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(54) Title: NOVEL 1-(1-OXO-1,2,3,4-TETRAHYDROISOQUINOLIN-7-YL)UREA DERIVATIVES AS N-FORMYL PEPTIDE RECEPTOR LIKE-1 (FPRL-1) RECEPTOR MODULATORS

(57) Abstract: The present invention relates to novel 1-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)urea derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of the N-formyl peptide receptor like-1 (FPRL-1) receptor.

**Novel 1-(1-OXO-1,2,3,4-TETRAHYDROISOQUINOLIN-7-YL)Urea Derivatives As
N-FORMYL Peptide Receptor Like-1 (FPRL-1) Receptor Modulators**

5

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 61/441,824, filed February 11, 2011, the disclosure of which is hereby incorporated in its entirety herein by reference.

10 **FIELD OF THE INVENTION**

The present invention relates to novel 1-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)urea derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of the N-formyl peptide receptor like-1 (FPRL-1) receptor. The invention relates specifically to the 15 use of these compounds and their pharmaceutical compositions to treat disorders associated with the N-formyl peptide receptor like-1 (FPRL-1) receptor modulation.

BACKGROUND OF THE INVENTION

The N-formyl peptide receptor like-1 (FPRL-1) receptor is a G protein-coupled receptor that is expressed on inflammatory cells such as monocytes and neutrophils, 20 as well as T cells and has been shown to play a critical role in leukocyte trafficking during inflammation and human pathology. FPRL-1 is an exceptionally promiscuous receptor that responds to a large array of exogenous and endogenous ligands, including Serum amyloid A (SAA), chemokine variant sCK β 8-1, the neuroprotective peptide humanin, anti-inflammatory eicosanoid lipoxin A4 (LXA4) and glucocorticoid-25 modulated protein annexin A1. FPRL-1 transduces anti-inflammatory effects of LXA4 in many systems, but it also can mediate the pro-inflammatory signaling cascade of peptides such as SAA. The ability of the receptor to mediate two opposite effects is proposed to be a result of different receptor domains used by different agonists.

Parmentier, Marc et al. Cytokine & Growth Factor Reviews 17 (2006) 501–519.

30 Activation of FPRL-1 by lipoxin A4 or its analogs and by Annexin I protein has been shown to result in anti-inflammatory activity by promoting active resolution of inflammation which involves inhibition of polymorphonuclear neutrophils (PMNs) and

eosinophils migration and also stimulate monocyte migration enabling clearance of apoptotic cells from the site of inflammation in a nonphlogistic manner. In addition, FPRL-1 has been shown to inhibit NK cytotoxicity and promote activation of T cells which further contributes to down regulation of tissue damaging inflammatory

5 signals. FPRL-1/ LXA4 interaction has been shown to be beneficial in experimental models of ischemia reperfusion, angiogenesis, dermal inflammation, chemotherapy-induced alopecia, ocular inflammation such as endotoxin-induced uveitis, corneal wound healing, re-epithelialization etc. FPRL-1 thus represents an important novel pro-resolutionary molecular target for the development of new therapeutic agents in

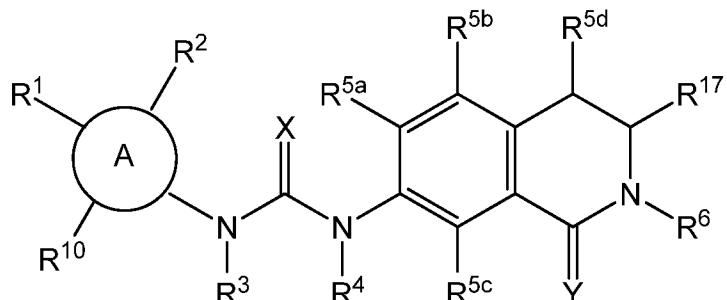
10 diseases with excessive inflammatory responses.

SUMMARY OF THE INVENTION

A group of novel compounds which are potent and selective FPRL-1 modulators has now been discovered. As such, the compounds described herein are useful in treating a wide variety of disorders associated with modulation of FPRL-1 receptor. 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 FPRL-1 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 FPRL-1 modulation.

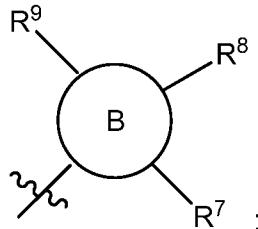
In one aspect, the invention provides a compound having **Formula I** or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof, or the geometrical isomers, enantiomers, diastereoisomers, tautomers, zwitterions and pharmaceutically acceptable salts thereof:



Formula I

wherein:

A is C_{6-10} aryl, Heterocyle, C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;



5 R¹⁷ is C_{1-6} alkyl or

B is C_{6-10} aryl, heterocyle, C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl;

R¹ is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R² is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$

10 alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R³ is H, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R⁴ is H, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^{5a} is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

15 R^{5b} is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R^{5c} is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R^{5d} is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$

20 alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R⁶ is H, $-S(O)_2R^{11}$, $-C_{1-6}$ alkyl, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl, C_{6-10} aryl, or heterocycle;

R⁷ is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$

25 alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R⁸ is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R⁹ is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R^{10} is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

X is O or S;

Y is O or S;

5 R^{11} is H, hydroxyl, $-C_{1-6}$ alkyl, C_{3-8} cycloalkyl or $NR^{13}R^{14}$;

R^{12} is H, hydroxyl, $-C_{1-6}$ alkyl, hydroxyl, C_{3-8} cycloalkyl, $NR^{13}R^{14}$ or $-OC_{1-6}$ alkyl;

R^{13} is H, $-C_{1-6}$ alkyl, C_{3-8} cycloalkyl, SO_2R^{11} or $C(O)R^{16}$;

R^{14} is H, $-C_{1-6}$ alkyl or C_{3-8} cycloalkyl;

R^{15} is $-C_{1-6}$ alkyl, or C_{3-8} cycloalkyl;

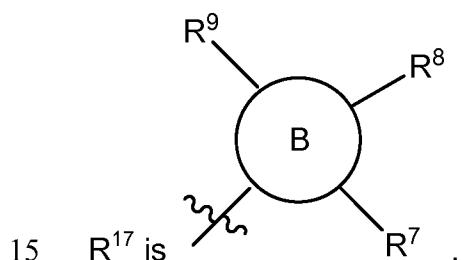
10 R^{16} is H, $-C_{1-6}$ alkyl or C_{3-8} cycloalkyl;

n is 1-4; and

m is 1-4.

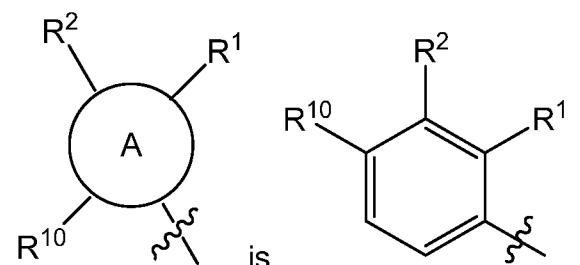
In another aspect, the invention provides a compound having **Formula I**

wherein:



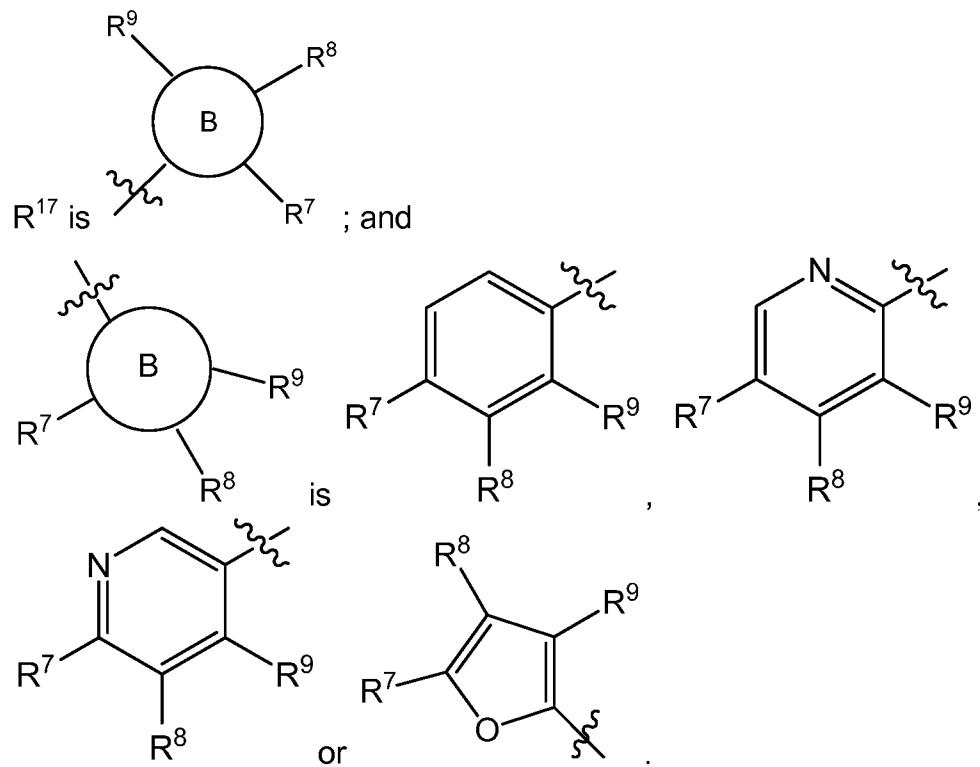
In another aspect, the invention provides a compound having **Formula I**

wherein:

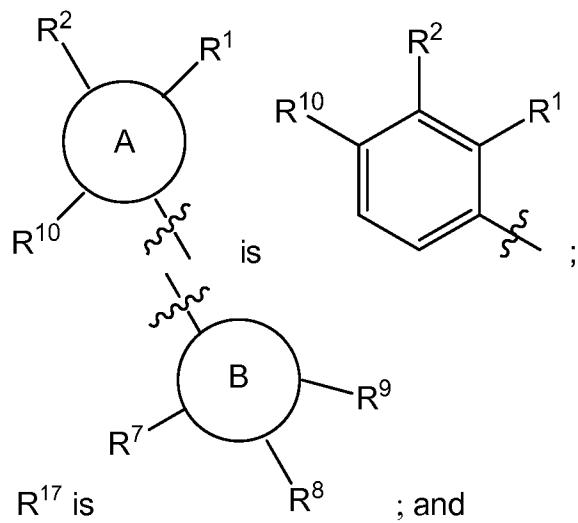


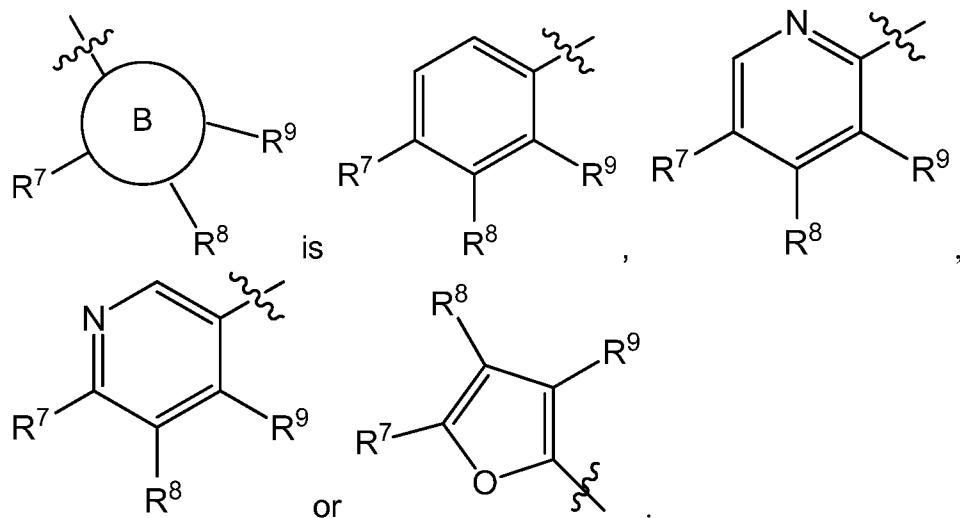
In another aspect, the invention provides a compound having **Formula I**

20 wherein:



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

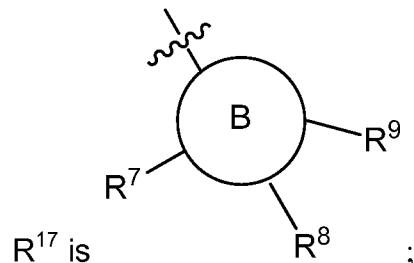




In another aspect, the invention provides a compound having **Formula I**

5 wherein:

A is C_{6-10} aryl;



B is C_{6-10} aryl, Heterocycle;

10 R¹ is H;

R² is H;

R³ is H;

R⁴ is H;

R^{5a} is H;

15 R^{5b} is H;

R^{5c} is H;

R^{5d} is H;

R⁶ is H, $-(CH_2)_n$ NR¹³R¹⁴, $-(CH_2)_m$ heterocycle or $-C_{1-6}$ alkyl;

R⁷ is H, halogen or cyano;

20 R⁸ is H or halogen;

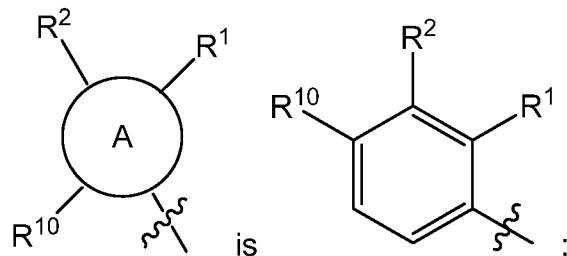
R⁹ is H;

R¹⁰ is halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl or $C(O)R^{12}$;

X is O;
 Y is O;
 R¹¹ is -C₁₋₆ alkyl;
 R¹² is -C₁₋₆ alkyl;
 5 R¹³ is H or -C₁₋₆ alkyl;
 R¹⁴ is H or -C₁₋₆ alkyl;
 R¹⁵ is -C₁₋₆ alkyl;
 n is 1-4; and
 m is 1-4.

10

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



15 R¹⁷ is C₁₋₆ alkyl;
 R¹ is H;
 R² is H;
 R³ is H;
 R⁴ is H;
 20 R^{5a} is H;
 R^{5b} is H;
 R^{5c} is H;
 R^{5d} is H;
 R⁶ is H, -(CH₂)_n NR¹³R¹⁴, -(CH₂)_m heterocycle or -C₁₋₆ alkyl;
 25 R¹⁰ is halogen, -S(O)R¹⁵, -S(O)₂R¹¹, -SC₁₋₆ alkyl, -C₁₋₆ alkyl or C(O)R¹²;
 X is O;
 Y is O;
 R¹¹ is -C₁₋₆ alkyl;
 R¹² is -C₁₋₆ alkyl;
 30 R¹³ is H or -C₁₋₆ alkyl;

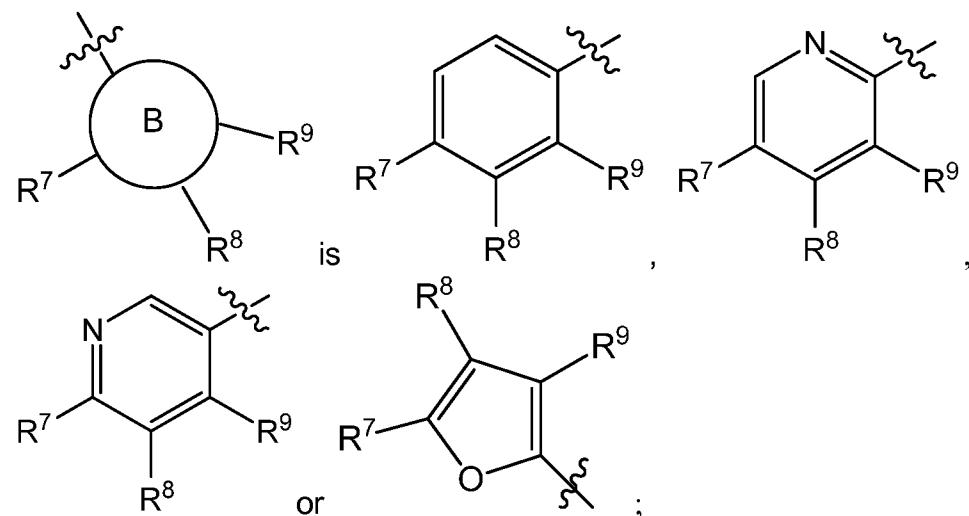
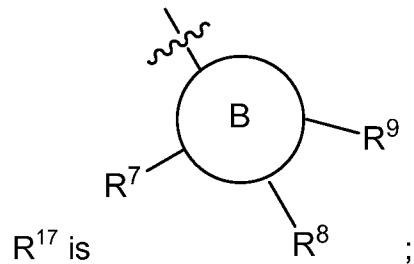
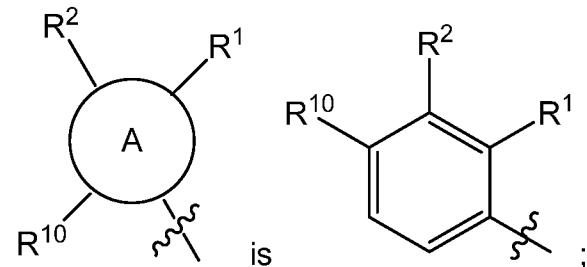
R^{14} is H or $-C_{1-6}$ alkyl;

R^{15} is $-C_{1-6}$ alkyl;

n is 1-4; and

m is 1-4.

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



R^1 is H;

R^2 is H;

15 R^3 is H;

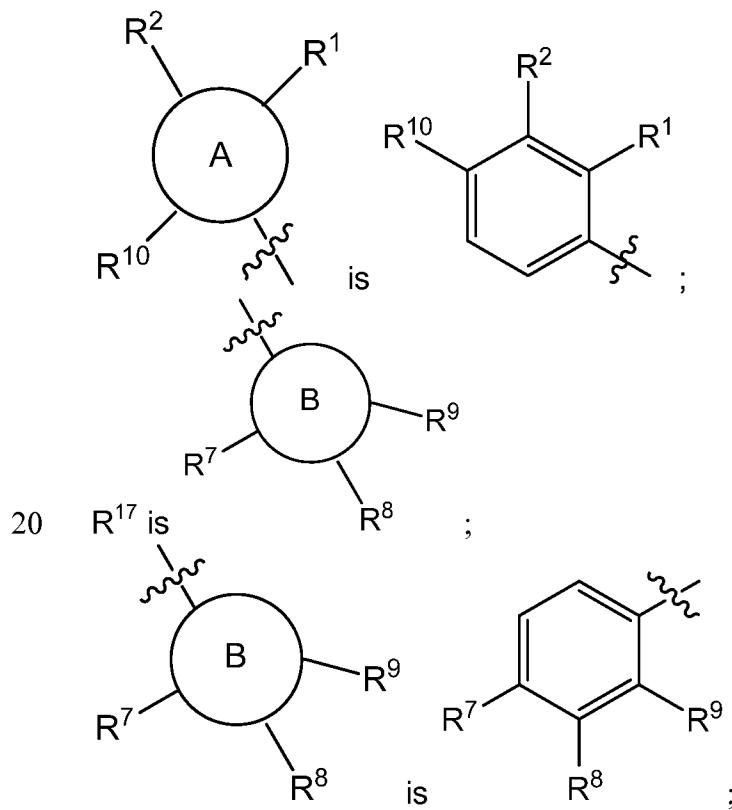
R^4 is H;

R^{5a} is H;

R^{5b} is H;

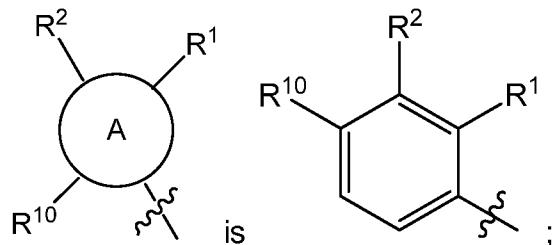
R^{5c} is H;
 R^{5d} is H;
 R^6 is H, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle or $-C_{1-6}$ alkyl;
 R^7 is H, halogen or cyano;
5 R^8 is H or halogen;
 R^9 is H;
 R^{10} is halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl or $C(O)R^{12}$;
 X is O;
 Y is O;
10 R^{11} is $-C_{1-6}$ alkyl;
 R^{12} is $-C_{1-6}$ alkyl;
 R^{13} is H or $-C_{1-6}$ alkyl;
 R^{14} is H or $-C_{1-6}$ alkyl;
 R^{15} is $-C_{1-6}$ alkyl;
15 n is 1-4; and
 m is 1-4.

