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Two Novel and Potent 3-[(*o*-Methoxyphenyl)piperazinylethyl]-5-phenylthieno[2,3-*d*]pyrimidine-2,4-diones Selective for the α_{1D} Receptor

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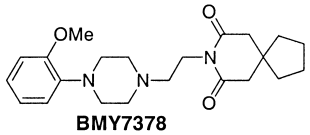
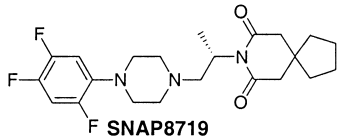
Abstract—The synthesis and in vitro characterization of A-119637 and A-123189, two novel, selective and potent α_{1D} antagonists, are described.

To date, three distinct subtypes of the α_1-receptor have been identified by both molecular biological (α_{1a}, α_{1b}, and α_{1d}) and classical pharmacological (α_{1A}, α_{1B}, and α_{1D}) means.[1] Defining the physiological roles of the α_1 subtypes in various organs has been the subject of intensive research efforts. The preponderance of evidence currently supports the hypothesis that the α_{1A} receptor is primarily responsible for mediating adrenergic prostatic tone.[2] The therapeutic relevance of these findings has been borne out in the clinical setting with BPH patients where tamsulosin (α_{1a}:α_{1b} selectivity $\approx 20\times$)[3] has been reported to possess improved prostate selectivity relative to earlier non-subtype selective agents.[4] Equally well-defined roles for the α_{1B} and α_{1D} subtypes have yet to be established. Several lines of evidence point to the importance of the α_{1B}[5] and α_{1D}[6] receptors in the maintenance of vascular tone. In the human bladder detrusor, α_{1d} mRNA has been shown to be the dominant α_1 subtype.[7] In a related study, the α_{1D} selective antagonist BMY7378 reportedly inhibited involuntary detrusor contractions in a rat model of bladder outlet obstruction.[8] Thus, it has been suggested that α_{1D} receptor blockade may ameliorate the irritative symptoms of BPH that result from involuntary contractions of the bladder smooth muscle.

A major factor that has limited the ability to conduct definitive in vivo studies on the role of the α_{1D} receptor has been the absence of highly potent and selective ligands devoid of ancillary pharmacology. For example, BMY7378 possesses equal affinity at the rat 5-HT_{1A} and α_{1d} receptors.[9] Likewise, the α_{1d} selective benzazepines SK&F 104856 and SK&F 106686 possess significant activity at the α_{2b} receptor.[10] More recently, SNAP8719, an analogue of BMY7378, has been described as an α_{1d} ligand with similar or improved selectivity versus the other α_1 receptor subtypes and inactive at a range of other receptors.[11] In vitro functional characterization of SNAP8719 has yet to be described in the literature. Unlike many of the selective α_{1A} antagonists, all of the currently known α_{1d} selective ligands have an affinity for this receptor of around 1 nM or greater. Therefore, the discovery of more potent subtype selective ligands would undoubtedly facilitate study of the physiological role played by the α_{1D} receptor. We describe herein two novel α_{1d} selective antagonists with potencies of less than 1 nM in both radioligand binding and in vitro functional assays.



BMY7378



SNAP8719

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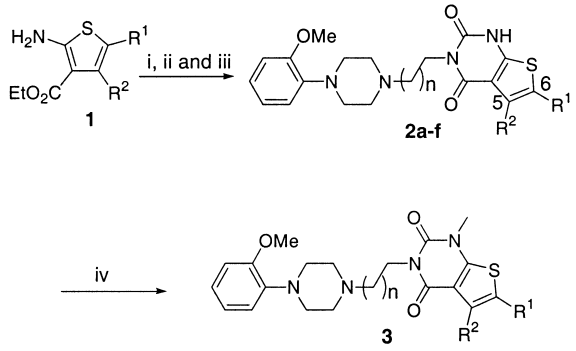
The title compounds described in this report were prepared in a straightforward fashion according to the method of Russell et al.[12,13] (Scheme 1). Briefly, the 2-amino-3-carboethoxythiophenes (**1**) were condensed with an ω-chloroalkylisocyanate in toluene at reflux, followed by reaction of the intermediate ω-chloroalkylureas with 2-methoxyphenylpiperazine and cyclization to the thienopyrimidine-2,4-diones by treatment with potassium *tert*-butoxide. Methylation of the N-1 position was accomplished by reaction with NaH then MeI. The starting substituted 2-amino-3-carboethoxythiophenes were synthesized as described by Gewald.[14]

Compounds were evaluated for their binding affinities at the cloned human and rat α_{1d} receptors versus the human α_{1a} and α_{1b} receptors as well as the bovine α_{1a} and tissue derived rat α_{1A} from the rat submaxillary gland.[3] Functional antagonism was demonstrated using the rat vas deferens, spleen and aorta as tissue models of the α_{1A}, α_{1B}, and α_{1D} receptors respectively.[3] Ancillary binding affinities at the α_{2a}, α_{2B}, α_{2c}, D_1, D_2, 5-HT_1, and 5-HT_2 receptors were determined for two compounds.

