Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 517–520

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Biphenylsulfonamide Endothelin Receptor Antagonists. Part 3: Structure–Activity Relationship of 4′-Heterocyclic Biphenylsulfonamides

Natesan Murugesan,* Zhengxiang Gu, Philip D. Stein, Steven Spergel, Sharon Bisaha, Eddie C.-K. Liu, Rongan Zhang, Maria L. Webb, Suzanne Moreland and Joel C. Barrish

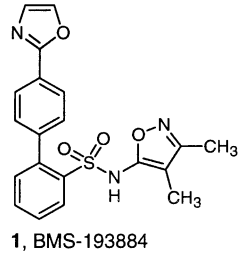
Department of Chemistry, Cardiovascular Agents, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543-5400, USA

Received 13 September 2001; accepted 19 November 2001

Abstract—A number of 4′-heterocyclic biphenylsulfonamide derivatives, formally derived from BMS-193884 (**1**) by replacing the oxazole ring with other heterocyclic rings, are potent and selective endothelin A (ET_A) receptor antagonists. Among the analogues examined, the pyrimidine derivative **18** is the most potent ($K_i = 0.9$ nM) and selective for the ET_A receptor, approximately equivalent to **1**.

The endothelins (ET-1, ET-2, and ET-3) constitute a family of highly potent endogenous vasoconstrictor agents with a wide range of additional biological activities.[1,2] The actions of these 21-amino acid peptides are mediated through two membrane associated, G-protein coupled membrane receptors, termed ET_A and ET_B.[3,4] The ET_A receptor, which is selective for ET-1, is expressed predominately in vascular smooth muscle cells where it mediates vasoconstrictive and proliferative responses. The isopeptide nonselective ET_B receptor mediates both vasoconstriction or vasodilation depending on the tissue type. Several ET_A and ET_B selective as well as nonselective receptor antagonists with a wide range of therapeutic potential have been described in the literature.[5,6] A number of these antagonists are currently being investigated to determine the role of endothelin and its receptors in mediating various pathophysiologies.[7–9]

In recent articles, our group has described a series of *N*-isoxazolyl biphenylsulfonamides, exemplified by the clinical candidate BMS-193884 (**1**), as potent and highly selective ET_A antagonists (Fig. 1).[10,11] The structure–activity relationship (SAR) studies on these analogues have shown that the oxazole moiety present in BMS-193884 was in large part responsible for its ET_A selectivity and potency.[11] The SARs have also indicated that substitution on the oxazole ring was not tolerated and generally led to loss of activity. In order to further investigate the role of the oxazole group, we have examined its replacement by various other heterocyclic rings. We report herein the synthesis and SAR of a series of 4′-heterocyclic biphenylsulfonamides as potent and selective ET_A antagonists.

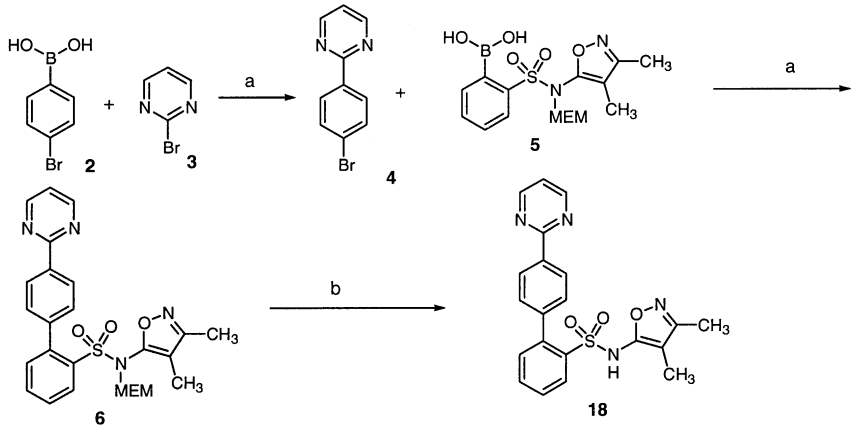


1, BMS-193884
ET_A K_i = 1.4 nM

Figure 1. Structure of BMS-193884.

*Corresponding author. Fax: +1-609-818-3450; e-mail: natesan.murugesan@bms.com

0960-894X/02/$ - see front matter
PII: S0960-894X(01)00791-0

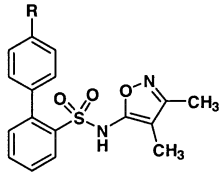


Scheme 1. Synthesis of compound **18**: (a) $(Ph_3P)_4Pd$, aq Na_2CO_3, EtOH/toluene; (b) 6 N aq HCl/EtOH.