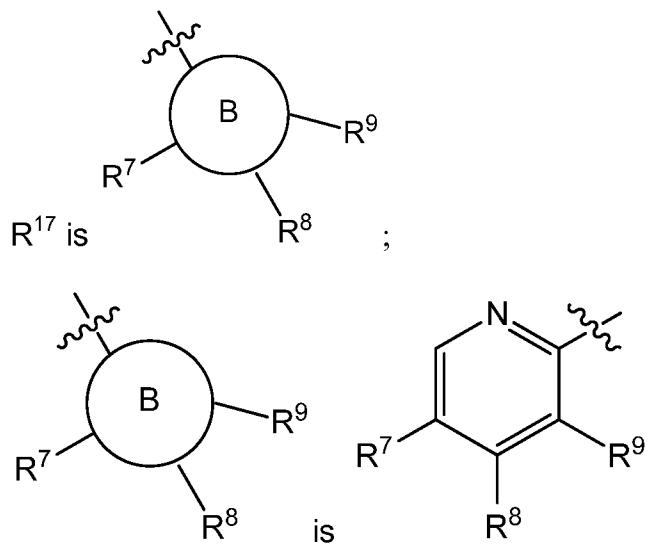
In another aspect, the invention provides a compound having **Formula I** wherein:



R^1 is H;
 R^2 is H;
 R^3 is H;
5 R^4 is H;
 R^{5a} is H;
 R^{5b} is H;
 R^{5c} is H;
 R^{5d} is H;
10 R^6 is H, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle or $-C_{1-6}$ alkyl;
 R^7 is halogen or cyano;
 R^8 is H or halogen;
 R^9 is H;
 R^{10} is halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl or $C(O)R^{12}$;
15 X is O;
 Y is O;
 R^{11} is $-C_{1-6}$ alkyl;
 R^{12} is $-C_{1-6}$ alkyl;
 R^{13} is H or $-C_{1-6}$ alkyl;
20 R^{14} is H or $-C_{1-6}$ alkyl;
 R^{15} is $-C_{1-6}$ alkyl;
 n is 1-4; and
 m is 1-4.

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





5 R^1 is H;
 R^2 is H;
 R^3 is H;
 R^4 is H;
 R^{5a} is H;

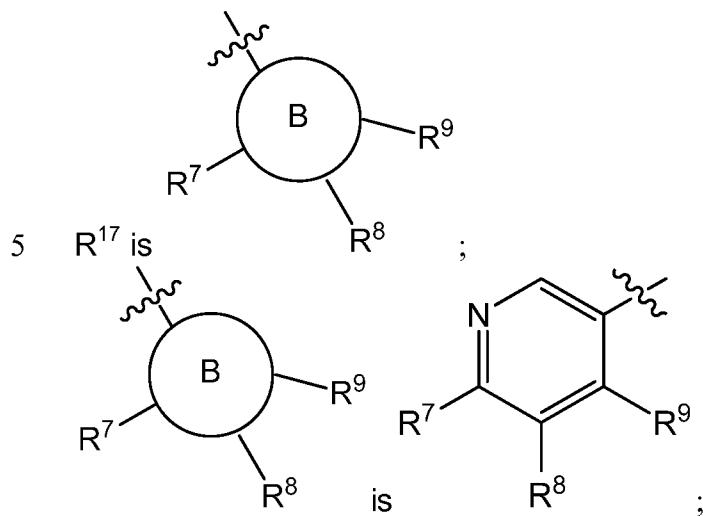
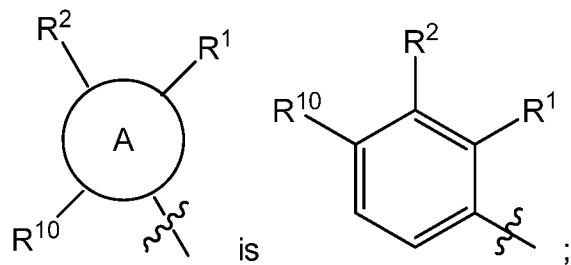
10 R^{5b} is H;
 R^{5c} is H;
 R^{5d} is H;
 R^6 is H, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle or $-C_{1-6}$ alkyl;
 R^7 is halogen;

15 R^8 is H;
 R^9 is H;
 R^{10} is $-S(O)R^{15}$, $-S(O)_2R^{11}$, $-SC_{1-6}$ alkyl, or $C(O)R^{12}$;
 X is O;
 Y is O;

20 R^{11} is $-C_{1-6}$ alkyl;
 R^{12} is $-C_{1-6}$ alkyl;
 R^{13} is H or $-C_{1-6}$ alkyl;
 R^{14} is H or $-C_{1-6}$ alkyl;
 R^{15} is $-C_{1-6}$ alkyl;

25 n is 1-4; and
m is 1-4.

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



R¹ is H;

R² is H;

10 R³ is H;

R⁴ is H;

R^{5a} is H;

R^{5b} is H;

R^{5c} is H;

15 R^{5d} is H;

R⁶ is H, -(CH₂)_n NR¹³R¹⁴, -(CH₂)_m heterocycle or -C₁₋₆ alkyl;

R⁷ is halogen;

R⁸ is H;

R⁹ is H;

20 R¹⁰ is -SC₁₋₆ alkyl or C(O)R¹²;

X is O;

Y is O;

R¹² is -C₁₋₆ alkyl;

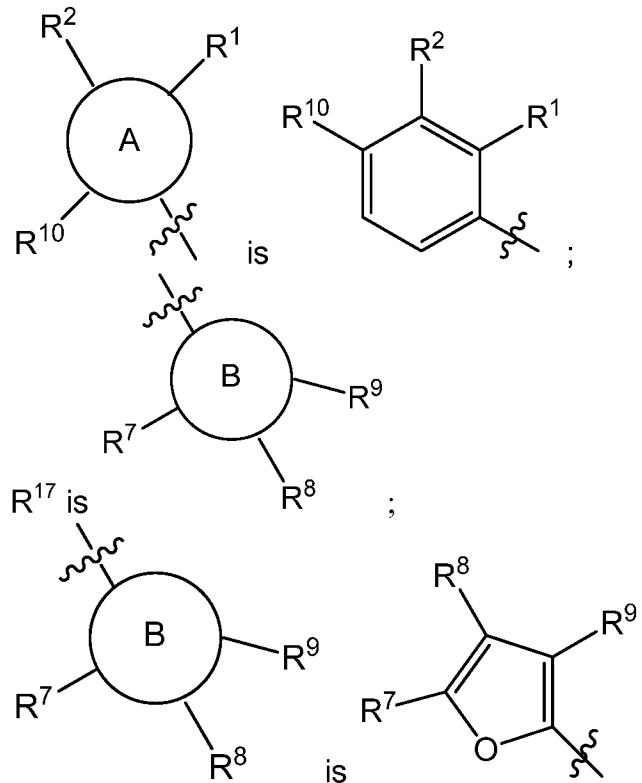
R^{13} is H or $-C_{1-6}$ alkyl;

R^{14} is H or $-C_{1-6}$ alkyl;

n is 1-4; and

m is 1-4.

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



10

R^1 is H;

R^2 is H;

R^3 is H;

R^4 is H;

15 R^{5a} is H;

R^{5b} is H;

R^{5c} is H;

R^{5d} is H;

R^6 is H, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle or $-C_{1-6}$ alkyl;

20 R^7 is H or halogen;

R^8 is H;

R^9 is H;

R^{10} is $-SC_{1-6}$ alkyl;

X is O;

Y is O

R^{13} is H or $-C_{1-6}$ alkyl;

5 R^{14} is H or $-C_{1-6}$ alkyl;

n is 1-4; and

m is 1-4.

The term "alkyl", as used herein, refers to saturated, monovalent or divalent hydrocarbon moieties having linear or branched moieties or combinations thereof 10 and containing 1 to 6 carbon atoms. One methylene ($-CH_2-$) group, of the alkyl can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, $-C(O)NH-$, $-S(O)_2NH-$, by a divalent C_{3-6} cycloalkyl, by a divalent heterocycle, or by a divalent aryl group. Alkyl groups can be independently substituted by halogen 15 atoms, hydroxyl groups, cycloalkyl groups, amine groups, heterocyclic groups, carboxylic acid groups, phosphonic acid groups, sulphonic acid groups, phosphoric acid groups, nitro groups, amide groups, sulfonamides groups.

The term "cycloalkyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms derived from a saturated cyclic hydrocarbon. Cycloalkyl groups can be monocyclic or polycyclic. Cycloalkyl can be independently substituted 20 by halogen, nitro groups, cyano groups, $-OC_{1-6}$ alkyl groups, $-SC_{1-6}$ alkyl groups, $-C_{1-6}$ alkyl groups, $-C_{2-6}$ alkenyl groups, $-C_{2-6}$ alkynyl groups, C_{3-8} cycloalkyl groups, carboxylic acid groups, ester groups, ketone groups, aldehyde groups, amide groups, amine groups, sulfonamide groups or hydroxyl groups.

The term "cycloalkenyl", as used herein, refers to a monovalent or divalent 25 group of 3 to 8 carbon atoms derived from a saturated cycloalkyl having at least one double bond. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be independently substituted by halogen atoms, nitro groups, cyano groups, $-OC_{1-6}$ alkyl groups, $-SC_{1-6}$ alkyl groups, $-C_{1-6}$ alkyl groups, $-C_{2-6}$ alkenyl groups, $-C_{2-6}$ alkynyl groups, carboxylic acid groups, ester groups, ketone groups, 30 aldehyde groups, amide groups, amine groups, sulfonamide groups, C_{3-8} cycloalkyl groups or hydroxyl groups.

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 moiety 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. Alkenyl groups can be substituted by C₁₋₃ alkyl, as defined above, or by halogen.

5 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. Alkynyl groups can be substituted by C₁₋₃ alkyl, as defined above, or by halogen.

10 The term “heterocyle” as used herein, refers to a 3 to 10 membered ring, which can be aromatic or non-aromatic, saturated or unsaturated, 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 and N heteroatoms can be oxidized. Heterocyles can be monocyclic or polycyclic.

15 Heterocyclic ring moieties can be substituted by halogen, nitro groups, cyano groups, -OC₁₋₆ alkyl groups, -SC₁₋₆ alkyl groups, -C₁₋₆ alkyl groups, -C₂₋₆ alkenyl groups, -C₂₋₆ alkynyl groups, carboxylic acid groups, ester groups, ketone groups, aldehyde groups, amide groups, amine groups, sulfonamide groups, C₃₋₈ cycloalkyl groups or hydroxyl groups. Usually, in the present case, heterocyclic groups are 5 or 20 6 membered rings such as but not limited to: furan, 2-furyl and 3-furyl derivatives; thiophene, 2-thienyl and 3-thienyl derivatives; pyrrole, oxazole, thiazole, pyrrolidine, pyrrolidine, imidazole, pyrazole, pyrazoline, isoxazole, isothiazole, pyrazolidine, imidazoline, thiazoline, oxazoline, dihydrothiophene, 2-pyridyl, 3-pyridyl, 4-pyridyl, dihydrofuran, tetrazole, triazole, oxadiazole, 1,2,5-oxadiazole, thiadiazole, 1,2,3-25 triazole, 1,2,4-triazole, pyrrolidinone, pyrrol-2(3H)-one, imidazolidin-2-one, or 1,2,4-triazol-5(4H)-one and the like 5-membered heterocyclic rings.

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 halogen atoms, nitro groups, cyano groups, -OC₁₋₆ alkyl groups, -SC₁₋₆ alkyl groups, -C₁₋₆ alkyl groups, -C₂₋₆ alkenyl groups, -C₂₋₆ alkynyl groups, carboxylic acid groups, ester groups, ketone groups, aldehyde groups, amide groups, amine groups, sulfonamide groups, C₃₋₈ cycloalkyl groups or hydroxyl groups. Usually aryl is phenyl. Preferred substitution

site on aryl are the meta and the para positions. Most preferred substitution sites on aryl are the para positions.

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

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

5 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 "-SO₂".

The term "sulfate" as used herein, represents a group of formula "-O-S(O)₂-O-".

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

10 The term "nitro" as used herein, represents a group of formula "-NO₂".

The term "cyano" as used herein, represents a group of formula "-CN".

The term "amide" as used herein, represents a group of formula "-C(O)NR^XR^Y", wherein R^X and R^Y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

15 The term "amine" as used herein, represents a group of formula "-NR^XR^Y", wherein R^X and R^Y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "ketone" as used herein, represents an organic compound having a carbonyl group linked to a carbon atom such as -(CO)R^X wherein R^X can be alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

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

The term "ester" as used herein, represents a group of formula "-C(O)OR^X", wherein R^X can be alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

The term "sulfonamide" as used herein, represents a group of formula "-

25 S(O)₂NR^XR^Y" wherein R^X and R^Y can be the same or independently H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle as defined above.

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".

30 The term "phosphoric acid" as used herein, represents a group of formula "-OP(O)(OH)₂".

The term "sulphonic acid" as used herein, represents a group of formula "-S(O)₂OH".

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.

Compounds of the invention are:

5 1-(4-acetylphenyl)-3-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;
1-(4-acetylphenyl)-3-[2-(2-aminoethyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;
1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;
10 1-(4-acetylphenyl)-3-[3-(4-cyanophenyl)-2-[2-(methylamino)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(trifluoromethyl)phenyl]urea;
15 1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(trifluoromethyl)phenyl]urea;
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;
20 1-(4-acetylphenyl)-3-{3-(3,4-dichlorophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-(4-bromophenyl)urea;
25 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;
1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;
30 1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;
1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

1-{3-(6-fluoropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea;

5 1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

1-{3-(2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

10 1-{3-(5-chloro-2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-(4-acetylphenyl)-3-{3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

15 1-{3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-(4-acetylphenyl)-3-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

20 1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea;

(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

25 (R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

30 (S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

(R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea.

5 Preferred compounds of the invention are:

1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(trifluoromethyl)phenyl]urea;

10 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-(4-acetylphenyl)-3-{3-(3,4-dichlorophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-(4-bromophenyl)urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

20 1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea;

1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

1-{3-(6-fluoropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-

25 tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea;

1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

30 (S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-{3-(2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-{3-(5-chloro-2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

5 1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea;

1-{3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

10 (R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea.

15 Most Preferred compounds of the invention are:

1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

20 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

1-{3-(6-fluoropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea;

25 1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

1-{3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

30 1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea.;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea;

(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea.

5 Some compounds of Formula I and some of their intermediates have at least one asymmetric center in their structure. This asymmetric 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.

10 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.

15 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, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; or an organic acid such as for example, acetic acid, hydroxyacetic acid, propanoic acid, lactic acid, pyruvic acid, malonic acid, fumaric acid, maleic acid, oxalic acid, tartaric acid, succinic acid, malic acid, 20 ascorbic acid, benzoic acid, tannic acid, pamoic acid, citric acid, methylsulfonic acid, ethanesulfonic acid, benzenesulfonic acid, formic and the like (Handbook of Pharmaceutical Salts, P.Heinrich Stahal& Camille G. Wermuth (Eds), Verlag Helvetica Chemica Acta- Zürich, 2002, 329-345).

25 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. (Handbook of Pharmaceutical Salts, P.Heinrich Stahal& Camille G. Wermuth (Eds), 30 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 N-formyl peptide receptor like-1 receptor.

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

15 In a further embodiment of the invention, there are provided methods for treating disorders associated with modulation of the N-formyl peptide receptor like-1 receptor.

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.

Therapeutic utilities of the N-formyl peptide receptor like-1 receptor
20 modulators are ocular inflammatory diseases including, but not limited to, wet and dry age-related macular degeneration (ARMD), uveitis, dry eye, Keratitis, allergic eye disease and conditions affecting the posterior part of the eye, such as maculopathies and retinal degeneration including non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, diabetic
25 retinopathy (proliferative), retinopathy of prematurity (ROP), acute macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; infectious keratitis, uveitis, herpetic keratitis, corneal angiogenesis, lymphangiogenesis, uveitis, retinitis, and choroiditis such as acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot
30 retinochoroidopathy, infectious (syphilis, lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (mewds), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-and Harada syndrome; vasuclar diseases/ exudative diseases such as retinal arterial occlusive disease,

central retinal vein occlusion, cystoids macular edema, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angiod streaks, familial exudative vitreoretinopathy, and Eales disease; traumatic/ surgical conditions such as sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, post surgical corneal wound healing, conditions caused by 5 laser, conditions caused by photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, and bone marrow transplant retinopathy; proliferative disorders such as proliferative vitreal retinopathy and epiretinal membranes, and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis 10 syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis 15 pigmentosa, systemic disorders with accosiated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes 20 such as retinal detachment, macular hole, and giant retinal tear; tumors such as retinal disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, 25 retinal astrocytoma, and intraocular lymphoid tumors; and miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigment epitheliitis, systemic inflammatory diseases such as stroke, coronary artery disease, obstructive airway diseases, HIV- 30

mediated retroviral infections, cardiovascular disorders including coronary artery disease, neuroinflammation, neurological disorders, pain and immunological disorders, asthma, allergic disorders, inflammation, systemic lupus erythematosus, eczema, psoriasis, CNS disorders such as Alzheimer's disease, arthritis, sepsis, 5 inflammatory bowel disease, cachexia, angina pectoris, post-surgical corneal inflammation, blepharitis, MGD, dermal wound healing, burns, rosacea, atopic dermatitis, acne, psoriasis, seborheic dermatitis, actinic keratoses, viral warts, photoaging, rheumatoid arthritis and related inflammatory disorders, alopecia, glaucoma, branch vein occlusion, Best's vitelliform macular degeneration, retinitis 10 pigmentosa, proliferative vitreoretinopathy (PVR), and any other degenerative disease of either the photoreceptors or the RPE (Perretti, Mauro et al. *Pharmacology & Therapeutics* 127 (2010) 175-188.)

