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Phenyl substituted prostaglandin analogs for glaucoma treatment

Johan Stjernschantz and Bahram Resul
Glaucoma Research Laboratories, Kabi Pharmacia Ophthalmics, S-75182 Uppsala, Sweden.

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Introduction

In the eye prostaglandins have generally been associated with inflammation. This misconception goes back to the late 1960s and 1970s and was, to a large extent, due to studies designed to prove the inflammatory role of prostaglandins in the eye. One problem with these studies was that large quantities of prostaglandins were administered to the eye, and usually by direct injection. Another problem was that in many of the studies, rabbits were used as experimental animals. The rabbit eye is prone to reacting to a variety of stimuli with increased blood flow and disruption of the blood-aqueous barrier in the anterior uvea. This protective mechansim of the rabbit eye (1) is in sharp contrast to primate and human eyes, which generally are much less sensitive to trauma. It is conceivable that endogenous prostaglandins may play an important role in this protective mechanism of the rabbit eye.

The first study to demonstrate a clear-cut reduction in intraocular pressure (IOP) after topical administration of prostaglandins was that of Camras *et al.* (2). In this study a biphasic response in IOP could be obtained with small doses of prostaglandins, *e.g.*, prostaglandin F_{2alpha} (PGF_{2alpha}) **1** (Scheme 1); first an increase and then a sustained decrease. A topical dose of 5 mcg induced only a decrease in IOP (2). Unfortunately, however, this study was performed in rabbits, a species exhibiting marked tachyphylaxis to prostaglandins, and is therefore not representative for the human and primate eye in which prostaglandins lower IOP by another mechanism of action. In subsequent studies it has been demonstrated that prostaglandins indeed reduce IOP in primates and cats as well as in dogs (3-10).

The most relevant animal model with respect to the human eye is the monkey eye and mechanism studies performed with prostaglandins in monkeys will therefore be described. Several independent studies clearly indicate that the main mechanism of action to reduce IOP, at least of PGF_{2alpha} and its isopropyl ester, is increased uveoscleral outflow of aqueous humor (11-14). Aqueous humor is produced in the ciliary processes behind the iris. It then flows through the pupil from the posterior chamber into the anterior chamber between the iris and the cornea (Fig. 1). Normally, most of the aqueous humor exits the eye through the trabecular meshwork and Schlemm's canal situated in the chamber angle. Schlemm's canal is directly connected to episcleral veins outside the eye. However, part of the aqueous humor bypasses this exit route and leaves the eye through the so-called uveoscleral outflow pathway (15). In this pathway aqueous humor percolates through the ciliary muscle from the anterior chamber to enter into the supraciliary and suprachoroidal spaces from which the fluid relatively easily can pass out from the eye through the sclera (Fig. 1). The main resistance in this pathway is constituted by the ciliary muscle.

In glaucoma the drainage of aqueous humor from the anterior chamber is obstructed in the trabecular meshwork and/or the tissue adjacent to Schlemm's canal. Thus, if part of the fluid could be shunted out from the eye through another route this would be very attractive from a pathophysiological and clinical point of view. In fact, theoretically, since the pressure gradient forcing fluid into the uveoscleral outflow pathway is very small, if all aqueous humor were to exit the eye through this route an IOP close to the episcleral venous pressure would ensue. Such a pressure level, around 10 mmHg, would be very desirable in glaucoma management.

