THE RECENT DEVELOPMENT ON PROSTAGLANDIS AND PROSTANOIDS

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Summary

Prostaglandin's and prostanoids and their developments in field of medicinal chemistry are amazing. Due to their wide variety of uses and applications; the significant researches have been undertaken. Cyclopentane ring with alkyl chains have known for their excellent SAR studies. In this regard we have attempted to carry on the extensive review on the above topic to explore a treasure of knowledge for their effective therapeutic uses. The present review is confined to discuss the chemistry of prostaglandins and prostanoids; the mechanism and pharmacology of prostaglandins and prostanoids are better understood.

Key words: Prostaglandin's, prostanoids, SAR.

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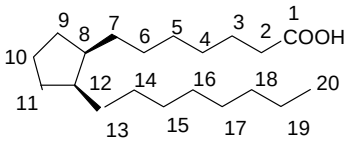
Introduction

As the name indicates prostaglandins mainly occurs in seminal fluid secreted by prostate gland. Prostaglandin are group of cyclopentane derivatives, naturally occurring 20 C fatty acids produced by oxidative metabolism of 5,8,11,14-eicosatetraenoic acid (arachidonic acid) in microsomal fraction of cells by mult enzyme complex pathway. Structurally prostaglandins are derivative of prostanoic acid [(octyl cyclopentyl) heptanoic acid].



Prostanoic acid

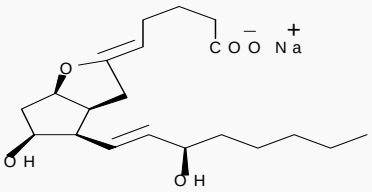
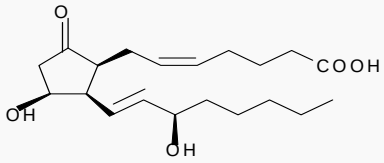
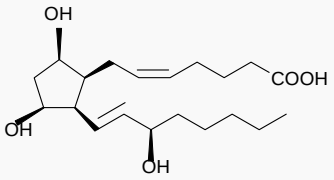
Analogue of prostaglandin are found useful in treatment of osteoporosis, glaucoma, prevention of post partum hemorrhage, inhibition of apoptosis therapy for pyometritis, vasodialation, treatment for primary dysmenorrhoea, protection of striated neurons against excitotoxic, injury, antitumour activity, atherogenesis, induction of labor, inhibition of platelet aggregation, photo affinity probes, local anesthetics, gastric protective, treatment of diseases associated with stress and Inflammation and many more pharmacological functions. [14]

Function:

There are currently nine known prostaglandin receptors on various cell types. Prostaglandins ligate a subfamily of cell surface seven-transmembrane receptors, G-protein-coupled receptors. These receptors are termed DP1-2, EP1-4, FP, IP, and TP, corresponding to the receptor that ligates the corresponding prostaglandin (e.g., DP1-2 receptors bind to PGD2).These varied receptors mean that Prostaglandins thus act on a variety of cells, and have a wide variety of actions:

- cause constriction or dilation in vascular smooth muscle cells
- cause aggregation or disaggregation of platelets
- sensitize spinal neurons to pain
- decrease intraocular pressure
- regulate inflammatory mediation
- regulate calcium movement
- control hormone regulation
- control cell growth

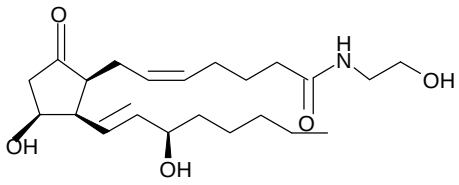
Table 1: comparison of the prostaglandin types Prostaglandin I_2 (PGI_2), Prostaglandin E_2 (PGE_2) and Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)[6]

Structure & Name	Receptor	Function
 PGI2	IP	• vasodilatation • inhibit platelet aggregation • bronchodilatation
 PGE2 s	EP_1	• bronchoconstriction • GI tract smooth muscle contraction
	EP_2	• bronchodilatation • GI tract smooth muscle relaxation • vasodilatation
	EP_3	• ↓ gastric acid secretion • ↑ gastric mucus secretion • uterus contraction (when pregnant) • GI tract smooth muscle contraction • lipolysis inhibition • ↑ autonomic neurotransmitters [6]
	Unspecified	• hyperalgesia[6] • pyrogenic
 $PGF_{2\alpha}$	FP	• uterus contraction • bronchoconstriction

PROSTANOID DERIVATIVES:

Amide derivative:

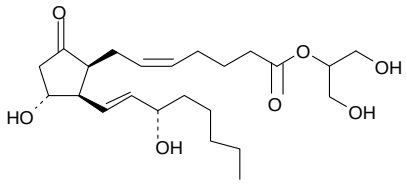
Novel amide derivatives of prostaglandins, prostaglandin ethanolamides (or prostamides) were shown to be formed by cyclooxygenase (COX-2) with anandamide as substrate, prostaglandin E_2 being the major prostanoid product produced by human COX-2.



Anandamide (arachidonoyl ethanol amide) must be previously cleaved from a phosphatidylethanolamine derivative by the action of phospholipase D in response to various stimuli. Later metabolic studies have shown that COX-2 was also able to generate ethanolamides of PGE_2, PGD_2 and $PGF_{2\alpha}$ It was also shown that endocannabinoid-derived prostanoids of the D-, E-, I-series and thromboxane are generated by the sequential actions of COX-2 and the corresponding prostaglandin synthase at rates comparable to those observed with the presumed natural substrate, arachidonic acid Prostamides were shown to have prominent pharmacological actions possibly by interaction with novel receptors The in vivo formation of prostamides D_2, $F_{2\square}$ and E_2 has been investigated using fatty acid hydrolase knockout mice. Synthetic analogues of endogenous prostamides, as Bimatoprost, are in development as hypotensive agent for the treatment of glaucoma and ocular hypertension. [9]

Ester derivatives:

It was demonstrated in 2000 that cyclooxygenase-2 was able to oxygenate the endocannabinoid, 2-arachidonoylglycerol, to glyceryl prostaglandins with intact macrophages or with purified enzyme, 2-acylglycerol being the preferred substrate. The first metabolite, prostaglandin H_2 glycerol ester is a substrate for cellular PGD synthase leading to prostaglandin D_2 and E_2 esters (PGE_2-G).



