Title: DIPHENYL UREA DERIVATIVES AS FORMYL PEPTIDE RECEPTOR MODULATORS

Abstract: The present invention relates to diphenyl urea derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of the N-formyl peptide receptor 2.
DIPHENYL UREA DERIVATIVES AS FORMYL PEPTIDE RECEPTOR MODULATORS

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RELATED APPLICATIONS

This application claims the benefit of United States Provisional Patent Application Serial No. 61/879,786 filed September 19, 2013, the disclosure of which is hereby incorporated in its entirety by reference.

FIELD OF THE INVENTION

The present invention relates to diphenyl urea derivatives, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals as modulators of the N-formyl peptide receptor 2 (FPR2). The invention relates specifically to the use of these compounds and their pharmaceutical compositions to treat disorders associated with the FPR2 modulation.

BACKGROUND OF THE INVENTION

The FPR2 is a G protein-coupled receptor that is expressed on inflammatory cells such as monocytes and neutrophils, as well as T cells and has been shown to play a critical role in leukocyte trafficking during inflammation and human pathology. FPR2 is an exceptionally promiscuous receptor that responds to a large array of exogenous and endogenous ligands, including Serum amyloid A (SAA), chemokine variant sCK38-1, the neuroprotective peptide human, anti-inflammatory eicosanoid lipoxin A4 (LXA4) and glucocorticoid-modulated protein annexin A1. FPR2 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).

Activation of FPR2 by LXA4 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 neutrophil (PMN) and eosinophil migration and also stimulate monocyte migration enabling clearance of apoptotic cells from the site of inflammation in a nonphlogistic manner. In addition, FPR2 has been shown to inhibit natural killer (NK) cell cytotoxicity and promote...
activation of T cells which further contributes to down regulation of tissue damaging inflammatory signals. FPR2/ 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. FPR2 thus represents an important novel pro-resolutionary molecular target for the development of new therapeutic agents in diseases with excessive inflammatory responses.

Journal of Combinatorial Chemistry (2007), 9(3), 370-385 teaches a thymidinyl dipeptide urea library with structural similarity to the nucleoside peptide class of antibiotics:

![Chemical Structure]

Helvetica Chimica Acta (1998), 81(7), 1254-1263 teaches the synthesis and spectroscopic characterization of 4-chlorophenyl isocyanate (1-chloro-4-isocyanatobenzene) adducts with amino acids as potential dosimeters for the biomonitoring of isocyanate exposure:

![Chemical Structure]

Yingyong Huaxue (1990), 7(1), 1-9 teaches the structure-activity relations of di- and tripeptide sweeteners and of L-phenyl analine derivatives:
FR 2533210 discloses L-phenyl analine derivatives as synthetic sweeteners:

WO2005047899 discloses compounds which selectively activate the receptor represented by the following scaffolds:
US 2013/0109866 discloses compounds of general structure

![Chemical Structure](image)

as FPR2 modulators.

Compound

is taught in WO2001025190 for the treatment of diseases caused by abnormal propagation of vascular smooth muscle cells.

**SUMMARY OF THE INVENTION**

A group of diphenyl urea derivatives, which are potent and selective FPR2 modulators, has been discovered. As such, the compounds described herein are useful in treating a wide variety of disorders associated with modulation of FPR2 receptor. The term "modulator" as used herein, includes but is not limited to: receptor agonist, antagonist, inverse agonist, inverse antagonist, partial agonist, and partial antagonist.

This invention describes compounds of **Formula I**, which have FPR2 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 FPR2 modulation.

In one aspect, the invention provides a compound represented by **Formula I** or the individual geometrical isomers, individual enantiomers, individual diastereoisomers, individual tautomers, individual zwitterions or a pharmaceutically acceptable salt thereof:
wherein:

$R^1$ is $OR^{11}$ or $NR^{12}R^{13}$;

$R^2$ is halogen, $NR^{14}R^{15}$, $-CF_3$, $-NO_2$, $-OR^{20}$, $-S(0)_mR^{16}$ or $-C(0)R^{17}$;

$R^3$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl, halogen, $NR^{14}R^{15}$, $-CF_3$, $-S(0)_mR^{18}$-$C(0)R^{19}$ or $-OR^{20}$;

$R^4$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl, halogen, $NR^{14}R^{15}$, $-CF_3$, $-S(0)_mR^{18}$-$C(0)R^{19}$ or $-OR^{20}$;

$R^5$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl, halogen, $NR^{14}R^{15}$, $-CF_3$, $-S(0)_mR^{18}$-$C(0)R^{19}$ or $-OR^{20}$;

$R^6$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl, halogen, $NR^{14}R^{15}$, $-CF_3$, $-S(0)_mR^{18}$-$C(0)R^{19}$ or $-OR^{20}$;

$R^7$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl, halogen, $NR^{14}R^{15}$, $-CF_3$, $-S(0)_mR^{18}$-$C(0)R^{19}$ or $-OR^{20}$;

$R^8$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl, halogen, $NR^{14}R^{15}$, $-CF_3$, $-S(0)_mR^{18}$-$C(0)R^{19}$ or $-OR^{20}$;

$R^9$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl, halogen, $NR^{14}R^{15}$, $-CF_3$, $-S(0)_mR^{18}$-$C(0)R^{19}$ or $-OR^{20}$;

$R^10$ is $OR^{11}$ or $NR^{12}R^{13}$;
R\(^{10}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl, optionally substituted C\(_{3-8}\) cycloalkenyl, halogen, NR\(^{14}\)R\(^{15}\), -CF\(_3\), -S(0)\(_m\)R\(^{19}\) - C(0)R\(^{19}\) or -OR\(^{20}\);
R\(^{11}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl, optionally substituted C\(_{3-8}\) cycloalkenyl;
R\(^{12}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl, optionally substituted C\(_{3-8}\) cycloalkenyl or R\(^{12}\) together with R\(^{13}\) may form a heterocyclic ring;
R\(^{13}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl, optionally substituted C\(_{3-8}\) cycloalkenyl or R\(^{13}\) together with R\(^{12}\) may form a heterocyclic ring;
R\(^{14}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl or optionally substituted C\(_{3-8}\) cycloalkenyl;
R\(^{15}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl or optionally substituted C\(_{3-8}\) cycloalkenyl;
R\(^{16}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl or optionally substituted C\(_{3-8}\) cycloalkenyl;
R\(^{17}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl or optionally substituted C\(_{3-8}\) cycloalkenyl or OR\(^{20}\);
R\(^{18}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl or optionally substituted C\(_{3-8}\) cycloalkenyl;
R\(^{19}\) is H, hydroxyl, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl, optionally substituted C\(_{3-8}\) cycloalkenyl or -OR \(^{20}\);
R\(^{20}\) is H, optionally substituted C\(_{1-8}\) alkyl, optionally substituted C\(_{3-8}\) cycloalkyl, optionally substituted heterocycle, optionally substituted C\(_{6-10}\) aryl or optionally substituted C\(_{3-8}\) cycloalkenyl;

n is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and
m is 0, 1 or 2; and except compound:

