

Conformationally Constrained Congeners of 6-Aryl-5-methyl-4,5-dihydro-3(2H)-pyridazinones Active on the Cardiovascular System: Conformational Studies by Molecular Mechanics Calculations and ¹H NMR Spectroscopy

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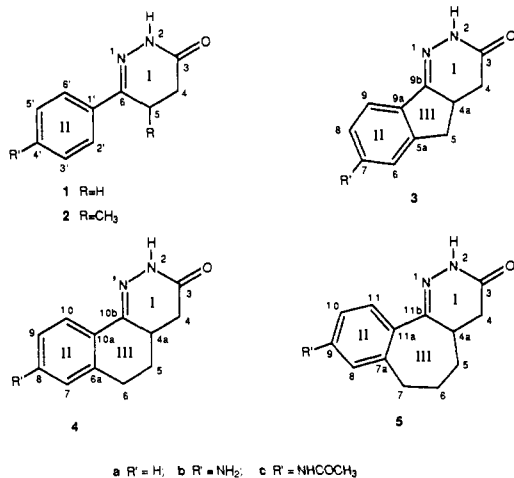
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Unsubstituted phenylpyridazinones **1a** and **2a** and their tricyclic analogues indenopyridazinone **3a**, benzocinnolinone **4a**, and benzocycloheptapyridazinone **5a** were submitted to conformational analysis with Allinger's MM2(85) program in order to better define the relationship between the cardiovascular properties of some derivatives and their preferred conformations. Structures 1-4, giving rise to highly active compounds, were found to exist in a conformation showing a near-planar arrangement of the phenyl and the pyridazinone ring. On the contrary, **5**, whose derivatives were inactive, shows two significantly populated conformations both markedly deviated from planarity. ¹H NMR analysis of the tricyclic systems 3-5 was in full agreement with the molecular mechanics calculations.

Pyridazinone cardiotonics with inotropic and vasodilator activities (e.g. **1** or **2** in which R' = imidazolyl, amino, acetylamino) are thought to elicit their positive inotropic response by selectively inhibiting the hydrolysis of adenosine 3',5'-cyclic monophosphate (cAMP) to adenosine monophosphate effected by cAMP phosphodiesterase III (cAMP PDE III).¹

Several models have been proposed² for the cAMP PDE III receptor in order to rationalize the inhibiting properties of a wide range of compounds with different chemical structures. As the modeling of a receptor active site may be based on the overall features of its substrates and/or inhibitors, the knowledge of the conformational properties of these substances is of utmost importance.

We have³ synthesized and tested for their antihypertensive, antithrombotic, and cardiotoxic activity (Table I) some conformationally restricted analogues of **1** and **2** (**3-5**, R' = amino, acetylamino) in which the incorporation of a penta-, hexa-, or heptacarbon ring (III) strongly reduces the relative mobility of rings I and II. The size of ring III plays a major role in determining the conformational properties of these tricyclic molecules, but its influence is, in principle, not easily predictable.



We now report conformational analysis of compounds **3-5** carried out through molecular mechanics calculations

Table I. Pharmacological Activities of Compounds **3-5**^a

compd	antihypertensive activity: ^b ED ₅₀ , mg/kg po	antithrombotic activity: ^c in the mouse, po	Inotropic activity ^d
3b	11.0 (6.52-14.62)	87	5.05 ± 0.06
3c	7.10 (3.50-12.82)	100	5.95 ± 0.02
4b	3.50 (2.50-6.40)	73	4.93 ± 0.05
4c	3.10 (1.67-5.40)	100	5.54 ± 0.04
5b	inactive	45	inactive
5c	inactive	46	inactive

^a Reference **3a, b**. ^b Dose that lowered the blood pressure by 50 mmHg in conscious, spontaneously hypertensive rats (SHR) (peak effect). In parentheses are confidence limits for $P = 0.05$. ^c Protection vs control percent; dose equimolar to 20 mg/kg ASA (1.1×10^{-4} mol/kg). ^d Evaluated in vitro on guinea pig spontaneously beating atria. Expressed as mean pD₂ after cumulative administration starting from 2×10^{-8} M, according to J. M. van Rossum (Van Rossum, J. M. *Arch. Int. Pharmacodyn.* 1963, 143, 299).

and ¹H NMR spectroscopy, which allowed a better determination of the preferred conformations for all of the compounds under our investigation.

