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Original Article

Targeting microsomal prostaglandin E synthase 1 to develop drugs treating the inflammatory diseases

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Abstract: Microsomal prostaglandin E synthase 1 (mPGES-1) is the terminal synthase of prostaglandin E2 (PGE2) which plays a crucial role in inflammatory diseases. Thus, mPGES-1 inhibitors are promising agents for their better specificity in blocking the production of PGE2, a potent inflammatory mediator, compared with non-steroidal anti-inflammatory drugs (NSAIDs). Currently, two mPGES-1 inhibitors are undergoing clinical trials and more novel inhibitors are being developed. In this review, we focus on the advances in the development of mPGES-1 inhibitors and the potential of these inhibitors to treat different inflammatory diseases, and discuss the existing challenges. The insights from this review will increase the understanding on the current status of mPGES-1-targeted anti-inflammatory drug development and the potential of these drugs in treating inflammation in diseases.

Keywords: mPGES-1, inhibitor, anti-inflammatory drug, inflammation, prostaglandin E2

Introduction

Prostaglandins (PGs) are a type of lipid mediators that have functional roles in both physiological and pathological conditions. The biosynthesis of PGs is initiated by the action of phospholipase A2, leading to the release of arachidonic acid (AA) from the membrane phospholipids. AA is converted by cyclooxygenases (COX-1 and COX-2) to intermediate prostaglandin G2 (PGG2), which is then converted into prostaglandin H2 (PGH2). Prostaglandins (PGD2, PGE2, PGI2, PGF2α, and TXA2) are synthesized from the same precursor PGH2 by different synthases (PGD synthase, PGE synthase, PGI synthase, PGF synthase, and TXA synthase). Among these PGs, prostaglandin E2 (PGE2) synthases play important roles in mediating inflammation (**Figure 1**). There are three types of PGE2 synthases, including microsomal prostaglandin E synthase 1 (mPGES-1), mPGES-2, and cytosolic PGES (cPGES). mPGES-2 and cPGES are constitutively expressed and their roles on PGE2 production are still controversial [1, 2]. mPGES-1 normally shows a low expression level in most tissues, while it is inducible under different pathological states. Compared with COX-2, mPGES-1 is a more selective target in blocking PGE2 production, and strategies targeting mPGES-1 are expected to be more specific and effective in treating inflammatory diseases.

In the past decades, a number of mPGES-1 inhibitors were developed and examined under pathological and/or physiological conditions with two inhibtitors entered the clinical trials [3, 4]. Thus, the translational potential of mPGES-1 inhibitors in treating human diseases is becoming promising. In this review, we will discuss mPGES-1 inhibitors in terms of their classifications, applications in inflammatory diseases, and the remaining problems, providing new insights into the research and clinical application of mPGES-1 inhibitors.

Structure and general function of mPGES-1

mPGES-1 is a membrane associated protein and shares a similar sequence with microsomal glutathione-S-transferase (GST)-1-like 1

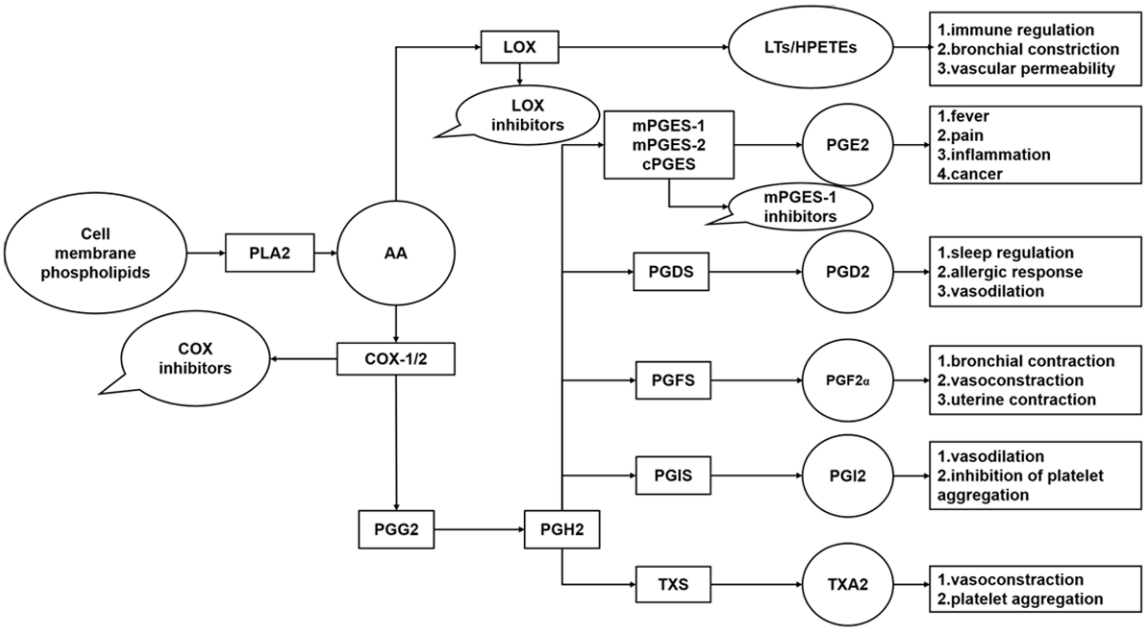


Figure 1. Arachidonic acid metabolic pathway and the function of prostaglandins. Phospholipases (PL) A2 release polyunsaturated fatty acids including arachidonic acid (AA) from membrane phospholipids. Oxygenation of AA by cyclooxygenases (COX-1/2) and lipoxygenases (LO) and further metabolization lead to the production of various lipid mediators with diverse functions. AA, arachidonic acid; COX, cyclooxygenase; LOX, lipoxygenase; PGG/H2, prostaglandin G/H2; mPGES-1/2, microsomal prostaglandin E synthetase1/2; cPGES, cystosolic PGES; PGD/F/I S, prostaglandin D/F/I synthetase; PGE/D/F/I, prostaglandin D/E/F/I; TXS, thromboxane synthetase; TXA2, thromboxane A2; HPETE, hydroperoxyeicosatetraenoicacid; LTs, leukotrienes.

(MGST-1), 5-lipoxygenase (LOX)-activating protein (FLAP), and leukotriene C4 synthase (LTC4S) [5]. mPGES-1 is an inducible terminal synthase that mostly couples to COX-2 to mediate PGE2 production. Physiologically, PGE2 acts as an important mediator in cell protection (including gastric mucosa defense and neuro-protection) [6, 7], water-electrolyte metabolism and blood pressure regulation [8], and cell growth and differentiation [9]. PGE2 also participates in various pathological processes, such as pyrexia, inflammation, pain sensation, and cancer [10]. Inflammation is a defensive response to extrinsic or intrinsic stimuli. During this process, enhanced expression of COX-2 and mPGES-1 leads to the overproduction of PGE2, contributing to the development of various inflammatory diseases.

Role of mPGES-1 in inflammatory diseases

mPGES-1 in cardiovascular disease

Cardiovascular disease threatens human health and is tightly associated with inflammation. mPGES-1 was reported to be associated with kinds of cardiovascular events by inducing the production of PGE2. In atherosclerosis, PGE2 was reported to increase the instability of atherosclerotic plaque by upregulating the matrix metalloproteinase (MMP)-2/9 in macrophages [11]. On the other hand, mPGES-1 depletion alleviated atherogenesis by suppressing PGE2 production and restrained thrombosis by augmenting PGI2 production [12]. Furthermore, it was discovered that mice with mPGES-1 deletion in myeloid cell displayed ameliorated atherosclerosis evidenced by smaller area of involved lesions, reduced inflammatory response, and alleviated oxidative stress, whereas mPGES-1 disruption in vascular smooth muscle cells, endothelial cells, or both showed little effect on atherogenesis [13]. Besides, mice lacking mPGES-1 conditionally in macrophage (Mac-mPGES-1-KO) also exhibited increased post-myocardial infarction (MI) survival rate but undetectable post-MI cardiac remodeling, reflected by comparative post-MI hypertrophy and fibrosis compared with WT (wild-type) mice [14]. Above evidence suggest that strategies targeting mPGES-1 in macrophage might be promising to treat and prevent

cardiovascular inflammatory diseases like atherosclerosis and myocardial infarction. In addition, mPGES-1 also participates in blood pressure regulation. Some reports stated that mPGES-1 deletion showed no effects on blood pressure of mice fed normal or high-salt diet [15, 16]. On the contrary, Jia and Zhang observed elevated blood pressure in mPGES-1 KO mice challenged with salt loading and angiotensin II (Ang II) infusion [17, 18]. Using mice with different genetic background of DBA/1lacJ and 129/SvEv, Carie S Facemire further explored the effects of mPGES-1 on blood pressure. In this study, 129-mPGES-1(-/-) mice exhibited exacerbated hypertension and albuminuria, while mPGES-1 deletion in mice with DBA/1 background showed little effect [19], which suggest that genetic background may determine the impact of mPGES-1 on blood pressure regulation.

