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The Use of Sulfonylamido Pyrimidines Incorporating an Unsaturated Side Chain as Endothelin Receptor Antagonists

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Abstract—A series of compounds structurally related to bosentan **1** featuring an unsaturated side chain at position 6 of the core pyrimidine have been studied for their potential to block the ET_A and ET_B receptor. Incorporation of a 2-butyne-1,4-diol linker bearing a pyridyl carbamoyl moiety led to in vitro highly potent endothelin receptor antagonists (e.g., **70** and **75**). The propargyl derivative **26** significantly reduced blood pressure in in vivo model studies with hypertensive salt-sensitive Dahl rats.

In 1988, endothelin-1 (ET-1) was isolated from the supernatant of cultured porcine endothelium cell monolayers.[1] The 21 amino acid peptide was characterised as the most potent vasoconstrictor ever reported. As it turned out, there are three different endothelins (ET-1, ET-2, ET-3) in man[2] that act through specific binding to two closely related G-protein coupled receptors, the endothelin receptors ET_A and ET_B. These receptors show different selectivities for the three endothelins. While the ET_A receptor strongly binds ET-1 and ET-2 but shows considerably lower affinity towards ET-3, the ET_B receptor does not discriminate among the three peptides.[3] ET-receptors are found in almost all organs.[3,4] However, the ratio of ET_A and ET_B receptors varies greatly in the various tissues. Pharmacological activation of the ET_A and ET_B receptor leads to a vasoconstriction. On the other hand, activation of the ET_B receptor can also trigger vasodilation, for example, due to coupling to NO release. Apart from these rather immediate effects, activation of the ET-receptors has been reported to induce cell proliferation and to effect hormone production, and therefore has long term effects on angiogenesis, inflammation and cardiac and vascular remodelling.[5] A wealth of renal, cardiac as well as vascular diseases such as renal failure, hypertension, atherosclerosis, acute myocardial infarction, congestive heart failure (CHF), pulmonary arterial hypertension (PAH), or cerebral vasospasm appear to be associated with elevated levels of endothelins, in particular ET-1.[5–7] The endothelin receptor antagonists are therefore thought to represent a novel class of drugs to treat such disorders. Indeed, a first non-peptidic orally active endothelin receptor antagonist, bosentan **1** (Fig. 1), has recently been approved for the treatment of pulmonary arterial hypertension in the USA, Canada, the European Union and Switzerland. A number of other non-peptidic endothelin receptor antagonists are in late clinical trials[8–10] [e.g., atrasentan (Abbott) for prostate cancer (PC); darusentan (Abbott) for CHF, enrasentan (GlaxoSmithKline) for CHF; sitaxsentan (Texas-Biotechnology) for CHF, PAH; T-0201 (Tanabe) for CHF; Y-598 (Yamanouchi) for PC]. In this paper, we disclose some of our results on structures related to bosentan **1**. In particular, we focus on the structure–activity–relationship (SAR) of unsaturated side chains replacing the ethylene glycol residue at position 6 of the core pyrimidine.

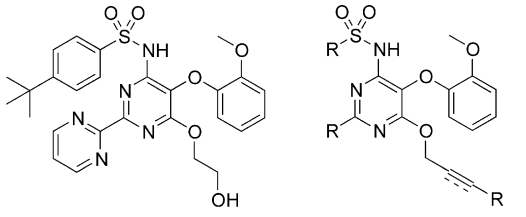

Figure 1.

