3D-QSAR And ADMET Prediction Of Triazine Derivatives For Designing Potent Anticancer Agents

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ABSTRACT

The three-dimensional quantitative structure–activity relationship (3D-QSAR) on triazine derivatives as anticancer agents have been carried out using VLifeMDS 4.3 software. The stepwise 3D-QSAR kNN-MFA method was applied to derive QSAR model. Also, ADMET prediction was performed using FAF Drugs 2 which runs on Linux OS. The information rendered by 3D-QSAR models may lead to a better understanding and designing of novel anticancer molecules. ADMET prediction of these compounds showed good drug like properties. The combination of the 3D-QSAR and ADMET prediction is an important tool in understanding the structural requirements for design of novel, potent and anticancer agents and can be employed to design new drug discovery and can be used for triazine derivatives of with specific anticancer activity.

Keywords: *3D-QSAR, Triazine derivatives, Anticancer agents, ADMET prediction*

1. INTRODUCTION

Among all heterocycles, the triazine scaffold occupies a prominent position, possessing a broad range of biological activities[1]. Triazine is found in many potent biologically active molecules with promising biological potential like anti-inflammatory, anti-mycobacterial, anti-viral, anti-cancer etc. which makes it an attractive scaffold for the design and development of new drugs. The wide spectrum of biological activity of this moiety has attracted attention in the field of medicinal chemistry[2-3]. The 1,3,5-triazine scaffold was extensively studied due to a wide variety of biological properties such as antimicrobial, antiviral, anti-inflammatory activities etc[4]. Moreover, a great deal of attention has been paid to 1,3,5-triazine derivatives endowed with antitumor activity. In the latest years literature reported four reviews dealing with the chemistry and the biological properties of 1,3,5-triazine derivatives. Three of them deal with uncondensed 1,3,5-triazine derivatives with various biological activities, whereas, the first one deals

with uncondensed derivatives possessing antitumor activity mainly dedicated to kinases inhibitors and deals, with 1,3,5-triazine and their hetero-fused derivatives have shown antitumor activity[5]. Herein, the synthesis, the antitumor activity, the Structure Activity Relationship (SAR) and, whenever reported, the possible mechanism of action, of the most promising 1,3,5-triazine derivatives are described. The first derivatives to be described are the disubstituted 1,3,5-triazines then the trisubstituted ones followed by the hetero-fused systems (fused with five and six membered rings and polycyclic systems)[6-9]. As triazine derivative were prepared by microwave method. Conventional methods for different chemical synthesis is very well documented and practiced. The methods for synthesis of organic compounds had continuously modified from the last 10 years[10-18]. The application of green chemistry principles and practices renders regulation, control, clean-up, and remediation of the environment. In year 1855 Robert Bunsen invented the burner acts as energy source for heating reaction vessel this was latter superseded by isomental, oil bath but the drawback of the heating though method remains the same[19-27]. Microwave Assisted Organic Synthesis had developed in now years which has been considered superior to traditional heating. Microwave assisted organic synthesis has as a new “lead” in the organic synthesis. The technique offers clean, simple, efficient, fast and economic for the synthesis of a number of organic molecules such reaction has new tool in the organic synthesis. Important advantage of this technology includes highly accelerated rate of the reaction time with an improvement in yield and quality of product. This technique is considered as important approach toward green chemistry because this technique is more environments friendly and this technology is used in the laboratory and has the potential to have a large impact on the fields of combinatorial chemistry, screening, medicinal chemistry and drug development. Conventional method of organic synthesis usually requires longer heating time, tedious apparatus setup which result in higher cost of process and the excessive use of solvents or reagents lead to environmental pollution[28-30]. Computational studies are the crucial steps in the drug designing. Docking study is the computational routine to determine probable binding manners of a ligand to the dynamic site of a receptor. It makes an image of the dynamic site with interaction points known as grid. Then it fits the ligand in the binding site either by grid search or energy search. Due to failure of ADME so it necessary to perform docking studies before pharmacological activity. An outbreak of coronavirus disease (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) raises an unparalleled challenge in the discovery of appropriate drugs for prevention and treatment. Given the rapid pace of scientific research and clinical data produced by the large number of people quickly infected with SARS-CoV-2, clinicians need reliable proof of successful medical care for this infection as in intial stage with help of molecular docking software it is easy to do in-silico study[31-50]. The chemical modification of drug delivery system for protein and peptide drugs is important in improving both enzymatic stability and membrane permeations can help to have good biological activity from any heterocyclic compound modification.

