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In-silico Comparative Study and 2D QSAR Analysis of Some Structural and Physiochemical Descriptors of Levetiracetam Analogs.

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Abstract

Levetiracetam is a new generation drug act as an intigrase inhibitor of Glioblastoma (Brain Cancer). The potential inhibition has been tested from the clinical trial data. Here the work basically deals with the QSAR analysis by considering some of the physiochemical descriptors and structural descriptors of the drug analogs. The descriptors were calculated from Molegro Package Software and the multiple linear regression equation models were built by using Minitab tools. The different combinations of structural and physiochemical descriptors were considered for model derivation. The best 5 model were chosen by observing high R-Sq value, high F-value and low residual errors. The P values for the 5 models were observed as 0.000 indicates the considered descriptors are significant. The results obtained with these models suggest, for this particular drug physiochemical descriptors are mainly depends strongly on the activity rather than structural descriptors.

Keywords: Structural descriptor, Physiochemical descriptor, QSAR, Multiple regression analysis, Integrase inhibitor.

Introduction

According to NIH (National Institute of Health) report almost 22020 people are newly infected with Glioblastoma, and the death rate per day is around 13140. Still it is in a

pandemic state hence currently a great international concern [1]. Glioblastoma multiforme (GBM) tumors almost invariably recur despite initial treatments. Correct diagnosis using a variety of imaging techniques and the involvement of a multidisciplinary tumor board are critical for evaluating each stage of a patient's progression and determining optimal management. Standard therapies for recurrence generally include repeated resection, radiation therapy, chemotherapy, and supportive care; however, salvage therapy must be highly individualized, and not all patients are eligible for every type of standard therapy. Factors such as the size and location of the tumor, previous treatment, and general health of the patient must be taken into consideration [2]. Findings suggest that PDE5 inhibitors may effectively modulate BTB permeability, and enhance delivery and therapeutic efficacy of monoclonal antibodies in hard-to-treat brain metastases from different primary tumors that had metastasized to the brain [3]. Microsatellite instability implying multiple replication errors (RER+ phenotype) characterizes a proportion of colorectal carcinomas, particularly those from patients with the hereditary non-polyposis colorectal carcinoma syndrome. Reported studied indicate the incidence of microsatellite instability in more than 500 sporadic tumors representing 6 different types of cancer. Apart from colorectal carcinoma the RER+ phenotype was found in 18% (6 of 33) of gastric carcinomas and 22% (4 of 18) of endometrial carcinomas. In contrast, no evidence of this abnormality was detected in cancers of the lung ($N = 85$), breast ($N = 84$), and testis ($N = 86$). Importantly, the first three cancers, as opposed to the latter three, are characteristic of the hereditary non-polyposis colorectal carcinoma syndrome. These findings suggest that the cancers belonging to the hereditary non-polyposis colorectal carcinoma tumor spectrum may have essential pathogenetic steps in common, including a tendency to multiple replication errors. [4]. Drug levetiracetam to treat autism and other problems with the brain. There are a few studies that look at whether or not levetiracem is safe and helpful for children with autism. One study showed that the drug did not help with behavior problems in children with autism. Leviracetam can cause a wide spectrum of behavioural adverse effects. Leviracetum has been shown to cause *psychosis* when given to some children with epilepsy. [5]

To analyse different potential drug molecules the quantitative structure-activity relationship (QSAR) method is a useful approach.QSAR is basically used to study the biological activities with various properties associated with the structures, which is helpful to explain how structural features in a drug molecule influence the biological activities. Also a successful in silico based QSAR analysis provides the advantages of higher speed and lower costs for bioactivity evaluation as compared to experimental testing [6]. Therefore, correlating the physicochemical properties or structural features of the integrase inhibitor compounds with their biological activity will surely provide useful information for the design of new anti Glioblastoma drugs. To address this issue, an in silico approach has been taken to calculate some selected physiochemical and structural descriptors of Levetiracetam analogs. Quantitative structural activity relationship study has been done by taking combinations of different physiological and structural descriptors by multiple linear regressions analysis to figure out the major molecular factor as associated with the activity of the drug molecule.

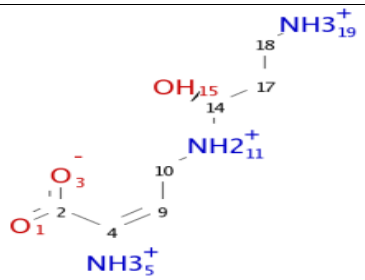
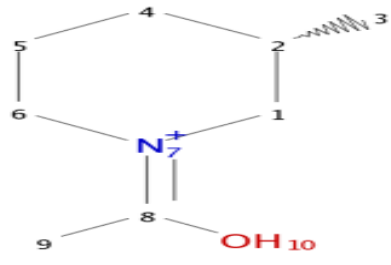
Materials and methods

