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QSAR AND DOCKING STUDIES OF APHORPHINE DERIVATIVES AS EFFICACIOUS PARTIAL ANTAGONISTS FOR PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is caused due to enhanced dopaminergic activity in the substantia nigra, a region of the midbrain. Dopamine Receptors are the main drugs used in the treatment of Parkinson's disease. In this work, docking studies have been performed in order to understand the interaction between Aphorphine inhibitor and Dopamine Receptors (D2). An increase in the calculated binding affinities between inhibitor and D2, reflects the experimental inhibitory activity, expressed in terms of the half maximal inhibitory concentration (IC_{50}), which is found to be in the range 0.0004 to 11.5 µm, for the inhibitors employed. The AM1 and PM3 semi-empirical methods have been used to estimate the predictive power of final QSAR equations. QSAR coupled with molecular docking studies indicated that, [6aR]-6, 10 dimethyl-5, 6, 6a, 7-tetrahydro-4H dibenzo [de, g] quin derivative of Aphorphine showed the highest percentage of concentration and can become a potential lead for treating Parkinson's disease.

KEYWORDS: **Inhibitor, Aphorphine derivatives, QSAR, Semi-empirical methods, Regression analysis, DOCKING, DOPAMINE Receptors (D2).**

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1. INTRODUCTION

Parkinson's Disease (PD) is a brain disorder developed after an age of 50 years that causes a gradual loss of muscle control. The symptoms of Parkinson's tend to be mild at first and can sometimes be overlooked. Distinctive signs of the disease include tremors, stiffness, slowed body movements, and poor balance. Parkinson's was originally called a "shaking palsy", but not everyone with Parkinson's has a tremor. The degradation processes of macromolecules, such as serotonin, norepinephrine, dopamine, and other neurotransmitters of dopaminergic neurons in substantia nigra, catalyzed by monoamine oxidase are critically important not only for the regulation of emotional behavior, but also for other neural functions. As a consequence, the brains of PD patients are subject to high levels of oxidative stress. The dopaminergic cell loss and disease progression are accompanied by the accumulation of high iron levels, associated with aggregation of synuclein (especially in the mutated form found in familial Parkinson's disease). Increasing evidence indicates that multiple biochemical and cellular factors are involved in neuronal death in PD, some of them involve protein dyshomeostasis, mitochondrial impaired function and metal-induced toxicity [1-2]. These processes contribute to the oxidative stress and damage and inflammatory response in brain of PD patients. The dopamine agonists include ergot derivatives, non-ergoline derivatives (pramipexole, rapinirole and piribedil) and apomorphine. Most dopamine agonists have their specific pharmacological profile.Treating PD was achieved through inhibiting the anomalous action of DOPAMINE by various specific D2 inhibitors such as

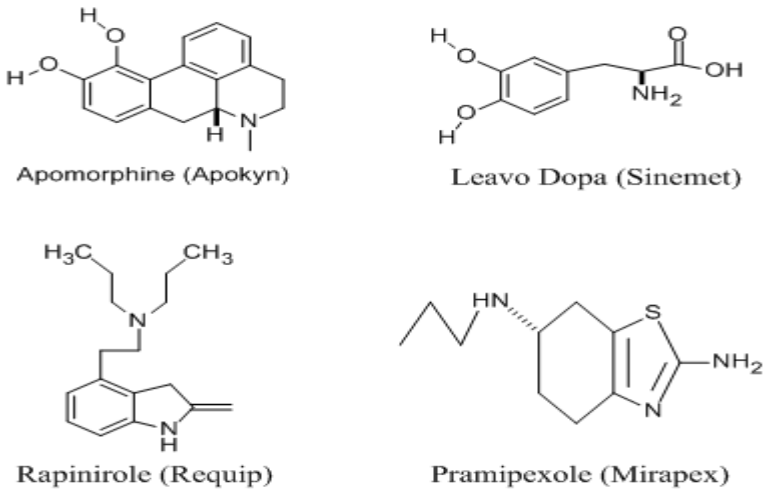


Figure1
Marketed drugs for the treatment of Parkinson's disease.

Aphorphine ($C_{17}H_{17}N$) is too basic heterocyclic Quinoline compound. It is a raw material used for the production of dyes and some valuable drugs. Many aphorphines have anti-protozoal properties. Aphorphine and related derivatives bind to DNA and RNA through intercolation mode [3--5]. Few pharmacokinetic and pharmacodynamic data are available regarding centrally acting antimuscarinic drugs. They are characterized by rapid absorption after oral intake, large volume of distribution and low clearance relative to hepatic blood flow, with extensive metabolism. Complex of the anti-parkinson's drug Apomorrphine with Dopamine Receptor centrally active Dopamenergic inhibitor that has been used to counter the effects of muscle relaxants as a respiratory stimulant and in the treatment of Parkinson's

disease and other central nervous system disorders.

2. MATERIALS AND METHODS

Bioassay

In the present investigation bioassay of 25 derivatives of Aphorphine found in the literature [6] with known IC_{50} values has been performed. The criteria for selection of molecules are

1) Against same target.
2) Which have available biological activity data.
3) Molecules possessing Aphorphine Scaffold.

More than 20 molecules showed IC_{50} below 1 µm (micro molar) concentration. These were further supported by docking studies using GOLD and Argus Lab 4.0.1 Software.[25]

