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Theoretical study of O^6-methylguanine-DNA methyltransferase inhibitors

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ABSTRACT

Human DNA repair protein O^6 – methylguanine-DNA methyltransferase (MGMT) can provide resistance to alkylating agents by DNA damage reversal. Methylation of genes promoter may play a significant role in carcinogenesis. Hence new approaches need to be considered to enhance the inactivation of this protein in order to overcome the resistance to alkylating agents which are still some of the preferred drugs in cancer chemotherapy. In this work different mathematical models are constructed by using quantum chemical parameters and graph theoretical indices. The models are verified and it is observed that both the parameters are suitable for screening these inhibitors. This study opens the door to the development of a new generation of a MGMT inhibitors.

Keywords: O^6 – methylguanine-DNA methyltransferase inhibitors, regression analysis, Alkylating agents

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INTRODUCTION

Alkylating agents are used in chemotherapy to treat several forms of cancer. This group of drugs essentially damage DNA and eventually resulting in the death of cancer cells. This phenomenon is essentially a mutation that takes away the cancer cell's ability to multiply. Therefore understandably cellular DNA repair mechanisms [1,2] can influence both their antitumor efficacy and their dose limiting toxicities. [3]

Human DNA repair protein O^6 – methylguanine-DNA methyltransferase (MGMT) can provide resistance to alkylating agents by DNA damage reversal. This enzyme is key to the removal of highly promutagenic and cytotxic o^6–alkylating adducts from guanine bases in DNA. [4-7]

Hence new approaches need to be considered to enhance the inactivation of this protein in order to overcome the resistance to alkylating agents which are still some of the preferred drugs in cancer chemotherapy. [8]

Methylation of genes promoter may play a crucial role in the development of nearly all types of cancer. In patients with glioblastoma multiforme, an aggressive brain tumor, as well as for treating melanoma form of skin cancer the methylation state of the MGMT gene determined, whether tumor cells would be responsive to an oral alkylating agent (temozolamide). If the promoter was methylated, temozolamide was more effective. [9-10]

Other methylating agents such as streptozotocin, Procasbazine, Dacarbazine are also clinically used in several diseases. [11] Chloroethylating agents such as BCNU, CCNU, Fotemustine are also used in several cancer diseases. The mechanism of cell killing by o^6-methylguanine and o^6- chloroethylguanine is substantially different, but in both DNA replication plays an essential part.

In this study, we intend to find correlation between pharmacological activity and different molecular descriptors of chemicals and also to construct regression model for predicting activity. This study opens the door to the development of a new generation of a MGMT inhibitors.

EXPERIMENTAL SECTION

The activity data of derivatives was collected from site Binding db (www.bindingdb.org)**.** A major part of the current research in COMPUTATIONAL chemistry, chemical graph theory, and quantitative structure-activity/property relationship studies involves topological indices.

Here we consider different topological indices such as Winner index (W) [[12], Harary index(H) [13], Randic connectivity index of zeroth order ($^0\chi$) and first order ($^1\chi$) [14,15], Balban index (J) [16] . All these topological indices are calculated by using our own code written in F77.

Calculations of quantum mechanical descriptors namely HOMO, LUMO, Dipole moment, Polarisability of the MGMT inhibitors are performed by DFT/ B3LYP calculation using Gamess[17] . Log P and Molar Volume (MV) are calculated by using ACDLABS 10.0[18]. By using the above topological and quantum chemical indices we performed regression analysis.

RESULTS AND DISCUSSION

This communication has been prepared with the list of the chemical structure and value of the inhibition activity (logIC50) of 25 training compounds and 8 test compounds taken from the literature are given in Table 1 and Table 2 respectively from the site of Binding db[19-21].

Quantum mechanical descriptors and graph theoretical indices of 25 training compounds and 8 test compounds are presented in Table 3 & table 4 respectively. To scaling the data we have converted the Winner index(W), Harray index(H), molar volume(MV) and Ic50 into their natural logarithm. In Table 3 it is evident that HOMO energy for compounds ranges between -0.2411 kcal/mol to -0.1516 kcal/mol. LUMO energy for compounds ranges between -0.0024 kcal/mol to -0.0925 kcal/mol. In Table 5 the correlation matrix among all parameters shows that there is a good correlation between Harray index and activity and moderate correlation with Balban index & χ^1. Thus these three indices have a good effect on predicting activity. There are also good inter correlation between $^0\chi$ and winner index and between molar volume and χ^1. So it is seem that the Harray index, χ^1 and Balban index has much important correlation towards Ic50 values.

