohen et al., U.S. Pat. No. 5,574,009; Chang et al., *N. Engl. J. Med.* 346: 165-73 (2002), each of which is incorporated by reference in its entirety. However, there remains an urgent need to devise additional therapies for MS and other demyelination and dismyelination disorders.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can promote myelination or remyelination. A method can include administering a compound of the invention, or a pharmaceutically acceptable salt thereof, to cells. A method of promoting oligodendrocyte progenitor cell differentiation can include administering a compound of the invention, or a pharmaceutically acceptable salt thereof, to cells. A method of treating multiple sclerosis can include administering a compound of the invention, or a pharmaceutically acceptable salt thereof, to a subject.

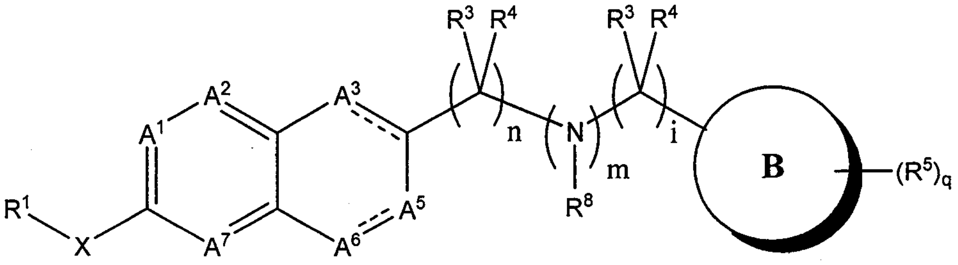
A number of studies have shown that ATX is expressed in non-pathological conditions, throughout development, with high expression levels in the CNS among other tissues. ATX mRNA was identified as highly upregulated during oligodendrocyte differentiation and ATX protein expression is also apparent in maturing ODCs, temporally correlated with the process of myelination. Finally, in the adult brain ATX is expressed in secretory epithelial cells, such as the choroid plexus, ciliary, iris pigment, and retinal pigment epithelial cells, whereas there is evidence for ATX expression in leptomenigneal cells and cells of the CNS vasculature. See, for example, Fuss, B., et al., J Neurosci 17, 9095-9103 (1997); Kawagoe, H., et al. Genomics 30, 380-384 (1995); Lee, H.Y., et al. J Biol Chem 271, 24408- 24412 (1996); Narita, M., et al., J Biol Chem 269, 28235-28242 (1994); Bachner, D., et al., Mechanisms of Development 84, 121- 125 (1999); Awatramani, R., et al., Nat Genet 35, 70-75 (2003); Li, Y., et al., J Neurol Sci 193, 137-146 (2002); Dugas, J.C., et al., J Neurosci 26, 10967-10983 (2006); Fox, M.A., et al., Molecular and Cellular Neuroscience 27, 140- 150 (2004); Hoelzinger, D.B., et al., Neoplasia 7, 7-16 (2005); and Sato, K., et al., J Neurochem 92, 904-914 (2005); each of which is incorporated by reference in its entirety.

Although neurons and astrocytes do not seem to express ATX under physiological conditions, ATX is highly upregulated in astrocytes following brain lesion. Two hallmarks of disease, Bassen-Kornzweig syndrome, metachromatic leukodystrophy (MLD), adrenoleukodystrophy, and nerve damage due to pernicious anemia; viral infection such as progressive multifocal leukoencephalopathy (PML), Lyme disease, or tabes dorsalis due to untreated syphilis; toxic exposure due to chronic alcoholism (which is a possible cause of Marchiafava-Bignami disease), chemotherapy, or exposure to chemicals such as organophosphates; or dietary deficiencies such as vitamin B12 deficiency, vitamin E deficiency and copper deficiency. Other demyelination disorders may have unknown causes or multiple causes such as trigeminal neuralgia, Marchiafava-Bignami disease and Bell's palsy. One particularly successful approach to treating demyelination disorders which are caused by autoimmune dysfunction has been to attempt to limit the extent of demyelination by treating the patient with immunoregulatory drugs. However, typically this approach has merely postponed but not avoided the onset of disability in these patients. Patients with demyelination due to other causes have even fewer treatment options. Therefore, the need exists to develop new treatments for patients with demyelination diseases or disorders.

SUMMARY

A compound of formula (I), or a pharmaceutically acceptable salt thereof, can be an S1P modulating agent and/or an ATX modulating agent, e.g., an S1P4 antagonist or ATX inhibitor.

In one aspect, a compound is represented by formula (I):



(I)

or a pharmaceutically acceptable salt thereof.

In formula (I), X can be O, $S(O)_r$, NR^{12}, C(O) or CH_2, in which r is 0, 1, or 2.

A^1, A^2, and A^7 can each independently be CR^2 or N.

A^3, A^5, and A^6 can each independently be CR^2, $C(R^2)_2$, N, or NR^{19}, wherein at least three of A^1, A^2, A^3, A^5, A^6, and A^7 are CR^2 or $C(R^2)_2$.

"------" indicates a double or a single bond.

reactive astrogliosis can be induced by LPA itself: hypertrophy of astrocytes and stress fiber formation. This may indicate an autoregulation loop of astrocytic activation, in which astrocytes upregulate the LPA- generating enzyme ATX and become activated by its metabolite LPA, while increased amounts of the metabolite inhibit the catalytic activity of ATX. See, e.g., Savaskan, N.E., et al., Cell Mol Life Sci 64, 230-243 (2007); Ramakers, G.J, & Moolenaar, W.H., Exp Cell Res 245, 252-262 (1998); and van Meeteren, L.A., et al., J Biol Chem 280, 21155-21161 (2005); each of which is incorporated by reference in its entirety.

ATX expression levels were shown to be elevated in glioblastoma multiform samples, and ATX was shown to augment invasiveness of cells transformed with ras, a key signaling molecule that promotes gliomagenesis. ATX expression was also detected in primary tumor tissues from neuroblastoma patients and retinoic acid induced expression of ATX in N-myc-amplified neuroblastoma cells.

There is significant evidence for ATX signaling in demyelination processes and in other neurodegenerative conditions. As noted above, it has been reported that addition of LPA to dorsal root fibers in *ex vivo* culture causes demyelination, whereas LPC fails to cause significant demyelination of nerve fibers in *ex vivo* cultures without further addition of recombinant ATX to the culture. Addition of recombinant ATX caused significant demyelination at equivalent levels to LPA presumable due to conversion of LPC to LPA through the enzymatic activity of ATX. In addition, injury induced demyelination was attenuated by about 50% in atx$^{+/-}$ mice over their wild type counterparts (Nagai, *et al.*, *Molecular Pain* (2010), *6*:78).

ATX protein levels were found deregulated in an animal model of MS (experimental autoimmune encephalitis; EAE) at the onset of clinical symptoms. See, e.g., Hoelzinger, D.B., et al. Neoplasia 7, 7-16 (2005); Nam, S.W., et al., Oncogene 19, 241-247 (2000); Kawagoe, H., et al., Cancer Res 57, 2516-2521 (1997); Dufner-Beattie, J., et al., Mol Carcinog 30, 181- 189 (2001); Umemura, K., et al., Neuroscience Letters 400, 97-100 (2006); and Fuss, B., et al., J Neurosci 17, 9095-9103 (1997); each of which is incorporated by reference in its entirety. Moreover, significant ATX expression was been detected in the cerebrospinal fluid of patients suffering with multiple sclerosis (MS), while completely lacking from the control samples, suggesting a role for ATX in maintenance of cerebrospinal fluid homeostasis during pathological/ demyelinating conditions. Hammack, B.N., et al. Proteomic analysis of multiple sclerosis cerebrospinal fluid. Mult Scler 10, 245-260 (2004); and Dennis, J., et al., J Neurosci Res 82, 737-742 (2005); each of which is incorporated by reference in its entirety.

Interestingly, ATX mRNA expression was found to be elevated in the frontal cortex of Alzheimer-type dementia patients indicating a potential involvement for ATX signaling in neurodegenerative diseases. LPA receptors are enriched in the CNS and their expression patterns suggest their potential involvement in developmental process including neurogenesis, neuronal migration, axon extension and myelination. Noteworthy, only two receptors have the same spatiotemporal expression as ATX in the CNS (Contos, J.J., et al., Mol Cell Biol 22, 6921-6929 (2002); Jaillard, C, ei al, Edg8/Sl P5: an oligodendroglial receptor with dual function on process retraction and cell survival. J Neurosci 25, 1459-1469 (2005); and Saba, J.D. Journal of cellular biochemistry 92, 967-992 (2004); each of which is incorporated by reference in its entirety). LPAi and SIP5 are specific for ODCs, and their expression highly correlates with the process of myelination. LPA1 is expressed in restricted fashion within the neuroblasts of the neuroproliferatve Ventricular Zone (VZ) of the developing cortex, in the dorsal olfactory bulb, along the pial cells of neural crest origin, and in developing facial bone tissue. Expression is observed during E11-E18, corresponding to a time period during which neurogenesis occurs. LPA1 expression is undetectable in the VZ after this point, to reappear during the first postnatal week within ODCs. Notably, Schwann cells (the myelinating cells of the Peripheral Nervous System; PNS) express high levels of LPA1 early in development and persistently throughout life, suggesting an influence of LPA on myelinating processes (Weiner. J.A. & Chun, J., Proc Natl Acad Sci U S A 96, 5233-5238 (1999), which is incorporated by reference in its entirety).

The above data strongly support a critical role for ATX and LPA signaling in neuronal development, oligodendrocyte differentiation and myelination, as well as possibly in the autoregulation of astrocyte activation. Moreover, the regulation of ATX and thus LPA production at local sites of CNS injury, inflammatory or autoimmune, could contribute to tissue homeostasis through the numerous effects of LPA. As demyelination and deregulated cerebrospinal fluid homeostasis are the hallmarks of multiple sclerosis, a role of ATX and LPA signaling in the pathophysiology of multiple sclerosis seems very likely.

The S1P modulating agents and/or ATX modulating agents of the invention can be used to various forms of MS including relapsing-remitting, secondary-progressive, primary-progressive, and progressive-relapsing forms. In addition, S1P modulating agents and/or ATX modulating agents of the invention can be used alone or in conjunction with other agents to treat or prevent MS. In a preferred embodiment, the compounds of the invention can be used to treat or prevent MS in combination with an immunomodulating therapy such as corticosteroids, beta interferon-1a (such as Avonex® or Rebif®), beta interferon-1b (Betaseron®), natalizumab (Tysabri®), glatiramer,and mitoxantrone.

Pain Mediation

Pain experienced by mammals can be divided into two main categories: acute pain (or nociceptive) and chronic pain which can be subdivided into chronic inflammatory pain and chronic neuropathic pain. Acute pain is a response to stimulus that causes tissue injury and is a signal to move away from the stimulus to minimize tissue damage. Chronic pain, on the other hand, serves no biological function and develops as a result of inflammation caused by tissue damage (inflammatory pain) or by damage to the nervous system such as demyelination (neuropathic pain). Chronic pain is generally characterized by stimulus-independent, persistent pain or by abnormal pain perception triggered by innocuous stimuli.

LPA has been found to be a mediator of both inflammatory pain and neuropathic pain. The transient receptor potential channel TRPV1 is known to be the originator of inflammatory pain. LPA has been shown to directly activate TRPV1 thereby creating pain stimulus by binding to its intracellular C-terminus (Tigyi, *Nature Chemical Biology* (January 2012), *8*:22-23). Thus, compounds which inhibit the formation of LPA by inhibiting the action of ATX would be useful in treating inflammatory pain.

