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PM3-Based Study of Cyclam and their Complexes

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Abstract: Six QSAR models of a series of cyclam & bicyclam derivatives have been developed using Heat of Formation, Molar Refractivity, Total Energy, Conformation Minimum Energy, Log P, Molecular Weight and Valence Connectivity Index (order 0, standard) descriptors. The analysis of variance (ANOVA) has been estimated using F-value, P-value and R.S.S. parameters. The correlation coefficient values are above 0.80. Overall best QSAR model is given by combination of Conformation Minimum Energy as first descriptor, LogP as second descriptor, Molecular Weight as third descriptor and Valence Connectivity Index (order 0, standard) as fourth descriptor. It has been noticed that N-substituted derivatives of cyclam & bicyclam compounds are more effective as compared to unsubstituted compounds. 15 new derivatives of bicyclam have been identified and their cytotoxic activities have been predicted with the help of best QSAR model. The proposed new compounds appear to have better cytotoxic effect.
Key Words: Cyclam, PM3, conformation minimum energy, valence connectivity index, cytotoxic activity.

Introduction

A series of bis-tetraazamacrocyclic compounds[1], consisting of two cyclam units linked in the way shown in Fig.-1 via an aliphatic linker or a linker containing an aromatic moiety, have been studied for their anti-HIV and cytotoxic effect[2, 3].

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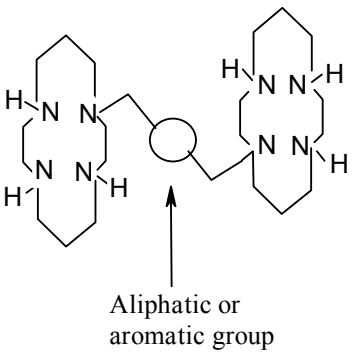

Figure-1.

QSAR [4, 5] has become increasingly helpful in understanding many aspect of chemical biological activity in drug research and pharmacological sciences [6-8].

QSAR study of bis-tetraazamacrocyclic compounds of this type (shown in fig-1) have been done [9], performing the Partial Least Square (PLS) analysis [10], resulting in models with high predictive ability (r^2=0.79). The best descriptors deduced from the analysis were the metal affinities for both rings, the metal- metal distance in the complex, ring size, and the angle and torsion between the planes defined to represent the face of each macrocyclic ring.

Recently a number of descriptors have been tried on testosterone [11, 12], estrogen [13] and alcohol [14, 15] derivatives. The QSAR models developed with these descriptors have shown high predictive power. In this paper, we have used these descriptors for QSAR development of cyclam and bicyclam derivatives. The descriptors used are Heat of Formation, Molar Refractivity, Total Energy, Conformation Minimum

Energy, Log P, Molecular Weight and Valence Connectivity Index (order 0, standard).

Material and Method

The study material of this paper are 22 cyclam derivatives and 12 metal complexes of cyclam, whose CC_{50} (in μM) against HIV-1 is reported. CC_{50} is 50% Cytotoxic Concentration. At CC_{50}, the cell viability of mock infected MT-4 cells is half that of untreated cells. Higher the value of CC_{50}, lower will be the toxicity of compound. The structural formulae of the compounds are given in Table-1. The 3D modeling and geometry optimization of all the compounds and evaluation of values of descriptors have been done with the help of CAche software using the semiemperical PM3 Hamiltonian. The values of various descriptors have been evaluated by solving the equations given in theory. The descriptors that have been used are,

1. Heat of Formation
2. Molar Refractivity
3. Total Energy
4. Conformation Minimum Energy
5. Log P
6. Molecular Weight
7. Valence Connectivity Index (order 0, standard)

Theory:

Heat of Formation (ΔH_f) [16]

It is defined as,the energy released or used when a molecule is formed from elements in their standard states or the heat released or absorbed (enthalpy change) during the formation of a pure substance from its elements, at constant pressure

Molar refractivity [17]

It is a constitutive-additive property that is calculated by the Lorenz-Lorentz formula,

$$MR = \frac{n^2 - 1}{n^2 + 2} * \frac{M}{\rho}$$

Where *M* is the molecular weight, *n* is the refraction index and ρ is the density.

Total Energy

The total energy is the work required to separate the electrons and nuclei infinitely far apart.

Conformation Minimum Energy

It is the energy calculated for an optimized conformation of the chemical sample. Depending on which procedure is used, the calculated energy may be steric energy (from Mechanics), heat of formation (from MOPAC) or total energy (from ZINDO).

