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Bioorganic & Medicinal Chemistry Letters 18 (2008) 821–824
Bioorganic & Medicinal Chemistry Letters

Synthesis and evaluation of a γ-lactam as a highly selective EP_2 and EP_4 receptor agonist

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Received 24 October 2007; revised 7 November 2007; accepted 8 November 2007
Available online 13 November 2007

Abstract—γ-Lactam analogs (**2**) of EP_4 receptor agonists were identified by substitution of the pyrazolidinone ring (**1**) with a pyrrolidinone ring. Several compounds (such as **2a**, **2h**) with high potency, selectivity and acceptable PK profiles were discovered. These were assessed in animal models of ovulation induction and bronchoconstriction.

Prostaglandins are known to have a broad range of biological actions in diverse tissues through binding to specific receptors on the plasma membrane.[1] Four subtypes of the PGE_2 receptor have been identified: EP_1, EP_2, EP_3, and EP_4, which mediate a wide variety of biological activities.[1] Of these four receptors, three are involved in the modulation of cAMP levels.[2] Activation of the EP_3 receptor results in a reduction of the intracellular cAMP level. In contrast, activation of EP_2 receptor and the EP_4 receptor increases the intracellular cAMP level, which is linked to the treatment of infertility. The EP_1 receptor is involved in regulating intracellular calcium levels. The EP_2 and the EP_4 receptors are interesting pharmacological targets because of their important regulatory roles in numerous physiological processes, suggesting that agonists may be useful in preventing and/or treating preterm labor, ovulation induction, asthma, fertility disorders, undesired blood clotting, sexual dysfunction, bone resorption, and inflammatory disorders, and other diseases. Additional roles for EP receptors have been reported, including smooth muscle relaxation in cat trachea for EP_2, vasodilation and anti-inflammatory activity for EP_4.[3] EP_2 and EP_4 receptor agonists have been proven to be beneficial for the treatment of preterm labor by suppressing uterine contraction and inducing oophorus maturation required for fertilization.[1b]

Several research groups have been investigating the improvement of pharmacological properties of PGE_2, which shows non-selective binding to the EP receptors (in-house binding data K_i = 9.1, 4.9, 0.33, and 0.79 nM for h-EP_1, h-EP_2, h-EP_3, and h-EP_4, respectively) and chemical and metabolic instability.[4] Until now, efforts to improve the selectivity and chemical stability of PGE_2 have been focused on only two general chemical modifications;[5] replacement of the α-alkenyl side chain with the more chemically stable phenylethyl group and substitution of heterocyclic rings for the 11-hydroxy cyclopentanone moiety.[5]

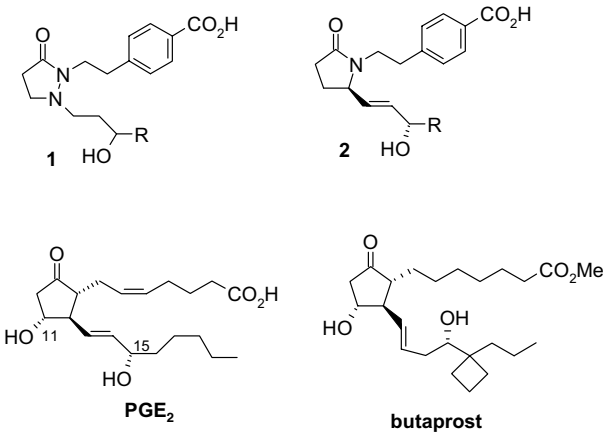

Figure 1. PGE_2 and prostaglandin derivative.

Keywords: Prostaglandin; EP_2 receptor; EP_4 receptor.
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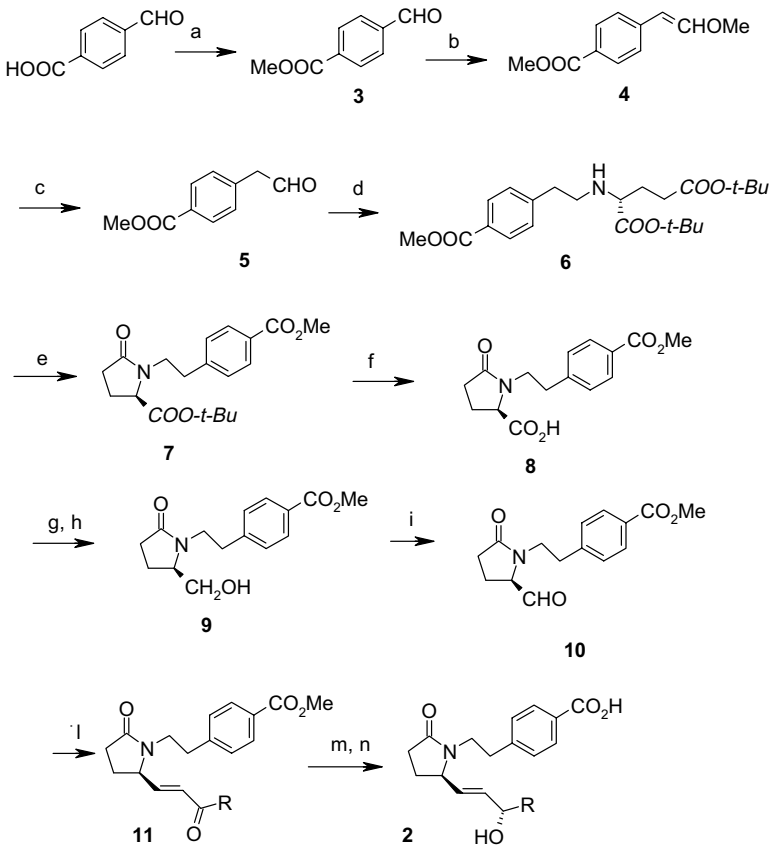
doi:10.1016/j.bmcl.2007.11.020

