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Biarylimidazoles as inhibitors of microsomal prostaglandin E_2 synthase-1

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ABSTRACT

Microsomal prostaglandin E_2 synthase (mPGES-1) represents a potential target for novel analgesic and anti-inflammatory agents. High-throughput screening identified several leads of mPGES-1 inhibitors which were further optimized for potency and selectivity. A series of inhibitors bearing a biaryl imidazole scaffold exhibits excellent inhibition of PGE_2 production in enzymatic and cell-based assays. The synthesis of these molecules and their activities will be discussed.

Inducible microsomal prostaglandin E_2 synthase-1 (mPGES-1) appears to be the predominant synthase involved in cyclooxygenase-2 (COX-2) mediated PGE_2 production.[1] Mice deficient in mPGES-1 show both a reduction in the production of inflammatory PGE_2 and a decrease in inflammatory responses in the collagen-induced arthritis model.[2,3] Furthermore, mPGES-1 knock-out mice exhibited no thrombogenesis nor blood pressure changes.[4] Thus, mPGES-1 inhibitors may achieve coxib-like efficacy in relieving pain and inflammation, while avoiding the adverse cardiovascular consequences associated with COX-2 mediated PGI_2 suppression.

An indole carboxylic acid series of mPGES-1 inhibitors derived from the FLAP (5-lipoxygenase activating protein) inhibitor, MK-886, has been previously described.[5] However, this series suffered from high protein binding, which resulted in decreased potency in cells. Hence, high-throughput screenings were carried out to search for other molecular scaffolds that may address this issue. The assay involved a 30-s mPGES-1 enzymatic reaction followed by detection of PGE_2 using EIA (enzyme immune assay).[6] Compound **2** was identified as a moderately potent mPGES-1 inhibitor (IC_{50} = 660 nM; Table 1). In IL-1β stimulated A549 epithelial lung carcinoma cells in presence of 2% and 50% FBS, compound **2** inhibited the production of PGE_2 (IC_{50} = 3100 and 7000 nM, respectively) but not $PGF_{2\alpha}$ (data not shown). Given its low molecular weight and structural simplicity, structural–activity relationship (SAR) studies were initiated on this series of compound.

The biarylimidazole scaffold could be divided into four segments for SAR analysis: the 2-imidazole position, the central imidazole ring, the 4-imidazole position, and the 5-imidazole position. At the 2-imidazole position, three compounds have been prepared. Compound **1** which contains a mono-*ortho*-cyanophenyl (IC_{50} = 1400 nM) and compound **3** with a bis-*ortho*-cyanofluoro phenyl (IC_{50} = 1000 nM) showed less affinity for the mPGES-1 enzyme (Table 1). Hence, the inhibitors described hereafter all contain the bis-*ortho*-chlorofluoro substitution pattern at the 2-imidazole position as in compound **2** (IC_{50} = 660 nM).

Moving the nitrogen on the central imidazole ring led to reduced activity against mPGES-1 (Table 2). Replacement of the central imidazole ring with an oxadiazole resulted in the complete loss of activity (compound **5**). A triazole derivative (compound **6**) showed superior inhibition in both the enzymatic (mPGES-1) and whole cell (A549) assays. These preliminary results suggest that the position of the H-bond donating NH is important for mPGES-1 activity.

For the 4-imidazole position, SAR studies show that *para*-relationship between the imidazole and R^3 is better than *meta*- and *ortho*- (data not shown). Hydrophobic groups are generally tolerated at the R^3 position (Table 3). Added flexibility of the linker resulted in lost of potency as can be seen with the alkyne linkage (compound **14**; IC_{50} = 8 nM) which is superior over the alkene (compound **12**; IC_{50} = 35 nM) and the alkane (compound **13**; IC_{50} = 150 nM). However, any polar substitutions on the phenyl alkyne

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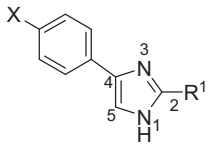
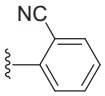
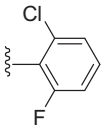
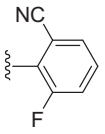
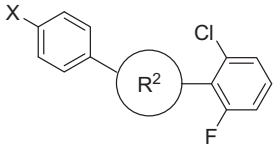
Table 1
SAR at the 2-imidazole position

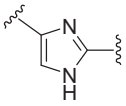
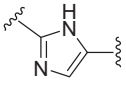
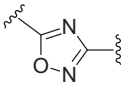
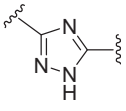


Entry	R^1	X	mPGES-1 IC_{50}[a] (nM)
1		Br	1400
2		Cl	660
3		Cl	1000

[a] Mean of two or more experiments.