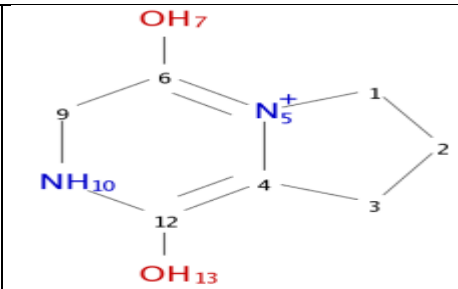
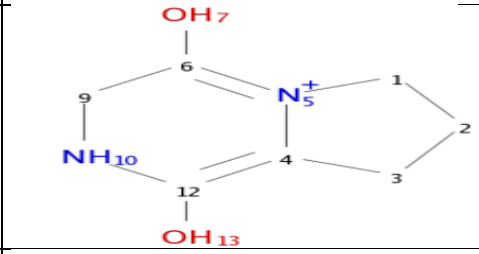
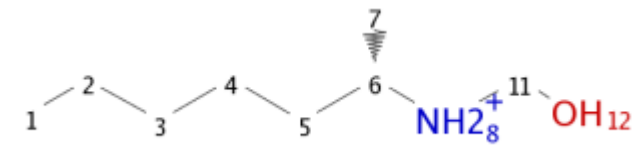
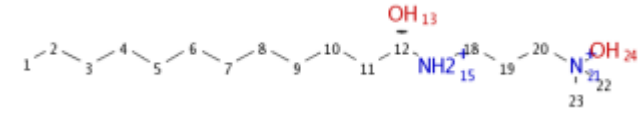
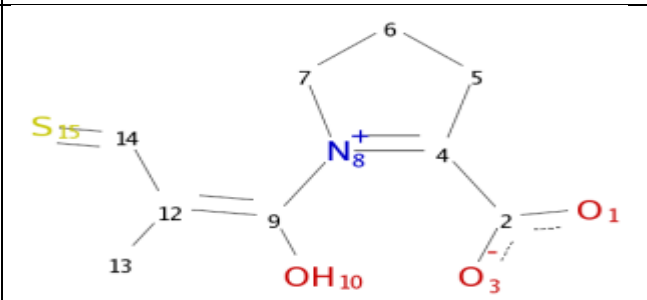
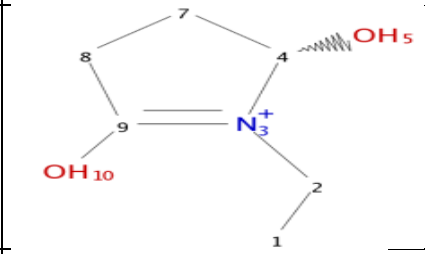
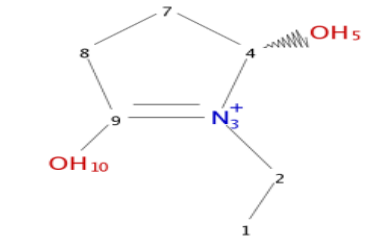
All total 72 analogs of the drug molecule Levetiracetam alongs with the EC50 value were obtained from Chembank [7] and corresponding log EC50 values were calculated. The derivatives of the Levetiracetam molecules were drawn in Marvin sketch 5.0 tools [8].Then the molecules were subjected to energy minimization by Prodrg server [9]. Prodrg is an on line server where the energy minimization of the molecule was performed by using Gromos 96 force field. The various descriptors were considered for the present work as physiochemical descriptors and structural descriptors for the molecules. All these descriptors were calculated by Molegro Package [10]. The different combinations of the above two types of descriptors were subjected to multiple regression analysis by MINITAB 14 software [11].For the best model selection various parameters like high F value, R-Sq and P value was chosen from regression analysis and equations were derived. From the equations the predicted and experimental Andrews value were compared.

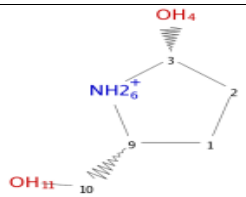
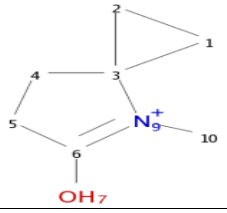
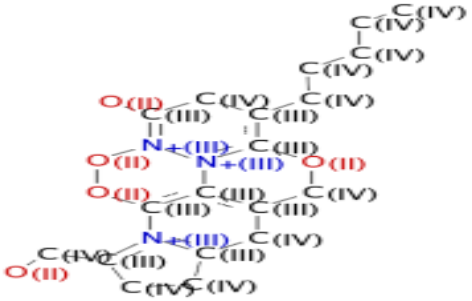
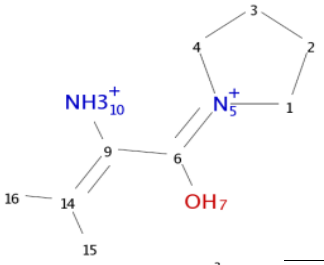
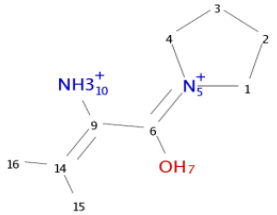
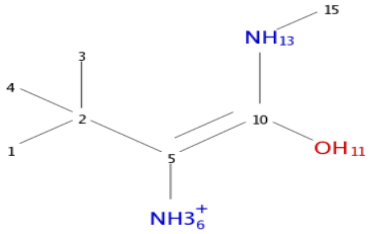
Results and Discussion

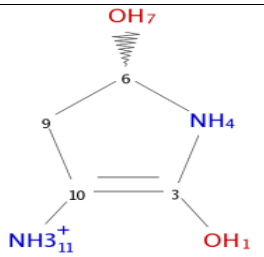
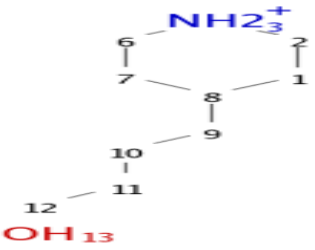
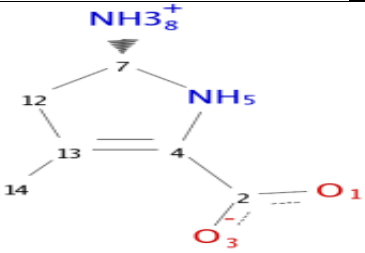
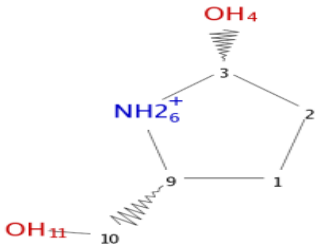
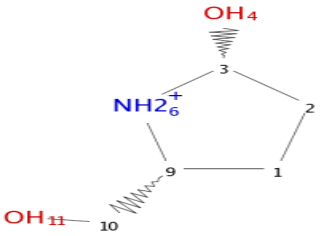
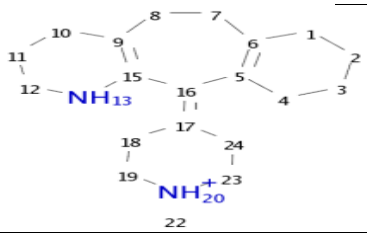
In the present study an attempt has been taken to develop the best QSAR model to explain the correlation between the combined effect of physiochemical and structural descriptors for the Glioblastoma integrase inhibitor Levetiracetam drug analogs (Table 1).

