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QSAR Studies in Substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-b]indoles—A Potent Class of Neuroleptics†

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Abstract—A series of nineteen substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3, 4-b]indoles analogues of neuroleptic drug, Centbutindole have been studied using quantitative structure–activity relationship analysis. The derived models display good fits to the experimental data ($r > \text{or} = 0.75$) having good predictive power ($r_{cv} > \text{or} = 0.688$). The best model describes a high correlation between predicted and experimental activity data ($r = 0.967$). Statistical analysis of the equation populations indicates that hydrophobicity (as measured by π_R, log*P*(o/w) and Slog*P*_VSA8), dipole y and structural parameters in terms of indicator variable, (In_1) and globularity are important variables in describing the variation in the neuroleptic activity in the series.

Introduction

Dopamine antagonists have been of current interest because of their use in the treatment of neurological disorders particularly Schizophrenia that affects about 1% of the population worldwide[1] and is characterised by disturbances in the areas of the brain that are associated with thought, perception, attention, motor behavior, emotion and life functioning. The classical neuroleptic agents like Chlorpromazine, Haloperidol and Fluphenazine are effective in controlling the positive symptoms of schizophrenia [presence of altered behaviors, such as delusions, hallucination (usually auditory),[2] extreme emotions, excited motor activity, and incoherent thoughts and speech], these drugs are less efficacious in attenuating negative symptoms[3] (a lack of behaviors, such as emotions, speech, social interaction and action) and are also associated with side effects including involuntary movement disorders or extra pyramidal side effects (EPS). These negative symptoms of schizophrenia are the primary target for new drugs from an effectiveness standpoint.[4–9] A plethora of theories have arisen to explain the deficits associated with schizophrenia including specific or 'global' changes in neurotransmission involving a given neurotransmitter, cell type or receptor, and a host of changes in brain function elicited by agents as diverse as stress, developmental aberrations and viral infection. One of the most famous and debatable, Dopamine hypothesis[10] proposes that brain of schizophrenic patients produces more dopamine than the normal brains. It is this increased dopamine that is believed to be responsible for the symptoms of the disease. However, there is much more debate in the scientific community as to the exact mechanism by which altered dopamine levels, especially in prefrontal cortex, striatum and limbic system, produce schizophrenia. The major support and refutation of the dopamine hypothesis has come from the examination of the dopamine receptors in these regions of the brain.

The dopamine receptors involved in these processes are categorised into D_1 family (D_1 and D_5 receptor subtypes) and D_2 family (D_2, D_3, and D_4 receptor subtypes). The D_1 and D_2 receptors are widely expressed in many neural systems, while D_3 and D_4 are found primarily in the limbic system. D_5 is much rarer than the other four receptors.[11] Their function is to bind to dopamine

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secreted by presynaptic nerve cells that trigger the changes in the metabolic activity of the postsynaptic nerve cells. It is these alterations in the presynaptic dopamine function constituted a part of the disrupted neural circuits that predispose people to schizophrenia.[12] The D_2 receptor blockade is the main target for antipsychotic drugs because there is a higher density of D_2 in schizophrenic brains and is associated both for controlling the symptoms of schizophrenia and for producing the neurological side effects, including EPS (Parkinsonism) and tardive dyskinesia like symptoms. The serotonergic $5HT_2$ receptor has been shown to attenuate the negative symptoms of schizophrenia[13] and for reducing EPS.[14] Hence the neuroleptics with right balance of Dopamine D_2 and $5HT_2$ receptor antagonism may be important for successful treatment of schizophrenia.