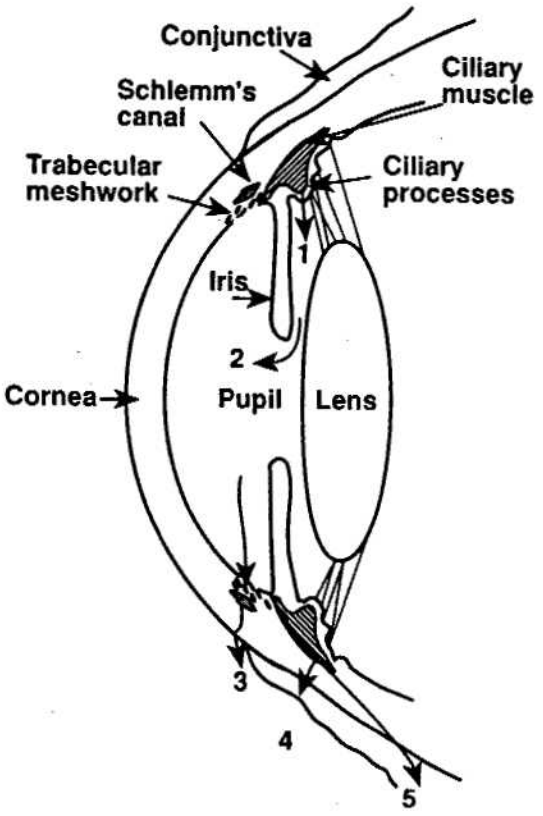


Fig. 1. Schematic picture of the anterior segment of the eye. The aqueous humor dynamics in the anterior segment determines the intraocular pressure together with the pressure in the blood vessels outside the eye. Aqueous humor is produced in the ciliary processes (1). It flows through the pupil into the anterior chamber (2), through the trabecular meshwork into Schlemm's canal and out into the blood vessels on the surface of the eye (3). Part of the aqueous humor exits through the uveoscleral pathway, traversing the ciliary muscle to enter into the supraciliary and suprachoroidal spaces, from where the fluid can leave the eye through the sclera (4 and 5, respectively).

PGF_{2alpha} and PGF_{2alpha} isopropyl ester (PGF_{2alpha}-ie) 2 (Scheme 1) have been shown effectively to reduce IOP both in normotensive healthy volunteers and in patients suffering from ocular hypertension or open angle glaucoma (16-23). However, both PGF_{2alpha} and PGF_{2alpha}-ie cause pronounced local side effects when applied topically on the eye. A diester prodrug, 15-propionate-PGF_{2alpha}-ie, was not found to significantly improve the therapeutic index of PGF_{2alpha} in the eye of human volunteers (24). These side effects comprise superficial irritation, mostly experienced as a grittyness or foreign body sensation and conjunctival hyperemia lasting for several hours (25). Because of the side effects it has not been possible to develop PGF_{2alpha} or an esterified prodrug of PGF_{2alpha} to a useful drug for glaucoma treatment in spite of the very good IOP lowering effect of this prostaglandin. It should be stressed, however, that PGF_{2alpha} and PGF_{2alpha}-ie have never been found to induce any intraocular side effects, and therefore from a clinical point of view, this class of drugs probably would be acceptable as long as the superficial ocular side effect profile is improved.

Attempts were made to reduce the local side effects of prostaglandins by a prodrug concept through esterification of different parts of the molecule. Esterification increases lipophilicity of the molecule and thus the bioavailability in the eye. The sites of esterification of PGF_{2alpha} used for the prodrug concept are illustrated in Scheme 1. These prodrugs of PGF_{2alpha} were prepared in the early 1980s. Unfortunately, the prodrugs did not significantly increase the therapeutic index of PGF_{2alpha} in the eye. However, substituting part of the omega chain with a phenyl ring (Scheme 2) has been shown to change the pharmacological profile of PGF_{2alpha} dramatically with respect to the side effects in the eye (26-29).

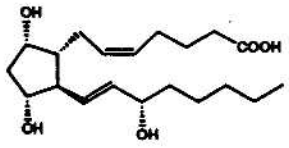
General method for synthesis of phenyl substituted PGF_{2alpha} analogues

The omega chains of the phenyl substituted PGF_{2alpha} analogues were synthesized from the appropriate phosphoranes (30-32) or phosphonates (33) as key reagents. Three general routes were utilized as outlined in Scheme 3.

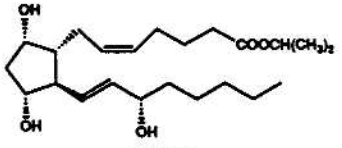
The acyl triphenylphosphorane I (Scheme 3) was prepared by addition of an aryl halide to lithiotriphenyl phosphinoacetonide (method A) or by reaction of methyl triphenylphosphonium bromide with aryl acid ester using potassium *t.* butoxide (method B). The reactive dimethyl (2-oxoalkyl) phosphonates were prepared by reaction of aryl halide and dimethyl (2- oxopropyl) phosphonate in THF using *n*-BuLi (method C). These precursors were prepared in 55-60% yield.

