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# $\alpha_1$-Adrenoceptor Agonists: The Identification of Novel $\alpha_{1A}$ Subtype Selective 2′-Heteroaryl-2-(phenoxymethyl)imidazolines

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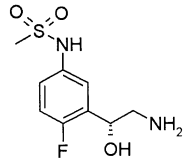
**Abstract**—Novel 2′-heteroaryl-2-(phenoxymethyl)imidazolines have been identified as potent agonists of the cloned human $\alpha_1$-adrenoceptors in vitro. The nature of the 2′-heteroaryl group can have significant effects on the potency, efficacy, and subtype selectivity in this series. $\alpha_{1A}$ Subtype selective agonists have been identified. 

$\alpha_1$-Adrenoceptors are 7TM G-protein coupled receptors that are activated by the neurotransmitter norepinephrine and the neurohormone epinephrine. Three $\alpha_1$-adrenoceptor subtypes ($\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$) have been confirmed via cloning techniques.[1] Included in the many functions of $\alpha_1$-adrenoceptors are important physiological roles in the cardiovascular and urogenital systems. Differential expression of $\alpha_1$ subtypes in various tissues is well documented, and therefore the development of subtype-specific ligands may result in more effective therapeutic agents with fewer side effects.[2] We have been particularly interested in the possibility that subtype-specific ligands may separate the cardiovascular and urogenital effects of $\alpha_1$ agonists, improving their utility for the treatment of stress urinary incontinence.

Stress urinary incontinence is characterized by the involuntary loss of urine due to a sudden increase in intra-abdominal pressure (e.g., pressure from sneezing, laughing, coughing, or strenuous exercise).[3] The cause can be weakened or damaged bladder neck and urethral muscle tissue. Activation of $\alpha_1$-adrenoceptors in the bladder neck and urethral smooth muscle causes muscle contraction, leading to increased bladder outlet resistance which can offset increases in intra-abdominal pressure. While $\alpha_1$ agonists are sometimes prescribed (off-label in the US) for stress urinary incontinence, typical $\alpha$-adrenergic side effects (cardiovascular and CNS) limit doses, and therefore likely limit clinical efficacy.[4] Some literature evidence suggests that $\alpha_{1A}$ may be the predominant subtype in urethral tissue.[5] Based on this, our initial goal was to identify novel, potent, highly selective $\alpha_{1A}$ agonists (vs $\alpha_{1B}$ and $\alpha_{1D}$) to test as agents for treatment of stress urinary incontinence with an improved side effect profile. This hypothesis was supported by reports that NS-49 (**1**), a selective $\alpha_{1A}$ agonist, exhibited good uroselectivity versus blood pressure in animal models[6] (Fig. 1).

Many 2-(anilinomethyl)imidazolines are adrenergic receptor ligands, and within that series novel, selective $\alpha_{1A}$ agonists have recently been identified.[7] A number of *ortho*-substituents on the anilino ring are tolerated for $\alpha_{1A}$ agonist activity in the 2-(anilinomethyl)imidazolines, including amides and esters (for example, diethylamide **2**).[8] We wanted to take advantage of the structure–activity relationships in the 2-(anilinomethyl)imidazoline




**1 (NS-49)**

**Figure 1.**

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series when looking for novel $\alpha_{1A}$ agonists in related series, such as the 2-(phenoxymethyl)imidazolines. Based on the 2-(anilinomethyl)imidazoline SAR, we focused on *ortho*-substituents on the phenol ring. However, while compound **2** was a potent $\alpha_{1A}$ agonist, the corresponding diethylamide in the 2-(phenoxymethyl)imidazoline series (**3**) was inactive at $\alpha_{1A}$. For compound **2**, a hydrogen bond between the amide carbonyl and the N–H of the aniline might be important for achieving the active conformation with the receptor, and compound **3** cannot make this hydrogen bond (Fig. 2).