Structural Skeleton of Aphorphine

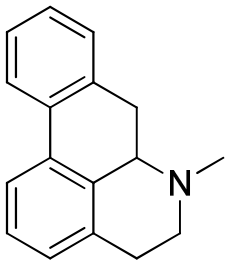
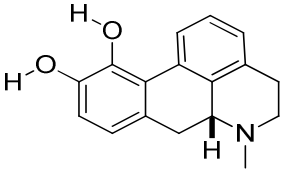
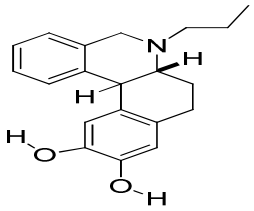
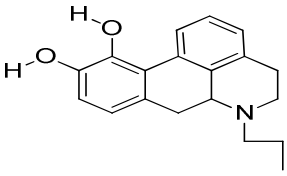
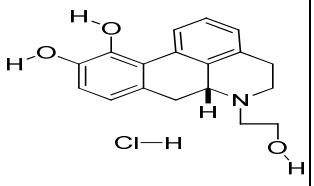
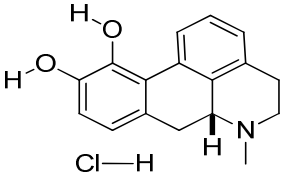
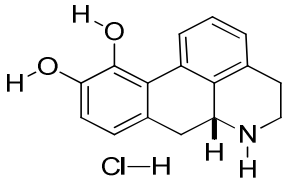
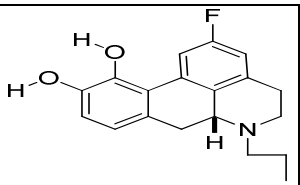
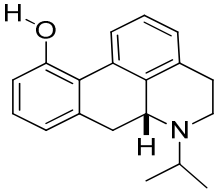
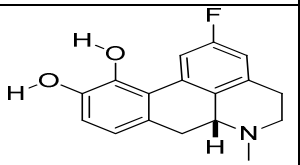
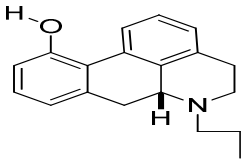
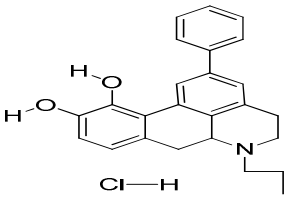
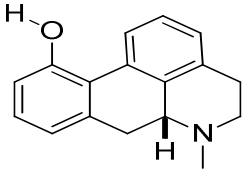
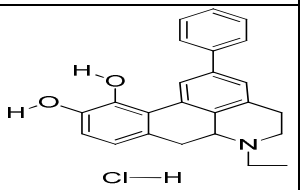
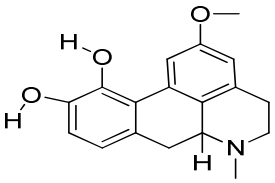
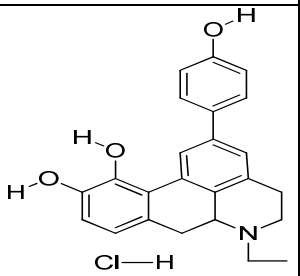
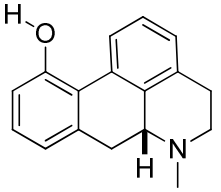
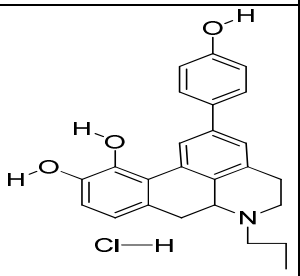
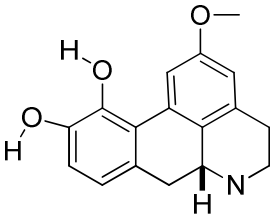
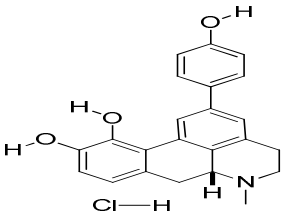
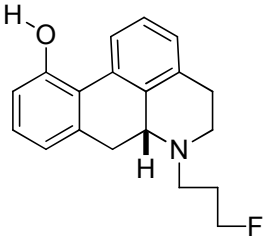
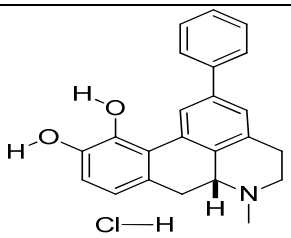
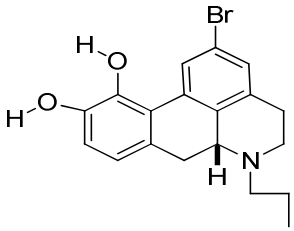
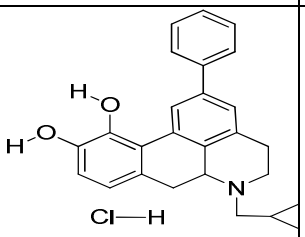
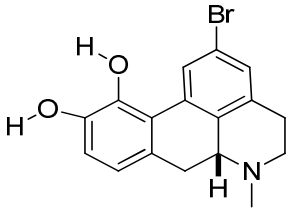
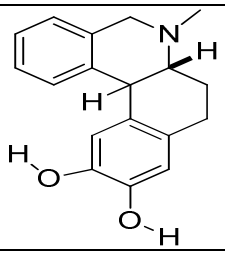


Figure 2
Aphorphine

Table 1
Derivatives of Aphorphine with IC_{50} values

COMPOUND	STRUCTURE	IC_{50}(µm)	COMPOUND	STRUCTURE	IC_{50}(µm)
1		0.0667	14		0.053
2		0.0048	15		1.46
3		0.087	16		1.19

4		7.1	17		1.01
5		0.00043	18		0.0127
6		0.192	19		0.0585
7		0.014	20		0.162
8		0.0015	21		11.5
9		0.002	22		0.0164
10		0.0085	23		0.86

11		0.0233	24		0.00089
12		0.00043	25		0.0177
13		0.136			

3.COMPUTATIONAL CALCULATIONS

Molecular Structure Building

Hyperchem software [7] was used in modelling studies on a series of 25 compounds tested for inhibitory activity in the present investigation. The molecules were generated and the geometry optimization was performed using molecular modeling programme (Force Field).

3.1 Data Set and Validation of QSAR Models

QSAR technique was applied to the Aphorphine analogues that were varied at the positions of different substituent's from structure to structure shown in Table 1. The appropriate descriptors or parameters for the identified compounds viz; vertical ionization potentials (IPV's), electron affinity (EA), electro negativity (χ), hardness (η), softness (S), electrophilicity index (ω), partition coefficient (LOGP), polarisability (POL) and hydration energy (HE) were used as independent variables for deciding in Dopamine (2) inhibitory activity.

3.2. CHEMICAL DESCRIPTORS

3.2.1. SEMI EMPIRICAL METHODS

Quantum chemical calculations at the DFT/RB3LYP/631G* (restricted B3LYP), RHF/6-31G* (restricted Hartree-Fock), AM1 and PM3 semi empirical theory levels, are employed for full optimization of the selected neutral compounds [8-10]. The geometrical structures of the radicals studied are optimized independently from the neutral molecules prior to the calculation of energies, treated as open shell systems [11-14]. All calculations are performed by using the program of Hyperchem software Inc. The calculated vertical ionization potential (IPV's) and electron affinity (EA) are corrected for zero-point energy, assuming a negligible error and thus saving computer-time. The IPV are calculated as the energy differences between a radical cation and the respective neutral molecule; IPV (E_{cation} – $E_{neutral}$) $_{DFT}$ and Koopmans's theorem (IPV = -ε $_{HOMO}$). The EA are computed as the energy differences between a neutral form and the anion molecule; EA=$E_{neutral}$ – E_{anion}. The AM1 reactivity descriptors are obtained from Eqs. (1) & (2) [15-17].