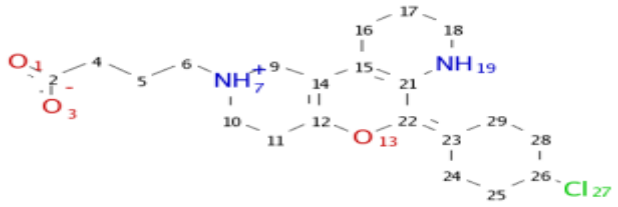
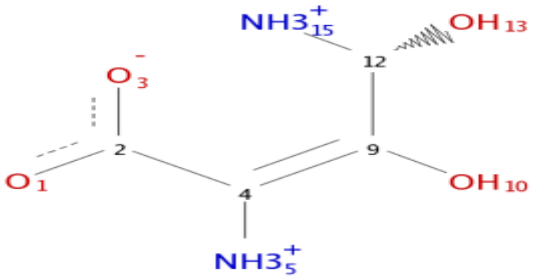
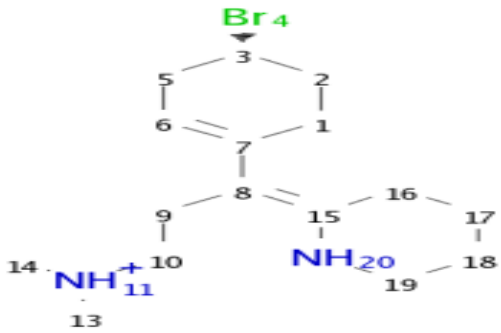
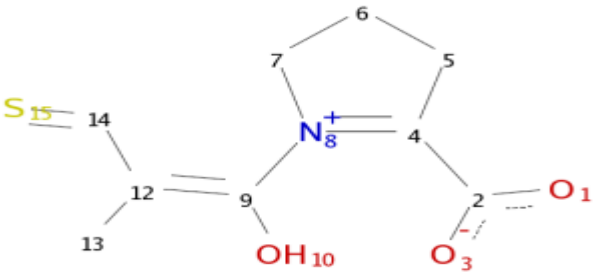
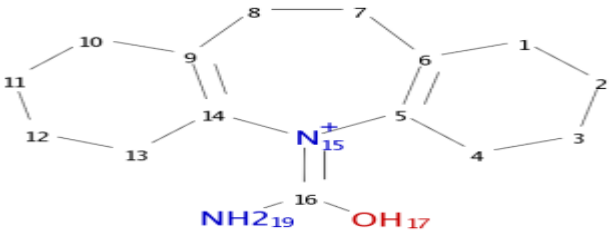
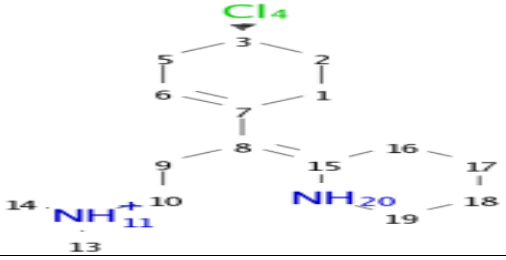
Table 1: Showing the Levetiracetam drug analogs along with their Log EC50 value.

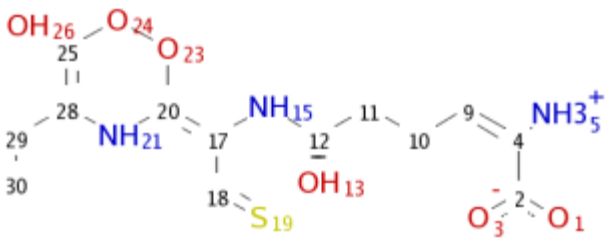
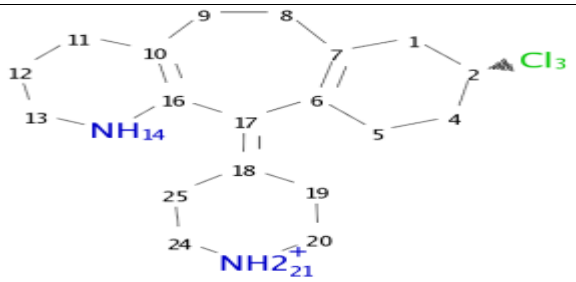
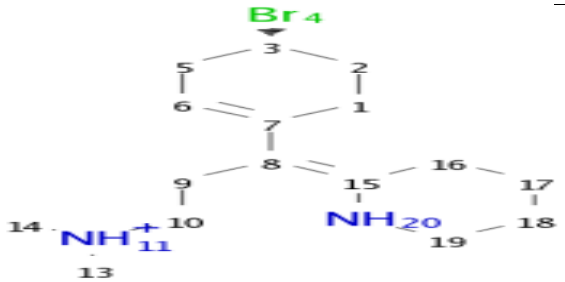
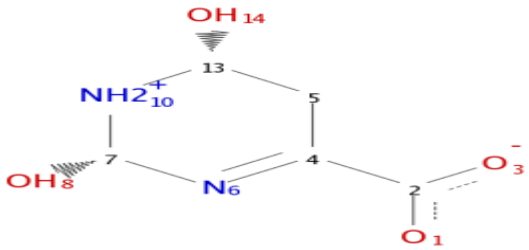
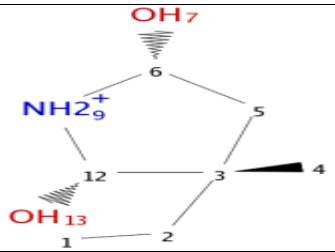
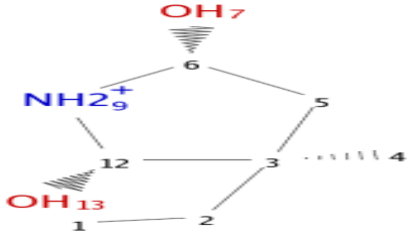
Serial number	Structure	Log EC50 value
1		5.20
2.		1.075