The phenyl substituted PGF_{2alpha} analogues were prepared from a commercially available bicyclic lactone (34, 35) corresponding to formula III as outlined in Scheme 4. The primary alcohol of lactone III was oxidized to aldehyde IV using dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the presence of anhydrous phosphoric acid in dimethoxyethylene (DME) (36-38). The crude aldehyde IV was reacted with the appropriate acyl phosphorane or acyl phosphonate I, II (Scheme 3) using a method described by Emmon-Horner (39, 40) affording alpha, beta unsaturated ketone V. The resulting enone V was treated with lithium tri *sec* butylboro hydride (lithium selectride) (41) at -120°C/-130°C, furnishing 70-75% *S* isomer VIa over *R* isomer VIb. Sodium borohydride and cerium chloride (41) were also used but with lower stereoselectivity. The isomers were separated by column chromatography on silica gel using toluene: AcOEt 2:1 as eluent. The phenyl benzoyl group was removed by using powdered potassium carbonate in methanol to give an 80% yield of the diol. The product was purified by column chromatography on silica gel using AcOEt as eluent. The diol was treated with diisobutyl aluminium hydride (DIBAL) (42) in dry THF at -78°C to afford lactol (triol) VII in 75-80% yield. The triol VII underwent Wittig reaction with 4-carboxy butyl triphenylphosphonium bromide and Kot.Bu in THF furnishing the phenyl PGF_{2a} acid VIII. This was further reacted without isolation with isopropyl iodide (iprI) and DBU in acetone (43) to give the corresponding ester in about 50% yield. The 15-allylic alcohol of the phenyl PGF_{2alpha} ester IX was oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (44, 45) in dioxane to give the

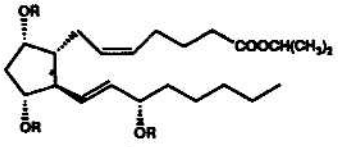
Scheme 1



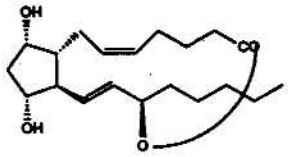
PGF2α
1



PGF2α ie
2



R=H, COCH3
3



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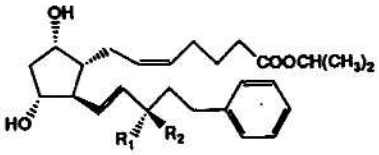
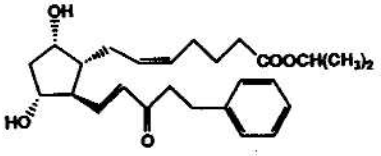
Scheme 2



5- R1=OH R2=H

6- R1=H R2=OH



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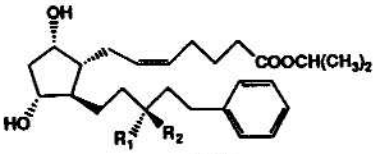
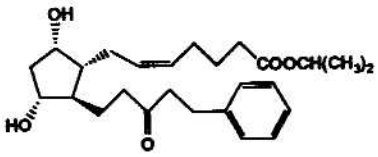


8- R1=OH R2=H

9- R1=H R2=OH



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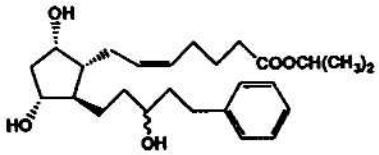
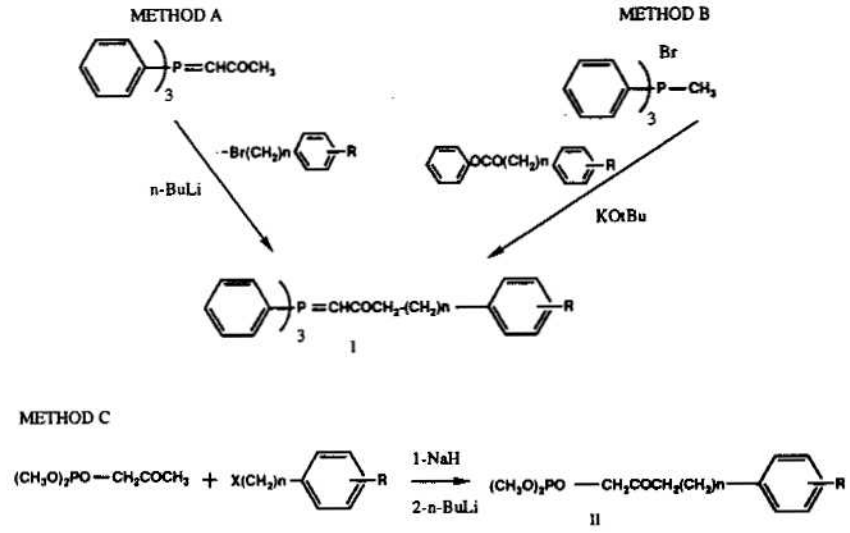


11

desired 15-keto phenyl PGF_{2alpha} analogue X in about 80% yield.

