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Research Paper / Makale

In Silico Study of 2, 4, 5-trisubstituted Thiazoles as Inhibitors of Tuberculosis Using 3D-QSAR, Molecular Docking, and ADMET Analysis

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Abstract: In order to discover new efficient drugs used as inhibitors of tuberculosis, three-dimensional quantitative structure-activity relationship (3D-QSAR) was executed on set of eighteen 2,4,5-trisubstituted thiazoles compounds. CoMFA and CoMSIA models were molded using 14 molecules as training set. They give a significant coefficient of R^2 (0.995 and 0.982 respectively) and important value of Q^2 (0.533 and 0.601, respectively). The robustness of these models was checked by an external validation using a test set of 4 molecules, affords significant R^2test values of 0.654 and 0.648 for CoMFA and CoMSIA models, respectively. CoMFA and CoMSIA contour maps provided much valuable information to identify the main regions impacting (decreasing or increasing) the antituberculosis activity. These outcomes guided us to design new entities with important activity. Molecular docking was put into effect to guess the types and modes of interactions between 2,4,5-trisubstituted thiazoles molecules and INHA receptor (PDB ID: 1ZID). In silico ADMET analysis was executed to evaluate the pharmacokinetic properties and to examine the toxicity of the newly designed molecules.

Keywords: Molecular docking, 3D-QSAR, anti-tuberculosis, thiazoles, ADMET

3D-QSAR, Moleküler Yerleştirme ve ADMET Analizleri ile 2, 4, 5-trisübstitüe Tiazollerin Tüberküloz İnhibitörleri Olarak Çalışılması

Öz: Tüberküloz inhibitörleri olarak kullanılan yeni etkili ilaçları keşfetmek için, on sekiz 2,4,5-trisübstitüe tiyazol bileşiği setinde üç boyutlu nicel yapı-aktivite ilişkisi (3D-QSAR) çalışması yapıldı. CoMFA ve CoMSIA modelleri, eğitim seti olarak 14 molekül kullanılarak kalıplanmıştır. Önemli bir R2 katsayısı (sırasıyla 0,995 ve 0,982) ve önemli Q2 değeri (sırasıyla 0,533 ve 0,601) verirler. Bu modellerin sağlamlığı, 4 molekülden oluşan bir test seti kullanılarak harici bir doğrulama ile kontrol edildi ve CoMFA ve CoMSIA modelleri için sırasıyla 0.654 ve 0.648'lik önemli R2test değerleri verdi. CoMFA ve CoMSIA kontur haritaları, antitüberküloz aktivitesini etkileyen (azalan veya artan) ana bölgeleri belirlemek için çok değerli bilgiler sağladı. Bu sonuçlar, önemli faaliyetlere sahip yeni oluşumlar tasarlamamıza rehberlik etti. 2,4,5-trisübstitüe tiyazol molekülleri ile INHA reseptörü (PDB ID: 1ZID) arasındaki etkileşim tiplerini ve modlarını tahmin etmek için moleküler yerleştirme devreye alındı. Yeni tasarlanan moleküllerin farmakokinetik özelliklerini değerlendirmek ve toksisitesini incelemek için in silico ADMET analizi yapıldı.

Anahtar Kelimeler: Moleküler yerleştirme, 3D-QSAR, anti-tuberculosis, thiazoles, ADMET

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1. Introduction

Tuberculosis (TB) is caused by Mycobacterium tuberculosis (Mtb) that distributes through the respiratory tract [1]. According to the WHO statistics, approximately 10 million people infected by TB and 1.4 million people died from this illness in 2019 [2]. Moreover, drug-resistant TB continues to be one of the medical challenges to which the whole world is making face. Therefore, it has become an urgency to try to discover new medications that can target resistant strains.

Compounds that possess sulfur atoms are present and much essential in living organisms [3]. In this case, one essential class of heterocyclic molecule that includes one sulfur atom is namely as thiazole. This class of compound is introduced in numerous natural and synthetic products with a diverse range of pharmacological activities, such as anticancer, antiviral, antibacterial, anticonvulsant, antifungal, anti-inflammatory, and anti-tuberculosis activities that could be well showed by the wide number of drugs in the market having this function group [4].

Three-dimensional quantitative structure-activity relationship (3D-QSAR) is considered as one of the most crucial methods in modern medicinal chemistry [5]. It was established to link the chemical structures of a series of molecules to their biological activities, thus, it used to discover novel candidate drugs. The Comparative Molecular Field Analysis (CoMFA) [6] and Comparative Molecular Similarity Indices Analysis (CoMSIA) [7] are the most privileged tools used in 3D-QSAR analysis to grasp the geometric information required to decisive the favored and unfavored entities for the biological activity.

Recently, a study conducted by Raja Sekhara Reddy et al. [8] showed that the Enoyl-ACP reductase (INHA) was found to be a relevant target in tuberculosis drug discovery. Bearing this in mind, we conducted a molecular docking study to gain a deeper insight into the binding modes and scrutinize the types of interactions between 2,4,5-trisubstituted thiazoles molecules and INHA receptor (PDB ID: 1ZID). In this study, new 2,4,5-trisubstituted thiazoles derivatives were proposed and designed with important antituberculosis activity by applying 3D-QSAR and molecular docking approaches. Further, in silico ADMET evaluation was executed to approve the use of the proposed inhibitors that can be used as antituberculosis drugs.

2. Material and Methods

2.1. Data Collection

For 3D-QSAR analysis, a set of eighteen 2,4,5-trisubstituted thiazoles with reported MIC values as antituberculosis agents, was taken from literature [9]. The antituberculosis activities MIC (µg/mL) were transformed into the corresponding pMIC values using the following expression pMIC = $-\log_{10}$ (MIC) and are listed with their corresponding structures in Table 1. The dataset was divided into two parts, fourteen molecules were selected randomly to mold a 3D-QSAR model (training set) and four molecules were employed to test the strength of the molded model (test set). The main structure of 2,4,5-trisubstituted thiazoles molecules is outlined in Figure 1.

