Conformational Analysis and Molecular Modeling of 1-Phenyl-, 4-Phenyl-, and 1-Benzyl-1,2,3,4-tetrahydroisoquinolines as D_1 Dopamine Receptor Ligands

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Conformational studies on a series of 1-phenyl-, 4-phenyl-, and 1-benzyl-1,2,3,4-tetrahydroisoquinolines that possess an identical substituent pattern to the prototypical D_1 dopamine receptor antagonist SCH23390 [(*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**1**)] were performed with use of molecular mechanics calculations {MM2(85), with newly developed aromatic halide bending and torsional parameters that are now incorporated into MM2(87)}, single-crystal X-ray analysis, and high-field NMR spectroscopy. The synthesis and biological testing of compounds **2–7** has been previously reported. The test compounds were compared both quantitatively and graphically to compound **1**. Calculations on both the free-base and protonated forms of each compound were carried out. To insure that conformation space was adequately sampled, the test compounds were energy minimized from different starting geometries; ring inversion of the heterocycle was employed, as were dihedral driver calculations on the phenyl or benzyl rings. For *N*-methyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2**), it was determined that the torsion angle τ(C8a–C1–C12–C17) had energy minima at approximately 60° and 240°. This finding was corroborated by NMR studies that indicated a dramatic upfield chemical shift of ArH8 after ring cyclization. The nitrogen lone pair or hydrogen vector was approximately orthogonal to the plane of the substituted aromatic ring in the tetrahydroisoquinolines; this explained the upfield chemical shift of the vicinal chiral proton (H1). In all instances, the 6-membered heterocyclic ring in the energy-minimized structures preferred the half-chair conformation with the phenyl rings pseudo-equatorial. Distance comparisons of the proposed pharmacophoric atoms (Cl, N, O, centroid of the phenyl or benzyl ring) showed that the phenyl or benzyl centroid to ammonium H distance, Cl to N distance, and distance of the nitrogen above or below the plane of the isoquinoline aromatic ring are the distances most highly correlated with biological activity (r = 0.82, 0.75, 0.81, respectively). Resolution and single-crystal X-ray analysis of compound **2** showed the most active enantiomer to possess the *S* absolute configuration, in contrast to the benzazepine (*R*)-**1**. Least-squares fitting of the energy-minimized structures with SYBYL molecular modeling software showed (*S*)-(+)-**2**, rather than (*R*)-(−)-**2**, gave a better fit to (*R*)-**1**. Volume determinations derived from SYBYL multifit analyses aided in receptor mapping to qualitatively describe areas of "active" pharmacophore space as well as areas of "inactive" substituent space. A correlation (r = 0.95) was found relating the calculated dipole moment orientations with D_1 receptor binding affinity.

The development of selective ligands for membranous central nervous system receptors has been difficult because of the low concentration of these receptors, the large number of different receptor systems, and the presence of multiple receptor subtypes. The macromolecular structures of the dopamine D_1 and D_2 receptors has not been clearly elucidated; therefore most of what we know about these molecular targets has come from analysis of small molecules known to interact with them. Knowledge of the interacting substituent groups, conformations, and configurations of structures conferring activity at a given receptor is the major "classical" route for obtaining information about the chemical nature of receptors and their important binding sites.

The structure activity requirements of both agonists and antagonists at the D_2 dopamine receptor have been studied,[1-6] but much less is known about D_1 receptors. Recently, several phenylbenzazepines have shown relative selectivity and high-affinity binding at D_1 receptors, and this knowledge has provided most of our present understanding of the D_1 receptor pharmacophore. One interesting compound to arise from this class is SCH23390

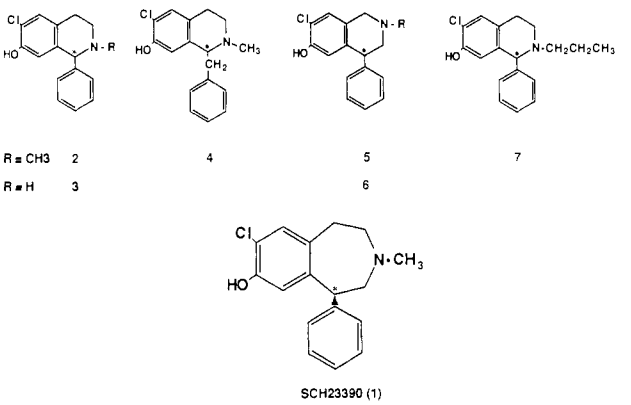

Figure 1. Test compounds (an asterisk denotes a chiral center).

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(1) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L.; Davidson, A. B.; Boff, E. *J. Med. Chem.* **1981**, *24*, 1026.

(2) Van De Waterbeemd, H.; Carrupt, P.-A.; Testa, B. *J. Med. Chem.* **1986**, *29*, 600.

(3) McDermed, J. D.; Freeman, H. S.; Ferris, R. M. In *Catecholamines: Basic and Clinical Frontiers*; Usdin, E., Koplin, I. J., Barchas, J., Eds.; Pergamon Press: New York, 1979; pp 568–570.

(4) Wikstrom, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.

(5) Seeman, P.; Watanabe, M.; Grigoriadis, D.; Tedesco, J. L.; George, S. R.; Svensson, U.; Nilsson, J. L. G.; Neumeyer, J. L. *Mol. Pharmacol.* **1985**, *28*, 391.

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[(*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1)] (Figure 1), which has become the prototypical D_1 receptor antagonist since its initial synthesis,[7] radiolabeling,[8] and subsequent pharmacological characterization.[9-13]

Computer-assisted molecular modeling based upon the conformational features of tetrahydroisoquinoline dopamine D_1 receptor antagonists (Figure 1) has led to some interesting conclusions regarding receptor–ligand interactions at the D_1 receptor. The synthesis, resolution, and pharmacological evaluation of these compounds, the measurement of their affinities at both D_1 and D_2 receptor sites, and their abilities to inhibit dopamine-stimulated adenylate cyclase (the biochemical marker for D_1 receptor activation) have been previously described.[14] D_1 affinity was determined by the ability of the test compounds to inhibit [^{3}H]benzazepine (compound 1) binding and the inhibition of dopamine-stimulated adenylate cyclase, while D_2 affinity was determined by the ability of these compounds to inhibit [^{3}H]spiperone binding. It was rationalized that derivatives **2** and **3** would serve as a direct comparison to compound 1 and its *N*-desmethyl derivative, SCH24518. The fact that these ring-contracted compounds possessed the same substitution pattern as compound 1, yet only retained one phenethylamine structure, was perceived to be an informative modification. 1-Benzyltetrahydroisoquinoline **4** was designed with use of this rationale along with the knowledge that it was structurally similar to the naturally occurring dopaminergic benzyltetrahydroisoquinolines.[15,16] Due to free rotation around the 1-benzyl bond, this compound could also provide some information about bulk tolerance in a hypothesized receptor pocket that accommodates the 1-phenyl substituent of compound 1.

Compound **7** was designed to probe the steric requirements in the area of the receptor believed to accommodate the *N*-methyl group of compound 1. Although the *N*-propyl substituent showed a decrease in activity in the phenylbenzazepine series,[17] the interatomic distance between the chlorine and the nitrogen is decreased in the tetrahydroisoquinoline series; therefore the alkyl substituent (i.e. *N*-propyl group) would not protrude as far into the receptor. The 4-phenyl derivatives **5** and **6** were of interest as dopamine receptor ligands since the 4-phenyl substituted dopamine agonist 3′,4′-dihydroxynomifensine[18] also possesses the tetrahydroisoquinoline nucleus.