Someday soon, you might be making your own medicines at home. That's because researchers have tailored a 3D printer to synthesize pharmaceuticals and other chemicals from simple, widely available starting compounds fed into a series[51-55]. Development of valuable methods for the preparation of many substances is still a challenge. The main issues in modern synthetic organic chemistry are selectivity, mildness, improvement of efficiency, and the avoidance of toxic reagents and by-products. From this point of view, considerable attention has been devoted to the development of new 1,3,5-triazine derivatives as reagents in organic synthesis. Quantitative structure-activity relationships (QSAR) present an attempt to correlate structural or property descriptors of compounds with activities. These physicochemical descriptors, which contain parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. Now the days QSAR are used in many disciplines, with many pertaining to drug design and environmental risk assessment. One of the importance characteristics of QSAR methodology is to increase predictive power of the model by subjecting results obtained by such model to rigorous validation and cross – validation studies. One of the most popular criteria for that the widely validation is leave- One –Out r^2 (LOO $q^{2)}$, but it has been reported that the widely accepted leave-One-Out (LOO) cross- validated $r^2(q^{2)}$ is an inadequate characteristic to assess the predictive ability of the models. Most practitioners seem to activity. Among the possible reasons proposed for this disappointment is chance evaluate the predictive ability of a QSAR model; its validation must be done using an external test set of compounds with known activities. Hence, it is needed to develop a methodology and practice in QSAR studies to improve its reliability and acceptance[56-57].

2. MATERIALS AND METHODS

Data Sets and Biological Activity

Molecular modeling studies 3D-QSAR, were performed using the molecular modeling software package VLife Molecular Design Suite (VLife MDS) version 4.3. A dataset of triazine derivatives with reported activities was used in present study. Since some compound exhibited insignificant/no inhibition, such compounds were excluded from the present study. The structures and their inhibitory activities in IC_{50} (μM) are listed in table 1.

Ligand Preparation

2D structure of triazine derivatives was drawn using VLife2 Draw tool. All structures were cleaned and 3D optimized. All the 3D structures were optimized using Merck molecular force field (MMFF) with

distance dependent dielectric function and energy gradient of 0.01 kcal/mol A with 10000 numbers of cycles. The total energy of a conformation can be calculated using MMFF by the relation;

Etotal = EB+ EA+ EBA+ EOOP+ ET+ Evdw + Eelec

Where,

EB = energy of bond stretching;

EA = energy of angle bending;

EBA = energy of bond stretching and angle bending;

EOOP = out-of-plane bending energy;

ET = torsion energy term;

Evdw = van der Waals energy;

Eelec = electrostatic energy.

3D-QSAR studies

Alignment of molecules

The molecules of the dataset were aligned by the template based technique, using the common structure of triazine derivatives with the help of VLifeMDS 4.3 template based alignment tool. This method is based on moving the molecules in 3D space, which is related to the conformational flexibility of molecules. The goal is to obtain optimal alignment between the molecular structures necessary for ligand–receptor interactions. The most active molecule was selected as a template for alignment of the molecules. A highly bioactive energetically stable conformation in this class of compounds is chosen as a reference molecule on which other molecules in the data set are aligned, considering template as a basis for the alignment.

