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Synthesis, Pharmacology and Pharmacokinetics of 3-(4-Arylpiperazin-1-ylalkyl)-uracils as Uroselective α_{1A}-Antagonists

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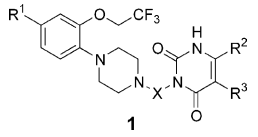
Abstract—Predominance in the urethra and prostate of the α_{1A}-adrenoceptor subtype, which is believed to be the receptor mediating noradrenaline induced smooth muscle contraction in these tissues, led to the preparation of α_{1A}-selective antagonists to be tested as uroselective compounds for the treatment of benign prostatic hyperplasia. Thus, a number of selective α_{1A}-adrenoceptor antagonists were synthesized and assayed in vitro for potency and selectivity. Dog pharmacokinetic parameters of **12** (RO700004) and its metabolite **40** (RO1104253) were established. The relative selectivity of intravenously administered **12**, **40** and standard prazosin to inhibit hypogastric nerve stimulation-induced increases in intraurethral prostatic pressure versus phenylephrine-induced increases in diastolic blood pressure in anesthetized dogs was 76, 71 and 0.6, respectively.

Competitive α_1-adrenoceptor antagonists such as doxazosin, terazosin, prazosin, alfuzosin and tamsulosin have been shown to be effective in relieving urinary outflow obstruction and reducing symptom scores in patients with benign prostatic hyperplasia (BPH).[1] However, the usefulness of α_1-adrenoceptor antagonists in BPH is offset by their dose-limiting cardiovascular effects, including postural hypotension, particularly during initial dosing.[2] The discovery and definition of the α_{1A}-, α_{1B}- and α_{1D}-adrenoceptor subtypes[3] offers the potential for more selective agents. Recently, much interest has focused on the role of the α_{1A}-adrenoceptor subtype in BPH, as a result of studies demonstrating that this subtype predominates in the urethra and prostate of man,[4] and it has been claimed to be the receptor mediating noradrenaline induced smooth muscle contraction in these tissues.[5] Thus, considerable effort has been dedicated to identify a subtype selective α_{1A}- over α_{1B}- and α_{1D}-adrenoceptor antagonist.[6] Our group[7] as well as groups at Merck/Synaptic,[8] Johnson & Johnson,[9] Kissei,[10] Abbott,[11] Japan Tobacco,[12] Recordati,[13] and others[14] have found potent and selective α_{1A}-adrenoceptor antagonists. However, clinical efficacy for the treatment of symptomatic BPH with these compounds has yet to be demonstrated.

In this study, we report the preparation and the in vitro α_1-adrenoceptor affinity profile of a series of α_{1A} adrenoceptor selective 3-(4-arylpiperazin-1-ylalkyl)-uracil antagonists. Pharmacokinetic data and in vivo pharmacology in dog of selected compounds are also presented.

Synthetic approaches to general structure **1** are presented in Schemes 1–4.



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Arylpiperazines **2** and **3** (Scheme 1) were the starting synthetic cores for all final compounds. Preparation of arylpiperazine **2** has been described before.[7] Preparation of **3** is presented in Scheme 1.[15] Thus, trifluoroethylation of 5-fluoro-2-nitrophenol **4** gave ether **5** in 98% yield.[16] Reduction of the nitro group with