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

- $R^1$ is OR$^{11}$;
- $R^2$ is halogen, NR$^{14}$R$^{15}$, -CF$_3$, -NO$_2$, -OR$^{20}$, -S(0)$_m$R$^{18}$ or -C(0)R$^{17}$;
- $R^3$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$^{14}$R$^{15}$, -CF$_3$, -S(0)$_m$R$^{18}$-C(0)R$^{19}$ or -OR$^{20}$;
- $R^4$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$^{14}$R$^{15}$, -CF$_3$, -S(0)$_m$R$^{18}$-C(0)R$^{19}$ or -OR$^{20}$;
- $R^5$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$^{14}$R$^{15}$, -CF$_3$, -S(0)$_m$R$^{18}$-C(0)R$^{19}$ or -OR$^{20}$;
- $R^6$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$^{14}$R$^{15}$, -CF$_3$, -S(0)$_m$R$^{18}$-C(0)R$^{19}$ or -OR$^{20}$;
- $R^7$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$^{14}$R$^{15}$, -CF$_3$, -S(0)$_m$R$^{18}$-C(0)R$^{19}$ or -OR$^{20}$;
- $R^8$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$^{14}$R$^{15}$, -CF$_3$, -S(0)$_m$R$^{18}$-C(0)R$^{19}$ or -OR$^{20}$.
R⁹ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₙR¹⁷⁻C(0)R¹⁹⁻OR¹⁰⁻OR²⁰⁻;
R¹⁰ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₙR¹⁷⁻C(0)R¹⁹⁻OR¹⁰⁻OR²⁰⁻;
R¹¹ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl;
R¹² is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;
R¹³ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;
R¹⁶ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;
R¹⁷ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl or OR²⁰⁻;
R¹⁸ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;
R¹⁹ is H, hydroxyl, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl or -OR²⁰⁻;
R²⁰ is H, optionally substituted C₁₋₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl or optionally substituted C₃₋₈ cycloalkenyl;
n is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and
m is 0, 1 or 2.

In another aspect, the invention provides a compound having Formula I, wherein:
R³ is OR¹¹;
R² is halogen;
R³ is H, optionally substituted C₁-s alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R⁴ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R⁵ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R⁶ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R⁷ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R⁸ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R⁹ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R¹⁰ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₅-10 ary1, optionally substituted C₃-8 cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)mR¹⁸-C(0)R¹⁹ or -OR²⁰;
R¹¹ is H, optionally substituted C₁₈ alkyl, optionally substituted C₃-8 cycloalkyl, optionally substituted heterocycle, optionally substituted C₆-io ary1, optionally substituted C₃-8 cycloalkenyl;
R¹⁵ is H, optionally substituted C₁⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻io aryl or optionally substituted C₃⁻₈ cycloalkenyl;
R¹⁶ is H, optionally substituted C₁⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻io aryl or optionally substituted C₃⁻₈ cycloalkenyl;
R¹⁷ is H, hydroxyl, optionally substituted C₁⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻io aryl, optionally substituted C₃⁻₈ cycloalkenyl or -OR²⁰;
R²⁰ is H, optionally substituted C₁⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻io aryl or optionally substituted C₃⁻₈ cycloalkenyl;
n is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and
m is 0, 1 or 2.

In another aspect, the invention provides a compound having Formula I, wherein:
R¹ is OR¹¹;
R² is halogen;
R³ is H, optionally substituted C₁⁻₈ alkyl;
R⁴ is H, optionally substituted C₁⁻₈ alkyl;
R⁵ is H, optionally substituted C₁⁻₈ alkyl;
R⁶ is H, optionally substituted C₁⁻₈ alkyl;
R⁷ is H, optionally substituted C₁⁻₈ alkyl;
R⁸ is H, optionally substituted C₁⁻₈ alkyl;
R⁹ is H, optionally substituted C₁⁻₈ alkyl;
R¹⁰ is H, optionally substituted C₁⁻₈ alkyl;
R¹¹ is H, optionally substituted C₁⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻io aryl, optionally substituted C₃⁻₈ cycloalkenyl; and
n is 0, 1 or 2.

In another aspect, the invention provides a compound having Formula I, wherein:
R¹ is OR¹¹;
R² is halogen;
R³ is H, optionally substituted C₁₀ alkyl;
R⁴ is H, optionally substituted C₈ alkyl;
R⁵ is H, optionally substituted C₈ alkyl;
R⁶ is H, optionally substituted C₈ alkyl;
R⁷ is H, optionally substituted C₈ alkyl;
R⁸ is H, optionally substituted C₈ alkyl;
R⁹ is H, optionally substituted C₈ alkyl;
R¹₀ is H, optionally substituted C₈ alkyl;
R¹¹ is H; and
n is 0, 1 or 2.

In another aspect, the invention provides a compound having Formula I, wherein:
R¹ is NR¹²R¹³;
R² is halogen, NR¹⁴R¹⁵, -CF₃, -NO₂, -OR²⁰, -S(0)ₚR¹₈ - C(0)R¹₉ or -OR²₀;
R³ is H, optionally substituted C₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₚR¹₈ - C(0)R¹₉ or -OR²₀;
R⁴ is H, optionally substituted C₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₚR¹₈ - C(0)R¹₉ or -OR²₀;
R⁵ is H, optionally substituted C₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₚR¹₈ - C(0)R¹₉ or -OR²₀;
R⁶ is H, optionally substituted C₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₚR¹₈ - C(0)R¹₉ or -OR²₀;
R⁷ is H, optionally substituted C₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₚR¹₈ - C(0)R¹₉ or -OR²₀;
R⁸ is H, optionally substituted C₈ alkyl, optionally substituted C₃₋₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆₋₁₀ aryl, optionally substituted C₃₋₈ cycloalkenyl, halogen, NR¹⁴R¹⁵, -CF₃, -S(0)ₚR¹₈ - C(0)R¹₉ or -OR²₀;
$R^9$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$_{14}^1$R$_{15}^1$, -CF$_3$, -S(0)$_m$R$_{19}^1$-C(0)R$_{19}^1$ or -OR$_{20}^1$;