Water/Octanol Partition coefficient (Log P)

The Water/Octanol partition coefficient [18] (LogP) is the logarithm of the ratio of concentrations of un-ionized compound between the two solutions or solvents.

$$log\ P_{oct/wat} = log\left(\frac{[solute]_{octanol}}{[solute]_{water}^{un-ionized}}\right)$$

Molecular Weight

It is the sum of atomic weights of all the atoms of the compound.

Valence Connectivity Index (order 0, standard)

It is called zeroth-order (atomic) valence molecular connectivity index for the chemical sample and it is defined by chemical graph theory [19, 20] as below,

$${}^1\chi = \sum_{paths} [d(\nu_i)\, d(\nu_j) \ldots d(\nu_l + 1)]^{-1/2}$$

where $d(\nu_i)\, d(\nu_j) \ldots d(\nu_l + 1)$ are valences of vertices $(\nu_i)\ (\nu_j) \ldots, \nu_l + 1$ in the considered path of length *l*. The valence-connectivity index in this paper is calculated by above equation.

Result and Discussion:

The values of seven descriptors of compounds listed in Table-1 have been calculated and are presented in Table-2 alongwith their observed toxicity (CC_{50}) in terms of μM. We have examined QSAR models using all possible combinations of descriptors. Following six QSAR models were found to have regression coefficient ($r^{\Lambda}2$) greater than 0.8 and cross validation coefficient ($rCV^{\Lambda}2$) greater than 0.5. The predicted toxicities of these QSAR models are given in Table-3.

1st QSAR model

The predicted toxicity of compounds have been obtained by the following regression equation,

RE1=0.0274364*∈-22.0422*LogP-2.98859* MW+ 74.4999* θ+7.88113

rCV^2=0.805827

r^2=0.872507

This regression equation contains Conformation Minimum Energy as first descriptor, Log P as second descriptor, Molecular Weight as third descriptor and Valence Connectivity Index (order 0, standard) as fourth descriptor. Correlation and cross validation coefficients indicate that, this model has high degree of predictive power as the values of $rCV^{\Lambda}2$ and $r^{\Lambda}2$ are 0.805827 and 0.872507 respectively. The values of predicted toxicities (PT1) of compounds are listed in Table-3.

2nd QSAR model

The predicted toxicity of compounds have been calculated by the following regression equation,

RE2=-21.723*LogP-2.91764*MW+73.1282*θ +2.66541

rCV^2=0.840669

r^2=0.871077

This regression equation involves LogP as first descriptor, Molecular Weight as second descriptor and Valence Connectivity Index (order 0, standard) as third descriptor. Correlation and cross validation coefficients indicate that, this model has good predictive power as the values of $rCV^{\Lambda}2$ and $r^{\Lambda}2$ are 0.840669 and 0.871077 respectively. The values of predicted toxicities (PT2) of compounds are listed in Table-3.

3rd QSAR model

The third predicted toxicity of compounds of Table-1 have been calculated by the following regression equation,

RE3=0.0885878*ΔHf-3.17118*ψ-
3.20893*MW+100.528*θ+6.86611

rCV^2=0.763525

r^2=0.827632

RE3 involves Heat of Formation as first descriptor, Molar Refractivity as second descriptor, Molecular Weight as third descriptor and Valence Connectivity Index (order 0, standard) as fourth descriptor. Correlation and cross validation coefficients indicate that, this regression gives good regression results as the values of $rCV^{\Lambda}2$ and $r^{\Lambda}2$ are 0.763525 and 0.827632 respectively. The values of predicted toxicities (PT3) of compounds are listed in Table-3.

4th QSAR model

The fourth predicted toxicity of compounds of Table-1 have been calculated by the following regression equation,

RE4= -3.29814*ψ+32.1277*Ω-3.25825 *MW +103.322
*θ-5.23329

rCV^2=0.774544

r^2=0.826451

This regression equation contains Molar Refractivity as first descriptor, Total Energy as second descriptor, Molecular Weight as third descriptor and Valence Connectivity Index (order 0, standard) as fourth descriptor. Correlation and cross validation coefficients indicate that, this model has high degree of predictive power as the values of $rCV^{\Lambda}2$ and $r^{\Lambda}2$ are 0.774544 and 0.826451 respectively. The values of predicted toxicities (PT4) of compounds are listed in Table-3.

