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Lactams as prostanoid receptor ligands. Part 4: 2-Piperidones as selective EP_4 receptor agonists

Todd R. Elworthy,* Emma R. Brill, Christopher C. Caires,† Woongki Kim, Leang K. Lach,‡ Jahari Laurant Tracy and San-San Chiou§

Roche Palo Alto, Department of Medicinal Chemistry, 3431 Hillview Avenue, Palo Alto, CA 94304-1397, USA

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To the memory of Woongki Kim, deceased 28 February 2005, a valued and dedicated colleague

Abstract—2-Piperidones were prepared bearing heptanoic acid or a thioether heptanoic acid at the 1-position as well as appropriately substituted at the 6-position to mimic the structure of prostaglandins. The stereochemical purity at the 6-position was determined to be $\geqslant$95% ee for an advanced synthetic intermediate. The 2-piperidones were identified as potent agonists at the EP_4 prostanoid receptor. They displayed a high affinity (K_i 5–130 nM) at EP_4 and subtype selectivity.

1. Introduction

Prostaglandin E_2 (PGE_2) acts on cells through at least four distinct receptors: the prostanoid EP_1, EP_2, EP_3, and EP_4 subtypes. Cyclohexanone **1**, a ring homologue of PGE_1, was reported in 1979 'to be less effective than the corresponding five-remembered ring counterparts' when tested under two in vivo settings.[1] However, these findings predate our current understanding of the plurality of EP receptor subtypes and the cellular effects fol-

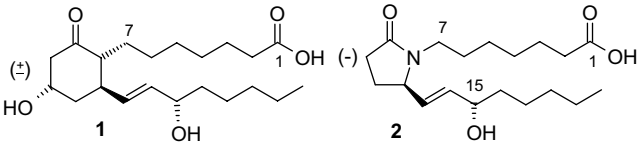
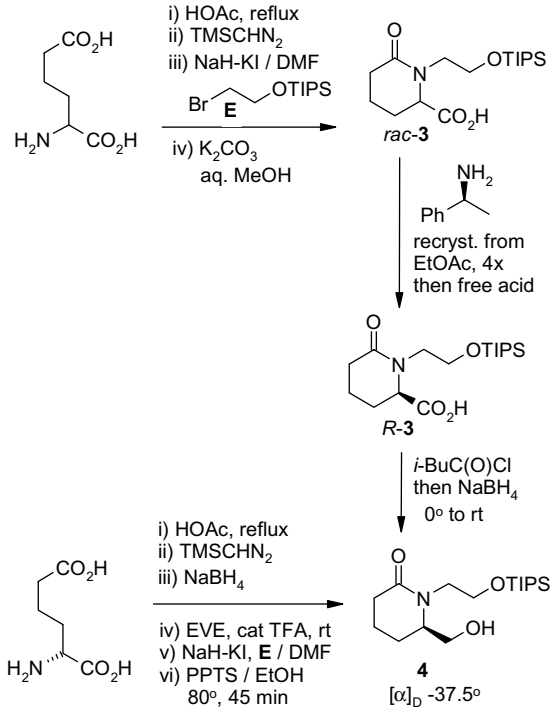


Figure 1. Structures of **1** and **2**.



Scheme 1. Preparation of *N*-substituted 6*R*-hydroxymethyl 2-piperidone.

Keywords: 2-Piperidone; EP4 agonist; Selective EP4 ligands; δ-Lactams as prostanoids.
* Corresponding author. Tel.: +1 650 852 3159; fax: +1 650 354 2442; e-mail: todd.elworthy@roche.com
† Roche 2002 Summer Intern (Medicinal Chemistry). Present address: Department of Chemistry, Stanford University, Stanford, CA 94305, United States.
‡ Present address: ARYx Therapeutics, 2338 Walsh Ave., Santa Clara, CA 95051, United States.
§ Present address: Élan Pharmaceuticals, 800 Gateway Blvd., South San Francisco, CA 94080, United States.