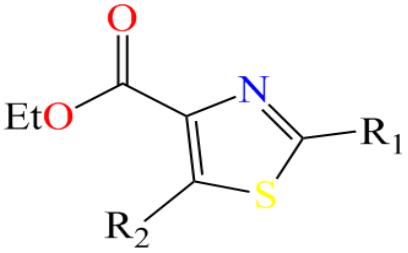
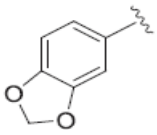
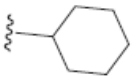
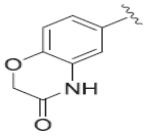
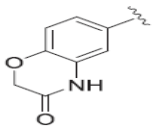
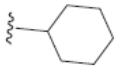
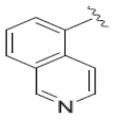
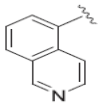
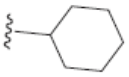
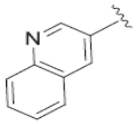
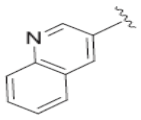
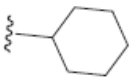
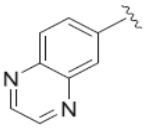
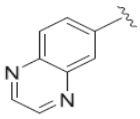
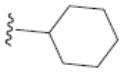
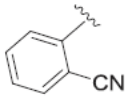
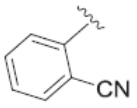
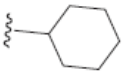
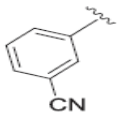
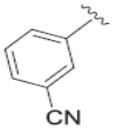
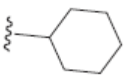
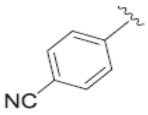
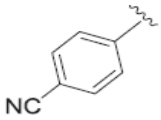
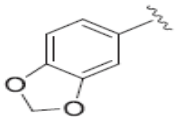
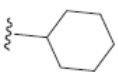
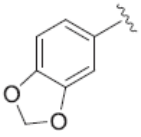
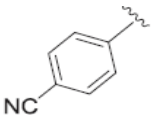


Figure 1. The chemical structure of the studied compounds.

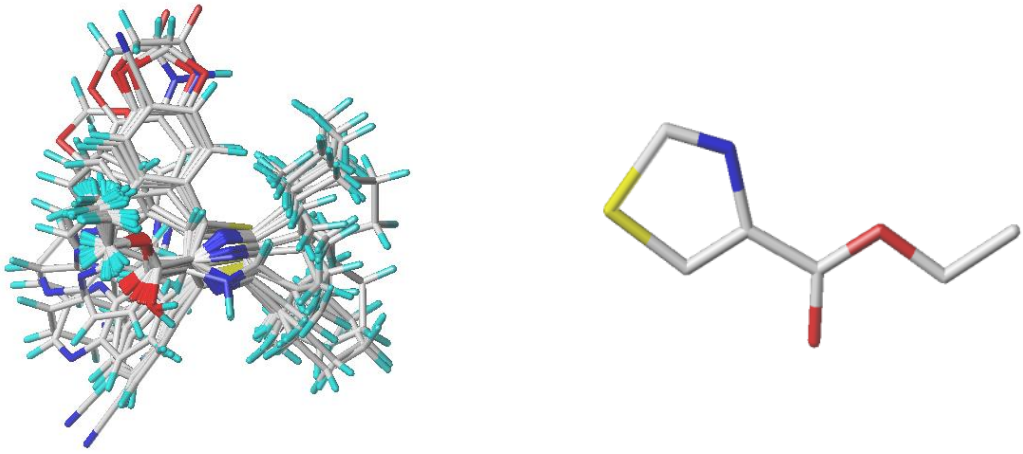
Table 1. Chemical structures and anti-tuberculosis activities of 2,4,5-trisubstituted thiazoles.

No	R1	R2	pMIC	No	R1	R2	pMIC
1			5.102	**10**			4.714
2			4.455	**11***			5.346
3*			4.787	**12**			5.346
4			5.397	**13**			5.346
5			5.091	**14***			5.376
6			4.823	**15***			5.376
7			4.823	**16**			5.677
8			5.744	**17**			4.866
9			5.050	**18**			4.838

* Test set molecules

2.2. Minimization and Alignment

In this study, SYBYL-X 2.0 molecular modeling package (Tripos Inc., St. Louis, USA) was adopted to execute all modeling studies. So, every structure of 18 2,4,5-trisubstituted thiazoles molecules was sketched and optimized using Tripos force field [10], Gasteiger Huckel charges [11] and with gradient convergence criteria of 0.01 kcal/mol [12]. The outcomes obtained by CoMFA and CoMSIA are strongly linked to the molecular alignment techniques [13]. Therefore, molecular alignment is considered as a sensitive step in the development of any 3D-QSAR analysis. Figure 2 displays the suggested alignment; the common core was taken and the eighteen concerned molecules were aligned to it using the ALIGN DATABASE algorithms existing in SYBYL-X 2.0 software and based on the inhibitor **8** which is the dataset's more active molecule. The compound **8** was selected as a template to align the database in 3D-QSAR analyses and to visualize the CoMFA and CoMSIA contour maps.



Aligned compounds CORE

Figure 2. The superposition and alignment of training data set using molecule **8** as a template.

2.3. CoMFA Studies

The CoMFA [6] technique was executed to compute the steric and electrostatic fields, and to institute relationships between these quantities and the antituberculosis activity. The aligned database was applied in a three dimensional (3D) regularly with a grid spacing of 2 Å in all Cartesians directions. During the computation, the energy cut-off value was set by default at 30kcal/mol [14].

2.4. CoMSIA Studies

The CoMSIA [7] model was accomplished in SYBYL-X 2.0 software utilizing the same grid box and the same training and test sets which are adopted for CoMFA analysis. In this part, we computed five fields' namely electrostatic, steric, hydrophobic effect and hydrogen bond acceptor and donor in order to mold a CoMSIA model. For the computation of hydrogen-bond and hydrophobic potentials, a probe atom with hydrogen bond donor or acceptor of +1 and hydrophobicity +1 was used and the attenuation factor was set by default at 0.3 [15].

2.4. Partial Least Square Analysis (PLS)

PLS [16] technique was undertaken to institute a linear correlation between antituberculosis activities and CoMFA, CoMSIA descriptors. So, PLS was accomplished to afford the coefficient of

cross-validation correlation (Q^2) and the optimum number of components (N) using for that leave-one-out cross-validation. In a similar vein, the non-cross-validation analysis was put into action to give the correlation coefficient (R^2), the standard error of estimate (SEE) and F-test value (F).

The greatest values of Q^2 and R^2 and lesser value of SEE were adopted to select the best 3D-QSAR model. The external validation was effected to assay the adeptness of the suggested model using 4 2,4,5-trisubstituted thiazoles molecules as a test set.

