Research Article

Computational Study of Substituted 5[H] - Phenanthradin-6-Ones as Poly (ADP-Ribose) Polymerase-1 (PARP-1) Inhibitors by Analog and Structure Based Methods

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ABSTRACT

The poly (ADP-ribose) polymerase-1 (PARP-1) is an abundant nuclear protein involved in DNA repair and programmed cell death. Substituted 5(H) phenanthradin-6-one analogs were found to be potent PARP-1 inhibitors. Semiempirical methods were used to estimate various physicochemical parameters. The hydration energy (HE), ionization potential (IP), electrophilic index (ω) and partition coefficient (LogP) were resulted as independent variables for inhibitory activity of the analogs. The overall increase of HE, IP, and EI and overall decrease of LogP enhance the efficacy of inhibitory nature of these analogs to PARP-1. Docking studies of 5(H) phenanthradin-6-one analogs with PARP-1 were also performed in support of the findings of QSAR studies. Analysis of results of both QSAR and docking studies suggested that remarkable inhibitory activity is exhibited by molecules **9b**, **10b1** and **10b2**. The hydrogen bond interactions along with hydrophobic and electrostatic interactions are mapped to confirm their potencies.

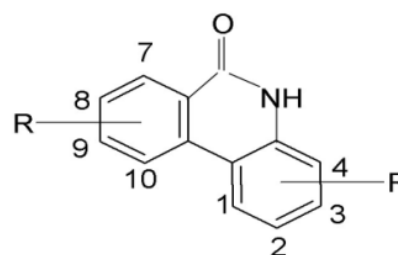**Keywords:** Computational study, structure based methods

INTRODUCTION

The PARP (ADP-Ribose) polymerase-1 family consists of 17 members (10 putative). They have all very different structures and functions in the cell. The members that have confirmed PARP activity are PARP-1(Fig.2), PARP-2, VPARP (PARP-4), Tankyrase-1 and -2 (PARP-5a or TNKS, and PARP-5b or TNKS2). Others include PARP-3, PARP-6, TIPARP (or "PARP7"), PARP-8, PARP-9, PARP-10, PARP-11, PARP-12, PARP-14, PARP-15, and PARP-16. PARP-1(Poly (ADP-ribose) polymerase-1) is nuclear DNA repair enzyme as component of base excision repair complex. PARP-1 is also known as NAD^+ ADP-ribosyltransferase-1 or poly (ADP-ribose) synthase-1 is an enzyme that in humans is encoded by the PARP-1 gene[1]. It is a protein involved in a number of cellular processes involving mainly DNA repair and programmed cell death. PARP-1 is also involved and finds applications in differentiation, proliferation, and tumor transformation, may participate in the path physiology of type I diabetes[2] . It is theorized that PARP-1 inhibitors may prove highly effective therapy for cancers with BRCAness, due to the high sensitivity of the tumors to the inhibitor and the lack of deleterious effects on the remaining healthy cells with functioning BRCA HR pathway. This is in contrast to conventional chemotherapies which are highly toxic to all cells and can induce DNA damage in healthy cells, leading to secondary cancer generation[3,4].

A common structural feature for the classical PARP-1 inhibitors is a carbaxamide attached to an aromatic ring or a fused aromatic aromatic lactam or imide[5]. Most of these inhibitors are structurally planar and show limited solubility in both organic and aqueous solvents.
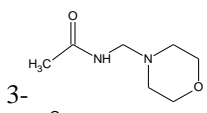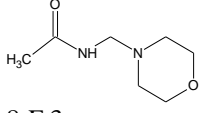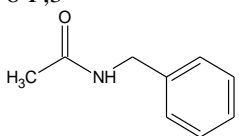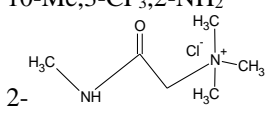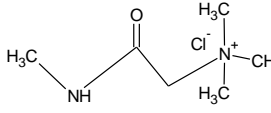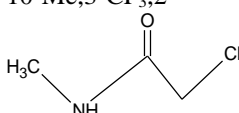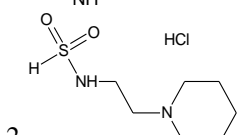
5[H] phenanthradin-6-ones (figure 3 and table 1) was initially identified as a moderate PARP-1 inhibitor[6]. In vivo testing of this compound is hindered by its poor solubility in bio-compatible vehicles. It was also found to cross inhibitor heterophil arginine ADP–ribose transferase (IC-%50- 47µm)[7]. Recently, to improve the efficacy of this class of inhibitors appropriate substituent(s) onto 5[H] phenanthradin-6-ones were made, the **29** analogs were synthesized.

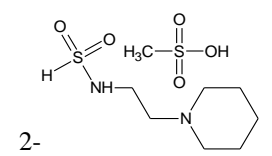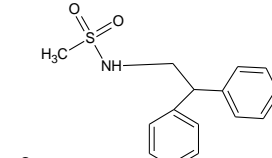It prompted us to carry out molecular modeling studies for arriving the best chemical improvement to have high inhibitory efficacy of 5[H] phenanthradin-6-one analogs. It is an attempt to elucidate the QSAR study of 5[H] phenanthradin-6-one analogs as PARP-1 inhibitor by using different physicochemical parameters like ionization potentials(IP), hydration energy(HE), polarisability (Pol),

Structure A

Table 1: Structural skeleton and Inhibition effect of 5[H] Phenanthradin-6-one analogs PARP-1 activities (Figure.3).

