

PHENYL BICYCLIC METHYL AMINE DERIVATIVES AS SPHINGOSINE-1 PHOSPHATE RECEPTORS MODULATORS

By inventors: Janet A. Takeuchi, Ling Li and Wha-Bin Im

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 61/475,352, filed April 14, 2011, the disclosure of which is hereby incorporated in its entirety herein by reference.

FIELD OF THE INVENTION

The present invention relates to novel phenyl bicyclic methyl amine derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of sphingosine-1-phosphate receptors. The invention relates specifically to the use of these compounds and their pharmaceutical compositions to treat disorders associated with sphingosine-1-phosphate (S1P) receptor modulation.

BACKGROUND OF THE INVENTION

Sphingosine-1 phosphate is stored in relatively high concentrations in human platelets, which lack the enzymes responsible for its catabolism, and it is released into the blood stream upon activation of physiological stimuli, such as growth factors, cytokines, and receptor agonists and antigens. It may also have a critical role in platelet aggregation and thrombosis and could aggravate cardiovascular diseases. On the other hand the relatively high concentration of the metabolite in high-density lipoproteins (HDL) may have beneficial implications for atherogenesis. For example, there are recent suggestions that sphingosine-1-phosphate, together with other lysolipids such as sphingosylphosphorylcholine and lysosulfatide, are responsible for the beneficial clinical effects of HDL by stimulating the production of the potent antiatherogenic signaling molecule nitric oxide by the vascular endothelium. In addition, like lysophosphatidic acid, it is a marker for certain types of cancer, and there is evidence that its role in cell division or proliferation may have an influence on the development of cancers. These are currently topics that are attracting great

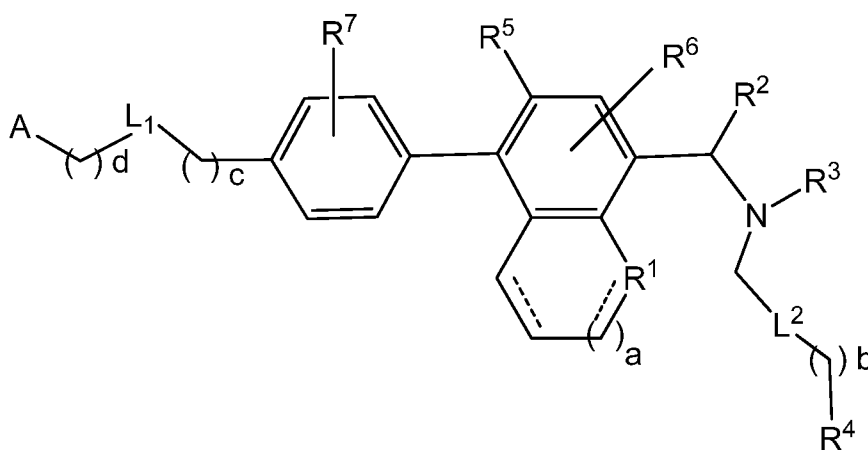
interest amongst medical researchers, and the potential for therapeutic intervention in sphingosine-1-phosphate metabolism is under active investigation.

SUMMARY OF THE INVENTION

We have now discovered a group of novel compounds which are potent and selective sphingosine-1-phosphate modulators. As such, the compounds described herein are useful in treating a wide variety of disorders associated with modulation of sphingosine-1-phosphate receptors. The term "modulator" as used herein, includes but is not limited to: receptor agonist, antagonist, inverse agonist, inverse antagonist, partial agonist, partial antagonist.

This invention describes compounds of Formula I, which have sphingosine-1-phosphate receptor biological activity. The compounds in accordance with the present invention are thus of use in medicine, for example in the treatment of humans with diseases and conditions that are alleviated by S1P modulation.

In one aspect, the invention provides a compound having **Formula I** or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof, or the geometrical isomers, enantiomers, diastereoisomers, tautomers, zwitterions and pharmaceutically acceptable salts thereof:



Formula I

wherein:

$\text{---}\xi\text{---}\text{---}\xi\text{---}$ represents a single $\text{---}\xi\text{---CH}_2\text{---CH}_2\text{---}\xi\text{---}$ or a double bond

$\text{---}\xi\text{---CH=CH\text{---}\xi\text{---}}$;

A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C₅₋₈ cycloalkyl, substituted or unsubstituted C₅₋₈ cycloalkenyl or hydrogen;

R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN,

5 C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

10 R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

15 R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;

R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹⁰ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;

L¹ is O, S, NH or CHR¹²;

20 L² is O, S, NH or CHR¹³;

R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;

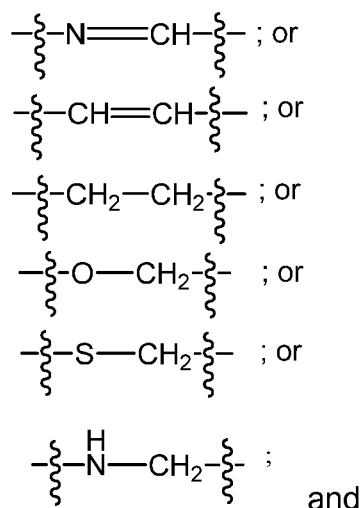
a is 0 or 1;

b is 0, 1, 2 or 3;

25 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4; with the provisos

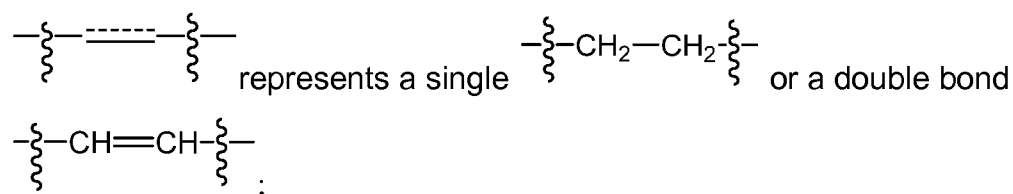
when a is 1 then $\begin{array}{c} \text{---}\zeta\text{---} \\ | \\ \text{---}\zeta\text{---} \end{array} \text{R}^1 \text{---}\text{---}\text{---} \begin{array}{c} \text{---}\zeta\text{---} \\ | \\ \text{---}\zeta\text{---} \end{array}$ represents



when a is 0 then R¹ is O, S, NH, or CH₂.

In another embodiment, the invention provides a compound having **Formula I**

5 wherein:



A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C₅₋₈ cycloalkyl, substituted or unsubstituted C₅₋₈

10 cycloalkenyl, or hydrogen;

R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -

15 S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

20 R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;

R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

L^2 is O, S, NH or CHR^{13} ;

5 R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

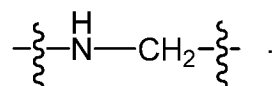
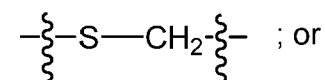
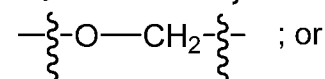
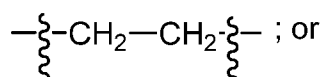
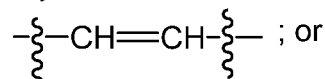
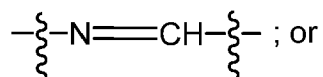
a is 1;

b is 0, 1, 2 or 3;

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

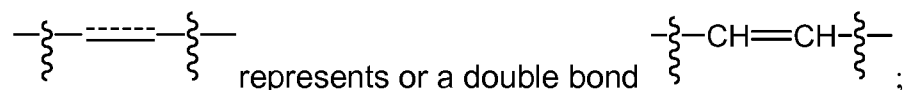
10 d is 1, 2, 3 or 4;

$\text{---}\xi\text{---}R^1\text{---}\xi\text{---}$ represents



In another embodiment, the invention provides a compound having **Formula I**

15 wherein:



A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C_{5-8} cycloalkyl, substituted or unsubstituted C_{5-8} cycloalkenyl, or hydrogen;

20 R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, -
 $S(O)_2H$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,
 NR^9R^{10} or hydroxyl;

5 R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,
 NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,
 NR^9R^{10} or hydroxyl;

R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

10 R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

L^2 is O, S, NH or CHR^{13} ;

15 R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

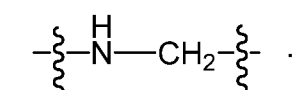
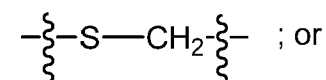
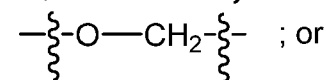
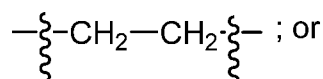
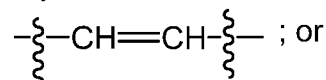
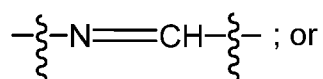
a is 1;

b is 0, 1, 2 or 3;

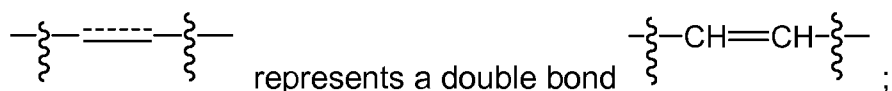
c is 0, 1, 2, 3 or 4;

20 d is 1, 2, 3 or 4;

$\text{---}\xi\text{---}R^1\text{---}\xi\text{---}$ represents

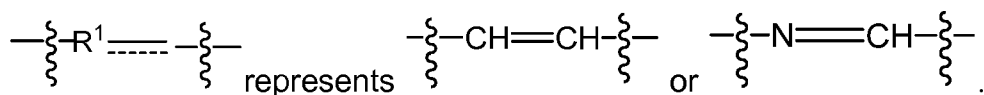


In another embodiment, the invention provides a compound having **Formula I**
 wherein:

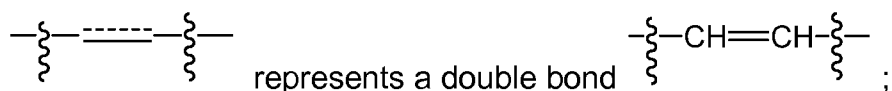


A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C₅₋₈ cycloalkyl, substituted or unsubstituted C₅₋₈ cycloalkenyl, or hydrogen;

- 5 R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;
 R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;
 R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;
- 10 R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;
 R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;
 R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;
- 15 R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;
 R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;
 R¹⁰ is H or substituted or unsubstituted C₁₋₃ alkyl;
 R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;
- 20 L¹ is O, S, NH or CHR¹²;
 L² is O, S, NH or CHR¹³;
 R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;
 R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;
 a is 1;
- 25 b is 0, 1, 2 or 3;
 c is 0, 1, 2, 3 or 4;
 d is 1, 2, 3 or 4;



- 30 In another embodiment, the invention provides a compound having **Formula I** wherein:

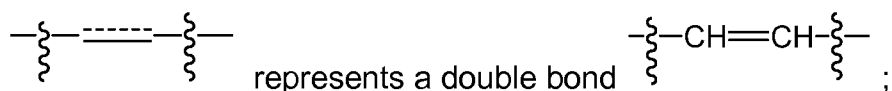


A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C₅₋₈ cycloalkyl, substituted or unsubstituted C₅₋₈ cycloalkenyl, or hydrogen;

- 5 R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;
 R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;
 R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;
- 10 R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;
 R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;
 R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸,
 15 NR⁹R¹⁰ or hydroxyl;
 R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;
 R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;
 R¹⁰ is H or substituted or unsubstituted C₁₋₃ alkyl;
 R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;
- 20 L¹ is O, S, NH or CHR¹²;
 L² is O, S, NH or CHR¹³;
 R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;
 R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;
 a is 1;
- 25 b is 0, 1, 2 or 3;
 c is 0, 1, 2, 3 or 4;
 d is 1, 2, 3 or 4; and



- 30 In another embodiment, the invention provides a compound having **Formula I** wherein:



A is substituted or unsubstituted aryl;

R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

5 R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

10 R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;

15 R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹⁰ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;

L¹ is O, S, NH or CHR¹²;

L² is O, S, NH or CHR¹³;

20 R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;

a is 1;

b is 0, 1, 2 or 3;

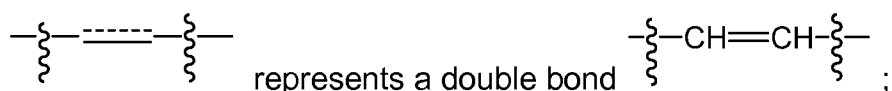
c is 0, 1, 2, 3 or 4;

25 d is 1, 2, 3 or 4;



In another embodiment, the invention provides a compound having **Formula I**

30 wherein:



A is substituted or unsubstituted aryl;

R² is hydrogen, substituted or unsubstituted C₁₋₃ alkyl;

R³ is hydrogen;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, or OR¹¹;

5 R⁵ is H, halogen;

R⁶ is H, halogen;

R⁷ is H, halogen;

R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;

L¹ is CHR¹²;

10 L² is CHR¹³;

R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;

a is 1;

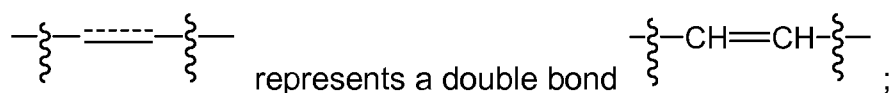
b is 0, 1;

15 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;



20 In another embodiment, the invention provides a compound having **Formula I** wherein:



A is substituted or unsubstituted C₆ aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C₅₋₈ cycloalkyl, substituted or unsubstituted C₅₋₈

25 cycloalkenyl, or hydrogen;

R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -

30 S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

5 R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

10 L^2 is O, S, NH or CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

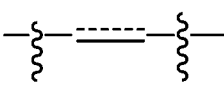
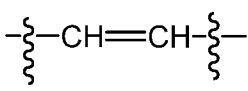
b is 0, 1, 2 or 3;

15 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;

" R^1 -----" represents " $—CH=CH—$ ".

In another embodiment, the invention provides a compound having **Formula I** wherein:

20  represents a double bond  ;

A is substituted or unsubstituted aryl;

R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

25 R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, - $S(O)_2H$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

30 R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

5 L^1 is O, S, NH or CHR^{12} ;

L^2 is O, S, NH or CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

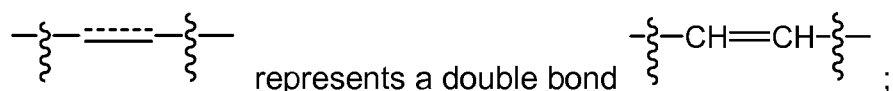
10 b is 0, 1, 2 or 3;

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

d is 1, 2, 3 or 4;

" R^1 -----" represents " $—CH=CH—$ ".

15 In another embodiment, the invention provides a compound having **Formula I** wherein:



A is substituted or unsubstituted aryl;

R^2 is hydrogen, substituted or unsubstituted C_{1-3} alkyl;

20 R^3 is hydrogen;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , or OR^{11} ;

R^5 is H, halogen;

R^6 is H, halogen;

R^7 is H, halogen;

25 R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is CHR^{12} ;

L^2 is CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

30 a is 1;

b is 0, 1;

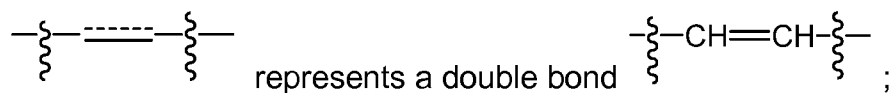
c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;

"R¹-----" represents " ---CH=CH--- ".