Table 2
Replacing the central imidazole ring



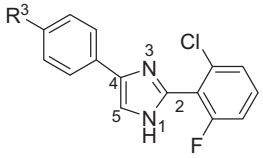
Entry	R^2	X	mPGES-1 IC_{50}[a] (nM)	A549 PGE_2 (2%/50% FBS) IC_{50}[a] (nM)
2		Cl	660	3100/7000
4		Br	3700	N/A
5		Br	>30,000	N/A
6		Br	110	620/1900

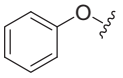
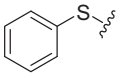
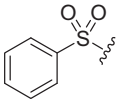
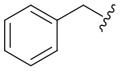
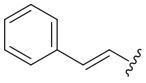
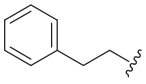
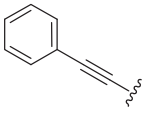
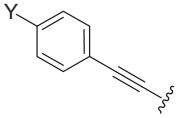
[a] Mean of two or more experiments.

(e.g., carboxylic acid, amide, sulfone, sulfonamide, and tertiary alcohol, compounds **15a–e**) led to the complete loss of enzyme inhibition. Although polar groups are not tolerated at all in the R^3 region of the inhibitors, introduction of a nitrogen atom on the 4-phenyl ring boosted cellular activities of PGE_2 synthesis inhibition, as exemplified by comparing compound **16** (Table 4) with compound **14** (Table 3). Subsequent derivatization all contained a triple bond linker extending from the 4-pyridyl group. Non-polar substituents on the phenyl alkyne afforded good mPGES-1 inhibitors, as did cyclohexyl (**19**) and cyclohexenyl (**20**) alkynes. The smaller cyclopropyl alkyne moiety (**21**) gave an inhibitor with slightly decreased potency, while the terminal alkyne analog (**22**) showed dramatically reduced potency. More polar heterocycle substituted alkynes were less potent inhibitors as well (compound **23**).

Addition of a substituent at the 5-imidazole position affected mPGES-1 activity (Table 5). In general, electron-withdrawing groups further increased the enzymatic potency (compounds **24**

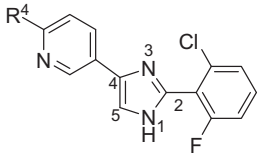
Table 3
SAR extending from the 4-phenyl group

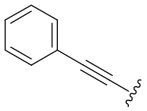
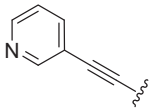
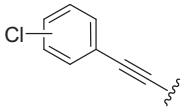
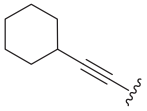
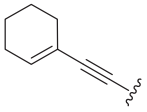
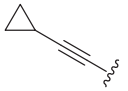
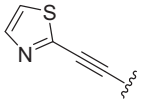


Entry	R^3	mPGES-1 IC_{50}[a] (nM)	A549 PGE_2 (2%/50% FBS) IC_{50}[a] (nM)
2		660	3100/7000
7		320	2100/27,000
8		180	1700/27,000
9		1400	>5000/>50,000
10		110	380/8700
11		570	1600/19,000
12		35	190/3300
13		150	920/13,000
14		8	280/3200
15a–e	 Y = CO_2H, $CONH_2$, SO_2CH_3, SO_2NH_2, $C(CH_3)_2OH$	>5000	NA

[a] Mean of two or more experiments.

Table 4
SAR extending from the 4-pyridyl group



Entry	R^4	mPGES-1 IC_{50}[a] (nM)	A549 PGE_2 (2%/50% FBS) IC_{50}[a] (nM)
16		23	29/520
17		480	410/1800
18a–c		ortho-9 meta-4 para-31	43/610 64/640 28/280
19		33	290/620
20		13	82/400
21		170	350/1800
22		2500	3300/4000
23		940	440/1400

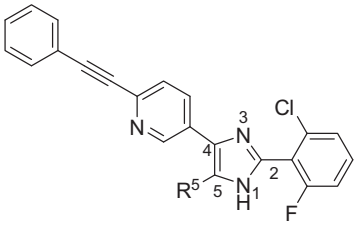
[a] Mean of two or more experiments.

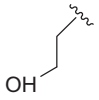
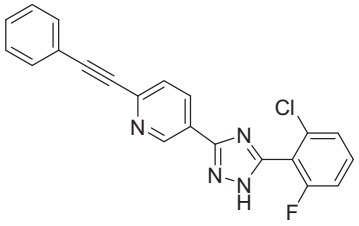
and **25**). Selected inhibitors were also tested in the human whole blood assay (HWBA) for inhibition of lipopolysaccharide-induced PGE_2 production.[7] Compound **25**, containing a bromo substituent on the 5-imidazole position, showed an IC_{50} of 1.6 μM in the HWBA, which is only threefold less active than rofecoxib (IC_{50} = 0.53 μM) and 1.5-fold less active than etoricoxib (IC_{50} = 1.1 μM).[8,9] Compound **25** also showed excellent bioavailability (127%) and a half-life of 4.8 h in rats (PO: 20 mpk in 60% PEG 200; IV: 5 mpk in 80% PEG 200). Inhibitors bearing a triazole (e.g., compound **28**) were not pursued further, since they generally exhibited lower potencies compared with the 5-bromo imidazoles.