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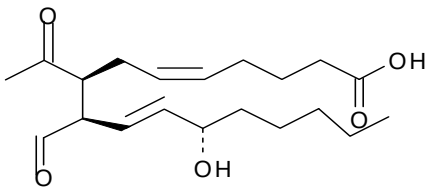
PGE_2-G

It was also shown that endocannabinoid-derived prostanoids of the D-, E-, I-series and thromboxane are generated by the sequential actions of COX-2 and the corresponding prostaglandin synthase at rates comparable to those observed with the presumed natural substrate, arachidonic acid Pharmacological studies revealed that macrophage production of these compounds is calcium-dependent and mediated by diacylglycerol lipase and COX-2

Later, it was shown that PGE_2-G was able to trigger specifically calcium mobilization, inositol-P3 synthesis, and activation of protein kinase C in macrophage cells.

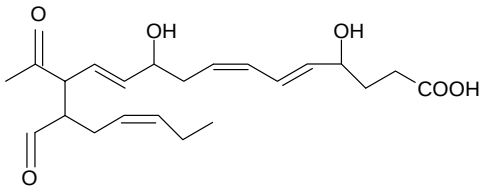
Aldehyde derivative:

PGH_2 produced by the cyclooxygenase action on arachidonic acid was shown to rearrange nonenzymatically to generate named levuglandins (LG) (secoprostanoic acid levulinaldehydes). These aldehydes were shown to react with lysyl residues on proteins to form adducts that partition to pyrrole derivatives and are able to form intra- and intermolecular protein-protein cross-links LG adducts are considered one of the first modifications of plasma lipropoteins (LDL) during their free radical oxidation These lipid-derived proteins may serve as dosimeters of oxidative injury since it was determined that elevated plasma levels of isoLG-protein epitopes were associated with atherosclerosis independently of total cholesterol Two main levuglandins were studied, LGD_2 whose structure is similar to PGE_2 and LGD_2 similar to PGE_2 .



Levugladin E_2

Later, it was shown that the two stereo isomers LGD2 and LGE2 may be produced by the cyclooxygenase pathway but also by the isoprostane pathway (rearrangement of isoprostane endoperoxides). Furthermore, the isoprostane pathway was shown to produce several structural isomers of levuglandins with the same chemical properties which were named isolevuglandins. The biosynthesis of isolevuglandins and the mechanism of their adduction to proteins have been extensively reviewed. The free radical-induced peroxidation of DHA may lead after molecular rearrangement via the neuroprostane pathway to the formation of highly reactive α-keto-aldehydes. These compounds were named isoketals (or neuroketals) to distinguish them from levuglandins formed by rearrangement of the cyclooxygenase endoperoxide. Eight regioisomers may be formed (each with eight racemic diastereomers). Of these eight regioisomers, four have a 1, 4-Pentadiene structure and four have a 1, 4, 7-octatriene structure on one of the side chains. [21]



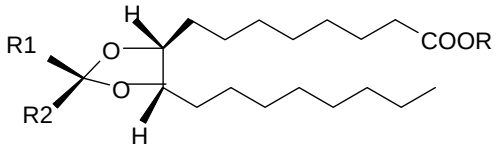
One Neuroketal

CLINICAL USES:

- To induce childbirth (parturition) or abortion (PGE_2 or PGF_2, with or without mifepristone, a progesterone antagonist);
- To prevent closure of patent ductus arteriosus in newborns with particular cyanotic heart defects (PGE_1)
- To prevent and treat peptic ulcers (PGE)
- As a vasodilator in severe Raynaud's phenomenon or ischemia of a limb
- In pulmonary hypertension
- In treatment of glaucoma (as in bimatoprost ophthalmic solution, a synthetic prostamide analog with ocular hypotensive activity)
- To treat erectile dysfunction or in penile rehabilitation following surgery (PGE1 as alprostadil).[20]
- To treat egg binding in small birds . [21]

RECENT DEVLOPMENTS:

Ganginell T S, Bertko R. J in 1985 synthesized some heterocyclic prostanoids substituted 1, 3-dioxanes (PGE_1 derivatives), which causes relaxation of guinea pig tracheal chain and intestine. They are also anesthetic. [1]



R=R1=C_2H_5, R2=CH_3, Ethyl (2- Ethyl, 2-methyl, 5-n-octyl, 1, 3-dioxolan) 4-yl.

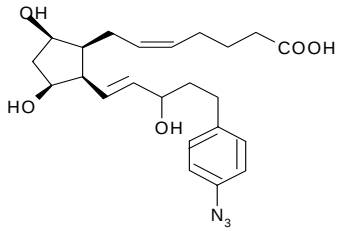
R=C_2H_5, R1=C_6H_5, R2=H, Ethyl (2-methyl, 2-phenyl, 5-octyl) 4-yl octanoate.

R=R1=R2=H, 5-n-octayl 1, 3-dioxalan 4-yl octanoic acid.

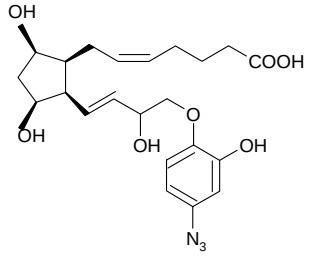
R=C_2H_5, R1=H, R2=CH_3, Ethyl, 2-methyl, 5-octyl, 1,3-dioxolan,4-yl octanoate.

