Discovery of Novel Seven-Membered Prostacyclin Analogues as Potent and Selective Prostaglandin FP and EP3 Dual Agonists

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Supporting Information

ABSTRACT: A novel series of prostaglandin analogues with a seven-membered ring scaffold was designed, synthesized, and evaluated for the functional activation of prostaglandin receptors to identify potent and subtype-selective FP and EP3 dual agonists. Starting from the prostacyclin derivative **5b**, a nonselective agonist for prostaglandin receptors, replacement of the core structure with an octahydro-2*H*-cyclopenta[*b*]oxepine scaffold led to the discovery of the potent and selective FP and EP3 dual agonist **11b** as a lead compound for the development of an antiglaucoma agent.

KEYWORDS: Prostaglandin, dual agonist, FP receptor, EP3 receptor, GPCR, glaucoma

EC₅₀	
FP	7.1 nM
EP3	3.6 nM
IP	47 nM

EC₅₀	
FP	28 nM
EP3	4.0 nM
IP	>10000 nM

Prostaglandins are the products of cyclooxygenase-catalyzed metabolism of arachidonic acid that exert a wide variety of biological actions through G-protein coupled prostaglandin receptors. Prostaglandin E₂ (PGE₂), PGF_{2α}, PGD₂, PGI₂, and thromboxane A₂ (TXA₂) preferentially activate the EP, FP, DP, IP, and TP receptor, respectively. There are four distinct subtypes of EP receptor, EP1, EP2, EP3 and EP4, as well as two subtypes of DP receptor, DP1 and DP2.

Glaucoma is a chronic ocular disease characterized by progressive optic neuropathy and visual field loss. There are many types of treatment for glaucoma based on various mechanisms. The primary treatment is to control intraocular pressure (IOP) by topical administration of an IOP lowering agent. Prostaglandin analogues (PGAs) such as latanoprost,¹ travoprost,² and tafluprost^{3,4} (Figure 1) reduce IOP by targeting the prostaglandin FP receptor. Currently, such FP agonists are the most effective IOP-lowering agents. However, recently, a novel mechanism of action for PGAs via the prostaglandin EP3 receptor has been reported.^{5,6} Topically applied EP3 receptor agonists have demonstrated the potential to reduce IOP in animals.⁷ These findings inspired us to identify a small molecule that selectively activates both the FP and EP3 receptors, which could potentially have a superior IOP-lowering effect compared with PGAs.⁸ Herein, we report discovery of the first highly selective FP and EP3 dual agonists with a novel seven-membered prostacyclin scaffold, (5*aR*,8*aS*)-octahydro-2*H*-cyclopenta[*b*]oxepine.

Figure 1. Launched antiglaucoma prostaglandin analogues.

To the best of our knowledge, no potent and selective FP and EP3 dual agonists have been reported. We conducted compound screening of our in-house compound libraries to identify compounds possessing FP and EP3 dual agonist activity. Through this screening, compounds **4**, **5a**, and **5b** were found to show the desired activities. The activity profiles are summarized in Table 1, including data for latanoprost acid (**1**), travoprost acid (**2**), and sulprostone (**3**, Figure 2)⁹ for comparison. Latanoprost and travoprost selectively stimulate

Received: October 19, 2016

Accepted: December 13, 2016

Published: December 13, 2016

Table 1. Activity Profiles of Identified Compounds

compound	functional assay (EC ₅₀ , nM) ^a		
	hFP	hEP3	hIP
4	16	0.89	NT ^b
5a	4.1	4.1	26
5b	7.1	3.6	47
1	12	8600	>10000
2	3.6	3400	>10000
3	1800	0.34	>10000

^aAssay protocols are provided in the Supporting Information. EC₅₀ values represent the mean of at least two experiments. ^bNot tested.