5th QSAR model

The fifth predicted toxicity of compounds of Table-1 have been calculated by the following regression equation,

RE5= -2.95021*ψ-3.05122*MW +96.4448 *θ-7.45108

rCV^2=0.801356

r^2=0.821901

This regression equation involves Molar Refractivity as first descriptor, Molecular Weight as second descriptor, and Valence Connectivity Index (order 0, standard) as third descriptor. Correlation and cross validation coefficients indicate that, this QSAR model gives good regression results as the values of $rCV^{\Lambda}2$ and $r^{\Lambda}2$ are 0.801356 and 0.821901 respectively. The values of predicted toxicities (PT5) of compounds are given in Table-3.

6th QSAR model

The sixth predicted toxicity (PT6) of compounds, given in Table-1, have been obtained by the following regression equation,

RE6=5.22359*ψ-33.8163*Ω-34.032*LogP-1.46946*
MW +133.631

rCV^2=0.510815

r^2=0.806081

RE6 involves Molar Refractivity as first descriptor, Total Energy as second descriptor, LogP as third descriptor and Molecular Weight as fourth descriptor. Correlation and cross validation coefficients indicate that, this model has good predictive power as the values of $rCV^{\Lambda}2$ and $r^{\Lambda}2$ are 0.510815 and 0.806081 respectively. The values of predicted toxicities (PT6) of compounds are given in Table-3.

The values of cross validation coefficient and correlation coefficient of all the six models are presented collectively in Table-4 in their decreasing order, alongwith the combination of descriptors providing the various models. The 1st QSAR model is the best model having the correlation coefficient value above 0.87 and also the cross validation coefficient value above 0.8.The combination of descriptors providing the best model (1st QSAR model) are Conformation Minimum Energy,

LogP, Molecular Weight and Valence Connectivity Index (order 0, standard).

Analysis of Variance, ANOVA:

In order to asses the quality of regression, analysis of variance of all the six QSAR models have been performed. The parameters used for ANOVA and their values, obtained by Statistica software, are included in Table-5. It is clear from the table, that all the six models are dependable.

Relationship Between Toxicity and Individual Descriptor:

A close look at Table-2 indicates that, Conformation Minimum Energy shows an inverse relationship with CC_{50} of the compound. To examine the relationship between reported CC_{50} and Conformation Minimum Energy, the values are placed in Table-6. To provide sequential relationship Table-6 has been divided into three subgroups A, B and C. A few compounds do not follow this trend. Generally, as the value of Conformation Minimum Energy increases, the value of CC_{50} decreases. It implies that a compound with lower value of Conformation Minimum Energy will be less toxic on human body. In the case of bicyclam compounds, in which two cyclam units are linked via a benzene ring, substitution at remaining four positions of benzene ring decreases the value of CC_{50}. An increase in the carbon chain between nitrogen of cyclam unit and benzene ring increases the value of CC_{50}, so that leads to a less toxic compound. Hence Conformation Minimum Energy is an important parameter for the study of cyclam and bicyclam compounds.

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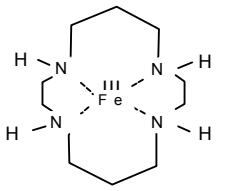
Again a close look at Table-2 indicates that, Molecular Weight shows an inverse relationship with CC_{50} of the compound. To examine the relationship between reported CC_{50} and Molecular Weight, values are placed in Table-7. To provide sequential relationship Table-7 has been divided into four subgroups A, B, C and D. Some of the compounds do not follow this trend. Generally, the compounds with lower value of Molecular Weight in its class (cyclam, bicyclam or cyclam-complex) have higher value of CC_{50}. As the value of Molecular Weight of compound increases, the value of CC_{50} decreases, therefore, making compound more toxic. Hence Molecular Weight is an important parameter for the study of cyclam and bicyclam compounds.

New Proposed Compounds:

It has been noticed that N-substitution on cyclam/bicyclam increases its Anti-HIV activity. [3, 21] We have introduced a set of 15 new N-substituted bicyclam compounds, which are listed in Table-8. Values of seven descriptors have been calculated and are presented in Table-9. With the help of best QSAR model (PT1), the CC_{50} of the compounds of Table-8 have been predicted and are included in Table-10 in decreasing order of their CC_{50}. Highest value of CC_{50} (377.985 μM) has been observed for the proposed compound PC11, it may be synthesized and tested for its toxicity. It has been noticed that proposed compounds PC-3, PC-6 and PC-9 have higher value of predicted toxicity than that of their respective unsubstituted bicyclam compounds. So these (PC-3, PC-6 and PC-9) compounds may be synthesized and tested for its toxicity

Table-1: Structures of cyclams and their complexes



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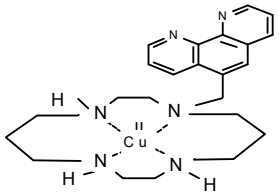