R=C_2H_5, R1=R2=CH_3, Ethyl 2,2- dimetyl , 1,3-dioxolan 5-octyl, 4-yl octanoate

Then in 1989 Kawada Kenji and Kurt Dolence E have synthesized Azide substituted 16-phenoxy and 17-phenyl PGF2 a prostaglandin. They were biologically in active as a result of hydrophilic phenoxy hydroxyl group. In second approach, iodination of 17-(4-aminophenyl 18,19,20-trinor prostaglandin $F_{2\alpha}$ derivative delivered 17-(4-azido 3-iodophenyl) 18, 19, 20 –Trinor prostaglandin $F_{2\alpha}$ which exhibited competitive binding with natural [3H] PG F_2a to ovine luteal cells and to plasma membrane of bovine corposa lutea. [^{125}I] 17-(4-azido 3-iodophenyl). 18,19,20-trinor prostaglandin F_2a was utilized in a preliminary photo affinity cross linking expt. [2]

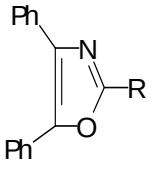


17-(4-Azido, 2-hydroxy, 19, 20- Trnor prostaglandin $F_{2\alpha}$



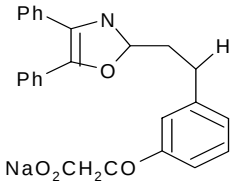
16-(4-azido, 2-hydroxy Phenoxy) 17, 18, 19, 20-Tetranor prostaglandin F2α

Nicholas A and Michael Rosenfeld in 1992 discovered that 4,5–diphenyl oxazole derivatives as prostacyclin mimetics found to inhibit ADP induced aggregation of human platelets with an IC_{50} of 2,5nm.By inserting a phenoxy ring into side chain moiety and systematically varying the pattern of substitution length,more potent inhibitors of platelet aggregation were identified .The substituted cis-(ethenyl phenoxy)acetic acid. [3]



R= $(CH_2)_8$ COOH

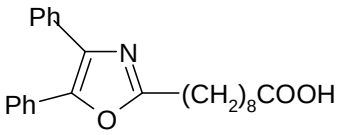
4,5-Diphenyl azile nonenaic acid



Most potent platelet aggregation inhibitors Trans olefinic isomer of this is 72 fold weaker as inhibitors of ADP induced platelet aggregation.

Recent studies by Zheng-Hong and Yumei Weng J. in 1992 on diphenyl heterocyclic moiety which is a prostacyclin mimetic, that inhibits ADP, induced aggregation of human platelets.

4,5 –Diphenyl 2- ozazolenonanoic acid



2-(3-(2-(4,5–diphenyl 1,2-oxezolyl) ethyl) phenoxy) acetic acid

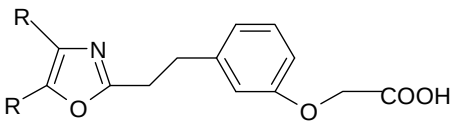
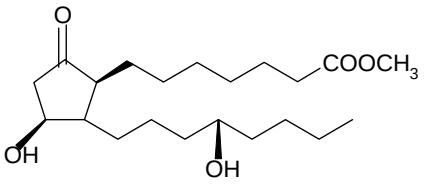


Table 2:Substituents with enhanced potency.

R	Inhibition of ADP induced aggregation (IC_{50})
C_6H_5	1.2
2-FC_6H_4	1.4
2-CH_3 C_6H_4	11.6
3-F C_6H_4	17.7
3-Cl C_6H_4	768
3-CH_3 C_6H_4	775
3-CH_3 O C_{6H4}	7.2
4-F C_6H_4	4.8
4-Cl C_6H_4	17.1

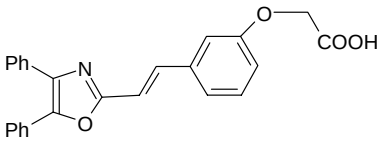
4-Br C_6H	12.6
4-CH_3 C_6H_4	0.34
4-CH_3 CH_2 C_6H_4	28.3
4-CF_3 C_6H_4	>60
4-CH_3 S C_6H_4	5.2
4-CH_3 OC_6H_4	704
2-Thionyl	17.0
3-Thionyl	>78
C-C_6H11	>20
2,2'-$(C_6H_4)_2$	

Anton Sadjak , Sabine Supanz have worked on di-isopropyl analog which showed efficiency equal to misoprostol against indomethacin induced gastric damage and no diarrhea at highest dose tested. [6]



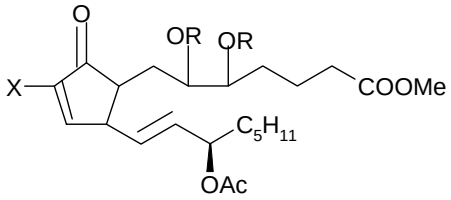
Misoprostol

Ashok Trehan K and Kimwright J. J have showed the structure activity relationship associated with (3-(4-(4,5-diphenyl 2- oxazolyl phenoxy) acetic acid (prostacyclin mimetics).



It inhibits ADP induced aggregation of human platelets with an IC_{50} of 0.18 nm.Effect of cis-olefin moiety of systems was examined. [5] C (10)- Halogenated prostaglandins were synthesized in 1995 by Paul Collins W. and William Perkins E. which possess good cytoprotective and antisecretory effects, whilst displaying fewer side-effects characteristic of prostaglandins. Halogenated PGE derivatives, which display enhanced stability. The cytoprotective activity was determined against ethanol-induced ulcerations in rats whilst inhibition of gastric acid secretion was demonstrated in a gastric pouch model in beagles, over a 4-hour period. Most of the compounds did not induce diarrhea in rats at 3.2mg/kg *(ig).*

The preferred example had a minimum effectual dose of 1 μg/kg *(po)* in rats and an ED_{50} of 0.03 μg/kg *(ig)* in dogs. The disclosure is illustrated by ten compounds, which are prepared via conventional Wittley and organocuprate reactions. A variety of methods are employed for producing the desired degree of fluorination. Methyl 7-[2β-[6-(1-cyclopenten-1-yl)-4R-(fluoromethyl)-4-hydroxy-1E, 5E-hexadienyl]-3α-5-oxo-1R, 1α-cyclopentyl] -4Z-heptenoate is the only specifically claimed compound.