Comp.	Substitution	IC$_{50}$ (μM)	Activity (3 + log1/IC$_{50}$)
1a	R = H	0.52	3.2839
1b	2-SO$_3$H,8-F	0.01	5.0000
1c	3-cl,8-cl	0.24	3.6197
1d	3-NH$_2$,8-NH$_2$	3.26	2.4868
1e	3-NO$_2$,8-NO$_2$	35	1.4549
5a1	3-COOMe	0.184	3.7351
5a2	8-F,3-COOMe	0.037	4.4317
5c1	3-	0.035	4.4559
5c2	8-F,3-	0.014	4.8538
5c3	8-F,3-	0.15	3.8239
9a	1-COOH	2.01	2.6968
9b	4-NH$_2$	0.312	3.5058
9c	4-NO$_2$	6.1	2.2146
9d	10-Me,3-F	0.092	4.0362
9e	10-COOH	>60	1.1523
10a1	10-Me,3-CF$_3$,NO$_2$	0.136	3.8664
10a2	2-NO$_2$	0.156	3.8068
10b1	2-NH$_2$	0.18	3.7447
10b2	3-NH$_2$,2-NH$_2$	0.18	3.7447
10b3	10-Me,3-CF$_3$,2-NH$_2$	0.044	4.3565
10c1	2-	0.03	4.5228
10c2	3-Me,2-	0.195	4.7086
10c3	10-Me,3-CF$_3$,2-	0.033	4.4814
11a1	2-	0.03	4.5228
11a2	2-	0.036	4.4436
11a3	2-	14	1.8535

LogP, etc…Recently Lien.et. Al[8] have reported on QSAR study of phenols with antioxidant activity by employing descriptors calculated by semi empirical methods AM1 and PM3 (Table 2, 3) A theoretical study of phenolic compounds with antioxidant property was also made on quantitative basis in which four computational methods density functional (DF), HF (Hartree-Fock) and AM1 and PM3 were employed to explore and determine various electronic descriptors with better accuracy to make the necessary improvement in the QSAR models. Vertical ionization potentials(IPv's), electrophilic index (ω), Ionization potential(IP), electron affinity (EA), electronegativity (χ), hardness (η), softness (S), polarisability (Pol) charges and other properties were obtained for 41 phenolic compounds which have antioxidant activity[8-10].

To correlate the biological activity of 5[H] phenanthradin-6-one analogs with ionization potentials, electron affinity, electronegativity, hardness(η), partition coefficient (LogP), softness(S), hydration energy(HE) and polarisability(Pol) from computational methods AM1 and PM3 (Table 6,7).GOLD and Argus lab 4.0.1 is Molecular modeling and Drug Docking software's[11-12]. 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.

Computational Methodology Calculations
Data Set
The physicochemical parameters ,such as vertical ionization potentials (IPv's) electron affinity (EA) , electronegativity (χ), hardness (η), softness (S), electrophilic index (ω), partition coefficient (LogP), charges, hydration energy(HE) and polarisability (Pol) were obtained for 26 5[H] phenanthradin-6-one compounds which have PARP-1 inhibitory activity.

Molecular Structure Building
A series of compounds tested for inhibitory activity was selected for the present study and the program of window Hyperchem software inc.[13] was used in modeling studies. The molecules were generated and the energy was minimized using molecular modeling pro. The window version software SPSS10[14] was used in the regression analysis.

Building of QSAR Models
QSAR technique was applied to the analogs of 5[H] phenanthradin-6-ones that were varied at the "R" position. The suitable descriptors or parameters for the compounds,

Table 2: Values obtained for the AM1 computational method.