In this study, we have constructed several regression equations namely Model 1, Model 2, Model 3 and Model 4 respectively by choosing the different no. & types of parameters. The Model 1 is constructed by using the descriptors molar volume (MV), Winner index(W), Harray index (H), Balban index (J), χ^0, χ^1. This regression model shows the value of correlation co-efficient between predicted and experimental $LogIC_{50}$ is 0.759 and the Fisher F-value is equal to 26.368463.The resulting regression equation is

Ic50=-87.64689+MV(11.8957)+LnW(-1.3694)+LnH(15.6905)+J(-0.9463)+Ki0(0.0951)+Ki1(-2.4783)

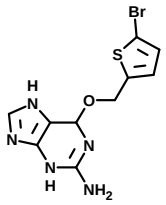
The Model 2 is constructed by using the quantum chemical descriptors (HOMO, LUMO, Dipole moment). The Value of correlation co-efficient between predicted and experimental $LogIC_{50}$ is 0.831. The Fisher F-value is equal to 13.468310.The resulting regression equation is

Ic50=-1.8231371E-01+ HOMO(20.2777)+LUMO(-43.3954)+DM(0.1811)

Here Model 2, based on quantum chemical descriptors shows better correlation between predicted and experimental activity than Model 1 which is completely based on graph theoretical indices.

Table 1: Chemical structure and activity of 25 training compounds

A1)Ic50=5.0



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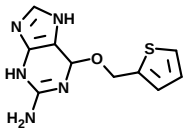

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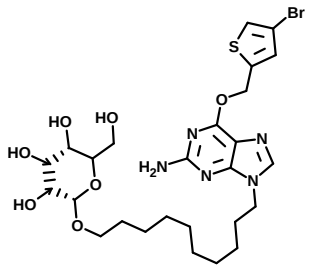

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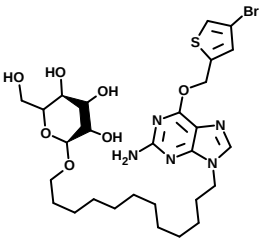

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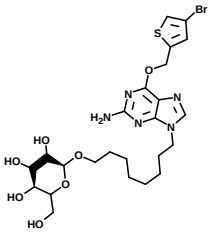

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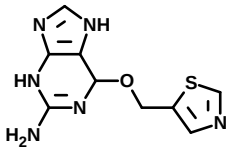

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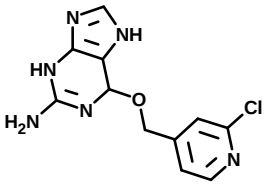

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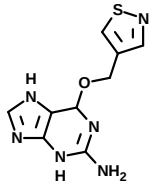
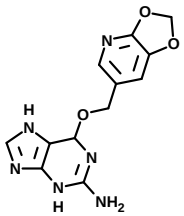


A9)Ic50=90.0



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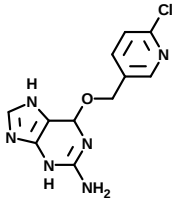

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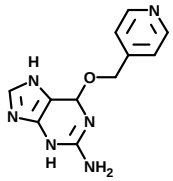

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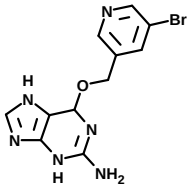

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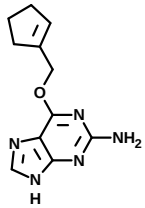

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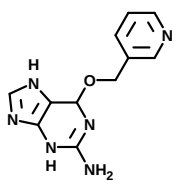

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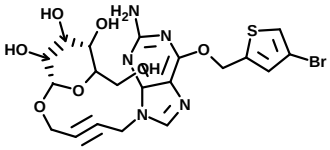
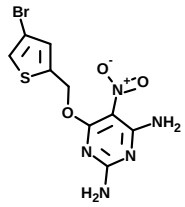
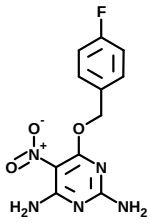