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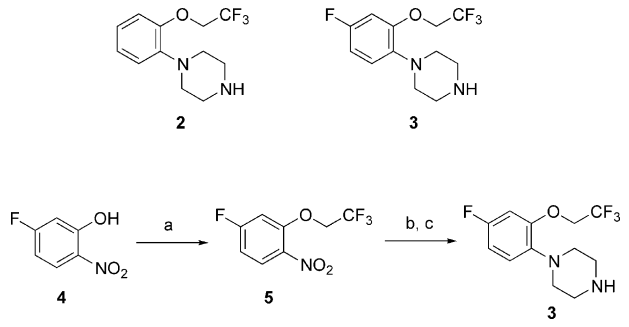
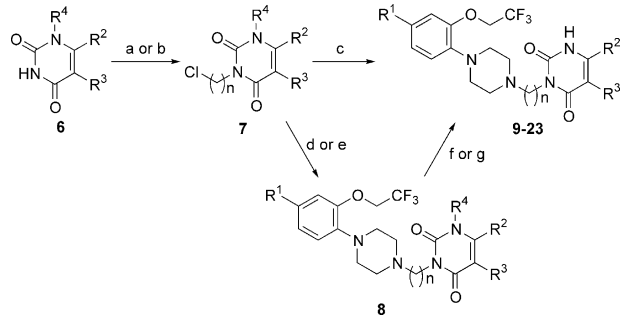
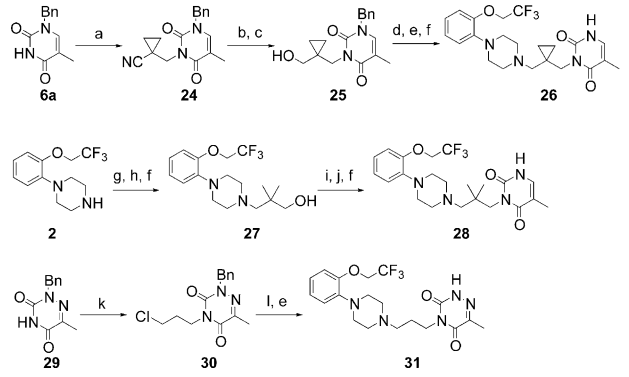


Scheme 1. Reagents and conditions: (a) CF_3CH_2OTf, Cs_2CO_3, NMP, 98%; (b) Ni_2B, 1 M HCl, MeOH, 60 °C; (c) $(ClCH_2CH_2)_2NH{\cdot}HCl$, K_2CO_3, Diglyme, 220 °C, 40% two steps.

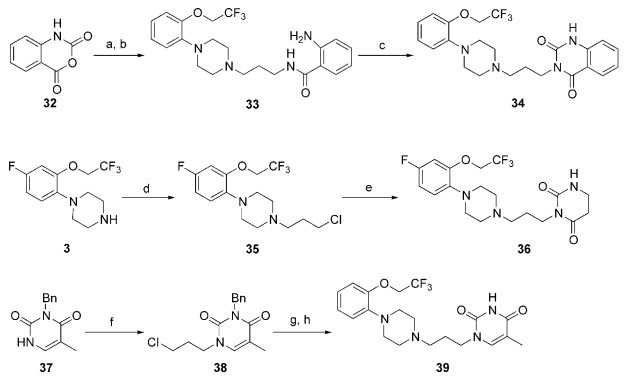


Scheme 2. Reagents and conditions: (a) for R^4 = Bn or SEM: K_2CO_3, $Cl(CH_2)_nBr$, DMF, 60–96%; (b) for R^4 = BOC: NaH, $Cl(CH_2)_nBr$, DMF, 34–89%; (c) for R^4 = BOC: **3**, neat, 210 °C, 22–69%; (d) for R^4 = Bn: **2**, K_2CO_3, NaI, CH_3CN, reflux, 52–80%; (e) for R^4 = SEM: **3**, K_2CO_3, NaI, CH_3CN, reflux, 61–88%; (f) for R^4 = Bn: HCO_2NH_4, Pd/C, MeOH, reflux, 31–57%; (g) for R^4 = SEM: *n*-Bu_4NF, THF, or 40% HF, CH_3CN, 70 °C, 62–88%.



Scheme 3. Reagents and conditions: (a) NaH, 1-cyanocyclopropylmethyl methanesulfonate, DMF, 50 °C, 70%; (b) HCl concd, acetic acid, reflux, 90%; (c) methyl chloroformate, THF, −5 °C; $NaBH_4$, H_2O, 90%; (d) MsCl, Et_3N, DCM, 0–5 °C; (e) **2**, K_2CO_3, NaI, CH_3CN, reflux, 65-84%; (f) HCO_2NH_4, Pd/C, MeOH, 62–85%; (g) 3-benzyloxy-2,2-dimethylpropionyl chloride, benzene, 0 °C, 86%; (h) $LiAlH_4$, THF, reflux, 96%; (i) *p*-TsCl, Et_3N, DMAP, DCM, 95%; (j) NaH, HMPA, **6a**, 85 °C, 73%; (k) 1-bromo-3-chloropropane, *n*-Bu_4NF, THF, 97%.