3.3. Correlation Analysis

The window version software SPSS [18] was used in the regression analysis. A relation between biological activity, expressed as Log ($1/IC_{50)}$, and the physicochemical parameters and QSAR was analyzed statistically by fitting

the data to correlation equations consisting of various combinations of these parameters. The statistical optimization was used to propose the best correlation model. The matrix correlation uses the Pearson product moment correlation to measure the degree of linear relationship between two variables. The coefficient assumes a value between -1 and +1. If one variable tends to increase the other decreases, the correlation coefficient is negative. Conversely, if the two variables tend to increase together the correlation coefficient is positive. We obtained the correlation matrix between inhibitory activity and respective calculated properties for twenty five Aphorphine derivatives. The more relevant regression models were selected: The correlation coefficient (R), the Fisher ratio values (F) and the standard deviations(s), standard error estimate (SEE), percentage of effective variable(%EV) and R^2adjusted (AdjR^2). The best equation was also tested for their predictive power using a cross- validation procedure .The cross-validation is a practical and reliable method for testing this significance. In principle, the so-called "leave-one-out" approach consists in developing a number of models with one sample omitted at the time [19]. After developing each model, the omitted data is predicted and the differences between actual and predicted reduction potential (y) values are calculated .The sum of squares of these differences is computed and finally the performance of the model (its predictive ability) is given by PRESS (Predictive Sum of Squares) and S_{PRESS} (Standard deviation of cross validation**).** The predictive ability of the model was also quantified in terms of the Q^2.

3.4. Docking Studies and Validation

GOLD and Argus lab 4.0.1 are Molecular Docking software**.** This helps in computational virtual screening to find the lead compounds. Molecular docking started with Fischer's lock and key theory, where, every receptor has its unique ligand to catalyze the reaction [20-22]. Now-a-days docking is used as a tool to predict the binding orientations and affinities of small molecules of drug candidates to their protein targets. The GOLD Score was calculated by defining the site using the list of atom numbers and retaining all the other default parameters. The 3D structure of Dopamine (2) was retrieved from Protein Data Bank (PDB ID 4DUB) [23] with an X-ray resolution of $2A^O$. Docking poses were obtained by applying Gold score, fitness functions available for scoring. All the results reported in the present paper are referred to the ChemScore and GOLD fitness functions. These complexes were prepared for docking studies by adding hydrogen atoms, removing water molecules and co-crystallized inhibitors and refined by using the DeepView/SwissPdbViewer3.7(SP5)(Guex N, Peitsch MC).

Swiss Model and the Swiss Pdb-Viewer

Deep View/Swiss PdbViewer3.7 (SP5) Enzyme-inhibitor interactions within a radius equal to 10Å centered on reported bound inhibitors were taken into account. As a conclusive part of docking we expect, generated results should yield RMSD values below 1.5 Å. Successful docking has been performed for the selected set of Aphorphines inhibitors and their corresponding ChemScore with their RMSD have been produced in the Table 2.

Table 2
Energy, ChemScore and gold fitness values of the docked ligands.

Compound	Activity(IC_{50} in µm)	GOLD Software		ArgusLab(Energy Values)
		CHEMSCORE	FITNESS	
1	0.0667	22.85	-659.07	-6.15282
2	0.0048	-1.67	-2220.84	-5.84064
3	0.087	21.19	-644.49	0
4	7.1	-6.18	-2702.19	-5.92985
5	0.00043	19.25	-169.68	0
6	0.192	17.77	-197.43	0
7	0.014	17.47	-382.01	0
8	0.0015	18.22	-236.39	0
9	0.002	-14.01	-2507.59	0
10	0.0085	20.18	-152.69	0
11	0.0233	21.80	-781.13	0
12	0.00043	-17.66	-2831.96	0
13	0.136	18.00	-242.52	-6.00111
14	0.053	20.75	22.88	0
15	1.46	22.37	-193.28	0
16	1.19	21.05	28.47	0
17	1.01	21.03	-71.86	0
18	0.0127	21.02	-75.81	0
19	0.0585	22.10	-174.85	-5.97376
20	0.162	21.96	-706.75	-5.36663
21	11.5	17.14	35.01	-5.32874
22	0.0164	22.36	-708.23	-5.36872
23	0.86	19.69	-38.10	-5.6611
24	0.00089	-7.97	-2811.36	-5.57776
25	0.0177	20.90	-962.37	-5.80796

3. RESULTS AND DISCUSSION

4.1. Simple linear regression model

The biological activity data and the physicochemical properties IPV, IP, EA, EI, EN, Hardness, Softness, LOGP, HE and POL of the Aphorphine derivatives are given in Table 3. The data from this table was subjected to regression analysis [24]. The Correlation matrices were generated with 25 analogs (Table 4). The term close to 1 indicates high co-linearity, while the value below 0.5 indicates that no co-linearity exist between more than the two parameters. The perusal of correlation matrix (Table 5) indicates that Hardness, Softness and EA are the predicted parameters from AM1 method. Hardness, Softness and EA were found to be explainable variable from regression methods backward, forward, removed and stepwise.

Predicted Activity = (3.116*EA) + (3.033*Hardness) + (-82.631*Softness) ----------→ (1)

N=25; R=0.957; R^2 =0.917; AdjR^2=0.905; %EV = 91.7; SEE = 1.09568; F= 80.644; Q=0.87343;
In addition, the plot of observed activity versus predicted activity was not found to be satisfactory. Hence, the predictive ability of the model is not good. Eq.1 shows that the values of %EV are less and to improve its value, outliers were sought and eliminated.
After the elimination of the outlier (2, 3, 4, 5, 6, 7, 10, 12, 15, 16, 17, 18, 22 and 24), a second model was developed. Overall, there is an increase in R and %EV (91.7-99.6) values, and a decrease in SEE (1.09568-0.25176).