$R^{10}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$_{14}^2$R$_{15}^2$, -CF$_3$, -S(0)$_m$R$_{19}^2$-C(0)R$_{19}^2$ or -OR$_{20}^2$;

$R^{12}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1, optionally substituted C$_{3-8}$ cycloalkenyl or $R^{12}$ together with $R^{13}$ may form a heterocyclic ring;

$R^{13}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1, optionally substituted C$_{3-8}$ cycloalkenyl or $R^{13}$ together with $R^{12}$ may form a heterocyclic ring;

$R^{14}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1 or optionally substituted C$_{3-8}$ cycloalkenyl;

$R^{15}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1 or optionally substituted C$_{3-8}$ cycloalkenyl;

$R^{16}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1 or optionally substituted C$_{3-8}$ cycloalkenyl;

$R^{17}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1, optionally substituted C$_{3-8}$ cycloalkenyl or OR$_{20}^1$;

$R^{18}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1 or optionally substituted C$_{3-8}$ cycloalkenyl;

$R^{19}$ is H, hydroxyl, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1, optionally substituted C$_{3-8}$ cycloalkeny1 or -OR$_{20}^1$;

$R^{20}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ ary1 or optionally substituted C$_{3-8}$ cycloalkeny1;

$n$ is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and
m is 0, 1 or 2; and except compound:

![Chemical Structure](image)

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

- $R^1$ is $NR^{12}R^{13}$;
- $R^2$ is halogen;
- $R^3$ is H;
- $R^4$ is H;
- $R^5$ is H;
- $R^6$ is H;
- $R^7$ is H;
- $R^8$ is H;
- $R^9$ is H;
- $R^{10}$ is H;
- $R^{12}$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkeny1 or $R^{12}$ together with $R^{13}$ may form a heterocyclic ring;
- $R^{13}$ is H, optionally substituted $C_{1-8}$ alkyl, optionally substituted $C_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted $C_{6-10}$ aryl, optionally substituted $C_{3-8}$ cycloalkenyl or $R^{13}$ together with $R^{12}$ may form a heterocyclic ring;

$n$ is 0, 1 or 2.

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

- $R^1$ is $NR^{12}R^{13}$;
- $R^2$ is halogen;
R^3 is H;
R^4 is H;
R^5 is H;
R^6 is H;
R^7 is H;
R^8 is H;
R^9 is H;
R^{10} is H;
R^{12} is optionally substituted C_{1-8} alkyl, optionally substituted C_{1-8} cycloalkyl, optionally substituted heterocycle, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkenyl;
R^{13} is H, optionally substituted C_{1-8} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted heterocycle, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkenyl;
n is 0, 1 or 2.

In another aspect, the invention provides a compound having Formula I, wherein:
R^1 is NR^{12}R^{13};
R^2 is halogen;
R^3 is H;
R^4 is H;
R^5 is H;
R^6 is H;
R^7 is H;
R^8 is H;
R^9 is H;
R^{10} is H;
R^{12} is optionally substituted C_{1-8} alkyl;
R^{13} is H; and
n is 0, 1 or 2.
$R^1$ is $NR^2 R^3$;
$R^2$ is halogen;
$R^3$ is $H$;
$R^4$ is $H$;
$R^5$ is $H$;
$R^6$ is $H$;
$R^7$ is $H$;
$R^8$ is $H$;
$R^9$ is $H$;
$R^{10}$ is $H$;
$R^{12}$ is optionally substituted $C_{1-8}$ alkyl by halogen atoms, hydroxyl groups, cycloalkyl groups, amino groups, heterocyclic groups, aryl groups, carboxylic acid groups, phosphonic acid groups, sulphonic acid groups, phosphoric acid groups, nitro groups, amide groups, sulfonamide groups, ester groups or ketone groups;
$R^{13}$ is $H$; and
$n$ is 0, 1 or 2.

The term "alkyl", as used herein, refers to saturated, monovalent or divalent hydrocarbon moieties having linear or branched moieties or combinations thereof and containing 1 to 8 carbon atoms. One methylene (-CH$_2$-) group, of the alkyl group can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, sulfate, sulfonate, amide, sulfonamide, by a divalent C$_{3-8}$ cycloalkyl, by a divalent heterocycle, or by a divalent aryl group. Alkyl groups can have one or more chiral centers. Alkyl groups can be independently substituted by halogen atoms, hydroxyl groups, cycloalkyl groups, amino groups, heterocyclic groups, aryl groups, carboxylic acid groups, phosphonic acid groups, sulphonic acid groups, phosphoric acid groups, nitro groups, amide groups, sulfonamide groups, ester groups, ketone 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 by halogen atoms, sulfonyl C$_{1-8}$ alkyl groups, sulfoxide C$_{1-8}$ alkyl groups, sulfonamide groups, nitro groups, cyano groups, -OC$_{1-8}$ alkyl groups, -SC$_{1-8}$ alkyl groups, -Ci$_{1-8}$ alkyl groups, -C$_{2-6}$
alkenyl groups, -C_2-6 alkynyl groups, ketone groups, alkylamino groups, amino groups, aryl groups, C_2-8 cycloalkyl groups or hydroxyl groups.

The term "cycloalkenyl", as used herein, refers to a monovalent or divalent group of 3 to 8 carbon atoms derived from a saturated cycloalkyi having at least one double bond. Cycloalkenyl groups can be monocyclic or polycyclic. Cycloalkenyl groups can be independently substituted by halogen atoms, sulfonyl groups, sulfoxide groups, nitro groups, cyano groups, -OC_1-6 alkyl groups, -SC_1-6 alkyl groups, -Ci_6 alkyl groups, -C_2-6 alkenyl groups, -C_2-6 alkynyl groups, ketone groups, alkylamino groups, amino groups, aryl groups, C_3-8 cycloalkyi 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 radical having 2 to 6 carbon atoms, derived from a saturated alkyl, having at least one double bond. One methylene (-CH_2-) group, of the alkenyl can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, sulfate, sulfonate, amide, sulfonamide, by a divalent C_3-8 cycloalkyi, by a divalent heterocycle, or by a divalent aryl group. C_2-6 alkenyl can be in the E or Z configuration. Alkenyl groups can be substituted by alkyl groups, as defined above or by halogen atoms.