mPGES-1 in brain disease

mPGES-1 also plays a crucial role in brain-associated inflammatory diseases. For example, mPGES-1 was remarkably induced, along with the increased production of PGE2, after cerebral cortex transient ischemia in a rat middle cerebral artery occlusion-reperfusion (MCAO) model [20]. In this experimental setting, deficiency of mPGES-1 significantly ameliorated cortex infraction, edema, neuron apoptosis, and behavioral neurological dysfunction, as evidenced by decreased infract volume, fewer terminal deoxynucleotidyl transferase nick-end-labeling (TUNEL) and caspase-3 positive nerve cells, lower neurological score, and higher motor activity [20]. mPGES-1 also plays a part in Alzheimer's disease (AD). Akitake observed increased expression of mPGES-1 in patients with AD and Tg2576 mice (a transgenic AD mouse model) [21]. They further discovered that microglia accumulation around senile plaques and learning disorders were ameliorated in mPGES-1-deficient Tg2576 mice. Interestingly, in mixed neuron-glial culture, mPGES-1 was induced together with COX-2 in LPS-stimulated microglia but not in neurons, astrocytes, and oligodendrocytes. Consistently, enhanced expression of mPGES-1 was detected in activated microglia in the rat substantia nigra after local injection of LPS [22]. Although multiple findings indicated a role of mPGES-1 in diverse cerebral inflammatory diseases, yet the exact functions of mPGES-1 in different types of cerebral cells remain to be further investigated.

mPGES-1 in arthritis and periodontitis

mPGES-1 is also involved in the pathology of arthritis and periodontitis. In a rat adjuvant-induced arthritis (AIA) model, the mRNA and protein level of mPGES-1 in treated paws were significantly increased [23]. mPGES-1-deficient mice displayed attenuated inflammation and pain response as well as reduced severity of disease evidenced by less pannus formation and joint erosion in collagen-induced arthritis (CIA) and collagen antibody-induced arthritis (CAIA) models [24, 25]. Besides, mPGES-1 is also related to osteoarthritis (OA). Remarkably elevated mRNA and protein levels of mPGES-1 were detected in cartilage and synovial tissues of patients with OA. And in vitro experiments also showed that pro-inflammatory factors could induce mPGES-1 expression in chondrocytes from patients with OA [26]. Anti-inflammatory drugs predominate in the treatment of arthritis; therefore, it is urgent to find more effective therapeutic strategies with fewer side effects, and mPGES-1 might be a promising target. Besides arthritis, mPGES-1 might also play a role in periodontitis. One research found that the expression of mPGES-1 was upregulated in tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β)-treated gingival fibroblasts and smooth muscle cells (SMCs). However, similar effects were not observed in gingival endothelial cells and mast cells [27], which suggested that different types of cells might play diverse roles in affording to mPGES-1-associated inflammation.

Classifications of mPGES-1 inhibitors

mPGES-1 was firstly identified as prostaglandin E synthase by Jackobsson in 1999 [28]. An insufficient understanding of the structure and function of mPGES-1 led scientists to mainly focus on the known anti-inflammatory drugs and proteins related to AA metabolism to look for potential mPGES-1 inhibitors. NSAIDs and selective COX2 inhibitors, exemplified by sulindac and NS-398, elicited mPGES-1 inhibition in the low micromolar range [29]. Beside, endogenous lipids like cysteinyl leukotrienes (LTC4) [29], PGs derivatives such as 15-deoxy-

$\Delta^{12,14}$-PGJ_2, fatty acid like AA, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) also had some inhibitory activity against mPGES-1 [30]. This inhibition of mPGES-1 may contribute to their anti-inflammatory properties to some extent. Later, a number of synthetic compounds and natural derivatives with the property of mPGFES-1 inhibition were developed as potential mPGES-1 inhibitors (**Tables 1** and **2**).

mPGES-1 inhibitors from synthetic compounds

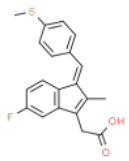
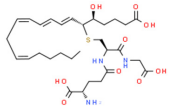
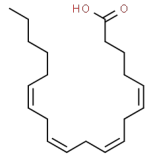
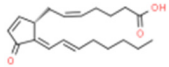
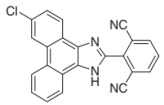
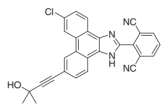
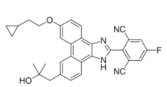
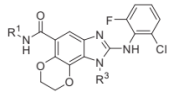
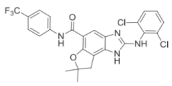
Phenanthrene imidazoles

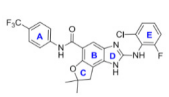
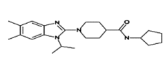
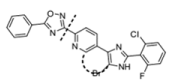
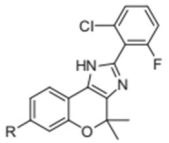
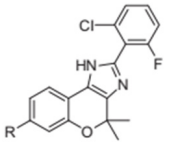
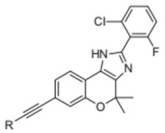
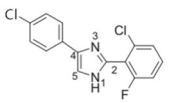
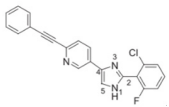
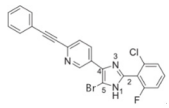
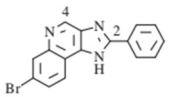
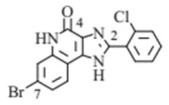
The janus kinase (JAK) inhibitor, azaphenanthrenone, was identified as a lead structure for mPGES-1 inhibitors by using an high-throughput screening (HTS) strategy [31]. Coˆte further carried out an internal HTS and structure-activity relationship (SAR) study, which contributed to the identification of MF63, the first reported mPGES-1 inhibitor with a satisfactory inhibitory activity against mPGES-1. MF63 significantly inhibited human mPGES-1 in cell-free assays (half maximal inhibitory concentration (IC50) = 1 nM), A549 cells (IC50 = 0.42 μM), and HWB assays (IC50 = 1.3 μM) [32]. When administrated orally at 100 mg/kg, MF63 completely inhibited hyperalgesic response in guinea pigs [33]. Further, in an equine inflammation model, MF63 only decreased the extracellular PGE2 level (IC50 = 0.1147 μM), while both NS-398 (a COX-2 inhibitor) (IC50 = 0.0528 μM) and indomethacin (a nonselective COX inhibitor) (IC50 = 0.0159 μM) reduced multiple prostaglandins, including PGE2, thromboxane A2 (TXA2), and PGI2 [34]. Besides, MF63 treatment maintained a higher PGE2 level compared with COX inhibitors at baseline, which preserved PGE2's homeostatic physiological function [34]. By constant SAR and pharmacokinetic (PK) analysis of the disubstituted phenanthrene imidazoles, Giroux and his team identified another two phenanthrene imidazole derivatives (compound 26 and 44) as more competent mPGES-1 inhibitors [35]. Compound 44 showed satisfactory inhibition of mPGES-1 in an enzyme assay (IC50 = 0.0009 μM) and an HWB assay (IC50 = 0.14 μM), good selectivity (nearly no effects on other prostaglandins), preferable PK profiles with a significantly shortened half-life (2.3 h in mice), faster metabolic rate, better thermal stability, and enhanced oral efficacy (50% effective dose (ED50) = 14 mg/kg) in guinea pigs. However, no further investigations of this kind of mPGES-1 inhibitor have been reported since 2009.

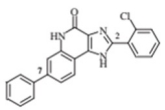
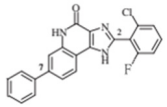
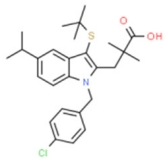
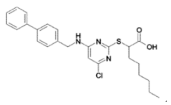
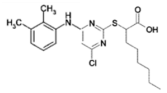
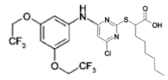
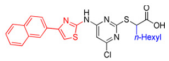
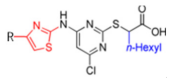
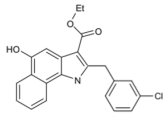
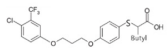
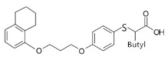
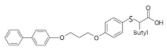
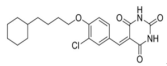
Benzimidazoles

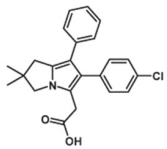
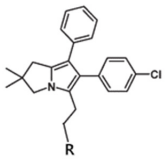
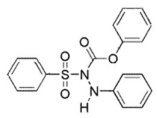
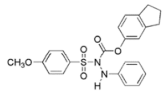
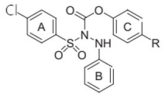
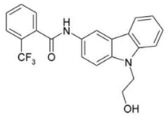
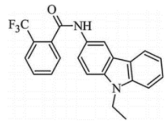
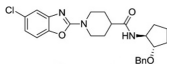
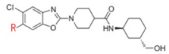
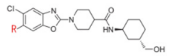
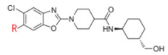
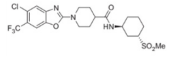
Muthukaman's team described some dioxane-fused tricyclic benzo[d] imidazole derivatives as potent mPGES-1 inhibitors [36]. Among these derivatives, compound 17d exhibited favorable human mPGES-1 enzyme inhibition (IC50 = 8 nM), A549 cell activity (IC50 = 16.24 nM), and HWB potency (IC50 = 249.9 nM), as well as guinea pig mPGES-1 inhibition (IC50 = 10.79 nM). Unfortunately, compound 17d showed no inhibition against rat or mouse mPGES-1 enzyme. Still, it displayed good selectivity, excellent metabolic stability, and reasonable oral PK profiles. Furthermore, the hyperalgesic response was markedly attenuated by compound 17d in LPS-induced thermal hyperalgesia pain model (ED50 = 36.7 mg/kg). These properties qualified compound 17d for a preclinical toxicity study. Additionally, a series of furan-fused tricyclic benzo[d]imidazole analogs were further synthesized, and compound 8l and 8m displayed potent mPGES-1 enzyme inhibition (IC50 = 3.7 and 3.9 nM, respectively) in guinea pigs [37]. In particular, compound 8m exhibited higher efficiency in guinea pig whole blood (IC50 = 222 nM), favorable selectivity (> 1000-fold over COX-1/2, mPGES-2, and cPGES), good metabolic stability, acceptable cytochrome P450 (CYP) inhibition, and moderate ether-a-go-go-related gene potassium channel (hERG) (patch clamp) liability. Specially, compound 8m also displayed adequate brain penetration (brain/plasma ratio = 0.22), satisfactory PK data across species in rats, guinea pigs, dogs, and cynomolgus monkey, and high oral bioavailability in rats and monkeys. Through combination of different substituents on A, D, and E ring of compound 8m, a series of compounds with comparative inhibitory potency in HWB assays, IC50 value ranging from 160 to 950 nM, were identified. Among them, compounds 21j, 21m, and 21p displayed excellent PK profiles, adequate CNS penetration, and high oral bioavailability, with fewer CYP and hERG liabilities [38]. Owing to the above properties, these compounds are expected to enter into clinical trials.