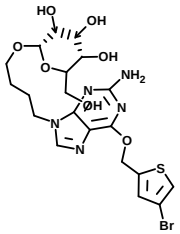
A16)Ic50=320.0



A17)Ic50=350.0



A18)Ic50=450.0



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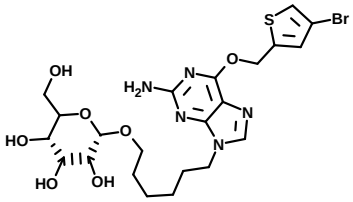
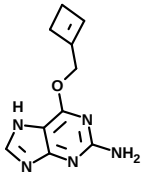
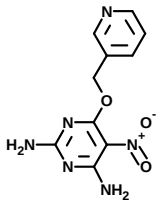


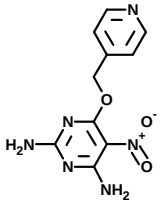
A20)Ic50=550.0



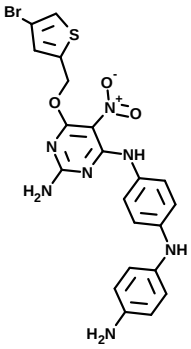
A21)Ic50=1600.0



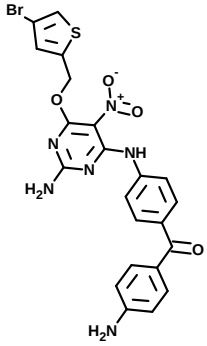
A22)Ic50=1900.0



A23)Ic50=4700.0



A24)Ic50=5700.0



A25)Ic50=13000.0

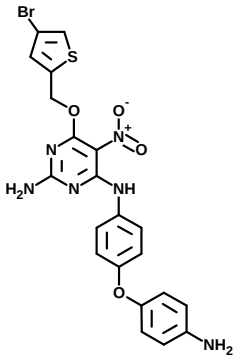
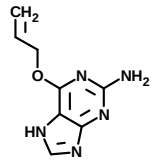


Table 2: Chemical structure and activity of 8 test compounds

B1)Ic50=2700.0



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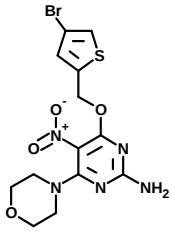
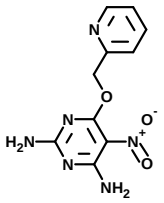
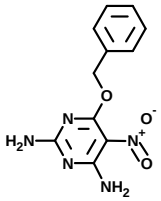


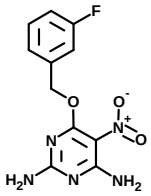
B3)Ic50=18000.0



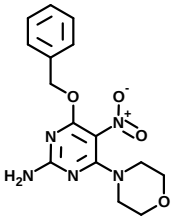
B4)Ic50=1300.0



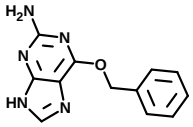
B5)Ic50=2500.0



B6)Ic50=19000.0



B7)Ic50=2500.0



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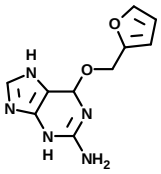

The Model 3 is constructed by using the quantum chemical descriptors (HOMO, LUMO, Dipole moment) and log P. The Value of correlation co-efficient between predicted and experimental $LogIC_{50}$ is 0.886 which is better than Model 2. The Fisher F-value is equal to 40.31470. The resulting regression equation is

Ic50=11.095030+ HOMO(47.2244)+LUMO(-64.0090)+DM(0.3537)+LogP(-0.5155)

Finally we performed regression with all the parameters i.e. HOMO, LUMO, dipole moment, logp, Balban index, winner index, Harray index, molar volume χ^0 & χ^1 and obtained Model 4. The resulting regression equation is

Ic50=48.41386+HOMO(51.5904)+LUMO(-70.4277)+DM (0.2028)+ Log p (-0.6498)+MV x(0.6674)+Ln W(2.8476)+H(-15.1298)+J(-3.1732)+Ki0(1.6709)+ Ki1 (-1.5339)

n=25, r=0.92, r^2=0.85, F=17.89

The above model gives a good correlation between predicted and experimental activity (r=0.92) and F value (17.89) also reveals the good agreement with the equation. The above model is also validated by test set and it gives correlation coefficient (0.70).The experimental and predicted activity of training and test set is shown in Table 5 and Table 6.

