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4-OXOSPIRO[BENZOPYRAN-2,4'-PIPERIDINES] AS SELECTIVE α_{1a}-ADRENERGIC RECEPTOR ANTAGONISTS

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Abstract: The 4-oxospiro[benzopyran-2,4'-piperidine] ring system is contained within potent class III antiarrhythmic agents. We highlight how these agents can be chemically transformed into a new class of potent (<1 nM) and selective (>25-fold) α_{1a}-receptor subtype adrenergic antagonists.

Benign prostatic hyperplasia (BPH) is the progressive enlargement of the prostate, a chronic condition that commonly affects elderly men.[1] This affliction has been managed by surgical techniques[2] and by pharmacological means[3] employing type-2 5α-reductase inhibitors or α_1-adrenergic receptor antagonists. Recent advances in pharmacology and molecular biology have prompted renewed investigations of α_1-adrenergic receptor antagonists with particular emphasis on α_{1a}-subtype selective compounds for the treatment of BPH.[4,5] We[6] and others[7-10] have recently reported on α_1-receptor subtype selective adrenergic antagonists. In the present disclosure, we extend our earlier work to demonstrate that the 4-oxospiro[benzopyran-2,4'-piperidine] ring system may serve as a useful scaffold for constructing potent and selective α_{1a}-receptor antagonists.

4-Oxospiro[benzopyran-2,4'-piperidines] have previously been reported as class III antiarrhythmic agents.[11] These compounds exert the effect of prolonging myocardial refractoriness by blocking the outward repolarizing potassium current. Our attention was drawn to these compounds by the observation that selected members of this structural class displayed modest affinity for α_1-adrenergic receptors. Moreover, it appeared that both the affinity for α_1-receptors and the level of antiarrhythmic activity of these agents might be subject to adjustment by straightforward structural modifications.[11,12] Based on this rudimentary analysis, we began our investigations with the known compounds **1**, **2**, and **3**.[11]

At the outset, the immediate objective was to test the concept that compounds with good α_1 potency could be derived from known antiarrhythmic agents but lacking the cardiovascular effects of the latter. To this end, we focused on three regions of the prototype compound **1**: (a) the core template of the 4-oxospirobenzopyran (b) the aryl ethyl side chain and (c) the 6- and 7-positions of the benzopyran ring. Compounds were evaluated for their ability to displace [^{125}I]-HEAT[13] from cloned human α_{1a}-, α_{1b}- and α_{1d}-adrenergic receptors stably expressed in CHO, LM, and HEK cells, respectively.[5] In addition, selected compounds were tested for potential

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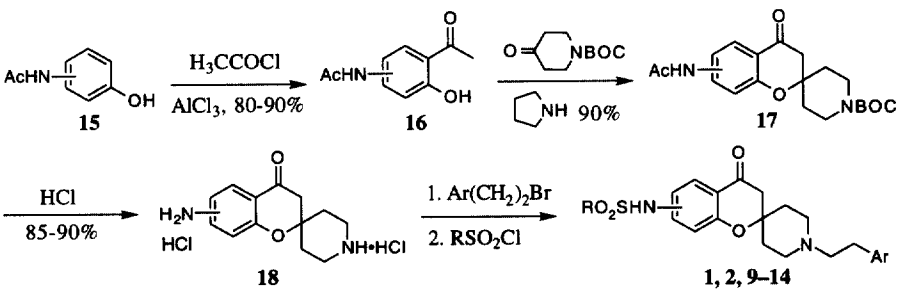
antiarrhythmic activity in vitro using isolated ferret papillary muscle preparations; the endpoint in this assay is related to the increase in effective refractory period (ERP) above the baseline value.[14]

The preparation of the compounds in Table 1 were, for the most part, carried out according to literature procedures as outlined in Scheme 1.[11,15,16]

Scheme 1 Synthesis of 4-Oxospiro[benzopyran-2,4'-piperidines]