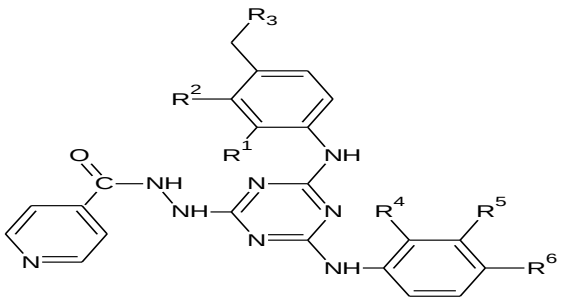

Table 1. Structures and biological activity of triazine derivatives

Sr. No	R Groups						IC_{50} (µM)
	R_1	R_2	R_3	R_4	R_5	R_6	
1	H	Cl	H	H	H	NO_2	1.428
2	NO_2	H	NO_2	H	H	NO_2	6.932
3	H	NO_2	H	H	H	NO_2	0.529
4	NO_2	H	NO_2	H	H	OCH_3	16.731
5	NO_2	H	NO_2	H	H	NO_2	6.272
6	H	H	Br	NO_2	H	NO_2	0.894
7	H	H	Br	NO_2	H	OCH_3	5.218
8	H	Cl	H	H	H	OCH_3	0.417
9	H	H	Br	H	H	NO_2	3.712
10	H	Cl	H	H	H	OCH_3	0.316
11	H	H	OCH_3	H	H	NO_2	1.692
12	H	H	OCH_3	H	H	Br	1.476
13	NO_2	H	NO_2	H	H	NO_2	0.267
14	H	NO_2	H	H	H	OCH_3	0.977
15	H	Cl	H	NO_2	H	NO_2	0.225
16	H	H	NO_2	H	H	OCH_3	0.016

17	H	H	NO_2	H	H	NO_2	0.048
18	H	H	NO_2	H	H	NO_2	0.061
19	NO_2	H	NO_2	H	H	NO_2	0.021
20	H	H	Br	H	H	OCH_3	0.032
21	NO_2	H	NO_2	NO_2	H	NO_2	0.059
22	H	H	NO_2	NO_2	H	NO_2	0.207
23	H	H	Br	H	H	NO_2	0.042

3D-QSAR kNN-MFA Model

Like many 3D-QSAR methods, k-nearest neighbor molecular field analysis (kNN-MFA) requires suitable alignment of given set of molecules. This is followed by generation of a common rectangular grid around the molecules. The steric and electrostatic interaction energies are computed at the lattice points of the grid using a methyl probe of charge +1. These interaction energy values are considered for the relationship generation and utilized as descriptors to decide nearness between molecules. The term descriptor is utilized in the following discussion to indicate field values at the lattice points. The optimal training and test sets were generated using the sphere exclusion algorithm. This algorithm allows the construction of training sets covering descriptor space occupied by representative points. Once the training and test sets were generated, kNN methodology was applied to the descriptors generated over the grid. The standard kNN method is implemented simply as follows:

- Calculate distances between an unknown object and all the objects in the training set,· Select k objects from the training set most similar to object u, according to the calculated distances.
- Classify object u with the group to which the majority of the k objects belong.

An optimal k value is selected by optimization through the classification of a test set of samples or by leave-one out cross validation. kNN-MFA with stepwise (SW) variable selection method was used to generate 3D-QSAR equations. This method employs a stepwise variable selection procedure combined with kNN to optimize (*i*) the number of nearest neighbors (k) and (*ii*) the selection of variables from the original pool. The step by-step search procedure begins by developing a trial model with a single independent variable and adds independent variables, one step at a time, examining the fit of the model at

each step. The method continues until there are no more significant variables remaining outside the model[58-59].

ADMET Prediction

ADMET prediction for the various physicochemical descriptors and pharmaceutically relevant properties was performed using FAFDrugs2 which runs on Linux OS. This tool is freely available and used for *in silico* ADMET filtering. This approach has been widely used as a filter for substances that would likely be further developed in drug design programs. In particular, we calculated thecompliance of compounds to the Lipinski's rule of five and Veber's rule. We have also assessed the parameters like number of rotatable bonds (>10) and number of rigidbonds which signify that compound may have good oral bioavailability and good intestinal absorption[60-64].

3. RESULTS AND DISCUSSION

3D-QSAR Studies

In the present study, kNN-MFA model is developed coupled with stepwise variable selection method to develop 3D-QSAR models of triazine as anticancer agents based on steric and electrostatic fields. A highly bioactive energetically stable conformation in this class of compounds is chosen as a reference molecule on which other molecules in the data set are aligned, considering template as a basis for the alignment. The aligned view of triazine is presented in figure. The total data set was divided into training and test sets using the sphere exclusion algorithm for diversity of the sampling procedure. This approach resulted in selection of compounds 2, 3, 4, 10, 11, 14, and 17 as the test set and the remaining 16 compounds as the training set. Selection of molecules in the training set and test is a key and important feature of any QSAR model. Therefore the care was taken in such a way that biological activities of all compounds in test lie within the maximum and minimum value range of biological activities of training set of compounds. The Uni Column statistics for training set and test set were generated to check correctness of selection criteria for trainings and test set molecules and result reflected the correct selection of test and training sets. Several statistically significant 3D-QSAR models using stepwise variable selection method were generated, of which the corresponding best model is reported herein. The best 3D-QSAR *k*NN MFA model selected based on the value of statistical parameters has a $q^2 = 0.7187$ and pred_$r^2 = 0.2075$.