nickel boride,[17] followed by treatment with bis(chloroethyl)amine at 220 °C gave **3**. Different uracil derivatives **6** were then utilized to prepare most of the final compounds (Scheme 2). Uracils **6**, N-1 protected as benzyl,[18] 2-(trimethylsilyl)ethoxymethyl (SEM)[19] or *tert*-butoxycarbonyl (BOC),[20] were transformed to the N-3 chloroalkyl intermediates **7**. The reaction of 1-BOC-3-chloroalkyluracils **7** and arylpiperazine **3** at 200–220 °C



Scheme 4. Reagents and conditions: (a) $Br(CH_2)_3NH_2{\cdot}HBr$, Et_3N, toluene, reflux, 13%; (b) **2**, $NaHCO_3$, CH_3CN, reflux, 43%; (c) $COCl_2$, toluene, reflux, 77%; (d) $Cl(CH_2)_3Br$, K_2CO_3, CH_3CN, 63%; (e) 5,6-dihydrouracil, *n*-Bu_4NF, THF, 26%; (f) $Cl(CH_2)_3Br$, *n*-Bu_4NF, THF, 83%; (g) **2**, K_2CO_3, NaI, CH_3CN, reflux, 68%; (h) HCO_2NH_4, Pd/C, MeOH, reflux, 81%.

Table 1. Compounds prepared according to Scheme 2

Entry	*n*	R^1	R^2	R^3	R^4 in **6**
9	2	F	H	Me	BOC
10	4	F	H	Me	BOC
11	3	H	H	Me	Bn
12	3	F	H	Me	BOC
13	3	F	H	H	SEM
14	3	F	H	Et	SEM
15	3	F	H	*i*-Pr	BOC
16	3	H	Me	Me	Bn
17	3	F	Me	H	Bn
18	3	F	H	F	BOC
19	3	F	H	Cl	SEM
20	3	F	H	OMe	SEM
21	3	F	H	NMe_2	SEM
22	3	H	H	CF_3	Bn
23	3	F	H	CH_2OH	SEM

gave the final deprotected products directly, while the treatment of 1-benzyl and 1-SEM-3-chloroalkyluracils **7** with arylpiperazines **2** and **3**, respectively, furnished intermediate **8**. Hydrogenation or treatment with *n*-Bu_4NF or HF deprotected **8** (R^4 = benzyl, R^4 = SEM, respectively) to give the final products.[21] Table 1 shows all products prepared by these synthetic routes. Also indicated in the table is the protecting group R^4 used in the starting uracil derivatives **6** for each compound.

Scheme 3 shows the preparation of compounds **26**, **28** and **31**.[21] Deprotonation of 1-benzylthymine **6a**[18a] with sodium hydride followed by treatment with 1-cyanocyclopropylmethyl methanesulfonate[22] provided cyclopropyl intermediate **24**. Subsequent hydrolysis of the cyano group and reduction of the resulting carboxylic acid in a two-step sequence (methyl chloroformate/sodium borohydride) gave alcohol **25**. Activation of the alcohol as its mesylate and treatment with arylpiperazine **2** gave, after removal of the benzyl group, cyclopropyl derivative **26**. For the preparation of *gem*-dimethyl derivative **28**, arylpiperazine **2** was treated with 3-benzyloxy-2,2-dimethylpropionyl chloride,[23] followed by reduction of the resulting amide and debenzylation to obtain alcohol **27**. The hydroxyl group was activated as the tosylate, which was reacted with the sodium salt of 1-benzylthymine in

HMPA at 85 °C to obtain, after removal of the benzyl group, compound **28**. Azathymine derivative **31** was prepared from 1-benzyl-6-azathymine **29**[24] following standard conditions. Scheme 4 shows the preparation of **34**, **36** and **39**. Isatoic anhydride **32** was opened with 3-bromopropylamine, and the resulting bromide was coupled with arylpiperazine **2** to obtain **33**. Closure to the quinazolinedione system was achieved with phosgene in toluene at reflux to furnish **34**. For the preparation of the dihydrouracil **36**, arylpiperazine **3** was reacted with 1-bromo-3-chloropropane to obtain chloride **35**, which was then treated with 5,6-dihydrouracil. Derivative **39**, in which the propyl chain is attached to the uracil ring N-1 rather than N-3, was obtained starting from 3-benzylthymine **37**[25] following standard conditions.