LPA has also been shown to play a role in neuropathic pain. For example, sciatic nerve injury has been shown to induce demyelination, down-regulation of myelin-associated glycoprotein (MAG) and damage to Schwann cell partitioning of C-fiber-containing Remak bundles in the sciatic nerve and dorsal root. However, demyelination, MAG down-regulation and Remak bundle damage in the dorsal root were abolished in LPA_1 receptor-deficient ($Lpar1^{-/-}$) mice (Nagai, *et al.*, *Molecular Pain* (2010), *6*:78). These results indicate that compounds that inhibit the formation of LPA by inhibiting the action of ATX would decrease dorsal root demyelination following nerve injury and decrease or eliminate neuropathic pain.

Thus the compounds of the invention are useful in treating or preventing chronic pain such as inflammatory pain and neuropathic pain in mammals.

Rheumatoid Arthritis (RA)

Studies in human and animal models of RA suggest that ATX plays a role in the development and progress of the disease. For example, increased ATX mRNA expression was detected in synovial fibroblasts (SFs) from animal models of RA during differential expression profiling, and human RA SFs were shown to express mRNA for both ATX and LPARs (Aidinis, V., et al., PLoS genetics 1, e48 (2005); Zhao, C, et al., Molecular pharmacology 73, 587-600 (2008); each of which is incorporated by reference in its entirety). ATX is overexpressed from activated SFs in arthritic joints, both in animal models and human patients (see WO 2011/151461). ATX expression was shown to be induced from TNF, the major pro-inflammatory factor driving RA.

Disease development was assessed in well-established animal models of RA. When ATX expression was conditionally ablated specifically in SFs, the lack of ATX expression in the joints resulted in marked decreased inflammation and synovial hyperplasia. This suggested an active involvement of the ATX-LPA axis in the pathogenesis of the disease. Similar results were also obtained with pharmacologic inhibition of ATX enzymatic activity and LPA signaling. A series of ex vivo experiments on primary SFs revealed that ATX, through LPA production, stimulates rearrangements of the actin cytoskeleton, proliferation and migration to the extracellular matrix (ECM), as well as the secretion of proinflammatory cytokines and matrix metalloproteinases (MMPs). Moreover, the LPA effect was shown to be synergistic with TNF and dependent on the activation of MAPK cellular signaling pathways. See, e.g., Armaka, M., et al., The Journal of experimental medicine 205, 331-337 (2008); which is incorporated by reference in its entirety.

In one embodiment a method for treating an individual with RA or the individual at risk of suffering thereof comprises administering to said individual an S1P modulating agent and/or ATX modulating agent of the invention in conjunction with an anti-TNF antibody for use in the treatment of RA. Examples of suitable anti-TNF antibodies are adalimumab, etanercept, golimumab, and infliximab (Taylor PC, Feldmann M. Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. Nat Rev Rheumatol. 2009 Oct;5(10):578-82).

Pulmonary Fibrosis

Evidence also suggests a role for ATX in pulmonary fibrosis. Mice lacking lysophosphatidic acid (LPA) receptor 1(LPAR1) were protected from Bleomycin (BLM)-induced pulmonary fibrosis and mortality, suggesting a major role for LPA in disease pathophysiology. The majority of circulating LPA is produced by the phospholipase D activity of Autotaxin (ATX) and the hydrolysis of lysophosphatidylcholine (LPC). Increased ATX expression has been previously reported in the hyperplastic epithelium of fibrotic lungs of human patients and animal models.

Therefore, we hypothesized that genetic or pharmacologic inhibition of ATX activity would reduce local or circulating LPA levels and hence attenuate disease pathogenesis.

Lung Cancer

Increased ATX expression has been detected in a large number of malignancies, including mammary, thyroid, hepatocellular and renal cell carcinomas, glioblastoma and neuroblastoma, as well as NSCLC. Strikingly, transgenic overexpression of ATX was shown to induce spontaneous mammary carcinogenesis. In accordance, in vitro ATX overexpression in various cell types promotes proliferation and metastasis while inhibiting apoptosis. LPA's actions are concordant with many of the "hallmarks of cancer", indicating a role for LPA in the initiation or progression of malignant disease. Indeed LPA levels are significantly increased in malignant effusions, and its receptors are aberrantly expressed in several human cancers.

See, for example: Euer, N., et al., Anticancer Res 22, 733-740 (2002); Liu, S., et al., Cancer Cell 15, 539-550 (2009); Zhang, G., et al., Chin Med J (Engl) 112, 330- 332 (1999); Stassar, M.J., et al., Br J Cancer 85. 1372- 1382 (2001); Kishi, Y., et al., J Biol Chem 281, 17492- 17500 (2006); Kawagoe, H., et al., Cancer Res 57, 2516-2521 (1997); Yang, Y., et al., Am J Respir Cell Mol Biol 21, 216-222 (1999); and Toews, M.L., et al. Biochim Biophys Acta 1582, 240-250 (2002); each of which is incorporated by reference in its entirety.

In cases where a compound of the invention can be sufficiently basic or acidic to form stable nontoxic acid or base salts, preparation and administration of the compounds as pharmaceutically acceptable salts may be appropriate. Examples of pharmaceutically acceptable salts can be organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, or α-glycerophosphate. Inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts from inorganic bases, can include but are not limited to, sodium, potassium, lithium, ammonium, calcium or magnesium salts. Salts derived from organic bases can include, but are not limited to, salts of primary, secondary or tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, or mixed di- and tri-amines where at least two of the substituents on the amine can be different and can be alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, or heterocyclic and the like. Also included can be amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Non-limiting examples of amines can include, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, or N-ethylpiperidine, and the like. Other carboxylic acid derivatives can be useful, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, or dialkyl carboxamides, and the like.

Pharmaceutical compositions can include a compound of the invention, or a pharmaceutically acceptable salt thereof. More particularly, such compounds can be formulated as pharmaceutical compositions using standard pharmaceutically acceptable carriers, fillers, solubilizing agents and stabilizers known to those skilled in the art. For example, a pharmaceutical composition including a compound of the invention, or a salt, analog, derivative, or modification thereof, as described herein, is used to administer the appropriate compound to a subject.

The compounds of the invention, or a pharmaceutically acceptable salt thereof, are useful for treating a disease or disorder associated with S1P receptor activity, and/or ATX activity. In one embodiment, a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, is administered to a subject in need thereof. In another embodiment, a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically-acceptable carrier is administered to a subject in need thereof.

The compounds of the invention can be used in combination with at least one further active ingredient, such as a medicament used in the treatment of multiple sclerosis such as Tysabri®, dimethyl fumarate, an interferon (such as pegylated or non-pegylated interferons, preferably interferon β-1a or pegylated interferon β -1a), glatiramer acetate, a compound improving vascular function, an immunomodulating agent (such as Fingolimod, cyclosporins, rapamycins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporine A, cyclosporine G, FK-506, ABT-281, ASM981, rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin etc.); corticosteroids; cyclophosphamide; azathioprine; mitoxanthrone, methotrexate; leflunomide; mizoribine; mycophenolic add; mycophenolate mofetil; 15-deoxyspergualine; diflucortolone valerate; difluprednate; Alclometasone dipropionate; amcinonide; amsacrine; asparaginase; azathioprine; basiliximab; beclometasone dipropionate; betamethasone; betamethasone dipropionate; betamethasone phosphate sodique; betamethasone valerate; budesonide; captopril; chlormethine chlorhydrate; clobetasol propionate; cortisone acetate; cortivazol; cyclophosphamide; cytarabine; daclizumab; dactinomycine; desonide; desoximetasone; dexamethasone; dexamethasone acetate; dexamethasone isonicotinate; dexamethasone metasulfobenzoate sodique; dexamethasonephosphate; dexamethasone tebutate; dichlorisone acetate; doxorubicinee chlorhydrate; epirubicine chlorhydrate; fluclorolone acetonide; fludrocortisone acetate; fludroxycortide; flumetasone pivalate; flunisolide; fluocinolone acetonide; fluocinonide; fluocortolone; fluocortolone hexanoate; fluocortolone pivalate; fluorometholone; fluprednidene acetate; fluticasone propionate; gemcitabine chlorhydrate; halcinonide; hydrocortisone; hydrocortisone acetate; hydrocortisone butyrate; hydrocortisone hemisuccinate; melphalan; meprednisone; mercaptopurine; methylprednisolone; methylprednisolone acetate; methylprednisolone hemisuccinate; misoprostol; muromonab-cd3; mycophenolate mofetil; paramethansone acetate; prednazoline, prednisolone; prednisolone acetate; prednisolone caproate; prednisolone metasulfobenzoate sodique; prednisolone phosphate sodique; prednisone; prednylidene; rifampicine; rifampicine sodique; tacrolimus; teriflunomide; thalidomide; thiotepa; tixocortol pivalate; triamcinolone; triamcinolone acetonide hemisuccinate; triamcinolone benetonide; triamcinolone diacetate; triamcinolone hexacetonide; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4,CD7, CD20 (e.g., rituximab and ocrelizumab), CD25, CD28, B7, CD40, CD45, CD56 (e.g., daclizumab), or CD58 or their ligands; or other immunomodulating agenty compounds, e.g. CTLA41g, or other adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including Selectin antagonists and VLA-4 antagonists (such as Tysabri®); remyelinating agents such as BIIB033. Compounds of the invention can also be used in combination with agents which treat the symptoms of multiple sclerosis such as fampridine.

The dose of a compound of the invention, or a pharmaceutically acceptable salt thereof, administered to a subject can be less than 10 µg, less than 25 µg, less than 50 µg, less than 75 µg, less than 0.10 mg, less than 0.25 mg, less than 0.5 mg, less than 1 mg, less than 2.5 mg, less than 5 mg, less than 10 mg, less than 15 mg, less than 20 mg, less than 50 mg, less than 75 mg, less than 100 mg, or less than 500 mg.

Administering can include administering by topical, enteral, parenteral, transdermal, transmucosal, inhalational, intracisternal, epidural, intravaginal, intravenous, intramuscular, subcutaneous, intradermal or intravitreal administration. In addition, the term "administer" or "administering" encompasses delivering a compound of the invention as a prodrug which is converted or metabolized in the body of the mammal into a compound of the invention. In one embodiment, a compound of the invention is administered in a non-prodrug form. In another embodiment, the compound is administered as a prodrug which is metabolized to a compound of the invention in the body of a mammal.

The duration of administering can be less than 30 seconds, less than 1 minute, about 1 minute, between 1 minute and 5 minutes, between 5 minutes and 10 minutes, between 10 minutes and 20 minutes, between 20 minutes and 30 minutes, between 30 minutes and 1 hour, between 1 hour and 3 hours, between 3 hours and 6 hours, between 6 hours and 12 hours, between 12 hours and 24 hours or for more than 24 hours.

Administering the inhibitor or compound can include multiple administrations. The duration between administrations can be less than 30 seconds, less than 1 minute, about 1 minute, between 1 minute and 5 minutes, between 5 minutes and 10 minutes, between 10 minutes and 20 minutes, between 20 minutes and 30 minutes, between 30 minutes and 1 hour, between 1 hour and 3 hours, between 3 hours and 6 hours, between 6 hours and 12 hours, between 12 hours and 24 hours or for more than 24 hours.

The duration between successive administrations can be less than 30 seconds, less than 1 minute, about 1 minute, between 1 minute and 5 minutes, between 5 minutes and 10 minutes, between 10 minutes and 20 minutes, between 20 minutes and 30 minutes, between 30 minutes and 1 hour, between 1 hour and 3 hours, between 3 hours and 6 hours, between 6 hours and 12 hours, between 12 hours and 24 hours, between 24 hours and 48 hours, between 48 hours and 72 hours, between 72 hours and 1 week or between 1 week and 2 weeks.

