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Original Article

QSAR and Molecular Docking Studies of 5-benzylide-no-2-adamantylthiazol[3,2-b][1,2,4]triazol-6(5H)ones Derivatives as Antimicrobial Activity

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ABSTRACT

Aim and Background: Bacterial Infection is a leading cause of death worldwide. Triazoles and thiazolinones (fused) have been reported to possess many biological activities including antibacterial activity. To study 2D and 3D QSAR followed by Molecular Docking studies to generate new chemical entities (NCE's) containing as pharmacophore for antibacterial activity. **Materials and Methods:** In the presented studies we have reported the results of QSAR studies for the 21 derivatives of triazole-thiazolinone synthesized by Tratrat *et al*. 2D and 3D QSAR studies were done by using V-Life software. The NCE's were designed by using Lead grow tool in V-Life Software and screened by Lipinski screen. The designed compounds having the Lipinski score 5 were subjected to molecular docking studies with *Staphylococcus aureus* (DNA gyrase) enzyme by using autodock software. **Results:** The r^2 and q^2 for the 2D QSAR and 3D QSAR was found to be 0.9000 and 0.8730 respectively. Large number of molecules were generated by using Lead grow tool in V Life. **Conclusion:** The substitution pattern was established by using QSAR tool for better Antibacterial activity.

Keywords: Triazole-thiazolinone, Antibacterial, QSAR, Combilib, Docking, Molecular modelling studies.

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INTRODUCTION

Antimicrobial resistance (AMR) is a specific type of drug resistance developed by micro-organisms like bacteria, fungi, viruses and parasites have ability to survive against the antimicrobial drugs. There is increase in the rate of morbidity and mortality due to the AMR, as per WHO report.[1-2] Antibiotic resistance is increasing at an alarming rate around the world. New resistance mechanisms are arising and spreading throughout the world, posing a threat to our ability to treat common infectious diseases. As medicines become less efficient, a rising range of bacterial infections are becoming more difficult to cure. The gram-positive bacterium *Staphylococcus aureus* is a prevalent source of bacterial infections. Infections with methicillin-resistant *Staphylococcus aureus* (MRSA) are 64% more likely to cause death than infections with drug-sensitive bacteria.[3] Various 1,2,4-triazole derivatives with plethora of pharmacological activities viz., antibacterial,[4-5] antitumor,[6] antitubercular,[7] analgesic,[8] antifungal,[9-10] antiviral are seen in the literature.[11-12] Similarly, Thiazolinone have also exhibit anti-hyperglycaemic,[13] anti-inflammatory, anti-microbial, anti-viral, anti-fungal, and anti-bacterial activities.[14-16]

To overcome the drug resistance and enhance biological activity, hybridization is the best strategy. Hybrids of 1,2,4-triazole were found to be highly active against drug-resistant pathogens and shown potential antibacterial activity.[4] Hence, 1,2,4-triazole and thiazolinone together as a hybrid have been reported to possess *Staphylococcus aureus* antibacterial activity.[17] Quantitative Structure-Activity relationship (QSAR) is a powerful tool for drug design. It gives an idea about the relationship between chemical structure and biological activity.[18-19] In present study we have attempted to optimize the triazole-thiazolinone pharmacophore for antibacterial activity by two dimensional (2D) and three-dimensional Quantitative structure activity relationship (3D QSAR). New compounds were designed by using Combilib tool in V-Life software and were screened by Lipinski filter. The compounds having the Lipinski score of 5 were subjected to the molecular docking process by using the autodock software.

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MATERIALS AND METHODS

Materials

QSAR studies (2D, 3D and Lead grow) were performed by using the software V-life MDS (V-Life MDS 4.4). The molecular docking studies were performed with autodock Software.[19-21] ChemDraw Ultra 8.0 software was used to draw the structures of all the designed molecules. 2D structures were changed to 3D format. The 3D optimization and energy minimization steps were performed by using the force field charge as Molecular Merck force field (MMFF) along with distance dependent-dielectric function and energy gradient of 0.001kcal/mol Å.