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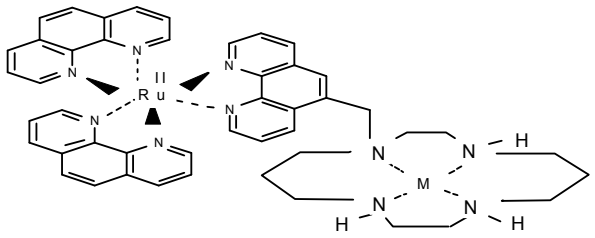
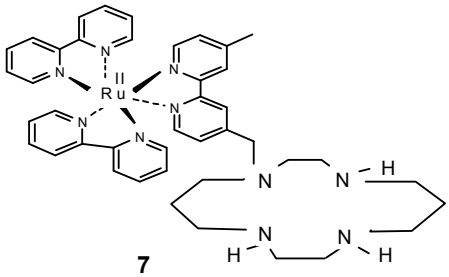


3 [M = Zn (II)], 4 [M = Cu (II)]
5 [M = Fe (III)], 6 [M = Co (III)]



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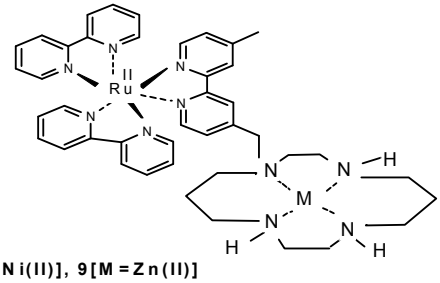
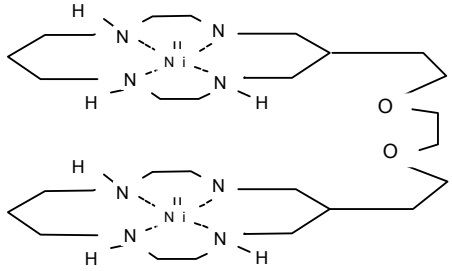


8 [M = Ni (II)], 9 [M = Zn (II)]
10 [M = Cu (II)], 11 [M = Fe (III)], 12 [M = Co (III)]



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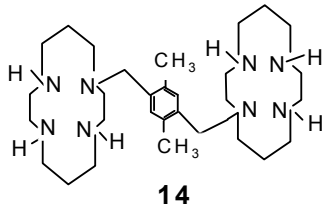

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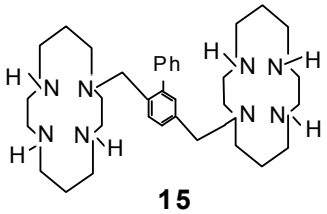

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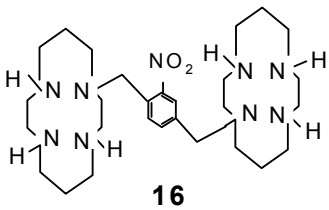

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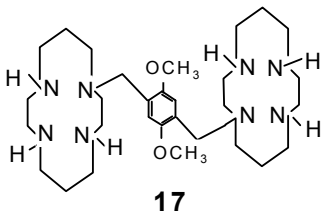

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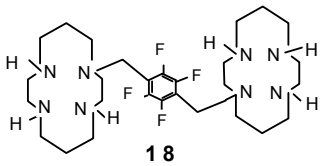

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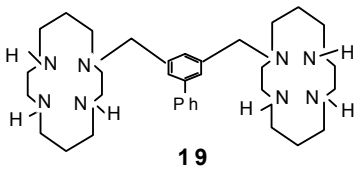

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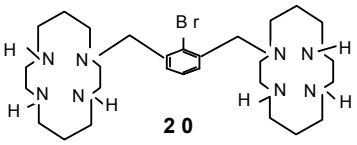

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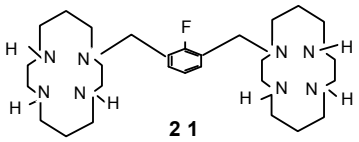

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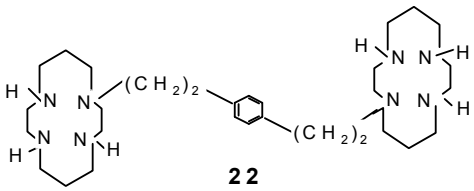