Predicted Activity = (3.780*EA) + (3.503*Hardness) + (-100.078*Softness) ----------→ (2)

N=11; R=0.998; R^2=0.996; AdjR^2=0.994; %EV=99.6; SEE=0.25176; F=654.952; Q=3.96409;
Eq.2 is an improved model since it explains the biological activity to the extent of 99.6%. In this way, the predictive molecular descriptors EA, Hardness and Softness were considered as variables.
In an attempt to investigate the predictive potential of proposed models, the cross-validation parameters (q^2_{cv} and PRESS) were calculated and used. The predictive power of the equations was confirmed by cross-validation method where, compounds are deleted one after another and prediction of the activity of the deleted compound is made based on QSAR model. The cross-validation evaluates the validity of a model by how well it predicts the data rather than how well it fits the data. The cross-validation parameter, q^2_{cv}, is mentioned in the respective equations (Table 6).

$$q^2_{cv} = \frac{(SD - PRESS)}{SD}$$

Where the PRESS (predictive residual sum of squares) and SD (standard deviation) values are obtained as
PRESS = $\sum (\text{property}_{observed} - \text{property}_{predicted})^2$.
SD = $\sum (\text{property}_{observed} - \text{property}_{mean})^2$.
The PRESS, SD, q^2_{cv} values for the twenty five Aphorphine derivatives (AM1 method) is given by
PRESS=26.4287, SD=36.98494, q^2_{cv}=0.285420.
The PRESS, SD, q^2_{cv} values for the eleven Aphorphine derivatives (AM1 method) is given by
PRESS=0.5053, SD=3.205454, q^2_{cv}=0.957999.
From the above observations, AM1 method gave a good q^2_{cv}values, which should be always smaller than %EV. A model is considered to be significant when q^2_{cv}>0.3.
Another cross-validation parameter, PRESS which is the sum of the squared differences between the actual and that predicted when the compound is omitted from the fitting process, also supports the predictive ability of Eq.2. Its value decreases from Eq.1.
The quality factor Q, is defined as the ratio of regression constants (R) to the standard error estimation (SEE), i.e. Q = R/SEE. This indicates that the higher the value of R, and the lower the value of SEE, the higher is the magnitude of Q and the better will be the correlation. In present case, Q increases from 0.87343 to 3.96409 (Eq. 1 & 2).

4.2. *Docking Analysis*

The compounds were then docked in to protein active site using docking software [25]. The ChemScore and GOLD fitness of two docking software's are presented in Table 2. The binding energies obtained in Argus Lab ranged from -5.32874 to - 6.15282 kJ/mol. The results of CCDC GOLD can be analyzed both in terms of energy values ranging from -17.66 to 22.85 and -2831.96 to 35.01. The docking simulation of the most active Aphorphine derivatives 25 towards Dopamine (2) (PDB ID 4DUB) showed that the enzyme–inhibitor complex was stabilized by hydrophobic interactions occurring between the aromatic moieties of the ligand and lipophilic residues of the binding site [26]. The compounds 8, 13, 14, 19, 21 and 23 were oriented towards the hydrophobic region lined by ASP110A, PHE346A, GLU1011, LEU1032, ASP1020A and GLU1022A. Result of docking studies has proved that the molecule number 21 shows Chemscore, Gold fitness and RMSD values as 17.14, 35.01 and 1.5 Å respectively (Table2). The molecule 21 has been reported with appreciable IC_{50} values of 11.5µM. All the poses of molecule 21(chosen as best in docking studies) and its interactions in the active pocket of Dopamine (2) have been illustrated in Figure 4.

Table 3
Values obtained for the AM1 computational method.

Compound	IPV	EA	EN(μ)	Hardness(η)	Softness(S)	EI(ω)	ACT	HE	LOGP	POL(Aº3)
1	8.27	0.89	4.58	3.69	0.14	2.84	3.18	-7.29	-0.17	30.1
2	8.41	0.91	4.66	3.75	0.13	2.9	4.32	-10.83	-0.05	34.02
3	8.62	1.29	4.96	3.67	0.14	3.35	3.06	-10.68	0.74	35.36
4	8.55	1.12	4.84	3.71	0.13	3.15	1.15	-10.52	-0.66	33.92
5	8.58	1.16	4.87	3.71	0.13	3.2	5.37	-11.37	-1.47	30.25
6	8.55	1.44	4.99	3.55	0.14	3.51	2.72	-11.04	2.16	48.69
7	8.34	1.19	4.77	3.58	0.14	3.18	3.85	-9.26	0.88	46.61
8	8.78	1.47	5.12	3.66	0.14	3.59	4.82	-18.36	0.66	47.5
9	8.83	1.48	5.15	3.67	0.14	3.61	4.7	-17.96	1.13	49.33
10	8.53	1.42	4.97	3.55	0.14	3.48	4.07	-18.97	0.32	45.66
11	8.52	1.03	4.78	3.74	0.13	3.05	3.63	-11.77	1.34	45.02
12	8.69	1.86	5.28	3.42	0.15	4.08	5.37	-10.25	1.45	40.09
13	8.47	0.13	4.3	4.17	0.12	2.22	2.87	-12.88	-0.22	32.18
14	8.47	0.13	4.3	4.17	0.12	2.21	3.28	-12.24	0.59	35.85
15	8.49	1.39	4.94	3.55	0.14	3.44	1.84	-15.66	0.19	39.67
16	8.66	1.27	4.96	3.69	0.14	3.33	1.92	-13.07	0.38	33.53
17	8.35	0.81	4.58	3.77	0.13	2.78	2	-5.16	0.91	33.38
18	8.35	0.79	4.57	3.78	0.13	2.77	3.9	-5.07	0.97	33.38
19	8.36	0.83	4.59	3.77	0.13	2.8	3.23	-5.92	0.16	29.71
20	8.37	0.98	4.67	3.7	0.14	2.95	2.79	-12.9	-1.86	32.82
21	7.82	1.43	4.62	3.2	0.16	3.34	0.94	-10.81	0.78	30.19
22	8.37	0.97	4.67	3.7	0.14	2.95	3.79	-12.9	-1.86	32.82
23	8.14	0.94	4.54	3.6	0.14	2.86	2.07	-5.43	0.91	33.48
24	8.54	1.14	4.84	3.7	0.14	3.17	5.05	-10.39	0	36.64
25	8.55	1.15	4.85	3.7	0.14	3.18	3.75	-11.08	-0.81	32.97

Table 4
Correlation matrix between the selected variables, by using AM1 method.