These compounds are useful for the treatment of mammals, including humans, with a range of conditions and diseases that are alleviated by the N-formyl 15 peptide receptor like-1 receptor modulation: including, but not limited to the treatment of wet and dry age-related macular degeneration (ARMD), diabetic retinopathy (proliferative), retinopathy of prematurity (ROP), diabetic macular edema, uveitis, retinal vein occlusion, cystoids macular edema, glaucoma, branch vein occlusion, Best's vitelliform macular degeneration, retinitis pigmentosa, proliferative 20 vitreoretinopathy (PVR), and any other degenerative disease of either the photoreceptors or the RPE.

In still another embodiment of the invention, there are provided methods for treating disorders associated with modulation of the FPRL-1 receptor. Such methods can be performed, for example, by administering to a subject in need 25 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 30 the treatment of ocular inflammatory diseases including, but not limited to, wet and dry age-related macular degeneration (ARMD), uveitis, dry eye, Keratitis, allergic eye disease and conditions affecting the posterior part of the eye, such as maculopathies and retinal degeneration including non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, diabetic

retinopathy (proliferative), retinopathy of prematurity (ROP), acute macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; infectious keratitis, uveitis, herpetic keratitis, corneal angiogenesis, lymphangiogenesis, uveitis, retinitis, and choroiditis such as acute

5 multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, infectious (syphilis, lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (mewds), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-and Harada syndrome;

10 vascular diseases/ exudative diseases such as retinal arterial occlusive disease, central retinal vein occlusion, cystoids macular edema, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery

15 occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, and Eales disease; traumatic/ surgical conditions such as sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, post-surgical corneal wound healing, conditions caused by

20 laser, conditions caused by photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, and bone marrow transplant retinopathy; proliferative disorders such as proliferative vitreal retinopathy and epiretinal membranes, and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis

25 syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis

30 pigmentosa, systemic disorders with accosiated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes

such as retinal detachment, macular hole, and giant retinal tear; tumors such as retinal disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma, and intraocular lymphoid tumors; and miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigment epitheliitis, systemic inflammatory diseases such as stroke, coronary artery disease, obstructive airway diseases, HIV-mediated retroviral infections, cardiovascular disorders including coronary artery disease, neuroinflammation, neurological disorders, pain and immunological disorders, asthma, allergic disorders, inflammation, systemic lupus erythematosus, eczema, psoriasis, CNS disorders such as Alzheimer's disease, arthritis, sepsis, inflammatory bowel disease, cachexia, angina pectoris, post-surgical corneal inflammation, blepharitis, MGD, dermal wound healing, burns, rosacea, atopic dermatitis, acne, psoriasis, seborrheic dermatitis, actinic keratoses, viral warts, photoaging, rheumatoid arthritis and related inflammatory disorders, alopecia, glaucoma, branch vein occlusion, Best's vitelliform macular degeneration, retinitis pigmentosa, proliferative vitreoretinopathy (PVR), and any other degenerative disease of either the photoreceptors or the RPE.

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, direct injection, application at the back of the eye or formulations that may further enhance the long duration of actions such as a slow releasing pellet, suspension, gel, or sustained delivery devices such as any suitable drug delivery system (DDS) known

in the art. While topical administration is preferred, this compound may also be used in an intraocular implant as described in U.S. U.S. Patent 7,931,909, 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

5 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

10 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

15 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

20 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.

25 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

30 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 5 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 10 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 15 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 20 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 25 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.

The compounds of the invention may also be administered in the form of 30 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.

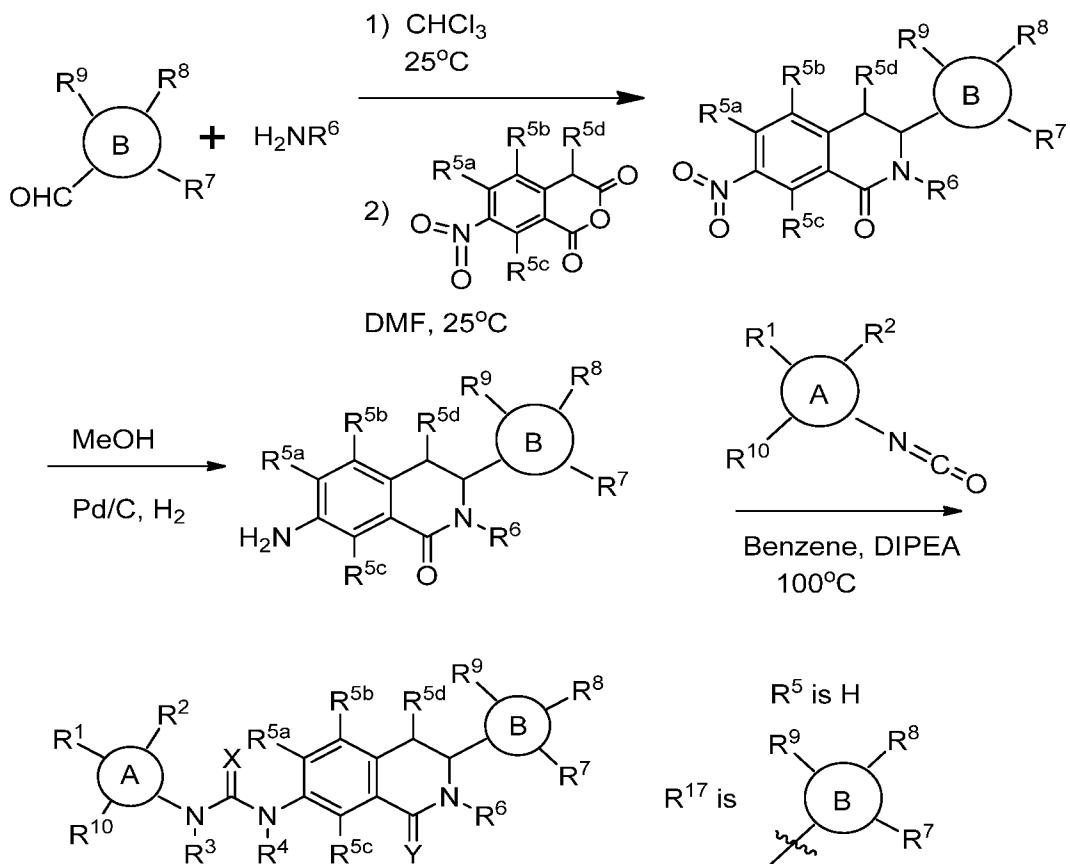
5 The compounds and pharmaceutical compositions described herein are useful as medicaments in mammals, including humans, for treatment of diseases and/or alleviations of conditions which are responsive to treatment by agonists or functional antagonists of the N-formyl peptide receptor like-1 (FPRL-1) receptor. Thus, in further embodiments of the invention, there are provided methods for

10 10 treating a disorder associated with modulation of the N-formyl peptide receptor like-1 (FPRL-1) receptor. 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 amount" means the amount of the

15 15 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 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. Synthetic Scheme 1 set forth below, illustrates how the compounds according to the invention can be made.

Scheme 1



Formula I

Compounds within the scope of the invention may be prepared as depicted in Scheme 1. In general, an aldehyde, such as 4-cyanobenzaldehyde, and an amine, such as *N*¹-boc-1,3-diamino-n-propane can be reacted in a suitable solvent (eg., THF or chloroform) to form an imine intermediate. The solvent may then be evaporated under reduced pressure, and the residue redissolved in DMF. The imine is then reacted with 7-nitro-homophthallic anhydride, (i.e., 7-Nitro-1*H*-2-benzopyran-1,3(4*H*)-dione) to produce a 7-nitro-3,4-dihydroisoquinolin-1(2*H*)-one, such as *tert*-butyl (3-(3-(4-cyanophenyl)-7-nitro-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)propyl)carbamate (Intermediate 1). The nitro group of the 7-nitro-3,4-dihydroisoquinolin-1(2*H*)-one can then be treated with a reducing agent, such as hydrogen in the presence of 10% palladium on carbon, in a suitable solvent (MeOH) to give a 7-amino-3,4-dihydroisoquinolin-1(2*H*)-one, such as *tert*-butyl (3-(7-amino-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)propyl)carbamate (Intermediate 13). The 7-amino-3,4-dihydroisoquinolin-1(2*H*)-one may be dissolved

in a suitable solvent (eg., benzene) and then be treated with an organic isocyanates, such as 4-acetylphenyl isocyanates, in the presence of a strong base (eg, DIPEA) to produce a urea, such as *tert*-butyl {3-[7-({[(4-acetylphenyl)amino] carbonyl}amino)-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate

5 (Intermediate 23), a compound which falls under the scope of the invention. At this stage, those skilled in the art will appreciate that many additional compounds that fall under the scope of the invention may be prepared by performing various common chemical reactions. For instance, a sulfide group may be oxidized to sulfoxide or sulfone groups by treatment with a suitable oxidizing agent (eg., m-chloroperbenzoic acid). Or, for example, the *t*-butylcarbamate group may be removed by treatment with a strong acid, such as trifluoroacetic acid, to give an amine product, such as 1-(4-acetylphenyl)-3-[2-(2-aminoethyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea (Compound 2). Details of certain specific chemical transformations are provided in the examples.

10 15 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.

DETAILED DESCRIPTION OF THE INVENTION

20 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 the plural unless specifically stated otherwise.

25 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 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 30 within the scope of the invention.

The present invention includes all pharmaceutically acceptable isotopically 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, use of deuterium may increase the in vivo half-life by altering the metabolism (rate) 5 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 10 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.

15 Compound names were generated with ACD version 11.0; and Intermediates and reagent names used in the examples were generated with softwares such as Chem Bio Draw Ultra version 12.0, ACD version 11.0 or Auto Nom 2000 from MDL ISIS Draw 2.5 SP1.

In general, characterization of the compounds is performed using NMR 20 spectra, 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. The optical rotation was recorded on Perkin Elmer Polarimeter 341, 589 nm at 20 °C, Na/Hal lamp.

All the reagents, solvents, catalysts for which the synthesis is not described 25 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, Chem-Impex, MIC-scientific, Ltd; however some known intermediates, were prepared according to published procedures.

30 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 chiral resolution was performed using chiral HPLC:

5

Preparative methods: Chiralpak AD-H (2 x 15cm)
 30% ethanol/CO₂, 100 Bar
 65ml/min, 220nm.

Analytical method: Chiralpak AD-H (25 x 0.46cm)
 40% ethanol (DEA)/CO₂, 100 Bar
 3ml/min, 220nm.

The following abbreviations are used in the examples:

NH ₃	ammonia
CH ₃ CN	acetonitrile
10 DMF	<i>N,N</i> -dimethylformamide
MeOH	methanol
CD ₃ OD	deuterated methanol
Na ₂ SO ₄	sodium sulfate
EtOAc	ethyl acetate
15 mW	microwave Biotage Initiator Eight
Auto-column	automated flash liquid chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Na ₂ CO ₃	sodium carbonate
20 N	normality
Pd/C	palladium(0) on carbon
EtOH	ethanol
SnCl ₂	stannous chloride
Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
25 Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
boc	tert-Butyloxycarbonyl

The following synthetic schemes illustrate how compounds according to the invention can be made. Those skilled in the art will be routinely able to modify and/or adapt the following schemes to synthesize any compound of the invention covered by Formula I.

Example 1**Intermediate 1****tert-butyl (3-(3-(4-cyanophenyl)-7-nitro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)propyl)carbamate**

5 To a solution of 4-cyanobenzaldehyde (150 mg, 1.15 mmol) in 6 mL of anhydrous THF was added *N*¹-boc-1,3-diamino-n-propane (219 mg, 1.27 mmol) and the mixture was stirred at 25°C for 30 minutes. The solvent was evaporated and then 2 mL of DMF and 7-nitro-1H-2-benzopyran-1,3(4H)-dione (CAS 36795-25-2) (288mg, 1.15 mmol) were added. Mixture was stirred at 25°C for 12 hours. The 10 solvent was evaporated and the residue was purified by medium pressure liquid chromatography on silica gel using ethyl acetate : hexane (8:2) to yield **Intermediate 1** as a yellow solid.

15 ¹H NMR (300 MHz, CD₃OD) δ: 8.80 (d, J = 2.3 Hz, 1H), 8.24 (dd, J = 8.2, 2.3 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 5.24 (d, J = 6.7 Hz, 1H), 4.07 - 4.22 (m, 1H), 3.79 - 3.91 (m, 1H), 3.31 - 3.37 (m, 1H), 3.15 - 3.23 (m, 1H), 3.03 - 3.13 (m, 1H), 2.89 - 2.98 (m, 1H), 1.78 - 1.90 (m, 2H), 1.41 (s, 9H).

20 **Intermediates 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12** were prepared from the corresponding starting materials and 7-nitro-1H-2-benzopyran-1,3(4H)-dione in a similar manner to the procedure described in **Example 1** for **Intermediate 1**. The reagents, reactants used and the results are described below in **Table 1**.

Table 1

Interm. No.	IUPAC name	Reagent(s) Reactant(s)	¹ H NMR δ (ppm) for Intermediate	Features
2	tert-butyl (2-(3-(4-cyanophenyl)-7-nitro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)carbamate	4-cyanobenz aldehyde 1-boc-ethylene diamine anhydrous THF	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.73 - 8.87 (m, 1H), 8.16 - 8.34 (m, 2H), 7.92 - 8.04 (m, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.32 (s, 1H), 5.19 - 5.30 (m, 1H), 4.18 - 4.42 (m, 1H), 3.81 - 4.02 (m, 1H), 3.38 - 3.60 (m, 2H), 2.90 - 3.05 (m, 2H), 1.37 (s, 9H)	yellow solid
3	4-(2-(2-(1H-imidazol-4-yl)ethyl)-7-nitro-1-oxo-1,2,3,4-tetrahydroisoquinolin	4-cyanobenz aldehyde histamine	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.87 - 2.98 (m, 1 H), 2.99 - 3.11 (m, 1 H), 3.15 - 3.28 (m, 2 H),	pink solid

	n-3-yl)benzonitrile	anhydrous THF	3.61 (dd, $J=16.7, 6.74$ Hz, 1 H), 4.28 - 4.44 (m, 1 H), 4.98 (d, $J=5.3$ Hz, 1 H), 6.91 (s, 1 H), 7.26 (d, $J=8.2$ Hz, 2 H), 7.33 (d, $J=8.5$ Hz, 1 H), 7.59 (s, 1 H), 7.61 - 7.66 (m, 2 H), 8.23 (dd, $J=8.4, 2.5$ Hz, 1 H), 8.79 (d, $J=2.3$ Hz, 1 H)	
4	tert-butyl (2-(3-(4-cyanophenyl)-7-nitro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)(methyl)carbamate	4-cyanobenzaldehyde N-boc-N-methylethylene diamine anhydrous THF	1 H NMR (300 MHz, CD ₃ OD) δ : 2.65 - 2.88 (m, 1 H), 2.95 (s, 3 H), 3.11 - 3.25 (m, 1 H), 3.36 - 3.47 (m, 1 H), 3.68 - 3.86 (m, 1 H), 3.87 - 4.06 (m, 1 H), 4.51 - 4.72 (m, 1 H), 5.27 (dd, $J=5.0, 4.4$ Hz, 1 H), 7.32 (d, $J=8.2$ Hz, 2 H), 7.36 - 7.40 (m, 1 H), 7.64 (d, $J=8.2$ Hz, 2 H), 8.20 - 8.30 (m, 1 H), 8.79 (d, $J=3.5$ Hz, 1 H)	yellow solid
5	2-(2-(1H-imidazol-4-yl)ethyl)-3-(3,4-dichlorophenyl)-7-nitro-3,4-dihydroisoquinolin-1(2H)-one	3,4-dichlorobenzaldehyde histamine anhydrous THF	1 H NMR (300 MHz, CD ₃ OD) δ : 2.85 - 3.11 (m, 2 H), 3.16 - 3.27 (m, 2 H), 3.50 - 3.62 (m, 1 H), 4.35 (dd, $J=18.8, 7.9$ Hz, 1 H), 4.89 (d, $J=4.7$ Hz, 1 H), 6.90 (s, 1 H), 6.95 (dd, $J=8.5, 2.1$ Hz, 1 H), 7.26 (d, $J=2.1$ Hz, 1 H), 7.36 (d, $J=8.8$ Hz, 1 H), 7.37 (d, $J=8.2$ Hz, 1 H), 7.61 (d, $J=1.2$ Hz, 1 H), 8.25 (dd, $J=8.2, 2.3$ Hz, 1 H), 8.79 (d, $J=2.6$ Hz, 1 H)	orange solid
6	2-(2-(1H-imidazol-4-yl)ethyl)-3-(5-fluoropyridin-2-yl)-7-nitro-3,4-dihydroisoquinolin-1(2H)-one	5-fluoro-2-formyl pyridine histamine anhydrous THF	1 H NMR (300 MHz, CD ₃ OD) δ : 2.83 - 2.98 (m, 1 H), 2.98 - 3.13 (m, 1 H), 3.17 - 3.26 (m, 1 H), 3.33 - 3.42 (m, 1 H), 3.49 - 3.62 (m, 1 H), 4.39 (ddd, $J=13.3, 7.5, 5.6$ Hz, 1 H), 4.90 (d, $J=6.7$ Hz, 1 H), 6.92 (s, 1 H), 7.20 (dd, $J=8.6, 4.2$ Hz, 1 H), 7.32 (d, $J=8.2$ Hz, 1 H), 7.45 (td, $J=8.6, 2.8$ Hz, 1 H), 7.66 (s, 1 H), 8.20 (dd, $J=8.4, 2.5$ Hz, 1 H), 8.28 (d, $J=2.9$ Hz, 1 H), 8.75 (d, $J=2.6$ Hz, 1 H)	brown-orange solid
7	2-(2-(1H-imidazol-4-yl)ethyl)-3-(5-chlorofuran-2-yl)-7-	5-chloro-2-furylaldehyde	1 H NMR (300 MHz, CD ₃ OD) δ : 2.86 - 3.12 (m, 3 H), 3.19 - 3.28 (m,	yellow-brown solid