Administering an inhibitor or compound to cells can include cells of an in vitro or in vivo system or model. The cells can be part of a cell line. The cell line can be a primary or secondary cell line. The cell line can be an immortal cell line. The cells can be ruptured and be in the form of a cell lysate. The cells can be part of a living organism, i.e., a subject, for example, a mammal. A mammal can include a rat, a mouse, a gerbil, a hamster, a rabbit or a human. The human can be a subject or a patient.

A method can further include monitoring a property of a sample or a subject. A sample can be removed from a subject. For instance, a sample can include a sample of cells or a tissue from a subject. A sample can include blood, plasma, or neuronal tissue including neurons or glial cells. A sample can also remain in the subject. For example, a sample can be a tissue or cells that are observed within the patient.

A method can further include providing untreated control cells, sample or subject and measuring a property of a sample of the untreated control cells, sample or subject.

A property can include the presence or absence of a molecule, the concentration of a molecule, for example myelin basic protein, myelin associated glycoprotein or myelin oligodendrocyte glycoprotein. In some embodiments, determining the presence of a molecule can include determining the concentration of the molecule, determining the purity of the molecule or determining the quantity of the molecule.

A property can be the conductivity of a tissue or cell. A property can be an emission, for example, electromagnetic radiation.

Monitoring a property can include observing the property of the sample or subject alone. Monitoring a property can include monitoring the property before the sample or subject has been administered a compound of the invention. Monitoring a property can include monitoring the property after the sample or subject has been administered a compound. Monitoring a property can include monitoring a property after the sample or subject has been administered a known concentration of a compound.

Monitoring a property of a sample or subject can include observing the property through a microscope. Monitoring a property of the composition can include measuring the property using a microscope. Monitoring a property of the composition can include monitoring the property using still photography or movies. The photography or movies can be on film media or digital form. Monitoring a property can include taking a scan, for example, an MRI or CT scan.

Promoting myelination, remyelination or oligodendrocyte progenitor cell differentiation can prevent or can treat a pathological condition or symptom in a mammal. A number of diseases or disorders involve demyelination of the central or peripheral nervous system which can occur for a number of reasons such as immune dysfunction as in multiple sclerosis, encephalomyelitis, Guillain-Barre Syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), transverse myelitis, and optic neuritis; demyelination due to injury such as spinal cord injury, traumatic brain injury, stroke, acute ischemic optic neuropathy, or other ischemia, cerebral palsy, neuropathy (e.g. neuropathy due to diabetes, chronic renal failure, hypothyroidism, liver failure, or compression of the nerve), post radiation injury, and central pontine myelolysis (CPM); inherited conditions such as Charcot-Marie-Tooth disease (CMT), Sjogren-Larsson syndrome, Refsum disease, Krabbe disease, Canavan disease, Alexander disease, Friedreich's ataxia, Pelizaeus–Merzbacher disease, Bassen-Kornzweig syndrome, metachromatic leukodystrophy(MLD), adrenoleukodystrophy, and nerve damage due to pernicious anemia; viral infection such as progressive multifocal leukoencephalopathy (PML), Lyme disease, or tabes dorsalis due to untreated syphilis; toxic exposure due to chronic alcoholism (which is a possible cause of Marchiafava-Bignami disease), chemotherapy, or exposure to chemicals such as organophosphates; or dietary deficiencies such as vitamin B12 deficiency, vitamin E deficiency, and copper deficiency. Some demyelination disorders can have unknown or multiple causes such as trigeminal neuralgia, Marchiafava-Bignami disease and Bell's palsy. In addition, demyelination can contribute to neuropathic pain. Compounds of the invention are expected to be useful in treating demyelination disorders.

Since LPA is a proinflammatory factor reducing the amount of LPA producted by inhibiting ATX is useful for treating inflammatory disorders such as asthma, allergies, arthritis, inflammatory neuropathies, transplantation rejection, Crohn's disease, ulcerative colitis, lupus erythematosis, psoriasis, an inflammatory bowel condition, and diabetes.

LPA has been shown to be involved in wound healing and stimulates the proliferation and migration of endothelial cells promoting processes such as angiogenesis. However, these same processes when deregulated can promote tumor growth and metastasis, and LPA is thought to contribute to the development, progression, and metastasis of several types of cancer including ovarian, prostate, melanoma, breast, head and neck cancers (see Gendaszewska-Darmach, Acta Biochimica Polonica (2008), 55(2):227-240). In addition, since ATX is located outside the cell in circulation, ATX inhibitors are expected to be of most benefit outside the cell. Therefore, ATX inhibitors are expected to be useful in treating cancer, particularly multidrug resistant (MDR) cancers where drug efflux mechanisms are the largest contributor to the drug resistance.

A compound of the invention, or a pharmaceutically acceptable salt thereof, formulated as a pharmaceutical composition and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, e.g., orally or parenterally, as eyedrops, by intravenous, intramuscular, topical or subcutaneous routes.

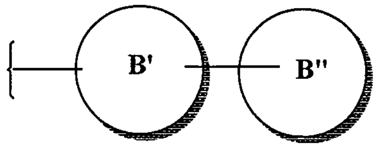
Thus, compound of the invention, or a pharmaceutically acceptable salt thereof, may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard

R^1 can be a $C_{6\text{-}20}$alkyl, a $C_{3\text{-}14}$carbocyclyl, a 3- to 15-membered heterocyclyl, a $C_{6\text{-}10}$aryl, or a five- to 14-membered heteroaryl, wherein R^1 may be optionally substituted with from one to six independently selected R^6.

R^2, for each occurrence, can be independently selected from the group consisting of hydrogen, halo, hydroxyl, nitro, cyano, carboxy, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}8}$cycloalkyl, $C_{3\text{-}8}$halocycloalkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$haloalkoxy, $C_{3\text{-}8}$cycloalkoxy, $C_{3\text{-}8}$halocycloalkoxy, $C_{1\text{-}6}$alkanoyl, amino, N-($C_{1\text{-}6}$alkyl)amino, N,N-di-($C_{1\text{-}6}$alkyl)amino, $C_{1\text{-}6}$alkoxycarbonyl, $C_{1\text{-}6}$alkanoyloxy, carbamoyl, N-($C_{1\text{-}6}$alkyl)carbamoyl, N,N-di-($C_{1\text{-}6}$alkyl)carbamoyl, $C_{1\text{-}6}$alkylamido, mercapto, $C_{1\text{-}6}$alkylthio, $C_{1\text{-}6}$alkylsulfonyl , sulfamoyl, N-($C_{1\text{-}6}$alkyl)sulfamoyl, N,N-di-($C_{1\text{-}6}$alkyl)sulfamoyl, and $C_{1\text{-}6}$alkylsulfonamido.

each R^3 and each R^4 can each independently be hydrogen, a carboxy, $C_{1\text{-}6}$alkyl, or a $C_{2\text{-}6}$alkenyl; or R^3 and R^4 together with the carbon to which they are attached are -C(=O)-, a $C_{3\text{-}8}$spirocycloalkyl, or a 3- to 8-membered spiroheterocycloalkyl.

B can be a fused ring system, a bridged ring system, a spiro ring system, or a combination thereof; or B is a bicyclic ring system represented by the following formula:



wherein B' and B" are each independently selected from the group consisting of monocyclic $C_{3\text{-}8}$carbocyclyl, a monocyclic 3- to 8-membered heterocyclyl, phenyl, or a 5- to 6- membered heteroaryl, wherein the heterocyclyl and the heteroaryl comprises 1 to 3 heteroatoms independently selected from N, S, or O; provided that when B is a fused ring system it is not 1H-benzo[d][1,2,3]triazole.

R^5, for each occurrence, can be independently hydroxyl, halo, $C_{1\text{-}6}$alkyl, or $-(CR^{17}R^{18})_p-R^7$; or two R^5 on the same carbon atom may be =O.

R^6, for each occurrence, can be independently selected from the group consisting of halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$haloalkyl, $C_{3\text{-}8}$cycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}6}$alkoxy-$C_{1\text{-}6}$alkyl, and tri-($C_{1\text{-}6}$alkyl)silyl; or two R^6 that are attached to the same carbon atom may form $C_{3\text{-}8}$spirocycloalkyl or 3- to 8-membered spiroheterocycloalkyl.

R^7 can be -OH, $-C(O)OR^{15}$, $-C(O)N(R^{16})_2$, $-C(O)N(R^{15})-S(O)_2R^{15}$, $-S(O)_2OR^{15}$, $-C(O)NHC(O)R^{15}$, -Si(O)OH, $-B(OH)_2$, $-N(R^{15})S(O)_2R^{15}$, $-S(O)_2N(R^{15})_2$, $-O-P(O)(OR^{15})_2$, $-P(O)(OR^{15})_2$, -CN, $-S(O)_2NHC(O)R^{15}$, $-C(O)NHS(O)_2R^{15}$, -C(O)NHOH, -C(O)NHCN, or a heteroaryl or a heterocyclyl selected from the group consisting of formulae (a)-(i'):

or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, or wafers, and the like. Such compositions and preparations should contain at least about 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions can be such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like can include the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; or a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl or propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

Exemplary pharmaceutical dosage forms for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, or nontoxic glyceryl esters, and mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, or thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation can be vacuum drying and the freeze drying techniques, which can yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, a compound of the invention may be applied in pure form, e.g., when they are liquids. However, it can be generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Exemplary solid carriers can include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts or esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of the invention to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508), each of which is incorporated by reference in its entirety.

Useful dosages of the compounds of the invention can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949, which is incorporated by reference in its entirety.

Generally, the concentration of the compound(s) of the invention in a liquid composition, such as a lotion, can be from about 0.1 to about 25 weight percent, preferably from about 0.5-10 weight percent. The concentration in a semi-solid or solid composition such as a gel or a powder can be about 0.1-5 wt-%, preferably about 0.5-2.5 weight percent based on the total weight of the composition.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment can vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and can be ultimately at the discretion of the attendant physician or clinician. In general, however, a dose can be in the range of from about 0.1 to about 10 mg/kg of body weight per day.

The compound can be conveniently administered in unit dosage form; for example, containing 0.01 to 10 mg, or 0.05 to 1 mg, of active ingredient per unit dosage form. In some embodiments, a dose of 5 mg/kg or less can be suitable.