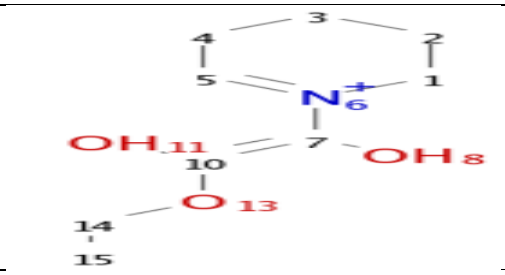
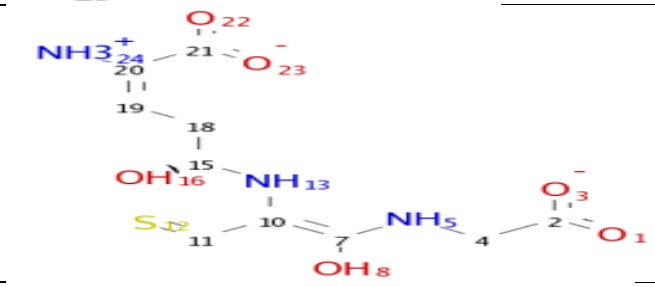
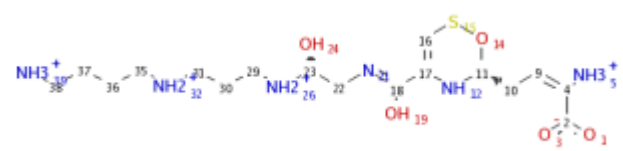
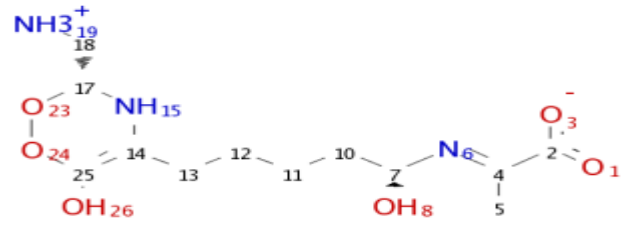
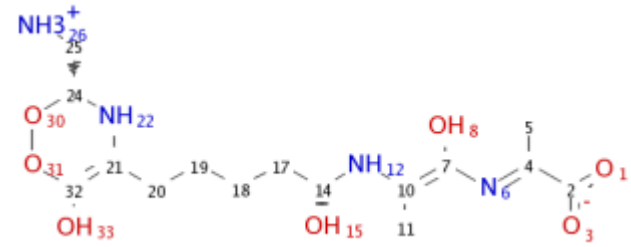
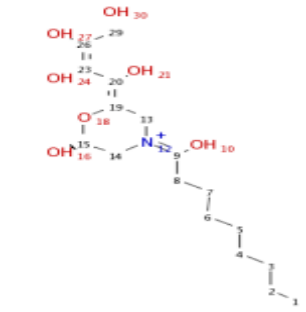
3		-0.342
4.		-0.342
5.		4.273
6.		6.467
7.		1.187
8.		0.196
9.		0.196

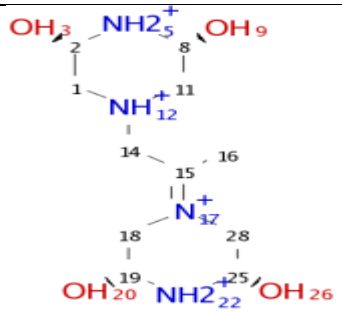
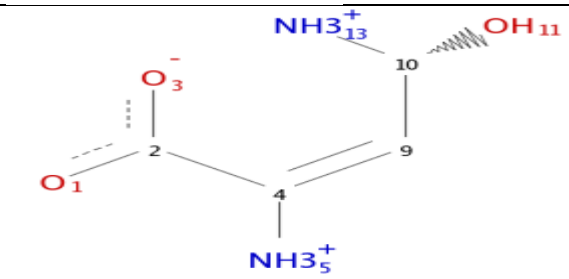
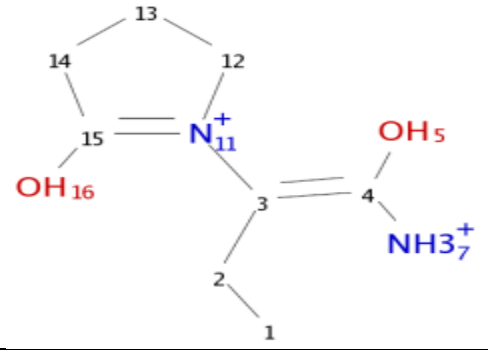
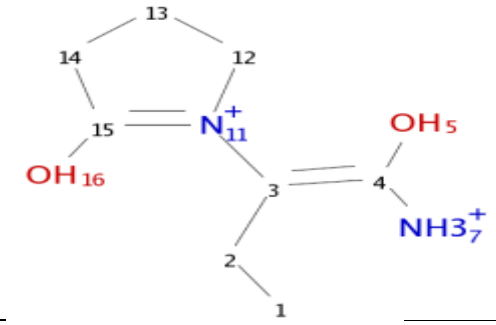
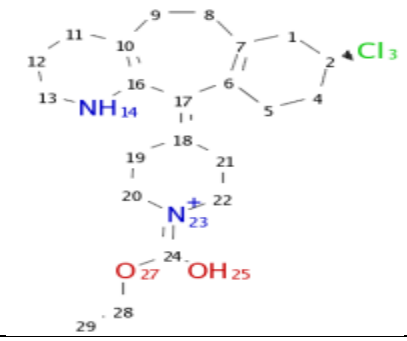
10.		0.226
11.		-0.689
12.		0.69
13.		5.880
14.		5.880
15.		9.511