The correlation graph between predicted and experimental activity of training set is shown in Figure 1.The graph shows a good agreement with equation. Figure 2 represents the same for test set.

We have constructed a cladogram by using Unweighted Pair Group Method with Arithmetic Mean (UPGMA) of 25 training compounds depending on the correlation between indices and activity in Figure 3. Through cladistic analysis one can estimate the compounds having similar molecular properties are in the same clade, and activity also are comparable with few exceptions. As an illustration it is found that compound A3 and A4 is in the same branch and these are very similar. Compound A5 and A19 are present in same clade, although there are large differences in their activities. This change in activity is due to difference in stereo bond in phenolic OH. Compound A5 has up stereo bond, whereas compound A19 has down stereo bond.

Table 3: Chemical structures of 25 training set

compound	HOMO	LUMO	DM	logP	Ln(MV)	lnW	lnH	J	χ^1	χ^1	Ln(Ic50)
A1	-0.1817	-0.0182	0.2706	2.17	5.0575	6.4473	4.0337	1.5104	12.5352	8.7203	1.6094
A2	-0.1903	-0.0182	1.7807	1.23	4.9747	6.2748	3.9528	1.2864	11.6649	8.3265	2.8903
A3	-0.2061	-0.0343	7.1481	3.4	5.9753	8.4329	5.0276	1.5528	28.4846	19.3674	3.4011
A4	-0.1989	-0.0233	7.0757	4.29	6.0537	8.4549	5.0664	1.9564	29.8988	20.3674	3.4011
A5	-0.2044	-0.0322	6.1523	2.51	5.8905	8.4222	4.9901	1.3935	27.0703	18.3674	3.4657
A6	-0.191	-0.0024	3.235	0.11	4.8926	6.2748	3.9528	1.2864	11.6649	8.3265	3.4965
A7	-0.1924	-0.0369	4.3718	0.93	5.077	6.6012	4.1099	1.4314	13.2423	9.2203	3.6889
A8	-0.1954	-0.0041	4.6999	0.29	4.8926	6.2748	3.9528	1.2864	11.6649	8.3265	4.2484
A9	-0.1814	-0.0378	3.312	0.32	5.0206	6.8824	4.2699	1.0781	14.2338	10.2928	4.4998
A10	-0.1992	-0.0141	4.0441	0.93	5.077	6.6619	4.0729	1.5683	13.8281	9.0586	4.7874
A11	-0.1911	-0.0259	2.8487	0.1	5.0173	6.4983	3.9973	1.67	12.9578	8.7027	4.8675
A12	-0.1925	-0.0279	2.5319	0.87	5.0968	6.6013	4.1099	1.4314	13.2423	9.2203	5.2983
A13	-0.1986	-0.0343	4.1095	0.33	5.0986	6.2748	3.9528	1.2864	11.6649	8.3265	5.2983
A14	-0.1809	-0.0415	2.8474	0.1	5.0173	6.4489	4.0308	1.5035	12.372	8.8265	5.3936
A15	-0.1963	-0.0196	7.4347	0.63	5.6951	8.2496	4.8973	1.1721	24.2419	16.3674	5.5214
A16	-0.2306	-0.0925	5.3121	3.1	5.2073	6.5889	4.0988	1.6891	13.9912	8.9692	5.7683
A17	-0.2284	-0.0871	5.8634	2.56	5.199	6.7499	4.1684	1.8494	14.6983	9.4692	5.8579
A18	-0.2024	-0.0296	4.7523	0.74	5.6951	8.2496	4.8973	1.1721	24.2419	16.3674	6.1092
A19	-0.2038	-0.0315	6.5998	1.63	5.7976	8.3507	4.9457	1.178	25.6561	17.3674	6.1092
A20	-0.1836	-0.0346	3.7244	0.85	4.9843	6.1026	3.8615	1.3681	10.9578	7.8265	6.3099
A21	-0.2411	-0.0851	5.4509	1.2	5.137	6.5903	4.096	1.6819	13.8281	9.0754	7.3778
A22	-0.2153	-0.084	5.678	1.2	5.137	6.5903	4.096	1.6819	13.8281	9.0754	7.5496
A23	-0.1516	-0.105	4.0527	6.63	5.7516	8.1554	4.8758	1.2461	23.3717	15.8682	8.4553
A24	-0.1617	-0.1171	2.6224	6.65	5.7893	8.2239	4.9266	1.2331	24.2419	16.2957	8.6482
A25	-0.1601	-0.1157	2.2217	6.69	5.7658	8.1554	4.8758	1.2461	23.3718	15.8682	9.4727

