

# Prostanoid Receptors

## Key References

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## Overview

Prostanoids comprise prostaglandins (PGs) and thromboxanes (Tx). Prostanoid receptors can be classified into five types on the basis of sensitivity to the five naturally-occurring ligands; PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2</sub>, PGI<sub>2</sub> and TxA<sub>2</sub>. These receptors are termed P receptors, with a preceding letter indicating the natural prostanoid to which each receptor is most sensitive - i.e. DP, EP, FP, IP and TP, respectively. Furthermore, EP receptors have been subdivided into four groups, EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub> and EP<sub>4</sub>, originally on the basis of their relative sensitivities to a range of selective agonists and antagonists, but subsequently, all have been cloned. It is important to appreciate that the recombinant EP<sub>4</sub> receptor was originally identified as EP<sub>2</sub>, and all publications referring to recombinant EP<sub>2</sub> receptors prior to 1995 actually refer to EP<sub>4</sub> receptors. Recently, evidence for a second subtype of DP receptor has been published, found in T-lymphocytes, and originally termed CRTH<sub>2</sub>. Interestingly, this receptor is unrelated to the other prostanoid receptors, being more similar to the FPR and BLT chemotactic receptors. Indomethacin acts as an agonist at this receptor, and the TP antagonist, ramatroban, has antagonist activity. This 'new' DP-receptors may now tentatively be termed DP<sub>2</sub>, with the existing DP receptor re-designated DP<sub>1</sub>, although this is yet to be made official. Although there is now a substantial body of evidence for subdivision within IP and TP receptors, this has yet to be formally accepted and incorporated within the classification. Isoprostanes, prostanoids synthesized through non-enzymatic conversion of arachidonic acid have been suggested to act at their own receptors, distinct from those for other prostanoids, but the evidence is ambiguous, and the case not proven. In addition, it has been suggested that certain prostaglandins ethanolamides

(prostamides) also act at receptors distinct from the 'classical' prostanoid receptors, but definitive evidence is still awaited.

The original basis for the classification was functional, and there are many agonists selective for the various prostanoid receptors. However, few agonists are truly selective for one type of receptor over all of the others, exceptions being BW245C at DP (DP<sub>1</sub>) receptors, fluprostenol at FP receptors, and cicaprost at IP receptors. There are potent antagonists for DP, EP<sub>1</sub>, EP<sub>4</sub> and TP receptors; EP<sub>3</sub> antagonists are just emerging, but there are still no well characterized potent selective antagonists at EP<sub>2</sub>, FP or IP receptors.

Although it is now known that there are splice variants of FP, TP and EP<sub>1</sub> receptors, they are particularly well established for EP<sub>3</sub> receptors, where at least ten splice variants have been reported to date across a variety of species (four of which have been found in man). In all cases, the splicing occurs in the intracellular C-terminal region, and while there is no evidence that it affects ligand affinities, it does appear to influence the receptors' coupling to particular signal transduction processes. The splice variant of the EP<sub>1</sub> receptor is distinct, in that the splice region incorporates the sixth and seventh intracellular domains, and the resulting receptor does not appear to couple directly to any recognized signal transduction process.

Prostanoid-induced effects are mainly transduced through modulation of the activity of either adenylyl cyclase or inositol phospholipid hydrolysis and calcium mobilization. DP<sub>1</sub>, EP<sub>2</sub>, EP<sub>4</sub> and IP receptors couple positively to adenylyl cyclase through binding to a G<sub>q/11</sub> protein. EP<sub>3</sub> receptors can

either couple negatively to adenylyl cyclase through binding to a G<sub>i</sub> protein, or like EP<sub>1</sub>, FP and TP receptors, via G<sub>q/11</sub> binding to inositol phospholipid hydrolysis and calcium mobilization. IP receptors appear to be most unusual among the prostanoid receptors, and indeed among G protein-coupled receptors in general, in that the receptor protein requires isoprenylation in order to optimize agonist-induced activation.

