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DESIGN AND SYNTHESIS OF NOVEL DIHYDROPYRIDINE ALPHA-1A ANTAGONISTS

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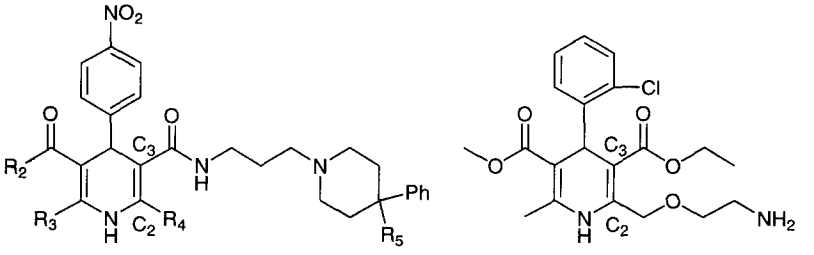
Abstract: A series of analogs of SNAP 5150 containing heteroatoms at C_2 or C_6 positions is described. Herein, we report that the presence of alkyl substituted heteroatoms at the $C_{2(6)}$-positions of the dihydropyridine are well tolerated. In addition, **15** inhibited the phenylephrine induced contraction of dog prostate tissue with a K_b of 1.5 nM and showed a K_b (DBP, dogs, μg/kg)/K_b (IUP, dogs, μg/kg) ratio of 14.8/2.5.

Introduction: Benign Prostatic Hyperplasia (BPH) is characterized by a nodular enlargement of prostatic tissue resulting in obstruction of the urethra.[1] This condition occurs in over 50% of the male population above age 60, and leads to a variety of urological symptoms including increased frequency in urination, nocturia, a poor urine stream and hesitancy or delay in starting urine flow. The urinary obstruction in men affected by BPH results from a combination of two components: mechanical constriction of the urethra due to increased prostatic mass



SNAP 5089: R_2=OMe, R_3=Me, R_4=Me, R_5=Ph
SNAP 5150: R_2=NH_2, R_3=Me, R_4=Me, R_5=Ph

Amlodipine

Figure 1. Amlodipine and Dihydropyridine α_{1a} Antagonists

and a dynamic component attributable to increased noradrenergic tone in the hyperplastic prostate. Several α_{1a} adrenoceptor antagonists of the quinazoline class such as prazosin, terazosin, doxazosin, and alfuzosin have

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been approved for treatment of BPH. They work by relaxing the smooth muscle of the prostate and other urinary tract tissues by the blockage of the adrenergic neurosystem.[2] These agents also show hypotensive side effects,[3] presumably as a result of their lack of selectivity for any one of the three α_1 adrenoceptor subtypes[4-6] (e.g., See Prazosin, Table 1).

Recently, we reported that dihydropyridine analogs SNAP 5089[7] and SNAP 5150[8] (Figure 1) are high affinity and selective α_{1a} antagonists, which are devoid of calcium channel antagonist activity associated with niguldipine. As part of a program to optimize the properties of SNAP 5150 analogs, we planned to introduce heteroatoms at C_2 and C_6 positions of the dihydropyridine ring. We had previously found that the presence of C_2 and C_6-alkyl group substitutions larger than an ethyl group on the dihydropyridine ring were accompanied with loss of activity and/or selectivity.[8] In addition, SNAP 5150 was found to have relatively short plasma half life typical of classical dihydropyridine Ca^{++} channel antagonists ($t_{½}$ < 2 h, bioavailability <10% in rat). The dihydropyridine Ca^{++} channel antagonist amlodipine (Figure 1) contains an aminoethoxymethyl group at C_2/C_6 of the dihydropyridine.[9a] In addition to being a potent Ca^{++} channel antagonist, amlodipine was reported to have long $t_{1/2}$ (>20 h) and >60% bioavailabilities in rat and dog.[9b] The favorable pharmacokinetic properties of amlodipine have partially been attributed to its high basicity (pK_a 8.7) and water solubility.[9b] We were interested in probing whether the introduction of similar substituents onto the SNAP 5150 template would lead to selective α_{1a} antagonists without Ca^{++} channel activity while maintaining desirable pharmacokinetic properties. The initial focus was to establish whether heteroatoms at C_2 and C_6 positions were compatible with α_{1a} antagonism.

