Synthesis and Evaluation of 2-[(5-Methylbenz-1-ox-4-azin-6-yl)imino]imidazoline, a Potent, Peripherally Acting α_2 Adrenoceptor Agonist†

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We have synthesized 2-[(5-methylbenz-1-ox-4-azin-6-yl)imino]imidazoline, **3**, a potent, peripherally acting α_2 adrenoceptor agonist. The agent is conveniently prepared in five steps from 2-amino-*m*-cresol. The agent has demonstrated good selectivity for α_2 adrenoceptors in binding and functional studies. When applied topically to eyes, the agent is efficacious for the reduction of intraocular pressure. The agent does not penetrate the blood−brain barrier and, as a consequence, does not lower blood pressure or induce sedation when administered topically or intravenously. We have determined the pK_a and log *P* in water versus both octanol and dodecane of **3** and a set of related agents. The best physical parameter to explain its lack of central nervous system penetration appears to be log *P* measured in octanol versus water.

Introduction

Agents stimulating α_2 adrenoceptors have been demonstrated to mediate a variety of physiologic functions including reduction of blood pressure, sedation, and inhibition of fluid secretion.[1,2] We have been interested in designing novel α_2 adrenoceptor agonists to reduce elevated intraocular pressure (IOP). This is a condition often associated with glaucoma.[3] Reduction of IOP is a peripherally mediated α_2 adrenoceptor process in both rabbit and human. This class of agents was first used to reduce IOP in 1966, when Makabe demonstrated that clonidine (**1**), a potent α_2 adrenoceptor agonist, lowered IOP in man.[4] A major limitation of peripheral application of clonidine for the treatment of elevated IOP is the ability of this agent to cross the blood−brain barrier. This property leads to centrally mediated side effects including sedation and reduction in blood pressure upon topical administration of the agent.[5] Polar compounds including *p*-aminoclonidine (**2**) have been introduced as central nervous system (CNS)-limited agents.[6,7] One drawback of *p*-aminoclonidine is its potency at α_1 receptors. That agent proved to be less than 100-fold selective for α_2 versus α_1 adrenoceptors under our assay conditions. An agent possessing enhanced selectivity for α_2 relative to α_1 adrenoceptors would minimize α_1 adrenoceptor-mediated effects including ocular vasoconstriction and mydriasis and would have a distinct advantage over existing agents in this class.[8] A second drawback of **2** is the allergy induced upon topical administration.[9] We have recently proposed that the induced allergic response to **2** is a consequence of its facile oxidation to an electrophilic *p*-quinonediimide followed by addition of thiol nucleophiles.[10] This process models well-known hapten formation reactions.[11] Oxidative instability is also a potential liability of long term use for **5**. It is a useful compound to assess hydrogen-bonding capacity, log *P*, and membrane penetration.[12,13] Herein, we describe full details of our studies with 2-[(5-methylbenz-1-ox-4-azin-6-yl)imino]imidazoline (AGN 193080, **3**), a potent, selective α_2 adrenoceptor agonist that does not cross the blood−brain barrier. Agent structures are shown in Figure 1.

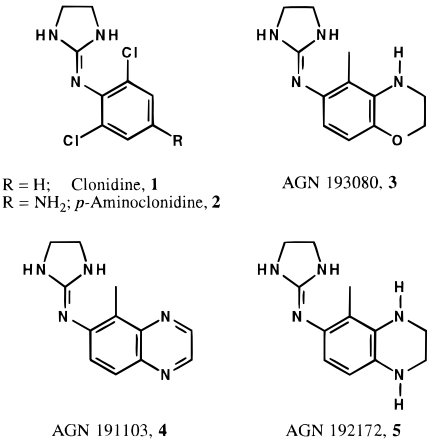

Figure 1.

Agent Synthesis

The synthesis of 6-amino-5-methylbenz-1-ox-4-azin-3-one (**10**), the amine intermediate for assembly of **3**, is shown in Scheme 1. Treatment of 2-amino-*m*-cresol (**6**) with chloroacetyl chloride afforded the cyclic amide **7**. This amide provided a convenient protecting group for the 4-nitrogen during the subsequent nitration reaction and during installation of the imidazoline subunit. This material was carefully nitrated in cold sulfuric acid to obtain the desired 6-nitro isomer **8** as the major product. Compound **8** and the 8-nitro isomer **9** proved difficult to separate. We therefore reduced the nitrated products directly to obtain the mixture of amines which proved easier to separate. The reduction, accomplished with hydrogen and palladium, afforded the key intermediate **10** for the assembly of **3**. The regiochemistry of the major product **10** was confirmed by NOE−NMR analysis.