However, there are potent $\alpha_{1A}$ agonists in the 2-(anilinomethyl)imidazoline series that do not have a hydrogen bond donor on the *ortho*-substituent of the anilino ring and therefore cannot form this type of intramolecular H-bond (e.g., compound **6**, which has a $pEC_{50}$ at $\alpha_{1A}$ of 8.1). This fact, coupled with the knowledge that there are known 2-(phenoxymethyl)imidazolines (such as cirazoline, **4**) that are $\alpha_1$ agonists, assured us that the anilino N–H was not critical for $\alpha_1$ agonist activity in all compounds from these series.[9] Additionally, 2′-phenyl-2-(phenoxymethyl)imidazoline (**5**) was as potent at $\alpha_{1A}$ as the corresponding 2′-phenyl-2-(anilinomethyl)imidazoline (**6**).[10] In the 2-(anilinomethyl)imidazoline series, replacement of the 2′-phenyl group with heteroaryl rings led to the identification of compounds that were potent, selective $\alpha_{1A}$ agonists. Therefore, we decided to explore the SAR of 2′-heteroaryl-2-(phenoxymethyl)imidazolines in search of novel $\alpha_{1A}$ agonists (Fig. 3).

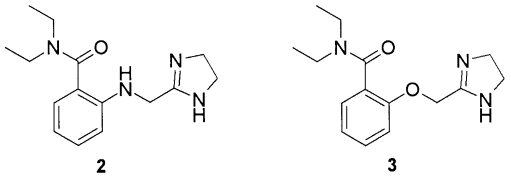



**Figure 2.**

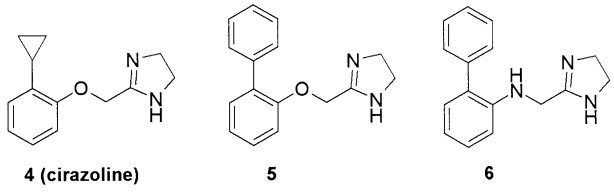



**Figure 3.**

## Chemistry[11]

A large number of 2′-heteroaryl-2-(phenoxymethyl)-imidazolines were prepared and evaluated for agonist activity at the $\alpha_1$-adrenoceptor subtypes. A representative set of 2′-heteroaryl-2-(phenoxymethyl)imidazolines was selected to illustrate the SAR in this series (Fig. 4).

All of these analogues of compound **5** were prepared using a two-step approach from phenols using chloroacetonitrile followed by heating in neat ethylenediamine (Scheme 1).[12]

The 2-(heteroaryl)phenols used in the syntheses of compounds **7**–**14**, **16**–**20**, and **24**–**26** were prepared via Suzuki couplings.[13] Generally, the commercially available heteroarylhalide was coupled with 2-methoxyphenylboronic acid, followed by demethylation using pyridine hydrochloride, to generate the appropriate phenol (e.g., the synthesis of the phenol for compound **20** is shown in Scheme 2).[14] The phenols for compounds **15**, **22**, **28**, and **29** were prepared from chromones as described in the literature (see Scheme 3).[15,16] The phenol for compound **23** was synthesized using a modification of a literature method (see Scheme 4).[17]

The phenol for compound **21** was prepared using a straightforward approach to pyrazoles,[18] and the phenol for compound **27** was prepared by a standard thiazole synthesis.[19] Compound **30** was made from the commercially available phenol.