Conformational studies based on single-crystal X-ray diffraction, NMR spectroscopy, and molecular mechanics methods were employed to determine conformational similarities or differences to compound 1. It was anticipated that this analysis could explain the enantioselectivity in the tetrahydroisoquinoline series. In addition, various graphical and statistical methods were also used to help develop a pharmacophore model for this class of D_1 dopamine antagonists.

Although the minimum-energy conformations of the compounds **1–7** might not be the biologically active conformations, these structures are nonetheless informative. The global versus local minimum problem associated with molecular mechanics calculations has been described elsewhere.[19] To circumvent such problems and to assure that all conformers studied were at their global minima, a thorough conformational search was undertaken. Different starting geometries, ring inversions, and dihedral driver calculations on the positioning of the phenyl and benzyl substituents were employed to probe the potential energy surface and to find the global minimum by using MM2(85) developed by Allinger and co-workers.[20] Dihedral driver options, present in most molecular mechanics programs, allow one to "scan" a part of the potential energy surface to determine the energy minima corresponding to rotation around a specific torsion angle.

Another ubiquitous problem in the quantitative molecular mechanics approach is the lack of necessary parameters for the structures one desires to study. Such was the case here: certain torsional and bond angle parameters for aromatic halogen substituents were developed for the MM2(85) program in the course of another investigation and used for the theoretical work described herein.[21]

X-ray crystal coordinates for both compounds **1**[22] and **2** were used as input geometries. Calculations and molecular modeling comparisons of both the free base and protonated forms of each compound were carried out. Distance comparisons of the proposed pharmacophoric elements (Cl, N, O, center of unsubstituted phenyl or benzyl ring) were also undertaken. The distance of the ring nitrogen above or below the plane of the substituted phenyl ring was studied as a possible correlate with the D_1 antagonist potency of the compounds. The preferred conformation of the 6-membered heterocyclic ring in the energy-minimized structures was also studied in conjunction with the conformation of the 1-phenyl or 1-benzyl substituent. The nitrogen lone pair or hydrogen vector was evaluated with regard to its possible receptor-binding orientation. Predictions of enantioselectivity were also performed and compared to assignment of absolute stereochemistry by X-ray crystallography of the biologically active isomer.

Finally, a quantitative structure–activity relationship (QSAR) was established in conjunction with these mo-

(6) Tonani, R.; Dunbar, J.; Edmonston, B.; Marshall, G. R. *J. Comp. Aided Molec. Des.* **1987**, *1*, 121.

(7) Gold, E. H.; Chang, W. K. U.S. Patent 4,349,472, September 14, 1982.

(8) Wyrick, S. D.; Mailman, R. B. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 189.

(9) Schulz, D. W.; Wyrick, S. D.; Mailman, R. B. *Eur. J. Pharmacol.* **1984**, *106*, 211.

(10) Schulz, D. W.; Stanford, E. J.; Wyrick, S. D.; Mailman, R. B. *J. Neurochem.* **1985**, *45*, 1601.

(11) Billard, W.; Ruperto, V.; Crosby, G.; Iorio, L. C.; Barnett, A. *Life Sci.* **1984**, *35*, 1885.

(12) Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 462.

(13) Mailman, R. B.; Schulz, D. W.; Lewis, M. H.; Staples, L.; Rollema, H.; DeHaven, D. L. *Eur. J. Pharmacol.* **1984**, *101*, 159.

(14) Charifson, P. S.; Wyrick, S. D.; Hoffman, A. J.; Ademe-Simmons, R. M.; Bowen, J. P.; McDougald, D. L.; Mailman, R. B. *J. Med. Chem.* **1988**, *31*, 1941.

(15) Clement-Cormier, Y. C.; Meyerson, L. R.; Phillips, H.; Davis, V. E. *Biochem. Pharmacol.* **1979**, *28*, 3123.

(16) Sandler, M.; Bonham Carter, S.; Hunter, K. R.; Stern, G. M. *Nature* **1973**, *241*, 439.

(17) Iorio, L. C.; Barnett, A.; Billard, W.; Gold, E. H. In *Neurobiology of Central D1-Dopamine Receptors*; Breese, G. R., Creese, I.; Eds., Plenum Press: New York, 1986; pp 1–14.

(18) Poat, J. A.; Woodruff, G. N.; Watling, K. J. *J. Pharm. Pharmacol.* **1978**, *30*, 495.

(19) Boyd, D. B.; Lipkowitz, K. B. *J. Chem. Educ.* **1982**, *59*, 269.

(20) Allinger, N.; et al. MM2(85) software, Molecular Design, Ltd.

(21) Bowen, J. P.; Reddy, V. V.; Patterson, D. G.; Allinger, N. *J. Org. Chem.* **1988**, *53*, 5471.

(22) Unpublished results graciously supplied from Schering Co.

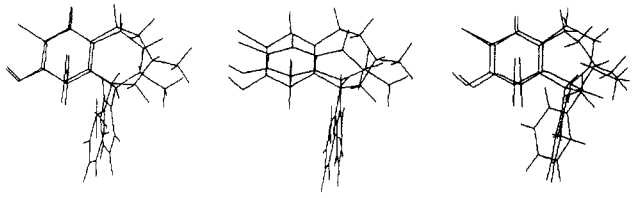

Figure 2. Superpositions of a, (*S*)-(+)-**2** (left); **b**, (*R*)-(−)-**2** (middle); and **c**, (*S*)-(+)-**4** (right) with (*R*)-(−)-**1**.

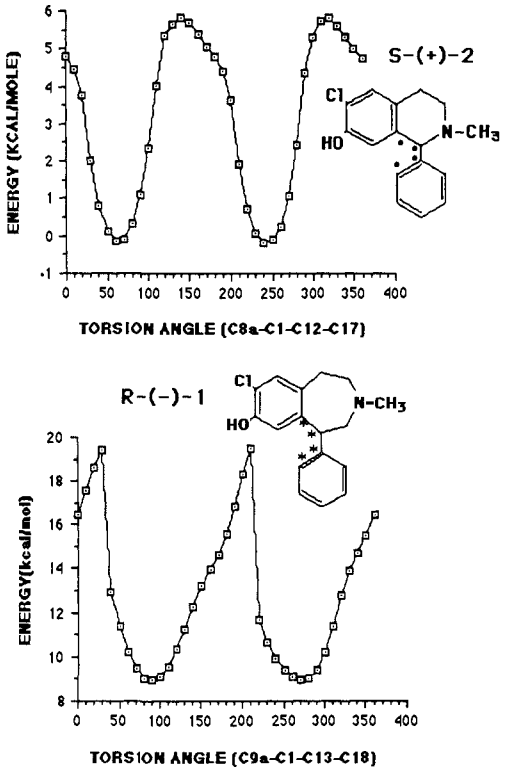

Figure 3. Torsion angle vs final steric energy (MM2(85)); atoms involved in the torsion are highlighted. **a**, (*S*)-(+)-**2** (above); **b**, (*R*)-(−)-**1** (below).

lecular modeling studies to aid in the refinement of a model that could be used to predict new, more potent analogues. Quantitative structure–activity relationships classically involve the use of multiple regression analyses to evaluate the correlation of the substituent parameter(s) with biological activity. We have searched for the absolute minimum number of predictor variables for these tetrahydroisoquinolines to aid in the description of the D_1 pharmacophore. From this work, an electronic descriptor seemed adequate to describe the observed D_1 binding data. The descriptor was defined as the angle between the dipole vector and the normal to the plane of the proposed pharmacophore. This single-variable model possessed better predictive power than models that included either hydrophobic or steric parameters.

