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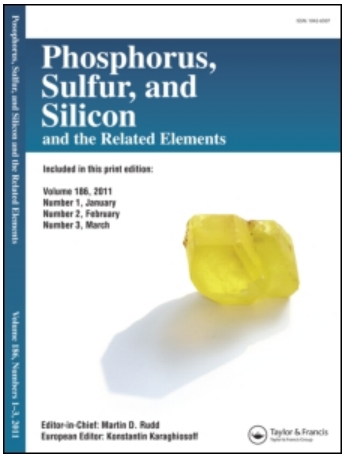

Phosphorus, Sulfur, and Silicon and the Related Elements

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The Rational Design of Drugs with Phos-phonic/phinic Acids as Enzyme Inhibitors Isosteric Receptor Ligands

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THE RATIONAL DESIGN OF DRUGS WITH PHOS-PHONIC/PHINIC ACIDS AS ENZYME INHIBITORS ISOSTERIC RECEPTOR LIGANDS

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Phosphonic/phosphinic acid analogs have been studied for inhibitory and ligand activity in farnesyl pyrophosphate synthase, prostaglandin, and other GPCR's.

Keywords: Isosteres; peptidomimetic; phosphinic/phosphonic acids; prostaglandins

INTRODUCTION

Phosphonic and phosphinic acids play an increasing role as active moieties within medicinally useful compounds. Furthermore, their role and potential as components of competitive binders and isosteric mimics in enzymes and receptors is becoming clearer. As the capabilities in our laboratories develop to understand key ligand/protein interactions, we are now demonstrating more success with rational design utilizing these building blocks. Recently, farnesyl diphosphate synthase was identified as the enzymatic target of the bisphosphonates, within the osteoclast, in their bone antiresorptive mechanism of action.[1] This further confirmed the suggestion of a stereochemical recognition event, hypothesized from the structure-activity relationships, under evaluation in our laboratories for a number of years.[2] The additional need for bone anabolic agents for osteoporosis and our interest in G-protein coupled

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receptor modeling has also led us to the design of new organophosphorus based receptor agonists. Prostaglandin F analogs have attracted recent interest as potential bone anabolic agents.[3] Guided by molecular modeling, we investigated the replacement of the C_1 acid by various suitable functional groups. Most of these replacements resulted in a significant loss of activity at the human FP receptor, the primary cellular mediator of the effects of the F analogs.[4] For example, the phosphonic acid analog of $PGF_{2\alpha}$(5.0 nM), 2-decarboxy-2-phosphono-$PGF_{2\alpha}$, has only a 1.0 micromolar hFP IC_{50} in our binding assay.[5] Therefore, we have extended this investigation to the phosphinic acid analogs of prostaglandins in attempt to better satisfy the requirements of the FP receptor. Finally, these research efforts have now extended to isosteric mimicry of peptide hormome ligands of the G-protein coupled receptors, where interactions in the receptor extracellular loops as well as intramembrane interactions must be studied. Among our approaches to peptidomimetic amide bond replacement for this purpose are included the use of asymmetrically pure phosphinyl dipeptide $\Psi[PO_2HCH_2]$ building blocks.

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RESULTS AND DISCUSSION

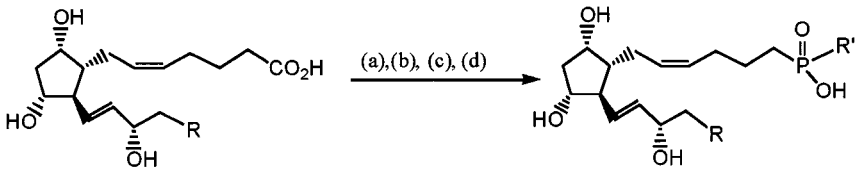
FP Receptor Modeling: Analysis of the C_1 Carboxylic Acid Binding Region

We focused on the previously constructed homology model of the hFP receptor that maximized the hypothesized ionic, hydrogen bonding, and hydrophobic interactions with the prostaglandin $PGF_{2\alpha}$.[6] Although X-ray coordinate information is currently unavailable for prostaglandin receptors, they are members of the G-protein coupled receptor (GPCR) family type and therefore possess structural similarity to the Swiss Institute rhodopsin template, upon which this model is based. In this work, we focused on the C_1 carboxylate region of the ligand, which forms an ionic interaction with a conserved arginine residue (amino acid 291 in hFP) found across all prostaglandin receptors and which has been shown previously via site-directed mutagenesis studies to be a key component of the prostaglandin ligand/receptor binding. It was also observed that, adjacent to the common ionic interaction between the C_1 carboxylic acid and this conserved arginine residue on the 7th transmembrane helix, there appeared to be a unique serine-118 residue in the 3rd transmembrane helix of the hFP receptor model that differentiated it structurally from the other prostaglandin receptors, which all possess a phenylalanine at this location. The sequence

difference at this location therefore suggested that a larger C_1 carboxylic acid isostere may be better tolerated in the hFP receptor and provide improved selectivity for the FP receptor relative to the other receptors.