X= Cl, Br, I

R= H= 5,6- dihydroxy prostanoids

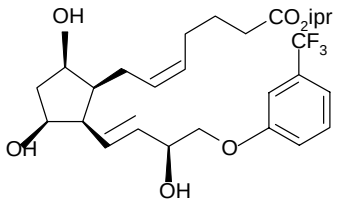
R= Ac= Acetylated compounds

The synthesis of halogenated prostaglandins at position C (10), starting from prostaglandin A2, has been accomplished, as well as an efficient regioselective hydroxylation of the upper chain of the prostanoid structure. Evaluation of the inhibitory effects on the proliferation of the K-562 cell line in vitro is presented. When the prostaglandin was modified in the upper chain, the antimitotic activity for bromo derivatives 4b, c and iodo derivative 5b had shown substantial improvements in their activities according to their ID50 values (28, 25, and 22 micrograms/mL, respectively). Attention is called to the significance of chloro derivative 3a in terms of its high potency, determined by its ID50 value (0.06 micrograms/mL).

Jose Dominques N. and Antonieta Teddez in 1996 showed that the prostaglandin decreases the risk of maternal infection (chorioammionitis) and does not appears to increase rate of caesarean section. In 1998, it was studied that prostaglandin analog such as Latanoprost (Xalantan) and Isopropyl unprostane (Regula) was highly effective in treating glaucoma.

Recently, Travoprost was synthesized which is a potent antiglaucoma agent A total of 22 synthetic steps are required to provide the single enantiomer prostanoid, with the longest linear sequence being 16 steps from 3-hydroxybenzotrifluoride. The route is based upon a cuprate-mediated coupling of the single enantiomer vinyl iodide 13 and the tricyclic ketone 5, of high stereochemical purity, to yield the single isomer bicyclic ketone 15. A Baeyer−Villiger oxidation provides the lactone 16 as a crystalline solid, thus limiting the

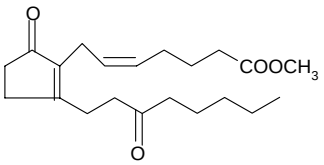
need for chromatographic purification. DIBAL-H reduction, Wittig reaction, esterification, and silyl group deprotection complete the synthesis of travoprost.



Travoprost

Lindsey K. and Jager A K. in 1999 studied that oral administration of garlic oil (diallyl disulphide) or corn oil decreases the arachidonic acid.

In 2000 Anjanyulu A. S, R. Krishnamurthy M V R. Found a rare prostaglandin from soft coral sacrophyton crassocaule from Indian Ocean.



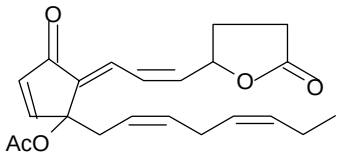
Methyl (5Z) -9,15-Dioxoprosta 5,8 (12) diene 1-oate

A detailed examination of Indian ocean soft corals sacrophyton crassocule resulted in isolation of 17 compounds of which two are novel 17B, 20B – Epoxy steroids and 1 is a new dihydroxygorgost 5-en the other compound includes 4 hippurin steroids and some new derivatives such as methyl arachidonate, butyl alcohol, a mixture of monohydroxy sterols, 3B –hydroxy pregn 5-en 20-one, 2prostaglandin (PGB2 acids and its methyl ester) and 9-oxo 9,11,seco gorgost 5-en 3B 11-diol.

The rare prostaglandin methyl (5Z)-9,15-dioxoprosta-5, 8(12)-dien-1-oate (1), hitherto unreported as a natural product, has been isolated from the Indian Ocean soft coral Sarcophyton crassocaule. Its structure was elucidated using detailed spectral ((1) H and (13)C NMR, DEPT, H-H COSY, C-H COSY, HRMS, and HMBC) analysis.

Shoko Fujiwara and Mikio T. Suzuki in 1998 three marine prostanoids were isolated from the extract of the Okinawan soft coral Clavularia viridis. The structures of these compounds were assigned based on the results of spectroscopic analysis. Compound 1 was shown to be preclavulone-A methyl ester, and this is the first isolation of the ester of preclavulone-A as a

natural product. Preclavulone-A is proposed to be the key intermediate in the biosynthesis of marine prostanoids exemplified by clavulones in C. viridis. The new prostanoid 3 was suggested to be a biosynthetic intermediate from preclavulone-A to clavulones, and a possible biogenetic pathway via 3 is proposed.



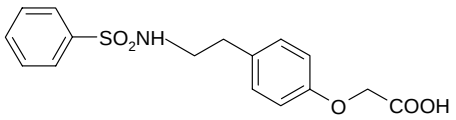
Clavulactone

Peterklimko and Terry Davis in 2000 isolated three new prostaglandins from carribbean soft corral plexaura nina . [18]

Recently Anton Sadjak and Sabine Supanz found linotroban which is a potent and selective TXA2 receptor antagonist having anti thrombotic effect. Thromboxane A_2 (TXA_2), an unstable arachidonic acid metabolite, elicits diverse physiological/pathophysiological actions, including platelet aggregation and smooth muscle contraction. TXA_2 has been shown to be involved in allergies, modulation of acquired immunity, atherogenesis, neovascularization, and metastasis of cancer cells. The TXA_2 receptor (TP) communicates mainly with G_q and G_{13}, resulting in phospholipase C activation and RhoGEF activation, respectively. In addition, TP couples with G_{11}, G_{12}, G_{13}, G_{14}, G_{15}, G_{16}, G_i, G_s and G_h. TP is widely distributed in the body, and is expressed at high levels in thymus and spleen. The second extracellular loop of TP is an important ligand-binding site, and Asp^{193} is a key amino acid. There are two alternatively spliced isoforms of TP, TPα and TPβ, which differ only in their C-terminals. [6]

