Drugs of the Future 2005, 30(8): 765-770

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.08.929953

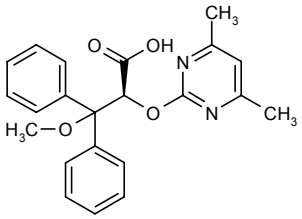
Ambrisentan

Prop INN; USAN

Treatment of Pulmonary Arterial Hypertension
Endothelin ET_A Receptor Antagonist

BSF-208075
LU-20807

(+)-2(*S*)-(4,6-Dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid



$C_{22}H_{22}N_2O_4$
Mol wt: 378.4212
CAS: 177036-94-1
EN: 282368

Abstract

Pulmonary artery hypertension (PAH) is a group of rare and progressive lung disorders. Because of the low incidence of the disease, progress in the search for treatments for PAH has been slow. Conventional therapy for mild to moderate PAH consists of diuretics, calcium channel blockers and anticoagulants, while options for patients with moderate to severe PAH are more limited (prostacyclin infusion and balloon atrial septostomy). However, research efforts in this field have intensified with several novel agents currently under active development. One such agent is the pyrimidine-derived ambrisentan, an endothelin receptor antagonist that is highly selective for ET_A. As compared to nonselective endothelin receptor antagonists, ambrisentan displays enhanced efficacy, a low propensity to cause liver toxicity and adverse drug interactions, a high oral bioavailability and a half-life enabling once-daily dosing. The efficacy of ambrisentan was demonstrated in clinical trials in patients with WHO class II and III PAH and it is presently undergoing phase III development for the treatment of PAH.

Synthesis

The condensation of benzophenone (I) with methyl 2-chloroacetate (II) by means of NaOMe in THF gives 3,3-diphenyloxirane-2-carboxylic acid methyl ester (III), which by treatment with BF_3/Et_2O and methanol yields 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid methyl ester (IV). The condensation of compound (IV) with 4,6-dimethyl-2-(methylsulfonyl)pyrimidine (V) by means of K_2CO_3 in DMF affords 2-(4,6-dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid methyl ester (VI), which is finally hydrolyzed with KOH in hot dioxane (1, 2). Scheme 1.

The pure (*S*)-enantiomer of the free acid from ester (IV) can be obtained by crystallization with a chiral amine (1, 2).