Comp	IPv = $-\varepsilon_{HOMO(AM1)}$	IP	EA	EN	η	S	ω	LogP	HE	Pol(A°³)
1a	-8.7239	-1.6328	-9.7562	-5.6945	4.0617	.1231	3.9918	-.1300	-4.9500	22.590
1b	-9.3494	-1.3256	-8.8659	-5.0957	3.7702	.1326	3.4437	-2.0900	-14.610	24.280
1c	-8.9245	-1.4390	-9.4149	-5.4269	3.9880	.1254	3.6925	-.5800	-4.3000	26.450
1d	-7.9670	-1.0160	-8.9810	-4.9985	3.9825	.1255	3.1368	-3.5700	-14.630	25.290
1e	-8.9963	-1.2508	-9.1688	-5.8352	3.9590	.1263	4.3003	-1.7600	-16.060	26.020
5a1	-8.9749	-1.5016	-9.2147	-5.3581	3.8566	.1296	3.7221	-.7200	-5.3400	26.980
5a2	-9.0465	-1.4559	-9.1135	-5.2847	3.8288	.1306	3.6471	-1.3200	-5.1100	26.890
5c1	-8.9280	-1.4540	-9.2322	-5.3431	3.8891	.1286	3.6704	-1.7300	-7.4100	38.090
5c2	-9.0004	-1.4134	-9.1263	-5.2698	3.8565	.1297	3.6006	-2.3300	-7.1700	38.000
5c3	-6.5223	-2.1071	-6.5885	-4.3478	2.2407	.2231	4.2182	-.1800	-4.7700	39.490
9a	-8.9731	-1.5391	-9.5204	-5.5297	3.9907	.1253	3.8312	-.7500	-10.820	25.150
9b	-8.5340	-1.3244	-9.5166	-5.4205	4.0961	.1221	3.5866	-1.8500	-8.5900	23.940
9c	-8.5003	-2.1052	-8.1946	-5.1499	3.0447	.1642	4.3554	-.9500	-8.6500	24.310
9d	-8.7787	-1.5080	-9.5797	-5.5438	4.0359	.1239	3.8076	-.5800	-3.7400	24.340
9e	-7.0360	-1.3021	-6.8920	-4.0770	2.7950	.1789	2.9736	-.7500	-4.5100	25.150
10a1	-9.2148	-1.3528	-9.2349	-5.2938	3.9411	.1269	3.5554	-.2300	-7.0200	27.700
10a2	-8.8470	-1.4413	-9.5241	-5.4827	4.0414	.1237	3.7190	-.9500	-11.060	24.310
10b1	-7.9881	-1.5388	-9.0620	-5.3004	3.7616	.1329	3.7343	-1.8500	-9.6500	23.940
10b2	-8.0535	-1.1460	-9.0118	-5.0789	3.9329	.1271	3.2794	-3.5700	-13.400	25.290
10b3	-8.4997	-1.1962	-8.8429	-5.0195	3.8234	.1308	3.2949	-1.1300	-6.3900	27.340
10c1	-8.3155	-.6528	-9.0961	-4.8744	4.2217	.1184	2.8140	-2.0000	-4.8400	36.290
10c2	-8.5398	-.3780	-9.2835	-4.8307	4.4528	.1123	2.6204	-1.8500	-3.6400	38.130
10c3	-8.7737	-1.1870	-8.9654	-5.0762	3.8892	.1286	3.3127	-.7100	-2.7000	33.020
11a1	-9.2042	-1.2009	-9.7923	-5.4966	4.2957	.1164	3.5166	-1.0700	-6.3800	38.500
11a2	-9.1742	-1.2500	-9.7232	-5.4866	4.2366	.1180	3.5527	-1.0700	-8.6000	38.500
11a3	-8.9663	-.9818	-9.6100	-5.2959	4.3141	.1159	3.2506	1.3100	-7.8200	48.260

vertical ionization potentials(IPv's), electron affinity (EA), electronegativity(χ), electrophilic index (ω), hardness(η), softness(S), partition coefficient (LogP) charges, polarisability (Pol) and hydration energy (HE) were used as indepedndent variables for desiding in PARP-1 inhibitory activity.

Chemical Descriptors
Calculated Properties
Quantum chemical calculations at the DFT/RB3LYP/631G* (restricted B3LYP), RHF/6-31G* (restricted Hartree-Fock)[15] and AM1[16] and PM3[17] [semiempirical theory levels, are employed for full

optimization of the selected neutral compounds. 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. All calculations are performed by using the program of window Hyperchem software inc.
In this work, the more relevant electronic properties for phenolic compounds such as vertical ionization potential (IPv), electron affinity(EA), electronegativity (χ), hardness(η), softness(S), electrophilic index(ω), partition coefficient (Log P), charges (Mulliken's charges),