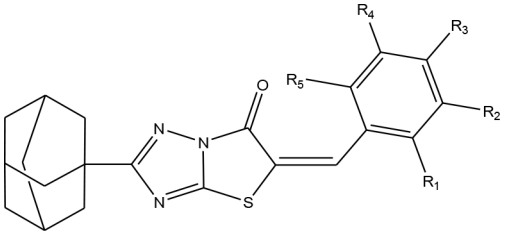
QSAR

Data Set

Tratrat *et al.* reported 25 derivatives of 5-benzylideno-2-adamantylthiazol[3,2-*b*][1,2,4]triazol-6(5H)ones among this data set of 21 derivative with antibacterial activity were selected for QSAR studies are displayed in Table 4. The minimal inhibitory concentration (MIC) of biological activity was integrated into pMIC [pMIC =log(1/MIC)].[17]

Molecular descriptors represent the mathematical values that describe properties of a molecule. 2D descriptors like physicochemical and alignment independent also called as topological descriptors were generated. All the invariable columns of descriptors were deleted.

The QSAR studies employed the antibacterial activity represented as pMIC values as dependent factors and the molecular descriptors as independent variables. The full data set was separated into a training set (to produce regression models) and a test set for the creation of the QSAR model (to evaluate the predictive ability of these models). The test compounds were selected on the basis of structural variety and antibacterial activity distribution. Uni-Column statistics for training set and test set were generated to check correctness of selection criteria for training and test set molecules.[20-21]



Methods

2D QSAR

For generation of 2D QSAR models, methods such as multiple linear regression (MLR), partial least square (PLS), and principal component regression (PCR) were used. Various descriptors such as physico-chemical and alignment were utilized to develop the models. Statistical parameters such as correlation coefficient (r^2), Cross-validated correlation coefficient (q^2), predicted r^2, r^2 se, Alpha Rand Predicted r^2, etc. were used to evaluate the QSAR model.[21]

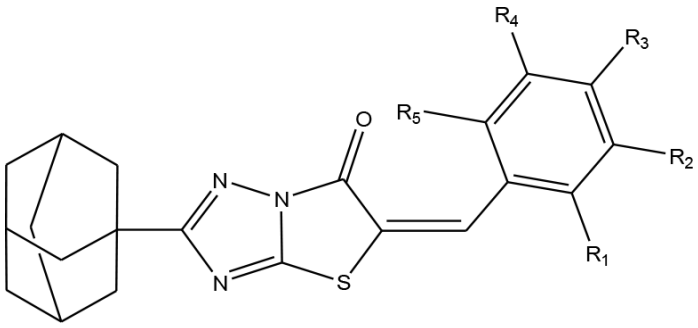


Figure 1: Common template used for alignment of triazole-thiazolinone derivatives.

3D QSAR

The 3D QSAR models were generated by k nearest neighbour molecular field analysis (kNN MFA) using simulated annealing (SA) variable selection method. The optimized molecules were aligned by using a template-based alignment method (Figure 1). 3D QSAR model was developed using the obtained set of molecules. This was followed by generation of rectangular grid around the molecule. The steric, hydrophobic and electrostatic interaction energies were computed at the lattice point of the grid. Further the generated QSAR model was evaluated by using various statistical parameters.[22]

Design of New Chemical Entities (NCE's) using LEADGROW tool

Information and correlation of structure with activity obtained from QSAR studies guided us to design the NCE's by using Lead grow tool in V-Life MDS software. Large library of the compounds having the triazole-thiazolinone nucleus were designed and screened through the Lipinski rule. Based on their Lipinski score the designed NCE's were selected for further docking study.[18]