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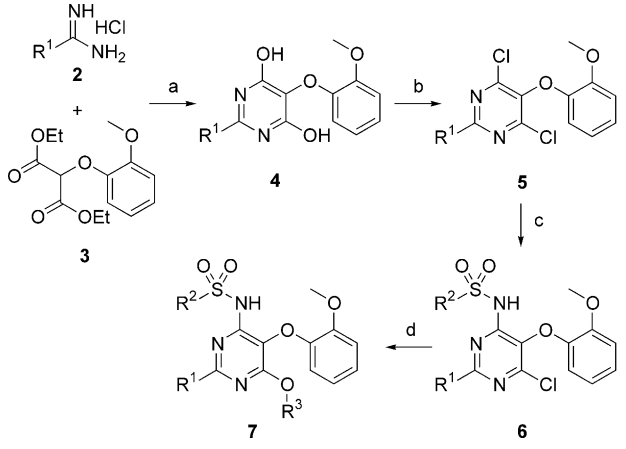
In general, the preparation of the compounds **23**–**78** was achieved in analogy to literature procedures and is outlined in Scheme 1. The necessary key intermediates **5** were prepared via a classical pyrimidine synthesis by condensing the corresponding amidines **2** with malonate **3** followed by chlorination of the obtained 4,6-dihydroxypyrimidines **4**. The 4,6-dichloropyrimidines **5** were then reacted with an excess of the sulfonamide potassium salts to give the 6-chloro-4-sulfonylamino-pyrimidine derivatives **6**. Conversion of the monochlorides **6** to the desired pyrimidines **7** was effected by treating the chloro compound with the corresponding alcoholate at elevated temperatures.

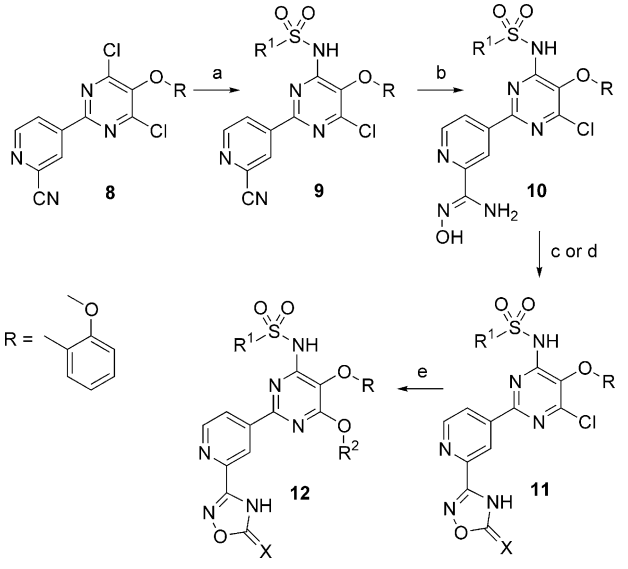
A number of compounds incorporating a five-membered heterocycle at the 2-position of the pyridine at position 2 of the core pyrimidine have been studied (Scheme 2, Table 4). Their preparation starts from the nitrile **8**.[11] Prior to the assembly of the heterocycle, the sulfonamide part was introduced by treating compound **8** with the corresponding sulfonamide potassium salt. The 4H-5-oxo-[1,2,4]oxa-diazole and the 4H-5-thio-[1,2,4]oxadiazole ring was built up in a two-step process.[12] Upon treatment with sodium methylate, the nitrile in compound **9** transformed to the iminoether which was then quenched with hydroxylamine hydrochloride to give the amidoxime **10**. Smooth ring closure to the corresponding oxadiazoles **11** was achieved by reacting **10** with either carbonyl diimidazole or thiocarbonyl diimidazole. Substitution of the chlorine in position 6 of **11** with the appropriate alcoholate completed the synthesis of the tetrasubstituted pyrimidines **12**. On the other hand, treating compound **9** with an excess of hydrazine hydrate furnished the amidrazones **13** which were then efficiently transformed to the tetrazole derivatives **14** under rather mild conditions using sodium nitrite (Scheme 3).[13] As mentioned above the synthesis was completed by the introduction of the unsaturated side chain.