Table 3: Values obtained for the PM3 computational method.   The

Compound	IPv = -$\varepsilon_{HOMO(PM3)}$	IP	EA	EN	η	S	Ω	Log P	HE	Pol(A°³)
1a	-8.6813	-	-	-	3.9676	.1260	4.0911	-.1300	-4.9500	22.5900
1b	-9.2011	1.7301	9.6654	5.6977	3.7336	.1339	3.6078	-	-	24.2800
1c	-8.7873	-	-	-	3.9724	.1258	3.5587	2.0900	14.3900	26.4500
1d	-8.1270	1.4568	8.9241	5.1904	4.0479	.1235	3.0551	-.5800	-4.3000	25.2900
1e	-9.4444	-	-	-	5.0542	.0989	2.1280	-	-	26.0200
5a1	-8.8870	1.3449	9.2897	5.3173	3.7512	.1332	3.8382	3.5700	14.6300	26.9800
5a2	-9.0117	-.9254	-	-	3.7242	.1342	3.7982	-	-	26.8900
5c1	-8.9175	.4162	9.0213	4.9733	3.7963	.1317	3.7357	1.7600	16.0600	38.0900
5c2	-9.0338	-	-	-	3.7909	.1318	3.6853	-.7200	-5.3400	38.0000
5c3	-6.4179	1.6150	9.6922	4.6380	1.9484	.2566	4.9794	-	-5.1100	39.4900
9a	-8.8949	-	-	-	3.8526	.1298	3.8881	1.3200	-6.4800	25.1500
9b	-8.5055	1.5744	9.1175	5.3662	4.0196	.1243	3.5903	-	-7.1700	23.9400
9c	-9.0057	-	-	-	3.4514	.1448	3.8064	1.7300	-4.7700	24.3100
9d	-8.7907	1.5295	9.0635	5.3189	3.9671	.1260	3.9063	-	-	24.3400
9e	-7.2564	-	-	-	2.4970	.2002	2.8074	2.3300	10.8200	25.1500
10a1	-9.0578	1.9951	9.1221	5.3258	4.2100	.1187	2.7859	-.1800	-8.5900	27.7000
10a2	-8.7379	-	-	-	4.3656	.1145	2.9180	-.7500	-9.1600	24.3100
10b1	-8.2565	2.4566	9.0770	5.2860	3.9619	.1262	3.3892	-	-3.7400	23.9400
10b2	-8.1353	-	-	-	3.9064	.1279	3.3550	1.8500	-4.5100	25.2900
10b3	-8.5452	1.6209	6.3534	4.4050	3.8078	.1313	3.2759	-.9500	-7.0200	27.3400
10c1	-8.2833	-	-	-	4.0071	.1247	2.9589	-.5800	-	36.2900
10c2	-8.4383	1.3529	9.3262	5.4735	4.1789	.1196	2.7648	-.7500	10.4100	38.1300
10c3	-9.1368	-	-	-	4.2519	.1175	2.9843	-.2300	-9.6500	33.0200
11a1	-9.2730	1.6745	9.3921	5.3725	4.2622	.1173	3.5543	-.9500	-	38.5000
11a2	-9.1441	-	-	-	4.0365	.1238	3.6608	-	13.4000	38.5000
11a3	-8.8681	1.6001	8.5774	5.1259	4.6213	.1087	2.4061	1.8500	-6.4000	48.2600
		-	-	-				-	-4.8400	
		1.2464	9.5343	5.5672				3.5700	-3.6400	
		-.6364	-	-				-	-2.6600	
		-.6827	6.2404	3.7434				1.1300	-5.1500	
		-	-	-				-	-8.6000	
		1.2204	9.0565	4.8446				2.0000	-7.8200	
		-	-	-				-		
		1.2153	9.4139	5.0483				1.8500		
		-	-	-				-.7100		
		1.1872	9.1443	5.1823				-		
		-.8641	-	-				1.0700		
		-.6292	9.0281	5.1217				-		
		-.7878	-	-				1.0700		
		-	8.8028	4.9950				1.3100		
		1.2425	-	-						
		-	8.8783	4.8712						
		1.4014	-	-						
		-.0826	8.9871	4.8081						
			-	-						
			9.2916	5.0397						
			-	-						
			9.7669	5.5047						
			-	-						
			9.4745	5.4379						
			-	-						
			9.3263	4.7049						

hydration energy(HE) and polarisability (Pol) on some key atoms are calculated.

calculated vertical ionization potenti als (IPv's) and electron affinity (EA) are corrected for zero-point energy, assuming a negligible error and thus saving computer-

Table 4: Observed activity and predicted activity values of 5 [H] Phenanthradin-6-one analogs by using **AM1** Eqs.

Compound	Observed	Eq. (1)		Eq. (2)	
		Predicted	Residual	Predicted	Residual
1a	3.2839	3.9235	-.6396	3.9396	-.6557
1b	5.0000	2.7149	2.2851	-	-
1c	3.6197	4.1036	-.4839	4.1077	4880.
1d	2.4868	3.5432	-1.0564	-	-
1e	1.4549	2.8502	-1.3953	-	-
5a1	3.7351	3.9260	-.1909	3.9680	.2329
5a2	4.4317	4.2801	.1516	4.3329	.0988
5c1	4.4559	4.1276	.3283	4.2400	.2159
5c2	4.8538	4.4838	.3700	4.6081	.2457
5c3	3.8239	2.8494	.9745	3.6483	.1756
9a	2.6968	3.0048	-.3080	3.1636	-.4668
9b	3.5058	4.0336	-.5278	4.1665	-.6607
9c	2.2146	3.2364	-1.0218	-	-
9d	4.0362	4.3135	-.2773	4.3067	-.2705
9e	1.1523	3.0237	-1.8714	-	-
10a1	3.8664	3.2360	.6304	3.2891	.5773
10a2	3.8068	3.0411	.7657	3.2030	.6038
10b1	3.7447	3.7220	.0227	3.9036	-.1589
10b2	3.7447	3.8549	-.1102	4.1570	-.4123
10b3	4.3565	3.6846	.6719	3.7564	.6001
10c1	4.5228	4.4063	.1165	4.5897	-.0669
10c2	4.7086	4.5142	.1944	4.7938	-.0852
10c3	4.4814	4.2037	.2777	4.1817	.2997
11a1	4.5228	4.0536	.4692	4.1222	.4006
11a2	4.4436	3.6056	.8380	3.7181	.7255
11a3	1.8535	2.1277	-.2742	2.1916	-.3381

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 Koopman's theorem (IPv = $-\varepsilon_{HOMO}$). The electron affinity are computed as the energy differences between a neutral form and the anion molecule; EA=$E_{neutral} - E_{anion}$. The AM1 and PM3-based reactivity parameters are obtained from Eqs. (1) – (4)[18-22].

