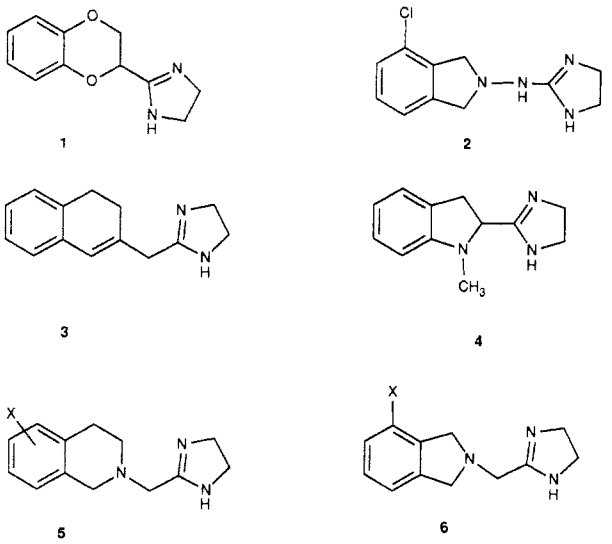
Affinity of 2-(Tetrahydroisoquinolin-2-ylmethyl)- and 2-(Isoindolin-2-ylmethyl)imidazolines for α-Adrenoceptors. Differential Affinity of Imidazolines for the [^{3}H]Idazoxan-Labeled α_2-Adrenoceptor vs the [^{3}H]Yohimbine-Labeled Site[1]

Robin D. Clark,*,† Jacob Berger,† Pushkal Garg,† Klaus K. Weinhardt,† Michael Spedding,*,‡ Andrew T. Kilpatrick,‡ Christine M. Brown,‡ and Alison C. MacKinnon‡

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304, and Syntex Research Center, Edinburgh, Scotland EH14 4AP. *Received January 17, 1989*

A series of 2-(tetrahydroisoquinolin-2-ylmethyl)- and 2-(isoindolin-2-ylmethyl)imidazolines were prepared and tested for α_1- and α_2-adrenoceptor affinity with radioligand binding. Several compounds, 5-fluoro- (**5h**), 5-chloro- (**5j**), 5,8-dimethoxy- (**5r**), and 5,8-dimethoxy-1-methyl- (**5s**) 2-(tetrahydroisoquinolin-2-ylmethyl)imidazoline, were found to be selective α_2-adrenoceptor ligands on the basis of displacement of [^{3}H]yohimbine from rat cerebral cortical membranes. One compound, 2-[(8-chloro tetrahydroisoquinolin-2-yl)methyl]imidazoline (**5m**), showed a 36-fold difference in affinity for the [^{3}H]idazoxan-labeled α_2-adrenoceptor relative to the [^{3}H]yohimbine-labeled site, which may be evidence for α_2-adrenoceptor subtypes.

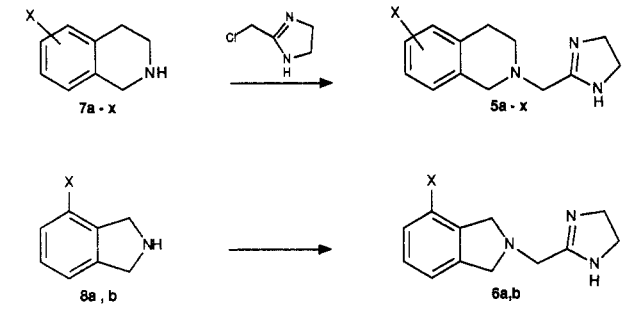
The synthesis and pharmacological evaluation of selective α_2-adrenoceptor antagonists remains an active area of research.[2] Such selective antagonists will be of use in defining the functional roles of α_2-adrenoceptors and may ultimately be of therapeutic use, e.g. for the treatment of depression.[3] A number of imidazoline derivatives have been reported to be α_2-adrenoceptor antagonists with various degrees of selectivity for the α_2 as opposed to the α_1-adrenoceptor.[2] Among these are the benzodioxane idazoxan (**1**),[4] the isoindoline BDF-6143 (**2**),[5] the dihydronaphthalene napamezole (**3**),[6] and the indoline **4**.[7] On the basis of their structural similarities with some of these agents, we were interested in evaluating 2-(tetrahydroisoquinolin-2-ylmethyl)- and 2-(isoindolin-2-ylmethyl)imidazolines (**5** and **6**,[8] respectively) as α_2-adrenoceptor antagonists. Reported herein are the results of structure–affinity relationship studies based on ligand-binding methodology which indicate that a number of these compounds are selective, high affinity α_2-adrenoceptor ligands and that several may differentiate between subtypes of the α_2-adrenoceptor.



