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Discovery of diphenylcarbamate derivatives as highly potent and selective IP receptor agonists: Orally active prostacyclin mimetics. Part 3

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Abstract—The new classes of diphenylcarbamate derivatives with a tetrahydronaphthalene skeleton as highly potent and selective IP agonists have been discovered. The optimized diphenylcarbamate type compound FK-788: (*R*)-**4** exhibited potent antiaggregative potency with an IC_{50} of 18 nM and high binding affinity for the human recombinant IP receptor with K_i values of 20 nM and selectivity for human IP over all other members of the human prostanoid receptor family. Compound (*R*)-**4** was shown to exhibit good pharmacokinetic properties in rats and dogs, and also good bioavailability in healthy volunteers.

1. Introduction

Prostanoid receptors are members of the G-protein coupled receptor superfamily. Recently, eight prostanoid receptors have been cloned and characterized.[1] PGE_2 will bind preferentially to the EP_1, EP_2, EP_3, and EP_4 receptors, PGD_2 to the DP receptor, $PGF_{2\alpha}$ to the FR receptor, PGI_2 to the IP receptor and TXA_2 to the TP receptor. The molecular characterization of these receptors has resulted in renewed interest in the field because the selectivity of compounds to human prostanoid receptors can now be determined.[2] However, success has been limited by the problems of identifying suitably selective ligands. Many of the problems encountered have been due to the existence of multiple prostanoid receptor subtypes and the lack of the selectivity of prostaglandin analogs.

Prostacyclin (PGI_2) is primarily derived from the vascular endothelium and plays an extremely important inhibitory role in platelet aggregation and as a vasodilator in maintaining homeostatic circulation.[3] Some groups have already disclosed novel PGI_2 analogs without a PG skeleton, which led us to create a novel PGI_2 mimetic with improved chemical and metabolic stability.[4] Hamanaka and co-workers disclosed AP-227 (**3**), which has a tetrahydronaphthalene scaffold with a benzhydrylimine group instead of the natural PG structure.[5] We have previously disclosed the new diphenyloxazole derivatives FR181157 (**1**) and FR193262 (**2**) as potent and orally active prostacyclin mimetics (Fig. 1). We explored a second structural series with improved potency and selectivity over all the other human PG receptors, and good pharmacokinetic profiles. Optimization of the benzhydrylimine moiety of **3** rapidly led to the identification of the potent diphenylcarbamate compound **11** in Figure 2. Despite high potency for the human IP receptor, compound **11** exhibited a lack of selectivity for the EP_3 receptor and poor PK properties, hindering further pharmacological evaluation. After extensive research, we selected FK-788: (*R*)-**4** as a potential candidate, since it exhibited highly potent and selective IP receptor activity and improved solubility and bioavailability. In this paper, we report the SAR of a series of diphenylcarbamate derivatives and the biological and pharmacokinetic profile of (*R*)-**4**.

Keywords: Diphenylcarbamate; Prostacyclin mimetic; IP receptor.
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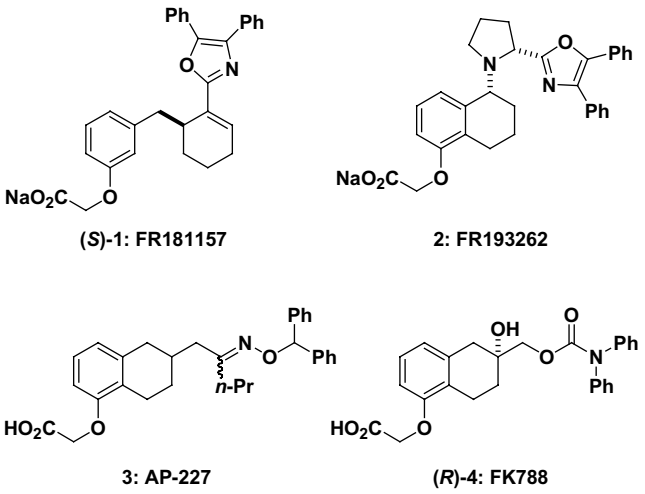


Figure 1.

