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2-(Anilinomethyl)imidazolines as α_1 Adrenergic Receptor Agonists: α_{1a} Subtype Selective 2′-Heteroaryl Compounds

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Abstract—The structure–activity relationship of 2′-pyrrole, pyrazole and triazole substituted 2-(anilinomethyl)imidazolines as α_1 adrenergic agonists was investigated. The size and orientation of substituents, as well as the position of the heteroatoms, were found to have a profound effect on the potency and selectivity of the molecules. Potent α_{1A} subtype selective agonists have been identified.
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Among other functions, α_1 adrenergic receptors are involved in smooth and cardiac muscle contraction.[1] It has been shown that the three α_1 adrenergic receptor subtypes that have been cloned and characterized, α_{1A}, α_{1B}, and α_{1D}, have varying expression levels in different tissues.[2] Thus, subtype selective ligands may be useful pharmacological tools and could potentially result in drugs with improved therapeutic profiles.[3] We are particularly interested in evaluating selective α_{1A} adrenergic agonists for the treatment of stress urinary incontinence due to evidence that α_{1A} is the predominant α_1 subtype in the urethra.[4] A suggestion that this approach may be successful is found in comparison of the α_{1A} selective antagonist tamsulosin and the non-selective antagonist terazosin in the treatment of benign prostatic hyperplasia. Tamsulosin has been found to have fewer cardiovascular side effects than terazosin.[5]

Warner Lambert patented 2′-carboxylic acid and methyl ester 2-(anilinomethyl)imidazolines as potent pressor agents in 1971.[6] Our evaluation of the methyl ester **1** (Fig. 1) at the three cloned human α_1 adrenergic receptors revealed that it was very potent and nonselective [α_{1A} ($pEC_{50}=9.1$), α_{1B} ($pEC_{50}=9.4$), and α_{1D} ($pEC_{50}=9.3$)].[7,8] Recently, investigation of a series of 2′-esters and amides revealed α_{1A} subtype selective 2-(anilinomethyl)imidazolines.[9] Further efforts in this area have focused on isosteric replacement of the ester or amide functionality.[10] Herein is described a series of five-membered nitrogen containing heterocycles that typify the structure–activity relationship of 2′-heteroaryl-2-(anilinomethyl)imidazolines at the cloned human α_{1A}, α_{1B}, and α_{1D} adrenergic receptors.

Two approaches were used to synthesize target molecules. Cyclocondensation of hydrazine derivatives with **3**, generated from reaction of **2** with an acetal or ketal, gave ready access to 2′-pyrazole and triazole compounds **4** and **5** (Scheme 1). Isomeric pyrazoles, were made similarly.[11] Pyrrole compounds of structure **7** were made via palladium coupling with 1-bromo-2-nitrobenzene **6** (Scheme 2).[12,13]

Reduction of the arylnitro group with hydrogen and palladium, followed by heating the anilines, **8**, with 2-(chloromethyl)imidazoline hydrochloride in a protic

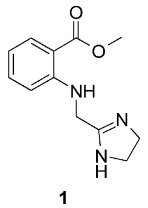

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Figure 1.

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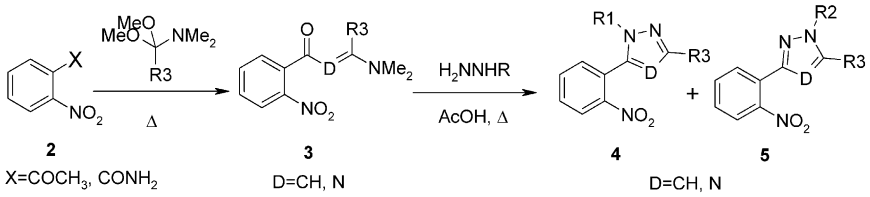
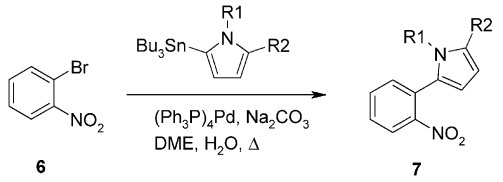


Scheme 1.