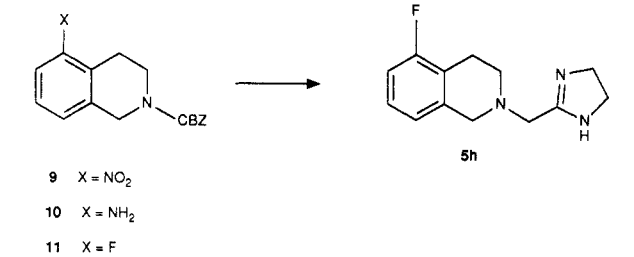
Chemistry

The 2-(tetrahydroisoquinolin-2-ylmethyl)- and 2-(isoindolin-2-ylmethyl)imidazolines **5a–x** and **6a,b** were prepared by condensation of tetrahydroisoquinolines **7a–x** and isoindolines **8a,b**, respectively, with 2-(chloromethyl)-

Scheme I



Scheme II



imidazoline[9] (Scheme I). The requisite 1,2,3,4-tetrahydroisoquinolines **7a–x** either were known compounds, **7b**,[10] **7f**,[11] **7i,l–p**,[12] **7q**,[13] **7r**,[14] **7t**,[15] **7u**,[16] **7v**,[17] and **7w**,[18] or

† Syntex Research, Palo Alto.
‡ Syntex Research, Edinburgh.

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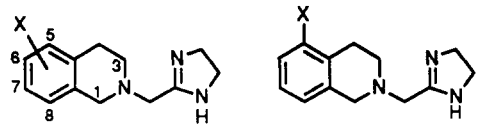
Table I. Physical Properties and Ligand Binding Data



5a–x **6a,b**

compd	X	% yield[b]	mp, °C	formula[c]	rat cerebral cortex radioligand binding, pK_i [^{3}H]prazosin (α_1)	[^{3}H]yohimbine (α_2)	[^{3}H]idazoxan (α_2)	selectivity ratio[d] (α_2/α_1)	ratio I/Y[e]
5a	H	84	250–254	$C_{13}H_{17}N_3 \cdot 2HCl$	5.67	6.32 ± 0.10	7.77 ± 0.11	5	28
5b	1-CH_3	34	225–228	$C_{14}H_{19}N_3 \cdot 2HCl \cdot 0.25H_2O$	5.14	7.19 ± 0.09	7.32 ± 0.07	110	1
5c	1-C_2H_5	35	indef	$C_{15}H_{21}N_3 \cdot 2HCl$[f]	<5	6.16 ± 0.05	6.31 ± 0.06	14	1
5d	1-allyl	23	135–137	$C_{16}H_{21}N_3 \cdot 2HCl \cdot 0.5H_2O$	<5	5.97	6.41 ± 0.03	9	3
5e	1,1-$(CH_3)_2$	42	220–223	$C_{15}H_{21}N_3 \cdot 2HCl$	<5	6.00	6.68 ± 0.05	10	5
5f	3-CH_3	10	210–213	$C_{14}H_{19}N_3 \cdot 2HCl$[g]	<5	6.90 ± 0.12	7.38 ± 0.15	80	3
5g	5-CH_3	20	240–241	$C_{14}H_{19}N_3 \cdot 2HCl$	5.26	6.57 ± 0.15	7.38 ± 0.10	20	6
5h	5-F	22	245–248	$C_{13}H_{16}FN_3 \cdot 2HCl \cdot 0.5H_2O$	5.55	7.48 ± 0.12	8.39 ± 0.08	86	8
5i	8-F	50	214–216	$C_{13}H_{16}FN_3 \cdot 2HCl$	5.50	7.25 ± 0.07	8.27 ± 0.09	56	10
5j	5-Cl	12	233–234	$C_{13}H_{16}ClN_3 \cdot 2HCl$	5.68	7.65 ± 0.08	7.80 ± 0.20	93	1
5k	5-Cl, 1-CH_3	7	220–221	$C_{14}H_{18}ClN_3 \cdot 2HCl \cdot H_2O$	5.20	6.74 ± 0.08	7.62 ± 0.12	35	8
5l	6-Cl	44	238–239	$C_{13}H_{16}ClN_3 \cdot 2HCl \cdot 0.5H_2O$	<5	6.18	6.83 ± 0.13	15	4
5m	8-Cl	55	220–222	$C_{13}H_{16}ClN_3 \cdot 2HCl$	5.80	6.67 ± 0.14	8.23 ± 0.08[h]	7	36
5n	5,8-$(Cl)_2$	34	234–237	$C_{13}H_{15}Cl_2N_3 \cdot 2HCl$	5.50	7.14 ± 0.09	8.12 ± 0.06	44	10
5o	5,6-$(Cl)_2$	57	247–248	$C_{13}H_{15}Cl_2N_3 \cdot 2HCl$	<5	6.42 ± 0.18	7.67 ± 0.16	26	18
5p	7,8-$(Cl)_2$	45	221–222	$C_{13}H_{15}Cl_2N_3 \cdot 2HCl$	<5	6.52 ± 0.10	7.68 ± 0.09	33	14
5q	5-OCH_3	56	240–241	$C_{14}H_{19}N_3O \cdot 2HCl \cdot H_2O$	4.72	7.07 ± 0.07	8.00 ± 0.04	225	9
5r	5,8-$(OCH_3)_2$	31	232–235	$C_{15}H_{21}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$	4.80	7.51 ± 0.13	7.80 ± 0.10	502	2
5s	5,8-$(OCH_3)_2$,1-CH_3	76	270–272	$C_{16}H_{23}N_3O_2 \cdot 2HCl$	5.19	7.71 ± 0.11	7.02 ± 0.10	332	0.2
5t	5,6-$(OCH_3)_2$	10	235–236	$C_{15}H_{21}N_3O_2 \cdot 2HCl \cdot H_2O$	<5	6.44 ± 0.21	6.24 ± 0.05	28	0.6
5u	6,7-$(OCH_3)_2$	51	239–240	$C_{15}H_{21}N_3O_2 \cdot 2HCl \cdot H_2O$	<5	5.87	6.13 ± 0.29	7	2
5v	6,8-$(OCH_3)_2$	45	232–233	$C_{15}H_{21}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$	<5	6.29	7.20 ± 0.11	20	8
5w	5-NO_2	41	250–252	$C_{13}H_{16}N_4O_2 \cdot 2HCl \cdot 0.5H_2O$	<5	6.13	7.14 ± 0.21	13	10
5x	5-NH_2	66	248–250	$C_{13}H_{18}N_4 \cdot 3HCl \cdot H_2O$[j]	<5	6.17	6.99 ± 0.14	15	7
6a	H	10	220–224	$C_{12}H_{15}N_3 \cdot 2HCl \cdot 0.5H_2O$	5.43	6.91 ± 0.08	8.07 ± 0.08	30	14
6b	Cl	28	231–233	$C_{12}H_{14}ClN_3 \cdot 2HCl$	6.05	7.71 ± 0.05	8.38 ± 0.10	46	5
idazoxan					6.10 ± 0.08	7.96 ± 0.04[k]	8.12 ± 0.05[k]	72	1
yohimbine					6.40 ± 0.03	7.90 ± 0.03[k]	7.25 ± 0.07[k]	32	0.2
rauwolscine						8.15 ± 0.10	7.09 ± 0.07		0.1