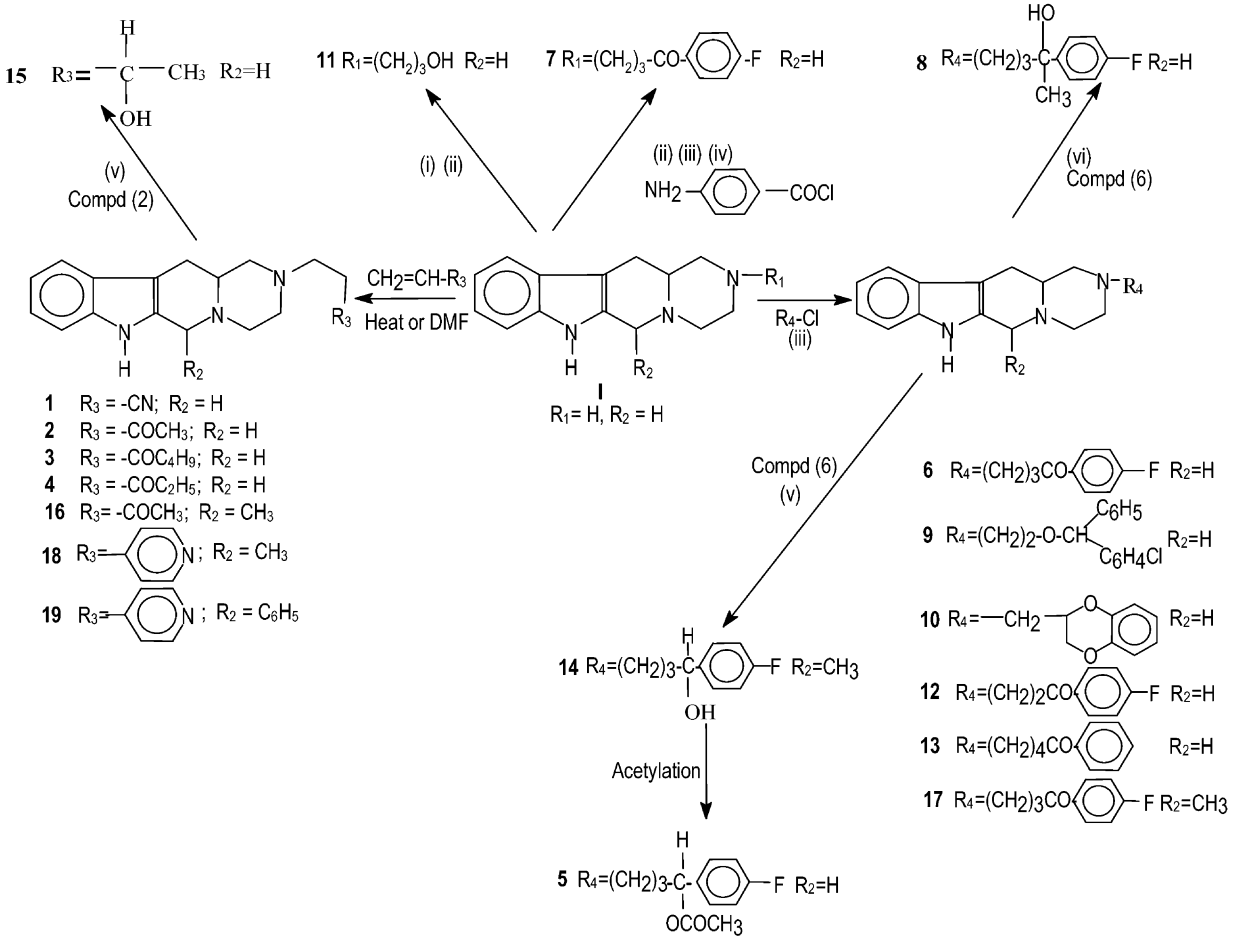
Quantitative structure–activity relationship (QSAR) is a very useful tool in contemporary drug designing. It is a scientific achievement and an economic necessity to reduce an empiricism in drug design to ensure that every drug synthesized and pharmacologically tested should be as meaningful as possible. In view of the above and in order to understand the influence of physiochemical and structural parameters for neuroleptic activity for some selected compounds of the 2-substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-b]indoles including one of the most active neuroleptic molecule, 2-γ-(p-flourobenzoyl)propyl - 1,2,3,4,6,7,12,12a - octahydropyrazino - [2′,1′:6,1]pyrido[3,4-b]indole (Biriperone, Centbutindole),[15] an approved drug for marketing, which mainly acts as Dopamine D_2 receptor and $5HT_2$ receptor blocker,[16] the 2D QSAR studies have been carried out and presented in this paper.

Chemistry

Different congeners of 2-γ-(*p*-flourobenzoyl)propyl-1,2,-3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-b]indole were synthesised from the key intermediate 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]-pyrido[3,4-b]indole ($R_1=H$, $R_2=H$)[20] and ($R_1=H$, $R_2=CH_3/C_6H_5$)[17] essentially according to our earlier reported methods (Scheme 1).