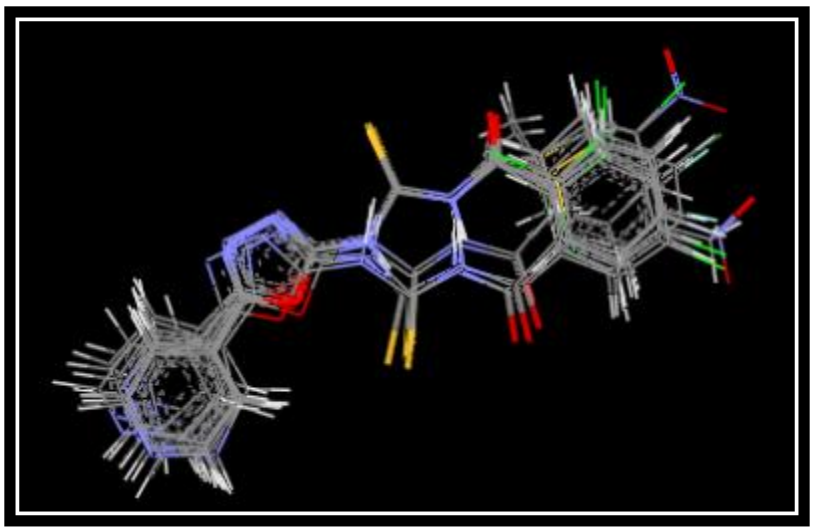

Fig 1. Alignment of the molecules

Table 2. Observed and predicted activity by QSAR equation along with residual

Code	Sets	PIC_{50}		Residual
		Exp.	Pred.	
1	Training	-0.655	0.464	-1.119
2	Test	-0.114	0.015	-0.129
3	Test	-1.159	-0.142	-1.017
4	Test	-0.655	0.464	-1.119
5	Training	0.324	-0.356	0.68
6	Training	-0.654	-0.256	-0.398
7	Training	-0.772	-0.528	-0.244
8	Training	0.333	0.358	-0.025
9	Training	-0.654	-0.256	-0.398
10	Test	0.153	0.533	-0.38
11	Test	0.917	0.397	0.52
12	Training	-0.169	-0.014	-0.155
13	Training	0.562	0.299	0.263
14	Test	0.010	-0.395	0.405

15	Training	0.647	0.739	-0.092
16	Training	0.193	0.398	-0.205
17	Test	0.826	0.353	0.473
18	Training	0.385	0.034	0.351
19	Training	1.677	1.359	0.318
20	Training	1.494	1.434	0.060
21	Training	1.229	1.580	-0.351
22	Training	0.754	-0.070	-34.859
23	Training	1.376	0.467	0.909

Table 3. Uni Column statistics of the training and test sets for QSAR models

Data set	Column name	Average	Max.	Min.	Std. deviation	Sum
Training	PIC_{50}	0.4063	1.6780	-1.1600	0.8327	6.5000
Test	PIC_{50}	-0.0870	0.9170	-0.8860	0.6333	-0.6090

Table 4. Statistical results of 3D-QSAR *k*NN MFA model generated by stepwise variable selection method

Sr. No.	Statistical parameter	Results
1	n (Training/Test)	16/7
2	k Nearest Neighbor	4
3	N	16
4	Degree of freedom	13
5	q2	0.7187
6	q2_se	0.4416
7	$Predr^2$	0.7368
8	pred_r^2se	S_1021-0.0542-0.0488
9	Descriptors(Range)	S_853 0.0400 0.2043

From table, it is evident that predicted activities of all the compounds are in good agreement with their corresponding experimental activities. The plots of observed versus predicted activity of both training & test sets molecules helped in crossvalidation of *k*NN-MFA QSAR model and are depicted in Fig..