Results and Discussion

Conformational Analysis. Some interesting stereochemical observations have been made regarding the titled compounds. The tetrahydroisoquinolines behave as stereochemical opposites of the benzazepines. The *R* enantiomers of the benzazepines are highly potent and selective D_1 ligands; the *S* isomer of compound **1**, SCH23388, is much less active as a D_1 antagonist.[17] In contrast, of the tetrahydroisoquinolines examined here, the *S* enantiomers are more effective competitors at ^{3}H-labeled compound **1** binding sites; X-ray analysis of the biologically active (+) antipode of **2** led to this assignment. This stereochemical

Table I. Receptor Binding Potencies[a]

compd	D_1 K_i[c]	pD_1 K_i	D_2 K_i[d]	pD_2 K_i	DSAC K_i[e]	pDSAC K_i
(*R*)-**1**	0.43	9.37	900	6.05	0.47	9.33
(*S*)-**2**	6.64	8.18	1850	5.73	6.58	8.18
(*R*)-**2**	442	6.35	19200	4.72	568	6.25
(*S*)-**3**	140	6.85	3750	5.43	109	6.96
(*S*)-**4**[b]	26.6	7.57	143.4	6.84	6.26	8.20
(*S*)-**5**[b]	86.8	7.06	261.1	6.58	102	6.99
(*S*)-**6**[b]	283	6.55	1810	5.74	628	6.20
(*S*)-**7**	179	6.75	1900	5.72	202	6.69

[a] Biological activity expressed as pK_i (−log K_i in M). [b] K_i's of racemates halved for comparison purposes of estimated *S* enantiomers. [c] D_1 potency was determined from competition binding experiments with [^{3}H]-SCH23390 (**1**). [d] D_2 potency was determined from competition binding experiments with [^{3}H]spiperone. [e] DSAC inhibitory potency was determined by the conversion of [^{32}P]-ATP to [^{32}P]-cAMP.

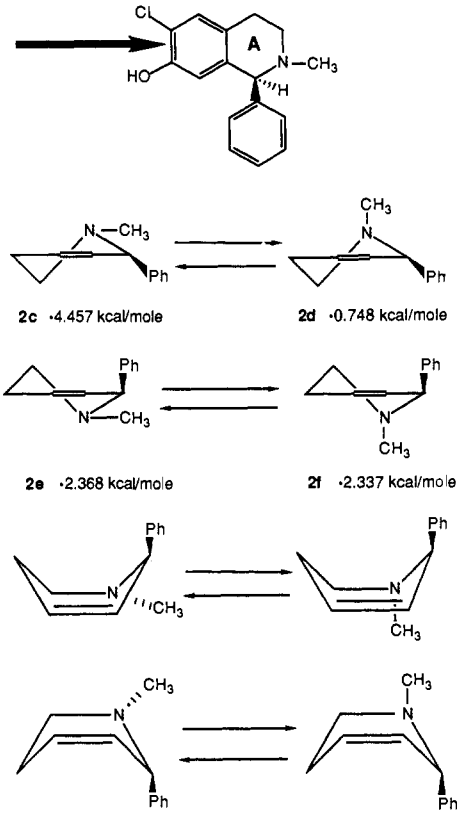

Figure 4. Eight theoretical conformers of tetrahydroisoquinoline ring A.

trend also holds true in terms of D_1 selectivity (Table I). Thus (*S*)-(+)-**2** is approximately 300 times more selective in competing for D_1 sites versus D_2 sites, while (*R*)-(−)-**2** has considerably less selectivity. This point is well illustrated via least-squares-fitted SYBYL comparisons of MM2(85) energy optimized structures: the (*S*)-(+) enantiomer (Figure 2a) of compound **2** possesses a much superior fit to (*R*)-**1** than does the (*R*)-(−) enantiomer (Figure 2b).

All of the tetrahydroisoquinolines that we have studied to date showed a significant preference for the phenyl or benzyl substituents to be pseudo-equatorial in the energy-minimized conformations. Dihedral driver calculations were indicative of the torsion angle τ(C8a–C1–C12–C17) allowing minima at 60° and 240° for the representative tetrahydroisoquinoline **2c** (Figure 3a). The corresponding torsion angle τ(C9a–C1–C13–C18) in compound **1** (Figure 3b) allows minima at approximately 90° and 270°. This calculated torsional preference is also borne out experimentally in the proton NMR spectrum, as shown by the

Table II. Pharmacophore Mapping

	2	2a[a]	2b[b]	2c[c]	2d[d]	2e[e]	2f[f]	3	3c	4	4c
dist, Å											
Cl–N	6.80	6.68	6.76	6.80	6.80	6.77	6.79	6.77	6.77	6.71	6.72
O–N	6.17	6.05	6.12	6.20	6.20	6.17	6.18	6.16	6.18	6.08	6.12
N–X[i]	2.44	2.53	2.51	2.47	2.49	2.54	2.47	2.43	2.45	3.85	3.86
Cl–X	6.65	6.70	6.68	6.67	6.82	6.67	6.75	6.71	6.72	6.74	6.76
O–X	5.12	5.52	5.29	5.13	5.19	5.30	5.39	5.14	5.16	4.97	5.00
N–Y[j]	5.02	5.07	5.12	5.03	5.05	5.14	5.02	5.00	4.99	6.51	6.53
Cl–Y	8.40	8.60	8.50	8.47	8.84	8.50	8.71	8.53	8.58	7.73	7.73
O–Y	6.46	7.44	6.89	6.51	6.69	6.90	7.16	6.50	6.58	5.27	5.29
Nϕ[g,k]	0.16	0.57	0.36	0.20	0.26	0.33	0.37	0.26	0.26	0.53	0.53
center[h] ϕ											
Cl	7.45	7.59	7.52	7.49	7.77	7.51	7.66	7.55	7.58	7.12	7.12
N	3.69	3.77	3.77	3.70	3.72	3.81	3.70	3.67	3.67	5.16	5.18
O	5.66	6.41	5.98	5.69	5.82	5.99	6.18	5.69	5.74	4.93	4.95
AmH				4.61	3.75	4.74	3.42		3.52		5.80
final steric energy, kcal/mol	−0.18		2.25	−4.46	−0.75	−2.37	−2.34	−4.59	−6.41	4.09	1.49

	1	1a[l]	1b[b]	1c[m]	5	5c[m]	6	6c[m]	7	7c[m]
dist, Å										
Cl–N	7.10	7.16	7.10	7.09	6.44	6.47	6.43	6.47	6.82	6.84
O–N	6.79	6.85	6.80	6.79	6.43	6.44	6.42	6.43	6.19	6.23
N–X	3.82	3.79	3.83	3.85	3.12	3.00	3.04	2.98	2.46	2.50
Cl–X	6.78	6.78	6.78	6.77	6.67	6.69	6.69	6.69	6.58	6.58
O–X	5.04	5.04	5.00	5.03	5.34	5.40	5.39	5.42	5.13	5.14
N–Y	6.44	6.42	6.49	6.53	5.35	5.17	5.24	5.15	5.05	5.08
Cl–Y	8.63	8.60	8.67	8.64	8.51	8.58	8.58	8.59	8.22	8.23
O–Y	6.20	6.16	6.16	6.20	7.00	7.71	7.13	7.21	6.47	6.51
Nϕ[g]	1.37	1.15	1.34	1.43	0.41	0.39	0.39	0.36	0.02	0.02
center[h] ϕ										
Cl	7.63	7.64	7.65	7.64	7.52	7.45	7.56	7.57	7.32	7.32
N	5.11	5.08	5.14	5.17	4.15	7.56	4.41	3.97	3.72	3.75
O	5.47	5.47	5.43	5.47	6.06	6.19	6.16	6.22	5.66	5.70
AmH		5.07	5.16	5.80		3.24		3.24		3.46
final steric energy, kcal/mol	9.05		6.95	8.41	−0.02	−3.94	−4.56	−5.28	2.97	−0.53