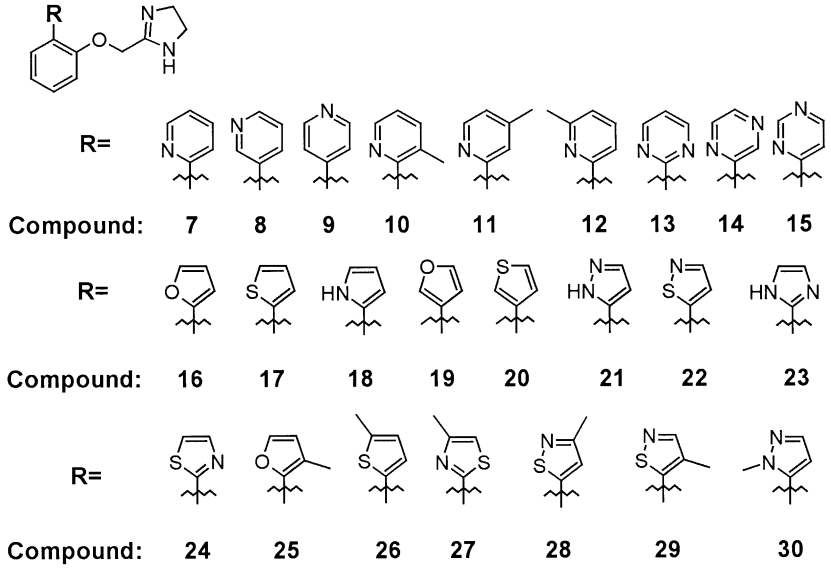


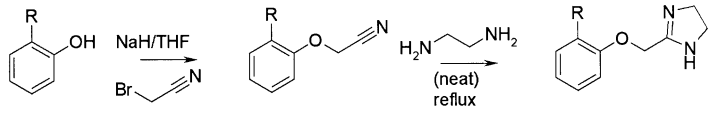

**Figure 4.**

## Results

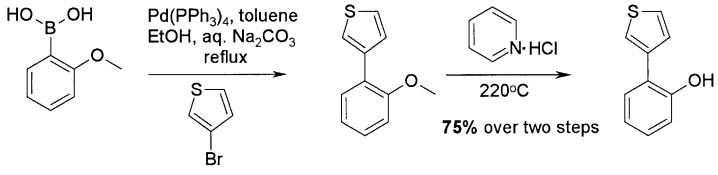
To model the potential ability of ligands to activate the individual $\alpha_1$ subtypes in humans, all compounds were evaluated in a cell-based functional assay using the cloned human receptors expressed in rat-1 fibroblasts.[20] The agonist potency (expressed as the $pEC_{50}$) and efficacy (expressed as a percent of the maximal effect of the $\alpha_1$-adrenoceptor agonist standard, phenylephrine) of selected 2′-heteroaryl-2-(phenoxymethyl)imidazolines are reported in Table 1.

2′-Phenyl-2-(phenoxymethyl)imidazoline (**5**) is a potent and selective $\alpha_{1A}$ agonist (it did not interact with the $\alpha_{1B}$ or $\alpha_{1D}$ in a manner to activate the receptors) and subtle changes to the 2-aryl ring result in interesting effects on the $\alpha_{1A}$ agonist activity and selectivity. The 2-pyridyl compound (**7**) retained most of the potency and $\alpha_{1A}$ selectivity of **5**; however, the 3-pyridyl (**8**) picked up agonist activity at the other two $\alpha_1$ receptors, and the 4-pyridyl (**9**) had *no* agonist activity at any of the $\alpha_1$ receptors. These effects of nitrogens at the 3- and 4-positions were also observed in the pyrazine (**14**), which had more agonist activity at $\alpha_{1B}$ than **7**, and the pyrimidine (**15**), which was inactive at all three subtypes. The steric requirements are also interesting, as a methyl at the 5- or 6-position (relative to the aryl ring, compounds **11** and **10**, respectively) of the 2-pyridyl caused a loss of all $\alpha_1$ agonist activity, while a methyl at the 3-position (**12**) resulted in some loss of $\alpha_{1A}$ (without picking up agonist activity at the other two subtypes).