[a] Values represent means of three separate determinations (n = 3) with SEM unless otherwise noted. Values without SEM are means of two determinations (n = 2). [b] Yield refers to the last step in each reaction sequence. [c] Elemental analyses were within 0.4% of theory unless otherwise noted. [d] Antilog of the [^{3}H]yohimbine pK_i minus the [^{3}H]prazosin pK_i. For [^{3}H]prazosin pK_i of less than 5, a pK_i of 5 was used to calculate the selectivity ratio. [e] Antilog of the [^{3}H]idazoxan pK_i minus the [^{3}H]yohimbine pK_i. [f] C: calcd, 56.97; found, 57.46. [g] C: calcd, 55.63; found, 53.30. [h] n = 5. [i] N: calcd, 16.37; found, 15.95. [j] C: calcd, 43.65; found, 46.72. [k] n = 4.

were prepared by standard literature procedures, **7c–e** (alkylation of 2-(bis(dimethylamino)phosphinoyl)-1-lithio-1,2,3,4-tetrahydroisoquinoline[10]), **7g,k,s**[19] (Bischler–Napieralski cyclization[20] followed by sodium borohydride reduction), and **7i** (intramolecular Friedel–Crafts alkylation[21]). The 5-fluoro compound (**5h**) was prepared as shown in Scheme II. The diazonium tetrafluoroborate, prepared from aniline **10** by the boron trifluoride–*tert*-butyl nitrite method,[22] decomposed upon storage at room temperature to give the intermediate fluoro compound **11**. Amino derivative **5x** was prepared by catalytic hydrogenation of **5w**.

Isoindolines **10a,b** were prepared by reduction of the corresponding phthalimides with borane–methyl sulfide.[23]

Pharmacological Testing

The relative affinities of the imidazolines for α-adrenoceptors were determined by measurement of radioligand displacement from rat cerebral cortical membrane binding sites. [^{3}H]Yohimbine and [^{3}H]prazosin were used to label α_2- and α_1-adrenoceptors, respectively, and for determination of α_2/α_1 selectivity ratios. The ability of compounds to displace the imidazoline ligand [^{3}H]idazoxan from rat cerebral cortical α_2-adrenoceptors was also determined. The results are presented in Table I.

Results and Discussion

Structure–Affinity Relationships Based on α_1-Adrenoceptor Affinity Assessed by [^{3}H]Prazosin Binding and α_2-Adrenoceptor Affinity Based on [^{3}H]Yohimbine Binding. None of the imidazolines in Table I were potent displacers of [^{3}H]prazosin from α_1-adrenoceptors and only one compound (**6b**) had a pK_i value of greater than 6.[24]

In the 2-(tetrahydroisoquinolin-2-ylmethyl)imidazoline series (**5a–x**) it was found that while the parent compound

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(24) Compound **8b** was subsequently found to be a partial α_1-agonist in functional assays (contraction of rabbit aortic strip) and to elevate blood pressure directly in pithed rats. Partial α_1-agonist activity has been reported for idazoxan (**1**) and BDF-6143 (**2**), ref 2 and citations therein, and for compound **4**, ref 7b.