	nitro-3,4-dihydroisoquinolin-1(2H)-one	histamine anhydrous THF	1 H), 3.35 - 3.49 (m, 1 H), 4.28 - 4.44 (m, 1 H), 4.80 (d, <i>J</i> =4.4 Hz, 1 H), 6.08 (s, 2 H), 6.91 (s, 1 H), 7.51 (s, 1 H), 7.65 (s, 1 H), 8.31 (d, <i>J</i> =5.9 Hz, 1 H), 8.75 (s, 1 H)	
8	3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-7-nitro-3,4-dihydroisoquinolin-1(2H)-one	6-chloropyridine carboxaldehyde histamine anhydrous THF	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.87 - 3.11 (m, 2 H), 3.17 - 3.29 (m, 2 H), 3.61 (dd, <i>J</i> =16.4, 6.4 Hz, 1 H), 4.34 (dt, <i>J</i> =13.2, 6.6 Hz, 1 H), 4.98 (d, <i>J</i> =5.0 Hz, 1 H), 6.91 (s, 1 H), 7.26 - 7.33 (m, 1 H), 7.37 (d, <i>J</i> =8.8 Hz, 1 H), 7.46 (dd, <i>J</i> =8.4, 2.5 Hz, 1 H), 7.63 (s, 1 H), 8.13 (d, <i>J</i> =2.3 Hz, 1 H), 8.27 (d, <i>J</i> =8.2 Hz, 1 H), 8.79 (d, <i>J</i> =2.3 Hz, 1 H)	orange solid
9	3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-7-nitro-3,4-dihydroisoquinolin-1(2H)-one	5-chloro-formylpyridine anhydrous CH ₃ CN histamine mW 130 °C 4 minutes	¹ H NMR (600 MHz, CD ₃ OD) δ: 8.75 (d, <i>J</i> = 2.6 Hz, 1H), 8.37 (d, <i>J</i> = 2.6 Hz, 1H), 8.21 (dd, <i>J</i> = 8.4, 2.5 Hz, 1H), 7.64 - 7.72 (m, 2H), 7.32 (d, <i>J</i> = 8.5 Hz, 1H), 7.16 (d, <i>J</i> = 8.5 Hz, 1H), 6.92 (s, 1H), 4.90 (dd, <i>J</i> = 6.7, 1.8 Hz, 1H), 4.37 - 4.42 (m, 1H), 3.53 - 3.58 (m, 1H), 3.38 (dd, <i>J</i> = 16.6, 2.2 Hz, 1H), 3.24 (dt, <i>J</i> = 13.4, 7.5 Hz, 1H), 3.05 (dt, <i>J</i> = 14.7, 7.4 Hz, 1H), 2.89 - 2.95 (m, 1H)	brown-red solid
10	(S)-<i>tert</i>-butyl {3-[3-(4-cyanophenyl)-7-nitro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	chiral HPLC Intermediate 13	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.80 (d, <i>J</i> = 2.3 Hz, 1H), 8.24 (dd, <i>J</i> = 8.2, 2.3 Hz, 1H), 7.63 (d, <i>J</i> = 8.2 Hz, 2H), 7.36 (d, <i>J</i> = 8.2 Hz, 1H), 7.30 (d, <i>J</i> = 8.2 Hz, 2H), 5.25 (d, <i>J</i> = 7.0 Hz, 1H), 4.10 - 4.25 (m, 1H), 3.85 (dd, <i>J</i> = 17.0, 6.4 Hz, 1H), 3.31 - 3.36 (m, 1H), 3.13 - 3.24 (m, 1H), 3.01 - 3.13 (m, 1H), 2.87 - 3.01 (m, 1H), 1.75 - 1.93 (m, 2H), 1.41 (s, 9H)	yellow solid >99% ee, [α] _D = -47.1° (c=1.32, CH ₂ Cl ₂) Single crystal X-ray crystallography confirmed .
11	(R)-<i>tert</i>-butyl {3-[3-	chiral HPLC	¹ H NMR (300 MHz,	yellow

	(4-cyanophenyl)-7-[([4-(methylthio)phenyl]amino]carbonyl)amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	Intermediate 13	^1H NMR (CD_3OD) δ : 8.80 (s, 1H), 8.25 (d, J = 9.1 Hz, 1H), 7.63 (d, J = 7.0 Hz, 2H), 7.36 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 7.6 Hz, 2H), 5.24 (d, J = 7.3 Hz, 1H), 4.10 - 4.22 (m, 1H), 3.85 (dd, J = 16.4, 7.3 Hz, 1H), 3.33 - 3.37 (m, 1H), 3.13 - 3.25 (m, 1H), 3.02 - 3.13 (m, 1H), 2.88 - 3.01 (m, 1H), 1.77 - 1.91 (m, 2H), 1.41 (s, 9H)	solid >99% ee, [α] _D = +47.0° c=1.51, CH_2Cl_2
12	tert-butyl [3-(3-methyl-7-nitro-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)propyl]carbamate	Acetaldehyde 1-boc-propylenediamine 7-nitro-1H-2-Benzopyran-1,3(4H)-dione (CAS 36795-25-2)	^1H NMR (CD_3OD) δ : 8.70 (d, J = 2.1 Hz, 1H), 8.33 (dd, J = 8.4, 2.2 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 3.92 - 4.12 (m, 2H), 3.46 (dd, J = 16.6, 6.0 Hz, 1H), 3.04 - 3.26 (m, 3H), 2.98 (d, J = 16.7 Hz, 1H), 1.78 - 1.94 (m, 2H), 1.43 (s, 9H), 1.17 (d, J = 6.4 Hz, 3H)	yellow oil

Example 2

Intermediate 13

tert-butyl (3-(7-amino-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)propyl)carbamate

To a solution of **Intermediate 1** (350 mg, 0.78 mmol) in 20 mL of MeOH was added 10%Pd/C (40 mg). A balloon filled with hydrogen gas was attached, and the reaction was stirred at 25°C for 12 hrs. The mixture was filtered through Celite pad and the solvent was evaporated. The residue was purified by medium pressure liquid chromatography on silica gel using ethyl acetate : hexane (8:2) to yield **Intermediate 13** as a yellow solid.

^1H NMR (300 MHz, CD_3OD) δ : 7.52 - 7.70 (m, 2H), 7.18 - 7.37 (m, 3H), 6.69 - 6.86 (m, 2H), 4.97 - 5.14 (m, 1H), 3.50 - 3.74 (m, 1H), 3.00 - 3.24 (m, 1H), 2.78 - 2.98 (m, 4H), 1.69 - 1.88 (m, 2H), 1.41 (s, 9H).

Intermediates 14, 15, 16, 17, 18, 19, 20, 21 and 22 were prepared from the corresponding nitro intermediate in a similar manner to the procedure described in **Example 2** for **Intermediate 13**. The reactants used and the results are described below in **Table 2**.

Table 2

Interm. No.	IUPAC name	Nitro Interm. No.	^1H NMR δ (ppm) for Intermediate	Features
14	<i>tert</i> -butyl (2-(7-amino-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)carbamate	2	^1H NMR (300 MHz, CD ₃ OD) δ : 7.55 - 7.63 (m, 2H), 7.29 - 7.35 (m, 1H), 7.21 - 7.29 (m, 2H), 6.68 - 6.82 (m, 2H), 4.98 - 5.09 (m, 1H), 4.12 - 4.28 (m, 1H), 4.02 - 4.15 (m, 2H), 3.60 - 3.76 (m, 1H), 2.79 - 3.01 (m, 2H), 1.38 (s, 9H)	yellow solid
15	4-(2-(2-(1H-imidazol-4-yl)ethyl)-7-amino-1-oxo-1,2,3,4-tetrahydroisoquinolin-3-yl)benzonitrile	3	^1H NMR (300 MHz, CD ₃ OD) δ : 2.80 - 3.21 (m, 4 H), 3.34 - 3.43 (m, 1 H), 4.30 (ddd, J =13.0, 7.6, 5.4 Hz, 1 H), 4.75 - 4.83 (m, 1 H), 6.71 - 6.75 (m, 2 H), 6.88 (s, 1 H), 7.20 (s, 1 H), 7.23 (s, 1 H), 7.32 (d, J =1.8 Hz, 1 H), 7.56 (s, 1 H), 7.59 (s, 1 H), 7.61 (s, 1 H)	yellow-orange solid
16	<i>tert</i> -butyl (2-(7-amino-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)ethyl)(methyl)carbamate	4	^1H NMR (300 MHz, CD ₃ OD) δ : 1.34 (s, 9 H), 2.65 - 2.76 (m, 1 H), 2.94 (br. s., 3 H), 3.16 - 3.26 (m, 1 H), 3.52 - 3.92 (m, 2 H), 4.14 - 4.27 (m, 0 H), 4.41 - 4.57 (m, 1 H), 5.03 - 5.11 (m, 1 H), 6.69 - 6.81 (m, 2 H), 7.26 (s, 1 H), 7.29 (s, 1 H), 7.32 (br. s., 1 H), 7.59 (s, 1 H), 7.62 (s, 1 H)	yellow solid
17	2-(2-(1H-imidazol-4-yl)ethyl)-7-amino-3-(3,4-dichlorophenyl)-3,4-dihydroisoquinolin-1(2H)-one	5	^1H NMR (300 MHz, CD ₃ OD) δ : 2.78 - 3.21 (m, 4 H), 3.32 - 3.43 (m, 1 H), 4.27 (ddd, J =13.1, 7.5, 5.7 Hz, 1 H), 4.66 - 4.76 (m, 1 H), 6.72 - 6.80 (m, 2 H), 6.91 - 6.98 (m, 1 H), 6.98 - 7.06 (m, 1 H), 7.13 - 7.23 (m, 2 H), 7.33 (d, J =1.5 Hz, 1 H), 7.73 - 7.81 (m, 1 H)	yellow solid
18	2-(2-(1H-imidazol-4-yl)ethyl)-7-amino-3-(5-fluoropyridin-2-yl)-3,4-dihydroisoquinolin-1(2H)-one	6	^1H NMR (300 MHz, CD ₃ OD) δ : 2.83 - 2.95 (m, 1 H), 2.96 - 3.09 (m, 2 H), 3.09 - 3.21 (m, 1 H), 3.24 - 3.29 (m, 1 H), 4.32 - 4.43 (m, 1 H), 4.70 (d, J =5.9 Hz, 1 H), 6.67 - 6.77 (m, 2 H), 6.88 (s, 1 H), 7.03 (dd,	yellow solid

			$J=8.5, 4.4$ Hz, 1 H), 7.29 (d, $J=1.8$ Hz, 1 H), 7.40 (td, $J=8.6, 2.8$ Hz, 1 H), 7.62 (s, 1 H), 8.33 (d, $J=2.9$ Hz, 1 H)	
19	7-amino-3-(2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-3,4-dihydroisoquinolin-1(2H)-one	7	^1H NMR (300 MHz, CD ₃ OD) δ : 2.80 - 3.06 (m, 3 H), 3.09 - 3.21 (m, 1 H), 3.23 - 3.29 (m, 1 H), 4.29 (ddd, $J=13.3, 7.8, 5.0$ Hz, 1 H), 4.65 (d, $J=4.1$ Hz, 1 H), 5.89 (d, $J=3.2$ Hz, 1 H), 6.19 (dd, $J=3.2, 1.8$ Hz, 1 H), 6.74 - 6.81 (m, 1 H), 6.87 (s, 1 H), 6.90 (s, 1 H), 7.27 (d, $J=2.3$ Hz, 1 H), 7.32 (s, 1 H), 7.62 (s, 1 H)	yellow solid
20	(S)-tert-butyl {3-[3-(4-cyanophenyl)-7-[(4-(methylthio)phenyl)amino]carbonyl]amino}-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	10	^1H NMR (300 MHz, CD ₃ OD) δ : 7.60 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 1.8$ Hz, 1H), 7.26 (d, $J = 7.9$ Hz, 2H), 6.73 - 6.78 (m, 2H), 5.04 (d, $J = 6.2$ Hz, 1H), 4.02 - 4.16 (m, 1H), 3.60 (dd, $J = 16.1, 6.2$ Hz, 1H), 3.11 - 3.23 (m, 1H), 3.00 - 3.11 (m, 1H), 2.80 - 2.99 (m, 2H), 1.73 - 1.85 (m, 2H), 1.41 (s, 9H).	off-white solid $[\alpha]_D = -65.2^\circ$ (c=1.31, CH ₂ Cl ₂).
21	(R)-tert-butyl {3-[3-(4-cyanophenyl)-7-[(4-(methylthio)phenyl)amino]carbonyl]amino}-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	11	^1H NMR (300 MHz, CD ₃ OD) δ : 7.60 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 2.1$ Hz, 1H), 7.26 (d, $J = 8.2$ Hz, 2H), 6.70 - 6.83 (m, 2H), 5.04 (d, $J = 6.7$ Hz, 1H), 4.02 - 4.17 (m, 1H), 3.60 (dd, $J = 16.3, 6.6$ Hz, 1H), 3.10 - 3.24 (m, 1H), 3.00 - 3.10 (m, 1H), 2.80 - 3.00 (m, 2H), 1.72 - 1.87 (m, 2H), 1.41 (s, 9H).	white solid $[\alpha]_D = +69.6^\circ$ (c=1.20, CH ₂ Cl ₂)
22	tert-butyl [3-(7-amino-3-methyl-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)propyl]carbamate	12	^1H NMR (CD ₃ OD) δ : 7.26 (d, $J = 2.1$ Hz, 1H), 6.99 (d, $J = 8.2$ Hz, 1H), 6.81 - 6.87 (m, 1H), 4.01 (dt, $J = 13.7, 7.1$ Hz, 1H), 3.77 - 3.85 (m, 1H), 3.21 - 3.28 (m, 1H), 3.12 - 3.21 (m, 1H), 2.97 - 3.10 (m, 2H), 2.62 (d, $J = 15.2$ Hz, 1H), 1.76 - 1.86 (m, 2H), 1.43 (s, 9H), 1.12 (d, $J = 6.4$ Hz, 2H).	light yellow solid

Example 3**Intermediate 23*****tert-butyl {3-[7-({[(4-acetylphenyl)amino]carbonyl}amino)-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate***

5 To a solution of **Intermediate 13** (100 mg, 0.24 mmol) and 10 mL of anhydrous benzene under argon at 25 °C was added 4-acetylphenyl isocyanate (43 mg, 0.26 mmol) and triethylamine (50 mg, 0.48 mmol). The resulting mixture was heated to 100°C for 12 hours and the reaction was quenched with water. The product was extracted with EtOAc, the layers were separated, and the organic layer 10 was washed with brine, and dried over Na₂SO₄, and filtered, and concentrated under reduced pressure. The residue was purified by medium pressure liquid chromatography on silica gel using ethyl acetate : hexane (85:15) to yield **Intermediate 23** as a light yellow solid.

15 ¹H NMR (300 MHz, CD₃OD) δ: 7.88 - 8.10 (m, 3H), 7.52 - 7.70 (m, 5H), 7.22 - 7.35 (m, 2H), 6.95 - 7.11 (m, 1H), 5.08 - 5.22 (m, 1H), 4.06 - 4.26 (m, 1H), 3.61 - 3.81 (m, 0H), 2.99 - 3.27 (m, 4H), 1.69 - 1.95 (m, 2H), 1.42 (s, 9H).

20 **Intermediates 24, 25, 26, 27, 28, 29, 30 and 31** were prepared from the amino derivative in the presence of anhydrous benzene and the corresponding isocyanate in a similar manner to the procedure described in **Example 3** for **Intermediate 23**. The reactants and reagents used and the results are described below in **Table 3**.

Table 3

Interm. No.	IUPAC name	Reactant Reagent(s)	¹ H NMR δ (ppm) for Intermediate	Features
24	<i>tert-butyl {2-[7-({[(4-acetylphenyl)amino]carbonyl}amino)-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]ethyl}carbamate</i>	Interm. 2 4-acetylphenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 7.98 - 8.05 (m, 1H), 7.95 (d, <i>J</i> = 8.8 Hz, 2H), 7.53 - 7.69 (m, 5H), 7.29 (d, <i>J</i> = 8.5 Hz, 2H), 6.96 - 7.07 (m, 1H), 5.05 - 5.22 (m, 1H), 4.13 - 4.34 (m, 1H), 3.67 - 3.86 (m, 1H),	yellow solid

			3.35 - 3.45 (m, 1H), 3.01 - 3.16 (m, 1H), 2.82 - 3.00 (m, 1H), 2.56 (s, 3H), 1.39 (s, 9H)	
25	tert-butyl {2-[7-({[(4-acetylphenyl)amino]carbonyl}amino)-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]ethyl}methylcarbamate.	Interm. 16 4-acetylphenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 1.34 (s, 9 H), 2.55 (s, 3 H), 2.68 - 2.79 (m, 1 H), 2.95 (br. s., 3 H), 3.03 - 3.17 (m, 1 H), 3.62 - 3.96 (m, 2 H), 4.19 - 4.31 (m, 1 H), 4.47 - 4.62 (m, 1 H), 5.02 (br. s., 1 H), 5.14 (br. s., 1 H), 7.00 (br. s., 1 H), 7.29 (s, 1 H), 7.32 (s, 1 H), 7.54 - 7.66 (m, 5 H), 7.93 (s, 1 H), 7.96 (s, 1 H), 8.01 (br. s., 1 H)	yellow solid
26	tert-butyl {3-[3-(4-cyanophenyl)-1-oxo-7-[({{4-(trifluoromethyl)phenyl]amino}carbonyl)amino]-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	Interm.13 α,α,α - trifluoro-p-tolyl-isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 1.74 - 1.91 (m, 2 H), 2.84 - 2.98 (m, 1 H), 3.00 - 3.13 (m, 2 H), 3.13 - 3.24 (m, 1 H), 3.70 (dd, <i>J</i> =16.3, 6.6 Hz, 1 H), 4.06 - 4.19 (m, 1 H), 5.12 (d, <i>J</i> =5.9 Hz, 1 H), 7.02 (d, <i>J</i> =8.2 Hz, 1 H), 7.28 (d, <i>J</i> =8.2 Hz, 2 H), 7.51 - 7.68 (m, 7 H), 8.01 (d, <i>J</i> =2.3 Hz, 1 H)	white solid
27	tert-butyl {3-[3-(4-cyanophenyl)-7-[({{4-(methylthio)phenyl]amino}carbonyl)amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	Interm. 13 4-(methylthio)-phenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 1.41 (s, 9 H), 1.76 - 1.87 (m, 2 H), 2.90 (ddd, <i>J</i> =14.2, 7.0, 6.9 Hz, 1 H), 3.00 - 3.12 (m, 2 H), 3.12 - 3.24 (m,	white solid

			0 H), 3.69 (dd, $J=16.4, 6.4$ Hz, 1 H), 4.12 (ddd, $J=14.0, 7.3, 7.1$ Hz, 1 H), 5.11 (d, $J=5.9$ Hz, 1 H), 7.00 (d, $J=8.2$ Hz, 1 H), 7.20 - 7.31 (m, 3 H), 7.34 - 7.37 (m, 2 H), 7.37 - 7.40 (m, 1 H), 7.55 (d, $J=2.6$ Hz, 1 H), 7.56 - 7.60 (m, 1 H), 7.62 (s, 1 H), 7.98 (d, $J=2.3$ Hz, 1 H)	
28	<i>tert</i>-butyl {3-[7-({[4-bromophenyl]amino}carbonyl)amino]-3-(4-cyanophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propyl}carbamate	Interm. 13 4-bromophenyl isocyanate	^1H NMR (300 MHz, CD ₃ OD) δ : 1.41 (s, 9 H), 1.73 - 1.89 (m, 2 H), 2.82 - 2.99 (m, 1 H), 2.99 - 3.13 (m, 2 H), 3.12 - 3.25 (m, 1 H), 3.69 (dd, $J=16.7, 6.4$ Hz, 1 H), 4.04 - 4.21 (m, 1 H), 5.11 (d, $J=5.0$ Hz, 1 H), 7.01 (d, $J=7.9$ Hz, 1 H), 7.28 (d, $J=7.9$ Hz, 2 H), 7.33 - 7.44 (m, 4 H), 7.52 - 7.65 (m, 3 H), 7.98 (d, $J=2.1$ Hz, 1 H)	white solid
29	(S)-<i>tert</i>-butyl {3-[3-(4-cyanophenyl)-7-[(4-(methylthio)phenyl]amino]carbonyl)amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propyl}carbamate	Interm. 20 4-(methylthio)-phenyl isocyanate	^1H NMR (300 MHz, CD ₃ OD) δ : 7.97 (d, 1H), 7.58 - 7.64 (m, 2H), 7.56 (d, $J = 2.6$ Hz, 1H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.21 - 7.32 (m, 4H), 7.01 (d, $J = 8.2$ Hz, 1H), 5.11 (d, $J = 6.4$ Hz, 1H), 4.07 - 4.16 (m, 1H), 3.64 - 3.75 (m, 1H), 3.13 - 3.22 (m, 1H), 3.02 - 3.12	yellow solid $[\alpha]_D = -55.9^\circ$ (c=0.72, CH ₂ Cl ₂).

