Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1621–1624

BIOORGANIC &
MEDICINAL
CHEMISTRY
LETTERS

Phenylacetamides as Selective α-1A Adrenergic Receptor Antagonists

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Received 6 April 2000; accepted 22 May 2000

Abstract—A novel class of potent and selective α-1a receptor antagonists has been identified. The structures of these antagonists were derived from truncating the 4-aryl dihydropyridine subunit present in known α-1a antagonists. The design principles which led to the discovery of substituted phenylacetamides, the synthesis and SAR of key analogues, and the results of select in vitro and in vivo studies are described. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Two mechanistically distinct drug classes are currently available to physicians for the clinical management of the urological disorder, benign prostatic hyperplasia (BPH). They are 5α-reductase inhibitors that function by reducing prostatic mass and thus help alleviate mechanical constriction of the urethra, and α-1 adrenergic receptor antagonists that act by relaxing tissue in the lower urinary tract (LUT) and thereby facilitate urine flow. Recently, the α-1 receptors have been divided into three subclasses: the α-1A, α-1B, and α-1D.[1,2] Among these, the α-1A receptor is believed to be primarily responsible for mediating smooth muscle contraction in the LUT and prostate.[3] While the physiological roles of the α-1B and α-1D receptors remain to be clearly defined in humans, they are associated with hypotensive effects induced by nonselective α-1 receptor antagonists. Therefore, a selective α-1A antagonist may be an efficacious agent for the treatment of BPH and could be devoid of ancillary cardiovascular effects.

Our goal at the incipient stage of this work was to synthesize potent and selective α-1A antagonists for the treatment of BPH. The approach described herein focused on identifying a suitable structural replacement for the highly functionalized 4-aryl dihydropyridine subunit found within known α-1a antagonists such as **1** (Fig. 1).[4]

Results and Discussion

Structure–activity relationships

Our plan to simplify the structures of the known 4-aryl dihydropyridine-containing α-1a antagonists was formulated based on an assessment of the structural components housed within compound **1**. Examination of **1** revealed to us that a cinnamide group was embedded within the structure. We reasoned that excising the dihydropyridine moiety might eliminate some of the metabolic liabilities associated with this structural class. We, therefore, replaced the 4-aryl dihydropyridine with the dihydrocinnamic acid shown in **3** without altering the remainder of the core structure. The consequence of this modification was a 67-fold decrease in α-1a binding affinity.[5] Our next course of action was to complete a systematic study that focused on varying the tether lengths between the piperidine nitrogen and the amide N-H and between the 4-nitrophenyl group and the amide carbonyl (Table 1). Substituting a phenylacetamide (**5**) for the dihydrocinnamide (**3**) produced a 4-fold potency enhancement. Studies examining substituent effects on the aryl-portion of the phenylacetamide revealed that

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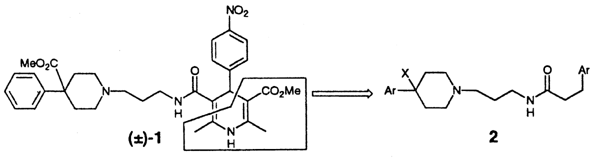
PII: S0960-894X(00)00307-3



α-1a = 3.6 nM
α-1b = 700 nM
α-1d = 1100 nM

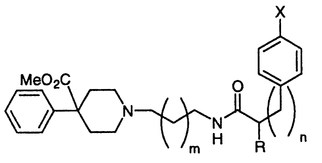
Figure 1.

the 4-nitro and 4-methyl substituted phenyl compounds have equivalent receptor binding profiles (cf **5** and **6**, Table 1).

Since the 4-aryl dihydropyridine includes structural elements at the positions linking the carbonyl attachment point and the 4-aryl group, we investigated phenylacetamides bearing similar forms of branching adjacent to the carbonyl of attachment. The addition of a methyl group on the methylene portion of the phenylacetamide subunit in **5** provided a modest boost in α-1a binding affinity (**7**). However, when a larger group, 4-methylphenyl (**8**) was installed at this position, the α-1a affinity increased by >10-fold relative to **6**. The potency enhancing bis(4-methylphenyl)acetamide group found in **8** was utilized in studies directed toward optimizing the amine-portion of these antagonists.