Results and Discussion

A preliminary classical 2D QSAR analysis was carried out for neuroleptic activity measured as $-\text{Log } ED_{50}$, for conditioned avoidance response (CAR) as dependent variable and lipophilicity (R_M and π_R) and Molar Refractivity (MR) as independent variables on the



Scheme 1. (i) CH_2=CH–CH_2Cl (ii) LiH_4, THF (iii) DMF 80° $NaCO_3$, NaI (iv) Cl CH_2CN (v) $NaBH_4$, MeOH (vi) CH_3 MgI.

compounds (**1** to **15**, Table 1) of neuroleptic activity. The intercorrelation among different parameters is shown in Table 2 while the results are summarised in Table 3.

The lipophilicity (π_R) and MR were found collinear ($r = 0.793$) and so were not considered together in the regression analysis. The analysis showed no linear correlation of neuroleptic activity with lipophilicity π_R ($r = 0.089$) or MR ($r = 0.032$). The parabolic model fitted better with π_R ($r = 0.540$) than with MR ($r = 0.374$) however, none of the correlation was statistically significant and the most active compound Centbutindole along with compound **8** were among the most deviated compounds.

The inclusion of an indicator, (In_1) describing the presence of substructure in which neuroleptic nitrogen is separated from an aromatic ring by four carbon atoms (Fig. 1), did improve the correlation from 0.540 to 0.725 (eq 3). Further the positive coefficient with (In_1) supports the earlier suggested,[21,22] minimal structural

Table 1. 2-substituted 1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-b]indoles, various molecular descriptors and their antipsychotic activity

Comp. No.[a]	Physicochemical parameters							Structural parameters		Neuroleptic activity		Eq 11		Eq 10	
	R_M	π_R	MR	+Log*P*(o/w)	DipoleY	Slog*P*_VSA8	Glob	In_1	In_2	ED_{50} ±SEM (nM)	−Log ED_{50}	Estd.	Pred.	Estd.	Pred.
1	0.64	0.16	15.57	1.41	−0.66	18.87	0.05	0	0	93.79±1.96	−1.97	−2.14	−2.18	−1.45	−1.26
2	0.88	0.29	20.42	1.60	0.19	18.87	0.05	0	0	17.48±3.44	−1.24	−1.49	−1.52	−1.43	−1.48
3	2.13	1.88	34.28	2.96	0.41	75.47	0.06	0	0	5.78±2.10	−0.76	−0.20	0.16	−1.43	−1.53
4	1.13	0.79	25.04	2.08	0.41	37.74	0.04	0	0	5.85±1.96	−0.77	−1.04	−1.11	−1.40	−1.47
5	2.38	1.90	54.92	4.68	−0.50	44.21	0.14	1	0	3.56±2.05	−0.55	−0.60	−0.62	−0.38	−0.32
6	2.41	2.53	44.11	3.86	0.36	37.74	0.17	1	0	0.10±0.00	0.98	0.37	−0.15	−0.16	−0.54
7	0.59	0.21	49.3	2.08	0.08	0.00	0.12	0	0	81.68±1.99	−1.91	−1.13	−0.92	−1.40	−1.35
8	3.66	3.25	50.03	4.90	0.08	37.74	0.17	1	0	40.60±1.97	−1.61	—	—	—	—
9	3.91	4.18	70.21	6.04	−0.44	6.47	0.09	0	0	145.48±1.97	−2.16	−1.81	−1.74	−2.37	−3.51
10	2.44	0.96	43.62	3.13	−0.12	0.00	0.09	0	0	90.38±1.97	−1.96	−1.56	−1.49	−1.45	−1.36
11	0.80	0.34	16.46	1.58	−0.04	18.87	0.05	0	0	44.77±3.79	−1.65	−1.65	−1.65	−1.43	−1.38
12	2.13	2.03	39.49	3.42	−0.51	18.87	0.03	0	0	68.90±3.45	−1.84	−2.32	−2.45	−1.49	−1.42
13	2.23	3.08	48.84	4.15	−0.82	56.61	0.05	0	0	111.58±1.96	−2.05	−1.75	−1.55	−1.64	−1.54
14	1.77	2.95	45.41	4.15	0.26	56.61	0.09	1	0	2.35±0.73	−0.37	−0.34	−0.33	−0.23	−0.18
15	1.12	0.61	21.08	2.05	−0.34	18.87	0.10	0	0	7.58±1.98	−0.88	−1.38	−1.44	−1.40	−1.46
16	0.75	0.29	20.42	2.07	0.11	22.85	0.06	0	1	19.39±3.53	−1.29	−1.33	−1.33	−1.40	−1.42
17	2.26	2.53	44.11	4.32	0.17	71.72	0.05	1	1	12.36±3.22	−1.09	−1.10	−1.10	−0.27	−0.01
18	1.50	1.72	32.3	2.78	0.29	3.98	0.04	0	1	39.43±1.98	−1.96	−1.70	−1.73	−1.43	−1.40
19	1.88	1.72	32.3	4.39	0.32	3.98	0.08	0	1	21.99±4.24	−1.34	−1.30	−1.29	−1.70	−1.79