Table 2 shows the biological data for all compounds. Binding affinity estimates (pK_i) refer to the inhibition of [^{3}H]-prazosin binding to CHO-K1 cell membranes or whole cells expressing human cloned α_{1A}-, α_{1B}-, α_{1D}-adrenoceptors. Below the α_{1B} and α_{1D} pK_i values, in parenthesis, is the ratio of α_{1B} over α_{1A}, and α_{1D} over α_{1A} affinities, respectively. Functional affinity estimates (pA_2/pK_B) refer to the antagonist inhibition of in vitro noradrenaline-stimulated contractions of rabbit bladder neck (RBN) and rat aortic rings, representative of α_{1A}- and α_{1D}-adrenoceptors, respectively.[26] Below the rat aorta pA_2/pK_B values, in parenthesis, is the ratio of rat aorta over RBN affinities. As can be observed, there is good correlation of pK_i with pA_2/pK_B values at α_{1A}- and α_{1D}-adrenoceptors. The majority of compounds bind to the α_{1A}-adrenoceptor in the nanomolar range, and demonstrate selectivity over the other two subtypes in both radioligand binding and functional affinity assays.

The length and substitution pattern of the linker between the uracil and the piperazinyl rings seem optimal for a straight 3-carbon chain. Thus the pA_2/pK_B selectivity of **11** (RS-100329) or **12** (RO700004) is higher than that of **9** or **10**, while the cyclopropyl and *gem*-dimethyl compounds, **26** and **28**, offer no improvement. Uracil derivative **13**, with no substitution at either the 5- or 6-position, and dihydrouracil **36** are somewhat less selective (α_{1D}/α_{1A} or rat aorta/RBN ratio) than analogue **12**. Substitution at the uracil ring provides further insight into different sterically and electronically demanding groups. 5-Ethyl and 5-isopropyl-uracil derivatives, **14** and **15**, respectively, although potent and selective, offer no advantage over **11** or **12**. However, 5,6-dimethyl-uracil **16** displays both very high affinity (pK_i 10.4, pA_2/pK_B 9.5) and selectivity ($\alpha_{1B/D}/\alpha_{1A}$ over 100). Quinazolinedione **34** also shows high potency at the α_{1A}-adrenoceptor subtype (pK_i 10.2, pA_2/pK_B 9) but low selectivity (rat aorta/RBN ratio 4). Among derivatives with electron-withdrawing groups at uracil ring position 5, such as **18**, **19** and **22**, the fluorouracil derivative **18** compares very well to analogue **12**. However, compounds **20** and **21**, which have electron-donating groups at C-5 of the uracil ring, do not show improvement in potency or selectivity. 6-Azathymine derivative **31** shows nanomolar potency at subtype α_{1A}, but low selectivity over α_{1D}. Attachment of the propyl side chain at N-1 of uracil ring, rather than at N-3, lowers the α_{1A}- over α_{1D}-adrenoceptor selectivity to 10 from 50 (**39** vs **11**).

Metabolism of compound **12** was assessed by incubation with hepatic microsomes from rat, dog, monkey and human in the presence of NADPH. Figure 1 shows the radiochromatograms of [^{14}C]-**12** metabolism in the four species. The similarity of dog and human profiles is clear. Table 3 shows the relative rate of metabolism of selected compounds by dog liver microsomes. The diminution of metabolism rate of compound **12** (0.6) compared to **11** (1.0) can be attributed to blockade of aromatic hydroxylation by fluoro-substitution. Indeed, phenol [(i.e., **1**, $R^1 = OH$, $X = (CH_2)_3$, $R^2 = H$ and

Table 2. Affinity estimates (pK_i and pA_2/pK_B)[a] for compounds described in Schemes 2–4