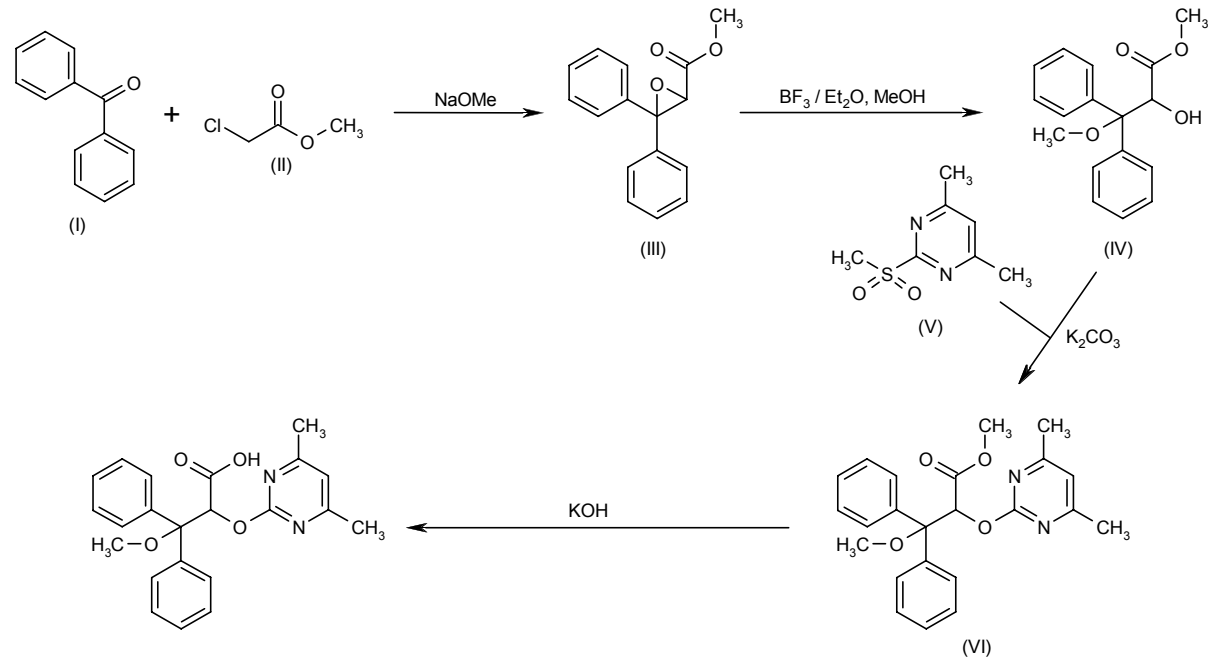
Introduction

Pulmonary artery hypertension (PAH) is a group of rare and progressive lung disorders characterized by identical obstructive pathological changes of the pulmonary microvasculature. It includes primary pulmonary hypertension (PPH), secondary pulmonary hypertension (PH) which occurs as a result of other medical conditions or drug use (*e.g.*, scleroderma, chronic obstructive pulmonary disease [COPD], systemic lupus erythematosus, HIV infection, portal hypertension, appetite-suppressant drug use, cocaine inhalation), and persistent pulmonary hypertension of the newborn (PPHN), occurring when a neonate is unable to successfully transfer from gas exchange by the placenta to that of the lungs. In adults, PAH is characterized by an increase in mean blood pressure in the pulmonary artery to > 25 mmHg at rest and > 30 mmHg during exercise. The progressive increase in pulmonary vascular resistance usually leads to right ventricular heart failure and death. The cause(s) of PPH is unknown, although genetic components (*e.g.*, mutations in the *BMPR2* gene) may be involved to some extent (3-5).

PPH is relatively rare, with an estimated total incidence of 35,000-70,000 patients worldwide. As a result of the low incidence of the disease, progress in the search for treatments for PAH has been slow. Initial treatment strategies starting in the 1950s included attempts to

L.A. Sorbera, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Ambrisentan



decrease pulmonary artery pressure with acute administration of vasodilators. Later in the 1980s and 1990s, the use of oral anticoagulants and high-dose calcium channel antagonists (nifedipine and diltiazem) was implemented. The development of continuous i.v. administration of prostacyclin (epoprostenol) occurred in the 1990s, with favorable results. Unfortunately, this method involves an awkward form of delivery. Later, balloon atrial septostomy was proposed and also showed favorable results. To date, conventional therapies for mild to moderate PAH consist of diuretics, calcium channel blockers and anticoagulants. Options for patients with moderate to severe PAH are more limited (prostacyclin infusion and balloon atrial septostomy). However, since 2000, research efforts to identify novel compounds for the treatment of PAH have intensified. Agents currently under active development for the treatment of PAH are shown in Table I (3, 6-12).

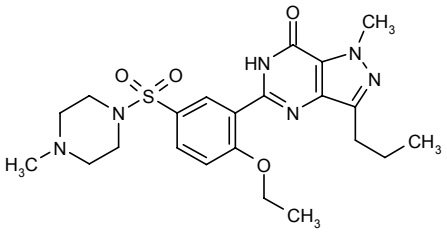
Of those novel agents currently under investigation, three are endothelin antagonists and show particular promise. Endothelins are a family of three isopeptides (ET-1, ET-2 and ET-3), composed of 21 amino acids and two internal disulfide bonds, that have potent mitogenic, vasoconstricting and/or bronchoconstricting effects. ET-1 has been found in abundance in endothelial and epithelial cells, where it acts as an autocrine/paracrine mediator. It has been demonstrated to play a role in the modulation of vascular tone, cell proliferation and apoptosis, and has therefore been implicated in several cardiovascular and noncardiovascular conditions, including PAH, where high endothelin concentrations strongly correlate with disease severity.