The active ingredient can be administered so as to achieve a desired peak plasma concentration of the active compound. The desired peak plasma concentration can be from about 0.5 µM to about 75 µM, preferably, about 1 µM to 50 µM, or about 2 µM to about 30 µM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing between about 1 mg to about 100 mg of the active ingredient.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four, or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

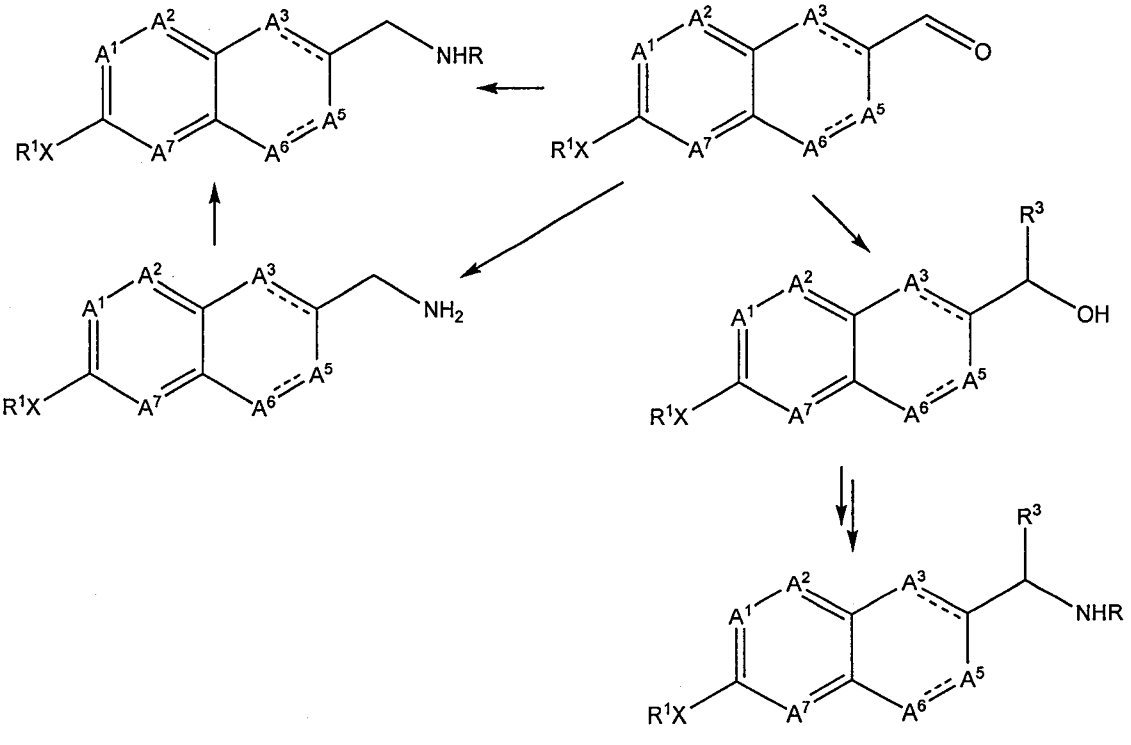
The disclosed method can include a kit comprising a compound of the invention and instructional material which can describe administering the compound or a composition comprising the compound to a cell or a subject. This should be construed to include other embodiments of kits that are known to those skilled in the art, such as a kit comprising a (preferably sterile) solvent for dissolving or suspending the compound or composition prior to administering the compound or composition to a cell or a subject. Preferably, the subject can be a human.

In accordance with the disclosed methods, as described above or as discussed in the Examples below, there can be employed conventional chemical, cellular, histochemical, biochemical, molecular biology, microbiology, and in vivo techniques which are known to those of skill in the art. Such techniques are explained fully in the literature.

EXAMPLES

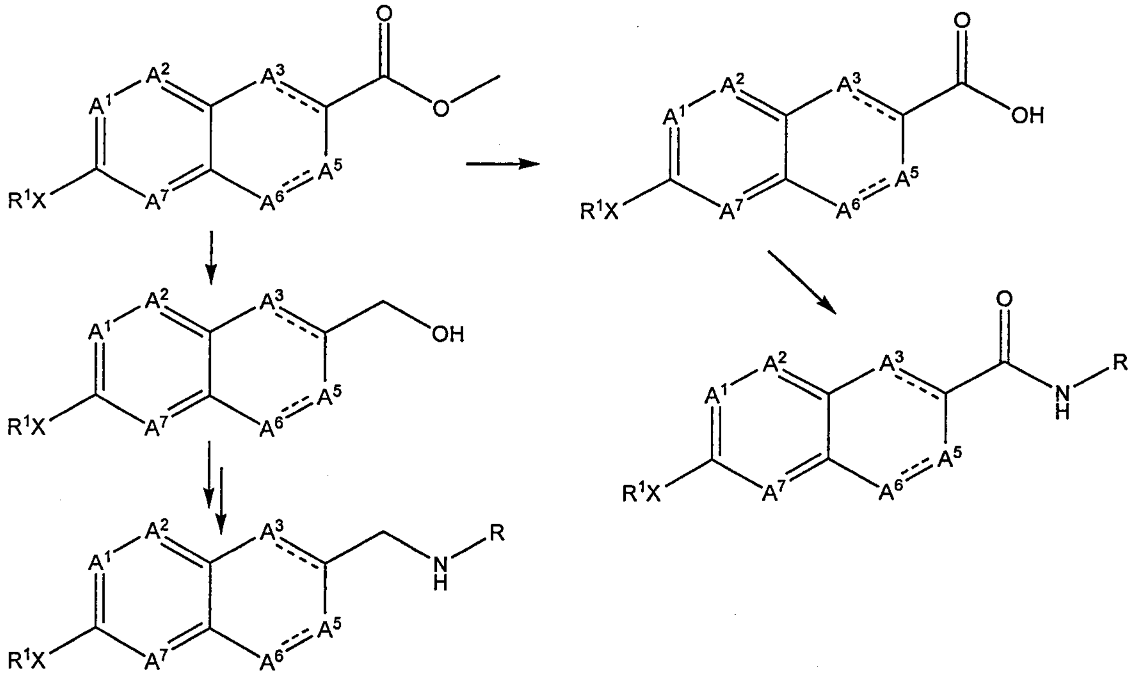
In one embodiment, certain compounds of the invention, and pharmaceutically acceptable salts thereof, may be prepared according to general scheme 1:

Scheme 1



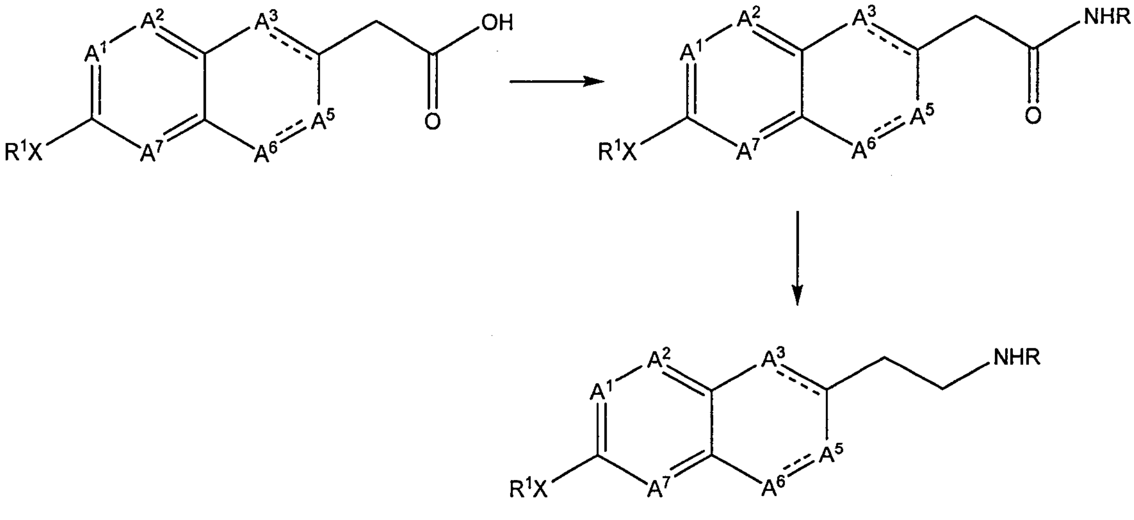
In one embodiment, certain compounds of the invention, and pharmaceutically acceptable salts thereof, may be prepared according to general scheme 2:

Scheme 2



In one embodiment, certain compounds of the invention, and pharmaceutically acceptable salts thereof, may be prepared according to general scheme 3:

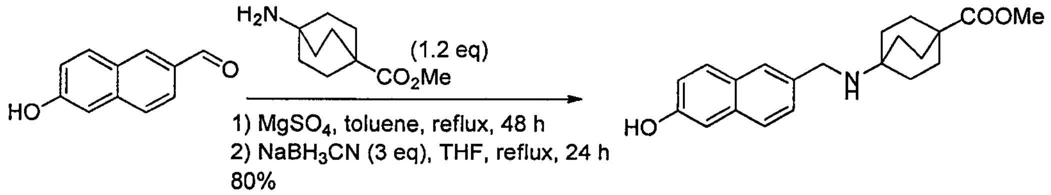
Scheme 3



Example 1: 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino) bicyclo[2.2.2]octane-1-carboxylic acid

Step 1:

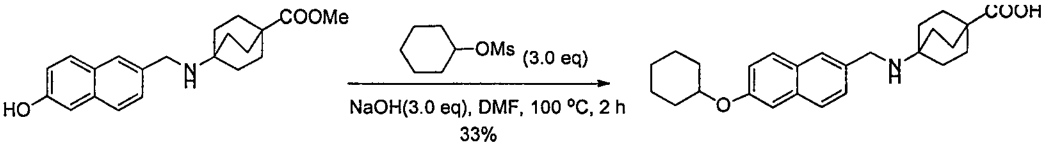
4-(((6-hydroxynaphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate



6-hydroxy-2-naphthaldehyde (520 mg, 3.02 mmol, 1.0 eq) and methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate (663 mg, 3.62 mmol, 1.2 eq) were dissolved in toluene (100 mL). Magnesium sulfate (72 mg, 0.60 mmol, 0.2 eq) was added to the solution and refluxed for 48 h. The solvent was removed in vacuo. The residue was dissolved in THF (150 mL) and sodium cyanoborohydride (571 mg, 9.06 mmol, 3.0 eq) was added. The mixture was refluxed for 24 h. The solvent was removed in vacuo. Water (50 mL) was added to the residue and extracted with EtOAc (2×150 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. The organic phase was concentrated to give methyl 4-(((6-hydroxynaphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate as yellow solid (819 mg, Y: 80%). ESI-MS $(M+H)^+$: 340.2. ^1H NMR (400 MHz, DMSO-d_6) δ: 9.98 (s, 1H), 8.91 (br, 1H), 7.89 (s, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.47 (dd, J = 8.4, 1.6 Hz, 1H), 7.15 (s, 1H), 7.14 (dd, J = 8.0, 2.4 Hz, 1H), 4.17 (s, 2H), 3.60 (s, 3H), 1.91-1.87 (m, 12H).

Step 2:

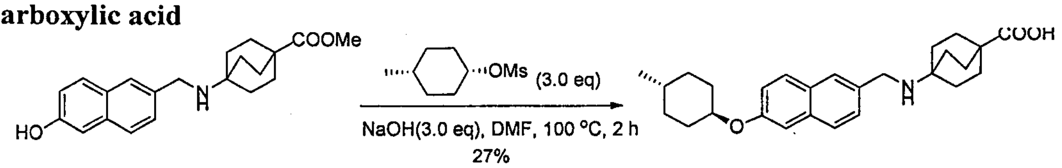
4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



Methyl 4-(((6-hydroxynaphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate (100 mg, 0.295 mmol, 1.0 eq), cyclohexyl methanesulfonate (100 mg, 0.885 mmol, 3.0 eq) and sodium hydroxide (35 mg, 0.875 mmol, 3.0 eq) were dissolved in DMF (2 mL). The mixture was stirred at 100 °C for 2 h. After cooling to rt, 1 N HCl was added to adjust pH = 6-7 and extracted with DCM (2×40 mL). The organic phase was washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by prep-HPLC (65% MeOH/H_2O) to give 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid as a white solid (40 mg, yield: 33% in two steps). ESI-MS $(M+H)^+$: 408.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.89 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.49 (dd, J = 8.8, 2.0 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.8, 2.4 Hz, 1H), 4.52-4.48 (m, 1H), 4.24 (s, 2H), 2.04-1.99 (m, 14H), 1.86-1.83 (m, 2H), 1.63-1.47 (m, 6H).

