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Communications to the Editor

De Novo Design of a Novel Oxazolidinone Analogue as a Potent and Selective α_{1A} Adrenergic Receptor Antagonist with High Oral Bioavailability

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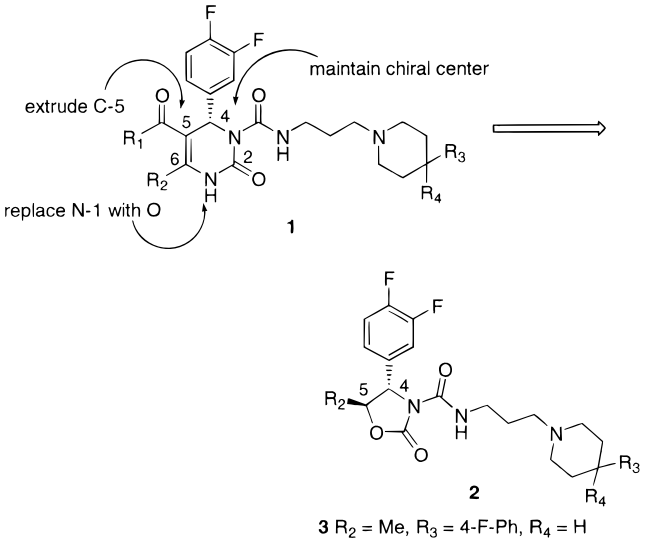
Introduction. Benign prostatic hyperplasia (BPH),[1] a urological disorder which results in obstruction to urine flow, is currently treated with a number of non-subtype-selective α_1 adrenoceptor antagonists such as terazosin,[2] doxazosin,[3] and tamsulosin.[4] These clinical agents, however, are associated with a number of cardiovascular side effects such as postural hypotension, presumably via blockade of vascular α_1 adrenergic receptors in addition to the prostatic α_1 adrenoceptors. It has been postulated that selective blockade of the α_{1A} adrenoceptor, the predominant α_1 receptor in the prostate, could provide symptomatic relief of BPH without the need for the dose titration which is required for several of the nonselective α_1 antagonists.[5]

Chart 1



3 R_2 = Me, R_3 = 4-F-Ph, R_4 = H

A number of α_{1A} subtype-selective antagonists representing different structural classes of compounds such as SNAP 5089 (dihydropyridine),[6] GG818 (oxazole),[7] and A-131701 (benz[*e*]isoindole)[8] have been reported in the literature over the past few years. We have recently reported that the dihydropyrimidinones, represented by general structure **1** (Chart 1), show subnanomolar binding affinity for α_{1A} with greater than 300-fold selectivity over α_{1B}, α_{1D}, and α_2 adrenoceptors.[9,10] Many of these compounds, however, show marginal bioavailabilities (0−30%) and short plasma half-lives (<4 h) in rats and dogs. Modification of the piperidine moiety or the linker portion ($-CONHCH_2CH_2CH_2-$) did not improve the pharmacokinetic profile of the resulting compounds.[10] Therefore, we decided to replace the dihydropyrimidinone moiety in **1** with another heterocycle by utilizing the known structure−activity relationship (SAR) in the dihydropyrimidinone series. The SAR for **1** reveals that (1) the chiral center at the C-4 position of the dihydropyrimidinone is important for the observed binding affinity for the α_{1A} receptor, (2) a number of modifications at the C-5 and C-6 positions of the