Results and Discussion

Though all the pyridazinone cAMP PDE III inhibitors have an electron-rich system such as an imidazolyl or amino or acetylamino group on ring II, our studies were performed on the unsubstituted systems since it is likely that the phenyl substituent has only a minor influence on the relative arrangement of rings I and II.

Calculations were carried out with the MM2(85)⁴ program both for the open compounds **1a** and **2a** and for their analogues **3a**, **4a**, and **5a**. Table II reports the geometric features of the conformations which contribute at least 0.1% to the overall population for each compound.

- (1) (a) Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Wyss, V.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *J. Med. Chem.* 1986, 29, 1832. (b) Erhardt, P. W. *J. Med. Chem.* 1987, 30, 231.
- (2) (a) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. *J. Med. Chem.* 1984, 27, 1101. (b) Moos, W. H.; Humblet, C. C.; Sircar, I.; Rithner, C.; Weishaar, R. E.; Bristol, J. A.; McPhail, A. T. *J. Med. Chem.* 1987, 30, 1963. (c) Erhardt, P. W.; Hagedorn, A. A., III; Sabio, M. *Mol. Pharmacol.* 1988, 33, 1. (d) Davis, A.; Warrington, B. H.; Vinter, J. G. *J. Comput.-Aided Mol. Des.* 1987, 1, 97.
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- (4) Tai, J. C.; Allinger, N. L. *J. Am. Chem. Soc.* 1988, 110, 2050.

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Table II. Selected Geometrical Parameters, Relative Energies (kcal/mol), and Equilibrium Percentages (30 °C) for Conformations of Compounds **1a**, **2a**, **3a**, **4a**, and **5a**

conformn	ϕ_1^a	ϕ_2^b	ω^c	E_{rel}	equil percent
1A	+13	+16	30	0.0	100.0
1B ^d	17 ^e	+13			
1C ^d	23 ^e	+7			
1D ^f	+3 ^g	+10			
2A ^h	+9	+16	26	0.0	98.7
2B ⁱ	-36	-14	51	2.6	1.3
2C ^j	10 ^e	+19			
3A	-9	+15	9	0.0	100.0
4A	+4	+16	21	0.0	99.9
4B	-23	+17	11	4.1	0.1
5A	+31	+19	50	0.0	81.8
5B	-31	-16	47	1.0	15.8
5C	-48	+15	31	2.5	1.3
5D	-59	-16	75	2.6	1.1

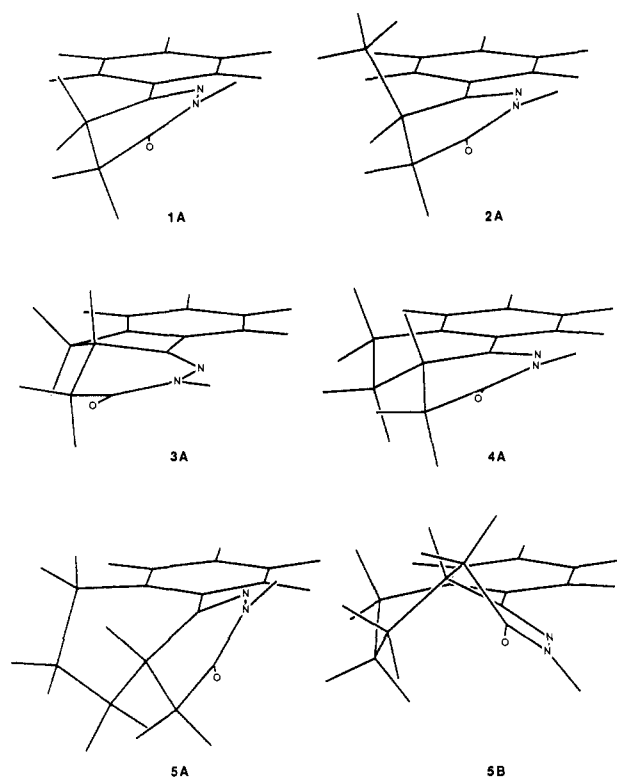
^aC=C—C=N torsional angle. ^bC=N—NH—CO torsional angle. ^cAngle between the pyridazinone amido group and the aromatic ring. ^dValues for two crystallographically independent cations in crystals of **1** (R' = imidazolyl) maleate monohydrate.^{2b} ^eAngle between the least-square planes of rings I and II. ^fValues from X-ray data of 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-2H-indol-2-one.⁶ ^gC5—C6—C1'—C2' torsional angle. ^hAxial methyl group (N1—C6—C5—CH₃ = +90°). ⁱEquatorial methyl group (N1—C6—C5—CH₃ = +146°). ^jValues from X-ray data of **2** (R' = imidazolyl) maleate;^{2b} axial methyl group.