[a] X-ray data (free base). [b] X-ray geometry as input for minimization. [c] Ammonium form of half-chair **2c** (Figure 4) from MODEL input geometries. [d] Ammonium form of half-chair **2d** (Figure 4) from MODEL input geometries. [e] Ammonium form of half-chair **2e** (Figure 4) from MODEL input geometries. [f] Ammonium form of half-chair **2f** (Figure 4) from MODEL input geometries. [g] Distance of N above or below plane of substituted phenyl ring. [h] Distance to center of unsubstituted phenyl ring. [i] X = 1′-position of unsubstituted phenyl ring. [j] Y = 4′-position of unsubstituted phenyl ring. [k] ϕ = center of pendant phenyl or benzyl ring. [l] X-ray data (cation). [m] Ammonium form from MODEL input geometries.

dramatic upfield chemical shift of ArH8 in the tetrahydroisoquinolines or ArH9 in the benzazepines. For compound **2**, the chemical shift of ArH8 is δ 6.11, which is probably due to its positioning within the shielding cone of the adjacent phenyl ring. Weinstock et al. also noted this upfield chemical shift in a series of 5,6-ethano-bridged 3-benzazepines[23] and further indicated that the benzazepine ring preferred the chair conformation for this series of compounds, which is in agreement with our data for the tetrahydroisoquinolines studied here.

The heterocyclic ring in the tetrahydroisoquinoline series could theoretically exist in either the half-chair or the boat conformation. This would allow for eight possible conformations (four half-chairs and four boats) with respect to the preferences of the *N*-alkyl substituent and the phenyl or benzyl substituents (i.e. axial vs equatorial). Figure 4 shows these possible conformers viewed down an imaginary axis toward the heterocycle. In studying all of these possible conformers, it was apparent that the boat forms were not stable. When constraints were applied to force the conformation into the various boat forms and then released prior to minimization, no minima corresponding to boat conformers were observed. In fact, every time one of the theoretically possible boat structures was used as the starting point for minimization, the half-chair conformer **2d** (Table II, Figure 4) was obtained. Similarly, Olefirowicz and Eliel[24] could not find any conformational minima corresponding to the boat in an extensive conformational analysis of variously substituted tetrahydroisoquinolines.

Both molecular mechanics calculations and proton NMR analyses predict that alkyl substituents on the nitrogen prefer to be equatorial. Prior to N-alkylation, the chemical shift of H1 is at δ 5.1; however, after N-methylation, the chemical shift of this proton moves upfield to δ 4.2. One possible explanation for this observation is that by virtue of the equatorial preference of the methyl group, the nitrogen lone pair is forced into an axial orientation and thereby exerting shielding effects on the H1 proton. In the desmethyl precursor to the N-methylated compounds, the nitrogen lone pair is most likely equilibrating between both equatorial and axial positions via inversion. This axial orientation of the lone pair (or ammonium hydrogen) in the alkylated compounds may be necessary for receptor interaction, since the desmethyl compounds **3** and **6** are much less potent than the corresponding *N*-methyl derivatives **2** and **5**, respectively. Both the unprotonated and protonated species were evaluated in this conformational study; however, the results of the pK_a determination supported the modeling emphasis on the protonated species. The pK_a was 7.33 ± 0.03 for the phenol and 8.95 ± 0.03 for the amine. Independent pK_a determinations at the isosbestic point (264 nM) were in agreement with those determined from the same titration curve: phenol pK_a = 7.32 ± 0.04, amine pK_a = 8.91 ± 0.03.

(23) Weinstock, J.; Oh, H.-J.; DeBrosse, C. W.; Eggleston, D. S.; Wise, M.; Flaim, K. E.; Gessner, G. W.; Sawyer, J. L.; Kaiser, C. *J. Med. Chem.* **1987**, *30*, 1303.

(24) Olefirowicz, E., Doctoral Dissertation under the direction of Ernest Eliel, 1988, University of North Carolina at Chapel Hill.

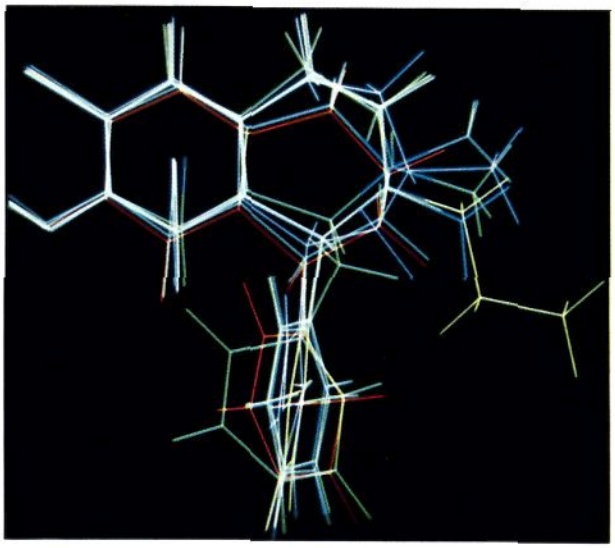

Figure 5. Result of multifit for the *S* isomers of **2–7** and compound (*R*)-**1**.

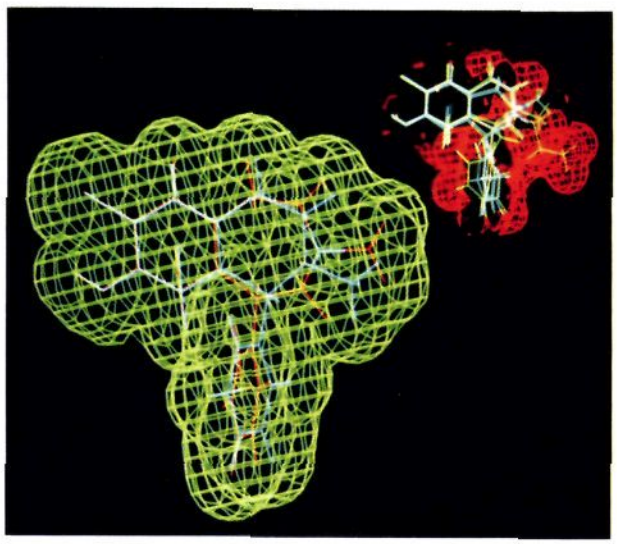

Figure 6. Molar volume representation of (*S*)-**2** and (*R*)-**1** illustrating "negative image" of an accommodating receptor pocket (green). Molar volume representation of (*S*)-**3**, **4**, **5**, **6**, and **7** illustrating unacceptable substituent space (red).

The molecular mechanics calculations predict the hydroxyl proton oriented toward the chlorine, indicating an intramolecular hydrogen bond. This is opposed to the X-ray crystal structures of (*S*)-(+)-**2** and (*R*)-**1** in which the hydroxyl proton is oriented away from the chlorine presumably due to an intermolecular hydrogen bond with water. An increase in stability of 1.5 kcal/mol for the calculated hydroxyl orientation (toward the chlorine) supports the premise of an intramolecular H bond. Although the gas-phase prediction does not consider the competition of hydrogen bonding with water in an aqueous biological medium, it is conceivable that within the microenvironment of a largely hydrophobic receptor site, an intramolecular hydrogen bond might possibly contribute either to loss of the phenolic proton or to hydrogen-bond exchange with a residue at this site.