† A preliminary account of these studies has been presented: Munk, S. A.; Harcourt, D.; Burke, J.; Lai, R.; Roberts, D.; Small, D.; Gluchowski, C.; Manlapaz, C.; Padillo, E.; Kharlamb, A.; Runde, E.; Wheeler, L.; Garst, M. Synthesis and Biological Evaluation of AGN 193080. A Potent and Selective Ocular Antihypertensive Agent. 209th American Chemical Society National Meeting, Anaheim, CA, April 1995; MEDI 193.

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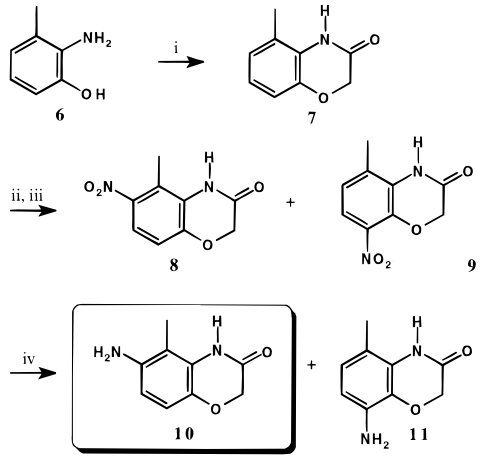
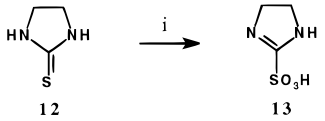
Scheme 1[a]



[a] Reagents and conditions: (i) triethylamine, 4-(dimethylamino)-pyridine, chloroacetyl chloride, methylene chloride; (ii) concentrated nitric acid, concentrated sulfuric acid, −15 °C; (iii) saturated sodium bicarbonate, ice; (iv) 10% palladium−carbon, H_2, methanol−tetrahydrofuran (1:1).

Scheme 2[a]



[a] Reagents and conditions: H_2O_2, $Na_2MoO_4 \cdot 2H_2O$, NaCl, −10 to −5 °C.

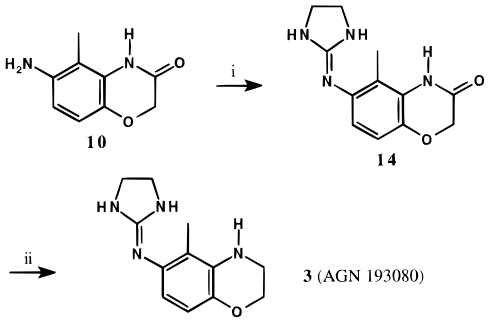
Methods for the synthesis of amidino-2-sulfonic acids, potential reagents for the construction of guanidines, have been reported.[14,15] The synthesis of imidazoline-2-sulfonic acid (**13**), the primary reagent for the assembly of aminoimidazolines including **3**, proved inconsistent in our hands initially. We therefore investigated the reaction to define a reproducible procedure for the preparation of reagent **13**. Internal temperature of the reaction mixture was found to be the critical variable after considering a variety of reaction conditions. The molybdenum-promoted H_2O_2 oxidation of the thiourea to imidazoline-2-sulfonic acid proved very exothermic. The rate of addition of H_2O_2 determined the internal temperature. The rate must be sufficiently slow to prevent the internal reaction temperature from rising above −4 °C. Careful monitoring of the internal temperature afforded reproducible yields of the reagent. A detailed procedure for the reaction shown in Scheme 2 is provided below.

The final assembly of **3** is shown in Scheme 3. The imidazoline subunit was installed in a single step upon treatment of the amine with imidazoline-2-sulfonic acid in acetonitrile and triethylamine. Amide **14** was reduced with borane−dimethyl sulfide to afford the agent for biological evaluation.

Pharmacologic Evaluation

Structure−activity studies within this series based on α_2 adrenergic receptor binding affinities have been communicated previously.[16−18] The earlier data allowed us to develop a summary of the key functional features of the agent that are responsible for agent−α_{2A} adrenoceptor binding. The summary is presented in Figure 2. Those studies revealed the importance of the imidazoline ring, conformational preorganization of both the imidazoline ring and the substituents appended to the aromatic core, and hydrogen bonding, as well as steric effects on α_{2A} adrenoceptor activity.