		IPV	EA	EN	η	S	EI	ACT	HE	LOGP	POL
IPV	Pearson Correlation	1	.284	.647**	.248	-.295	.404*	.531**	-.535**	.071	.512**
	Sig. (2-tailed)		.168	.000	.231	.152	.045	.006	.006	.736	.009
	N	25	25	25	25	25	25	25	25	25	25
EA	Pearson Correlation	.284	1	.915**	-.858**	.828**	.987**	.185	-.334	.262	.476*
	Sig. (2-tailed)	.168		.000	.000	.000	.000	.377	.103	.206	.016
	N	25	25	25	25	25	25	25	25	25	25
EN	Pearson Correlation	.647**	.915**	1	-.577**	.533**	.955**	.370	-.491*	.238	.594**
	Sig. (2-tailed)	.000	.000		.003	.006	.000	.068	.013	.251	.002
	N	25	25	25	25	25	25	25	25	25	25
η	Pearson Correlation	.248	-.858**	-.577**	1	-.994**	-.781**	.098	.051	-.227	-.207
	Sig. (2-tailed)	.231	.000	.003		.000	.000	.643	.810	.276	.322
	N	25	25	25	25	25	25	25	25	25	25
S	Pearson Correlation	-.295	.828**	.533**	-.994**	1	.754**	-.129	-.057	.244	.186
	Sig. (2-tailed)	.152	.000	.006	.000		.000	.539	.788	.240	.373
	N	25	25	25	25	25	25	25	25	25	25
EI	Pearson Correlation	.404*	.987**	.955**	-.781**	.754**	1	.250	-.406*	.290	.532**
	Sig. (2-tailed)	.045	.000	.000	.000	.000		.229	.044	.160	.006
	N	25	25	25	25	25	25	25	25	25	25
ACT	Pearson Correlation	.531**	.185	.370	.098	-.129	.250	1	-.236	-.042	.327
	Sig. (2-tailed)	.006	.377	.068	.643	.539	.229		.255	.843	.110
	N	25	25	25	25	25	25	25	25	25	25
HE	Pearson Correlation	-.535**	-.334	-.491*	.051	-.057	-.406*	-.236	1	.110	-.555**
	Sig. (2-tailed)	.006	.103	.013	.810	.788	.044	.255		.601	.004
	N	25	25	25	25	25	25	25	25	25	25
LOGP	Pearson Correlation	.071	.262	.238	-.227	.244	.290	-.042	.110	1	.565**
	Sig. (2-tailed)	.736	.206	.251	.276	.240	.160	.843	.601		.003
	N	25	25	25	25	25	25	25	25	25	25
POL	Pearson Correlation	.512**	.476*	.594**	-.207	.186	.532**	.327	-.555**	.565**	1
	Sig. (2-tailed)	.009	.016	.002	.322	.373	.006	.110	.004	.003	
	N	25	25	25	25	25	25	25	25	25	25

Table 5
Correlation matrix between the selected variables, by using AM1 method.

		IPV	EA	EN	η	S	EI	ACT	HE	LOGP	POL
IPV	Pearson Correlation	1	.061	.552	.475	-.530	.209	.967**	-.685*	.049	.746**
	Sig. (2-tailed)		.858	.078	.140	.093	.537	.000	.020	.885	.008
	N	11	11	11	11	11	11	11	11	11	11
EA	Pearson Correlation	.061	1	.866**	-.850**	.809**	.986**	.177	-.296	.201	.428
	Sig. (2-tailed)	.858		.001	.001	.003	.000	.604	.377	.553	.189
	N	11	11	11	11	11	11	11	11	11	11
EN	Pearson Correlation	.552	.866**	1	-.472	.411	.929**	.632*	-.590	.193	.731*
	Sig. (2-tailed)	.078	.001		.142	.210	.000	.037	.056	.570	.011
	N	11	11	11	11	11	11	11	11	11	11
η	Pearson Correlation	.475	-.850**	-.472	1	-.994**	-.759**	.355	-.101	-.151	.017
	Sig. (2-tailed)	.140	.001	.142		.000	.007	.284	.768	.657	.961
	N	11	11	11	11	11	11	11	11	11	11
S	Pearson Correlation	-.530	.809**	.411	-.994**	1	.718*	-.422	.097	.168	-.054
	Sig. (2-tailed)	.093	.003	.210	.000		.013	.196	.776	.622	.874
	N	11	11	11	11	11	11	11	11	11	11
EI	Pearson Correlation	.209	.986**	.929**	-.759**	.718*	1	.310	-.434	.229	.546
	Sig. (2-tailed)	.537	.000	.000	.007	.013		.354	.182	.498	.082
	N	11	11	11	11	11	11	11	11	11	11
ACT	Pearson Correlation	.967**	.177	.632*	.355	-.422	.310	1	-.604*	.094	.736**
	Sig. (2-tailed)	.000	.604	.037	.284	.196	.354		.049	.783	.010
	N	11	11	11	11	11	11	11	11	11	11
HE	Pearson Correlation	-.685*	-.296	-.590	-.101	.097	-.434	-.604*	1	-.095	-.765**
	Sig. (2-tailed)	.020	.377	.056	.768	.776	.182	.049		.782	.006
	N	11	11	11	11	11	11	11	11	11	11
LOGP	Pearson Correlation	.049	.201	.193	-.151	.168	.229	.094	-.095	1	.523
	Sig. (2-tailed)	.885	.553	.570	.657	.622	.498	.783	.782		.099
	N	11	11	11	11	11	11	11	11	11	11
POL	Pearson Correlation	.746**	.428	.731*	.017	-.054	.546	.736**	-.765**	.523	1
	Sig. (2-tailed)	.008	.189	.011	.961	.874	.082	.010	.006	.099	
	N	11	11	11	11	11	11	11	11	11	11

IPV→Vertical Ionization Potential, *EA→Electron Affinity, *EN→Electro Negativity, *EI→Electophilicity Index, *ACT→Observed Activity, *HE→Hydration Energy, *LOGP→Partition Coefficient, *POL→Polarizability

Table 6
Observed Activity and Predicted Activity values of Aphorphine derivatives by using AM1 equations.

