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ANALOGS OF UK 14,304 AS α_2-ADRENOCEPTOR AGONISTS. TWIST AND AGENT POLARITY AS DESIGN ELEMENTS.

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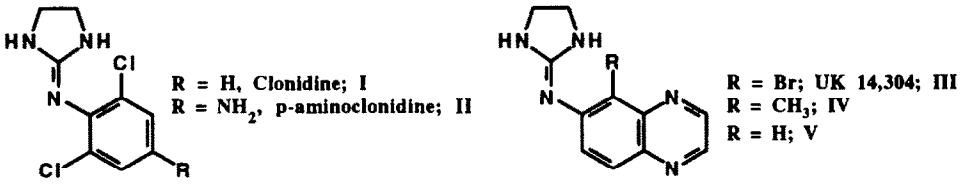
Abstract: Tetrahydroquinoxaline analogs of UK 14,304 were prepared. These agents proved to be highly polar, potent, and selective α_2-adrenoceptor agonists. This study suggested that agents bearing a twist of the imidazoline ring relative to the quinoxaline nucleus prove more potent than planar analogs.

Agents stimulating α_2 adrenoceptors have been demonstrated to elicit a variety of physiologic responses including lowering of blood pressure, cognition enhancement, and inhibition of fluid secretion.[1] We were interested in designing novel α_2 adrenoceptor agonists to reduce high intraocular pressure (IOP), a condition often associated with glaucoma.[2] This class of agents was first used to treat high IOP in 1966 when Mackabe demonstrated that clonidine, I, lowered IOP in man.[3] Since that time, many α_2 agonists including UK 14,304, III,

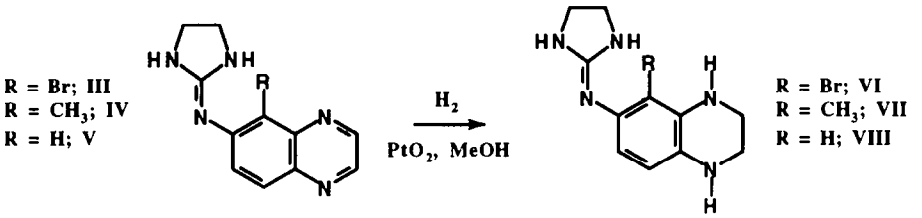
Figure I



have been used to treat ocular hypertension.[4] A major drawback of topical α_2 agonist therapy for the treatment of high IOP has been that centrally mediated effects including hypotension and bradycardia accompany a reduction in IOP.[5] Previous workers have observed that many of these untoward effects can be mitigated through increased agent polarity.[6] Thus *p*-aminoclonidine, II, was shown to have an improved therapeutic index compared to the parent for the treatment of elevated IOP. We therefore prepared a series of reduced, tetrahydroquinoxaline

analogs of UK 14,304. These agents proved to be more polar than the starting materials from which they were derived. This is seen upon comparison of the distribution coefficients of the quinoxalines to the corresponding reduced analogs. This study revealed the importance of steric effects in maintaining the relative orientation of the quinoxaline and imidazoline subunits. Sterically induced twist enhances α_2 adrenoceptor agonist activity.

Scheme I



A set of quinoxalines including UK 14,304 (R = Br) was treated with H_2 and PtO_2 in methanol at 50 psi to afford the analogs VI-VIII shown below.[7] These agents proved unstable as free bases and were best handled as dihydrochloride salts. The agents were purified by treatment with decolorizing carbon followed by recrystallization from ethanol. Satisfactory analytical and spectroscopic data was obtained for the compounds.