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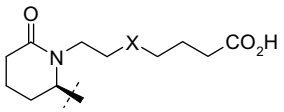
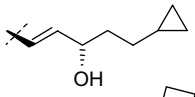
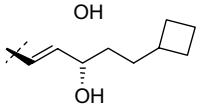
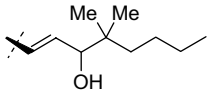
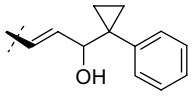
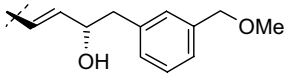
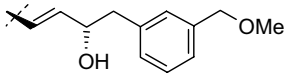
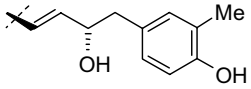
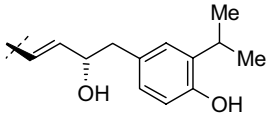
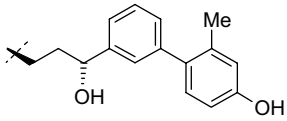
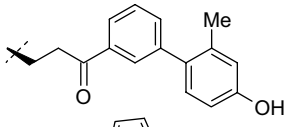
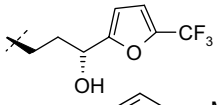
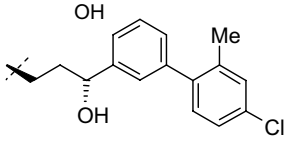
Table 1. EP prostanoid receptor profile of δ-lactams

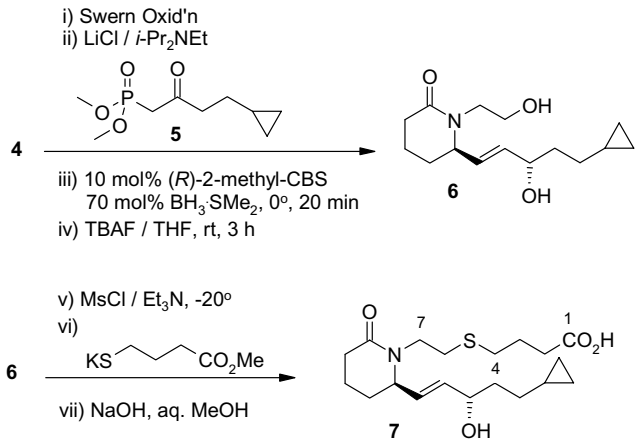
Compound		X	Binding affinity, K_i (nM)[a]			Activity, EC_{50} (nM)[a] EP_4
			EP_2	EP_3	EP_4	
7		S	>10,000	>10,000	21 (6)	190 (6)
8		S	3800	>10,000	7.3	34 (6)
9[b]		S	>10,000	nd[c]	86	290 (6)
10[b]		S	>10,000	>10,000	17	260 (9)
11		S	>10,000	>10,000	22	44 (9)
12		C	>10,000	nd	8.7	44 (9)
13		C	>10,000	>10,000	7.4	280
14		C	>10,000	nd	130	1730 (9)
15		C	>10,000	> 10,000	25	110 (9)
16		C	nd	nd	nd	21,000 (6)
17		S	>10,000	>10,000	105	630 (9)
18		S	1600	>10,000	4.8 (6)	6.1 (6)

[a] The values are the average of three determinations except where noted in parentheses.
[b] The straight line denotes a dr of 1 (at the hydroxyl carbon) for the ligand.
[c] nd = Not determined.

lowing EP_4 activation.[2] We, and others, have recently reported that the chemically simplified 8-aza-11-deoxy-prostaglandin E_1 **2** and related γ-lactams are selective ligands for the EP_4 receptor.[3] Thus, we investigated the question whether the ring homologue of **2** would also be an agonist for the EP_4 subtype. The focus of this letter is to describe the preparation, establishment of stereochemical purity (at the 6-position of the δ-lactam system) and selected in vitro pharmacological data of 2-piperidone ligands (Fig. 1).

2. Results and discussion

The generation of the substituted δ-lactam **4** is outlined in Scheme 1 and was achieved via two routes. Lactam **4** was the pivotal intermediate to access the thioether lactams (see Table 1). Classical resolution of *rac*-**3,** derived from racemic 2-aminoadipic acid, was accomplished using (*S*)-(−)-α-methyl benzylamine.[4] (*R*)-**3** could be enriched to 95% ee.[5] This optical purity is comparable to the 98% ee[5] obtained for **4** following the process of



Scheme 2. Preparation of thioether piperidone ligands.

cyclodehydration of (*R*)-2-aminoadipic acid (Scheme 1, lower).[6] In addition, (6*R*)-hydroxymethyl-2-piperidone[7a] was used to supplement our supply of **4** as well as to generate the all-C ligands described in this letter.