Endothelins exert their action via G-protein-coupled receptors, of which two types have been cloned: ET_A and ET_B. ET_A is expressed in vascular smooth muscle cells, cardiomyocytes and fibroblasts, and exhibits greater affinity for ET-1 over ET-2 and ET-3. Thus, this receptor is thought to predominantly mediate the vasoconstrictive and proliferative effects of ET-1. ET_B is expressed in medial smooth muscle of human arteries, where it also mediates vasoconstriction. This receptor type is thought to be counterregulatory, protecting against excessive vasoconstriction by mediating clearance mechanisms for excess endothelins and by virtue of its involvement in the feedback and regulation of endothelin synthesis and secretion; ET_B has also been shown to have antiproliferative effects in human cells. Thus, in the treatment of PAH, selective antagonism of ET_A over ET_B would appear to be optimal in that the damaging effects of vasoconstriction and proliferation of endothelin would be blocked, while the beneficial effects of ET_B would be preserved (3, 13-16).

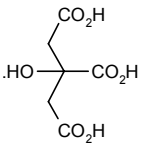
Ambrisentan is a pyrimidine-based endothelin receptor antagonist that is highly selective for ET_A. It also possesses enhanced efficacy and a low propensity to cause liver toxicity (*versus* sitaxsentan and bosentan) and adverse drug interactions (*versus* anticoagulants). Moreover, the agent has a high oral bioavailability and a half-life that would enable once-daily dosing. Ambrisentan was therefore chosen for further development as a treatment for PAH (2, 15, 16).

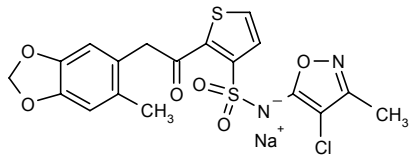
Table I: Drugs under active development for PAH (from Prous Science Integrity®).

Drug	Mechanism of action	Source	Phase
1. Sildenafil citrate (Revatio™)	Phosphodiesterase 5 (PDE5) inhibitor	Pfizer	L-2005
2. Sitaxsentan sodium (Thelin™)	Endothelin ET_A receptor antagonist	Encysive Pharmaceuticals	Prereg.
3. Ambrisentan	Endothelin ET_A receptor antagonist	Myogen	III
4. Aviptadil	Synthetic VIP	Mondobiotech	II/III
5. UK-369003*	Phosphodiesterase 5 (PDE5) inhibitor	Pfizer	II
6. PRX-08066*	5-HT_{2B} antagonist	Predix Pharmaceuticals	I
7. TBC-3711	Endothelin ET_A receptor antagonist	Encysive PharmaceuticalsS	I

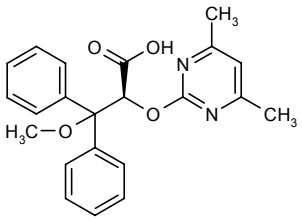


1

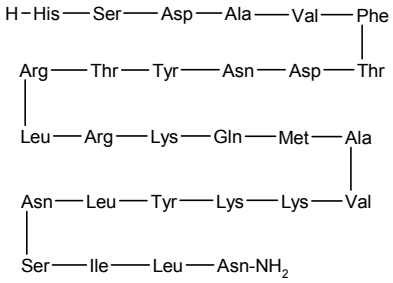




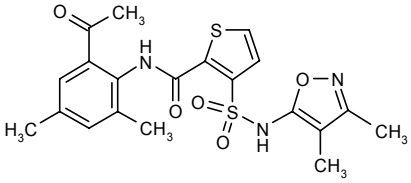
2



3



4



7

* Structure not available.

Pharmacological Actions

In experiments using membranes from stably transfected CHO cells expressing human ET_A or ET_B receptors incubated with [^{125}I]-ET-1, ambrisentan proved to be highly selective for ET_A over ET_B, with K_i values of 1 ± 0.9 and 195 nM, respectively (2) (Table II).