Table 4: Chemical structures of 8 test set

Compound	HOMO	LUMO	DM	Logp	MV	LnW	Ha	J	χ^0	χ^1	Ln(Ic50)
B1	-0.2022	-0.0267	4.5982	0.68	4.9119	5.6971	3.6619	1.9189	9.9663	6.8089	7.901
B2	-0.1725	-0.1047	5.6458	3.17	5.4955	7.1974	4.4604	1.5088	17.1041	11.5417	6.9078
B3	-0.2362	-0.0929	4.4194	1.28	5.137	6.107	3.8474	1.6414	11.5436	7.7027	9.7981
B4	-0.242	-0.0789	5.5552	2.42	5.1756	6.5903	4.096	1.6819	13.8281	9.0754	7.1701
B5	-0.2327	-0.0855	6.5577	2.56	5.199	6.7346	4.1721	1.8759	14.6983	9.4692	7.824
B6	-0.1464	-0.098	5.5776	2.48	5.4723	7.1982	4.4585	1.505	16.9409	11.6479	9.8522
B7	-0.2119	-0.0392	4.8814	1.71	5.1269	6.4489	4.0308	1.5035	12.372	8.8265	4.0604
B8	-0.1838	-0.0343	1.2243	0.38	4.9178	6.2748	3.9528	1.2864	11.6649	8.3265	4.382

Table 5: Correlation Table

	HOMO	LUMO	DM	logP	Ln(MV)	lnW	H	Balban	χ^0	χ^1	Ln(Ic50)
HOMO	1	-0.0835	-0.5634	0.4128	0.1436	0.0883	0.0933	-0.118	0.1429	0.1347	0.0717
LUMO	-0.0835	1	0.0075	-0.7177	-0.2861	-0.2869	0.0414	0.1317	-0.2664	-0.0726	-0.3158
DM	-0.5634	0.0075	1	-0.0022	0.5153	0.3327	0.2005	0.051	0.3477	0.4781	0.1397
logP	0.4128	-0.7177	-0.0022	1	0.6699	0.2708	0.3143	0.0593	0.4195	0.5279	0.3988
Ln(MV)	0.1436	-0.2861	0.5153	0.6699	1	0.4536	0.502	0.0778	0.6538	0.8999	0.3708
lnW	0.0883	-0.2869	0.3327	0.2708	0.4536	1	-0.5063	-0.8204	0.9327	0.0831	-0.4573
H	0.0933	0.0414	0.2005	0.3143	0.502	-0.5063	1	0.8638	-0.2894	0.7977	0.8082
Balban	-0.118	0.1317	0.051	0.0593	0.0778	-0.8204	0.8638	1	-0.6617	0.4382	0.7261
Ki0	0.1429	-0.2664	0.3477	0.4195	0.6538	0.9327	-0.2894	-0.6617	1	0.2994	-0.3744
Ki1	0.1347	-0.0726	0.4781	0.5279	0.8999	0.0831	0.7977	0.4382	0.2994	1	0.613
Ln(ic50)	0.0717	-0.3158	0.1397	0.3988	0.3708	-0.4573	0.8082	0.7261	-0.3744	0.613	1

Table 5: Experimental and predicted Ic50 value for training set

Compound Name	Experimental Ic50	Predicted Ic50
A1	3.4011	2.4119
A2	3.4657	4.804562
A3	3.4965	3.278919
A4	4.2484	3.351768
A5	4.4998	5.101704
A6	4.7874	4.316422
A7	4.8675	5.269375
A8	5.2983	3.854702
A9	5.2983	5.305355
A10	5.3936	5.606117
A11	5.5214	5.643261
A12	5.7683	6.578651
A13	5.8579	6.080311
A14	6.1092	5.417366
A15	6.1092	5.709682
A16	6.3099	5.82526
A17	7.3778	6.36541
A18	7.5496	7.665027
A19	8.455301	8.550847
A20	8.648201	8.870053
A21	9.4727	8.465234
A22	2.8903	3.459877
A23	3.6889	4.814358
A24	1.6094	2.448307
A25	3.4011	4.33184