The all-C α-chain ligands (**12**–**16** of Table 1) as well as the requisite ketophosphonates (e.g., **5** of Scheme 2) were prepared similarly to our previously described work on the γ-lactams.[8] The preparation of the more complex 5-thia derivatives via diol **6** is detailed in Scheme 2. Oxidation of **4** to its aldehyde and condensation with **5** afforded an enone which was treated with borane and (*R*)-2-methyl oxazaborolidine [(*R*)-2-methyl-CBS from Aldrich Co.]. The desired allylic alcohol was purified to >94% dr (silica gel chromatography, eluant: 4% *i*-PrOH in 3:1 ethyl acetate:hexane)[8] and exposure to tetrabutylammonium fluoride reveals diol **6**. Generation of the ligand **7** from diol **6** without resorting to a secondary hydroxyl blocking group is representative.

The 2-piperidone ligands were first evaluated for their functional activity at the EP_4 receptor[9] and then profiled for their affinity at the available EP receptors. We elected not to assay these acids for affinity at the EP_1 based on earlier findings that related γ-lactams failed to display measurable affinity for that receptor.[3c,9]

The data in Table 1 demonstrate the 2-piperidones are ligands with a high affinity (K_i 5–130 nM) at the EP_4 receptor and behave as agonists. Ligands **9** and **10** highlight the tolerance of substitution at an ω-chain position to potentially block PG-based metabolism and retain agonist activity. A polar feature is also tolerated at the terminus of the ω-chain as illustrated by the phenolic ligands **13** and **15**. However, the feature does not enhance agonist activity as exemplified by the comparison of pairs **12** and **13** or **15** and **18**. Potency is lost for a ligand bearing a carbonyl in replacement for the hydroxyl (e.g., **15** vs **16**). Heteroaryl terminated ligands display modest potency (e.g., **17**).

Pharmacological similarities between the γ- and δ-lactams are revealed for some ω-chain substitutions, which leads to more potent agonists at EP_4.[3a,c,9] Ligands terminated in cyclobutyl and appropriate *meta*-substituted phenyl confer high activity. Biphenyl bearing ligands **15** and **18** display high potency consistent with our earlier findings.[9] Furthermore; similarities are seen between the δ-lactams and the recently reported cyclopentanone derivatives. The decrease in potency observed for **12**, **13**, and **14** supports the binding model of the distal features of the ω-chain proposed by Maruyama et al. [10] whereas the *meta*-methoxymethyl of **12** is preferential. In contrast, enhancement of activity was not observed for the δ-lactams when the carbon at the 5-position of the upper chain is replaced by sulfur. Fivefold improvement was seen for the γ-lactams[3e] whereas δ-lactams **11** and **12** are equipotent.

3. Conclusions

Elaborated 2-piperidones act as potent agonists at the EP_4 prostanoid receptor and are typically 500-fold selective for that subtype. When compared to their 2-pyrrolidinone counterparts, a loss of 2- to 10-fold in both activity and affinity at the EP_4 receptor is observed. Be that as it may, we were surprised to find that 2-piperidone ligands display functional potency at EP_4 despite the conspicuous absence of reports of active cyclohexanone prostaglandins. It is not clear whether ring homologues were not previously pursued because they were investigated in systems not sensitive to the then unknown EP_4 receptor or whether the carbocyclic homologues suffer significantly reduced activity as compared to the lactams. The coplanarity of the C-7 to N-8 bond of the δ-lactam presents differences to that of the tetrahedral presentation of the upper side chain of synthetic cyclohexanone **1**. These differences likely reside in the placement of the carboxylate at C-1 and its relation to the carbonyl at C-9. Those requirements for receptor activation are apparently preserved while accommodating the ring homologue.

Acknowledgments

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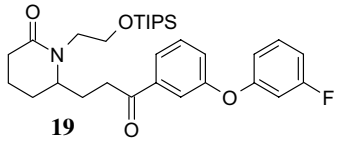
5. δ-Lactam **4** displays a rotation of $[\alpha]_D$ −37.5 (*c* 1.0, CH_3CN) when prepared from (*R*)-2-aminoadipic acid (Sigma–Aldrich) and corresponds to 98% ee. Ketone **19** was produced[8] to assess enantiomeric purity and was resolved by chiral stationary phase HPLC with a Chiralcel AD column, eluant: 3% *i*-PrOH in *n*-hexane at 1.0 mL/min. Enantiomeric excesses reported for Scheme 1 materials were based on their respective conversion to enriched **19**. This ketone was chosen to assess ee due to the ease UV detection and the stringency of being an advanced intermediate of the sequence that is not susceptible to racemization.



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