Figure 2. Structures of sulprostone and prostacyclin (PGI₂).

the FP receptor, while sulprostone is a potent EP3 receptor agonist. All three hit compounds have a terminal phenyl ring in their ω -chain, which is a structural feature shared with latanoprost, travoprost, and sulprostone. These results indicate that the terminal phenoxy group may be a privileged structure for potent FP and EP3 receptor dual agonists. Although 16-phenoxy tetranor PGE₂ (4) exhibited agonist activity against both the FP and EP3 receptors, the chemical lability of 4 in aqueous solution because of the β -hydroxyl ketone structure was a major drawback for development as an ocular formulation. Therefore, we turned our attention to 5a and 5b previously reported by the Upjohn group.¹⁰ Both 5a and 5b showed potent EP3 and FP activity, as well as the expected chemical stability in aqueous solution as required for an ocular formulation, but also demonstrated agonist activity against the IP receptor. It has been reported that activation of the IP receptor may cause conjunctival irritation.^{11,12} We therefore attempted to identify compounds possessing potent and selective agonist activity for both the FP and EP3 receptors over the IP receptor by the structural modification of 5a and 5b (Figure 3).

Figure 3. Compounds with dual FP and EP3 agonist activity found from compound libraries.

Since prostacyclin, PGI₂, exhibits highly potent activity for the IP receptor, the IP agonist activity of 5a and 5b is probably due to their core structural similarity to prostacyclin. Compounds 5a and 5b have a homoprostacyclin scaffold, octahydrocyclopenta[*b*]pyran. Further homologation, namely, ring expansion from a six- to a seven-membered ring, should affect their physicochemical and pharmacological properties in a predictable fashion. First, the extra methylene group in the core structure should increase the lipophilicity and the volume

of the molecule in the receptor binding site. Second, the seven-membered ring scaffold may more effectively mimic the conformationally flexible structure of natural prostaglandins, such as E₂ and F_{2 α} compared with the six-membered ring. If the FP and EP3 receptors prefer a ligand with conformationally flexible features for the active binding mode, a prostacyclin analogue with a seven-membered ring might more effectively stimulate these receptors. If the IP receptor prefers a more rigid ligand structure in its binding, a ligand with a seven-membered ring would be less potent toward the IP receptor. Finally, variations in the length, position, and configuration of the carboxylic acid chain on the seven-membered ring scaffold will effectively change the three-dimensional relationship between the carboxyl group and the terminal phenyl ring. The relative position of these groups is likely to be important for the active binding mode stimulating both FP and EP3 receptors. Therefore, varying the positions of these groups could change the potency and selectivity of the compounds toward the receptors, and the appropriate positions of the groups for an FP and EP3 dual agonist can be explored. Thus, ring expansion from a six- to a seven-membered prostacyclin analogue would be a rational and promising entry toward the discovery of an FP and EP3 dual agonist with high potency and subtype selectivity. To our knowledge, no prostacyclin analogues of this type containing a seven-membered ring have been reported to date.

Based on the above-mentioned findings and considerations, we designed and synthesized a collection of novel prostacyclin analogues containing a seven-membered ring structure with variations in the length, position, and configuration of the carboxylic acid chain (Figure 4). All the compounds have a common terminal phenoxy group in their ω -chains, suggesting potent agonist activity against both FP and EP3 receptors. Type A compounds (6–9) have an unsaturated core structure, 5,5a,6,7,8,8a-hexahydro-2*H*-cyclopenta[*b*]oxepine, with a carboxylic acid chain at the 3-position. Type B (10a–12b) and

Figure 4. Designed compounds with seven-membered ring scaffolds.