5a had a low affinity for the [^{3}H]yohimbine-labeled α_2-adrenoceptor, substituted analogues were considerably more active. Substitution at C-1 with methyl gave a higher affinity compound (**5b**), but larger groups (**5c,d**), 1,1-disubstitution (**5e**), or moving the methyl group to C-3 was detrimental (**5f**). In the aromatic ring, C-5 appeared to be particularly amenable to substitution with fluorine (**5h**), chlorine (**5j**), and to a lesser degree with methoxy (**5q**). Among the disubstituted analogues, substitution at C-5 and C-8 was beneficial in the dimethoxy case (**5r**), although less so in the dichloro compound (**5n**). Any substitution involving C-6 and/or C-7 was clearly not tolerated relative to the C-5 and C-5,8 substituted examples (e.g., **5j** vs **5o**, **5r** vs **5v**). Substitution of methyl at C-1 of the two highest affinity compounds, **5j** and **5r**, was carried out to determine if the enhancement in affinity seen in going from **5a** to **5b** was general. However, while the derived **5s** was of higher affinity than the related **5r**, the trend was the opposite in the chloro case as **5k** was over a log order less active than **5j**. In terms of α_2/α_1 selectivity within this series, the general trend among the C-1 and substituted aromatic derivatives of **5a** was toward increased α_2-selectivity due to increased α_2-affinity with a concomitant maintanence (e.g., **5j**) or decrease in α_1-affinity (e.g., **5r,s**). The highest affinity compound in the series, **5s**, was approximately $^1/_2$ as active as idazoxan in the ligand binding assay while displaying a 5-fold-enhanced selectivity for the [^{3}H]yohimbine-labeled α_2-adrenoceptor.

In the 2-(isoindolin-2-ylmethyl)imidazoline series, 4-chloro derivative **6b** (which corresponds to 5-chlorotetrahydroisoquinoline **5j**) was also of higher affinity than the parent (**6a**). However, this compound was less selective for the α_2-adrenoceptor than the tetrahydroisoquinoline analogues.

α_2-Adrenoceptor Affinity Assessed by [^{3}H]Idazoxan Binding. Although many of the compounds had essentially similar potency displacing [^{3}H]idazoxan and [^{3}H]-yohimbine, there were also marked discrepancies with ratios of pK_i values (Table I, I/Y), ranging from 0.2 (yohimbine selective) to 36 (idazoxan selective). Some of the compounds were very potent in displacing [^{3}H]idazoxan, and seven compounds (**5h, 5i, 5m, 5n, 5q, 6a, 6b**) had pK_i values greater than or equal to 8. In contrast, the most potent ligands in displacing [^{3}H]yohimbine (**5s, 6b**) had pK_i values of 7.71. In this series the affinity for [^{3}H]idazoxan appeared to relate more to functional effectiveness as an α_2-adrenoceptor antagonist, e.g., **6b** was found to have a pA_2 value of 8.5 as an antagonist of the α_2-selective agonist UK14304 in the guinea pig ileum. The most [^{3}H]idazoxan-selective agent (**5m**, I/Y ratio = 36) had a pA_2 value of 8.2 in this preparation,[25] which was identical with the pK_i value.

Relative structure–affinity relationships (SAR) based on [^{3}H]idazoxan binding were also somewhat different from those based on [^{3}H]yohimbine displacement. For example, the enhancement of affinity upon 1-methylation ([^{3}H]yohimbine binding) was reversed in several cases (e.g., **5a** vs **5b**, **5r** vs **5s**) based on [^{3}H]idazoxan binding. Among the chlorinated 2-(tetrahydroisoquinolin-2-ylmethyl)-imidazolines, the 8-substituted isomers (**5m**, **5n**, **5p**) showed a 14–36-fold enhancement in [^{3}H]idazoxan binding as compared to virtually no enhancement for the 5-chloro isomer (**5i**). There thus appear to be differences in the selectivity of certain of these imidazolines for the sites labeled by [^{3}H]idazoxan and [^{3}H]yohimbine.[26]

On the basis of extensive SAR studies, three major binding sites were proposed for idazoxan type compounds at the α_2-adrenoceptor.[27] These were a planar hydrophobic area that interacts with the benzene ring, a site which binds one or both of the benzodioxane oxygens, and an imidazoline binding site which is presumably anionic in nature. Aromatic substitution was not tolerated. The ability of the 2-position of idazoxan to accommodate alkyl and methoxy groups with an enhancement in α_2-affinity has also suggested either an additional binding site or a preferential skewed pseudoequitorial orientation of the imidazoline ring.[27] 2-(Tetrahydroisoquinolin-2-ylmethyl)imidazoline (**5**) fits this model in a general sense with the proviso that either the benzodioxan oxygen binding site is not accomodated or the nitrogen of the tetrahydroisoquinoline binds to this site. However, series **5** differs in that aromatic substitution is allowable for significant binding to the α_2-adrenoceptor labeled by either [^{3}H]yohimbine or [^{3}H]idazoxan. This suggests that the additional methylene spacer between the tetrahydroisoquinoline and the imidazoline rings may induce these compounds to bind in a somewhat different manner than idazoxan.