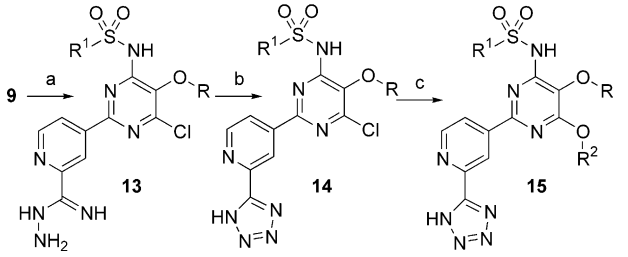
Scheme 1. General reaction pathway for the preparation of 4-sulfonylamino pyrimidines. Reagents and conditions: (a) 3 equiv NaOMe, MeOH, rt, 18 h, 80–100%; (b) $POCl_3$, $PhNMe_2$, 120 °C, 2–18 h, 50–90%; (c) R^2SO_2NHK, DMSO or DMF, rt to 60 °C, 18–72 h, 50–95%; (d) R^3ONa, R^3OH, neat or in DME, DMF or DMPU, 60–120 °C, 4–48 h, 30–95%.

Additionally, compounds incorporating a 2-hydroxymethyl pyridine substituent at position 2 of the core pyrimidine have been prepared (Scheme 4). The pivotal 2-methyl-pyridine substituted 4,6-dichloropyrimidine **17** was prepared starting from 2-methyl-4-cyanopyridine **16**.[14] Compound **17** was then transformed to its pyridine *N*-oxide **18** by treatment with peracetic acid. The next steps involved the introduction of the sulfonamide moiety and the unsaturated side chain. The *N*-oxide **19** smoothly rearranged in refluxing acetic anhydride[14] to the corresponding acetoxymethyl pyridine derivative which upon hydrolysis yielded the desired hydroxymethyl pyridine **20**.

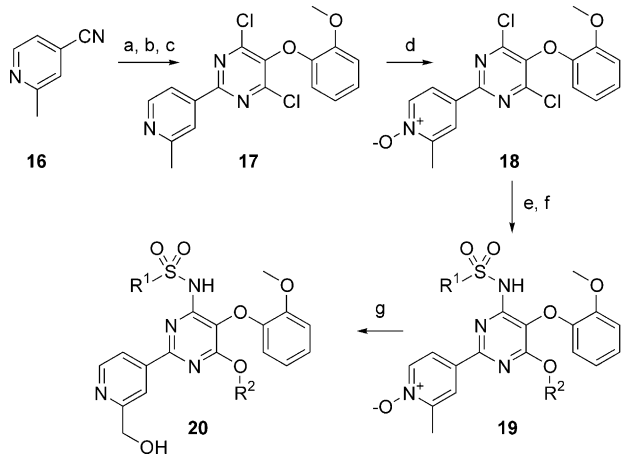
The free alcohol functionality of the butynediol derivatives **21** was further reacted with an isocyanate in the presence of DMAP to furnish the corresponding carbamates **22** in good yields (Scheme 5). In case R^3 represents a pyridine or pyrazine, the necessary isocyanate was generated in situ prior to the addition of the alcohol **21** from the corresponding carboxylic acid azide[15,16] in refluxing chloroform.



Scheme 2. Reagents and conditions: (a) 1.5 equiv R^1SO_2NHK, 1 equiv Hünig's base, DMSO, rt 18–48 h, 72–92%; (b) (i) 1.3 equiv NaOMe, MeOH, 45 °C 24 h; (ii) 1.3 equiv $NH_2OH{\cdot}HCl$, 45 °C 15 min, 77–93%; (c) (X=O) 1.1 equiv Im_2CO, 4 equiv DBU or DBN, MeCN, rt 48–72 h, 67–78%; (d) (X=S) 1.1 equiv Im_2CS, 4 equiv DBU or DBN, MeCN, rt 48–72 h, 62–78%; (e) 10–20 equiv NaH, 40–80 equiv R^2OH, THF, DMF, 60–80 °C 16–24 h, 57–74%.



