



## Selective $\alpha_{1a}$ Adrenergic Receptor Antagonists Based on 4-Aryl-3,4-dihydropyridine-2-ones

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**Abstract**—A series of  $\alpha_{1a}$  receptor antagonists derived from a 4-aryl-3,4-dihydropyridine-2-one heterocycle is disclosed. Potency in the low nanomolar to picomolar range along with high selectivity was obtained. In vivo efficacy in a prostate contraction model in rats was observed with a few derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

### Introduction

Benign prostatic hyperplasia (BPH), which is characterized by an enlargement of the prostate resulting in urinary obstruction, is a common condition<sup>1</sup> in males over the age of 50. Increased prostatic mass can be clinically treated with 5- $\alpha$ -reductase inhibitors, such as finasteride,<sup>2</sup> thus blocking the conversion of testosterone to dihydrotestosterone<sup>3</sup> which is found in excess in the enlarged prostate.  $\alpha_1$  Receptor antagonists such as terazosin,<sup>4</sup> originally developed as antihypertensive agents, have been used for treating BPH (relaxation of prostatic and urethral adrenergic tone), but with hypotensive side effects. Recent pharmacological and binding studies followed by cloning experiments have indicated the existence of three subclasses of  $\alpha_1$  receptors:  $\alpha_{1a}$ ,  $\alpha_{1b}$  and  $\alpha_{1d}$ .<sup>5</sup> Distribution of  $\alpha_1$  receptor subtypes among tissues is heterogeneous and it was later shown that the  $\alpha_{1a}$  receptor is the major subtype in prostatic tissue while less prevalent in cardiovascular tissues.<sup>6</sup> Selective  $\alpha_{1a}$  receptor antagonists should, therefore, have a better therapeutic index with regard to cardiovascular side effects for the treatment of BPH. Tamsu-

losin, although only slightly selective for the  $\alpha_{1a}$  receptor subtype, has shown a better tolerability profile than nonselective compounds when used to treat BPH.<sup>7</sup> The search for more selective antagonists may thus provide agents completely devoid of cardiovascular side effects.

Previous studies from our laboratories and others have shown that compounds such as **1**, incorporating a 4-aryl-5-carboxamide-dihydropyrimidinone (DHP) heterocyclic moiety are selective  $\alpha_{1a}$  receptor antagonists (Fig. 1).<sup>8</sup> The unsubstituted DHP derivatives ( $R_1$ ,  $R_2 = H$ ) generally demonstrated a poor pharmacokinetic profile, which was originally attributed to poor absorption due to the fairly high polarity ( $\log P < 1$ ) of these compounds. SAR studies around the DHP series have led us to propose a pharmacophore model **2** as a working hypothesis. A locked  $sp_3/sp_2$  configuration at C4-C5, which insures the proper orientation between the C4 aryl group and the C5 carboxamide, seemed to be an important feature regarding potency.<sup>8</sup> According to these results the replacement of the N-3 of DHP by a methylene unit should fit the pharmacophore model and may be advantageous regarding potency, selectivity,<sup>9</sup> and pharmacokinetic profile (increased  $\log P$ ) of the resulting dihydropyridinone derivatives of type **3**.

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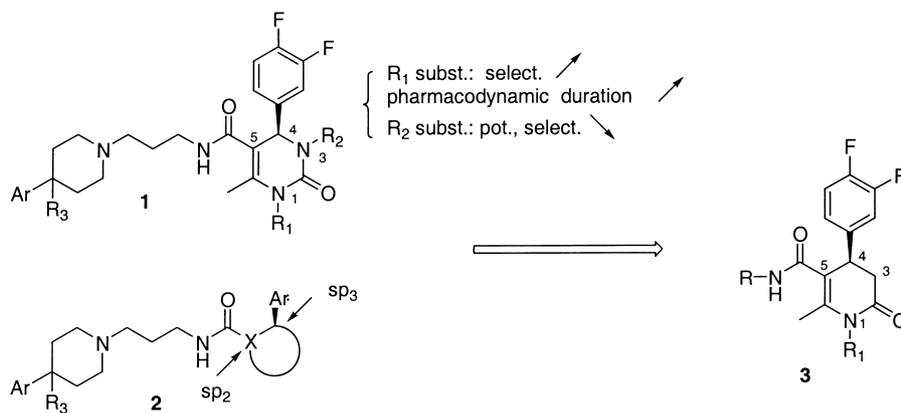


