ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Autotaxin Inhibitors May Treat Pain and Osteoarthritis

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Title:	Pyrido- or Pyrrolo-Fused Pyrimidine Derivatives as Autotaxin Inhibitors for Treating Pain		
Patent/Patent Application Number:	WO 2014/110000 A1	**Publication Date:**	17 July 2014
Priority Application:	US 61/751,363 and US 61/777,201	**Priority Date:**	11 January 2013 and 12 March 2013
Inventors:	Beauchamp, T. J.; Dao, Y.; Jones, S. B.; Norman, B. H.; Pfeifer, L. A.		
Assignee Company:	Eli Lilly and Company; Lilly Corporate Center, Indianapolis, IN 46206, USA		
Disease Area:	Nerve injury-induced neuropathic pain and pain associated with osteoarthritis	**Biological Target:**	Autotaxin inhibition

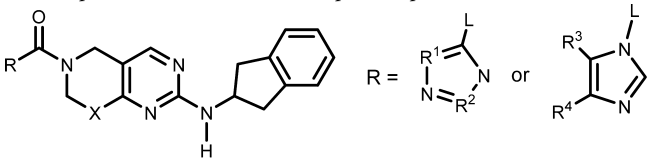
Summary:

The invention in this patent application relates to pyrido- or pyrrolo pyrimidine derivatives represented generally by formula (I). These compounds are autotaxin inhibitors and may be useful for the treatment of nerve injury-induced neuropathic pain particularly pain associated with osteoarthritis.

Autotaxin is an enzyme that is responsible for the biosynthesis of lysophosphatidic acid (LPA) from lysophosphatidylcholine. LPA is an intracellular lipid mediator, which influences several biological and biochemical processes including the up-regulation of pain-related proteins through LPA1, which is one if its cognate receptors. Inhibition of the autotaxin-mediated LPA biosynthesis may provide a novel mechanism to prevent nerve injury-induced neuropathic pain. The most common form of arthropathies is osteoarthritis (OA), which affects more than 20 million Americans. The pain associated with osteoarthritis is reported to be the primary symptom leading to lower extremity disability in OA patients. The currently approved treatments for OA pain may be invasive, may not be appropriate for treating all patients, and may lose efficacy with long-term use.

Autotaxin inhibitors that block the production of LPA can potentially offer a desirable treatment for patients suffering from pain associated with OA. Thus, there is a need for the discovery of novel autotaxin inhibitors such as the compounds described in this patent application to provide effective treatments for pain and pain associated with OA.

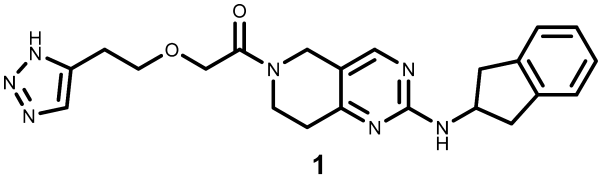
Important Compound Classes:



Formula (I)

Key Structures:

The inventors reported synthesis procedures and structures of 25 compounds of formula (I). The following two compounds are representative examples:



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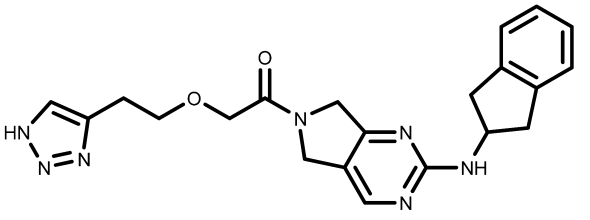

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Biological Assay:

- Inhibition of Autotaxin as Measured by Choline Release
- Reduction of LPA in the Presence of Human Plasma

Biological Data:

The inventors test results from the above two assays for compounds 1 and 2. The IC_{50} data for the two compounds are listed in the following table:

Inhibition of Autotaxin: Choline Release Assay			Reduction of LPA in Human Plasma		
Compound	IC_{50} (nM)	n	Compound	IC_{50} (nM)	n
1	5.7	7	**1**	10	6
2	<1.7	5	**2**	2.2	4

Recent Review Articles:

1. Barbayianni, E.; Magrioti, V.; Moutevelis-Minakakis, P.; Kokotos, G. *Expert Opin. Ther. Pat.* **2013**, *23* (9), 1123−1132.
2. Albers, H. M. H. G.; Ovaa, H. *Chem. Rev.* **2012**, *112* (5), 2593−2603.
3. Federico, L.; Pamuklar, Z.; Smyth, S. S.; Morris, A. J. *Curr. Drug Targets* **2008**, *9* (8), 698−708.

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Notes

The authors declare no competing financial interest.