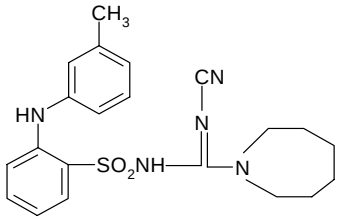
The stable PGI2-analogue iloprost and the TXA2-receptor antagonist sulotroban (BM 13177) were investigated for possible synergistic effects on platelet aggregation in human platelet rich plasma in vitro. Iloprost and sulotroban synergistically inhibited U 46619, collagen, and the second wave of ADP-induced platelet aggregation. Iloprost and sulotroban at concentrations showing little or no inhibition alone resulted, in combination, in marked or complete inhibition of U 46619 or collagen-induced aggregation. Combination of iloprost 10(-10) M, which had no effect on the concentration-response curve (CRC) to U 46619, with sulotroban 5 x 10(-6) M, which shifted the CRC to U 46619 by a factor of 3 to the right, resulted in a rightward shift of the U 46619 CRC by a factor of 4.5. To attain a 4.5-fold shift with either compound alone, a concentration of 5 x 10(-10) M iloprost or 10(-5) M sulotroban

was required. A similar mutual enhancement of inhibitory effects was seen for combinations of the PGI2-analogue cicaprost (ZK 96.480) with sulotroban or the TXA2-receptor antagonist SQ 29548 with iloprost. When the TXA2-dependent part of collagen-induced aggregation was fully inhibited by sulotroban, the concentrations of iloprost necessary for 90% inhibition were reduced by a factor of 2.5 - 3. In the presence of acetylsalicylic acid, the synergistic action of sulotroban and iloprost was reduced and merely additive effects against U 46619-induced platelet aggregation were found, suggesting that the release of endogenous TXA2 plays an important role for the synergistic effect of the two compounds. The combination of a PGI2-analogue and a TXA2-antagonist may lead to a safer and more effective control of platelet activation than with eithercompound alone.

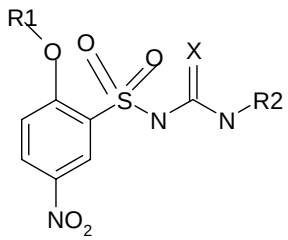


Sulotroban

Then in 2001 Dr. Valentin J.synthesised N-isopropyl N (2-(3-Methyl phenyl amine) 5-nitrobenzene sulphonyl) urea from TXA2 Antagonist, which prevent prevent platelet aggregation.



The synthesis and SAR Study of a Series of *N*-Alkyl-*N*'-[2-(aryloxy)-5 nitrobenzenesulfonyl]ureas and -cyanoguanidine as Selective Antagonists of the TPα and TPβ Isoforms of the Human Thromboxane A_2 Receptor was carried out. [13]



R1 = methylphenyl , halophenyl ,alkoxyphenyl

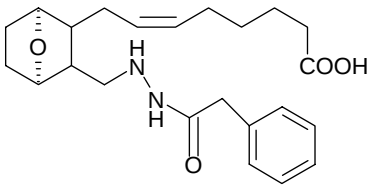
R2 = t-butyl, n-phenyl, i-propyl, n-butyl

X = O, N-CN

The prostanoid thromboxane (TX) A2 exerts its proaggregant and constrictive actions upon binding to the specific TXA_2 receptor (TP), a member of the G-protein coupled receptor superfamily. In humans, TXA_2 signals through two distinct TP isoforms, TPα and TPβ. Herein, we describe the design, synthesis, and SAR study of a series of original *N*-alkyl-*N*'-[2-(aryloxy)-5-nitrobenzenesulfonyl] ureas and -cyanoguanidine. The SAR study was based on the results of a functional assay, TP-mediated intracellular calcium ($[Ca^{2+}]_i$) mobilization performed on the two separate isoforms. Optimal nature and position of several structural moieties was defined for both activity and selectivity toward TPα and TPβ isoforms. Three compounds (9h, 9af, and 9ag), showing increased selectivity for TPβ relative to TPα (23.2:1, 18.1:1, 19.9:1, respectively), were selected for further experiments, and their activity was confirmed in a platelet aggregation assay. This study represents the first extended SAR study dealing with the identification of isoform selective antagonists for the human TXA_2 receptor.

M. L. Ogletree, D. N. Harris, R. Greenberg, M. F. Haslanger and M. Nakane is working on SQ 29,548, [1S-[1 alpha, 2 beta (5Z), 3 beta,4 alpha]-7-[3-[[2- [(phenylamino) carbonyl]hydrazino]methyl]-7-oxabicyclo[2.2.1] hept-2- yl]-5-heptenoic acid, and the racemic modification, +/- SQ 29,548, were identified as active inhibitors of human platelet aggregation induced by arachidonic acid, collagen, epinephrine (2 degrees phase) and the thromboxane A2 mimics, 9,11-azo prostaglandin (PG) H2 and 11,9- epoxymethano PGH2. SQ 29,548 did not inhibit aggregation induced by ADP, and it did not prevent PGD2 from inhibiting ADP-induced platelet aggregation. Inhibition of platelet function by +/- SQ 29,548 was not associated with inhibition of cyclooxygenase or thromboxane synthetase or with changes in platelet cyclic AMP. In guinea-pig trachea and rat aorta, +/- SQ 29,548 competitively antagonized the activity of 9,11-azo PGH2 with pA2 values of 7.8 and 8.4, respectively. The chiral compound, SQ 29,548 competitively antagonized contractions of guinea-pig tracheal spirals caused by 11,9-epoxymethano PGH2 with a pA2 value of 9.1. The +/- SQ 29,548 competitively antagonized tracheal responses to 11,9- epoxymethano PGH2 and PGD2 with pA2 values of 8.2 and 8.3, respectively, indicating that PGD2 and the thromboxane A2 mimic probably act at the same receptor in guinea-pig tracheal smooth muscle. Contractions of guinea-pig tracheal spirals induced by PGE2 were not antagonized,

and those caused by PGF2 alpha were only partially antagonized by +/- SQ 29,548. The +/- SQ 29,548 also significantly inhibited the aorta contracting activity of 11,9-epoxymethano PGH2 (pA2 = 9.1) and thromboxane A2 released from perfused guinea-pig lungs upon arachidonic acid challenge.