Ambrisentan exhibited potent ET_A blockade in several *in vitro* and *in vivo* models. Efficacy was demonstrated in pig models of in-stent restenosis and hepatic ischemia/reperfusion injury, and in a gerbil model of global cerebral ischemia. The agent potently and concentration-dependently inhibited big ET-1- and ET-1-induced contraction of isolated rat basilar artery segments *in vitro* (see Table III), an effect mediated by the ET_A receptor; however, big ET-1- and ET-1-induced relaxation was only observed in the presence of ambrisentan and was inhibited at higher concentrations of the drug, suggesting ET_B receptor affinity. The agent was also active in protecting against graft pancreatitis and ischemia/reperfusion-induced pancreatic injury in a pig pancreas transplantation model, improving glucose balance and gastrointestinal function in a rat model of type 2 diabetes, and preventing the development of hypertension in stroke-prone spontaneously hypertensive rats (17-26).

Clinical Studies

The efficacy of ambrisentan (1, 2.5, 5 or 10 mg/day p.o. for 12 weeks, followed by a 12-week open-label dose-adjustment period) as a treatment for PAH was demonstrated in a randomized trial conducted in 23 WHO class II (baseline 6-min walk distance [6MWD] = 390 m) and 41 WHO class III (baseline 6MWD = 316 m) patients with idiopathic PAH or PAH associated with collagen vascular disease, anorexigen use or HIV infection. Treatment was well tolerated, with a low incidence and severity of

Table II: Endothelin receptor affinities of ambrisentan compared to other selected ET_A antagonists (from Prous Science Integrity®).

Drug	ET_A	ET_B	ET_A selectivity	Ref.
Ambrisentan	1.00	195[c]	195	2
97-139	1.00[a]	1000[b]	1000	32
Atrasentan	0.03	63.3	2110	33, 34
Bosentan	26.7	228	8.5	35-46
Clazosentan	0.81	1930	2383	47
Darusentan	1.70	189	111	42, 46, 48, 49
J-104132	0.03	0.10	3.3	39, 50
SB-234551	0.13	500	385	43
Sitaxsentan	0.43[d]	9800*	22,790	51, 52
TBC-3711	0.08*	26,300*	328,750	53
ZD-4054	5.40	>10,000	>1852	54

Competitive binding affinity (K_i, nM or * IC_{50}, nM) for endothelin ET_A and ET_B receptors evaluated by displacement of [^{125}I]-ET-1 or ET-3 in cells transfected with the human receptor except when otherwise pointed out: [a] in rat aorta; [b] in human heart; [c] in guinea pig cerebellum; [d] in TE671 human medulloblastoma cells. ET_A receptor selectivity is the ratio of ET_B/ET_A receptor affinities.

aminotransferase abnormalities. Treatment with all doses resulted in a similar improvement in 6MWD from baseline for both class II and class III patients at weeks 12 (37.7 and 35.2 m, respectively) and 24 (58.3 and 51.9 m, respectively). There was a trend toward greater improvement in the Borg dyspnea index (BDI) in class III patients compared to class II patients at week 12 (–1.1 and –0.4, respectively). At week 24, class III patients had a significantly greater improvement in BDI over class II patients (–1.6 and 0, respectively) (27, 28).

The long-term safety and efficacy were assessed in 54 patients from this trial who continued on open-label drug for 48 weeks. Treatment was well tolerated, with a low incidence of aminotransferase abnormalities reported. Adverse events were not dose-related and no drug interactions were observed. Two patients developed increased serum aminotransferase requiring either dose reduction or discontinuation. When dose groups were combined, a significant increase in mean 6MWD (54.5 ± 54.9 m) and a significant improvement in BDI (–0.9 ± 2.1) were observed at 48 weeks. According to Kaplan-Meier analysis, 57% of the patients had a WHO class improvement, while only 5% deteriorated. The survival at this time was 93% in contrast to 77% as predicted by the NIH Registry formula (29).

Two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III trials (ARIES1: 5 and 10 mg p.o. once daily for 12 weeks; ARIES2: 2.5 and 5 mg p.o. once daily for 12 weeks) have been initiated to examine the safety and efficacy of ambrisentan in approximately 186 patients/trial with idiopathic PAH or PAH associated with collagen vascular disease, anorexigen use or HIV infection (WHO class I-IV symptoms; 6MWD = 150-450 m; mean pulmonary artery pressure = 25 mmHg or greater; pulmonary vascular resistance > 3 mmHg/l/min; pulmonary capillary wedge pressure and left ventricular end diastolic pressure < 15 mmHg; total lung capacity 70% or greater than predicted normal; FEV_1 = 65% or greater than predicted normal); pediatric patients and subjects with congenital heart disease were excluded. The primary efficacy endpoint is exercise capacity. Secondary endpoints are BDI, WHO functional class and quality of life assessment (30, 31).