Moreover, from the calculated geometries of compounds **3a**, **4a**, and **5a** the ¹H NMR coupling constants for the vicinal hydrogen atoms of rings I and III were obtained through a suitable Karplus equation.⁵ The calculated constants reported in Table III are the weighted averages of the constants obtained for each conformation; the experimental coupling constants reported in the same table were obtained from the 500-MHz spectra of the same compounds.

To explain the cAMP PDE III inhibitory potency of arylpyridazinones, Bristol et al.^{2a,b} proposed a model having the pyridazinone (ring I) and the aryl group (ring II) essentially coplanar, while, according to the Erhardt et al.^{2c} model, the plane of the amido function of ring I deviates about 20° from the plane of ring II. Actually, owing to the puckering of ring I, the two models stress a different aspect of the same conformation.

A complete description of the overall topography of such molecules should, therefore, involve both torsional angles C=C—C=N (ϕ_1) and C=N—NH—CO (ϕ_2) which, respectively, indicate the degree of deflection from planarity at the junction between rings I and II and the mode of puckering of ring I. The algebraic sum of ϕ_1 and ϕ_2 is very close to the angle between the plane of the pyridazinone amido group and the aromatic ring, which is named ω in the following discussion.

In order to check the reliability of the molecular mechanics calculations, we compared the conformational preferences of the pyridazinones **1** and **2** to crystallographic X-ray data that have been reported^{2b,6} for some closely related compounds. As shown in Table II, the calculated conformations resemble the X-ray data in the puckering of ring I and in the relative orientation of the two rings. While **1** presents only one energy minimum (**1A**), con-

Chart I

formational analysis of **2** is more complex owing to the presence of a 5-methyl group, which may be axially or equatorially oriented. The axial orientation (**2A**), also confirmed by the X-ray data, was found to be largely preferred over the equatorial conformation (**2B**).

Analysis of compounds **3–5**, in which the free rotation of rings I and II is restricted, was then undertaken.

In indenopyridazinone **3**, only one minimum (**3A**) with $\omega = 9^\circ$ was revealed. This value derives from two opposite deviations from planarity ($\phi = -9^\circ$, $\phi_2 = +15^\circ$), and it is lower than the value of 15° supposed by Erhardt et al.^{2c} The preferred conformations of **3** and **2** evidenced a very similar puckering in the ring I with identical ϕ_2 , but also evidenced an opposite sign for ϕ_1 .

Benzocinnilone **4** also showed only one conformation significantly populated (**4A**), though a higher energy conformation does exist (**4B**). Ring I is puckered in the usual way ($\phi_2 = +16^\circ$), while the ϕ_1 angle is very close to 0° , thus indicating that the 21° angle ω mainly derives from the puckering of ring I rather than from a deviation from planarity in the overall topography.

Finally, the greater flexibility of **5** was confirmed by the existence of two conformations **5A** and **5B**, both giving a significant contribution to the overall population. Puckering of ring I resulted in a torsional angle ϕ_2 of $+19^\circ$ in **5A** and -16° in **5B**; the values of ϕ_1 ($+31^\circ$ and -31° , respectively) and of ω angles (50° and 47°) indicate a marked deviation from planarity for both conformations.

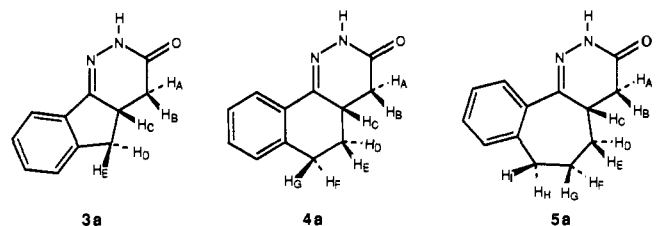
The significant conformations for each compound are depicted in Chart I.

The conformational features just outlined were experimentally confirmed by the ¹H NMR data (Table III); in particular by the vicinal coupling constants for each pair of adjacent hydrogen atoms in rings I and III.