2.6. Y-Randomization Test

Y-Randomization test is a technique of validation effectuated to know if the proposed models are strong or not [17]. For that reason, the pMIC values of fourteen molecules as a training set were arbitrarily shuffled more than once and after every shuffle, a new 3D-QSAR model is molded. Indeed, the new suggested models have to be lower values of R^2 and Q^2 than those in the original models. If it's not the case, the proposed models should be rejected due to the structural redundancy and chance correlation.

2.7. Molecular Docking

The molecular docking is an important computational method used to give a deeper insight into the kinds and modes of interactions between a macromolecule called receptor and a small molecule called ligand [18]. Enoyl ACP Reductase (INHA) is an important enzyme involved in the fatty acid biosynthesis in mycobacterium. It is responsible for the cell wall synthesis in mycobacteria [8]. Molecular docking was executed with two programs; Autodock Vina [19] and Autodock tools 1.5.6 [20] to determine the binding mode of the more active molecule in dataset (molecule **8**) and the best proposed molecule (molecule **Y1**) to the active site residues of the target INHA for anti-tubercular activities. The crystallographic structure of the INHA receptor (PDB ID: 1ZID) was downloaded from the protein databank with resolution 2.70Å [8]. The extracted INHA receptor was prepared by eliminating of all water molecules founded in this INHA receptor and adding the polar hydrogen atoms using Discovery Studio 2016 software [21]. The active site has been defined and it corresponds to the coordinates: x= -4.346, y = 34.669 and z= 13.433. The grid size was set at 30×30×30 xyz points with grid spacing of 1 Å to cover the folic acid binding site in the enzyme and was generated by using the co-crystallized ligand as the center for docking. For ligand and enzyme preparations; an extended PDB format, termed PDBQT, is employed for coordinate files, which includes atomic partial charges and atom types using Autodock tools 1.5.6. Torsion angles were calculated to assign the flexible and non-bonded rotation of molecules. The engendered outcomes were analysed using PyMol [22] and Discovery Studio 2016 [21] software's.

2.8. ADMET Analysis

The success of a medication journey through the body is measured based on his pharmacokinetics parameters (adsorption, distribution, metabolism, excretion and toxicity; ADMET). For this goal, the new suggested molecules were assessed for their ADMET properties using pkCSM [23] and SwissADME [24] online tools. So, the main goal of this analysis is to determine the pharmacokinetics properties of the suggested molecules, thus, avoid expensive reformulation, preferably before synthesis.

3. Results and Discussion

3.1. CoMFA Results

CoMFA model was proposed and its statistical parameters are disposed in Table 2. Outcomes of this Table point out that CoMFA model has a value of R^2 of 0.984, Q^2 value of 0.533, three as

optimum number of components, small estimation error Scv (0.054), and F value of 199.560. The external predictive proficiency of CoMFA model was checked and tested by using a test set molecules. The external validation gave high value of R^2test of 0.654; indicating the high predicted power of CoMFA model. Moreover, the rations of steric and electrostatic contributions were almost found to be 41:59 which makes clear that electrostatic interactions are much more important than steric interactions.

3.2. CoMSIA Results

In this analysis, CoMSIA model was established based on combination between steric, electrostatic, hydrophobic, acceptor, and donor descriptors. The key statistical parameters like R^2, Q^2, R test^2, F-test, and Scv were determined using SYBYL-X 2.0 and listed in Table 2.

Table 2. PLS Statistics of CoMFA and CoMSIA models.

							Fractions				
Model	Q^2	R^2	Scv	F	N	R^2test	Ster	Elec	hyd	Acc	Don
CoMFA	0.533	0.984	0.054	199.560	3	0.654	0.418	0.582	-	-	-
CoMSIA	0.601	0.959	0.085	78.938	3	0.648	0.105	0.321	0.162	0.224	0.189

R^2: Non-cross-validated correlation coefficient, Q^2: Cross-validated correlation coefficient, N: Optimum number of components, Scv: Standard error of the estimate, F: F-test value, R^2test: External validation correlation coefficient.

Table 3. Observed and predicted activities of eighteen 2,4,5-trisubstituted thiazoles molecules.

		CoMFA		CoMSIA	
N^o	pMIC	Predicted	Residuals	predicted	Residuals
1	5.102	5.140	-0.038	4.949	0.153
2	4.455	4.449	0.006	4.787	-0.332
3*	4.787	5.048	-0.261	5.049	-0.262
4	5.397	5.449	-0.052	5.197	0.200
5	5.091	5.129	-0.038	5.238	-0.147
6	4.823	4.825	-0.002	5.269	-0.446
7	4.823	4.838	-0.015	5.277	-0.454
8	5.744	5.653	0.091	5.274	0.470
9	5.050	4.978	0.072	4.765	0.285
10	4.714	4.698	0.016	4.745	-0.031
11*	5.346	5.071	0.275	5.068	0.278
12	5.346	5.378	-0.032	5.332	0.014
13	5.346	5.358	-0.012	5.381	-0.035
14*	5.376	5.383	-0.007	5.375	0.001
15*	5.376	5.387	-0.011	5.392	-0.016
16	5.677	5.704	-0.027	5.328	0.349
17	4.866	4.936	-0.070	4.848	0.018
18	4.838	4.788	0.05	4.882	-0.044

* Test set molecules

Outcomes of Table 2 hint that CoMSIA model has high Cross and non-cross validated correlation coefficients with Q^2 (0.601) and R^2 (0.959) respectively, F-test value of 78.938, lower standard error of the estimate S_{cv} of 0.085, and 3 as optimal number of components. Additionally, the

predicted capability of the molded model was examined by using an external validation; the R^2test value obtained is 0.648. These statistics results proved the good stability and the powerful predictive capability of CoMSIA model.

The observed and predicted antituberculosis activities of eighteen 2,4,5-trisubstituted thiazoles molecules are elucidated in Table 3. The small residuals values between observed and predicted activities clearly hinted the good predictive ability of CoMFA and CoMSIA models.

The plots of experimental pMIC versus predicted pMIC employing for the CoMFA and CoMSIA models are revealed in Figure 3. It may be viewed that the blue and orange circle solid points were close to the line Y = X, suggesting that experimental and predicted antituberculosis activity of the 18 2,4,5-trisubstituted thiazoles molecules had a robust linear relationship.