Scheme 1. Synthesis of Type A and Type B Compounds^a

^aReagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) DIBAL, toluene, -60°C ; (c) $\text{Ph}_3\text{PCH}_2\text{Br}$, *t*-BuOK, 0°C , 95% in 3 steps; (d) NaH, 2,3-dibromopropene, DMF, 0°C , 82%; (e) $\text{EtO}_2\text{C}(\text{CH}_2)_{n+1}\text{ZnBr}$, $\text{Pd}(t\text{-Bu}_3\text{P})_2$, toluene, THF, 80°C , 86–97%; (f) $(\text{SiMe}_3)\text{Ru}(\text{PCy}_3)_2(\text{Ind})\text{Cl}_2$, toluene, 80°C , 83–92%; (g) aq. NaOH, EtOH, rt; (h) 2-iodopropane, K_2CO_3 , DMF, 40°C , 90–99%; (i) TBAF, THF, rt, 47–96%; (j) $\text{SO}_3 \cdot \text{pyridine}$, *i*-Pr₂NEt, AcOEt, 0°C ; (k) dimethyl (2-oxo-3-phenoxypropyl)phosphonate, K_3PO_4 , THF, rt, 43–69% in 2 steps; (l) (*R*)-2-methyl-CBS-oxazaborolidine, $\text{BH}_3 \cdot \text{SMe}_2$, THF, rt; (m) AcOH, H_2O , THF, 60°C , 20–67% in 2 steps; (n) aq. NaOH, MeOH, rt, 94%–quant.; (o) H_2 , Pd/C, *i*-PrOH, rt or H_2 , PtO_2 , AcOEt, rt or H_2 , $[\text{Ir}(\text{cod})(\text{PCy}_3)(\text{py})]\text{PF}_6$, CH_2Cl_2 , rt; (p) HPLC or SFC separation.

Scheme 2. Synthesis of Type C Compounds^a

^aReagents and conditions: (a) $\text{RuClH}(\text{CO})(\text{PPh}_3)_3$, toluene, 60°C , 94%; (b) *t*-butyl bromoacetate, NaH, DMF, rt, 72%; (c) aq. NaOH, MeOH, THF, rt; (d) allyl bromide, K_2CO_3 , DMF, rt, 90% in 2 steps; (e) LDA, TMSCHN₂, THF, -78°C to rt; (f) TMSCHN₂, MeOH, AcOEt, rt, 32% and 35% in 2 steps; (g) $(\text{SiMe}_3)\text{Ru}(\text{PCy}_3)_2(\text{Ind})\text{Cl}_2$, toluene, 80°C , 80–85%; (h) LiAlH_4 , THF, 0°C , 89–92%; (i) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{iPr}$, 2-iodoxybenzoic acid, DMSO, rt, 83–90%; (j) H_2 , Pd/C, NaHCO_3 , *i*-PrOH, rt, 75–86%; (k) TBAF, THF, rt, 78–87%; (l) $\text{SO}_3 \cdot \text{pyridine}$, *i*-Pr₂NEt, AcOEt, 0°C ; (m) dimethyl(3-phenoxy-2-oxopropyl)phosphonate, K_3PO_4 , THF, rt, 44–46% in 2 steps; (n) (*R*)-2-methyl-CBS-oxazaborolidine, $\text{BH}_3 \cdot \text{SMe}_2$, THF, rt; (o) AcOH, H_2O , THF, 60°C , 56–63% in 2 steps; (p) aq. NaOH, MeOH, rt, quant.

Table 2. Functional Potency toward Human Prostaglandin Receptors for Compounds 6–13

Type	Core	Compd	Linker	Functional assay (EC ₅₀ , nM) ^a		
				hFP	hEP3	hIP
A		6	(CH ₂) ₂ C2	530	2700	>10000
		7	(CH ₂) ₃ C3	640	4700	>10000
		8	(CH ₂) ₄ C4	73	13	>10000
		9	(CH ₂) ₅ C5	880	6400	>10000
B		10a	(CH ₂) ₂ (3α, C2)	1000	870	>10000
		11a	(CH ₂) ₃ (3α, C3)	280	2.3	>10000
		12a	(CH ₂) ₄ (3α, C4)	110	130	>10000
	10b	(CH ₂) ₂ (3β, C2)	110	4800	>10000
		11b	(CH ₂) ₃ (3β, C3)	28	4.0	>10000
		12b	(CH ₂) ₄ (3β, C4)	43	540	>10000
C		13a	(CH ₂) ₂ (2α, C2)	3.8	27	2000
		13b	(CH ₂) ₂ (2β, C2)	22	18	>10000