Compound	Observed Activity	Equation(1)		Equation(2)	
		Predicted	Residual	Predicted	Residual
1	3.18	2.78	-0.39	2.75	-0.43
2	4.32	3.18	-1.14	-	-
3	3.06	3.88	0.82	-	-
4	1.15	3.64	2.49	-	-
5	5.37	3.75	-1.62	-	-
6	2.72	3.63	0.92	-	-
7	3.85	3.01	-0.85	-	-
8	4.82	4.36	-0.46	4.67	-0.16
9	4.7	4.5	-0.2	4.84	0.14
10	4.07	3.57	-0.5	-	-
11	3.63	3.52	-0.11	3.64	0
12	5.37	4.07	-1.3	-	-
13	2.87	3.16	0.29	3.11	0.25
14	3.28	3.15	-0.13	3.1	-0.17
15	1.84	3.48	1.64	-	-
16	1.92	3.97	2.05	-	-
17	2	2.99	1	-	-
18	3.9	2.98	-0.91	-	-
19	3.23	3.03	-0.21	3.03	-0.2
20	2.79	3.08	0.29	3.11	0.32
21	0.94	1.22	0.28	0.95	0.01
22	3.79	3.08	-0.7	-	-
23	2.07	2.38	0.32	2.28	0.21
24	5.05	3.6	-1.45	-	-
25	3.75	3.65	-0.11	3.79	0.04

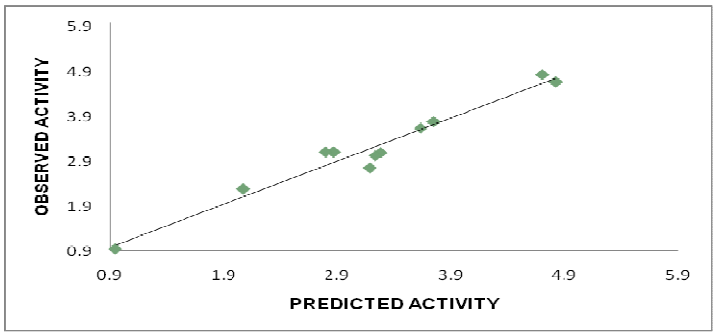


Figure 3
Plot of Observed Verses Predicted activity (AM1 Method)

The most active compounds docked successfully into the active site of the inhibited enzyme. Inhibitory activity of the most potent compounds was explained mostly by hydrophobic interactions. The compounds 1, 8, 9, 11, 13, 14, 19, 20, 21, 23 and 25 were found to present high antiprotozoal activity and significant inhibitory activity on Dopamine (2). The information rendered by QSAR models and the docking interactions may afford valuable clues to optimize the lead and design of new potential inhibitors. The order of the more effective and the higher activity of the remaining eleven Aphorphine compounds 21, 14, 23, 19, 8, 13, 1, 20, 25, 11 and 9. Best pose of the more effective and the higher activity of the Aphorphine compound21 is as follows.

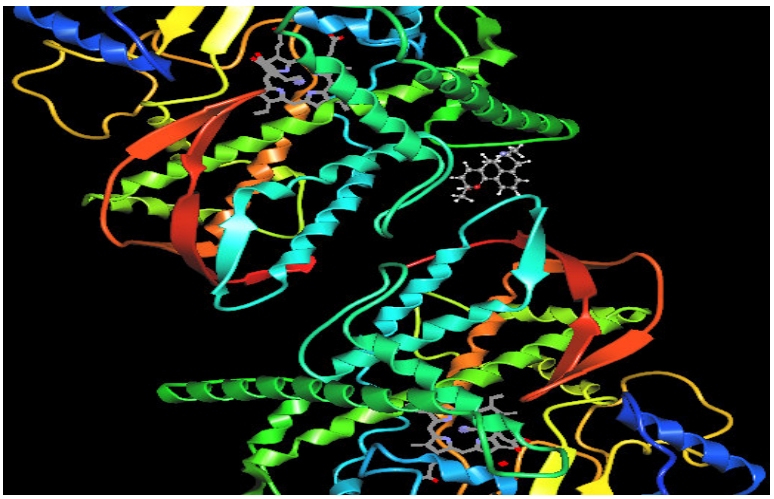


Figure 4
Best pose of molecule 21 and secondary structure of Dopamine (2) (PDB ID 4DUB)

SUPPORTING INFORMATION

Table 7
Values obtained for the PM3 computational method.

Compound	IPV	EA	EN(μ)	Hardness(η)	Softness(S)	EI(ω)	ACT	HE	LOGP	POL(A°3)
1	8.46	0.92	4.69	3.77	0.13	2.91	3.18	-7.27	-0.17	30.1
2	8.59	0.91	4.75	3.84	0.13	2.94	4.32	-11.04	-0.05	34.02
3	8.72	2.78	5.75	2.97	0.17	5.56	3.06	-10.72	0.74	35.36
4	8.7	1.14	4.92	3.78	0.13	3.2	1.15	-10.76	-0.66	33.92
5	8.73	1.19	4.96	3.77	0.13	3.27	5.37	-11.62	-1.47	30.25
6	8.82	1.49	5.15	3.67	0.14	3.62	2.72	-11.28	2.16	48.69
7	8.65	2.17	5.41	3.24	0.15	4.51	3.85	-9.3	0.88	46.61
8	8.83	2.49	5.66	3.17	0.16	5.05	4.82	-19.24	0.66	47.5

9	10.1	1.5	5.8	4.3	0.12	3.92	4.7	-18.18	1.13	49.33
10	8.82	1.81	5.32	3.5	0.14	4.03	4.07	-19.14	0.32	45.66
11	8.66	1.61	5.14	3.53	0.14	3.74	3.63	-11.95	1.34	45.02
12	8.72	2.24	5.48	3.24	0.15	4.64	5.37	-10.04	1.45	40.09
13	8.6	0.05	4.32	4.27	0.12	2.19	2.87	-12.93	-0.22	32.18
14	8.59	0.05	4.32	4.27	0.12	2.18	3.28	-12.25	0.59	35.85
15	8.78	1.89	5.34	3.44	0.15	4.14	1.84	-16.14	0.19	39.67
16	8.89	2.35	5.62	3.27	0.15	4.83	1.92	-12.68	0.38	33.53
17	8.51	0.82	4.67	3.84	0.13	2.83	2	-5.36	0.91	33.38
18	8.52	0.82	4.67	3.85	0.13	2.84	3.9	-5.27	0.97	33.38
19	8.57	0.88	4.73	3.85	0.13	2.9	3.23	-6.13	0.16	29.71
20	8.55	0.96	4.75	3.8	0.13	2.98	2.79	-13.12	-1.86	32.82
21	8.03	1.57	4.8	3.23	0.15	3.57	0.94	-12.57	0.78	30.19
22	8.55	0.96	4.75	3.8	0.13	2.98	3.79	-13.12	-1.86	32.82
23	8.44	1	4.72	3.72	0.13	2.99	2.07	-5.59	0.91	33.48
24	8.68	1.16	4.92	3.76	0.13	3.21	5.05	-10.65	0	36.64
25	8.69	1.16	4.92	3.76	0.13	3.22	3.75	-11.34	-0.81	32.97

IPV→Vertical Ionization Potential, *EA→Electron Affinity, *EN→Electro Negativity,
EI→Electophilicity Index, *ACT→Observed Activity, *HE→Hydration Energy,
LOGP→Partition Coefficient, *POL→Polarizability

Table 8
Correlation matrix between the selected variables, by using PM3 method.