5

In another embodiment, the invention provides a compound having **Formula I** wherein:



A is hydrogen;

10 R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

15 R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

20 R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;

R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹⁰ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;

25 L¹ is O, S, NH or CHR¹²;

L² is O, S, NH or CHR¹³;

R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;

a is 1;

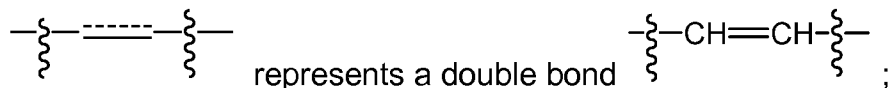
30 b is 0, 1, 2 or 3;

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

d is 1, 2, 3 or 4;



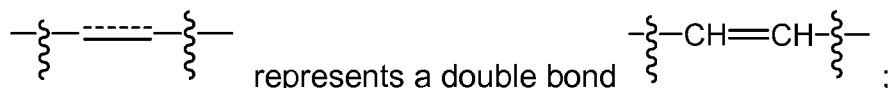
In another embodiment, the invention provides a compound having **Formula I** wherein:



- 5 A is hydrogen;
 R^2 is hydrogen, substituted or unsubstituted C_{1-3} alkyl;
 R^3 is hydrogen;
 R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , or OR^{11} ;
 R^5 is H, halogen;
 10 R^6 is H, halogen;
 R^7 is H, halogen;
 R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;
 L^1 is CHR^{12} ;
 L^2 is CHR^{13} ;
 15 R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;
 R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;
a is 1;
b is 0, 1;
c is 0, 1, 2, 3 or 4;
 20 d is 1, 2, 3 or 4;



- 25 In another embodiment, the invention provides a compound having **Formula I** wherein:



- A is hydrogen;
 R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN,
 30 $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, -

$S(O)_2H$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,

5 NR^9R^{10} or hydroxyl;

R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,

NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,

NR^9R^{10} or hydroxyl;

10 R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

15 L^2 is O, S, NH or CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

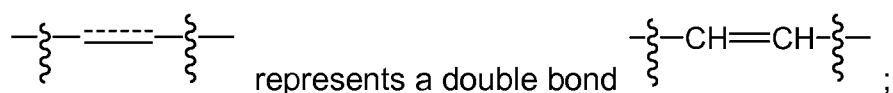
b is 0, 1, 2 or 3;

20 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;



25 In another embodiment, the invention provides a compound having **Formula I** wherein:



A is hydrogen;

R^2 is hydrogen, substituted or unsubstituted C_{1-3} alkyl;

30 R^3 is hydrogen;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , or OR^{11} ;

R^5 is H, halogen;

R^6 is H, halogen;

R^7 is H, halogen;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is CHR^{12} ;

5 L^2 is CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

b is 0, 1;

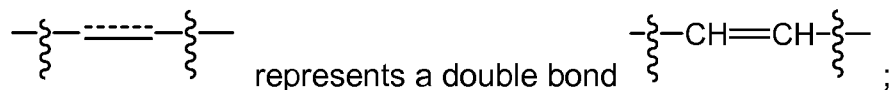
10 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;



15

In another embodiment, the invention provides a compound having **Formula I** wherein:



A is substituted or unsubstituted C_{5-8} cycloalkyl;

20 R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, $-S(O)_2H$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{11} ;

25 R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,

30 NR^9R^{10} or hydroxyl;

R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

L^2 is O, S, NH or CHR^{13} ;

5 R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

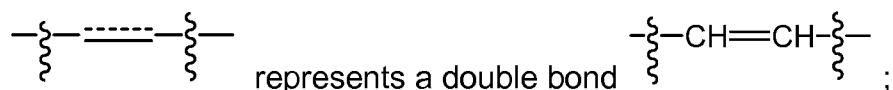
b is 0, 1, 2 or 3;

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

10 d is 1, 2, 3 or 4;



In another embodiment, the invention provides a compound having **Formula I** wherein:



15 A is substituted or unsubstituted C_{5-8} cycloalkyl;

R^2 is hydrogen, substituted or unsubstituted C_{1-3} alkyl;

R^3 is hydrogen;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , or OR^{11} ;

R^5 is H, halogen;

20 R^6 is H, halogen;

R^7 is H, halogen;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is CHR^{12} ;

L^2 is CHR^{13} ;

25 R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

b is 0, 1;

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

30 d is 1, 2, 3 or 4;



In another embodiment, the invention provides a compound having **Formula I** wherein:



A is substituted or unsubstituted C₅₋₈ cycloalkyl;

R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

10 R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

15 R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;

R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;

20 R¹⁰ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;

L¹ is O, S, NH or CHR¹²;

L² is O, S, NH or CHR¹³;

R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;

25 R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;

a is 1;

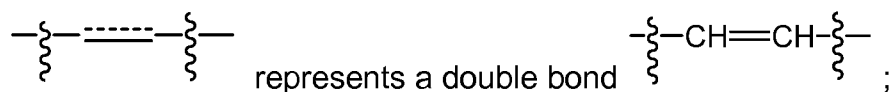
b is 0, 1, 2 or 3;

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

d is 1, 2, 3 or 4;



In another embodiment, the invention provides a compound having **Formula I** wherein:



- 5 A is substituted or unsubstituted C₅₋₈ cycloalkyl;
 R² is hydrogen, substituted or unsubstituted C₁₋₃ alkyl;
 R³ is hydrogen;
 R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, or OR¹¹;
 R⁵ is H, halogen;
 10 R⁶ is H, halogen;
 R⁷ is H, halogen;
 R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;
 L¹ is CHR¹²;
 L² is CHR¹³;
 15 R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;
 R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;
 a is 1;
 b is 0, 1;
 c is 0, 1, 2, 3 or 4;
 20 d is 1, 2, 3 or 4;



- 25 The term "alkyl", as used herein, refers to saturated, monovalent or divalent hydrocarbon moieties having linear or branched moieties or combinations thereof and containing 1 to 6 carbon atoms. One methylene (-CH₂-) group, of the alkyl can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, or by a divalent C₃₋₆ cycloalkyl. Alkyl groups can be substituted by halogen, hydroxyl,
 30 cycloalkyl, amino, non-aromatic heterocycles, carboxylic acid, phosphonic acid groups, sulphonic acid groups, phosphoric acid.

The term "cycloalkyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, preferably 3 to 5 carbon atoms derived from a saturated cyclic hydrocarbon. Cycloalkyl groups can be monocyclic or polycyclic. Cycloalkyl can be substituted by 1 to 3 C₁₋₃ alkyl groups or 1 or 2 halogens.

5 The term "cycloalkenyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms, preferably 3 to 6 carbon atoms derived from a saturated cycloalkyl having one double bond. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be substituted by 1 to 3 C₁₋₃ alkyl groups or 1 or 2 halogens.

10 The term "halogen", as used herein, refers to an atom of chlorine, bromine, fluorine, iodine.

The term "alkenyl", as used herein, refers to a monovalent or divalent hydrocarbon radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one double bond. C₂₋₆ alkenyl can be in the E or Z configuration.

15 Alkenyl groups can be substituted by 1 to 2 C₁₋₃ alkyl.

The term "alkynyl", as used herein, refers to a monovalent or divalent hydrocarbon radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one triple bond.

20 The term "heterocycle" as used herein, refers to a 3 to 10 membered ring, which can be aromatic or non-aromatic, saturated or non-saturated, containing at least one heteroatom selected from O or N or S or combinations of at least two thereof, interrupting the carbocyclic ring structure. The heterocyclic ring can be saturated or non-saturated. The heterocyclic ring can be interrupted by a C=O; the S heteroatom can be oxidized. Heterocycles can be monocyclic or polycyclic.

25 Heterocyclic ring moieties can be substituted by hydroxyl, 1 to 2 C₁₋₃ alkyl or 1 to 2 halogens. Usually, in the present case, heterocyclic groups are 5 or 6 membered rings. Usually, in the present case, heterocyclic groups are pyridine, furan, azetidine, thiazol, thiophene, oxazol, pyrazol.

30 The term "aryl" as used herein, refers to an organic moiety derived from an aromatic hydrocarbon consisting of a ring containing 6 to 10 carbon atoms by

removal of one hydrogen, which can be substituted by 1 to 3 halogen atoms or by 1 to 2 C₁₋₃ alkyl groups. Usually aryl is phenyl. Preferred substitution site on aryl are meta and para positions.

The term "hydroxyl" as used herein, represents a group of formula " --OH ".

5 The term "carbonyl" as used herein, represents a group of formula " --C(O) ".

The term "carboxyl" as used herein, represents a group of formula " --C(O)O-- ".

The term "sulfonyl" as used herein, represents a group of formula " --SO_2 ".

The term "sulfate" as used herein, represents a group of formula " $\text{--O-S(O)}_2\text{--O--}$ ".

10 The term "carboxylic acid" as used herein, represents a group of formula " --C(O)OH ".

The term "sulfoxide" as used herein, represents a group of formula " --S=O ".

The term "phosphonic acid" as used herein, represents a group of formula " --P(O)(OH)_2 ".

15 The term "phosphoric acid" as used herein, represents a group of formula " --(O)P(O)(OH)_2 ".

The term "boronic acid", as used herein, represents a group of formula " --B(OH)_2 ".

20 The term "sulphonic acid" as used herein, represents a group of formula " $\text{--S(O)}_2\text{OH}$ ".

The formula " H ", as used herein, represents a hydrogen atom.

The formula " O ", as used herein, represents an oxygen atom.

The formula " N ", as used herein, represents a nitrogen atom.

The formula " S ", as used herein, represents a sulfur atom.

Some compounds of the invention are:

- [3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
- [3-({[4-(4-hexylphenyl)-1-naphthyl]methyl}amino)propyl]phosphonic acid;
- 2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethyl dihydrogen phosphate;
- 5 3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)propanoic acid;
- {3-[(5-[4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- (3-[(5-[4-[3-(2-methylphenyl)propyl]phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- [3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)butyl]phosphonic acid;
- 10 {3-[(5-[3-fluoro-4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- [3-({[5-(2-fluoro-4-heptylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
- [3-({[5-(3-fluoro-4-heptylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
- {3-[(5-[4-(3-ethylheptyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- 15 [3-({[5-(4-octylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
- [3-({[5-(3-fluoro-4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
- {3-[(5-[4-(2-cyclohexylethyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- 2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethanol;
- 20 (3-[(5-[3-fluoro-4-[3-(2-methylphenyl)propyl]phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- (3-[(5-[3-fluoro-4-[3-(3-methylphenyl)propyl]phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- (3-[(5-[3-fluoro-4-[3-(4-methylphenyl)propyl]phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- 25 {3-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- {3-[(5-[4-(2-cyclohexylethyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
- 30 2-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethanol;
- 2-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethyl dihydrogen phosphate.

Some compounds of Formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in an R or S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-13.

- 5 The term “pharmaceutically acceptable salts” refers to salts or complexes that retain the desired biological activity of the above identified compounds and exhibit minimal or no undesired toxicological effects. The “pharmaceutically acceptable salts” according to the invention include therapeutically active, non-toxic base or acid salt forms, which the compounds of Formula I are able to form.
- 10 The acid addition salt form of a compound of Formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, such as for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, fumaric acid,
- 15 maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pantoic acid, citric, methylsulfonic, ethanesulfonic, benzenesulfonic, formic and the like (Handbook of Pharmaceutical Salts, P.Heinrich Stahl& Camille G. Wermuth (Eds), Verlag Helvetica Chemica Acta- Zürich, 2002, 329-345).
- 20 The base addition salt form of a compound of Formula I that occurs in its acid form can be obtained by treating the acid with an appropriate base such as an inorganic base, for example, sodium hydroxide, magnesium hydroxide, potassium hydroxide, calcium hydroxide, ammonia and the like; or an organic base such as for example, L-Arginine, ethanolamine, betaine, benzathine, morpholine and the like.
- 25 (Handbook of Pharmaceutical Salts, P.Heinrich Stahl& Camille G. Wermuth (Eds), Verlag Helvetica Chemica Acta- Zürich, 2002, 329-345).

Compounds of Formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

With respect to the present invention reference to a compound or compounds, is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different
5 polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

The compounds of the invention are indicated for use in treating or preventing conditions in which there is likely to be a component involving the sphingosine-1-phosphate receptors.

10 In another embodiment, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier.

In a further embodiment of the invention, there are provided methods for treating disorders associated with modulation of sphingosine-1-phosphate receptors.
15 Such methods can be performed, for example, by administering to a subject in need thereof a pharmaceutical composition containing a therapeutically effective amount of at least one compound of the invention.

These compounds are useful for the treatment of mammals, including humans, with a range of conditions and diseases that are alleviated by S1P
20 modulation: not limited to the treatment of diabetic retinopathy, other retinal degenerative conditions, dry eye, angiogenesis and wounds.

Therapeutic utilities of S1P modulators are ocular diseases, such as but not limited to: wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, geographic atrophy, angiogenesis
25 inhibition, glaucomatous optic neuropathy, chorioretinopathy, hypertensive retinopathy, ocular ischemic syndrome, prevention of inflammation-induced fibrosis in the back of the eye, various ocular inflammatory diseases including uveitis, scleritis, keratitis, and retinal vasculitis; or systemic vascular barrier related diseases such as but not limited to: various inflammatory diseases, including acute lung injury,
30 its prevention, sepsis, tumor metastasis, atherosclerosis, pulmonary edemas, and

ventilation-induced lung injury; or autoimmune diseases and immunosuppression such as but not limited to: rheumatoid arthritis, Crohn's disease, Graves' disease, inflammatory bowel disease, multiple sclerosis, Myasthenia gravis, Psoriasis, ulcerative colitis, autoimmune uveitis, renal ischemia/perfusion injury, contact hypersensitivity, atopic dermatitis, and organ transplantation; or allergies and other inflammatory diseases such as but not limited to: urticaria, bronchial asthma, and other airway inflammations including pulmonary emphysema and chronic obstructive pulmonary diseases; or cardiac protection such as but not limited to: ischemia reperfusion injury and atherosclerosis; or wound healing such as but not limited to: scar-free healing of wounds from cosmetic skin surgery, ocular surgery, GI surgery, general surgery, oral injuries, various mechanical, heat and burn injuries, prevention and treatment of photoaging and skin ageing, and prevention of radiation-induced injuries; or bone formation such as but not limited to: treatment of osteoporosis and various bone fractures including hip and ankles; or anti-nociceptive activity such as but not limited to: visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains; or central nervous system neuronal activity in Alzheimer's disease, age-related neuronal injuries; or in organ transplant such as renal, corneal, cardiac or adipose tissue transplant.

In still another embodiment of the invention, there are provided methods for treating disorders associated with modulation of sphingosine-1-phosphate receptors. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of at least one compound of the invention, or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual isomers, enantiomers, and diastereomers thereof.

The present invention concerns the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of ocular disease, wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, geographic atrophy, glaucomatous optic neuropathy, chorioretinopathy, hypertensive retinopathy, ocular ischemic syndrome, prevention of inflammation-induced fibrosis in the back of the eye, various ocular inflammatory diseases including uveitis, scleritis, keratitis, and

retinal vasculitis; or systemic vascular barrier related diseases , various inflammatory diseases, including acute lung injury, its prevention, sepsis, tumor metastasis, atherosclerosis, pulmonary edemas, and ventilation-induced lung injury; or autoimmune diseases and immunosuppression , rheumatoid arthritis, Crohn's disease, Graves' disease, inflammatory bowel disease, multiple sclerosis, Myasthenia gravis, Psoriasis, ulcerative colitis, autoimmune uveitis, renal ischemia/perfusion injury, contact hypersensitivity, atopic dermatitis, and organ transplantation; or allergies and other inflammatory diseases , urticaria, bronchial asthma, and other airway inflammations including pulmonary emphysema and chronic obstructive pulmonary diseases; or cardiac protection , ischemia reperfusion injury and atherosclerosis; or wound healing, scar-free healing of wounds from cosmetic skin surgery, ocular surgery, GI surgery, general surgery, oral injuries, various mechanical, heat and burn injuries, prevention and treatment of photoaging and skin ageing, and prevention of radiation-induced injuries; or bone formation, treatment of osteoporosis and various bone fractures including hip and ankles; or anti-nociceptive activity , visceral pain, pain associated with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains; or central nervous system neuronal activity in Alzheimer's disease, age-related neuronal injuries; or in organ transplant such as renal, corneal, cardiac or adipose tissue transplant.

The actual amount of the compound to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the severity of the condition, the age and weight of the patient, the patient's general physical condition, the cause of the condition, and the route of administration.