Table III: Inhibition of ET-1-induced vasoconstriction by ambrisentan compared to other selected ET_A antagonists (from Prous Science Integrity®).

Drug	Parameter	Value	Source	Ref.
Ambrisentan	pA_2	6.51	Rat basilar artery	21
97-139	pA_2	8.80	Rat aorta	32
Atrasentan	pIC_{50}	6.54	Rat aorta	33
Bosentan	pA_2	7.08	Rat aorta	55-57
		9.50	Rat aorta	
Clazosentan	pA_2	8.24	Rat basilar artery	47, 58
J-104132	pA_2	9.70	Rabbit iliac artery	50
SB-234551	pK_B	9.05	Human pulmonary artery	43

Source

Myogen, Inc. (US) (licensed from Abbott Laboratories).

References

1. Riechers, H., Klinge, D., Amberg, W., Kling, A., Müller, S., Baumann, E., Rheinheimer, J., Vogelbacher, U.J., Wernet, W., Unger, L., Raschack, M. (Abbott GmbH & Co. KG). *New carboxylic acid derivatives, their preparation and their use.* EP 0785926, EP 1110952, JP 1998507190, WO 1996011914.

2. Riechers, H., Albrecht, H.-P., Amberg, W. et al. *Discovery and optimization of a novel class of orally active nonpeptidic endothelin-A receptor antagonists*. J Med Chem 1996, 39: 2123-8.

3. Prous Science Drug R&D Backgrounders: *Pulmonary hypertension (online publication).* Updated August 19, 2005.

4. Rubin, L.J. *Primary pulmonary hypertension*. New Engl J Med 1997, 336: 111-7.

5. Gaine, S.P., Rubin, L.J. *Primary pulmonary hypertension*. Lancet 1998, 352: 719-25.

6. Weir, E.K., Rubin, L.J., Ayres, S.M. et al. *The acute administration of vasodilators in primary pulmonary hypertension. Experience from the National Institutes of Health Registry on Primary Pulmonary Hypertension.* Am Rev Respir Dis 1989, 140: 1623-30.

7. Reeves, J.T. *Hope in primary pulmonary hypertension*. New Engl J Med 1980, 302: 112-3.

8. Fuster, V., Steele, P.M., Edwards, W.D., Gersh, B.J., McGoon, M.D., Frye, R.L. *Primary pulmonary hypertension: Natural history and the importance of thrombosis.* Circulation 1984, 70: 580-7.

9. Rich, S., Kaufmann, E., Levy, P.S. *The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension*. New Engl J Med 1992, 327: 76-81.

10. Rubin, L.J., Mendoza, J., Hood, M., McGoon, M., Barst, R., Williams, W.B., Diehl, J.H., Crow, J., Long, W. *Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial*. Ann Intern Med 1990, 112: 485-91.

11. Barst, R.J., Rubin, L.J., Long, W.A. et al. *A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group.* New Engl J Med 1996, 334: 296-302.

12. Sandoval, J., Gaspar, J., Pulido, T., Bautista, E., Martínez-Guerra, M.L., Zeballos, M., Palomar, A., Gómez, A. *Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment*. J Am Coll Cardiol 1998, 32: 297-304.

13. Yanagisawa, M., Kurihara, H., Kimura, S., Tomobe, Y., Kobayashi, M., Mitsui, Y., Yazaki, Y., Goto, K., Masaki, T. *A novel potent vasoconstrictor peptide produced by vascular endothelial cells.* Nature 1988, 332: 411-5.

14. Lüscher, T.F., Barton, M. *Endothelins and endothelin receptor antagonists. Therapeutic considerations for a novel class of cardiovascular drugs*. Circulation. 2000, 102: 2434-40.