Correlation Analysis

A relation between biological activity, expressed as Log1/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 association 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. On the other hand, if the two variables tend to increase simultaneously the correlation coefficient is positive. We obtained the correlation matrix between inhibitory activity and respective calculated properties for **26** 5[H] phenanthradin-6-one analogs. The more significant regression models were selected following criteria: 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(R^2_{adj}).

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 consist in developing a number of models with one sample omitted at the time.

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)+23.

The predictive ability of the model was also quantified in terms of the Q^2 [24].

Docking Studies and Validation

The GOLD Score was calculated by defining the site using the list of atom numbers and retaining all the other default parameters. Now a days docking is frequently to predict the binding orientations of small molecules of drug candidates to their protein targets in order to predict the affinity of the small molecules[25]. The 3D structure of PARP-1 was retrieved from Protein Data Bank (PDB ID **3SE2**) with an X-ray resolution of 2.3A^{O26}. Docking poses were obtained by applying both Gold score and Chemscore, fitness functions available for scoring. As easily interpretable results were obtained based on a recently published, all the results reported in the present paper are referred to the Gold score and Chemscore fitness functions. These complexes were prepared for docking

Table 5: Observed activity and predicted activity values of 5 [H] Phenanthradin-6-one analogs by using **PM3** Eqs.

Compound	Observed	Eq. (3)		Eq. (4)	
		Predicted	Residual	Predicted	Residual
1a	3.2839	4.0759	-.7920	3.7643	-.4804
1b	5.0000	3.0310	1.9690	-	-
1c	**3.6197**	**4.0850**	-.4653	**3.9281**	-.3084
1d	2.4868	3.5402	-1.0534	-	-
1e	1.4549	2.1172	-.6623	-	-
5a1	**3.7351**	**4.0213**	-.2862	**3.8788**	-.1437
5a2	4.4317	4.3173	.1144	4.3668	.0649
5c1	4.4559	4.2964	.1595	4.4125	.0434
5c2	4.8538	4.4442	.4096	3.7683	1.0855
5c3	3.8239	3.0322	.7917	4.1410	-.3171
9a	2.6968	3.2067	-.5099	3.0752	-.3784
9b	**3.5058**	**4.0411**	-.5353	**4.2107**	-.7049
9c	2.2146	3.2893	-1.0747	-	-
9d	4.0362	4.3915	-.3553	4.1973	-.1611
9e	1.1523	2.7962	-1.6439	-	-
10a1	3.8664	3.0526	.8138	3.0905	.7759
10a2	**3.8068**	**3.0134**	.7934	**3.2294**	.5774
10b1	**3.7447**	**3.7014**	.0433	**3.9041**	-.1594
10b2	**3.7447**	**3.8730**	-.1283	**4.5129**	-.7682
10b3	4.3565	3.7310	.6255	3.7528	.6037
10c1	4.5228	4.3194	.2034	4.6732	-.1504
10c2	4.7086	4.3930	.3156	4.8370	-.1284
10c3	4.4814	4.1890	.2924	4.2630	.2184
11a1	4.5228	4.3445	.1783	4.3393	.1835
11a2	4.4436	3.7081	.7355	3.6676	.7760
11a3	1.8535	2.0356	-.1821	2.1346	-.2811

studies by adding hydrogen atoms, removing water molecules and co-crystallized inhibitors and refined by using the DeepView/SwissPdbViewer3.7(SP5)[27]. Enzyme-inhibitor interactions within a radius equal to 10 Å centered on information bound inhibitors were taken into explanation. 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 **26** 5[H] phenanthradin-6-one inhibitors and their corresponding Gold score ,Chemscore and binding energy values with their respective RMSD have been produced, in the table 8. All docking runs were carried out using standard default settings with a population size of 100, a selection pressure 1.1,a maximum of 100000 operations , number of islands as 5,a niche size of 2,migrate 10,a mutation and crossover rate of 95.

Argus Lab 4.0.1 is Molecular modeling and Drug Docking software. It is very flexible and can imitated crystallographic binding orientations. Argus lab, which provides a user-friendly graphical interface and uses Shape Dock algorithm, was used to carry out docking studies of the PARP-1.

RESULTS AND DISCUSSIONS
Simple linear regression model
The biological activity data and the physicochemical properties IPv, IP, EA, EI, EN, Hard, Soft, LogP, HE and Pol of the 5[H] Phenanthridin-6-one analogs are given in Tables 1-3. The data from these tables were subjected to regression analysis. The Correlation matrices were generated with 26 analogs (**Tables 4,4a and 5,5a**). 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.

Table 6: Inhibition of Poly (ADP-ribose) Polymerase-1 (PARP-1) GOLD Scores and Arguslabs Energy values of 5 [H] Phenanthradin-6-one analogs.

