ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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LPM7 Inhibitors May Potentially Treat Autoimmune Diseases

Ahmed F. Abdel-Magid*

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

Title:	Ketoamide Immunoproteasome Inhibitors		
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Priority Application:	US 61/712,312	**Priority date:**	11 October 2012
Inventors:	Lynch, S. M.; Narayanan, A.; Steiner, S.		
Assignee Company:	F. Hoffmann-La Roche AG; Grenzacherstrasse 124, CH-4070 Basel (CH) (for all designated States except US) Hoffmann-La Roche Inc.; 340 Kingsland Street, Nutley, New Jersey 07110, USA (for US only)		
Disease Area:	Autoimmune and inflammatory diseases and disorders such as rheumatoid arthritis, lupus, and irritable bowel disease (IBD)	**Biological Target:**	Inhibition of the low-molecular mass polypeptide-7 (LMP7)

Summary:

The invention in this patent application relates to keto amide derivatives represented generally by formula (I). These compounds are LMP7 inhibitors and may potentially be useful in treating inflammatory diseases and disorders such as rheumatoid arthritis, lupus, and irritable bowel disease (IBD).

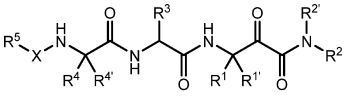
Immunoproteasome plays an essential role in generating antigenic peptide repertoire and shaping MHC (major histocompatibility complex) class I restricted CD8+ T cell response. Studies in mouse models of inflammatory disease have indicated its role in preventing the accumulation of harmful protein aggregates. An essential component of the immunoproteasome is the low-molecular mass polypeptide-7 (LMP7), which is mainly expressed in immune cells (such as T/B lymphocytes and monocytes) and nonimmune cells that have been exposed to inflammatory cytokines, including IFN-y and TNFa. Recent studies have suggested that LPM7 regulates inflammatory cytokine production and immune cell functions beyond the regulation of MHC class I mediated antigen presentation.

The inventors referred to the known LMP7 inhibitor, PR-957 (also named ONX-0914). PR-957 has shown potential therapeutic benefits in several preclinical autoimmune disease models. It has significantly decreased disease score and reduced inflammation and bone erosion in mouse CAIA and CIA arthritis models. It reduced plasma cell numbers and levels of anti-dsDNA IgG and prevented disease progression in MRL/lpr lupus-prone mice model. It also reduced inflammation and tissue destruction in a DSS-induced colitis model in mice and protected LMP7 knockout mice from disease in IBD models.

The above data strongly suggest a close connection between LMP7 activity and the functions of B/T lymphocytes and production of inflammatory cytokines, which are confirmed pathways in the pathogenesis of rheumatoid arthritis, lupus, and IBD. Therefore, there is a strong rationale to pursue LMP7 inhibition as a viable therapeutic target to treat autoimmune disease.

In recognizing the disadvantage and potential liability of the long-term usage of covalent LPM7 inhibitors in treating chronic autoimmune diseases, it is thus desirable to design new small molecule LMP7 inhibitors that possess either covalent−reversible or noncovalent properties.

Important Compound Classes:



Formula (I)

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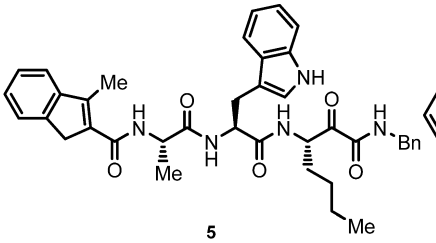
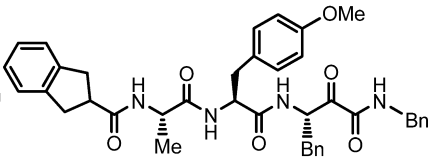
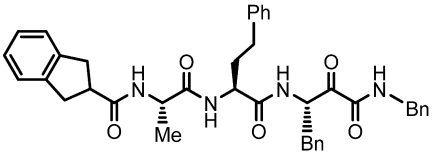
Key Structures: The inventors reported the structures of 59 examples of formula (I) including the following representative compounds:



5



19



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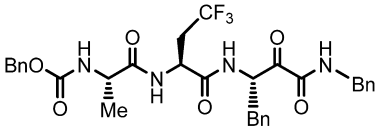

57

Biological Assay:

- Cell-Based Proteasome Activity/Selectivity Assay
- Modified PBMC Proteasome Activity Assay
- PBMC IP-10 Assay

Biological Data: The results of the above assays for the representative compounds **5**, **19**, **42**, and **57** (structures above) are listed in the following Table:

Compound	IC_{50} (μM) ramos:ac-(anw)2-r110	IC_{50} (μM) ramos:rh110 -(wla)2	IC_{50} (μM) ramos:rh110 -(kql)2	IC_{50} (μM) ramos:rh110 -(pal)2	IC_{50} (μM) ramos:rh110 -(Ile)2	EC_{50} (μM)
5	0.018	0.56	20	0.142	3.345	1.216
19	0.003	0.055	20	0.234	20	0.695
42	0.004	0.014	20	0.968	18.085	0.379
57	0.524	6.164	20	2.729	20	5.030

Claims: Claims 1−15: Composition of matter, variations of formula (I)
Claim 16: Composition of matter, 59 specific examples of formula (I)
Claim 17: Composition of matter, 4 specific examples of formula (I)
Claim 18: A pharmaceutical composition
Claims 19−22: Use of compounds to treat diseases and disorders
Claim 23: A method for treating an inflammatory disease or disorder
Claim 24: General claim

Recent Review Articles:
1. Basler, M.; Kirk, C. J.; Groettrup, M. *Curr. Opin. Immunol.* **2013**, *25* (1), 74−80.
2. Ebstein, F.; Kloetzel, P.-M.; Krueger, E.; Seifert, U. *Cell. Mol. Life Sci.* **2012**, *69* (15), 2543−2558.

AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.