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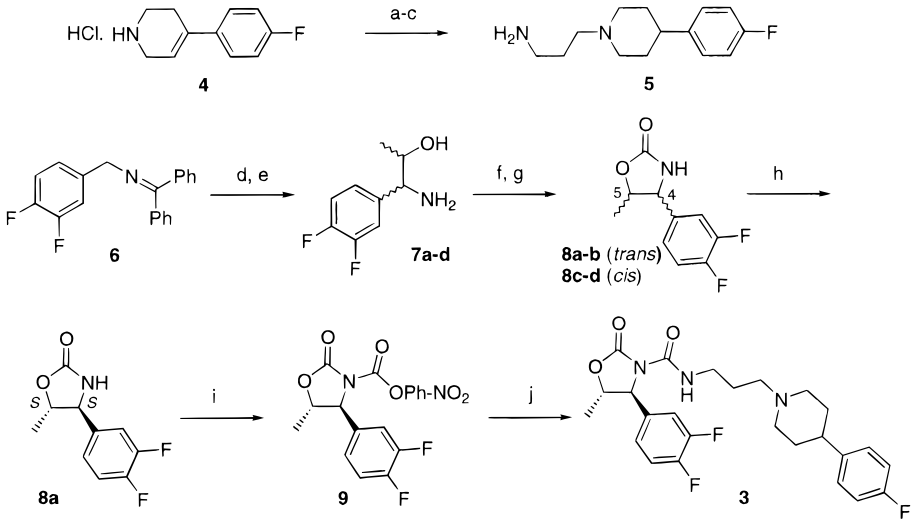
Scheme 1[a]



[a] (a) H_2, Pd−C, MeOH, 95%; (b) 3-bromopropylphthalimide, K_2CO_3, DMF, 88%; (c) hydrazine, MeOH, reflux, 93%; (d) *t*-BuLi, THF, CH_3CHO; (e) CH_3ONH_2·HCl, MeOH, 68% for two steps; (f) Boc_2O, $CHCl_3$, 91%; (g) NaH, THF, 89%; (h) separation of the diastereomers by column chromatography and separation of the enantiomers by chiral phase HPLC, 16%; (i) *n*-BuLi, THF, 4-nitrophenyl chloroformate, 75%; (j) **5**, THF, 89%.

dihydropyrimidinone are tolerated, suggesting a less critical role for the substituents at these positions in achieving an optimum binding and selectivity profile, and (3) the hydrogen on the N-1 of the dihydropyrimidinone can be replaced without significant loss in binding affinity for the α_{1A} receptor.[11] We envisioned the replacement of the dihydropyrimidinone with an oxazolidinone moiety **2**, where the chiral center from **1** is maintained, the C-5 carbon atom is extruded, and the nitrogen at the 1-position is replaced with an oxygen atom. In this Communication, we describe the synthesis of such a novel oxazolidinone (**3**, SNAP 7915) and the in vitro and in vivo profile of this compound.

Chemistry. The synthesis of compound **3** is depicted in Scheme 1. Commercially available 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (**4**) was converted into 3-[4-(4-fluorophenyl)piperidin-1-yl]propylamine (**5**) by a three-step sequence in high yield. The vicinal amino alcohols **7a**−**d** synthesized from **6** by a known procedure[12] were cyclized into oxazolidinones **8a**−**d** via a two-step process. The trans isomers **8a**,**b** (in which the protons at the C-4 and C-5 positions of the oxazolidinone ring are in trans spatial orientation) were separated from the cis isomers **8c**,**d** by column chromatography. The relative stereochemistry was assigned using the NOE observed between the C-4 and C-5 protons. The two enantiomers of the *trans*-oxazolidinone were resolved by chiral phase HPLC.[13] The (+)-trans enantiomer **8a**, which was found to possess 4*S*,5*S* absolute stereochemistry,[14] was treated with *n*-BuLi and the resulting solution was converted to the *p*-nitrophenyloxycarbonyl derivative **9** in 75% yield. Treatment of **9** with amine **5** led to formation of the desired product **3** in high yield.

Results and Discussion. Compound **3** showed subnanomolar (0.17 nM) binding affinity for the recombinant human α_{1A} adrenoceptor and greater than 700fold selectivity over α_{1B} and α_{1D} receptors in competition binding assays using [^{125}I]HEAT (Table 1).[15] High binding affinity for the α_{1A} adrenoceptor was also observed for the rat and dog recombinant α_1 receptors (0.36 and 0.23 nM, respectively), indicating no significant species difference in the α_1 binding of **3**. Compound **3** did not show significant affinity for the rat L-type calcium channel and a number of G-protein coupled receptors such as α_2 adrenergic, histamine, and serotonin receptors (Table 1).[16−22] In addition, compound **3** did not exhibit significant cross-reactivity when screened against a panel of more than 30 G-protein coupled receptors.[23] The binding affinity and selectivity of **3** for the α_{1A} receptor are similar to those observed for a number of dihydropyrimidinones such as **1**.[9,10]

