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Synthesis and Evaluation of Furo[3,4-*d*]pyrimidinones as Selective α_{1a}-Adrenergic Receptor Antagonists

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Abstract—Furo[3,4-*d*]pyrimidinones were found to be metabolites of dihydropyrimidinones such as **1a**–**b** that are subtype-selective antagonists of the α_{1a}-adrenergic receptor. A versatile synthesis that provides access to furo[3,4-*d*]pyrimidinones in high yield and in enantiomerically pure forms is described along with structure–activity relationships in the series.

Alpha-1-adrenergic receptor antagonists are used for the treatment of benign prostatic hyperplasia (BPH), a urological disorder prevalent in the elderly male population that results in the obstruction of urine flow.[1,2] We have recently reported that dihydropyrimidinones such as **1a**–**b** are α_{1a} selective antagonists with a potential for the treatment of BPH with fewer side effects than the nonselective α_1 adrenergic antagonists.[3] These compounds exhibit good binding affinity (<1 nM) and excellent selectivity (>300-fold) for the α_{1a} receptor over α_{1b} and α_{1d} subtypes. The in vitro metabolism studies[4] revealed that the dihydropyrimidinones **1a**–**b** give rise to furo[3,4-*d*]pyrimidinone (**2**) as one of the metabolites, presumably via intermediate **1c**. A synthetic route was needed to confirm the structural identity of **2** and to determine whether it contributes to the in vivo activity of the parent compounds as an active metabolite. The synthesis and structure–activity relationships (SAR) of furo-[3,4-*d*]pyrimidinones such as **2** are presented in this letter.

The initial attempts to synthesize furo[3,4-*d*]pyrimidinones were modeled on the route used for the synthesis of **1** (Scheme 1, eq. (1)), where an appropriate β-ketoester was condensed with an aromatic aldehyde to obtain benzylidene **4** which was then reacted with *O*-methylisourea in presence of $NaHCO_3$ to obtain dihydropyrimidine **5** in good yield.[5] An analogous condensation of tetronic acid (**7**) with aromatic aldehydes, however, required strongly acidic conditions (conc HCl as solvent).[6] Furthermore, benzylidene **8** failed to give the desired furo[3,4-*d*]pyrimidinone under conditions used to obtain **5** (Scheme 1, eq (2)).

An alternate synthesis of furo[3,4-*d*]pyrimidinones **9**, has been reported, albeit in low yields (4–18%).[7] We therefore developed a novel synthetic route for the synthesis of the target compounds in high yields by modification of a previously reported synthesis (Scheme 2).[8,9] Thus intermediate **6** was obtained from the dihydropyrimidine **5** (as a racemic mixture or pure enantiomers) by known procedures[3,5] and was treated with bromine in $CHCl_3$ at 0 °C to obtain bromide **10** in good yield. Compound **10** was heated (neat) in an oil bath at 130 °C for 5 h, cooled and washed with chloroform to obtain the furo[3,4-*d*]pyrimidinone **11** in quantitative yield.[10] Intermediate **11**, without purification, was treated with several primary amines to yield the desired compounds represented by general structure **12**.

Some noteworthy features of this route include: (1) the presence of *p*-nitrophenyloxycarbonyl group on the N-1