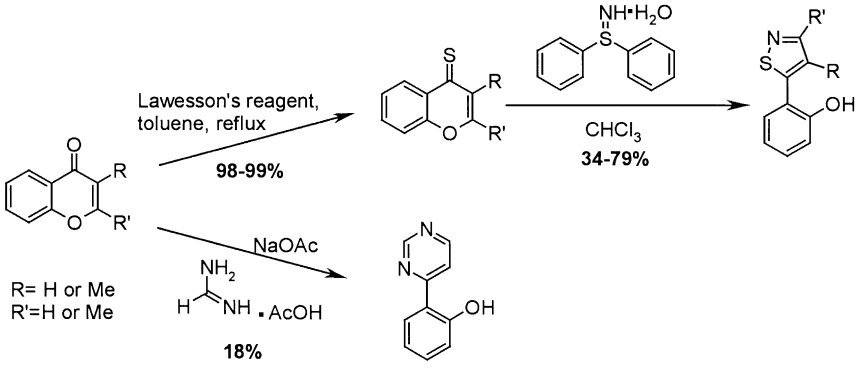
The five-membered heterocyles with one heteroatom and no additional substitution were able to potently activate all three of the $\alpha_1$ receptors (**16**–**20**). Adding an additional heteroatom often led to some $\alpha_{1A}$ subtype selectivity (e.g., **21** and **23**). However, there were exceptions, for instance thiazole **24** was slightly more selective than the corresponding pyrrole (**18**), but no more selective than the corresponding thiophene (**17**). Addition of a methyl group to the *ortho* heterocyclic ring often led to improved selectivity (e.g., methylfuran **25** and methylthiophene **26**), and the addition of a second heteroatom and a methyl group also resulted in com-



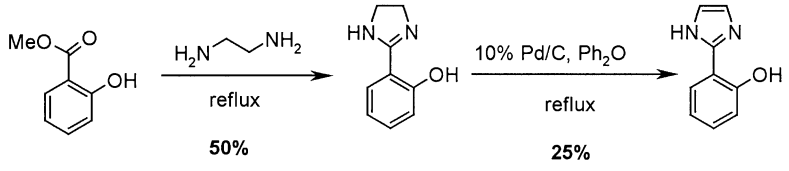

**Scheme 1.**




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

pounds with $\alpha_{1A}$ selectivity (**27**–**30**). The role of increased steric bulk [on the 2′-substituent of the 2-(phenoxymethyl)imidazolines] on subtype selectivity is clearly exemplified in the selectivity improvement seen by adding a methyl group to thiazole **24** (compound **24** is ~10-fold selective vs $\alpha_{1B}$ and $\alpha_{1D}$ while methylthiazole **27** is >2000-fold selective).

Consistent with literature reports and receptor theory, the $\alpha_{1A}$ subtype selectivity observed in the cell-based agonist functional assays did not correlate directly with subtype selectivity in receptor binding assays, as illustrated by the affinity data for selected 2′-heteroaryl-2-(phenoxymethyl)imidazolines shown in Table 2.[22]