Molecular docking

Intermolecular interactions between compound 1-19 with DNA gyrase 2 were investigated by Molecular Docking. The topoisomerase ATPase inhibitor site was used as the binding site and ligands were docked via Lamarckian genetic algorithm (LGA) as implemented in Autodock 4.2 program.[23-24] DNA gyrase is a member of type IIA family of topoisomerases which has a unique ability to introduce negative supercoils into covalently closed DNA in an ATP- and Mg^{2+} -dependent manner. It is composed of two hetero-tetrameric subunits each of GyrA and GyrB. The GyrB subunit is important for ATP-dependent negative supercoiling of DNA, which is essential for the replication process to maintain DNA topology.[25]

Protein Preparation: The crystal structure of DNA gyrase B (GyrB) protein structure of *Staphylococcus aureus* (PDB ID: 3TTZ, Resolution: 1.63 Å) was retrieved from the source of Research Collaboratory for Structure Bioinformatics (RCSB) protein data bank (https://www.rcsb.org). The protein (PDB ID: 3TTZ) is selected by using the Basic Local Alignment Search Tool (BLAST) which is an algorithm used for calculating sequence similarities between DNA and protein sequences from National Centre for Biotechnology Information (NCBI) database.[26] Protein was prepared by using Biovia Discovery studio visualizer v21.1.0.20298 via retaining one chain A and the water molecules, chain B, ligand group present were deleted. One water molecule interact with Thr173 in the binding site was considered for the docking.

Ligand Preparation

The structures of ligand were drawn using ChemDraw Ultra 8.0 software. The energy minimization and ligand optimization were performed in Avogadro 1.2.0 using force field MMFF94.

Autodock grid generation

Auto grid tool was used for the preparation of the grid map type. The grid was prepared by centring it on to the site II residues of BSA with dimensions of 56×70×46 Å and a 0.375 Å grid spacing.

Docking

Docking was performed by using Autodock 4.2. program. In ADT tools ADT assigned polar hydrogens, united atom Kollman charges, gasteiger charges, polar hydrogens and fragmental volumes added to the protein. Further, all other parameters were maintained at their default value.

RESULTS

2D QSAR

The results for 2D QSAR were obtained by various methods, amongst them the MLR has shown the best results (Table 1). The following equation was generated -

PMIC = 0.6400 (SsCH3count) + 0.5576 (T_O_O_4) -0.9695 (T_O_O_0) + 0.3076 (T_2_2_2) +0.8745 (T_N_S_6) Eq. 1

An idea about the requirement of different physico-chemical descriptors and alignment descriptors and their contribution for antibacterial activity was obtained from the 2D QSAR analysis. $SsCH_3$count (i.e., the total number of $-CH_3$ group connected with single bond), T_O_O_4 (the count of number of Oxygen atom separated from any Oxygen atom by 4 bond distance in a molecule) and T_2_2_2 (the count of number of double bounded atoms separated from any other double bonded atom by 2 bonds in a molecule),T_N_S_6(the count of number of Nitrogen atoms separated from Sulphur atom by 6 bonds in a molecule) contributes positively towards the activity in the formation of the new chemical entities and T_O_O_0 (the count of number of Oxygen atom separated from any Oxygen atom) contributes negatively in the activity.

Table 1: Results of 2D QSAR for 5-benzylideno-2-adamantylthiazol[3,2-*b*][1,2,4]triazol-6(5H)ones derivatives.

Statistics parameter	Score
Optimum Components	3
N	16
Degree of freedom	10
r^2	0.9000
q^2	0.6999
F test	17.9904
r^2_se	0.2313
q^2_se	0.1626
Pred_ r^2	0.9949
Pred_ r^2_se	0.0416
ZScore r^2	5.15721
ZScore q^2	2.47681
Best Rand r^2	0.47949
Best Rand q^2	-0.10654
Alpha Rand r^2	0.00001
Alpha Rand q^2	0.01000
Z Score Pred r^2	1.99977
Best Rand Pred r^2	0.62334
Alpha Rand Pred r^2	0.05000
Descriptors	SsCH3count T_O_O_4 T_O_O_0 T_2_2_2 T_N_S_6
Coefficients	0.6400 0.5576 -0.9695 0.3076 0.8745

Table 2: Results of 3D QSAR.

