ACS Medicinal Chemistry Letters
Cite This: ACS Med. Chem. Lett. 2017, 8, 1132-1133
Patent Highlight
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# Selective Inhibitors of Phosphodiesterase 4B (PDE-4B) May Provide a Better Treatment for CNS, Metabolic, Autoimmune, and Inflammatory Diseases

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|---|---|---|---|
| **Patent Application Title:** | 6,7-Dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine-2-carboxamide Compounds | | |
| **Patent Application Number:** | WO 2017/145013 A1 | **Publication date:** | 31 August 2017 |
| **Priority Application:** | US 62/298,657 | **Priority date:** | 23 February 2016 |
| **Inventors:** | Chappie, T. A.; Patel, N. C.; Verhoest, P. R.; Helal, C. J.; Sciabola, S.; Lachapelle, E. A.; Wager, T. T.; Hayward, M. M. | | |
| **Applicants:** | Pfizer Inc.; 235 East 42nd Street, New York, NY 10017, USA | | |
| **Disease Area:** | Central nervous system (CNS), metabolic, autoimmune, and inflammatory diseases | **Biological Target:** | Phosphodiesterase 4B (PDE-4B) |

**Summary:**

The invention in this patent application relates to 6,7-dihydro-5*H*-pyrazolo[5,1-*b*][1,3]oxazine derivatives represented generally by formula I. These compounds are inhibitors of PDE-4 isozymes, especially with a binding affinity for the PDE-4B isoform, and may be useful for the treatment of central nervous system (CNS), metabolic, autoimmune, and inflammatory diseases or disorders.

The cyclic nucleotides, 3′,5′-cyclic adenosine monophosphate (cAMP) and guanosine 3′,5′-cyclic guanosine monophosphate (cGMP), are examples of second messengers that regulate many intracellular processes. They are intracellular signaling molecules released by cells to initiate intracellular signal transduction cascades, which cause the occurrence of several biological processes such as proliferation, differentiation, migration, survival, and apoptosis. An example of their activities is the cAMP activation of the cAMP-dependent kinases in the neurons of the central nervous system to initiate the phosphorylation of specific proteins to regulate synaptic transmission as well as neuronal differentiation and survival.

The level of intracellular cAMP is regulated by a balance between the activities of two types of enzyme: adenylyl cyclases (AC), which catalyze the formation of cAMP from adenosine triphosphate (ATP), and phosphdiesterases (PDEs), which degrade cAMP. There are at least ten known families of adenylyl cyclases and 11 families of phosphodiesterases to achieve this balance, a testament to the complexity and importance of the cyclic nucleotide signaling process.

Phosphodiesterases (PDEs) are intracellular enzymes that hydrolyze cAMP and cGMP into the nonsignaling molecules 5′-adenosine monophosphate (AMP) and 5′-guanosine monophosphate (GMP), respectively. In addition to the main families of PDEs, different types of neurons are known to express multiple isozymes of each of these families of enzymes, and there is good evidence for compartmentalization and specificity of function for different isozymes within a given neuron.

The 11 known families of PDEs are encoded by 21 different genes; each gene typically yields multiple splice variants that further contribute to the isozyme diversity. The PDE families are distinguished functionally based on cyclic nucleotide substrate specificity, mechanism(s) of regulation, and sensitivity to inhibitors. Furthermore, PDEs are differentially expressed throughout the organism, including in the central nervous system. As a result of these distinct enzymatic activities and localization, different PDE isozymes can serve distinct physiological functions. Therefore, selective inhibitors of distinct PDE isozymes may have the advantage of delivering specific therapeutic effects, fewer side effects, or both.

The compounds described in this patent application display a binding affinity for the PDE4 family of enzymes (PDE-4A, PDE-4B, PDE-4C, and PDE-4D), particularly for the PDE-4A, PDE-4B, and PDE-4C isoforms.

The function of PDE-4 isozymes can be inhibited by known selective PDE-4 inhibitors such as Roflumilast (Daliresp), which was approved for the treatment of severe chronic obstructive pulmonary disease (COPD) and Apremilast (Otezla), which was approved for the treatment of adults with active psoriatic arthritis.