**Table 1.** In vitro functional agonism activity[a]

| R | $\alpha_{1A}$ | | $\alpha_{1B}$ | | $\alpha_{1D}$ | |
|---|---|---|---|---|---|---|
| | $pEC_{50}$ | %Max[b] | $pEC_{50}$ | %Max[b] | $pEC_{50}$ | %Max[b] |
| **1 (NS-49)** | 6.5 | 86 | <4.0 | — | <4.0 | — |
| **2** | 7.5 | 105 | 5.7 | 32 | <5.3 | — |
| **3** | <5.3 | — | <5.3 | — | <5.3 | — |
| **4 (cirazoline)** | 7.9 | 93 | 7.2 | 72 | 6.9 | 31 |
| **5** | 8.5 | 96 | <4.0 | — | <4.0 | — |
| **6** | 8.1 | 101 | <4.0 | — | 6.1 | 20 |
| **7** | 7.9 | 104 | <4.0 | — | <4.0 | — |
| **8** | 8.7 | 109 | 7.1 | 111 | 6.8 | 38 |
| **9** | <4.0 | — | <4.0 | — | <4.0 | — |
| **10** | <4.0 | — | <4.0 | — | <4.0 | — |
| **11** | <4.0 | — | <4.0 | — | <4.0 | — |
| **12** | 6.9 | 80 | <4.0 | — | <4.0 | — |
| **13** | 5.9 | 90 | <4.0 | — | <4.0 | — |
| **14** | 8.6 | 97 | 6.2 | 46 | <4.0 | — |
| **15** | <4.0 | — | <4.0 | — | <4.0 | — |
| **16** | 8.9 | 106 | 8.0 | 110 | <4.0 | — |
| **17** | 9.0 | 101 | 8.4 | 112 | 7.8 | 93 |
| **18** | 8.9 | 99 | 9.0 | 104 | 8.2 | 111 |
| **19** | 9.3 | 104 | 8.3 | 111 | 8.3 | 126 |
| **20** | 9.6 | 98 | 7.8 | 103 | 7.9 | 120 |
| **21** | 8.3 | 119 | 7.1 | 39 | <4.0 | — |
| **22** | 8.3 | 99 | 7.9 | 56 | 7.6 | 82 |
| **23** | 7.0 | 122 | <4.0 | — | <4.0 | — |
| **24** | 8.6 | 102 | 7.7 | 100 | 7.5 | 113 |
| **25** | 8.5 | 99 | <4.0 | — | <4.0 | — |
| **26** | 7.6 | 97 | <4.0 | — | <4.0 | — |
| **27** | 7.6 | 104 | <4.0 | — | <4.0 | — |
| **28** | 6.8 | 75 | <4.0 | — | <4.0 | — |
| **29** | 7.9 | 104 | <4.0 | — | <4.0 | — |
| **30** | 7.4 | 107 | <4.0 | — | <4.0 | — |

[a]See ref 20 for a description of the assay. Each entry represents the mean of at least two experiments, with $pEC_{50}$s having an average SEM of ±0.11.
[b]% of phenylephrine response (40 μM).

**Table 2.** Binding affinities for selected phenoxymethylimidazolines[a]

| | $\alpha_{1A}$ | $\alpha_{1B}$ | $\alpha_{1D}$ |
|---|---|---|---|
| | $pIC_{50}$ (±SEM)[b] | $pIC_{50}$ (±SEM) | $pIC_{50}$ (±SEM) |
| **5** | 7.56 (±0.03) | 6.13 (±0.03) | 6.49 (±0.02) |
| **7** | 6.94 (±0.01) | 5.69 (±0.02) | 5.95 (±0.07) |
| **8** | 7.30 (±0.03) | 5.89 (±0.06) | 6.59 (±0.01) |
| **11** | 5.89 (±0.07) | 5.61 (±0.09) | 5.85 (±0.11) |
| **18** | 7.49 (±0.06) | 6.57 (±0.01) | 7.27 (±0.10) |
| **25** | 7.46 (±0.08) | 6.11 (±0.01) | 6.38 (±0.02) |

[a]See ref 21 for a description of the assay.
[b]Each entry is the mean of at least two experiments.

## Conclusions

A number of novel $\alpha_1$ agonists have been identified in the 2′-heteroaryl-2-(phenoxymethyl)imidazoline series, including some compounds with sub-nanomolar agonist potencies at the cloned human $\alpha_{1A}$-adrenoceptor (**19** and **20**). Several compounds in the series displayed agonist subtype selectivity for the cloned human $\alpha_{1A}$-adrenoceptor, with compounds **7**, **25**, **26**, **27**, **29** and **30** exhibiting greater than 1000-fold selectivity versus the cloned human $\alpha_{1B}$- and $\alpha_{1D}$-adrenoceptors in our functional agonism assay. These selective $\alpha_{1A}$-adrenoceptor agonists are useful tools to test the relationship between $\alpha_{1A}$-subtype selectivity and uroselectivity in animal models.

