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2-(Anilinomethyl)imidazolines as α_{1A} Adrenergic Receptor Agonists: 2′-Heteroaryl and 2′-Oxime Ether Series

Frank Navas, III,[a,*] Michael J. Bishop,[a] Deanna T. Garrison,[a] Stephen J. Hodson,[a] Jason D. Speake,[a] Eric C. Bigham,[a] David H. Drewry,[a] David L. Saussy,[b] James H. Liacos,[b] Paul E. Irving[b] and M. Jeffrey Gobel[b]

[a]*Division of Chemistry, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709, USA*
[b]*Division of Pharmacology and Molecular Therapeutics, GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, NC 27709, USA*

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Abstract—A series of 2′-heteroaryl and 2′-oxime anilinomethylimidazolines was prepared and evaluated in in vitro functional assays for cloned human α_{1A}, α_{1B}, and α_{1D} receptor subtypes. Potent and selective α_{1A} agonists have been identified in these series.

Alpha$_1$ adrenergic receptors have an important physiological role in the cardiovascular and urogenital systems.[1–3] Three α_1 adrenergic receptor subtypes (i.e., α_{1A}, α_{1B}, and α_{1D}) have been confirmed via cloning techniques.[4–9] The expression levels of these subtypes varies in different tissues; therefore, development of subtype specific ligands may result in drugs with improved therapeutic profiles.[10] For example, the selective α_{1A} antagonist tamsulosin has been shown to have fewer side effects in the treatment of benign prostatic hyperplasia than the non-selective α_1 antagonist terazosin.[11,12] Similarly, the selective α_{1A} agonist NS-49 may be effective in the treatment of stress urinary incontinence with a lower potential for systemic blood pressure effects.[13,14] The improved therapeutic profile of NS-49 is due to the predominance of the α_{1A} subtype in urethal smooth muscle. We are interested in evaluating selective α_{1A} agonists as potential therapeutic agents for the treatment of stress urinary incontinence.

2′-Carboxylic acid and methyl ester 2-(anilinomethyl)-imidazolines were reported to be potent pressor agents and believed to be acting through α_1 adrenergic activation.[15] Our evaluation of a 2′-methyl ester (Fig. 1) at the three cloned human α_1 adrenergic receptors[16] revealed that it was a potent full agonist at all three subtypes: α_{1A} ($pEC_{50} = 9.1$); α_{1B} ($pEC_{50} = 9.4$); α_{1D} ($pEC_{50} = 9.3$).

Efforts to develop a selective α_{1A} agonist focused on the replacement of the methyl ester. Heterocycles[17–23] and oxime ethers[24–27] have been used as ester bioisosteres. Isosteric replacement of the methyl ester with a variety of heterocycles and oxime ethers resulted in the discovery of α_{1A} agonists that are both potent and selective. The preparation and biological activity of a series of 2′-heteroaryl and 2′-oxime ethers of 2-(anilinomethyl)-imidazolines are described herein.

The 2′-substituted 2-(anilinomethyl)imidazolines were prepared according to the general synthetic scheme illustrated in Scheme 1.

The requisite nitro intermediates were prepared by a variety of synthetic methods. 2-(2-Nitrophenyl)oxazole,[28,29] 3-methyl-5-(2-nitrophenyl)isoxazole,[30] 5-(2-nitrophenyl)-isoxazole,[31] and 4-(2-nitrophenyl)isoxazole[31] were prepared

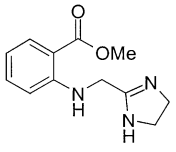

Figure 1.