Entry	pK_i α_{1A}	pK_i α_{1B} (α_{1B}/α_{1A})	pK_i α_{1D} (α_{1D}/α_{1A})	pA_2/pK_B RBN	pA_2/pK_B rat aorta (Aorta/RBN)
9	9.3±0.05	7.8±0.1(32)	8.6±0.04 (5)	8.5±0.05	8.0±0.1 (2.9)
10	9.8±0.1	8.0±0.1(63)	ND[c]	9.2±0.2	8.3±0.2 (7.9)
11	9.6±0.1	7.5±0.1 (126)	7.9±0.1 (50)	9.2±0.1	7.9±0.2 (20)
12	8.9±0.1	7.1±0.1 (63)	7.2±0.1 (50)	8.9±0.1	6.8±0.1 (126)
13	8.9±0.1	7.0±0.2 (79)	7.5±0.1 (25)	8.5[b]±0.02	7.0±0.1 (32)
14	9.1±0.1	7.1±0.1 (100)	7.6±0.2 (32)	9.1±0.2	7.2±0.1 (79)
15	8.6±0.2	7.0±0.2 (40)	ND[c]	8.4±0.1	6.8±0.1 (40)
16	10.4±0.5	7.8±0.05 (398)	8.3±0.1 (126)	9.5±0.2	7.1±0.2 (251)
17	8.8±0.2	6.8±0.2 (158)	7.3±0.2 (50)	8.7[b]±0.1	7.3±0.2 (50)
18	9.6±0.1	7.0±0.1 (398)	7.6±0.03 (100)	8.9±0.05	7.1±0.2 (63)
19	9.0±0.2	7.3±0.2 (50)	8.0±0.2 (10)	8.7±0.1	7.0±0.1 (50)
20	8.8±0.2	6.8±0.2 (100)	7.5±0.2 (20)	8.8±0.04	6.8±0.1 (100)
21	8.2±0.2	6.7±0.3 (32)	7.0±0.2 (16)	8.2[b]±0.03	6.4±0.04 (63)
22	ND[c]	7.7±0.2	8.2±0.3	9.1[b]±0.2	7.5±0.3 (40)
26	9.1±0.1	7.2±0.1 (79)	7.8±0.1 (18)	8.6±0.05	7.3±0.1 (25)
28	8.4±0.05	6.4±0.1 (100)	6.9±0.1 (32)	7.8±0.1	6.3[b]±0.3 (32)
31	9.5±0.1	7.4±0.02 (126)	8.1±0.2 (25)	8.7±0.01	7.7±0.2 (10)
34	10.2±0.1	8.3±0.1 (79)	8.7±0.2 (32)	9.0±0.1	8.4±0.1 (4)
36	9.0±0.05	6.9±0.1 (126)	7.5±0.1 (32)	8.6[b]±0.05	6.9±0.1 (50)
39	8.7±0.3	7.0±0.1 (50)	7.7±0.2 (10)	8.5[b]±0.2	7.1±0.1 (25)

[a]Values are mean±SE mean, $n \geq 3$, unless otherwise noted.
[b]$n = 2$.
[c]Not determined.

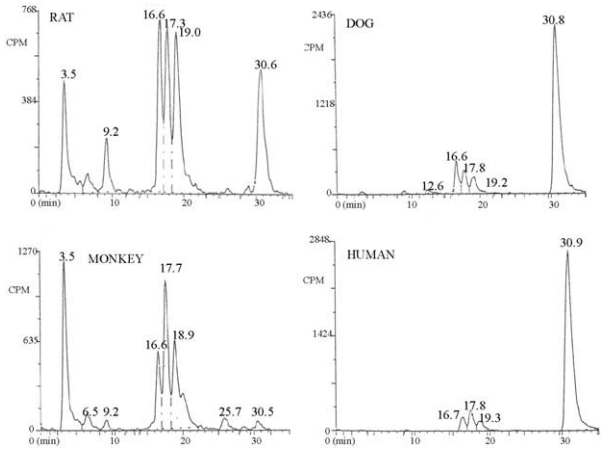


Figure 1. Metabolism of [^{14}C]-**12** by hepatic microsomes.