Scheme 3[a]



[a] Reagents and conditions: (i) imidazoline-2-sulfonic acid, triethylamine, acetonitrile, reflux; (ii) borane−dimethyl sulfide complex, tetrahydrofuran, reflux.

***In Vitro* Evaluation.** The agent was evaluated in a variety of binding assays. The α_1 adrenergic membrane preparation was from human brain and has a mixed population of subtypes. Binding studies were conducted using α_2 adrenergic membrane preparations from cloned receptors transfected into Chinese hamster ovary (CHO) cells to determine the subtype selectivity. The α_{2A} preparation was the human C-10 receptor; the α_{2B} preparation was the rat RNG receptor; the α_{2C} preparation was the human C-2 receptor.[19]

Preliminary *in vitro* functional studies were conducted using tissue baths. The rabbit vas deferens was used to assess α_2 adrenergic activity, and the rabbit aorta was used to assess α_1 adrenergic activity. Prostatic ends of the vas deferens from albino rabbits were mounted between platinum electrodes and field stimulated. Cumulative concentration−response curves in 0.25 log units were obtained for each agent. Contractile responses from aortic rings from albino rabbit were determined in 0.5 log units. The EC_{50} was determined as the concentration that produced a 50% contractile response relative to the maximum response to norepinephrine.

Agent **3** (AGN 193080) proved to be 400-fold selective for the α_{2A} adrenoceptor subtype relative to the α_1 adrenoceptor in both binding and function assay systems. Functional evaluation of the agents demonstrated that **3** was a full agonist in the vas deferens assay and proved more selective than *p*-aminoclonidine (90-fold selective) or clonidine (66-fold selective) for the α_{2A} receptor versus the α_1 receptor. Table 1 summarizes the results of the *in vitro* evaluation of **3** (AGN 193080) and several analogs.

***In Vivo* Evaluation.** A single drop of either clonidine or **3** was applied unilaterally to rabbit eyes and the IOP was monitored for 6 h postadministration. The concentration was 0.001% for each agent. The results of the study are presented in Figure 3. From this study, both agents proved effective for the reduction of intraocular pressure; however, **3** proved to have enhanced efficacy compared to clonidine. Agent **3** decreased IOP 25% at the peak (2 h) compared to a peak reduction of only 10% for clonidine. The duration of action of **3** was superior to that of clonidine. The IOP had not returned to the base-line level at 6 h postadministration of **3** in contrast to clonidine, where a return to base line was

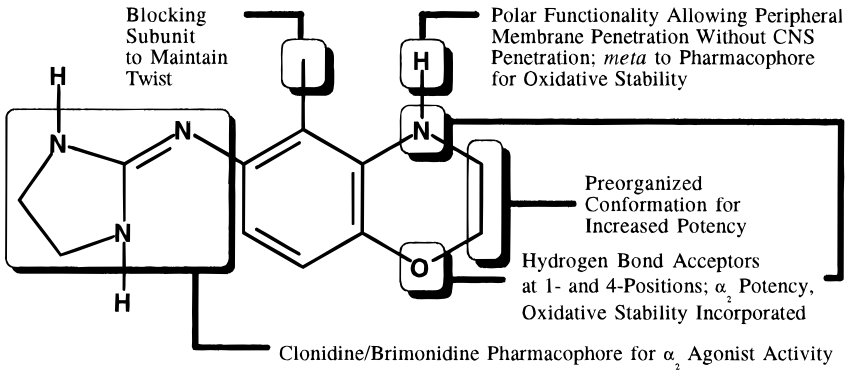


Figure 2. Functional features of agent **3** designed to be a peripherally acting α_2 agonist.

Table 1

	binding affinities (K_i, nM)				functional response (EC_{50}, nM)	
agent	α_1	α_{2A}	α_{2B}	α_{2C}	α_1	α_2
clonidine	510 ± 110	3.8 ± 0.41	8.3 ± 0.21	30 ± 2.0	290 ± 47	4.4 ± 0.43
p-NH_2-clonidine	180 ± 18	2.9 ± 0.25	4.8 ± 1.2	30 ± 7.7	180 ± 9.5	1.9 ± 0.19
3	470 ± 21	1.2 ± 0.19	30 ± 2.1	8.9 ± 2.1	480 ± 75	1.2 ± 0.10
4	1400 ± 200	2.0 ± 0.58	17 ± 1.9	27 ± 7.0	4700 ± 100	0.26 ± 0.016
5	8700 ± 320	9.6 ± 1.2	140 ± 7.7	120 ± 9.6	790 ± 100	3.5 ± 1.7