*Corresponding author. Tel.: +1-919-483-8066; fax: +1-919-315-5668; e-mail: fn28689@gsk.com

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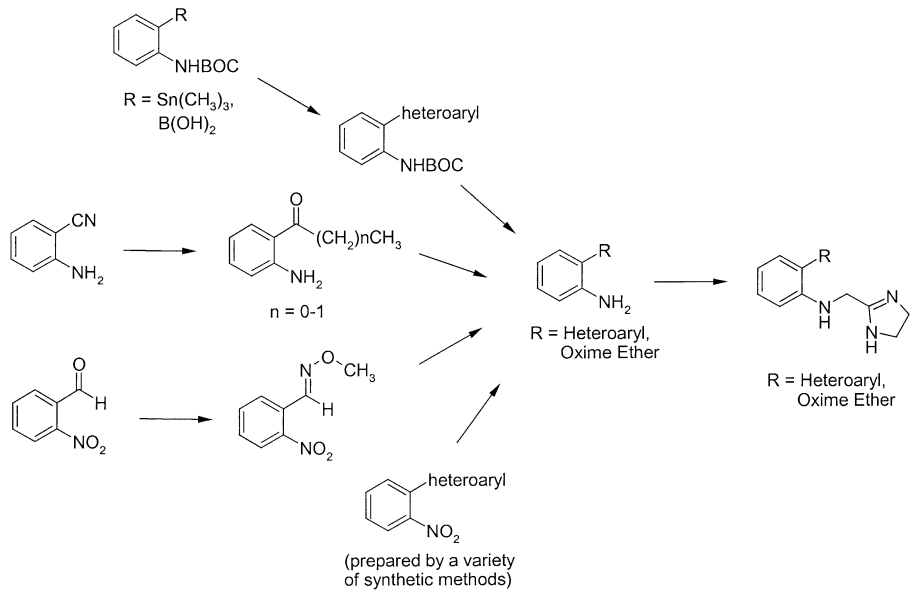


Scheme 1.

according to literature procedures. The nitro intermediate for compound **21** was prepared by a method analogous to that described for 5-(2-nitrophenyl)isoxazole in which guanidine hydrochloride was used in the presence of catalytic NaOH to form the 2-aminopyrimidine ring. The nitro intermediates for compounds **12**–**13**, **17**, and **19** were prepared under Ullmann cross-coupling conditions using 2-bromonitrobenzene and the corresponding bromo- or iodo-substituted heterocycles.[32] 2-(2-Nitrophenyl)furan was prepared by Stille[33] coupling of 2-nitrobromobenzene and 2-tributylstannylfuran in DMF with tetrakis(triphenylphosphine)palladium as a catalyst. The analogous thiophene intermediate was obtained in a similar manner using 2-nitroiodobenzene, 2-tributylstannylthiophene, and dichlorobis(triphenylphosphine)palladium (II) as a catalyst. The nitro intermediates for oxadiazoles **14** and **15** were prepared according to the general procedures described by Orlek and co-workers.[17] 4-Methyl-5-(2-nitrophenyl)oxazole was prepared from 2-nitrobenzaldehyde and 1-(toluene-4-sulfonyl)ethyl isocyanide[34] using the general procedure described by Possel et al.[35] The nitro intermediate for oxazole **6** was prepared from 2-bromo-2′-nitroacetophenone using potassium acetate and acetic acid followed by ammonium acetate and acetic acid under refluxing conditions. 2-Methyl-4-(2-nitrophenyl)thiazole was prepared from 2-bromo-2′-nitroacetophenone and thioacetamide. Treatment of 2-bromo-2′-nitroacetophenone with tetrabutylammonium azide in acetonitrile between 0 and 25 °C followed by treatment of the resultant azide with polymer-bound triphenylphosphine and acetyl chloride in toluene at room temperature gave the nitro intermediate for methyloxazole **3**. The reaction of 2-nitrobenzaldehyde with methoxylamine hydrochloride in refluxing EtOH gave the desired nitro intermediate for oxime **26**.

Reduction of the previously described nitro intermediates as well as commercially available 5-(2-nitrophenyl)oxazole provided the majority of desired anilines. The nitro groups of the isoxazole intermediates were reduced with stannous chloride and HCl.[31] 2-(2-Nitrophenyl)furan and 2-(2-nitrophenyl)pyridine were reduced with 35% hydrazine in EtOH in the presence of 10% Pd/C. The nitro intermediates for oxadiazoles **14** and **15** and oxime **26** were reduced with sodium sulfide using the general conditions described by Lin and Lang.[36] Commercially available 5-(2-nitrophenyl)furfural was reduced by the general method described by Kano and co-workers using titanium (IV) chloride and sodium borohydride to give the desired aniline intermediate for compound **16**.[37] 4-(2-Nitrophenyl)-2-methylthiazole was reduced by catalytic hydrogenation with platinum oxide in ethanol. Catalytic hydrogenation of 2-(2-nitrophenyl)thiophene was carried out in ethanol and acetic acid using 10% palladium on carbon to give the desired aniline. The remaining nitro intermediates for compounds **1**, **3**, **6**–**7**, **10**, **12**–**13**, **19**, **21**, and **26** were reduced by catalytic hydrogenation using 10% Pd/C in EtOH.