Due to our concern about the potential metabolic generation of the known opioid ligand, nor-meperidine,[6] which could form via oxidative dealkylation of the piperidine nitrogen, our focal point shifted to alternative 4-aryl piperidines and piperazines. The structures and in vitro binding profiles of select examples are summarized in Table 2. Two important discoveries emerged from this investigation. The installation of a cyano group at the 4-position of 4-arylpiperdines increases binding selectivity for the α-1a receptor (**9** versus **11** and **12** versus **13**). Furthermore, an *ortho* substituent on the 4-piperidine aryl group enhances α-1 potency (**14** versus **15**). These two moieties were incorporated into the structures of the antagonists highlighted in Table 3. Two of the *ortho* substituents examined, 2-methyl- and 2-chloro-phenyl (**16** and **18**, respectively), further enhanced the in vitro binding profiles relative to the unsubstituted phenyl analogue, **11**. Overall, the in vitro profiles of

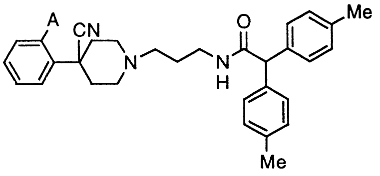
Table 1. α-1 Binding data



	m	n	R	X	K_i (nM)[a] α-1a	α-1b	α-1d
3	1	1	H	NO_2	240	910	1300
4	0	1	H	NO_2	380	>3000	1500
5	1	0	H	NO_2	75	3300	6300
6	1	0	H	Me	74	>3000	3400
7	1	0	Me	NO_2	47	1700	1700
8	1	0	4-MePh	Me	5.1	450	960

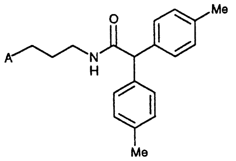
[a] All K_is are calculated for competition binding assays (I^{125}-HEAT) utilizing cloned human α-1 receptors ($n \geq 2$).[5]

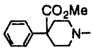
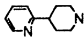
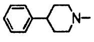
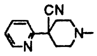
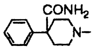
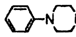
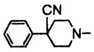
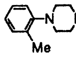
Table 3. α-1 Binding data



	A	K_i (nM) α-1a	α-1b	α-1d
11	H	7.3	>2000	1400
16	Me	1.3	360	1100
17	CF_3	22	1900	3200
18	Cl	0.99	280	660
19	OMe	7.5	570	710

Table 2. α-1 Binding data



	A	K_i (nM) α-1a	α-1b	α-1d		A	K_i (nM) α-1a	α-1b	α-1d
8		5.1	450	960	**12**		27	670	3600
9		8.8	34	230	**13**		25	>2000	>5000
10		570	570	3300	**14**		12	23	120
11		7.3	>2000	1400	**15**		1.1	6.6	34

compounds **16** and **18** are improved relative to our initial dihydropyridine lead, **1**, and the molecular weight is more than one hundred daltons lower. At this point, the pharmacokinetics of **16** were evaluated in two species.

Although the in vitro profile of **16** is significantly improved when compared with the initial dihydrocinnamic acid lead structure **5**, the pharmacokinetic profile is poor (rat: 10% F, 18 min $t_{1/2}$ and dog: $\leqslant$F, 60 min $t_{1/2}$, $C_{max} \leqslant 20$ nM at 3 mpk po). A number of basic strategies were employed in an attempt to enhance the pharmacokinetic profile of **16**. One approach focused on further reducing molecular weight and modifying potential sites of metabolism.

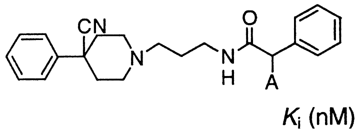
Since the optimal size for an α-substitutent at the phenylacetamide methylene position remained ambiguous based on the limited data set in Table 1, three α-alkyl phenylacetamides (**21**, **22**, and **23**) were prepared (Table 4). These compounds all have similar α-1 binding profiles, but the isopropylphenylacetamide (**23**) reduces molecular weight to the greatest extent. Therefore, the isopropylphenylacetamide was utilized in conjunction with the potency enhancing groups already described in an effort to improve pharmacokinetics. For example, replacement of the 4-cyano-4-phenyl piperidine (**21**) with 4-cyano-4-(2-methylphenyl) piperidine (**24**) produced a 10-fold α-1a potency enhancement. This potency increase may be attributable to conformational changes induced by the 2-methyl group on the orientation of the 4-phenyl group and/or of the piperidine ring.

Based on in vitro metabolism studies of a related compound, we anticipated that the 4-methyl substituent on the phenylacetamide present in **16** might be a site of metabolic oxidation.[7] Therefore, several halo-substituted phenylacetamides were prepared (Table 5). The 4-methyl- and 4-chloro-phenylacetamides have comparable in vitro binding profiles. However, the 4-fluorophenylacetamide has 3-fold lower affinity for the α-1a receptor relative to **24** and **25**, but the 3-fluoro- (**27**) and 3,4-difluoro-phenyl (**28**) acetamides are equipotent to **24** and **25**. Compounds **27** and **28** possess α-1 binding profiles comparable to that of the higher molecular weight bis(4-methylphenyl)acetamide **16** but should be devoid of the previously described metabolic liability.

The racemates, **27** and **28**, were separated utilizing chiral HPLC (Chiralcel OD column). The in vitro binding data for one enantiomeric pair is highlighted in Figure 2. It is clear from the data that a single enantiomer is responsible for the high in vitro binding affinity specifically for the α-1a receptor. The more potent isomer, **(+)-28**, was chosen for further characterization.