Statistical Parameters	SA-KNN Score
k Nearest Neighbor	3
N	16
Degree of Freedom	10
q^2	0.8730
q^2_se	0.2178
Pred_r^2	0.7161
Pred_r^2se	0.2655

3D QSAR

In continuation with the 2D QSAR, 3D QSAR models were also generated to predict and interpret the activity. The 3D QSAR was performed by using 5 molecules as test set and remaining 16 molecules as training set. The KNN method was used for performing the 3D QSAR. Various parameters such as q^2, q^2_se

etc. were used for selection of best models using 2 fields i.e., steric and electrostatic. The results of 3D QSAR are included in Table 2 and the generated data points are shown in Figure 1.

Design of NCE's containing triazole-thiazolinone pharmacophore

More than 500 compounds were generated using Lead grow tool of V-Life software which follows the Lipinski rule. Only 19 most active molecules (Table 3) on the basis of their Lipinski score was selected for the further process. The various parameters were generated in Lead grow tool result i.e., H-Acceptor Count which indicates Number of hydrogen bond acceptor atoms, molecular weight signifies the molecular weight of the compound and the polar surface area is the surface sum over all polar molecules.

Table 3: Result of Combilib study.

Sl. No	R_1	R_2	R_3	R_4	R_5	H-Acceptor Count	Mol. Wt.	Polar Surface Area	Lipinski Screen Score
1	F	Pyrrole	Acetate	Allyl	Benzopyrrole	4	642.64	143.85	5
2	F	Pyrrole	Allyl	Methyl ketone	Benzopyrrole	5	598.61	145.13	5
3	F	Pyrrole	Allyl	Methyl ketone	Pyridine	4	657.68	143.85	5
4	F	Pyrrole	Allyl	Methyl ketone	Cyclopentane	4	594.62	128.06	5
5	F	Pyrrole	Allyl	Cl	Pyridine	4	609.66	128.06	5
6	F	Allyl	Cl	Allyl	Pyridine	2	553.98	98.86	5
7	F	Allyl	Cl	$-O-C_2H_5$	Benzopyrrole	4	600.61	118.89	5
8	F	Allyl	Cl	Methyl ketone	Cyclopentane	3	598.03	110.99	5
9	F	Allyl	Cl	Cyclopentane	Pyridine	3	547.99	103.04	5
10	F	Pyrrole	S	Methyl ketone	Benzopyrrole	2	569.01	98.86	5
11	F	Allyl	Cl	Allyl	Benzopyrrole	4	619.65	134.62	5
12	F	Allyl	S	Allyl	Benzopyrrole	2	592.03	101.76	5
13	F	Allyl	Cl	$-O-C_2H_5$	Pyridine	3	588.64	101.76	5
14	F	Allyl	Cl	$-O-C_2H_5$	S	3	559.98	108.09	5
15	F	Allyl	Cl	Methyl ketone	Pyridine	3	557.97	115.93	5
16	F	Allyl	Cl	Methyl ketone	Benzopyrrole	3	596.02	118.83	5
17	F	Allyl	S	Methyl ketone	Pyridine	4	554.58	115.93	5
18	F	Allyl	S	Allyl	Cyclobutane	3	540.62	85.97	5
19	F	Allyl	S	Allyl	S	6	537.57	120.11	5

Table 4: Data set used for QSAR study.

