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Viewpoint

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Prostaglandin E_2 Synthase-1 Inhibitors as Potential Treatment for Osteoarthritis

Patent Highlight

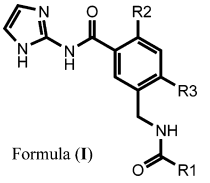
Ahmed F. Abdel-Magid*

Therachem Research Medilab (India) Pvt. Ltd., Jaipur, India

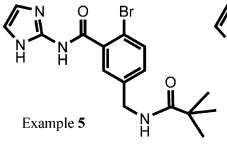
Title:	Novel Imidazole-2-benzamide Compounds Useful for the Treatment of Osteoarthritis		
Patent Application Number:	WO 2012/087771A1	**Publication Date:**	June 28, 2012
Priority Application:	US 61/425,478	**Priority Date:**	December 21, 2010
Inventors:	Kuklish, S. L.; Schiffler, M. A.; York, J. S.		
Assignee Company:	Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, United States		
Disease Area:	Osteoarthritis	**Biological Target:**	Microsomal Prostaglandin E_2 Synthase-1 (mPGES-1)

Summary: This patent application introduces compounds of formula (I) as novel inhibitors of mPGES-1 that may be useful for treating patients suffering from pain and/or inflammation associated with osteoarthritis. The application claims variations of the compound of formula (I) and the specific compound of formula (II) as well as their use in a method for treating inflammation and pain resulting from osteoarthritis. The inhibition of the enzyme mPGES-1 would result in reduced formation of Prostaglandin E_2 (PGE_2). PGE_2 is a main mediator of the osteoarthritis conditions, such as fever, pain, and inflammation. Its biosynthesis from arachidonic acid is mediated by several enzymes including cyclooxygenases and PGE_2 synthases (PGES). Cyclooxygenase-2 (COX-2) inhibitors (such as Celebrex and Vioxx) reduce PGE2 production to treat pain and inflammation, but they may also cause severe adverse effects including increased risk of heart attacks, thrombosis, and stroke. Vioxx was withdrawn from the market in 2004 because of concerns over potential serious complications. Similar to Cox-2 inhibitors, the inhibitors of the enzyme mPGES-1, which is involved in the conversion of the unstable intermediate PGH_2 into PGE_2 in a later stage of the biosynthesis, can also reduce the production of PGE_2. mPGES-1 inhibitors may be beneficial as an alternative treatment for osteoarthritis conditions, particularly if they prove safer to use and do not cause serious adverse effects.

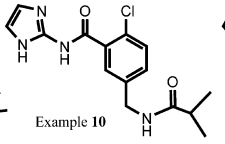
Important Compound Classes:



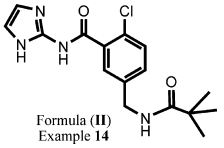
Formula (**I**)



Example **5**



Example **10**



Formula (**II**)
Example **14**

Biological Data: Three biological assays were reported for the same examples:

Human mPGES-1 enzyme inhibition assay

Example#	Human mPGES-1 Inhibition, IC_{50} (μM, mean ± std. dev.)
5	0.18 ± 0.046 (n = 2)
10	0.89 ±0.35 (n = 2)
14	0.24 ± 0.085 (n = 6)

Cell Based Assay for measuring Eicosanoid Selectivity

Example#	PGE_2 Inhibition, IC_{50} (μM, mean ± std. dev.)
5	0.19
10	2.77± 1.51 (n=3)
14	0.87 ± 0.42 (n = 5)

Human Whole Blood Assay

Example#	PGE_2 Inhibition, IC_{50} (μM, mean ± std. dev.)
5	0.607 ± 0.502 (n = 3)
10	0.792 ± 0.462 (n = 3)
14	0.74 ± 0.31 (n=6)

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Recent Review Articles:

Kawabata, A. *Biol. Pharm. Bull.* **2011**, *34* (8), 1170−1173.
Kojima, F.; Matnani, R. G.; Kawai, S.; Ushikubi, F.; Crofford, L. J. *Inflammation Regener.* **2011**, *31* (2), 157−166.
Kapoor, M.; Pelletier, J.-P.; Martel-Pelletier, J. In *Prostaglandins*; Goodwin, G. M., Ed.; 2010; pp 103−111.

AUTHOR INFORMATION

Corresponding Author

*Address: 1383 Jasper Drive, Ambler, Pennsylvania, 19002, United States. Tel: 215-913-7202. E-mail: afmagid@comcast.net.

Notes

The authors declare no competing financial interest.