New Phosphinyl Prostaglandin Analogs

Early generation receptor agonists in this class are characterized by poor selectivity and relatively short half-lives, the latter likely due in part to the C_1 carboxylic acid, which is subject to *beta* oxidation. Following the previously reported synthetic strategy to prepare the phosphonic acid series,[5] a series of phosphinic acids were prepared from their native prostaglandins. Utilizing this improved Barton variation of the Hunsdiecker reaction, the commercially available prostaglandins (**1a**, **1b**) were protected as tris-acetates, and the carboxylic-thiohydroxamic anhydride formed from N-hydroxypyridine-2-thione was refluxed in CH_2Cl_2 in the presence of a light source and CF_3CH_2I to induce a halodecarboxylation which produces the corresponding iodo intermediate in 50–60% yields (Figure 1). In a subsequent step, the iodide was treated with a variety of alkyl phosphinites via the Arbuzov reaction to provide the protected prostaglandin derivatives, which were saponified to provide the appropriate C_1 phosphinic acids **2a** & **2b**.[7] On *in vitro* analysis, binding potency appeared to track to size in the $PGF_{2\alpha}$ series **2a**, as $R^1 = CH_3$ (hFP $IC_{50} = 311$ nM) was significantly more potent than butyl (hFP $IC_{50} = 6700$ nM). Most interestingly, an analog of the potent but non-selective 16-phenoxy prostaglandin series, phosphinic acid 1-*nor*-2-(*P*-methyl)-phosphino-16-phenoxy-16-tetranor $PGF_{2\alpha}$ **2b**, proved to be potent (hFP $IC_{50} = 42$ nM) and selective (IC_{50}'s > 10,000 nM at all other prostaglandin receptors tested, including EP_1,



1a, R = $(CH_2)_3CH_3$, R' = H, CH_3, butyl
1b, R = OPh, R' = CH_3

2a, R = $(CH_2)_3CH_3$, R' = CH_3, butyl
2b, R = OPh, R' = CH_3

FIGURE 1 Key: (a) 30 equiv. Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; then sat. aq. Na_2CO_3, 99% (b) $(COCL)_2$, DMF, CH_2Cl_2; then CF_3CH_2I, DMAP, sodium salt of N-hydroxypyridine-2-thione, CH_2Cl_2, hν, reflux, 65%; (c) $P(OEt)_2R'$, reflux, 50–85%; (d) NaOH, EtOH–H_2O, 25–70%.

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EP_4, TP & IP). It was also found to be a bone anabolic agent, as demonstrated by the increase in vertebral bone volume above the pretreatment ovariectomized control group ($p < .05$). Interestingly, the *in vivo* ED_{50} was approximately 10 times better than predicted by FP binding. This is an encouraging sign that the metabolic stability was increased, although more studies will be required to confirm that our goal to reduce β-oxidation was accomplished.

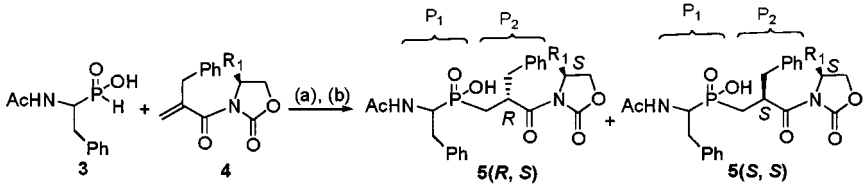
New Synthetic Entry into Phosphinyl Peptidomimetic Building Blocks

The availability and ease of making four individual isomers of the phosphinic acid bearing pseudodipeptidic unit can greatly facilitate peptidomimetic research. Methodology in the literature[8] leads to epimeric and racemic mixtures of phosphinyl dipeptide analogs. Thus, we evaluated a phosphinic acid involved asymmetric Michael addition reaction to achieve chiral induction at the α-position (P_2) of acrylate derivatives of Evans oxazolidinone type auxiliaries.

We found that reaction of (1-(*N*-Ac-amino)-2-phenylethyl)-phosphonous acid **3** with TMSCl at low temperature led to a mild and versatile Michael addition to simple acrylate analogs in very high yield. As shown in Table I, these conditions also led to useful asymmetric induction. Thus, the phosphinic acid **3** was treated with TMSCl in the presence of *N*,*N*-diisopropylethylamine at room temperature for 3 hrs. Michael addition to **4a** was then accomplished at room temperature over 24 hrs followed by an ethanol quench at -10°C to yield dipeptidomimetic **5a** (94%) in a 3:1 ratio of two diastereomers.

This asymmetric addition reaction was further studied using the diphenylmethyl auxiliary derivative **4b**. As also shown in Table I, even higher asymmetric induction was achieved in a similar overall yield of

TABLE I Asymmetric Michael Addition Reaction with Two Auxiliaries



Entry	Phosphinic acid	Acrylate: R_1	Product	(*R*, *S*)/(*S*, *S*)
1	**3**	**4a:** $PhCH_2$	**5a**	3/1
2	**3**	**4b:** Ph_2CH	**5b**	86/1

Key: (a) TMSCl, iPr$_2$NEt, DCM, 0°C-r.t., 24 hr; (b) EtOH, -10°C.

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5b (90%). Note that these results reflect products **5a** and **5b**, utilizing a racemic mixture of **3**. To investigate whether or not the chiral center at P_1 affected asymmetric induction, the Cbz protected form of **3** in the pure *R* configuration was added to **4a** under the same conditions. A 3:1 R/S ratio at P_2 of **5b** with was also observed. A similar chiral induction was demonstrated with nucleophiles bearing no asymmetry at P_1.[9] We now also believe the chiral carbon at the P_2 side chain position of the phosphinyl dipeptide structures **5a** and **5b** is formed preferentially in the *R* configuration. This stereochemical proposal is supported by X-ray crystallographic evidence, which will be published in due course.

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