[a]**Ref. 17**: compounds 1–5, 11–15, 17–19; **Ref. 18**: compounds 1, 7, 8, 9; **Ref. 19**: compounds 6, 16; **Ref. 20**: compounds 10.

Table 2. Correlation matrix for intercorrelations between different physiochemical and structural parameters and their correlation with neuroleptic activity (−log ED_{50})

	MR	π_R	R_M	In_1	In_2	Log*P*(o/w)	Dipole Y	Slog*P*_VSA8	Glob	−Log ED_{50}
MR	1.000									
π_R	0.793	1.000								
R_M	0.799	0.885	1.000							
In_1	0.432	0.495	0.434	1.000						
In_2	0.733	0.552	0.497	0.782	1.000					
Log*P*(o/w)	−0.177	−0.039	−0.124	−0.015	−0.127	1.000				
Dipole Y	0.852	0.900	0.878	0.443	0.612	0.039	1.000			
Slog*P*_VSA8	−0.196	−0.109	−0.136	0.180	0.085	0.358	−0.189	1.000		
Glob	0.135	0.389	0.213	0.540	0.248	−0.074	0.174	0.118	1.000	
−Log ED_{50}	−0.032	0.089	0.007	0.597	0.328	−0.091	0.009	0.473	0.475	1.000

Table 3. Statistically significant QSAR models for modeling neuroleptic activity

S.no.	Regression equations	n	r	s	f
1	$-\text{Log } ED_{50} = -2.635\ (\pm 1.256) + 0.089(\pm 0.069)\ \text{MR} - 0.001(\pm 0.001)\ (\text{MR})^2$	15	0.374	0.864	0.98
2	$-\text{Log } ED_{50} = -1.993(\pm 0.448) + 1.294\ (\pm 0.585)\ \pi_R - 0.324(\pm 0.147)\ (\pi_R)^2$	15	0.540	0.784	2.48
3	$-\text{Log } ED_{50} = -1.719(\pm 0.401) + 0.602\ (\pm 0.582)\ \pi_R - 0.191(\pm 0.138)\ (\pi_R)^2 + 1.131(\pm 0.486)\ In_1$	15	0.725	0.670	4.06
4	$-\text{Log } ED_{50} = -2.542\ (\pm 0.817) + 1.606\ (\pm 0.864)\ R_M - 0.381(\pm 0.197)\ (R_M)^2$	15	0.488	0.813	1.87
5	$-\text{Log } ED_{50} = -2.043(\pm 0.651) + 0.880(\pm 0.707)\ R_M - 0.264(\pm 0.157)\ (R_M)^2 + 1.255(\pm 0.413)\ In_1$	15	0.765	0.627	5.17
6	$-\text{Log } ED_{50} = -1.609\ (\pm 0.338) + 0.496\ (\pm 0.474)\ \pi_R - 0.170\ (\pm 0.116)\ (\pi_R)^2 + 1.032(\pm 0.396)\ In_1 - 0.229\ (\pm 0.366) In_2$	19	0.696	0.624	3.29
7	$-\text{Log } ED_{50} = -1.620\ (\pm 0.330) + 0.420\ (\pm 0.449)\ \pi_R - 0.150\ (\pm 0.109)\ (\pi_R)^2 + 1.054\ (\pm 0.387)\ In_1$	19	0.686	0.611	4.43
8	$-\text{Log } ED_{50} = -1.578\ (\pm 0.318) + 0.403\ (\pm 0.450)\ \pi_R - 0.137(\pm 0.111)\ (\pi_R)^2 + 1.251(\pm 0.395)\ In_1 - 0.269\ (\pm 0.345)\ In_2$	18	0.756	0.587	4.33
9	$-\text{Log } ED_{50} = -1.592\ (\pm 0.313) + 0.317\ (\pm 0.430)\pi_R - 0.115\ (\pm 0.105)\ (\pi_R)^2 + 1.270(\pm 0.389)\ In_1$	18	0.742	0.579	5.73
10	$-\text{Log } ED_{50} = -1.765\ (\pm 0.923) + 0.319\ (\pm 0.586)\ \text{LogP} - 0.069\ (\pm 0.081)\ In_1 + 1.410\ (\pm 0.382)\ (\text{LogP})^2$	18	0.753	0.569	6.11
11	$-\text{Log } ED_{50} = -2.461\ (\pm 0.255) + 11.380\ (\pm 2.616)\ \text{glob} + 0.840\ (\pm 0.259)\text{Dipole Y} + 0.014\ (\pm 0.004)\ \text{SlogP\_VSA8}$	18	0.872	0.422	14.85

