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Discovery of 4′-[(Imidazol-1-yl)methyl]biphenyl-2-sulfonamides as Dual Endothelin/Angiotensin II Receptor Antagonists

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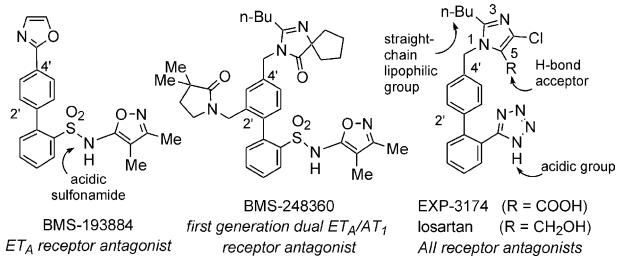
Abstract—A series of 4′-[(imidazol-1-yl)methyl]biphenylsulfonamides has potent antagonist activity against both angiotensin II AT_1 and endothelin ET_A receptors. Such dual-acting antagonists could have utility in the treatment of hypertension, heart failure, and other cardiovascular diseases in a broad patient population. Certain compounds in the present series are orally active in a rat model of angiotensin II-mediated hypertension.

Angiotensin II subtype 1 (AT_1) receptor antagonists are clinically useful for the management of hypertension and heart failure,[1] while endothelin subtype A (ET_A) receptor antagonists show promise for treatment of similar indications.[2] We have been engaged in a program to develop single agents with the ability to antagonize both AT_1 and ET_A receptors,[3] and our efforts resulted in the discovery of BMS-248360, a potent (human ET_A $K_i = 2$ nM; rat AT_1 $K_i = 6$ nM) dual-action receptor antagonist.[4] BMS-248360 bears structural features of both irbesartan, a marketed AT_1 receptor antagonist, and BMS-193884, an ET_A receptor antagonist discovered at Bristol-Myers Squibb (BMS).[5] We sought to expand on this work by merging features of various other reported AT_1 receptor antagonists with those of BMS-193884. In this communication, we report that potent dual antagonist activity has been found in an imidazole series related to the AT_1 receptor antagonist losartan. Furthermore, certain compounds in this new class possess promising oral efficacy in a rat model of angiotensin II-mediated hypertension.



With few exceptions, angiotensin II receptor antagonists are structurally similar to Dupont's biphenyl-2-tetrazole series, exemplified by EXP-3174.[6] These compounds are generally selective for the AT_1 receptor subtype over the AT_2 subtype. Many biphenyl 4′ substituents are known, and certain structural features are required for good AT_1 receptor binding affinity.[7] Notable is the requirement for a hydrogen-bond acceptor in the space occupied by the imidazole C-5 substituent in EXP-3174. In contrast, endothelin receptor antagonism has been found in a wide range of chemotypes,[8] including a series of biphenyl-2-sulfonamides discovered at BMS.[5,9] These compounds, exemplified by BMS-193884, are ET_A receptor subtype-selective and superficially can be seen to resemble AT_1 receptor antagonists. An acidic heteroaryl-substituted sulfonamide is required for ET_A receptor

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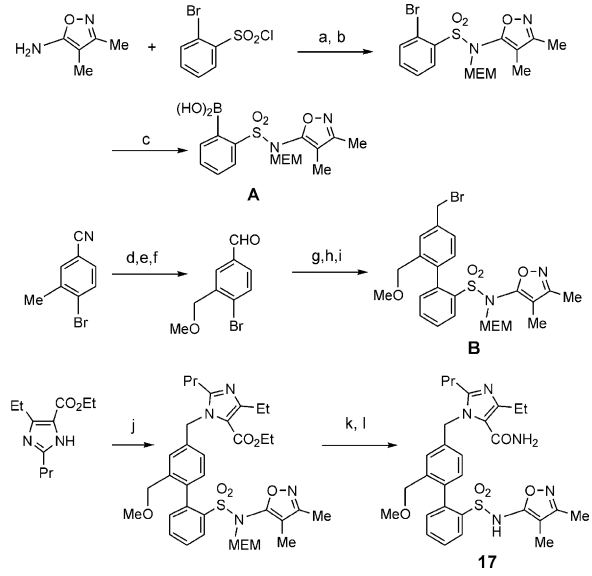
antagonism, and particularly good activity is found with a 3,4-dimethyl-5-isoxazolyl pharmacophore.