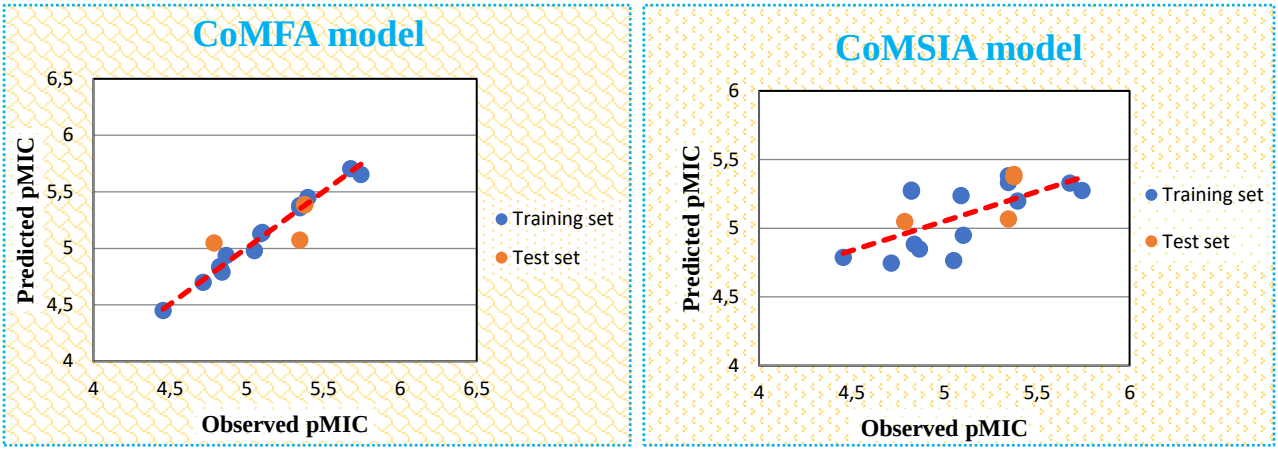


Figure 3: Predicted pMIC versus observed pMIC of training set and test set molecules using the CoMFA and CoMSIA models.

3.5. Y-Randomization

Table 4. Q^2 and R^2 values after Y-randomization test.

Iteration	CoMFA		CoMSIA	
	Q^2	R^2	Q^2	R^2
1	-0.10	0.87	-0.20	0.83
2	-0.35	0.86	-0.14	0.81
3	-1.18	0.90	-0.14	0.86
4	-0.13	0.94	0.05	0.91
5	-0.42	0.95	-0.21	0.92
Original	0.53	0.98	0.60	0.95

The proposed CoMSIA and CoMFA models were tested for their proficiency using Y-randomization test. Hence, diver's random shuffles of the dependent variable were put into effect and after every shuffle; a 3D-QSAR was established. The generated outcomes are given in Table 4. The lower values of Q^2 and R^2 clearly indicate that our original CoMFA and CoMSIA models are not due to chance correlation of the training set.

3.3. CoMFA Contour Map

In order to know the influence of steric and electrostatic moieties on activity of 2,4,5-trisubstituted

thiazoles molecules, CoMFA contour maps were produced and their outcomes are presented in Figure 4.

Green colored portions found around R_1 and nitrile groups reveal that bulky entities in these positions would enriched the activity (Figure 4 (A)). This finding can explain the high activity of compound **16** (pMIC = 5.677) that has a bulky moiety in R_1 position. On the other hand, yellow contour cover ethoxy group points out the beneficial role of tiny entities to ameliorate the activity (Figure 4 (A)).

In CoMFA electrostatic contour maps (Figure 4 (B)), the red contour around nitrile entity clearly indicates that groups with electron withdrawing nature might enhance the potency. While, the blue contour around methyl group of R_1 moiety and *meta* position of R_2 entity make clear the importance of insertion of groups with electron donating character to upsurge the antituberculosis activity (Figure 4 (B)).

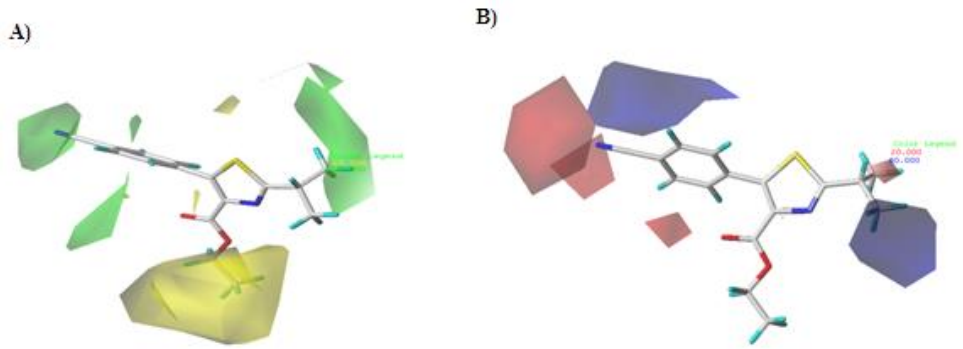


Figure 4. Contour maps of CoMFA model, A) Steric, B) Electrostatic.

3.4.CoMSIA Contour Map

CoMSIA contour maps were molded to explain structure activity relationship and then determine the favorable and unfavorable moieties impacting the activity. The produced outcomes are presented in Figure 5.

Yellow contour around ethoxy group (-OC_2H_5) shows that this position should not be occupied by large groups to ameliorate the activity. Green contour around R1 moiety hints that huge entities could increase the activity (Figure 5 (A)). This result can explain the low activity of compound **18** (pMIC= 4.838) that has a small group (methyl) in R_1 position.

In CoMSIA electrostatic contour maps (Figure 5 (B)), the blue contours around *ortho* and *meta* positions of R_2 group mention that groups with electron donating character in these positions would ameliorate the potency. On the other hand, tiny red contour around nitrile group points out the crucial role of entities with electron withdrawing character to upsurge the potency of molecules.

Yellow regions cover R1 group and around *ortho*, *meta* positions of R_2 moiety (Figure 5 (C)) pinpoint the importance of hydrophobic entities in increased activity of the compounds. White colors cover nitrile moiety and around thiazole ring make clear the introduction of hydrophilic groups in these regions improving the antituberculosis activity (Figure 5 (C)).

CoMSIA H-bond acceptor contour maps (Figure 5 (D)), red contours around ethoxy group and near to *ortho*, *meta* positions of R_2 moiety suggest that groups with hydrogen bond acceptor character

can ameliorate the activity. On the other hand, magenta contour near to nitrile moiety points out those only groups with hydrogen bond acceptor character can increase the activity (Figure 5 (D)).

In CoMSIA H-bond donor contour maps (Figure 5 (E)), cyan contour cover R_1 group makes clear the meaningful role of entities with hydrogen bond donor character in ameliorated the potency of molecules. These crucial results provided much useful information to determine the preferred and unpreferred groups, thus, they pave the way to design new molecules with significant antituberculosis activities.