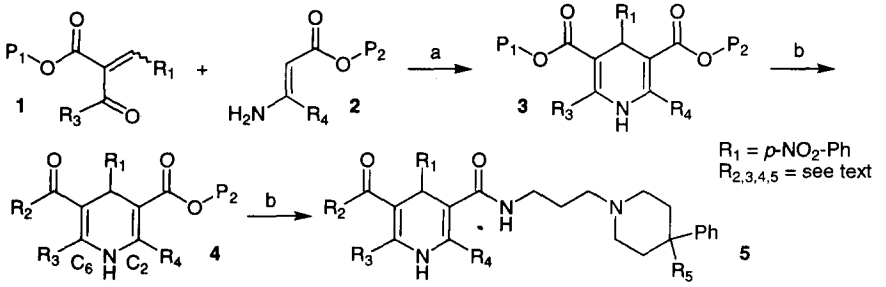
Table 1. Binding Affinities (K_i, nM) of Amlodipine , Prazosin, SNAP 5089, and SNAP 5150 at Human α-Adrenoceptors and Rat C-Type Ca^{++} Channel

Compound	**h α_{1a}**	h α_{1b}	h α_{1d}	h α_{2a}	h α_{2b}	h α_{2c}	r Ca^{++}	h $\alpha_{1b,1d,2a,2b,2c}$/h α_{1a}	rCa^{++}/h α_{1a}
Amlodipine	**2344**	7943	5370	-	-	-	2.0	>2	<1
Prazosin	**0.58**	0.55	0.33	-	-	-	-	<1	NA
SNAP 5089	**0.35**	220	540	2417	1088	912	670	>600	>1000
SNAP 5150	**1.87**	367	398	369	420	324	>1000	>150	>500

Biological Methods: The binding assays[7,8] (n = 3, ±5%) and functional α1 antagonism[10] in isolated prostate tissue are reported elsewhere.

Synthesis: We recently reported a general synthetic methodology for the syntheses of the dihydropyridine analogs described herein.[11] This methodology requires a Hantzsch cyclocondensation of protected benzylidene **1** and enamide **2** to form the doubly protected dihydropyridine intermediate **3** (Scheme 1). The resulting doubly protected dihydropyridine intermediate **3** (Scheme 1) was sequentially deprotected followed by attachment of the desired groups at C_3 and C_5-positions using conventional coupling agents such as DCC, ECD, or CDI to

give the final product **5**. Our previous studies[7,8] had indicated that 4-nitrophenyl functionality was an optimal substituent at the C_4-position of the dihydropyridine. The present study focuses predominately on molecules with a 4-(4-nitrophenyl)dihydropyridine functionality. The synthesis of the aminopropylpiperidine side chains is described elsewhere.[7,8] The terminal azido groups of our $C_{2(6)}$-substituted analogs were reduced with trimethylphosphine in ethyl acetate and quenched with water.[12] Using double protection strategy, we were able to examine the SAR of a variety of $C_{3,5}$-carboxylic acid derivatives described herein.



P_1 and P_2 = one of CH_2CH_2CN, Benzyl, CH_2CH_2TMS or *t*-Bu
(a) EtOH, *t*-BuOH, heat; (b) NaOH if CH_2CH_2CN, H_2/Pd/C if Benzyl, F^- if CH_2CH_2TMS and formic acid if *t*-Bu, then, amine + coupling agent such as DCC

Scheme 1. Synthesis of Dihydropyridines Using Doubly Protected Intermediates

Table 2. The Effect of C_2-Substituted Alkyl Chains on the Binding Affinities (K_i, nM)

Compound	R_2	R_3	R_4	R_5	h α_{1a}	h α_{1b}	h α_{1d}	h α_{2a}	h α_{2b}	h α_{2c}	$\alpha_{1\,b,1d,2a,2b,2c}/\alpha_{1a}$
6	NHEt	ethyl	propyl	Ph	**3.8**	181	380	955	507	442	>45
7	NHEt	ethyl	pentyl	Ph	**127**	127	380	-	-	-	>1

Table 3. The Effect of Heteroatoms at the C_2-Position on the Binding Affinities (K_i, nM)