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. One methylene (-CH_2-) group, of the alkynyl can be replaced by oxygen, sulfur, sulfoxide, nitrogen, carbonyl, carboxyl, sulfonyl, sulfate, sulfonate, amide, sulfonamide, by a divalent C_3-8 cycloalkyi, by a divalent heterocycle, or by a divalent aryl group. Alkynyl groups can be substituted by alkyl groups, as defined above, or by halogen atoms.

The term "heterocycle" 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 form oxygen, nitrogen, sulfur, or combinations of at least two thereof, interrupting the carbocyclic ring structure. The heterocyclic ring can be interrupted by a C=O; the S and N heteroatoms can be oxidized. Heterocycles can be monocyclic or polycyclic. Heterocyclic ring moieties can be substituted by halogen atoms, sulfonyl groups, sulfoxide groups, nitro groups, cyano groups, -OC_1-6 alkyl groups, -SC_1-6 alkyl groups, -Ci_6 alkyl groups, -C_2-6 alkenyl groups, -C_2-6 alkynyl groups

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, ketone groups, alkylamino groups, amino groups, aryl groups, C₃-8 cycloalkyi groups or hydroxyl groups.

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 atom. Aryl can be substituted by halogen atoms, sulfanyl C₁-6 alkyl groups, sulfoxide C₁-6 alkyl groups, sulfonamide groups, carboxyclic acid groups, C₁-6 alkyl carboxylates (ester) groups, amide groups, nitro groups, cyano groups, -OCI₆alkyl groups, -SCI₆alkyl groups, -CIC₆alkyl groups, -C₂-6 alkenyl groups, -C₂-6 alkynyl groups, ketone groups, aldehydes, alkylamino groups, amino groups, aryl groups, C₃-8 cycloalkyi groups or hydroxyl groups. Aryls can be monocyclic or polycyclic.

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)-".

The term "ketone" as used herein, represents an organic compound having a carbonyl group linked to a carbon atom such as -C(0)R x wherein R x can be alkyl, aryl, cycloalkyi, cycloalkenyl, heterocycle as defined above.

The term "ester" as used herein, represents an organic compound having a carbonyl group linked to a carbon atom such as -C(0)OR x wherein R x can be alkyl, aryl, cycloalkyi, cycloalkenyl, heterocycle as defined above.

The term "amide" 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, cycloalkyi, cycloalkenyl, heterocycle as defined above.

The term "carboxyl" as used herein, represents a group of formula "-C(0)0-".

The term "sulfonyl" as used herein, represents a group of formula "-SO₂-".

The term "sulfate" as used herein, represents a group of formula "-0-S(0)₂-O-".

The term "sulfonate" as used herein, represents a group of the formula "-S(0)₂-0-".

The term "carboxylic acid" as used herein, represents a group of formula "-C(0)OH".

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(0)NR xR y" wherein R x and R y can be the same or independently H, alkyl, aryl, cycloalkyi, cycloalkenyl, heterocycle as defined above.
The term "sulfonamide" as used herein, represents a group of formula \(-S(0)_{2}NR'_{x}R''_{y}\) wherein \(R'\) and \(R''\) 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(0)(OH)_{2}\".

The term "phosphoric acid" as used herein, represents a group of formula "-OP(0)(OH)_{2}\".

The term "sulphonic acid" as used herein, represents a group of formula "-S(0)_{2}OH\".

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

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

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

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

Compounds of the invention are:

- 3-\{3-(2-(((4-Bromophenyl)carbamoyl)amino)phenyl)propanoyl]amino\} propanoic acid;
- Methyl3-\{3-(2-(((4-Bromophenyl)carbamoyl)amino)phenyl)propanoyl]amino\} propanoate;
- 4-\{3-(2-(((4-Bromophenyl)carbamoyl)amino)phenyl)propanoyl]amino\} butanoic acid;
- Methyl4-\{3-(2-(((4-Bromophenyl)carbamoyl)amino)phenyl)propanoyl]amino\} butanoate;
- 3-(2-(((4-Bromophenyl)carbamoyl)amino)phenyl)propanoic acid;
- \{3-(2-(((4-Bromophenyl)carbamoyl)amino)phenyl)propanoyl]amino\} acetic acid;
- Methyl \{3-(2-(((4-Bromophenyl)carbamoyl)amino)phenyl)propanoyl]amino\} acetate.

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.
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.

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, ascorbic acid, benzoic acid, tannic acid, pamoic acid, citric acid, methysulfonic acid, ethanesulfonic acid, benzenesulfonic acid, formic and the like (Handbook of Pharmaceutical Salts, P. Heinrich Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zurich, 2002, 329-345).

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 Stahl & Camille G. Wermuth (Eds), Verlag Helvetica Chimica Acta- Zurich, 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 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 2.

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

In a further embodiment of the invention, there are provided methods for treating disorders associated with modulation of the N-formyl peptide receptor 2.

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 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 retinopathy (proliferative), retinopathy of prematurity (ROP), acute macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; infectious keratitis, herpetic keratitis, corneal angiogenesis, lymphangiogenesis, retinitis, and choroiditis such as acute 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; 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 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 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 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 pigmentosa, systemic disorders with associitated 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, 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 (Perretti, Mauro et al. Pharmacology & Therapeutics 127 (2010) 175-188.)

The compounds of the invention are useful for the treatment of mammals, including humans, with a range of conditions and diseases that are alleviated by the N-formyl peptide receptor 2 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 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 FPR2 receptor. Such methods can be performed, for example, by administering to a subject in need thereof a therapeutically effective amount of at least one compound of the invention, or any combination thereof, or pharmaceutically acceptable salts, individual enantiomers, and diastereomers thereof.

The present invention concerns the use of a compound of Formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of ocular 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 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; 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, 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 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 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 pigmentosa, systemic disorders with associated 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, 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, back to the eye, intramuscular, intravenous, and intrarectal modes of delivery. Additionally, the formulations may be designed to delay release of the active compound over a given period of time, or to carefully control the amount of drug released at a given time during the course of therapy.

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

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

Pharmaceutical compositions containing invention compounds may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing invention compounds in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

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

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

Pharmaceutical compositions containing invention compounds may be in a form suitable for topical use, for example, as oily suspensions, as solutions or suspensions in aqueous liquids or nonaqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable salt thereof, as an active ingredient with conventional ophthalmically acceptable pharmaceutical excipients and by preparation of unit dosage suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 2.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional pharmaceutically acceptable preservatives, stabilizers and surfactants. Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose cyclodextrin and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers,
citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar manner an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place of or in conjunction with it.