^a Assay protocols are provided in the [Supporting Information](#). EC₅₀ values represent the mean of at least two experiments.

type C (**13a** and **13b**) compounds have a 3,4,5,5a,6,7,8,8a-octahydro-2H-cyclopenta[b]oxepine core scaffold substituted with carboxylic acid chains at the 3- and 2-positions, respectively.

The syntheses of type A and B compounds are shown in [Scheme 1](#). A THP-protected Corey lactone **14**¹³ was converted to allyl cyclopentanol **15** in three steps. Cyclopentanol **15** was alkylated with 2,3-dibromopropene to afford **16**. The Negishi coupling reaction with corresponding zinc-reagents, followed by a ring-closing metathesis reaction catalyzed by a ruthenium-indenylidene precatalyst [(SIMes)Ru(PCy₃)(Ind)Cl₂]¹⁴ afforded cyclized compounds **18a–d**. Deprotection of the TBS group with TBAF gave alcohols **20a–d**. Oxidation of the alcohols, followed by Horner–Emmons olefination with dimethyl (3-phenoxy-2-oxopropyl)phosphonate afforded the enones. Stereoselective reduction with (*R*)-2-methyl-CBS-oxazaborolidine¹⁵ and borane-dimethylsulfide complex followed by deprotection of the THP group and saponification gave acids **6–9**. For the synthesis of type B compounds, hydrogenation of tetrahydrooxepine **19a–c** with palladium on carbon, platinum dioxide, or [Ir(cod)(PCy₃)(py)]PF₆ (Crabtree's catalyst)¹⁶ gave a diastereomeric mixture of oxepane derivatives. After deprotection of the TBS group, introduction of the ω-chain was carried out in a similar manner as above to afford isopropylesters **22a–c**. High-pressure liquid chromatography (HPLC) or supercritical fluid chromatography (SFC)

purification followed by saponification gave diastereomerically pure acids **10a–12a** and **10b–12b**.

The syntheses of the type C compounds are outlined in [Scheme 2](#). Isomerization of the allyl group of compound **15** with RuClH(CO)(PPh₃)₃ gave the inner alkene **23** as a 1:1 mixture of *E* and *Z* isomers. O-Alkylation of alcohol **23** followed by transesterification produced allyl ester **24**. Ireland–Claisen rearrangement of **24** in the presence of LDA and chlorotrimethylsilane followed by methylation of the resulting carboxylic acid with trimethylsilyldiazomethane gave methyl esters **25** and **26**, which were readily separable by silica gel chromatography. Ring-closing metathesis catalyzed by (SIMes)Ru(PCy₃)(Ind)Cl₂ gave tetrahydro-oxepines **27** and **28**. After reduction with LiAlH₄, oxidation of the alcohols to aldehydes, followed by Wittig condensation with (isopropoxy-carbonylmethylene) triphenylphosphorane gave the unsaturated esters. Hydrogenation with palladium on carbon and deprotection of the TBS group with TBAF gave alcohols **29** and **30**. The resulting alcohols were converted to the corresponding carboxylic acids **13a** and **13b** as described above.

The activity profiles of the novel prostacyclin derivatives with a seven-membered ring structure are summarized in [Table 2](#). The agonist activities of the compounds were evaluated using intracellular Ca²⁺ signaling responses in Chinese hamster ovary (CHO) cells expressing human FP and EP3 receptors and cAMP signaling responses in CHO cells expressing human IP receptors.