Comp	GOLD Data (fitness score)	ArgusLab (Energy values)
1a	40.67	-6.6781
1b	--	-6.6928
1c	**60.66**	**-6.1410**
1d	59.12	-8.7438
1e	--	0
5a1	**64.86**	**-8.6126**
5a2	--	-8.1840
5c1	--	0
5c2	--	0
5c3	**-**	**0**
9a	-	-9.3420
9b	**66.00**	**-9.1464**
9c	--	-8.6442
9d	--	-10.3000
9e	--	-9.9468
10a1	--	-6.5610
10a2	**59.93**	**-9.4263**
10b1	**49.88**	**-9.9319**
10b2	**51.27**	**-9.7834**
10b3	--	0
10c1	--	-6.3379
10c2	--	0
10c3	--	0
11a1	--	0
11a2	--	0
11a3	--	0

The perusal of correlation matrix (**Table 4a and Table 5a**) indicates that HE, IP and EN are the predicted parameters from AM1 method. From regression methods backward, forward, removed and stepwise. HE, EN, and LogP were found to be explainable variables.

The regression technique was applied through the origin using these reasonable parameters.

Activity = 0.198 x HE (0.058) – 0.847 x EN (0.08) – 0.618 x LogP (0.197)   (1)
N = 26; R = 0.976; R^2 = 0.952; R^2_{adj}=0.946; %EV = 95.20; SEE = 0.8785;
F= 153.73; Q = 1.1116;

In addition, the plot of observed activity versus predicted activity was not found to be satisfactory. Hence, the predictive capability of the model is not good. Eq.1 show that the values of %EV are less and to improve its value, outliers were sought and eliminated.

After the elimination of the outlier (1b, 1d, 1e, 9c and 9e), a second model was developed. Overall, there is an increase in R and %EV (95.2 – 98.90) values, and a decrease in SEE (**0.8785 - 0.4698**).

Activity = 0.176 x HE (0.042) – 0.648 x LogP (0.117) + 1.633 x IP (0.50) + 1.852 x EI (0.215) (2)
N = 21; R= 0.994; R^2= 0.989; R^2_{adj}=0.986; %EV = 98.9; SEE = 0.4698;
F = 374.145; Q = 2.1194;

Eq.2 is an improved model since it explains the biological activity to the extent of (98.9%). In this way, the predictive molecular descriptors HE, IP, EI and LogP were considered as variables.

From the correlation matrix table, it reveals HE, EN and LogP are found to be explainable variables. A tri parametric QSAR equation with HE, EN and LogP was generated in PM3 method also.

Activity = 0.168 x HE (0.048) – 0.85 x EN(0.07) – 0.618 LogP(0.197)   (3)
N = 26; R = 0.981; R^2= 0.962; R^2_{adj}=0.957; %EV = 96.2; SEE = 0.7870; F = 193.422; Q = 1.2465;

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 (**1b, 1d, 1e, 9c and 9e**), a second model was developed.

Activity = 0.166 HE (0.049)-0.748 x LogP [0.137] +1.896 x IP [0.411] +1.899 x EI   (4)
N = 21; R = 0.992; R^2 = 0.985; R^2_{adj}=0.981; %EV = 98.5; SEE = 0.5431;
F = 278.984; Q = 1.8268;

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 leave-one-out (LOO) cross-validation method [28]. Here, 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 and 7).

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

Where the PRESS (predictive residual sum of squares) and SD (standard deviation) valves are obtained as
PRESS = $\sum$ (property $_{observed}$ – property $_{predicted}$)^2,
SD = $\sum$ (property $_{observed}$ – property $_{mean}$)^2.
Eq.2 and 4 of AM1 and PM3 methods respectively give 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.
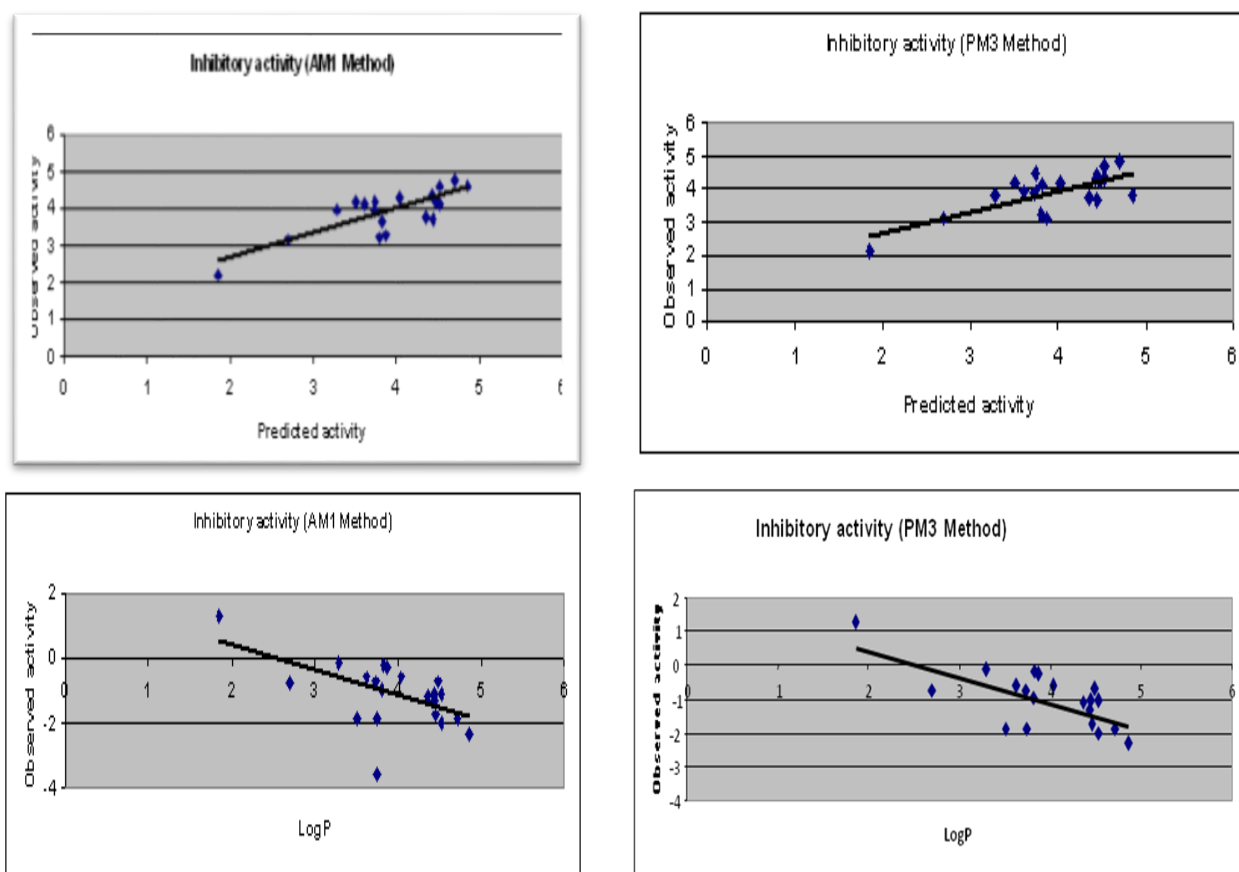
Figure 1: Observed activity Vs Predicted activity.