The ingredients are usually used in the following amounts:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>active ingredient</td>
<td>about 0.001-5</td>
</tr>
<tr>
<td>preservative</td>
<td>0-0.10</td>
</tr>
<tr>
<td>vehicle</td>
<td>0-40</td>
</tr>
<tr>
<td>tonicity adjustor</td>
<td>0-10</td>
</tr>
<tr>
<td>buffer</td>
<td>0.01-10</td>
</tr>
<tr>
<td>pH adjustor</td>
<td>q.s. pH 4.5-7.8</td>
</tr>
<tr>
<td>antioxidant</td>
<td>as needed</td>
</tr>
<tr>
<td>surfactant</td>
<td>as needed</td>
</tr>
<tr>
<td>purified water</td>
<td>to make 100%</td>
</tr>
</tbody>
</table>

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses. Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five units doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 µl.
The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butandiol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

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

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

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 2. Thus, in further embodiments of the invention, there are provided methods for treating a disorder associated with modulation of the N-formyl peptide receptor 2. 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 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.
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
Compounds of Formula I were prepared as depicted in Scheme 1. In general, a t-butyl ester derivative of 2-nitrocinnamic acid was hydrogenated with hydrogen gas in the presence of a palladium catalyst to produce a 2-aminophenyl propionate. The product was subsequently reacted with a phenylisocyanate to produce a phenylurea derivative. The t-butyl ester protecting group was then removed under acidic conditions and gave the amino acid urea. The carboxylic acid group could be converted to an amide by treating the compound with activating reagents, such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and hydroxybenzotriazole (HOBt) in the presence of an amine, or by other methods known to those skilled in the art. Those skilled in the art will appreciate that carboxylic acid or ester groups are versatile functional groups which can be chemically transformed into many other functional groups, and thus these compounds are useful intermediates for producing many other homologs and derivatives.

The following abbreviations are used in the general scheme and in the examples:

- Et₃N: triethylamine
- CH₂Cl₂: dichloromethane
- CD₃OD: deuterated methanol
- Na₂SO₄: sodium sulfate
- DMF: N,N-dimethylformamide
- EDCI/EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
- HOBt: hydroxybenzotriazole
- THF: tertahydrofuran
- EtOAc: ethylacetate
- HCO₂H: formic acid
- DMAP: 4-dimethylaminopyridine
MeOH methanol
Pd/C palladium on carbon
HCl hydrochloric acid
NaOH sodium hydroxide
CDCl₃ deuterated chloroform

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. Details of certain specific chemical transformations are provided in the examples.

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

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.

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 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 hydrogen ¹H (or H) or use of ¹³C enriched material in place of ¹²C 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) of the
compounds of the invention. These compounds can be prepared in accord with the preparations described by use of isotopically enriched reagents.

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

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

Compound names were generated with ACDLabs version 12.5. Some of the intermediate and reagent names used in the examples were generated with software such as Chem Bio Draw Ultra version 12.0 or Auto Norn 2000 from MDL ISIS Draw 2.5 SP1.

In general, characterization of the compounds is performed according to the following methods; NMR spectra are recorded on 300 or 600 MHz Varian and acquired at room temperature. Chemical shifts are given in ppm referenced either to internal TMS or to the solvent signal.

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

Usually the compounds of the invention were purified by medium pressure liquid chromatography, unless noted otherwise.

**Example 1**

**Intermediate 1**

(trans)-tert-Butyl 3-(2-Nitrophenyl)acrylate
To a solution of irans-2-nitrocinnamic acid (3.23 g, 16.7 mmol) and 100 mL of THF at 25 °C was added di-tert-butyl dicarbonate (7.29 g, 33.4 mmol) and DMAP (611 mg, 5.01 mmol). The resulting mixture was stirred at 25°C for 12 hours. The mixture was concentrated to an oil and the residue was purified by medium pressure liquid chromatography on silica gel using ethyl acetate: hexane (8:92) to yield Intermediate 1 as light yellow solid.

$^1$H NMR (CDCl$_3$, 300MHz) $\delta$: 8.04 (s, 2H), 7.63 (d, J = 3.8 Hz, 2H), 7.48 - 7.56 (m, 1H), 6.30 (d, J = 15.8 Hz, 1H), 1.54 (s, 9H).

**Example 2**

**Intermediate 2**

**tert-Butyl 3-(2-Aminophenyl)propanoate**

A solution of Intermediate 1 (1.26 g, 5.06 mmol) and 100 mL of methanol was added 150 mg of 10%Pd-C and hydrogen balloon. The mixture was stirred at 25 °C for 2.5 hours. The resulting reaction was filtered through celite pad and concentrated to yield Intermediate 2 as yellow oil.

$^1$H NMR (CDCl$_3$, 300MHz) $\delta$: 6.96 - 7.08 (m, 2H), 6.61 - 6.77 (m, 2H), 3.62 - 3.87 (br s, NH), 2.72 - 2.84 (m, 2H), 2.57 (d, J = 7.6 Hz, 2H), 1.43 (s, 9H).

**Example 3**

**Intermediate 3**

**tert-Butyl 3-(2-(3-(4-Bromophenyl)ureido)phenyl)propanoate**
To a solution of Intermediate 2 (500 mg, 2.26 mmol) and 15 mL of pyridine at 25 °C was added 4-bromo-phenyl isocyanate (446 mg, 2.26 mmol). The resulting mixture was stirred at 25°C for 1 hour. The mixture was quenched with 10%HCl (15 mL), and the product was extracted with ethyl acetate (10 mL). The layers were separated, and the organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by medium pressure liquid chromatography on silica gel using ethyl acetate: hexane (4 : 6) to yield Intermediate 3 as a white solid.

¹H NMR (CD₃OD, 300MHz) δ: 7.53 (d, J = 7.3 Hz, 1H), 7.42 (br. s., 4H), 7.16 - 7.26 (m, 2H), 7.07 - 7.15 (m, 1H), 2.86 - 2.95 (m, 2H), 2.57 (t, J = 7.3 Hz, 2H), 1.39 (s, 9H).