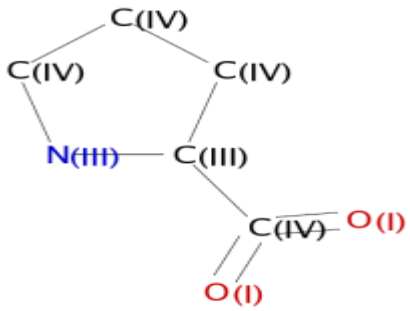
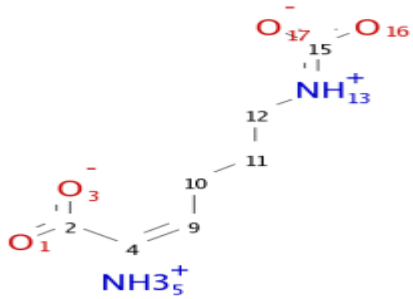
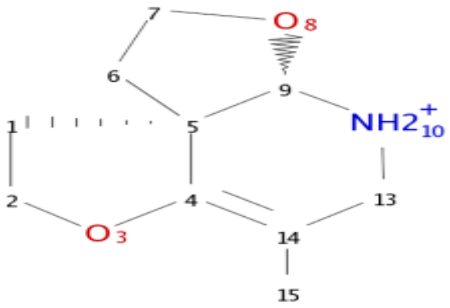
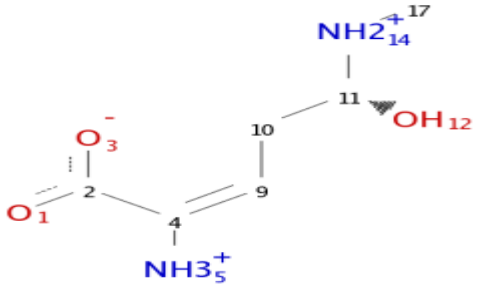
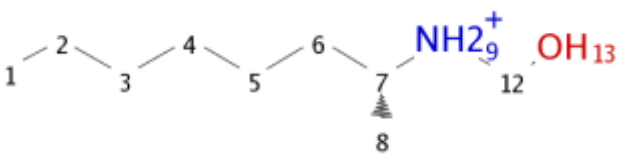
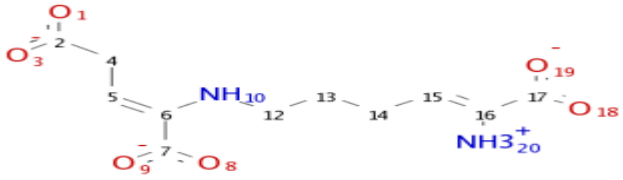
16.		0.877
17.		-0.747
18.		3.058
19.		0.226
20.		0.226
21.		31.974

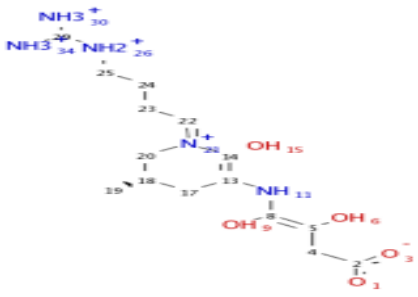
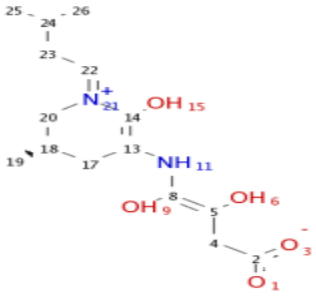
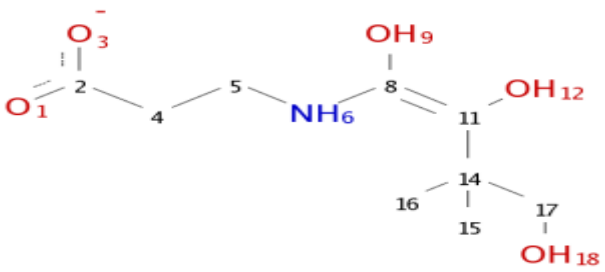
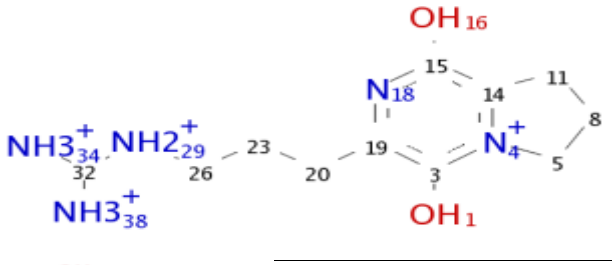
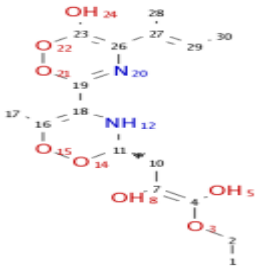
22.		24.523
23.		6.873
24.		11.658
25.		1.187
26.		15.218
27.		11.457

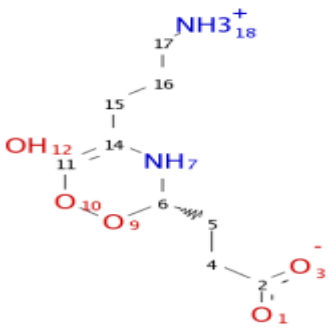
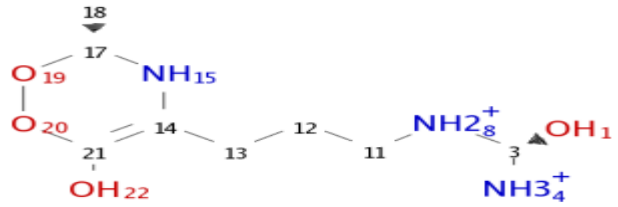
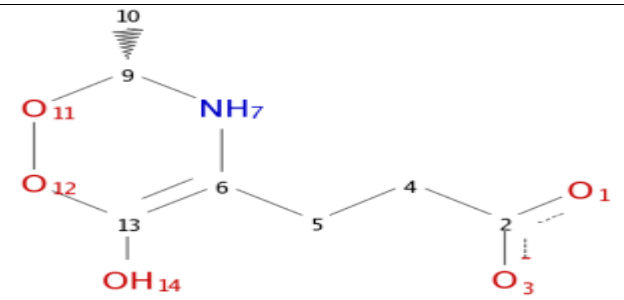
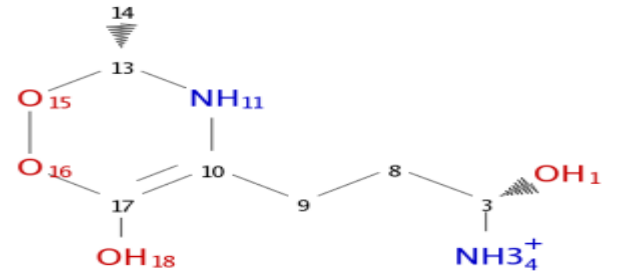
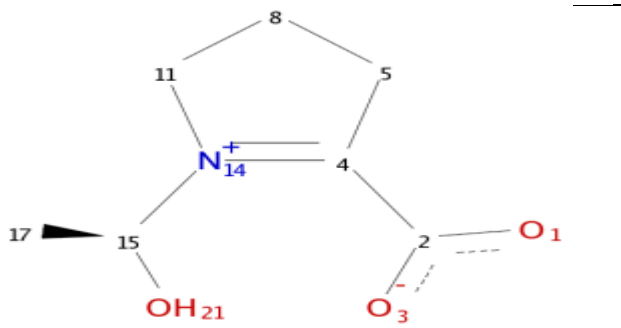
28		1.149
29		32.268
30		11.658
31		0.597
32		1.202
33		1.202

