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Discovery of a novel EP2/EP4 dual agonist with high subtype-selectivity

Tohru Kambe *, Toru Maruyama, Masayuki Nakano, Yoshihiko Nakai, Tadahiro Yoshida, Naoki Matsunaga, Hiroji Oida, Akira Konaka, Takayuki Maruyama, Hisao Nakai, Masaaki Toda

Minase Research Institute, Ono Pharmaceutical Co., Ltd, Shimamoto, Mishima, Osaka 618-8585, Japan

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ABSTRACT

A series of γ-lactam prostaglandin E_1 analogs bearing a 16-phenyl moiety in the ω-chain and aryl moiety in the α-chain were synthesized and biologically evaluated. Among the tested compounds, γ-lactam PGE analog **3** designed as a structural hybrid of **1** and **2** was discovered as the most optimized EP2/EP4 dual agonist with excellent subtype-selectivity (K_i values: mEP2 = 9.3 nM, mEP4 = 0.41 nM). A structure–activity relationship study is presented.

Receptors for prostaglandin E_2 (PGE_2) can be classified into four subtypes, EP1, EP2, EP3 and EP4, each of which mediates different effects in various tissues and cells.[1] The EP4 receptor is distributed in thymus, lung, heart, kidney, bone, womb and other organs, and mediates an increase of the intracellular c-AMP concentration. Various biological actions of PGE_2, including a cytoprotective action, improvement of blood flow, regulation of inflammatory cytokine production and bone resorption/formation, are thought to mediate the EP4 subtype. A recent report suggests that an EP4 agonist is capable of restoring bone mass and strength normally lost in rats subjected to ovariectomy or immobilization.[2] EP2 receptor agonists have been shown to have an anabolic effect on bone formation in various animal models.[3] These findings led us to development of a novel EP2/EP4 dual agonist which could prove to be a more beneficial agent for the treatment of bone diseases such as osteoporosis and fracture healing in humans. Several research groups have been investigating the improvement of pharmacological properties of PGE_2.[4–7] Efforts to improve the selectivity and chemical stability of PGE_2 have been focused mainly on two general chemical modifications: replacement of the α-alkenyl side chain with the phenylethyl group and replacement of the γ-hydroxycyclopentanone moiety with 2-pyrrolidinone.

Our purpose was to develop PGE_2 analogs with subtype-selectivity and high potency for both receptor subtypes EP2 and EP4 because of their presumed therapeutic potential for the treatment of bone diseases.

In our previous reports, we described 8-aza-5-thia PGE_1 analog **1** (Fig. 1), an EP4 receptor agonist with high subtype-selectivity and high potency which showed potent inhibitory activity of LPS-induced production of TNF-α in rats.[8] Compound **2** was also reported to be an EP4 receptor agonist.[4] We focused on the activity profiles of **2** because it displayed weak to moderate binding affinity (K_i = 340 nM for mEP2, in-house data) for the EP2 subtype in addition to potent EP4 subtype affinity and moderate EP3 subtype affinity (Table 1). Based on the information described above, more detailed chemical modification of the benzoic acid moiety of **2** was predicted to lead us to the discovery of a new structure which possesses a desirable activity profile as an EP2/EP4 dual agonist with subtype-selectivity and high potency.

Herein we report on the discovery of a novel PGE analog of structure **3** (Fig. 1) consisting of a structurally novel α-chain beneficial for EP2/EP4 receptor affinity, a ω-chain beneficial for EP4 subtype-selectivity and a γ-lactam ring as a replacement for the chemically unstable γ-hydroxycyclopentanone.

Synthesis of test compounds listed in Tables 1–3 is described in Schemes 1–6. Synthesis of **3** and **10**–**12** are presented in Scheme 1a. Ethanolysis of the *S*-acetyl group of **16**[9] followed by *S*-arylation with ethyl 2-bromothiazole-4-carboxylate and ethyl 2-bromothiazole-5-carboxylate resulted in **17** and **22**, respectively. Deprotection of the *tert*-butyldimethylsilyl (TBS) group with tetrabutylammonium fluoride (TBAF) afforded **18a** and **23**, respectively. Compound **18a** and **23** were transformed to the enones **20a**–**c** and **24**, respectively by DMSO oxidation followed by Horner–Emmons reaction using an optional phosphonate chosen from among **26a**–**c** (Scheme 1c). Stereoselective reduction of **20a**–**c** and **24** yielded **21a**–**c** and **25**, respectively. Alkaline hydrolysis of **21a** and **25** afforded **3** and **10**, respectively. Alkaline hydrolysis of **21b** and **21c** afforded **11** and **12**, respectively.

Synthesis of **13**–**15** is outlined in Scheme 1b. The ethyl ester **17** was transformed to the corresponding butyl ester **18b**, which was

* Corresponding author. Tel.: +81 75 961 1151; fax: +81 75 962 9314.
E-mail addresses: kanbe@ono.co.jp, t-kam@iris.dti.ne.jp (T. Kambe).