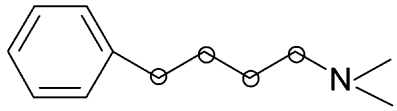


Figure 1. Depiction of the substructure in which neuroleptic nitrogen is separated from an aromatic ring by four carbon atoms.

requirement for active neuroleptics, which is also a crude measure of distance between centre of the aromatic ring and the neuroleptic N-atom.

In order to improve the correlations and to substitute hydrophobic parameters π_R by experimentally determined R_M for all compounds at physiological pH (=7.4) similar correlations were studied using R_M. Eqs 2 and 3 are parallel with eqs 4 and 5 respectively and give the same information, though the correlations are little poorer with R_M. The inclusion of four more compounds (**16**–**19**) where substitution at 6-position by $-CH_3/C_6H_5$ (presence indicated by indicator variable, In_2) has been carried out, resulted in eq 6. The comparison of regression coefficient of eq 6 with eq 3 justified the inclusion.

Exclusion of compound **8** (identified with its larger residuals) yielded eq 8 with improved correlation ($r=0.756$) and was also found to be statistically significant >95% ($F_{4,13\ \alpha\ 0.05}=4.00$; $F_{4,13}=4.33$). Since the regression coefficient with In_2 was less significant, its exclusion from the equation resulted in the three parameter equation for eighteen compounds which has little lower correlation ($r=0.742$) but was statistically more significant >98% ($F_{3,14\ \alpha\ 0.02}=5.56$; $F_{3,14}=5.73$) indicating that lipophilicity of the whole molecule is important and is, however, not parameterised using indicator variable, (In_2). Hence the new software, MOE (molecular operating environment) was used and the log*P*(o/w) values for the whole molecule were computed, which did correlate with the π_R values ($r=0.94$) for 15 compounds. The statistical significance of the resulting equation (eq 9) was found to be >98% ($F_{3,14\ \alpha\ 0.02}=5.56$; $F_{3,14}=611$). Prediction power of eq 10 ($r_{cv}=0.688$) was confirmed by cross validation by **L**eave **O**ne **O**ut method (LOO)[23] predicted values as shown in Table 1.

Further, a database containing structure along with experimental activities for 18 molecules was built and a set of descriptors was calculated, which was pruned to obtain a more relevant set using contingency analysis, a statistical application in MOE for data reduction. QSAR-contingency assists in the selection of descriptors in order to select the optimum set for the molecules under consideration by performing a bivariate contingency analysis for each descriptor and the activity or property value. It suggests a set of descriptors that best describes the molecules in the training set. Recommended ranges for the indices helps to choose descriptors for QSAR analysis to obtain a better model. We, therefore, on the basis of contingency analysis and relative importance of each descriptor with respect to activity chose Dipole Y, Slog*P*_VSA8 and globularity (glob) (description of each given in the experimental section), and tried to fit it into a QSAR model (eq 11; Table 3) which was found to be statistically significant >99.99% ($F_{3,14\ \alpha\ 0.001}=11.3$; $F_{3,14}=14.85$). This model is satisfactory in both statistical significance and predictive ability. It shows excellent, high predictive ability as $r_{cv}=0.842$ (Fig. 2).