			(m, 2H), 2.86 - 2.96 (m, 1H), 2.44 (s, 3H), 1.77 - 1.86 (m, 2H), 1.41 (s, 9H)	
30	(R)-tert-butyl {3-[3-(4-cyanophenyl)-7-[(4-(methylthio)phenyl]amino]carbonyl]amino}-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propyl}carbamate	Interm.21 4-(methylthio)-phenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 7.98 (s, 1H), 7.52 - 7.62 (m, 3H), 7.37 (d, J = 8.8 Hz, 2H), 7.25 (dd, J = 13.8, 8.2 Hz, 4H), 6.99 (d, J = 8.5 Hz, 1H), 5.10 (d, J = 5.3 Hz, 1H), 4.05 - 4.18 (m, 1H), 3.68 (dd, J = 16.1, 6.7 Hz, 1H), 3.12 - 3.24 (m, 1H), 3.00 - 3.12 (m, 2H), 2.83 - 2.96 (m, 1H), 2.43 (s, 3H), 1.75 - 1.87 (m, 2H), 1.41 (s, 9H)	yellow solid [α] _D = +52.1° (c=1.49, CH ₂ Cl ₂)
31	tert-butyl (3-{3-methyl-7-[(4-(methylthio)phenyl]amino]carbonyl}amino)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propyl}carbamate	4-(methylthio)-phenyl isocyanate Triethylamine Interm.22	¹ H NMR (CD ₃ OD) δ: 7.84 (d, J = 2.1 Hz, 1H), 7.70 (dd, J = 8.1, 2.2 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.18 - 7.27 (m, 3H), 4.03 (dt, J = 13.8, 7.2 Hz, 1H), 3.82 - 3.91 (m, 1H), 3.32 - 3.35 (m, 0H), 3.13 - 3.25 (m, 0H), 3.01 - 3.13 (m, 2H), 2.69 - 2.80 (m, 1H), 2.44 (s, 3H), 1.77 - 1.89 (m, 2H), 1.43 (s, 9H), 1.15 (d, 3H).	light yellow solid

Example 4**Intermediate 32**

7-amino-3-(5-chloro-2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-3,4-dihydroisoquinolin-1(2H)-one

To a solution of **Intermediate 13** (445 mg, 1.15 mmol) in 20 mL of EtOH was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (1.04 g, 4.60 mmol). The mixture was heated to 80°C for 3 hrs. The solvent was evaporated and the residue was purified by medium pressure liquid chromatography on silica gel using 10% 7N $\text{NH}_3\text{-MeOH} : \text{CH}_2\text{Cl}_2$ (80:20) to yield

5 **Intermediate 32** as a yellow solid.

^1H NMR (300 MHz, CD_3OD) δ : 2.81 - 3.06 (m, 3 H), 3.12 (d, $J=5.9$ Hz, 1 H), 3.21 - 3.28 (m, 1 H), 4.25 - 4.39 (m, 1 H), 4.63 (d, $J=4.7$ Hz, 1 H), 5.93 (d, $J=3.2$ Hz, 1 H), 6.04 (d, $J=3.2$ Hz, 1 H), 6.75 - 6.84 (m, 1 H), 6.86 - 6.96 (m, 2 H), 7.27 (d, $J=2.6$ Hz, 1 H), 7.66 (s, 1 H).

10 **Intermediates 33 and 34** were prepared from the corresponding nitro intermediate in the presence of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ in a similar manner to the procedure described in **Example 4** for **Intermediate 32**. The reactants and the results are described below in **Table 4**.

Table 4

Interm. No.	IUPAC name	Nitro Interm No.	^1H NMR δ (ppm) for Intermediate	Features
33	7-amino-3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-3,4-dihydroisoquinolin-1(2H)-one	8	^1H NMR (300 MHz, CD_3OD) δ : 2.80 (d, 1 H), 2.85 - 2.95 (m, 1 H), 2.94 - 3.07 (m, 1 H), 3.19 (ddd, $J=13.4, 7.8, 7.5$ Hz, 1 H), 3.37 (dd, $J=15.7, 6.3$ Hz, 1 H), 4.20 - 4.32 (m, 1 H), 4.78 (d, $J=6.7$ Hz, 1 H), 6.72 - 6.81 (m, 2 H), 6.88 (s, 1 H), 7.24 - 7.30 (m, 1 H), 7.32 (d, $J=2.1$ Hz, 1 H), 7.42 (dd, $J=8.4, 2.5$ Hz, 1 H), 7.62 (s, 1 H), 8.06 (d, $J=2.6$ Hz, 1 H)	yellow solid
34	7-amino-3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-3,4-dihydroisoquinolin-1(2H)-one	9	^1H NMR (300 MHz, CD_3OD) δ : 8.42 (d, $J = 2.3$ Hz, 1H), 7.60 - 7.66 (m, 2H), 7.29 (d, $J = 2.1$ Hz, 1H), 7.00 (d, $J = 8.2$ Hz, 1H), 6.89 (s, 1H), 6.70 - 6.75 (m, 2H), 4.69 (d, $J = 6.2$ Hz, 1H), 4.32 - 4.46 (m, 1H), 3.20 - 3.28 (m, 1H), 3.15 (dd, $J = 13.0, 7.2$ Hz, 1H), 2.97 - 3.10 (m, 2H), 2.83 - 2.96 (m, 1H)	off-white solid

Example 5**Intermediate 35****tert-butyl {3-[3-(4-cyanophenyl)-7-[(4-(methylsulfinyl)phenyl]amino]carbonyl]amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate**

5 To a solution of **Intermediate 27** (62 mg, 0.11 mmol) and 10 mL of anhydrous THF at 0 °C was added *meta*-chloroperbenzoic acid (20 mg, 0.11 mmol). The mixture was stirred at 0 °C for 2 hours. The reaction was quenched with 2N Na₂CO₃ solution and product was extracted with EtOAc. The organic extracts were combined and washed with water, and brine, and dried over Na₂SO₄, and filtered, 10 and concentrated under reduced pressure. The residue was purified by medium pressure liquid chromatography on silica gel using methanol : dichloromethane (1:9) to yield **Intermediate 35** as a white solid.

15 ¹H NMR (300 MHz, CD₃OD) δ: 1.42 (s, 9 H), 1.75 - 1.90 (m, 2 H), 2.79 (s, 3 H), 2.84 - 2.98 (m, 1 H), 3.00 - 3.13 (m, 2 H), 3.13 - 3.25 (m, 1 H), 3.70 (dd, *J*=15.8, 7.0 Hz, 1 H), 4.05 - 4.19 (m, 1 H), 5.12 (d, *J*=6.2 Hz, 1 H), 7.02 (d, *J*=8.2 Hz, 1 H), 7.29 (d, *J*=8.2 Hz, 2 H), 7.53 - 7.75 (m, 7 H), 8.02 (d, *J*=2.3 Hz, 1 H).

20 **Intermediates 36, 37 and 38** were prepared from the thio derivative in the presence of *meta*-chloroperbenzoic acid in a similar manner to the procedure described in **Example 5** for **Intermediate 35**. Using 5.0 equivalents of *meta*-chloroperbenzoic acid in the procedure of **Example 5** and stirring the reaction mixture at 25 °C for 0.5 h lead to the sulfonyl derivatives **Intermediate 39** and **40**. The reactant used and the results are described below in **Table 5**.

Table 5

Interm. No.	IUPAC name	Thio Interm. No.	¹ H NMR δ (ppm) for Intermediate	Features
36	(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	29	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.03 (d, <i>J</i> = 1.8 Hz, 1H), 7.53 - 7.73 (m, 7H), 7.27 (d, <i>J</i> = 8.2 Hz, 2H), 7.00 (d, <i>J</i> = 8.2 Hz, 1H), 5.11 (d, <i>J</i> = 5.6 Hz, 1H), 4.06 - 4.19 (m, 1H), 3.69 (dd, <i>J</i> =	white solid

			16.0, 6.6 Hz, 1H), 3.13 - 3.24 (m, 1H), 3.00 - 3.12 (m, 2H), 2.84 - 2.97 (m, 1H), 2.78 (s, 3H), 1.75 - 1.90 (m, 2H), 1.41 (s, 9H).	
37	<i>(R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea.</i>	30	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.03 (d, J = 1.8 Hz, 1H), 7.53 - 7.73 (m, 7H), 7.27 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.2 Hz, 1H), 5.11 (d, J = 5.6 Hz, 1H), 4.06 - 4.19 (m, 1H), 3.69 (dd, J = 16.0, 6.6 Hz, 1H), 3.13 - 3.24 (m, 1H), 3.00 - 3.12 (m, 2H), 2.84 - 2.97 (m, 1H), 2.78 (s, 3H), 1.75 - 1.90 (m, 2H), 1.41 (s, 9H).	white solid [α] _D = +77.2° (c=0.64, CH ₂ Cl ₂).
38	<i>(S)-tert-butyl {3-[3-(4-cyanophenyl)-7-[({[4-(methylsulfonyl)phenyl]amino}carbonyl)amino] -1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate</i>	30	¹ H NMR (CD ₃ OD) δ: 8.03 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.54 - 7.64 (m, 3H), 7.28 (d, J = 7.9 Hz, 2H), 7.02 (d, J = 8.2 Hz, 1H), 5.12 (d, J = 6.4 Hz, 1H), 4.07 - 4.19 (m, 1H), 3.70 (dd, J = 16.1, 7.0 Hz, 1H), 3.14 - 3.24 (m, 1H), 3.09 (s, 3H), 3.05 - 3.13 (m, 2H), 2.84 - 2.96 (m, 1H), 1.77 - 1.89 (m, 2H), 1.41 (s, 9H).	white solid [α] _D = -62.1° (c=1.14, CH ₂ Cl ₂).

39	<i>tert</i> -butyl {3-[3-(4-cyanophenyl)-7-[({[4-(methylsulfonyl)phenyl]amino}carbonyl)amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	27	¹ H NMR (300 MHz, CD ₃ OD) δ: 1.42 (s, 9 H), 1.76 - 1.88 (m, 2 H), 2.85 - 3.07 (m, 2 H), 3.09 (s, 3 H), 3.10 - 3.23 (m, 2 H), 3.70 (dd, <i>J</i> =16.8, 6.6 Hz, 1 H), 4.06 - 4.19 (m, 1 H), 5.12 (d, <i>J</i> =7.0 Hz, 1 H), 7.03 (d, <i>J</i> =8.2 Hz, 1 H), 7.29 (d, <i>J</i> =8.2 Hz, 2 H), 7.57 (d, <i>J</i> =2.3 Hz, 1 H), 7.60 (s, 1 H), 7.62 - 7.64 (m, 1 H), 7.66 - 7.75 (m, 2 H), 7.85 (q, <i>J</i> =4.7 Hz, 1 H), 8.03 (d, <i>J</i> =2.3 Hz, 1 H).	yellow solid
40	(<i>R</i>)- <i>tert</i> -butyl {3-[3-(4-cyanophenyl)-7-[({[4-(methylsulfonyl)phenyl]amino}carbonyl)amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propyl}carbamate	30	¹ H NMR (CD ₃ OD) δ: 8.03 (d, <i>J</i> = 2.1 Hz, 1H), 7.85 (d, <i>J</i> = 8.8 Hz, 2H), 7.70 (d, <i>J</i> = 8.8 Hz, 2H), 7.54 - 7.64 (m, 3H), 7.28 (d, <i>J</i> = 7.9 Hz, 2H), 7.02 (d, <i>J</i> = 8.2 Hz, 1H), 5.12 (d, <i>J</i> = 6.4 Hz, 1H), 4.07 - 4.19 (m, 1H), 3.70 (dd, <i>J</i> = 16.1, 7.0 Hz, 1H), 3.14 - 3.24 (m, 1H), 3.09 (s, 3H), 3.05 - 3.13 (m, 2H), 2.84 - 2.96 (m, 1H), 1.77 - 1.89 (m, 2H), 1.41 (s, 9H).	white solid [α] _D = +63.3° (c=1.16, CH ₂ Cl ₂).
41	<i>tert</i> -butyl (3-{3-methyl-7-[({[4-(methylsulfonyl)phenyl]amino}carbonyl)amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propyl)carbamate	31	¹ H NMR (CD ₃ OD) δ: 7.90 (d, <i>J</i> = 2.1 Hz, 1H), 7.84 (d, <i>J</i> = 8.5 Hz, 2H), 7.69 (d, <i>J</i> = 8.5 Hz, 3H), 7.21 (d, <i>J</i> = 8.2 Hz, 1H), 4.03 (dt, <i>J</i> = 13.8, 7.0 Hz, 1H), 3.82 - 3.91 (m, 1H), 3.31 (s, 3H),	

		3.24 - 3.29 (m, 1H), 3.13 - 3.22 (m, 1H), 3.01 - 3.07 (m, 2H), 2.73 (d, J = 16.1 Hz, 1H), 1.77 - 1.89 (m, 2H), 1.43 (s, 9H), 1.14 (d, 3H).	
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Example 6**Intermediate 42**

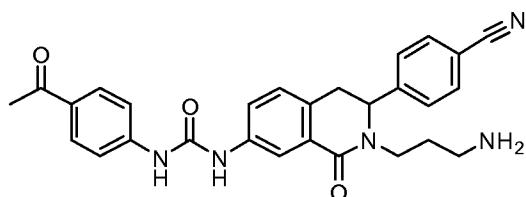
tert-butyl {3-[3-(4-cyanophenyl)-7-[{[4-(ethylthio)phenyl]amino}carbonyl]amino]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propyl}carbamate

In a sealed tube, a solution of **Compound 6** (85 mg, 0.14 mmol) and 8 mL of 1,4-dioxane was purged under argon at 25 °C and ethanethiol (0.05 ml, 0.70 mmol), Pd₂(dba)₃ (12 mg, 0.014 mmol), Xantphos (16 mg, 0.028 mmol) and 5 diisopropylethylamine (0.1 mL, 0.56 mmol) were added. The resulting mixture was heated to 110°C for 12 hours. The mixture was concentrated and the residue was purified by medium pressure liquid chromatography on silica gel using ethyl acetate : 10 hexane (7:3) to yield **Intermediate 42** as a yellow solid.

¹H NMR (600 MHz, CD₃OD) δ: 7.98 (d, J = 2.3 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 15 7.57 (dd, J = 8.2, 2.3 Hz, 1H), 7.34 - 7.41 (m, 2H), 7.24 - 7.33 (m, 4H), 7.00 (d, J = 8.2 Hz, 1H), 5.11 (d, J = 6.2 Hz, 1H), 4.12 (td, J = 13.4, 7.2 Hz, 1H), 3.69 (dd, J = 16.1, 6.5 Hz, 1H), 3.15 - 3.24 (m, 1H), 3.02 - 3.11 (m, 2H), 2.89 - 2.93 (m, 1H), 2.87 (q, J = 7.3 Hz, 2H), 1.76 - 1.88 (m, 2H), 1.42 (s, 9H), 1.20 - 1.27 (m, 3H).

Example 7**Compound 1**

1-(4-acetylphenyl)-3-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea



To a solution of **Intermediate 23** (75 mg, 0.13 mmol) and 4 mL of anhydrous 25 CH₂Cl₂ under argon at 25 °C was added TFA (0.2 mL). The resulting mixture was

stirred for 2 hours and the reaction was quenched by the addition of 7N NH₃-MeOH (0.2mL) at 0 °C. Silica gel (100mg) was added and the mixture was concentrated to dryness. The resulting product was purified by medium pressure liquid chromatography on silica gel using an eluent of 10% 7N NH₃-MeOH : CH₂Cl₂ (80:20)

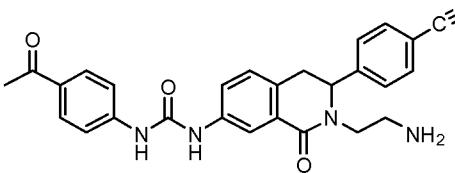
5 to yield **Compound 1** as a light yellow solid.

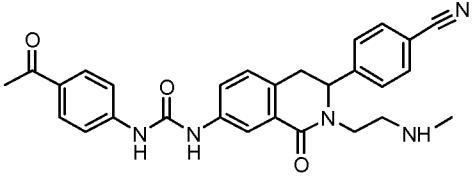
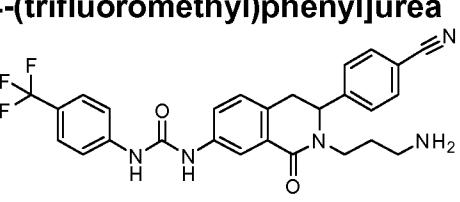
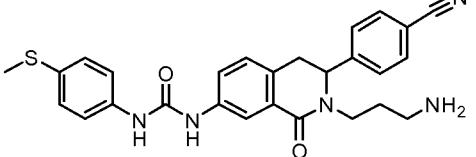
¹H NMR (300 MHz, CD₃OD) δ: ¹H NMR (CD₃OD) δ: 7.88 - 8.10 (m, 3H), 7.52 - 7.70 (m, 5H), 7.22 - 7.35 (m, 2H), 6.95 - 7.11 (m, 1H), 5.08 - 5.22 (m, 1H), 4.06 - 4.26 (m, 1H), 3.61 - 3.81 (m, 0H), 2.99 - 3.27 (m, 4H), 1.69 - 1.95 (m, 2H), 1.42 (s, 9H).

10 **Compounds 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17** were prepared from the amino intermediate derivative in the presence of trifluoroacetic acid and the corresponding protected amine in a similar manner to the procedure described in **Example 7 for Compound 1**. The intermediate used and the results are described below in **Table 6**.

