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Viewpoint

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Factor D Inhibitors for the Treatment of AMD

Patent Highlight

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Title:	Indole Compounds or Analogues Thereof Useful for the Treatment of Age-Related Macular Degeneration (AMD)		
Patent Application Number:	WO 2012/093101 A1	**Publication Date:**	July 12, 2012
Priority Application:	US 61/429,730	**Priority Date:**	January 4, 2011
Inventors:	Altmann, E.; Hommel, U.; Lorthiois, E. L. J.; Maibaum, J. K.; Ostermann, N.; Quancard, J.; Randl, S. A.; Simic, O.; Vulpetti, A.; Rogel, O.		
Assignee Company:	Novartis AG [CH/CH], Lichtstrasse 35, CH-4056 Basel (CH)		
Disease Area:	Age-Related Macular Degeneration (AMD)	**Biological Target:**	Complement Alternative Pathway and Factor D

Summary:

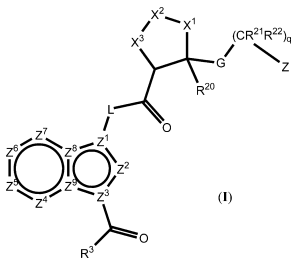
This invention relates to compounds of formula (I), which inhibit the alternative pathway of the complement system and particularly inhibit factor D. This inhibition may provide a treatment for patients suffering from conditions and diseases associated with activation of the complement alternative pathway such as age-related macular degeneration (AMD), diabetic retinopathy, and related ophthalmic diseases.

The macula is a small highly pigmented yellow spot about 5 mm in diameter in the center of the retina of the human eye. It is responsible for the sharp vision needed for reading, driving, or recognizing faces. AMD affects older adults and results in a progressive loss of visual acuity in the macula. The less advanced form is called dry (or atrophic) AMD; it occurs from the death of atrophic cells of the macula. The disease may advance to a second form known as wet (or neovascular) AMD. Wet AMD is characterized by the abnormal growth of blood vessels under the macula and vascular leakage. A scar tissue forms from leakage of fluid and blood that may destroy the central retina and can lead to blindness.

The complement system is part of the innate immune system. It consists of several inactive small proteins that are normally found in the blood. The complement proteins may be activated by any of three biochemical pathways: the classical complement pathway, the alternative complement pathway, and the lectin pathway. There is genetic evidence that links the activation of the alternative pathway to the pathogenesis of AMD. The inhibition of this activation process may provide possible treatment for AMD. Factor D is a protein that is involved in the activation of the alternative pathway of the complement system via activation of the complement C3 to C3 protease. Inhibition of factor D is a suitable target to inhibit the complement alternative pathway and treat patients with AMD.

The patent application claims the compounds of formula (I) with activities to modulate and inhibit factor D function and/or factor D-mediated complement pathway activation process. Additionally, these compounds may inhibit or suppress the amplification of the complement system caused by C3 activation irrespective of the initial mechanism of activation.

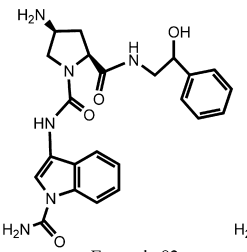
Important Compound Classes:



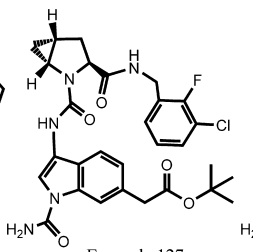
(I)

Key Structures:

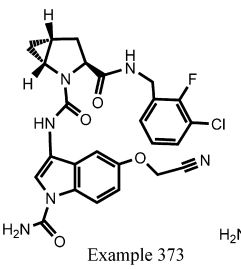
The following four structures are representative examples of compounds of formula (I). The patent application describes 773 specific compounds with reported synthesis procedures and IC_{50} values:



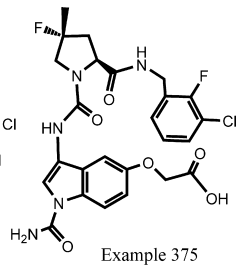
Example 82



Example 127



Example 373



Example 375

Published: August 27, 2012

Biological Assay:

Page 95: Human Complement Factor D Assay: Method 1

The test compound is incubated with recombinant human factor D for 1 h at room temperature at pH 7.5; the IC_{50} values were calculated from the percentage of inhibition of complement factor D activity as a function of test compound concentration.

Biological Data:

The application contains a table of IC_{50} values in nM for 773 compounds using method 1 above. IC_{50} values range from 1 nM for example 373 to 24750 nM for example 82:

Example	IC50 (nM)	Example	IC50 (nM)
82	24750	373	1
127	3	375	2

Claims:

Claims 1−16: composition of matter; variations of formula (I)

Claim 17: composition of matter: list of 620 compounds specifically by name

Claims 18 and 19: Pharmaceutical composition/combination

Claims 20−23: methods of treating disorders; claim 22 has a long list of potential disorders

Claims: 24−26: compounds as medicaments

Claim 27: composition of matter; four specific indole intermediates

Recent Review Articles:

Khandhadia, S.; Cipriani, V.; Yates, J. R. W.; Lotery, A. J. Age-related macular degeneration and the complement system. *Immunobiology* **2012**, *217* (2), 127−146.

de Oliveira Dias, J. R.; Rodrigues, E. B.; Mauricio, M.; Magalhaes, O., Jr.; Penha, F. M.; Farah, M. E. Cytokines in neovascular age-related macular degeneration: fundamentals of targeted combination therapy. *Br. J. Ophthalmol.* **2011**, *95* (12), 1631−1637.

Bradley, D. T.; Zipfel, P. F.; Hughes, A. E. Complement in age-related macular degeneration: A focus on function. *Eye (London, U. K.)* **2011**, *25* (6), 683−693.

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Notes

The authors declare no competing financial interest.