Table 1. Binding Affinity Profile of **3** for Recombinant Receptors and Tissue Preparations

assay	radioligand	K_i (nM)[a]	select[b]
human $\alpha_{1A}/\alpha_{1B}/\alpha_{1D}$	[^{125}H]HEAT	0.17 ± 0.03/119 ± 24/122 ± 6	>700
dog $\alpha_{1A}/\alpha_{1B}/\alpha_{1D}$	[^{125}H]HEAT	0.23 ± 0.01/121 ± 13/133 ± 8	>500
rat $\alpha_{1A}/\alpha_{1B}/\alpha_{1D}$	[^{125}H]HEAT	0.36 ± 0.09/79 ± 14/62 ± 9	>200
human $\alpha_{2A,2B,2C}$	[^{3}H]rauwolscine	>45	>250
rat L-type Ca-channel[c]	[^{3}H]nitrendipine	>1000	>5000
H_1 (human brain)[c]	[^{3}H]pyrilamine	54 ± 27	>200
human H_2	[^{3}H]tiotidine	>1000	>5000
5-$HT_{1A,1B,1D,2A}$	[^{3}H]serotonin	>500	>1000

[a] K_i values obtained using radioligands in competition binding assays with recombinant receptors unless otherwise noted. [b] Selectivity = K_i for other receptor/K_i for α_{1A} receptor. [c] Tissue preparation.

The comparison of functional potency of the α_{1A}-selective antagonist **3** and the nonselective α_1 antagonist terazosin in a number of in vitro and in vivo assays is shown in Table 2.[24] Compound **3** potently antagonized A-61603-[25] or phenylephrine-induced contraction of human, dog, and rat prostatic tissues. It is important to note that the antagonist potencies (K_b = 0.1−0.33 nM) observed for **3** in the functional assays were in close agreement with the binding affinities (K_i = 0.17−0.36 nM) for the cloned human, dog, and rat α_{1A} receptors.

In anesthetized rats, compound **3** showed higher functional potency (AD_{50} = 12 μg/kg) to inhibit the phenylephrine-induced contractile response of the in

Table 2. In Vitro and in Vivo Functional Profiles and Pharmacokinetics for **3** and Terazosin

assay	agonist	**3**	terazosin
K_b human prostate (nM)	A-61603	0.1 ± 0.035	25 ± 2.7
K_b dog prostate (nM)	phenylephrine	0.33 ± 0.05	130 ± 33
K_b rat prostate (nM)	A-61603	0.26 ± 0.13	25 ± 3
K_b rat aorta (nM)	norepinephrine	>1000	19 ± 2.4
AD_{50} in situ rat prostate (μg/kg)	phenylephrine	12 ± 1.8	52 ± 15
K_b dog IUP[a] (μg/kg)	phenylephrine	3.0	16
DBP_{15},[b] dog (μg/kg)	phenylephrine	>300	72
rat: F, $t_{1/2}$ (h)		25%,[c] 6.0 ± 1.2	49%, 7.5
dog: F, $t_{1/2}$ (h)		74 ± 17%,[d] >12	

[a] Intra-urethral pressure. [b] DBP_{15} is the dose of a compound required to cause a drop of 15 mmHg in diastolic blood pressure. [c] No SD available. Oral bioavailability was calculated using mean oral AUC values. iv: 1 mg/kg dose (n = 4), AUC = 559 ± 139 ng·h/mL; po: 3 mg/kg dose (n = 4), AUC = 419 ± 128 ng·h/mL. [d] iv: 1 mg/kg dose (n = 3), AUC = 2274 ± 488 ng·h/mL; po: 3 mg/kg dose (n = 3), AUC = 4900 ± 320 ng·h/mL; the values are mean ± SD.