Example 2:

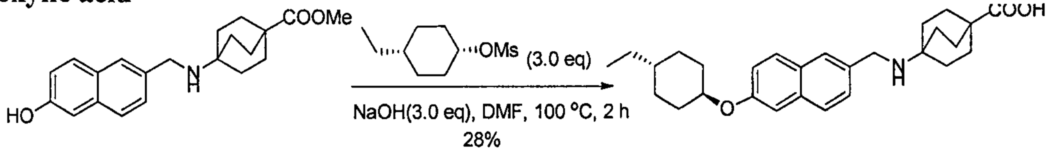
4-(((6-((trans-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 34 mg, white solid, yield: 27% in two steps. ESI-MS $(M+H)^+$: 422.3. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.78 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.37 (dd, J = 8.4, 2.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.07 (dd, J = 9.2, 2.4 Hz, 1H), 4.32-4.25 (m, 1H), 4.14 (s, 2H), 2.11-2.07 (m, 2H), 1.94-1.88 (m, 12H), 1.74-1.71 (m, 2H), 1.41-1.39 (m, 3H), 1.09-1.06 (m, 2H), 0.86 (d, J = 6.8 Hz, 3H).

Example 3:

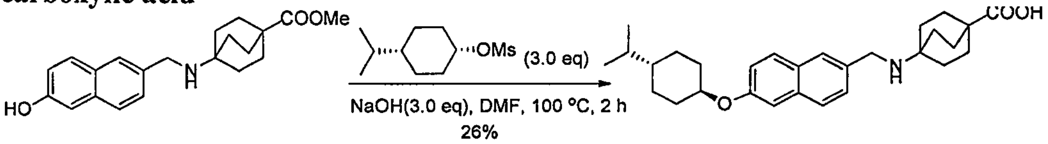
4-(((6-((trans-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 36 mg, white solid, yield: 28% in two steps. ESI-MS $(M+H)^+$: 436.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.89 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.48 (dd, J = 8.8, 2.0 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.18 (dd, J = 8.8, 2.4 Hz, 1H), 4.43-4.39 (m, 1H), 4.26 (s, 2H), 2.25-2.21 (m, 2H), 2.05-1.99 (m, 12H), 1.92-1.89 (m, 2H), 1.48-1.45 (m, 2H), 1.33-1.28 (m, 3H), 1.19-1.13 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H).

Example 4:

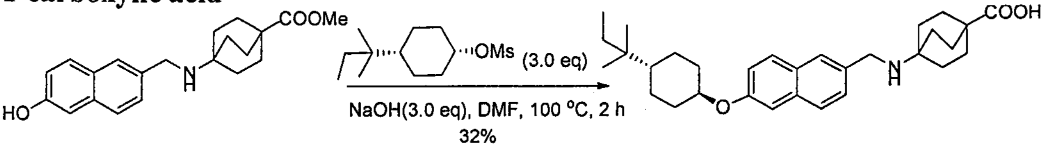
4-(((6-((trans-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 34 mg, white solid, yield: 26% in two steps. ESI-MS $(M+H)^+$: 450.3. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.78 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.37 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.07 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.30-4.25 (m, 1H), 4.14 (s, 2H), 2.16-2.13 (m, 2H), 1.94-1.88 (m, 12H), 1.78-1.75 (m, 2H), 1.41-1.32 (m, 3H), 1.19-1.09 (m, 3H), 0.83 (d, *J* = 6.8 Hz, 6H).

Example 5:

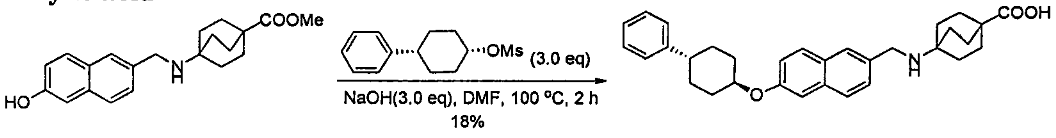
4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino) bicyclo[2.2.2]octane-1-carboxylic acid. 45 mg, white solid, yield: 32% in two steps. ESI-MS $(M+H)^+$: 478.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.78 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.38 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.30-4.21 (m, 1H), 4.12 (s, 2H), 2.18-2.15 (m, 2H), 1.93-1.90 (m, 12H), 1.76-1.73 (m, 2H), 1.32-1.14 (m, 8H), 0.76-0.72 (m, 8H).

Example 6:

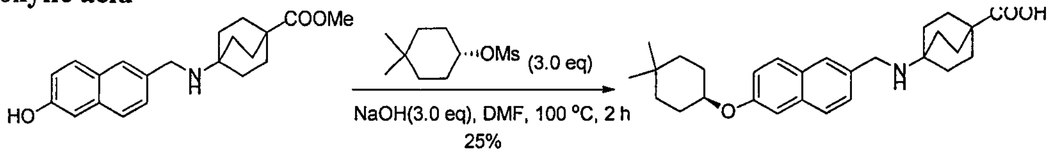
4-(((6-((trans-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 26 mg, white solid, yield: 18% in two steps. ESI-MS $(M+H)^+$: 483.3. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.90 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 8.8, 1.6 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.29-7.26 (m, 4H), 7.22 (dd, J = 9.2, 2.4 Hz, 1H), 7.20-7.17 (m, 1H), 4.59-4.52 (m, 1H), 4.25 (s, 2H), 2.67-2.61 (m, 1H), 2.37-2.34 (m, 2H), 2.05-1.98 (m, 14H), 1.78-1.71 (m, 2H) , 1.69-1.63 (m, 2H).

Example 7:

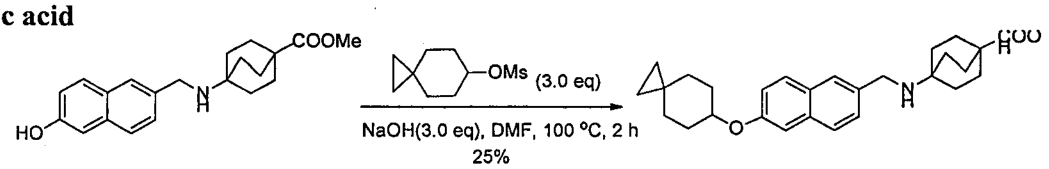
4-(((6-((4,4-dimethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((4,4-dimethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 32 mg, white solid, yield: 25% in two steps. ESI-MS $(M+H)^+$: 436.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.89 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.48 (dd, J = 8.4, 2.0 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.21 (dd, J = 8.8, 2.4 Hz, 1H), 4.51-4.49 (m, 1H), 4.26 (s, 2H), 2.05-1.94 (m, 14H), 1.79-1.74 (m, 2H), 1.59-1.56 (m, 2H), 1.40-1.35 (m, 2H), 1.01 (s, 3H), 1.00 (s, 3H).

Example 8:

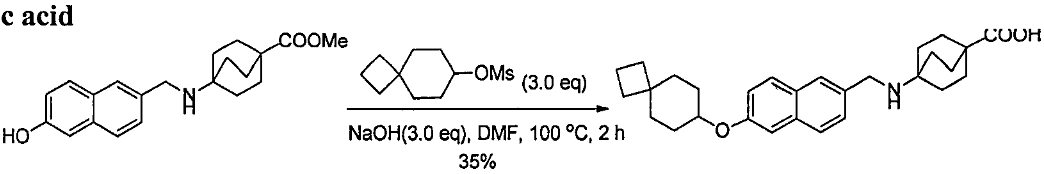
4-(((6-(spiro[2.5]octan-6-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-(spiro[2.5]octan-6-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 12 mg, white solid, yield: 25% in two steps. ESI-MS $(M+H)^+$: 434.2. ^{1}H NMR (400 MHz, CD$_3$OD) δ: 7.90 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.49 (dd, J = 8.8, 2.0 Hz, 1H), 7.31 (d, J = 2.0 Hz, 1H), 7.22 (dd, J = 8.4, 2.0 Hz, 1H), 4.64-4.60 (m, 1H), 4.26 (s, 2H), 2.04-1.99 (m, 14H), 1.83-1.74 (m, 2H), 1.60-1.54 (m, 2H), 1.43-1.39 (m, 2H), 0.38-0.29 (m, 4H).

Example 9:

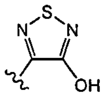
4-(((6-(spiro[3.5]nonan-7-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-(spiro[3.5]nonan-7-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 46 mg, white solid, yield: 35% in two steps. ESI-MS $(M+H)^+$: 448.3. ^{1}H NMR (400 MHz, CD$_3$OD) δ: 7.89 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.48 (dd, J = 8.8, 2.0 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 8.8, 2.4 Hz, 1H), 4.51-4.43 (m, 1H), 4.26 (s, 2H), 2.05-1.99 (m, 12H), 1.94-1.81 (m, 10H), 1.55-1.52 (m, 4H).

Example 10:

4-(((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid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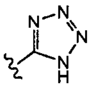
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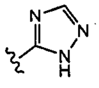
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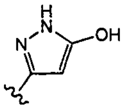
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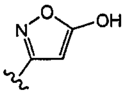
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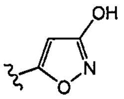
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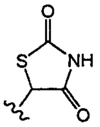
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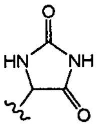
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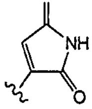
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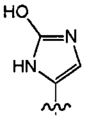
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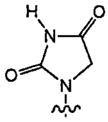
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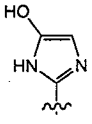
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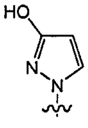
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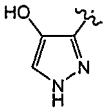
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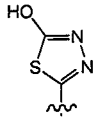
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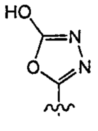
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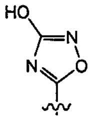
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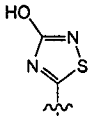
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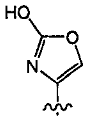
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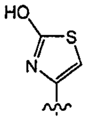
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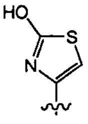
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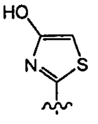
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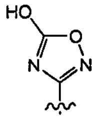
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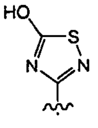
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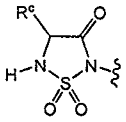
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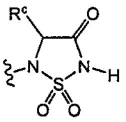
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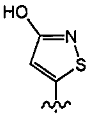
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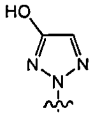
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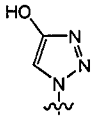
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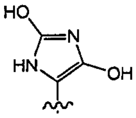
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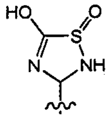
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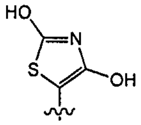
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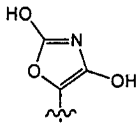
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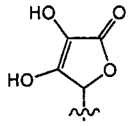
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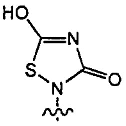
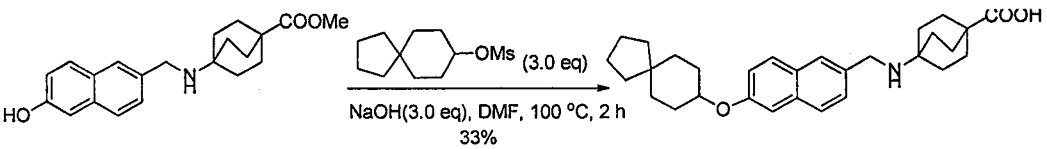

(i') .

