Molecular Connectivity Analysis of Hallucinogenic Mescaline Analogs

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Abstract □ The hallucinogenic (psychotomimetic) potency of 10 mescaline analogs was examined by molecular connectivity analysis. Potencies could be described by a two-term relating equation, which explained 94% of the variance in activity, on the basis of structural variation. 2,5-Dimethoxy substitution as well as the nature of the 4-position substituent played an important role in determining hallucinogenic potency. With the relating equation, reasonable potency predictions were made for six compounds not included in the initial investigation.

Keyphrases □ Mescaline analogs—hallucinogenic activity, structure—activity relationships, molecular connectivity analysis □ Hallucinogenic agents—mescaline, analogs, hallucinogenic activity, structure-activity relationships, molecular connectivity analysis □ Structure-activity relationships—mescaline analogs, molecular connectivity analysis

Molecular connectivity analysis was used recently in studies of the structure–activity relationships of hallucinogenic phenylisopropylamine (amphetamine) analogs (1). Hallucinogenic activity could be related to three structural descriptors (χ terms) by an equation that accounted for greater than 80% of the variance in hallucinogenic potency. The relating equation, generated from the amphetamine data, was used to predict the hallucinogenic potency of six phenethylamine derivatives (mescaline analogs) (1).

One χ term in the original equation encodes the presence of the α-methyl group of the amphetamine side chain. Being devoid of this α-methyl group, the phenethylamines were predicted correctly to be of lower hallucinogenic potency (1). The correct prediction of the six phenethylamine derivative activities may have been fortuitous since only one of these six compounds was experimentally more active than mescaline in humans.

Recently, data became available on additional phenethylamines with potency six to 35 times that of mescaline. In light of these findings and of the newly available active compounds, it was of interest to reexamine the phenethylamines as a separate hallucinogenic class.

EXPERIMENTAL

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 (2). The method used in this investigation was described previously (2) and has given good results in correlating biological activity with the structures of, for example, hallucinogenic amphetamine derivatives (1) and lysergide analogs (3). Molecular connectivity indexes or descriptors (χ terms) have been computed for each compound in this study. A multivariable search of connectivity terms was conducted in a regression analysis using a program that considers all variable combinations. The number of terms employed was limited necessarily by the molecular size and the number of observations and was governed by statistical considerations.

Psychotomimetic or hallucinogenic activity measurement is necessarily only semiquantitative. Hallucinogenic agent potencies are measured relative to a total dose of 350 mg of mescaline. For example, the dose of V required to produce an effect similar to that of 350 mg of mescaline is 40–60 mg (4); thus, for an average 50-mg dose, V is calculated to have a potency seven times that of mescaline, or 7 mescaline units. The variance in mescaline-unit data has been estimated as ~25% (5). Therefore, although V might possess an activity of ~5–9 mescaline units, a value of 7 mescaline units was used to perform the regression analysis.

Compounds I and IX are reported to possess an activity of "less than" 1 and 5 mescaline units, respectively (5). Again, to perform the regression, certain assumptions must be made. Thus, activities midway between inactivity and the reported activity (*i.e.*, 0.5 and 2.5 mescaline units, respectively) were assumed for these compounds. Although II has an activity of less than 1 mescaline unit, one study (6) reported an activity of 0.2 mescaline unit, and this latter value was used in the regression analysis.

RESULTS AND DISCUSSION

The relative hallucinogenic potencies of the 10 phenethylamine derivatives can be described by:

$$\text{mescaline units} = 129\ {}^{3}\chi_c^{v} - 4.45\ {}^{4}\chi_p - 14.54 \qquad \text{(Eq. 1)}$$

$$n = 10 \quad s = 3.02 \quad r = 0.97$$

Although the correlation is significant and explains 94% of the variation in hallucinogenic activity, the variation in biological activity measurement should be called to attention again.

The two molecular connectivity indexes important in the equation are weighted counts of structural fragments. The ${}^{3}\chi_c^{v}$ index describes a structural feature of three bonds converging at one atom (cluster). The v denotes the index valence form; that is, the atom δ assignments are based on the atomic valence rather than on the simple degree of adjacency. The ${}^{4}\chi_p$ index describes a structural feature of four contiguous bonds in which the atom δ values are based on the degree of adjacency. Several detailed descriptions of the molecular connectivity method and the calculation of the indexes were published recently (2).

From the relating equation, several generalizations can be derived about the impact of structural variation on activity. The ${}^{3}\chi_c^{v}$ term suggests that increasing the number of nuclear substituents will generally increase potency; compare the activities of I and II with those of III and IV. This is in accord, biologically, with previous findings (7) that those phenethylamines with high methoxylation serve less well as substrates for enzymatic degradation. In addition, the presence of the ${}^{3}\chi_c^{v}$ term implies that the lower the δ^{v} in the substituent, the higher the potency; *i.e.*, Br > CH_3 > OCH_3 (compare III, VII, and VIII).

The ${}^{4}\chi_p$ term is related to the phenethylamine ring substitution pattern. Because the coefficient for this term in the relating equation is negative, the greater the value of the term, the lower is the potency of the compound. In the monosubstituted phenethylamines, an *ortho*-substituent contributes two additional terms and a *meta*-substituent contributes one additional term as compared to a *para*-substituent. Therefore, the position of the substituent would be expected to enhance activity in the order: *ortho* < *meta* < *para*.