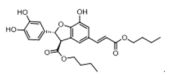
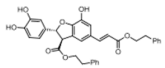
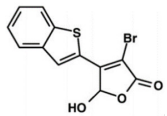
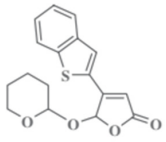
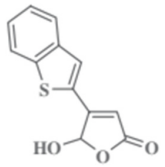
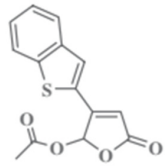
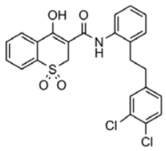
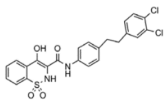
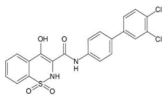
Table 1. Structures and efficacy of synthetic compounds

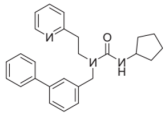
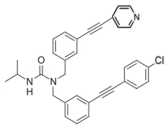
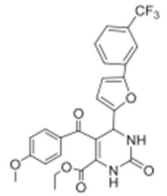
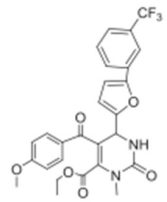
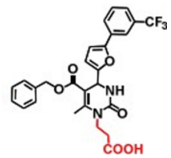
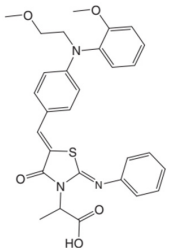
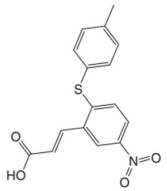
Classification	Name	Structure	IC50 in enzyme (human), A549 (2% FBS), and HWB assays	Citation
NSAIDs	Sulindac sulfide		Enzyme: 80 μM	[29]
Cysteinyl leukotrienes	LTC4 (cysteinyl leukotriene C4)		Enzyme: 5 μM	[30]
Fatty acid	Arachidonic acid		Enzyme: 0.3 μM	
Fatty acid analog	15-deoxy-12,14-prostaglandin J2		Enzyme: 0.3 μM	
Phenanthrene imidazoles	MF63		Enzyme: 1 nM (human); 0.9 nM (Guinea pig) A549: 0.42 μM (50% FBS) HWB: 1.3 μM	[32]
	Compound 26		Enzyme: 1 nM A549: 0.02 μM (50% FBS) HWB: 0.2 μM	[35]
	Compound 44		Enzyme: 0.9 nM A549: 0.01 μM (50% FBS) HWB: 0.14 μM	
Benzimidazoles	Compound 17d (R^1 = 3CF3, 5F-Phenyl R^3 = Me)		Enzyme: 8 nM (human); 10.79 nM (Guinea pig) A549: 16.24 nM HWB: 249.9 nM	[36]
	Compound 8l		Enzyme: 3.7 nM (human); 2.6 nM (Guinea pig) A549: 4.4 nM HWB: 234 nM	[37]

	Compound 8m		Enzyme: 3.9 nM (human); 6.3 nM (Guinea pig) A549: 10 nM HWB: 275 nM	
	Compound III		Enzyme: 90 nM (human); 0.9 μM (Rat) A549: 100% inhibition at 10 μM HWB: 100% inhibition at 80 μM	[39]
Tricyclic 4,4-dimethyl-3,4-dihydrochromeno[3,4-d]imidazole derivatives	Compound IX		Enzyme: 56 nM	[40]
	Compound 7 (R = 3CF3-phenyl)		Enzyme: 92.94 nM A549: 616.6 nM	
	Compound 9 (R = 3CF3O-phenyl)		Enzyme: 56.89 nM A549: 839.7 nM	
	Compound 11l (R = 2F, 5Cl-Phenyl)		Enzyme: 36.28 nM A549: 838.7 nM	
Biarylimidazoles	Compound 2		Enzyme: 660 nM A549: 3.1 μM	[41]
	Compound 16		Enzyme: 23 nM A549: 29 nM HWB: 3.3 μM	
	Compound 25		Enzyme: 1 nM A549: 13 nM HWB: 1.6 μM	
Imidazoquinoline Derivatives	Compound 1		60% enzyme inhibition at 10 μM	[42]
	Compound 33		Enzyme: 9.1 nM	

	Compound 17		Enzyme: 7.9 nM	[43]
	Compound 39		Enzyme: 4.1 nM A549: 33 nM	
Indole carboxylic acid derivatives	MK886		Enzyme: 1.6 μM	[44]
Pirinixic acid derivatives	Compound 7b		Enzyme: 1.3 μM	[47]
	YS121		Enzyme: 3.4 μM HWB: 3 μM	[48]
	LP105		Enzyme: 2.6 μM	[49]
	Compound 16		Enzyme: 0.94 μM	[50]
	Compound 13		Enzyme: 0.4 μM	[51]
Benzo[g]indol-3-carboxylates	Compound 7a		Enzyme: 0.6 μM A549: 2 μM	[54]
2-mercaptohexanoic acids	Compound 17		Enzyme: 1.7 μM	[55]
	Compound 19		Enzyme: 2.2 μM	
	Compound 21		Enzyme: 2.2 μM	
Benzylidenebarbituric acid derivatives	Compound 4b		Enzyme: 33 nM Mouse: 157 nM	[57]

Arylpyrrolizines (Licofelone derivatives)	Licofelone		Enzyme: 6 μM	[58]
	Compound 11f (R = CO-NH-SO2-Tol)		Enzyme: 2.1 μM	[59]
Phenylsulfonyl Hydrazide Derivatives	Compound 1		Enzyme: > 10 μM RAW264.7 cells: 5.7 μM	[60]
	Compound 8n		Enzyme: 70 nM RAW264.7 cells: 4.5 nM	[61]
	PBCH (R = BnO)		A549: 193.66 nM RAW264.7 cell: 60 nM HWB: 428.64 nM	[62, 63]
Benzamides	AF3485		A549: 1.98 μM	[64]
	AF3442		Enzyme: 0.06 μM Monocyte: 0.41 μM HWB: 29 μM	[65]
Benzoxazoles	Compound 37		Enzyme: 18 nM Fetal fibroblast: 34.7 nM HWB: 7.56 μM	[66]
	Compound 23 (R = CF3)		Enzyme: 33 nM HWB: 174 nM	[67]
	Compound 26 (PF4693627) (R = 4-Chlorophenyl)		Enzyme: 3 nM HWB: 109 nM	
	Compound 29 (R = 4-(Trifluoromethoxy) phenyl)		Enzyme: 2 nM HWB: 53 nM	
	Compound 35		Enzyme: 19 nM HWB: 250 nM	[68]

Dihydrobenzofuran derivatives	Compound 19		Enzyme: 2.1 μM	[69]
	Compound 20		Enzyme: 2.0 μM	
γ-hydroxybutenolide derivatives	BTH		RAW264.7 cells: 1.8 μM	[71]
	Compound 14g		RAW264.7 cells: 0.85 μM	[73]
	Compound 16g		RAW264.7 cells: 1.25 μM	
	Compound 18		RAW264.7 cells: 0.79 μM	
Oxciams	Compound 9		Enzyme: 1.68 μM Fetal fibroblast cell: 3.4 μM	[74]
	Compound 10		Enzyme: 0.11 μM	
	Compound 13j (PF-9184)		Enzyme: 16 nM	

Trisubstituted Ureas	Compound 3		88% enzyme inhibition at 10 μM	[76]
	Compound 42		Enzyme: 2 nM A549: 0.34 μM (50% FBS) HWB: 2.1 μM	
Dihydropyrimidin Derivatives	Compound 34		Enzyme: 4.16 μM	[77]
	Compound 35		Enzyme: 7.56 μM	
	Compound 4		Enzyme: 0.41 μM	[78]
Other scaffolds	Compound 3		Enzyme: 3.5 μM	[56]
	Compound 4		Enzyme: 4.6 μM	