Conclusion

Previously, both [^{3}H]yohimbine and [^{3}H]idazoxan have been used as radioligands to define α_2-adrenoceptor affinity. However, there have been suggestions that there may be different subtypes of α_2-adrenoceptors.[28-32] On the basis of autoradiographic[31] and pharmacological[32] studies, [^{3}H]rauwolscine, an isomer of yohimbine, and [^{3}H]idazoxan appear to label different areas of rat brain. This evidence indicates that [^{3}H]idazoxan and [^{3}H]rauwolscine label a heterogeneous population of α_2-adrenoceptors.[31-32] It was therefore of interest that the imidazolines reported herein showed a wide spectrum of selectivity ratios in displacing [^{3}H]yohimbine and [^{3}H]idazoxan from rat cerebral cortex with a rank order of potencies different for the two ligands. This is consistent with the concept that these compounds may have different affinities for subtypes of the α_2-adrenoceptor, although we cannot exclude the possibility that [^{3}H]yohimbine and [^{3}H]idazoxan bind at different sites, or affinity states, of a single receptor. Further detailed studies with the most selective compounds may resolve this issue. Nevertheless, this report shows that compounds may have differential affinities

(25) Compound **5m** was also found to be a partial α_2-adrenoceptor agonist in the guinea pig ileum, but only at high concentrations (1 μM, 50% inhibition of electrically evoked contractions at 9 μM).

(26) The observed pK_i differences did not appear to result from the different buffers used in the α_2-adrenoceptor binding assays (Tris HCl, pH 7.4 for [^{3}H]yohimbine binding; physiological salt solution, pH 7.4, for [^{3}H]idazoxan binding). For example, in the [^{3}H]idazoxan binding assay using physiological buffer, pK_i values of 7.25 ± 0.07 and 8.12 ± 0.05 were determined for the standards yohimbine and idazoxan, respectively, compared with values of 7.36 ± 0.10 and 8.09 ± 0.10, respectively, in the Tris HCl buffer. In the same assay, **5m** had pK_i values of 8.23 ± 0.08 in the physiological buffer and 8.55 ± 0.15 in the Tris HCl buffer.

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in displacing two ligands which are thought to label the α_2-adrenoceptor.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded for all compounds with Varian A-60 or Bruker WM 300 instruments and were consistent with the assigned structures. Microanalyses were performed by the Syntex Analytical Department and, where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

General Procedure for the Preparation of 5a–x and 6a,b. 2-[(1,2,3,4-Tetrahydro-5,8-dimethoxy-1-methylisoquinolin-2-yl)methyl]-4,5-dihydro-1*H*-imidazole Dihydrochloride (5s). Isoquinoline **7s** was prepared by Bischler–Napieralski cyclization of *N*-acetyl-2,5-dimethoxyphenethylamine (phosphorus oxychloride, acetonitrile, 60 °C)[20] followed by $NaBH_4$ reduction (27%): HCl salt, mp 229–230 °C. A mixture of isoquinoline **7s** (5.3 g, 26 mmol), 2-(chloromethyl)imidazoline hydrochloride[9] (4.65 g, 30 mmol), and *N,N*-diisopropylethylamine (10 mL, 60 mmol) in 30 mL of dichloromethane was stirred at room temperature for 12 h. The mixture was added to water and extracted with dichloromethane and the extract was evaporated. After addition of toluene, solvents were removed in vacuo and this procedure was repeated twice to remove *N,N*-diisopropylethylamine. The residue was dissolved in hot ethanol and the resulting hot solution was filtered with charcoal and acidified with ethanolic HCl. The product crystallized upon cooling the solution to room temperature and filtration afforded 7.0 g (76%) of **5s**: mp 270–272 °C; NMR (Me_2SO-d_6) δ 1.38 (d, J = 7 Hz, 3 H), 2.78 (m, 2 H), 3.10 (m, 1 H), 3.28 (m, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.90 (s, 4 H), 3.92 (AB quartet, J = 15 Hz, 2 H), 4.18 (q, J = 7 Hz, 1 H), 6.85 (s, 2 H), 10.5 (br s, 2 H, exchanges with D_2O).