We first investigated type A compounds bearing unsaturated core ring structures. However, the FP and EP3 agonist activities of compound **7** with a C-3 linker were markedly decreased in comparison with **5a** and **5b**. Shortening the linker in **6** (C2) had a smaller effect on agonist activity. Extension of the linker in **8** (C4) improved the potency for FP and EP3 receptors, while further extension of the linker in **9** (C5) resulted in less potency. However, it was noteworthy that IP agonist activity was completely abolished in all the type A compounds.

We next evaluated type B compounds for agonist activity. Surprisingly, compound **11a** (3 α , C3), which has a carboxylic acid chain with a C-3 linker at the 3- α position, exhibited a remarkable improvement in EP3 agonist activity and a modest improvement in FP activity, compared with the corresponding unsaturated type A analogue **7** (C3). The 3-epimer **11b** (3 β , C3) was found to have more potent FP activity than **11a**, while preserving potent EP3 agonist activity. Moreover, the IP agonist activity of **11a** and **11b** was completely abolished. Hence, replacement of the six-membered ring core structure of **5a** and **5b** with the seven-membered scaffold has a beneficial impact on subtype selectivity for the FP and EP3 receptors over the IP receptor. The extra methylene group in the core structure is unfavorable for an activation of the IP receptor probably due to steric hindrance. Compounds **12a** and **12b** with a C-4 linker maintained FP receptor potency, while the EP3 agonist activity was greatly reduced. Shortening of the linker to C-2 in **10a** and **10b** resulted in a loss of potency for both FP and EP3 receptors.

We next tested type C compounds, which are regioisomers of type B. Compound **13b** (2 β , C2) with a C-2 carboxyl acid side chain showed the desired potent FP and EP3 agonist activity, and IP agonist activity was completely abolished. The 2-epimer **13a** (2 α , C2) exhibited excellent FP and good EP3 agonist activity, as well as poor IP receptor activity compared with **5a**.

Evaluation of the prostacyclin analogues containing a seven-membered ring revealed that the 2- α congener with a C-2 linker **13a** (2 α , C2) was the most potent FP agonist among them. Interestingly, the activity profiles of type B and C compounds showed an opposite tendency regarding the configuration of the carboxylic acid chain substituents on the core scaffolds. In type C compounds, the FP agonist activity of **13a** (2 α , C2) was 6-fold more potent than that of the corresponding epimer **13b** (2 β , C2). For the type B compounds, however, the congener **11b** (3 β , C3) was a 10-fold more potent FP agonist than the corresponding **11a** (3 α , C3).

The clear difference in FP agonist activity for these derivatives, as described above, indicates that the conformation and configuration of the seven-membered scaffold is critical for FP receptor recognition. Therefore, we investigated the conformation of these prostacyclin compounds with seven-membered ring scaffolds by molecular modeling and ^1H NMR. The results of conformational analysis of type B and C scaffolds using LIGPREP¹⁷ and MACROMODEL¹⁸ are shown in Figure 5. To simplify the calculations, we employed model compounds B- α , B- β , C- α , and C- β , in which the flexible alkyl carboxylic acid side chain at the 3- or 2-position and the ω -chain at the 6-position of the octahydrocyclopenta[*b*]oxepine were replaced with methyl and vinyl groups, respectively. Generally, the conformation of seven-membered ring systems can be described as a combination of chair/twist-chair and boat/twist-boat pseudorotational cycles.¹⁹ Our calculations showed that the lowest-energy core ring conformations of B- β and C- α ,

Figure 5. Lowest-energy conformations for the more potent congeners of (a) type C and (b) type B. Superposition of low-energy conformations for less potent congeners of (c) type C and (d) type B.

which correspond to molecules with the β -configuration of the type B scaffold and the α -configuration of the type C scaffold, respectively, exclusively existed as a chair conformation where the methyl group occupied a pseudoequatorial position (Figure 5a,b). In all the low-energy structures of B- β and C- α observed within 10 kJ/mol from the global minimum, the conformations of the seven-membered ring scaffold region were identical to the most stable conformation. However, the low-energy conformations of B- α and C- β , which corresponded to the molecules with the α -configuration of the type B scaffold and the β -configuration of the type C scaffold, existed as mixtures of chair/twist-chair and boat conformations (Figure 5c,d).