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 Eqs.2 and 4. Its value decreases from Eq.1 to Eq.4.

The quality factor Q [23], is defined as the ratio of regression constants (R) to the standard error estimation (SEE), that is, 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 1.1116 to 2.1194 and 1.2465 to 1.8268 (**Eq.1 to 4**).

Docking Analysis

The compounds were then docked using each of the three docking software's. The Gold score, Chemscore and binding energy values with their respective RMSD have been produced, from the two docking software's are indicated in **Table 8**. The binding energies obtained in Argus Lab ranged from **-6.3379** to **-10.30 kJ/mol** .The results of CCDC GOLD can be analyzed both Gold score and Chemscore in terms of values ranging from **-29647.95 to 66.00** and **-19.50 to 43.35.**
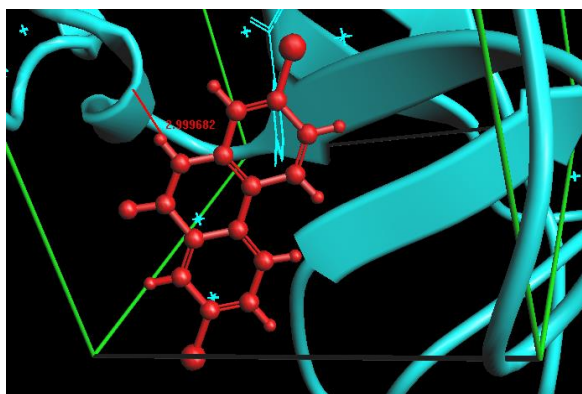
The docking simulation of the most active 5[H] Phenanthridin-6-one analogs are **1c,5a1,9b, 10a2,10b1** and **10b2** toward PARP-1 (**PDB ID 3SE2**) showed that the most enzyme–inhibitor complex was stabilized by hydrophobic interactions occurring between the aromatic moieties of the ligand and lipophilic residues of the binding site.
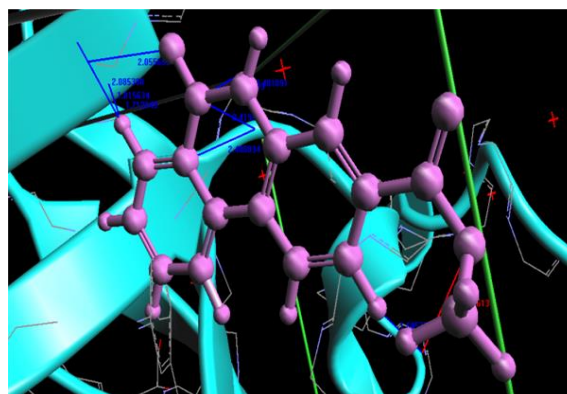
In particular the 5[H] Phenanthridin-6-one analogs are **1c,5a1,9b, 10a2,10b1** and **10b2** was oriented towards the hydrophobic region lined by ASN1549,ILE1570,GLY1602,SER1641,ASN1614,SER1 544,ASN1572,GLU1713,TYR1711, ILE1675,TYR1646 and HET7979. Result of docking studies has proved that the molecule numbered **1c, 5a1, 9b, 10a2, 10b1** and **10b2** shows Gold score, Chemscore and RMSD values as in the **table 8.** All the poses of molecule **1c, 5a1, 9b, 10a2, 10b1** and **10b2** (chosen as best in docking studies) and its interactions in the active pocket of PARP-1 have been illustrated in **figure 8.**
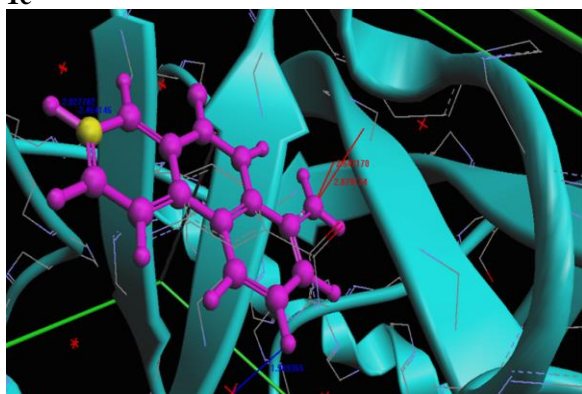
CONCLUSION

