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DESIGN AND SYNTHESIS OF N-ALKYLATED SACCHARINS AS SELECTIVE α-1A ADRENERGIC RECEPTOR ANTAGONISTS†

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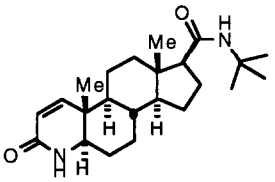
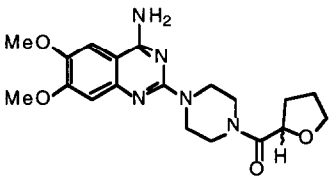
Abstract: Benign prostatic hyperplasia can be managed pharmacologically with α-1 adrenergic receptor antagonists. Agents that demonstrate selectivity for the α-1a receptor subtype may offer advantages in clinical applications with respect to hypotensive side effects. The N-alkylated saccharins reported here represent a new class of subtype selective α-1a adrenergic receptor antagonists which demonstrate potent effects on prostate function in vivo and are devoid of blood pressure side effects. © 1998 Elsevier Science Ltd. All rights reserved.

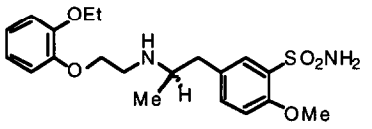
Benign prostatic hyperplasia (BPH) is a common condition in elderly men.[1] Historically, it has been managed surgically with transurethral resection of the prostate.[2] More recently, pharmacological management of the condition has become possible.[3] Finasteride **1**, a potent type 2 5α-reductase inhibitor, has been shown to be effective for the treatment of BPH.[4] Other therapies utilize α-1 adrenergic receptor antagonists. Currently available agents, such as terazosin **2**,[5] were originally developed as antihypertensive agents and thus have clinical drawbacks when used for BPH. Tamsulosin **3** represents the first of a class of "prostate selective" agents for the treatment of BPH.[6]



Finasteride **1**



Terazosin **2**



Tamsulosin **3**

Recent advances in pharmacology and molecular biology have demonstrated that the α-1 adrenergic receptor consists of three subtypes: α1a, α1b, and α1d. Further, studies have shown that blockade of

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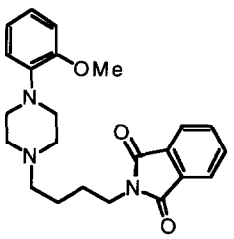
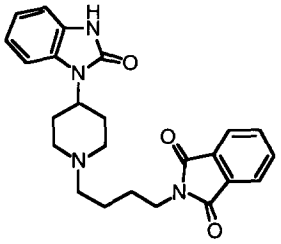
contraction in human prostate tissue by antagonists is positively associated with affinity for the α1a subtype.[7,8] Thus, agents that demonstrate subtype selectivity for the α–1a adrenergic receptor may offer advantages over nonselective α1 antagonists with respect to cardiovascular side effects. Several investigators have disclosed α–1a subtype selective adrenergic receptor antagonists for the treatment of BPH.[9,10]

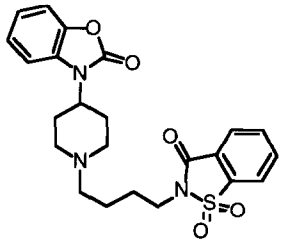
Our own strategy began with the study of the known serotonin 1A ($5\text{-}HT_{1A}$)/α1 receptor ligand NAN-190 **4**.[11] This compound is reported to have comparable affinity for the $5\text{-}HT_{1A}$ receptor (K_i = 0.6 nM) and the α1 receptors (K_i = 0.8 nM). Our goal was to design a compound based on **4** with an acceptable α1 subtype selectivity profile but devoid of significant affinity for other G-protein coupled receptors. Our initial approach was to replace the aryl piperazine moiety in **4** and then to systematically investigate alternative aromatic heterocycles to replace the phthalimide ring system. Compounds were tested for their ability to displace β-([^{125}I]-iodo-4-hydroxyphenyl)ethylaminomethyl tetralone from human cloned α1a, α1b, and α1d receptors stably expressed in CHO, LM and HEK cells respectively.[8,12]



NAN-190 **4** Ki (nM)
α1: 0.8 $5\text{-}HT_{1A}$: 0.6



5 Ki (nM): α1a: 0.28
α1b: 3.0 (11x)
α1d: 16 (56x)



6 Ki (nM): α1a: 0.12
α1b: 14 (115x)
α1d: 41 (350x)

We found that the 4-(2-keto-1-benzimidazolinyl) piperidine **5** was a suitable replacement for the aryl piperazine and offered modest selectivity for the α1a receptor over α1b (11x) and α1d (56x). Two more changes provided the subnanomolar α1a antagonist **6**, which has acceptable selectivity for α1b (115x) and α1d (350x). First, replacing the phthalimide with the 1,2-benzisothiazole-3(2H)-one-1,1-dioxide (saccharin) ring system afforded better selectivity against α1b. When this change was combined with the replacement of the 2-keto-1-benzimidazoline ring in **5** with benzoxazolone, the selectivity was improved further.