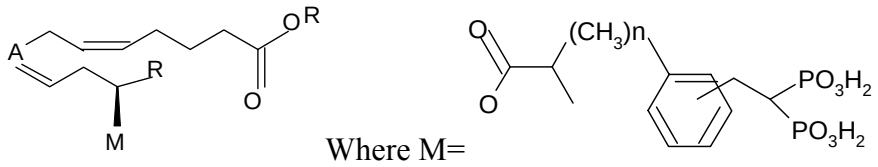


SQ-29548

In the present study it was investigated that effect of a 100 mg single oral dose of a newly developed thromboxane A2 receptor antagonist on collagen-induced thrombogenesis in flowing human non-anticoagulated blood. Blood was drawn directly from an antecubital vein over immobilised collagen type III fibrils on a cover slip placed in a parallel-plate perfusion chamber. Shear rates at the collagen surface were characteristic for medium sized (650 s-1) and moderately stenosed (2,600 s-1) arteries. Blood-collagen interactions were morphologically quantified as platelet-collagen adhesion, fibrin deposition and thrombus volume. Activation peptides of coagulation, fibrinopeptide A (FPA), and of platelets, beta-thromboglobulin (beta-TG), were measured immediately distal to the perfusion chamber. HN-11500 ingestion reduced significantly the thrombus volume by 32% at 2,600 s-1, but not at 650 s-1. However, transmission electron microscopy revealed loosely packed and less degranulated platelets at 650 s-1. The beta-TG plasma levels were also reduced at both shear rates by the HN-11500 ingestion. The platelet-collagen adhesion was significantly enhanced at both shear rates. This was apparently a consequence of higher platelet concentrations at the collagen surface, because fewer platelets were consumed by the thrombi after the drug ingestion. In contrast, the coagulation, as measured by fibrin deposition and FPA plasma levels, was not significantly affected by HN-11500. Thus, it appears that the thromboxane A2 receptor antagonist HN-11500 reduces the thrombotic response by primarily impairing the platelet function at arterial blood flow conditions, and particularly at high wall shear rates.

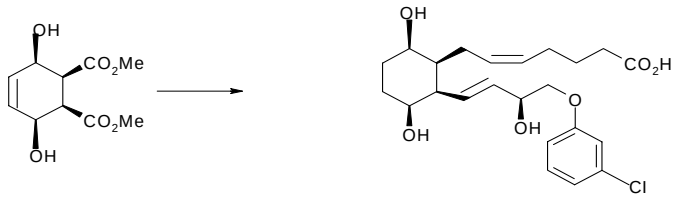
In 2001 it was discovered that the prostaglandin therapy was used for pyometritis . Pyometritis (greek ;pyo =pus and metritis =inflammation of uterus has long been a disease feared by the purebred dog breeder . The disease usually affects middle to older bitches. A combination of hormonal changes along with a contamination of pathogenic bacteria with in

the uterus allows the infection to begin. The bacteria and their by products fills the uterine cavity .The signs of bitch with pyometritis are fever (frequently 104 -106 degree fahrenheit) ,weakness and foul vaginal discharge.the toxin produced by bacteria are absorbed by bloodstream, hence affecting multiorgans.Various prostaglandin conjgates were introduced by Michael balazy and Takefumi Iesaki in 2001 which prevent bone diseases (oestoporosis in cytostatic disorders) .

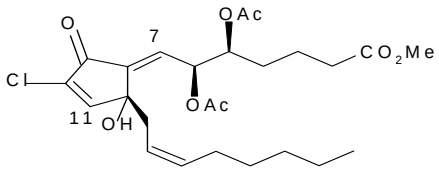


R=H or alkyl

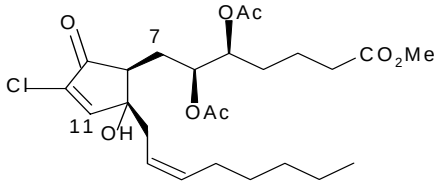
Potent prostaglandin FP agonist cloprostenol was synthesized.The racemic cyclohexane for cyclopentane ring substitution analogue of the potent prostaglandin FP agonist cloprostenol was synthesized from cyclohexenediol in 21 steps and 0.07% yield .In a prostaglandin FPreceptor-linked send messenger assay , racemic analogue exhibited an EC_{50} value of 319 nm (72% response relative to cloprostenol), the corresponding value for PGF_{2a} and cloprostenol were 23 nm (91% relative response) and 1nm (defined as 100% response) respectively . Key features of the synthesis were the selective manipulation of four hydroxyl group to direct independent elaboration of alpha and omega chains and a new method for synthesis of aryloxy terminated omega chain involved Horner-Emmons elongation of an aldehyde to a methyl enone , regioselective bromination adjacent to the carbonyl and phenoxide displacement of bromine. [12]



Punaglandins, Chlorinated Prostaglandins, Function as Potent Michael Receptors To Inhibit Ubiquitin Isopeptidase Activity.



Pundaglandin 4



Pundaglandin 6

Cyclopentenone prostaglandins exhibit unique antineoplastic activity and are potent growth inhibitors in a variety of cultured cells. Recently the dienone prostaglandin, Δ^{12}-PGJ_2, was shown to preferentially inhibit ubiquitin isopeptidase activity of the proteasome pathway. It is theorized that isopeptidase inhibition and general cytotoxicity of prostaglandins depend on olefin−ketone conjugation, electrophilic accessibility, and the nucleophilic reactivity of the endocyclic β-carbon. Δ^{12}-PGJ_2, which contains a cross-conjugated α,β-unsaturated ketone, was a potent inhibitor of isopeptidase activity, whereas PGA_1 and PGA_2 with simple α,β-unsaturated pentenones were significantly less potent and PGB_1 with a sterically hindered α,β-unsaturated ketone was inactive. To further investigate the proposed mechanism, punaglandins, which are highly functional cyclopentadienone and cyclopentenone prostaglandins chlorinated at the endocyclic α-carbon position, were isolated from the soft coral *Telesto riisei*. They were then assayed for inhibition of ubiquitin isopeptidase activity and antineoplastic effects. The punaglandins were shown to inhibit isopeptidase activity and exhibit antiproliferative effects more potently than A and J series prostaglandins. Also, the cross-conjugated dienone punaglandin was more potent than the simple enone punaglandin. The ubiquitin−proteasome pathway is a vital component of cellular metabolism and may be a suitable target for antineoplastic agents. These newly characterized proteasome inhibitors may represent a new chemical class of cancer therapeutics.