In Figure 6, we abstracted all information extracted from CoMFA and CoMSIA contour maps results, which could be much useful to scrutinize the structural requirements that influence the activity and consequently propose new potent 2,4,5-trisubstituted thiazoles molecules with important inhibitory activity.

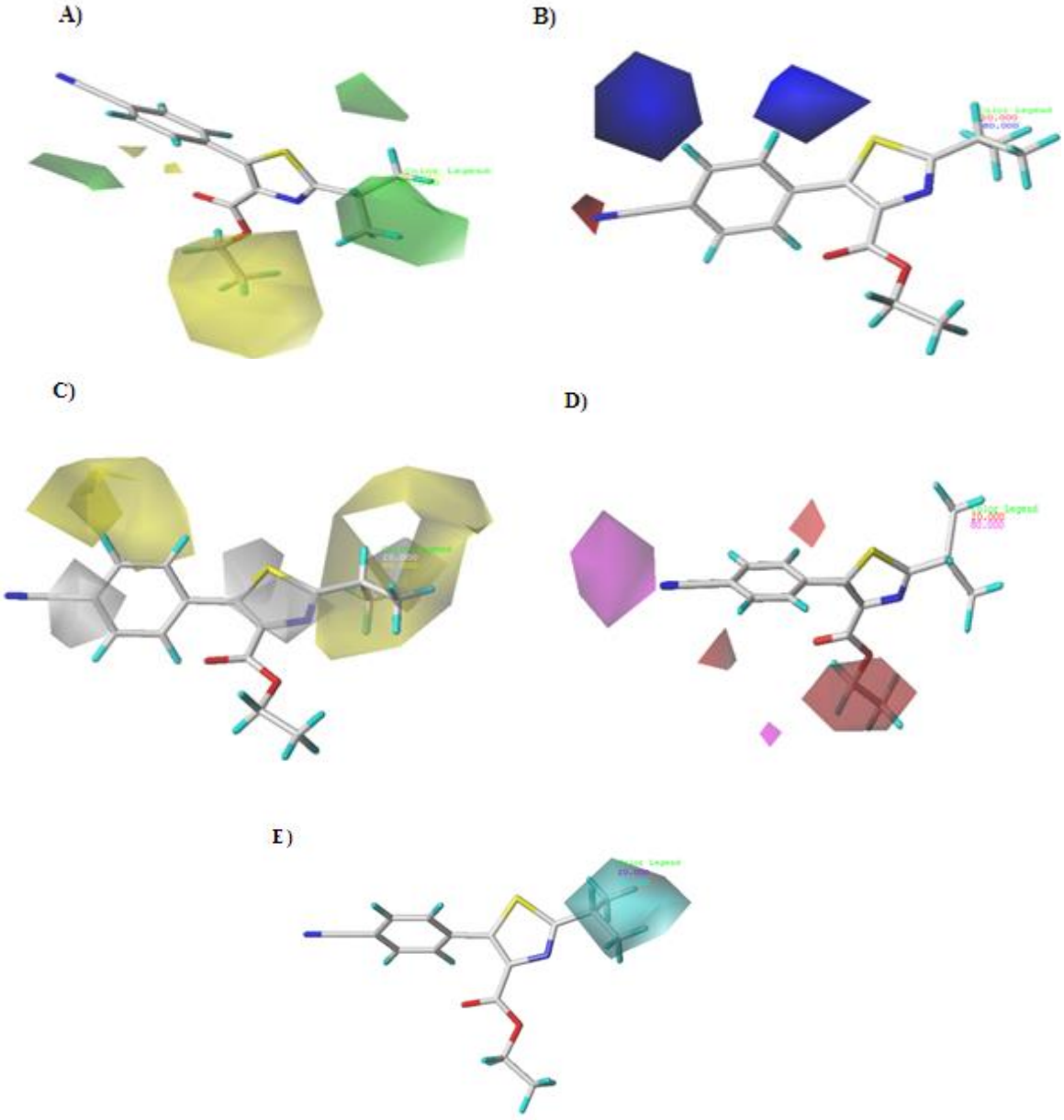


Figure 4. Contour maps of CoMSIA model. A) Steric, B) Electrostatic, C) Hydrophobic, D) H-bond acceptor, E) H-bond donor.

3.6. Design of New Molecules

Contour maps extracted from CoMFA and CoMSIA models enabled us to determine the sites influencing on activity of molecules. So, the key structural factors were investigated to design two new molecules by modifying the 2,4,5-trisubstituted thiazoles entity. The new molecules **Y1** and **Y2** present higher activity than molecule **8** which is the more active molecule in dataset (Table 5). The chemical structures of newly suggested molecules are elucidated in Figure 7.