2-[(4-Chloro-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-4,5-dihydro-1*H*-imidazole Dihydrochloride (6b). 3-Chlorophthalic anhydride[33] was converted to 3-chlorophthalimide by heating with aqueous NH_4OH.[34] To a solution of the phthalimide (60 g, 0.33 mol) in 1 L of THF was slowly added 100 mL (1 mol) of borane–methyl sulfide complex and the resulting solution was heated under reflux for 12 h. The solution was cooled in an ice bath and treated carefully with 100 mL of 6 M HCl. The mixture was heated under reflux for 2 h, filtered, and concentrated in vacuo. The residue was partitioned between water and ethyl acetate, and the aqueous layer was basified with NH_4OH and extracted 3× with CH_2Cl_2. The CH_2Cl_2 extracts were combined and evaporated to an oil, which was purified by Kugelrohr distillation, bp 80–85 °C (ca. 1 mm), to afford 15.3 g (30%) of 4-chloroisoindoline (**8b**) as a white solid mp 48–50 °C, which rapidly darkened at room temperature and was stored in a freezer prior to use. This material was converted to **6b** as described for the preparation of **5s**.

***N*^{2}-(Carbobenzyloxy)-5-amino-1,2,3,4-tetrahydroisoquinoline (10).** 5-Nitro-1,2,3,4-tetrahydroisoquinoline[18] was converted to the CBz derivative **9** with benzyl chloroformate (ethyl acetate–aqueous K_2CO_3): mp 68–69 °C; IR 1685 cm^{-1}. Anal. ($C_{17}H_{16}N_2O_4$) C, H, N.

To a solution of **9** (7.3 g, 23 mmol) in 55 mL of acetic acid was added a solution of stannous chloride dihydrate (20 g, 89 mmol) in 25 mL of 10% HCl, and the resulting homogenous mixture was stirred for 48 h at room temperature. The mixture was poured into a mixture of ice–aqueous NaOH and extracted with ethyl acetate. The ethyl acetate was dried (K_2CO_3) and evaporated to 6.3 g (97%) of **10**: mp 75–81 °C. A small sample was converted to the HCl salt (ethanol–ether): mp 193–194 °C. Anal. ($C_{17}H_{18}N_2O_2$·HCl) C, H, N.

***N*-(Carbobenzyloxy)-5-fluoro-1,2,3,4-tetrahydroisoquinoline (11).**[22] Boron trifluoride etherate (1.1 mL, 8.5 mmol) was cooled to −15 °C and a solution of **10** (1.55 g, 5.5 mmol) in 10 mL of dichloromethane was added. To the slightly cloudy mixture was added *tert*-butyl nitrite (0.8 mL, 6.7 mmol) in 4 mL of dichloromethane over a 10-min period at −15 °C. After the addition was complete, the clear solution was stirred for 25 min at ca. 3 °C. Pentane (20 mL) was added and a gummy precipitate formed. The mixture was allowed to remain at room temperature for 72 h during which time a slow evolution of gas bubbles was noted. The supernatant was decanted from the now-solid precipitate and evaporated to an oil, which was purified by silica gel chromatography (10% ethyl acetate–hexane) to afford 0.55 g (35%) of **11** as an oil: IR (film) 1695 cm^{-1}; NMR ($CDCl_3$) δ 2.82 (m, 2 H), 3.72 (t, 2 H), 4.65 (s, 2 H), 5.12 (s, 2 H), 6.88 (apparent t, 2 H, H-7, H-8), 7.14 (q, J = 8, 13.5 Hz, 1 H, H-6), 7.34 (m, 5 H); MS m/e 285 (M^+), 240, 194, 150, 91.

2-[(5-Fluoro-1,2,3,4-tetrahydroisoquinolin-2-yl)methyl]-4,5-dihydro-1*H*-imidazole Dihydrochloride (5h). A mixture of **11** (0.5 g, 1.75 mmol) and 10% palladium on carbon (80 mg) in 15 mL of ethanol was hydrogenated at atmospheric pressure for 20 min. The catalyst was filtered off and to the filtrate was added 2-chloromethyl-2-imidazoline hydrochloride[9] (0.3 g, 1.9 mmol) and the resulting mixture was heated under reflux for 16 h. The mixture was concentrated in vacuo and the residue was partitioned between dichloromethane and aqueous NH_4OH. The dichloromethane was evaporated and the residue was purified by silica gel chromatography (5% methanol–dichloromethane, 1% NH_4OH) to afford 130 mg (32%) of free base **5h**: mp 129–130 °C. This was converted to the bis HCl salt with ethanolic HCl: mp 245–248 °C.

Adrenoceptor Binding Assays. Membrane Preparation. Male Sprague–Dawley rats (150–200 g) were killed by cervical dislocation; the brains were rapidly removed and dissected on ice. Cerebral cortices were homogenized in 25 volumes of Tris buffer (50 mM Tris HCl, 5 mM EDTA; pH 7.4 at 4 °C) using a polytron PT 10 tissue disrupter. The homogenate was then centrifuged at 38000*g* for 15 min. The pellet obtained was washed 3× by resuspension and centrifugation in Tris assay buffer (50 mM Tris HCl, 0.5 mM EDTA; pH 7.4 at 4 °C). The final pellet was resuspended in assay buffer to a protein concentration of 1.0 mg/mL and stored under liquid nitrogen until required.