In ring I the two vicinal coupling constants $J_{A,C}$ and $J_{B,C}$ confirmed the mode of puckering of the ring. An unexpectedly high coupling constant of about 16 Hz was found in **3** and **4** for the trans pseudodaxial hydrogen atoms H_A and H_C, which strongly contrasts with the value of about

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Table III. ¹H NMR Data of Compounds 3a, 4a, and 5a (CDCl₃, 500 MHz)


Chemical Shifts, δ										
	H _A	H _B	H _C	H _D	H _E	H _F	H _G	H _H	H _I	NH
3a	2.35	2.75	3.17	3.43	2.92					8.58
4a	2.27	2.68	2.82	1.64	2.19	2.89	2.84			8.69
5a	2.31	2.57	2.92	1.64	1.70	1.80	1.90	2.77	2.83	8.66

Coupling Constants, Hz																
	J _{A,B}	J _{A,C}	J _{B,C}	J _{C,D}	J _{C,E}	J _{D,E}	J _{D,F}	J _{D,G}	J _{E,F}	J _{E,G}	J _{F,G}	J _{F,H}	J _{F,I}	J _{G,H}	J _{G,I}	J _{H,I}
3a ^a	-16.5	16.0	6.0	8.5	7.5	-16.5										
3a ^b		12.3	4.0	9.5	8.6											
4a ^a	-16.5	16.0	6.0	12.5	4.5	-12.5	4.0	13.0	3.5	4.0	-16.0					
4a ^b		12.3	4.2	12.3	3.3		3.4	13.3	2.9	3.4						
5a ^a	-16.5	12.0	6.0	11.0	3.0	-14.0	6.5	9.0	4.0	6.5	-14.0	5.0	11.5	4.5	5.0	-15.0
5a ^b		10.5	4.1	11.4	1.8		6.8	9.4	2.7	7.0		4.1	12.3	3.1	4.3	

^a Experimental values. ^b Calculated values.

12 Hz obtained by the application of the Karplus equation on the calculated conformations 3A and 4A. Conversely, in compound 5 the experimental value of $J_{A,C}$ (12 Hz) is closer to the calculated one (10 Hz). It seems reasonable that the abnormally high $J_{A,C}$ values in 3 and 4 are indicative of a rigid conformation, while lower $J_{A,C}$ values, as in 5, reflect an equilibrium between two (or more) conformations.

In addition, the experimental and calculated coupling constant values for the vicinal hydrogens of the alicyclic ring in 3–5 are very close, thus inferring that the conformations predicted by the calculations are a realistic picture of the conformations in solution.

Interesting to note, the most active systems of the arylpyridazinone series (2)^{2a,b} and of their tricyclic congeners (4)³ have a preferred conformation with quite similar torsional angles (for 2, $\phi_1 = +9^\circ$, $\phi_2 = +16^\circ$; for 4, $\phi_1 = +4^\circ$, $\phi_2 = +16^\circ$). In this regard, it seems worthy to note that derivatives of system 3, having $\phi_1 = -9^\circ$ and $\phi_2 = +15^\circ$, were slightly less active and that a loss of activity was observed in derivatives of system 5, which mainly exist as two conformers with $\phi_1 = +31^\circ$, $\phi_2 = +19^\circ$ and, respectively, with $\phi_1 = -31^\circ$, $\phi_2 = -16^\circ$.

Overall, these structure–activity relationships lead to the conclusion that optimal activity is obtained when rings I and II are almost coplanar (ϕ_1 is $+9^\circ$ for 2 and $+4^\circ$ for 4); moreover, these results are in strong support of the Erhardt model, which requires for optimal activity an ω angle of about 20° (for 2 it is 26° and for 4 is 20°).

Among the structural features of 4,5-dihydropyridazinones, Bristol et al.^{2a,b} had also indicated that a 5-methyl group axially oriented (as in 2) is able to fit into a small lipophilic pocket on the PDE III receptor surface. To support this point, it was noticed that dehydrogenation of the dihydropyridazinone ring, converting the C-5 atom from sp^3 to sp^2 , changes the orientation of the methyl group and causes a considerable reduction of activity, because of the missed hydrophobic interaction.⁷ Actually, it should be stressed that in this case the methyl group also

induces a marked deviation from coplanarity of pyridazinone and phenyl rings,⁸ which could significantly account for the loss in potency observed for arylpyridazinones. On the other hand, tricyclic congeners 3 and 4 gave highly active derivatives in spite of the pseudoequatorial orientation of the $-CH_2-$ or the $-CH_2CH_2-$ chain at C4a, which make improbable any efficient fitting into the hypothetical pocket. In addition, dehydrogenation of the dihydropyridazinone moiety of 4 left the activity almost unchanged,^{3b} contrary to the aromatization of 2.

