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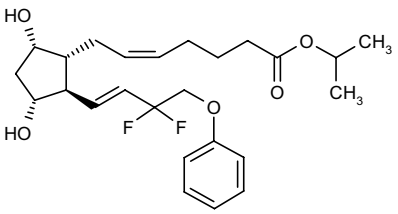
Tafluprost

Prop INN

Prostanoid FP Receptor Agonist
Antiglaucoma Drug

AFP-168
DE-085

15-Deoxy-15,15-difluoro-16-phenoxy-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ isopropyl ester



$C_{25}H_{34}F_2O_5$
Mol wt: 452.5313

CAS: 209860-87-7

EN: 268411

Abstract

Prostaglandin analogues have been extensively studied and used for lowering/controlling the elevated intraocular pressure (IOP) that causes glaucoma. In the search for a drug candidate with stronger and more consistent IOP-lowering activity while producing milder side effects than currently available drugs, tafluprost was synthesized and selected for further evaluation. Preclinical studies carried out in mice, cats and monkeys showed that tafluprost at a concentration of 0.005% has a potent IOP-lowering effect. Pharmacokinetic studies demonstrated rapid absorption into ocular tissues and entry into the systemic circulation. Results from phase I and II clinical trials indicated that tafluprost had a stronger IOP-lowering effect than latanoprost, with fewer and milder local side effects. The compound has been submitted for regulatory approval in Japan by Santen.

Synthesis

Tafluprost is synthesized by the following procedure:

The Wittig condensation of the bicyclic carbaldehyde (I) with the dimethyl phosphonate (II) by means of LiCl and Et_3N or NaH in DMF gives the adduct (III), which is fluorinated by means of morpholino-sulfur trifluoride (IV) in dichloromethane to yield the difluorinated compound (V). The hydrolysis of the benzoate ester group of (V) by means of K_2CO_3 in methanol affords the hydroxylic compound (VI). The reduction of the lactone group of (VI) by means of diisobutyl aluminum hydride in THF/toluene provides the lactol (VII), which is condensed with the phosphonium salt (VIII) by means of NaHMDS or KHMDS in THF/toluene to give the prostaglandin $F_{2\alpha}$ derivative (IX). Finally, this compound is esterified with isopropyl iodide (X) and DBU in acetone to provide the target prostaglandin $F_{2\alpha}$ isopropyl ester (1-7). Scheme 1.

Background

Glaucoma is a common eye disease that can lead to blindness if not treated appropriately. Based on published studies and United Nations population projections, approximately 60 million people worldwide are expected to have glaucoma in 2010. Glaucoma is the second leading cause of blindness worldwide after cataracts, and glaucoma-associated blindness represents a significant burden on healthcare systems. Although no cure for glaucoma exists, further damage and blindness can be prevented by early detection and treatment (8).

Intraocular pressure (IOP) is considered one of the main risk factors for glaucoma and is one of the few that can be clinically modified. Thus, the objective in treating glaucoma is nearly always the reduction in IOP in order to prevent additional optic nerve damage and preserve remaining vision. Since the discovery that topically applied prostaglandins (PGs) could reduce IOP, PG analogues have been extensively studied for the potential treatment of glaucoma and ocular hypertension. These compounds decrease IOP by increasing uveoscleral outflow. Several PG derivatives, including unoprostone isopropyl ester, latanoprost, bimatoprost and travoprost, have been launched as antiglaucoma drugs, with latanoprost used as first-line therapy. However, currently available antiglaucoma drugs, including latanoprost, produce local side effects, such as conjunctival hyperemia, irritation and headache. New agents with greater IOP-