The patient will be administered the compound orally in any acceptable form, such as a tablet, liquid, capsule, powder and the like, or other routes may be desirable or necessary, particularly if the patient suffers from nausea. Such other routes may include, without exception, transdermal, parenteral, subcutaneous, intranasal, via an implant stent, intrathecal, intravitreal, topical to the eye, back to the eye, intramuscular, intravenous, and intrarectal modes of delivery. Additionally, the formulations may be designed to delay release of the active compound over a given

period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

In another embodiment of the invention, there are provided pharmaceutical compositions including at least one compound of the invention in a pharmaceutically acceptable carrier thereof. The phrase "pharmaceutically acceptable" means the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a patch, a micelle, a liposome, and the like, wherein the resulting composition contains one or more compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. Invention compounds may be combined, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. Invention compounds are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing invention compounds may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing invention compounds in admixture with non-toxic

pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the invention compounds are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the invention compounds are mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

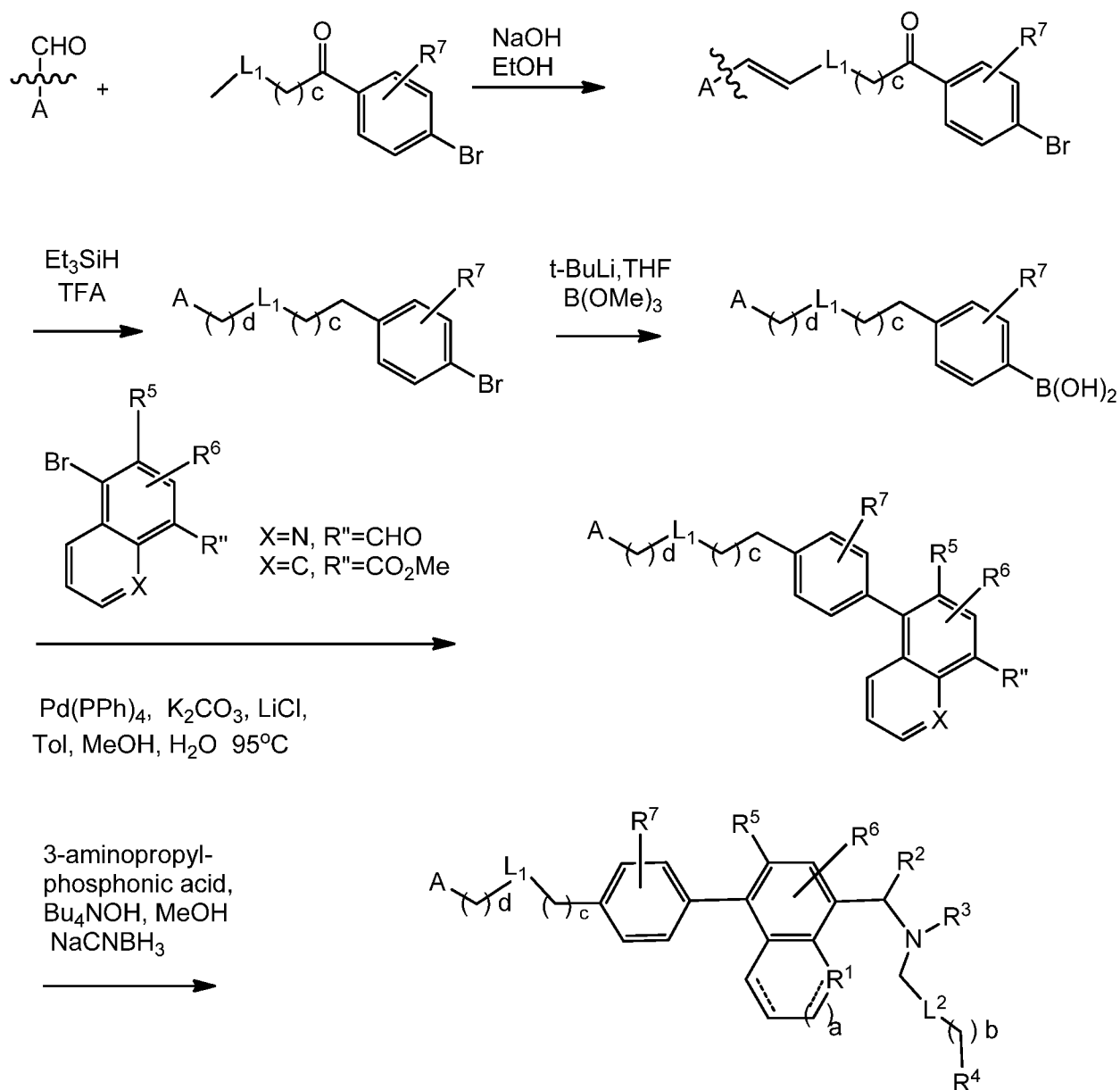
The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Invention compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the invention compounds with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

5 The compounds and pharmaceutical compositions described herein are useful as medicaments in mammals, including humans, for treatment of diseases and/or alleviations of conditions which are responsive to treatment by agonists or functional antagonists of sphingosine-1-phosphate receptors. Thus, in further embodiments of the invention, there are provided methods for treating a disorder
10 associated with modulation of sphingosine-1-phosphate receptors. Such methods can be performed, for example, by administering to a subject in need thereof a pharmaceutical composition containing a therapeutically effective amount of at least one invention compound. As used herein, the term "therapeutically effective
15 amount" means the amount of the pharmaceutical composition that will elicit the biological or medical response of a subject in need thereof that is being sought by the researcher, veterinarian, medical doctor or other clinician. In some embodiments, the subject in need thereof is a mammal. In some embodiments, the mammal is human.

20 The present invention concerns also processes for preparing the compounds of Formula I. The compounds of formula I according to the invention can be prepared analogously to conventional methods as understood by the person skilled in the art of synthetic organic chemistry. The synthetic schemes set forth below, illustrate how compounds according to the invention can be made.



To a solution of appropriately substituted bromophenone in ethanol is added sodium hydroxide followed by a solution of aldehyde. The reaction mixture is stirred at room temperature and then an extraction with water and ethyl acetate is performed. The ene-one formed is reduced in the presence of trifluoroacetic acid and triethylsilane to afford the corresponding saturated arylbromide. This arylbromide will be reacted with the desired bromoquinolone aldehyde or bromo naphthylmethylester after treated with t-butyllithium and trimethylborate. The compound of Formula I is obtained from the reaction between the quinolone aldehyde or the naphthylmethylester and the phosphoric derivative.

Those skilled in the art will be able to routinely modify and/or adapt the following scheme to synthesize any compounds of the invention covered by Formula I.

BRIEF DESCRIPTION OF THE INVENTION

5 **Figure 1** shows that Compounds 9, 10, 11 and 14 lowered lymphocyte count after 24 hours in a lymphopenia assay in mice, by measuring the *in vivo* blood lymphocyte depletion after dosing.

Figure 2 shows that Compounds 15, 17, 18 and 20 lowered lymphocyte count after 24 hours in a lymphopenia assay in mice, by measuring the *in vivo* blood
10 lymphocyte depletion after dosing.

DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the use of the singular includes
15 the plural unless specifically stated otherwise.

It will be readily apparent to those skilled in the art that some of the compounds of the invention may contain one or more asymmetric centers, such that the compounds may exist in enantiomeric as well as in diastereomeric forms. Unless it is specifically noted otherwise, the scope of the present invention includes
20 all enantiomers, diastereomers and racemic mixtures. Some of the compounds of the invention may form salts with pharmaceutically acceptable acids or bases, and such pharmaceutically acceptable salts of the compounds described herein are also within the scope of the invention.

The present invention includes all pharmaceutically acceptable isotopically
25 enriched compounds. Any compound of the invention may contain one or more isotopic atoms enriched or different than the natural ratio such as deuterium ^2H (or D) in place of protium ^1H (or H) or use of ^{13}C enriched material in place of ^{12}C and the like. Similar substitutions can be employed for N, O and S. The use of isotopes may assist in analytical as well as therapeutic aspects of the invention. For example,
30 use of deuterium may increase the *in vivo* half-life by altering the metabolism (rate)

of the compounds of the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

The following examples are for illustrative purposes only and are not intended, nor should they be construed as limiting the invention in any manner. Those skilled in the art will appreciate that variations and modifications of the following examples can be made without exceeding the spirit or scope of the invention.

As will be evident to those skilled in the art, individual isomeric forms can be obtained by separation of mixtures thereof in conventional manner. For example, in the case of diastereoisomeric isomers, chromatographic separation may be employed.

Compound names were generated with ACD version 8; and Intermediates and reagent names used in the examples were generated with software such as Chem Bio Draw Ultra version 12.0 or Auto Nom 2000 from MDL ISIS Draw 2.5 SP1.

In general, characterization of the compounds is performed according to the following methods:

NMR spectra are recorded on 300 and/or 600 MHz Varian and acquired at room temperature. Chemical shifts are given in ppm referenced either to internal TMS or to the solvent signal.

All the reagents, solvents, catalysts for which the synthesis is not described are purchased from chemical vendors such as Sigma Aldrich, Fluka, Bio-Blocks, Combi-blocks, TCI, VWR, Lancaster, Oakwood, Trans World Chemical, Alfa, Fisher, Maybridge, Frontier, Matrix, Ukrorgsynth, Toronto, Ryan Scientific, SiliCycle, Anaspec, Syn Chem, AK Scientific, AMFineCom, Carbocore, Chem-Impex, MIC-scientific, Ltd; however some known intermediates, were prepared according to published procedures.

Usually the compounds of the invention were purified by column chromatography (Auto-column) on an Teledyne-ISCO CombiFlash with a silica column, unless noted otherwise.

The following abbreviations are used in the examples:

	DMF	<i>N,N</i> -dimethylformamide
	CDCl ₃	deuterated chloroform
	CD ₃ OD	deuterated methanol
	MPLC	medium pressure liquid chromatography
5	THF	tetrahydrofuran
	MeOH	methanol
	AcOH	acetic acid
	RT	room temperature
	NaOH	sodium hydroxide
10	MgSO ₄	magnesium sulfate
	TFA	trifluoroacetic acid
	DIBAL	diisobutylaluminium hydride
	NMO	N-methylmorpholine-N-oxide
	LiCl	lithium chloride
15	HCl	hydrochloric acid

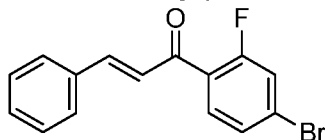
Those skilled in the art will be able to routinely modify and/or adapt the following schemes to synthesize any compound of the invention covered by Formula I.

Some compounds of this invention can generally be prepared in one step from commercially available literature starting materials.

Example 1

Intermediate 1

(2E)-1-(4-bromo-2-fluorophenyl)-3-phenylprop-2-en-1-one



25

To a solution of 4-bromo-2-fluoroacetophenone (CAS 625446-22-2) (2.5g, 11.5mmol) in ethanol (20 mL) were added to a NaOH solution (576 mg in 4.4 mL water) followed by a solution of benzaldehyde (1.22g) in ethanol (7 mL) with stirring. After stirring for 16h at RT, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over

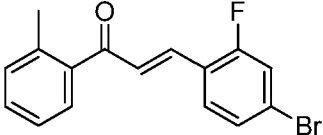
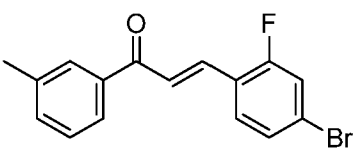
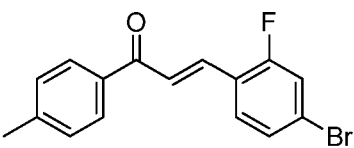
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MgSO₄, and concentrated under reduced pressure. Purification by MPLC (5% ethyl acetate in hexanes) gave 737 mg of the **Intermediate 1** as colorless solid.

¹H NMR (600 MHz, CDCl₃) δ 7.75 (dd, *J* = 1.76, 15.85 Hz, 1H), 7.72 (t, *J* = 8.07 Hz, 1H), 7.61 - 7.63 (m, 2H), 7.41 - 7.43 (m, 4H), 7.34 - 7.38 (m, 2H).

- 5 **Intermediates 2-4** were prepared from the corresponding bromo-acetophenone and aldehyde, in a similar manner to the procedure described in **Example 1** for Intermediate 1. The results are tabulated below in **Table 1**.

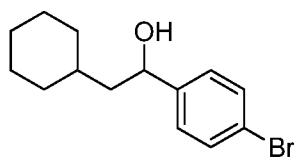
Table 1

Interm No.	IUPAC name Structure	¹ H NMR δ (ppm)
2	(2E)-3-(4-bromo-2-fluorophenyl)-1-(2-methylphenyl)prop-2-en-1-one 	¹ H NMR (600 MHz, CDCl ₃) δ: 7.55 (d, <i>J</i> = 16.1 Hz, 1H), 7.52 (d, <i>J</i> = 8.2 Hz, 1H), 7.46 (dd, <i>J</i> = 8.1 Hz, 1H), 7.40 (dd, <i>J</i> = 7.9 Hz, 1H), 7.27 - 7.35 (m, 4H), 7.24 (d, <i>J</i> = 16.7 Hz, 1H), 2.46 (s, 3H)
3	(2E)-3-(4-bromo-2-fluorophenyl)-1-(3-methylphenyl)prop-2-en-1-one 	¹ H NMR (600 MHz, CDCl ₃) δ: 7.80 - 7.83 (m, 3H), 7.63 (d, <i>J</i> = 15.8 Hz, 1H), 7.52 (t, <i>J</i> = 8.2 Hz, 1H), 7.38 - 7.42 (m, 2H), 7.33 - 7.36 (m, 2H), 2.45 (s, 3H)
4	(2E)-3-(4-bromo-2-fluorophenyl)-1-(4-methylphenyl)prop-2-en-1-one 	¹ H NMR (600 MHz, CDCl ₃) δ: 7.93 (d, <i>J</i> = 8.2 Hz, 2H), 7.81 (d, <i>J</i> = 15.8 Hz, 1H), 7.63 (d, <i>J</i> = 15.8 Hz, 1H), 7.51 (dd, <i>J</i> = 8.5 Hz, 1H), 7.32 - 7.36 (m, 2H), 7.31 (d, <i>J</i> = 7.9 Hz, 2H), 2.44 (s, 3H)

10 Example 2

Intermediate 5

1-(4-bromophenyl)-2-cyclohexylethanol



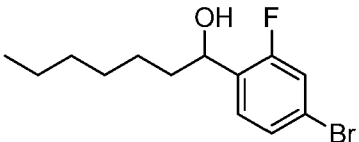
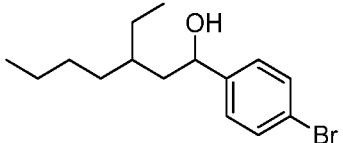
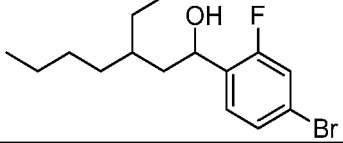
To a solution of 4-bromo benzaldehyde (2.34g, 12.64 mmol) in diethyl ether (20 mL)
 15 at -25 °C was added cyclohexylmethylmagnesium bromide (25.3 mL, 12.64 mmol).

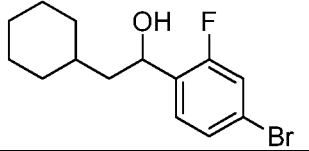
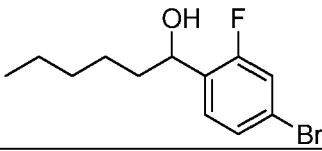
After stirring at 0 °C for 1h, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with ether. The combined ethereal layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. Purification by MPLC (10% ethyl acetate in hexanes) gave (1.75 g, 49%) **Intermediate 5** as colorless oil.

¹H NMR (600 MHz, CDCl₃) δ: 7.46 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 4.76 (dd, J = 8.7, 5.1 Hz, 1H), 1.77 - 1.81 (m, 1H), 1.63 - 1.74 (m, 6H), 1.46 - 1.51 (m, 1H), 1.35 - 1.43 (m, 1H), 1.14 - 1.26 (m, 2H), 0.95 (quint, J = 12.4, 12.0, 2.9 Hz, 2H).

Intermediates 6-10 were prepared from the corresponding aldehyde and the magnesium bromide, in a similar manner to the procedure described in **Example 2** for **Intermediate 5**. The results are tabulated below in **Table 2**.

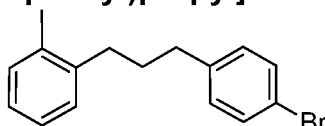
Table 2

Interm No.	IUPAC name Structure	¹ H NMR δ (ppm)
6	1-(4-bromo-2-fluorophenyl)heptan-1-ol 	¹ H NMR (600 MHz, CDCl ₃) δ: 7.50 (dd, J = 8.2, 7.0 Hz, 1H), 7.14 (dd, J = 9.5, 1.9 Hz, 1H), 7.00 (dd, J = 8.2, 1.8 Hz, 1H), 4.65 (dd, J = 7.3, 5.9 Hz, 1H), 1.80 (br. s., 1H), 1.64 - 1.78 (m, 3H), 1.34 - 1.42 (m, 1H), 1.23 - 1.33 (m, 8H), 0.87 (t, J = 7.0 Hz, 3H)
7	1-(4-bromophenyl)-3-ethylheptan-1-ol 	¹ H NMR (600 MHz, CDCl ₃) δ: 7.47 (d, J = 8.22 Hz, 2H), 7.23 (d, J = 8.22 Hz, 2H), 4.72 (dd, J = 5.28, 8.51 Hz, 1H), 1.71 (dddd, J = 5.43, 8.51, 10.27, 13.94 Hz, 2H), 1.50 - 1.57 (m, 1H), 1.20 - 1.42 (m, 8H), 0.82 - 0.90 (m, 6H)
8	1-(4-bromo-2-fluorophenyl)-3-ethylheptan-1-ol 	
9	1-(4-bromo-2-fluorophenyl)-2-cyclohexylethanol	¹ H NMR (300 MHz, CDCl ₃) δ: 7.18 - 7.46 (m, 3H), 5.08 (dd, J = 4.98, 8.79 Hz, 1H), 1.60 - 1.81 (m, 5H), 1.39 - 1.59 (m, 2H), 1.13 - 1.35 (m, 4H), 0.85 - 1.04 (m, 2H)

		
10	1-(4-bromo-2-fluorophenyl)hexan-1-ol 	^1H NMR (600 MHz, CDCl_3) δ 7.35 (t, J = 8.20 Hz, 1H), 7.29 (dd, J = 1.47, 8.22 Hz, 1H), 7.20 (dd, J = 1.76, 9.68 Hz, 1H), 4.96 (dd, J = 5.72, 7.48 Hz, 1H), 1.67 - 1.81 (m, 3H), 1.39 - 1.46 (m, 1H), 1.26 - 1.33 (m, 4H), 0.88 (t, J = 6.50 Hz, 3H)

Example 3**Intermediate 11**

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1-[3-(4-bromophenyl)propyl]-2-methylbenzene

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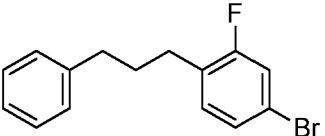
To a solution of (2*E*)-1-(4-bromophenyl)-3-(2-methylphenyl)prop-2-en-1-one (CAS 264229-42-7) (3.85g, 12.8mmol) in TFA (70mL) at 0 °C was added triethylsilane (10.2 mL, 63.9 mmol) dropwise. After stirring at RT for 16h, the reaction mixture was concentrated under reduced pressure. Purification by MPLC (hexanes) gave 2.7 g of **Intermediate 11** as colorless oil.