Scheme 3. (R, R^1 as in Scheme 2) Reagents and conditions: (a) 4 equiv NH_2NH_2HCl or $NH_2NH_2H_2O$, DMF, rt 24–72 h, 69–99%; (b) 1.83 equiv $NaNO_2$, concd HCl/H_2O, DMF, rt 2 h, 82–95%; (c) 10 eq. NaH, 40–60 equiv R^2OH, THF, DMF, 55–80 °C 3–18 h, 52–64%.

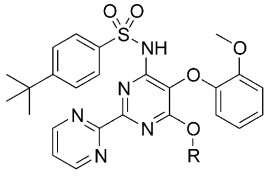


Scheme 4. Reagents and conditions: (a) 0.1 equiv NaOMe, 1.1 equiv NH_4Cl, MeOH, rt 24 h, 60–72%; (b) 3 equiv NaOMe, 1.1 equiv **3**, MeOH, rt 16 h, 71%; (c) $POCl_3$, 120–145 °C 12–16 h, 45–56%; (d) 3 equiv CH_3COOOH, MeCN, 95 °C 48 h, 68–95%; (e) 2.2 equiv R^1SO_2NHK, DMSO, rt 24 h, 60–95%; (f) 10 equiv NaH, 40–60 equiv R^2OH, DMF, THF, 70 °C 18 h, 78–87%; (g) (i) Ac_2O, 140 °C 45–90 min; (ii) 0.2 N NaOH, THF, MeOH, H_2O, 0 °C 1 h, 45–62%.

The receptor affinities (IC_{50} values) were determined in radio-ligand competition binding studies on membranes of CHO cells expressing the human recombinant ET_A or ET_B receptor using ^{125}I-labelled ET-1 as described earlier.[17] The functional inhibitory potency on ET_A receptors (pA_2 values) of the compounds was assessed by their inhibition of the contraction induced by ET-1 on rat aortic rings.[18] All compounds behaved as competitive antagonists.

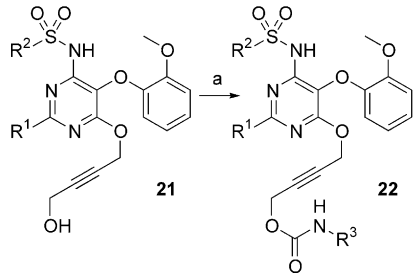
First, a number of olefinic and propargylic alcohols have been introduced to position 6 of the core pyrimidine. As shown in Table 1, the side chains incorporating a double bond give compounds (**23**–**25**) inferior in potency to bosentan **1**, although the in vitro potency on the ET_A receptor gradually improves with increasing chain length. The corresponding compounds with a

Table 1. Inhibition of [^{125}I]-ET-1 binding to membranes of CHO-cells expressing the ET_A or ET_B receptor



Compd	R	IC_{50} ET_A (nM)	IC_{50} ET_B (nM)
Bosentan **1**	$-CH_2CH_2OH$	40	280
23	$-CH_2CH{=}CH_2$	373	2085
24	$-CH_2CH{=}CH{-}CH_3$	239	3330
25	$-CH_2CH{=}CH{-}CH_2{-}CH_3$	165	2970
26	$-CH_2{-}C{\equiv}CH$	97	1190
27	$-CH_2{-}C{\equiv}C{-}CH_3$	85	3169
28	$-CH_2{-}C{\equiv}C{-}CH_2{-}CH_3$	59	2280
29	$-CH_2{-}C{\equiv}C{-}CH_2{-}OH$	51	832
30	$-CH_2{-}C{\equiv}C{-}CH_2{-}OCH_3$	13	1140
31	$-CH_2{-}C{\equiv}C{-}CH_2{-}O{-}C_6H_5$	139	973
32	$-CH_2{-}C{\equiv}C{-}CH_2{-}O{-}CH_2{-}C_6H_5$	1280	199

Values represent results of single experiment.