Levels of COX-2 isoenzyme and certain prostaglandins like PGE2, PGF2̣ and PGE1 are found to be higher in certain cancers like colorectal carcinoma, squamous cell carcinoma of head and neck and certain types of breast cancer. They have been shown to aid

carcinogenesis by altering cell proliferation, tumor angiogenesis, apoptosis, immunity and carcinogen metabolism. Decreasing the high levels of COX-2 and above-mentioned prostaglandins has shown to decrease carcinogenesis. Cyclopentanone prostaglandins like PGJ2 and PGA1 have been shown to have anti-tumor effects. These act directly by suppressing the oncogenes or indirectly by preventing efflux of anti-neoplastic agents from resistant cancer cells. COX-2 inhibitors, PGA1 and PGJ2 may be of vital importance in future cancer therapy.

1. Effects of Prostaglandin D_2, 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2, and Selective DP_1 and DP_2 Receptor Agonists on Pulmonary Infiltration of Eosinophils in Brown Norway Rats:

Prostaglandin (PG) D_2 is an arachidonic acid metabolite that is released by allergen-stimulated mast cells. It is a potent in vitro chemoattractant for human eosinophils, acting through the DP_2 receptor/chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). Furthermore, there is in vivo evidence that PGD_2 contributes to allergen-induced pulmonary eosinophilia via its classic DP_1 receptor. The PGD_2-derived product 15-deoxy-$\Delta^{12,14}$-PGJ_2 is widely used as a peroxisome proliferator-activated receptor γ agonist and has been shown to have anti-inflammatory properties. However, this substance can also activate eosinophils in vitro through the DP_2 receptor. The objectives of the present study were to determine whether PGD_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 can induce pulmonary eosinophilia, and, if so, to examine the abilities of selective DP_1 and DP_2 receptor agonists to induce this response. Brown Norway rats were treated by intratracheal instillation of PGs. Vehicle and 5-oxo-6,8,11,14-eicosatetraenoic acid were used as negative and positive controls, respectively. Lung eosinophils were identified by immunostaining of lung sections with an antibody to major basic protein. Both PGD_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 induced robust eosinophilic responses that were apparent by 12 h and persisted for at least 48 h. Two selective DP_2 receptor agonists, 15R-methyl-PGD_2 and 13–14-dihydro-15-keto-PGD_2, induced similar responses, the former being more potent than PGD_2, whereas the latter was less potent. The selective DP_1 receptor agonist BW245C [(4*S*)-(3-[(3*R*,*S*)-3-cyclohexyl-3-hydroxypropyl]-2,5-dioxo)-4-imidazolidineheptanoic acid] was completely inactive. We conclude that PGD_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 induce eosinophil infiltration into the lungs through the DP_2 receptor. The potent in vitro DP_2 receptor agonist 15R-methyl-PGD_2 is also very active in vivo and should be a useful tool in examining the role of this receptor.[17]

2. Vicinal nitrohydroxyeicosatrienoic acids: vasodilator lipids formed by reaction of nitrogen dioxide with arachidonic acid:

Nitric oxide (NO)-derived species could potentially react with arachidonic acid to generate novel vasoactive metabolites. We studied the reaction of arachidonic acid with nitrogen dioxide (NO2), a free radical that originates from NO oxidation. The reaction mixture contained lipid products that relaxed endothelium-removed bovine coronary arteries. Relaxation to the lipid mixture was inhibited approximately 20% by indomethacin and approximately 70% by a soluble guanylate cyclase (sGC) inhibitor (ODQ). Thus, novel lipid products, which activate sGC presumably through a mechanism involving NO, appeared to have contributed to the observed vasorelaxation. Lipids that eluted at 9 to 12 min during high-performance liquid chromatography fractionation accounted for about one-half of the vasodilator activity in the reaction mixture, which was inhibited by ODQ. Lipid products in fractions 9 to 12 were identified by electrospray tandem mass spectrometry to be eight isomers having molecular weight of 367 and a fragmentation pattern indicative of arachidonic acid derivatives containing nitro and hydroxy groups and consistent with the structures of vicinal nitrohydroxyeicosatrienoic acids. These lipids spontaneously released NO (183 +/- 12 nmol NO/15 min/micromol) as detected by head space/chemiluminescence analysis. Mild alkaline hydrolysis of total lipids extracted from bovine cardiac muscle followed by isotopic dilution gas chromatography/mass spectrometry analysis detected basal levels of nitrohydroxyeicosatrienoic acids (6.8 +/- 2.6 ng/g tissue; n = 4). Thus, the oxidation product of NO, NO2, reacts with arachidonic acid to generate biologically active vicinal nitrohydroxyeicosatrienoic acids, which may be important endogenous mediators of vascular relaxation and sGC activation.[19]

3. Use of prostaglandin therapy for pyometritis:

Pyometritis (greek ;pyo =pus and metritis =inflammation of uterus has long been a disease feared by the purebred dog breeder . The disease usually affects middle to older bitches. A combination of hormonal changes along with a contamination of pathogenic bacteria with in the uterus allows the infection to begin. The bacteria and their by products fills the uterine cavity .The signs of bitch with pyometritis are fever (frequently 104 -106 degree fahrenheit) ,weakness and foul vaginal discharge . the toxin produced by bacteria are absorbed by bloodstream, hence affecting multiorgans.

The treatment for pyometritis have been found strictly surgical. Currently medical management of pyometritis ,involves the use of prostaglandins. This treatment is hormonal rather than surgical. By giving daily injection of prostaglandin over a 2 to 10 days period , the uterus is stimulated to contrat and expel the fetid discharge.Prostaglandin are used in conjugation with IV fluid and antibiotics.