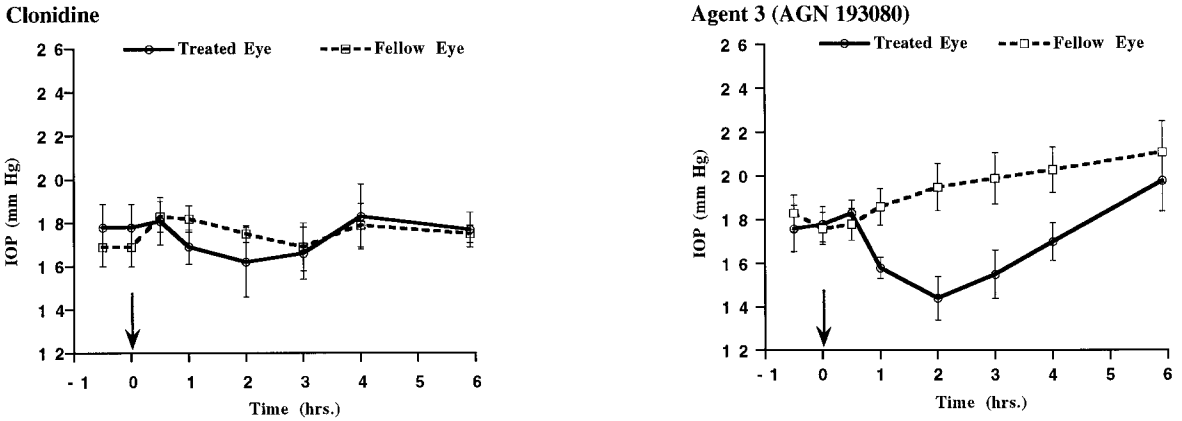


Figure 3. Intraocular pressure upon topical, unilateral administration of a single drop of a 0.001% solution of the agent to rabbit eye. The untreated (fellow) eye served as the control. The mean values reported are the result of six animals in each group.

observed at 3 h. While the data are not presented, topical administration of **4** lowered IOP in the rabbit while **5** had little effect on IOP in that species at comparable concentrations.

Figure 4 details the effect that the agents had on blood pressure in the cynomolgus monkey following intravenous (peripheral) administration of the agents. Clonidine showed a dramatic, dose-dependent reduction in blood pressure upon peripheral administration of the agent, panel A. This centrally mediated effect observed upon peripheral administration demonstrated that the agent crossed the blood−brain barrier. In addition, a similar dose-dependent decrease in blood pressure was observed with agent **4**, panel B. In sharp contrast, **3** did not demonstrate any appreciable hypotensive activity upon peripheral administration, panel C. A lack of hypotensive activity was also observed upon administration of agent **5**, panel D.

Similarly, clonidine proved to be a potent hypotensive agent following intravenous administration to rabbit. Agent **3**, in contrast, did not affect blood pressure following intravenous administration to rabbit. These results, presented in Figure 5, panel A, suggest that **3** did not cross the blood−brain barrier upon peripheral administration to rabbit.

These results are in sharp contrast to those obtained when either clonidine or **3** was injected directly into the fourth ventricle of the rabbit brain, Figure 5, panel B. Clonidine lowered blood pressure 20% relative to control (saline). Agent **3** showed a 70% reduction in blood pressure compared to control. These results demonstrated that **3** was very efficacious for the reduction of blood pressure when administered directly to the site of action, reflecting the enhanced potency and efficacy of **3** in functional assays for α_2 adrenergic activity relative to clonidine. These experiments support the premise that **3** does not cross the blood−brain barrier in the rabbit.

Sedation is a commonly observed centrally mediated response to α_2 adrenergic agonists. Rat activity after intravenous administration to the tail vein is a good model to evaluate that response. Similar results to those obtained for the peripheral administration resulting in centrally mediated processes were obtained using this model. Clonidine and **4** cross the blood−brain barrier and sedate the rat. Complete sedation upon administration of clonidine intravenously to the rat was observed at a concentration of 100 μg/kg. In contrast, after treatment with **3** or **5** intravenously at a concen-