Sl. No	$-R_1$	$-R_2$	$-R_3$	$-R_4$	$-R_5$	$-R_6$	MIC(μM)	pMIC
1.	-H	-OH	-H	-OH	-H	-H	345	3.995
2.	-H	-OH	-H	-H	-H	-H	101	3.448
3.**	-H	-H	-H	-OH	-H	-H	356	4.026
4.	-H	-H	$-OCH_3$	$-OCH_3$	-H	-H	94	3.816
5.	-H	-H	-H	-H	-H	-H	154	4.614
6.	-H	- H	$-OCH_3$	$-OCH_3$	$-OCH_3$	-H	23	4.600
7.*,**	-H	-H	-H	$-C_2H_5$	-H	-H	25	3.785
8.	-H	$-NO_2$	-H	-H	-H	-H	163	4.786
9.**	-H	-H	$-NO_2$	-H	-H	-H	19	4.031
10.	-H	-H	-H	$-NO_2$	-H	-H	93	4.873
11.*,**	-H	-H	-F	-H	-H	-H	13.2	4.950
12.	-H	-H	-H	-F	-H	-H	11	4.880
13.	-H	-Cl	-H	-H	-H	-H	13	5.306
14.*	-H	-H	-Cl	-H	-H	-H	5	4.950
15.	-H	-H	-H	-Cl	-H	-H	11	4.920
16.*	-H	-Cl	-Cl	-H	-H	-H	12	4.881
17.*,**	-H	-Cl	-H	-Cl	-H	-H	13	4.880
18.	-H	-Cl	-H	-H	-H	-Cl	13	4.955
19.	-H	-Br	-H	-H	-H	-H	11	4.952
20.	-H	-H	-Br	-H	-H	-H	11	4.952
21.	-H	-H	-H	-Br	-H	-H	11	3.462

*Test set of 2D QSAR, **test set of 3D QSAR remaining molecules.

Table 5: Docking scores and major interaction.

Comp No.	Pose number	Docking Score(kcal/mol)	Major interactions
1	1	-7.7	H-Bond: Thr104 VdW: Val21, Gly24, Leu25, Ala27, Val28, Val130 Polar/Charged: Gln20, Ser128, Ser129, Glu50
2	1	-7.9	VdW: Val21, Leu25, Ala27, Val28, Tyr35 Polar/Charged: Gln20, Glu23, Thr104, Ser128, Ser129
3	3	-7.1	VdW: Tyr35, Ala27, Gly24, Val21, Ile102, Val130 Polar/Charged: Glu23, Thr104, Ser128, Ser129, Asn54
4	2	-7.4	VdW: Val131, Val130, Ile51, Leu103, Ile102, Pro87, Ile86 Polar/Charged: Ser129, Ser128, Asn54, Glu58
5	6	-6.9	VdW: Val130, Tyr35, Ile102, Pro87, Ile86 Polar/Charged: Ser128, Asn54, Arg84, Glu58, Glu50, Metal Interaction
6	5	-6.9	VdW: Val130, Ile102, Ile86, Pro87 Polar/Charged: Asn54, Ser55, Thr173, Asp173, Asp81, Glu58, Glu50, Ser128, Ser129, Metal-N Interaction
7	1	-7.8	VdW: Val21, Leu25, Tyr35, Ala27, Val28, Val130, Ile102 Polar/Charged: Gln20, Thr104, Ser128, Ser129, Asn54
8	1	-8.3	VdW: Pro87, Ile86, Gly85, Tyr35, Val131, Val130, Ile51, Leu103, Ile102 Polar/Charged: Thr173, Arg84, Glu58, Glu50, Ser128, Ser129, Asn54
9	7	-7.4	VdW: Ile102, Pro87, Ile86, Tyr35, Val131, Val130, Ile52 Polar/Charged: Ser128, Ser129, Asn54
10	1	-7.8	VdW: Val21, Leu25, Tyr35, Ala27, Val28, Ile102 Polar/Charged: Gln20, Thr104, Ser128, Ser129, Asn54
11	4	-7.8	VdW: Val21, Leu25, Val28, Ile102, Val130 Polar/Charged: Gln20, Thr104, Ser128, Ser129, Glu50, Asn54
12	1	-7.6	VdW: Val21, Leu25, Val28, Ile102 Polar/Charged: Gln20, Thr104, Ser128, Ser129, Asn54
13	7	-6.6	H-Bond: Glu58, Arg84 VdW: Tyr63, Ala61, Leu60, Ile86, Pro87 Polar/Charged: Asp57, Asn54, Thr173, Metal-NH
14	1	-7.4	VdW: Val130, Leu103, Ile102, Pro87, Ile86, Gly85 Polar/Charged: Glu50, Ser128, Ser129, Asn54, Thr173, Arg84, Glu58
15	3	-7.1	H-Bond: Gln91 VdW: Val101, Ile102, Pro87, Ile86 Polar/Charged: Ser128, Lys93, Asn54, Glu58
16	1	-7.6	VdW: Val130, Ile102, Leu103, Pro87, Ile86 Polar/Charged: Glu50, Asn54, Glu58, Thr173, Arg84
17	1	-8.3	VdW: Tyr35, Val131, Val130, Ile151, Leu103, Ile102, Pro87, Ile87 Polar/Charged: Ser128, Ser129, Asn54, Glu58, Arg84
18	4	-6.9	H-Bond: Arg84 VdW: Tyr63, Ala61, Leu60, Ile86, Ile102, Pro87 Polar/Charged: Asn54, Thr173, Glu58, Asp57
19	3	-7.1	VdW: Tyr35, Val130, Leu103, Ile102, Pro87, Ile86 Polar/Charged: Ser128, Ser129, Thr173, Asn54, Ser55, Arg54, Glu58
Ampicillin	1	-7.5	VdW: Ileu51, Ileu175, Ileu86, Val99, Val142, Val140, Ile102, Val79, Gly172, Gly85 Polar/Charged: Asn54, Ser55, Asp57 H-bond: Thr173, Asp81, water

