JOURNAL OF
MEDICINAL
CHEMISTRY

Volume 40, Number 20 September 26, 1997

Communications to the Editor

Synthesis and Pharmacological Characterization of 3-[2-((3a*R*,9b*R*)-*cis*-6-Methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]isoindol-2-yl)ethyl]pyrido-[3′,4′:4,5]thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (A-131701): A Uroselective α_{1A} Adrenoceptor Antagonist for the Symptomatic Treatment of Benign Prostatic Hyperplasia[1]

Michael D. Meyer,*,† Robert J. Altenbach,† Fatima Z. Basha,† William A. Carroll,† Irene Drizin,† Steven W. Elmore,† Paul P. Ehrlich,† Suzanne A. Lebold,† Karin Tietje,† Kevin B. Sippy,† Michael D. Wendt,† Daniel J. Plata,‡ Fred Plagge,‡ Steven A. Buckner,† Michael E. Brune,† Arthur A. Hancock,† and James F. Kerwin, Jr.†

Neurological and Urological Diseases Research, D-47C, and Process Research, D-45L, Abbott Laboratories, Abbott Park, Illinois 60064-3500

Received June 2, 1997

Pharmacological management of benign prostatic hyperplasia (BPH) has most successfully been achieved by administration of α_1 antagonists, which function via relaxation of prostatic smooth muscle. Terazosin[2] (**2**), doxazosin[3] (**3**), and alfuzosin[4] (**4**), agents currently approved for this indication, were originally developed as antihypertensives, and their ameliorative effects in the treatment of benign prostatic hyperplasia (BPH) were not observed until after their introduction into clinical practice. Consequently, these agents suffer from significant cardiovascular side effects when administered for the BPH indication. Tamsulosin[5] (**5**), recently approved in Japan, is the first "uroselective" α_1 antagonist developed for the treatment of BPH (Figure 1).

Within the past several years, the heterogeneity of the α_1 receptor has been realized both on a molecular and pharmacological level. Three subtypes of the human α_1 receptor have been cloned and expressed: α_{1a}, α_{1b}, and α_{1d}.[6] In several studies, antagonist blockade of norepinephrine- or phenylephrine-induced contraction of human prostate tissues has been found to correlate with affinity for the α_{1a} subtype.[7,8] Consequently, an agent which demonstrates selectivity for the α_{1a} subtype may have efficacy in the treatment of BPH with significantly reduced cardiovascular side effects.

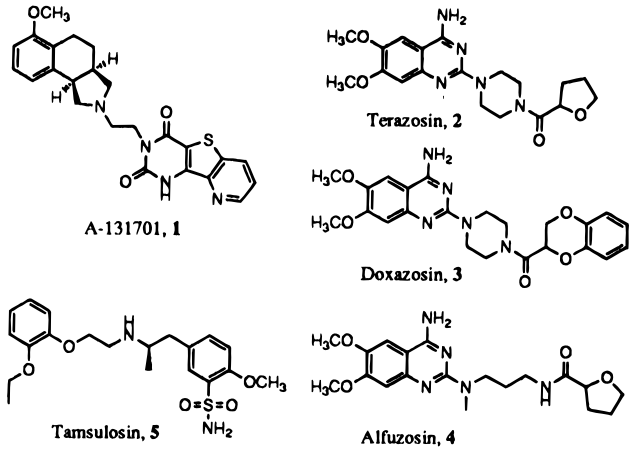


Figure 1.

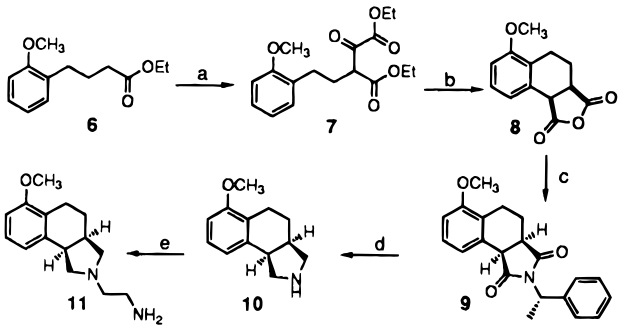
Results and Discussion

The title compound was prepared in enantiomerically pure form in nine steps from ethyl 2-methoxyphenylbutyrate. Synthesis of the enantiomerically resolved benz[*e*]isoindole substructure is described in Scheme 1. Base-promoted condensation of the ester **6**[9] with diethyl oxalate yielded the keto diester **7**, which upon treatment with sulfuric acid, followed by hydrogenation, produced the racemic *cis*-fused anhydride **8**. Dehydrative condensation of the anhydride **8** with (*S*)-α-methylbenzylamine yielded a diastereomeric mix of imides, from which the desired 3a*R*,9b*R* imide **9** was selectively crystallized. Reduction of the pyrrolidinedione **9** in refluxing 1.0 M BH_3·THF solution, followed by hydrogenolytic removal of the α-methylbenzyl group, yielded the enantiomerically resolved benz[*e*]isoindole core **10**. Alkylation of the secondary amine **10** with chloroaceto-