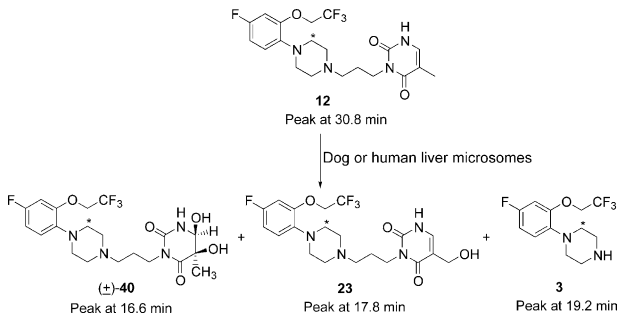
Table 3. In vitro relative rate of metabolism of selected compounds by dog liver microsomes

Entry	Rel. rate met.[a]	Entry	Rel. rate met.[a]
11	1.0	**18**	0.5
12	0.6	**20**	0.2
13	1.1	**21**	0.4
14	1.4	**36**	1.0
16	6.4		

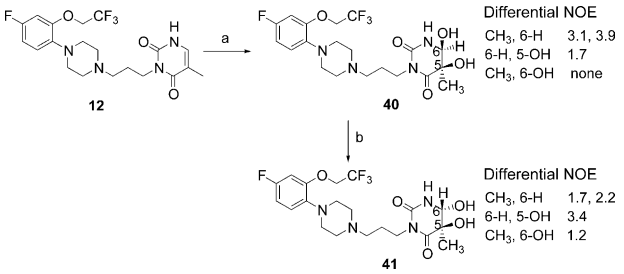
[a]Rates of metabolism relative to compound **11** that is set to 1.0.

R^3 = Me)] was isolated and identified as one of the metabolites from incubation of compound **11** with dog liver microsomes. On the other hand, compounds **18**, **20** and **21** are quite comparable to **12**, and the very potent and selective compound **16** (see Table 2) undergoes metabolism six times as fast as **11**.

Metabolites of compound **12** formed in dog liver microsomes were isolated and identified by mass spectrometric analysis, and structure formulas are shown in Scheme 5. Peak numbers under each compound refer to the retention times of the compounds in the radiochromatogram from dog liver microsomes (see Fig. 1). Syntheses (Scheme 2 for **23** and Scheme 6 for **40**) of different metabolites confirmed the assignment. Isolation of milligram quantities of **40** from a microsomal incubation was accomplished for enantiomeric analysis. Chiral HPLC studies[27] with both biological and synthetic



Scheme 5. Formation of metabolites of **12** from dog and human liver microsomes. The peak numbers refer to the retention times in radiochromatogram shown in Figure 1, and the asterisk in structures shows the radiolabeled carbon.



Scheme 6. Reagents and conditions: (a) NBS, CF_3CO_2H, H_2O, DMSO; 10% $NaHCO_3$, 57%; (b) *p*-TsOH, H_2O, DMSO, 60 °C, 33%.

40 show that both enantiomers are present in about 1:1 ratio in biologically produced **40**. Relative stereochemistry of this diol compound was assigned by the synthetic preparation of both *cis*- and *trans*-diols and by NOE NMR studies (Scheme 6).

Table 4 shows the affinity at the α_{1A}-, α_{1B}- and α_{1D}-adrenoceptor subtypes, the selectivity (α_{1B}/α_{1A} and α_{1D}/α_{1A} ratios), and the relative rate of metabolism in dog microsomes of metabolites **23** and **40**. Parent compound **12** is included for comparison purposes. Both **23** and **40** showed higher metabolic stability during incubation with microsomes than **12** or any derivative in Table 3. In addition, the *cis*-diol **40** showed a selectivity for the α_{1A}- over $\alpha_{1B/D}$-adrenoceptors of over 30 in both radioligand and functional studies, and an affinity of over pK_i 8 at the α_{1A} subtype. The pharmacokinetic profiles of **12** and **40** in dogs are shown in Table 5. Compound **40** has a terminal half life about 4 times longer than **12** following iv administration to dogs (11 vs 2.5 h) as a result of a 4-fold increase in the volume of distribution (4.0 vs 0.93 L/kg, respectively), while clearance remains about the same.

The effects on the prostate versus diastolic blood pressure (DBP) of **12** and **40**, compared to the non-selective α_1-adrenoceptor antagonist prazosin, were studied in dogs to evaluate their in vivo selectivity. Thus, pentobarbital-anesthetized male mongrel dogs were administered non-cumulative intravenous doses (0.03–300 μg/kg) of prazosin, **12** or **40** to inhibit increases in intraurethral pressure (IUP; balloon catheter) induced by hypogastric nerve stimulation (HGNS; 20–50 V, 10 Hz, 10 s) as well as phenylephrine (PE)-induced increases in diastolic blood pressure (DBP; femoral artery).[28] Prazosin non-selectively inhibited PE-induced increases in DBP (PE-DBP) and HGNS-induced increases in IUP (HGNS-IUP) yielding a selectivity ratio of 0.6 (PE-DBP/HGNS-IUP). In marked contrast both **12** and **40** selectively inhibited HGNS-IUP over PE-DBP yielding selectivity ratios of 76[28] and 71, respectively.