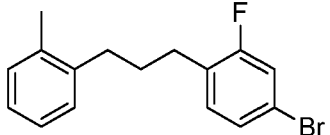
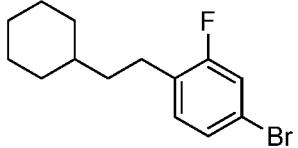
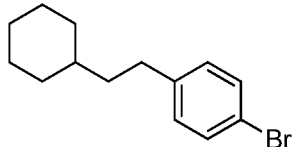
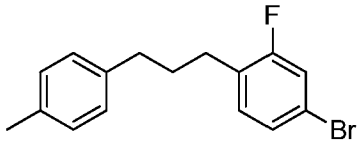
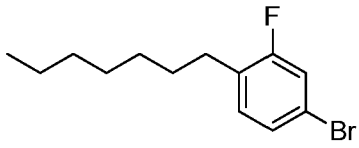
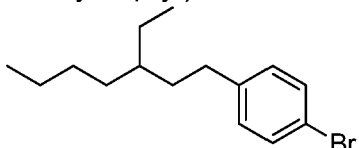
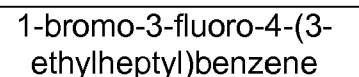
^1H NMR (600 MHz, CDCl_3) δ : 7.34 - 7.36 (m, 2H), 7.06 - 7.11 (m, 4H), 7.00 - 7.02 (m, 2H), 2.59 (q, J = 8.80 Hz, 4H), 2.23 (s, 3H), 1.81 - 1.87 (m, 2H).

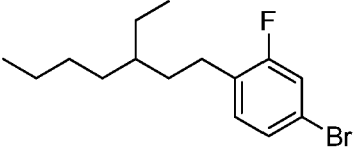
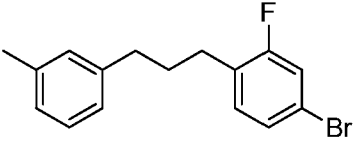
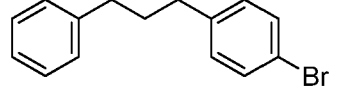
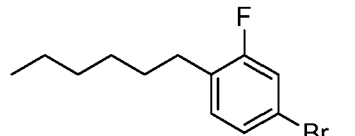
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Intermediates 12-22 were prepared from the corresponding ene-ones, TFA and triethylsilane, in a similar manner to the procedure described in **Example 3** for **Intermediate 11**. The results are tabulated below in **Table 3**.

Table 3

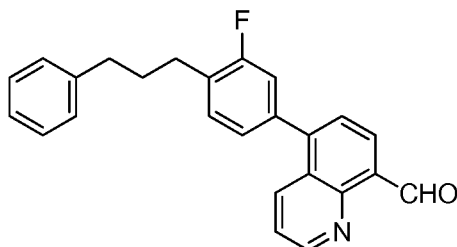
Interm. No.	IUPAC name Structure	Starting material	^1H NMR δ (ppm)
12	4-bromo-2-fluoro-1-(3-phenylpropyl)benzene 	Intermediate 1	^1H NMR (600 MHz, CDCl_3) δ 7.28 (td, J = 1.80, 7.63 Hz, 2H), 7.17 - 7.20 (m, 5H), 7.03 - 7.06 (m, 1H), 2.64 (dt, J = 7.78, 11.74 Hz, 4H), 1.89 - 1.95 (m, 2H)

13	4-bromo-2-fluoro-1-[3-(3-methylphenyl)propyl]benzene 	Intermediate 2	^1H NMR (600 MHz, CDCl_3) δ 7.17 - 7.21 (m, 2H), 7.05 - 7.14 (m, 5H), 2.68 (t, J = 7.63 Hz, 2H), 2.63 (t, J = 7.90 Hz, 2H), 2.27 (s, 3H), 1.84 - 1.90 (m, 2H)
14	4-bromo-1-(2-cyclohexylethyl)-2-fluorobenzene 	Intermediate 9	^1H NMR (300 MHz, CDCl_3) δ 7.15 - 7.21 (m, 2H), 7.05 (dd, J = 7.62, 8.50 Hz, 1H), 2.56 - 2.62 (m, 2H), 1.60 - 1.80 (m, 5H), 1.41 - 1.50 (m, 2H), 1.11 - 1.31 (m, 4H), 0.89 - 0.99 (m, 2H)
15	1-bromo-4-(2-cyclohexylethyl)benzene 	Intermediate 5	^1H NMR (600 MHz, CDCl_3) δ 7.38 (d, J = 8.22 Hz, 2H), 7.04 (d, J = 8.22 Hz, 2H), 2.54 - 2.58 (m, 2H), 1.63 - 1.76 (m, 5H), 1.44 - 1.49 (m, 2H), 1.11 - 1.28 (m, 4H), 0.92 (dtd, J = 3.50, 11.20, 12.30 Hz, 2H)
16	4-bromo-2-fluoro-1-[3-(3-methylphenyl)propyl]benzene 	Intermediate 4	^1H NMR (600 MHz, CDCl_3) δ 7.17 - 7.20 (m, 2H), 7.02 - 7.10 (m, 5H), 2.61 (q, J = 7.34 Hz, 4H), 2.32 (s, 3H), 1.90 (quin, J = 7.78 Hz, 2H)
17	4-bromo-2-fluoro-1-heptylbenzene 	Intermediate 6	^1H NMR (300 MHz, CDCl_3) δ 7.18 - 7.21 (m, 1H), 7.15 - 7.18 (m, 1H), 7.04 (dd, J = 7.62, 8.50 Hz, 1H), 2.57 (t, J = 7.62 Hz, 2H), 1.57 (quin, J = 7.30 Hz, 2H), 1.24 - 1.34 (m, 8H), 0.88 (t, J = 6.90 Hz, 3H)
18	1-bromo-4-(3-ethylheptyl)benzene 	Intermediate 7	^1H NMR (600 MHz, CDCl_3) δ 7.38 (d, J = 7.34 Hz, 2H), 7.05 (d, J = 8.22 Hz, 2H), 2.51 - 2.54 (m, 2H), 1.52 (ddd, J = 5.50, 5.72, 10.78 Hz, 2H), 1.23 - 1.36 (m, 9H), 0.90 (t, J = 7.04 Hz, 3H), 0.85 (t, J = 7.34 Hz, 3H)
19	1-bromo-3-fluoro-4-(3-ethylheptyl)benzene 	Intermediate 8	^1H NMR (300 MHz, CDCl_3) δ 7.15 - 7.21 (m, 2H), 7.05 (t, J =

			8.20 Hz, 1H), 2.52 - 2.58 (m, 2H), 1.47 - 1.55 (m, 2H), 1.18 - 1.39 (m, 8H), 0.89 (t, $J = 7.00$ Hz, 3H), 0.83 (s, 3H)
20	4-bromo-2-fluoro-1-[3-(3-methylphenyl)propyl]benzene 	Intermediate 3	^1H NMR (600 MHz, CDCl_3) δ 7.16 - 7.20 (m, 3H), 7.05 (t, $J = 8.07$ Hz, 1H), 6.96 - 7.01 (m, 3H), 2.62 (dt, $J = 8.10, 10.12$ Hz, 4H), 2.32 (s, 3H), 1.88 - 1.93 (m, 2H)
21	1-bromo-4-(3-phenylpropyl)benzene 	2-Propen-1-one, 1-(4-bromophenyl)-3-phenyl-, (2E)- (CAS 22966-23-0)	^1H NMR (600 MHz, CDCl_3) δ 7.39 (d, $J = 8.22$ Hz, 2H), 7.28 (t, $J = 7.30$ Hz, 2H), 7.16 - 7.20 (m, 3H), 7.05 (d, $J = 8.51$ Hz, 2H), 2.63 (t, $J = 7.63$ Hz, 2H), 2.60 (t, $J = 7.63$ Hz, 2H), 1.90 - 1.96 (m, 2H)
22	4-bromo-2-fluoro-1-hexylbenzene 	Intermediate 10	^1H NMR (300 MHz, CDCl_3) δ 7.15 - 7.20 (m, 2H), 7.04 (t, $J = 8.20$ Hz, 1H), 2.58 (t, $J = 7.76$ Hz, 2H), 1.57 (quin, $J = 7.90$ Hz, 2H), 1.25 - 1.36 (m, 6H), 0.88 (t, $J = 7.30$ Hz, 3H)

Example 4**Intermediate 23****5-[3-fluoro-4-(3-phenylpropyl)phenyl]quinoline-8-carbaldehyde**

5



To a solution of **Intermediate 12** (500 mg, 1.7 mmol) in THF (15 mL) at -78°C was added t-butyllithium (1.7 M in pentane, 2.0 mL) slowly dropwise. After stirring at -78°C for 1h, trimethyl borate (0.39 mL, 3.46 mmol) was added. The reaction mixture

10

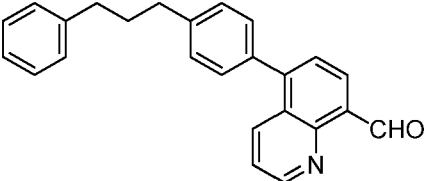
was warmed at RT over 2h. After stirring at RT for 15 min, the reaction mixture was quenched with saturated solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with HCl (10% solution), brine, and dried (MgSO₄), filtered, and concentrated under reduced pressure to give 415 mg boronic acid as a colorless solid.

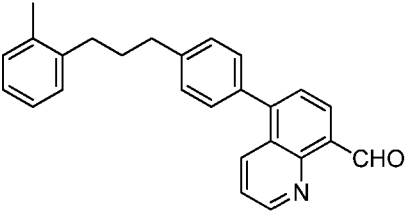
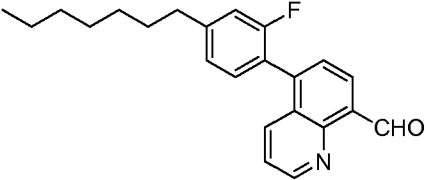
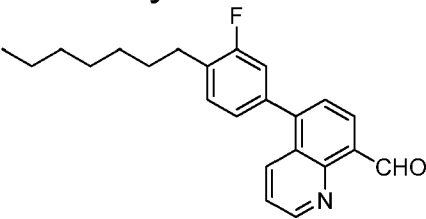
To a solution of the resulting boronic acid (4.07 mg, 1.5 mmol) and 5-bromoquinoline-8-carbaldehyde (CAS 885267-41-4) (292 mg, 1.4 mmol) in toluene (30 mL) were added potassium carbonate (436 mg, 3.15 mmol) and LiCl (67 mg) with stirring. After bubbling with Argon for 10min, tetrakis(triphenylphosphine)palladium(0) (36 mg) was added and heated at 95 °C for 16h. After the reaction mixture was cooled at RT, it was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, and dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was purified by MPLC (15% ethyl acetate in hexanes) gave 320 mg of **Intermediate 23** as colorless solid.

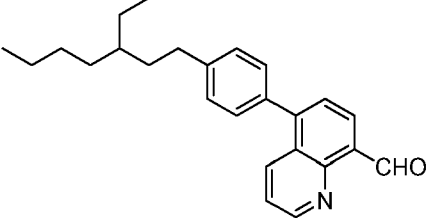
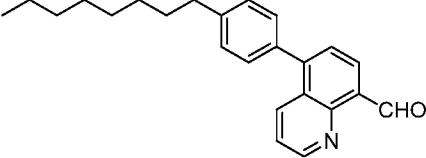
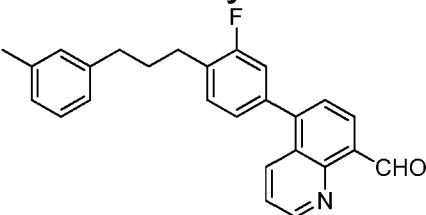
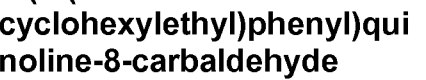
¹H NMR (600 MHz, CDCl₃) δ 11.49 (s, 1H), 9.06 (dd, *J* = 1.61, 3.96 Hz, 1H), 8.36 (d, *J* = 7.63 Hz, 1H), 8.32 (dd, *J* = 1.76, 8.51 Hz, 1H), 7.62 (d, *J* = 7.34 Hz, 1H), 7.48 (dd, *J* = 4.11, 8.51 Hz, 1H), 7.28 - 7.36 (m, 3H), 7.19 - 7.25 (m, 3H), 7.17 (dd, *J* = 1.61, 7.78 Hz, 1H), 7.14 (dd, *J* = 1.47, 10.27 Hz, 1H), 2.80 (t, *J* = 7.63 Hz, 2H), 2.75 (t, *J* = 7.60 Hz, 2H), 2.02 - 2.08 (m, 2H).

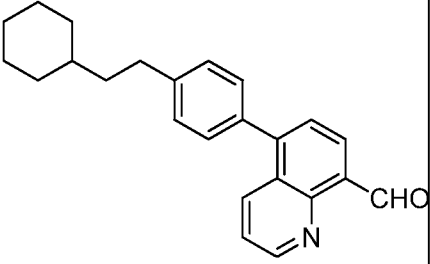
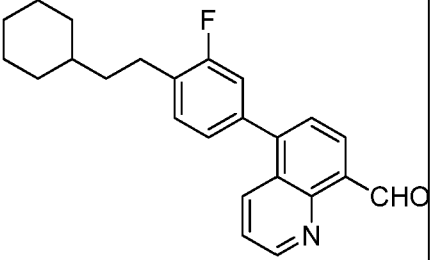
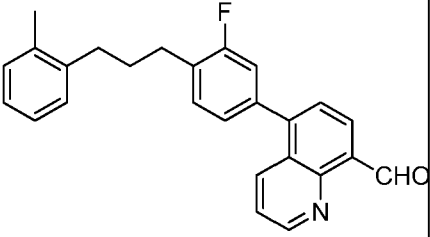
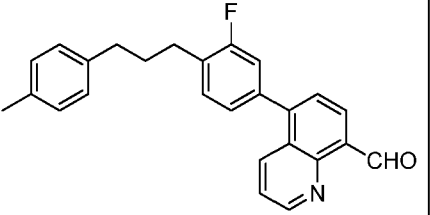
Intermediates 24-38 were prepared from the corresponding bromide in a similar manner to the procedure described in **Example 4** for **Intermediate 23**. The results are tabulated below in **Table 4**.