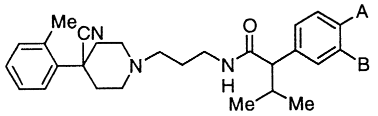
When examined in counterscreens, **(+)-28** was found to be >50-fold selective against the other G-protein coupled receptors (human α-2a, α-2b, α-2c, dopamine-1,-2,-3,-4,-5, and 5-HT receptors) tested. The study of the functional activity of **(±)-28** in isolated rat prostate tissue revealed that **(±)-28** competitively antagonizes phenylephrine-induced contraction with a K_b value of 110 nM. Prior to the delineation of the stereochemistry of the preferred enantiomer, **(+)-28**, the bioavailability of **(±)-28** was measured in rats (8% F and 120 min $t_{1/2}$ at 10 mpk po/3 mpk iv) and dogs (19% F and 120 min $t_{1/2}$ at 3 mpk po/1 mpk iv). Reasonable plasma levels of **(±)-28** were detected in both species. In particular, the high oral C_{max} (1.3 uM),

Table 4. α-1 Binding data

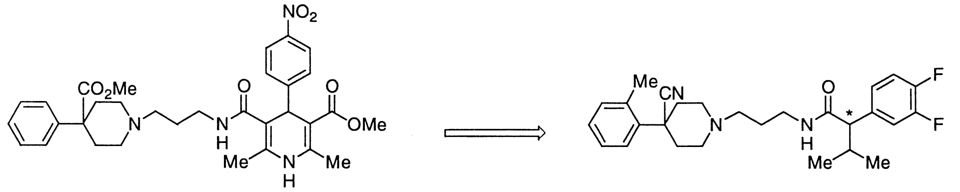


		K_i (nM)		
		α-1a	α-1b	α-1d
20	Phenyl	28	840	3300
(±)-21	*i*-Propyl	72	1200	2900
(±)-22	Cyclopentyl	50	2000	2300
(±)-23	Cyclohexyl	61	1100	2500

Table 5. α-1 Binding data



			K_i (nM)		
	A	B	α-1a	α-1b	α-1d
24	Me	H	7.4	650	1100
25	Cl	H	6.4	870	1300
26	F	H	24	960	2400
27	H	F	3.4	680	2700
28	F	F	2.0	900	1600



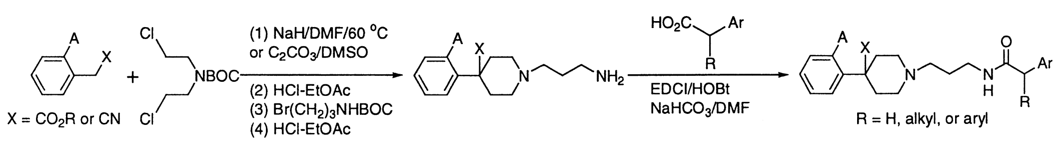
(±)-1
MW 590.67
α-1a = 3.6 nM
α-1b = 700 nM (194x)
α-1d = 1100 nM (306x)

(+)-28
α-1a = 2.0 nM
α-1b = 1400 nM (700x)
α-1d = 2100 nM (1050x)

MW 453.57

(-)-28
α-1a = 50 nM
α-1b = 1200 nM (24x)
α-1d = 2600 nM (52x)

Figure 2.



Scheme 1.

low volume of distribution (0.79 L/kg), and moderate clearance rate (6.7 mL/min/kg) observed in dogs represent promising results.

Synthesis

The 4-aryl piperidines were synthesized utilizing a spiro-annulation reaction of phenylacetic esters or benzylnitriles and *N*-Boc-bis-chloroethylamine (Scheme 1).[8] Deprotection, alkylation, and a second deprotection completes the assembly of the prerequisite propyl amines. The coupling reactions of these amines to the phenylacetic acids were conducted utilizing standard EDCI/HOBt conditions. The phenylacetic acids employed were either commercially available or synthesized utilizing literature methods.[9]

Conclusion

A series of phenylacetamides has been identified as potent and selective α-1a antagonists. These antagonists have lower molecular weights and have improved in vitro profiles relative to the known 4-aryl dihydropyridine-containing α-1A antagonists. The meperidine-like group within **1** has been replaced with 4-aryl-4-cyanopiperidines which provided α-1a potency and specificity enhancements. For example, (+)-**28** exhibits improved specificity for the α-1a receptor, has a lower molecular weight than **1** and displays acceptable pharmacokinetics. Based on the data presented, a significant stereochemical preference exists for optimizing α-1a binding affinity of α-alkyl phenylacetamides.

Acknowledgements

The authors thank Drs. Timothy V. Olah and Kelem Kassahun for LCMS analysis of plasma samples from select pharmacokinetic studies, Carl F. Homnick for assistance with chiral HPLC separations of enantiomers, and Dr. Roger Freidinger.

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