In conclusion, the conformational studies of 1–5, when compared with the pharmacological properties of their derivatives, suggest that an almost planar topology is an essential requirement for activity of aryl-dihydropyridazinones, as well as of their tricyclic congeners, i.e., in agreement to the Bristol model,^{2a,b} ϕ_1 should be about 5 – 10° and, in agreement to the Erhardt model,^{2c} ω should be about 20° . The importance of the small alkyl substituent on the pyridazinone moiety seems confined to the former class of derivatives.

Experimental Section

6-Phenyl- and 5-methyl-6-phenyl-4,5-dihydro-3(2H)-pyridazinones (1a and 2a, respectively),⁹ 2,4,4a,5-tetrahydro-3H-indeno[1,2-c]pyridazin-3-one (3a),¹⁰ 4,4a,5,6-tetrahydrobenzo[h]cinnolin-3(2H)-one (4a),¹¹ and 2,4,4a,5,6,7-hexahydro-3H-benzo[6,7]cyclohepta[1,2-c]pyridazin-3-one (5a)¹¹ are known in the literature.

¹H NMR spectra were recorded on a Bruker AM-500 spectrometer at 30°C in CDCl₃ solution. Chemical shifts and coupling

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(8) The dihedral angle between the planes formed by the two rings is approximately 50° in 6-aryl-5-methylpyridazinones. This value is supported by X-ray and NMR studies on the structurally related milrinone (1,6-dihydro-2-methyl-6-oxo-3,4'-bipyridine-5-carbonitrile). See: Robertson, D. W.; Beedle, E. E.; Swartzendruber, J. K.; Jones, N. D.; Elzey, T. K.; Kauffman, R. F.; Wilson, H.; Hayes, J. S. *J. Med. Chem.* 1986, 29, 635.
 (9) (a) Aubagnac, J. L.; Bourgeon, D.; Jacquier, R. *Bull. Soc. Chim. Fr.* 1975, 309. (b) Dixon, S.; Gregory, H.; Wiggins, L. *J. Chem. Soc.* 1949, 2139.
 (10) Cignarella, G.; Grella, G.; Loriga, M.; Curzu, M. M.; Schiatti, G. *Farmaco, Ed. Sci.* 1978, 33, 866. The name used for 3a in this reference and in ref 3 was 4,4a-dihydro-5H-indeno[1,2-c]pyridazin-3-one.
 (11) Holava, H. M.; Partyka, R. A. *J. Med. Chem.* 1971, 14, 262.

Table IV. Force Field Parameters^a

Natural Bond Length, Stretching Force Constant, and Bond Moment			
bond	l_0 , Å	K_s , mdyn/Å	moment, D
N:-N	1.33	5.6	0.0
Natural Bond Angles and Bonding Constants			
angle	θ_0 , deg	k_θ , mdyn Å/rad ²	
C-N:-N	115.0	0.43	
N-N:-LP	122.5	0.50	
C'-N-N:	120.0	0.43	
H-N-N:	113.0	0.36	
out of plane bending			
N:-N		0.05	
N-N:		0.05	
Torsional Constants, kcal/mol			
angle	V_1	V_2	V_3
A-N:-N-B	0.0	1.825	0.0
N:-N-C'=O	0.0	5.0	0.0
N:-N-C'-C''	0.0	5.0	0.0
N-N:-C-D	0.0	10.0	0.0
C''-C''-C-N:	-0.044	0.24	0.06

^aC (C_{sp2} , alkene, imine); C' (C_{sp2} , carbonyl); C'' (C_{sp3}); LP (lone pair); N: (imine), N (amide); A (C, LP); B (H, C'); D (C, C'').

constant values of compound **3a** have been evaluated with a first-order approach. Some signals in the spectra of **4a** and **5a** were partially overlapped; a spin system simulation using the PANIC program of Brüker allowed the determination of the spectral parameters and a straightforward assignment of all the signals.