† Neurological and Urological Diseases Research.
‡ Process Research.

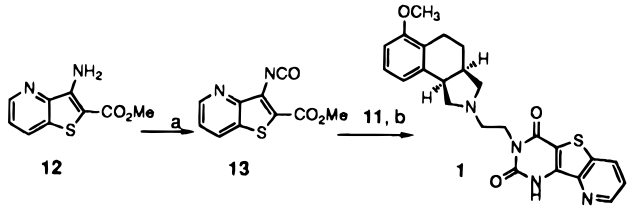
S0022-2623(97)00364-6 CCC: $14.00

Scheme 1[a]



[a] Reagents and conditions: (a) KOtBu, diethyl oxalate; (b) (i) H_2SO_4, (ii) H_2, Pd; (c) (*S*)-α-methylbenzylamine, refluxing xylene; (d) (i) BH_3·THF, reflux, (ii) H_2, Pd; (e) (i) chloroacetonitrile, ethyldiisopropylamine, (ii) $LiAlH_4$.

Scheme 2[a]



[a] Reagents and conditions: (a) phosgene, triethylamine; (b) (i) **11**, CH_2Cl_2, rt, (ii) KOtBu, THF.

nitrile, followed by $LiAlH_4$ reduction, gave the primary amine **11**. The heterocyclic substructure was prepared from the known thienopyridine **12**.[10] The amine **12** was reacted with phosgene to yield the isocyanate **13**, which upon condensation with the primary amine **11**, and subsequent *in situ* cyclization, yielded the final product **1** (A-131701) (Scheme 2).

Radioligand binding studies revealed **1** to be a moderately selective agent with sub-nanomolar affinity for the α_{1a} subtype of the α_1 adrenergic receptor. The nomenclature guidelines proposed by Bylund et al.,[11] using upper case letters to describe tissue-derived receptors and lower case letters to describe recombinant receptors, have been used throughout. **1** was approximately 32-fold selective for the human α_{1a} binding site vs the human α_{1b} site. Selectivity was observed, as well, over a range of related G-protein-coupled receptors. Selectivity over the α_2 sites ranged from 60- to 430-fold; the D_2 site showed moderate affinity at 19.7 nM. Results are summarized in Table 1.

Screening against a large battery of receptors, ion channels, amine uptake sites, and enzymes (data not shown) revealed no sites for which **1** possessed affinity within 3 orders of magnitude relative to the α_{1a} binding site. Radioligand binding assays were performed essentially as described by Knepper et al.[12]

Comparison of **1** to terazosin and tamsulosin, two agents currently used clinically for the treatment of BPH, revealed that **1** showed superior *in vitro* selectivity to these agents. Tamsulosin demonstrated a comparable level of receptor binding selectivity to **1**. The results are summarized in Table 2.

Functional assays for pharmacologically defined α_1 adrenoceptors were used to further characterize **1**. Functional activity was determined using phenylephrine (PE) challenge in dog prostate and rat vas deferens (α_{1A}); rat spleen (α_{1B}); and rat aorta (α_{1D})[13,14] isolated tissues. In each of these models, agonist dose−response curves were repeated against increasing concentrations of test agent. Schild analysis was then applied to determine the pA_2 value. In these experiments, **1** showed an 11−13-fold selectivity for the α_{1A} response (vs α_{1B}). Tamsulosin was approximately 1.4-fold selective for the α_{1B} response, and terazosin was 4−14-fold selective for the α_{1B} response. In these isolated tissue models, **1** differentiated from tamsulosin, showing approximately 20-fold greater selectivity for the α_{1A} response. The results are summarized in Table 3.