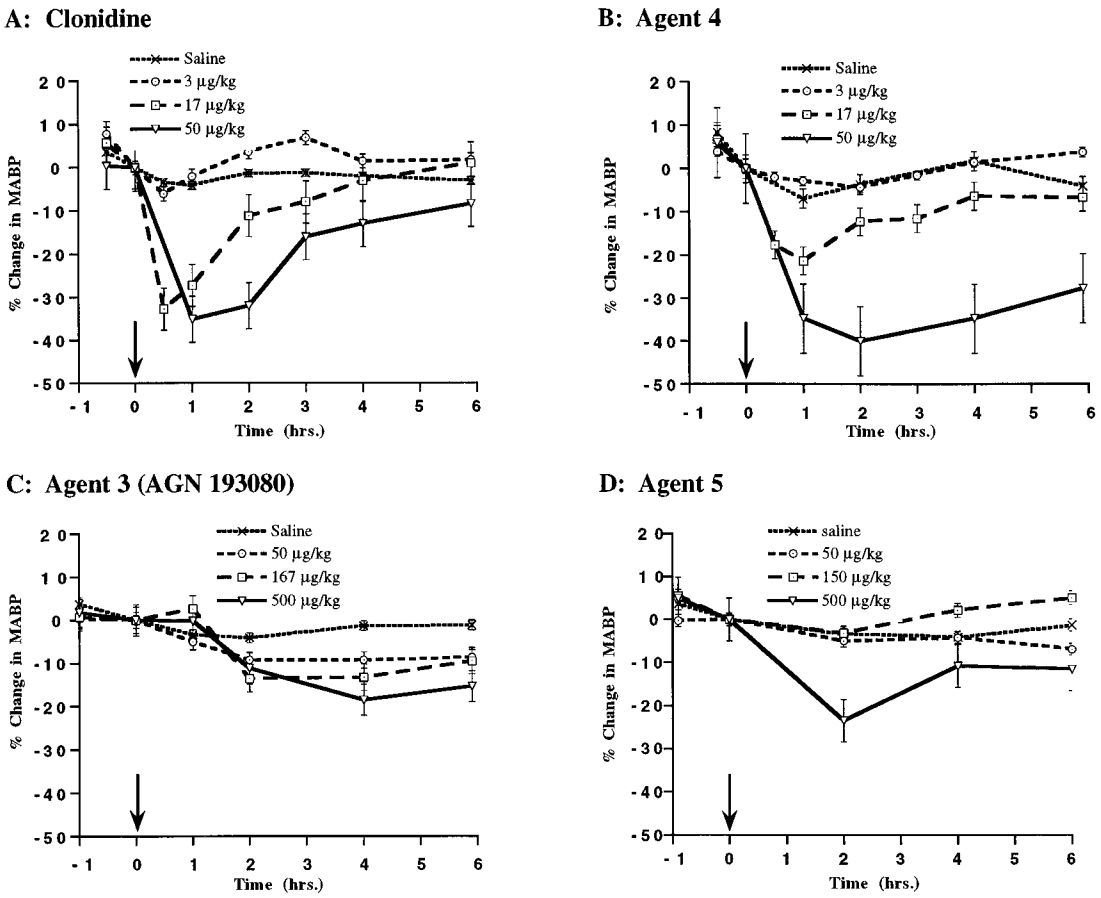


Figure 4. Mean arterial blood pressure (MABP) versus time upon intravenous administration to cynomolgus monkey. Saline served as a control. Each agent was evaluated at three concentrations specified in the given panel. Each reported percent change is the mean result from six animals.