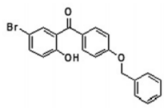
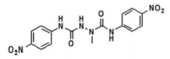
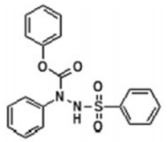
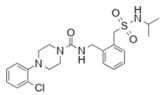
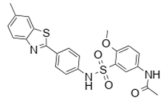
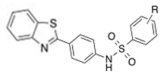
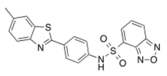
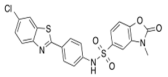
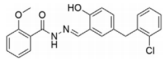
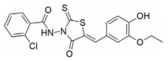
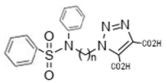
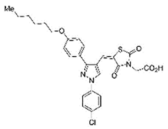
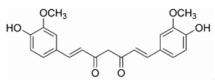
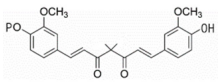
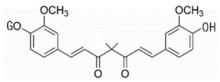
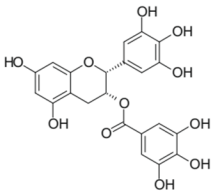
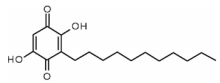
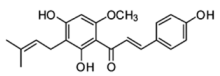
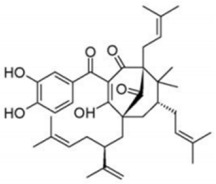
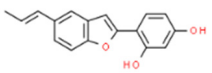
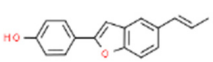
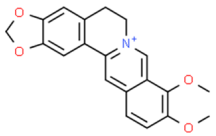
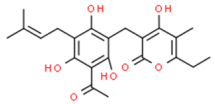
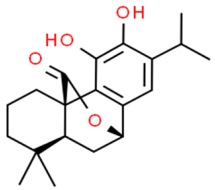
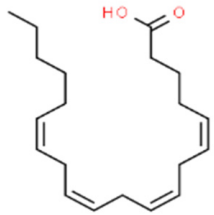
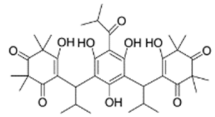
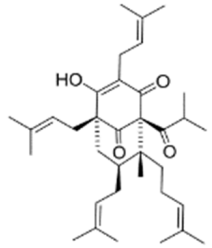
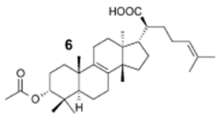
Compound 1a		Enzyme: 1.4 μM	[79]
Compound 2d		Enzyme: 0.9 μM	
Compound 3b		Enzyme: 1.7 μM	
Compound 6		Enzyme: 1.2 μM	[80]
Compound 8		Enzyme: 1.3 μM	
Compound 15 (R = 4-NHAc)		Enzyme: 0.6 μM	
Compound 19		Enzyme: 0.6 μM	
Compound 20		Enzyme: 0.3 μM	
Compound 6		Enzyme: 4.5 μM	[81]
Compound 7		Enzyme: 3.8 μM	
Compound 6f		Enzyme: 1.1 μM	[82]
Compound 14f		Enzyme: 36 nM	[83]

Table 2. Structures and efficacy of natural derivatives

Plant name	Compound	Structure	IC50 in enzyme, A549, and HWB assays	Citation
Zingiber officinale	Curcumin		Enzyme: 0.22 μM	[84]
	Compound 5		Enzyme: 0.93 μM	
	Compound 9		Enzyme: 1.02 μM	
Green tea	Epigallocatechin-3-gallate (EGCG)		Enzyme: 1.8 μM HWB: > 3 μM	[86]
Embelia ribes	Embelin		A549: 0.21 μM	[87]
Humulus lupulus L	Xanthohumol		A549: 32.3% residual activity (10 μM)	[88]
Garcinia	Garcinol		Enzyme: 0.3 μM A549: 1.2 μM HWB: 30 μM	[89]
Karameria lappacea	Lignans (Compound 6)		Enzyme: 7.4 μM	[90]
	Lignans (Compound 8)		Enzyme: 5.3 μM	
Berberis vulgaris	Berberine		71% inhibition against mPGES-1 at 50 μM (Hela cell)	[91]

Helichrysum italicum	Arzanol		A549: 0.4 μM	[93]
Salvia officinalis	Carnosol (CS)		Enzyme: 10.9 μM	[94]
	Carnosic acid (CA)		Enzyme: 14.9 μM HWB: 9.3 μM	
Myrtus communis	Myrtucommulone (MC)		Enzyme: 1 μM	[96]
Hypericum perforatum	Hyperforin (Hyp)		Enzyme: 1 μM HWB: 0.03-1 μM	[97]
Boswellia	3α-acetoxy-8,24-dienetirucallic acid		Enzyme: 0.4 μM	[98]

Compound III, also belonging to benzimidazoles, was characterized by Leclerc [39]. Compound III dose-dependently inhibited the human mPGES-1 enzyme (IC50 = 0.09 μM), as well as PGE2 synthesis in A549 cells and HWB assays. Notably, it also showed inhibition against recombinant rat mPGES-1 (IC50 = 0.9 μM) and suppressed PGE2 generation in mouse peritoneal macrophages challenged with LPS. And no detectable inhibition against COX-1, COX-2, PGIS, or H-PGDS was observed after using compound III, even up to 50 μM. For this compound, dual inhibition against human and murine mPGES-1 enzyme and excellent selectivity were considered to be of greater advantage than some other mPGES-1 inhibitors. Unlike the reduction of 6 keto-prostaglandin F1α (PGF1α) and thromboxane B2 (TXB2) induced by NS-398, compound III treatment resulted in PGH2 switching to the prostacyclin pathway, increasing the formation of PGF1α and TXB2 in IL-1β-stimulated A549 cells [39]. In the mouse air pouch model, both mPGES-1 depletion and compound III administration reduced PGE2 synthesis. However, mPGES-1 deficiency led to an increase of TXB2, while compound III had no apparent shunting, but accompanied by a trend of general downregulation of other prostanoids (PGE2, TXB2, and 6keto-PGF1α). The difference between genetic deletion and enzymatic inhibition suggests that partial inhibition of gene may be more beneficial than its complete blockade in some settings. Overall, all these evidences showed that compound III might serve as a promising human and murine mPGES-1 inhibitor.

Tricyclic 4,4-dimethyl-3,4-dihydrochromeno[3,4-d]imidazole derivatives

Based on the known compound IX containing a non-acid core, Muthukaman identified the conformationally rigid tricyclic 3,4-dihydrochromeno [3, 4-d] imidazole (X) as a novel scaffold using a lead hopping strategy [40]. Lead hopping, which mainly includes ring opening or closure, replacements of hetercycle, and topology-based hopping, is a common strategy to discover novel scaffolds with enhanced properties. In this experimental setting, different substituents in different sites of X derived a series of novel mPGES-1 inhibitors, among which, compound 7, 9, and 11l showed remarkable inhibitory potency towards mPGES-1 (IC50 = 92.94, 56.89, and 36.28 nM, respectively), excellent mPGES-1 selectivity (> 150-fold over COX-2, > 70-fold over COX-1), good metabolic stability in liver microsomes of humans, rats and guinea pigs, and no significant CYP inhibition. Despite of the favorable PK profiles, compound 9 (200 mg/kg, 38%) and 11l (100 mg/kg, 26%) did not significantly alleviate hyperalgesic response in an LPS-induced hyperalgesia model in guinea pigs. This may be explained by the low brain penetration, poor cellular potency, and unspecific binding with plasma protein in this experimental model.

Biarylimidazoles

Serum protein binding is the primary barrier to drug design. To address this issue, Wu conducted an HTS strategy, leading to the identification of biarylimidazoles as mPGES-1 inhibitors [41]. SAR analysis of the four segments of biarylimidazole scaffold including the 2, or 4, or 5-imidazole position and the central imidazole ring yielded some novel compounds, represented by compound 2 (IC50 = 660 nM), compound 16 (IC50 = 23 nM), and compound 25 (IC50 = 1 nM). Compound 25 was the most effective, with favorable inhibitory activity in enzyme (IC50 = 1 nM), A549 cell (EC50 = 13 nM/2% FBS, 160 nM/50% FBS, respectively) as well as in the HWB assays (IC50 = 1.6 μM). It also showed favorable bioavailability (127%) and less half-life (4.8 h) in rats, suggesting its promising PK properties. Indeed, some of these biarylimidazole derivatives are less shifted in serum, yet some still manifested a mild serum shift probably due to their high lipophilicity. Unfortunately, no further preclinical or follow-up studies have been reported yet.

Imidazoquinolines

To identify novel potent mPGES-1 inhibitors, Shiro investigated imidazoquinolines [42]. Through an HTS strategy, imidazoquinoline derivative 1 with moderate inhibition towards mPGES-1 (60% at 10 μM) was recognized. Chemical modification of compound 1, 2-chlorophenyl group at the C(2)-position and the quinolone structure at the C(4)-position in particular, resulted in the identification of compound 33 which exhibited excellent mPGES-1 inhibi-

tion (IC50 = 9.1 nM) and mPGES-1 selectivity (> 1000-fold over COX-1/2) [42]. When the bromine at C(7)-position of compound 33 was replaced by phenyl group, compound 17 was generated with more inhibition against mPGES-1 (IC50 = 7.9 nM) [43]. Additional SAR studies led to the recognition of compound 39, which displayed more suppression on mPGES-1 (IC50 = 4.1 nM), potent cell-based functional activity (IC50 = 33 nM), impressive mPGES-1 selectivity (700-fold over COX), excellent *in vitro* absorption, distribution, metabolism, and excretion (ADME) profiles and good oral absorption in rats [43]. In consideration of these features, compound 39 deserved to be further evaluated. However, no relevant literature was published later.