		IPV	EA	EN	η	S	EI	ACT	HE	LOGP	POL
IPV	Pearson Correlation	1	.252	.609**	.241	-.200	.317	.376	-.506**	.181	.598**
	Sig. (2-tailed)		.225	.001	.246	.338	.123	.064	.010	.387	.002
	N	25	25	25	25	25	25	25	25	25	25
EA	Pearson Correlation	.252	1	.921**	-.879**	.892**	.989**	.112	-.348	.337	.493*
	Sig. (2-tailed)	.225		.000	.000	.000	.000	.593	.088	.100	.012
	N	25	25	25	25	25	25	25	25	25	25
EN	Pearson Correlation	.609**	.921**	1	-.623**	.651**	.938**	.244	-.489*	.349	.645**
	Sig. (2-tailed)	.001	.000		.001	.000	.000	.240	.013	.088	.001
	N	25	25	25	25	25	25	25	25	25	25
η	Pearson Correlation	.241	-.879**	-.623**	1	-.993**	-.835**	.073	.100	-.248	-.199
	Sig. (2-tailed)	.246	.000	.001		.000	.000	.728	.636	.231	.340
	N	25	25	25	25	25	25	25	25	25	25
S	Pearson Correlation	-.200	.892**	.651**	-.993**	1	.864**	-.065	-.131	.275	.216
	Sig. (2-tailed)	.338	.000	.000	.000		.000	.759	.533	.183	.300
	N	25	25	25	25	25	25	25	25	25	25
EI	Pearson Correlation	.317	.989**	.938**	-.835**	.864**	1	.140	-.384	.352	.513**
	Sig. (2-tailed)	.123	.000	.000	.000	.000		.506	.058	.084	.009
	N	25	25	25	25	25	25	25	25	25	25
ACT	Pearson Correlation	.376	.112	.244	.073	-.065	.140	1	-.207	-.042	.327
	Sig. (2-tailed)	.064	.593	.240	.728	.759	.506		.322	.843	.110
	N	25	25	25	25	25	25	25	25	25	25
HE	Pearson Correlation	-.506**	-.348	-.489*	.100	-.131	-.384	-.207	1	.106	-.541**
	Sig. (2-tailed)	.010	.088	.013	.636	.533	.058	.322		.615	.005
	N	25	25	25	25	25	25	25	25	25	25
LOGP	Pearson Correlation	.181	.337	.349	-.248	.275	.352	-.042	.106	1	.565**
	Sig. (2-tailed)	.387	.100	.088	.231	.183	.084	.843	.615		.003
	N	25	25	25	25	25	25	25	25	25	25
POL	Pearson Correlation	.598**	.493*	.645**	-.199	.216	.513**	.327	-.541**	.565**	1
	Sig. (2-tailed)	.002	.012	.001	.340	.300	.009	.110	.005	.003	
	N	25	25	25	25	25	25	25	25	25	25

IPV→Vertical Ionization Potential, *EA→Electron Affinity, *EN→Electro Negativity,
EI→Electophilicity Index, *ACT→Observed Activity, *HE→Hydration Energy,
LOGP→Partition Coefficient, *POL→Polarizability

Table 9
Correlation matrix between the selected variables, by using PM3 method.

		IPV	EA	EN	η	S	EI	ACT	HE	LOGP	POL
IPV	Pearson Correlation	1	.197	.605	.336	-.299	.245	.794*	-.640	.400	.631
	Sig. (2-tailed)		.611	.084	.376	.435	.526	.011	.063	.286	.069
	N	9	9	9	9	9	9	9	9	9	9
EA	Pearson Correlation	.197	1	.900**	-.857**	.871**	.989**	.365	-.018	.402	.493
	Sig. (2-tailed)	.611		.001	.003	.002	.000	.335	.962	.283	.177
	N	9	9	9	9	9	9	9	9	9	9
EN	Pearson Correlation	.605	.900**	1	-.547	.574	.912**	.649	-.300	.505	.681*
	Sig. (2-tailed)	.084	.001		.128	.106	.001	.059	.433	.166	.043
	N	9	9	9	9	9	9	9	9	9	9
η	Pearson Correlation	.336	-.857**	-.547	1	-.993**	-.821**	.067	-.319	-.176	-.142
	Sig. (2-tailed)	.376	.003	.128		.000	.007	.864	.403	.650	.715
	N	9	9	9	9	9	9	9	9	9	9
S	Pearson Correlation	-.299	.871**	.574	-.993**	1	.852**	-.070	.316	.214	.136
	Sig. (2-tailed)	.435	.002	.106	.000		.004	.859	.407	.580	.728
	N	9	9	9	9	9	9	9	9	9	9
EI	Pearson Correlation	.245	.989**	.912**	-.821**	.852**	1	.356	-.037	.442	.476
	Sig. (2-tailed)	.526	.000	.001	.007	.004		.347	.926	.233	.196
	N	9	9	9	9	9	9	9	9	9	9
ACT	Pearson Correlation	.794*	.365	.649	.067	-.070	.356	1	-.583	.636	.909**
	Sig. (2-tailed)	.011	.335	.059	.864	.859	.347		.099	.065	.001
	N	9	9	9	9	9	9	9	9	9	9
HE	Pearson Correlation	-.640	-.018	-.300	-.319	.316	-.037	-.583	1	-.082	-.541
	Sig. (2-tailed)	.063	.962	.433	.403	.407	.926	.099		.834	.133
	N	9	9	9	9	9	9	9	9	9	9
LOGP	Pearson Correlation	.400	.402	.505	-.176	.214	.442	.636	-.082	1	.665
	Sig. (2-tailed)	.286	.283	.166	.650	.580	.233	.065	.834		.051
	N	9	9	9	9	9	9	9	9	9	9
POL	Pearson Correlation	.631	.493	.681*	-.142	.136	.476	.909**	-.541	.665	1
	Sig. (2-tailed)	.069	.177	.043	.715	.728	.196	.001	.133	.051	
	N	9	9	9	9	9	9	9	9	9	9

IPV→Vertical Ionization Potential, *EA→Electron Affinity, *EN→Electro Negativity,
EI→Electophilicity Index, *ACT→Observed Activity, *HE→Hydration Energy,
LOGP→Partition Coefficient, *POL→Polarizability

Table 10
Observed Activity and Predicted Activity values of Aphorphine derivatives by using PM3 Equations.