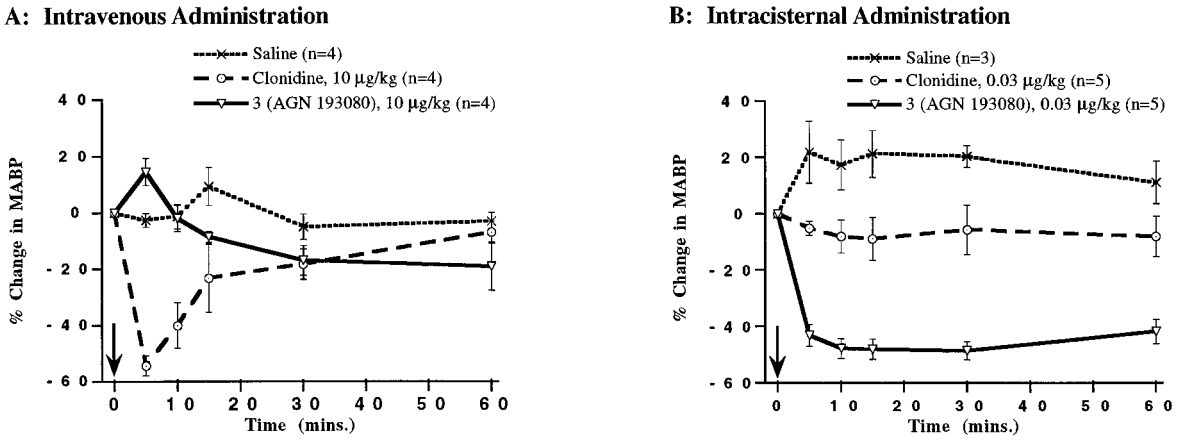


Figure 5. MABP versus time upon either intravenous or intracisternal administration of clonidine or agent **3** to rabbit. Saline served as a control. Each agent was evaluated at the same concentration in the given model. The concentration is specified in the given panel. Each reported percent change is the mean result of the specified number of separate animals.

tration of over 1000 μg/kg, the animals remained active. These results are not shown.

Physicochemical Evaluation of Agents

log *P* and log DC (the distribution coefficient at a given pH) are physical properties employed in early studies to assess blood−brain barrier penetration.[20] A negative log DC does not, however, guaranty minimal access to the CNS. A summary of the data that we obtained is shown in Table 2. The measured pK_as of the aniline nitrogens are all well below 5. These nitrogens are not protonated at physiologic pH, and the pK_as are therefore not reported. Agent **4** has a log DC of −0.80 at pH 7.4 and proved centrally active in a variety of animal models. This is one among many examples of agents possessing a low log DC that does penetrate the CNS.[21]

Table 2

agent	log DC_{oct} (pH = 7.4)	log P_{oct}	log $P_{dodecane}$	Δlog *P*	pK_a(guanidine subunit)
3	−3.4	0.35	−0.34	0.69	11.1
4	−0.80	0.90	−3.00	3.90	9.4
5	−3.9	0.04	−0.39	0.43	11.3

Seiler first applied the concept of Δlog *P*, the difference of the log *P*s determined in water versus octanol and water versus a hydrocarbon, as an improved parameter to explain CNS penetration.[22] Agents possessing a large Δlog *P* should not penetrate the blood−brain barrier. Later, in a series of elegant studies, a group originally at Smith Kline used Δlog *P* in the design of peripherally acting histamine antagonists.[12] We evaluated this parameter to explain the lack of CNS activity observed with **3**. Dodecane was used as the hydrocarbon to minimize loss of the solvent through evaporation during the titration studies. Agent **4**, which penetrated the blood−brain barrier, had a very large Δlog *P* in contrast to either **3** or **5**. Those data suggest that Δlog *P* cannot explain the lack of CNS activity for **3**.

The most meaningful correlation to lack of CNS penetration appears to be the log *P* in our series. Agent **4** is basic and has a negative log DC at pH = 7.4 but a log *P* = 0.9. This agent had the most negative log *P* in dodecane of any agent examined within our series suggesting that it should not penetrate the CNS. This agent penetrates the blood−brain barrier upon peripheral administration, which was surprising. Agents **3** and **5** are extremely basic, having pK_as around 11. Basicity alone does not appear to control peripheral membrane penetration. Agent **3**, which had a log P_{oct} of 0.35, was able to penetrate peripheral membranes as shown by its efficacy for the reduction of IOP. That agent did not, however, penetrate the blood−brain barrier upon peripheral administration. Agent **5**, which had a log P_{oct} close to zero, did not penetrate any biological membranes well as shown by its poor ability to lower IOP or elicit any other biological response *in vivo* at doses comparable to those employed for the evaluation of the other agents.

Conclusions

We have prepared **3** (AGN 193080) using a convenient five-step process. The agent is a potent, selective agonist at the α_2 adrenergic receptor. The agent is among the most efficacious α_2 adrenergic agonists for the reduction of intraocular pressure that we have evaluated. The agent does not cross the blood−brain barrier and, as a consequence, is not sedating, nor does it affect blood pressure upon peripheral administration. This agent will have utility for applications requiring peripheral α_2 adrenergic agonist activity.