R^8, R^{12}, and R^{19} can each independently be hydrogen or a C_{1-6}alkyl.

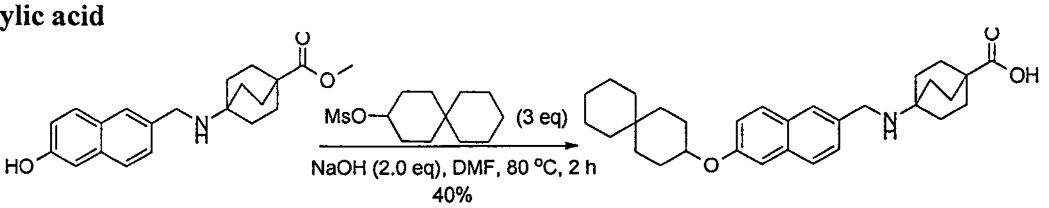
R^{15} for each occurrence can be independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, C_{6-10}aryl, a 5 to 14 membered heteroaryl, and a 3 to 15 membered heterocyclyl; wherein the heteroaryl or heterocyclyl comprises from 1 to 10 heteroatoms independently selected from O, N, or S; and wherein R^{15} may be optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, C_{1-4}alkoxy, C_{1-4}alkyl, cyano, nitro, hydroxyl, amino, N-(C_{1-4}alkyl)amino, N,N-di-(C_{1-4}alkyl)amino, carbamoyl, N-(C_{1-4}alkyl)carbamoyl, N,N-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylamido, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonamido, sulfamoyl, N-(C_{1-4}alkyl)sulfamoyl, and N,N-(C_{1-4}dialkyl)-sulfamoyl.

R^{16} can be R^{15}; or two R^{16} together with the nitrogen atom to which they are attached can form a 5 to 14 membered heteroaryl or a 3 to 15 membered heterocyclyl, wherein the heteroaryl or heterocyclyl comprises from 1 to 10 heteroatoms independently selected from O, N, or S; and wherein the heteroaryl or heterocyclyl may be optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, C_{1-4}alkoxy, C_{1-4}alkyl, cyano, nitro, hydroxyl, amino, N-(C_{1-4}alkyl)amino, N,N-di-(C_{1-4}alkyl)amino, carbamoyl,



The preparation of 4-(((6-(spiro[4.5]decan-8-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 45 mg, white solid, yield: 33% in two steps. ESI-MS $(M+H)^+$: 462.3. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.89 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.48 (dd, J = 8.4, 1.6 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.8, 2.4 Hz, 1H), 4.53-4.51 (m, 1H), 4.25 (s, 2H), 2.05-1.99 (m, 14H), 1.73-1.65 (m, 8H), 1.54-1.42 (m, 6H).

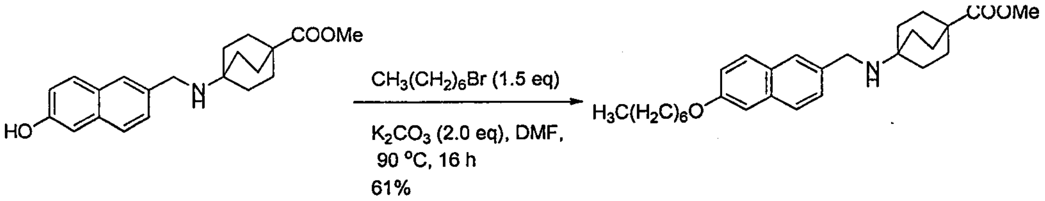
Example 11: 4-(((6-(spiro[5.5]undecan-3-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-(spiro[5.5]undecan-3-yloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 50 mg, white solid, yield: 40% in two steps. ESI-MS $(M+H)^+$: 476.3. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.89 (s, 1H), 7.86-7.79 (m, 2H), 7.48 (dd, J = 8.4, 1.2 Hz, 1H), 7.28 (d, J = 1.2 Hz, 1H), 7.20 (dd, J = 8.8, 1.2 Hz, 1H), 4.52-4.48 (m, 1H), 4.26 (s, 2H), 2.05-1.92 (m, 14H), 1.75-1.66 (m, 4H), 1.47 (br, 8H), 1.37-1.30 (m, 4H).

Example 12: 4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid

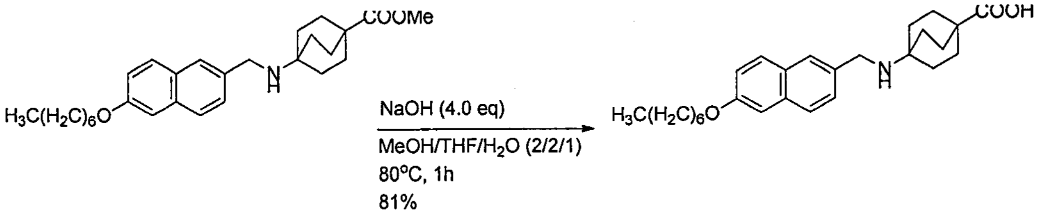
Step 1: methyl 4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate



To a solution of methyl 4-(((6-hydroxynaphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate (153 mg, 0.45 mmol, 1.0 eq) in DMF (3 mL) was added 1-bromoheptane (119 mg, 0.68 mmol, 1.5 eq) and K_2CO_3 (124 mg, 0.9 mmol, 2.0 eq). The mixture was stirred at 90 °C for 16 h. After cooling down to room temperature, the mixture was diluted with brine (50 mL) and extracted with EtOAc (60 mLx3). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by pre-HPLC to give methyl 4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate as a white solid (120 mg, yield: 61%). ESI-MS $(M+H)^+$: 321.1.ESI-MS $(M+H)^+$: 438.3. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.73 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.34 (dd, J = 8.4, 2.0 Hz, 1H), 7.13 (dd, J = 8.8, 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 3.98 (t, J = 6.8 Hz, 2H), 3.85 (d, J = 2.4 Hz, 2H), 3.60 (s, 3H), 1.83-1.80 (m, 2H), 1.50-1.30 (m, 20H) , 0.90 (t, J = 7.2 Hz, 3H).

Step 2:

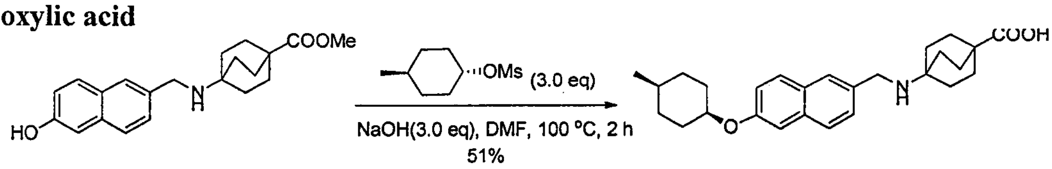
4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



To a solution of methyl 4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino) bicyclo[2.2.2]octane-1-carboxylate (120 mg, 0.27 mmol, 1.0 eq) in $MeOH/THF/H_2O$ (2:2:1, 10 mL) was added NaOH (43 mg, 1.08 mmol, 4.0 eq). The mixture was stirred at reflux for 1 h. After cooling down to room temperature, the mixture was adjusted to pH = 6 with 1 N HCl and extracted with DCM (30 mLx2). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by pre-HPLC to give 4-(((6-(heptyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid as a white solid (94 mg, yield: 81%). ESI-MS $(M+H)^+$: 424.2. ^1H NMR (400 MHz, CD_3OD) δ: 7.90 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.49 (dd, J = 8.4, 1.6 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.25 (s, 2H), 4.11 (t, *J* = 6.4 Hz, 2H), 2.05-2.01 (m, 12H), 1.87-1.83 (m, 2H), 1.55-1.50 (m, 2H), 1.42-1.33 (m, 6H), 0.93 (t, *J* = 7.2 Hz, 3H).

Example 13:

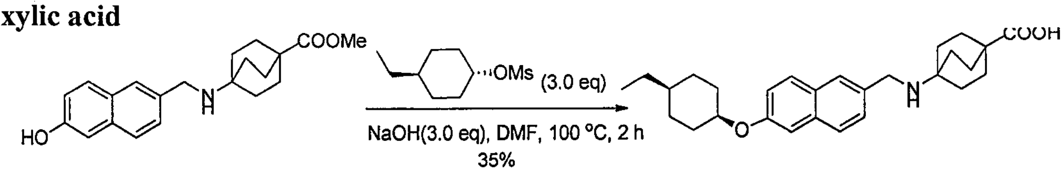
4-(((6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 64 mg, white solid, yield: 51% in two steps. ESI-MS $(M+H)^+$: 422.3. ^{1}H NMR (500 MHz, CD_3OD) δ: 7.91 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 9.5 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.24 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.76-4.74 (m, 1H), 4.26 (s, 2H), 2.09-2.00 (m, 14H), 1.72-1.68 (m, 2H), 1.57-1.54 (m, 3H), 1.46-1.43 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H).

Example 14:

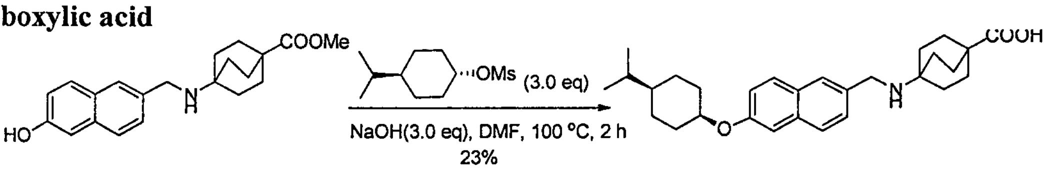
4-(((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 45 mg, white solid, yield: 35% in two steps. ESI-MS $(M+H)^+$: 436.2. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.89 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.48 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.77-4.73 (m, 1H), 4.25 (s, 2H), 2.10-1.99 (m, 14H), 1.67-1.59 (m, 4H), 1.44-1.30 (m, 5H), 0.94 (t, *J* = 7.2 Hz, 3H).

Example 15:

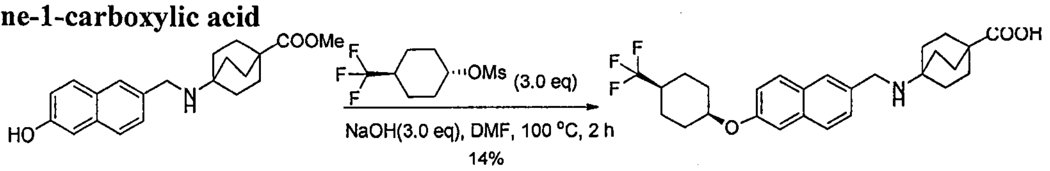
4-(((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((cis-4-isopropylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 30 mg, white solid, yield: 23% in two steps. ESI-MS $(M+H)^+$: 450.3. ^1H NMR(400 MHz, CD_3OD) δ: 7.78 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.37 (dd, J = 8.4, 1.6 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.11 (dd, J = 8.8, 2.4 Hz, 1H), 4.64-4.63 (m, 1H), 4.12 (s, 2H), 2.03-2.00 (m, 2H), 1.93-1.87 (m, 12H), 1.52-1.38 (m, 7H), 1.12-1.05 (m, 1H), 0.82 (d, J = 6.8 Hz, 6H).