## References and Notes

1. (a) The pharmacologically-defined native $\alpha_1$-adrenoceptors are identified as $\alpha_{1A}$, $\alpha_{1B}$ and $\alpha_{1D}$. The corresponding subtypes characterized by molecular cloning techniques are designated as $\alpha_{1a}$, $\alpha_{1b}$ and $\alpha_{1d}$. For a brief review of $\alpha_1$-adrenoceptor molecular pharmacology and a recent discussion of adrenoceptor classification, see: Zhong, H.; Minneman, K. P. *Eur. J. Pharmacol.* **1999**, *375*, 261. (b) Guarino, R. D.; Perez, D. M.; Piascik, M. T. *Cell. Signal.* **1996**, *8*, 323. (c) Hieble, J. P. *Pharm. Acta Helv.* **2000**, *74*, 163. (d) Alexander, S.; Peters, J.; Mead, A. *Trends Pharmacol. Sci.* **1998**, *Suppl*, 1.
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10. 2′-Phenyl-2-(phenoxymethyl)imidazoline is not a novel compound; see: Pigini, M.; Bousquet, P.; Brasili, L.; Carrieri, A.; Cavagna, R.; Dontenwill, M.; Gentili, F.; Gianella, M.; Leonetti, F.; Piergentili, A.; Quaglia, W.; Carotti, A. *Bioorg. Med. Chem.* **1998**, *6*, 2245.

11. All yields are unoptimized. Most reactions were run only once and the reported yield represents the recovery of isolated clean material from that single reaction.
12. This is a variation of a common approach to 2-(phenoxymethyl)imidazolines. For example, see: Monkovic, I.; Wllner, D.; Adam, M. A.; Brown, M.; Crenshaw, R. R.; Fuller, C. E.; Juby, P. F.; Luke, G. M.; Matiskella, J. A.; Montzka, T. A. *J. Med. Chem.* **1988**, *31*, 1548.
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14. The phenol for compound **18** was prepared via the Suzuki coupling of commercially available 1-*tert*-butoxycarbonyl-2-pyrrolylboronic acid and 2-bromophenol.
15. Isothiazoles were formed as described in: Buggle, K.; Fallon, B. *J. Chem. Res. Miniprint* **1988**, *11*, 2664.
16. The pyrimidine was formed in a manner similar to that described in: Khilya, V. P.; Kornilov, M. Y.; Gorbulenko, N. V.; Golubushina, G. M.; Kovtun, E. N. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1985**, *21*, 1273.
17. (a) This two-step procedure is based on literature precedent. Step one: Hill, A. J.; Aspinall, S. R. *J. Am. Chem. Soc.* **1939**, *61*, 822. (b) Step two: Amemiya, Y.; Miller, D. D.; Hsu, F.-L. *Synth. Commun.* **1990**, *20*, 2483.
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20. Human $\alpha_{1A}$ (clone #137-12)-, $\alpha_{1B}$ (clone #37-11)- and $\alpha_{1D}$ (clone #16-7)-adrenoceptors were expressed in Rat-1 fibroblast cells. Receptor activation was determined via calcium mobilization through the Gq coupled PLC pathway using calcium-sensitive fluorescent dyes (Calcium Green-Molecular Probes C 3011), measured by a Fluorescent Light Imaging Plate Reader (FLIPR). Eleven-point concentration–response curves were calculated as percent of the 40 μM phenylephrine response, with the highest sample concentration typically 5 μM. The assay results for NS-49 and cirazoline are shown for comparative purposes.
21. Affinity of compounds at $\alpha_1$-adrenoceptor subtypes was determined by radioligand binding techniques using membranes prepared from Rat-1 fibroblasts expressing human $\alpha_{1A}$-, $\alpha_{1B}$-, and $\alpha_{1D}$-adrenoceptors as previously described. See: Gobel, J.; Saussy, D. L.; Goetz, A. S. *J. Pharmacol. Toxicol.* **1999**, *42* (4), 237.
22. Other researchers have noted this phenomenon, and usually attribute it to the compounds having different intrinsic activities at the different subtypes. For a discussion, see ref 1(a), p. 264.