15. Channick, R.N., Sitbon, O., Barst, R.J., Manes, A., Rubin, L.J. *Endothelin receptor antagonists in pulmonary arterial hypertension.* J Am Coll Cardiol 2004, 43(12, Suppl. S): 62S-7S.

16. Kirchengast, M., Luz, M. *Endothelin receptor antagonists. Clinical realities and future directions.* J Cardiovasc Pharmacol 2005, 45: 182-91.

17. Kirchengast, M. *Endothelin receptor blockade and in-stent restenosis*. J Cardiovasc Pharmacol 2001, 38(Suppl. 2): S31-4.

18. Uhlmann, D., Armann, B., Gaebel, G. et al. *Endothelin A receptor blockade reduces hepatic ischemia/reperfusion injury after warm ischemia in a pig model*. J Gastrointest Surg 2003, 7: 331-9.

19. Hauck, E.F., Hoffmann, J., Schin, M., Kempski, O. *Effect of endothelin-A receptor antagonist BSF 208075 on leukocyte-endothelium-interactions and neuronal cell death after transient global cerebral ischemia assessed by intravital videomicroscopy*. 33rd Annu Meet Soc Neurosci (Nov 8-12, New Orleans) 2003, Abst 236.6.

20. Vatter, H., Zimmermann, M., Jung, C., Weyrauch, E., Lang, J., Seifert, V. *Effect of the novel endothelin$_A$ receptor antagonist LU 208075 on contraction and relaxation of isolated rat basilar artery.* Clin Sci (1979) 2002, 103(Suppl. 48): 408S-13S.

21. Vatter, H., Zimmermann, M., Weyrauch, E., Lange, B.N., Setzer, M., Raabe, A., Seifert, V. *Cerebrovascular characterization of the novel nonpeptide endothelin-A receptor antagonist LU 208075.* Clin Neuropharmacol 2003, 26: 73-83.

22. Uhlmann, D., Ludwig, S., Escher, E., Armann, B., Gäbel, G., Teupser, D., Tannapfel, A., Hauss, J., Witzigmann, H. *Protective effect of a selective endothelin a receptor antagonist (BSF 208075) on graft pancreatitis in pig pancreas transplantation*. Transplant Proc 2001, 33: 3732-4.

23. Witzigmann, H., Ludwig, S., Armann, B. et al. *Endothelin$_A$ receptor blockade reduces ischemia/reperfusion injury in pig pancreas transplantation*. Ann Surg 2003, 238: 264-74.

24. Uhlmann, D., Lauer, H., Serr, F., Hauss, J., Witzigmann, H. *Reduction of pancreatic ischemia/reperfusion injury by an endothelin$_A$ receptor antagonist*. Am Transpl Congr (May 21-25, Seattle) 2005, Abst 1184.

25. Balsiger, B., Rickenbacher, A., Boden, P.J., Biecker, E., Tsui, J., Dashwood, M., Reichen, J., Shaw, S.G. *Endothelin A-receptor blockade in experimental diabetes improves glucose balance and gastrointestinal function*. Clin Sci (1979) 2002, 103(Suppl. 48): 430S-3S.

26. Barandier, C.E., Yang, Z., Luscher, T.F. *Effects of chronic ET$_A$-receptor blockade in stroke-prone spontaneously hypertensive rats*. Hypertension 2000, 36(4): Abst P38.

27. Rubin, L., Galie, N., Badesch, D. et al. *Ambrisentan improves exercise capacity and clinical measures in pulmonary arterial hypertension (PAH).* Am J Respir Crit Care Med 2004, 169(7, Suppl.): A210.

28. Frost, A., Manes, A., Keogh, A. et al. *Ambrisentan improves 6-minute walk distance comparably for WHO class II and III PAH patients*. Proc Amer Thorac Soc 2005, Abstracts Issue: A198.

29. Galie, N., Keogh, A., Frost, A. et al. *Ambrisentan long-term safety and efficacy in pulmonary arterial hypertension - One year follow-up*. Proc Amer Thorac Soc 2005, Abstracts Issue: A299.

30. *Clinical trials - Ambrisentan*. Myogen Website June 28, 2005.