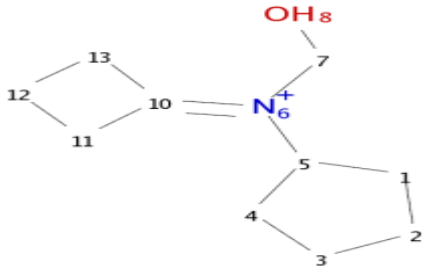
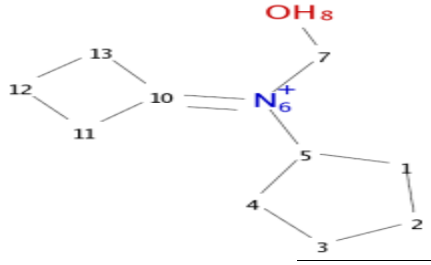
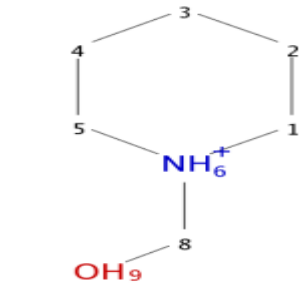
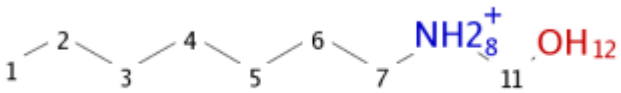
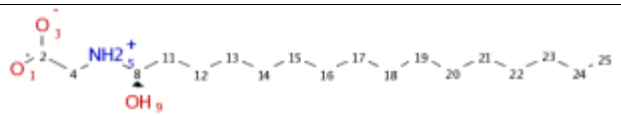
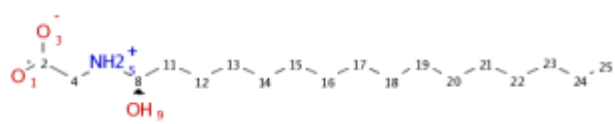
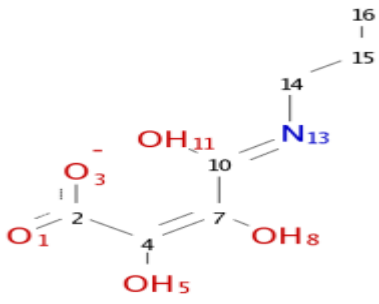
34		0.829
35		5.157
36		1.212
37		-0.089
38		0.574
39		0.777

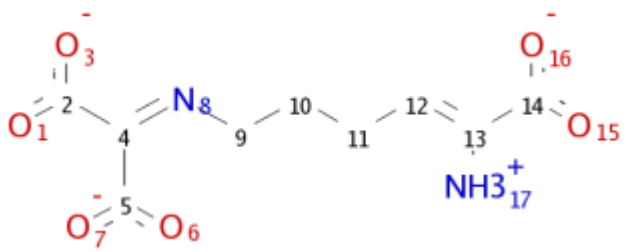
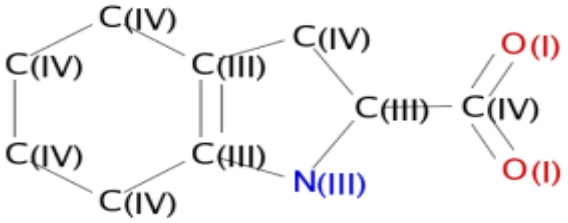
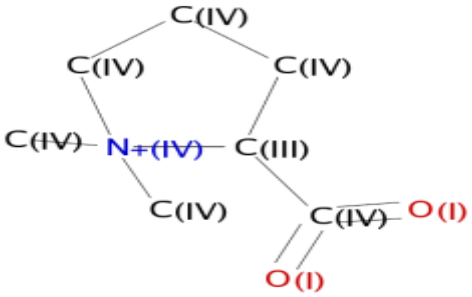
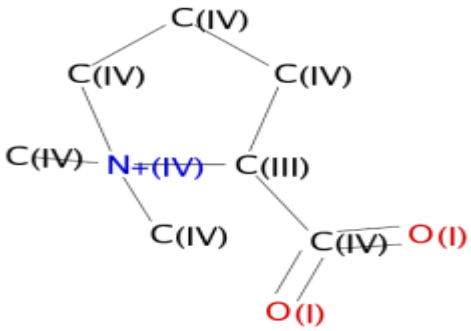
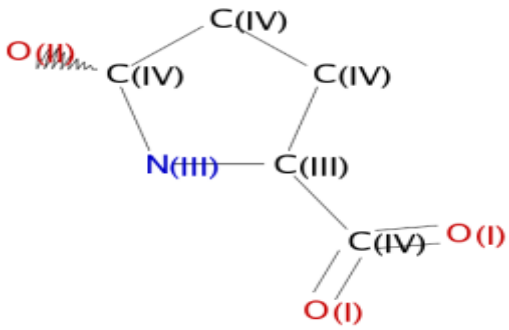
40		-2.147
41		4.733
42		0.812
43		0.812
44		28.119