Compound **1**, terazosin, and tamsulosin were examined in two *in vivo* models: a challenge intraurethral pressure (cIUP) model as a measure of efficacy and the spontaneously hypertensive rat (SHR) model as a measure of selectivity. The cIUP model used aged male anesthetized dogs, in which a pressure transducer was inserted through the urethra to the region of the prostate. Phenylephrine caused a dose-related increase in intraurethral pressure, which was blockable by α_1 antagonists. Dose−response curves were generated at varying antagonist doses. From these data, a pseudo pA_2 value could be generated.[15] A similar strategy was used in the SHR model. Using an ascending iv dose paradigm, and measuring the decrease in blood pressure over a 60 min period, an ED_{50} value for dose required to produce a 50% decrease in mean arterial pressure relative to mean arterial pressure in normotensive rats was calculated. Pseudo pA_2 values from the IUP model

Table 1. Radioligand Binding Profile of **1**

receptor[a]	K_i (nM)	95% confididence limits
human α_{1a}	0.220	0.091−0.533
human α_{1b}	6.95	6.03−8.00
human α_{1d}	0.97	0.825−1.13
human α_{2a}	94.9	46.5−194
rat α_{2B}	13.1	6.29−27.2
human α_{2c}	16.6	3.82−72.2
β_1	10 600	6770−16700
β_2	3 870	3010−4980
D_1	717	486−1060
D_2	19.7	5.22−74.3
5-HT_1	3 380	2070−5520
5-HT_2	83	12.1−563

[a] The following radioligands were used: [^{3}H]prazosin for α_1 assays; [^{3}H]rauwolscine for α_2; [^{3}H]DHA for β_1 and β_2; [^{3}H]SCH-23390 for D_1; [^{3}H]spiroperidol for D_2; [^{3}H]serotonin for 5-HT_1; [^{3}H]ketanserin for 5-HT_2.

Table 2. Radioligand Binding (K_i, nM) Comparison of **1** to Other α_1 Antagonists

receptor	1	terazosin[a]	tamsulosin[a]
human α_{1a}	0.22	2.0 (1.5, 2.8)	0.029 (0.022, 0.038)
human α_{1b}	6.90	2.68 (2.1, 3.4)	0.61 (0.23, 1.6)
human α_{1d}	0.97	0.85 (0.66, 1.1)	0.058 (0.036, 0.085)
human α_{2a}	95	1500 (740, 3100)	13.4 (7.9, 23)
rat α_{2B}	13.1	7.7 (5, 12)	6.8 (1.9, 24)
human α_{2c}	16.6	78 (33, 190)	7.9 (2, 32)

[a] 95% Confidence limits indicated in parentheses.

Table 3. *In Vitro* Profile (pA_2) of **1** and Other Adrenergic Antagonists in Functional Screens of α_1 Antagonism

	1	terazosin	tamsulosin
α_{1A}			
dog prostate	9.0 (±0.15)	7.44 (±0.24)	9.54 (±0.17)
rat vas deferens	8.93 (±0.18)	8.04 (±0.45)	9.47 (±0.21)
α_{1B}			
rat spleen	7.89 (±0.22)	8.60 (±0.46)	9.69 (±0.44)
α_{1D}			
rat aorta	9.11 (±0.20)	8.65 (±0.29)	10.60 (±0.43)

Table 4. Comparison of Pseudo pA_2 and pED_{50} Values of Antagonists in the IUP and SHR Models

antagonist	IUP (pseudo pA_2)	SHR (pED_{50})	selectivity ratio
1	8.17 (±0.57)	5.33 (±0.74)	690
terazosin	7.02 (±0.66)	6.64 (±0.76)	2.4
tamsulosin	8.87 (±0.46)	7.33 (±0.30)	35

and pED_{50} values from the SHR model for **1**, terazosin, and tamsulosin are reported in Table 4. The ratio of the values then offers a relative index of prostate selectivity for these three compounds. The *in vivo* measurements are in good agreement with the *in vitro* selectivities observed in isolated tissue preparations, with **1** being approximately 20-fold more selective than tamsulosin and approximately 2 orders of magnitude more selective than terazosin.

Compound **1** represents a novel structural type exhibiting high affinity and moderate selectivity for the α_{1a} subtype of the α_1 adrenergic receptor. Numerous studies have correlated affinity to this subtype with modulation of prostatic tone in a variety of animal species, including man. These data further corroborate that correlation. In *in vitro* functional models predictive of α_1 subtype specificity and in *in vivo* models predictive of prostatic vs vascular tone, **1** demonstrates a very high degree of uroselectivity, significantly greater than that observed for tamsulosin, the only uroselective α_1 antagonist currently in use clinically for the treatment of BPH. These data suggest that **1** may have clinical utility for the symptomatic treatment of BPH with significantly reduced cardiovascular side effects.