It is apparent from the data in the Table that the 6-methanesulfonamide group in compound **1** affects both antiarrhythmic activity and α_1-receptor affinity (cf. compounds **1**, **2**, and **3**). The boost in α_{1a} potency realized when the methanesulfonamide group is absent, as in **3**, could be further augmented by increasing the electron density of the appended aromatic ring.[17] Thus, substituting naphthyl for pyridyl resulted in a 15-fold increase in α_{1a} receptor binding potency (cf. **3** and **4**). Further exploration of various 4-oxospirobenzopyran analogs (**5-8**)[11,16] related to **4** did not result in significant improvements in either α_{1a}-binding affinity or selectivity. However, when a 7-methanesulfonamide group was reintroduced in **4**, the resulting product **9** displayed an additional two-fold enhancement in α_{1a}-receptor binding potency and gave evidence of slight α_1-receptor subtype selectivity. Importantly, this change also held antiarrhythmic activity in check. Continued electronic tuning of the accessory aryl pharmacophore in **9** eventually led to the 2-methylindole derivative **11**. In essence, therefore, by varying the arylethyl appendage of **2**, affinity for the α_{1a}-adrenergic receptor subtype was increased more than 200-fold with the concomitant elimination of antiarrhythmic activity (cf. **2** and **11**).

An alternative, albeit counterintuitive, method for improving the α_1-receptor binding profile of **4** was discovered when a sulfonamide group was coupled to the benzopyran ring in the 6-position. In this way, the α_{1a}-receptor binding potency of **11** could be nearly duplicated, given the important proviso that the methanesulfonamide function is substituted (e.g., as in **12**). Surprisingly, when the 1-naphthyl ring in **12** was replaced with 2-methylindole, the expected incremental improvement in α_1-receptor binding affinity was not obtained (data not shown). Further examination of structural variants of the benzenesulfonamide analog **12** ultimately guided us to the 3,5-dimethylisoxazole derivative **14** which combines subnanomolar α_{1a}-receptor binding affinity with no measurable antiarrhythmic activity.

Table 1 Receptor Binding Affinity and in vitro Antiarrhythmic Acitivity

	K_i, nM (selectivity) (n ≥ 2)[a]			EC_{25}, μM[b]
	α-1d	α-1b	α-1a	ERP
1	3841	>2000	>2000	0.033
2	3250	>2000	1670	6.6
3	1515	1294	793	0.16
4	67 (1.3x)	48 (1x)	53	–
5	60 (1.3x)	137 (3x)	45	–
6	149 (5x)	49 (1.6x)	31	–
7	200 (2.8x)	53 (0.7x)	71	–
8	99 (1.8x)	55 (1x)	56	–
9	136 (7x)	149 (7.5x)	20	9.0
10	94 (14x)	175 (27x)	6.5	3.8
11	115 (14x)	221 (28x)	8	>30
12	53 (4x)	24 (1.8x)	13	>30
13	24 (3x)	53 (6.6x)	8	>30
14	18 (26x)	24 (35x)	0.69	>30

[a]Values represent the numerical average of at least duplicate experiments.

[b]EC_{25} refers to that concentration required to increase the effective refractory period (ERP) 25% above baseline.

Compound **14** was subsequently tested in various tissue preparations to determine if its high receptor binding potency would be maintained in tissues that have an abundance of α_{1a}-receptors.[5] In these assays, **14** showed binding affinity of <10 nM in prostatic tissue (rat and human). Additionally, compound **14** showed antagonist activity in a functional assay (K_b = 31 nM, isolated rat prostate).

By carrying out limited SAR studies, we have shown in this work how potent class III antiarrhythmic agents can be transformed into α_{1a}-adrenergic antagonists. Our results broaden the structural diversity among antagonists with affinity for the α_{1a}-receptor subtype and hold promise for the discovery of additional novel ligands using this generalized approach.

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