The attachment of two optimal substituents onto the core skeleton resulted in the water – soluble compounds, **1c**, **5a1**, which exhibits a 5-fold increase in inhibitory activity as compared to the core structure of 5(H)Phenanthradin-6-one **1a**. The variation of substituents at 1-,2-, 3-, 4-, 8-, and 10- position of the tri cyclic ring of 5[H] phenanthradin-6-ones resulted increase and decrease the inhibitory activity with reference to core. The indicative molecular parameters from both AM1 and PM3 are found to be HE, IP, EI and LogP by a regression analysis. The valid modeled equations 2 and 4 reveal the overall
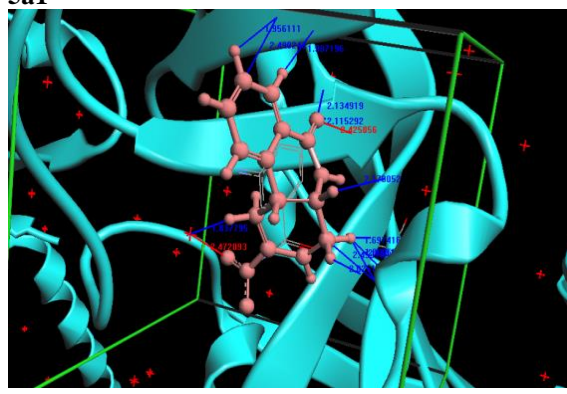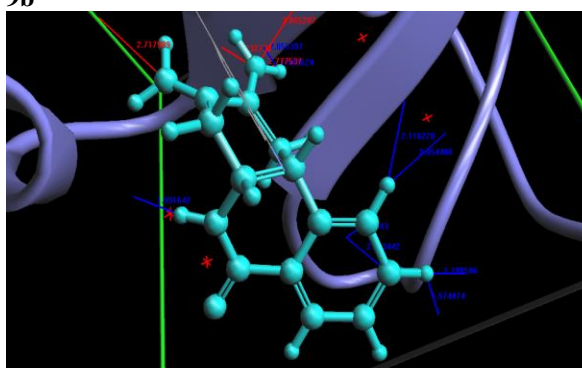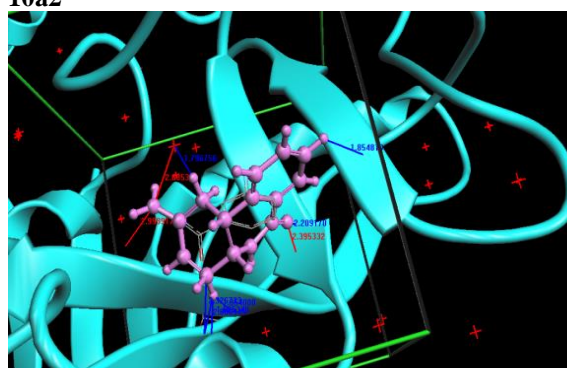
1c

5a1

9b

10a2

10b1

10b2

increase of HE,IP, and EI and overal decrease of LogP enhance the efficacy of inhibitory nature of these analogs to PARP-1 **figure 4.**

The increase of HE which enhances inhibitory activity indicates replacing of water molecules present in the active site of PARP-1 by interaction. Inhibition trend of 4-substituted compounds appeared 4- amino **9b>1a>4-** nitro **9c**.

The electronic nature of 2-or 3- substituents appears a significant affect the inhibition. This was exemplified by the electron withdrawing 2-nitro compound **10a2** and electron donating 2-amino compounds **10b1** and 2, 3-diamino **10b2.** This supported by the indicative parameters IP and EI. The EI is related to LUMO and describes the compounds ability to interact with electron pair donars of active site. This index, quantifies the electrophilic character of the substrates and to describes spatial localization within the molecular volume (at Michael acceptor sites or on other parts of the molecules).The

decrease of inhibitory activity by 5(H) Phenanthradin-6-one analogs with increase of LogP indicates the liphophilic character of the drug candidate is unfavorable. This infers the presence of polar groups of amino acids residues are expected in the active site of PARP-1. The linear dependence of inhibitory activity on LogP is evident from **Figure 6 and 7**. 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 in **figure 8**.

Figure.5: Binding orientations of database hit compounds **1c, 5a1, 9b, 10a2, 10b1** and **10b2**, and crystallographic conformation of PARP-1 active site (**PDB ID 3SE2**).Hydrogen bonds are shown in red colour dotted lines.

providing laboratory facility.

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