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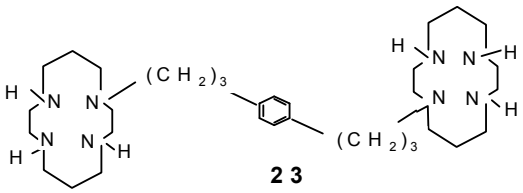

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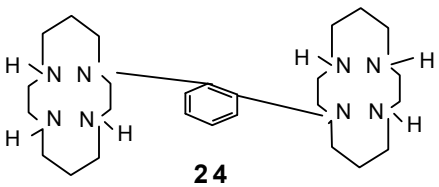

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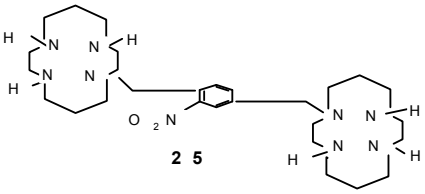

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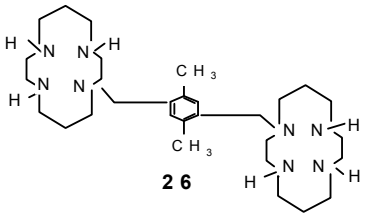

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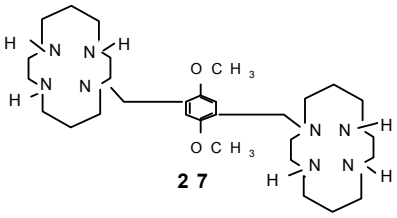

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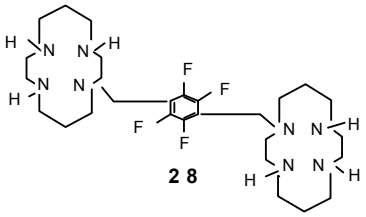

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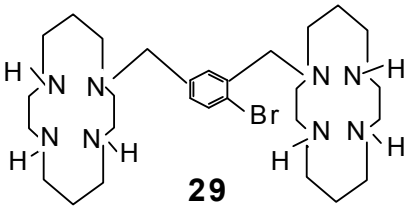

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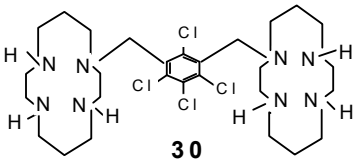

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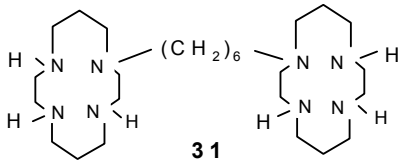

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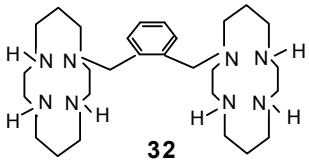

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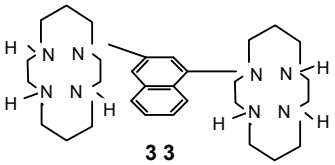

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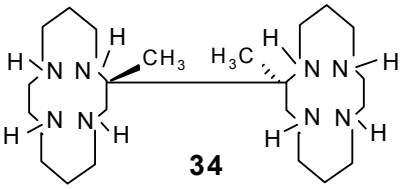

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Table-2: Values of descriptors and observed toxicities of cyclam compounds