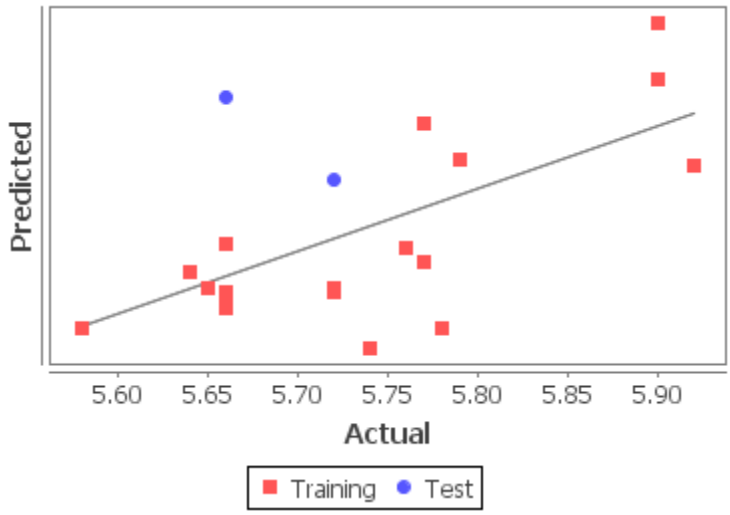

Fig 2. Comparison of observed activity versus predicted activity for training set & test set compounds according to 3D QSAR model by SW-*k*NN MFA method

From stepwise 3D-QSAR kNN-MFA (SW-*k*NN MFA) model, the points generated are S_1021 (-0.0542 -0.0488) and S_853 (0.0400 0.2043) i.e. steric interaction at their corresponding spatial grid points. These points suggested the significance and requirement of steric properties for better biological activities. It is observed that negative range at grid point S_1021 on phenyl moiety indicating that negative steric potential is favorable for increase in the activity of triazine derivatives and hence less bulky substituents are preferred in that region. Therefore, less steric groups will be preferable for enhancing biological activity. Positive range at S_853 grid point on phenyl moiety indicates that positive steric potential is favorable for increase in the activity and hence more bulky substituent groups are preferred in that region. Therefore bulky substituents were preferred at the position of generated data point S_853 around triazine pharmacophore for maximum activity. These results are in close agreement with the experimental observations that compounds 12, 14, 15, 19, 20, 21, 22 and 23 with bulky substituent at R3 position and less steric groups at of phenyl ring showed greater activities.

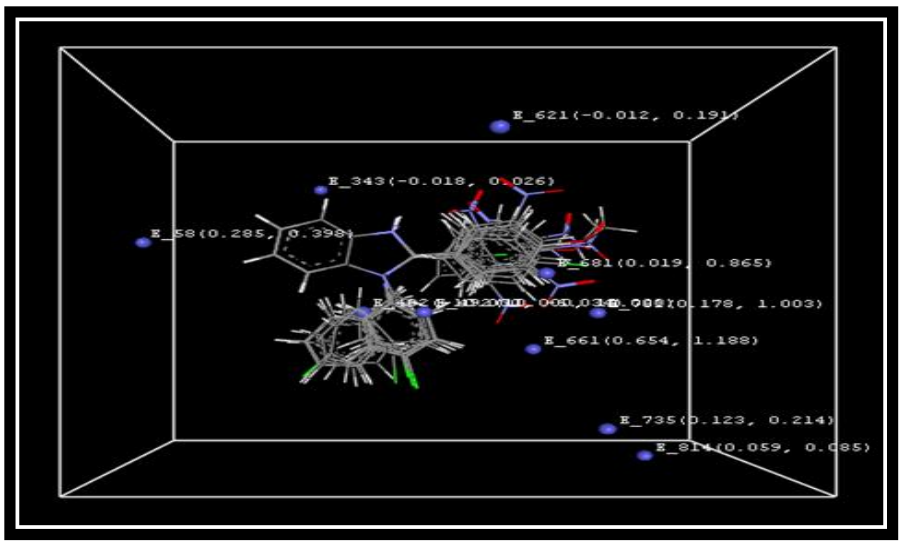

Fig. 3. Stereo view of the molecular rectangular field grid around the superposed molecular units of triazine series of compounds using SW method

Thus, the contribution plot arising out of 3D-QSAR studies provide some useful insights for better understanding of the structural features of these compounds responsible for producing significant anticancer activity.