Experimental Section

General. Reagents used were the highest quality available commercially. Reaction solvents were obtained from Aldrich in Sure-Seal bottles. Unless otherwise noted, all reactions were carried out under an argon atmosphere and temperatures refer to the temperature of the bath. Organic extracts were dried with magnesium sulfate ($MgSO_4$) or potassium carbonate (K_2CO_3). Flash chromatography was conducted using the procedure described by Still.[23] Proton and carbon NMR spectra were measured on either a Varian Gemini 300 or a Varian Unity Plus 500 spectrometer in the solvents specified. Chemical shifts are reported in ppm downfield from TMS as an internal standard, and coupling constants are reported in Hertz. Mass spectra (LRMS and HRMS) were recorded on a VG 7070E Sector magnetic 70 eV mass spectrometer. Combustion analyses were conducted by Robertson Microlit Laboratories, Madison, NJ.

Imidazoline-2-sulfonic Acid (13). A slurry of imidazoline-2-thione (33.2 g, 0.324 mol), $Na_2MoO_4 \cdot 2H_2O$ (2.50 g, 0.0103 mol), and NaCl (7.5 g; to depress freezing point of the water) in water (150 mL; deionized) was prepared and chilled to −10 to −5 °C internal temperature (bath temperature −20 to −15 °C). H_2O_2 (30% in water; 250 mL, 2.45 mol; density = 1.110; Aldrich, personal communication) was added to this mechanically mixed slurry in a Morton flask. The first 125 mL was added at a rate of 0.23 mL/min via syringe pump. This rate insured that the internal temperature did not rise above −4 °C as the reaction is extremely exothermic. The second 125 mL was added via addition funnel at a rate of 10 drops/min overnight and did not cause an exotherm (note the first 0.972 mol of peroxide should be sufficient to complete the oxidation). The reaction was warmed to 0−5 °C to melt ice that had formed overnight. The white solid was collected via vacuum filtration, washed with chilled deionized water, and dried under vacuum to afford 20.4 g (48%) of **13**: ^{1}H NMR (DMSO) 3.88 (s, 4H), 10.15 (br s, 1H); ^{13}C NMR (DMSO) 45.0, 169.3; mp 133−135 °C. Anal. ($C_3H_6N_2O_3S$) C, H, N.

5-Methylbenzox-4-azin-3-one (7). To 2-amino-*m*-cresol (**6**; 14.7 g, 120 mmol), triethylamine (35.0 mL, 251 mmol) and 4-(dimethylamino)pyridine (0.29 g, 2.39 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added chloroacetyl chloride (10.0 mL, 0126 mmol) dropwise via syringe. After the addition was complete, the resulting solution was warmed at reflux for 24 h. The organic material was washed successively with phosphoric acid (0.5 M), saturated sodium bicarbonate, water, and brine and then dried ($MgSO_4$). The organic solution was concentrated, and the solid was dissolved in THF to which Et_2O was then added. The resulting crystals were collected by filtration to afford pure **7** (12.3 g) in 63% yield: ^{1}H NMR ($CDCl_3$) 2.27 (s, 3H), 4.59 (s, 2H), 6.80−6.92 (m, 3H), 8.05 (br s, 1H); ^{13}C NMR ($CDCl_3$) 16.3, 67.1, 114.6, 123.5, 124.2, 124.3, 124.8, 143.9, 165.9.

Nitration of 5-Methylbenzox-4-azin-3-one (8 and 9). To **7** (14.64 g, 89.7 mmol) dissolved in concentrated H_2SO_4 (65 mL) at −10 °C was added 70% concentrated HNO_3 (8.08 g, 89.7 mmol) in concentrated H_2SO_4 (25 mL) with rapid mechanical stirring at a rate such that the internal temperature was maintained below −5 °C. As soon as the addition was complete, the mixture was poured onto crushed ice (500 mL), and the resulting solids were collected by filtration and then slurried in cold water (300 mL). Sufficient NaOH was added to adjust the pH to 7. The resulting yellow powder was collected by filtration. The solid was then dissolved in THF, adhered to silica gel, and purified by flash chromatography with 60% hexane in ethyl acetate to afford the nitrated product as a mixture of two regioisomers: the desired 6-substituted aromatic **8** (55%) and the 8-substituted byproduct **9** (22%). These isomers could be separated with difficulty at this point. It proved operationally easier to carry the mixture directly to the next step: MS calcd for $C_9H_8N_2O_4$ = 208, *m*/*z* obsd at 208 (M^+).

