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PSYCHOTOMIMETIC PHENALKYLAMINES AS SEROTONIN AGONISTS: AN SAR ANALYSIS

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Summary

The structure-activity relationships of a series of psychotomimetic phenethylamine and phenylisopropylamine analogs were examined using a molecular connectivity analysis. Greater than 90% of the variance in their activity as serotonin agonists in a model system can be explained on this basis.

Our laboratories have been investigating various theoretical aspects of hallucinogenic agents in an attempt to elucidate their mechanism of action. Our investigations have not only dealt with hallucinogenic activity (1,2; Glennon, Kier and Shulgin, submitted for publication) but also with the conformation of the serotonin (5-hydroxytryptamine, 5-HT) molecule (1,3) and the ability of hallucinogenic agents to interact with 5-HT receptors of various model systems (4,5; Glennon and Kier, submitted for publication). Recently, our attention has been focussed on the hallucinogenic phenethylamines (mescaline analogs) and phenylisopropylamines (amphetamine analogs) (6,7; Glennon, Liebowitz and Mack, submitted for publication).

Using a molecular connectivity approach, a relating equation was obtained between the hallucinogenic potency and structural variation of a series of phenylisopropylamine analogs (7). Although the initial results indicated that this same relating equation might adequately describe the activity of phenethylamine analogs as well, it was later found that this might have been fortuitous because of the low activity of the analogs initially examined. Using a somewhat larger set of phenethylamines, which included more potent compounds, a second relating equation was obtained to describe their activity (Glennon, Kier and Shulgin, submitted for publication).

One of the problems inherent to such investigations is the subjective nature of the hallucinogenic response. It was felt that molecular connectivity might more accurately describe activity if there was more precision in the biological response. Perhaps a surrogate measure of activity might be employed if such activity parallels hallucinogenic potency and secondly, offers more precision.

Barfnecht, et al. (8), have reported that a very modest correlation exists between the lipophilicity, as measured by octanol-water partition coefficients, and hallucinogenic activity of a series of phenylisopropylamines. Nichols, et al. (9), have found a relationship between this physicochemical parameter and the ability of these compounds, together with phenethylamine analogs, to stimulate 5-HT receptors of sheep umbilical artery preparations. Though we have found that several hallucinogenic phenylisopropylamine analogs possess a rel-

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atively high affinity for the 5-HT receptors of a model system (unpublished data employing an isolated rat fundus preparation), Nichols, et al. (9), have recently suggested that the ability of such compounds to interact with the 5-HT receptors of isolated sheep umbilical artery, in conjunction with their lipophilicity, may be predictive of hallucinogenic potential in man. Using the method of molecular connectivity, we now wish to explore the structural aspects of the phenethylamines and phenylisopropylamines, and their relationships to the 5-HT agonist activity reported by Nichols, et al. (9).

Methods

Molecular structures can be analyzed in terms of the number of atoms, kinds of atoms, bonding types and adjacency environment by the molecular connectivity method (7,10). Molecular indices or descriptors (chi terms) have been computed for each of the compounds in this study. A multi-variable search for connectivity terms was conducted in a regression analysis using a program which considers all possibilities of variables. The number of chi terms employed in this investigation is necessarily limited by both the size of the molecule and the number of observations and is governed by statistical considerations.

Results and Discussion

A prime consideration is whether stimulation of 5-HT receptors in the sheep umbilical artery preparation is a valid model which parallels hallucinogenic potency. The logarithm of the relative biological response (log RBR) (9) was compared with the logarithm of hallucinogenic activity in mescaline units (log MU) for those compounds for which data were available. Linear regression analysis resulted in a correlation coefficient of r = .88 (n = 11). In spite of the 25% variation in MU data (11), this correlation suggests the possibilities of using the sheep umbilical artery as an easily obtainable correlate of hallucinogenic potency.

The log RBR of compounds 1-17 as 5-HT agonists in the isolated sheep umbilical artery preparation was found to relate to three connectivity indices according to the following expression:

$$\log RBR = 11.07\ {}^{3}\chi_p^v - 2.78({}^{3}\chi_p^v)^2 + 6.89\,{}^{4}\chi_p^v - 21.19$$

$$r = .95 \qquad s = .196 \qquad n = 17$$

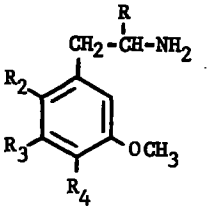
$$F = 39.6$$

where r is the regressinn coefficient, s is the standard deviation and n is the number of observations. The relating equation explains greater than 90% of the variance in activity. The compounds and the observed and calculated values for log RBR are shown in Table I.