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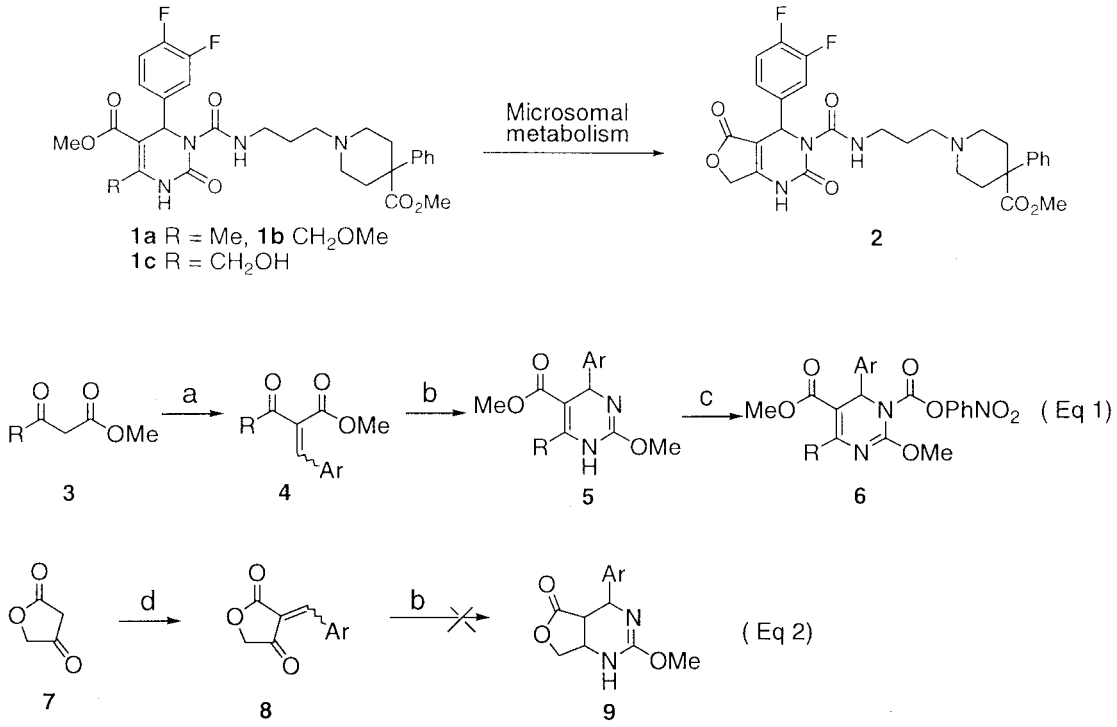
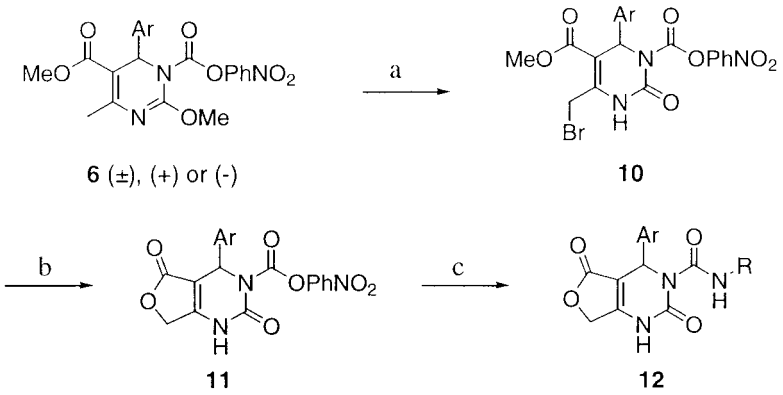


Scheme 1. (a) ArCHO, PhH, >90%; (b) *O*-methylisourea, $NaHCO_3$, DMF, 60–70%; (c) *p*-nitrophenylchloroformate, CH_2Cl_2, DMAP, 90%; (d) ArCHO, concd HCl, 40–58%.



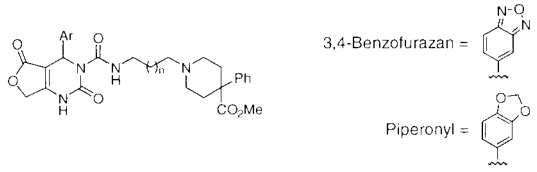
Scheme 2. Br_2, $CHCl_3$; (b) heat, 130 °C; (c) RNH_2, THF or CH_2Cl_2, 60–80% yield from **6**.

position enables the introduction of a variety of side chains from a common intermediate, (2) the route provides access to enantiomerically pure furo[3,4-*d*]pyrimidinones, (3) the synthetic sequence is concise, and (4) the compounds are obtained in high yield.

The generality of the synthetic route is highlighted by the preparation of compounds **13**–**22** shown in Tables 1 and 2. A number of compounds were screened against recombinant human α_1 receptors in binding assays using [^{3}H]-prazosin as the radioligand and the results are shown in Tables 1 and 2. Compound **13**, with an electron-donating substituent on the C-6 phenyl ring, shows lower binding affinity and selectivity while compounds **14** and **15** containing electron-withdrawing substituents exhibit good affinity and high selectivity for the recombinant α_{1a} receptor. The three-carbon tether is the optimal length for the linker resulting in compounds **16**, **17**, and **18** with the desired binding and selectivity profiles. The structure–activity relationship for furo[3,4-*d*]pyrimidinones parallels that observed for compounds such as **1a**–**b** as previously described.[3] Compound **16**, which contains a 3,4-difluorophenyl substituent, shows a particularly noteworthy binding and selectivity profile and as such was further characterized.

Both enantiomers of compound **16** were synthesized starting from the pure enantiomers of compound **5**.[3] The (+)-enantiomer showed better binding affinity and selectivity for the cloned human α_{1a} receptor than the (−)-enantiomer or the racemate.[11] Encouraged by the binding affinity of **(+)-16**, we decided to explore the SAR of analogues of **(+)-16**, in which the 4-methoxycarbonyl-4-phenyl piperidine moiety was replaced with the preferred substituted piperidines[12] or piperazines[13] as shown in Table 2.

