# Prostanoid

**Overview:** Prostanoid receptors (nomenclature agreed by the NC-IUPHAR Subcommittee on Prostanoid Receptors, see Coleman *et al*., 1994) are activated by the endogenous ligands prostaglandin (PG) $D_2$ (D), $PGE_2$ (E), $PGF_{2\alpha}$ (F), $PGH_2$ (H), prostacyclin [$PGI_2$ (I)] and thromboxane $A_2$ (T). Measurement of the potency of $PGI_2$ and $TXA_2$ is hampered by their instability in physiological salt solution; they are often replaced by cicaprost and U46619, respectively, in receptor characterization studies.

| Nomenclature | $DP_1$ | $DP_2$ | FP | IP | TP |
|---|---|---|---|---|---|
| Other names | – | CRTh2, GPR44 | – | – | – |
| Ensembl ID | ENSG00000168229 | ENSG00000183134 | ENSG00000122420 | ENSG00000160013 | ENSG00000006638 |
| Principal transduction | $G_s$ | $G_{i/o}$ | $G_{q/11}$ | $G_s$ | $G_{q/11}$ |
| Rank order of potency | D >> E > F > I,T | D >> F, E > I, T | F > D > E > I,T | I >> D,E,F > T | T = H >> D,E,F,I |
| Selective agonists | L644698, BW245C, ZK118182, RS93520, SQ27986 | 13,14-dihydro-15-oxo $PGD_2$, 15*R*-15-methyl $PGD_2$ (Hata *et al*., 2003; Monneret *et al*., 2003) | Fluprostenol, latanoprost-free acid, AL12180 (Sharif *et al*., 2006) | Cicaprost, AFP07, BMY45778 (Seiler *et al*., 1997) | U46619, $STA_2$, I-BOP, AGN192093 |
| Selective antagonists | BWA868C (9.3, Giles *et al*., 1989), S5751 (8.8, Arimura *et al*., 2001), laropiprant (10.1, Sturino *et al*., 2007) | Ramatroban (Sugimoto *et al*., 2003), CAY10471 (Mathiesen et al *et al*., 2006) | AS604872 (Cirillo *et al*., 2007) | RO1138452 (8.8, Bley *et al*., 2006) | BMS180291 (9.3–10.0), ONO3708 (8.9), GR32191 (8.3–9.4, Lumley *et al*., 1989), SQ29548 (8.1–9.1, Swayne *et al*., 1988) |
| Probes | [$^3$H]-$PGD_2$ (13–34 nM) | [$^3$H]-$PGD_2$ (6–11 nM) | [$^3$H]-$PGF_{2\alpha}$ (2–4 nM), [$^3$H]-(+)-fluprostenol (34 nM) | [$^3$H]-Iloprost (1–20 nM) | [$^3$H]-SQ29548 (5–40 nM), [$^{125}$I]-SAP (0.2–1.0 nM), [$^{125}$I]-I-BOP (0.3–5.0 nM) |

Ramatroban is also a TP receptor antagonist. Cicaprost exhibits moderate $EP_4$ receptor agonist potency (Abramovitz *et al*., 2000). Iloprost also binds to $EP_1$ receptors. The TP receptor exists in α and β isoforms due to alternative splicing of the cytoplasmic tail (Raychowdhury *et al*., 1994).

| Nomenclature | $EP_1$ | $EP_2$ | $EP_3$ | $EP_4$ |
|---|---|---|---|---|
| Ensembl ID | ENSG00000160951 | ENSG00000125384 | ENSG00000050628 | ENSG00000171522 |
| Principal transduction | $G_{q/11}$ | $G_s$ | $G_{i/o}$ | $G_s$ |
| Rank order of potency | E > F,I > D,T | E >F,I > D,T | E > F,I > D,T | E > F,I > D,T |
| Selective agonists | 17-Ph-ω-trinor-$PGE_2$, ONO-DI-004 | Butaprost, CP533536 (Cameron et al *et al*., 2009), ONO-AE1–259 | Sulprostone, SC46275, ONO-AE-248 | ONO-AE1–329, L902688 (Young *et al*., 2004) |
| Selective antagonists | ONO8711 (9.2), GW848687 (9.1, Giblin *et al*., 2007), SC51322 (8.8) | – | L798106 (7.7) | GW627368 (9.2), ONO-AE3–208 (8.5), L161982 (8.5), BGC201531 (7.8, Maubach *et al*., 2009), CJ042794 (8.6, Murase *et al*., 2008) |
| Probes | [$^3$H]-$PGE_2$ (1–25 nM) | [$^3$H]-$PGE_2$ (5–22 nM) | [$^3$H]-$PGE_2$ (0.3–7 nM) | [$^3$H]-$PGE_2$ (0.6–24 nM |

17-Ph-ω-trinor-$PGE_2$ also shows agonist activity at $EP_3$ receptors. Sulprostone also has affinity for $EP_1$ receptors. Butaprost and SC46275 may require de-esterification within tissues to attain full agonist potency. There is evidence for subtypes of FP (Liljebris *et al*., 1995), IP (Wise *et al*., 1995; Takechi *et al*., 1996) and TP (Krauss *et al*., 1996) receptors. mRNA for the $EP_1$ and $EP_3$ receptors undergo alternative splicing to produce two (Okuda-Ashitaka *et al*., 1996) and at least six variants, respectively, which can interfere with signalling (Okuda-Ashitaka *et al*., 1996) or generate complex patterns of G protein ($G_{i/o}$, $G_{q/11}$, $G_s$ and $G_{12,13}$) coupling (e.g. Kotani *et al*., 1995; Negishi *et al*., 1995). The possibility of additional receptors for the isoprostanes has been suggested (Pratico *et al*., 1996). Receptors (prostamide F, which as yet lack a molecular correlate) that preferentially recognize $PGF_{2\alpha}$-1-ethanolamide and its analogues (e.g. bimatoprost) have been identified, together with moderate-potency antagonists (e.g. AGN 211334) (see Woodward *et al*., 2008).

**Abbreviations: AFP07**, 7,7-difluoro-16*S*,20-dimethyl-18,19-didehydro-$PGI_2$; **AGN192093**, (*Z*)-7-([1α,5α,6α,7β]-7-[{1*E*,3*S*}-3-hydroxy-1-octenyl]-3-oxo-2,4-dioxobicyclo[3.2.1]oct-6-yl)-5-heptenol; **AH23848**, (1α[*z*],2β,5α)-(±)-7-(5-[{(1,1′-biphenyl)-4-yl}methoxy]-2-[4-morpholinyl]-3-oxocyclopentyl)-4-heptenoate; **AL12180**, 5,6-dihydro-4,5-didehydro-11-deoxy-11-oxa-16-(3-chlorophenoxy)-ω-tetranor-$PGF_{2\alpha}$; **AS604872**, (2*S*)-3-([1,1-biphenyl]-4-ylsulphonyl-*N*-[(*R*)-phenyl(2-pyridinyl)-methyl]-1,3-thiazolidine-2-carboxamide; **BGC201531**, (*N*-(4-[4-(5-methoxypyridin-2-yl)phenoxymethyl]-5-methylfuran-2-carbonyl)-2-methylbenzenesulphonamide; **BMS180291**, (1*s*-(1α,2α,3α,4α)-2-([3-{4-

([pentylamino]carbonyl)-2-oxazolyl}-7-oxabicyclo{2.2.1}hept-2-yl]methyl)benzenepropanoic acid; also known as ifetroban; **BMY45778**, 3-(4-[4,5-diphenyl-2-oxazolyl]-5-oxazolyl)phenoxyacetic acid; **BW245C**, 5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin; **BW848687**, 6-[2-(5-chloro-2-{[(2,4-difluorophenyl)methyl]oxy}phenyl)-1-cyclopenten-1-yl]-2-pyridinecarboxylic acid; **BWA868C**, 3-benzyl-5-(6-carboxyhexyl)-1-(2-cyclohexyl-2-hydroxyethylamino)hydantoin; **CAY10471**, (+)-3-([{4-fluorophenyl}sulfonyl]methylamino)-1,2,3,4-tetrahydro-9*H*-carbazole-9-acetic acid; **CJ042794**, 4-{(1*S*)-1-[({5-chloro-2-[(4-fluorophenyl)oxy]phenyl}carbonyl)amino]ethyl} benzoic acid, **CP533536**, N-(4-*t*-butylbenzyl)-pyridyl-3-yl-sulphonamidomethylphenoxyacetic acid; **GR32191**, [1*R*-[1(*Z*),2$\alpha$,3$\beta$,5]]-(+)-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid; **GW627368**, *N*-(2-[4-{4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl]-acetyl)benzenesulphonamide; **I-BOP**, (1*S*-[1$\alpha$,2$\beta${5*z*},3$\alpha$[1*e*,3*s*,],4$\alpha$])-7-(3-[hydroxy-4-{4′-iodophenoxy}-1-butenyl]-7-oxabicyclo[2.2.1]hept-2-yl)-5-heptanoate; **L161982**, 5-butyl-2,4-dihydro-[[2′-[*N*-(5-methyl-2-thiophenecarbonyl)sulphamoyl]biphenyl-4-yl]methyl]-2-[(2-trifluoromethyl)phenyl]-1,2,4-triazol-3-one; **L644698**, 4-(3-{3-[3-hydroxyoctyl]-4-oxo-2-thiazolidinyl}propyl)benzoate racemate; **L798106**, 5-bromo-2-methoxy-*N*-[3-(naphthalen-2-yl-methylphenyl)-acryloyl]-benzenesulphonamide; **L902688**, 8-aza-1-decarboxy-11-deoxy-16,16-difluoro-16-phenyl-ω-tetranor-1-(5-tetrazolo) $PGE_1$; **ONO3708**, (9,11)-(11,12)-dideoxa-9$\alpha$,11$\alpha$-dimethylmethano-11,12-methano-13,14-dihydro-13-aza-14-oxo-15-cyclopentyl-16,17,18,19,20-pentanor-15-epi-$TXA_2$; **ONO8711**, 6-[(2*S*,3*S*)-3-(4-chloro-2-methylphenylsulphonylaminomethyl)-bicyclo[2.2.2]octan-2-yl]-5*Z*-hexenoic acid; **ONO-AE-248**, 11,15-*O*-dimethyl-$PGE_2$; **ONO-AE1-259**, 16*s*-9-deoxy-9$\beta$-chloro-15-deoxy-16-hydroxy-17,17-propano-19,20-didehydro-$PGE_2$; **ONO-AE1-329**, 16-(3-methoxymethyl)phenyl-ω-tetranor-3,7-dithia-$PGE_1$; **ONO-AE3-208**, 2-(2-(2-methyl-2-naphth-1-ylacetylamino)-phenylmethyl)-benzoic acid; **ONO-DI-004**, 17*S*-17,20-dimethyl-2,5-ethano-6-oxo $PGE_1$; **RO1138452**, 4,5-dihydro-1*H*-imidazol-Z-yl)-[4-(4-isopropoxybenzyl)phenyl]amine; **RS93520**, *Z*-4-([C3′*S*,1*R*,2*R*,3*S*,6*R*]-2C3′-cyclohexyl-3′-hydroxyprop-1-ynyl)-3-hydroxybicyclo(4.2.0)oct-7-ylidene butyrate; **S5751**, ((*Z*)-7-[1*R*,2*R*,3*S*,5*S*)-2-(5-hydroxybenzo[b]thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid); **SAP**, 7-([1*R*,2*S*,3*S*,5*R*]-6,6-dimethyl-3-benzenesulphonamino-bicyclo[3.1.1]hept-2-yl)-5z-heptenoic acid; **SC46275**, methyl-7-(2$\beta$-[6-{1-cyclopenten-1-yl}-4*R*-hydroxy-4-methyl-1*e*,5*e*-hexadienyl]-3$\alpha$-hydroxy-5-oxo-1*R*,1$\alpha$-cyclopentyl)-4z-heptenoic acid; **SC51322**, 8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[3-[furanylmethyl)-thio]-1-oxopropyl] hydrazide; **SQ29548**, (1*S*-[1$\alpha$,2$\beta${5*z*},3$\beta$,4$\beta$])7-(3-[[2-(phenylamino)carbonyl}hydrazino]methyl)-7-oxabicyclo[2.2.1]hept-2-yl-5-heptenoate; **SQ27986**, [1*S*-[1B,2B(5*Z*),3A(1*E*,3*S*)4B]]7-[3-(3-cyclohexyl-3-hydroxy-1-propenyl)-7-oxabicyclo[2.2.1]hept-2-y]5-heptenoic acid; **$STA_2$**, 11$\alpha$-carba-9$\alpha$,11$\beta$-thia-$Txa_2$; **U46619**, 11$\alpha$,9$\alpha$-epoxymethano-$PGH_2$; **ZK118182**, (5*Z*,13E)-(9*R*,11*R*,15*S*)-9-chloro-15-cyclohexyl-11,15-dihydroxy-3-oxa-16,17,18,19,20-pentanor-5,13-prostadienoic acid; **ZK138357**, (5*Z*)-7-([2*RS*,4*S*,5*S*]-2-[2-chlorophenyl]-5-[{1*E*}-{3*R*,*S*}-3-hydroxy-3-cyclohexyl-1-propenyl]-1,3-dioxolan-4-yl)-5-heptanoic acid

## Further Reading


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