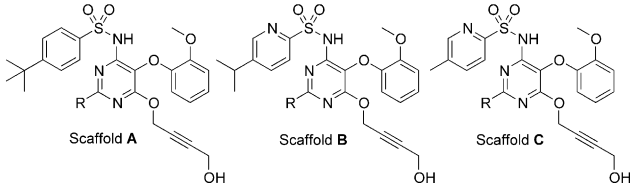


Scheme 5. Reagents and conditions: (a) 1–2-equiv R^3NCO, 0.5–1 equiv DMAP, $CHCl_3$, 75 °C 18 h, 43–89%; or (i) 2.5–4 equiv R^3CON_3, 1 equiv DMAP, $CHCl_3$, 75 °C 1–2 h; (ii) addition of **21**, 75 °C 18 h, 58–76%.

triple bond (**26**–**29**) are about four times more potent when compared to the allylic derivatives. Compound **29** incorporating the 2-butyne-1,4-diol is about as potent as bosentan **1**. Interestingly, masking the terminal alcohol functionality in **29** with a methyl group (**30**) improves the compound's affinity towards the ET_A receptor. The phenyl ether **31** and in particular the benzyl ether **32**, however, show poorer IC_{50}-values for the ET_A receptor blockade. It is noteworthy that the benzylether side chain in **32** leads to a compound preferentially blocking the ET_B receptor.

The series incorporating a propargyl or a butyne-1,4-diol side chain have been investigated in more detail. While we have been evaluating a number of substitutents at position 2 of the core pyrimidine, we focused our studies on the 4-*tert*-butylbenzene, the 5-isopropyl-2-pyridine and the 5-methyl-2-pyridine sulfonamides as these have been found to furnish the most promising compounds.[19–21] The examples in Tables 2 and 3 illustrate the effect of the sulfonamide and the 2-substituent on the SAR of the tetrasubstituted pyrimidines.

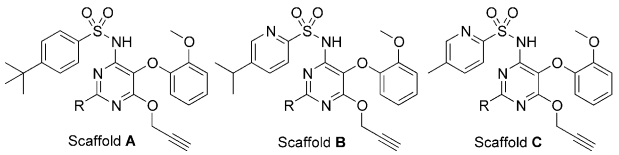
Table 2. Inhibition of [^{125}I]-ET-1 binding to membranes of CHO cells expressing the ET_A or ET_B receptor

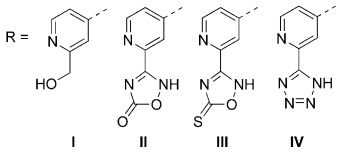


Compd	Scaffold	R	IC_{50} ET_A (nM)	IC_{50} ET_B (nM)
29	A	2-Pyrimidyl	51	832
33	A	4-Pyridyl	125	44
34	A	4-Morpholinyl	155	50
35	A	Hydrogen	561	744
36	B	2-Pyrimidyl	53	2030
37	B	4-Pyridyl	26	77
38	B	4-Morpholinyl	16	49
39	B	Hydrogen	166	183
40	C	2-Pyrimidyl	339	> 10,000
41	C	4-Pyridyl	22	1520
42	C	4-Morpholinyl	18	612
43	C	Methyl	452	2880

Values represent results of single experiment.

Table 3. Inhibition of [^{125}I]-ET-1 binding to membranes of CHO cells expressing the ET_A or ET_B receptor





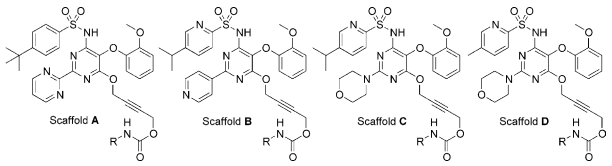
Compd	Scaffold	R	IC_{50} ET_A (nM)	IC_{50} ET_B (nM)
26	A	2-Pyrimidyl	97	1190
44	A	2-Pyrazinyl	186	903
45	A	4-Pyridyl	176	295
46	A	I	38	100
47	A	II	66	238
48	A	III	84	258
49	B	2-Pyrimidyl	96	1950
50	B	2-Pyrazinyl	339	2620
51	B	4-Pyridyl	125	823
52	B	4-Morpholinyl	121	746
53	B	I	24	205
54	B	II	22	294
55	B	III	27	366
56	B	IV	23	221
57	C	2-Pyrimidyl	339	>10000
58	C	4-Pyridyl	94	4580
59	C	I	11	>1000
60	C	II	13	2500
61	C	III	12	1670
62	C	IV	5	1030

Values represent results of single experiment.