Of the seventeen compounds for which Nichols, et al. (9), report agonist activity, variation in structure divides these compounds into several structural types. The compounds a) either posseas (phenylisopropylamine analogs) or are devoid (phenethylamine analogs) of an α-methyl group and b) possess either a 2-methoxy or a 3-methoxy substituent. The major structural alteration is at the 4-position, which includes bromo alkoxy, methylthio and alkyl derivatives and one example of a nitro derivative. It has been demonstrated that the 3,4,5-trisubstituted compounds are about as active as 2,4,5-trisubstituted compounds of comparable log P in this model system (9). For this reason, and because the major structural variation is at the 4-position, it might be expected that molecular connectivity indices will focus on these 4-position substi-

TABLE 1.

Serotonin Receptor Agonist Activity



					Log RBR		
	R_2	R_3	R_4	R	Obs.[a]	Calc.	Δ
1	H	OCH_3	OCH_3	H	0.00	-0.06	.06
2	H	OCH_3	OC_2H_5	H	0.31	0.40	.09
3	H	OCH_3	OC_3H_7	H	0.56	0.48	.07
4	H	OCH_3	O-i-C_3H_7	H	0.45	0.74	.29
5	H	OCH_3	Br	H	0.88	0.78	.10
6	OCH_3	H	SCH_3	H	0.83	0.97	.14
7	OCH_3	H	SCH_3	CH_3	1.31	1.15	.16
8	OCH_3	H	NO_2	CH_3	0.67	0.64	.03
9	OCH_3	H	Br	CH_3	1.57	1.64	.07
10	OCH_3	H	CH_3	CH_3	1.00	0.78	.22
11	OCH_3	H	C_2H_5	CH_3	1.59	1.31	.28
12	OCH_3	H	nC_3H_7	CH_3	1.84	2.06	.22
13	OCH_3	H	nC_4H_9	CH_3	1.62	1.30	.32
14	OCH_3	H	nC_5H_{11}	CH_3	.88	1.02	.14
15	OCH_3	H	tC_4H_9	CH_3	1.39	1.44	.05
16	H	OCH_3	O-n-C_4H_9	H	0.10	0.30	.20
17	H	OCH_3	$OCH_2C_6H_5$	H	0.48	0.51	.03

[a] Data from Nichols, et al. (9).

tuents.

Although each molecular connectivity index is interrelated with each other it is possible, however, to consider each term of the equation and to discuss the major structural feature which it is describing. Both $^3X_p^v$ and $^4X^v$ can be related to the α-methyl group and suggest an enhanced activity when this group is present. The $^3X_p^v$ index also increases by one subgraph as the length of the substituent in the 4-position increases. Because, in the second term, this index is negative and squared, increasing the length of the chain will result in a rapidly diminishing effect on activity. Thus, this second term $(^3X_p^v)^2$ governs a maximum potency value with an intermediate length side chain. This appears with 3 in the phenethylamine series with 12 in the phenylisopropylamine series. The great size of the benzyloxy side chain of compound 17 contributes adversely to activity.

The emergence of valence chi terms in the equation indicates that the nature of atoms is of more than passing importance. That means that heteroatoms are playing a role more than just space filling comparable to carbon isosteres. The valence chi terms indicate that ring substituents with heteroatoms are going to differ in potency from alkyl substituents of the same length. The magnitude of the difference depends on the overall size of the substituent and whether its length is less than or exceeds the maximum value governed by the two $^3X_p^v$ indices.

We have previously detailed the structure-activity relationship (SAR) of the phenylisopropylamines in relation to hallucinogenic potency and have developed a relating equation which explains 85% of the variance in activity (7). In this study we have shown, as suggested by Nichols, et al. (9), that the 5-HT agonist activity of phenethylamines and phenylisopropylamines in the sheep umbilical artery preparation relates to their hallucinogenic potency and is thus a valid model for the investigation. An investigation of the SAR of these data should afford further insight as to the importance of various structural features which effect 5-HT agonists activity. The initial study included a total of twenty-three phenylisopropylamine analogs which varied in ring substituents at all positions (7). This present study examines a series of phenethylamines, as well as phenylisopropylamines, where the major structural variation influencing activity occurs at the 4-position. The relating equation generated includes data on both types of compounds and explains greater than 90% of the variance in 5-HT agonist activity.

Nichols, et al. (9) have demonstrated a possible hydrophobic region of the receptor which corresponds to the 4-position of the substituted phenyl nucleus. They have discussed the importance of lipophilicity and have found that this parameter correlates with activity if an indicator parameter, necessary to limit the steric length of the 4-position substituent, is additionally introduced into the equation. It would appear that this model might be very useful in predicting hallucinogenic potency, and that the hydrophobic region of the receptor will need to be considered. Molecular connectivity can be used to describe the structure of molecules in an SAR study of these compounds and so might also prove to be a useful tool in predicting agonistic activity.

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