Pharmacophore Mapping. As a result of exhaustive SAR work performed on the benzazepine D_1 selective ligands, substitution patterns have evolved for both D_1 agonists and antagonists.[17] The positioning of the halogen and hydroxyl group has been given much attention over

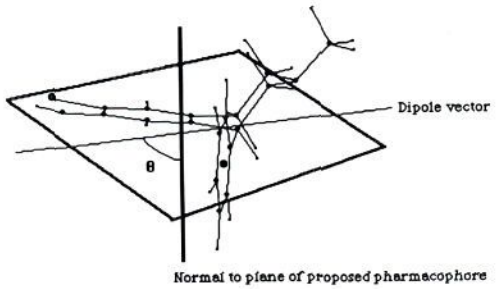

Figure 7. Description of dipole vector with respect to proposed pharmacophore. The least-squares plane was calculated with Cl, N, O, and the centroid of the phenyl.

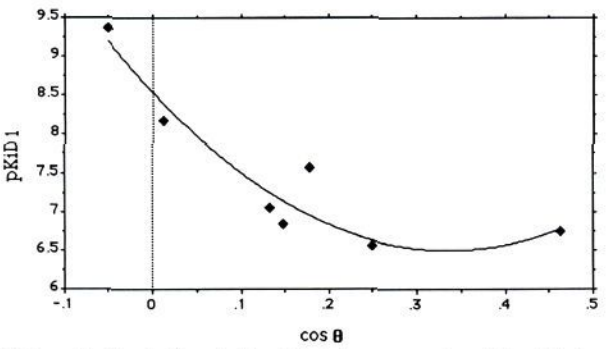

Figure 8. Parabolic relationship between cos θ and D_1 affinity.

the past decade, and the data are conclusive that compound **1** embodies the maximal positioning of these groups as related to D_1 inhibitory potency. The present study on tetrahydroisoquinolines **2–7** relies largely on the previous benzazepine SAR work. An initial attempt at pharmacophore mapping was accomplished by a comparison of interatomic distances from MM2 optimized structures. The distances chosen for measurement are listed in Table II. Additionally, the distance of the nitrogen above or below the plane of the isoquinoline aromatic ring and the distance between the ammonium hydrogen and the centroid of the phenyl or benzyl substituent were measured. Distances were measured for both the neutral species and the protonated forms, and are presented in Table II along with their final steric energies. The legend of Table II designates the source of the input geometries (X-ray vs MODEL) used in the MM2 optimizations. It is evident from this table that of the four possible half-chair conformations mentioned earlier, conformer **2c** (Table II, Figure 4), with both the methyl and phenyl groups equatorial (or pseudo-equatorial), is the most energetically favorable.

Statistical analysis of these data has been performed to determine individual interatomic distance vs activity correlations (see Table III). The 1-phenyl centroid to ammonium H distance, Cl to N distance, and distance of the nitrogen above or below the plane of the isoquinoline aromatic ring are the distances most highly correlated with the biological activity (expressed as the $-\log K_i$ D_1 in M, i.e. pK_iD_1) in this series of simple regressions. Although multiple regression can, in some instances, provide more insight into the relationship among variables, it was not feasible in this case due to the small data set ($n = 7$ observations vs 13 regressors). This inherent statistical limitation is cause for judicious interpretation of these results. The fact that the 1-phenyl centroid to ammonium hydrogen distance is highly correlated, yet the 1-phenyl centroid to nitrogen distance is so poorly correlated, is cause for questioning the utility of this approach. Also of interest is the variability (Table II) of the distances of the

Table III. Correlation between Distances and Biological Activity[a]

distance	slope	r	r^2	p
Cl–N	+	0.75	0.56	0.05
O–N	+	0.56	0.32	0.19
N–X	+	0.55	0.30	0.20
Cl–X	+	0.54	0.29	0.21
O–X	–	0.61	0.38	0.14
N–Y	+	0.65	0.43	0.11
Cl–Y	+	0.10	0.01	0.83
O–Y	–	0.41	0.17	0.36
N plane ϕ	+	0.81	0.65	0.03
ϕ–Cl	+	0.24	0.06	0.61
ϕ–N	+	0.12	0.02	0.79
ϕ–O	–	0.47	0.22	0.29
ϕ–AmH	+	0.82	0.67	0.03

[a] Compounds: 1, 2, 3, 4, 5, 6, 7 (ammonium forms). Biological activity expressed as pD_1K_i (K_i's of racemates halved).

nitrogen above or below the plane of the isoquinoline aromatic ring. For the benzazepine 1 this distance is 1.367 Å in the X-ray structure and 1.429 Å in the MODEL-generated protonated form. The most potent tetrahydroisoquinoline, 2, however, only measures 0.162 Å (X-ray) and 0.201 Å (MODEL-generated protonated form) for this same distance. Given that these are different structural classes, it could be rationalized that a smaller distance is required for tetrahydroisoquinolines to act as D_1 antagonists. The *N*-propyl derivative 7 showed a considerably smaller distance for the nitrogen to the plane of isoquinoline aromatic ring (0.022 Å) which can be explained by movement of the 1-phenyl substituent away from the *N*-propyl group to minimize steric interactions, thus causing a notable flattening of the heterocyclic ring.

Least-Squares Fit of "Pharmacophore" Atoms. Although the distance–activity analysis presented above is insufficient to describe the necessary structural requirements for the test compounds to act as selective D_1 antagonists, some insight can be gained if these observations are viewed in conjunction with proposed dopamine receptor models. The generally accepted hypothesis of *m*-hydroxyphenethylamine as the dopaminergic pharmacophore has been described.[25] Because this hypothesis assumes involvement of the hydroxyl group in binding to the receptor, it seems reasonable to include the oxygen atom in the search for a D_1 antagonist pharmacophore. In compound 1 the hydroxyl group is meta to one of the two possible phenethylamine moieties, while in the 1-phenyltetrahydroisoquinolines, the hydroxyl is para to the phenethylamine moiety. The 4-phenyltetrahydroisoquinoline 5 also possesses a hydroxyl group meta to the phenethylamine moiety, yet is much less potent than its 1-phenyl congener. Therefore, it might be concluded that the hydroxyl group need not be oriented meta to phenethylamine as a prerequisite for D_1 antagonism. More importantly, the spatial orientation with respect to the other pharmacophoric atoms is the significant feature of this description. The oxygen, nitrogen, chlorine, and phenyl (or benzyl) centroids of the *S* tetrahydroquinolines were thus determined as being suitable points for a least-squares comparison with (*R*)-1. Table IV shows root mean square (rms) fits of these atoms for each derivative with compound 1. The relative potency data for the compounds are also provided using the estimated K_i's of the racemates as previously described. (*R*)-2 is also included to illustrate the lack of "fit" to this model. Figure 2a,b shows a graphical representation of the least squares

Table IV. Least-Squares Fit to Proposed Benzazepine Pharmacophore

compd	Cl	O	N	Cϕ[a]	rms	pD_1 K_i
(*S*)-2	0.13	0.35	0.86	0.73	0.5534	8.18
(*R*)-2	0.75	1.05	1.18	1.59	1.1331	6.35
(*S*)-3	0.12	0.33	0.85	0.74	0.5507	6.85
(*S*)-4	0.29	0.60	0.32	0.43	0.4140	7.57
(*S*)-5	0.29	0.58	0.76	0.69	0.5741	7.06
(*S*)-6	0.38	0.95	0.95	0.90	0.7814	6.55
(*S*)-7	0.29	0.64	0.79	0.76	0.6157	6.75

[a] Cϕ represents the phenyl or benzyl centroid. $y = -1.827x + 8.25$; $r = 0.677$; $p = 0.095$.

fitted (*S*)-2 and (*R*)-2 with (*R*)-1, while Figure 2c shows the least-squares fit of compound 4 with (*R*)-1.