In the butyne-1,4-diol series, the combination of R representing a 4-pyridyl or a 4-morpholine residue with a pyridine sulfonamide gives the most potent compounds (**37**, **38**, **41**, **42**). This finding, however, does not fully translate to the propargyl series (Table 3). Here, the above combination furnishes compounds with somewhat inferior potency than the 2-pyrimid-2-yl-pyrimidine derivatives **26**, **49** and **57**. The most potent examples in the propargyl series are all characterised by a 2-pyridin-4-yl-pyrimidine scaffold where the pyridine bears a polar group in position 2. In fact, the tetrazole at this position yields as good results as the bioisosteric 4H-[1,2,4]oxadiazoles (**56** vs **54**, **55**; **62** vs **60**, **61**). Surprisingly, in this study the much smaller hydroxymethylene group in **46**, **53** and **59** appears to be an equipotent replacement for such polar five-membered rings.

Interestingly, in both the propargyl as well as the butyne-1,4-diol series the compounds incorporating the 5-methyl-2-pyridine sulfonamide are as potent inhibitors of ET_A but about ten times less potent on ET_B as the corresponding 5-isopropyl-2-pyridine sulfonamide derivatives. Compounds **40** and **57**, both basing on the 2-pyrimid-2-yl-pyrimidine scaffold appear to be the only exceptions to this rule.

Table 4. Inhibition of [^{125}I]-ET-1 binding to membranes of CHO-cells expressing the ET_A or ET_B receptor



Compd	Scaffold	R	IC_{50} ET_A (nM)	IC_{50} ET_B (nM)	pA_2
63	A	2-Pyridyl	293	1060	
64	A	2-Pyrazinyl	204	1400	
65	B	*n*-Butyl	157	18	6.37
66	B	Phenyl	35	32	6.25
67	B	2-Pyridyl	7	123	7.57
68	B	2-Pyrazinyl	14	236	7.70
69	C	Phenyl	13	28	6.68
70	C	2-Pyridyl	1	42	7.70
71	C	2-Pyrazinyl	0.4	13	7.58
72	D	*n*-Butyl	196	207	
73	D	Cyclohexyl	753	603	
74	D	Phenyl	18	589	6.64
75	D	2-Pyridyl	1	197	7.56
76	D	3-Pyridyl	21	920	6.30
77	D	4-Pyridyl	12	656	7.29
78	D	2-Pyrazinyl	2	241	8.11

Values represent results of single experiment. pA_2-values on rat aortic rings ($n \geq 2$).

Note also the trend of selectivity for the ET_B receptor observed with the derivatives **33** and **34** (Table 2). However, based on these results no rules to achieve ET_B receptor selectivity can be postulated.

When the butyne-diol linker was further derivatised to form a carbamate, highly potent compounds could be identified. The SAR of such carbamates is illustrated in Table 4. While the *n*-butyl and cyclohexyl carbamates **65**, **72**, and **73** exhibit inferior binding affinities when compared to the corresponding compounds with the free alcohol moiety (**37**, **42**), the phenyl carbamates **69** and **74** are about as potent as their corresponding free alcohols **38** and **42**, respectively. The affinity towards the ET_A receptor could be improved further when pyridine carbamates were employed. However, the position of the nitrogen appears to be critical. While the 3-pyridine and 4-pyridine carbamates show moderate potency, the 2-pyridine derivatives clearly give the best results (e.g., **75**–**77**). The 2-pyrazine carbamate furnishes compounds with potencies comparable to those of the 2-pyridine derivatives (e.g., **78**). The high affinity of compounds **70**, **75**, and **78** in the binding assay is also reflected in good pA_2-values on rat aortic rings. Surprisingly, the 2-pyridine as well as the 2-pyrazine carbamate yield rather poor ET-receptor antagonists in combination with the 2-pyrimidin-2-yl-pyrimidine scaffold **A**.