Indole carboxylic acid derivatives (MK886 derivatives)

mPGES-1 shows a homology and similarity with FLAP. Thus, scientists turned to FLAP inhibitors, such as MK886, that was deemed to be the first identified mPGES-1 inhibitor [44]. Riendeau later developed about thirty MK886 derivatives via a SAR study, among which some possessed low nanomolar potency against mPGES-1. However, due to the poor whole blood cell activity of these derivatives, further development of these indole carboxylic acid derivatives was limited [45]. Later, a plausible binding mode between the indole derivatives and mPGES-1 was described by San Juan and Cho by performing three-dimensional (3D)-quantitative structure-activity relationship (QSAR)-comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) [46]. They found that steric, electrostatic, hydrophobic, and hydrogen bond donors significantly increased the activity of these compounds, providing strategies to improve the activity of mPGES-1 inhibitors. Based on a developed HTS and SAR strategy, several novel mPGES-1 inhibitors were identified, which showed better inhibition of mPGES-1.

Pirinixic acid derivatives

Based on the structure of pirinixic acid (PA), Koeberle presented a series of α-substituted PA derivatives as dual mPGES-1 and 5-LOX inhibitors [47]. Of these PA derivatives, compound 7b showed potent inhibition of mPGES-1 and 5-LOX (IC50 = 1.3 and 1 μM, respectively) as well as repression of PGE2 generation in intact cells, with less pronounced suppression of COX-1/2 [47]. YS121, an α-(*n*-hexyl)-substituted pirinixic acid (IC50 = 3.4 μM), was found to concentration-dependently inhibit PGE2 production in LPS-stimulated HWB assays (IC50 = 3 μM), and it showed little effect on TXB2 and 6-keto-PGF1α synthesis. However, in a carrageenan-induced pleurisy model in rats, YS121 (1.5 mg/kg) was found to significantly inhibit exudate formation (62%) and cell infiltration (40%) accompanied by a reduced level of PGE2, leukotriene B4 (LTB4), as well as 6-keto-PGF1α [48]. Reduction of LTB4 and PGE2 may synergize to provide higher anti-inflammatory efficacy. LP105, another PA derivative, also displayed multiple enzyme inhibition, including mPGES-1 (IC50 = 2.6 μM), 5-LOX (IC50 = 1.5 μM), and COX-1 (IC50 = 5~8 μM) [49]. Moreover, Hieke characterized a novel class of α-naphthyl pirinixic acids, among which compound 16 exhibited optimal *in vitro* pharmacological profiles with potent inhibition of mPGES-1 and 5-LOX (IC50 = 0.94 and 0.1 μM, respectively) [50]. However, the efficacy of compound 16 on PGE2 production in cells was not evaluated. There were also some aminothiazole-featured pirinixic acids, among which compound 13 suppressed mPGES-1 (IC50 = 0.4 μM) and 5-LOX (IC50 = 0.3 μM) in cell-free assays, while it induced the activation of peroxisome proliferator-activated receptor gamma (PPARγ) (EC50 = 1.3 μM) [51]. In zymosan-induced peritonitis mouse model, compound 13 was observed to decrease vascular permeability and to reduce inflammatory cell infiltration, accompanied by reduced cysteinyl-leukotrienes and PGE2 [52]. Although some of these inhibitors have demonstrated efficacy in animal models, their detailed *in vivo* efficacy and potential side effects are unclear.

Benzo[g]indol-3-carboxylates

It was reported that diverse indol-3-carboxylates possess 5-LOX inhibition exemplified by compound 2, which showed potent inhibition of 5-LOX in a cell-based assay (IC50 = 2.4 μM) and a cell-free assay (IC50 = 0.3 μM) [53]. Modification of compound 2 introduced compound 7a, which inhibited human mPGES-1 in cell-free assays (IC50 = 0.6 μM) and in A549 cells (IC50 = 2 μM) [54]. Despite having some

inhibition against COX-1/2, compound 7a did not significantly suppress 6-keto-PGF1α formation, till the concentration of 30 μM. Simultaneously, in carrageenan-induced paw edema mouse model and rat pleurisy model, compound 7a significantly ameliorated the inflammatory response by reducing PGE2 and LTB4, which suggested that the *in vivo* anti-inflammatory activity could represent the effects of double inhibition of mPGES-1 and 5-LOX.

2-mercaptohexanoic acids

2-mercaptohexanoic acids were identified as dual inhibitors of mPGES-1 and 5-LOX [55]. The lead compounds (17, 19 and 21) showed similar mPGES-1 inhibition (IC50 = 1.7, 2.2, and 2.2 μM, respectively) and 5-LOX inhibition. Besides, they showed no significant inhibitory effects on COX-1/2, cPLA2, and other human LOs (12/15-LO), indicating good selectivity for mPGES-1 and 5-LOX. However, cell-based and HWB assays were not performed, and the detailed function of these compounds deserve further exploration.

Benzylidenebarbituric acid derivatives

L2, a structure scaffold, was found to bind to a conserved region of the active site of human and murine mPGES-1 enzyme in a virtual screening [56]. Ding and his team designed a preferable scaffold (L3) by modifying L2 and synthesized a series of benzylidenebarbituric acid derivatives [57]. All these compounds exhibited mPGES-1 inhibition in human (IC50 = 33-620 nM) and mice (IC50 = 157 nM-19 μM), among which compound 4b was determined as the most potent one, with an IC50 of 33 nM in human and 157 nM in mice. Compound 4b also showed great selectivity, with almost no inhibition of COX-1/2 at the concentration of 100 μM. In mouse air-pouch model, compound 4b markedly decreased the PGE2 level after either subcutaneous or oral administration, and it showed no toxicity even at a high dose (1 g/kg), while the control drug, celecoxib, resulted in serious gastrointestinal toxicity at a lower dose of 50 mg/kg [57]. Compound 4b was expected to be a next-generation anti-inflammatory drug for its excellent potency, selectivity, safety, and oral availability.

Arylpyrrolizines (licofelone derivatives)

Licofelone (ML3000), the first proposed mPGES-1 and 5-lipoxygenase (5-LOX) inhibitor, showed mPGES-1 inhibition (IC50 = 6 μM) in cell-free assays and potently inhibited PGE2 production in IL-1β-treated A549 cells (IC50 < 1 μM) [58]. Based on the structure of licofelone, a series of arylpyrrolizine derivatives were synthesized and evaluated [59]. Substitution of sulfonimides at the free acid group improved the inhibitory potency toward mPGES-1 while retaining the sub-micromolar 5-LOX inhibition. Among these derivatives, compound 11f was about 3.2-fold superior to licofelone and was considered equipotent to MK886 (IC50 = 2.1 μM). In addition, compound 11f showed less inhibition against COX-1/2 compared with licofelone, indicating better specificity [59]. Additional investigations are needed to provide in-depth information regarding the *in vivo* activity of this kind of compounds.

Phenylsulfonyl hydrazide derivatives

By using the HTS strategy, researchers identified compound 1, which possessed a phenylsulfonyl hydrazide core and inhibited PGE2 production (IC50 = 5.7 μM) in LPS-induced macrophages, as an mPGES-1 inhibitor [60]. SAR studies of compound 1 resulted in the introduction of compound 8n, showing potent inhibition against mPGES-1 enzyme (IC50 = 70 nM) and LPS-induced PGE2 production (IC50 = 4.5 nM) [61]. It was further found that phenylsulfonyl hydrazide could be separated into two regioisomers, and kinetic product 7 exhibited powerful inhibition against mPGES-1 while thermodynamic product 8 possessed low inhibitory activity [62]. Kinetic product compound 7d, which was later named PBCH, markedly inhibited PGE2 production in RAW264.7 macrophages (IC50 = 60 nM), A549 cells (IC50 = 193.66 nM), and HWB assays (IC50 = 428.64 nM) [62, 63]. Besides, PBCH significantly alleviated edema in either croton oil applied ears or carrageenan-inoculated paws of rats [63].

Benzamides

AF3485 [64], emerging from benzamide derivatives, inhibited human recombinant mPGES-1 in bacterial membrane and microsomal mPGES-1 from transfected A549 cells. In addition, AF3485 completely suppressed PGE2 formation at 100 μM in IL-1β-stimulated A549 cells (IC50 = 1.98 μM) while PGF2α production was inhibited only at 100 μM, indicating good selectivity of AF3485. Unfor-

tunately, no *in vivo* study of AF3485 is available. AF3442 [65], inhibited mPGES-1 activity and PGE2 formation in LPS-induced monocytes (IC50 = 0.06 μM and 0.41 μM). In HWB assay, PGE2 production was inhibited (IC50 = 29 μM) by approximately 70% at 100 μM, and AF3442 exhibited no significant effects on other PG synthases, even up to 100 μM. Further *in vivo* experiments are expected to provide more information regarding its efficacy and toxicity.

Benzoxazoles

Benzoxazoles were found to restrain mPGES-1 by HTS [66]. Of them, compound 37 markedly inhibited mPGES-1 activity and PGE2 production (IC50 = 18 nM and 34 nM), along with good selectivity and oral bioavailability. Further SAR studies resulted in the discovery of more potent compounds [67]. The selected compounds (23, 26, and 29) showed significant inhibition against mPGES-1, with IC50 values of 33, 3, and 2 nM, respectively. These three compounds inhibited PGE2 production by approximately 60% in air pouch model in guinea pigs while 6-keto-PGF1α formation was not restrained. Besides, HWB/1483 and human fetal fibroblast assays verified that compound 26 (PF-4693627) was selective against relevant human enzymes, including TXAS, PGDS, 5-LOX, 15-LOX, 12-LOX and COX-2 [67]. The satisfactory *in vitro* and *in vivo* efficacy, good PK and safety profiles, and ease of synthesis allowed PF-4693627 to become a candidate for treating rheumatoid arthritis (RA) and osteoarthritis (OA) [67]. Notably, compound 35, another substituted benzoxazole, displayed better overall profiles than PF-4693627, suggesting that compound 35 might serve as a valuable alternative to PF-4693627 [68].