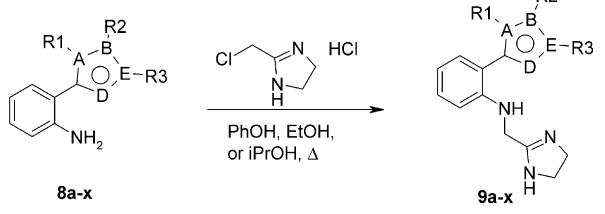
Scheme 2.

solvent such as phenol provided the desired 2′-heteroaryl-2-(anilinomethyl)imidazolines of structure **9** (Scheme 3).[14]

The activity of select compounds is shown in Table 1. Several trends in the SAR are worth noting. To begin with, the unsubstituted heterocycles are typically potent and efficacious at all three receptor subtypes. The triazole and the isomeric pyrazoles, **9a**, **9j**, and **9r**, respectively, all have a pEC_{50} at the α_{1A} subtype of ~9 and are fully efficacious. Triazole **9a** and pyrazole **9j** have very similar profiles at the α_{1B} subtype, pEC_{50} 8.3 and full efficacy, with pyrazole **9r** being less potent and slightly less efficacious. At the α_{1D} subtype, the two pyrazoles share a similar profile, being somewhat less potent and efficacious than the triazole.

It is also interesting to note the impact that alkyl substitution on the heterocycle has on agonist activity at the three receptors. In general, substitution is better tolerated at the α_{1A} subtype than at α_{1B} and α_{1D}, though potency is almost always negatively affected to some extent at all three subtypes.

In the triazole series, **9a**–**9i**, increasing alkyl chain length at R1 from methyl to butyl causes potency and efficacy to drop at all three receptors. Methyl and ethyl substitution were approximately equal to each other in their effects at α_{1A} and α_{1B}, causing a slight decrease in potency at α_{1A} and approximately an order of magnitude decrease in potency at α_{1B}, with little effect on receptor activation. At the α_{1D} subtype, methyl substitution caused an order of magnitude decrease in potency with no effect on efficacy. Upon moving to ethyl, the potency at α_{1D} continued to drop slightly, but

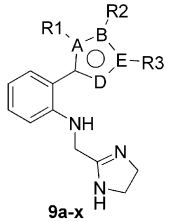


Scheme 3.

the compound was no longer a full agonist. The propyl and butyl substituents continued this downward trend in both potency and efficacy at all three subtypes. Interestingly, isopropyl substitution, compound **9f**, was intermediate between ethyl and *n*-propyl, **9c** and **9d**, respectively, in its impact on potency at the α_{1A} subtype, but had a much more pronounced negative effect on potency and efficacy at the α_{1B} and α_{1D} subtypes. Trifluoroethyl compound **9g** lost all activity at α_{1B} and α_{1D}, but was still efficacious at α_{1A}, though with somewhat reduced potency. Substitution at R3 on the triazole ring, **9h** and **9i**, was not well tolerated at any of the α_1 receptors.

The C5-linked pyrazoles, **9j**–**9o**, revealed a trend similar to the triazoles, but the effects of substitution were much more pronounced. All of the substitutions at R1

Table 1. In vitro agonist activity of 2′-heteroaryl-2-(anilinomethyl)-imidazolines[a]



	A	B	E	D	R^1	R^2	R^3	α_{1A}		α_{1B}		α_{1D}	
								pEC_{50}	%Max	pEC_{50}	%Max	pEC_{50}	%Max
9a	N	N	C	N	H		H	9.1	135	8.3	100	8.4	123
9b	N	N	C	N	Me		H	8.7	91	7.4	93	7.2	116
9c	N	N	C	N	Et		H	8.9	107	7.2	94	6.9	55
9d	N	N	C	N	nPr		H	7.9	96	6.5	74	6.6	57
9e	N	N	C	N	nBu		H	6.7	86	6.7	83	6.4	66
9f	N	N	C	N	iPr		H	8.2	104	<4.0	0	5.5	37
9g	N	N	C	N	CH_2CF_3		H	7.1	91	<4.0	0	<4.0	0
9h	N	N	C	N	H		Me	6.1	87	<5.3	0	<5.3	0
9i	N	N	C	N	Me		Me	6.0	98	<5.3	0	<5.3	0
9j	N	N	C	C	H		H	9.0	104	8.3	95	7.7	54
9k	N	N	C	C	Me		H	8.0	108	<4.0	0	<4.0	0
9l	N	N	C	C	Et		H	7.2	81	<4.0	0	<4.0	0
9m	N	N	C	C	nPr		H	6.6	59	<4.0	0	<4.0	0
9n	N	N	C	C	iPr		H	<4.0	0	<4.0	0	<4.0	0
9o	N	N	C	C	CH_2CF_3		H	6.5	76	<4.0	0	<4.0	0
9p	N	N	C	C		Me	H	8.5	116	7.3	33	7.8	29
9q	N	N	C	C		Et	H	7.6	78	<4.0	0	<4.0	0
9r	C	N	N	C	H	H		8.9	112	7.1	72	7.7	62
9s	C	N	N	C	H	Me		6.4	39	<4.0	0	<4.0	0
9t	C	N	N	C	H	Et		<4.0	0	<4.0	0	<4.0	0
9u	N	C	C	C	Me	H	H	7.7	103	<4.0	0	6.6	32
9v	N	C	C	C	Et	H	H	8.6	93	<4.0	0	<4.0	0
9w	N	C	C	C	Me	Me	H	7.3	78	<4.0	0	<4.0	0
9x	N	C	C	N	Me	H	H	8.2	88	7.4	104	6.7	92