# Prostanoid Receptors

CURRENTLY ACCEPTED NAME	EP <sub>1</sub>	EP <sub>2</sub>	EP <sub>3</sub>	EP <sub>4</sub>
ALTERNATE NAME	—	—	—	—
STRUCTURAL INFORMATION	402 aa (human)	358 aa (human)	4 splice variants: 390, 388, 365, 374 aa (human)	488 aa (human)
SUBTYPE SELECTIVE AGONISTS	17-Ph- $\omega$ -PGE <sub>2</sub> , Iloprost <sup>a</sup>	Butaprost ( <b>B6309</b> ), AH-13205 ( <b>A9102</b> ), CP-533,536, ONO-AE1-259	SC-46275, GR63799, Sulprostone ( <b>S8692</b> ), <sup>d</sup> ONO-AE-248	ONO-AE1-734, ONO-AE1-329
SUBTYPE SELECTIVE ANTAGONISTS	SC-19220 ( <b>S3065</b> ), AH6809 ( <b>A1221</b> ), SC-51809	AH-6809 ( <b>A1221</b> ) <sup>c</sup>	L-798,106	AH23848 ( <b>A8227</b> ), <sup>e</sup> L-161,982, ONO-AE3-208, GW627368
RECEPTOR SELECTIVE AGONISTS	PGE <sub>2</sub> ( <b>P5640</b> )	PGE <sub>2</sub> ( <b>P5640</b> )	PGE <sub>2</sub> ( <b>P5640</b> ), Misoprostol ( <b>M6932</b> )	PGE <sub>2</sub> ( <b>P5640</b> )
RECEPTOR SELECTIVE ANTAGONISTS	Not known	Not known	Not known	Not known
SIGNAL TRANSDUCTION MECHANISMS	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>s</sub> (increase cAMP)	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG) G <sub>i</sub> (cAMP modulation)	G <sub>s</sub> (increase cAMP)
RADIOLIGANDS OF CHOICE	[ <sup>3</sup> H]-PGE <sub>2</sub>	[ <sup>3</sup> H]-PGE <sub>2</sub>	[ <sup>3</sup> H]-PGE <sub>2</sub> [ <sup>3</sup> H]-Sulprostone	[ <sup>3</sup> H]-PGE <sub>2</sub>
TISSUE EXPRESSION	Kidney, myometrium, GI smooth muscle	Myometrium, airway smooth muscle, GI smooth muscle	Myometrium, kidney, GI mucosa	Ductus arteriosus, kidney, lymphocytes, mononuclear cells
PHYSIOLOGICAL FUNCTION	Modulation of pain, diuresis & natriuresis	Control of uterine contractility	Control of uterine contractility natriuresis, GI cytoprotection	Control of ductus, bone metabolism
DISEASE RELEVANCE	Inflammatory pain, diabetic nephropathy	Pre-term labor	Pre-term labor, gastric ulcer	Patent ductus, colonic inflammation

## Abbreviations

**AH-6809:** 6-Isopropoxy-9-oxoxanthene-2-carboxylic acid  
**AH-13205:** trans-2-(4-(1-Hydroxyhexyl)phenyl)-5-oxocyclopentaneheptanoic acid  
**AH-23848:** [1a(Z),2b,5a]-(±)-7-[5-[[[(1,1-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid  
**CP-533,536:** (3-[4-Tert-butyl-benzyl(pyridine-3-sulfonyl)-amino-methyl]-phenoxy)-acetic acid  
**GR 63799:** 7-(3-Hydroxy-2-(2-hydroxy-3-phenoxypropoxy)-5-oxocyclopentyl)-4-(benzoylamino)phenyl ester,(1R-(1a(Z),2b(R\*),3a)-4-heptenoic acid  
**GW 627368:** (N-[2-[4-(4,9-Diethoxy-1-oxo-1,3-dihydro-2H-benzo[*f*]isoindol-2-yl)phenyl]-acetyl]benzenesulphonamide)  
**L-161,982:** [4'-[3-Butyl-5-oxo-1-(2-trifluoromethyl-phenyl)-1,5-dihydro-[1,2,4]triazol-4-ylmethyl]-biphenyl-2-sulfonic acid (3-methyl-thiophene-2-carbonyl)-amide]  
**L-798,106:** 5-Bromo-2-methoxy-N-[3-2-(naphthalen-2-yl-methyl)phenyl]-acryloyl]-benzenesulphonamide  
**ONO-AE1-259:** (16S-9-Deoxy-9 $\beta$ -chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro PGE-2)  
**ONO-AE1-329:** (16-(3-Methoxymethyl)phenyl-omega-tetranor-3,7-dithia PGE-1)  
**ONO-AE1-734:** Methyl-7-[(1R,2R,3R)-3-hydroxy-2-[(E)-(3S)-3-hydroxy-4-(m-methoxymethylphenyl)-1-butenyl]-5-oxocyclopentyl]-5-thiaheptanoate  
**ONO-AE3-208:** 4-[4-Cyano-2-[2-(*f*-fluoronaphthalen-1-yl)propionylamino] phenyl]butyric acid  
**SC 19220:** 1-Acetyl-2-[8-chloro-10,11-dihydrodibenz(b,f)(1,4)oxazepine-10-carbonyl]hydrazine  
**SC 46275:** Methyl-7-(2b-(6-(1-cyclopentyl-yl)-4R-hydroxy-4-methyl-1E,5E-hexadienyl)-3a-hydroxy-5-oxo-1R,1a-cyclopentyl)-4Z-heptenoate  
**SC 51809:** (8-Chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[1-oxo-3-(4-pyridinyl)propyl]hydrazide, monohydrochloride)

## FOOTNOTES

**a** Iloprost is a partial agonist at EP<sub>1</sub> receptors, but is a potent full agonist at IP receptors.  
 Sulprostone is more potent as an EP<sub>3</sub> agonist.  
**b** Misoprostol is also an EP<sub>3</sub> agonist.

**c** Human EP<sub>2</sub> receptors only; also antagonist at EP<sub>1</sub> and DP receptors.  
**d** Sulprostone also has moderate EP<sub>1</sub> agonistic activity.  
**e** AH23848 is also a potent TP receptor blocking drug.

# Prostanoid Receptors

CURRENTLY ACCEPTED NAME	DP <sup>a</sup>	FP	IP	TP
ALTERNATE NAME	—	—	—	—
STRUCTURAL INFORMATION	359 aa (human)	358 aa (human)	386 aa (human)	343 aa (human)
SUBTYPE SELECTIVE AGONISTS	Not known	Not known	Not known	AGN 192093
SUBTYPE SELECTIVE ANTAGONISTS	Not known	Not known	Not known	Not known
RECEPTOR SELECTIVE AGONISTS	PGD <sub>2</sub> ( <b>P5172</b> ), BW245C ( <b>B9305</b> ), ZK 110841, RS 93520, SQ 27986, L-644,698	PGF <sub>2a</sub> ( <b>P0424</b> ), Fluprostenol ( <b>F8549</b> ), Cloprostenol ( <b>C9530</b> ), Latanoprost ( <b>L1167</b> )	PGI <sub>2</sub> ( <b>P6188</b> ), Cicaprost, Iloprost, <sup>b</sup> BMY 45778, Beraprost, ONO-1301 ( <b>O2264</b> )	U-46619 ( <b>D8174</b> ), STA2, I-BOP, AGN 192093, SQ 26655
RECEPTOR SELECTIVE ANTAGONISTS	BWA868C ( <b>B9180</b> ), AH6809 ( <b>A1221</b> ), S-5751, ZK 138,357	Not known	Not known	GR32191 ( <b>G5044</b> ), SQ 29548, BM 13505 ( <b>D7441</b> ), EP092, L-655,240 ( <b>L9539</b> ), ICI 192605, ONO 3708, BMS 180291, Ramatroban, KW-3635
SIGNAL TRANSDUCTION MECHANISMS	G <sub>s</sub> (increase cAMP)	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>s</sub> (increase cAMP) G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)
RADIOLIGANDS OF CHOICE	[ <sup>3</sup> H]-PGD <sub>2</sub>	[ <sup>3</sup> H]-PGF <sub>2a</sub> [ <sup>3</sup> H]-17-Phe-ω-PGF <sub>2a</sub>	[ <sup>3</sup> H]-PGI <sub>2</sub> [ <sup>3</sup> H]-Iloprost	[ <sup>3</sup> H]-U-46619 [ <sup>3</sup> H]-SQ 29548 [ <sup>125</sup> I]-BOP
TISSUE EXPRESSION	Blood platelets, myometrium, ciliary muscle, basophils	Corpus luteum, myometrium, ciliary body	Blood platelets, vascular smooth muscle, sensory nerves	Blood platelets, vascular smooth muscle, airways smooth muscle
PHYSIOLOGICAL FUNCTION	Regulation of sleep	Luteolysis, labor	Control of platelet aggregation, vasodilatation, pain	Control of platelet aggregation, vasoconstriction, bronchoconstriction,
DISEASE RELEVANCE	Not known	Not known	Not known	Diabetic vascular occlusion

## Abbreviations

**AGN 192093:** (5Z,9a,11a,13E,15S)-Prosta-5,13-diene-1,9,11,15-tetrol-cyclic-9,11-carbonate

**AH-6809:** 6-Isopropoxy-9-oxoxanthene-2-carboxylic acid

**Beraprost:** (rac-(1R\*,2R\*,3aS\*,8bS\*)-2,3,3a,8b-Tetrahydro-2-hydroxy-1-[(E)-(3S\*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1H-cyclopenta[b]benzofuran-5-butylate)

**BM 13505 (Daltroban):** 4-(2-(4-Chlorobenzenesulfonylamino)ethyl)benzeneacetic acid

**BMS 180291 (Ifetroban):** 1S-(1a,2a,3a,4a)]-2-[[3-[4-[[++Pentylamino]carbonyl]-2-oxazolyl]-7-oxabicyclo[2.2.1]hept-2-yl]methyl]benzenepropanoic acid

**BMY 45778:** (3-(4,5-Diphenyl(2,4'-bioxazol)-5'-yl)phenoxy)acetic acid

**1-BOP:** [1S[1a,2a(Z),3b(1E,3S\*),4a]]-7-[3-[3-Hydroxy-4-(4-iodophenoxy)-1-butenyl]-7-oxabicyclo-[2.2.1]hept-2-yl]5-heptanoic acid

**BW A868C:** 3-Benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)hydantoin

**BW 245C:** 3-(3-Cyclohexyl-3-hydroxypropyl)-2,5-dioximidazolidine-4-heptanoic acid

**EP092:** (1a,2b(Z),3a,4a)-(±)-7-(3-(1-(((Phenylamino)thioxomethyl)hydrazono)ethyl)bicyclo(2.2.1)hept-2-yl)-5-heptenoic acid

**GR 32191:** (4Z)-7-[(1R,2R,3S,5S)-5-[(1,1'-Biphenyl)-4-ylmethoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid

**ICI 192605:** (4Z)-rel-6-[(2R,4R,5S)-2-(2-Chlorophenyl)-4-(2-hydroxyphenyl)-1,3-dioxan-5-yl]-4-hexenoic acid

**KW-3635:** Sodium (E)-11-[2-(5,6-dimethyl-1-benzimidazolyl)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate monohydrate

**L-644,698:** ±(4-(3-(3-Hydroxyoctyl)-4-oxo-2-thiozolidinyl)propyl) benzoic acid

**L-655,240:** 3-(1-(4-Chlorobenzyl)-5-fluoro-3-methylindol-2-yl)-2,2-dimethylpropanoic acid

**ONO3708:** (1S-(1-a,2-b(Z),3-a(S\*),5-a))-7-(3-((Cyclopentylhydroxycetyl)amino)-6,6-dimethylbicyclo(3.1.1)hept-2-yl)-5-heptenoic acid

**ONO-1301:** [7,8-dihydro-5-[(E)-[[a-(3-pyridyl)benzylidene]-amino]oxy]ethyl]-1-naphthyl]oxy]acetic acid

**Ramatroban:** (+)-(3R)-3-(4-fluorophenylsulfonamido)-1,2,3,4-tetrahydro-9-carbazolepropanoic acid

**RS 93520:** (4Z)-4-[(1R,2R,3S,6R)-2-[(3S)-3-Cyclohexyl-3-hydroxy-1-propynyl]-3-hydroxybicyclo[4.2.0]oct-7-ylidene]butanoic acid

**S-5751:** ((Z)-7-[(1R,2R,3S,5S)-2-(5-hydroxybenzo[b]thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid)

**SQ 26655:** 9-α,11α-epoxy-10a-homo-15S-hydroxy-prosta-5Z,13E-dienoic acid

**SQ 27986:** 7-(3-(3-Cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo(2.2.1)hept-2-yl)-5-heptenoic acid

**SQ 29548:** 7-(3-((2-((Phenylamino)carbonyl)hydrazino)methyl)-7-oxabicyclo(2.2.1)hept-2-yl)-5-heptenoic acid

**STA2:** (5Z)-7-[(1S,2R,3R,5S)-3-[(1E,3S)-3-Hydroxy-1-octenyl]-6-thiabicyclo[3.1.1]hept-2-yl]-5-heptenoic acid

**U-46619:** (5Z)-7-[(1R,4S,5S,6R)-6-[(1E,3S)-3-Hydroxy-1-octenyl]-2-oxabicyclo[2.2.1]hept-5-yl]-5-heptenoic acid

**ZK 110841:** 9-Deoxy-9-chloro-16,17,18,19,20-pentano-15-cyclohexyl-PGF<sub>2a</sub>

**ZK 138,357:** (5Z)-7-[(2RS,4S,5S)-2-(2-chlorophenyl)-5-[(1E)-(3RS)-3-hydroxy-3-cyclohexyl-1-propenyl]-1,3-dioxolan-4-yl]-5-heptanoic acid

## FOOTNOTES

<sup>a</sup> DP receptor may now be re-designated DP<sub>1</sub>, with CRTH2 re-designated as DP<sub>2</sub> (see text).

<sup>b</sup> Iloprost is also a potent but partial EP<sub>1</sub> agonist.