While the rms fits do not correlate as well as expected with the biological activity, pharmacophoric resolution in the 0.5–0.6-Å range for such a series of antagonists is not unreasonable. One reason for a lack of a better correlation is that the 1-benzyl compound 4 aligns the center of its pendant aromatic ring quite well with that of compound 1 in the least squares fitting procedure. However, the regression analysis does not consider that the aromatic ring of 4 is almost perpendicular to the aromatic ring of compound 1 (and the other tetrahydroisoquinolines, Figure 2c). The receptor does not appear to exhibit much bulk tolerance in this region as evidenced by the diminished D_1 affinity of 4 with its increased substituent width in this part of the molecule. Similarly, the *N*-propyl group of compound 7 is not considered in this method, and this might contribute to some inaccuracy because this bulky substituent is probably the reason for the poor affinity and activity, although the rms fits are reasonable. Also, the desmethyl compounds 3 and 6 give a much better rms fit than would be expected from their poor affinity for D_1 sites. The lack of an *N*-methyl substituent is not considered by this analysis; therefore, a much better fit is calculated on the basis of only the four atoms chosen. Removal of the outlier (compound (*S*)-2) from the regression analysis improves the relationship between rms fit and D_1 affinity among the remaining compounds ($r = 0.861$, standard error = 0.243, $p = 0.0275$). Since (*S*)-2 has been determined to be the only tetrahydroisoquinoline in the present study to possess significant D_1 antagonist potency, this implies that its mode of binding to the D_1 dopamine receptor is different from that of its tetrahydroisoquinoline congeners. Although (*S*)-2 differs stereochemically from compound 1, its conformational resemblance to the benzazepine is closer than the other compounds studied. This may allow for a mode of binding to the D_1 receptor analogous to compound 1, which is unattainable by the other tetrahydroisoquinoline test compounds.

Multifit Analysis: Receptor Mapping. Classical structure–activity relationship studies require many assumptions to be made about receptor sites, which may be incorrect due to limited information regarding the molecular target or receptor. In the case where the receptor is unknown, developing a pharmacophore hypothesis provides a mechanism for understanding the three-dimensional structural pattern in the ligand that facilitates receptor binding (and receptor activation in the case of agonists). If one can assume that a single pharmacophore exists for a set of compounds active at a given pharmacological receptor, a Multifit analysis (more commonly referred to as the "Active Analogue Approach") can be implemented by using the program SYBYL.[26] The object

(25) Kaiser, C.; Jain, T. *Med. Res. Res.* **1985**, *5*, 145.

(26) SYBYL version 5.05, Tripos and Associates, St. Louis, MO, 1987.

of such methodology is to examine the possible three-dimensional arrangement of the hypothetically significant atoms to see if a similar three-dimensional arrangement of the proposed groups is energetically feasible.

As mentioned in the Experimental Section, a spring force constant of 20 mdynes/Å was applied to link the chlorines, oxygens, nitrogens, and pendant phenyl (or benzyl) centroids for the *S* isomers of compounds **2–7** and compound (*R*)-**1**. This conglomerate was minimized and is shown in Figure 5. One method for evaluating the results of a Multifit analysis involves the construction of molar volume representations that are pseudo-electron density maps. This approach can give some useful qualitative information regarding "active" vs "inactive" receptor space. Figure 6 shows the results of such a volume representation. In Figure 6, the calculated volume in green represents accommodatable receptor space. The most potent tetrahydroisoquinoline, (*S*)-**2**, and the benzazepine **1** have been used to determine this region. The red volume illustrates unfavorable receptor space and has been determined by compounds **3–7**. The *N*-propyl substituent of compound **7** and the perpendicular benzyl ring of compound **4** constitute the majority of the inactive region. The *N*-methyl group of **5** also contributes to this inactive area.

The potential use of such modeling is to aid in the design of new compounds. For example, in the prediction of a new D_1 antagonist, one would expect that an active compound could successfully occupy the "active" region with the important pharmacophoric constituents in roughly the same region as those in this model. One would also want to ascertain that a proposed compound did not enter "inactive" space, as this region is occupied by the receptor. However, it must be realized that if a substituent from a proposed compound extended out of the "active" region into an area not defined by "inactive" space, no definitive conclusions could be drawn at this time since these areas have not been explored.

Dipole Orientation as a Quantitative Structure–Activity Determinant. Over the past two decades, quantitative structure–activity relationships (QSAR) have emerged as an invaluable tool in drug design. Computers allow statistical analyses on large datasets, and this has led to the development of new models correlating physicochemical features with specific biological effects. However, there is a risk of arriving at random high correlations when too many variables are screened relative to the number of available observations. Topliss and Edwards have addressed the phenomenon of chance correlations when the number of variables screened is large compared to the number of observations.[27] They have concluded that some correlations are less significant than their standard *p* values indicate and have provided guidelines for the approximate incidence of chance correlations at specified r^2 values for various combinations of observations and screened variables.

In the present study, only seven observations (compounds **2–7** and compound **1**) are considered. For this reason, it was desirable to derive a quantitative structure–activity relationship with as few variables as possible to describe the dataset adequately. It became apparent that many combinations of descriptor variables modeled after a classic Hansch approach were "regressor heavy" for our purposes. If *C* log *P* (*C* = calculated), Verloop steric parameter(s), and variable electronic descriptors were employed, good correlations were obtained. However, the use of these three or four regressor models to explain seven observations obviously suffers from the very problems that Topliss and Edwards have described.

Table V. Development of an Equation Relating Dipole Vector Variable, cos θ, with D_1 Affinity[a]

compd	cos θ	pK_iD_1 (exp)	pK_iD_1 (calcd)
(*R*)-**1**	−0.051	9.37	9.19
(*S*)-**2**	0.011	8.18	8.40
(*S*)-**3**	0.148	6.85	7.13
(*S*)-**4**	0.178	7.57	6.95
(*S*)-**5**	0.132	7.06	7.25
(*S*)-**6**	0.249	6.55	6.63
(*S*)-**7**	0.463	6.75	6.78

[a] $pK_iD_1 = 8.53 - 12.08 \cos\theta + 17.908 \cos\theta^2$. $R = 0.95$, $R^2 = 0.902$, SE = 0.384, $p = 0.0096$.

