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Alleviating CYP and hERG liabilities by structure optimization of dihydrofuran-fused tricyclic benzo[*d*]imidazole series – Potent, selective and orally efficacious microsomal prostaglandin E synthase-1 (mPGES-1) inhibitors: Part-2

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ABSTRACT

In an effort to identify CYP and hERG clean mPGES-1 inhibitors from the dihydrofuran-fused tricyclic benzo[*d*]imidazole series lead **7**, an extensive structure-activity relationship (SAR) studies were performed. Optimization of A, D and E-rings in **7** afforded many potent compounds with human whole blood potency in the range of 160–950 nM. Selected inhibitors **21d**, **21j**, **21m**, **21n**, **21p** and **22b** provided selectivity against COX-enzymes and mPGES-1 isoforms (mPGES-2 and cPGES) along with sufficient selectivity against prostanoid synthases. Most of the tested analogs demonstrated required metabolic stability in liver microsomes, low hERG and CYP liability. Oral pharmacokinetics and bioavailability of lead compounds **21j**, **21m** and **21p** are discussed in multiple species like rat, guinea pig, dog, and cynomolgus monkey. Besides, these compounds revealed low to moderate activity against human pregnane X receptor (hPXR). The selected lead **21j** further demonstrated *in vivo* efficacy in acute hyperalgesia (ED_{50}: 39.6 mg/kg) and MIA-induced osteoarthritic pain models (ED_{50}: 106 mg/kg).

Microsomal PGE synthase-1 (mPGES-1) is a dominant source of biologically active PGE_2, during the biosynthesis in the downstream of the COXs in arachidonic acid (AA) pathway. PGES is a terminal enzyme, which is classified into three isoforms, namely microsomal PGES-1 (mPGES-1), microsomal PGES-2 (mPGES-2) and cytosolic PGES (cPGES).[1] The role of prostaglandins (PGs) in inflammatory pain is well established. Binding of PGs to prostanoid receptors (EP1, EP2, EP3 and EP4) sensitizes pain specific neurons to stimulate pain in central nociceptive systems and mPGES-1 expression was strongly up-regulated in the brain and spinal cord during inflammation.[2] An inducible enzyme mPGES-1, which is functionally coupled to COX-2, is responsible for the release of PGE_2 in response to inflammatory stimuli, such as IL-1β, TNF-α, and LPS. A previous study by Akira group has shown that PGE_2 production by LPS is completely suppressed in peritoneal macrophages derived from mPGES-1 knockout mice.[3] This enabled the use of mPGES-1 knockout mice as models for various diseases, such as collagen induced arthritis, pain hypersensitivity and neuropathic pain.[4] An mPGES-1 knockout study in mice exhibits rediversion of the PGH_2 substrate by a PG synthases into several prostanoids ($PGF_{2\alpha}$, PGD_2 and PGI_2), including PGE_2 and thromboxane A_2 (TXA_2).[4] Therefore, it is expected that mPGES-1 inhibitors may not increase the risk of cardiovascular side effects associated with COX-2 inhibitor, as they do not inhibit PGI_2 production.[5] Similarly, additional knockout studies demonstrated devoid of gastrointestinal and renal toxicity, which are associated with COX-1 inhibitors.[6] Further, these knockout animals revealed viable, fertile, and normal phenotype, which signifies that mPGES-1 inhibitors could possess anti-inflammatory potential with minimum or negligible side effect profile.[4] Therefore, selective inhibition of mPGES-1 might be a promising approach for the design of an effective anti-inflammatory drugs lacking NSAID related side effects.[7]

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Although development of novel mPGES-1 inhibitors has received great attention recently, numerous inhibitors with variety of chemo types are reported with only general SAR[8] and the available *in vivo* efficacy data is still limited to very few compounds in the literature. Some notable examples are, MF-63 (**1**) from Merck,[9] pyridine-3-carboxamide (**2**) from Eli Lilly[10] and PF-4693627 (**3**) from Pfizer[11] demonstrated *in vivo* efficacy in guinea pig hyperalgesia model (Fig. 1). As well, we have recently reported *in vivo* efficacy to few potent mPGES-1 inhibitors, such as quinazolinone (**4**), aminobenzimidazole-5-carboxamide (**5**) and 1,4-dihydrochromeno[3,4-*d*]imidazole (**6**) in hyperalgesia pain model.[12,13] Further, mPGES-1 inhibitors from Eli Lilly (LY-3023703)[14] and our group (GRC27864)[15] have completed Ph-I clinical trials for the treatment of pain and an inflammatory diseases.

In the preceding communication,[16] the design, synthesis and initial SAR (structure-activity relationship) optimization of potent dihydrofuran-fused benz[*d*]imidazole series, as exemplified by lead **7** was described (Fig. 2). The mPGES-1 lead **7** and its analogs were highly potent both in human and guinea pig enzymes, cell permeable, selective against COX-enzymes with adequate PGE_2 release human whole blood potency. In addition, it had adequate brain penetration, orally bioavailable and was efficacious in animal models of pain. However, compound **7** and other analogs from this series suffered cytochrome P450 (CYP) enzyme (CYP3A4, CYP2C9 and CYP2C19) and hERG liability, which was expected to cause adverse drug-drug interaction (DDI)[17] and potential QTc prolongation safety issues[18] if taken to clinical development. Overall, analogs from this series with nitrogen incorporated in the E-ring exhibited higher CYP3A4 liability, whereas compounds with *meta*- and *para*-substituted phenyl as A-ring revealed CYP2C9 and CYP2C19 liabilities.[16a] Further, compounds with substituted pyridine as A-ring tested so far had shown decreased enzyme, cell and human whole blood potency along with moderate to low metabolic stability.[16a] Therefore, additional SAR optimization of lead **7** is warranted in order to completely eliminate CYP and hERG liabilities for further development.