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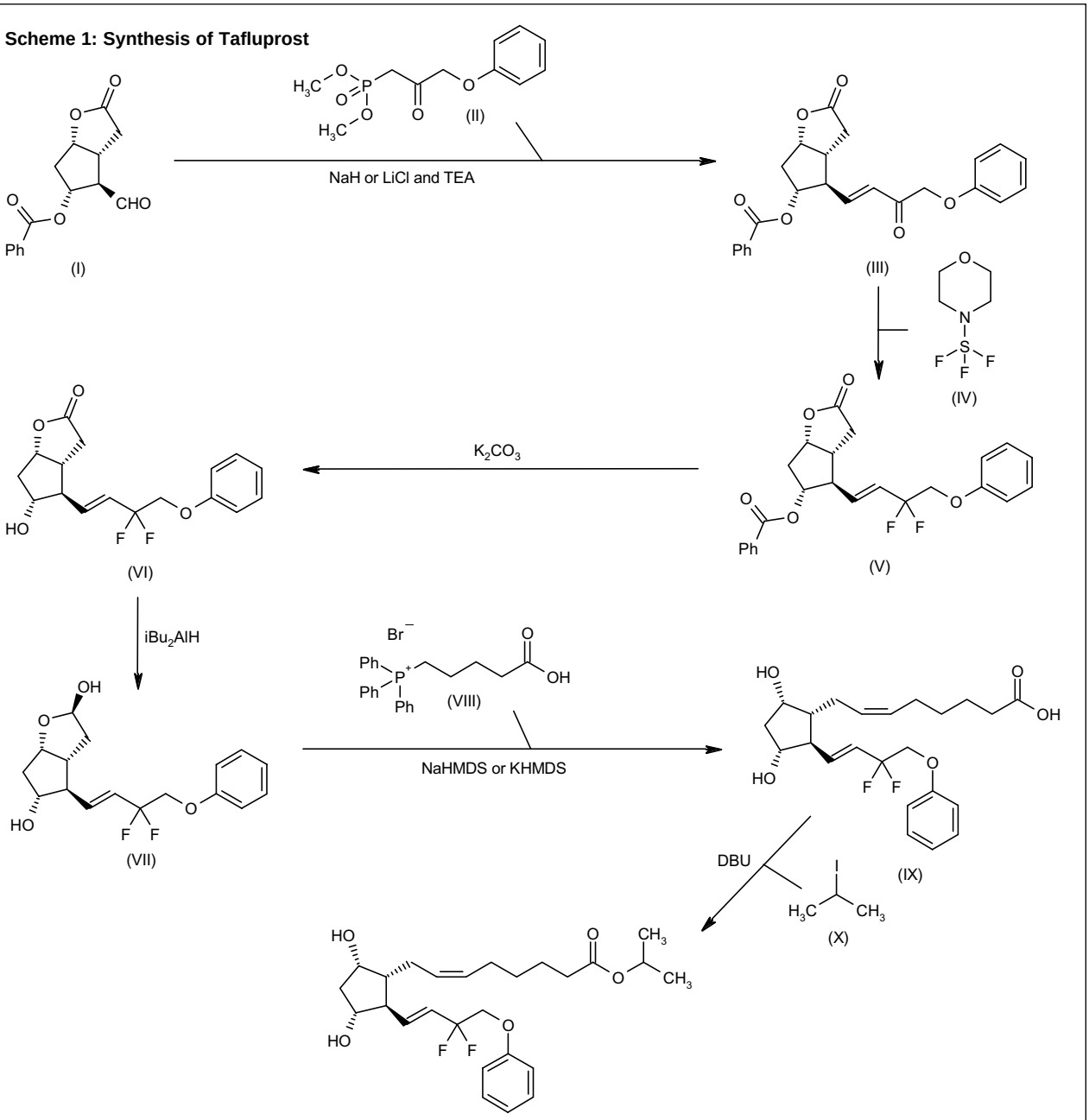
Scheme 1: Synthesis of Tafluprost



lowering efficacy and milder local side effects are therefore needed (8).

Recently, a new PG analogue, tafluprost, was developed as a potential new ocular hypotensive drug. Tafluprost is being co-developed by Santen and Asahi Glass and was recently submitted for approval in Japan for the reduction in IOP in primary open-angle glaucoma and ocular hypotension (1, 9, 10).

Preclinical Pharmacology

The carboxylic acid of tafluprost (AFP-172) displayed high affinity for the PGF (FP) receptor (K_i = 0.4 nM), over 10 times that of the carboxylic acid of latanaprost (1, 11, 12).