The agents were evaluated for their ability to discriminate between α_2 and α_1 adrenoceptors by determining binding affinities (K_i) for HT-29 (α_2 adrenoceptors)[8] and human brain (α_1 adrenoceptors)[9] preparations. Potent and selective agents were assessed for functional efficacy (EC_{50}) through their ability to inhibit the contractile response of an electrically stimulated rabbit *vas deferens*.[10]

The data presented in Table I are striking in that agents bearing an electron donating substituent (methyl; IV and VII) and agents bearing an electron withdrawing substituent (Br; III and VI) at the 5-position of the quinoxaline nucleus both demonstrate increased potency and selectivity for α_2 adrenoceptors versus the unsubstituted cases. Agents III and IV as well as agents VI and VII proved to be of comparable potency and almost an order of magnitude more active than the analogs bearing a 5-hydrogen in the HT-29 binding assay. The agents demonstrating single digit nanomolar binding affinity were evaluated for functional activity. Reduced agents VI and VII were shown to be potent agonists in the *vas deferens* assay and were similar in activity to UK 14,304.

A modeling study was conducted to compare the conformation of these agents.[11] The minimum energy conformations for agents VIII and VII are presented in Figure II, shown below. Substitution at the 5-position of the tetrahydroquinoxaline nucleus induced a twist about the carbon-nitrogen bond at the 6-position, a 1.6 Å shift in the position of the proximal nitrogen, and a 0.76 Å shift in the position of the distal nitrogen. Similar results were obtained for the minimum energy conformation of the 5-bromo analog VI. This could also be predicted from consideration of the steric parameters for bromine and methyl subunits.[12] We therefore conclude that this twist is a key element affording increased α_2 activity of agents VI and VII versus VIII.

Table I

Agent	K_i (nM)[a]		EC_{50}[a]	logDC[b]
	α_1	α_2	α_2	
III; UK 14,304	1,900 +/- 100	2.4 +/- 0.2	1.0 +/- 0.1	1.5
IV	1,400 +/-100	1.3 +/- 0.1	0.3 +/- 0.3	0.16
V	11,000 +/-1,000	64 +/-7.1	not tested	not tested
VI	1,100 +/-120	6.0 +/ 1.0	2.0 +/-0.6	-1.74
VII	8,700 +/-1,000	6.8 +/-0.8	3.5 +/-1.7	-2.08
VIII	5,100 +/-2,300	46 +/-6.5	not tested	not tested

a) All experiments were replicated at least three separate times.
b) logDC represents the partition coefficient between octanol and pH7.2 phosphate buffer

Figure II

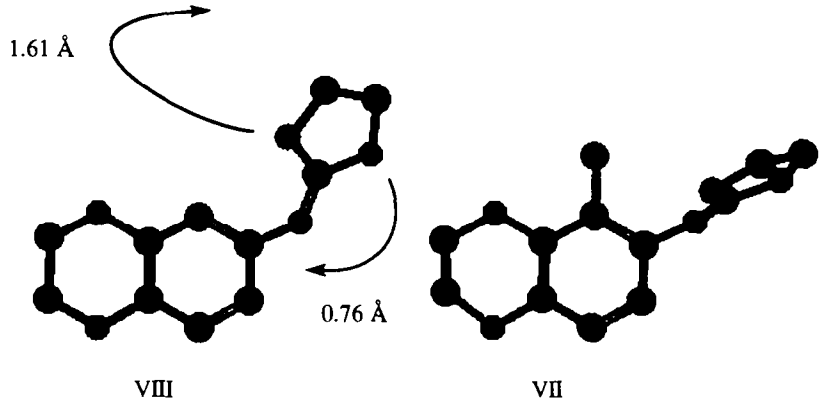


Table I also presents data for the distribution coefficients of UK 14,304, IV, and the corresponding reduced analogs. Agents VI and VII proved to have negative log DCs. This demonstrated that these agents are relatively organic insoluble when protonated (pH = 7.4). This is in contrast to the aromatic analogs. Both UK 14,304 and agent IV proved to have positive logDCs demonstrating that they are moderately organic soluble.

Reduced analog VII was shown to be selective for the α_2 versus α_1 adrenoceptor subtype by three orders of magnitude. Preliminary *in vivo* experiments conducted with glaucomatous cynomologus monkeys and the highly polar analog VII suggest that the agent reduces intraocular pressure when applied as a topical solution. Full details of our studies with this set of agents will be reported in due course.

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