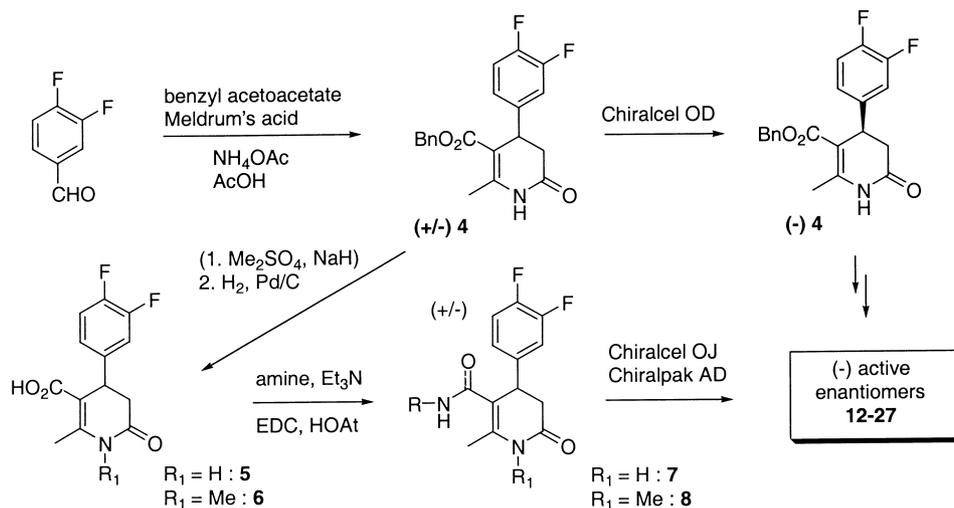
Figure 1.

### Chemistry

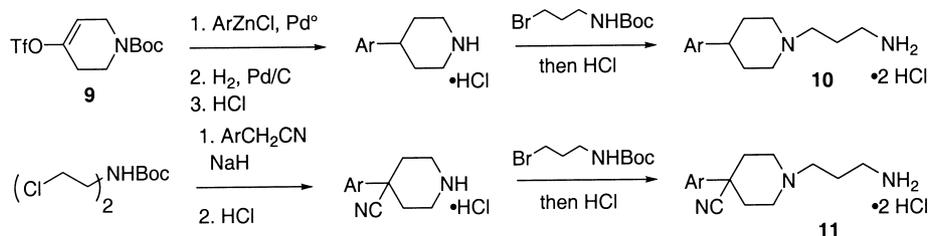
The dihydropyridinone ring was prepared<sup>10–12</sup> from 3,4-difluorobenzaldehyde in racemic form, as shown in Scheme 1. Optional methylation at N-1 followed by hydrogenolysis of the benzyl ester provides the acid derivatives **5** and **6**, which are readily coupled to various amines (Scheme 2) under standard conditions. The racemic amides **14**, **15**, **18**, **19**, **22** and **23** were resolved by preparative chiral HPLC.<sup>13</sup> In each case the (–) enantiomer was significantly more active than the (+) enantiomer and was assigned as R, by analogy with previous DHP derived antagonists.<sup>8</sup> Dihydropyridinone

**4** was also resolved by preparative chiral HPLC<sup>14</sup> and the (–) enantiomer, identified as the ‘active’ enantiomer,<sup>15</sup> was utilized for the direct preparation of the 4R amides.

A general preparation of the amines to be coupled to the dihydropyridinone moiety is presented in Scheme 2. Various aryl zincates were prepared from the corresponding aryl halides and coupled to triflate **9**.<sup>8</sup> Introduction of the propylamine chain via alkylation or reductive amination gave access to piperidines **10**. Piperidines **11** containing a 4-cyano substituent in addition to the 4-aryl group were derived from phenylacetone nitriles and bis-(2-chloroethyl)-Boc-amine.

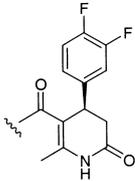
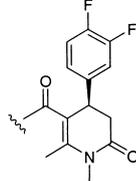
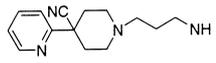
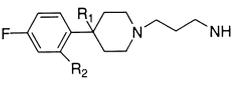
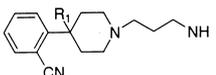


Scheme 1.



Scheme 2.

**Table 1.** Primary screen/in vitro data

					
		Compound no.	$K_i$ (nM) $\alpha_{1a}, \alpha_{1b}, \alpha_{1d}$	Compound no.	$K_i$ (nM) $\alpha_{1a}, \alpha_{1b}, \alpha_{1d}$
		<b>12</b>	42, >2000, >5000	<b>13</b>	257, >2000, >5000
	$R_1 = H, R_2 = H$	<b>14</b>	0.4, 37, 200	<b>15</b>	0.7, 54, 250
	$R_1 = H, R_2 = CN$	<b>16</b>	0.2, 100, 150	<b>17</b>	0.8, 366, 590
	$R_1 = CN, R_2 = H$	<b>18</b>	1.8, 1040, 1050	<b>19</b>	1.9, 425, 880
	$R_1 = CN, R_2 = CN$	<b>20</b>	1.4, >2000, >5000	<b>21</b>	7, >2000, >5000
	$R_1 = CN, R_2 = F$	<b>22</b>	1, 805, 588	<b>23</b>	1.1, 842, 1155
	$R_1 = H$	<b>24</b>	1, 330, 330	<b>25</b>	3, 1200, 682
	$R_1 = CN$	<b>26</b>	3.2, >2000, >5000	<b>27</b>	13, >2000, >5000