Molecular mechanics calculations were performed with the MM2(85)-PC program⁴ obtained from QCPE. The parameter set was updated with the parameter list MM2(1987)-VAX kindly furnished by Prof. Allinger. Moreover, in the KOMEGA.FOR subroutine, three lines above line 135, the instruction IPOMG(NTPI) = IOMG(NTPI) was modified to IPOMG(NTPI) = IOMG(I). This correction was necessary in order to properly calculate molecules containing both an unsaturated and a saturated moiety; without the modification the V_2 torsional parameter for the bonds in the conjugated moiety are not correctly reduced as a function of the bond order. The program was then extensively tested, particularly on the molecules whose calculations are re-

ported in ref 4, and gave satisfactory results.

A value of 4.7 for the dielectric constant was used during the calculations. The six phenyl carbon atoms and C and N imine atoms were considered π atoms. The parameters not included in the parameter list were chosen by analogy with similar atomic arrangements and are reported in Table IV. The natural bond length of the N1-N2 bond as well as the V_2 torsional parameters involving the same bond were chosen on the basis of MNDO calculations^{12,13} performed by us on the model compound C-H₂=NNHCHO. In order to test the influence of the values of these parameters on the calculations, they were varied over a reasonable range; these variations do not significantly affect the results.

The conformational space relative to the rotation of the phenyl ring of compounds **1a** and **2a** with respect to the dihydropyridazinone ring was explored by using the MM2 dihedral driver (NDRIVE = -1, 5° incremental changes). By examination of molecular models the candidate starting geometries of compounds **3a**, **4a**, and **5a** were identified and the energy was minimized. Moreover, extensive application of the dihedral driver (NDRIVE = 1, 5° incremental changes) to the bonds in rings II and III allowed the full exploration of their conformational space. Several local minima were found for compounds **4a** (three minima) and **5a** (eight minima) and the most significant are reported in Table II.

Vicinal ¹H NMR coupling constants were calculated with the Haasnoot et al.⁵ modification of the Karplus equation utilizing the 3JHPC program.¹⁴

Acknowledgment. We thank Dr. Pierangela Ciuffreda for the 500-MHz ¹H NMR spectra and Ministero della Pubblica Istruzione (Rome) for financial support.

Registry No. **1a**, 1011-46-7; **2a**, 110766-33-1; **3a**, 69099-74-7; **3b**, 103422-53-3; **3c**, 103422-54-4; **4a**, 25823-48-7; **4b**, 103422-66-8; **4c**, 103422-56-6; **5a**, 25742-87-4; **5b**, 103603-08-3; **5c**, 103603-09-4.

Supplementary Material Available: MM2-calculated atomic coordinates of the minimum energy conformers of compounds **1a**, **2a**, **3a**, **4a**, and **5a** (9 pages). Ordering information is given on any current masthead page.

(12) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* 1977, 99, 4899.

(13) QCPE program no. QCMP002.

(14) QCPE program no. QCMP025.

Conformation-Activity Relationship Study of 5-HT₃ Receptor Antagonists and a Definition of a Model for This Receptor Site

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A conformation-activity relationship study of 5-HT₃ receptor antagonists was used to define a pharmacophore and receptor map to qualitatively account for their activity. The design and synthesis of specific keto-amino-indole derivatives that are potent 5-HT₃ receptor antagonists gave some support to the model.

There is now substantial evidence for the existence of multiple 5-HT receptor subtypes, recently classified into three major categories designated "5-HT₁-like", 5-HT₂, and 5-HT₃.¹ The remarkable recent advances in our understanding of 5-HT neurotransmission reflect, in large part, the increasing availability of compounds with selectivity and potency for individual 5-HT receptor subtypes,² which

led to proposals of models for the corresponding recognition sites.³⁻⁵

It is perhaps in the 5-HT₃ receptor area where the most spectacular developments have occurred.⁶ In particular,

- (1) Bradley, P. B.; Engel, G.; Feniuk, W.; Fozard, J. R.; Humphrey, P. P. A.; Middlemiss, D. N.; Mylecharane, E. J.; Richardson, B. P.; Saxena, P. R. *Neuropharmacology* 1986, 25, 563.
- (2) Fozard, J. R. *Trends Pharmacol. Sci.* 1987, 8, 501.

(3) Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *J. Med. Chem.* 1988, 31, 1087.

(4) Hibert, M. F.; McDermott, I.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *Eur. J. Med. Chem.* 1989, 24, 31.

(5) Hibert, M. F. *Actual. Chim. Ther.* 1989, 16.

(6) Fozard, J. R. *5-Hydroxytryptamine: Prospective Therapeutic Applications*; Saxena, P. R., Ed.; Kluwer: Dordrecht, in press.