Conclusion

It appears that no doubt lipophilicity is one of the most important parameters as the transport of the drug to CNS being the rate limiting step and that the variation in neuroleptic activity is difficult to parameterise by normal physicochemical parameters alone because of high stereo specificity of the receptors. Hence the structural parameters like indicator variable, (In_1) and globularity describe the variation in the neuroleptic activity. The positive contribution by indicator variable (In_2) substantiate that this substructure can mimic the

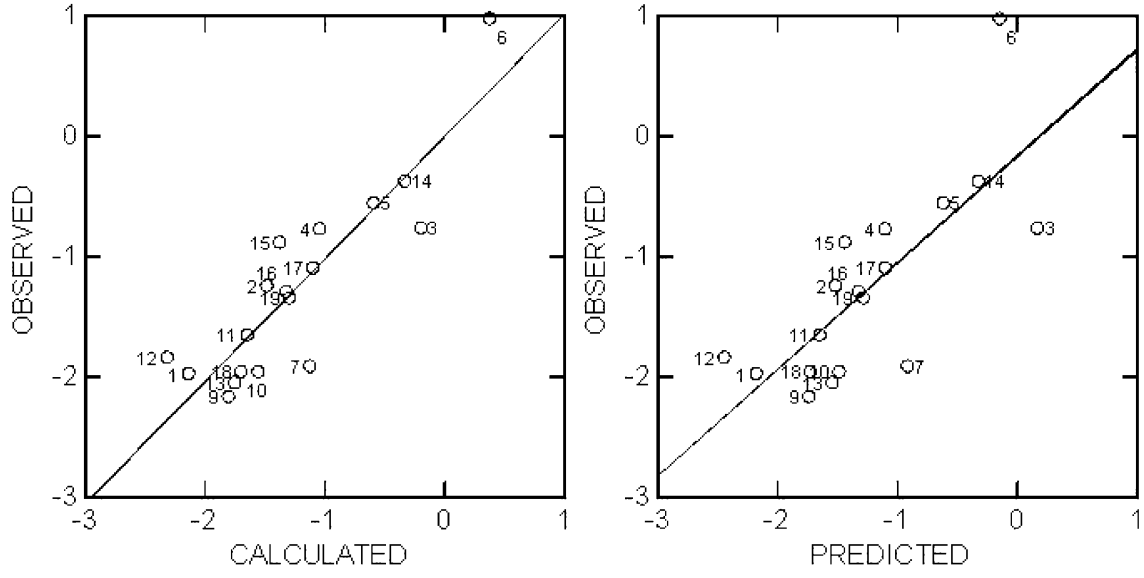


Figure 2. Plots of observed versus calculated (left) and observed versus predicted, $r_{cv}=0.842$, (right) for eq 11.

dopamine moiety as also proposed earlier in case of Haloperidol and Chlorpromazine.[24,25] Thus the incorporation of this substructure with judicious modulation of the physicochemical properties particularly lipophilicity and dipole may be very useful in designing of new neuroleptic drug.

Material and Methods

General method for determination of partition coefficient

Accurately weighed amount of compound was partitioned between measured volume of purified carbon dioxide-free *n*-octanol saturated with water (V_1 mL) and measured volume of water saturated with *n*-octanol (V_2 mL) on a mechanical shaker at 37°, till the equilibrium was reached (120 h). The octanol layer was separated and centrifuged at 2000 rpm, kept standing overnight. The concentration of the compound in octanol layer before and after partition was determined from the standard curve between the concentration and O.D. at 283 mμ in case of compounds **1** and **5** and at 247 mμ in case of Centbutindole. If C_1 and C_2 are the amount of the compound before partitioning and after partitioning in *n*-octanol layer (V_1 mL) and aqueous phase (V_2 mL), the concentration of the compound in octanol layer = C_2/V_1 mg/mL and the concentration of the compound partitioned into water layer = C_1-C_2/V_2 mg/mL.