The remaining aniline intermediates were prepared by a variety of synthetic methods as described below. Stille coupling of 2-chloropyrazine and (2-trimethylstannylphenyl-carbamic acid *tert*-butyl ester[38] with tetrakis(triphenylphosphine)palladium (0) in the presence of catalytic copper (I) bromide followed by deprotection with trifluoroacetic acid provided 2-(2-aminophenyl)-pyrazine en route to **18**. Suzuki coupling of [2-(*N*-*t*-boc-amino)phenyl]boronic acid with 2-bromo-3-methylpyridine and 2-bromo-3-trifluoromethylpyridine according to the general procedure described by Snieckus[39] followed by *N*-deprotection with trifluoroacetic acid provided the aniline intermediates for compounds **20** and **22**, respectively. Finally, the aniline intermediates for oximes **23**–**25** and **27** were prepared by treatment of the corresponding anilino ketones with the *O*-alkyl hydroxylamine hydrochlorides in EtOH under refluxing conditions. The requisite anilino ketones for compounds **25**

and **27** were obtained via Grignard reaction between anthranilonitrile and ethylmagnesium chloride followed by hydrolysis with sulfuric acid. The anilino ketones for compounds **23** and **24** were commercially available.

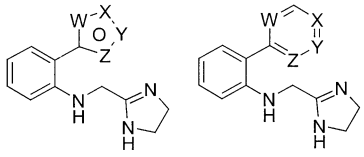
The anilines described above were coupled to 2-(chloromethyl)-2-imidazoline hydrochloride[40] as described in the literature.[41,42] All compounds except **3**–**4**, **14**–**15**, **18**, and **23**–**24** were converted to either their hydrogen chloride or fumarate salts. ^{1}H NMR and mass spectroscopic data were consistent for all final products. Representative ^{1}H, ^{13}C NMR, and mass spectroscopic data are provided for compound **20**.[43]

The 2′-heteroaryl substituted 2-anilinomethylimidazolines listed in Table 1 range from weak partial agonists to potent full agonists at the α_{1A} receptor. The α_{1A} agonists oxymetazoline, naphazoline, and cirazoline are included for comparison.

Potency and efficacy at the α_{1A} receptor as well as selectivity versus the α_{1B} and α_{1D} subtypes are influenced by the heteroatoms of the 2′-heteroaromatic ring. The relative positions of the heteroatoms can significantly impact potency and selectivity. For example, isoxazole **8** is a potent full agonist at all three receptor subtypes whereas isoxazole **11** is a less potent but selective α_{1A} agonist. A similar comparison can be made for oxazoles **10** and **1**, respectively. Heteroatom substitution may also influence activity at the three receptor subtypes. For example, oxazole **1** was a moderately potent and selective α_{1A} agonist that was inactive at the α_{1B} and α_{1D} subtypes. However, replacement of the oxazole nitrogen with a carbon resulted in a compound (i.e., furan **2**) that was significantly more potent at all three receptor subtypes and fully efficacious at α_{1B} and α_{1D}. While pyridine **17** and pyrazine **18** are both potent full agonists at the α_{1A} receptor, the presence of the second nitrogen in the pyrazine ring resulted in a significant loss of potency and efficacy at the α_{1B} receptor. Finally, a comparison between thiophene **12** and furan **16** reveals that substitution of oxygen for sulfur resulted in an increase in α_{1A} potency and efficacy. These observations suggest that the heteroatoms of the 2′-aromatic ring contribute significantly to the ligand–receptor interactions at all three receptor subtypes. These heteroatoms (i.e., oxygen and nitrogen) may act as hydrogen-bond acceptors, which in turn could either facilitate or inhibit receptor activation.

