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Patent Highlight

Novel Difluorocyclohexyl Derivatives as IL-17 Modulators for Treating Inflammatory and Autoimmune Diseases

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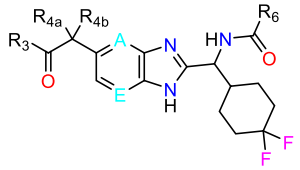
Important Compound Classes.



Title. Difluorocyclohexyl Derivatives as IL-17 Modulators

Patent Publication Number. WO 2021/204801 A1

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Priority Application. GB 2005153.8 and GB 2009617.8

Priority Date. April 7, 2020, and June 24, 2020

Inventors. Chovatia, P. T.; Foley, A. M.; Haslett, G. W.; Hutchings, M. C.; Johnson, J. A.; Lecomte, F. C.; Monck, N. J. T.; Quincey, J. R.; Rampalakos, K.; Reuberson, J. T.; Smalley, A. P.; Trani, G.; Vaidya, D. G.

Assignee Company. UCB Biopharma SRL, Belgium

Disease Area. Inflammatory and autoimmune diseases

Biological Target. IL-17

Summary. The interleukin (IL)-17 or IL-17A is a proinflammatory cytokine and the founder member of the IL-17 family. Subsequently, five additional members of the family (IL-17B to IL-17F) have been identified, including the most closely related, IL-17F (ML-1), which shares approximately 55% amino acid sequence homology with IL-17A. IL-17A and IL-17F are expressed by the recently defined autoimmune related subset of T helper cells, TH17, that also express IL-21 and IL-22 signature cytokines. IL-17A and IL-17F are expressed as homodimers but may also be expressed as the IL-17A/F heterodimer. IL-17A and IL-17F signal through the receptors IL-17R, IL-17RC, or an IL-17RA/RC receptor complex. Both IL-17A an IL-17F have been associated with a number of autoimmune diseases.

The present application describes a series of novel difluorocyclohexyl derivatives as IL-17 modulators for the treatment of inflammatory and autoimmune diseases. Further, the application discloses compounds, their preparation, use, pharmaceutical composition, and treatment.

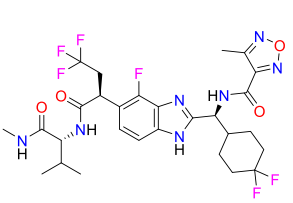
Definitions. A = C-R_1 or N; E = C-R_2 or N; R_3 = $-NR_{3a}R_{3b}$;

R_{4a} = H, F, OH; or R_{4a} = C_{1-4} alkyl, optionally substituted by one or more substituents;

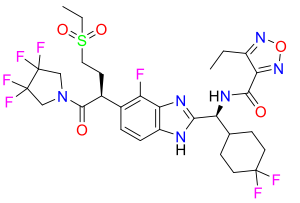
R_{4b} = H, F, or C_{1-4} alkyl; and

R_6 = $-OR_{6a}$ or $-NR_{6b}R_{6c}$ or R_6 = C_{1-6} alkyl, C_{3-9} cycloalkyl, C_{3-9} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6}) alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6}) alkyl), any of which group may be optionally substituted by one or more substituents.

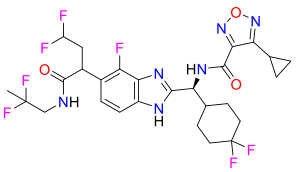
Key Structures.



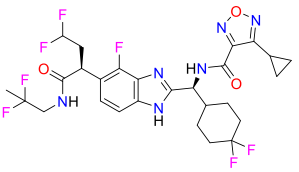
Compound 9



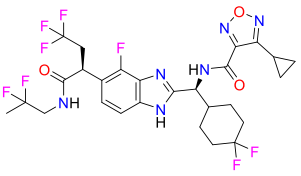
Compound 31



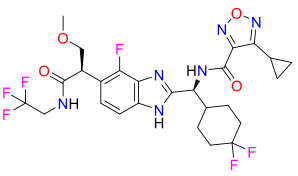
Compound 59



Compound 61



Compound 67



Compound 76

Biological Assay. The inhibition of IL-17A-induced IL-6 release from the human dermal fibroblast (HDF) cell line assay was performed. The compounds described in this application were tested for their ability to inhibit IL-17. The IL-17 pIC_{50} are shown in the following table.

Biological Data. The table below shows representative compounds were tested for IL-17 inhibition. The biological data

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obtained from testing representative examples are listed in the following table.

Compound No.	pIC_{50}
9	8.9
31	8.8
59	8.9
61	9.1
67	8.8
76	8.9

Claims. Total claims: 21
Compound claims: 15
Pharmaceutical composition claims: 2
Method of treatment claims: 2
Use of compound claims: 2

Recent Review Articles.

1. Ghoreschi, K.; Balato, A.; Enerback, C.; Sabat, R. *Lancet* **2021**, *397*, 754.
2. Loft, N.; Halling, A.; Egeberg, A.; Skov, L. *J. Am. Acad. Dermatol.* **2021**, *84*, 130.
3. Marson, J. W.; Snyder, M. L.; Lebwohl, M. G. *Med. Clin. North Am.* **2021**, *105*, 627.
4. Griffiths, C. E. M.; Armstrong, A. W.; Gudjonsson, J. E.; Barker, J. N. W. N. *Lancet* **2021**, *397*, 1301.
5. Stober, C. *Best Pract. Res. Clin. Rheumatol.* **2021**, *35*, 101694.
6. Higgins, E. *Medicine* **2021**, *49*, 361.

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Notes

The author declares no competing financial interest.

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