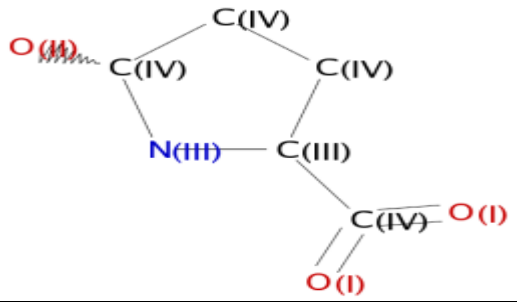
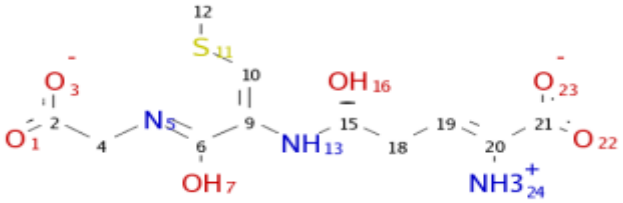
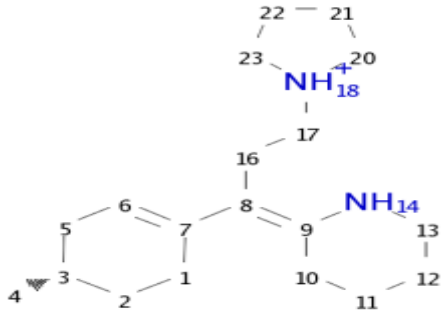
45		1.10
46		10.196
47		8.162
48		2.481
49		4.493
50		12.129

51		-0.853
52		-0.408
53		4.901
54		3.612
55		2.013

56		-0.222
57		0.426
58		-0.017
59		-0.438
60		-0.355

61		-1.303
62		-1.303
63		0.064
64		3.805
65		6.037
66		6.037
67		4.123

68		14.513
69		1.4
70		0.06
71		3.00
72		6.2

73		5.9
74		4.273
75		12.935

After calculation of descriptors for all molecules and multiple linear regression analysis by MINITAB 14 tool the following best 5 equations were derived.

1. Andrews = - 7.13 + 0.241 H - 0.120 C + 3.40 N + 0.561 O + 0.395 OH + 4.29 CO2minus + 0.465 HD-HD-Min - 0.431 HD-HA-Min (Eq.1)
2. Andrews = - 5.94 + 4.70 HD + 2.00 HA + 0.645 Rings - 2.70 Nother + 1.46 CO2minus - 4.78 OH + 0.147 HD-HD-Min - 0.651 HD-HA-Min (Eq.2)
3. Andrews = - 7.18 - 0.0465 C + 3.84 N + 0.889 O - 0.013 OH + 3.63 CO2minus+ 0.212 HD-HD-Min - 0.296 HD-HA-Min (Eq.3)
4. Andrews = - 5.63 - 0.040 Rot2 + 4.75 HD + 1.96 HA + 0.663 Rings - 2.62 Nother + 1.58 CO2minus - 4.75 OH - 0.663 HD-HA-Min (Eq.4)
5. Andrews = - 7.19 - 0.048 Rot2 + 4.75 HD + 1.96 HA + 0.569 Rings - 2.45 Nother+ 1.36 CO2minus - 4.87 OH + 0.169 HD-HD-Min (Eq.5)

In order to confirm our results predicted the Andrews value from the above equations and these results were compared to previously calculated one .Such correlations for the above 5 equations have been given in the Figure 1, Figure 2 , Figure 3, Figure 4, Figure 5 respectively.

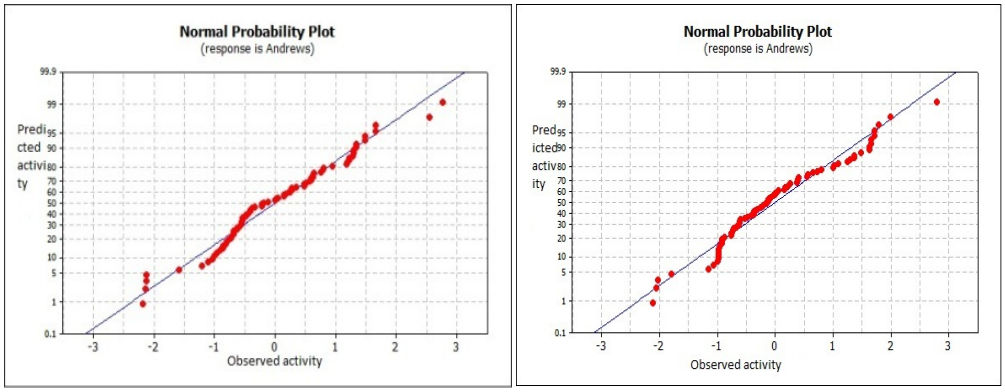


Figure 1,2: Plot between calculated and predicted value for Andrews: Model 1&2.