In the ^1H NMR spectra of **11b** (3 β , C3, type B), the presence of a diaxial $^3J_{\text{HH}}$ coupling of 12 Hz and a higher magnetic field shift for the H2 signal compared with that for **11a** (3 α , C3) (2.9 versus 3.4 ppm) indicated that the H3 was in a pseudoaxial position on the seven-membered ring (Figure S1 in the Supporting Information). In the ^1H NMR spectrum of the type C compounds, the H2 signal of **13a** (2 α , C2) was found at higher magnetic field at 3.2 ppm than **13b** (2 β , C2) at 3.8 ppm. These observations indicated that the carboxylic acid chains of **11b** (3 β , C3, type B) and **13a** (2 α , C2, type C) occupied pseudoequatorial sites.

The results of modeling and ^1H NMR indicate that the most potent FP agonist **13a** (2 α , C2, type C) exclusively adopts a chair conformation, in which the carboxylic acid chain occupies a pseudoequatorial position. Compound **11b** (3 β , C3, type B), which is the most potent of the type B compounds, also adopts a chair conformation with the carboxylic acid chain in the pseudoequatorial site. These results suggest that the rigid chair conformation of the seven-membered core scaffold and the position of the carboxylic acid group are critical for effective activation of the FP receptor.

In contrast, EP3 agonist activity was not affected by the structure of the core ring moiety. Compound **11a** (3 α , C3) was the most potent EP3 agonist, while the 3-epimer **11b** (3 β , C3) was almost equipotent, regardless of the configuration at the 3-position. The EP3 agonist activities of **11a** and **11b**, with a C-3 linker, were 300-fold and 1000-fold more potent than compounds **10a** and **10b** with a C-2 linker, respectively, as well as 50-fold and 100-fold more potent than **12a** and **12b** (C-4 linker). These results indicate that the configuration of substituents is not strictly recognized by the EP3 receptor, and the length of carboxylic acid chain has a more dominant effect on EP3 agonist activity.

Therefore, we concluded that **11b**, which has a C-3 linked carboxylic acid side chain with a 3 β configuration on a type B scaffold, was the most appropriate lead compound for further optimization since it was a potent FP and EP3 dual agonist

(EC₅₀, 28 and 4.0 nM, respectively) but inactive toward the IP receptor (EC₅₀ > 10 μM). Further evaluation of **11b** also showed that it had less EP1 agonist activity (EC₅₀, 140 nM) compared with its FP and EP3 activities, and it was inactive toward EP2 and EP4 receptors with EC₅₀ values of more than 10 μM.

In summary, we have designed and synthesized a novel series of prostacyclin derivatives with a seven-membered ring scaffold. Starting from prostacyclin derivative **5b**, which is a nonselective agonist for prostaglandin receptors, replacement of the core structure of **5b** with the novel octahydro-2H-cyclopenta[*b*]-oxepine scaffold led us to discover the potent FP and EP3 dual agonist **11b**, which exhibits excellent selectivity over other prostaglandin receptors. Thus, we have identified **11b** as a promising lead compound for a novel antiglaucoma agent. This is the first report of seven-membered prostacyclin analogues, which demonstrates that these novel scaffolds can be useful for developing new prostaglandin-related compounds with pharmacological relevance. Further optimization of the lead compound will be reported in due course.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.6b00415.

Experimental procedures, characterization data, and conditions for the biological assays (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Mr Satoshi Nakayama and Mr. Tomohiro Karakawa for their efforts on the biological tests, and Ms. Aki Fukunaga for her help in the SFC separation of compounds.

■ ABBREVIATIONS

THP, tetrahydropyranyl; TBS, *tert*-butyldimethylsilyl; TBAF, tetra-*n*-butylammonium fluoride; LDA, lithium diisopropylamide

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