We next explored structure–activity relationships (SAR) on the benzoxazolone ring system of **6** as summarized in Table 1. In general, most substitutions decreased potency at the α1a receptor. However, fluoro-substitution at the 6-position as in **19**, provided increased potency and similar selectivity for α1a over α1b and α1d. Other substituents at the 6-position and other substitution patterns were not advantageous.

Table 1

SAR of the Benzoxazolone Ring Substituents

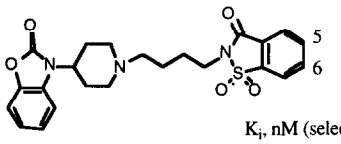
	K_i, nM (selectivity)		
	α 1d	α 1b	α 1a
6	41 (350x)	14 (115x)	0.12
13	1019 (7x)	1152 (8x)	147
14	644 (208x)	301 (97x)	3.1
15	224 (11x)	108 (5x)	20
16	136 (117x)	37 (32x)	1.2
17	894 (10x)	676 (7.5x)	90
18	2750 (5.5x)	1650 (3.3x)	499
19	25 (298x)	7.3 (87x)	0.084
20	3429 (3x)	1958 (2x)	1033

In an effort to further refine the α-1 receptor selectivity profile of **6**, we examined the consequences of variously substituting the saccharin ring system, as summarized in Table 2. Many of the substituents we prepared in the 5- and 6-positions led to potent α1a antagonists. A wide range of groups with different electronic characteristics and steric demands provided subnanomolar antagonists and often good selectivity for α1b and α1d. Several of these compounds showed efficacy in in vitro functional models and good oral pharmacokinetics in animal models. To demonstrate the utility of these compounds in vivo, chlorosaccharin **28** was further evaluated.

Radioligand binding studies demonstrated that **28** is greater than 50-fold selective for the α1a adrenergic receptor with respect to a wide range of related G-protein coupled receptors including α-2, β, dopamine, serotonin, and muscarine and various enzymes (data not shown).

Table 2

SAR of Saccharin Modifications



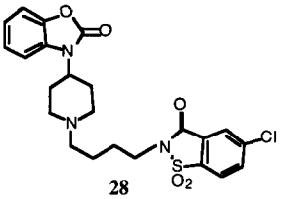
K_i, nM (selectivity)

Compd	5	6	α 1d	α 1b	α 1a
6	H	H	41 (350x)	14 (115x)	0.12
21	NO_2	H	351 (2752x)	133 (1044x)	0.13
22	H	NO_2	75 (479x)	75 (477x)	0.16
23	SCH_3	H	59 (1023x)	10 (176x)	0.057
24 [a]	H	SO_2CH_3	210 (88x)	6.8 (3x)	2.4
25	CH_3	H	73 (735x)	20 (201x)	0.099
26	OCH_3	H	76 (1188x)	15 (234x)	0.064
27	F	H	71 (266x)	50 (188x)	0.27
28	Cl	H	85 (1104x)	24 (312x)	0.077

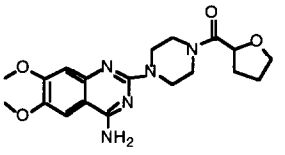
[a] receptors were expressed in COS-7 cells[13]

Chlorosaccharin **28** was tested in various tissue preparations to determine if potent in vitro receptor subtype selectivity would translate to the expected higher affinity in tissues which have a greater abundance of α1a receptors.[8] In the assay, both human and dog prostatic and aortic tissues were used (Table 3). Compound **28** was shown to be more potent in prostate tissue affinity in both human (530x) and dog (310x) prostatic tissue relative to aortic tissue.

Table 3



28



Terazosin **2**

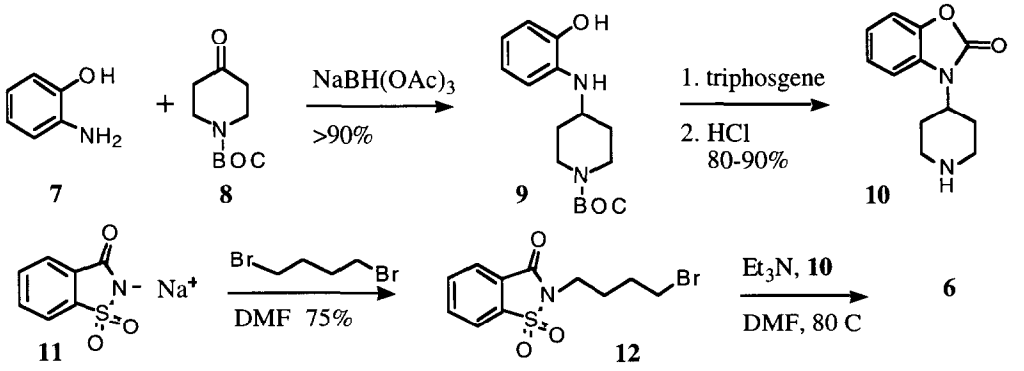
Binding Studies		K_i(nM)	
human α1d	85		2.0
human α1b	24		1.2
human α1a	0.08		4.2
Human Prostate	0.17		2.9
Human Aorta	90		2.4
Dog Prostate	0.24		32
Dog Aorta	74		2.0
In Vitro Functional Assays		**K_b (nM)**	
Rat Prostate	2.0		27
Rat Aorta	110		19
Dog Prostate	1.7		---
Dog Aorta	>100		---
In Vivo Dog Assays		**K_b (μg/kg)**	
Phenylephrine increase in urethal pressure	5.5		16
Phenylephrine increase in diastolic pressure	156		17
Selectivity	28x		1x