Substitution of the 2′-heteroaryl ring may also have a significant effect on subtype potency, efficacy, and selectivity. The α_{1B} and α_{1D} receptors appear to be

Table 1. In vitro agonist activity of 2′-heteroaryl series[a]

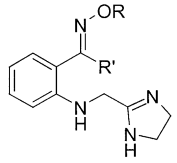


1–16 **17–22**

Compd	W	X	Y	Z	pEC$_{50}$ (% Max. of phenylephrine)[b]		
					α_{1A}	α_{1B}	α_{1D}
Oxymetazoline					7.7 (74)	<5.3	<5.3
Naphazoline					7.2 (72)	<5.3	<5.3
Cirazoline					7.9 (93)	7.2 (72)	6.9 (31)
1	C	N	C	O	7.76 (107)	<5.30	<5.30
2	C	C	C	O	9.33 (101)	8.2 (95)	7.79 (90)
3	C	N	C–Me	O	6.96 (126)	<5.30	<5.30
4	N	C–Me	S	C	8.35 (98)	7.16 (21)	<5.30
5	C	C	C	S	8.65 (99)	8.24 (103)	7.74 (59)
6	C	O	C–Me	N	6.49 (64)	<5.30	<5.30
7	O	C	N	C–Me	7.82 (95)	<4.00	<4.00
8	C	C	N	O	9.10 (134)	8.43 (97)	8.54 (114)
9	O	N	C–Me	C	7.41 (86)	7.02 (27)	<4.00
10	O	C	C	N	9.18 (121)	8.79 (123)	8.3 (103)
11	C	N	O	C	7.34 (99)	<4.00	<4.00
12	C	C	C–Me	S	7.44 (49)	<4.00	<4.00
13	S	C	C	C–Me	9.07 (104)	6.95 (78)	7.31 (83)
14	O	N	C–Me	N	6.18 (92)	<5.30	<5.30
15	N	O	C–Me	N	6.14 (57)	6.17 (43)	<5.30
16	C	C	C–Me	O	8.57 (98)	7.33 (48)	<5.70
17	N	C	C	C	8.17 (103)	7.52 (101)	7.38 (35)
18	N	C	N	C	8.34 (94)	6.47 (48)	6.74 (38)
19	N	C	C	N	8.00 (105)	7.11 (102)	7.09 (60)
20	C–Me	C	C	N	7.61 (104)	<4.00	<4.00
21	C	N	C–NH$_2$	N	7.37 (97)	<5.30	7.54 (44)
22	C–CF$_3$	C	C	N	6.17 (78)	<4.00	<4.00

[a]See ref 16 for description of the assay. Each entry represents the mean of at least two experiments, with an average SEM of ±0.12.
[b]% of phenylephrine response (40 μM).

Table 2. In vitro agonist activity of 2′-oxime series[a]



Compd	Isomer	R	R′	pEC_{50} (% Max. of phenylephrine)[b]		
				α_{1A}	α_{1B}	α_{1D}
23	*E*	CH_3	CH_3	7.68 (92)	<5.30	<5.30
24	*E*	CH_2CH_3	CH_3	7.28 (102)	<5.30	<5.30
25	*E*	CH_3	CH_2CH_3	8.48 (112)	<4.00	<4.00
26	*E*	CH_3	H	7.29 (94)	<5.30	<5.30
27	*Z*	CH_3	CH_2CH_3	7.06 (141)	<5.30	<5.30

[a]See ref 16 for description of the assay. Each entry represents the mean of at least two experiments, with an average SEM of ±0.12.
[b]% of phenylephrine response (40 μM).

