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Patent Highlight

Thienopyridinyl and Thiazolopyridinyl Compounds as IRAK4 Inhibitors

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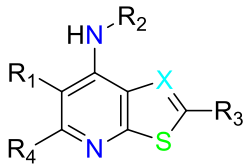
Important Compound Classes.



Title. Thienopyridinyl and Thiazolopyridinyl Compounds Useful as IRAK4 Inhibitors

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Priority Application. US 62/877,334

Priority Date. July 23, 2019

Inventors. Ahmad, S.; Li, L.; Wu, H.; Hynes, J.

Assignee Company. Bristol-Myers Squibb Company, USA

Disease Area. Inflammatory and autoimmune diseases, cancer

Biological Target. Interleukin-1 receptor-associated kinase 4 (IRAK4)

Summary. Toll/IL-1 receptor family members are important regulators of inflammation and host resistance. The Toll-like receptor (TLR) family recognizes molecular patterns derived from infectious organisms including bacteria, fungi, parasites, and viruses. With the exception of TLR3, all TLRs recruit the adaptor molecule MyD88. Members of the interleukin-1 receptor-associated kinase (IRAK) family of serine/threonine kinases are recruited to the receptor via interactions with MyD88. The family consists of four members. Several lines of evidence indicate that IRAK4 plays a critical and nonredundant role in initiating signaling via MyD88 dependent TLRs and IL-1R family members. IRAK4 directly interacts with MyD88 and subsequently recruits either IRAK1 or IRAK2 to the receptor complex to facilitate downstream signaling.

IRAK4 is the only member of the IRAK family whose kinase activity has been shown to be required for initiation of signaling. IRAK4 inhibitors will block all MyD88 dependent signaling. MyD88 dependent TLRs have been shown to contribute to the pathogenesis of multiple sclerosis, rheumatoid arthritis, cardiovascular disease, metabolic syndrome, sepsis, systemic lupus erythematosus, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, autoimmune uveitis, asthma, allergy, type I diabetes, and allograft rejection.

Oncogenically active MyD88 mutations in diffuse large B cell lymphomas have been identified that are sensitive to IRAK4 inhibition. Whole genome sequencing also identified mutations in MyD88 associated with chronic lymphatic leukemia suggesting that IRAK4 inhibitors have utility in treating leukemias.

The present application describes a series of novel thienopyridinyl and thiazolopyridinyl compounds as IRAK4 inhibitors for the treatment of inflammatory diseases, autoimmune diseases, and cancer. Further, the application discloses compounds and their preparation, use, pharmaceutical composition, and treatment.

Definitions. X = CR_4 or N;

R_1 = (i) $-C(O)NHR_{1a}$ or $-C(O)NH(CH_2)_{1-3}R_{1b}$; or

(ii) pyrazolyl, imidazolyl, isooxazolyl, or triazolyl, each substituted with 0 or 1 R_{1c};

R_2 = (i) C_{1-6} alkyl substituted with 0 to 4 substituents independently selected from F, Cl, OH and CN; or

(ii) a cyclic group selected from C_{3-6} cycloalkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and pyrazolyl, wherein said cyclic group is substituted with 0 to 3 substituents independently selected from F, OH, CN, C_{1-2} alkyl, C_{1-2} fluoroalkyl and C_{1-2} hydroxyalkyl;

R_3 = R_{3a} or -NHR_{3a}; and

R_4 = H, F, Cl, CH_3 or CF_3.

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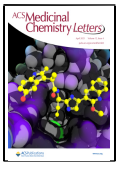
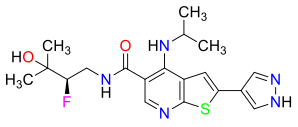
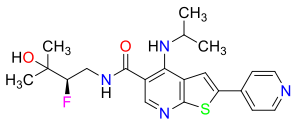
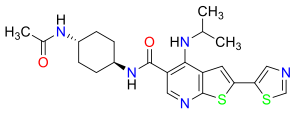
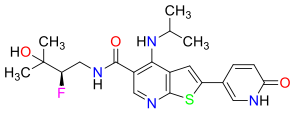


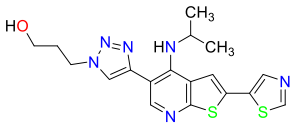
Key Structures.

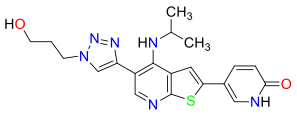

Compound 21


Compound 23


Compound 45


Compound 59


Compound 79


Compound 80

Biological Assay. The IRAK4 inhibition assay was performed. The compounds described in this application were tested for their ability to inhibit IRAK4. The IRAK4 IC_{50} (μM) are shown in the following table.

Biological Data. The table below shows representative compounds were tested for IRAK4 inhibition. The biological data obtained from testing representative examples are listed in the following table.

Compound No.	IRAK4 IC_{50} (μM)
21	0.0024
23	0.0048
45	0.0037
59	0.0038
79	0.0023
80	0.0052

Claims. Total claims: 10
Compound claims: 9
Pharmaceutical composition claims: 1

Recent Review Articles.

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2. Su, L.; Xu, W.; Huang, A. *Autoimmun. Rev.* **2020**, *19*, 102461.
3. Patra, M. C.; Shah, M.; Choi, S. *Semin. Cancer Biol.* **2020**, *64*, 61.
4. Fitzgerald, K. A.; Kagan, J. C. *Cell* **2020**, *180*, 1044.
5. Bu, L.; Baba, H.; Yasuda, T.; Uchihara, T.; Ishimoto, T. *Cancer Sci.* **2020**, *111*, 3468.
6. Robertson, S. A.; Hutchinson, M. R.; Rice, K. C.; Chin, P.; Modenhauer, L. M.; Stark, M. J.; Olson, D. M.; Keelan, J. A. *Clin. Transl. Immunol.* **2020**, *9*, e1121.

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Notes

The author declares no competing financial interest.

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