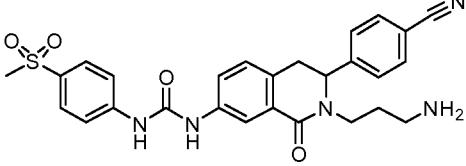
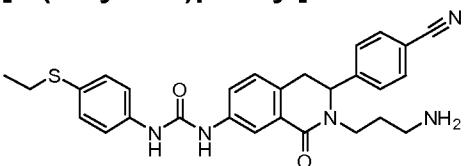
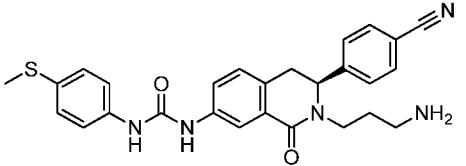
15

Table 6

Comp No.	IUPAC name	Amino. Interm	¹ H NMR δ (ppm) for Compound	Features
2	1-(4-acetylphenyl)-3-[2-(2-aminoethyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea 	24	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.05 (d, <i>J</i> = 2.3 Hz, 1H), 7.94 (d, <i>J</i> = 8.5 Hz, 2H), 7.49 - 7.67 (m, 5H), 7.29 (d, <i>J</i> = 8.5 Hz, 2H), 7.02 (d, <i>J</i> = 8.2 Hz, 1H), 5.06 - 5.20 (m, 1H), 4.06 - 4.26 (m, 1H), 3.67 - 3.86 (m, 1H), 3.01 - 3.15 (m, 1H), 2.83 - 3.01 (m, 3H), 2.55 (s, 3H).	white solid
3	1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(methylamino)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea	25	¹ H NMR (CD ₃ OD) δ: 2.41 (s, 3 H), 2.55 (s, 3 H), 2.81 - 2.90 (m, 2 H), 2.93 - 3.12 (m, 2 H), 3.75 (dd,	white solid

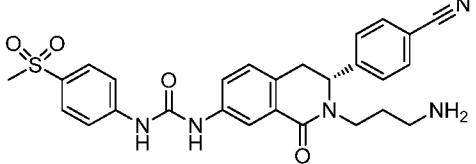
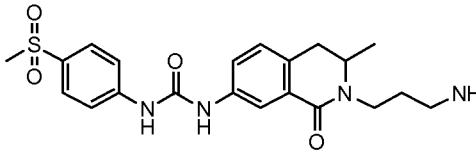
			<i>J</i> =16.0, 6.9 Hz, 1 H), 4.24 (ddd, <i>J</i> =13.4, 7.0, 6.8 Hz, 1 H), 5.13 (d, <i>J</i> =5.9 Hz, 1 H), 7.01 (d, <i>J</i> =8.2 Hz, 1 H), 7.27 (s, 1 H), 7.30 (s, 1 H), 7.53 - 7.64 (m, 5 H), 7.93 (s, 1 H), 7.95 (s, 1 H), 8.04 (d, <i>J</i> =2.3 Hz, 1 H)	
4	1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(trifluoromethyl)phenyl]urea 	26	¹ H NMR (CD ₃ OD) δ: 1.70 - 1.93 (m, 2 H), 2.70 (t, <i>J</i> =6.3 Hz, 2 H), 2.96 (dt, <i>J</i> =13.4, 6.6 Hz, 1 H), 3.08 (d, <i>J</i> =16.1 Hz, 1 H), 3.65 (dd, <i>J</i> =16.0, 6.3 Hz, 1 H), 4.09 - 4.25 (m, 1 H), 5.10 (d, <i>J</i> =5.9 Hz, 1 H), 7.00 (d, <i>J</i> =8.2 Hz, 1 H), 7.29 (d, <i>J</i> =8.5 Hz, 2 H), 7.51 - 7.67 (m, 7 H), 8.04 (d, <i>J</i> =2.1 Hz, 1 H)	white solid
5	1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea 	27	¹ H NMR (CD ₃ OD) δ: 1.72 - 1.88 (m, 1 H), 1.89 - 2.03 (m, 1 H), 2.43 (s, 3 H), 2.70 (t, <i>J</i> =7.3 Hz, 1 H), 2.88 - 3.02 (m, 1 H), 3.07 (d, <i>J</i> =16.1 Hz, 1 H), 3.24 - 3.29 (m, 1 H), 3.65 (dd, <i>J</i> =15.8, 11.1 Hz, 1 H), 4.02 - 4.25 (m, 1 H), 5.12 (d, <i>J</i> =7.9 Hz, 1 H), 6.99 (d, <i>J</i> =8.2 Hz, 1 H), 7.19 - 7.32 (m, 4 H), 7.33 -	yellow solid

			7.42 (m, 2 H), 7.50 - 7.64 (m, 3 H), 8.00 (d, <i>J</i> =2.6 Hz, 1 H)	
6	1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-(4-bromophenyl)urea	28	¹ H NMR (CD ₃ OD) δ: 1.75 - 1.92 (m, 2 H), 2.71 (t, <i>J</i> =7.6 Hz, 2 H), 2.90 - 3.02 (m, 1 H), 3.08 (d, <i>J</i> =16.1 Hz, 1 H), 3.66 (dd, <i>J</i> =15.8, 6.7 Hz, 1 H), 4.10 - 4.27 (m, 0 H), 5.10 (d, <i>J</i> =5.3 Hz, 1 H), 7.00 (d, <i>J</i> =8.2 Hz, 1 H), 7.29 (d, <i>J</i> =8.8 Hz, 2 H), 7.33 - 7.45 (m, 4 H), 7.55 (dd, <i>J</i> =8.2, 2.3 Hz, 1 H), 7.59 (s, 1 H), 7.62 (s, 1 H), 8.01 (d, <i>J</i> =2.3 Hz, 1 H)	white solid
7	1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	35	¹ H NMR (CD ₃ OD) δ: 1.76 - 1.98 (m, 2 H), 2.71 - 2.77 (m, 1 H), 2.92 - 3.04 (m, 1 H), 3.09 (dd, <i>J</i> =16.0, 1.6 Hz, 1 H), 3.67 (dd, <i>J</i> =16.0, 6.6 Hz, 1 H), 4.10 - 4.26 (m, 1 H), 5.11 (d, <i>J</i> =5.3 Hz, 1 H), 7.02 (d, <i>J</i> =8.2 Hz, 1 H), 7.30 (d, <i>J</i> =8.5 Hz, 2 H), 7.55 (dd, <i>J</i> =8.2, 2.3 Hz, 1 H), 7.58 - 7.74 (m, 6 H), 8.07 (d, <i>J</i> =2.3 Hz, 1 H)	white solid
8	1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-	39	¹ H NMR (CD ₃ OD) δ: 1.75 - 1.95 (m,	white solid

	[4-(methylsulfonyl)phenyl]urea 		2 H), 2.75 (td, <i>J</i> =6.9, 2.1 Hz, 2 H), 2.98 (m, 1 H), 3.09 (s, 3 H), 3.11 - 3.14 (m, 1 H), 3.67 (dd, <i>J</i> =15.5, 6.7 Hz, 1 H), 4.10 - 4.26 (m, 1 H), 5.12 (d, <i>J</i> =5.3 Hz, 1 H), 7.02 (d, <i>J</i> =8.2 Hz, 1 H), 7.29 (d, <i>J</i> =8.2 Hz, 2 H), 7.50 - 7.66 (m, 3 H), 7.66 - 7.75 (m, 2 H), 7.81 - 7.92 (m, 2 H), 8.07 (d, <i>J</i> =2.3 Hz, 1 H)	
9	1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea 	42	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.00 (d, <i>J</i> = 1.5 Hz, 1H), 7.51 - 7.66 (m, 3H), 7.34 - 7.43 (m, 2H), 7.29 (dd, <i>J</i> = 8.4, 2.5 Hz, 4H), 6.99 (d, <i>J</i> = 8.2 Hz, 1H), 5.10 (d, <i>J</i> = 5.9 Hz, 1H), 4.07 - 4.25 (m, 1H), 3.65 (dd, <i>J</i> = 16.1, 6.4 Hz, 1H), 3.07 (d, <i>J</i> = 16.1 Hz, 1H), 2.79 - 3.01 (m, 3H), 2.70 (t, <i>J</i> = 6.4 Hz, 1H), 1.74 - 1.91 (m, 2H), 1.14 - 1.34 (m, 3H)	white solid
10	(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea 	29	¹ H NMR (CD ₃ OD) δ: 8.13 (s, 1H), 7.62 (d, <i>J</i> = 7.3 Hz, 2H), 7.48 (d, <i>J</i> = 8.5 Hz, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 2H), 7.30 (d, <i>J</i> = 7.3 Hz, 2H), 7.23 (d, <i>J</i> = 7.3 Hz, 2H), 7.01 (d, <i>J</i> = 7.9 Hz, 1H),	white solid [α] _D = -71.7° (c=1.09, CH ₂ Cl ₂)

			5.16 (d, $J = 6.7$ Hz, 1H), 4.07 - 4.22 (m, 1H), 3.70 (dd, $J = 15.7, 7.2$ Hz, 1H), 2.88 - 3.14 (m, 4H), 2.44 (s, 3H), 1.91 - 2.12 (m, 2H)	
11	(R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	30	¹ H NMR (CD ₃ OD) δ: 8.13 (d, $J = 2.1$ Hz, 1H), 7.61 (d, $J = 8.2$ Hz, 2H), 7.47 (dd, $J = 8.2, 2.1$ Hz, 1H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.20 - 7.26 (m, 2H), 7.00 (d, $J = 8.2$ Hz, 1H), 5.14 (d, $J = 5.9$ Hz, 1H), 4.07 - 4.20 (m, 1H), 3.69 (dd, $J = 16.1, 6.7$ Hz, 1H), 2.88 - 3.14 (m, 4H), 2.43 (s, 3H), 1.89 - 2.09 (m, 2H)	white solid [α] _D = +77.4° (c=1.33, CH ₂ Cl ₂)
12	(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	36	¹ H NMR (CD ₃ OD) δ: 8.13 (d, $J = 2.1$ Hz, 1H), 7.61 (d, $J = 8.2$ Hz, 2H), 7.47 (dd, $J = 8.2, 2.1$ Hz, 1H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.20 - 7.26 (m, 2H), 7.00 (d, $J = 8.2$ Hz, 1H), 5.14 (d, $J = 5.9$ Hz, 1H), 4.07 - 4.20 (m, 1H), 3.69 (dd, $J = 16.1, 6.7$ Hz, 1H), 2.88 - 3.14 (m, 4H), 2.43 (s, 3H),	white solid [α] _D = -57.9° (c=1.03, CH ₂ Cl ₂)

			1.89 - 2.09 (m, 2H)	
13	(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	37	¹ H NMR (CD ₃ OD) δ: 8.17 (d, J = 2.1 Hz, 1H), 7.60 - 7.74 (m, 6H), 7.49 (dd, J = 8.2, 2.3 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 7.9 Hz, 1H), 5.16 (d, J = 7.3 Hz, 1H), 4.07 - 4.20 (m, 1H), 3.72 (dd, J = 16.0, 7.2 Hz, 1H), 2.95 - 3.16 (m, 4H), 2.79 (s, 3H), 1.93 - 2.12 (m, 2H)	white solid [α] _D = +63.3° (c=1.16, CH ₂ Cl ₂)
14	(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	38	¹ H NMR (CD ₃ OD) δ: 8.18 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.68 - 7.76 (m, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.51 (dd, J = 8.2, 2.3 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 1H), 5.17 (d, J = 7.0 Hz, 1H), 4.07 - 4.21 (m, 2H), 3.73 (dd, J = 16.6, 5.4 Hz, 1H), 3.11 - 3.15 (m, 1H), 3.09 (s, 3H), 2.96 - 3.06 (m, 3H), 1.95 - 2.12 (m, 2H)	white solid [α] _D = -53.6° (c=0.89, CH ₂ Cl ₂)
15	(R)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	40	¹ H NMR (CD ₃ OD) δ: 8.18 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.68	white solid [α] _D =

			- 7.76 (m, 2H), 7.63 (d, J = 8.2 Hz, 2H), 7.51 (dd, J = 8.2, 2.3 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 1H), 5.17 (d, J = 7.0 Hz, 1H), 4.07 - 4.21 (m, 2H), 3.73 (dd, J = 16.6, 5.4 Hz, 1H), 3.11 - 3.15 (m, 1H), 3.09 (s, 3H), 2.96 - 3.06 (m, 3H), 1.95 - 2.12 (m, 2H)	+50.5° (c=0.61, CH ₂ Cl ₂)
16	1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea 	31	¹ H NMR (CD ₃ OD) δ: 7.90 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.17 - 7.28 (m, 3H), 4.06 (dt, J = 14.0, 7.2 Hz, 1H), 3.83 - 3.91 (m, 1H), 3.22 - 3.28 (m, 1H), 3.15 (dt, J = 13.3, 6.4 Hz, 1H), 2.69 - 2.81 (m, 3H), 1.82 - 1.94 (m, 2H), 1.15 (d, J = 6.4 Hz, 3H).	light yellow solid
17	1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea 	41	¹ H NMR (CD ₃ OD) δ: 8.03 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 9.1 Hz, 2H), 7.72 (d, J = 9.1 Hz, 2H), 7.63 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 7.9 Hz, 1H), 3.98 - 4.12 (m, 1H), 3.83 - 3.95 (m, 1H), 3.30 (s, 3H), 3.20 - 3.29 (m, 1H), 2.88 - 2.99 (m, 2H), 2.71 - 2.83 (m, 2H), 1.95	

			- 2.06 (m, 2H), 1.18 (d, J = 6.7 Hz, 6H).	
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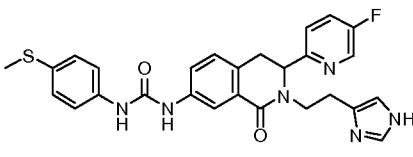
Compounds 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 and 28 were prepared from the amino intermediate derivative in the presence of anhydrous benzene and the corresponding isocyanate in a similar manner to the procedure described in

5 **Example 3 for Intermediate 23.** The reactants and reagents used and the results are described below in **Table 7**.

Table 7

Comp. No.	IUPAC name	Reactants	^1H NMR δ (ppm) for Compound	Features
18	1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea	Interm. 15 4-acetylphenyl isocyanate	^1H NMR (300 MHz, CD_3OD) δ : 2.56 (s, 3 H), 2.84 - 3.25 (m, 3 H), 3.41 - 3.56 (m, 1 H), 4.28 - 4.40 (m, 1 H), 4.86 - 4.90 (m, 1 H), 6.89 (s, 1 H), 6.99 (d, J =8.5 Hz, 1 H), 7.23 (s, 1 H), 7.26 (s, 1 H), 7.54 - 7.64 (m, 6 H), 7.92 - 7.95 (m, 1 H), 7.95 - 7.98 (m, 1 H), 8.01 (d, J =2.3 Hz, 1 H)	white solid
19	1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(trifluoromethyl)phenyl]urea	Intrem. 15 α,α,α - trifluoro-p-tolyl-isocyanate	^1H NMR (300 MHz, CD_3OD) δ : 2.83 - 3.23 (m, 4 H), 3.46 (dd, J =16.1, 7.0 Hz, 1 H), 4.34 (ddd, J =13.0, 7.5, 5.3 Hz, 1 H), 4.90 (s, 1 H), 6.89 (s, 1 H), 6.98 (d, J =8.2 Hz, 1 H), 7.22 (s, 1 H), 7.25 (s, 1 H),	yellow solid

			7.50 - 7.66 (m, 8 H), 8.02 (d, <i>J</i> =2.3 Hz, 1 H)	
20	1-(4-acetylphenyl)-3-{3-(3,4-dichlorophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea	Interm.17 4-acetylphenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.55 (s, 3 H), 2.84 - 3.22 (m, 4 H), 3.44 (dd, <i>J</i> =15.8, 7.0 Hz, 1 H), 4.26 - 4.38 (m, 1 H), 4.76 (d, <i>J</i> =5.0 Hz, 1 H), 6.91 (s, 1 H), 6.98 (d, <i>J</i> =8.2 Hz, 1 H), 7.04 (d, <i>J</i> =6.2 Hz, 2 H), 7.14 - 7.25 (m, 2 H), 7.57 (d, <i>J</i> =8.5 Hz, 2 H), 7.69 (s, 1 H), 7.93 (s, 1 H), 7.96 (s, 1 H), 8.01 (d, <i>J</i> =2.3 Hz, 1 H)	yellow solid
21	1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea	Interm. 15 4-(methylthio)-phenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.43 (s, 3 H), 2.82 - 3.21 (m, 4 H), 3.45 (dd, <i>J</i> =16.0, 6.6 Hz, 1 H), 4.27 - 4.39 (m, 1 H), 4.86 - 4.90 (m, 1 H), 6.89 (s, 1 H), 6.96 (d, <i>J</i> =8.5 Hz, 1 H), 7.20 - 7.27 (m, 4 H), 7.36 (s, 1 H), 7.39 (s, 1 H), 7.50 - 7.64 (m, 4 H), 7.97 (d, <i>J</i> =2.1 Hz, 1 H)	white solid
22	1-{3-(6-fluoropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea	Interm. 18 (methylthio)-phenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.42 (s, 3 H), 2.82 - 2.96 (m, 1 H), 2.97 - 3.10 (m, 1 H), 3.10 - 3.24 (m, 2 H),	yellow solid

			3.32 - 3.45 (m, 1 H), 4.33 - 4.48 (m, 1 H), 4.76 (d, <i>J</i> =5.3 Hz, 1 H), 6.89 (s, 1 H), 6.95 (d, <i>J</i> =7.9 Hz, 1 H), 7.08 (dd, <i>J</i> =8.6, 4.2 Hz, 1 H), 7.22 (d, <i>J</i> =8.8 Hz, 2 H), 7.31 - 7.45 (m, 3 H), 7.53 (dd, <i>J</i> =8.1, 2.2 Hz, 1 H), 7.61 (s, 1 H), 7.94 (d, <i>J</i> =1.8 Hz, 1 H), 8.32 (d, <i>J</i> =2.6 Hz, 1 H)	
23	1-[3-(2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	Interm. 19 4-(methylthiophenyl)isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.41 (s, 3 H), 2.81 - 3.12 (m, 3 H), 3.17 - 3.29 (m, 1 H), 3.33 - 3.40 (m, 1 H), 4.31 (ddd, <i>J</i> =13.3, 7.7, 5.4 Hz, 1 H), 4.71 (d, <i>J</i> =4.7 Hz, 1 H), 5.93 (d, <i>J</i> =2.9 Hz, 1 H), 6.19 (br. s., 1 H), 6.87 (s, 1 H), 7.08 (d, <i>J</i> =8.2 Hz, 1 H), 7.21 (d, <i>J</i> =8.5 Hz, 2 H), 7.31 (s, 1 H), 7.35 (s, 1 H), 7.37 (s, 1 H), 7.59 (d, <i>J</i> =2.3 Hz, 1 H), 7.63 (s, 1 H), 7.90 (d, <i>J</i> =2.1 Hz, 1 H).	yellow solid
24	1-[3-(5-chloro-2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	Interm. 32 4-(methylthiophenyl)isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.42 (s, 3 H), 2.81 - 3.10 (m, 3 H), 3.16 - 3.28 (m, 1 H), 3.32 - 3.39 (m, 1 H), 4.25 - 4.41 (m, 1 H), 4.68 (d,	yellow solid