ADMET Prediction

All the compounds showed significant values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five. The 23 compounds werewithin the range of accepted values. None of the compounds had violated Veber rule (Rotatable bonds ≤ 10 and PSA ≤ 140). The compounds except 1, 5, 6, 7, 13, 19, 22, and 23 had violated one rule i.e. log $p \geq 5$ of the Lipinski's rule. A molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: log*P* (octanol-water partition coefficient) ≤5, molecular weight ≤500, number of hydrogen bond acceptors ≤10 and number of hydrogen bond donors ≤5. Thus, all these compounds followed the criteria for orally active drug and therefore, these compounds can be further developed as oral drug candidates. All the compounds except 17, 18, and 21 were non toxic.

Table 5. Prediction of ADMET properties of compounds

Code	MW	log *p*	PSA	Rot. bond	Rig. bond	HBD	HBA	Lipinski violation	Veber violation	Toxicity
1	492.87	4.97	44.56	5	23	1	2	1	FALSE	NT
2	548.42	5.28	45.65	4	23	1	3	0	FALSE	NT
3	537.50	5.32	46.21	4	23	1	3	0	FALSE	NT
4	531.48	5.76	54.46	4	23	1	3	0	FALSE	NT
5	533.41	4.37	58.12	4	22	1	3	0	FALSE	NT
6	616.40	4.12	54.29	7	22	2	3	0	FALSE	NT
7	556.43	4.82	58.32	6	24	1	3	0	FALSE	NT
8	511.98	5.68	69.21	5	24	1	3	0	FALSE	NT
9	571.40	4.23	44.23	4	22	1	3	0	FALSE	NT
10	477.90	3.54	48.92	4	24	1	2	0	FALSE	NT
11	537.32	4.67	45.10	5	25	1	3	1	FALSE	NT
12	522.35	4.29	62.56	5	22	1	3	1	FALSE	NT
13	582.50	4.21	55.17	6	24	2	3	1	FALSE	NT
14	473.44	4.92	43.92	4	23	1	2	1	FALSE	NT
15	537.87	5.32	52.27	5	23	1	3	0	FALSE	NT
16	473.44	6.23	41.87	4	24	2	2	1	FALSE	NT
17	488.41	4.34	47.18	5	22	1	2	1	FALSE	NT
18	488.41	4.91	48.23	5	22	1	3	1	FALSE	NT
19	518.44	4.88	45.12	5	24	2	2	0	FALSE	NT
20	507.34	4.12	48.31	4	24	1	2	0	FALSE	NT
21	578.41	6.19	49.19	6	25	1	2	0	FALSE	NT
22	533.41	5.29	48.10	5	23	2	3	0	FALSE	NT
23	537.32	4.68	48.32	5	22	2	2	0	FALSE	NT

MW: molecular weight; log *p*: logarithm of partition coefficient of compound between n-octanol and water; PSA: polar surface area; Rot. bond: rotatable bond; Rig. bond: rigid bond; HBD: hydrogen bond donor; HBA: hydrogen bond acceptor; T: toxic; NT: non toxic.

4. CONCLUSION

The stepwise method is applied for optimization and selection of suitable descriptors for development of 3D-QSAR kNN-MFA model for a series of triazine derivatives as polo-like kinase 1 inhibitors using VLifeMDS 4.3 drug design software. The 3D-QSAR results revealed that bulky substituent and less steric groups at position of phenyl ring were preferred for enhancing biological activity of triazine analogs. This finding supports the experimental observations, where presence of bulky groups at less steric groups of phenyl ring signifies increase in activities of compounds. From the molecular docking studies, it is evident that bulky groups at of phenyl ring of triazine forms strong hydrophobic interactions with active site of hydrophobic amino acid residues. The pharmacophore patterns of triazine derivatives were developed using MolSign Module of VLifeMDS 4.3. The chemical feature based best common pharmacophore has two aromatic carbon centers, one aliphatic carbon center, one hydrogen bond acceptor features. The ADMET prediction revealed that compounds can be further developed as good oral drug candidates. Hence, the combination of the above studies (3D-QSAR and ADMET prediction) are useful in understanding the structural requirements for design of novel, potent and cancer inhibitors and can be employed to design new derivatives triazine with specific anticancer activity.

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