13,14-dihydro phenyl PGF_{2alpha} analogues were synthesized as outlined in Scheme 5. The *trans* allylic double bond of compound VI was reduced under hydrogen atmosphere using pd-c as a catalyst in the presence of sodium nitrite (46) affording compound XI in quantitative yield. The product XI was isolated and reacted subsequently following a procedure described above to give the desired product XII (Schemes 4 and 5). The 9,11 dihydroxyl groups of the phenyl PGF_{2alpha} analogue XII were protected with benzene boronic acid (47) to give 9,11-phenyl boronate, which was further reacted without isolation with pyridinium chlorochromate (PCC) adsorbed on alumina (48) in CH_2Cl_2 to give the 15-keto analogue XIII. This was treated with hydrogen peroxide to deprotect the 9,11-phenyl boronate,

Scheme 3



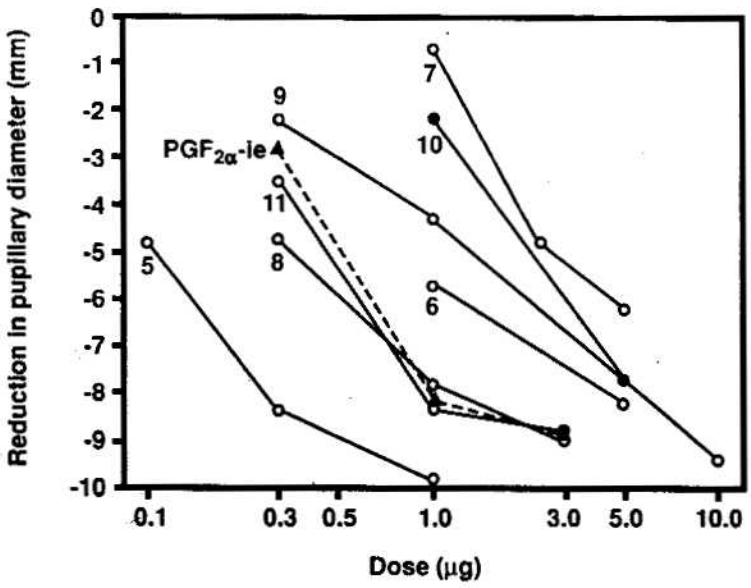
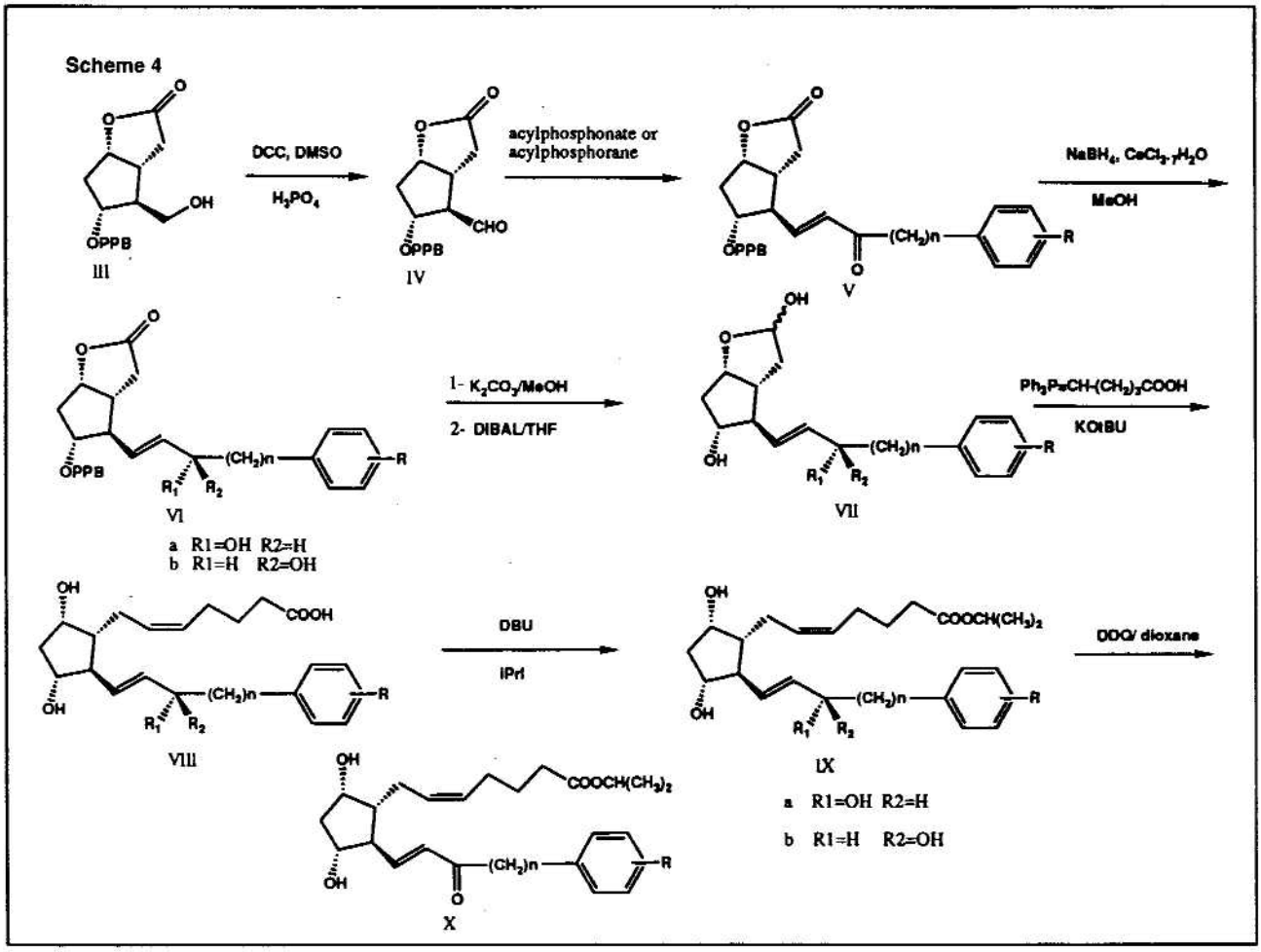