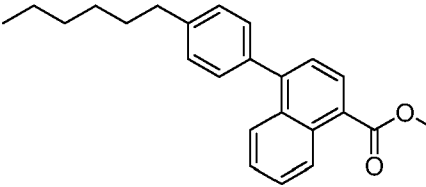
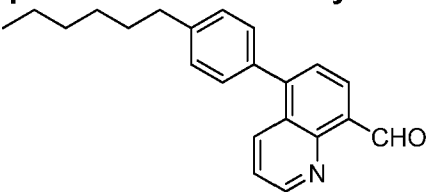
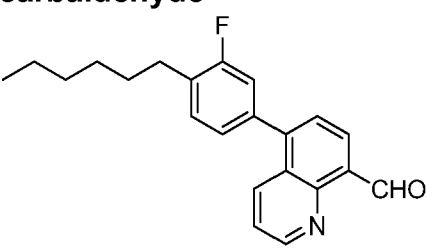
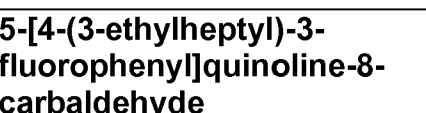
Table 4

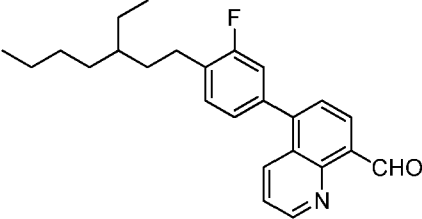
Interm No.	IUPAC name Structure	Starting material	¹ H NMR δ (ppm)
24	5-[4-(3-phenylpropyl) phenyl]quinoline-8-carbaldehyde 	Intermediate 21	¹ H NMR (600 MHz, CDCl ₃) δ 11.50 (d, <i>J</i> = 0.59 Hz, 1H), 9.06 (dd, <i>J</i> = 1.76, 4.11 Hz, 1H), 8.37 (d, <i>J</i> = 7.34 Hz, 1H), 8.35 (d, <i>J</i> = 1.76 Hz, 1H), 7.64 (d, <i>J</i> = 7.34 Hz, 1H), 7.46 (dd, <i>J</i> = 4.11, 8.51 Hz,

			1H), 7.35 - 7.40 (m, 4H), 7.29 - 7.33 (m, 2H), 7.20 - 7.24 (m, 3H), 2.77 (t, J = 7.60 Hz, 2H), 2.73 (t, J = 7.90 Hz, 2H), 2.03 - 2.09 (m, 2H)
25	5-4-[3-(2-methylphenyl)propyl]phenylquinoline-8-carbaldehyde 	Intermediate 11	¹ H NMR (600 MHz, CD ₃ OD) δ 8.98 (dd, J = 1.61, 4.26 Hz, 1H), 8.33 (dd, J = 1.47, 8.51 Hz, 1H), 7.92 (d, J = 7.34 Hz, 1H), 7.52 - 7.55 (m, 2H), 7.36 - 7.39 (m, 4H), 7.04 - 7.14 (m, 4H), 4.74 (s, 2H), 3.16 (t, J = 7.60 Hz, 2H), 2.79 (t, J = 8.20 Hz, 2H), 2.69 (t, J = 7.60 Hz, 2H), 2.27 (s, 3H), 2.00 - 2.07 (m, 2H), 1.92 - 1.98 (m, 2H), 1.63 - 1.73 (m, 2H)
26	5-(2-fluoro-4heptylphenyl)quinoline-8-carbaldehyde 	1-bromo-2-fluoro-4-heptylbenzene (CAS 256383-48-9)	¹ H NMR (CDCl ₃) δ 11.51 (d, J = 0.9 Hz, 1H), 9.06 (dd, J = 4.2, 1.9 Hz, 1H), 8.38 (d, J = 7.3 Hz, 1H), 8.12 (ddd, J = 8.5, 2.6, 1.8 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.48 (dd, J = 8.6, 4.2 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.13 (dd, J = 7.9, 1.8 Hz, 1H), 7.08 (dd, J = 10.8, 1.5 Hz, 1H), 2.69 - 2.74 (m, 2H), 1.70 (dt, J = 14.9, 7.5 Hz, 2H), 1.26 - 1.44 (m, 8H), 0.91 (t, J = 7.0 Hz, 3H)
27	5-(3-fluoro-4heptylphenyl)quinoline-8-carbaldehyde 	Intermediate 17	¹ H NMR (CDCl ₃) δ 11.50 (s, 1H), 9.08 (dd, J = 4.1, 1.8 Hz, 1H), 8.38 (d, J = 7.3 Hz, 1H), 8.36 (dd, J = 8.5, 1.8 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.50 (dd, J = 8.8, 4.1 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.17 (dd, J = 7.6, 1.8 Hz, 1H), 7.14 (dd, J = 10.3, 1.8 Hz, 1H),

			2.74 (t, J = 7.8 Hz, 2H), 1.70 (quin, J = 7.6 Hz, 2H), 1.29 - 1.44 (m, 8H), 0.91 (t, J = 7.0 Hz, 3H)
28	5-(4-(3-ethyl heptyl phenyl) quinoline-8-carbaldehyde 	Intermediate 18	¹ H NMR (CDCl ₃) δ 11.49 (s, 1H), 9.04 (dd, J = 4.1, 1.8 Hz, 1H), 8.36 (dd, J = 8.5, 1.8 Hz, 1H), 8.36 (d, J = 7.3 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.45 (dd, J = 8.8, 4.1 Hz, 1H), 7.35 - 7.39 (m, 4H), 2.69 (dd, J = 10.1, 6.0 Hz, 2H), 1.63 - 1.67 (m, 2H), 1.28 - 1.43 (m, 9H), 0.92 (dt, J = 7.1 Hz, 6H)
29	5-(4-octyl phenyl) quinoline-8-carbaldehyde 	1-bromo-4-octylbenzene (CAS 51554-93-9)	¹ H NMR (CDCl ₃) δ 11.50 (s, 1H), 9.05 (dd, J = 3.7, 1.6 Hz, 1H), 8.36 (d, J = 7.3 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.46 (dd, J = 8.5, 4.1 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 2.71 (t, J = 7.9 Hz, 2H), 1.70 (quin, J = 7.6 Hz, 2H), 1.25 - 1.43 (m, 10H), 0.90 (t, J = 6.7 Hz, 3H)
30	5-(3-fluoro-4-(3-(m-tolyl)propyl)phenyl)quinoline-8-carbaldehyde 	Intermediate 20	¹ H NMR (CDCl ₃) δ 11.50 (d, J = 0.9 Hz, 1H), 9.07 (dd, J = 4.1, 1.8 Hz, 1H), 8.38 (s, 1H), 8.34 (dd, J = 8.5, 1.8 Hz, 1H), 7.64 (dd, J = 7.5, 0.7 Hz, 1H), 7.49 (dd, J = 8.6, 4.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.12 - 7.22 (m, 3H), 6.96 - 7.06 (m, 3H), 2.80 (t, J = 7.8 Hz, 2H), 2.67 - 2.75 (m, 2H), 2.35 (s, 3H), 1.98 - 2.10 (m, 2H)
31	5-(4-(2-cyclohexylethyl)phenyl)quinoline-8-carbaldehyde 	Intermediate 15	¹ H NMR (CDCl ₃) δ 11.49 (d, J = 0.6 Hz, 1H), 9.04 (dd, J = 4.1, 1.8 Hz, 1H), 8.35 (d, J = 7.3 Hz, 1H), 8.36 (dd, J = 8.5, 2.3 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.45 (dd, J = 8.5, 4.1 Hz, 1H), 7.38 (d, J = 8.2

			Hz, 2H), 7.34 (d, $J = 7.9$ Hz, 2H), 2.70 - 2.74 (m, 2H), 1.82 (dd, $J = 13.5$, 2.1 Hz, 2H), 1.73 (ddd, $J = 12.8$, 3.2, 2.8 Hz, 2H), 1.66 - 1.69 (m, 1H), 1.57 - 1.61 (m, 2H), 1.30 - 1.39 (m, 1H), 1.15 - 1.30 (m, 3H), 0.98 (dtd, $J = 12.3$, 12.1, 3.2 Hz, 2H)
32	5-(4-(2-cyclohexylethyl)-3-fluorophenyl)quinoline-8-carbaldehyde 	Intermediate 14	^1H NMR (CDCl_3) δ 11.49 (d, $J = 0.6$ Hz, 1H), 9.06 (dd, $J = 4.1$, 1.8 Hz, 1H), 8.36 (d, $J = 7.6$ Hz, 1H), 8.34 (dd, $J = 8.5$, 1.8 Hz, 1H), 7.63 (dd, $J = 7.3$, 0.6 Hz, 1H), 7.48 (dd, $J = 8.5$, 4.1 Hz, 1H), 7.34 (t, $J = 7.9$ Hz, 1H), 7.11 - 7.18 (m, 2H), 2.69 - 2.78 (m, 2H), 1.65 - 1.87 (m, 5H), 1.54 - 1.62 (m, 2H), 1.15 - 1.47 (m, 4H), 0.99 (dtd, $J = 12.0$, 11.6, 2.8 Hz, 2H)
33	5-{3-fluoro-4-[3-(2-methylphenyl)propyl]phenyl}quinoline-8-carbaldehyde 	Intermediate 13	^1H NMR (300 MHz, CDCl_3) δ 11.48 (d, $J = 0.59$ Hz, 1H), 9.04 (dd, $J = 1.76$, 4.10 Hz, 1H), 8.34 (d, $J = 7.62$ Hz, 1H), 8.31 (dd, $J = 2.05$, 8.79 Hz, 1H), 7.61 (dd, $J = 0.59$, 7.62 Hz, 1H), 7.46 (dd, $J = 4.25$, 8.64 Hz, 1H), 7.36 (t, $J = 8.50$ Hz, 1H), 7.11 - 7.20 (m, 7H), 2.78 (dt, $J = 7.60$, 33.11 Hz, 4H), 2.31 (s, 3H), 1.94 - 2.04 (m, 2H)
34	5-{3-fluoro-4-[3-(4-methylphenyl)propyl]phenyl}quinoline-8-carbaldehyde 	Intermediate 16	^1H NMR (300 MHz, CDCl_3) δ 11.50 (d, $J = 0.88$ Hz, 1H), 9.10 (dd, $J = 1.76$, 4.40 Hz, 1H), 8.39 (d, $J = 7.62$ Hz, 1H), 8.37 (dd, $J = 1.76$, 8.50 Hz, 1H), 7.65 (dd, $J = 0.73$, 7.47 Hz, 1H), 7.52 (dd, $J = 4.25$, 8.64 Hz, 1H), 7.35 (t, $J = 7.90$ Hz, 1H), 7.07 - 7.19 (m, 7H), 2.75 (dt, $J =$

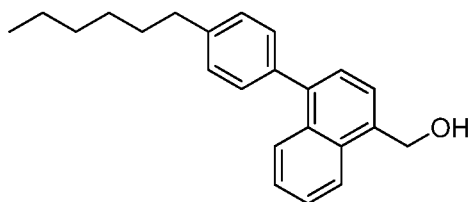
			7.90, 24.03 Hz, 4H), 2.33 (s, 3H), 1.99 - 2.07 (m, 2H)
35	methyl 4-(4-hexyl phenyl)-1-naphthoate 	1-bromo-4-hexylbenzene (CAS 237033-22-2)	¹ H NMR (300 MHz, CDCl ₃) δ 8.98 (ddt, <i>J</i> = 0.70, 0.88, 8.57 Hz, 1H), 8.20 (d, <i>J</i> = 7.62 Hz, 1H), 7.96 (ddd, <i>J</i> = 0.60, 1.47, 8.50 Hz, 1H), 7.61 (ddd, <i>J</i> = 1.47, 6.96, 8.57 Hz, 1H), 7.46 (ddd, <i>J</i> = 1.17, 6.89, 8.35 Hz, 1H), 7.43 (d, <i>J</i> = 7.33 Hz, 1H), 7.28 - 7.41 (m, 4H), 4.02 (s, 3H), 2.71 (t, <i>J</i> = 7.60 Hz, 2H), 1.65 - 1.75 (m, 2H), 1.26 - 1.44 (m, 6H), 0.91 (t, <i>J</i> = 7.00 Hz, 3H)
36	5-(4-hexylphenyl)quinoline-8-carbaldehyde 	1-bromo-4-hexylbenzene (CAS 237033-22-2)	¹ H NMR (300 MHz, CDCl ₃) δ 11.50 (s, 1H), 9.06 (dd, <i>J</i> = 1.61, 3.96 Hz, 1H), 8.37 (d, <i>J</i> = 7.33 Hz, 2H), 7.65 (d, <i>J</i> = 7.33 Hz, 1H), 7.47 (dd, <i>J</i> = 4.25, 8.64 Hz, 1H), 7.33 - 7.40 (m, 4H), 2.72 (t, <i>J</i> = 7.60 Hz, 2H), 1.65 - 1.75 (m, 2H), 1.31 - 1.46 (m, 6H), 0.91 (t, <i>J</i> = 6.70 Hz, 3H)
37	5-(3-fluoro-4-hexylphenyl)quinoline-8-carbaldehyde 	Intermediate 22	¹ H NMR (300 MHz, CDCl ₃) δ 11.49 (s, 1H), 9.05 (dd, <i>J</i> = 1.76, 4.10 Hz, 1H), 8.35 (d, <i>J</i> = 7.33 Hz, 1H), 8.34 (dd, <i>J</i> = 1.76, 8.79 Hz, 1H), 7.62 (d, <i>J</i> = 7.62 Hz, 1H), 7.48 (dd, <i>J</i> = 4.10, 8.79 Hz, 1H), 7.35 (t, <i>J</i> = 7.91 Hz, 1H), 7.15 (dd, <i>J</i> = 1.76, 19.05 Hz, 1H), 7.15 (s, 0H), 2.74 (t, <i>J</i> = 7.62 Hz, 2H), 1.64 - 1.74 (m, 2H), 1.30 - 1.47 (m, 6H), 0.91 (t, <i>J</i> = 6.70 Hz, 3H)
38	5-[4-(3-ethylheptyl)-3-fluorophenyl]quinoline-8-carbaldehyde 	Intermediate 19	¹ H NMR (300 MHz, CDCl ₃) δ 11.51 (d, <i>J</i> = 0.88 Hz, 1H), 9.10 (dd, <i>J</i> =

			1.90, 4.25 Hz, 1H), 8.39 (d, $J = 7.62$ Hz, 1H), 8.38 (dd, $J = 1.76, 8.79$ Hz, 1H), 7.65 (d, $J = 7.33$ Hz, 1H), 7.51 (dd, $J = 4.25, 8.64$ Hz, 1H), 7.36 (t, $J = 7.90$ Hz, 1H), 7.12 - 7.19 (m, 2H), 2.68 - 2.75 (m, 2H), 1.60 - 1.68 (m, 2H), 1.26 - 1.45 (m, 9H), 0.88 - 0.95 (m, 6H)
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Example 5

Intermediate 39

[4-(4-hexylphenyl)-1-naphthyl]methanol



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To a solution of **Intermediate 35** (297 mg, 1.1 mmol) in methylene chloride (10 mL) at -78 °C was added DIBAL (1M in methylene chloride, 2.8 mL, 2.8 mmol). After warming at RT over 3h, the reaction mixture was cooled to -10 °C and quenched with ethyl acetate, methanol, and 10% HCl solution. The mixture was diluted with water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. Purification by MPLC (30% ethyl acetate in hexanes) gave 378 mg of **Intermediate 39** as colorless oil.

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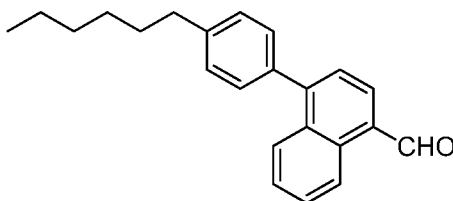
¹H NMR (300 MHz, CDCl₃) δ 8.20 (dd, $J = 0.59, 8.50$ Hz, 1H), 7.97 (dd, $J = 0.59, 8.50$ Hz, 1H), 7.56 (ddd, $J = 1.50, 6.70, 8.21$ Hz, 1H), 7.56 (d, $J = 8.50$ Hz, 1H), 7.45 (ddd, $J = 1.47, 7.03, 8.79$ Hz, 1H), 7.37 - 7.41 (m, 3H), 7.28 - 7.32 (m, 2H), 5.20 (s, 2H), 2.70 (t, $J = 7.60$ Hz, 2H), 1.65 - 1.75 (m, 2H), 1.31 - 1.46 (m, 6H), 0.92 (t, $J = 6.70$ Hz, 3H).

15

Example 6

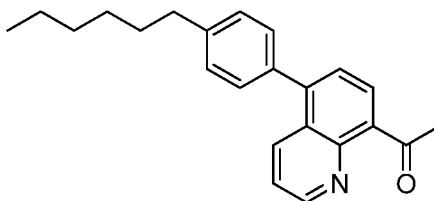
20

Intermediate 40

4-(4-hexylphenyl)-1-naphthaldehyde

To a solution of **Intermediate 39** (308 mg, 0.96 mmol), NMO (283 mg, 2.4 mmol),
5 and 4 Å molecular sieves (0.4g) in dichloromethane (10 mL) and acetonitrile (1.2 mL)
was added tetrapropylammonium perruthenate (TPAP, 10 mg). After stirring at RT
for 2h, the reaction mixture was filtered through a short column of silica gel, eluted
with ethyl acetate and concentrated under reduced pressure. Purification by MPLC
(2% ethyl acetate in hexanes) gave rise to 242 mg of **Intermediate 40** as colorless
10 solid.

¹H NMR (300 MHz, CDCl₃) δ 10.42 (s, 1H), 9.36 (d, *J* = 8.50 Hz, 1H), 8.02 (d, *J* =
7.33 Hz, 1H), 8.00 (d, *J* = 8.50 Hz, 1H), 7.70 (ddd, *J* = 1.17, 7.03, 8.50 Hz, 1H), 7.57
(d, *J* = 7.33 Hz, 1H), 7.53 (ddd, *J* = 1.47, 7.30, 8.20 Hz, 1H), 7.31 - 7.42 (m, 4H),
2.72 (t, *J* = 7.91 Hz, 2H), 1.65 - 1.76 (m, 2H), 1.31 - 1.46 (m, 6H), 0.92 (t, *J* = 6.70
15 Hz, 3H).

Example 7**Intermediate 41****1-[5-(4-hexylphenyl)quinolin-8-yl]ethanone**

To a solution of **Intermediate 36** (166 mg, 0.52 mmol) in THF (3 mL) at -78 °C was
added methyl lithium (1.6M in ether, 0.36 mL, 0.57 mmol) dropwise. After stirring at -
78 °C for 20 min, a solution of N-t-butylbenzenesulfinimidoyl chloride (169 mg, 0.78
mmol) in THF (1.2 mL) was added dropwise. After stirring the reaction mixture for
25 another 20 min at -78 °C, then at RT for 20 min, the black solution mixture was

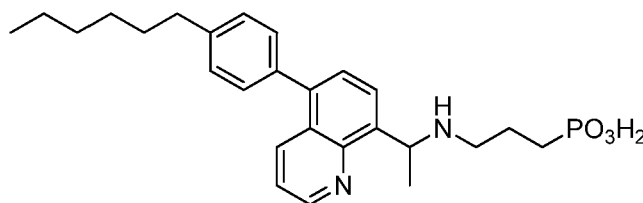
quenched with 2M HCl (3mL). The aqueous layer was extracted with ethyl acetate. The combined aqueous layers were then extracted well with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. Purification by MPLC (20% ethyl acetate in hexanes) gave 25 mg of **Intermediate 41** as brown oil.