Example 4

**Compound 1**

3-(2-(r(4-Bromophenyl)carbamovnamino)phenyl)propanoic Acid

A solution of Intermediate 2 (910 mg, 2.18 mmol) and 16 mL of formic acid was stirred at 25 °C for 4 hours. The resulting reaction was quenched with water (1 mL), and the product was extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was rinsed two times with acetone : hexanes (1 : 4) to yield Compound 1 as a white solid.

¹H NMR (CD₃OD, 300MHz) δ: 7.98 (br. s., NH), 7.58 (s, 1H), 7.40 (s, 4H), 7.14 - 7.29 (m, 2H), 7.03 - 7.13 (m, 1H), 3.15 (t, J = 5.7 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 2.50 (d, J = 14.7 Hz, 2H), 2.11 - 2.25 (m, 2H), 1.69 (quin, J = 7.2 Hz, 2H).
Example 5

**Compound 2**

Methyl 4-(3-(2-(4-Bromophenyl)carbamoyl)amino)phenyl)propanoylaminolbutanoate

To a solution of Compound 1 (150 mg, 0.41 mmol) and 10 mL of DMF was added EDCI (1.19 mg, 0.62 mmol), HOBt (84 mg, 0.62 mmol), N-methylmorpholine (84 mg, 0.82 mmol), and methyl 4-aminobutyrate hydrochloride (96 mg, 0.41 mmol). The resulting mixture was stirred at 25°C for 12 hours. The mixture was quenched with water (4 mL), and the product was extracted with ethyl acetate (20 mL). The layers were separated, and the organic layer was washed with water, brine, dried over Na2S04, filtered, and the filtrate was concentrated under reduced pressure. The resulting product was purified by medium pressure liquid chromatography on silica gel using ethyl acetate : hexane (4 : 6) to yield Compound 2 as white solid.

1H NMR (CD3OD, 300MHz) δ: 7.98 (br. s., NH), 7.58 (s, 1H), 7.40 (s, 4H), 7.14 - 7.29 (m, 2H), 7.03 - 7.13 (m, 1H), 3.15 (t, J = 5.7 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 2.50 (d, J = 14.7 Hz, 2H), 2.11 - 2.25 (m, 2H), 1.69 (quin, J = 7.2 Hz, 2H).

Compounds 3 and 6 were prepared from the corresponding carboxylic acid in a similar manner to the procedure described in Example 5 for Compound 2. The results are described below in Table 1.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>IUPAC name</th>
<th>Structure</th>
<th>1H NMR δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Methyl 3-{[3-(2-{[(4-bromophenyl)carbamoyl]amino]phenyl)propanoyl]amino}propanoate</td>
<td><img src="image_url" alt="Structure" /></td>
<td>1H NMR (CD3OD, 300MHz) δ: 8.02 (br s, NH), 7.58 (s, 1H), 7.40 (s, 4H), 7.15 - 7.24 (m, 2H), 7.02 - 7.13 (m, 1H), 3.62 (s, 3H), 3.37 (d, J = 4.7 Hz, 2H), 2.87 - 2.97 (m,</td>
</tr>
</tbody>
</table>
Example 6

**Compound 4**

4-fr3-(2-fr(4-Bromophenyl)carbamoyl)phenyl)propanoyl)amino)butanoic Acid

A solution of Compound 2 (145 mg, 0.31 mmol) and 10 mL of methanol was added 1 mL of 1N NaOH. The mixture was stirred at 25 °C for 12 hours. The resulting reaction was quenched with 10% HCl (1 mL), and the product was extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was rinsed twice with acetone : hexanes (1:9) to yield Compound 3 as a white solid.

\[ ^1H \text{ NMR (CD}_3\text{OD, 300MHz)} \delta: 7.98 \text{ (br. s., NH), 7.58 (s, 1H), 7.40 (s, 4H), 7.14 - 7.29 (m, 2H), 7.03 - 7.13 (m, 1H), 3.15 (t, J = 5.7 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 2.50 (d, J = 14.7 Hz, 2H), 2.11 - 2.25 (m, 2H), 1.69 (quin, J = 7.2 Hz, 2H). \]
Compound 5 and 7 were prepared from the corresponding ester in a similar manner to the procedure described in Example 6 for Compound 4. The results are described below in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>IUPAC name Structure</th>
<th>$^1$H NMR δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3-[[3-2-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoylamino]propanoic Acid</td>
<td>$^1$H NMR (CD$_3$OD, 300MHz) δ: 7.57 (d, J = 8.5 Hz, 1H), 7.40 (s, 4H), 7.16 - 7.27 (m, 2H), 7.10 (m, 1H), 3.37 (t, J = 6.9 Hz, 2H), 2.92 (t, J = 7.5 Hz, 3H), 2.49 (t, J = 7.5 Hz, 2H), 2.42 (t, J = 6.6 Hz, 2H).</td>
</tr>
<tr>
<td>7</td>
<td>{[3-2-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoylamino]acetic Acid</td>
<td>$^1$H NMR (CD$_3$OD, 300MHz) δ: 7.58 (d, J=7.6 Hz, 1H), 7.40 (s, 5H), 7.03-7.28 (m, 2H), 3.87 (s, 2H), 2.95 (t, J=7.6 Hz, 2H), 2.53-2.65 (m, 2H).</td>
</tr>
</tbody>
</table>

Biological Data

Biological activity of compounds according to Formula I is set forth in Table 3 below. CHO-Ga16 cells stably expressing FPRL1 were cultured in (F12, 10% FBS, 1% PSA, 400 µg/ml geneticin and 50 µg/ml hygromycin) and HEK-Gqi5 cells stable expressing FPR1 were cultured in (DMEM high glucose, 10% FBS, 1% PSA, 400 µg/ml geneticin and 50 µg/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 3
<table>
<thead>
<tr>
<th>IUPAC Name</th>
<th>FPR2 Ga16-CHO EC&lt;sub&gt;50&lt;/sub&gt; (nM) (Rel. eff.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-[[3-2-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoyl]amino]propanoic Acid</td>
<td>637 (1.00)</td>
</tr>
<tr>
<td>Methyl 4-[[3-2-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoyl]amino]butanoate</td>
<td>922 (0.96)</td>
</tr>
<tr>
<td>4-[[3-2-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoyl]amino]butanoic Acid</td>
<td>2041 (0.99)</td>
</tr>
<tr>
<td>Methyl 3-[[3-2-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoyl]amino]propanoate</td>
<td>311 (1.00)</td>
</tr>
<tr>
<td>3-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoic Acid</td>
<td>1230 (1.00)</td>
</tr>
<tr>
<td>Methyl [{3-2-[[4-bromophenyl]carbamoyl]amino]phenyl]propanoyl]amino]acetate</td>
<td>180 (0.80)</td>
</tr>
<tr>
<td>[{3-2-[[4-Bromophenyl]carbamoyl]amino]phenyl]propanoyl]amino]acetic Acid</td>
<td>410 (0.76)</td>
</tr>
</tbody>
</table>
What is claimed is:

1. A compound represented by Formula I, its enantiomers, diastereoisomers, tautomers, or a pharmaceutically acceptable salt thereof:

\[
\text{Formula I}
\]

wherein:

- \( R^1 \) is \( OR^{11} \) or \( NR^{12}R^{13} \);
- \( R^2 \) is halogen, \( NR^{14}R^{15} \), \(-\text{CF}_3\), \(-\text{N}0_{2}^{-}\), \(-\text{OR}^{20}\), \(-\text{S}(0)\text{m}_R^{18}\) or \(-\text{C}(0)R^{19}\) or \(-\text{OR}^{20}\);
- \( R^3 \) is \( H \), optionally substituted \( C_{1-8} \) alkyl, optionally substituted \( C_{3-8} \) cycloalkyl, optionally substituted heterocycle, optionally substituted \( C_{6-\text{io}} \) aryl, optionally substituted \( C_{3-8} \) cycloalkenyl, halogen, \( NR^{14}R^{15} \), \(-\text{CF}_3\), \(-\text{S}(0)\text{m}_R^{18}\) \(-\text{C}(0)R^{19}\) or \(-\text{OR}^{20}\);
- \( R^4 \) is \( H \), optionally substituted \( C_{1-8} \) alkyl, optionally substituted \( C_{3-8} \) cycloalkyl, optionally substituted heterocycle, optionally substituted \( C_{6-\text{io}} \) aryl, optionally substituted \( C_{3-8} \) cycloalkenyl, halogen, \( NR^{14}R^{15} \), \(-\text{CF}_3\), \(-\text{S}(0)\text{m}_R^{18}\) \(-\text{C}(0)R^{19}\) or \(-\text{OR}^{20}\);
- \( R^5 \) is \( H \), optionally substituted \( C_{1-8} \) alkyl, optionally substituted \( C_{3-8} \) cycloalkyl, optionally substituted heterocycle, optionally substituted \( C_{6-\text{io}} \) aryl, optionally substituted \( C_{3-8} \) cycloalkenyl, halogen, \( NR^{14}R^{15} \), \(-\text{CF}_3\), \(-\text{S}(0)\text{m}_R^{18}\) \(-\text{C}(0)R^{19}\) or \(-\text{OR}^{20}\);
- \( R^6 \) is \( H \), optionally substituted \( C_{1-8} \) alkyl, optionally substituted \( C_{3-8} \) cycloalkyl, optionally substituted heterocycle, optionally substituted \( C_{6-\text{io}} \) aryl, optionally substituted \( C_{3-8} \) cycloalkenyl, halogen, \( NR^{14}R^{15} \), \(-\text{CF}_3\), \(-\text{S}(0)\text{m}_R^{18}\) \(-\text{C}(0)R^{19}\) or \(-\text{OR}^{20}\);
- \( R^7 \) is \( H \), optionally substituted \( C_{1-8} \) alkyl, optionally substituted \( C_{3-8} \) cycloalkyl, optionally substituted heterocycle, optionally substituted \( C_{6-\text{io}} \) aryl, optionally
substituted C$_{3-8}$ cycloalkenyl, halogen, NR$_{14}$R$_{15}$, -CF$_3$, -S(0)$_m$R$_{18}$ -C(0)R$_{19}$ or -OR$_{20}$; 
R$^8$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$_{14}$R$_{15}$, -CF$_3$, -S(0)$_m$R$_{18}$ -C(0)R$_{19}$ or -OR$_{20}$; 
R$^9$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$_{14}$R$_{15}$, -CF$_3$, -S(0)$_m$R$_{18}$ -C(0)R$_{19}$ or -OR$_{20}$; 
R$^{10}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl, halogen, NR$_{14}$R$_{15}$, -CF$_3$, -S(0)$_m$R$_{18}$ -C(0)R$_{19}$ or -OR$_{20}$; 
R$^{11}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl; 
R$^{12}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl or together with R$^{13}$ may form a heterocyclic ring; 
R$^{13}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl, optionally substituted C$_{3-8}$ cycloalkenyl or together with R$^{12}$ may form a heterocyclic ring; 
R$^{14}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl or optionally substituted C$_{3-8}$ cycloalkenyl; 
R$^{15}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl or optionally substituted C$_{3-8}$ cycloalkenyl; 
R$^{16}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6-10}$ aryl or optionally substituted C$_{3-8}$ cycloalkenyl;
$R^{17}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6}$-io aryl, optionally substituted C$_{3-8}$ cycloalkenyl or OR$_{20}$; $R^{18}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6}$-io aryl or optionally substituted C$_{3-8}$ cycloalkenyl; $R^{19}$ is H, hydroxyl, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6}$-io aryl, optionally substituted C$_{3-8}$ cycloalkenyl or OR$_{20}$; $R^{20}$ is H, optionally substituted C$_{1-8}$ alkyl, optionally substituted C$_{3-8}$ cycloalkyl, optionally substituted heterocycle, optionally substituted C$_{6}$-io aryl or optionally substituted C$_{3-8}$ cycloalkenyl; $n$ is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and $m$ is 0, 1 or 2; and except compound:

![Chemical Structure](image)

2. A compound according to claim 1, wherein:
   $R^1$ is OR$_{11}$.

3. A compound according to claim 1, wherein:
   $R^1$ is NR$_{12}$R$_{13}$.

4. A compound according to claim 1, wherein:
   $R^1$ is OR$_{11}$;
R² is halogen;
R³ is H, optionally substituted C₁⁻₈ alkyl;
R⁴ is H, optionally substituted d-e alkyl;
R⁵ is H, optionally substituted d-e alkyl;
R⁶ is H, optionally substituted d-e alkyl;
R⁷ is H, optionally substituted d-e alkyl;
R⁸ is H, optionally substituted d⁻₈ alkyl;
R⁹ is H, optionally substituted d-s alkyl;
R¹⁰ is H, optionally substituted Ci⁻₈ alkyl;
R¹¹ is H, optionally substituted Ci⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻/io aryl, optionally substituted C₃⁻₈ cycloalkenyl; and
n is 0, 1 or 2.