2. Chemistry

The racemic diphenylcarbamate derivatives were synthesized by the routes shown in Scheme 1. Commercially available 5-hydroxytetralone **5** was converted in four steps to α,β-unsaturated ester **8**. Reduction of **8** with DIBAL in toluene, followed by acylation with diphenylcarbamoyl chloride in pyridine gave the desired carbamate **9**. Deprotection of phenol with tetrabutylammonium fluoride followed by *O*-alkylation with ethyl bromoacetate and hydrolysis afforded the phenoxyacetic acid **10**. Catalytic hydrogenation of **10** with Pd/C gave the corresponding unsaturated carbamate **11**. Similarly the α-alcohol **7** was transformed into α-alcohol carbamate derivatives, which were resolved into the two diastereoisomers (cis and trans at alcohol with a ratio 5:2) through chromatographic separation and followed by the same conditions to give *cis*-**14** and *trans*-**15** as racemates.

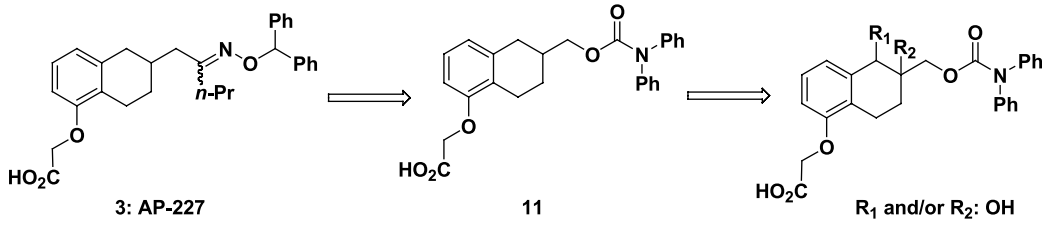
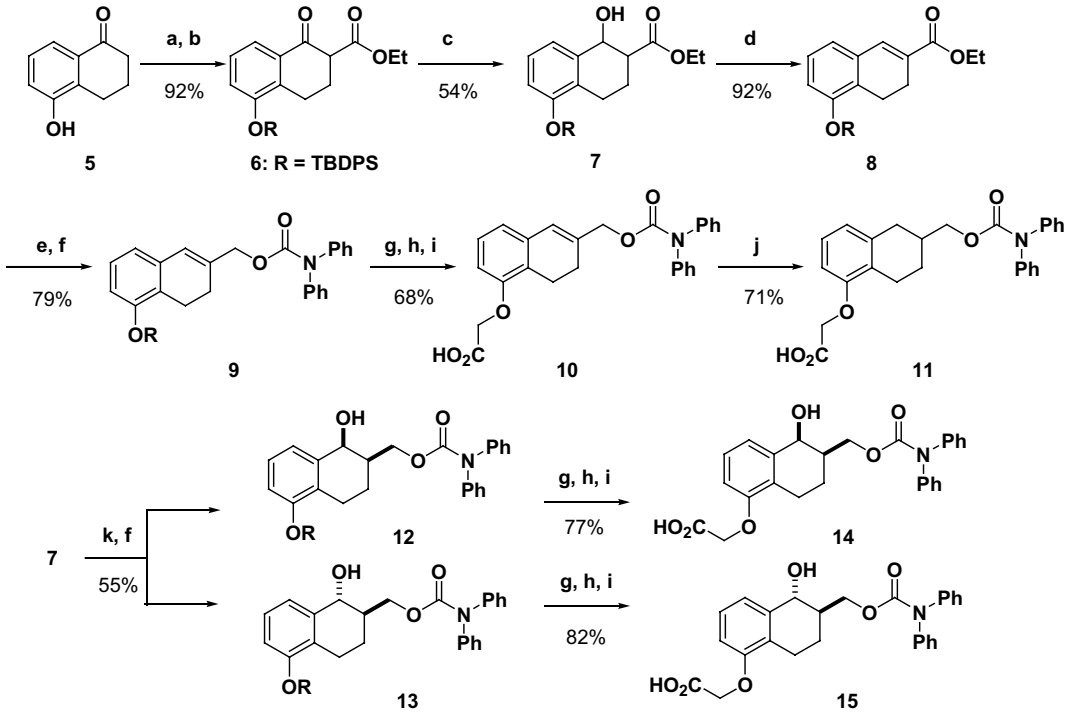


Figure 2.



Scheme 1. Reagents: (a) TBDPSiCl, imidazole, DMF; (b) $(EtO)_2CO$, NaH, Tol; (c) $NaBH_4$, EtOH–THF; (d) $KHSO_4$, Tol; (e) DIBAL-H, Tol; (f) $ClCON(Ph)_2$, Py; (g) *t*-BuNF, THF (h) ethyl bromoacetate, K_2CO_3, DMF; (i) NaOH, THF–EtOH; (j) Pd/C, AcOEt–EtOH; (k) $LiAlH_4$, THF.