Compd	R_2	R_3	R_4	R_5	h α_{1a}	h α_{1b}	h α_{1d}	h α_{2a}	h α_{2b}	h α_{2c}	$\alpha_{1\,b,1d,2a,2b,2c}/\alpha_{1a}$
8	NH_2	CH_3	$CH_2(CH_2)_3NH_2$	Ph	**4.4**	269	314	-	-	-	>70
9	NH_2	CH_3	$CH_2(CH_2)_2NH_2$	Ph	**3.8**	181	433	-	-	-	>45
10	NH_2	CH_2CH_3	$CH_2OCH_2CF_3$	Ph	**11.5**	177	417	2308	753	884	>15
11	NH_2	CH_2CH_3	CH_2OCH_3	Ph	**19.5**	192	729	575	288	513	>10
12	NH_2	CH_2CH_3	$CH_2(CH_2)_3OCH_3$	Ph	**5.1**	347	454	99	237	355	>20
13	NH_2	CH_2CH_3	$CH_2O(CH_2)_3NH_2$	Ph	**4.8**	447	948	813	1131	286	>60
14	NH_2	CH_2CH_3	$CH_2O(CH_2)_2N_3$	Ph	**3.3**	98.3	309	468	229	224	>30
15	NH_2	CH_2CH_3	$CH_2O(CH_2)_2NH_2$	Ph	**0.5**	326	514	403	902	204	>400

The Effect of C_2-Substitution (R_4): A systematic C_2-substitution using those listed in Table 3 were examined. We showed that the presence of heteroatoms at the C_2-position (R_4) effects the affinities and the selectivities of

the analogs differently than the alkyl chains (**6** and **7**, Table 2). For example, selected heteroatom substituted chains (R_4) such as methoxybutyl, aminopentyl, aminobutyl, methoxymethyl, aminoethoxymethyl and aminopropoxymethyl groups listed in Table 3 (**8–15**) gave rise to analogs with better affinity and selectivity profiles compared to compound **7** which contains a *n*-pentyl group at the C_2-position (Table 2). Interestingly, the potential photoaffinity ligand (compound **14**) containing a terminal azido group also binds with reasonable affinity and selectivity. The aminoethoxymethyl group at C_2-position was found to be the optimal substituent giving rise to excellent α_{1a} affinity and selectivity (e.g., **15**, SNAP 5399, Table 3, Figure 2). Furthermore, **15** showed negligible activity at the Ca^{++} channel binding assays (>10000 nM).

C_2- vs C_6-Substitution: Encouraged by the results obtained for compound **15**, we then examined compounds with aminoethoxymethyl groups at C_2 vs C_6 positions (Table 4). The α_{1a} affinities of analogs **16–18** containing aminoethoxymethyl groups at C_2 (R_4) or C_6 (R_3) remained at low nanomolar range. Nonetheless, the substitution of an aminoethoxymethyl group at the C_6-position was accompanied by a net loss of α_{1a} selectivity (**16** and **18**, Table 4).

Table 4. Effect of C_2 vs C_6-Substitution of Dihydropyridine Analogs on Binding Affinity (K_i, nM)

Compd	R_2	R_3	R_4	R_5	h α_{1a}	h α_{1b}	h α_{1d}	h α_{2a}	h α_{2b}	h α_{2c}	$\alpha_{1\,b,1d,2a,2b,2c}/\alpha_{1a}$
15	NH_2	Ethyl	$CH_2O(CH_2)_2NH_2$	Ph	**0.5**	326	514	403	902	204	>400
16	NH_2	$CH_2O(CH_2)_2NH_2$	ethyl	Ph	**1.7**	36.3	246	-	-	-	>20
17	NHEt	ethyl	$CH_2O(CH_2)_2NH_2$	Ph	**4.5**	785	1296	1698	2541	473	>100
18	NHEt	$CH_2O(CH_2)_2NH_2$	ethyl	Ph	**3.0**	254	447	-	-	-	>80

Characterization of the Enantiomers of SNAP 5399 (15): The enantiomers of SNAP 5399 were separated on a Chiralcel® AD column using a 84:3:13 mixture of hexane, ethanol and isopropanol (isopropanol contained 3% diethylamine). The (-)-enantiomer (1st HPLC eluent, $[\alpha]_{100} = -39.8$) was found to have higher affinity (0.4 nM)

Table 5. Binding Affinities (K_i, nM) for the Enantiomers of SNAP 5399 (**15**)

15	h α_{1a}	h α_{1b}	h α_{1d}	$\alpha_{1b,1d}/\alpha_{1a}$
(+/-)	**0.5**	326	514	>650
(+)	**5.9**	236	893	>40
(-)	**0.4**	505	1376	>1200

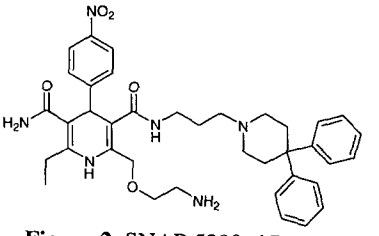


Figure 2. SNAP 5399, **15**

with selectivities greater than 1000-fold over the other human α-subtypes (Table 5). The (+)-isomer ($[\alpha]_{100}$ = +40.1) of SNAP 5399 exhibited an affinity of 5.9 nM at the α_{1a} receptor with >40 fold selectivity over the other α-subtypes.