So the partition coefficient (P)

$$= \frac{\text{Concentration of the octanol layer}}{\text{Concentration in the water layer}}$$

$$= (C_2/V_1)/[(C_1 - C_2)/V_2] = [C_2/(C_1 - C_2)].(V_2/V_1)$$

Thus, the log *P* values for the prototype compound (I. R_1 = H, R_2 = H), Centbutindole and compound **2** were found to be 0.36, 2.88 and 0.66, respectively. The experimental π_R-values 2.52 and 0.30 were obtained by subtracting the experimental log *P* value of the prototype compounds from experimental log *P* 2.88 and 0.66 for Centbutindole and compound **2**, respectively. As these values compared well with the calculated π_R values 2.53 and 0.29 for Centbutindole and compound **2**, respectively from Hansch method[26] as shown below, π_R values for other compounds were calculated similarly (Table 1).

$$\pi\text{-}(CH_2)_3COC_6H = F(p)$$

$$= \pi\text{-}(CH_2)_2 + \pi\text{-}(CH_3 - COCH_3)\text{-}\pi - CH_3) + \pi(C_6H_5F)$$

$$= (2\times 0.5) + (-0.24 - 0.50) + (2.27)$$

$$= 2.53$$

Determination of R_M

Silica gel plates ($60F_{254}$, 20×20 cm, thickness 0.2 mm) were impregnated by placing them in chromatographic chamber containing stationary phase [liquid paraffin (6.0 mL) + hexane (94.0 mL)] for 12–24 h till the solution had reached the top plates. The volatile component of stationary phase was allowed to evaporate at room temperature for 48 h. The approximate solutions of compounds in chloroform (0.3%) containing a few drops of methanol were prepared and 1 μL of each solution was spotted thrice on the impregnated plate at 1 cm apart from each other and 2 cm away from lower edge of the plate. Each plate was run in mobile phase containing 40% acetone phosphate buffer (pH 7.4) (V_1/V_2) at room temperature, then plates were taken out from the chamber and dried at room temperature for 5–6 h. The spot were located in UV light and R_f values were calculated. Thus, the R_f values at 50, 60, 70, and 80% acetone concentration was determined at different acetone concentration using the following formula.

$$R_M = \log\left[1/(R_f - 1)\right]$$

After determining R_M values for each concentration, a graph was plotted in R_M versus percentage of acetone concentration. From the computerized graph the R_M values were extrapolated at 0% concentration of acetone, which described the R_M values or partitioning values at physiological pH (= 7.4) as listed in the Table 1.

Calculation of molar refractivity (MR)

The MR values for substructure present at position 2 of 1,2,3,4,6,7,12,12a-Octahydropyrazino[2′,1′:6,1]pyrido[3,4-b]indoles in case of neuroleptic series listed above have been calculated by literature method[27] and are listed in Table 1.

Pharmacology

The neuroleptic activity for the compound was estimated as ED_{50} for the conditioned avoidance response (CAR).[19] A colony of male albino rats was trained to develop conditioned avoidance response (CR to buzzer) according to the method of Cook and Weidley.[28] Each dose of the drugs was administered ip to a group of 5 rats and the rats tested at the interval of 1 h. Minimum of three graded doses were used to calculate the ED_{50} value for each compound.

Log*P*(o/w) is a 2D molecular descriptor calculated from the connection table representation of a molecule (e.g., elements, formal charges and bonds, but not atomic coordinates). Log*P* (o/w) denotes Log of the octanol/water partition coefficient (including implicit hydrogens). This property is calculated from a linear atom type model[29] with $r^2 = 0.931$, RMSE = 0.393 on 1,847 molecules.

Slog*P*_VSA8 is a Subdivided Surface Area 2D molecular descriptor based on an approximate accessible van

der waals surface area calculation for each atom, v_i along with some other atomic property, p_i. The v_i are calculated using a connection table approximation. Each descriptor in a series is defined to be the sum of the v_i over all atoms i such that p_i is in a specified range (a, b]. Slog*P*_VSA8 denotes the sum of v_i such that L_i is in (0.30,0.40] where L_i denotes the contribution to log*P*(o/w) for atom-i as calculated in the Slog*P* descriptor (Log of the octanol/water partition coefficient (including implicit hydrogens). This property is an atomic contribution model[30] that calculates log*P* from the given structure.

Globularity (glob) is a 3-D molecular descriptor that depends on the structure connectivity and conformation. Globularity, or inverse condition number (smallest eigenvalue divided by the largest eigenvalue) of the covariance matrix of atomic coordinates. A value of 1 indicates a perfect sphere while a value of 0 indicates a two- or one-dimensional object.

Dipole Y is a conformation dependent molecular descriptor that depends upon the stored partial charges of the molecules and their conformations. It denotes the y component of the dipole moment (external coordinates) calculated from the partial charges of the molecule.

Computations

All the computations were carried out in Compaq PC model 486. Multiple regression analysis was carried out using Systat software version 7.0.1 and MOE 2001.01.

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