Interest in using either the dipole moment or the dipole orientation relative to some important substituent(s) as a predictor of electronic effects arose partly due to the relative ease of obtaining this information. Further, Young et al.[28] showed a good correlation between H_2 histamine antagonist potency, dipole moment orientation, and lipophilicity for a series of cimetidine analogues. These researchers discovered an optimum angle between the dipole moment orientation and a vector constructed along a nitrogen-variable substituent bond. In the work presented here, a least-squares plane defined by the proposed four point pharmacophore (Cl, N, O, phenyl or benzyl centroid) was constructed. A standard molecular orientation was chosen for the compounds. Angle, θ, was defined by the dipole moment vector and the normal to the pharmacophoric plane and is shown in Figure 7. Graphical analysis has shown that, for (*S*)-**2** and (*R*)-**1**, the dipole vectors are oriented in the same direction, implying that (*S*)-**2** is electronically capable of binding to the D_1 receptor in the same fashion as (*R*)-**1**. This finding is in agreement with the rms fit of (*S*)-**2** with (*R*)-**1**. A very good correlation was obtained between D_1 affinity, the cosine of this angle, and the square of the cosine. The addition of *C* log *P* to the regression analysis did not improve the correlation and, in fact, led to a poorer correlation. The actual value of the dipole moment, μ, was also tried in various models, as well as $\mu \cos\theta$. As in the work by Young et al.,[28] no improvement in the model was obtained. The results are shown in Table V and are illustrated in Figure 8. From these data, it appears that for potent D_1 binding affinity, a value of cos θ near zero or slightly negative is desired. It appears that the orientation of the least-squares pharmacophore plane is largely influenced by the 1-phenyl or 1-benzyl centroid. Since this is the only pharmacophore element that deviates substantially from the plane of the other three determinants (Cl, N, O), one can envision that the distance of the centroid above the plane of the Cl, N, and O affects the value of cos θ. Therefore, cos θ represents a coupling of the dipole moment orientation with hydrophobicity, since it is also descriptive of the phenyl or benzyl orientation with respect to the tetrahydroisoquinoline nucleus. This model presently stands as a correlation; however, only when a new chemical structure predicted from this model is synthesized and tested can the validity of this quantitative structure–activity relationship be evaluated.

The methodologies presented herein represent a multifaceted computational approach in the search for selective tetrahydroisoquinoline D_1 dopamine antagonists.

(27) Topliss, J. G.; Edwards, R. P. In *Computer-Assisted Drug Design*; Olson, E. C., Christofferson, R. E., Eds.; ACS Symposium Series 112; American Chemical Society: Washington, DC, 1979; pp 131–145.

(28) Young, R. C.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Graham, M. J.; Mitchell, R. C.; Prain, H. D.; Roantree, M. L. *J. Med. Chem.* **1986**, *29*, 44.

Characterization of the Cl, N, O, and phenyl or benzyl centroids as the four-point pharmacophore was determined largely by the interatomic distance vs biological activity correlations and confirmed by the least-squares superposition analysis. Utilization of these data in a multifit analysis, followed by molar volume calculations, defined the limits of steric tolerance allowed by the receptor. Studies on the dipole moment orientation with respect to the four-point pharmacophore led to the development of a QSAR equation with predictive ability for tetrahydroisoquinoline D_1 dopamine antagonists. While none of these computational methods alone can completely describe or predict new potential structures, the collection of models serves as a guide for the rational design of such agents.

Experimental Section

pK_a Determination of (*S*)-(+)-*N*-Methyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((+)-2). The pK_a of both the phenol and amine were determined via UV spectroscopy (Cary 2390 UV spectrophotometer) in a single solution multicomponent MOPS buffer (0.005 M) at 25 °C over a pH range of 0.5–11.0, with 1.0 N NaOH as a titrant according to the method of Minick and Brent.[29] Determination of the analytical wavelength (λ at which the largest deviation exists among superimposed pH–wavelength curves over the pH range) was accomplished by incremental titration of the pH upward. The pH was then adjusted downward to approximately 0.5 with 1.0 N HCl, and then the absorbance at the analytical wavelength (240 nM) was monitored while the pH was gradually raised. A titration curve of pH vs absorbance was generated and a nonlinear regression analysis was performed. The inflection point(s) on the curve is (are) extrapolated to give the pK_a's.

Single-Crystal X-ray Diffraction Determination of Absolute Configuration of (+)-*N*-Methyl-6-chloro-7-hydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline ((*S*)-(+)-2). Crystal Data. $C_{16}H_{16}ClNO$, M = 273.77, orthorhombic, a = 10.864 (3) Å, b = 16.480 (6) Å, c = 7.639 (1) Å, V = 1367.7 Å^3, Z = 4, D_{calcd} = 1.329 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 24.1 cm^{-1}. Space group $P2_12_12_1$ (D_2^4) uniquely determined from the systemic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$. Sample dimensions: 0.28 × 0.38 × 0.40 mm.

Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs. One octant of intensity data to θ = 67° was recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, incident beam graphite monochromator; ω–2θ scans). From a total of 1421 independent measurements, those 1320 reflections with $I > 3.0\sigma(I)$ were retained for the structure analysis. In addition to the usual Lorentz and polarization corrections, an empirical absorption correction (T_{max}:T_{min} = 1.00:0.83) was applied to these data. Refined unit-cell parameters were derived from the diffractometer setting angles for 25 reflections (57° < θ < 67°) widely separated in reciprocal space.

The crystal structure was solved routinely by direct methods; crystallographic calculations were performed on PDP11/44 and Microvax computers by use of the Enraf-Nonius Structure Determination Package incorporating the direct methods program MULTAN11/82. Initial non-hydrogen atom positions were obtained from an E map. A difference Fourier synthesis, evaluated following several rounds of full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic temperature factor parameters, revealed significant positive regions at calculated hydrogen atom positions. Continuation of the least-squares refinement of non-hydrogen atom parameters, with the hydrogen atoms included at their calculated positions, decreased R to 0.044 (R_w = 0.077). Introduction of the imaginary contributions to the anomalous dispersion corrections into the structure-factor calculations yielded R = 0.042 (R_w = 0.072) for the S enantiomer, whereas values for the mirror image at R = 0.053 (R_w = 0.088) were significantly higher. Several further rounds of least-squares refinement of parameters for this enantiomer led to convergence at R = 0.035 (R_w = 0.053). Neutral atom scattering factors used in the structure-factor calculations, as well as their anomalous dispersion corrections, were taken from ref 30. In the least-squares iterations, $\sum w\Delta^2[w = 1/\sigma^2(|F_o|), \Delta = (|F_o| - |F_c|)]$ was minimized. A view of the solid-state conformation is presented in Figure 9.

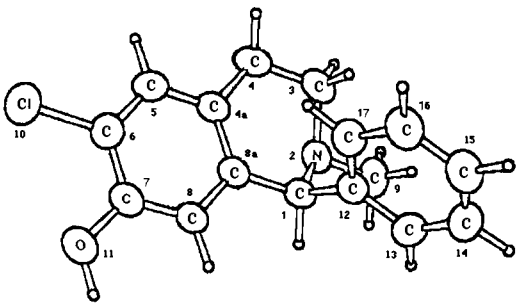

Figure 9. X-ray crystal structure of (*S*)-(+)-2.

Computer-Assisted Conformational Analysis and Molecular Modeling Methods. Molecular mechanics calculations were performed on the tetrahydroisoquinolines and benzazepines with use of MM2(85)[20] which contains both MM2 for nonconjugated systems and MMP2 for conjugated π or aromatic systems, on a MICROVAX II computer.