In our previous communication, we described pyrazolidinone analogs (**1** in Fig. 1) that were EP_4 receptor agonists.[6] Poor oral bioavailability limited assessment of these compounds in animal models. In order to overcome this problem, we investigated pyrrolidinone (γ-lactam) derivatives (**2** in Fig. 1). Derivatives (**2** in Fig. 1) showed good PK properties with high potency for the EP_4 receptor. In this report, we describe the synthesis, the structure-activity relationship of this series of compounds, as well as the results from in vivo animal model studies.

The approach for the synthesis of γ-lactams is outlined in Scheme 1. Alcohol **9** was the key intermediate for construction of the final γ-lactam derivatives **2**.The (*R*)-stereochemistry of compound **9** (corresponding to the natural PGE_2 stereochemistry) was inherited from the starting material H-D-Glu(O-*t*-Bu)-O-*t*-Bu·HCl (ee > 95%). Reductive amination of aldehyde **5** with H-D-Glu(O-*t*-Bu)-O-*t*-Bu·HCl smoothly provided triesters **6**, which underwent intramolecular cyclization to afford lactam **7**. The three-step conversion of **7** by hydrolysis, anhydride formation, and then reduction with $NaBH_4$ gave the key intermediate **9**.[7] Conversion of alcohol **9** into enone **11** was accomplished via Swern oxidation followed by Wittig olefination. The enone **11** can be reduced with $NaBH_4$ and $CeCl_3$ (for example R groups in compounds **2f**, **2g**) or by chiral reduction using Corey's procedure.[8] Saponification of the esters with NaOH in THF/MeOH/H_2O, followed by preparative reverse phase HPLC, furnished the desired target compound **2**.

Individual compounds were tested in vitro in the human EP_2/EP_4 receptor binding assays and also in the human EP_2/EP_4 functional assays.[5d] ^{3}H-PGE2/4 binding is evaluated by counting the plates on the top count using the ^{3}H SPA dpm2 program. % Binding and K_i values for inhibitors are calculated based on the one site competition parameter using the graphpad.? prism program. EP2/4 EC_{50} was evaluated by measuring total cAMP (intra- and extra- cellular) by using a cAMP-screen ELISA System (Tropix, #CS1000). The binding and functional data are summarized in Table 1. Compound **2a** with the $PGE_2\omega$-side chain showed high affinity binding against both EP_2 and EP_4 receptors (h-EP_2 K_i = 120 nM, h-EP_4 K_i = 2 nM). Interestingly, this compound also showed very good in vitro potency against the EP_4 receptor with an EC_{50} of 0.2 nM, about 15-fold more potent than PGE_2 itself (EC_{50} = 3.0 nM). In vitro activity of this compound displayed 60- or 750-fold selectivity for the EP_4 receptor versus the EP_2 receptor. Compounds with shorter alkyl groups (such as **2c**, **2d**,



Scheme 1. Reagents and conditions: (a) $SOCl_2$, MeOH, 91%; (b) $ClPh_3PCH_2OMe$, NaOMe, MeOH then benzene 73%; (c) aqueous H_2SO_4, THF, 94%; (d) i—H-D-Glu (O-*t*-Bu)-O-*t*-Bu.HCl, Et_3N; ii—HOAc, MeOH, $NaBH_3CN$; (e) xylene, reflux, 59%, 2 steps; (f) TFA, 0 °C to rt; (g) *N*-methylmorpholine, *i*-BuOC(O)Cl, THF; (h) $NaBH_4$, THF/H_2O, 54%, 3 steps; (i) $(COCl)_2$, DMSO, Et_3N, DCM, 92%; (l) i—NaH, THF, 0 °C; ii—$(MeO)_2P(O)CH_2C(O)R$, 0 °C to rt, 90%; (m) $NaBH_4$ and $CeCl_3$, MeOH, H_2O or (*R*)-2-methyl-CBS-oxazaborolidine, BH_3·THF, rt, 80%; (n) NaOH, H_2O/MeOH/THF, 100%.