Chemistry

The general synthesis of biphenylsulfonamides bearing a heterocyclic ring at the 4′-position is exemplified for the preparation of **18** in Scheme 1.[11] Suzuki-coupling of the 4-bromophenyl boronic acid **2** with 2-bromopyrimidine **3** afforded the 2-(4-bromophenyl)pyrimidine derivative **4**. Subsequent Suzuki-coupling of this material with our previously reported boronic acid derivative **5**[11] using palladium tetrakistriphenylphosphine as the catalyst gave the biphenylsulfonamide **6**. Removal of the MEM group was achieved using 6 N aqueous hydrochloric acid in refluxing ethanol to afford **18**. Compounds **7**–**15**, **17** and **19**–**22** were prepared by an analogous sequence to that shown in Scheme 1. The corresponding 4-bromophenyl heterocyclic intermediates

Table 1. Substitution of the 4′-position of biphenylsulfonamides with a five-membered ring heterocycle



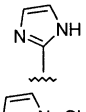
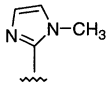
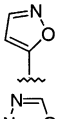
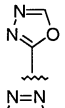
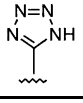
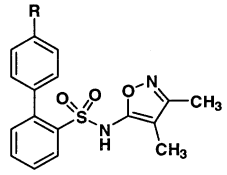
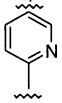
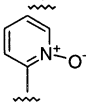
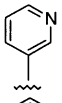
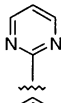
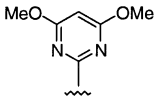
Compd	R	ET_A K_i (nM)	ET_A K_B (nM)	ET_B K_i (nM)	A/B selectivity ratio
1		1.4	19	18,700	13,350
7		5.6	66	52,000	9300
8		44	1600	150,000	3400
9		19	1400	120,000	6300
10		6.7	58	9400	1400
11		270	270	39,000	144
12		4	130	75,000	18,750
13		3800	ND	>200,000	52

Table 2. Substitution of the 4′-position of biphenylsulfonamides with a six-membered ring heterocycle



Compd	R	ET_A K_i (nM)	ET_A K_B (nM)	ET_B K_i (nM)	A/B selectivity ratio
14		38	130	20,000	526
15		2.3	99	6300	2739
16		37	610[a]	30,800	832
17		3.3	180	20,000	6060
18		0.9	21	16,000	17,800
19		6.2	34	22,000	3550
20		25	700[a]	130,000	5200
21		300	ND	170,000	566
22		220	ND	48,000	218

[a]Standard deviations are less than 10% of the mean values for all of the assays; ND, not determined. K_B [a] = K_B apparent.

used were prepared using methods described previously.[12] Compound **16** was prepared from **15** by oxidation using *m*-chloroperbenzoic acid.

Results and Discussion

The endothelin receptor binding assays were performed using CHO cells stably expressing human ET_A or ET_B receptors as previously described.[11] ET_A functional assays (inhibition of ET-1 induced contractions in rabbit carotid artery rings) were performed as previously described.[11] K_B values were obtained from experiments in which at least three different concentrations of test compound were studied. Apparent K_B values were calculated when only one antagonist concentration was used. The results are summarized in Tables 1 and 2 and, for comparative purposes, the binding affinities for **1** are also included.

The present study commenced with the replacement of the oxazole moiety in **1** with related five-membered ring heterocycles at the 4′-position of the pendant aromatic ring (Table 1). Analogues incorporating either a thiazole (**7**) or an oxadiazole (**12**) ring at this position were among the most potent five-membered heterocycles examined in this study. Both compounds showed no significant differences in their ET_A binding affinity compared to **1** while the selectivity was maintained. Analogues incorporating other alternate five-membered ring heterocycles such as imidazole (**8**), *N*-methyl imidazole (**9**), pyrazole (**10**) or an isoxazole (**11**) were all less potent compared to **1** at the ET_A receptor. We previously showed that an acidic group is not tolerated at the 4′-position of the biphenylsulfonamides.[11] The tetrazole analogue **13** is significantly less active, confirming our previous results.