31. *Product pipeline - Ambrisentan*. Myogen Website June 7, 2005.

32. Mihara, S., Nakajima, S., Matumura, S., Kohnoike, T., Fujimoto, M. *Pharmacological characterization of a potent nonpeptide endothelin receptor antagonist, 97-139.* J Pharmacol Exp Ther 1994, 268: 1122-8.

33. Chiou, W.J., Wessale, J.L., von Geldern, T., Opgenorth, T.J., Wu-Wong, J.R. *"Irreversible" endothelin-1 binding does not prohibit ABT-627 from reversing endothelin-1-induced effects*. J Cardiovasc Pharmacol 2000, 36(5, Suppl. 1): S48-52.

34. Winn, M., von Geldern, T.W., Opgenorth, T.J. et al. *2,4-Diarylpyrrolidine-3-carboxylic acids - Potent ET$_A$ selective endothelin receptor antagonists. 1. Discovery of A-127722*. J Med Chem 1996, 39: 1039-48.

35. Opgenorth, T.J., Adler, A.L., Calzadilla, S.V. et al. *Pharmacological characterization of A-127722: An orally active and highly potent ET$_A$-selective receptor antagonist*. J Pharmacol Exp Ther 1996, 276: 473-81.

36. Clozel, M., Breu, V., Gray, G.A. et al. *Pharmacological characterization of bosentan, a new potent orally active nonpeptide endothelin receptor antagonist*. J Pharmacol Exp Ther 1994, 270: 228-35.

37. Wu-Wong, J.R., Dixon, D.B., Chiou, W.J., Opgenorth, T.J. *Endothelin receptor antagonists: Effect of serum albumin on potency and comparison of pharmacological characteristics.* J Pharmacol Exp Ther 1997, 281: 791-8.

38. Williams, D.L., Murphy, K.L., Nolan, N.A. et al. *Pharmacology of L-754,142, a highly potent, orally active, nonpeptidyl endothelin antagonist*. J Pharmacol Exp Ther 1995, 275: 1518-26.

39. Nishikibe, M., Ohta, H., Okada, M. et al. *Pharmacological properties of J-104132 (L-753,037), a potent, orally active, mixed ET_A/ET_B endothelin receptor antagonist*. J Pharmacol Exp Ther 1999, 289: 1262-70.

40. Hoshino, T., Yamauchi, R., Kikkawa, K., Yabana, H., Murata, S. *Pharmacological profile of T-0201, a highly potent and orally active endothelin receptor antagonist.* J Pharmacol Exp Ther 1998, 286: 643-9.

41. Morimoto, H., Shimadzu, H., Kushiyama, E., Kawanishi, H., Hosaka, T., Kawase, Y., Yasuda, K., Kikkawa, K., Yamauchi-Kohno, R., Yamada, K. *Potent and selective ET-A antagonists. 1. Syntheses and structure-activity relationships of N-(6-(2-(aryloxy)ethoxy)-4-pyrimidinyl)sulfonamide derivatives.* J Med Chem 2001, 44: 3355-68.

42. Raschack, M., Gock, S., Unger, L., Hahn, A., Amberg, W., Jansen, R., Alken, P., Weber, A., Hergenroder, S. *LU 302 872 and its racemate (LU 224 332) show balanced endothelin-A/B receptor affinity, high oral activity, and inhibit human prostate tissue contractions*. J Cardiovasc Pharmacol 1998, 31(Suppl. 1): S241-4.

43. Ohlstein, E.H., Nambi, P., Hay, D.W.P., Gellai, M., Brooks, D.P., Luengo, J., Xiang, J.-N., Elliott, J.D. *Nonpeptide endothelin receptor antagonists. XI. Pharmacological characterization of SB 234551, a high-affinity and selective nonpeptide ETA receptor antagonist.* J Pharmacol Exp Ther 1998, 286: 650-6.

44. Yamada, K. et al. *Syntheses and structure-activity relationships of sulfonamide derivatives as endothelin antagonists: A potent and selective ET-A antagonist, TA-0201 and related compounds.* 216th ACS Natl Meet (Aug 23-27, Boston) 1998, Abst MEDI 057.