In summary, the present study shows a number of compounds to be high affinity antagonists at the α_{1A}-adrenoceptor subtype, with considerable selectivity over the α_{1B}- and α_{1D}-subtypes, in both radioligand binding and functional studies. Compound **12** has a similar in vitro profile in human and dog microsomes, forming mainly metabolites **3**, **23**, and racemic **40**. Metabolite **40** also shows nanomolar activity on the α_{1A}-subtype

Table 4. Affinity estimates (pK_i and pA_2/pK_B)[a] and in vitro rate of metabolism[c] of **12**, **23** and **40** by dog liver microsomes

Entry	pK_i α_{1A}	pK_i α_{1B} (α_{1B}/α_{1A})	pK_i α_{1D} (α_{1D}/α_{1A})	pA_2/pK_B RBN	pA_2/pK_B Rat aorta (aorta/RBN)	Rel rate met[c] (Dog)
12	8.9±0.1	7.1±0.1 (63)	7.2±0.1 (50)	8.9±0.1	6.8±0.1 (126)	0.6
23	8.1±0.2	6.8±0.2 (20)	7.2±0.1 (7.9)	8.2[b]±0.1	7.0±0.1 (16)	0.1
40	8.3±0.1	6.6±0.2 (63)	6.9±0.1 (33)	8.5±0.1	6.6±0.1 (79)	0

[a]Values are mean±SE mean, $n \geq 3$, unless otherwise noted.
[b]$n=2$.
[c]Relative rate of metabolism with respect to **11** (see Table 3).

Table 5. Single-dose pharmacokinetics of **12** and **40** in dogs[a]

Compd:	**12**		**40**	
Route:	IV	PO	IV	PO
$T_{1/2}$ (h)	2.5	2.8	11	10
CL (L/h/kg)	0.26	NC[b]	0.25	NC[b]
V_d (L/kg)	0.93	NC[b]	4.0	NC[b]
Bioavailability (%)	100	78	100	111

[a]0.3 mg/kg (**12** as hydrochloride salt, and **40** as oxalate salt) both PO and IV (four dogs in cross-over design for each **12** and **40**).
[b]Not calculated.

adrenoceptor, and selectivity over α_{1B}- and α_{1D}-subtypes higher than 30. Pharmacokinetic studies in dog showed both **12** and **40** to have a bioavailability of over 75%, although **40** has a terminal half life about 4 times as long as **12** (10–11 vs 2.5–2.8 h, respectively). Finally, in vivo preclinical pharmacological studies (HGNS-IUP vs PE-DBP) clearly demonstrate the uroselectivity of compounds **12** and **40** (RO1104253). **12** was assessed in clinical trials for the treatment of symptomatic BPH.[29] The cardiovascular effects of **12** were evaluated in two ascending-dose studies (single oral doses from 0.5 to 20 mg; multiple oral doses from 5 to 40 mg, once daily for 8 days) in healthy subjects (Phase 1). In the single-dose study, increases in supine and orthostatic heart rate (10–12 bpm) were observed with the 20 mg dose without clinical symptoms or hypotension. In the multiple-dose study, syncope associated with orthostatic hypotension was observed in one of six subjects in both the 30 and 40 mg groups. No clinically significant changes in blood pressure, or related symptoms, were observed at lower doses. In Phase 2, oral doses from 2.5 to 15 mg were administered once daily for 12 weeks. **12** was well tolerated in BPH patients (≥ 50 years) with increased mean peak urine flow rate (Q_{max}) of 2–3.5 mL/s. There was no apparent effect of **12** on vital signs or on orthostatic blood pressure compared to placebo. Development of **12** (RO700004, RS-100975) was discontinued, however, due to lack of clinically significant symptomatic improvement.[29]

References and Notes

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