5. A compound according to claim 1, wherein:
R¹ is NR²R³;
R² is halogen;
R³ is H;
R⁴ is H;
R⁵ is H;
R⁶ is H;
R⁷ is H;
R⁸ is H;
R⁹ is H;
R¹⁰ is H;
R¹² is H, optionally substituted C₁⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻/io aryl, optionally substituted C₃⁻₈ cycloalkenyl or R¹² together with R¹³ may form a heterocyclic ring;
R¹³ is H, optionally substituted Ci⁻₈ alkyl, optionally substituted C₃⁻₈ cycloalkyl, optionally substituted heterocycle, optionally substituted C₆⁻/io aryl, optionally substituted C₃⁻₈ cycloalkenyl or R¹³ together with R¹² may form a heterocyclic ring;
n is 0, 1 or 2.

6. A compound according to claim 1, wherein:
\( R^1 \) is \( NR^2 R^3 \);
\( R^2 \) is halogen;
\( R^3 \) is H;
\( R^4 \) is H;
\( R^5 \) is H;
\( R^6 \) is H;
\( R^7 \) is H;
\( R^8 \) is H;
\( R^9 \) is H;
\( R^{10} \) is H;
\( R^{12} \) is optionally substituted \( C_{1-8} \) alkyl, optionally substituted \( C_{3-8} \) cycloalkyl, optionally substituted heterocycle, optionally substituted \( C_{6-10} \) aryl or optionally substituted \( C_{3-8} \) cycloalkenyl;
\( R^{13} \) is H, optionally substituted \( C_{1-8} \) alkyl, optionally substituted \( C_{3-8} \) cycloalkyl, optionally substituted heterocycle, optionally substituted \( C_{6-10} \) aryl or optionally substituted \( C_{3-8} \) cycloalkenyl; and
\( n \) is 0, 1 or 2.

7. A compound according to claim 1, wherein:
\( R^1 \) is \( NR^2 R^3 \);
\( R^2 \) is halogen;
\( R^3 \) is H;
\( R^4 \) is H;
\( R^5 \) is H;
\( R^6 \) is H;
\( R^7 \) is H;
\( R^8 \) is H;
\( R^9 \) is H;
\( R^{10} \) is H;
\( R^{12} \) is optionally substituted \( C_{1-8} \) alkyl;
\( R^{13} \) is H;
\( n \) is 0, 1 or 2.

8. A compound according to claim 1, wherein:
R^1 is NR^{12}R^{13}; 
R^{12} is halogen; 
R^{13} is H; 
R^4 is H; 
R^5 is H; 
R^6 is H; 
R^7 is H; 
R^8 is H; 
R^9 is H; 
R^{10} is H; 
R^{12} is optionally substituted C_{1-6} alkyl by halogen atoms, hydroxyl groups, cycloalkyl 
groups, amino groups, heterocyclic groups, aryl groups, carboxylic acid groups, 
phosphonic acid groups, sulphonic acid groups, phosphoric acid groups, nitro groups, 
amide groups, sulfonamide groups, ester groups or ketone groups; 
R^{13} is H; and 
n is 0, 1 or 2.

9. A compound according to claim 1, selected from: 
3-[[3-(2-[[((4-Bromophenyl)carbamoyl]amino)phenyl]propanoyl]amino]propanoic acid; 
4-[[3-(2-[[((4-Bromophenyl)carbamoyl]amino)phenyl]propanoyl]amino]butanoic acid; 
Methyl4-[[3-(2-[[((4-bromophenyl)carbamoyl]amino)phenyl]propanoyl]amino]butanoate; 
3-(2-[[((4-Bromophenyl)carbamoyl]amino)phenyl]propanoic Acid; 
Methyl 3-(2-[[((4-bromophenyl)carbamoyl]amino)phenyl]propanoyl]amino)acetate; and 
10. A pharmaceutical composition comprising as active ingredient a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A pharmaceutical composition according to claim 10 wherein the compound is which is selected from:
   3-[[4-(Bromophenyl)carbamoyl]amino]phenyl]propanoic Acid;
   Methyl [[3-2-[[4-(bromophenyl)carbamoyl]amino]phenyl]propanoyl] amino]acetate; and
### INTERNATIONAL SEARCH REPORT

#### A. CLASSIFICATION OF SUBJECT MATTER

**INV.** C07C275/28 C07C275/30

**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)

C07C A61K

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 practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>US 2013/123496 AI (BEARD RICHARD L [US] ET AL) 16 May 2013 (2013-05-16) [0005]; [0007]; [0015]; examples; Tables 1-6; [0215]; claims 1-11</td>
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* Special categories of cited documents:

- **A** document defining the general state of the art which is not considered to be of particular relevance
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- **Z** document member of the same patent family

**Date of the actual completion of the international search**

16 January 2015

**Date of mailing of the international search report**

30/01/2015

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-3040,
Fax: (+31-70) 340-3016

Sen, Alina

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Form PCT/ISA210 (second sheet) (April 2005)
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<td>Y</td>
<td>IGOR A. SCHEPETKIN, LI L IYA N. KI RPOTINA, ANDREI I. KHELEBNI KOV, MARK A. JUTI LA AND MARK T. QUINN: &quot;Gastrin-Releasing Peptid/Neuromedi n B Receptor Antagoni sts PD176252, PD168368, and Related Analogs Are Potent Agonists of Human Formyl -Peptide Receptors&quot;, MOLECULAR PHARMACOLOGY, vol. 79, no. 1, 2011, pages 77-90, XP002734613, DOI: 10.1124/mol.110.068288 &quot;abstract&quot; ; page 83, Table 3; page 84, Tables 4 and 5; page 85, Table 6</td>
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<td>L. N. KI RPOTINA ET AL: &quot;Identifi cation of Novel Smal 1-Molecule Agonists for Human Formyl Peptide Receptors and Pharmacophore Model of Their Recognition&quot;, MOLECULAR PHARMACOLOGY, vol. 77, no. 2, 1 February 2010 (2010-02-01), pages 159-170, XP055047399, ISSN: 0026-895X, DOI: 10.1124/mol.109.060673 page 160, right-hand column, &quot;Cell Culture&quot; ; page 162, compound AG-09/10; page 162, Table 1 &quot;Activity of selected FPR1/FPR2 agonists&quot;</td>
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# INTERNATIONAL SEARCH REPORT

**International application No**
PCT/US2014/055944

## Information on patent family members

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