¹H NMR (600 MHz, CDCl₃) δ 8.97 (dd, *J* = 1.76, 4.11 Hz, 1H), 8.30 (dd, *J* = 1.76, 8.51 Hz, 1H), 7.97 (d, *J* = 7.63 Hz, 1H), 7.53 (d, *J* = 7.34 Hz, 1H), 7.32 - 7.40 (m, 5H), 2.98 (s, 3H), 2.71 (t, *J* = 8.20 Hz, 2H), 1.67 - 1.73 (m, 2H), 1.33 - 1.43 (m, 6H), 0.91 (t, *J* = 7.00 Hz, 3H).

Example 8

Compound 1

[3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)butyl]phosphonic acid



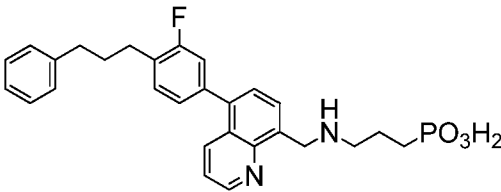
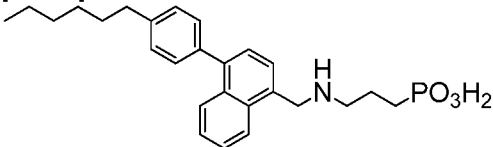
To a solution of **Intermediate 41** (68 mg, 0.21 mmol) and (3-aminopropyl)phosphonic acid (29 mg, 0.21 mmol) in methanol (3 mL) was added tetrabutylammonium hydroxide (1M in MeOH, 0.21 mL, 0.21 mmol). The reaction mixture was heated at 50 °C for 2h with stirring, then sodium cyanoborohydride (13 mg, 0.21 mmol) was added. The reaction mixture was heated at 50 °C with stirring for 3h. After cooling to RT, the mixture was concentrated and purified by MPLC (0-100% ethyl acetate in hexanes) to give 26 mg of **Compound 1** as yellow solid.

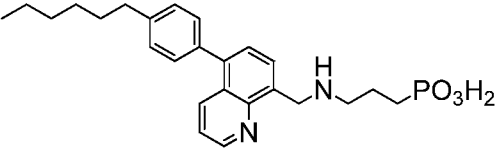
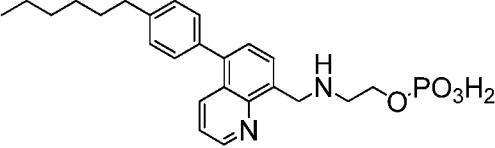
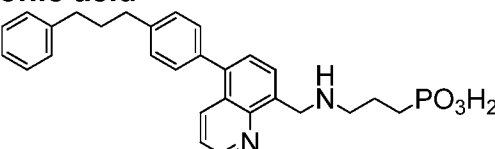
¹H NMR (600 MHz, CD₃OD) δ 8.96 (dd, *J* = 1.76, 4.11 Hz, 1H), 8.36 (dd, *J* = 1.76, 8.51 Hz, 1H), 7.86 (d, *J* = 7.34 Hz, 1H), 7.57 (d, *J* = 7.34 Hz, 1H), 7.55 (dd, *J* = 4.10, 8.22 Hz, 1H), 7.37 (d, *J* = 0.88 Hz, 4H), 5.03 (q, *J* = 6.75 Hz, 1H), 2.90 (s, 1H), 2.79 - 2.84 (m, 1H), 2.72 (t, *J* = 7.90 Hz, 2H), 1.88 - 1.95 (m, 2H), 1.85 (d, *J* = 7.04 Hz, 3H), 1.61 - 1.73 (m, 4H), 1.34 - 1.45 (m, 6H), 0.92 (t, *J* = 7.00 Hz, 3H).

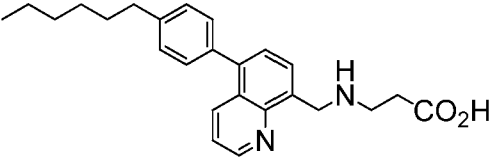
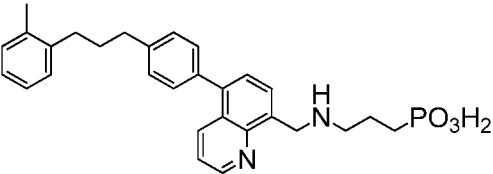
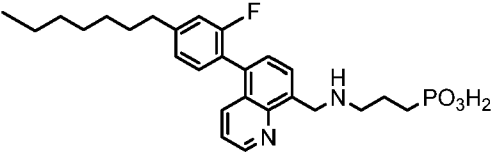
Compounds 2 through **20** were prepared from the corresponding aldehyde or methylester in a similar manner to the procedure described in **Example 8** for

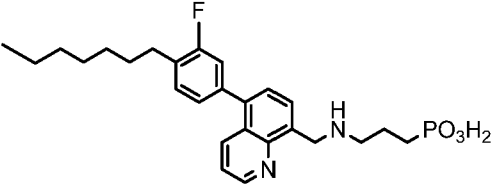
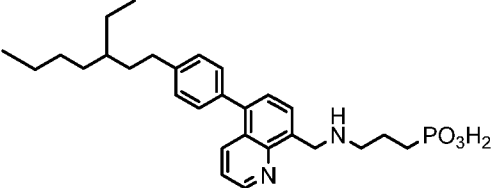
Compound 1 and in the general procedure described above. The results are tabulated below in **Table 5**.

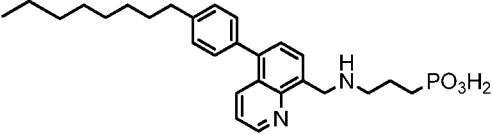
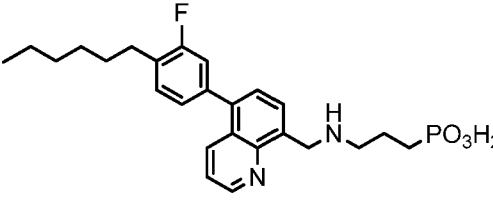
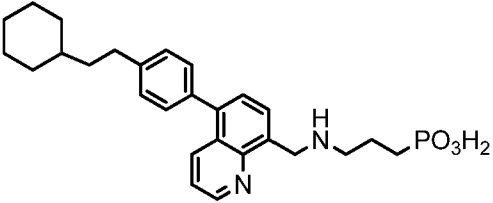
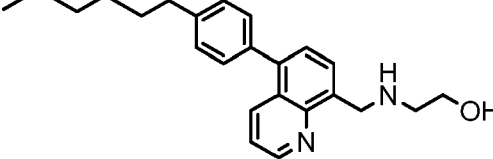
Table 5

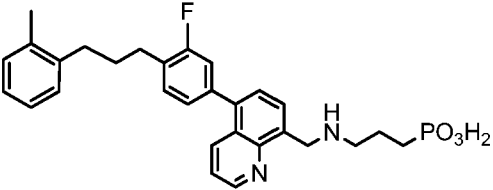
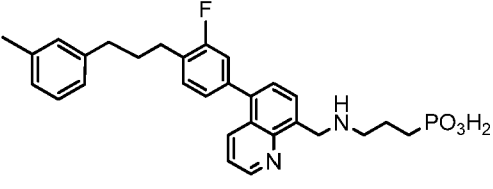
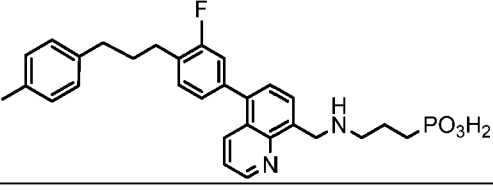
Comp. No.	IUPAC name Structure	Starting material	¹ H NMR δ (ppm)
2	{3-[(5-[3-fluoro-4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid 	Intermediate 23	¹ H NMR (600 MHz, CD ₃ OD) δ 9.00 (dd, <i>J</i> = 1.61, 4.25 Hz, 1H), 8.32 (dd, <i>J</i> = 1.61, 8.66 Hz, 1H), 7.94 (d, <i>J</i> = 7.34 Hz, 1H), 7.55 - 7.58 (m, 2H), 7.39 (t, <i>J</i> = 7.78 Hz, 1H), 7.13 - 7.28 (m, 7H), 4.75 (s, 2H), 3.18 (t, <i>J</i> = 6.60 Hz, 2H), 2.77 (t, <i>J</i> = 7.63 Hz, 2H), 2.71 (t, <i>J</i> = 7.63 Hz, 2H), 1.98 - 2.08 (m, 4H), 1.63 - 1.73 (m, 2H)
3	[3-({4-(4-hexylphenyl)-1-naphthyl}methyl)amino]propyl}phosphonic acid 	Intermediate 40	¹ H NMR (600 MHz, CD ₃ OD) δ 8.22 (d, <i>J</i> = 8.51 Hz, 1H), 7.94 (d, <i>J</i> = 8.22 Hz, 1H), 7.73 (d, <i>J</i> = 7.34 Hz, 1H), 7.66 (ddd, <i>J</i> = 1.17, 6.90, 8.36 Hz, 1H), 7.52 (ddd, <i>J</i> = 1.17, 6.90, 8.36 Hz, 1H), 7.45 (d, <i>J</i> = 7.34 Hz, 1H), 7.34 (d, <i>J</i> = 1.17 Hz, 4H), 4.69 (s, 2H), 3.26 (t, <i>J</i> = 6.31 Hz, 2H), 2.72 (t, <i>J</i> = 8.50 Hz, 2H), 2.00 - 2.08 (m, <i>J</i> = 6.60, 6.75, 18.93 Hz, 2H), 1.68 - 1.75 (m, 4H), 1.35 - 1.44 (m, 6H), 0.92 (t, <i>J</i> = 7.30 Hz, 3H)

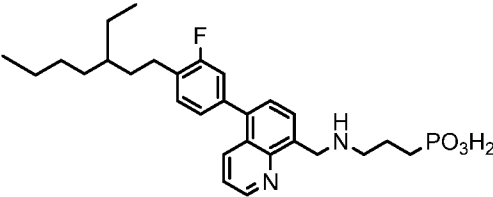
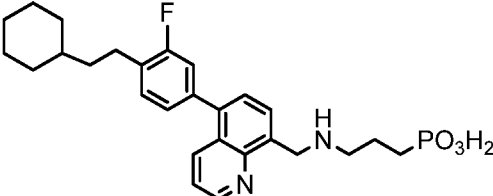
4	[3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid 	Intermediate 36	¹ H NMR (300 MHz, CD ₃ OD) δ 8.98 (dd, <i>J</i> = 1.47, 4.10 Hz, 1H), 8.33 (dd, <i>J</i> = 1.47, 8.50 Hz, 1H), 7.93 (d, <i>J</i> = 7.33 Hz, 1H), 7.47 - 7.59 (m, 2H), 7.35 (s, 4H), 4.75 (s, 2H), 3.18 (t, <i>J</i> = 6.59 Hz, 2H), 2.71 (t, <i>J</i> = 7.62 Hz, 2H), 1.97 - 2.12 (m, 2H), 1.61 - 1.76 (m, 4H), 1.32 - 1.46 (m, 6H), 0.92 (t, <i>J</i> = 6.70 Hz, 3H)
5	2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethyl dihydrogen phosphate 	Intermediate 36	¹ H NMR (600 MHz, CD ₃ OD) δ 8.99 (dd, <i>J</i> = 1.61, 4.26 Hz, 1H), 8.34 (dd, <i>J</i> = 1.61, 8.66 Hz, 1H), 7.94 (d, <i>J</i> = 7.34 Hz, 1H), 7.55 (d, <i>J</i> = 7.04 Hz, 1H), 7.54 (dd, <i>J</i> = 4.26, 8.66 Hz, 1H), 7.35 - 7.37 (m, 4H), 4.74 (s, 2H), 4.10 (tdd, <i>J</i> = 2.42, 2.79, 7.08 Hz, 2H), 2.72 (t, <i>J</i> = 7.60 Hz, 2H), 1.63 - 1.73 (m, 4H), 1.34 - 1.45 (m, 6H), 0.89 - 0.94 (m, <i>J</i> = 7.00, 7.00 Hz, 3H)
6	{3-[(5-[4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid 	Intermediate 24	¹ H NMR (600 MHz, CD ₃ OD) δ 8.98 (dd, <i>J</i> = 1.61, 4.26 Hz, 1H), 8.33 (dd, <i>J</i> = 1.76, 8.51 Hz, 1H), 7.92 (d, <i>J</i> = 7.34 Hz, 1H), 7.52 - 7.54 (m, 2H), 7.35 (s, 4H), 7.14 - 7.28 (m, 5H), 4.73 (s, 2H), 3.16 (t, <i>J</i> = 6.46 Hz, 2H), 2.73 (t, <i>J</i> = 7.30 Hz, 2H), 2.69 (t, <i>J</i> = 7.60 Hz, 2H), 1.98 - 2.07 (m, 4H), 1.63 - 1.73 (m, 2H)

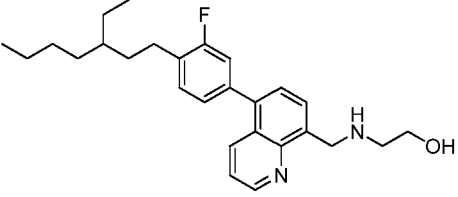
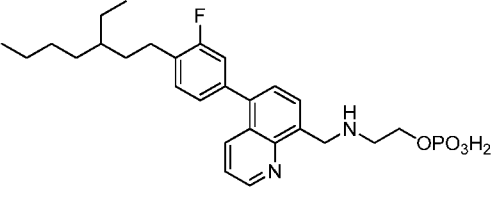
7	3-([5-(4-hexylphenyl)quinolin-8-yl]methyl)amino)propanoic acid 	Intermediate 36	¹ H NMR (600 MHz, CD ₃ OD) δ 9.01 (dd, <i>J</i> = 1.76, 4.40 Hz, 1H), 8.33 (dd, <i>J</i> = 1.76, 8.51 Hz, 1H), 7.87 (d, <i>J</i> = 7.04 Hz, 1H), 7.55 (d, <i>J</i> = 3.52 Hz, 1H), 7.53 (t, <i>J</i> = 2.05 Hz, 1H), 7.35 (s, 4H), 4.74 (s, 2H), 3.26 (t, <i>J</i> = 6.16 Hz, 2H), 2.72 (t, <i>J</i> = 7.90 Hz, 2H), 2.56 (t, <i>J</i> = 6.16 Hz, 2H), 1.67 - 1.72 (m, 2H), 1.34 - 1.43 (m, 6H), 0.92 (t, <i>J</i> = 7.30 Hz, 3H)
8	(3-([5-(4-[3-(2-methylphenyl)propyl]phenyl)quinolin-8-yl]methyl)amino)propyl)phosphonic acid 	Intermediate 25	¹ H NMR (600 MHz, CD ₃ OD) δ 8.98 (dd, <i>J</i> = 1.61, 4.26 Hz, 1H), 8.33 (dd, <i>J</i> = 1.47, 8.51 Hz, 1H), 7.92 (d, <i>J</i> = 7.34 Hz, 1H), 7.52 - 7.55 (m, 2H), 7.36 - 7.39 (m, 4H), 7.04 - 7.14 (m, 4H), 4.74 (s, 2H), 3.16 (t, <i>J</i> = 7.60 Hz, 2H), 2.79 (t, <i>J</i> = 8.20 Hz, 2H), 2.69 (t, <i>J</i> = 7.60 Hz, 2H), 2.27 (s, 3H), 2.00 - 2.07 (m, 2H), 1.92 - 1.98 (m, 2H), 1.63 - 1.73 (m, 2H)
9	[3-([5-(2-fluoro-4-heptylphenyl)quinolin-8-yl]methyl)amino)propyl]phosphonic acid 	Intermediate 26	¹ H NMR (CD ₃ OD) δ: 9.01 (dd, <i>J</i> = 4.1, 1.8 Hz, 1H), 8.09 (dt, <i>J</i> = 8.5, 1.9 Hz, 1H), 7.97 (d, <i>J</i> = 7.3 Hz, 1H), 7.54 - 7.61 (m, 2H), 7.32 (t, <i>J</i> = 7.8 Hz, 1H), 7.19 (dd, <i>J</i> = 8.2, 1.5 Hz, 1H), 7.13 (d, <i>J</i> = 11.2 Hz, 1H), 4.78 (d, <i>J</i> = 6.5 Hz, 2H), 3.21 (t, <i>J</i> = 6.6 Hz, 2H), 2.74 (t, <i>J</i> =