6-Amino-5-methylbenzox-4-azin-3-one (10). To a mixture of **8** and **9** (2.41 g, 11.6 mmol) dissolved in a solution of MeOH (300 mL) and THF (300 mL) under argon was added 10% palladium on carbon (1.20 g). The resulting mixture was stirred under an atmosphere of H_2 for 16 h. The catalyst was removed by filtration, and the resulting solution was concentrated *in vacuo* and subjected to flash chromatography on silica gel with 50% hexane/ethyl acetate to afford pure **10** (0.96 g) in 46% yield along with a mixture of **10** and **11** (0.33 g): ^{1}H NMR (DMSO) 1.95 (s, 3H), 4.31 (s, 2H), 4.57 (s, 2H), 6.24 (d, *J* = 8.5 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 10.01 (s, 1H); ^{13}C NMR (DMSO) 10.8, 67.0, 108.6, 109.0, 113.6, 126.1, 135.6, 142.2, 166.4.

2-[(5-Methyl-3-oxobenz-1-ox-4-azin-6-yl)imino]imidazoline (14). A mixture of **10** (1.20 g, 6.74 mmol), imidazoline-2-sulfonic acid (**13**; 2.02 g, 13.5 mmol), and triethylamine (2.35 mL, 16.9 mmol) was heated at reflux in anhydrous acetonitrile (50 mL) under argon for 48 h. At that time, additional amounts of imidazoline-2-sulfonic acid (1.01 g, 6.74 mmol) and triethylamine (1.41 mL, 10.1 mmol) were added, and the resulting mixture was stirred an additional 24 h. This solution was concentrated *in vacuo*, and the residue was dissolved in a solution of 25% *i*-PrOH/$CHCl_3$, washed successively with NaOH (1 N) and brine, dried ($MgSO_4$), and

concentrated *in vacuo*. The resulting foam was purified by flash chromatography with 20% MeOH (saturated with NH_3) in chloroform to give pure **14** (0.42 g) as a foam in 25% yield along with 55% recovered starting material. The HCl salt was recrystallized from EtOH/Et_2O to afford fine white needles: ^{1}H NMR (DMSO) 2.10 (s, 3H), 3.59 (s, 4H), 4.53 (s, 2H), 6.83 (d, J = 8.6 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 8.07 (br s, 2H), 10.15 (vbr s, 1H), 10.42 (s, 1H); ^{13}C NMR (DMSO) 11.8, 42.6, 66.6, 111.3, 121.7, 122.7, 126.8, 128.5, 143.4, 158.9, 165.3.

2-[(5-Methylbenz-1-ox-4-azin-6-yl)imino]imidazoline (AGN 193080, 3). To a slurry of **14**, the free base (0.41 g, 1.68 mmol), in anhydrous THF (200 mL) under argon in a 2-neck round-bottom flask equipped with a reflux condenser was added borane−dimethyl sulfide complex (3.76 mL, 7.57 mmol). The mixture was warmed at reflux until starting material was no longer observed via TLC (24 h). The reaction mixture was cooled to room temperature, and the reaction was carefully quenched by the dropwise addition of methanol. The resulting mixture was then warmed at reflux for an additional 5 min. The crude reaction mixture was concentrated *in vacuo* and purified by flash chromatography using 30% methanol (saturated with NH_3) in chloroform to give pure **3** (0.31 g) as a hydrochloride salt in 68% yield. The HCl salt was derived from acid present in the $CHCl_3$. The compound proved to be a hard foam: ^{1}H NMR (DMSO) 1.91 (s, 3H), 3.34 (m, 2H), 3.57 (s, 4H), 4.07 (m, 2H), 5.51 (s, 1H), 6.37 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 8.30 (vbr s, 3H); ^{13}C NMR (DMSO) 11.5, 40.2, 42.5, 63.9, 113.9, 114.8, 119.8, 126.6, 133.4, 142.4, 158.9; IR (KBr) 1485, 1601, 1656, 2700−3600 cm^{-1}; mass calcd for $C_{12}H_{16}N_4O$ = 232.1324, obsd = 232.1311. Anal. ($C_{12}H_{17}ClN_4O$) C, H, N.

Determination of pK_a, log DC, and log *P* Values. A Sirius PCA-101 automatic titrator with expert system software was used to determine the pK_a, log DC, and log *P* values of the agents from potentiometric titration data.[24] In a typical experiment, the instrument automatically added 0.15 M KCl in water to a weighed sample and then added an accurately measured amount of acid to dissolve the agent and reach a predetermined starting pH. After the agent had dissolved, the solution was titrated to the predetermined final pH. The pK_a values were calculated using the system software. The log *P* value of the agent was determined by adding either octanol or dodecane to the sample before titration. The log *P* values was derived from the known relationship between the aqueous pK_a and the pK_a determined in the presence of the partition solvent.

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