Example 16:

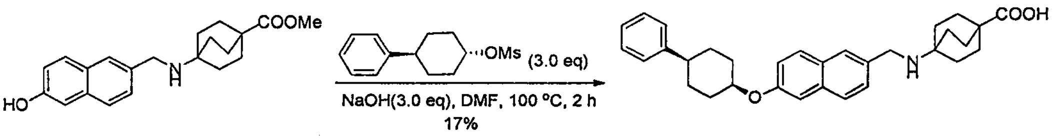
4-(((6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2] octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 20 mg, white solid, yield: 14% in two steps. ESI-MS $(M+H)^+$: 476.3. ^1H NMR (400 MHz, CD_3OD) δ: 7.80 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.39 (dd, J = 8.4, 2.4 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 4.72-4.70 (m, 1H), 4.13 (s, 2H), 2.13-2.08 (m, 3H), 1.93-1.88 (m, 12H), 1.67-1.65 (m, 6H).

Example 17:

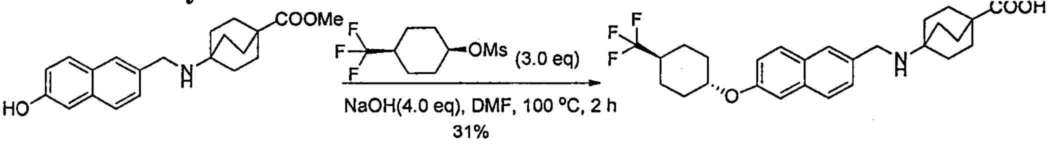
4-(((6-((cis-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((cis-4-phenylcyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 24 mg, white solid, yield: 17% in two steps. ESI-MS $(M+H)^+$: 484.3. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.91 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.50 (dd, J = 8.4, 1.2 Hz, 1H), 7.34-7.17 (m, 6H), 7.16-7.14 (m, 1H), 4.86-4.84 (m, 1H), 4.23 (s, 2H), 2.79-2.51 (m, 1H), 2.25-2.22 (m, 2H), 2.01-1.93 (m, 14H), 1.84-1.69 (m, 4H).

Example 18:

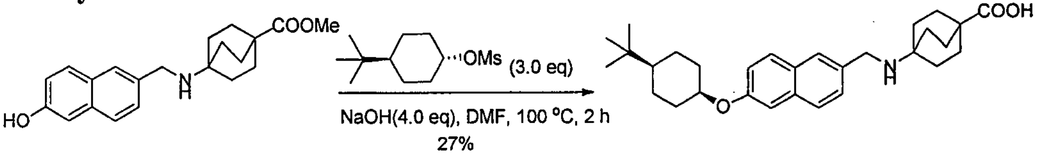
4-(((6-((trans-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-(trifluoromethyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 42 mg, white solid, yield: 31% in two steps. ESI-MS $(M+H)^+$: 476.3. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.91 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 8.8, 1.6 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 8.8, 2.4 Hz, 1H), 4.84-4.81 (m, 1H), 4.26 (s, 2H), 2.23-2.20 (m, 3H), 2.05-1.99 (m, 12H), 1.79-1.72 (m, 6H).

Example 19:

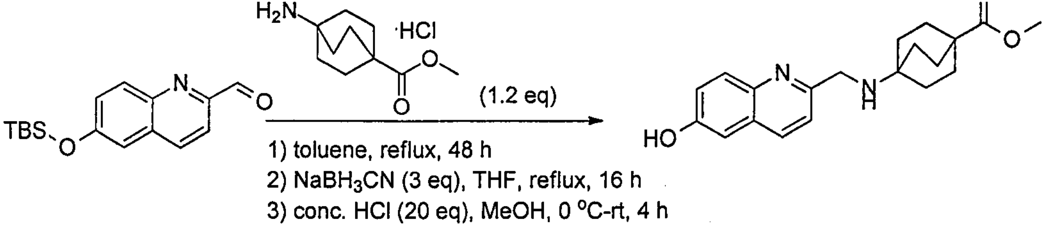
4-(((6-((cis-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((cis-4-(tert-butyl)cyclohexyl)oxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 37 mg, white solid, yield: 27% in two steps. ESI-MS $(M+H)^+$: 464.3. ^1H NMR (400 MHz, CD_3OD) δ: 7.90 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.49 (dd, J = 8.4, 2.0 Hz, 1H), 7.27 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 8.8, 2.4 Hz, 1H), 4.76-4.74 (m, 1H), 4.22 (s, 2H), 2.19-2.16 (m, 2H), 2.04-1.98 (m, 12H), 1.63-1.50 (m, 6H), 1.18-1.13 (m, 1H), 0.92 (s, 9H).

Example 20:
4-(((6-(cyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid

Step 1: Methyl 4-(((6-hydroxyquinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate



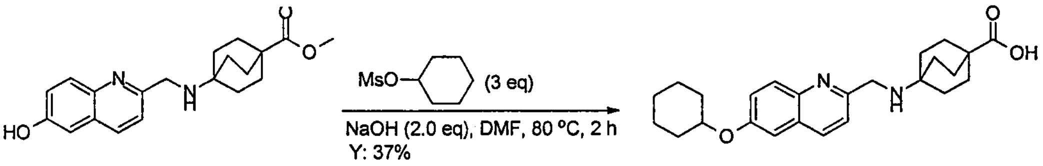
A mixture of 6-((tert-butyldimethylsilyl)oxy)quinoline-2-carbaldehyde (1 g, 3.48 mmol) and methyl 4-amino bicyclo[2.2.2]octane-1-carboxylate hydrochloride salt (766 mg, 4.18 mmol, 1.2 eq) in dry toluene (200 mL) was stirred at reflux for 48 h. Then the mixture was concentrated and the residue was dissolved in THF (150 mL), and $NaBH_3CN$ (658 mg, 10.44 mmol, 3 eq) was added. The reaction mixture was stirred at reflux for 16 h. After concentration, EA (200 mL) was added and the mixture was washed with H_2O (100 mL x2). The organic phase was dried and concentrated to give methyl 4-(((6-((tert-butyldimethylsilyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate as yellow solid (crude 1.5 g), which was used for the next step without further purification. ESI-MS $(M+H)^+$: 455.2.

To a solution of crude methyl 4-(((6-((tert-butyldimethylsilyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate (1.5 g, 3.3 mmol) in MeOH (100 mL) was added conc. HCl (5.5 mL, 12 M, 20 eq) slowly at 0 °C. Then the reaction mixture was stirred at room temperature for 4 h. The mixture was adjusted to pH = 8 with sat. $NaHCO_3$ and concentrated. The residue was extracted with EA

(200 mL) and washed with H_2O (200 mL x2). The organic phase was dried and concentrated to give methyl 4-(((6-hydroxyquinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylate as yellow solid (940 mg, yield: 80% in two steps). ESI-MS $(M+H)^+$: 341.2. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, J = 9.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.8, 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 3.93 (s, 2H), 3.66 (s, 3H), 1.96-1.92 (m, 6H), 1.83-1.79 (m, 6H).

Step 2:

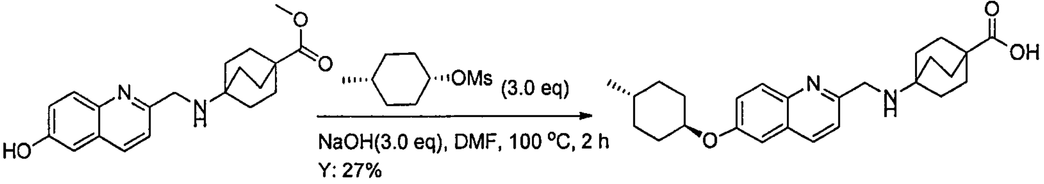
4-(((6-(cyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-(cyclohexyloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 40 mg, a yellow solid, yield: 37%. ESI-MS $(M+H)^+$: 409.2, HPLC: 100%. ^1H NMR (400 MHz, CD_3OD) δ: 8.26 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 9.2, 2.4 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 4.54-4.52 (m, 1H), 4.47 (s, 2H), 2.09-2.03 (m, 14H), 1.86-1.83 (m, 2H), 1.65-1.46 (m, 6H).

Example 21:

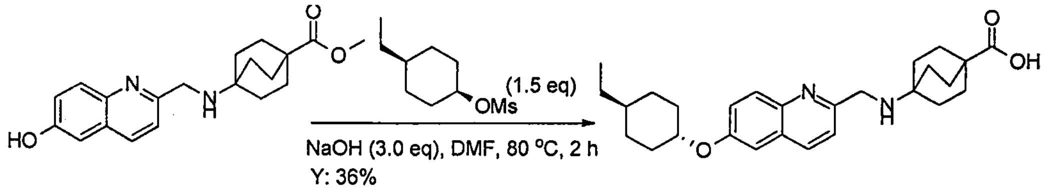
4-(((6-((trans-4-methylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-methylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 34 mg, a white solid, yield: 27%. ESI-MS $(M+H)^+$: 423.3, HPLC: 100%. ^1H NMR (400 MHz, CD_3OD) δ: 8.26 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 9.2, 2.8 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 4.47 (s, 2H), 4.44-4.40 (m, 1H), 2.22-2.20 (m, 2H), 2.04-2.00 (m, 12H), 1.84-1.81 (m, 2H), 1.50-1.44 (m, 3H), 1.20-1.17 (m, 2H), 0.96 (d, J = 6.4 Hz, 3H).

Example 22:

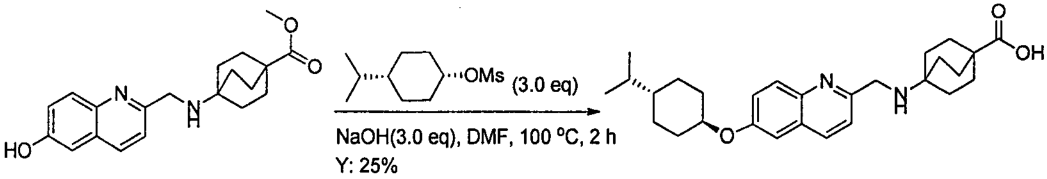
4-(((6-((trans-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-ethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 50 mg, a yellow solid, yield: 36%. ESI-MS $(M+H)^+$: 437.2, HPLC: 98.93%. ^1H NMR (400 MHz, CD_3OD) δ: 8.26 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 9.2, 2.4 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 4.47 (s, 2H), 4.45-4.40 (m, 1H), 2.25-2.22 (m, 2H), 2.06-2.00 (m, 12H), 1.93-1.90 (m, 2H), 1.53-1.49 (m, 2H), 1.35-1.27 (m, 3H), 1.20-1.10 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H).

Example 23:

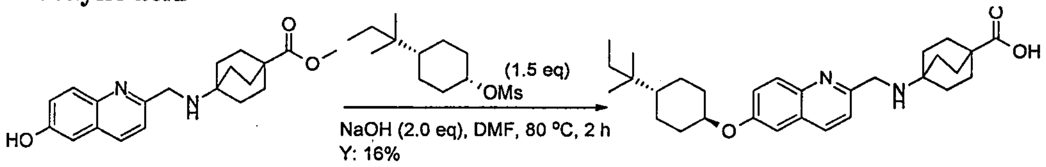
4-(((6-((trans-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-isopropylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 34 mg, a white solid, yield: 25%. ESI-MS $(M+H)^+$: 451.2, HPLC: 100%.^1H NMR (400 MHz, CD_3OD) δ: 8.27 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 8.8, 2.8 Hz, 1H), 7.32 (d, J = 2.8 Hz, 1H), 4.47 (s, 2H), 4.42-4.38 (m, 1H), 2.27-2.25 (m, 2H), 2.04-2.00 (m, 12H), 1.88-1.85 (m, 2H), 1.50-1.43 (m, 3H), 1.29-1.23 (m, 3H), 0.93 (d, *J* = 6.4 Hz, 6H).