			7.6 Hz, 2H), 2.05 (ddd, J = 17.5, 7.0, 6.9 Hz, 2H), 1.69 - 1.74 (m, 4H), 1.31 - 1.43 (m, 8H), 0.92 (t, J = 6.9 Hz, 3H)
10	[3-({[5-(3-fluoro-4-heptylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid 	Intermediate 27	¹ H NMR (CD ₃ OD) δ: 8.98 (dd, J = 4.3, 1.6 Hz, 1H), 8.27 (dd, J = 8.5, 1.5 Hz, 2H), 7.95 (d, J = 7.3 Hz, 1H), 7.52 (dd, J = 8.5, 3.8 Hz, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.12 (dd, J = 7.6, 1.5 Hz, 1H), 7.07 (dd, J = 10.4, 1.3 Hz, 1H), 4.73 (s, 2H), 3.16 (t, J = 6.6 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.03 - 2.10 (m, 2H), 1.64 - 1.73 (m, 4H), 1.28 - 1.46 (m, 8H), 0.90 (t, J = 7.0 Hz, 3H)
11	{3-[(5-[4-(3-ethylheptyl)phenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid 	Intermediate 28	¹ H NMR (CD ₃ OD) δ: 8.98 (dd, J = 4.1, 1.5 Hz, 1H), 8.31 (dd, J = 8.5, 1.8 Hz, 1H), 7.93 (d, J = 7.3 Hz, 1H), 7.51 - 7.53 (m, 2H), 7.33 (s, 4H), 4.74 (s, 2H), 3.17 (t, J = 6.6 Hz, 2H), 2.69 (dd, J = 9.2, 5.7 Hz, 2H), 2.01 - 2.08 (m, 2H), 1.63 - 1.70 (m, 4H), 1.29 - 1.37 (m, 9H), 0.90 - 0.94 (m, J = 7.0, 7.0 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H)
12	[3-({[5-(4-octylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid	Intermediate 29	¹ H NMR (CD ₃ OD) δ: 8.99 (dd, J = 4.3, 1.6 Hz, 1H), 8.35 (dd, J = 8.7, 1.6 Hz, 1H), 7.93 (d, J = 7.3 Hz, 1H), 7.54 - 7.57 (m, 2H), 7.36 (s, 4H), 4.75 (s,

			2H), 3.18 (t, J = 6.5 Hz, 2H), 2.70 - 2.73 (m, 2H), 2.00 - 2.07 (m, 2H), 1.63 - 1.74 (m, 4H), 1.28 - 1.44 (m, 10H), 0.90 (t, J = 6.7 Hz, 3H)
13	[3-({[5-(3-fluoro-4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid 	Intermediate 37	¹ H NMR (CD ₃ OD) δ: 9.01 (dd, J = 4.1, 1.5 Hz, 1H), 8.34 (dd, J = 8.7, 1.6 Hz, 1H), 7.94 (d, J = 7.0 Hz, 1H), 7.55 - 7.59 (m, 2H), 7.39 - 7.42 (m, 1H), 7.14 - 7.20 (m, 2H), 4.76 (s, 2H), 3.18 (t, J = 6.6 Hz, 2H), 2.75 (t, J = 7.8 Hz, 2H), 2.01 - 2.08 (m, 2H), 1.65 - 1.74 (m, 4H), 1.33 - 1.44 (m, 6H), 0.90 - 0.94 (m, 3H)
14	{3-[(5-[4-(2-cyclohexylethyl)phenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid 	Intermediate 31	¹ H NMR (CD ₃ OD) δ: 9.00 (dd, J = 4.1, 1.5 Hz, 1H), 8.36 (dd, J = 8.5, 1.5 Hz, 1H), 7.93 (d, J = 7.0 Hz, 1H), 7.55 - 7.57 (m, 2H), 7.36 (s, 4H), 4.77 (s, 2H), 3.21 (t, J = 6.6 Hz, 2H), 2.72 - 2.75 (m, 2H), 2.01 - 2.09 (m, 2H), 1.84 (d, J = 11.4 Hz, 2H), 1.66 - 1.76 (m, 5H), 1.57 - 1.61 (m, 2H), 1.18 - 1.37 (m, 4H), 1.00 (qd, J = 12.3, 3.2 Hz, 2H)
15	2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethanol 	Intermediate 36	¹ H NMR (CDCl ₃) δ: 8.91 (dd, J = 4.1, 1.5 Hz, 1H), 8.29 (dd, J = 8.5, 1.8 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.37 (dd, J = 8.5, 4.1 Hz, 1H), 7.30 - 7.35 (m, 4H), 4.40 (s, 2H), 3.77 (t, J = 3.8 Hz, 2H), 2.91 (t, J

			= 5.0 Hz, 2H), 2.70 (t, J = 7.9 Hz, 2H), 1.70 (dt, J = 15.3, 7.6 Hz, 2H), 1.38 - 1.44 (m, 2H), 1.32 - 1.38 (m, 3H), 1.25 (br. s., 1H), 0.91 (t, J = 7.0 Hz, 3H)
16	(3-{[(5-{3-fluoro-4-[3-(2-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid 	Intermediate 33	¹ H NMR (CD ₃ OD) δ: 9.00 (dd, J = 4.1, 1.8 Hz, 1H), 8.27 - 8.36 (m, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.54 - 7.59 (m, 2H), 7.42 (t, J = 7.9 Hz, 1H), 7.05 - 7.21 (m, 6H), 4.72 (s, 2H), 3.14 (t, J = 6.3 Hz, 2H), 2.82 (t, J = 7.6 Hz, 2H), 2.68 - 2.74 (m, 2H), 2.28 (s, 3H), 1.89 - 2.08 (m, 4H), 1.69 (dt, J = 17.2, 6.9 Hz, 2H)
17	(3-{[(5-{3-fluoro-4-[3-(3-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid 	Intermediate 30	¹ H NMR (CD ₃ OD) δ: 9.01 (dd, J = 4.2, 1.6 Hz, 1H), 8.35 (dd, J = 8.6, 1.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.56 - 7.61 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.12 - 7.22 (m, 3H), 6.96 - 7.04 (m, 3H), 4.76 (s, 2H), 3.19 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 2.31 (s, 3H), 1.94 - 2.12 (m, 4H), 1.71 (ddd, J = 17.4, 7.0, 6.9 Hz, 2H)
18	(3-{[(5-{3-fluoro-4-[3-(4-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid 	Intermediate 34	¹ H NMR (CD ₃ OD) δ: 9.00 (dd, J = 4.2, 1.6 Hz, 1H), 8.33 (dd, J = 8.6, 1.6 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.52 - 7.59 (m, 2H), 7.34 - 7.41 (m, 1H), 7.05 - 7.19 (m, 6H), 4.76 (s, 2H), 3.20 (t, J = 6.6 Hz, 2H), 2.62

			- 2.78 (m, 4H), 2.28 (s, 3H), 1.91 - 2.13 (m, 4H), 1.71 (ddd, J = 17.4, 7.0, 6.9 Hz, 2H)
19	{3-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid 	Intermediate 38	¹ H NMR (CD ₃ OD) δ: 9.00 (dd, J = 4.2, 1.6 Hz, 1H), 8.31 (dd, J = 8.5, 1.8 Hz, 1H), 7.95 (d, J = 7.3 Hz, 1H), 7.53 - 7.57 (m, 1H), 7.54 (d, J = 7.0 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.09 - 7.18 (m, 2H), 4.75 (s, 2H), 3.19 (t, J = 6.6 Hz, 2H), 2.67 - 2.75 (m, 2H), 2.06 (dq, J = 16.7, 7.0, 6.4 Hz, 2H), 1.59 - 1.77 (m, 4H), 1.28 - 1.46 (m, 9H), 0.92 (t, J = 7.0 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H)
20	{3-[(5-[4-(2-cyclohexylethyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid 	Intermediate 32	¹ H NMR (CD ₃ OD) δ: 9.01 (dd, J = 4.4, 1.8 Hz, 1H), 8.33 (dd, J = 8.5, 1.8 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.55 - 7.60 (m, 2H), 7.40 (t, J = 7.9 Hz, 1H), 7.15 - 7.20 (m, J = 9.2, 1.3 Hz, 1H), 7.15 (dd, J = 13.8, 1.5 Hz, 1H), 4.76 (s, 2H), 3.19 (t, J = 6.6 Hz, 2H), 2.72 - 2.78 (m, 2H), 2.05 (dq, J = 17.3, 7.0, 6.4 Hz, 2H), 1.84 (d, J = 12.6 Hz, 2H), 1.71 (dt, J = 17.2, 6.9 Hz, 5H), 1.57 (dt, J = 8.8, 7.0 Hz, 2H), 1.17 - 1.37 (m, 4H), 0.93 - 1.07 (m, 2H)
22	2-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethanol	Intermediate 38	¹ H NMR (600 MHz, CD ₃ OD) δ: 8.91 - 8.93 (m, 1H), 8.27 - 8.30 (m, 1H), 7.75 -

			7.78 (m, 1H), 7.47 - 7.51 (m, 3H), 7.39 (s, 2H), 4.39 (d, $J = 14.38$ Hz, 2H), 3.70 (q, $J = 5.60$ Hz, 2H), 2.70 - 2.82 (m, 4H), 1.61 - 1.67 (m, 2H), 1.40 - 1.45 (m, 2H), 1.31 - 1.38 (m, 7H), 0.90 - 0.95 (m, 6H)
23	2-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethyl dihydrogen phosphate 	Intermediate 38	^1H NMR (600 MHz, CD_3OD) δ : 9.04 (dd, $J = 1.61, 4.25$ Hz, 1H), 8.42 (dd, $J = 1.61, 8.66$ Hz, 1H), 7.94 (d, $J = 7.34$ Hz, 1H), 7.63 (dd, $J = 4.11, 8.51$ Hz, 1H), 7.62 (d, $J = 7.34$ Hz, 1H), 7.42 (t, $J = 7.78$ Hz, 1H), 7.22 (dd, $J = 1.61, 7.78$ Hz, 1H), 7.18 (dd, $J = 1.76, 10.56$ Hz, 1H), 4.88 (s, 2H), 4.32 - 4.35 (m, 2H), 3.46 (dd, $J = 4.26, 5.14$ Hz, 2H), 2.74 (dd, $J = 6.46, 9.68$ Hz, 2H), 1.65 (dt, $J = 5.30, 9.68$ Hz, 2H), 1.41 - 1.45 (m, 2H), 1.31 - 1.40 (m, 7H), 0.93 (t, $J = 7.60$ Hz, 3H), 0.93 (t, $J = 7.30$ Hz, 3H)

Example 9**Biological Data**

Compounds were synthesized and tested for S1P1 activity using the GTP $\gamma^{35}\text{S}$ binding assay. These compounds may be assessed for their ability to activate or block activation of the human S1P1 receptor in cells stably expressing the S1P1 receptor.

GTP $\gamma^{35}\text{S}$ binding was measured in the medium containing (mM) HEPES 25, pH 7.4, MgCl_2 10, NaCl 100, dithiothreitol 0.5, digitonin 0.003%, 0.2 nM GTP $\gamma^{35}\text{S}$,

and 5 µg membrane protein in a volume of 150 µl. Test compounds were included in the concentration range from 0.08 to 5,000 nM unless indicated otherwise.

Membranes were incubated with 100 µM 5'-adenylylimmidodiphosphate for 30 min, and subsequently with 10 µM GDP for 10 min on ice. Drug solutions and membrane
 5 were mixed, and then reactions were initiated by adding GTP $\gamma^{35}\text{S}$ and continued for 30 min at 25 °C. Reaction mixtures were filtered over Whatman GF/B filters under vacuum, and washed three times with 3 mL of ice-cold buffer (HEPES 25, pH7.4, MgCl_2 10 and NaCl 100). Filters were dried and mixed with scintillant, and counted for ^{35}S activity using a β -counter. Agonist-induced GTP $\gamma^{35}\text{S}$ binding was obtained
 10 by subtracting that in the absence of agonist. Binding data were analyzed using a non-linear regression method. In case of antagonist assay, the reaction mixture contained 10 nM S1P1 in the presence of test antagonist at concentrations ranging from 0.08 to 5000 nM.

Table 6 shows activity potency: S1P1 receptor from GTP $\gamma^{35}\text{S}$: nM, (EC_{50})

15

Table 6

IUPAC name	S1P1 EC_{50} (nM)
[3-({[4-(4-hexylphenyl)-1-naphthyl]methyl}amino)propyl]phosphonic acid	54.2
[3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid	0.6
2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethyl dihydrogen phosphate	31.1
3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)propanoic acid	872
{3-[(5-[4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid	8.3
(3-[(5-[4-[3-(2-methylphenyl)propyl]phenyl]quinolin-8-yl)methyl] amino} propyl) phosphonic acid	3.8
[3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)butyl]phosphonic acid	61.7
{3-[(5-[3-fluoro-4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl}phosphonic acid	5.95

[3-({[5-(2-fluoro-4-heptylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid	13.6
[3-({[5-(3-fluoro-4-heptylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid	223
{3-[(5-[4-(3-ethylheptyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid	6.97
[3-({[5-(4-octylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid	11.2
[3-({[5-(3-fluoro-4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid	1.3
{3-[(5-[4-(2-cyclohexylethyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid	1.5
2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethanol	192
(3-[(5-{3-fluoro-4-[3-(2-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid	1.0
(3-[(5-{3-fluoro-4-[3-(3-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid	0.3
(3-[(5-{3-fluoro-4-[3-(4-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid	1
{3-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid	2.5
{3-[(5-[4-(2-cyclohexylethyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid	1.68
2-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethyl dihydrogen phosphate	2.63
2-[(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethanol	137

Example 10

Lymphopenia Assay in Mice

Test drugs are prepared in a solution containing 3% (w/v) 2-hydroxy propyl β -cyclodextrin (HPBCD) and 1% DMSO to a final concentration of 1 mg/ml, and subcutaneously injected to female C57BL6 mice (CHARLES RIVERS) weighing 20-25 g at the dose of 10 mg/Kg. Blood samples are obtained by puncturing the

submandibular skin with a Goldenrod animal lancet at 5, 24, 48, 72, and 96 hrs post drug application. Blood is collected into microvettes (SARSTEDT) containing EDTA tripotassium salt. Lymphocytes in blood samples are counted using a HEMAVET Multispecies Hematology System, HEMAVET HV950FS (Drew Scientific Inc.).

5 (Hale, J. et al Bioorg. & Med. Chem. Lett. 14 (2004) 3351).

A lymphopenia assay in mice, as previously described, was employed to measure the *in vivo* blood lymphocyte depletion after dosing Compounds 9, 10, 11 and 14, (**Figure 1**) and Compounds 15, 17, 18 and 20, (**Figure 2**). These S1P agonists (or modulators) are useful for S1P-related diseases, and exemplified by the lymphopenia *in vivo* response. In general, test compounds were prepared in a solution containing 3% (w/v) 2-hydroxy propyl β -cyclodextrin (HPBCD) and 1% DMSO to a final concentration of 1 mg/ml, and subcutaneously injected to female C57BL6 mice (CHARLES RIVERS) weighing 20-25 g at the dose of 10 mg/Kg or 2 mg/Kg. Blood samples were obtained by puncturing the submandibular skin with a Goldenrod animal lancet at 24, 48, 72 and 96 hrs post drug application. Blood was collected into microvettes (SARSTEDT) containing EDTA tripotassium salt. Lymphocytes in blood samples were counted using a HEMAVET Multispecies Hematology System, HEMAVET HV950FS (Drew Scientific Inc.). Results are shown in Figures 1 and 2 that depict lowered lymphocyte count after 24 hours (<1 number of lymphocytes $10^3/\mu\text{L}$ blood).