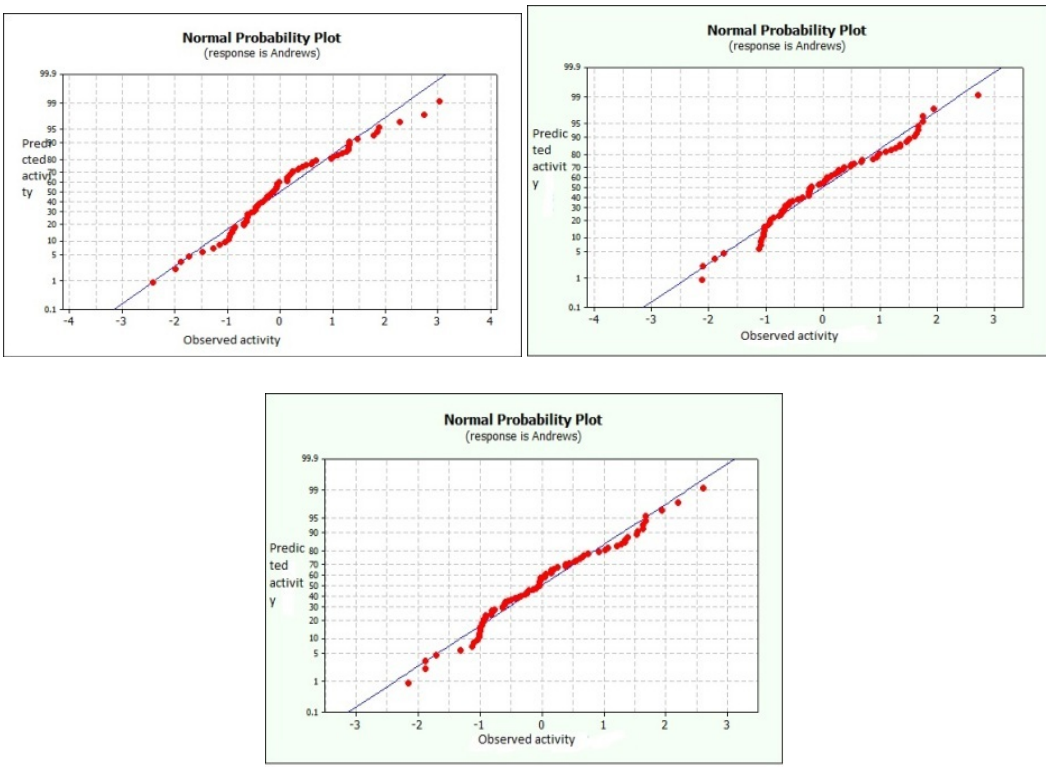


Figure 3,4,5: Plot between calculated and predicted value for Andrews: Model 3,4,5 respectively.

Comparing the variance value (R-Sq) among the equations (Table 2), the variances decreases when the more number of independent variable (descriptors) for the physiochemical type were considered. For same set of descriptors (Eq.4 and Eq.2) only two combination of structural descriptors shows less change in variance value (R-Sq), however when structural descriptors (Eq.3) were considered the variance value decreases significantly but not in F value. In general the physichemical and

structural descriptors are very important type of molecular descriptor for bioactivity prediction [12]. However, in our MLR regression analyses, it was observed that in comparison to structural descriptors they are less important for anti Glioblastoma activities.

Table 2: Calculation of statistical parameters for the best model consideration.

Model Number	R-Sq value (%)	F-value	P value
1	88.0	66.25	0.000
2	87.3	61.61	0.000
3	87.08	70.09	0.000
4	87.20	61.09	0.000
5	86.6	58.19	0.000

Conclusion

In the present study QSAR analysis has been carried out for the anti Glioblastoma drug Levetiracetam analogs by the help of available literature resources. Our results lead to the conclusion that Physiochemical parameters are best suited for the anti-Glioblastoma activity of the Levetiracetam derivatives rather than structural parameters. More over by similar type of descriptor analysis proposed models could be efficiently used to screen existing databases in order to identify novel potent compounds.

Acknowledgement

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References

[1] National Cancer Institute (Homepage on the internet).US: National Institute of Health. Available from http://www. cancer.gov/cancertopics/types/brain.

[2] Susan M. Chang, MD; Nicholas A. Butowski, MD; Patricia K. Sneed, MD; Ilona V. Garner, BS. Standard Treatment and Experimental Targeted Drug Therapy for Recurrent Glioblastoma Multiforme. Neurosurg Focus. 2006;20(4).

[3] Hu J, Ljubimova JY, Inoue S, Konda B, Patil R, Ding H, Espinoza A, Wawrowsky KA, Patil C, Ljubimov AV, Black KL.. Phosphodiesterase type 5 inhibitors increase Herceptin transport and treatment efficacy in mouse metastatic brain tumor models.. PLoS One. 2010 Apr 19;5(4):e10108.

[4] Päivi Peltomäki, Ragnhild A. Lothe, Lauri A. Aaltonen, Lea Pylkkänen, Minna Nyström-Lahti, Raquel Seruca, Leonor David, Ruth Holm, David Ryberg, Aage Haugen, Anton Brøgger, Anne-Lise Børresen, and Albert de la Chapelle. Microsatellite Instability Is Associated with Tumors That Characterize the Hereditary Non-Polyposis Colorectal Carcinoma Syndrome. *Cancer Res* December 15, 1993 53; 5853.

[5] Farooq, MY, Bhatt A., Majid A., Gupta R., Khasnis A., and Kassab MY Levetiracetam for Managing Neurologic and Psychiatric Disorders *Am J Health-Syst Pharm*, (2009).Volume 66, Issue 6, p. 541-561.

[6] David A. Winkler. The role of quantitative structure - activity relationships (QSAR) in biomolecular discovery. Briefings in Bioinformatics. 2002; 3:73-86.

[7] Chembank (Home page on the internet). For structural details of different chemical molecules. http://chembank.broadinstitute.org/welcome.htm

[8] Chemaxon .com (Home page on the internet).Marvin calculator plugin and chemical terms demo .Inc; c1999-2010.Available from http://www.chemaxon.com/marvin/sketch/index.jsp

[9] Schuettelkopf AW, VanAalten DMF. PRODRG - a tool for high-throughput crystallography of protein-ligand complexes.Acta Crystallographica.2004; 60: 1355-63.

[10] Molegro drug-development high-performance drug discovery solutions. http://www.molegro.com

[11] David J. Wild MINITAB Release 14. *J. Chem. Inf. Model.* 2005; 45:212

[12] Du Q, Mezey PG, Chou KC.Heuristic molecular lipophilicity potential (HMLP): a 2D-QSAR study to LADH of molecular family pyrazole and derivatives. J Comput Chem. 2005 Apr 15; 26(5):461-70.