Compound	Heat of Formation (kcal/mole)	Molar Refractivity	Total Energy (Hartree)	Conformation Minimum Energy (kcal/mole)	Log P	Molecular Weight	Valence Connectivity Index (order 0, standard)	Obsd. Toxicity
1	18.174	50.628	0.177	110.944	-2.547	256.173	10.529	52.8
2	88.18	108.081	0.321	201.689	-0.444	458.108	18.612	34.9
3	404.997	226.942	0.645	404.997	-3.591	925.461	36.196	10.9
4	402.335	226.942	0.641	402.335	-3.591	923.627	36.249	35.3
5	396.146	226.942	0.631	396.146	-3.591	915.928	36.463	29.9
6	400.107	226.942	0.638	400.107	-3.591	919.014	36.38	29.3
7	239.284	265.197	0.381	239.284	0.408	952.181	38.715	20.6
8	188.112	254.799	0.169	106.118	-0.828	1010.891	40.019	12.2
9	609.707	254.799	0.972	609.707	-0.828	1017.561	39.905	9.24
10	524.537	254.799	0.836	524.537	-0.828	1015.727	39.958	8.23
11	521.721	254.799	0.831	521.721	-0.828	1008.028	40.173	13.5
12	532.104	254.799	0.848	532.104	-0.828	1011.114	40.09	26.1
13	-51.713	130.682	-0.471	-295.538	-5.212	632.217	25.549	170
14	99.894	165.096	-0.009	-5.393	0.314	530.842	24.605	208
15	97.88	180.15	0.064	39.91	1.064	578.886	26.07	198
16	94.443	161.937	0.153	96.023	-0.573	547.786	23.947	203
17	87.895	167.94	-0.085	-53.406	-1.126	562.841	25.422	206
18	74.917	155.879	-0.242	-152.024	-0.063	574.75	23.963	47
19	93.741	180.15	0.063	39.247	1.064	578.886	26.07	198
20	83.38	162.636	0.037	23.291	0.171	581.684	24.647	144
21	80.338	155.23	-0.039	-24.587	-0.481	520.779	23.061	201
22	107.881	164.523	0.006	3.628	-0.117	530.842	24.174	201
23	103.785	173.725	-0.022	-14.085	0.675	558.895	25.589	283
24	127.927	146.785	0.031	19.745	0.134	474.735	21.346	168
25	84.657	161.937	0.148	92.658	-0.573	547.786	23.947	203
26	92.385	165.096	-0.014	-8.649	0.314	530.842	24.605	208
27	86.141	167.94	-0.098	-61.474	-1.126	562.841	25.422	206
28	66.19	155.879	-0.244	-153.161	-0.063	574.75	23.963	47
29	85.458	162.636	0.031	19.254	0.171	581.684	24.647	144
30	76.434	174.233	-0.006	-3.67	1.451	640.569	26.986	9
31	97.808	148.588	-0.05	-31.133	-1.009	482.798	22.279	290
32	94.279	155.013	0.02	12.631	-0.621	502.788	22.76	168
33	98.13	163.235	0.057	35.884	1.137	524.794	23.501	207
34	98.191	128.56	-0.01	-6.568	-2.447	426.691	19.752	319

Table3: Values of predicted toxicities PA1-PA6 of cylam compounds

Comp	PT1	PT2	PT3	PT4	PT5	PT6
1	85.865	80.525	84.325	86.648	76.991	102.358
2	40.657	36.739	72.885	78.981	70.886	29.261
3	28.899	27.436	-7.972	-8.549	-9.872	59.533
4	38.249	36.657	2.998	2.759	0.829	62.371
5	77.075	74.812	48.726	49.698	45.015	74.018
6	61.75	59.711	30.793	31.232	27.558	69.27
7	44.051	46.851	23.576	30.059	38.734	92.927
8	-10.663	-2.226	-5.307	0.959	16.022	1.611
9	-25.243	-29.995	-0.782	-6.728	-15.286	-35.329
10	-18.156	-20.773	2.878	0.355	-4.585	-28.044
11	20.762	17.381	48.905	47.467	39.601	-16.579
12	5.613	2.281	31.541	29.329	22.144	-21.673
13	128.643	139.682	127.573	128.53	142.089	80.531
14	247.454	246.398	262.28	262.654	258.836	205.586
15	197.657	196.998	207.377	210.059	209.036	185.657
16	170.056	168.041	151.2	154.974	152.904	188.905
17	243.071	244.023	231.597	230.918	231.557	225.008
18	72.612	79.456	83.772	76.061	90.054	113.631
19	197.639	196.998	207.01	210.025	209.036	185.693
20	102.515	104.177	109.62	110.846	114.945	121.335
21	179.445	180.066	168.841	167.399	169.671	196.924
22	225.086	224.236	221.469	220.466	218.951	216.774
23	228.648	228.587	244.071	243.923	242.599	197.598
24	176.946	175.634	175.2	170.364	169.688	197.137
25	169.964	168.041	150.333	154.802	152.904	189.086
26	247.365	246.398	261.615	262.488	258.836	205.762
27	242.85	244.023	231.442	230.505	231.557	225.443
28	72.581	79.456	82.999	76.003	90.054	113.693
29	102.404	104.177	109.804	110.639	114.945	121.552
30	71.873	75.652	118.467	121.087	126.702	53.267
31	246.182	245.192	234.756	231.964	229.772	236.362
32	214.911	213.603	198.273	197.576	196.209	224.972
33	166.215	165.376	176.364	176.456	176.223	174.529
34	257.994	255.356	224.34	221.022	216.365	261.805

PT=Predicted Toxicity

Table-4: QSAR models in decreasing order of predictive powers alongwith the Values of regression and cross-validation coefficients