Combining the AT_1 and ET_A receptor antagonist chemotypes requires four significant structural compromises. First, an 'AII group' at the 4′ position must be tolerated by the ET_A receptor. Second, the AT_1 receptor must tolerate the specific heteroaryl sulfonamide required for ET_A antagonism. Third, we have found that ET_A antagonism is enhanced by certain biphenyl 2′ substituents, yet these substituents may interfere with AT_1 antagonism. Finally, the resultant dual antagonist must possess oral bioavailability, which is difficult to achieve in large molecules (i.e., MW > 500). Since the biphenyl scaffold, the heteroaryl sulfonamide, and a 4′ 'AII group' were all required elements, we sought to find the smallest effective 4′ and 2′ substituents. The (imidazol-1-yl)methyl 4′ substituent present in losartan and its active metabolite EXP-3174 is one of the smallest high-potency 'AII groups' reported to date. Although the anionic carboxylate found in EXP-3174 would not be conducive to ET_A receptor antagonism[5] or to achievement of pharmacokinetic goals, replacement of this group with neutral hydrogen bond acceptors was precedented.[10]

Target compounds were prepared by variations of the synthetic route described for compound **17** (Scheme 1). At a minimum, compounds were characterized by ^1H NMR and LC/MS analysis. The preparation of boronic acid intermediate **A** has been described.[11] All imidazole precursors were prepared according to literature procedures.[6,12] The alkylation of imidazoles with intermediate **B** or analogues generally gave a mixture of N-1 and N-3 regioisomeric alkylation products, which were separated by silica gel chromatography. Structural assignments for these products were determined by ^1H NMR and were based on literature precedents.[10b,c]



Scheme 1. Reagents and conditions: (a) pyridine, DMAP, 55 °C, 16 h, 96%; (b) MEMCl, K_2CO_3, DMF, 0 °C to rt, 14 h, 92%; (c) (i) *n*-BuLi, THF, −90 °C, 15 min, (ii) $B(OMe)_3$, −90 °C to 0 °C, 1 h, (iii) HCl (aq), rt, 1 h, 85%; (d) NBS, CCl_4, $(BzO)_2$, reflux, 8 h, 58%; (e) NaOMe, DMF, rt, 3 h, 82%; (f) DIBAL-H, THF, 0 °C, 2 h, 88%; (g) toluene/EtOH (2:1), Na_2CO_3 (aq), compound A, $Pd(Ph_3P)_4$, 85 °C, 2 h, 83%; (h) $NaBH_4$, MeOH, 0 °C, 1 h, 95%; (i) CBr_4, Ph_3P, DMF, 0 °C, 4 h, 72%; (j) K_2CO_3, DMF, compound B, rt, 24 h, 39%; (k) (i) HCl, dioxane/EtOH (2:1), 60 °C, 8 h, (ii) KOH, H_2O/MeOH (1:2), 65 °C, 30 h, 95% crude (l) CDI, THF, rt, 2 h, then NH_3 (aq), rt, 10 min, 38%.

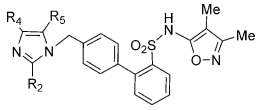
Our strategy for the optimization of binding affinity[13] was as follows: First, optimize for AT_1 receptor antagonism through choice of imidazole substituents with a 2′-unsubstituted biphenyl. Second, improve ET_A receptor antagonism by introducing a 2′ substituent, which we hoped could be done without compromising AT_1 receptor affinity.

Since various researchers have successfully substituted amides[10] for the carboxylate of EXP-3174, the 5-carboxamides became our starting point for imidazole substituent SAR. The primary carboxamide analogue **1** (Table 1), which possesses the identical 2-butyl and 4-chloro substituents found in losartan, showed moderate activity at the AT_1 receptor, but its ET_A receptor binding affinity was poor. Adjusting the imidazole C-2 substituent to propyl and the C-4 substituent to ethyl resulted in compound **3**, which possessed AT_1 receptor binding affinity within the range we sought, along with moderate ET_A receptor binding affinity.