In this manuscript, we describe the synthesis and structure-activity relationship (SAR) optimization based on lead **7**[16a] to afford mPGES-1 inhibitors with low CYP and hERG liability without altering the core scaffold. Therefore, we focused our attention on the A, D and E-rings of lead **7** for optimization (Fig. 2). It is well-known in the literature that reducing lipophilicity (or increasing polarity) and disturbing the geometry

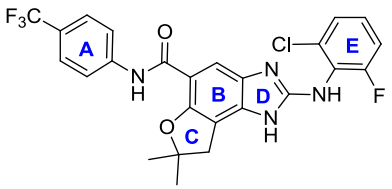

Fig. 2. mPGES-1 lead **7**. IC_{50}: 3.9 nM; A549 cell IC_{50}: 10.4 nM. Human whole blood IC_{50}: 275 nM. Guinea Pig whole blood IC_{50}: 222 nM. CYP liability: 2C9, 2C19 (>50% inhibition @10 μM). hERG liability: 56% inhibition @10 μM.

of molecule while performing lead optimization would provide compounds with reduced hERG and CYP liability.[19] With this hypothesis, we initially synthesized two compounds by introducing 2, 6-difluorophenyl (**21a**) and 2-trifluoromethylphenyl (**21b**) as A-ring along with 2, 6-dichlorophenyl group as E-ring without any modification done on the other rings (Table 1). The biological activity of **21a** and **21b** revealed comparable mPGES-1 enzyme and cell potency (IC_{50}s: <15 nM) similar to earlier lead **7** along with human whole blood potency (HWB IC_{50}s: 660 nM for **21a** and 506 nM for **21b**) similar to COX-2 inhibitor, Celecoxib (HWB IC_{50}: 540 nM).[8c,20] After having comparable human whole blood potency to Celecoxib, compounds **21a** and **21b** were further evaluated for CYP inhibition and unveiled low liability (<50%@ 10 μM) against five major CYP isoforms tested, namely CYP1A2, CYP2D6, CYP3A4, CYP2C9 and CYP2C19, respectively (Table 2).[21] Next analog **21c** with 2-trifluoromethylphenyl as A-ring and 2-chloro-6-fluorophenyl as d-ring afforded single digit enzyme and, cellular potency with a human whole blood IC_{50} of 536 nM, similar to compound **21b**. CYP inhibition study of **21c** also revealed low CYP liability against all five major isoforms tested. Encouraged with these results, additional SAR optimization was initiated to improve human whole blood potency in this series. Therefore, combination of 2-fluoro-5-trifluoromethylphenyl (**21d**), 2-fluoro-5-difluoromethylphenyl (**21e**), 2-fluoro-5-cyclopropyl phenyl (**21f** and **21g**), 2-fluoro-4-trifluoromethylphenyl (**21h**) and 2-methyl-4-trifluoromethyl phenyl (**21i**) analogs were synthesized and tested for mPGES-1 potency. All these compounds demonstrated single digit enzyme and A549 cell potency except **21g**, which displayed slightly lower enzyme potency (IC_{50}: 16 nM) and single digit cell potency (cell IC_{50}: 3.2 nM). Among the analogs (**21d–i**) tested for human whole blood potency, analogs **21d**, **21e**, **21g** and **21i** afforded enhanced whole blood potency (HWB IC_{50}s: <340 nM)

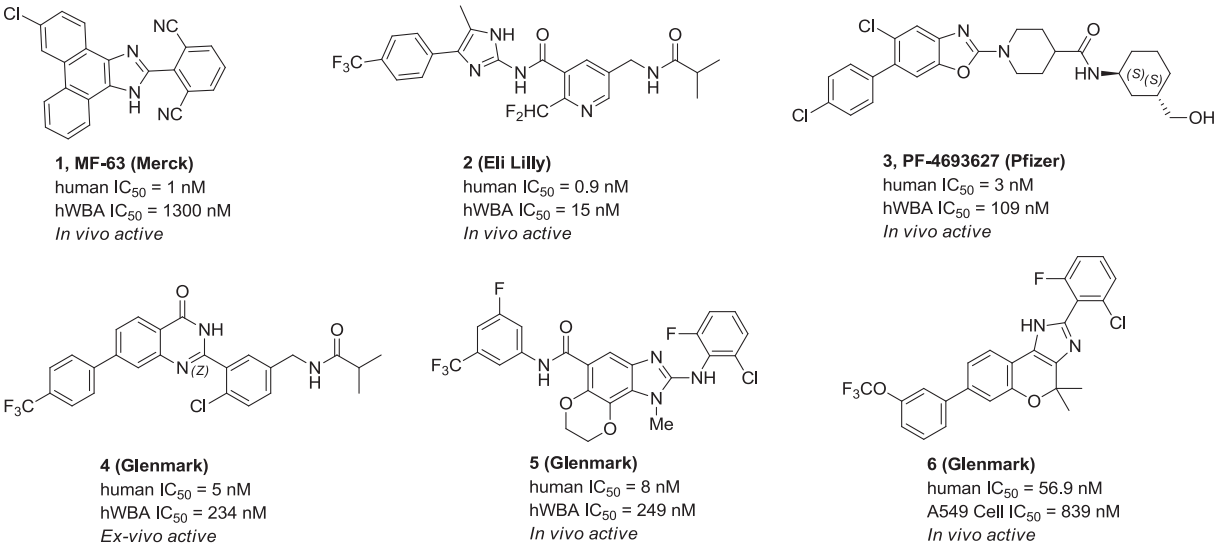

Fig. 1. Representative mPGES-1 inhibitors.