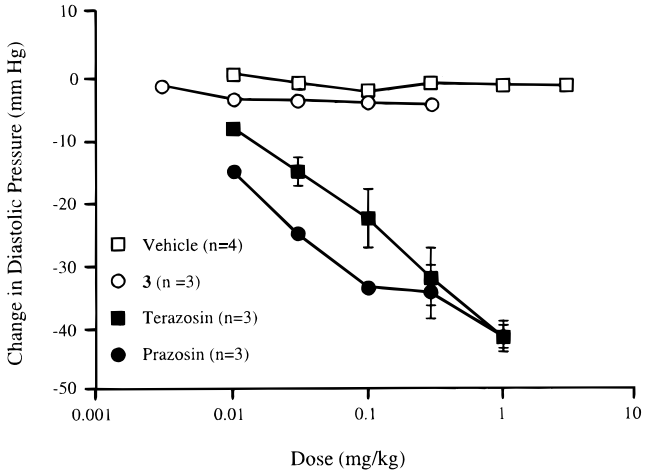


Figure 1. Effect of α_1 antagonists on baseline diastolic blood pressure in anesthetized male dogs (10 min post-intravenous administration). Data shown are mean ± SE. The error bars are not shown when smaller than the size of the symbols used.

situ prostate compared to terazosin (AD_{50} = 52 μg/kg). Compound **3** exhibited significantly lower potency to inhibit agonist-induced contractions of isolated rat aorta (K_b > 1 μM) relative to its potency to inhibit agonist-induced contractions of isolated rat prostate (K_b = 0.26 nM). The observed selectivity for inhibition of prostatic vs aortic contraction is consistent with the binding selectivity exhibited by **3** for the recombinant rat α_{1A} adrenoceptor over the α_{1D} adrenoceptor.[26] In contrast, terazosin displayed nearly equal potencies in the rat aorta and prostate tissue preparations (K_b ~ 20 nM).

Compound **3** failed to show any hypotensive effects in the dog even at a high dose of 300 μg/kg. Terazosin, on the other hand, showed hypotensive effects (defined as a 15% drop in diastolic blood pressure, DBP_{15}) at a dose of 72 μg/kg. In a separate experiment, both terazosin and prazosin, unlike compound **3**, showed a dose-dependent decrease in the diastolic blood pressure (Figure 1) in anesthetized male dogs.

The uroselectivity of compound **3** (defined as the ratio of DBP_{15} to K_b for inhibition of a phenylephrine-induced increase in intra-urethral pressure) was assessed in anesthetized mongrel dogs. Compound **3** displayed at least 100-fold uroselectivity, in contrast to the 4-fold selectivity observed for terazosin in these models. A significantly lower dose of **3** (3 μg/kg) compared to terazosin (16 μg/kg) was required to block the effect of phenylephrine. These observations support the hypothesis that an α_{1A}-selective antagonist may be able to provide symptomatic relief for BPH patients while causing fewer cardiovascular side effects.

Compound **3** exhibited significantly improved oral bioavailability and plasma half-life in rats (25% and 6 h) and dogs (74% and >12 h) compared to the dihydropyrimidinones represented by **1** (oral bioavailability < 25% and half-life < 6 h in rats and dogs).

On the basis of its high binding affinity and selectivity for the α_{1A} adrenoceptor, its unique structure, and its excellent pharmacokinetic and pharmacodynamic properties, compound **3** (SNAP 7915) has emerged as one of the most interesting α_{1A} antagonists reported to date.

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Supporting Information Available: Experimental procedures and characterization data for **3** and other intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Chiralcel OD column (20 × 250 mm) using 80% hexane/20% ^{i}PrOH/0.1% Et_2NH as the eluting system (12 mL/min) under isocratic conditions (UV 254 nm). Retention times for the two isomers of the *trans*-oxazolidinone were 12.1 min {$[\alpha]_D = +36.4$ (c = 0.25, acetone)} and 15.6 min {$[\alpha]_D = -30.8$ (c = 0.20, acetone)}, respectively.

(14) The absolute and relative stereochemistry of **3** was confirmed by a combination of NOE studies and an alternate synthesis from (*S*)-(+)-methyl lactate. The details will be published elsewhere.

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