An *N*,*N*-dimethylamide (**4**) showed diminished AT_1 receptor binding, but the *N*-methylamide (**5**) regained much of the AT_1 receptor affinity found in **3**, while also achieving the best ET_A receptor binding of any compound in the 2′-hydrogen series. Replacement of the 5-carboxamide group by a methyl ester (**6** vs **2**) or an acetyl group (**7** vs **2**) did not improve activity. Since our aim was to keep molecular weight (volume) to a minimum, we concluded that the imidazole substitution patterns in **3** and **5** were optimal or close to optimal for monocyclic imidazoles.

We also investigated fusion of the imidazole C-4 and C-5 substituents using the (oxo)cycloheptimidazole group reported by workers at Kotobuki Seiyaku.[12d] The resultant compound (**8**, Table 1) had an AT_1 receptor binding affinity of 8 nM, approximately as good as the best monocyclic compounds shown in Table 1. However, ET_A receptor binding was somewhat poorer.

Table 1. Variation of imidazole substituents[a]



Compd	R_2	R_4	R_5	AT_1 K_i (nM)	ET_A K_i (nM)
1	Bu	Cl	$CONH_2$	24 (4)	415 (170)
2	Pr	Cl	$CONH_2$	21 (1)	40 (30)
3	Pr	Et	$CONH_2$	7 (2)	55 (12)
4	Pr	Et	$CONMe_2$	51 (10)	55 (25)
5	Pr	Et	CONHMe	13 (4)	16 (6)
6	Pr	Cl	CO_2Me	23 (10)	460 (130)
7	Pr	Cl	COMe	40 (1)	40 (20)
8	Pr	$CH_2CH_2CH_2CH_2C(=O)$		8 (4)	105 (15)

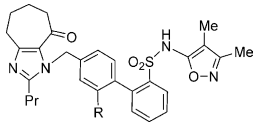
[a]Standard deviations are given in parentheses.

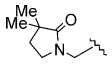
SAR at the biphenyl 2′ position was investigated initially in the fused imidazole series (Table 2). In the work that led to discovery of BMS-248360, a pyrrolidine-based 2′ substituent appeared to be optimal, providing potent AT_1 and ET_A receptor affinity. The substituent had little effect on AT_1 receptor affinity, but it enhanced ET_A receptor affinity in BMS-248360 by approximately 40-fold.[4] In the present fused imidazole series, addition of this substituent (**9**, Table 2) did indeed dramatically improve ET_A receptor binding over the 2′ unsubstituted analogue **8**. However, it also severely diminished AT_1 receptor binding.

This difference in behavior from BMS-248360 could be related to the difference in the placement of the hydrogen-bond acceptor groups on the two 4′ heterocycles. In the imidazolinone BMS-248360, the carbonyl oxygen is directly attached to the 5-membered ring, whereas in the imidazole series (both monocyclic and fused) there is an intervening carbon atom. This difference probably translates into a subtle difference in the optimal biphenyl torsion angle for AT_1 receptor-binding. A large 2′ substituent might interact with the AT_1 receptor in such a way as to force the torsion angle out of the optimal range for the imidazole but not for the imidazolinone. Alternately, a large 2′ substituent might have a direct steric interaction with the 4′ substituent, probably via the 4′ heterocycle's C-2 alkyl group. If so, then this interaction is tolerated with the imidazolinone but not with the imidazole.

Fortunately, smaller 2′ substituents were better tolerated by the AT_1 receptor (Table 2). The best substituent in the fused imidazole series appeared to be methyl (**10**), though other small lipophilic groups such as ethoxymethyl (**14**) and methoxymethyl (**15**) were similarly effective. In the monocyclic imidazole carboxamide series (Table 3), the same small 2′ substituents were even more effective, providing single digit nanomolar binding at both receptors (**17** vs **10**; **16** vs **15**). This series demonstrated that a properly-chosen biphenyl 2′ substituent can have a subtle *positive* effect on AT_1 receptor binding, in addition to the expected improvement in ET_A receptor binding. For three of the best 2′ substituents, the corresponding *N*-methylcarboxamide compounds were also prepared (Table 3). These compounds (**22**–**24**) were indistinguishable from the corresponding primary carboxamides in ET_A receptor binding. However, AT_1 receptor affinity diminished when the 2′ substituent was larger than methyl.