Supporting Information Available: Experimental details (4 pages). Ordering information is given on any current masthead page.

References

(1) Presented in part: 213th National Meeting of the American Chemical Society, San Francisco, CA, April 13−17, 1997, MEDI-291.

(2) Lepor, H.; Henry, D.; Laddu, A. R. The efficacy and safety of terazosin in the treatment of BPH. *Prostate* **1991**, *18*, 345−355.

(3) Holme, J. B.; Christensen, M. M.; Rasmussen, P. C.; Jacobsen, F.; Nielsen, J.; Norgaard, J. P.; Olesen, S.; Noer, I.; Wolf, H.; Husted, S. E. 29-Week Doxazosin treatment in patients with symptomatic benign prostatic hyperplasia. *Scand. J. Urol. Nephrol.* **1994**, *28*, 77−82.

(4) Jardin, A.; Bensadoun, H.; Delauche-Cavallier, M. C.; Stalla-Bourdillon, A.; Attali, P. Long-term treatment of benign prostatic hyperplasia with alfuzosin: a 24−30 month survey. *Br. J. Urol.* **1994**, *74*, 579−584.

(5) Kawabe, K.; Ueno, A.; Takimoto, Y.; Aso, Y.; Kato, H. Use of an α_1-blocker, YM617, in the treatment of benign prostatic hypertrophy. *J. Urol.* **1990**, *144*, 908−912.

(6) Price, D. T.; Schwinn, D. A.; Lomasney, J. W.; Allen L. F.; Caron, M. G.; Lefkowitz, R. J. Identification, quantitation, and localization of mRNA for three distinct alpha$_1$ adrenergic subtypes in human prostate. *J. Urol.* **1993**, *150*, 546−551.

(7) Marshall, I.; Burt, R. P.; Chapple, C. R. Noradrenaline contractions of human prostate mediated by α_{1A}-(α_{1C})-adrenoceptor subtype. *Br. J. Pharmacol.* **1995**, *115*, 781−786.

(8) Forray, C.; Bard, J. A.; Wetzel, J. M.; Chiu, G.; Chapiro, I.; Tang, R.; Lepor, H.; Hartig, P. R.; Weinshank, R. L.; Branchek, T. A.; Gluchowski, C. The α_1 adrenoceptor that mediates smooth muscle contraction in human prostate has the pharmacological properties of the cloned human α_{1c} subtype. *Mol. Pharmacol.* **1994**, *45*, 703−708.

(9) Winstein, S.; Heck, R. F. Aryl Participation in the Solvolysis of Some gen-Dimethyl-Substituted 4-Aryl-1-alkyl p-Bromobenzenesulfonates. *J. Org. Chem.* **1972**, *37*, 825−836.

(10) Dunn, A. D.; Norrie, R. Nucleophilic Displacements in Pyridine Rings. *J. Heterocycl.Chem.* **1994**, *24*, 85−89.

(11) Bylund, D. B.; Eikenberg, D. C.; Hieble, J. P.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Molinoff, P. B.; Ruffolo, R. R., Jr.; Trendelenburg, U. International Union of Pharamacology nomenclature of adrenoceptors. *Pharmacol. Rev.* **1994**, *46*, 121−136.

(12) Knepper, S. M.; Buckner, S. A.; Brune, M. E.; DeBernardis, J. F.; Meyer, M. D.; Hancock, A. A. A-61603, a potent α_1-adrenergic receptor agonist, selective for the α_{1A} receptor subtype. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 97−103.

(13) Aboud, R.; Shafii, M.; Docherty, J. R. Investigation of the subtypes of α_1 adrenoceptors mediating contractions of rat aorta, vas deferens and spleen. *Br. J. Pharmacol.* **1993**, *109*, 80−87.

(14) Buckner, S. A.; Oheim, K.; Morse, P.; Knepper, S.; Hancock, A. A. Alpha$_1$-adrenoceptor induced contractility in rat aorta is mediated by the alpha1D subtype. *Eur. J. Pharmacol.* **1996**, *297*, 241−248.

(15) Brune, M. E.; Buckner, S. A.; Polakowski, J.; Kerwin, J. F., Jr.; Hancock, A. A. Pharmacological Antagonism of Alpha-adrenergic Agonist Induced Increases in Canine Intra-urethral Pressure in vivo. *Drug Dev. Res.* **1995**, *34*, 267−275.

JM970364A