ACS Medicinal Chemistry Letters

Patent Highlight

pubs.acs.org/acsmedchemlett

Targeting CCR2 Receptor To Treat Inflammation Diseases and Disorders

Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

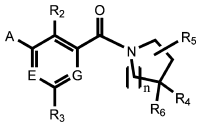
Title:	Novel and Selective CCR2 Antagonists		
Patent Application Number:	WO 2013/010839 A1	**Publication date:**	24 January 2013
Priority Application:	EP 11174198.9	**Priority date:**	15 July 2011
Inventors:	Ebel, H.; Frattini, S.; Giovannini, R.; Scheuerer, S.		
Assignee Company:	Boehringer Ingelheim International GMBH, Binger Str. 173, 55216 Ingelheim am Rhein (DE)		
Disease Area:	• COPD, asthma, cystic fibrosis • inflammatory and neuropathic pain • diabetes mellitus • peripheral atherosclerotic disease • diabetic nephropathy	**Biological Target:**	CC chemokine receptor 2 (CCR2)

Summary:

This patent application discloses novel compounds represented by formula I which are selective antagonists of the CC chemokine receptor 2 (CCR2) and can potentially treat conditions and diseases where activation of CCR2 plays a significant role. These conditions may include inflammatory diseases of the respiratory tracts such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibroses; neurologic disease, such as inflammatory and neuropathic pain disease; cardiovascular diseases, such as peripheral atherosclerotic disease and immune related diseases; such as diabetes mellitus, including diabetes nephropathy.

Inflammations are implicated in many of these conditions and diseases, and they are critically triggered and/or promoted by the activity of macrophages (produced by differentiation out of monocytes). CCR2 regulates monocyte trafficking and macrophage recruitment. It is thus necessary for macrophage-dependent inflammatory responses and the development of many inflammatory and immunoregulatory disorders and diseases as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Blocking the monocyte CCR2 receptor by an antagonist would diminish monocyte triggering and their move toward an inflammation area for conversion into macrophages and, hence, reduce macrophage-induced inflammation. Selective CCR2 antagonists such as those described in this patent application would potentially be useful in treating many of the above-mentioned disorders and diseases.

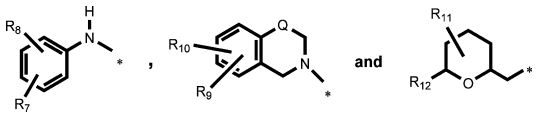
Important Compound Classes:



Formula (I)

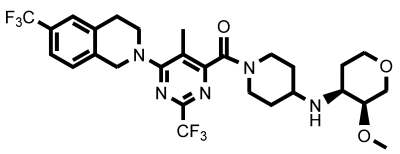
Definitions:

A is a group selected from:

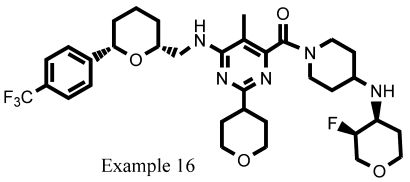


Received: February 12, 2013
Published: March 1, 2013

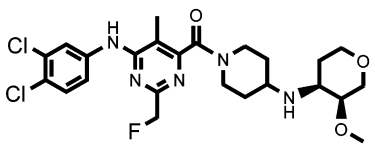
Key Structures: The patent application describes the synthesis of 46 examples of the compounds of formula I; four of these examples are illustrated here:



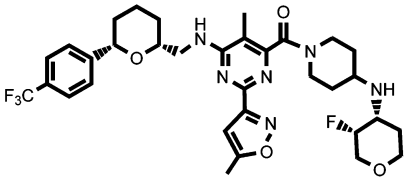
Example 2



Example 16



Example 20



Example 24

Biological Assay:

CCR2 binding assay

CCR5 binding assay

CCR2/CCRS-selectivity for chemokine receptor anatgonists:

Biological Data:

- All of the referenced examples have been found to have an activity in the CCR2 binding assay of 10 μM or less.
- The dissociation constants (hKi), representing the CCR2 and CCR5 affinities, are reported for all 46 examples; the data for examples 2, 16, 20, and 24 (structures above) are listed in the table:

Example	hKi (nM) CCR2	hKi (nM) CCR5	Example	hKi (nM) CCR2	hKi (nM) CCR5
2	2	150	20	0.6	31
16	1	210	24	1	50

Claims: Claims 1−13: Composition of matter, variations of formula I

Claims 14−19: Use of compounds as medicaments (inflammatory diseases of the respiratory tracts (preferably asthma, COPD) and cystic fibroses; neurological disease, preferably inflammatory and neuropathic pain disease; immune related diseases, preferably diabetes mellitus, including diabetes nephropathy and cardiovascular diseases, preferably peripheral atherosclerotic disease)

Recent Review Articles:

1. Kang, Y. S.; Cha, J. J.; Hyun, Y. Y.; Cha, D. R. *Expert Opin. Invest. Drugs* 2011, *20* (6), 745−756.

2. Struthers, M.; Pasternak, A. *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* 2010, *10* (13), 1278−1298.

3. Xia, M.; Sui, Z. *Expert Opin. Ther. Pat.* 2009, *19* (3), 295−303.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania, 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The author declares no competing financial interest.