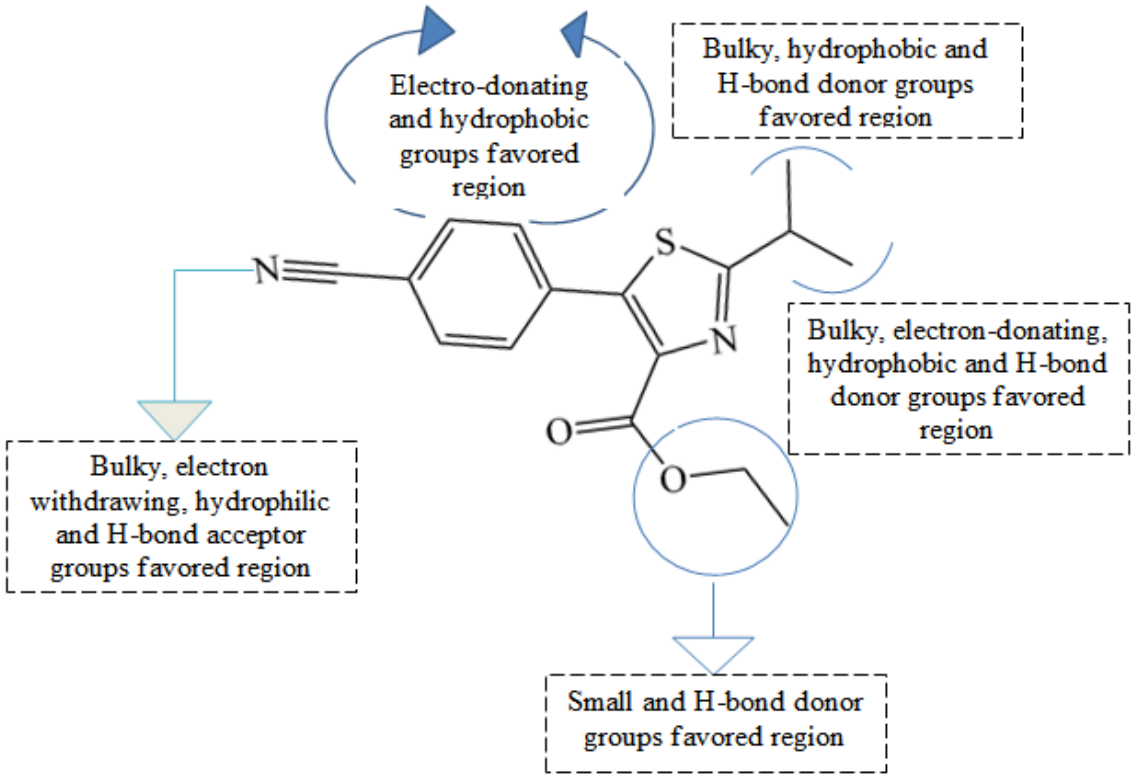


Figure 6. Summary of contour maps for anti-tuberculosis activity generated by CoMFA and CoMSIA models.

Table 5. Predicted pMIC of newly designed molecules.

N°	Predicted pMIC	
	CoMFA	CoMSIA
Y1	5.779	5.765
Y2	5.750	5.724

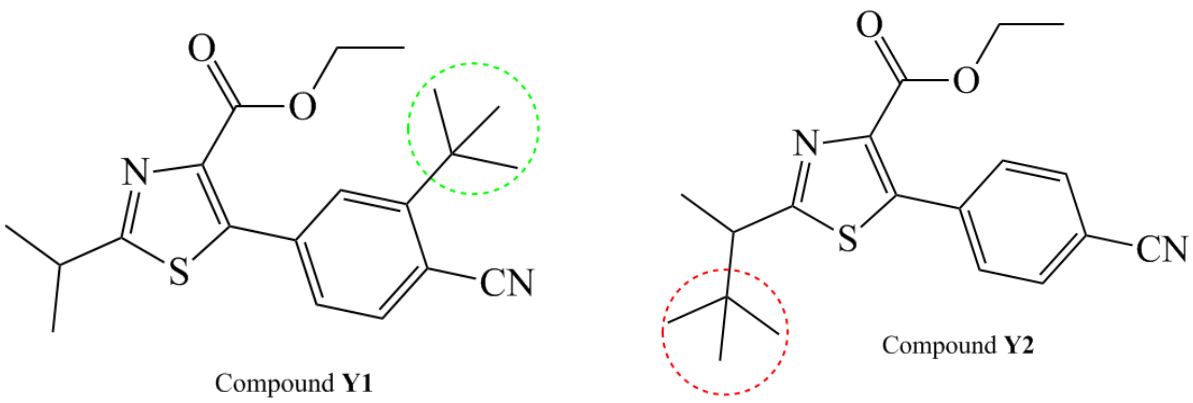


Figure 7. Structure of newly designed antituberculosis inhibitors.

3.7. Molecular Docking Results

To understand the binding interactions of the more active molecule (molecule **8**) and best proposed molecule (molecule **Y1**) in the potential interactions in the INHA receptor pocket (PDB ID: 1ZID), a molecular docking using Autodock vina program was put into practice. The obtained outcomes are shown in Figure 8 and Figure 9, respectively.

Docking interaction of molecule **8** with INHA receptor shows alkyl and pi-Alkyl interactions with Leu218 (4.90Å), Trp222 (4.95Å), Pro193 (3.26Å), Phe149 (4.62Å), Met161, 147, 155 residues at distances of 4.57Å, 5.09Å and 4.49Å, respectively (Figure 8). The phenyl ring makes pi-sigma interaction with Met199 residue at distance of 3.63Å, pi-alkyl interaction with Met161 residue at distance of 4.57Å and pi-sulfur interaction with Met103 residue at distance of 5.43Å, this interaction was also observed for the nitrile group at distance of 3.34Å. In addition, the thiazole ring forms pi-pi T-shaped interaction with Tyr158 residue at distance of 4.84Å, pi-pi stacked interaction Phe149 residue at distance of 3.61Å and pi-sulfur interactions with Tyr158 and Phe149 residues at distance of 3.45Å and 3.85Å, respectively. The methyl moiety located at the position two of the thiazole group affords pi-sigma interaction with Trp222 residue at distance of 3.34Å.

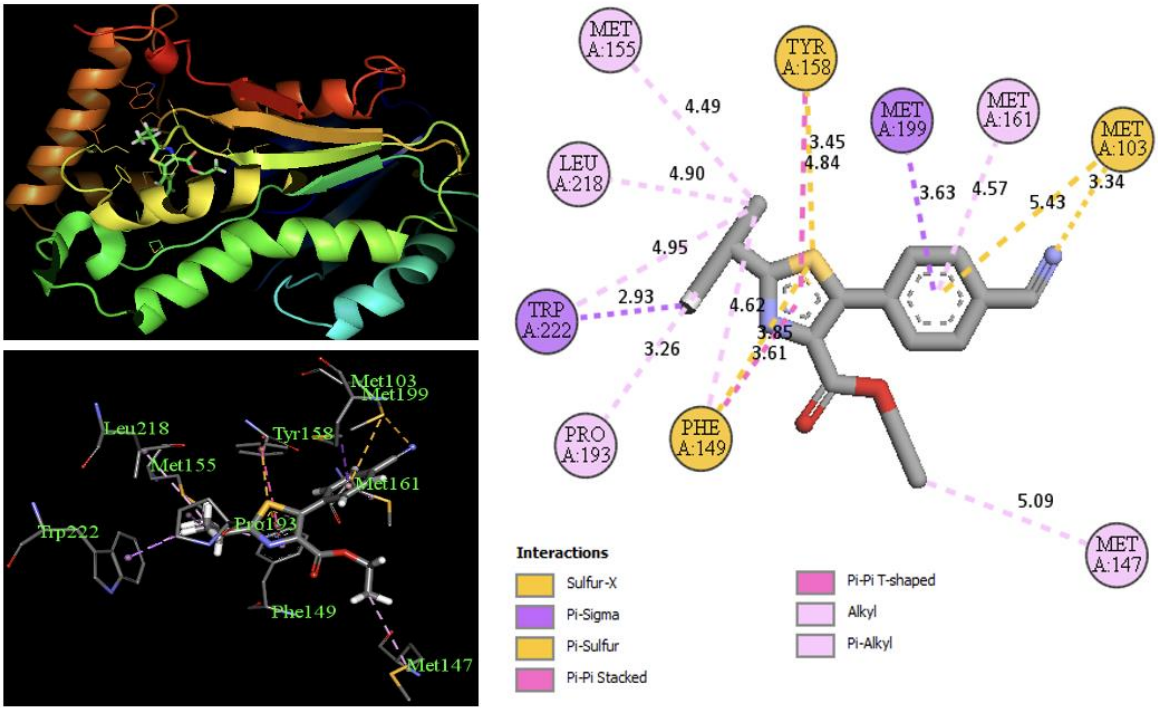


Figure 8. Docking interactions of the compound **8**.