Docking result

The ligands were minimized and possible ionization states were generated at pH 7. The docking scores of the ligands are shown in Table 5. We noted that exposed L shaped charged binding pocket was available for binding that was formed by the negatively charged residues. The resulting docking scores of the compounds were in range of -6.96 to -8.3kcal/mol and binding was majorly driven by Van der Waal and polar residues. Compound 1, 13, 15 and 18 form H-bonding with Thr104, Glu58, Gln91, Arg84 respectively. Cofactor Mg^{2+} interacts with compound 5, 6, and 13. In majority of the poses, the adamantly group orients towards hydrophobic pocket shared by Ileu86, Pro87, Ala61 and Leu60. Compound 1 comprise docking score of -7.7kcal/mol and form H-bond with Thr104 and Van der Waal interactions with Val21, Gly24, Leu25, Ala27, Val28, Val130.Compound 8 and 17 showed highest

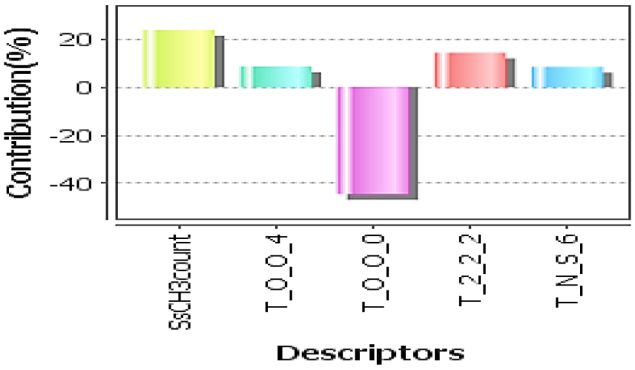


Figure 2: Contribution plot of descriptors by SA-MLR.

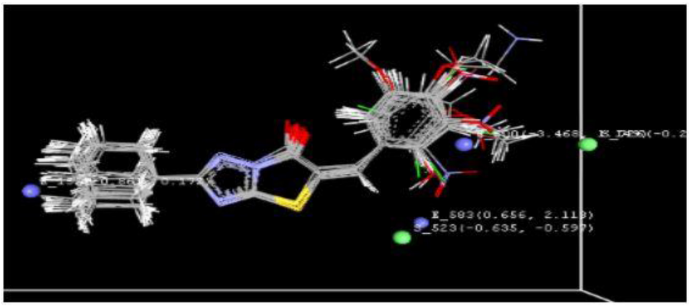


Figure 3: Generated data points in 3D QSAR.