Variations of the Arylpiperidine Side Chain in SNAP 5399 Series: Prior SAR[7,8] had indicated that the presence of a basic amino group of the piperidine as well as one terminal aromatic group was necessary to sustain the nanomolar affinities of our analogs. Therefore, we sought to change only one of the 4-phenyl groups of the piperidine ring to access the SAR of the 4,4-diphenylpiperidine ring (**19–22**, Table 6). These included substitution of one of the phenyl groups of the 4,4'-diphenylpiperidine with hydrogen (**19**), 4-methoxyphenyl (**20**), 4-carbomethoxy (**21**), and 4-dimethylaminomethyl (**22**) groups. Replacement of one of the phenyl groups of the diphenylpiperidine with a carbomethoxy group resulted in **21**, which showed low nanomolar α_{1a} affinity and good selectivity compared to the other alpha subtypes. Replacement of one of the phenyl groups of the diphenylpiperidine moiety with a hydrogen resulted in loss of selectivity of the analog while the affinity remained in the low nanomolar range (**19**, Table 6). In contrast, replacement of one of the phenyl groups of the diphenylpiperidine ring with dimethylaminomethyl moiety was found to be detrimental to the affinity (455 nM) of the analog, although, the selectivity of the analog **22** remained greater than 85-fold. Due to its favorable affinity, selectivity and polarity profile, SNAP 5522 (**21**) was selected as a tool compound for radioligand studies after the attachment of the Wood's reagent at the C_2-aminoethoxymethyl moiety.[10]

Table 6. The Effect of Piperidine Side Chains on the Binding Affinities K_i (nM) of SNAP 5399 Analogs

Compound	R_2	R_3	R_4	R_5	h α_{1a}	h α_{1b}	h α_{1d}	$\alpha_{1\,b,1d}/\alpha_{1a}$
19	NH_2	CH_3	$CH_2O(CH_2)_2NH_2$	H	**1.37**	17.9	166	>10
20	NH_2	CH_3	$CH_2O(CH_2)_2NH_2$	*p*-OCH_3-Ph	**6.31**	479	2073	>75
(5522) **21**	NH_2	CH_3	$CH_2O(CH_2)_2NH_2$	CO_2CH_3	**3.15**	840	1459	>260
22	NH_2	CH_3	$CH_2O(CH_2)_2NH_2$	$CH_2N(CH_3)_2$	**455**	38681	27542	>85

Conclusion: A series of high affinity and subtype selective a_{1a} antagonist analogs of SNAP 5150 containing alkyl substituted heteroatoms at C_2 and C_6 was designed and synthesized. The ex vivo activity of SNAP 5399 (**15**) was evaluated using isolated dog and human prostate tissues. The results show that **15** inhibited [^{3}H]prazosin binding with an IC_{50} of 0.6 nM in agreement with the results obtained from the cloned human α_{1a} receptor.[10] SNAP 5399 also inhibited the phenylephrine induced contraction of dog prostate with a K_b of 1.4–1.5 nM.[10] SNAP 5399 (**15**) and 5522 (**21**) exhibited over 200-fold selectivities with respect to the other α_1, α_2, Ca^{++}, 5-HT, D_1 ,D_2, D_3, and H_1 receptors. SNAP 5399, **15**, inhibited the phenylephrine induced contraction of dog prostate with a K_b of 1.5 nM and in vivo studies showed a DBP-K_b/IUP-K_b ratio of (14.8/2.5) 5.9. SNAP 5399 and SNAP 5522 displayed low bioavailabilities (<10%) and short $t_{1/2}$'s (<2 h) in rat and dog despite the presence of the aminoethoxymethyl functionality, which gave excellent pharmacokinetic properties to

amlodipine.[9b] This prompted us to search for other substitutes for the dihydropyridine ring. The design and synthesis of the new templates will be the subject of other reports which will be described in due course.

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