4. Prostaglandin E_2 Inhibits Fibroblast Migration by E-Prostanoid 2 Receptor–Mediated Increase in PTEN Activity :

An increased migratory phenotype exists in lung fibroblasts derived from patients with fibroproliferative lung disease. Prostaglandin E_2 (PGE_2) suppresses fibroblast migration, but the receptor(s) and mechanism(s) mediating this action are unknown. Our data confirm that treatment of human lung fibroblasts with PGE_2 inhibits migration. Similar effects of butaprost, an E-prostanoid (EP) 2 receptor–specific ligand, implicate the EP2 receptor in migration-inhibitory signaling. Further, migration in fibroblasts deficient for the EP2 receptor cannot be inhibited by PGE_2 or butaprost, confirming the central role of EP2 in mediating these effects. [19]

5. Prostanoids and isoprostanoids in atherogenesis:

Prostanoids and the enzymes responsible for their formation are both increased in atherogenesis, suggesting that these mediators participate in the pathogenesis of the disease and that drugs that inhibit their activity should modulate this disease. Although there is some controversy about the role of COX2 in atherogensis, consistent experimental data support a functional role for COX1 dependent prostanoids and TP receptor activation in the initiation and progression of this chronic vascular disease. Thus, TP receptor antagonism is at least as effective as selective inhibition of COX1 in retarding atherogenesis. Interestingly, this receptor can still be activated when TxA2 biosynthesis is suppressed by some isoprostanoids which are formed independently from COX, i.e. F2-iPs. Moreover, since F2-iPs levels increase during this disease and represent an independent risk marker for coronary artery disease in general they are also considered active in the development of atherosclerosis. Thus, recent evidence indicates that these lipid oxidation products, which also activate the TP receptor, mediate the vascular effects of inflammation and oxidative stress in experimental models of atherogenesis . [17]

6. COX-2 and prostanoid expression in micturition pathways after cyclophosphamide-induced cystitis in the rat :

The purpose of this study was to determine the role of cyclooxygenase-2 (COX-2) and its metabolites in lower urinary tract function after induction of acute (4 h), intermediate (48 h), or chronic (10 day) cyclophosphamide (CYP)-induced cystitis. Bladders were harvested from euthanized female rats for analyses. Conscious cystometry was used to assess the effects of a COX-2-specific inhibitor, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl2(5*H*)-furanone (DFU, 5 mg/kg sc), a disubstituted furanone, in CYP-induced cystitis. COX-2 mRNA was increased in inflamed bladders after acute (12-fold) and

chronic (9-fold) treatment. COX-2 protein expression in inflamed bladders paralleled COX-2 mRNA expression. Prostaglandin D_2-methoxime expression in the bladder was significantly ($P \leq 0.01$) increased in acute (3-fold) and chronic (5.5-fold) cystitis. Prostaglandin E_2 was significantly ($P \leq 0.01$) increased (2-fold) in the bladder with intermediate (1.7-fold) and chronic (2.6-fold) cystitis. COX-2-immunoreactive cell profiles were distributed throughout the inflamed bladder and coexpressed histamine immunoreactivity. Conscious cystometry in rats treated with CYP + DFU showed increased micturition intervals 4 and 48 h after CYP treatment and decreased intravesical pressures during filling and micturition compared with rats treated with CYP + vehicle. These studies suggest an involvement of urinary bladder COX-2 and its metabolites in altered micturition reflexes with CYP-induced cystitis. [(5)]

7. Prostaglandins and Prostanoid Receptors in Human Pregnancy and Parturition:

Prostaglandin's (PGs) are involved in several major signaling pathways. Their effects are terminated when they are transported across cell membranes and oxidized intracellularly. The transport step of PG metabolism is carried out by the prostaglandin transporter (PGT). Inhibition of PGT would therefore be expected to change local or circulating concentrations of prostaglandins, and thus their biological effects. To develop PGT-specific inhibitors with high affinity, we designed a library of triazine compounds and screened 1842 small molecules by using Madin-Darby canine kidney cells stably expressing rat PGT. We found several effective PGT inhibitors. Among them, the most potent inhibitor had a K_i of 3.7 ± 0.2 μM. These inhibitors allowed us to isolate the efflux process of PGE_2 and to demonstrate that PGT does not transport PGE_2 outwardly under physiological conditions.[(17)]

8. Protective effect of a synthetic analog of prostaglandin E_1 on the small intestinal damage induced by the administration of methotrexate to rats:

Antitumor drugs like methotrexate cause damage to the small intestine, resulting in malabsorption. The present study evaluated this damage by determining the small intestinal absorption of 3-*O*-methyl-d-glucose (3-OMG) and a poorly absorbable marker, fluorescein isothiocyanate-labeled dextran (FD-4; average molecular mass, 4.4 KDa) using the *in vitro* everted intestine and *in situ* intestinal loop techniques. Methotrexate (15 mg/kg body weight) was orally administered to rats once daily for 5 days. A synthetic analog of prostaglandin E_1, OP-1206 (17*S*,20-dimethyl-trans-Δ^2-prostaglandin E_1; 0.5 μg/kg body weight) was orally administered to rats twice a day for 5 days. The absorption clearance of FD-4 via the small intestine of the methotrexate-treated rats increased marked, but that of the methotrexate- and OP-1206-treated rats was significantly lower than that of the rats treated only with methotrexate. The absorption clearance of [^{3}H]-3-OMG via the small intestine of the

methotrexate-treated rats fell markedly, but that of the methotrexate- and OP-1206-treated rats was significantly greater than that of the rats treated only with methotrexate. The changes in AUC values of FD-4 and [^{3}H]-3-OMG obtained from *in situ* intestinal loop experiment showed the same trends as those seen in the absorption clearance from the *in vitro* everted intestine experiment. These results show that OP-1206 alleviates the methotrexate-induced damage to the small intestine of rats recently Ronni Wolf M D and Hagit Matz M D studied that Latanoprost, a prostaglandin analog, has been reported to stimulate eyelash growth in patients using it in eye preparations for glaucoma and body and scalp hair growth when used topically in various animal models. latanoprost (Xalatan®), as an intraocular pressure (IOP)-lowering drug for use in patients with glaucoma and ocular hypertension, the stimulating effect of this drug on eyebrow and eyelash hair growth and pigmentation was reported in an ophthalmology journal.(7)

Conclusion

There is a wide scope for the study on the recent developments on prostaglandins and prostanoids for their versatile activities. Medicinal uses from vasodialation to pulmonary disesase in all these, prostaglandins and their derivatives have been employed. The SAR, chemistry mechanism of action and pharmacology of these have helped to know better pharmacokinetic parameters. Prostaglandins and their derivatives will be the strong candidates for drug or regimen for the effective treatment of all major illness and diseases.

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