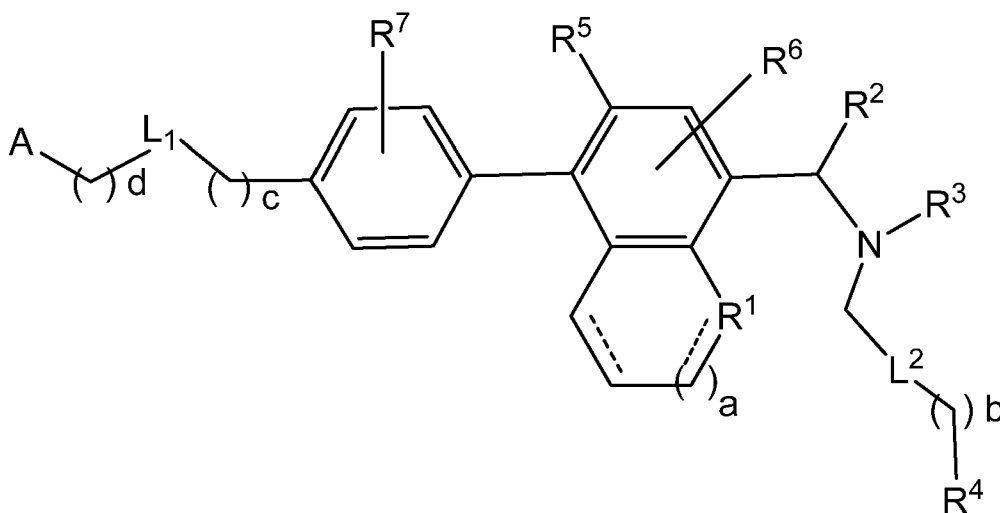
10

15

20

What is claimed is:

1. A compound having Formula I, its individual enantiomers, its individual diastereoisomers, its individual isomers, its individual tautomers or a pharmaceutically acceptable salt thereof



Formula I

wherein:

$\begin{array}{c} \text{---} \text{---} \text{---} \\ \text{---} \text{---} \text{---} \end{array}$
 represents a single
 $\begin{array}{c} \text{---} \text{---} \text{---} \\ \text{---} \text{---} \end{array}$
 or a double bond

$\begin{array}{c} \text{---} \text{---} \text{---} \\ \text{---} \text{---} \end{array}$
 ;

A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C₅₋₈ cycloalkyl, substituted or unsubstituted C₅₋₈ cycloalkenyl, or hydrogen;

R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

5 R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

L^2 is O, S, NH or CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

10 R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

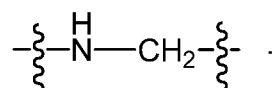
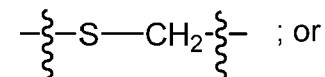
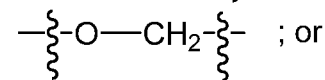
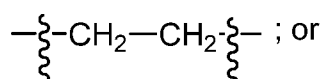
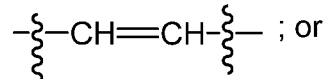
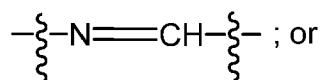
a is 1;

b is 0, 1, 2 or 3;

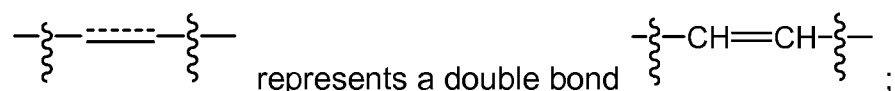
c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;

15 $\text{---}\xi\text{---}R^1\text{---}\xi\text{---}$ represents



2. A compound according to claim 1, wherein:



A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle,

20 substituted or unsubstituted C_{5-8} cycloalkyl, substituted or unsubstituted C_{5-8} cycloalkenyl, or hydrogen;

R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, -
 $S(O)_2H$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,

5 NR^9R^{10} or hydroxyl;

R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,
 NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$,
 NR^9R^{10} or hydroxyl;

10 R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

15 L^2 is O, S, NH or CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

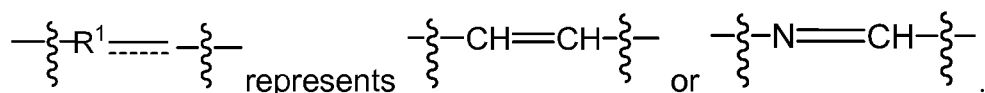
R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

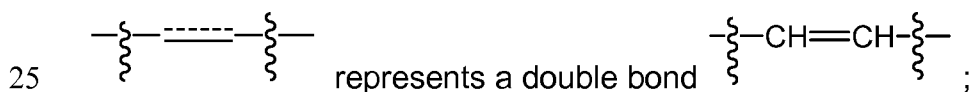
b is 0, 1, 2 or 3;

20 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;



3. A compound according to claim 1, wherein:



A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle,
substituted or unsubstituted C_{5-8} cycloalkyl, substituted or unsubstituted C_{5-8}
cycloalkenyl, or hydrogen;

R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN,

30 $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, - $S(O)_2H$, - $P(O)MeOH$, - $P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

5 R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

10 R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

L^2 is O, S, NH or CHR^{13} ;

15 R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

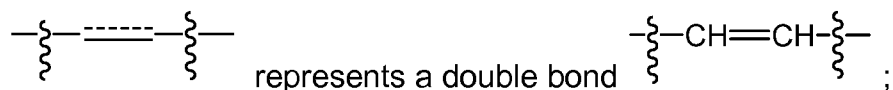
b is 0, 1, 2 or 3;

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

20 d is 1, 2, 3 or 4; and



4. A compound according to claim 1, wherein:



25 A is substituted or unsubstituted aryl;

R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, -

30 $S(O)_2H$, - $P(O)MeOH$, - $P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

5 R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

10 L^2 is O, S, NH or CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

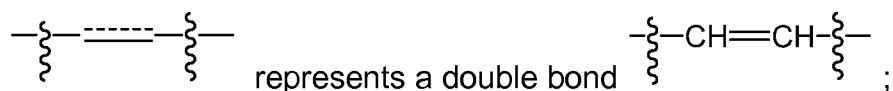
b is 0, 1, 2 or 3;

15 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;



5. A compound according to claim 1, wherein:



20 A is hydrogen;

R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, -

25 $S(O)_2H$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

30 R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

5 L^2 is O, S, NH or CHR^{13} ;

R^{12} is H or substituted or unsubstituted C_{1-3} alkyl;

R^{13} is H or substituted or unsubstituted C_{1-3} alkyl;

a is 1;

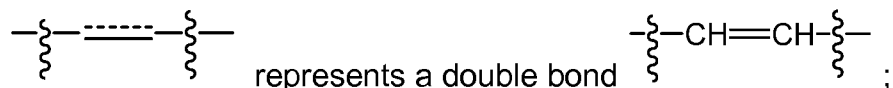
b is 0, 1, 2 or 3;

10 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;



6. A compound according to claim 1, wherein:



15 A is hydrogen;

R^2 is hydrogen, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^3 is hydrogen, halogen, substituted or unsubstituted C_{1-3} alkyl, $C(O)R^8$ or hydroxyl;

R^4 is OPO_3H_2 , carboxylic acid, PO_3H_2 , substituted or unsubstituted C_{1-6} alkyl, -

20 $S(O)_2H$, $-P(O)MeOH$, $-P(O)(H)OH$ or OR^{11} ;

R^5 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^6 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

25 R^7 is H, halogen, $-OC_{1-3}$ alkyl, substituted or unsubstituted C_{1-3} alkyl, CN, $C(O)R^8$, NR^9R^{10} or hydroxyl;

R^8 is H, OR^{11} or substituted or unsubstituted C_{1-3} alkyl;

R^9 is H or substituted or unsubstituted C_{1-3} alkyl;

R^{10} is H or substituted or unsubstituted C_{1-3} alkyl;

30 R^{11} is H or substituted or unsubstituted C_{1-3} alkyl;

L^1 is O, S, NH or CHR^{12} ;

L^2 is O, S, NH or CHR^{13} ;

R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;

a is 1;

b is 0, 1, 2 or 3;

5 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;



7. A compound according to claim 1 selected from:

- 10 [3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
 [3-({[4-(4-hexylphenyl)-1-naphthyl]methyl}amino)propyl]phosphonic acid;
 2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethyl dihydrogen phosphate;
 3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)propanoic acid;
 {3-[(5-[4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
 15 (3-[(5-{4-[3-(2-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
 [3-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)butyl]phosphonic acid;
 {3-[(5-[3-fluoro-4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
 20 [3-({[5-(2-fluoro-4-heptylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
 [3-({[5-(3-fluoro-4-heptylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
 {3-[(5-[4-(3-ethylheptyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
 [3-({[5-(4-octylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
 [3-({[5-(3-fluoro-4-hexylphenyl)quinolin-8-yl]methyl}amino)propyl]phosphonic acid;
 25 {3-[(5-[4-(2-cyclohexylethyl)phenyl]quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
 2-({[5-(4-hexylphenyl)quinolin-8-yl]methyl}amino)ethanol;
 (3-[(5-{3-fluoro-4-[3-(2-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl]phosphonic acid;
 30 (3-[(5-{3-fluoro-4-[3-(3-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl]phosphonic acid;

(3-([(5-{3-fluoro-4-[3-(4-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino)propyl)phosphonic acid;

{3-([(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino)propyl}phosphonic acid;

5 {3-([(5-[4-(2-cyclohexylethyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino)propyl}phosphonic acid;

2-([(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino)ethanol; and

2-([(5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino)ethyl dihydrogen phosphate.

10

8. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable adjuvant, diluents or carrier.

15 9. A pharmaceutical composition according to claim 8 wherein the compound is selected from:

[3-([(5-(4-hexylphenyl)quinolin-8-yl)methyl]amino)propyl]phosphonic acid;

[3-([(4-(4-hexylphenyl)-1-naphthyl)methyl]amino)propyl]phosphonic acid;

2-([(5-(4-hexylphenyl)quinolin-8-yl)methyl]amino)ethyl dihydrogen phosphate;

20 3-([(5-(4-hexylphenyl)quinolin-8-yl)methyl]amino)propanoic acid;

{3-([(5-[4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino)propyl}phosphonic acid;

(3-([(5-{4-[3-(2-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino)propyl)phosphonic acid;

[3-([(5-(4-hexylphenyl)quinolin-8-yl)methyl]amino)butyl]phosphonic acid;

25 {3-([(5-[3-fluoro-4-(3-phenylpropyl)phenyl]quinolin-8-yl)methyl]amino)propyl}phosphonic acid;

[3-([(5-(2-fluoro-4-heptylphenyl)quinolin-8-yl)methyl]amino)propyl]phosphonic acid;

[3-([(5-(3-fluoro-4-heptylphenyl)quinolin-8-yl)methyl]amino)propyl]phosphonic acid;

{3-([(5-[4-(3-ethylheptyl)phenyl]quinolin-8-yl)methyl]amino)propyl}phosphonic acid;

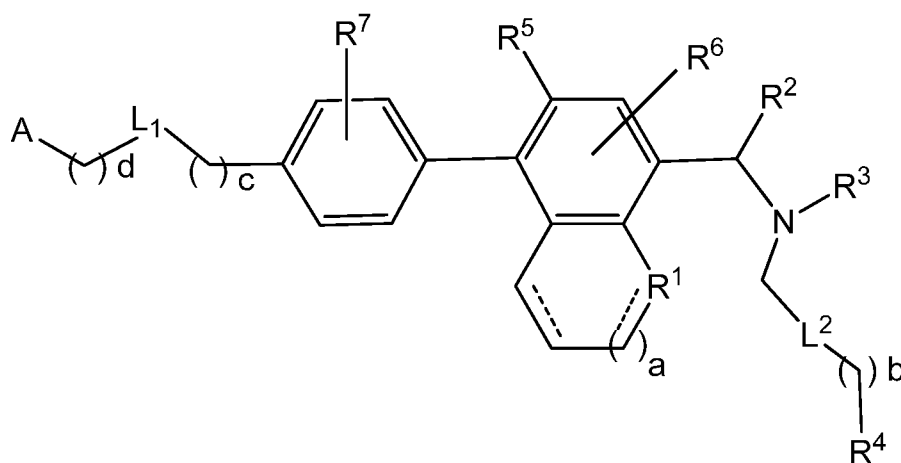
30 [3-([(5-(4-octylphenyl)quinolin-8-yl)methyl]amino)propyl]phosphonic acid;

[3-([(5-(3-fluoro-4-hexylphenyl)quinolin-8-yl)methyl]amino)propyl]phosphonic acid;

{3-([(5-[4-(2-cyclohexylethyl)phenyl]quinolin-8-yl)methyl]amino)propyl}phosphonic acid;

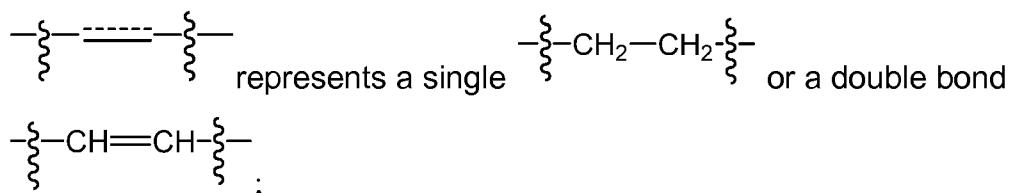
2-([(5-(4-hexylphenyl)quinolin-8-yl)methyl]amino)ethanol;

- (3-[[[5-{3-fluoro-4-[3-(2-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid;
 (3-[[[5-{3-fluoro-4-[3-(3-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid;
 5 (3-[[[5-{3-fluoro-4-[3-(4-methylphenyl)propyl]phenyl}quinolin-8-yl)methyl]amino}propyl)phosphonic acid;
 {3-[[[5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]propyl}phosphonic acid;
 {3-[[[5-[4-(2-cyclohexylethyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]propyl}
 10 phosphonic acid;
 2-[[[5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethanol; and
 2-[[[5-[4-(3-ethylheptyl)-3-fluorophenyl]quinolin-8-yl)methyl]amino]ethyl dihydrogen phosphate.
- 15 10. A method of treating a disorder associated with sphingosine-1-phosphate receptor modulation, which comprises administering to a mammal in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula I



Formula I

wherein:



A is substituted or unsubstituted aryl, substituted or unsubstituted heterocycle, substituted or unsubstituted C₅₋₈ cycloalkyl, substituted or unsubstituted C₅₋₈ cycloalkenyl, or hydrogen;

R² is hydrogen, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN,

5 C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R³ is hydrogen, halogen, substituted or unsubstituted C₁₋₃ alkyl, C(O)R⁸ or hydroxyl;

R⁴ is OPO₃H₂, carboxylic acid, PO₃H₂, substituted or unsubstituted C₁₋₆ alkyl, -S(O)₂H, -P(O)MeOH, -P(O)(H)OH or OR¹¹;

10 R⁵ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁶ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

R⁷ is H, halogen, -OC₁₋₃ alkyl, substituted or unsubstituted C₁₋₃ alkyl, CN, C(O)R⁸, NR⁹R¹⁰ or hydroxyl;

15 R⁸ is H, OR¹¹ or substituted or unsubstituted C₁₋₃ alkyl;

R⁹ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹⁰ is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹¹ is H or substituted or unsubstituted C₁₋₃ alkyl;

L¹ is O, S, NH or CHR¹²;

20 L² is O, S, NH or CHR¹³;

R¹² is H or substituted or unsubstituted C₁₋₃ alkyl;

R¹³ is H or substituted or unsubstituted C₁₋₃ alkyl;

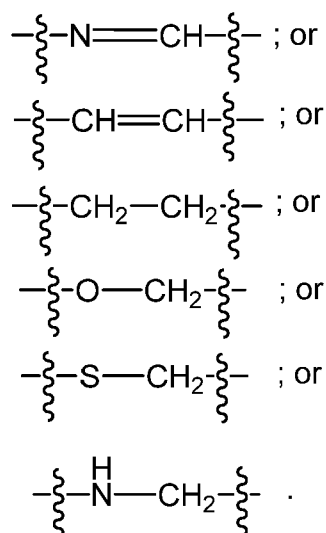
a is 1;

b is 0, 1, 2 or 3;

25 c is 0, 1, 2, 3 or 4;

d is 1, 2, 3 or 4;

$\text{---}\begin{array}{c} \text{ } \\ \text{ } \end{array} \text{R}^1 \text{---}\begin{array}{c} \text{ } \\ \text{ } \end{array}$ represents



11. A method of claim 10, wherein the pharmaceutical composition is administered to the mammal to treat ocular diseases, wet and dry age-related macular degeneration, diabetic retinopathy, retinopathy of prematurity, retinal edema, geographic atrophy, glaucomatous optic neuropathy, chorioretinopathy, hypertensive retinopathy, ocular ischemic syndrome, prevention of inflammation-induced fibrosis in the back of the eye, various ocular inflammatory diseases including uveitis, scleritis, keratitis, and retinal vasculitis; or systemic vascular barrier related diseases, various inflammatory diseases, including acute lung injury, its prevention, sepsis, tumor metastasis, atherosclerosis, pulmonary edemas, and ventilation-induced lung injury; or autoimmune diseases and immunosuppression, rheumatoid arthritis, Crohn's disease, Graves' disease, inflammatory bowel disease, multiple sclerosis, Myasthenia gravis, Psoriasis, ulcerative colitis, autoimmune uveitis, renal ischemia perfusion injury, contact hypersensitivity, atopic dermatitis, and organ transplantation; or allergies and other inflammatory diseases, urticaria, bronchial asthma, and other airway inflammations including pulmonary emphysema and chronic obstructive pulmonary diseases; or cardiac protection, ischemia reperfusion injury and atherosclerosis; or wound healing such as but not limited to: scar-free healing of wounds from cosmetic skin surgery, ocular surgery, GI surgery, general surgery, oral injuries, various mechanical, heat and burn injuries, prevention and treatment of photoaging and skin ageing, and prevention of radiation-induced injuries; or bone formation, treatment of osteoporosis and various bone fractures including hip and ankles; or anti-nociceptive activity, visceral pain, pain associated

with diabetic neuropathy, rheumatoid arthritis, chronic knee and joint pain, tendonitis, osteoarthritis, neuropathic pains; or central nervous system neuronal activity in Alzheimer's disease, age-related neuronal injuries; or organ transplant such as renal, corneal, cardiac or adipose tissue transplant.

- 5 12. The method of claim 11 wherein the mammal is a human.