Example 24:

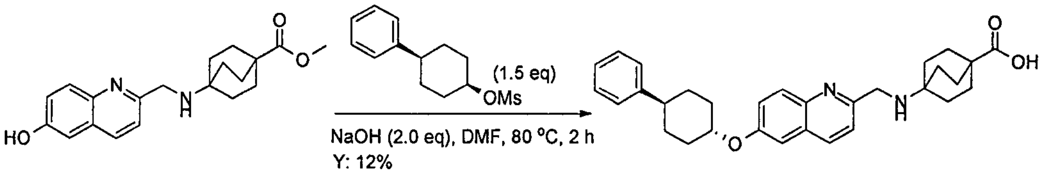
4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-(tert-pentyl)cyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 24 mg, a yellow solid, yield: 16%. ESI-MS $(M+H)^+$: 479.3, HPLC: 97.56%. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.25 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.39 (dd, J = 8.8, 2.4 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 4.46 (s, 2H), 4.41-4.35 (m, 1H), 2.30-2.27 (m, 2H), 2.02-1.97 (m, 12H), 1.87-1.84 (m, 2H), 1.47-1.41 (m, 2H), 1.38-1.22 (m, 5H), 0.88-0.81 (m, 9H).

Example 25:

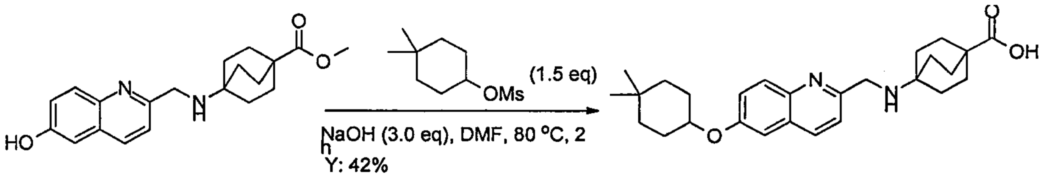
4-(((6-((trans-4-phenylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((trans-4-phenylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 40 mg, a yellow solid, yield: 12%. ESI-MS $(M+H)^+$: 485.2, HPLC: 95.88%. ^{1}H NMR (400 MHz, CD_3OD) δ: 8.26 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H), 7.30-7.24 (m, 4H), 7.19-7.14 (m, 1H), 4.58-4.51 (m, 1H), 4.38 (s, 2H), 2.63-2.56 (m, 1H), 2.35-2.32 (m, 2H), 1.98-1.93 (m, 14H), 1.78-1.57 (m, 4H).

Example 26:

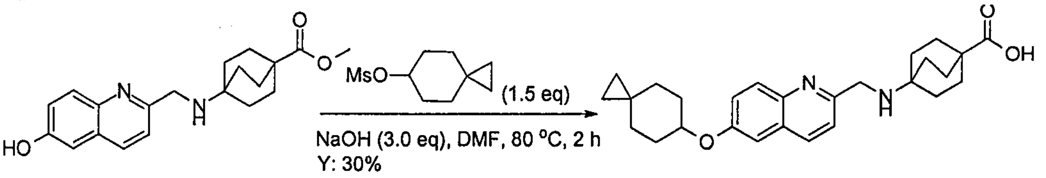
4-(((6-((4,4-dimethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



The preparation of 4-(((6-((4,4-dimethylcyclohexyl)oxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 50 mg, a yellow solid, yield: 42%. ESI-MS (M+H)$^+$: 437.3, HPLC: 100%.^{1}H NMR (400 MHz, CD$_3$OD) δ: 8.21 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.43 (dd, J = 9.2, 2.8 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 4.53-4.50 (m, 1H), 4.47 (s, 2H), 2.03-1.95 (m, 14H), 1.78-1.75 (m, 2H), 1.60-1.55 (m, 2H), 1.42-1.37 (m, 2H), 1.00 (s, 3H), 0.97 (s, 3H).

Example 27:

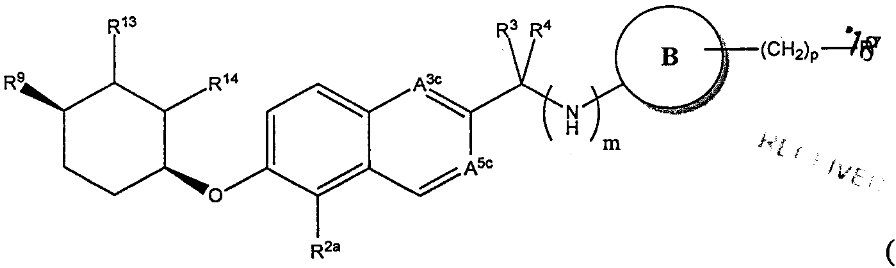
4-(((6-(spiro[2.5]octan-6-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid



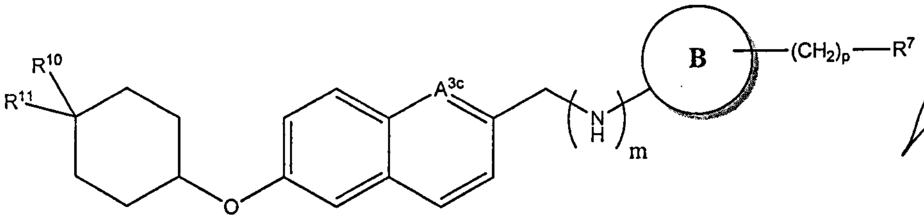
The preparation of 4-(((6-(spiro[2.5]octan-6-yloxy)quinolin-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid was the same as that of 4-(((6-(cyclohexyloxy)naphthalen-2-yl)methyl)amino)bicyclo[2.2.2]octane-1-carboxylic acid. 20 mg, a white solid, yield: 30%. ESI-MS (M+H)$^+$: 435.0, HPLC: 100%. ^{1}H NMR (400 MHz, CD$_3$OD) δ: 8.26 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 9.6 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 9.2, 2.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 4.65-4.61 (m, 1H), 4.47 (s, 2H), 2.04-2.01 (m, 14H), 1.83-1.75 (m, 2H), 1.60-1.55 (m, 2H), 1.43-1.39 (m, 2H), 0.37-0.30 (m, 4H).

CLAIMS

1. A compound represented by formula (IIa) or (III):



(IIa); or



(III)

or a pharmaceutically acceptable salt thereof, wherein:

A^{3c} and A^{5c} are N or CH, provided that only one of A^{3c} or A^{5c} is N;

R^{2a} is a halo, C_{1-6}haloalkyl or cyano;

R^9 is a halo, an C_{1-6}alkyl, or a C_{1-6}haloalkyl;

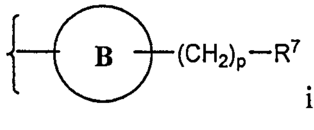
R^{13} and R^{14} are each independently hydrogen or a C_{1-6}alkyl;

R^{10} and R^{11} are each independently hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, tri-C_{1-6}alkylsilyl, or phenyl, wherein at least one of R^{10} or R^{11} is not hydrogen; or R^{10} and R^{11} together with the carbon to which they are attached form a C_{3-8}spirocycloalkyl or 3- to 8-membered spiroheterocycloalkyl;

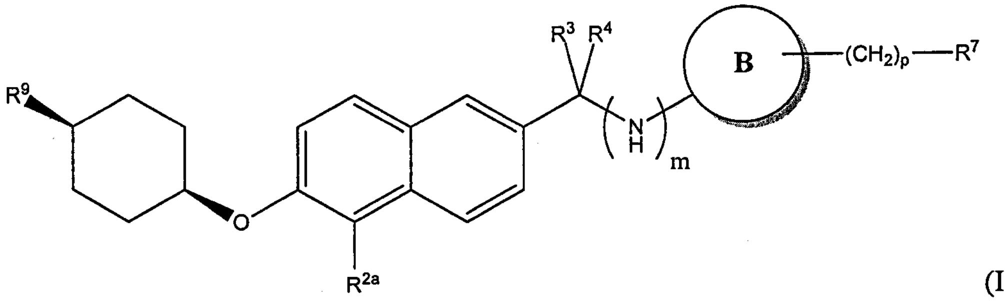
each R^3 and each R^4 are each independently hydrogen, a carboxy, C_{1-6}alkyl, or a C_{2-6}alkenyl; or R^3 and R^4 together with the carbon to which they are attached are -C(=O)-, a C_{3-8}spirocycloalkyl, or a 3- to 8-membered spiroheterocycloalkyl;

and

(i) m is 1;



is represented by the following formula:

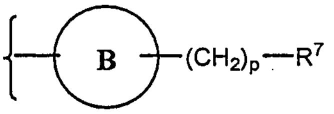


(IIb)

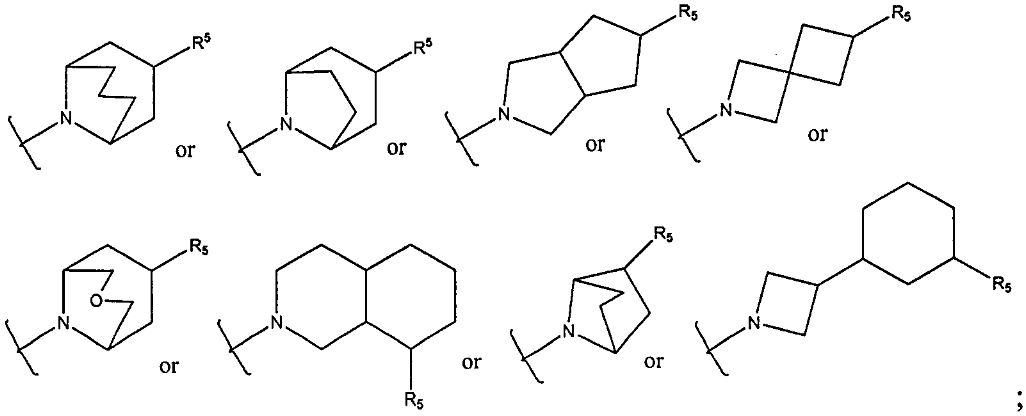
or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 3, or a pharmaceutically acceptable salt thereof, wherein:

m is 0;



is a ring system represented by the following formula:



;

wherein B is optionally further substituted by oxo, hydroxy, -NH$_2$, -CONH$_2$, or -CO$_2$H; and

R^5 is CO$_2$H.

5. The compound according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^{2a} is -Cl, -CF$_3$ or -CHF$_2$.

6. The compound according to Claim 5, or a pharmaceutically acceptable salt thereof, wherein R^9 is methyl, ethyl, -CF$_3$ or *tert*-butyl.

8-(1-(6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(5-cyano-6-((cis-4-(trifluoromethyl)cyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((5-cyano-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-((6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoro-methyl)naphthalen-2-yl)methyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)propyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(1-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(1-(5-chloro-6-((cis-4-methylcyclohexyl)oxy)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(5-chloro-6-((cis-4-ethylcyclohexyl)oxy)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

9-(1-(6-((cis-4-(1,1-difluoroethyl)cyclohexyl)oxy)-5-(trifluoromethyl)naphthalen-2-yl)ethyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

9-(5-cyano-6-((cis-4-methylcyclohexyl)oxy)-2-naphthoyl)-9-azabicyclo[3.3.1]nonane-3-carboxylic acid;

8-(5-cyano-6-((cis-4-methylcyclohexyl)oxy)-2-naphthoyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;

8-(1-(5-cyano-6-((cis-4-ethylcyclohexyl)oxy)naphthalen-2-yl)propyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid;