

# Endothelin Receptors

## Key References

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## Overview

Endothelins are a family of vasoactive peptides that were discovered in a search for the identity of a vasoconstricting factor known to exist in the media from cultured endothelial cells. The first member of this family, endothelin-1 or ET-1, was revealed in a seminal *Nature* article published in March, 1988. Subsequently, ET-2, ET-3 and several snake venom toxins, called sarafotoxins, were identified as members of a bicyclic 21 amino acid peptide family.

It is now known that the mammalian peptides, ET-1 and ET-3, are produced by a wide range of tissues and cells. ET-1 is the primary isoform circulating in plasma. ET-3 has been found in high levels in brain. ET-2 may be more selectively produced in the kidney and intestine, but its functional significance remains poorly defined. The endothelins are all coded from separate genes and the gene products require proteolytic processing to produce mature endothelins. A number of endothelin converting enzymes (ECE) have been identified which may be important in the final proteolytic cleavage step.

The endothelins function through their interaction with G protein-coupled receptors. To date, two subtypes have been cloned from mammalian cells, ET<sub>A</sub> and ET<sub>B</sub>. The ET<sub>A</sub> receptors have a much greater affinity for ET-1 over ET-3 and are expressed abundantly in vascular smooth muscle and stromal tissues. In humans and animals, *in vivo* and *in vitro* studies with selective antagonists have revealed that the vasoconstrictor and proliferative effects of ET-1 are primarily mediated by the ET<sub>A</sub> receptor. The ET<sub>B</sub> receptor binds both ET-1 and ET-3 with nearly equal affinity and is expressed abundantly on endothelial cells

and epithelial tissues. While the ET<sub>B</sub> receptor can mediate a vasoconstrictor response, its physiological role appears to be two-fold: i) mediation of ET-1-induced nitric oxide release from endothelial cells and an accompanying vasodilation response, and ii) clearance of ET peptides from the circulation. These conclusions are supported by studies with ET<sub>B</sub>-selective antagonists which block the transient vasodilation response observed upon bolus intravenous administration of ET-1 or studies showing that hypertension is associated with chronic administration of ET<sub>B</sub> antagonists, and the marked increase in plasma endothelin levels upon ET<sub>B</sub>-selective or non-selective receptor blockade, but not ET<sub>A</sub>-selective blockade. In addition to their vasoactive properties, these receptors are involved in regulation of cell proliferation. Gene disruption studies indicate that both receptor subtypes and both ET-1 and ET-3 play important roles in embryologic development.

Therapeutic interest in blocking the endothelin system has been high leading to the discovery of a large number of peptidic and non-peptide receptor antagonists. These antagonists may have utility in a number of cardiovascular diseases, including congestive heart failure, pulmonary hypertension, stroke, kidney failure, hypertension, angioplasty-induced restenosis, and a variety of non-cardiovascular conditions, such as asthma, chronic obstructive pulmonary disease, pain and cancer.

# Endothelin Receptors

CURRENTLY ACCEPTED NAME	ET <sub>A</sub>	ET <sub>B</sub>
STRUCTURAL INFORMATION	427 aa (human)	442 aa (human)
PREFERRED ENDOGENOUS PEPTIDES	ET-1 ( <a href="#">E 7764</a> ) = ET-2 ( <a href="#">E 9012</a> ) >> ET-3 ( <a href="#">E 9137</a> )	ET-1 ( <a href="#">E 7764</a> ) = ET-2 ( <a href="#">E 9012</a> ) = ET-3 ( <a href="#">E 9137</a> )
SUBTYPE SELECTIVE AGONISTS	None	[Ala <sup>1,3,11,15</sup> ]-ET-1 ( <a href="#">E 6877</a> ) Sarafotoxin 56c ( <a href="#">S 6545</a> ) IRL 1620 ( <a href="#">E-137</a> ) BQ-3020 ( <a href="#">E-139</a> )
SUBTYPE SELECTIVE ANTAGONISTS <sup>a</sup>	A-127722 <sup>b</sup> A-147627 (ABT 627, Atrasentan) A-216546 BQ-123 ( <a href="#">B-150</a> ) BQ-610 ( <a href="#">B-151</a> ) FR 139317 Lu-135252 (Darusentan) PD 151,242 ( <a href="#">P-208</a> ) PD 156,707 TBC-11251 (Saitaxsentan)	A-192621 BQ-788 ( <a href="#">B-157</a> ) RES-701-1 Ro 46-8443
NON-SELECTIVE ANTAGONISTS	A-186086 Ro-61-6612 (Tezosentan) SB-209670 SB-217242 (Enrasentan) PD 142,893 ( <a href="#">P 2959</a> ) PD 145,065 ( <a href="#">P 3084</a> ) Ro 47-0203 (Bosentan)	A-186086 Ro-61-0612 (Tezosentan) SB 209670 SB-217242 PD 142,893 ( <a href="#">P 2959</a> ) PD 145,065 ( <a href="#">P 3084</a> ) Ro 47-0203 (Bosentan)
SIGNAL TRANSDUCTION MECHANISMS	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG) <sup>c</sup>	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG) <sup>c</sup>
RADIOLIGANDS OF CHOICE	[ <sup>125</sup> I]-ET-1 [ <sup>3</sup> H]-BQ-123	[ <sup>125</sup> I]-ET-1 [ <sup>125</sup> I]-ET-3