## Results

The proposed N to methylene substitution in the DHP moiety was indeed tolerated. Table 1 shows the potency of a series of dihydropyridinone derived amides against the three subclasses of  $\alpha_1$  receptors. As observed in the DHP series,<sup>8</sup> N<sub>1</sub>-methylation slightly increases selectivity against  $\alpha_{1a}$  while potency is only slightly diminished. The choice of amines to be coupled to the central dihydropyridinone moiety was guided by previous results in the DHP series<sup>8</sup> and indeed, the SAR is very similar in both series. Introduction of a 2-fluoro substituent on the aryl-piperidine results in slightly increased potency and selectivity while a 2-cyano substituent improves selectivity drastically. The 4-cyano-4-(2-pyridyl)piperidine derivatives were found to be very selective but of marginal potency. Placement of fluorine at the aryl 4-position improves potency with little effect on the selectivity. Introduction of an angular 4-cyano group on the piperidine was beneficial to selectivity but at the expense of potency. The best combination is illustrated by compounds **16** and **17** with  $K_i$  against the  $\alpha_{1a}$  receptor subtype of 0.2 and 0.8 nM, respectively, and with selectivity against the other subtypes greater than  $450 \times$ .

A selection of the most active and selective antagonists was screened against the  $\alpha_2$  receptor subtypes and the human histamine type I (hH1) receptor (Table 2): while selectivity within the  $\alpha$  receptor subclass is still very good for both NH and N-Me derivatives, selectivity against hH1 is marginal for NH derivatives. Most of these compounds were evaluated in vivo in an in situ rat prostate model.<sup>16</sup> The most active compounds remain **16** and **17** with AD<sub>50</sub>, of 5 and 9  $\mu\text{g}/\text{kg}$  respectively, and with duration of action of 2.5 and 4 h, respectively (Tamsulosin: 3  $\mu\text{g}/\text{kg}/3.5$  h). Rat oral bioavailability for compounds **16** and **17** was found to be low. Further, the

$t_{1/2}$  for **16** and **17** (4.8 and 1.4 h respectively) does not correlate well with the observed pharmacodynamic duration. In the dog, bioavailability was improved only for **16** (34%). Short half-lives (< 1 h) and low bioavailability for compounds **19**, **22**, **23** confirmed the poor pharmacokinetic profile within this series. Metabolism and absorption studies within the related DHP series have suggested rapid N-dealkylation of the piperidine.<sup>8</sup> It is possible that a first pass effect is the reason for low bioavailability within both series.

In conclusion, a series of potent and selective  $\alpha_{1a}$  receptor antagonists derived from a 4-aryl-3,4-dihydropyridinone-2-one heterocycle was uncovered. In vivo efficacy was observed along with moderate pharmacodynamic duration in a few cases, setting the stage for further studies in this series.

**Table 2.** Selectivity screen/in vivo efficacy

Compound no.	$K_i$ (nM) $\alpha_{1a}, \alpha_{2a}, \alpha_{2b}, \alpha_{2c}$	hH1	insrp <sup>a</sup>
			AD <sub>50</sub> ( $\mu\text{g}/\text{kg}$ ) <sup>b</sup> /dur. <sup>c</sup>
<b>14</b>	0.4, 229, 162, 313	19	32
<b>16</b>	0.2, 1288, 145, 1479	58	5/2.5 h
<b>17</b>	0.8, 4519, 288, 3846	398	9/4 h
<b>18</b>	1.8	63	
<b>19</b>	1.9, 1862, 776, 1096	355	25
<b>20</b>	1.4, 7852, 676, 4677	91	
<b>21</b>	7, 13646, 1758, 6531	616	
<b>22</b>	1, 1972, 531, 1995	108	17/1.5 h
<b>23</b>	1.1, 3388, 955, 1905	302	29/1 h

<sup>a</sup>In situ rat prostate model.

<sup>b</sup>Dose of compound required to inhibit the prostate contractile response by 50% after challenge with the selective  $\alpha_{1a}$  agonist A61603.

<sup>c</sup>Duration of action in hours, after repeated challenge with the agonist.

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9. Within the DHP series,<sup>8</sup> substitution at N-1 (R=Me, COMe, CO<sub>2</sub>Me) resulted in improved selectivity and increased pharmacodynamic duration, while substitution at N-3 led to reduced potency and selectivity.
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13. Chiralpak AD 250×20 mm at 6 mL/min or Chiralcel OJ 250×20 mm at 8 mL/min, 15 to 35% EtOH in hexane containing 0.1% diethylamine.
14. Chiralcel OD 500×50 mm at 60 mL/min, 10% EtOH in hexane containing 0.1% diethylamine.
15. Originally, (+) **4** was converted to (+) **14**, the less active enantiomer, thus identifying (–) **4** as the enantiomer leading to more active enantiomers (–) **12–27**. Additionally, hydrogenolysis of (+) **4** followed by coupling with (*S*)-(–)- $\alpha$ -methylbenzylamine provided material suitable for X-ray crystallography. The structure results confirmed the *S* configuration at C4 for (+) **4** and, by default, the *R* configuration for (–) **4**.
16. The prostate of anesthetized rats is connected to a force transducer and compounds administered iv, are evaluated for inhibition of contractile response induced by the selective  $\alpha_1$  agonist A61603. Duration of action is obtained from repeated challenges with the agonist. For details see ref 8.