Input geometries were either generated by using interactive graphics programs such as MODEL version 2.91[31] or X-ray data for (*S*)-2 and compound 1[22] and then transferred to MM2(85) for quantitative studies. Initial energy minimizations were carried out on each compound with use of the dihedral driver option on all rotatable bonds in MM2(85), starting each minimization at one of the eight possible ring conformations (four half-chairs and four boats; see Figure 4). Once the low-energy conformations for each compound were determined, various interatomic distance measurements were taken and correlated with biological activity by linear regression analysis. Because compounds **4–6** were racemates, the K_i values for the S enantiomers were estimated as one-half of the racemate value. These data were then transformed into potencies (–log K_i in M) for purposes of the regression analysis.[32]

Once the study compounds had been conformationally characterized, the MM2(85) predicted geometries were loaded into the SYBYL program (version 5.05)[27] via software developed in our laboratories. Least-squares fitting of atoms used in the distance comparisons (i.e. Cl, O, N, center of either the phenyl or benzyl substituents) were carried out for each molecule with compound 1 as the reference molecule. Other combinations of fitted atoms, including ammonium hydrogens, center of isoquinoline phenyl rings, normals to the planes of the isoquinoline aromatic rings and 1-phenyl rings, were also tried, but with poor result. The root mean square distances of the proposed pharmacophoric atoms were then compared with biological activity. Next, SYBYL multifit analysis was performed on (*R*)-1 and the *S* enantiomers of compounds **2–7**, keeping the chlorines, oxygens, nitrogens, and 1-phenyl centroid's "linked" by a 20 mdynes/Å spring force constant for each atomic set. The results of the multifit analysis were attained, with each molecule having a geometry that insured conformational similarity of the pharmacophoric atoms. Volume calculations were then performed on these data by employing the Mvolume subroutine within SYBYL and defining (*S*)-2 and (*R*)-1 as the "active" compounds and the *S* enantiomers of **3–7** as the "inactive" compounds. Active pharmacophore space accommodated by the receptor was determined by application of the Mvolume addition algorithm to (*S*)-2 and (*R*)-1. Inactive substituent space was determined by the additive volumes of **3–7** minus the additive volumes of (*S*)-2 and (*R*)-1, since the inactive

(29) Minick, D.; Brent, D. *Automation of Pharmaceutical Operations*, Suppl.; Fraade, D. J., Ed.; Aster Publishing Co.: Springfield, OR, 1985; pp 31–36.

(30) *International Tables for X-Ray Crystallography*, The Kynoch Press, Birmingham, England: 1974; Vol. IV.

(31) Still, C.; Steliou, K.; et al. MODEL, version 2.91, K., Quebec, Canada.

(32) All statistical analyses were carried out with the StatView 512+ software package, Brain Power Inc., Calabasas, CA, 1986.

compounds also contain some of the structural features common to the active compounds.[33]

Determination of Dipole Orientation and Development of a Quantitative Structure-Activity Relationship. The energy-optimized final atomic coordinates from the molecular mechanics calculations were translated to the new center of mass and transferred into SYBYL. The calculated dipole moment vector from MM2(85) was added to the SYBYL graphics display for each molecule. This vector was extended to the plane of the proposed pharmacophore defined by the Cl, O, N, and 1-phenyl or 1-benzyl centroids. A normal was constructed to that plane through the center of mass. The angle, θ, between the dipole vector and the normal to the plane of the proposed pharmacophore (Figure 7) was measured for each molecule and its cosine was evaluated. The value of cos θ for (*R*)-1 was given a negative sign to account for the opposite stereochemistry from the *S* isomers of the tetrahydroisoquinoline test compounds. The cos θ values were evaluated in a second-order polynomial regression analysis with the D_1 binding potency of the test compounds. Biological activity was expressed as the $-\log K_i$ (with the K_i values of **4-6** halved as previously described) for purposes of the regression analysis.

(33) Marshall, G. R. In Macromolecular Structure and Specificity: Computer-Assisted Modeling and Applications. *Ann. N.Y. Acad. Sci.* **1985**, *439*, 162.

Acknowledgment. This work was supported by PHS Grants MH40537, ES01104, Center Grants HD03110 and MH33127, and a Burroughs Wellcome Fund Toxicology Scholar Award to R.B.M. We thank Tripos Associates, Evans & Sutherland, and Silicon Graphics for their support.

Supplementary Material Available: Tables of X-ray parameters for (+)-**2** (13 pages); observed and calculated structure amplitudes (10 pages). Ordering information is given on any current masthead page.

Synthesis and Anthelmintic Activity of a Series of Pyrazino[2,1-*a*][2]benzazepine Derivatives

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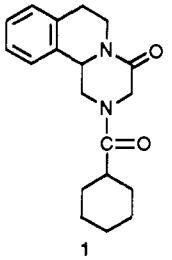
Received October 27, 1988

A series of 1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine derivatives was prepared and the cestocidal activity of the compounds evaluated in an in vitro *Taenia crassiceps* screen. Many of these derivatives proved to be highly active, and 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine, epsiprantel (BAN) (**22**), was selected for further development. The structure-activity relationships are discussed.

The discovery of the anthelmintic activity of various pyrazinoisoquinoline derivatives culminated in the development[1] of 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline (praziquantel, 1) as a potent cestocide. Many related heterocyclic systems were subsequently examined, but all were devoid of substantial anthelmintic activity.[2]

During our investigation of related heterocyclic systems we discovered the high cestocidal potency of derivatives of the pyrazino[2,1-*a*][2]benzazepine system (**2**). Here, we report on the synthesis and structure-activity relationships of these derivatives.



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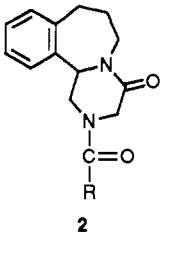
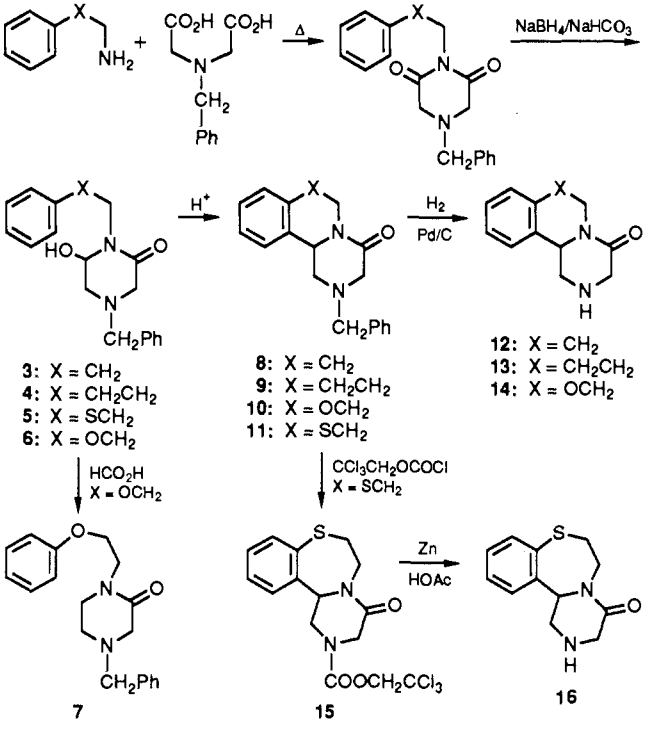


2

Chemistry

During our investigation of the pyrazino[2,1-*a*]isoquinoline ring system we developed a synthesis (Scheme I) of the nucleus based on the methodology of Speckamp[3] which utilizes the cyclization of an α-hydroxy lactam (**3**). Several other groups[4-6] have subsequently published related syntheses.

Scheme I



This synthesis was readily extended to give the ring-expanded analogues **2**, utilizing either polyphosphoric acid

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[‡] Beecham Pharmaceuticals Research Division, Great Burgh.
[§] Beecham Pharmaceuticals Research Division, Brockham Park.

(1) Seubert, J.; Pohlke, R.; Loebich, F. *Experientia* **1977**, *33*, 1036.
(2) Andrews, P.; Thomas, H.; Pohlke, R.; Seubert, J. *Med. Res. Rev.* **1983**, *3*, 147.

0022-2623/89/1832-2058$01.50/0