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PATENT HIGHLIGHT

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FPRL-1 Receptor Modulators May Provide Treatment for Inflammation

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Patent Application Title:	Amide derivatives of *N*-urea substituted amino acids as formyl peptide receptor like-1 (FPRL-1) receptor modulators		
Patent Application Number:	WO 2013/062947 Al	Publication date:	2 May 2013
Priority Application:	US 61/551772	Priority date:	26 October 2011
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Disease Area:	Inflammation	Biological Target:	Formyl peptide receptor like-1 (FPRL-1) receptor

Summary:

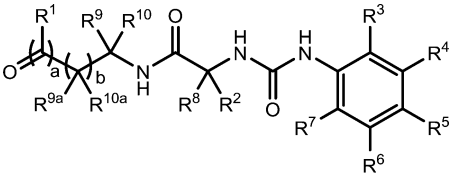
The invention in this patent application relates to amide derivatives of *N*-urea substituted amino acids represented generally by formula II that act as modulators of the *N*-formyl peptide receptor like-1 (FPRL-1) receptor. These compounds may potentially treat disorders associated with the FPRL-1 receptor modulation such as inflammation.

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, neutrophils, and T cells and plays a critical role in leukocyte trafficking during inflammation. This is a promiscuous receptor; it responds to different exogenous and endogenous ligands. While it transduces anti-inflammatory effects of lipoxin A4 (LXA4) and annexin A1, it can also mediate the pro-inflammatory signaling cascade of peptides such as serum amyloid A (SAA).

Activation of FPRL-1 by LXA4 and annexin A1 promotes inhibition of polymorphonuclear neutrophil (PMN) and migration of eosinophil as well as stimulation of monocyte migration to enable clearance of apoptotic cells from the site of inflammation in a nonphlogistic manner. FPRL-1 also inhibits natural killer (NK) cell cytotoxicity and promotes activation of T cells, which contributes to down regulation of tissue damaging inflammatory signals.

The interaction of FPRL-1 with LXA4 proved beneficial in several experimental inflammation models. The modulation of FPRL-1 thus represents a novel therapeutic target for the treatment of diseases with excessive inflammatory responses.

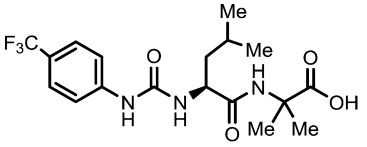
Important Compound Classes:



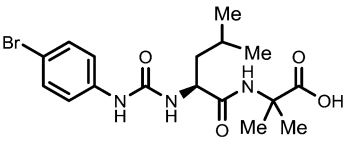
Formula II

Key Structures:

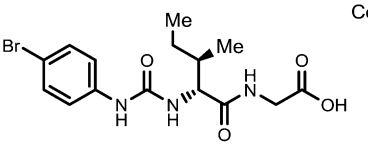
The patent application described the synthesis of 91 examples of the compounds of formula II, the three structures shown here are selected representative examples:



Compound 69



Compound 74



Compound 65

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Biological Data: The inventors tested the FPRL-1 activities of 98 compounds at concentrations ranging from 0.61 to 10 000 nM, and the results are expressed as EC_{50} (nM) and efficacy values. The IC_{50} results for three selected examples with variable IC_{50} values are listed in the table (structures shown above):

Compound	FPRL-1 Ga16-CHO EC_{50} (nM) (Rel. eff.)
69	2.3 (0.92)
74	1 (0.96)
65	19315 (0.45)

Claims: All claims are for composition of matter

Claims 1−14: variations of formula II

Claim 15: 98 specific compounds of formula II listed by chemical names

Recent Review Articles:

1. El Kebir, D.; Jozsef, L.; Filep, J. G. *J. Leukocyte Biol.* **2008**, *84* (3), 600−606.

2. Le, Y.; Zhou, Y.; Tao, H.; Wang, J. M. *Clin. Exp. Allergy Rev.* **2004**, *4* (Suppl. 2), 155−161.

3. Cui, Y.; Le, Y.; Yazawa, H.; Gong, W.; Wang, J.-M. *J. Leukocyte Biol.* **2002**, *72* (4), 628−635.

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Notes

The authors declare no competing financial interest.