The new suggested molecule **Y1** was docked by the same manner in the potential interactions in the INHA receptor pocket and makes more types and number of interactions (Figure 9). The isopropyl group which is located at the position two of the thiazole group makes alkyl interactions with Trp222 (4.07Å), Tyr158 (4.49Å), Leu218 (4.42 Å and 4.29Å) and Pro193 (3.42 Å and 4.05Å) residues. The thiazole ring also presents several interactions as pi-pi T-shaped, pi-sulfur, pi-alkyl and pi-donor hydrogen bond. In a similar vein, the ethyl methanoate group affords a conventional hydrogen bond interaction with Ile194 residue at distance of 3.27 Å, the same group provides also alkyl interactions with Ile21 (4.42Å), Ala191 (4.40Å) and Ile194 (3.70Å) residues. The phenyl ring forms pi-alkyl interaction with Met161 residue at distance of 5.13Å. The nitrile group makes a carbon hydrogen bond interaction with Gly96 residue at distance of 3.34Å. The isobutane moiety

provides an alkyl interaction with Met147 residue at distance of 5.46Å. Therefore, considering the important role of hydrogen bonding in the pharmacological effect of ligands, the proposed compound **Y1** is pharmacologically significant compared to compound **8** which is the dataset's more active molecule.

The surflex score and binding energy of the proposed molecules and compound **8** were determined as show in Table 6. It can be seen from results of Table 6, the compound **Y1** and **Y2** have better total scoring and binding energy than compound **8**. Of the two inhibitors mentioned, **Y1** demonstrated the lowest binding energy, so it was chosen for further study.

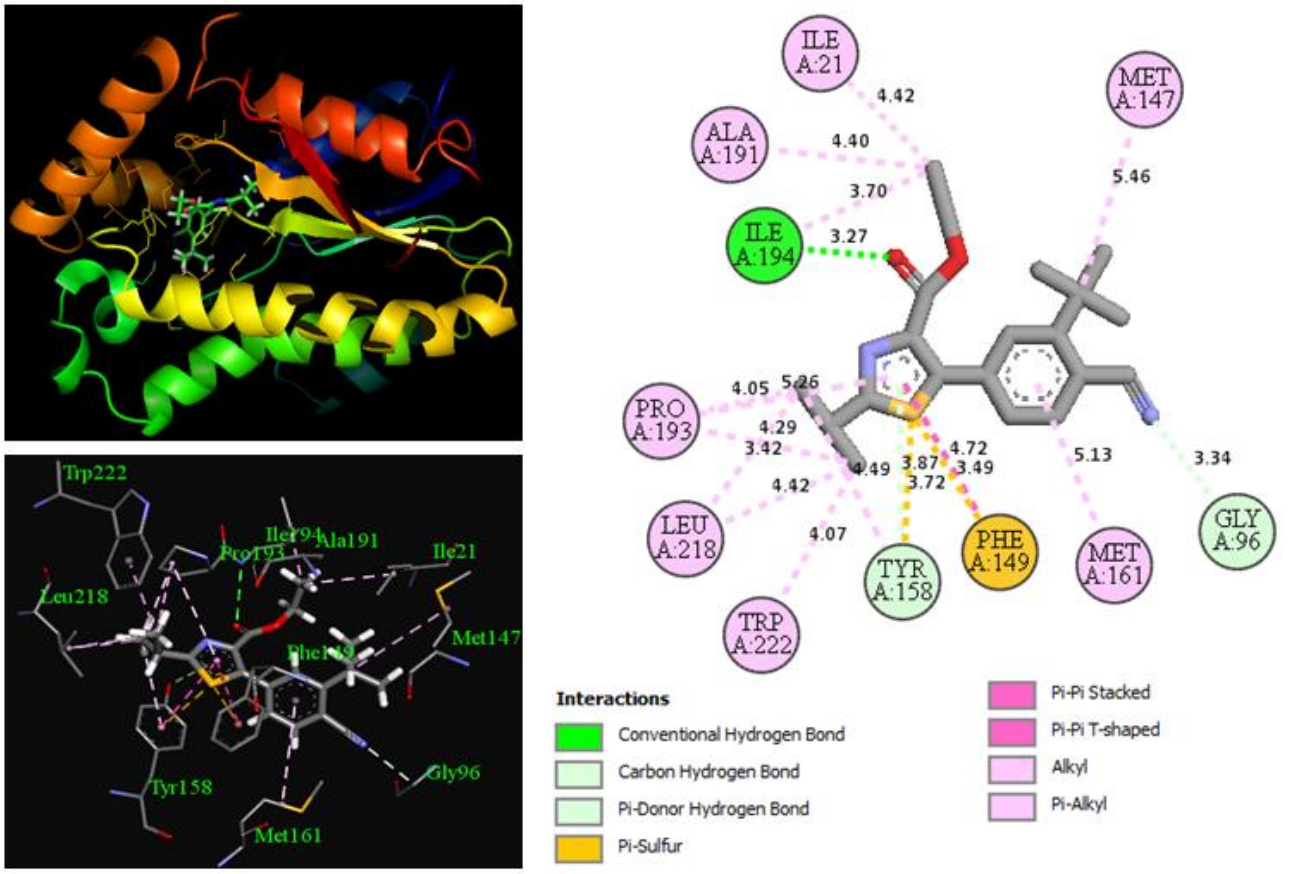


Figure 9. Docking interactions of the proposed compound **Y1**.

Table 6. Surflex score and binding energy of the proposed compounds and compound **8**.