[^{3}H]Yohimbine Binding. Competition α_2-adrenoceptor binding assays were performed by incubating washed rat cerebral membranes (500 μg of protein) with 1.5 nM [^{3}H]yohimbine (New England Nuclear, 80.9 Ci/mmol) in the presence or absence of a range of 12 concentrations of the competing ligand in a total volume of 500 μL of Tris assay buffer (50 mM Tris HCl, 0.5 mM EDTA; pH 7.4 at 25 °C). Nonspecific binding was defined as the concentration of bound ligand in the presence of 10 μM phentolamine. Specific binding represented ~70% of total binding at 1.5 nM [^{3}H]yohimbine. Following equilibrium (30 min at 25 °C), bound radioactivity was separated from free by filtration through a Brandel cell harvester. Bound radioactivity on the glass-fiber filters was determined by liquid-scintillation counting.

[^{3}H]Idazoxan Binding. EDTA-free membrane preparations were incubated with 1 nM [^{3}H]idazoxan (Amersham, 58 Ci/mmol) to equilibrium (30 min) at 25 °C in a final volume of 0.5 mL. The incubations were performed in a physiological salt solution: 118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.3 mM $CaCl_2$; pH 7.4; 25 °C. Nonspecific binding was determined using 3 μM phentolamine and represented ~40% of total binding.

[^{3}H]Prazosin Binding. EDTA-washed membranes (250 μg) were incubated with 0.5 nM [^{3}H]prazosin (New England Nuclear 85 Ci/mmol) for 30 min at 25 °C in Tris buffer (50 mM pH 7.4, 0.5 mM EDTA) in a volume of 0.5 mL. Nonspecific binding was defined by 10 μM phentolamine and represented ~15% of total binding.

Inhibition of specific ligand binding by the test compound was analyzed graphically to estimate the IC_{50} (concentration of test compound that displaced 50% specific binding). The inhibitory constant (K_i) was calculated from the IC_{50} using the equation of Cheng and Prusoff.[35] Hill coefficients were essentially equal to unity for all compounds tested.

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chemistry and Lani Russell and Nicole Grinder for preparing the manuscript.

Registry No. **5a**, 110706-41-7; **5a**·2HCl, 123621-18-1; **5b**, 123593-76-0; **5b**·2HCl, 123594-09-2; **5c**, 123593-77-1; **5c**·2HCl, 123594-10-5; **5d**, 123593-78-2; **5d**·2HCl, 123594-11-6; **5e**, 123593-79-3; **5e**·2HCl, 123594-12-7; **5f**, 123593-80-6; **5f**·2HCl, 123594-13-8; **5g**, 123593-81-7; **5g**·2HCl, 123594-14-9; **5h**, 123593-82-8; **5h**·2HCl, 123594-15-0; **5i**, 123593-83-9; **5i**·2HCl, 123594-16-1; **5j**, 123593-84-0; **5j**·2HCl, 123594-17-2; **5k**, 123593-85-1; **5k**·2HCl, 123594-18-3; **5l**, 123593-86-2; **5l**·2HCl, 123594-19-4; **5m**, 123593-87-3; **5m**·2HCl, 123594-20-7; **5n**, 123593-88-4; **5n**·2HCl, 123594-21-8; **5o**, 123593-89-5; **5o**·2HCl, 123594-22-9; **5p**, 123593-90-8; **5p**·2HCl, 123621-19-2; **5q**, 123593-91-9; **5q**·2HCl, 123594-23-0; **5r**, 123593-92-0; **5r**·2HCl, 123594-24-1; **5s**, 123593-93-1; **5s**·2HCl, 123594-25-2; **5t**, 123593-94-2; **5t**·2HCl, 123594-26-3; **5u**, 123593-95-3; **5u**·2HCl, 123594-27-4; **5v**, 123593-96-4; **5v**·2HCl, 123594-28-5; **5w**, 123593-97-5; **5w**·2HCl, 123594-29-6; **5x**, 123593-98-6; **5x**·3HCl, 123594-30-9; **6a**, 110706-35-9; **6a**·2HCl, 123594-31-0; **6b**, 110706-37-1; **6b**·2HCl, 123594-32-1; **7a**, 91-21-4; **7b**, 4965-09-7; **7c**, 25939-81-5; **7d**, 87443-63-8; **7e**, 41565-85-9; **7f**, 29726-60-1; **7g**, 123593-99-7; **7h**, 123594-00-3; **7i**, 123594-01-4; **7j**, 73075-43-1; **7k**, 123594-02-5; **7l**, 33537-99-4; **7m**, 75416-50-1; **7n**, 89315-57-1; **7o**, 75416-53-4; **7p**, 61563-24-4; **7q**, 103030-70-2; **7r**, 76019-13-1; **7s**, 123594-03-6; **7s**·HCl, 123594-05-8; **7t**, 52759-09-8; **7u**, 1745-07-9; **7v**, 88207-92-5; **7x**, 115955-90-3; **8a**, 496-12-8; **8b**, 123594-04-7; **9**, 123594-06-9; **10**, 123594-07-0; **10**·HCl, 123594-33-2; **11**, 123594-08-1; 2-(chloromethyl)-2-imidazoline hydrochloride, 13338-49-3; *N*-acetyl-2,5-dimethoxyphenethylamine, 106274-40-2; 5,8-dimethoxy-1-methyl-3,4-dihydroisoquinoline, 105901-26-6; 3-chlorophthalic anhydride, 117-21-5; 3-chlorophthalimide, 51108-30-6; 5-nitro-1,2,3,4-tetrahydroisoquinoline, 41959-45-9; [^{3}H]yohimbine, 146-48-5; [^{3}H]idazoxan, 79944-58-4; [^{3}H]prazosin, 19216-56-9.