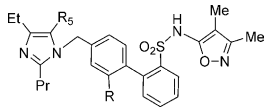
Table 2. Variation of biphenyl 2′ substituents in fused imidazole series[a]



Compd	R	AT_1 K_i (nM)	ET_A K_i (nM)
8	H	8 (4)	105 (15)
9		360 (140)	1 (0.6)
10	Methyl	2 (1)	13 (4)
11	Fluoro	16 (2)	20 (6)
12	Cyanomethyl	16 (5)	15 (7)
13	Hydroxymethyl	30 (10)	14 (3)
14	Ethoxymethyl	5 (1)	20 (7)
15	Methoxymethyl	4 (1)	17 (6)

[a]Standard deviations are given in parentheses.

Table 3. Variation of biphenyl 2′ substituents in monocyclic series[a]



Compd	R_5	R	AT_1 K_i (nM)	ET_A K_i (nM)
16	$CONH_2$	Methoxymethyl	0.6 (0.2)	4 (2)
17	$CONH_2$	Methyl	2 (1)	5 (2)
18	$CONH_2$	Ethoxymethyl	3 (1)	20 (6)
19	$CONH_2$	Chloro	35 (2)	700 (300)
20	$CONH_2$	Ethyl	1.3 (0.4)	7 (4)
21	$CONH_2$	2-Fluoroethoxymethyl	2 (0.6)	8 (3)
5	CONHMe	H	13 (3)	16 (6)
22	CONHMe	Methoxymethyl	8 (3)	7 (3)
23	CONHMe	Methyl	4 (1)	5 (2)
24	CONHMe	Ethoxymethyl	14 (4)	22 (2)

[a]Standard deviations are given in parentheses.

To screen for in vivo oral efficacy, we studied selected compounds in a rat angiotensin II oral pressor assay using conscious Sprague–Dawley rats.[14] In this assay, **10** was only poorly efficacious. In contrast, **17** and **23** both had potency (area-over-the-curve (AOC) value and maximum percent decrease of pressor response, Table 4) similar to that of BMS-248360, or approximately half that of irbesartan. Caco-2 cell permeability rates for both **17** and **23** were relatively low (Table 4), suggesting that poor absorption may be limiting their in vivo efficacy. Nonetheless, these results suggest that further optimization of this series could yield highly-potent, orally active dual receptor antagonists.

In conclusion, we have combined the features of the AT_1 receptor antagonist losartan with those of BMS-193884, an ET_A-selective endothelin receptor antagonist. The resultant 4′-[(imidazol-1-yl)methyl]-biphenylsulfonamides have potent in vitro activity. Inclusion of certain 2′ substituents on the biphenyl core

Table 4. In vivo evaluation of selected compounds[a]

Compd	Rat AII pressor effect po, 30 μmol/kg (AOC units)[b]	Max BP % decrease	Caco-2 Pc, nm/s pH 5.5/7.4
Irbesartan	11,900	84 (4)	
BMS-248360	5800	45 (14)	
10	1200	23 (13)	
17	5300	47 (17)	71/40
23	6700	64 (6)	59/37

[a]Values are means of four experiments, standard deviation is given in parentheses.
[b]Defined as the integral from 0 to 240 min on the graph of % inhibition of pressor response versus time.

of these compounds enhances both AT_1 and ET_A receptor binding affinity. Compounds **17** and **23** are orally active in a rat model of angiotensin-mediated hypertension.

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13. Binding to the human ET_A receptor was evaluated by incubating test compounds with CHO-K1 cells expressing the human ET_A receptor in the presence of 0.05 nM ^{125}I-labelled endothelin 1 according to ref 4. The K_d for endothelin 1 was 0.05 nM in this assay. Compounds were evaluated for AT_1 binding by incubation with rat aortic smooth muscle cells and 0.2 nM ^{125}I-labeled Sar-Ile-angiotensin II according to ref 4. The K_d for angiotensin II was 0.094 nM in this assay. Each reported K_i value is the mean of at least three individual experiments.
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