Table 3. Comparison of in vitro functional and binding data[a]

Compd	Functional assay (pEC_{50})[b]			In vitro binding (pIC_{50})		
	α_{1A}	α_{1B}	α_{1D}	α_{1A}	α_{1B}	α_{1D}
1	7.76 (107)	<5.30	<5.30	6.34	6.64	6.53
7	7.82 (95)	<4.00	<4.00	6.72	6.49	6.46
8	9.10 (134)	8.43 (97)	8.54 (114)	7.45	6.88	7.42
10	9.18 (121)	8.79 (123)	8.3 (103)	7.34	6.35	7.39
17	8.17 (103)	7.52 (101)	7.38 (35)	7.09	6.23	6.93
19	8.00 (105)	7.11 (102)	7.09 (60)	6.72	5.66	6.38
26	7.29 (94)	<5.30	<5.30	6.55	6.79	7.37

[a]See refs 16 and 46 for descriptions of the assays. Each entry represents the mean of at least two experiments, with an average SEM of ±0.12 for the functional assay and ±0.11 for the binding assay.
[b]% of phenylephrine response (40 μM).

less able to accommodate substitution of the 2′-heteroaromatic ring. For example, methyl substitutions of thiophene **5**, furan **2**, isoxazole **8**, and pyridine **17** to give compounds **12**, **16**, **9**, and **20**, respectively, result in a greater loss of potency and/or efficacy at the α_{1B} and α_{1D} receptors relative to α_{1A}. In fact, one may possibly exploit this steric constraint of the α_{1B} and α_{1D} receptors to design α_{1A} agonists with greater selectivity.

Finally, replacement of the methyl group of pyridine **20** with a trifluoromethyl group (i.e., **22**) resulted in a loss of potency at the α_{1A} receptor, suggesting that electron density of the heteroaromatic ring may be important for interaction with this receptor subtype.

The in vitro α_1 functional profiles of the 2′-oxime ethers are listed in Table 2. All of the compounds listed in this series are selective, full agonists at the α_{1A} receptor subtype. An increase in steric bulk of the (*E*)-*O*-methyl oxime ethers resulted in an increase in potency at the α_{1A} receptor. Thus, as size increased from the formyl (**26**) to the acetophenone (**23**) and finally the propiophenone derivative (**25**), potency at the α_{1A} receptor increased more than an order of magnitude. In contrast, an increase in size of the *O*-alkyl group resulted in a slight decrease in potency at the α_{1A} receptor (i.e., *O*-methyl oxime ether **23** vs *O*-ethyl oxime ether **24**). The effect of configuration about the oxime double bond on α_{1A} agonist activity was significant. While both compounds were fully efficacious at the α_{1A} receptor, the (*E*)-*O*-methyl oxime ether (**25**) was more than 25 times as potent as the corresponding *Z*-isomer (**27**).

While a number of compounds in the 2′-heteroaryl and 2′-oxime ether series were potent and selective for the α_{1A} receptor, none were selective for the α_{1B} and α_{1D} subtypes. This is consistent with the fact that most imidazoline-type α_1 adrenergic agonists exhibit some degree of selectivity for the α_{1A} subtype.[44,45] Furthermore, the functional activity observed at the three receptor subtypes did not generally correlate with their binding affinities.[46] For example, oxazoles **1** and **7** were at least 100-fold more potent at the α_{1A} receptor relative to α_{1B} and α_{1D}; however, the compounds bound equally well to all three subtypes (see Table 3). The lack of correlation between the α_1 subtype selectivity in the functional and binding assays has been attributed to a difference in intrinsic activity at the three receptor subtypes.[45]

2′-Heteroaryl and 2′-oxime anilinomethylimidazolines have been identified that were potent, selective, and fully efficacious at the α_{1A} receptor. Functional activity at the α_{1A}, α_{1B}, and α_{1D} subtypes did not generally correlate with receptor binding affinity. In the 2′-heteroaryl series, the heteroatoms appeared to play a significant role in ligand–receptor interactions. Also, the α_{1B} and α_{1D} receptor subtypes have greater steric constraints in the vicinity of the heteroaryl ring than does the α_{1A} receptor. All of the oxime ethers were fully efficacious at the α_{1A} receptor and selective. In this series, potency at the α_{1A} receptor progressively increased as steric bulk at the oxime carbon was increased. In the case of the *O*-methyl propiophenone derivative, the *E*-isomer was preferred.

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