With the exception of compound **2f**, all compounds displayed high affinity for the α_{1d} receptors (Table 1). A-119637 (**2a**) and A-123189 (**2b**) displayed selectivities between 10- to 20-fold for the α_{1d} receptor over the human α_{1a} and rat α_{1A} receptors. Slightly greater selectivities were observed for α_{1d} versus α_{1b}, with A-119637 being 18-fold selective and A-123189 29-fold selective at the human clones. Interestingly, A-119637 and A-123189 possess 10-fold greater affinity for the bovine α_{1a} receptor than for the human α_{1a} and rat α_{1A} receptors. Relative to the α_{1d} selective ligand BMY7378, both A-119637 and A-123189 have approximately 3× greater binding affinity for the human α_{1d} receptor, although also correspondingly lower selectivity for α_{1d} over α_{1a} and α_{1b}. The unsubstituted compound **2d** possesses only 4-fold selectivity for α_{1d} over α_{1b} and is nonselective for α_{1d} versus α_{1a}. Extending the chain length to three carbons results in a 40-fold decrease in affinity for the α_{1d} receptor and a total loss of selectivity (compound **2f**). Moving the phenyl substituent to the 6 position (compound **2e**) reduces the selectivity to a level comparable with the unsubstituted compound **2d**. The 6-methyl-5-phenyl substitution pattern (compound **2c**) produces α_{1d} selectivity qualitatively similar to A-119637 and A-123189. Moving the methyl group to the N-1 position (compound **3**) reduces affinity for the α_{1d} receptor while having little effect on the α_{1a} and α_{1b} subtypes. It appears therefore, that the 5-phenyl substituent is responsible for the α_{1d} selectivity versus α_{1a} and imparts additional selectivity over α_{1b} relative to the core structure.

Both A-119637 and A-123189 exhibit potent antagonism in the α_{1D} functional model, the rat aorta (Table 2) and show ~100-fold selectivity over the rat vas deferens and spleen. Both of these compounds display over 100-fold greater potency in the rat aorta than BMY7378. Relative to BMY7378, A-119637 and A-123189 are less α_{1d} selective in their binding affinities (see Table 1), however the tissue selectivities for the rat aorta are equivalent or superior. The reason for the discrepancy between these two readouts of α_{1D} selectivity is presently unknown.

Compounds A-119637 and A-123189 were also screened at the α_{2a}, α_{2B}, α_{2c}, D_1, D_2, 5-HT_1, and 5-HT_2 receptors



Scheme 1. (i) $Cl(CH_2)_nCH_2NCO$, toluene, reflux; (ii) 2-methoxyphenylpiperazine, Hünig's base, acetonitrile, reflux; (iii) KO*t*Bu, ethanol, reflux; (iv) NaH, DMF; MeI.

Table 2. In vitro functional activity[a]

Compound	Rat vas deferens[b] pA2	Rat spleen[c] pA2	Rat aorta[d] pA2
A-119637	8.07 (1.03)	8.69 (1.00)	10.6 (0.94)
A-123189	8.36 (1.01)	8.76 (0.81)	10.7 (0.77)
BMY7378	5.98 (0.80)	7.37 (0.92)	8.22 (1.18)

[a]Schild slopes shown in parentheses.
[b]α_{1A}.
[c]α_{1B}.
[d]α_{1D}.

Table 1. α_1 Subtype radioligand binding K_i (nM)[a]

Compound	R^1	R^2	n	α_{1A} (rat)	α_{1a} (human)	α_{1a} (bovine)	α_{1b} (human)	α_{1d} (human)	α_{1d} (rat)
2a (A-119637)	H	Ph	1	2.43	2.63	0.274	4.66	0.252	0.213
2b (A-123189)	H	*m*-Tolyl	1	3.47	4.17	0.348	9.09	0.312	0.170
2c	Me	Ph	1	1.97	2.63	0.377	3.70	0.466	0.251
2d	H	H	1	0.523	0.344	0.181	1.22	0.308	0.229
2e	Ph	H	1	0.578	0.868	0.248	1.86	NT	0.361
2f	H	Ph	2	9.58	8.49	1.25	15.8	7.15	8.20
3	H	Ph	1	2.62	3.10	0.436	4.47[b]	NT	0.710
BMY7378		—	—	112	130	43	94.3	0.778	0.959
SNAP8719	—	—	—	NA	14,900[c]	NA	165[c]	1.3[c]	NA

[a]K_i values the average of 3–6 determinations.
[b]Hamster clone.
[c]Value from ref 11. NT = not tested. NA = not available.

Table 3. Ancillary binding profiles of A-119637 and A-123189

Receptor[ab]	A-119637	A-123189
α_{2a}[e]	77.8	82.5
α_{2B}[f]	71.0	66.6
α_{2c}[e]	74.7	82.0
D_1[f]	6090	12300
D_2[f]	50.0	17.0[c]
5-HT_1[f]	5490[d] (0.98)	12,300[d] (1.4)
5-HT_2[f]	137	2190

[a]K_i (nM).
[b]Average of 3–6 determinations.
[c]Two determinations.
[d]Hill slope in parentheses.
[e]Cloned human receptor.
[f]Native rat receptor.

(Table 3) and found to have considerably less affinity for all these receptors relative to the α_{1d} receptor. The low affinities of A-119637 and A-123189 for the 5-HT_1 receptor with Hill slopes near unity suggest weak affinity for the 5-HT_{1A} receptor. This distinguishes these compounds from BMY7378, for which the affinity at the 5-HT_{1A} receptor could be a potential confounding factor in evaluating the in vivo functional role of the α_{1D} receptor. Activity at the D_2 receptor was the greatest source of cross reactivity for A-119637 and A-123189, although the affinities versus α_{1d} are still 50- to 100-fold weaker.

In conclusion, A-119637 and A-123189 are two novel, selective and potent α_{1D} antagonists in both the α_1 clonal cell lines and in in vitro tissue strips. These agents share with BMY7378 and SNAP8719 the common structural features of a substituted phenylpiperazine and a heterocycle attached via a two-carbon linker. The 5-phenyl substitution on the heterocyclic attachment was shown to impart the α_{1D} selectivity.[15]

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