45. Nambi, P., Pullen, M., Wu, H.L. et al. *Nonpeptide endothelin receptor antagonists. VII: Binding characteristics of [^{3}H]SB 209670, a novel nonpeptide antagonist of endothelin receptors.* J Pharmacol Exp Ther 1996, 277(3): 1567-71.

46. Stumpf, C., Goeck, S., Unger, L., Nebel, M., Riechers, H., Raschack, M. *LU 135 252 shows high endothelin-A receptor affinity and selectivity and oral efficacy leading to reduction of neointima formation in collared rabbit carotid arteries.* Naunyn-Schmied Arch Pharmacol 1997, 355(4, Suppl.): Abst 383.

47. Roux, S., Breu, V., Giller, T., Niedhart, W., Ramuz, H., Coassolo, P., Clozel, J.P., Clozel, M. *Ro 61-1790, a new hydrosoluble endothelin antagonist: General pharmacology and effects on experimental cerebral vasospasm*. J Pharmacol Exp Ther 1997, 283: 1110-8.

48. Münter, K., Hergenröder, S., Unger, L., Kirchengast, M. *Oral treatment with an ET_A-receptor antagonist inhibits neointima formation induced by endothelial injury*. Pharm Pharmacol Lett 1996, 6: 90.

49. Elger, B., Raschack, M., Riechers, H., Seega, J., Unger, L. *Selective endothelin A receptor antagonist LU 135 252 reduces focal cerebral oedema and infarction in spontaneously hypertensive rats.* Cerebrovasc Dis 1996, 6(Suppl. 2): Abst P219.

50. Nishikibe, M. *Pharmacology of J-104,132, a potent, orally-active, mixed ET_A/ET_B endothelin receptor antagonist.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.16.

51. Wu, C., Chan, M.F., Stavros, F., Raju, B., Okun, I., Mong, S., Keller, K.M., Brock, T., Kogan, T.P., Dixon, R.A.F. *Discovery of TBC11251, a potent, long acting, orally active endothelin receptor-A selective antagonist*. J Med Chem 1997, 40: 1690-7.

52. Wu, C., Decker, E.R., Blok, N. et al. *Endothelin antagonists: Substituted mesitylcarboxamides with high potency and selectivity for ETA receptors*. J Med Chem 1999, 42(22): 4485-99.

53. Perreault, T., Berkenbosch, J.W., Barrington, K.J., Decker, E.R., Wu, C., Brock, T.A., Baribeau, J. *TBC3711, an ET_A receptor antagonist, reduces neonatal hypoxia-induced pulmonary hypertension in piglets*. Pediatr Res 2001, 50: 374-83.

54. Curwen, J.O., Wilson, C. *ZD4054: A specific endothelin A receptor antagonist with potential utility in prostate cancer and metastatic bone disease*. Eur J Cancer 2002, 38(Suppl. 7): Abst 340.

55. Gray, G.A., Clozel, M. *Three endothelin receptor subtypes suggested by the differential potency of bosentan, a novel endothelin receptor antagonist, in isolated tissues*. Br J Pharmacol 1994, 112(Suppl.): Abst 120P.

56. Harada, H., Kazami, J., Watanuki, S., Tsuzuki, R., Sudoh, K., Fujimori, A., Tanaka, A., Tsukamoto, S., Yanagisawa, I. *Ethenesulfonamide derivatives, a novel class of orally active endothelin-A receptor antagonists.* Chem Pharm Bull 2001, 49: 606-12.

57. Bolli, M.H., Boss, C., Clozel, M., Fischli, W., Hess, P., Weller, T. *The use of sulfonylamido pyrimidines incorporating an unsaturated side chain as endothelin receptor antagonists.* Bioorg Med Chem Lett 2003, 13: 955-9.

58. Hortobagyi, T., Görlach, C., Benvò, M., Wahl, M. *In vitro characterization and in vivo action after brain trauma of a new endothelin receptor-A antagonist: RO 61-1790*. Fundam Clin Pharmacol 1999, 13(Suppl. 1): Abst PS154.