Dihydrobenzofuran derivatives

Di Micco pictured 2,3-dihydrobenzofuran as novel scaffold for mPGES-1 inhibitors design [69]. Consequently, compound 19 and 20 (IC50 = ~2 μM) were identified as new lead compounds targeting mPGES-1, which showed mPGES-1 inhibition approximately equivalent to that of MK886. Besides, they claimed that smaller hydrophobic groups could produce powerful Van Der Waals forces via deeper and tighter accommodation into the binding cavity. Additionally, the catechol moiety was preferred to establish H-bonds interaction to enhance the stability of these derivatives [69]. This provided new perspectives for the 2,3-dihydrobenzofuran core as a guiding structure for the design of mPGES-1 inhibitors. However, no further studies have been reported.

γ-hydroxybutenolide derivatives

Petrosaspongiolide M (PM), containing a γ-hydroxybutenolide scaffold, ameliorated inflammatory response in mouse colitis model [70]. Collection of PM analogs led to the generation of compound 4e (BTH) [71]. BTH inhibited PGE2 production via the downregulation of mPGES-1 with no effects on COX-2 in LPS-induced murine macrophage RAW264.7 cells and human monocytic THP-1 cells. Besides, in mouse air pouch model, BTH dose-dependently decreased the level of PGE2 and LTB4 in pouch exudates but only affected 6-keto-PGF1α level at the highest tested dose [72]. In another study, three compounds (14 g, 16 g, and 18) with more inhibition of PGE2 generation in RAW264.7 cells were identified by some structural changes of BTH [73]. All these evidence suggested that BTH could be a promising candidate of mPGES-1 inhibitor.

Oxicams

Based on the moderate inhibition of human mPGES-1 by benzothiopyran S-dioxides, exemplified by compound 9 (IC50 = 1.68 μM), Wang replaced the benzothiopyran with dioxobenzothiazinone (oxicam type) and identified compound 10 with better selectivity for mPGES-1 (IC50 = 0.11 μM) over COX-2 (IC50 > 68 μM) [74]. They then carried out a greater range of SAR by group substitution and changes of linkers. Results showed that the nature and position of the substituents on the D ring of the biphenyl analog (compound 13a) endowed these compounds with more inhibition against mPGES-1. Compound 13j, with 3,4-dichloro on the D ring, also termed PF-9184, exhibited the strongest inhibition against human mPGES-1 enzyme (IC50 = 0.016 μM) and in cell-based assays (IC50 = 0.42 μM). PF-9184 also displayed excellent mPGES-1 selectivity (> 238-fold over COXs) in IL-1β-stimulated fetal fibroblast cell assays while showing little effect on the production of 6-keto-PGF1α, PGF2α, and TXB2 (IC50 > 100 μM) [74]. In addition, com-

pared with a COX-2 inhibitor (SC-236), PF-9184 showed more desirable profiles on eicosanoid metabolism [75]. However, the inhibitory activity of PF-9184 in the HWB assay (IC50 = ~5 μM) was poor because of the high proportion of plasma protein binding.

Trisubstituted ureas

Using an HTS strategy, Chiasson identified a novel class of mPGES-1 inhibitor [76]. Trisubstituted urea (compound 3) was found to moderately inhibit human recombinant mPGES-1 with 88% enzyme inhibition (IC50 = 10 μM). The optimized trisubstituted ureas showed more inhibition against mPGES-1 (IC50 < 5 μM), among which compound 42, the most potent one, displayed good efficacy and selectivity in A549 cell assays (IC50 = 0.34 μM). However, these compounds showed worse potency in HWB assays (IC50 = 2.1-9.7 μM) compared with MF63 (IC50 = 1.3 μM) [76]. However, further PK properties and *in vivo* efficacy of this kind of compounds were not performed.

Dihydropyrimidin derivatives

Terracciano modified the dihydropyrimidin core (DHPM), which is endowed with several pharmacological effects, and identified decorated dihydropyrimidin-2(1H)-ones as novel promising mPGES-1 inhibitors [77]. Compound 34 and 35 inhibited mPGES-1 in a low micromolar range, with IC50 values of 4.16 μM and 7.56 μM, respectively. Some precise modifications were made based on the lead structure of compound 34. Consequently, three novel compounds were evaluated and compound 4 was identified as the most potent one with a DHPM scaffold (IC50 = 0.41 μM) [78].

Other scaffolds identified by virtual screening

Initially, compounds with mPGES-1 inhibition were explored using strategies based on SAR followed by HTS methods. Later, virtual screening approaches based on ligand or structure were employed to develop mPGES-1 inhibitors. Although virtual screening has brought in various novel scaffolds, none of them has been assessed in HBW assays or animal models. For example, screening a database containing 2.1 million structures resulted in 21 hits, which exhibited 10-83% inhibition of mPGES-1 at 10 μM. The most potent two, compound 3 and 4, inhibited the enzyme activity of mPGES-1 by 83% and were later determined to have an IC50 value of 3.5 μM and 4.6 μM, respectively [56]. Another screening of a chemical library led to three hits (1a, 2d, and 3b) with potent inhibition of mPGES-1 (IC50 = 1.4, 0.9, and 1.7 μM, respectively). Of the three, compound 3b significantly suppressed LPS-induced PGE2 production in RAW264.7 cells at 1 and 10 μM (59.94 ± 1.44% and 93.3 ± 2.27%, respectively) [79]. Furthermore, in a multi-step screening of a chemical library, two promising phenotypes (6 and 8) were identified as potent mPGES-1 inhibitors with IC50 values of 1.2 μM and 1.3 μM, respectively. Modification of chemotype 8 resulted in another three benzothiazole derivatives (15, 19, and 20) with increased inhibition (IC50 = 0.3-0.6 μM) [80]. Similarly, by screening the VITAS-M compound library (about 1.3 million lists) according to a multistep protocol, two compounds (6 and 7) showed satisfactory IC50 values of 4.5 μM and 3.8 μM toward mPGES-1 [81]. Additionally, Lee developed a novel strategy based on the replacement of glutathione with non-peptide mimics [82]. Consequently, 13 compounds with a broad range of IC50 values from 1.1 to 23.3 μM were qualified. The most active one, compound 6f, potently inhibited mPGES-1 (IC50 = 1.1 μM) and showed exceptional selectivity (> 1000 fold) over COX-1/2 in cell-free assays. Ding also characterized a series of compounds with increased inhibitory efficacy, among which compound 14f was identified as the most powerful one, with an IC50 value of 36 nM [83]. Together, virtual screening is a useful approach to explore novel inhibitors of mPGES-1 and it increases the diversity of mPGES-1 inhibitors, while the inhibitory potential of the acquired compounds still needs further evaluation.

mPGES-1 inhibitors from natural derivatives

Phenols

Curcumin, an acidic polyphenolic compound isolated from *Curcuma longa* (*Zingiber officinale*), moderately inhibited mPGES-1 (IC50 = 0.22 μM) [84]. With a similar structure to curcumin, 6-shogaol reduced the expression of mPGES-1 in IL-1β-stimulated A549 cells [85]. Small chemical modulation of curcumin led to

the identification of some curcumin prenylated derivatives, among which a monoisopentenylated derivative (compound 5) and a monogeranylated derivative (compound 9) exhibited potent inhibition of mPGES-1, with IC50 values of 0.93 μM and 1.02 μM, respectively [84]. Epigallocatechin-3-gallate (EGCG), a major polyphenol in green tea, was also found to display favorable inhibition of mPGES-1 (IC50 = 1.8 μM), moderate COX-1 inhibition (IC50 = 20~80 μM), and almost no COX-2 inhibition. It also suppressed PGE2 formation (≥ 3 μM) without affecting other concomitant prostaglandins synthesis in LPS-stimulated whole blood cell assays [86]. In addition, several kinds of natural derivatives showed dual inhibition towards mPGES-1 and 5-LOX. Embelin, the active constituent of the fruit of *Embelia ribes*, concentration-dependently inhibited PGE2 production in A549 cells treated with IL-1β (IC50 = 0.21 μM) and also showed potent inhibition against 5-LOX (IC50 = 0.06 μM) [87]. Xanthohumol, extracted from *Humulus lupulus L*, potently inhibited human mPGES-1 in A549 cells, with 32.3% residual enzymatic activity at a concentration of 10 μM and also displayed strong inhibition against 5-LOX (IC50 = 2.1 μM) [88]. Garcinol, isolated from *Garcinia,* showed mPGES-1 repression in enzyme, cell, and whole blood cell assays (IC50 = 0.3, 1.2 and 30 μM, respectively) [89]. Garcinol also showed inhibitory effects on COX-1 (IC50 = 12 μM) and 5-LOX (IC50 = 0.1 μM) in cell-free assays. Lignans, segregated from *Karameria lappacea* roots, exhibited pan inhibition targeting multiple enzymes, including mPGES-1, 5-LOX, and COX-1/2 [90]. Interestingly, most of these natural derivatives have inhibition of mPGES-1 and 5-LOX, making them suitable to be developed as dual mPGES-1 and 5-LOX inhibitors.