Table 6: Experimental and predicted Ic50 value for test set

Compound Name	Experimental Ic50	Predicted Ic50
B1	7.901	4.570259
B2	6.9078	8.739144
B3	9.798101	7.708316
B4	7.1701	5.13648
B5	7.824	5.702945
B6	9.8522	9.640333
B7	4.0604	3.284288
B8	4.382	5.330615

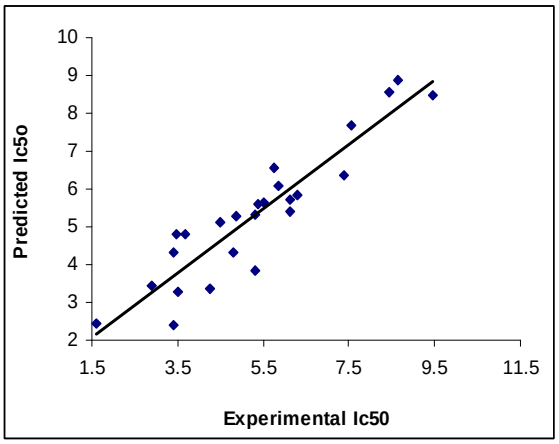

Figure 1 Correlation graph for Training set

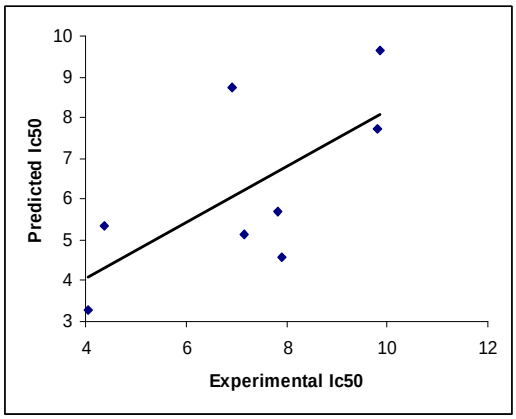

Figure 2 Correlation graph for Test set

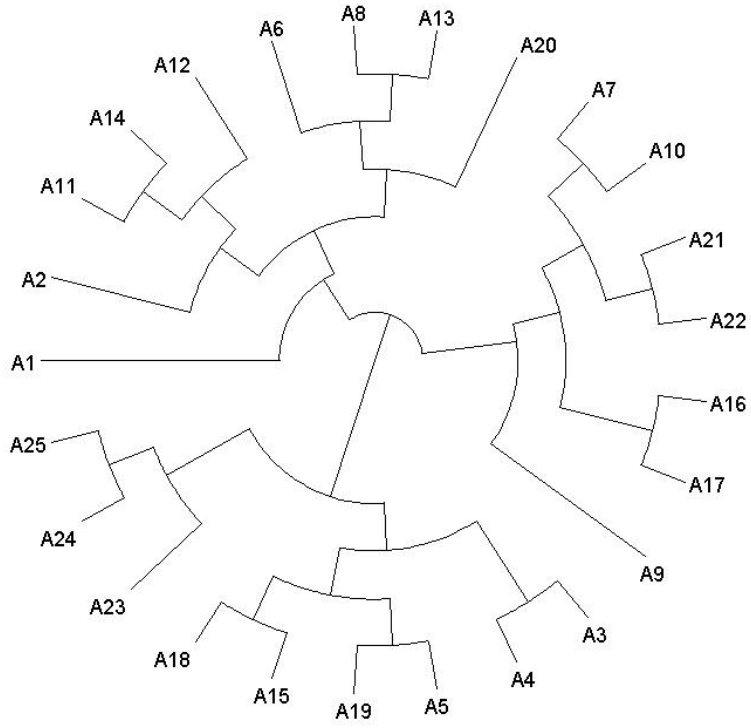

Figure 3: Cladogram using Unweighted Pair Group Method with Arithmetic Mean (UPGMA) of 50 training compounds.

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