Aporphines as Antagonists of Dopamine D-1 Receptors

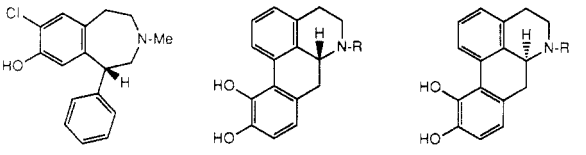
John M. Schaus,* Robert D. Titus, Mark M. Foreman, Norman R. Mason, and Lewis L. Truex

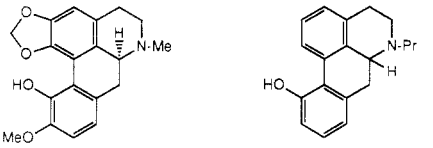
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285. *Received January 23, 1989*

The aporphine alkaloids are a class of compounds known to possess activity at both D-1 and D-2 dopamine receptors. (*R*)-Apomorphine and (*S*)-bulbocapnine are examples of compounds which have agonist and antagonist activity, respectively, at D-1 receptors. A series of optically pure aporphines was synthesized and their activity at D-1 and D-2 dopamine receptors was studied. The (*R*)-aporphines uniformly had greater affinity for both D-1 and D-2 receptors than their *S* antipodes. Dihydroxy compound (*R*)-apomorphine, in accord with previous studies, was found to be a D-1 agonist. Aporphines possessing a single hydroxy group at C-11 are antagonists at the D-1 receptor. The corresponding methoxy compounds are virtually inactive at dopamine receptors. The most potent compounds, (*R*)-11-hydroxyaporphine (*R*-**14**) and (*R*)-10-bromo-11-hydroxyaporphine (*R*-**26**), are more potent than bulbocapnine as D-1 antagonists but are not as selective. A model for binding of aporphines to the D-1 receptor was formulated in which binding interactions between the receptor and the basic nitrogen and the C-11 hydroxy group of the aporphine are required for high-affinity binding to the receptor. The absolute configuration at C-6a determines the orientation of the N-6 lone pair and binding is optimal for the 6a*R* series. The agonist or antagonist activity of an aporphine is determined by the presence or absence, respectively, of a hydroxy group at C-10. A hydrophobic binding site may be present and may account for the high antagonist activity of (*S*)-bulbocapnine.

Studies with dopaminergic agents have led to the identification of two distinct classes of central nervous system (CNS) dopamine receptors, D-1 and D-2. The D-1 receptors are located postsynaptically and are positively linked to adenylate cyclase as its second messenger. In contrast, D-2 receptors are located both pre- and postsynaptically and either are not coupled or are negatively coupled to adenylate cyclase.[1] While much research has concentrated on the function of D-2 receptors in the CNS, until relatively recently, little has been known of the significance of D-1 receptors. The discovery of the D-1 selective antagonist SCH-23390 (**1**) has greatly facilitated research on the function of D-1 receptors in the CNS.[2]

It is now known that functional interaction exists between D-1 and D-2 receptors in the CNS. In dopamine-depleted mice and rats, administration of either a D-1 or a D-2 agonist alone is ineffective in producing stereotypic behavior and increases in locomotor activity. However, when these agents are given in combination, similar increases in these behavioral indices are seen as when (*R*)-apomorphine (**2a**), an agonist at both D-1 and D-2 receptors, is given.[3-5] Similarly, climbing behavior in





normal mice identical with that induced by (*R*)-apomorphine is induced by concomitant administration of a D-1 and a D-2 agonist but not by either treatment alone.[6] Locomotor activity and stereotypy induced by either (*R*)-apomorphine or a selective D-1 or D-2 agonist can be blocked by antagonists selective for either D-1 or D-2 receptors.[7]

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