## ABBREVIATIONS

**A-127722:** *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid  
**A-147627 (ABT-627):** (2R,3R,4S)-(+)-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid  
**A-186086:** (2R,3R,4S)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid  
**A-192621:** (2R,3R,4S)-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2,6-diethylphenylaminocarbonylmethyl)-pyrrolidine-3-carboxylic acid  
**A-216546:** [2S-(2,2-Dimethylpentyl)-4S-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3R-carboxylic acid  
**BQ-123:** Cyclo (D- $\alpha$ -aspartyl-L-prolyl-D-valyl-L-leucyl-D-tryptophyl)  
**BQ-610:** N-[1-Formyl-N-[N-[(hexahydro-1H-azepin-1-yl)carbonyl]-L-leucyl]-D-tryptophyl]-D-tryptophan  
**BQ-788:** N-[N-[N-[(2,6-Dimethyl-1-piperidinyl)carbonyl]-4-methyl-L-leucyl]-1-(methoxycarbonyl)-D-tryptophyl]-D-norleucine

**BQ-3020:** N-Acetyl-[Ala<sup>11,15</sup>]-Endothelin-1(6-21)  
**ET-1:** Endothelin-1  
**ET-2:** Endothelin-2  
**ET-3:** Endothelin-3  
**FR 139317:** (R)2-[(R)-2-[(S)-2-[[1-(Hexahydro-1H-azepinyl)]carbonyl]amino-4-propionyl]amino-3-(2-pyridyl)propionic acid  
**IRL 1620:** N-Suc-[Glu<sup>9</sup>,Ala<sup>11,15</sup>]-Endothelin-1(8-21)  
**Lu 135252:** (+)-(S)-2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenyl-propionic acid  
**PD 142,893:** N-Acetyl- $\beta$ -Phenyl-D-Phe-Leu-Asp-Ile-Ile-Trp  
**PD 145,065:** N-Acetyl- $\alpha$ -[10,11-Dihydro-5H-dibenzo[a,d]cycloheptadien-5-yl]-D-Gly-Leu-Asp-Ile-Ile-Trp  
**PD 151,242:** N-[N-[N-[(Hexahydro-1H-azepin-1-yl)carbonyl]-L-leucyl]-1-methyl-D-tryptophyl]-D-tyrosine  
**PD 156,707:** Sodium 2-benzo[1,3]dioxol-5-yl-4-(4-methoxyphenyl)-4-oxo-3-(3,4,5-trimethoxybenzyl)-but-2-enoate

**RES-701-1:** cyclic (Gly<sup>1</sup>-Asp<sup>9</sup>) (Gly-Asn-Trp-His-Gly-Thr-Ala-Pro-Asp-Trp-Phe-Phe-Asn-Tyr-Trp)  
**Ro 46-8443:** N-[6-[(2R)-2,3-Dihydroxypropoxy]-5-(2-methoxyphenoxy)-2-(4-methoxyphenyl)-4-pyrimidinyl]-4-(1,1-dimethylethyl)-benzenesulfonamide  
**Ro 47-0203:** 4-Tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxyphenoxy)-2,2'-bipyrimidin-4-yl]-benzenesulfonamide  
**Ro 61-0612:** 5-Isopropyl-pyridine-2-sulfonic acid 6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-2-(2-1H-tetrazol-5-yl-pyridin-4-yl)-pyrimidin-4-ylamide  
**SB-209670:** ( $\pm$ )-(1S,2R,3S)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid  
**SB-217242:** 1-(1,3-Benzodioxol-5-yl)-2,3-dihydro-3-[2-(2-hydroxyethoxy)-4-methoxyphenyl]-5-propoxy-, -1H-indene-2-carboxylic acid  
**TBC-11251:** N-(4-Chloro-3-methyl-5-isoazoly)-2-[(6-methyl-1,3-benzodioxol-5-yl)acetyl]-3-thiophenesulfonamide

## FOOTNOTES

- a** "Subtype Selective Antagonists" means > 500-fold  
**b** A-127722 is the racemic version of A-147627 (ABT-627, Atrasentan).  
**c** Some evidence exists to suggest that endothelin receptors may signal through other signal transduction mechanisms.