A number of in vitro highly potent compounds have been screened for their in vivo activity in the rat. Hence, 30 mg/kg of the compound was administered orally to hypertensive Dahl salt-sensitive rats equipped with a telemetric system recording blood pressure and heart

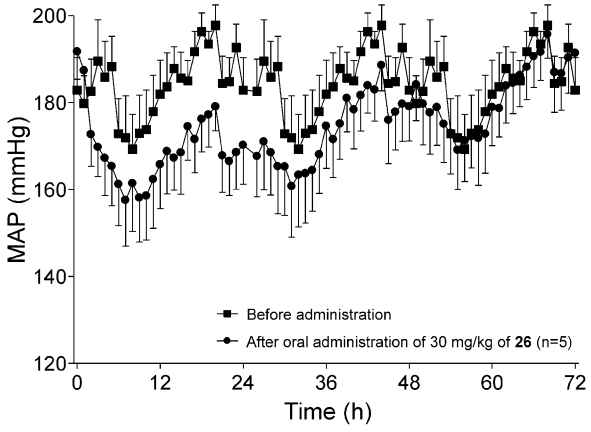


Figure 2. Mean arterial blood pressure recordings (MAP) before and after administration of 30 mg/kg of the propargyl derivative **26** to hypertensive Dahl salt-sensitive rats ($n = 5$). The heart rate remained unaffected (data not shown).

Table 5. Area between curves (ABC) calculated after oral administration of 30 mg/kg of the compounds to hypertensive Dahl salt-sensitive rats ($n = 5$) equipped with a telemetric system recording blood pressure and heart rate[a]

Compd	IC_{50} ET_A (nM)	IC_{50} ET_B (nM)	pA_2	ABC
Bosentan **1**	40	280	7.14	340
26	97	1190	6.97	661
27	85	3169	7.15	508
29	51	832	6.83	92
30	13	1140		332
68	14	236	7.70	25
70	1	42	7.70	29
78	2	241	8.11	26

[a]A compound with an ABC < 100 is considered to be inactive at the dose tested. The heart rate remained unaffected in all experiments. To enhance reading the IC_{50}- as well as the pA_2-values are given once more.

rate.[22] From the blood pressure recordings, the area between the curve (ABC) before and the one after treatment is calculated to assess the compound's efficacy. Bosentan **1** reaches an ABC of 340 at a dose of 30 mg/kg. At this dose, none of the three carbamates **68**, **70**, and **78** shows a significant effect on blood pressure. On the other hand, the propargyl compound **26** (Fig. 2, Table 5) as well as the 2-butyn-1-ol **27** (Table 5) significantly reduce blood pressure despite being considerably less potent in vitro when compared to the three carbamates **68**, **70**, and **78**. The in vivo activity is lost with the hydroxy compound **29**. However, the in vivo activity is restored when the free alcohol in **29** is protected as its methyl ether (**30**).

In conclusion, sulfonylamido pyrimidine derivatives incorporating a propargyl side chain in position 6 and a 4-pyridine substituent in position 2 which itself is substituted with a polar group in position 2, are potent antagonists of the ET_A receptor. In addition, the propargyl derivative **26** has been shown to reduce blood pressure in hypertensive Dahl salt-sensitive rats. Pyridine and pyrazine carbamoyl derivatives of compounds incorporating a 2-butyne-1,4-diol, such as **70**, **71**, **75**, and **78**, show high affinity towards the endothelin receptors and high functional potency in vitro. They are about as potent as their corresponding ethylene glycol analogues disclosed previously.[19] Further studies shall aim at improving the carbamate's in vivo profile.

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