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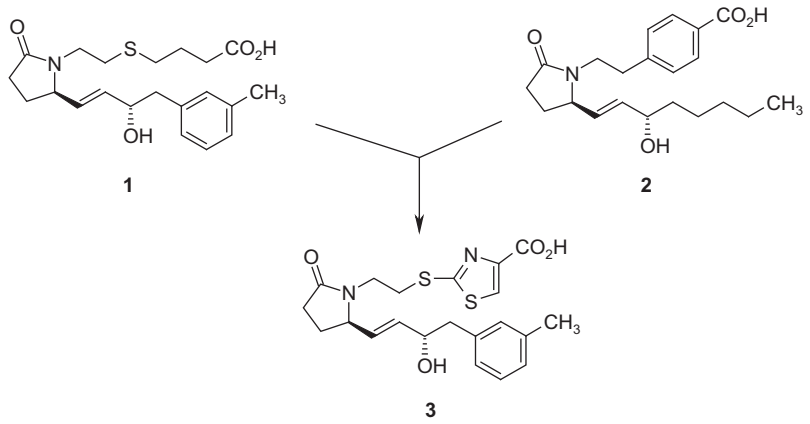
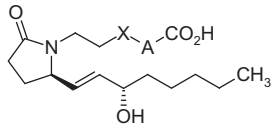


Figure 1. Molecular design of γ-lactam PGE analog **3** bearing the structurally novel ω-chain beneficial for EP2/EP4 dual selectivity.

Table 1
Effect of the α-chain structure of the γ-lactam PGE framework bearing the natural ω-chain on the activity profiles



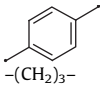
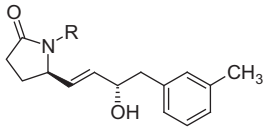
Compound	X	A	Binding assay (K_i, nM)			
			mEP1	mEP2	mEP3	mEP4
2	Bond		>10^4	340	86	1.7
4	CH_2	–$(CH_2)_3$–	>10^4	>10^4	39	9.2
5	S	–$(CH_2)_3$–	>10^4	2500	26	2.0
PGE_2			6.0	22	5.0	3.1

Table 2
Effect of the α-chain structure of the γ-lactam PGE framework bearing the 16-(3-methylphenyl) ω-chain on the activity profiles



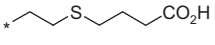
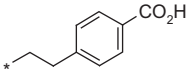
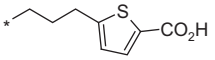
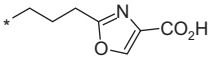
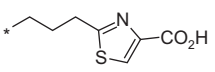
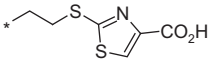
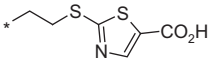
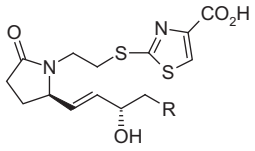
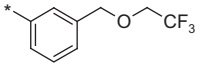
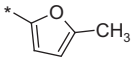
Compound	R	Binding assay[a] (K_i, nM)			
		mEP1	mEP2	mEP3	mEP4
1		>10^4	>10^4	5800	1.8
6		>10^4	410	>10^4	0.9
7		>10^4	127	1600	0.6
8		>10^4	240	>10^4	35
9		>10^4	84	>10^4	12
3		>10^4	9.3	540	0.41
10		>10^4	320	>10^4	5.5

Table 3
Activity profiles of γ-lactam PGE analogs bearing the 2-mercaptothiazole-4-carboxylic acid α-chain and miscellaneous ω-chain



Compound	R	Binding assay (K_i, nM)			
		mEP1	mEP2	mEP3	mEP4
11	–$(CH_2)_3CH_3$	3400	3.0	15	0.5
12		>10^4	19	770	1.5
13		1900	15	1200	1.4
14		>10^4	42	49	0.77
15		>10^4	13	85	43

converted to the enones **20d–f** by DMSO oxidation followed by Horner–Emmons reaction using an optional phosphonate chosen from among **26d–f** (Scheme 1c). Alkaline hydrolysis of enones **20d–f** afforded **13–15**, respectively.

To synthesize **6**, we developed an alternative synthetic method of 8-aza PGE analogs starting from *N*-Boc-D-glutamic acid as described in Scheme 2. Esterification of *N*-Boc-D-glutamic acid γ-ethyl ester **27** with *N*-hydroxysuccinimide followed by hydride reduction with lithium borohydride afforded **29**, Swern oxidation of which provided **30**. The aldehyde **30** was converted to allyl alcohol **31** by Horner–Emmons reaction using **26a** as a phosphonate followed by stereoselective reduction of the formed enone carbonyl. Acidic deprotection of **31** afforded **32**. Reductive alkylation of **32** with an appropriate aldehyde and sodium triacetoxyborohydride followed by *O*-protection with TBS chloride resulted in the cyclized product **33**. Palladium-catalyzed carbonyl insertion reaction of **33** followed by treatment with methanol afforded a methyl ester **34**, which was converted to **6** by acidic deprotection followed by alkaline hydrolysis.

Synthesis of **7** is outlined in Scheme 3. *N*-Alkylation of **35**[10] with methyl (5-bromopropyl)thiophene-2-carboxylate afforded **36**.