It is clear from the above that PDE-4 inhibitors can provide needed and beneficial pharmacological activities that have been realized into known therapies. However, their use has been associated with induction of common gastrointestinal side effects such as nausea, emesis, and diarrhea. It was hypothesized that these undesirable adverse effects are associated with the inhibition of the PDE-4D isoform. Thus, research efforts were directed to develop compounds with selective affinities for the inhibition of PDE-4B isoform over the PDE-4D isoform. It is anticipated that compounds with enhanced binding affinity for the PDE-4B isoform over the PDE-4D isoform can be useful in the treatment of various diseases and disorders of the central nervous system (CNS) with fewer side effects.

The compounds of formula I described in this patent application show selective affinity for the inhibition of PDE-4B isoform, and therefore, they have the potential to provide useful therapies for the treatment of various diseases and disorders of the central nervous system (CNS), as well as metabolic, autoimmune, and inflammatory diseases or disorders. Their use may also lead to decreased gastrointestinal side effects (e.g., nausea, emesis, and diarrhea) believed to be associated with inhibition of the PDE-4D isoform.

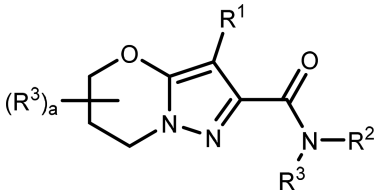
**Received:** October 15, 2017
**Published:** October 27, 2017





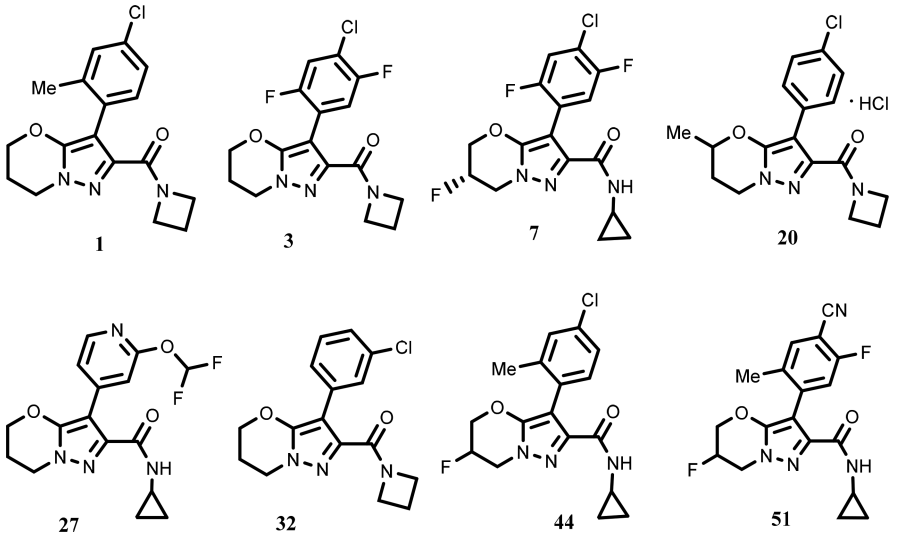
DOI: 10.1021/acsmedchemlett.7b00425
ACS Med. Chem. Lett. 2017, 8, 1132−1133

**Important Compound Classes:**



Formula I

**Key Structures:** The inventors reported the structures of 64 compounds of formula I, including the following representative examples. Few examples were resolved into enantiomers.



**Biological Assay:** The PDE-4A, PDE-4B, PDE-4C, and PDE-4D binding affinities for formula I compounds were determined.

**Biological Data:** The biological data obtained from testing the above representative examples are shown in the following table:

| example | Human PDE-4B1 FL $IC_{50}$ (nM) | Human PDE-4A3 FL $IC_{50}$ (nM) | Human PDE-4C1 FL $IC_{50}$ (nM) | Human PDE-4D3 FL $IC_{50}$ (nM) |
|---|---|---|---|---|
| **1** | 211[a] | 241[a] | 653[a] | >29800[a] |
| **3** | 27.6[a] | 31.9[a] | 104[a] | >15100[a] |
| **7** | 6.51 | 2.00 | 31.4 | 306 |
| **20** | 2970 | 11800 | >17000 | >30000 |
| **27** | 178[a] | 115 | 389 | >12800[a] |
| **32** | 207 | 188 | 48.2 | >12200 |
| **44** | 55.6 | 20.6 | 160 | 6420 |
| **51** | 26.7[a] | 12.0[a] | 108 | 558[a] |

a. Value represents the geometric mean of ≥7 determinations

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### Notes

The author declares no competing financial interest.



DOI: 10.1021/acsmedchemlett.7b00425
*ACS Med. Chem. Lett.* 2017, 8, 1132−1133