			$J=4.4$ Hz, 1 H), 5.96 (d, $J=3.2$ Hz, 1 H), 6.04 (d, $J=3.2$ Hz, 1 H), 6.89 (s, 1 H), 7.11 (d, $J=8.2$ Hz, 1 H), 7.22 (d, $J=8.5$ Hz, 2 H), 7.29 - 7.43 (m, 3 H), 7.57 - 7.67 (m, 2 H), 7.91 (d, $J=1.8$ Hz, 1 H).	
25	1-(4-acetylphenyl)-3-(3-(6-chloropyridin-3-yl)-2-[1H-imidazol-4-yl]ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea 	Interm. 33 4-acetylphenyl isocyanate	1 H NMR (300 MHz, CD ₃ OD) δ : 2.56 (s, 3 H), 2.87 - 3.09 (m, 3 H), 3.17 - 3.28 (m, 1 H), 3.47 (dd, $J=16.0, 6.6$ Hz, 1 H), 4.25 - 4.35 (m, 1 H), 4.87 (br. s., 1 H), 6.90 (s, 1 H), 7.04 (d, $J=8.2$ Hz, 1 H), 7.29 (d, $J=8.2$ Hz, 1 H), 7.45 (dd, $J=8.4, 2.5$ Hz, 1 H), 7.56 - 7.64 (m, 4 H), 7.94 (s, 1 H), 7.97 (s, 1 H), 8.02 (d, $J=2.1$ Hz, 1 H), 8.09 (d, $J=2.3$ Hz, 1 H)	white solid
26	1-[3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea 	Interm. 33 4-(methylthiophenoxy)-phenyl isocyanate	1 H NMR (300 MHz, CD ₃ OD) δ : 2.44 (s, 3 H), 2.85 - 3.09 (m, 3 H), 3.16 - 3.28 (m, 1 H), 3.46 (dd, $J=15.5, 6.4$ Hz, 1 H), 4.24 - 4.35 (m, 1 H), 4.87 (br. s., 1 H), 6.89 (s, 1 H), 7.01 (d, $J=8.2$ Hz, 1 H), 7.21 - 7.32 (m, 3 H), 7.38 (d, $J=8.8$ Hz, 2 H), 7.44	white solid

			(dd, <i>J</i> =8.2, 2.3 Hz, 1 H), 7.58 (d, <i>J</i> =2.3 Hz, 1 H), 7.61 (s, 1 H), 7.98 (d, <i>J</i> =2.1 Hz, 1 H), 8.09 (d, <i>J</i> =2.1 Hz, 1 H)	
27	1-(4-acetylphenyl)-3-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea	Interm. 34 4-acetylphenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.40 (s, 1H), 7.89 - 8.00 (m, 3H), 7.60 - 7.68 (m, 2H), 7.50 - 7.60 (m, 3H), 7.05 (d, <i>J</i> = 7.9 Hz, 1H), 6.97 (d, <i>J</i> = 8.2 Hz, 1H), 6.89 (s, 1H), 4.76 (d, <i>J</i> = 5.9 Hz, 1H), 4.33 - 4.48 (m, 1H), 3.33 - 3.45 (m, 1H), 3.12 - 3.26 (m, 2H), 2.96 - 3.12 (m, 1H), 2.83 - 2.96 (m, 1H), 2.54 (s, 3H)	yellow solid
28	1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea	Interm. 34 4-(methylthiophenoxy)-phenyl isocyanate	¹ H NMR (300 MHz, CD ₃ OD) δ: 8.39 (s, 1H), 7.95 (s, 1H), 7.56 - 7.66 (m, 2H), 7.51 (d, <i>J</i> = 8.2 Hz, 1H), 7.29 - 7.42 (m, 2H), 7.20 (d, <i>J</i> = 7.9 Hz, 2H), 7.03 (d, <i>J</i> = 8.5 Hz, 1H), 6.94 (d, <i>J</i> = 8.2 Hz, 1H), 6.88 (s, 1H), 4.75 (d, <i>J</i> = 6.2 Hz, 1H), 4.31 - 4.48 (m, 1H), 3.33 - 3.45 (m, 1H), 3.10 - 3.27 (m, 2H), 2.97 - 3.10 (m, 1H), 2.82 - 2.95 (m, 1H), 2.41 (s, 3H)	yellow solid

Compounds **29**, **30**, **31** and **32** were synthesized by using 5.0 equivalents of *meta*-chloroperbenzoic acid in the procedure of **Example 5** for **Intermediate 35** and stirring the reaction mixture at 25°C for 0.5 h lead to the sulfonyl derivatives. The starting materials used and the results are described below in **Table 8**.

5

Table 8

Comp No.	IUPAC name	Starting material	¹ H NMR δ (ppm) for Compound	Features
29	1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea	Interm. 15	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.43 (s, 3 H), 2.82 - 3.21 (m, 4 H), 3.45 (dd, J=16.0, 6.6 Hz, 1 H), 4.27 - 4.39 (m, 1 H), 4.86 - 4.90 (m, 1 H), 6.89 (s, 1 H), 6.96 (d, J=8.5 Hz, 1 H), 7.20 - 7.27 (m, 4 H), 7.36 (s, 1 H), 7.39 (s, 1 H), 7.50 - 7.64 (m, 4 H), 7.97 (d, J=2.1 Hz, 1 H).	white solid
30	1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea	Comp. 21	¹ H NMR (CD ₃ OD) δ: 2.84 - 3.07 (m, 4 H), 3.09 (s, 3 H), 3.10 - 3.22 (m, 1 H), 3.47 (dd, J=16.0, 6.6 Hz, 1 H), 4.34 (ddd, J=13.1, 7.7, 5.6 Hz, 1 H), 6.90 (s, 1 H), 6.99 (d, J=8.2 Hz, 1 H), 7.24 (d, J=8.2 Hz, 2 H), 7.52 - 7.58 (m, 2 H), 7.61 (d, J=7.6 Hz, 2 H), 7.68 (s, 1 H), 7.71 (s,	white solid

			1 H), 7.83 (s, 1 H), 7.86 (s, 1 H), 8.04 (d, <i>J</i> =2.3 Hz, 1 H).	
31	1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea	Comp. 22	¹ H NMR (300 MHz, CD ₃ OD) δ: 2.78 (s, 3 H), 2.84 - 2.96 (m, 1 H), 2.98 - 3.11 (m, 1 H), 3.11 - 3.25 (m, 2 H), 3.33 - 3.45 (m, 1 H), 4.35 - 4.48 (m, 1 H), 4.78 (d, <i>J</i> =6.4 Hz, 1 H), 6.90 (s, 1 H), 6.98 (d, <i>J</i> =8.5 Hz, 1 H), 7.10 (dd, <i>J</i> =9.2, 3.7 Hz, 1 H), 7.42 (t, <i>J</i> =9.2 Hz, 1 H), 7.55 (d, <i>J</i> =8.5 Hz, 1 H), 7.60 - 7.73 (m, 5 H), 7.97 (s, 1 H), 8.33 (s, 1 H).	white solid
32	1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea	Comp. 22	¹ H NMR (CD ₃ OD) δ: 2.84 - 2.97 (m, 1 H), 2.97 - 3.05 (m, 1 H), 3.08 (s, 3 H), 3.11 - 3.25 (m, 2 H), 3.32 - 3.44 (m, 1 H), 4.40 (dt, <i>J</i> =13.5, 6.7 Hz, 1 H), 4.78 (d, <i>J</i> =5.9 Hz, 1 H), 6.89 (s, 1 H), 6.97 (d, <i>J</i> =7.9 Hz, 1 H), 7.09 (dd, <i>J</i> =8.4, 3.7 Hz, 1 H), 7.40 (t, <i>J</i> =8.5 Hz, 1 H), 7.53 (d, <i>J</i> =8.2 Hz, 1 H), 7.62 (s, 1 H), 7.69 (d,	white solid

			$J=1.5$ Hz, 2 H), 7.78 - 7.86 (m, 2 H), 7.99 (s, 1 H), 8.31 (s, 1 H).	
34	1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea	Comp. 28	1 H NMR (CD ₃ OD) δ : 8.41 (d, $J = 1.2$ Hz, 1H), 7.98 (s, 1H), 7.84 (d, $J = 8.8$ Hz, 2H), 7.60 - 7.74 (m, 4H), 7.55 (d, $J = 6.7$ Hz, 1H), 7.06 (d, $J = 8.5$ Hz, 1H), 6.99 (d, $J = 7.9$ Hz, 1H), 6.89 (s, 1H), 4.77 (d, $J = 5.9$ Hz, 1H), 4.34 - 4.48 (m, 1H), 3.33 - 3.45 (m, 1H), 3.13 - 3.26 (m, 2H), 3.08 (s, 3H), 2.97 - 3.06 (m, 1H), 2.83 - 2.98 (m, 1H).	light yellow solid

Example 8

Biological Data

Biological activity of compounds according to Formula 1 is set forth in **Table 9** below. CHO-Ga16 cells stably expressing FPRL1 were cultured in (F12, 10% FBS, 1% PSA, 400 μ g/ml geneticin and 50 μ g/ml hygromycin) and HEK- Gqi5 cells stable expressing FPR1 were cultured in (DMEM high glucose, 10% FBS, 1% PSA, 400 μ g/ml geneticin and 50 μ g/ml hygromycin). In general, the day before the experiment, 18,000 cells/well were plated in a 384-well clear bottom poly-d-lysine coated plate. The following day the screening compound-induced calcium activity was assayed on the FLIPR^{Tetra}. The drug plates were prepared in 384-well microplates using the EP3 and the MultiPROBE robotic liquid handling systems. Compounds were tested at concentrations ranging from 0.61 to 10,000 nM. Results are expressed as EC₅₀ (nM) and efficacy values.

Table 9

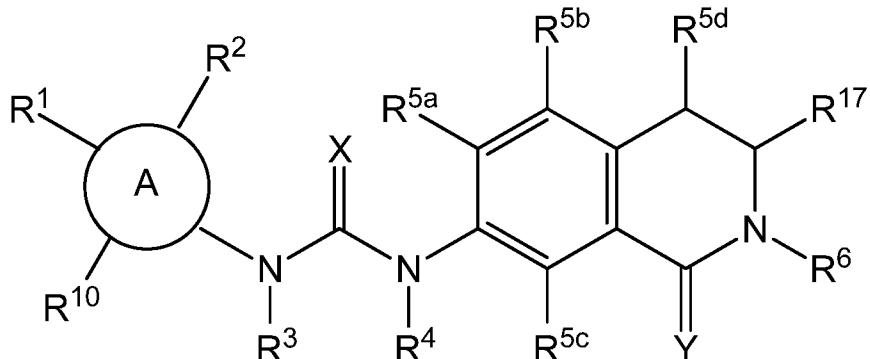
IUPAC name	FPRL-1 Ga16-CHO EC ₅₀ (eff)
1-(4-acetylphenyl)-3-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea	40 nM (1.00)
1-(4-acetylphenyl)-3-[2-(2-aminoethyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea	34 nM (0.90)
1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea	11 nM (0.80)
1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(methylamino)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea	32 nM (1.00)
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(trifluoromethyl)phenyl]urea	21 nM (0.78)
1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(trifluoromethyl)phenyl]urea	32 nM (0.78)
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	2.5 nM (0.70)
1-(4-acetylphenyl)-3-{3-(3,4-dichlorophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea	28 nM (1.04)
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-(4-bromophenyl)urea.	31 nM (1.00)
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	21 nM (0.92)
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	10 nM (0.86)
1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea	22 nM (0.96)
1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea	20 nM (1.00)
1-{3-(6-fluoropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-	12.6 nM (0.93)

(methylthio)phenyl]urea	
1-[3-(2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	19 nM (0.83)
1-[3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	11.8 nM (0.93)
1-[3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	10.5 nM (1.0)
1-[3-(5-chloro-2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	17 nM (0.81)
1-(4-acetylphenyl)-3-[3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea	24 nM (0.81)
1-[3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	6.3 nM (0.89)
1-(4-acetylphenyl)-3-[3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea	38.4 nM (81)
1-[3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	13.5 nM (0.91)
1-[3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	9.5 nM (0.99)
1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea	23 nM (1.0)
(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea.	299 nM (1.0)
(R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea.	3.3 nM (0.97)
(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	878 nM (0.85)
(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea	10.6 nM (0.94)
(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	ND (1.3)
(R)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	29 nM (0.90)
1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-	15 nM

tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea	(0.89)
1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea	150 nM (88)

What is claimed is:

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

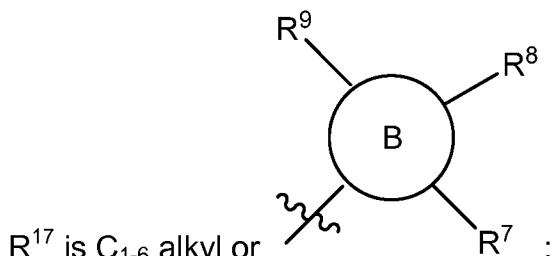


5

Formula I

wherein:

A is C₆₋₁₀ aryl, Heterocyle, C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl;



10

B is C₆₋₁₀ aryl, Heterocyle, C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl;

R¹ is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R² is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R³ is H, C₁₋₆ alkyl or C₃₋₈ cycloalkyl;

R⁴ is H, C₁₋₆ alkyl or C₃₋₈ cycloalkyl;

R^{5a} is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R^{5b} is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R^{5c} is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R^{5d} is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R^6 is H, $-S(O)_2R^{11}$, $-C_{1-6}$ alkyl, $C(O)R^{12}$, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle, $NR^{13}R^{14}$, C_{3-8} cycloalkyl, C_{6-10} aryl, or heterocycle;

5 R^7 is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R^8 is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

10 R^9 is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

R^{10} is H, halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, nitro, cyano, $-OC_{1-6}$ alkyl, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl, $-C_{2-6}$ alkenyl, $-C_{2-6}$ alkynyl, $C(O)R^{12}$, $NR^{13}R^{14}$, C_{3-8} cycloalkyl or hydroxyl;

X is O or S;

Y is O or S;

15 R^{11} is H, hydroxyl, $-C_{1-6}$ alkyl, C_{3-8} cycloalkyl or $NR^{13}R^{14}$;

R^{12} is H, hydroxyl, $-C_{1-6}$ alkyl, hydroxyl, C_{3-8} cycloalkyl, $NR^{13}R^{14}$ or $-OC_{1-6}$ alkyl;

R^{13} is H, $-C_{1-6}$ alkyl, C_{3-8} cycloalkyl, SO_2R^{11} or $C(O)R^{16}$;

R^{14} is H, $-C_{1-6}$ alkyl or C_{3-8} cycloalkyl;

R^{15} is $-C_{1-6}$ alkyl, or C_{3-8} cycloalkyl;

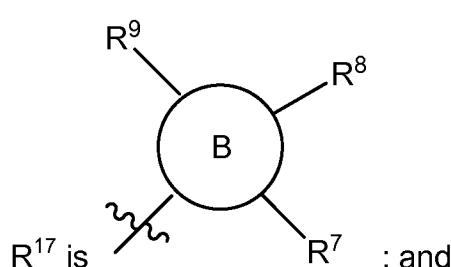
20 R^{16} is H, $-C_{1-6}$ alkyl or C_{3-8} cycloalkyl;

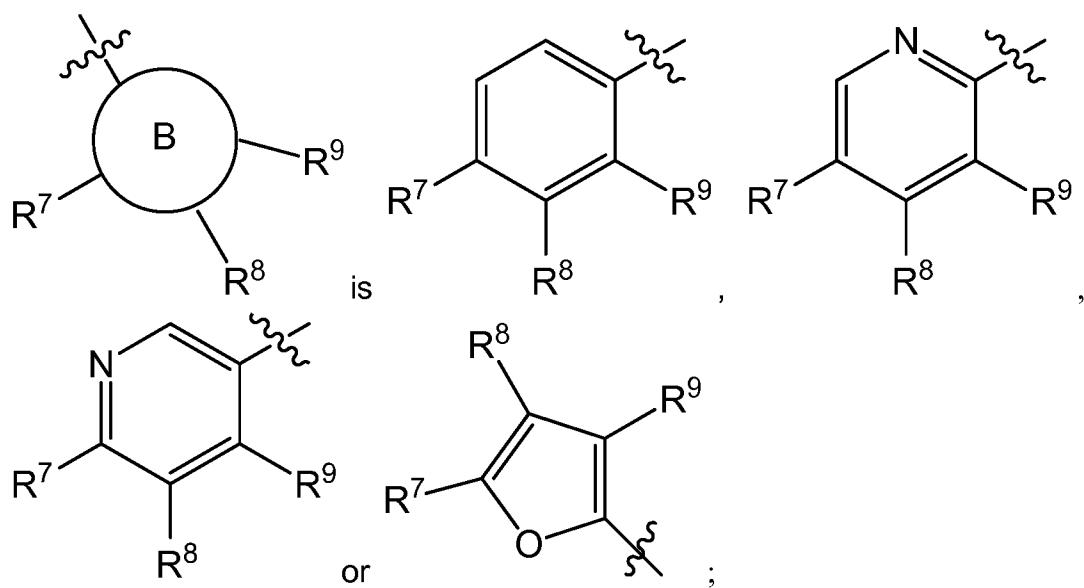
n is 1-4; and

m is 1-4.