S. No.	Predicted Toxicity	rCV^2	r^2	Combination of descriptors
1	PT1	0.805827	0.872507	Conformation Minimum Energy, Log P, Molecular Weight, Valence Connectivity Index (order 0, standard)
2	PT2	0.840669	0.871077	Log P, Molecular Weight, Valence Connectivity Index (order 0, standard)
3	PT3	0.763525	0.827632	Heat of Formation, Molar Refractivity, Molecular Weight, Valence Connectivity Index (order 0, standard)
4	PT4	0.774544	0.826451	Molar Refractivity, Total Energy, Molecular Weight, Valence Connectivity Index (order 0, standard)
5	PT5	0.801356	0.821901	Molar Refractivity, Molecular Weight, Valence Connectivity Index (order 0, standard)
6	PT6	0.510815	0.806081	Molar Refractivity, Total Energy, Log P, Molecular Weight

rCV^2=Cross Validation Coefficient; r^2= Correlation Coefficient

Table-5: Correlation Summary of six best QSAR models

S.No.	rCV^2	r^2	F value	R.S.S.	P value	V.C.
1	0.805827	0.872507	49.62327	275069.3	0.00	4
2	0.840669	0.871077	67.57468	274618.0	0.00	3
3	0.763525	0.827632	34.82313	260932.4	0.00	4
4	0.774544	0.826451	34.54203	260567.0	0.00	4
5	0.801356	0.821901	46.16188	259123.5	0.00	3
6	0.510815	0.806081	30.12485	254103.4	0.00	4

rCV^2=Cross Validation Coefficient; r^2= Correlation Coefficient;
R.S.S. =Residual sum square; V.C. =Variable Count

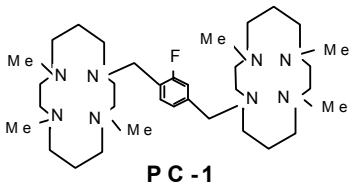
Table-6: Relationship between Conformation Minimum Energy and CC_{50}

Conformation Minimum Energy	CC_{50}	Compound No.
Subgroup-A		
-31.133	290	31
-14.085	283	23
-5.393	208	14
3.628	201	22
12.631	168	32
23.291	144	20
110.944	52.8	1
201.689	34.9	2
396.146	29.9	5
400.107	29.3	6
521.721	13.5	11
609.707	9.24	9
Subgroup-B		
-61.474	206	27
-24.587	201	21
39.91	198	15
402.335	35.3	4
404.907	10.9	3
524.537	8.23	10
Subgroup-C		
35.884	207	33
96.023	203	16
239.284	20.6	7

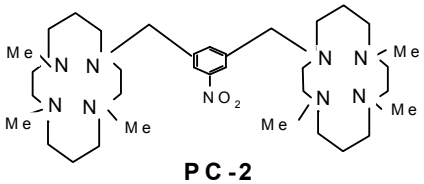
Table-7: Relationship between Molecular Weight and CC_{50}

Molecular Weight	CC_{50}	Compound No.
Subgroup-A		
426	319	34
482	290	31
524	207	33
562	206	27
578	198	15
632	170	13
915	29.9	5
919	29.3	6
952	20.6	7
1008	13.5	11
1010	12.2	8
1017	9.24	9
Subgroup-B		
530	208	14
547	203	16
581	144	20
923	35.3	4
1011	26.1	12
1015	8.23	10
Subgroup-C		
474	168	24
574	47	18
925	10.9	3
Subgroup-D		
256	52.8	1
458	34.9	2
640	9	30

Table-8: Structures of proposed compounds



PC-1



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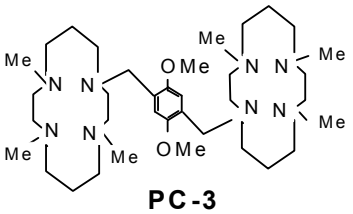

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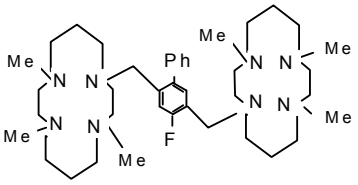

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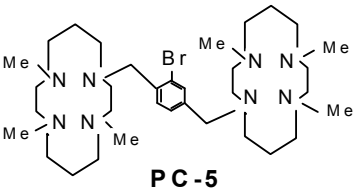

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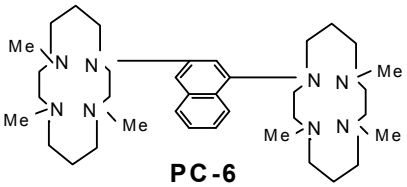