Other natural derivatives

Berberine, the major active component of *Berberis vulgaris,* dose-dependently suppressed PGE2 synthesis while showed no effects on COX-1/2 enzyme activity in air pouch model in Wistar rats [91]. In another study, berberine was determined to inhibit PGE2 production by 71.9% at a concentration of 50 μM in Hela cells [92]. Arzanol is the main anti-inflammatory constituents of *Helichrysum italicum*. It dose-dependently inhibited PGE2 formation, with an IC50 of 0.4 μM in IL-1β-stimulated A549 cells [93]. In carrageenan-induced pleurisy rat model, arzanol markedly alleviated exudate formation (by 59%) and cell infiltration (by 48%). Besides, arzanol also displayed potent semi-purified 5-LOX inhibition (IC50 = 3.1 μM) in cell-free assays [93]. Carnosol (CS) and carnosic acid (CA), as *Salvia officinalis* derivatives, were found to potently inhibit mPGES-1, with IC50 values of 10.9 μM and 14 μM, respectively. Meanwhile, they also showed inhibition of 5-LOX (CS: IC50 = 0.3 μM; CA: IC50 = 0.8 μM) [94]. In LPS-stimulated HWB assays, CA suppressed PGE2 synthesis (IC50 = 9.3 μM) while not inhibiting other prostanoids synthesis. Besides, it showed no effects on COX-1/2 activity in cell-free assays [95]. Myrtucommulone (MC) derived from *Myrtus communis* and the polyprenylated acylphloroglucinol hyperforin (Hyp) from *Hypericum perforatum* were claimed to possess inhibitory activity on mPGES-1 [96, 97]. MC and Hyp showed comparable mPGES-1 enzyme inhibition (IC50 = 1 μM) and also inhibited PGE2 formation in HWB assays at a low micromolar concentration. Besides, four pentacyclic triterpene acid compounds extracted from *Boswellia* species showed inhibition against mPGES-1, with IC50 values of 3-30 μM [98]. A 120-day follow-up clinical trial further verified that a novel *Boswellia serrata* extract (BSE) containing 3-acetyl-11-ketoβ-boswellic acid (AKBBA) and β-boswellic acid (BBA), significantly reduced pain, stiffness, knee joint gap, and osteophytes [99]. However, BSE only showed a mild inhibition against mPGES-1, and more effective derivatives are needed to be developed as selective mPGES-1 inhibitors. Although many plant-derived compounds have been characterized, most of them were just evaluated *in vitro* and few have entered into animal experiments.

mPGES-1 inhibitors in inflammatory diseases

To better understand the efficacy of mPGES-1 inhibitors, we will discuss some mPGES-1 inhibitors in several kinds of inflammatory diseases (**Figure 2**).

mPGES-1 inhibitors in cardiovascular diseases

It has been proposed that the shunting of PGH2 from PGE2 to prostacyclin contributes to the cardiovascular protection. To compare the

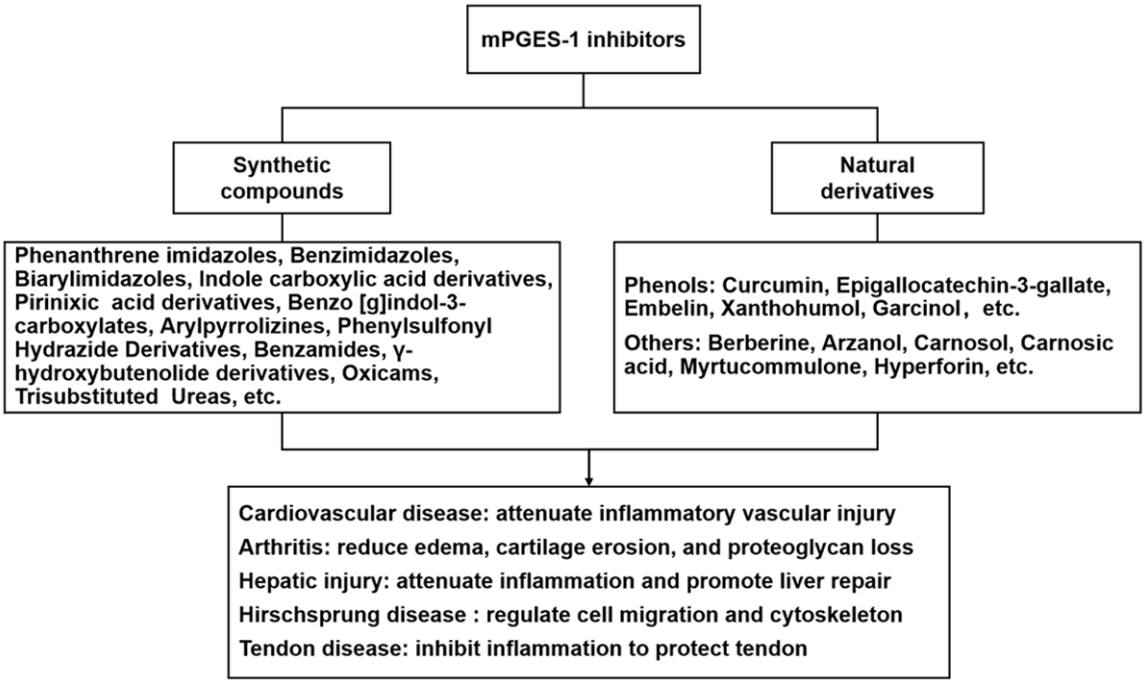


Figure 2. Classifications of mPGES-1 inhibitors and their roles in inflammatory diseases. In general, mPGES-1 inhibitors can be divided into two categories of synthetic compounds and natural derivatives. The roles of some mPGES-1 inhibitors have been investigated in diseases including cardiovascular diseases, arthritis, hepatic diseases, etc.

effects of mPGES-1 inhibitors and COX-2 inhibitors on vascular tone, Ozen established an *in vitro* model using the internal mammary artery (IMA) and saphenous vein (SV) with LPS and IL-1β stimulation [100]. The IMA and SV were obtained from patients who had undergone coronary artery bypass surgery. They found that an mPGES-1 inhibitor (Compound III, 10 μM) significantly suppressed vasocontraction induced by noradrenaline, while an IP-receptor antagonist (CAY10441, 1 μM) and a COX-2 inhibitor (DuP-697, 1 μM) increased the contraction of the IMA, although both Compound III (10 μM) and Dup-697 (1 μM) markedly decreased PGE2 release. However, Compound III elevated the level of 6-keto-PGF1α, while DuP-697 caused a remarkable decline of 6-keto-PGF1α in IMA and SV [39]. The attenuated vasocontraction by Compound III may attribute to the increased PGI2 synthesis after mPGES-1 inhibition. In another experiment, Larsson identified five compounds (934, 117, 118, 322, and 323) with dual human and mouse mPGES-1 inhibition (IC50 = 10-29 nM and 67-250 nM) and good selectivity [101]. These compounds inhibited PGE2 production in A549 cells stimulated with IL-1β (IC50 = 0.15-0.82 μM) and in HWB assays (IC50 = 3.3-8.7 μM). In addition, human *ex vivo* wire-myography analysis revealed that compound 118 exhibited better efficacy than Compound III at a 3-fold lower concentration (3 μM/10 μM), which notably reduced adrenergic vasoconstriction [101]. It was supposed that the cardiovascular side effects of COX-2 inhibitors, such as blood pressure elevation, could be greatly alleviated by the use of mPGES-1 inhibitors.

mPGES-1 inhibitors in arthritis

There have been some studies about mPGES-1 inhibitors in arthritis. The adjuvant-induced arthritis (AIA) model in rats is a well-established model that simulates human arthritis characteristics. In AIA model performed by Lee, PBCH significantly mitigated paw edema and reduced plasma prostaglandin E metabolite (PGEM) without affecting PGI2 and TXA2 production [63]. Besides, PBCH administration significantly decreased the *Ly6g6d* (lymphocyte antigen 6 family member G6D) mRNA level, the rheumatoid factor (RF) level, and the receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) ratio. With regard to the adverse effects, no significant changes in plasma parameters (alanine aminotransferase

(ALT), aspartate aminotransferase (AST), troponin I, and blood urea nitrogen (BUN)) were detected. Meanwhile, PBCH treatment did not cause gastric mucosal bleeding [63]. High efficacy and favorable safety make PBCH a promising mPGES-1 inhibitor for treating arthritis, and further investigations remain to be performed in other kinds of inflammatory diseases. Similarly, the *in vivo* efficacy of BTH in the chronic model of collagen-induced arthritis was also investigated. In this experimental setting, the arthritic incidence, together with the arthritic score, was remarkably reduced after BTH administration (5 mg/kg). Moreover, BTH markedly reduced inflammatory cell infiltration, cartilage erosion, and proteoglycan loss, accompanied by reduced PGE2 and LTB4 level [72]. These two representative compounds showed potent anti-inflammatory activity and low risk of cardiovascular and gastrointestinal side effects in arthritis models, and possible mechanism might be associated with mPGES-1 suppression accompanied by reduced PGE2 and LTB4, without affecting COX-2 expression and 6-keto-PGF1α level.