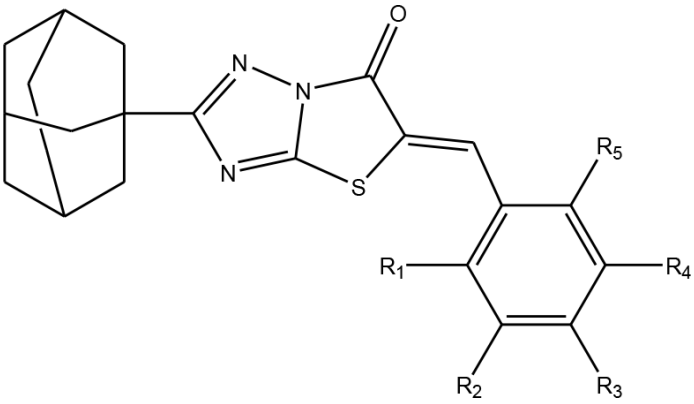


Figure 4: Structure of designed NCE's.

docking score of -8.3kcal/mol. In particular, compound 8 form Van der Waal contacts with Pro87, Ile86, Gly85, Tyr35, Val131, Val130, Ile51, Leu103, Ile102 and weak charged interactions with Thr173, Arg84, Glu58, Glu50, Ser128, Ser129, Asn54. Further details of the contacts formed by the compounds are provided in Table 5 and representative poses are depicted in Figure 5.

DISCUSSION

2D QSAR

From the results of 2D QSAR studies, the requirement of different chemical and physical parameters and their contribution to the potential antimicrobial activity is obtained. $SsCH_3$count (i.e., the total number of $-CH_3$ group connected with single bond),

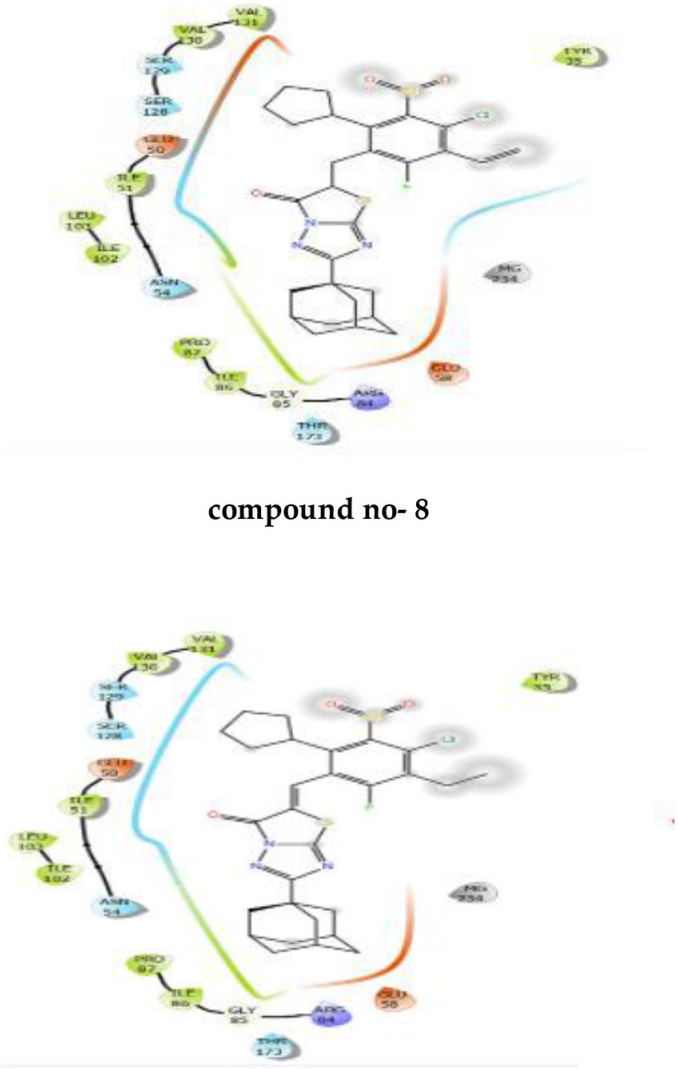


Figure 5: Interaction diagram of representative poses.