Compound	Observed Activity	Equation(1)		Equation(2)	
		Predicted	Residual	Predicted	Residual
1	3.18	2.71	-0.47	2.68	-0.5
2	4.32	3.06	-1.26	-	-
3	3.06	3.18	0.12	3.15	0.09
4	1.15	3.05	1.9	-	-
5	5.37	2.72	-2.64	-	-
6	2.72	4.38	1.67	-	-
7	3.85	4.19	0.34	4.15	0.29
8	4.82	4.27	-0.55	-	-
9	4.7	4.44	-0.26	4.39	-0.31
10	4.07	4.11	0.04	4.06	-0.01
11	3.63	4.05	0.42	4.01	0.37
12	5.37	3.61	-1.76	-	-
13	2.87	2.9	0.03	2.86	0
14	3.28	3.23	-0.05	3.19	-0.09
15	1.84	3.57	1.73	-	-
16	1.92	3.02	1.09	-	-
17	2	3	1.01	-	-
18	3.9	3	-0.89	-	-
19	3.23	2.67	-0.56	-	-
20	2.79	2.95	0.16	2.92	0.13
21	0.94	2.72	1.78	-	-
22	3.79	2.95	-0.83	-	-
23	2.07	3.01	0.95	-	-
24	5.05	3.3	-1.75	-	-
25	3.75	2.97	-0.78	-	-

From the correlation matrix table, it reveals POL is found to be explainable variables from regression methods backward, forward, removed and stepwise. A diparametric QSAR equation with POL was generated in PM3 method also.

Predicted Activity = (0.090*POL) ----------→ (3)

N=25; R=0.945; R^2=0.893; AdjR^2=0.889; %EV=89.3; SEE =1.18592; F=201.293; Q=0.79684;
Eq.3 shows that the values of %EV is less and to improve its value, outliers were sought and eliminated, In addition, the plot of observed activity versus predicted activity was not found to be satisfactory. Hence, the predictive ability of the model is not good. After the elimination of the outlier (2, 4, 5, 6, 8, 12, 15, 16, 17, 18, 19, 21, 22, 23, 24 and 25), a second model was developed.

Predicted Activity = (0.089*POL) ----------→(4)

N=9; R=0.997; R^2 =0.995; AdjR^2=0.994; %EV = 99.5; SEE=0.27372; F=1498.636; Q=3.64240;
The PRESS, SD, q^2_{cv} values for the twenty five Aphorphine derivatives (PM3 method) is given by PRESS=33.7563, SD=36.984944, q^2_{cv}=0.087296.
The PRESS, SD, q^2_{cv} values for the nine Aphorphine derivatives (PM3 method) is given by PRESS=0.6138, SD=3.149155, q^2_{cv}=0.805090.
From the above observations PM3 method given a good q^2_{cv} value i.e. q^2_{cv}>0.3 and Q value increases from 0.79684 to 3.64240 (Eqs. 3 & 4).

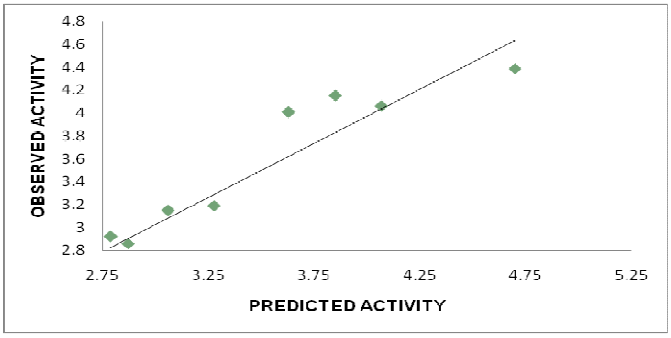


Figure 5
Plot of Observed Verses Predicted activity (PM3 Method)

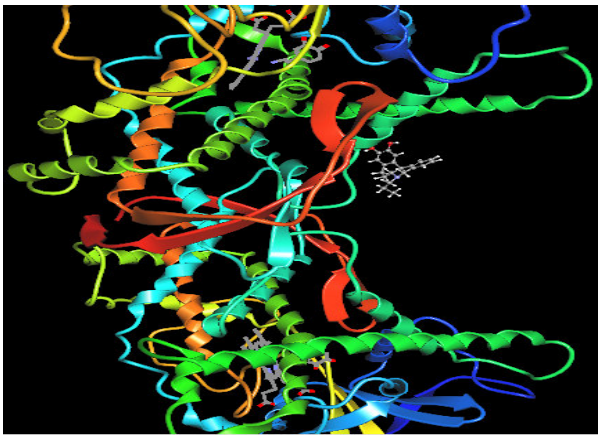


Figure 6
Best pose of molecule 14 and secondary structure of Dopamine (2) (PDB ID 4DUB)

5. CONCLUSION

Quantitative structure–activity relationship studies (QSAR) and molecular docking were performed on twenty five Aphorphine Dopamine (2) inhibitors to find out the structural relationship with the activity. The best predictive AM1 model resulted in cross-validated R^2 value of 0.996, AdjR^2 value of 0.994 and standard error of estimate 0.25176 (AM_1). Similarly the best predictive PM3 model was derived with R^2 of 0.995, AdjR^2 of 0.994 and standard error of estimate of 0.27372, comprising softness, hydration energy, hydrophobic and hydrogen bond donor fields. These models were able to predict the activity of test set molecules efficiently (best molecules 1, 8, 9, 11, 13, 14, 19, 20, 21, 23 and 25) within an acceptable error range. GOLD and Argus lab docking software were employed to dock the inhibitors into the active site of Dopamine (2) and these docking studies revealed the vital interactions and binding conformation of the inhibitors. Therefore, the present study showed that the QSAR studies and the docking approach of Aphorphine derivatives as Dopamine (2) inhibitors can be successfully modelled using the parametric equations. The Eq.2 from AM1, semi empirical calculations reveal EA, Hardness and Softness cause the inhibitory activity. Higher values of EA, Hardness and Softness were responsible for higher inhibitory activity nature for Dopamine (2) enzyme. The linear dependence of inhibitory nature on Hardness, Softness and HE were evident from Figure 3.

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