Replacement of the oxazole in **1** with a phenyl ring resulted in the terphenyl derivative **14** (Table 2). This compound was more than 30-fold less active for the ET_A receptor compared to **1** suggesting a putative hydrogen bond between the heteroatoms of the 4′-heterocycle and the receptor. The pyridyl analogues **15** and

17 were equipotent to **1** in their ET_A binding affinity indicating that the hydrogen bond between the heterocycle and the receptor may be accessed from either the 2- or 3-position of the heterocyclic ring. However, both compounds were less potent than **1** in their ET_A functional activity. Interestingly, the pyridine *N*-oxide derivative **16** was 20-fold less potent than the parent pyridine analogue **15**. The 2-pyrimidine analogue **18** exhibited the highest ET_A activity among the compounds prepared in this study. It showed subnanomolar ET_A activity (ET_A $K_i = 0.9$ nM; ET_B $K_i = 16{,}000$ nM) and was equipotent to **1** in its potency as well as selectivity. This compound was also equipotent to **1** in the ET_A functional assay (ET_A $K_B = 21$ nM). The pyridazine derivative (**19**), the 3-pyrimidine (**20**) and the 4-pyrimidine (**21**) analogues each display reduced binding affinity at ET_A relative to **1**. The 3,5-dimethoxy-2-pyrimidine derivative **22** was more than 200-fold less potent than the parent pyrimidine analogue **18** suggesting that substitution of the pyrimidine ring is not tolerated. This result is in agreement with our previous findings in the 4′-oxazole biphenylsulfonamide series.

In summary, a number of 4′-heterocyclic biphenylsulfonamide derivatives incorporating a five- or six-membered heterocycles were evaluated for their binding affinity to the ET_A and ET_B receptors. Several of these, such as oxadiazoles (**12**), 2- and 3-pyridyl (**15** and **17**) and pyrimidine (**18**), were found be effective replacements for the oxazole ring in **1**. Among the analogues examined, the pyrimidine analogue **18** was found be a subnanomolar ET_A antagonist and was equipotent to **1** in its potency, selectivity and functional activity.

References and Notes

1. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.
2. Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Masaki, T. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2863.
3. Rubanyi, G. M.; Polokoff, M. A. *Pharmacol. Rev.* **1994**, *46*, 325.
4. Ohlstein, E. H.; Elliott, J. D.; Feuerstein, G. Z.; Ruffolo, R. R., Jr. *Med. Res. Rev.* **1996**, *16*, 365.
5. Webb, M. L.; Meek, T. D. *Med. Res. Rev.* **1997**, *17*, 17.
6. Brunner, H. R. *Am. J. Hypertens.* **1998**, *11*, 103S.
7. Pousset, F.; Isnard, R.; Lecha, P.; Katlotka, H.; Carayon, A.; Maistre, G.; Escolano, S.; Thomas, D.; Komajda, M. *Eur. Heart J.* **1997**, *18*, 254.
8. Love, M. P.; McMurray, J. J. V. *Basic Res. Cardiol.* **1996**, *91*, 21.
9. Nguyen, B. N. T.; Johnson, J. A. *Pharmacotherapy* **1998**, *18*, 706.
10. Murugesan, N.; Gu, Z.; Stein, P. D.; Bisaha, S.; Spergel, S.; Girotra, R.; Lee, V. G.; Lloyd, J.; Misra, R. N.; Schmidt, J.; Mathur, A.; Stratton, L.; Kelly, Y. F.; Bird, E.; Waldron, T.; Liu, E. C. K.; Zhang, R.; Lee, H.; Serafino, R.; Abboa-Offei, B.; Mathers, P.; Giancarli, M.; Seymour, A. A.; Webb, M. L.; Moreland, S.; Barrish, J. C.; Hunt, J. T. *J. Med. Chem.* **1998**, *41*, 5198.
11. Murugesan, N.; Gu, Z.; Stein, P. D.; Bisaha, S.; Spergel, S.; Mathur, A.; Leith, L.; Liu, E. C. K.; Zhang, R.; Bird, E.; Waldron, T.; Marino, A.; Morrison, R. A.; Webb, M. L.; Moreland, S.; Barrish, J. C. *J. Med. Chem.* **2000**, *43*, 3111.
12. (a) Murugesan, N. US Patent 5612359, 1997; *Chem. Abstr.* **1997**, *126*, 293349. (b) Murugesan, N.; Barrish, J. C.; Stein, P. D. US Patent 5780473, 1998; *Chem. Abstr.* **1998**, *129*, 136175.