Terazosin **2** in the same assay is *less* potent in prostatic than in aortic tissue in both human and dog preparations. In in vitro functional assays in isolated prostate and aorta, compound **28** showed no agonist activity and was at least 50-fold more potent in antagonizing induced contractions in the prostate than aorta (rat and dog). Further, in vivo testing also demonstrated the selectivity for prostatic effects with respect to blood pressure effects.

Our hypothesis for the use of α1a subtype selective adrenergic antagonists for the treatment of BPH is that such an antagonist would inhibit the effects of the α-1 adrenergic system in the prostatic urethra but would be devoid of activity in the cardiovascular system. In an in vivo assay, dogs were intravenously challenged with the α-1 adrenergic agonist phenylephrine. Subsequent doses of an antagonist, **28** or terazosin **2**, were used to construct dose–response curves for both intraurethral pressure (IUP) and diastolic blood pressure (DBP). From these data, we conclude that **28** is a 28-fold selective antagonist for IUP vs. DBP and that terazosin **2** is not selective in this assay. Further evaluation of **28** (data not shown) demonstrated no effect on blood pressure in spontaneously hypertensive rats (3 mg/kg, iv dose), conscious dogs (1 mg/kg, iv dose) and conscious rhesus monkeys (1 mg/kg, iv dose). Thus, we have demonstrated that a compound which is selective in vitro for α1a over α1b and α1d adrenergic receptors is also selective in vivo for intraurethral pressure over diastolic blood pressure.

The preparation of **6** is depicted Scheme 1. 2-Aminophenol is reductively alkylated with 1-t-butoxycarbonyl-4-piperidone and the resulting aminophenol is cyclized with triphosgene. Deprotection under standard conditions provides the free piperidine. Sodium saccharin **11** is monoalkylated with 1,4-dibromobutane and the resulting bromide **12** is used to alkylate the piperidine which provides the target compound **6**. The preparation of compounds **13–20** was accomplished in an analogous way.

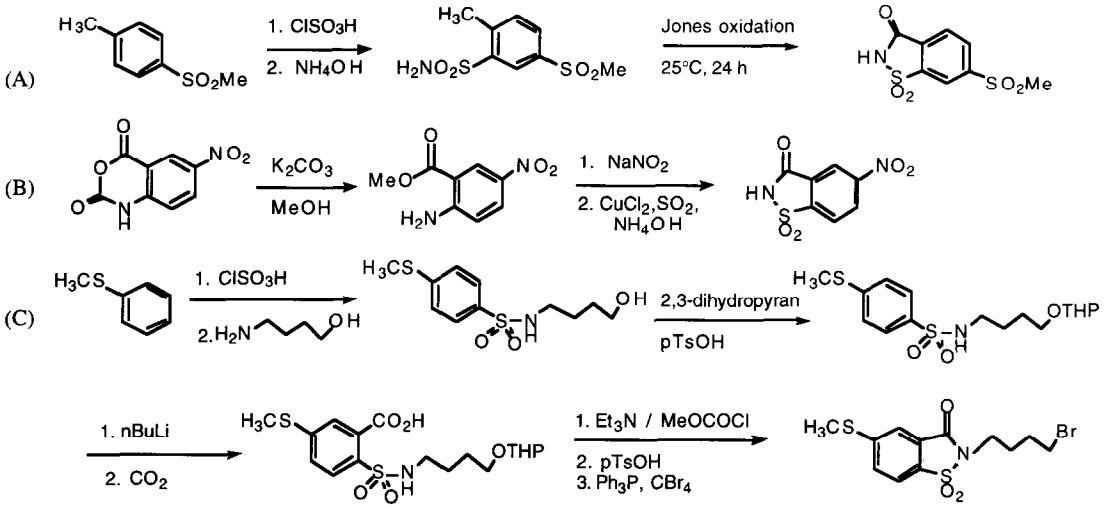
Scheme 1



The synthesis of various substitutions in the saccharin ring was accomplished as described in Scheme 2 and according to established literature methods.[14] Target compounds were prepared in analagous fashion to that in Scheme 1.

Scheme 2

Synthesis of Substituted Saccharins



Compound **28** is representative of a class of novel α1a adrenergic receptor antagonists with high affinity and selectivity. Functional studies both in vitro and in vivo demonstrate that compounds of this class can be useful for the reduction of intraurethral pressure while not affecting blood pressure. Further development of compounds in this class will be reported in due course.

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