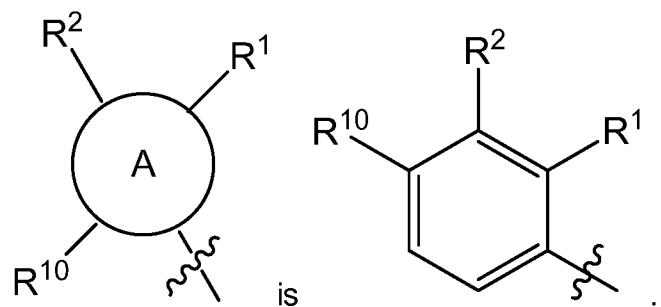
2. A compound according to claim 1, wherein:

25

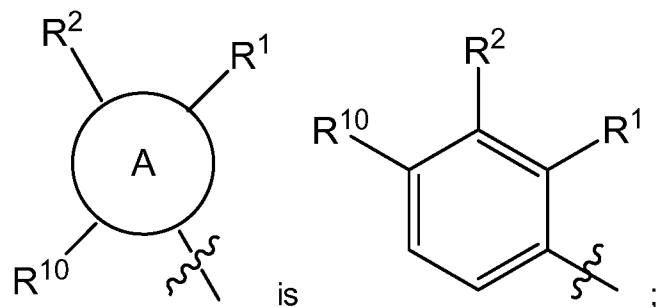




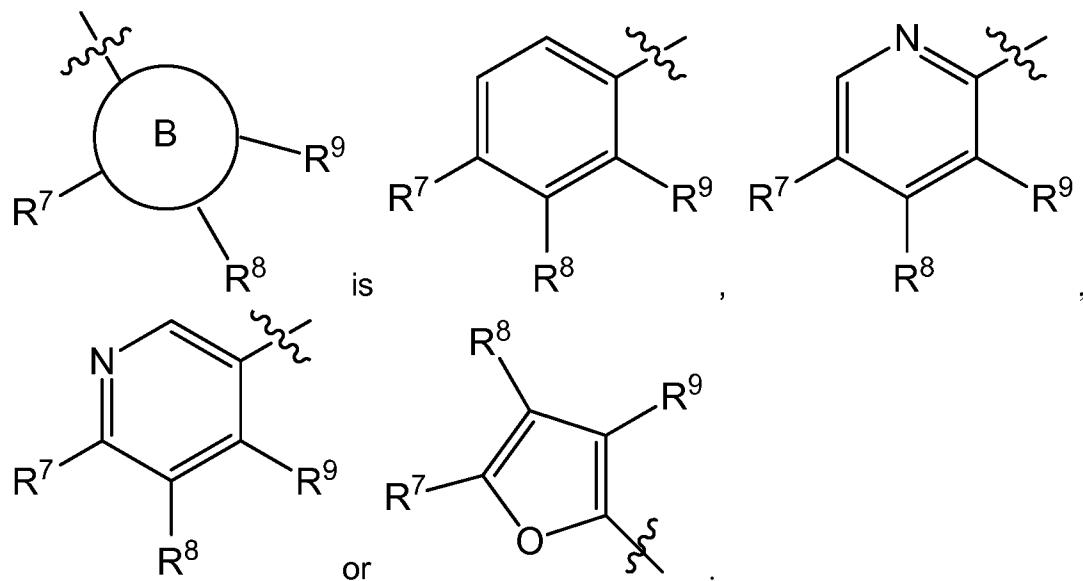
5 3. A compound according to claim 1, wherein:



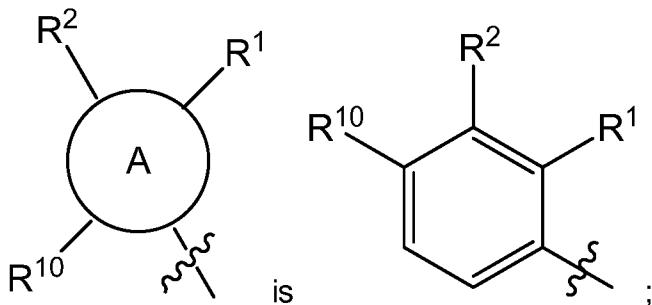
4. A compound according to claim 1, wherein:



10 R¹⁷ is ; and



5. A compound according to claim 1, wherein:



5 R^{17} is C_{1-6} alkyl;

10 R^1 is H;

R^2 is H;

R^3 is H;

R^4 is H;

R^{5a} is H;

R^{5b} is H;

R^{5c} is H;

15 R^{5d} is H;

R^6 is H, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle or $-C_{1-6}$ alkyl;

R^{10} is halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl or $C(O)R^{12}$;

X is O;

Y is O;

20 R^{11} is $-C_{1-6}$ alkyl;

R^{12} is $-C_{1-6}$ alkyl;

R^{13} is H or $-C_{1-6}$ alkyl;

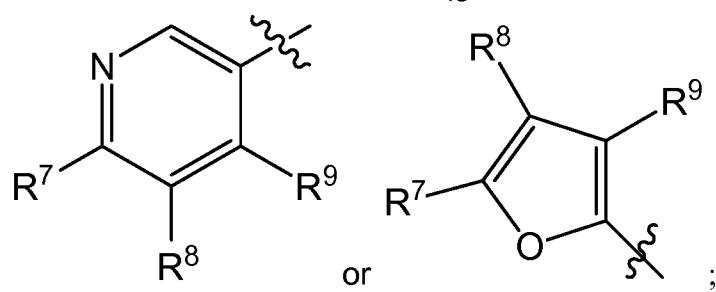
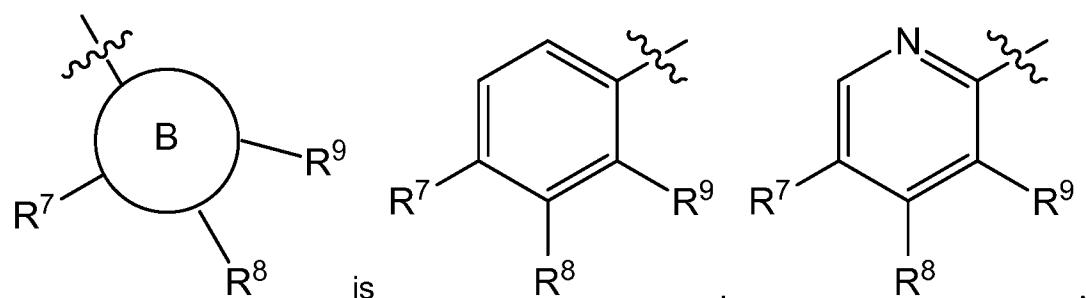
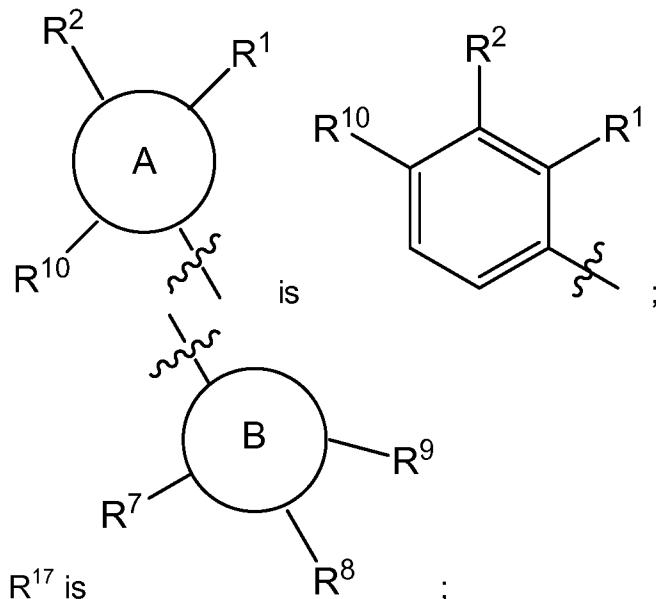
R^{14} is H or $-C_{1-6}$ alkyl;

R^{15} is $-C_{1-6}$ alkyl; and

n is 1-4; and

5 m is 1-4.

6. A compound according to claim 1, wherein:



15 R^1 is H;

R^2 is H;

R^3 is H;

R^4 is H;

R^{5a} is H;

R^{5b} is H;

R^{5c} is H;

R^{5d} is H;

5 R^6 is H, $-(CH_2)_n NR^{13}R^{14}$, $-(CH_2)_m$ heterocycle or $-C_{1-6}$ alkyl;

R^7 is H, halogen or cyano;

R^8 is H or halogen;

R^9 is H;

R^{10} is halogen, $-S(O)R^{15}$, $-S(O)_2R^{11}$, $-SC_{1-6}$ alkyl, $-C_{1-6}$ alkyl or $C(O)R^{12}$;

10 X is O;

Y is O;

R^{11} is $-C_{1-6}$ alkyl;

R^{12} is $-C_{1-6}$ alkyl;

15 R^{13} is H or $-C_{1-6}$ alkyl;

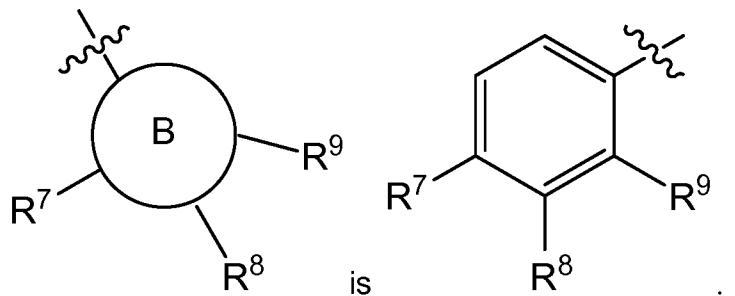
R^{14} is H or $-C_{1-6}$ alkyl;

R^{15} is $-C_{1-6}$ alkyl;

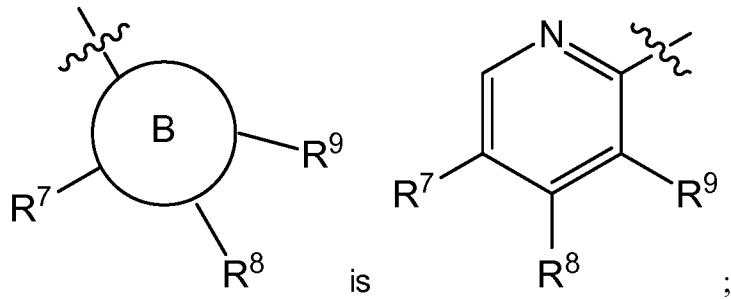
n is 1-4; and

20 m is 1-4.

7. A compound according to claim 6, wherein:



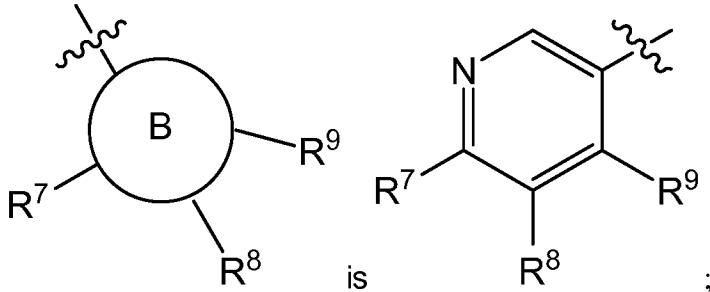
8. A compound according to claim 6, wherein:



25 R^7 is halogen;

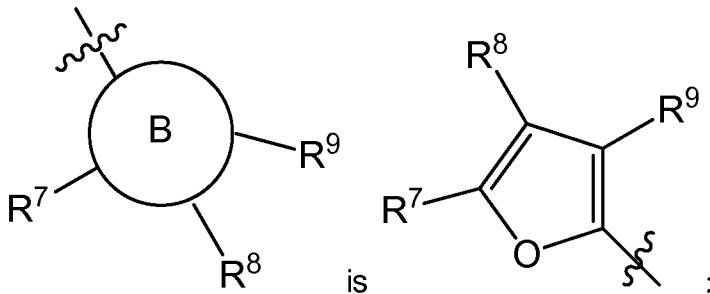
R^8 is H; and
 R^{10} is $-S(O)R^{15}$, $-S(O)_2R^{11}$, $-SC_{1-6}$ alkyl, or $C(O)R^{12}$.

9. A compound according to claim 6, wherein:



R^7 is halogen;
 R^8 is H; and
 R^{10} is $-SC_{1-6}$ alkyl or $C(O)R^{12}$.

10 10. A compound according to claim 6, wherein:



R^7 is H or halogen; and
 R^{10} is $-SC_{1-6}$ alkyl.

15 11. A compound according to claim 1 selected from:

1-(4-acetylphenyl)-3-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;
1-(4-acetylphenyl)-3-[2-(2-aminoethyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;
20 1-(4-acetylphenyl)-3-[3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;
1-(4-acetylphenyl)-3-[3-(4-cyanophenyl)-2-[2-(methylamino)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(trifluoromethyl)phenyl]urea;

1-[3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(trifluoromethyl)phenyl]urea;

5 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-(4-acetylphenyl)-3-[3-(3,4-dichlorophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;

10 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-(4-bromophenyl)urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

15 1-[3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-[3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

20 1-[3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

1-[3-(6-fluoropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

25 1-[3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

1-[3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

30 1-[3-(2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-[3-(5-chloro-2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-(4-acetylphenyl)-3-[3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;

1-[3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

1-(4-acetylphenyl)-3-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

5 1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea;

(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-

10 tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

(R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

15 (S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

(R)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-

20 tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea; and

1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea.

25

12. 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.

30 13. A pharmaceutical composition according to claim 12 wherein the compound is selected from:

1-(4-acetylphenyl)-3-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;

1-(4-acetylphenyl)-3-[2-(2-aminoethyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]urea;

5 1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-(4-acetylphenyl)-3-{3-(4-cyanophenyl)-2-[2-(methylamino)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

10 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(trifluoromethyl)phenyl]urea;

1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(trifluoromethyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

15 1-(4-acetylphenyl)-3-{3-(3,4-dichlorophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-(4-bromophenyl)urea;

20 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

25 1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea;

1-{3-(4-cyanophenyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

30 1-{3-(6-fluoropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfinyl)phenyl]urea;

1-{3-(5-fluoropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

1-{3-(2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

1-{3-(5-chloro-2-furyl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

5 1-(4-acetylphenyl)-3-{3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-{3-(6-chloropyridin-3-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

10 1-(4-acetylphenyl)-3-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl}urea;

1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylthio)phenyl]urea;

15 1-{3-(5-chloropyridin-2-yl)-2-[2-(1H-imidazol-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydro isoquinolin-7-yl}-3-[4-(methylsulfonyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(ethylthio)phenyl]urea;

(S)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

(R)-1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

20 20 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea;

(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

(S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfinyl)phenyl]urea;

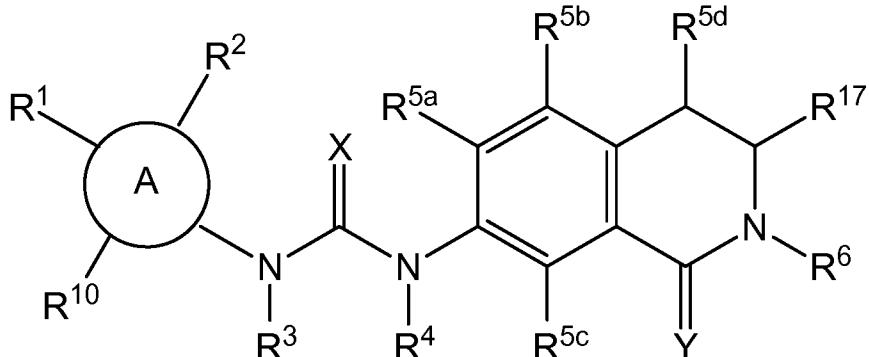
25 25 (S)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

(R)- 1-[2-(3-aminopropyl)-3-(4-cyanophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea;

1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylthio)phenyl]urea; and

30 30 1-[2-(3-aminopropyl)-3-methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl]-3-[4-(methylsulfonyl)phenyl]urea.

14. A method of treating a disorder associated with N-formyl peptide receptor like-1 (FPRL-1) 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

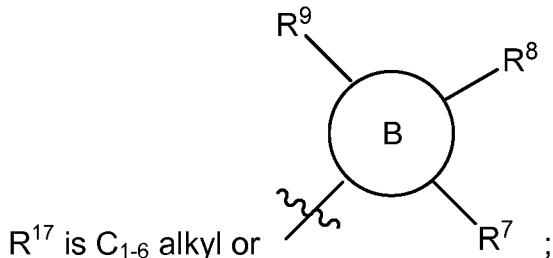


5

Formula I

wherein:

10 A is C₆₋₁₀ aryl, Heterocyle, C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl;



B is C₆₋₁₀ aryl, Heterocyle, C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl;

15 R¹ is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R² is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R³ is H, C₁₋₆ alkyl or C₃₋₈ cycloalkyl;

R⁴ is H, C₁₋₆ alkyl or C₃₋₈ cycloalkyl;

R^{5a} is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl,

20 -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R^{5b} is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R^{5c} is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R^{5d} is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R⁶ is H, -S(O)₂R¹¹, -C₁₋₆ alkyl, -(CH₂)_n NR¹³R¹⁴, -(CH₂)_m heterocycle, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl or heterocycle;

5 R⁷ is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R⁸ is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

10 R⁹ is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

R¹⁰ is H, halogen, -S(O)R¹⁵, -S(O)₂R¹¹, nitro, cyano, -OC₁₋₆ alkyl, -SC₁₋₆ alkyl, -C₁₋₆ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkynyl, C(O)R¹², NR¹³R¹⁴, C₃₋₈ cycloalkyl or hydroxyl;

X is O or S;

Y is O or S;

15 R¹¹ is H, hydroxyl, -C₁₋₆ alkyl, C₃₋₈ cycloalkyl or NR¹³R¹⁴,

R¹² is H, hydroxyl, -C₁₋₆ alkyl, hydroxyl, C₃₋₈ cycloalkyl, NR¹³R¹⁴ or -OC₁₋₆ alkyl;

R¹³ is H, -C₁₋₆ alkyl, C₃₋₈ cycloalkyl, SO₂R¹¹ or C(O)R¹⁶;

R¹⁴ is H, -C₁₋₆ alkyl or C₃₋₈ cycloalkyl;

R¹⁵ is -C₁₋₆ alkyl, or C₃₋₈ cycloalkyl ;

20 R¹⁶ is H, -C₁₋₆ alkyl, C₃₋₈ cycloalkyl;

n is 1-4; and

m is 1-4.

15. A method of claim 14, wherein the pharmaceutical composition is
25 administered to the mammal to treat ocular inflammatory diseases.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/024659

A. CLASSIFICATION OF SUBJECT MATTER				
INV.	C07D217/24	C07D401/06	C07D401/14	C07D405/14
	A61P27/02			A61K31/4725

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/016460 A1 (SNOW ROGER JOHN [US] ET AL) 7 February 2002 (2002-02-07)	1
A	Claims 32-33, intermediates of the formulae III and V; page 24, right column, penultimate formula; page 27, left column, first formula. -----	2-15
A	WO 2005/047899 A2 (ACADIA PHARM INC [US]; NASH NORMAN [US]; SCULLY AUDRA L [US]; GARDELL) 26 May 2005 (2005-05-26) Page 17, paragraph 0041, last sentence; claim 60 and page 23, paragraph 0058 to page 29, paragraph 0065: compounds of formula III; claims 10, 13. ----- -/-	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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15 March 2012

02/04/2012

Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer
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Weisbrod, Thomas

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/024659

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BURLI ET AL.: "Potent hFPRL1 (ALXR) agonists as potential anti-inflammatory agents", BIOORG. MED. CHEM. LETT., vol. 16, no. 14, 15 July 2006 (2006-07-15), pages 3713-3718, XP025106261, DOI: 10.1016/J.BMCL.2006.04.068 [retrieved on 2006-07-15]</p> <p>The whole document; e.g. schemes 1-2: compounds 24-58.</p> <p>-----</p>	1-15
A	<p>WO 2009/051670 A2 (RESOLVYX PHARMACEUTICALS INC [US]; GJORSTRUP PER [US]) 23 April 2009 (2009-04-23)</p> <p>Claims; page 6, line 21 to page 7, line 24; page 8, lines 9-12; page 49, line 1 to page 50, line 4: structure of lipoxin compounds.</p> <p>-----</p>	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2012/024659

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
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			BR PI0416272 A	09-01-2007	
			CA 2544983 A1	26-05-2005	
			EP 1692502 A2	23-08-2006	
			JP 2007516434 A	21-06-2007	
			KR 20060130064 A	18-12-2006	
			WO 2005047899 A2	26-05-2005	

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			EP 2214660 A2	11-08-2010	
			JP 2011500568 A	06-01-2011	
			KR 20100080798 A	12-07-2010	
			US 2009118243 A1	07-05-2009	
			WO 2009051670 A2	23-04-2009	