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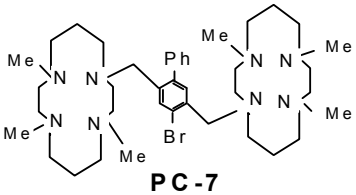

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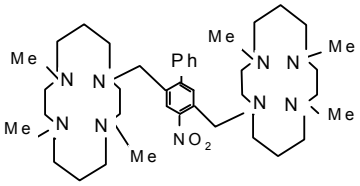

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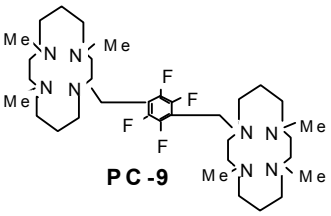

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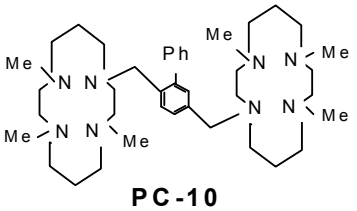

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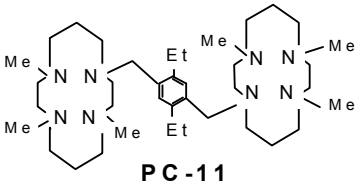
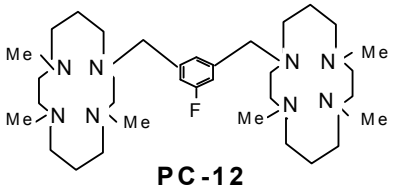


PC-11



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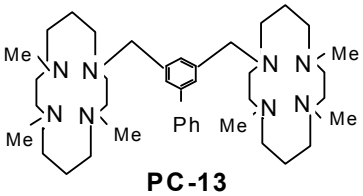

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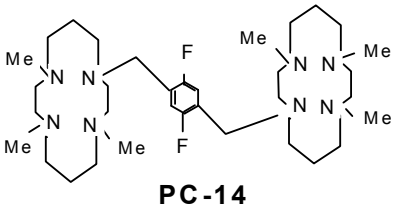

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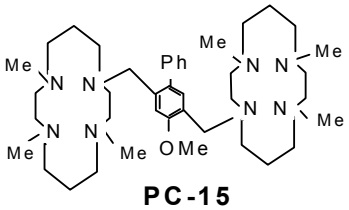

PC-15

Table-9: Values of descriptors and proposed toxicities of proposed cyclam compounds (given in Table-8)

Proposed Compounds	Heat of Formation (kcal/mole)	Molar Refractivity	Total Energy (Hartree)	Conformation Minimum Energy (kcal/mole)	Log P	Molecular Weight	Valence Connectivity Index (order 0, standard)	Proposed Toxicity
PC-1	43.441	186.998	0.108	68.079	1.687	604.939	28.744	306.074
PC-2	218.402	193.705	0.132	82.661	1.595	631.947	29.63	293.793
PC-3	-3.247	167.94	-0.005	31.309	-1.126	562.841	25.422	245.395
PC-4	72.6	212.134	0.116	56.4	3.372	681.037	32.053	287.707
PC-5	84.276	194.404	0.134	78.033	2.34	665.845	30.33	228.088
PC-6	151.949	195.004	0.146	91.384	3.305	608.955	29.184	291.827
PC-7	121.139	219.541	0.193	60.901	4.024	741.943	33.639	209.593
PC-8	247.071	218.841	0.394	75.638	3.28	708.044	32.939	275.557
PC-9	-79.867	187.647	0.129	80.855	2.106	658.911	29.646	203.088
PC-10	67.799	180.15	0.108	30.305	1.064	578.886	26.07	197.419
PC-11	50.338	206.066	0.08	82.112	3.275	643.056	31.703	377.985
PC-12	42.874	186.998	0.117	73.46	1.687	604.939	28.744	306.222
PC-13	82.011	180.15	0.024	15.299	1.064	578.886	26.07	197.007
PC-14	-34.019	155.446	0.058	36.441	-0.342	538.769	23.361	146.652
PC-15	76.997	218.381	0.123	70.658	2.98	693.073	33.084	337.578

Table-10: Proposed Toxicity of Proposed Compounds in descending order

Proposed Compounds	Proposed Toxicity in descending order
PC-11	377.985
PC-15	337.578
PC-12	306.222
PC-1	306.074
PC-2	293.793
PC-6	291.827
PC-4	287.707
PC-8	275.557
PC-3	245.395
PC-5	228.088
PC-7	209.593
PC-9	203.088
PC-10	197.419
PC-13	197.007
PC-14	146.652

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