For phenethylamines with more than one nuclear substituent, the ${}^{4}\chi_p$ term indicates that activity is enhanced when two substituents are *para* to one another (*para* > *meta* > *ortho*). Such substitution can only be realized, in disubstituted molecules for example, when the phenethylamine is 2,5-disubstituted.

These statements, which can be quantified using the χ terms, echo those structure–activity relationships that have evolved in a qualitative manner by inspection of a phenethylamine series. Shulgin (4) reported that if the *p*-methoxy group is replaced with another substituent (higher alkoxy, methyl, or halo), there is an unquestioned increase in potency. Shulgin (4) commented further that 2,4,5-orientation appears to be more effective than 3,4,5-orientation, although there are too few examples to establish this generality.

Investigations of structure–activity relationships can highlight those structural features that influence activity. However, because hallucino-

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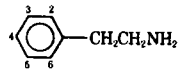
Table I—Chi Terms and Activities of Various Phenethylamine Analogs



Compound	Position 2	3	4	5	6	$^3\chi_c^v$	$^4\chi_p$	Mescaline Units Obs.	Calc.
I			OCH_3			0.186	2.34	<1	0–2.0
II		OCH_3	OCH_3			0.236	3.13	<1	0–4.9
III	OCH_3		OCH_3	OCH_3		0.279	3.77	1	1.9–7.9
IV		OCH_3	OCH_3	OCH_3		0.287	3.94	1	1.6–7.6
V		OCH_3	OCH_2CH_3	OCH_3		0.287	4.07	7	1.3–7.3
VI		OCH_3	$OCH_2CH_2CH_3$	OCH_3		0.287	4.18	6	0.9–6.9
VII	OCH_3		CH_3	OCH_3		0.364	3.47	20	14–20
VIII	OCH_3		Br	OCH_3		0.509	3.47	35	33–39
IX	OCH_3	—O—CH_2—O—				0.263	4.34	<5	0–3.7
X		OCH_3	—O—CH_2—O—			0.287	4.22	2	0.6–6.6
XI[a]		—O—CH_2—O—				0.236	3.47	~1	0–3.5
XII[a]	OCH_3	OCH_3	OCH_3			0.236	4.06	<1	0–4.3
XIII[a]	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	0.344	5.69	—[b]	1.5–7.5
XIV[a]	OCH_3		I	OCH_3		0.593	3.47	44	42–48
XV[a]	OCH_3		C_2H_5	OCH_3		0.322	3.77	18	7–13
XVI[a]		OCH_3	SCH_3	OCH_3		0.383	3.94	12	14–20

[a] Not used to derive the relating equation; activities were predicted using the equation. [b] Effective human intoxication levels have not been evaluated fully.

genic activity cannot be measured with great accuracy and because mescaline units do not reflect the route of administration, time of onset, and duration of action, one cannot expect to predict hallucinogenic potency confidently. Furthermore, the potencies used in the regression analysis span more than two orders of magnitude (from 0.2 mescaline unit for II to 35 mescaline units for VIII). In addition, several activities have been reported in uncertain terms, *i.e.*, "less than." This uncertainty is reflected by the standard deviations and results in broad ranges of predicted activity, particularly for compounds that are only weakly active. Conversely, compounds that are the most active and, subsequently, those from which the most information might be gleaned should be predicted rather well (*e.g.*, VII and VIII).

Application of the relating equation should, nevertheless, afford a relative prediction of activity. To test the relating equation, data from several compounds that have not yet been fully evaluated in humans and/or were not used in generating the relating equation were compared with their predicted potencies. Compounds XI and XII are relatively weak hallucinogenic agents with potencies similar to mescaline. Both compounds are predicted by the relating equation to possess low hallucinogenic activity.

Previous investigators (8), employing a modified Bovet-Gatti profile, found that 2,3,4,5,6-pentamethoxyphenethylamine (XIII) is behaviorally active in animal models with a potency about eight times that of mescaline. With the relating equation, XIII is predicted to have a potency of ~4.5 mescaline units. As another example, an iodinated derivative, 4-iodo-2,5-dimethoxyphenethylamine (XIV), recently was titrated in humans, but effective intoxication levels have not been explored fully. The iodo group, which is *para* to the side chain, possesses a δ^v that is even lower than that of a bromo group. In addition, this molecule possesses two methoxy groups *para* to one another (*i.e.*, 2,5-dimethoxy). On this basis, XIV is predicted by the relating equation to be ~42–48 times more active than mescaline. Shulgin[1] found that the threshold effects of XIV were clear at a total dose of 8 mg; this amount corresponds to an activity of ~44 mescaline units.

Compounds XV and XVI are an order of magnitude more potent than mescaline[1] but less active than XIV. Table I reveals that their activity was predicted reasonably well.

The indexes encode structural information about features contributing to hallucinogenic potency. When applied to several examples not included in the analysis, the relating equation gives reasonable predictions. The structural information derived from this analysis contributes to an understanding of structural influence on hallucinogenic potency.

[1] A. T. Shulgin, unpublished observations.

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