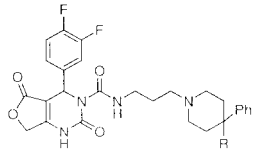
Table 1. Structure–activity relationship for furo[3,4-*d*]pyrimidinones



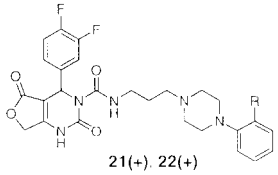
Compd.	Ar	*n*	K_i (nM)[a,b]		
			α_{1a}	α_{1b}	α_{1d}
13	Piperonyl	1	35	390	1900
14	4-NO_2-Ph	1	1.1	130	420
15	3,4-Benzofurazan	1	0.9	300	340
16	3,4-di-F-Ph	1	0.9	330	430
17	3,4-di-F-Ph	0	62	1200	1300
18	3,4-di-F-Ph	2	15	340	420
(+)-16	3,4-di-F-Ph	1	**0.4**	**500**	**230**
(−)-16	3,4-di-F-Ph	1	1.6	250	130

[a]K_i values obtained by displacement of [^{3}H]-prazosin from recombinant human receptors.
[b]All K_i values are ± 5% S.E. or less for $n > 2$. In cases where $n = 2$, both K_i values are within 2-fold of each other and the values shown are the average of the two experiments.

Table 2. Side chain modifications



16(+), 19(+), 20



21(+), 22(+)

Compound	R	K_i (nM)[a]		
		α_{1a}	α_{1b}	α_{1d}
(+)-16	CO_2Me	0.4	500	230
(+)-19	CN	5.8	970	1100
20	Ph	9.1	120	130
(+)-21	$CONH_2$	2.3	350	690
(+)-22	NO_2	0.6	210	180

[a]Please see footnote for Table 1.

Substitution of the ester functionality with a cyano group gave compound **(+)-19** that maintained the selectivity against the other α_1 subtypes (>166-fold), but showed lower binding affinity for the α_{1a} receptor (5.8 nM cf. 0.4 nM for **(+)-16**). Replacement of the methoxycarbonyl group by a phenyl substituent gave compound **20**, which showed a substantial decrease in binding affinity as well as selectivity for the α_{1a} receptor. Compounds **(+)-21** and **(+)-22** containing substituted phenyl-piperazine moieties[13] in place of the piperidine moieties exhibit comparable binding affinities (2.3 and 0.6 nM, respectively) for the α_{1a} receptor with good subtype-selectivity (>100-fold).

Compound **(+)-16** was evaluated in a number of in vitro and in vivo assays.[14] Compound **(+)-16** shows greater than 1500-fold selectivity over α_2 adrenoceptors and the rat L-type calcium channel.[15] In the functional studies, **(+)-16** shows good potency and selectivity to antagonize phenylephrine induced contraction of rat prostate tissue ($K_b = 0.28$ nM) compared to rat aorta ($K_b = 540$ nM). The selectivity observed in the functional assay is in good agreement with the selectivity for the cloned human α_{1a} receptor over α_{1d} receptor in the binding assays and can be regarded as a potential measure of uroselectivity. In the anesthetized rats, **(+)-16** potently antagonized A-61603[16] induced contraction of the rat prostate ($AD_{50} = 67$ μg/kg) over a 2 h period. These results suggest that compounds such as **(+)-16** may not only be active metabolites, but may also be an intrinsically interesting series of α_1 antagonists in their own right. Compound **(+)-16** shows a short plasma half-life (~1.5 h) in rats and dogs presumably due to the other metabolic pathways such as *N*-dealkylation as observed for compounds that are structurally similar to **1a**–**b**.[3,12]

In summary, a versatile, high yielding synthesis of furo[3,4-*d*]pyrimidinones has been developed that provides access to the desired compounds in enantiomerically pure forms. Select compounds show good binding affinity and selectivity for the α_{1a} receptor. Compounds such as **(+)-16**, show good uroselectivity in the functional assays as well and therefore, may be useful as α_{1a} selective antagonists for treatment of BPH.

Acknowledgements

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4. The in vitro metabolism was studied using suspensions of freshly isolated hepatocytes and microsomal preparations from rat, dog and humans. The compounds were incubated with liver microsomal protein and NADPH for 60 min. Following centrifugation, the supernatant was dried, reconstituted with 30% acetonitrile and analyzed by electrospray LC–MS/MS.
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10. Furo[3,4-*d*]pyrimidinone **11** (Ar = 3,4-difluorophenyl): ^{1}H NMR (DMSO-d_6) δ 4.94 (br s, 2 H), 6.08 (s, 1 H), 7.20–7.43 (m, 5 H), 8.35 (d, J = 10.2 Hz, 2 H).
11. Compound **(+)-16**: ^{1}H NMR ($CDCl_3$) δ 1.62–1.73 (m, 2 H), 1.91–1.98 (m, 2 H), 2.17–2.36 (m, 2 H), 2.40 (br t, J = 6.6 Hz, 2 H), 2.52–2.57 (m, 2 H), 2.76–2.93 (m, 2 H), 3.20–3.40 (m, 2 H), 3.61 (s, 3 H), 4.69 (s, 2 H), 6.30 (br s, 1 H), 6.38 (s, 1 H), 7.04–7.35 (m, 8 H), 9.09 (br t, 1 H). HCl salt. m.p. 142–145 °C; $[\alpha]_D$ +128° (c 0.52, $CHCl_3$). Anal. calcd for $C_{29}H_{31}N_4O_6F_2Cl.0.23\ CHCl_3$: C, 55.55; H, 4.98; N, 8.87. Found: C, 55.25; H, 5.03; N, 8.52.
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