mPGES-1 inhibitors in hepatic ischemia/reperfusion

Hepatic ischemia/reperfusion (I/R) injury is a common postoperative complication and under this condition, PGE2 has been reported to play a critical role. In a mouse model of hepatic I/R conducted by Nishizawa, the expression of mPGES-1 was largely induced, mainly in neutrophils and Kupffer cells, along with the increased expression of PGE2 [102]. In this experiment, compound III significantly attenuated hepatic IR injury, manifesting as attenuated inflammation, necrosis, and oxidative stress. In addition, results showed that both pre-treatment and post-treatment with compound III promoted the repair of injuried liver after hepatic I/R, which is in agreement with the results shown in mPGES-1-KO mice challenged with hepatic I/R [102]. Compound III was able to promote liver restoration after acute I/R injury; however, whether other kinds of mPGES-1 inhibitors possess similar effects still requires further investigation.

mPGES-1 inhibitors in hirschsprung disease (HSCR)

Inflammation plays an important part in HSCR. Wu reported that the expression of mPGES-1, PGE2, and PGE2R was notably increased in HSCR colon tissues [103]. They also stated that mPGES-1-derived PGE2 damaged the cytoskeleton and suppressed cell migration by upregulating EP2 while downregulating actin related protein 2/3 complex subunit 2 (ARP2/3). After treating with the mPGES-1 inhibitor, MK886, the damaged cell morphology and function were partly reversed [103]. This may provide new insights to reveal the complicated mechanism of HSCR.

mPGES-1 inhibitors in tendon disease

Tendon disease is a disorder that causes great pain and always leads to disability. Bergqvist investigated the role and underlined mechanisms of prostanoids in tendon diseases [104]. Increased expression of the prostacyclin receptor together with multiple enzymes, including COX-1, COX-2, PGIS, and mPGES-1 were detected in diseased tendon tissue. The selected mPGES-1 inhibitor (compound III, 10 μM) significantly reduced PGE2 production in diseased as well as normal tendon stromal cells (by 83% and 70%, respectively), but increased 6-keto-PGF1α production by 240% only in diseased tendon cells. Although the non-selective COX inhibitor naproxen (10 μM) and the selective COX-2 inhibitor NS-398 (10 μM) also remarkably inhibited PGE2 production (> 96%), both of them also showed suppression on prostacyclin (> 96%) [104]. Due to the protective role of prostacyclin in tendon diseases, selective manipulation of PGE2 production may be a more favorable therapeutic strategy.

mPGES-1 inhibitors in clinical trials

Although there have been numerous reported mPGES-1 inhibitors, only a few of them have entered into clinical trials, including LY3023703 [3] and GRC27864 [4]. Jin carried out a multiple ascending study consisting of 48 participants receiving different treatments including LY3023703, celecoxib, and placebo, once daily for 28 days [3]. Ex vivo whole-blood analysis revealed LY3023703 (30 mg) showed more inhibition of LPS-induced PGE2 production (> 90%) compared with that of celecoxib (82%). Simultaneously, LY3023703 increased PGI2 synthesis by 115%, while celecoxib decreased PGI2 by 44%. Compared with the placebo, the difference in blood pressure or pulse rate was not statistically significant after LY3023703 treatment. Unfortunately, one subject developed markedly elevated serum aminotransfer-

ase (10-fold over the normal upper limit) after 28 days of 30 mg LY3023703 dosing, which met criteria for a severe treatment emergent adverse event (TEAE). Although most TEAEs were mild, such as abdominal pain, diarrhea, and constipation, LY3023703 was ultimately terminated from the clinical trial because of drug-induced liver injury. Later, Norman found it might be the reactive metabolites formation induced by LY3023703 that resulted in the observed hepatotoxicity [105]. The failure of LY3023703 suggested that these agents could be relatively safe in preclinical studies, there still might be some unexpected and serious problems in clinical studies.

GRC27864, a substituted pyrimidine derivative, showed potent inhibition of human mPGES-1 (enzyme assay: IC50 = 5 nM, HWB assay: IC50 = 376 nM), guinea pig mPGES-1 (enzyme assay: IC50 = 12 nM, HWB assay: IC50 = 161 nM), and dog mPGES-1 (HWB assay IC50 = 154 nM). It also displayed excellent selectivity for mPGES-1 (> 1000-fold) over multiple prostaglandins synthases (COX-1/2, mPGES-2, and cPGES) and good metabolic stability across species [4]. Besides, GRC27864 effectively depressed PGE2 synthesis in synovial fibroblasts and chondrocytes from patients with RA and OA [4]. Therefore, based on all these properties, GRC27864 entered into clinical trials. The Phase 1 study was to make a comprehensive evaluation of single ascending dose in healthy volunteers in 2014 (NCT02179645) and of multiple ascending doses in healthy subjects as well as elderly subjects in 2015 (NCT02361034). It is currently in Phase 2 trials, and the detailed outcomes of the clinical trials are not available. We expect GRC27864 to be applied in clinical therapy in the near future.

Potential limitations of mPGES-1 inhibitors

Although the functional roles of mPGES-1 inhibitors have been observed in experimental models *in vitro* and *in vivo*, there are also some potential limitations of mPGES-1 inhibitors that have impeded their applications in the clinic.

Specificity

Firstly, structural analogs of mPGES-1 or other members of MAPEG superfamily, such as MGST-1, FLAP and LTC4S, can also be affected by the identified inhibitors of mPGES-1. Besides, although many reported mPGES-1 inhibitors show potent inhibition of mPGES-1, they also inhibit other PGSs to some extent. In this way, they may cause some unexpected adverse effects. For example, mPGES-1 inhibition significantly increased the incidence and severity of CAIA in mice by upregulating the level of neutrophils (~3.6) in the inflamed joint, which might be associated with the unsatisfactory specificity of mPGES-1 inhibitors [106].

Species selectivity

Species selectivity is a significant limiting factor in drug research and naturally is a restraint on mPGES-1 inhibitor development. MF63 was a potent inhibitor in HWB assays and displayed effects in rodents, yet it showed no effects on naive rats or mice [32]. YS121, a dual inhibitor of mPGES-1 and 5-LOX, significantly depressed exudation and leukocyte infiltration in carrageenan-induced rat pleurisy model, while it hardly affected mPGES-1 enzyme activity in murine RAW264.7 cells [48]. It was later found that the discrepancy in the sequence of mPGES-1 between the human and murine enzyme led to the failure of mPGES-1 inhibition in mice and rats. Three amino acid residues (in humans: Thr131, Leu135, and Ala138) located close to the active site of mPGES-1 are different in size between species [107]. The interspecies differences have impeded the preclinical progress of mPGES-1 inhibitors. However, scientists have introduced some novel approaches and found several inhibitors with dual human and mouse mPGES-1 inhibition [57, 101].

Safety and toxicity

Overall, compared with traditional NSAIDs or selective COX-2 inhibitors, mPGES-1 inhibitors, exemplified by compound 4b [57], PF4693627 [67], GRC27864 [4], and PBCH [63], indeed showed satisfactory safety and fewer side effects. However, mPGES-1 inhibitors may encounter some unexpected problems. In clinical trials, subjects suffered from mild TEAEs such as abdominal pain, diarrhea, and constipation after LY3023703 administration. Additionally, one subject developed a severe liver injury, which led to the withdrawal of LY3023703 from the clinical trial [3]. PGE2, as a downstream product of mPGES-1, its effects could be diverse via its actions on different

receptors (EP1-4). Thus, a comprehensive and systematic research of the complicated effects of mPGES-1 inhibitors should be conducted to better understand their safety and toxicity.

Conclusions

mPGES-1 plays a potent role in mediating PGE2 formation with no effects on the synthesis of other physiologically-relevant prostaglandins. Thus, targeting mPGES-1 might be prospective for anti-inflammatory drug design, which allows for the basal production of PEG2 and other prostaglandins that are of importance for the homeostatic processes in physiology. During the past years, the development of mPGES-1 inhibitors impressively advanced due to the progress in technology. Unfortunately, although a variety of mPGES-1 inhibitors have been developed over the past two decades, only a few are reported to be biologically active *in vivo* and currently none of them are available for clinical use. The present absence in clinical use of mPGES-1 inhibitors might be associated with the limitations mentioned above. Regarding these limitations, the toxicity of mPGES-1 inhibitors is the primary cause leading to the clinical trial failure. Therefore, more efforts are needed to better demonstrate the pharmacological profiles of new mPGES-1 inhibitors, which could improve the success rate of preclinical and clinical trials of these drugs. Although the clinical translation of mPGES-1 inhibitors in treating human diseases is undergoing some difficulties, we are still confident in the successful application of mPGES-1 inhibitors in clinic in the near future.

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Disclosure of conflict of interest

None.

Abbreviations

mPGES-1, microsomal prostaglandin E synthase 1; NSAIDs, nonsteroidal anti-inflammatory drugs; PGs, prostaglandins; AA, arachidonic acid; COX, cyclooxygenase; PGG/H/E2, prostaglandin G/H/E2; mPGES-1/2, microsomal prostaglandin E synthetase1/2; cPGES, cystosolic PGES; 5-LOX, 5-lipoxygenase; LT, leukotriene; TXA2, thromboxane A2; LPS, lipopolysaccharide; HTS, high-throughput screening; SAR, structure-activity relationship; PK, pharmacokinetics; HWB, human whole blood; IC50, 50% inhibitory concentration; ED50, 50% effective dose; CYP, cytochrome P450; hERG, human Ether-à-go-go Related Gene.

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