In *in vivo* studies, the maximal IOP reduction produced by tafluprost 0.0025% was greater than that produced by latanoprost 0.005% in both normotensive and ocular hypertensive monkeys (3.1 and 11.8 mmHg, respectively, *versus* 2.1 and 9.5 mmHg, respectively). Also, the peak time for IOP reduction on tafluprost was 8 h after administration, similar to on latanoprost, but the duration of the IOP reduction was longer on tafluprost than latanoprost. The primary mechanism of the IOP-lowering effect of tafluprost was via an increase in uveoscleral outflow, similar to other PG derivatives. In comparison

to latanaoprost, tafluprost was associated with less stimulation of melanogenesis in melanoma cells (11, 12).

In other experiments, tafluprost exhibited more potent FP receptor-agonist effects than latanoprost. The carboxylic acid AFP-172 induced contraction of isolated cat iris sphincters with an EC_{50} of 0.5 nM compared to 13.6 nM for the carboxylic acid of latanoprost. Tafluprost applied topically at 0.001-0.01% displayed more potent miotic effects than latanoprost in anesthetized cats. A similar reduction in IOP was seen in conscious normotensive monkeys administered tafluprost 0.0005% and latanoprost 0.005%, although the effect of tafluprost was of longer duration, with a significant reduction in IOP up to 8 h after administration. No increase in melanin content of B16 melanoma cells was observed for tafluprost at up to 100 μM, whereas latanoprost concentration-dependently increased melanin content at 1-100 μM (13).

The effect of tafluprost on IOP and retinal blood flow (RBF) in adult cats was also evaluated. A single drop was administered in 1 eye of cats anesthetized with enflurane and mechanically ventilated. Measurements carried out at 30 and 60 min after dosing showed a 16.1% and 21% IOP reduction, respectively, as well as an increase of 1% and 2.4% in mean vessel diameter, respectively. Increased mean blood velocity (17.4% and 13.7%, respectively) and mean RBF (20.7% and 18.8%, respectively) were also observed at 30 and 60 min after administration (14).

The effects of tafluprost on IOP were compared with those of latanoprost, timolol maleate and other ocular hypotensive agents in a study in male ddY mice housed under a 12-h light-dark cycle. The reduction in IOP was evaluated by analyzing the difference between treated and untreated eyes of the same mouse. The mean baseline IOP during the experiment was 17.9 ± 0.1 mmHg, and the maximal IOP reduction on tafluprost was 4.2 ± 0.8 mmHg, being the most potent compound studied. Concomitant administration of tafluprost and timolol or dorzolamide produced a further reduction in IOP (5.7 ± 0.5 and 5.0 ± 0.4 mmHg, respectively) (15).

In another preclinical study performed in mice, 3 μl of tafluprost or latanoprost was topically administered to 1 eye of ddY and C57BL/6J (B6) mice. Both tafluprost and latanoprost lowered IOP in a dose-dependent manner at night. In B6 mice, both tafluprost and latanoprost lowered IOP from 1 to 6 h after administration, but the effect of tafluprost was significantly stronger than that of latanoprost. In contrast, in EP1 and EP2 receptor knockout mice, a similar IOP-reducing effect was seen for both compounds. Furthermore, in FP receptor knockout animals, the compounds exhibited little effect and the IOP-lowering effect was significantly diminished in EP3 receptor knockout mice (16). Other experiments in EP1 and EP3 receptor-deficient mice also indicated a possible role for the EP3 receptor in the IOP-lowering effects of tafluprost, latanoprost, bimatoprost and travoprost (17).

The IOP-lowering effect of tafluprost was also compared with that of travoprost, unoprostone and latanoprost in mice over a 24-h period. The IOP was found to be higher at night than during the day. Area under the curve (AUC) analysis revealed dose-dependent IOP reductions for each agent tested. The maximum IOP reductions were –5.5 ± 1.0 mmHg on tafluprost 0.015%, –3.9 ± 0.6 mmHg on latanoprost 0.005%, –3.8 ± 0.8 mmHg on travoprost 0.004% and –2.0 ± 0.3 mmHg on isopropyl unoprostone 0.12%. Tafluprost 0.005% decreased IOP more than latanoprost 0.005% at 3, 6 and 9 h or 0.12% unoprostone at 2, 3 and 6 h, while no significant difference was observed between tafluprost and travoprost 0.004% (18).