[a]See ref 7 for a description of the assay. Each entry represents the mean of at least two experiments, with an average SEM of ±0.08 in the pEC_{50}. %Max refers to percent of the 40 μM phenylephrine response.

completely destroyed agonist activity at both the α_{1B} and α_{1D} subtypes, while still retaining activity at the α_{1A} receptor. Also, as size increased from methyl to propyl, there was a more rapid falloff in potency and efficacy at α_{1A} than that observed for analogous substitutions in the triazole series. Methyl compound **9k** reduced potency by an order of magnitude, while retaining efficacy. Ethyl substitution, **9l**, further reduced potency almost another order of magnitude, with some effect on efficacy, and propyl substitution, **9m**, continued the trend. Unlike the triazole series, isopropyl substitution was not tolerated, as demonstrated by the loss of all agonist activity of compound **9n**.

In the C3-linked pyrazoles, substitution at R2 with methyl and ethyl, compounds **9p** and **9q**, respectively, showed the same trend, but were slightly less dramatic in their impact on potency and efficacy than the analogous C5-linked pyrazoles **9k** and **9l**. Methyl substitution was not enough to completely remove efficacy at the α_{1B} and α_{1D} subtypes and only reduced potency at the α_{1A} subtype by $\sim$3-fold. Upon ethyl substitution, the agonist activity at the α_{1B} and α_{1D} subtypes was removed with, again, some reduction of potency and efficacy at the α_{1A} subtype.

Substitution of the C4-linked pyrazoles, compounds **9r–9t**, had an even more pronounced effect on agonism at all three α_1 receptor subtypes. Methyl substitution was enough to almost completely remove efficacy at all of the receptors, with only the α_{1A} subtype maintaining some weak agonism. Ethyl compound **9t** had no measurable agonist activity.

One exception to the observed trends occurs in the pyrrole series, compounds **9u–9w**. In this case ethyl substitution, **9v**, is actually somewhat more potent at the α_{1A} subtype than methyl, **9u**. However, at α_{1D} the previously observed trends held, in that **9u** still had some efficacy, while **9v** did not. Neither compound had any efficacy at the α_{1B} subtype. Additional substitution, **9w**, further reduced potency and efficacy at α_{1A} as expected.

A possible rationale for the observed SAR arises from consideration of the differing likely shapes of the molecules, determined at least in part, by whether or not they are able to form an intramolecular hydrogen bond to the aniline N–H. Those heterocycles that can readily make this H-bond, such as the unsubstituted triazole **9a**, and pyrazole **9j**, would likely be relatively planar with regard to the dihedral angle between the two aryl rings. However, compounds such as pyrazole **9k**, where the H-bond acceptor has been blocked by methyl substitution, may tend to be somewhat less planar. Further, compounds that have progressively larger substituents, either adjacent to the H-bond acceptor, **9p** and **9q** for instance, or adjacent to the biaryl bond, **9b–g**, for example, may also have increasing difficulty adopting a planar conformation. It appears that the α_{1A} receptor may be better able to accommodate this non-planarity and still achieve the appropriate conformation for receptor activation than either the α_{1B} or α_{1D} receptors. It should be noted that, consistent with previous reports, functional activity did not correlate well with affinity.[15] For instance, **9j** had a pIC_{50} of 7.6, 6.8, and 7.4 at α_{1A}, α_{1B}, and α_{1D}, respectively, while **9k** possessed a pIC_{50} of 6.7, 6.4, and 6.3 at the three receptors, a rather small difference considering the dramatic change in functional activity.[16] This incongruence has been attributed to differences in intrinsic activity of the ligands at the three receptors, and these types of ligands have been referred to as efficacy driven or efficacy dominant agonists.[17]

In conclusion, 2′-heteroaryl-2-(anilinomethyl)imidazolines have been identified that are potent, fully efficacious, and selective for the cloned human α_{1A} adrenergic receptor. The size and shape of the 2′-heteroaryl group were found to have a profound impact on functional activity at all three α_1 receptors. Compound **9j** was less than 10-fold selective for the α_{1A} receptor, while compound **9k** shows that an appropriately placed methyl group can confer $>$10,000-fold selectivity for activation of the α_{1A} receptor.

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