Fig. 2. Miotic effect of 17-phenyl substituted PGF_{2alpha}-ie analogues in cat eyes 3 hours after topical application (maximum effect). PGF_{2alpha}-ie included for comparison (n = 6).



giving the desired product, the 15-keto phenyl PGF_{2alpha} analogue XIV in good yield.

The analogues were identified with ^{13}C and ^{1}H NMR and the purity was determined with HPLC. All analogues were used as isopropyl esters to enhance bioavailability in the eye.

17-Phenyl substituted PGF_{2alpha} analogues

Structure-activity relationships of 17-phenyl substituted PGF_{2alpha}-ie analogues

The test compounds were administered topically on the eye in aqueous solution. All the 17-phenyl substituted PGF_{2alpha}-ie analogues (Scheme 2) exhibited marked and dose dependent miotic (pupillary constrictive) effect in the cat (Fig. 2). The horizontal pupillary diameter of the experimental eye was compared with that of the contralateral control eye treated with vehicle only. In fact, some of the phenyl substituted analogues such as compound **5** (Scheme 2) were more potent than PGF_{2alpha} (administered as the isopropyl ester),which is endogenous in the eye (Fig. 2). These results seem to be in fairly good agreement with those of previously reported studies with 17-phenyl-18,19,20-trinor-prostaglandins in other biological systems (49). In spite of the fact that PGF_{2alpha}-ie is very irritative in the cat eye, none of the phenyl substituted PGF_{2alpha}-ie analogues caused any ocular irritation as judged from the behavior of the animals as well as from the degree of lid closure after topical administration of the compunds (Table I). The marked miotic effect of these compounds in combination with the total lack of irritative effect strongly suggests that substitution of part of the omega chain with an aromatic ring structure either causes conformational alteration in the molecule or imposes a steric hindrance, which enables a discrimination between different prostaglandin receptor subtypes.

The IOP reducing effect of the new phenyl substituted PG analogues was investigated in cynomolgus monkeys using pneumatonometry. The pneumatonometer was calibrated for IOP measurement in monkeys using the closed stopcock method (50). Again the experimental eye was treated topically with the test compound while the contralateral eye received the vehicle only. It has to be emphasized that the IOP of the normotensive cynomolgus monkey is usually low, often around 10-14 mmHg, and consequently only pressure reductions of a few mmHg can be obtained. In spite of this, many of the analogues caused a clear-cut reduction in IOP (Fig. 3). Particularly analogues **5**, **8** and **11** were effective. These compounds were roughly equipotent with PGF_{2a}-ie. Least reduction was caused by the 15-epimers with the

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