Pharmacokinetics and Metabolism

To evaluate the distribution and metabolism of [^{3}H]-tafluprost in ocular tissues and to study IOP-lowering effects of the major metabolites of tafluprost, single ocular doses of [^{3}H]-tafluprost were administered to male/female cynomolgus monkeys (1 μg/eye for tissue distribution studies and 10 μg/eye for metabolic studies). Tafluprost was rapidly absorbed into ocular tissues and subsequently entered the systemic circulation. The highest concentrations of radioactivity were observed in the bulbar conjunctiva and the palpebral conjunctiva (323 and 180 ng eq/g, respectively) at 0.083 h after administration, and in the cornea (784 ng eq/g) at 0.25 h after administration. Nonvolatile radioactivity in plasma peaked (0.907 ng eq/g) at 0.083 h after administration and then declined steadily. Three major metabolites, AFP-172, 1,2-dinor-AFP-172 and 1,2,3,4-tetranor-AFP-172, accounted for most of the radioactivity in the aqueous humor and other ocular tissues. AFP-172 was demonstrated to be the most abundant and the only pharmacologically active metabolite in ocular tissues. A small amount of tafluprost was detected in the ciliary body, cornea and iris (19).

Clinical Studies

A double masked, placebo-controlled, ascending-dose phase I study was carried out in 16 non-Japanese and 8 Japanese healthy male subjects to determine an appropriate concentration of tafluprost for the treatment of glaucoma. Tafluprost was administered once daily on the first day of each treatment period and twice daily on the second day of the same treatment period. Four concentrations (0.0001%, 0.0005%, 0.0025% and 0.005%) were tested. Each of the concentrations demonstrated an IOP-lowering effect, although the two higher concentrations showed a stronger effect. No serious adverse events were reported, the most frequent adverse event on tafluprost being ocular hyperemia (20).

To further determine the safety, tolerability and pharmacokinetics of tafluprost, two phase I clinical trials were carried out in healthy non-Japanese (n=49) and Japanese volunteers (n=27). The subjects were randomized to receive either tafluprost eye drops at a concentration of 0.0025% or 0.005%, latanoprost 0.005% or placebo, 1 drop per eye once a day for 7 days. Among the non-Japanese males, tafluprost 0.005% showed a signif-

icantly greater IOP reduction than either latanoprost 0.005% or placebo at various times during the treatment. Among the Japanese males, a statistically significant IOP decrease was noted with tafluprost 0.005%, but not tafluprost 0.0025% or latanoprost 0.005%. The results indicate that tafluprost has a better IOP-lowering effect than latanoprost. In both trials, tafluprost was generally well tolerated, no serious adverse events were reported and no subjects withdrew due to adverse effects (21).

A prospective, multicenter, randomized, double-masked, active-controlled phase II study was carried out in a total of 38 patients with open-angle glaucoma or ocular hypertension to investigate the IOP-lowering effect and tolerability of tafluprost 0.0015%. The patients were divided into two parallel groups, and the IOP-lowering effect and tolerability of tafluprost were compared with those of latanoprost 0.005% as eye drops for 6 weeks. Eighteen patients in each group completed the study. No statistically significant difference in the IOP-lowering effect of tafluprost 0.0015% and latanoprost 0.005% was seen at the end of the 6-week treatment period. The mean diurnal IOP decrease from baseline to day 42 was 33% for both groups and the IOP values remained stable for both tafluprost and latanoprost up to at least 24 h after administration, slowly increasing from 36 h after dosing. Very few adverse events were observed and tafluprost showed a relatively low incidence of mild conjunctival redness (22).

Several phase III studies, including comparative studies of tafluprost and latanoprost, have been conducted in Japan and Europe. Results from the Japanese study indicated the noninferiority of tafluprost as compared to latanoprost, while initial results from the European study did not demonstrate its noninferiority to latanoprost. A U.S. and European study is also under way comparing tafluprost and timolol maleate 0.5% (9). Santen has filed for regulatory approval in Japan for the use of tafluprost in reducing elevated IOP in primary open-angle glaucoma and ocular hypertension (10).

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Santen Pharmaceutical Co., Ltd. (JP); Asahi Glass Co., Ltd. (JP).

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