T_O_O_4 (the count of number of Oxygen atom separated from any Oxygen atom by 4 bond distance in a molecule) and T_2_2_2 (the count of number of double bounded atoms separated from any other double bonded atom by 2 bonds in a molecule),T_N_S_6(the count of number of Nitrogen atoms separated from Sulphur atom by 6 bonds in a molecule) contributes positively towards the activity in the formation of the new chemical entities and T_O_O_0 (the count of number of Oxygen atom separated from any Oxygen atom) contributes negatively in the activity. contribution of these descriptors is shown in Figure 2.

3D QSAR

Some useful aspects are provided by the 3D QSAR study for a comprehensive understanding of the structural features of triazole-thiazolinone pharmacophore. The generated 3D data points are shown in Figure 3.

Design of NCE's

Among the 500 generated compounds only 19 most active molecules were selected for the further process on the basis of their Lipinski score. The general structure of these designed NCE's is shown in Figure 4.

Docking

The obtained docking results are the representation of binding affinity of the designed compounds towards target for antimicrobial activity calculated in the form of dock score. In majority of the poses, the adamantly group orients towards hydrophobic pocket shared by Ileu86, Pro87, Ala61 and Leu60. Compound 1 comprise docking score of -7.7kcal/mol and form H-bond with Thr104 and Van der Waal interactions with Val21, Gly24, Leu25, Ala27, Val28, Val130. Compound 8 and 17 showed highest docking score of -8.3kcal/mol. In particular, compound 8 form Van der Waal contacts with Pro87, Ile86, Gly85, Tyr35, Val131, Val130, Ile51, Leu103, Ile102 and weak charged interactions with Thr173, Arg84, Glu58, Glu50, Ser128, Ser129, Asn54. Further details of the contacts formed by the compounds are provided in Table 5 and interaction diagram of representative poses are depicted in Figure 5.

CONCLUSION

In the present study 21 derivatives of triazole-thiazolinone synthesized by Tratrat *et al* were studied using 2D and 3D QSAR, for pharmacophore optimization for antibacterial activity. Best model generated showed correlation coefficient r^2= 0.9000 and q^2 = 0.6999 for 2D QSAR and q^2 = 0.8730 for 3D QSAR. Therefore, the new chemical entities were designed based on their various properties such as electrostatic, steric, hydrophobic and topological requirements and the substitution pattern is based upon the 2D, 3D QSAR studies. Thus, the library of triazole-thiazolinone derivatives was designed based on QSAR results and screened through the Lipinski screen. The molecules with higher Lipinski score subjected to molecular docking studies and the binding affinity of the molecules with DNA gyrase inhibitor was reported. The compounds with Lipinski score 5 were subjected to molecular docking studies. The outcome of docking studies is that the docking score of compounds is in the range of compound -6.96 to -8.3kcal/mol. Compound 8 and 17 showed highest docking score of -8.3kcal/mol. It is worth to mention that few compounds have docking score greater than that of standard reference compound i.e., ampicillin (-7.5kcal/mol).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QSAR: Quantitative Structure Activity Relationship; **NCE:** New Chemical Entities; **AMR:** Antimicrobial resistance; **WHO:** World Health Organization; **MRSA:** Methicillin-resistant *Staphylococcus aureus*; **MMFF:** Molecular Merck force field; **MIC:** Minimum inhibitory concentration; **LGA:** Lamarckian genetic algorithm; **NCBI:** National Centre for Biotechnology Information.

SUMMARY

Hybrids of 1,2,4-triazole and thiazolinone are reported as potential antibacterial agents. The new chemical entities were designed based on their various properties such as electrostatic, steric, hydrophobic and topological requirements and the substitution pattern is based upon the 2D, 3D QSAR studies. The molecules with higher Lipinski score subjected to molecular docking studies and the binding affinity of the molecules with DNA gyrase inhibitor was reported. The substitution pattern was established by using QSAR tool for better antibacterial activity.

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