The synthesis of compound **25** and similar biarylimidazole analogs is described in Scheme 1. Starting from commercially available arylmethylketones **29**, alpha bromination using bromine under acidic conditions gave alpha-bromoketones **30**. Intermediates **30** were then condensed with amidine **31** in refluxing aqueous $KHCO_3$/THF.[10] The amidine was prepared in a separate reaction by addition of LHMDS to the corresponding benzonitrile, followed by cleavage of the silyl groups under aqueous acidic conditions.[11] The resulting imidazoles **32** were coupled with alkynes under standard Sonogashira coupling conditions. Compounds **33** were brominated through an electrophile substitution using *N*-bromosuccinimide, followed by aqueous workup, to give the desired 5-bromo-biarylimidazoles **34**.

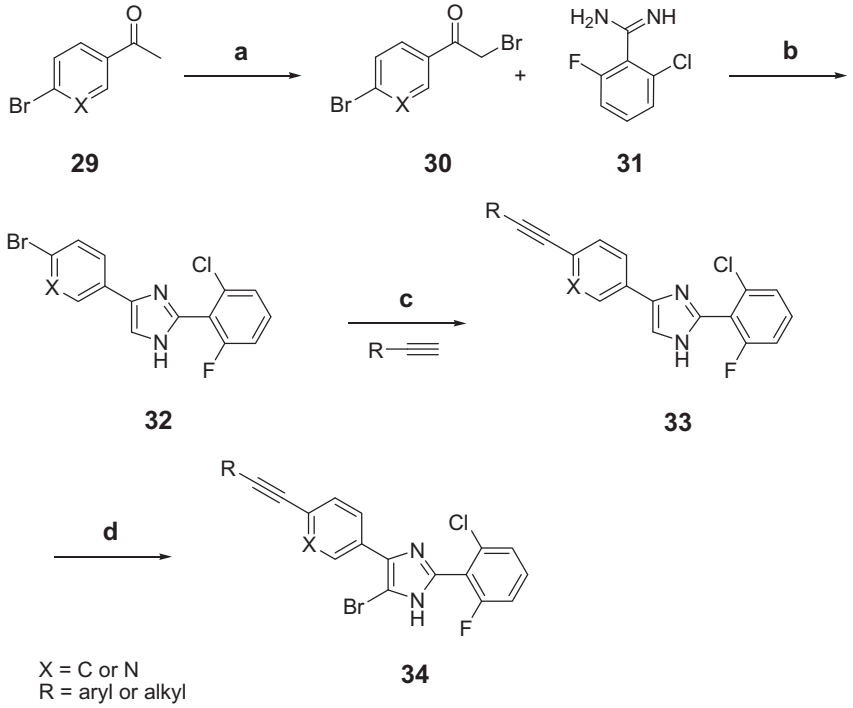
In summary, the present study demonstrates that biarylimidazole can serve as an excellent scaffold to design potent and selective mPGES-1 inhibitors with good rat pharmacokinetic properties. Even though this series still display a large serum shift, probably due to their high lipophilicity, several biarylimidazole inhibitors are less shifted in presence of serum proteins when compared to the indole carboxylic acid series.[5] In HWBA, the activity of compound **27** is approaching that of extensively-characterized COX-2 inhibitors rofecoxib and etoricoxib. It remains to be seen if inhibitors of mPGES-1 will demonstrate equivalent efficacy in inflammatory pain.

Table 5
SAR at the 5-imidazole position



Entry	R^5	mPGES-1 IC_{50}[a] (nM)	A549 PGE_2 (2%/50% FBS) IC_{50}[a] (nM)	HWBA IC_{50}[a] (nM)
16	H	23	29/520	3300
24	Cl	5	25/480	6800
25	Br	1	13/160	1600
26	CH_3	20	21/340	4800
27		180	160/700	N/A
28		16	130/850	9500

[a] Mean of two or more experiments.



Scheme 1. Reagents and conditions: (a) Br_2, HBr, AcOH, 0–40 °C, 1 h (54–74%); (b) $KHCO_3$ aq, THF, reflux, 3 h (50–70%); (c) $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 65 °C, 18 h (50–80%); (d) NBS, CCl_4, rt, 2 h; 1% HBr aq (65–85%).

References and notes

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Carty, T. J.; Perez, J. R.; Audoly, L. P. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 9044.
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