Compound	Surflex score (-logki)	Autodock binding energy (kcal/mol)
Y1	3.446	-7.000
Y2	3.336	-6.900
8	2.679	-6.600

3.8. Docking Validation Protocol

To confirm the obtained outcomes from molecular docking procedure, a re-docking of the co-crystallized ligand was executed. Figure 10 clarifies the superposition view between the docked ligand conformation and the co-crystalized ligand.

The finding of docking validation demonstrates that the co-crystalized ligand bound in a comparable position compared to that observed for the docked ligand conformation. On the other hand, the root mean square distance (RMSD) of the docked ligand is 0.851Å which was within the reliable range of 2 Å [25]. Subsequently, the obtained RMSD value was confirmed after docking protocol that the docked ligand could interact with the crystal structure of 1ZID similarly to the original co-crystallized ligand. Hence, the docking validation outcome demonstrated the good proficiency of molecular docking.

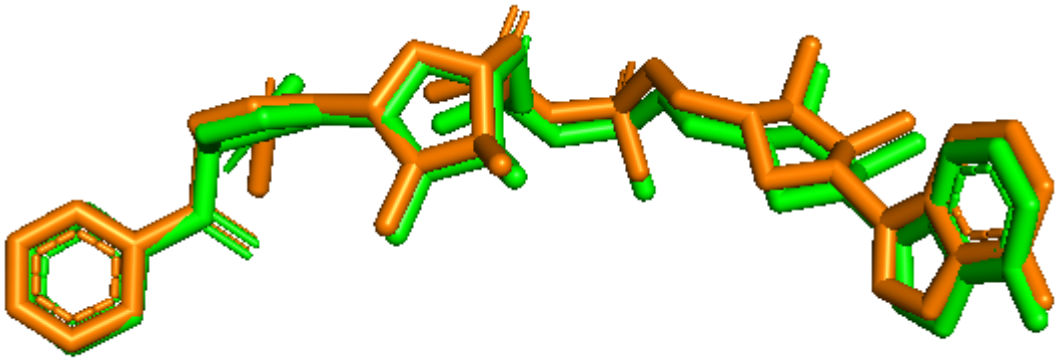


Figure 10. Re-docking pose with the RMSD value of 0.851Å (Orange = Original, Green = Docked).

The interaction between co-crystalized structure and the potential interactions in the INHA receptor shows numerous conventional hydrogen bond interactions as Ile194 (3.29Å), Lys165 (3.38Å and 3.16Å), Ile21 (3.30Å), Ser20 (3.02Å), Gly14 (3.09Å), Val65 (3.09Å) and Asp64 (3.12Å) residues (Figure 11). The 9H-purine ring makes carbon hydrogen bond interaction with Phe41 (3.64Å), pi-alkyl interaction with Val65 (4.87Å), Ile122 (5.01Å and 5.02Å), Ile95 (4.67Å) residues and pi-pi stacked interaction with Phe41 residue at distance of 4.30Å and 3.99Å. The pyridine ring affords pi-pi stacked interaction with Phe149 (4.43Å) residue, pi-sulfur interaction with Met155 (5.39Å) residue and pi-alky interaction with Pro193 (4.82Å) residue. The co-crystalized structure forms carbon hydrogen bond interactions with Pro193 (3.50Å) and Ser94 (3.64Å) residues.

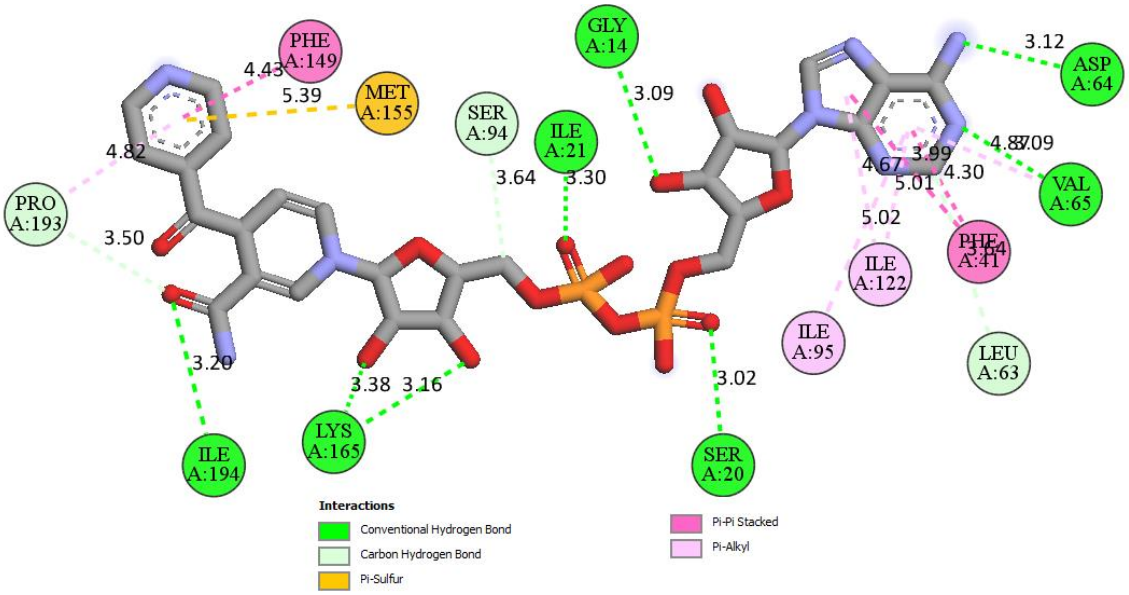


Figure 11. Docking interactions of the co-crystalized structure.

3.8. Pharmacokinetic Properties Results

Determination of pharmacokinetic properties of a molecule is deemed as an essential step to know whether molecule respect Lipinski's rule or not. For this reason, pharmacokinetic properties of the proposed molecules **Y1** and **Y2** were defined using pkCSM [23] online tool and their outcomes are embodied in Table 7.

The new molecules **Y1** and **Y2** have a molecular weight (MW) less than 500 Da, hydrogen-bond acceptors (HBA) not over than 10 and Hydrogen bond donors (HBD) less than 5, Log P not more than 5 (except molecule **Y1** has a value superior a bit of 5), total polar surface area (TPSA) not more than 140 Å and rotatable bonds (nrotb) less than 10, exhibiting that the proposed molecules **Y1** and **Y2** have good pharmacokinetic properties, thus they are fulfill of Lipinski's rule of five for oral bioavailability [26]. Moreover, the new suggested molecules were examined for their synthetic accessibility. Table 7 points out that the synthetic accessibility (SA) of the molecules **Y1** and **Y1** is 3.87 and 4.22, respectively, thus, they are easy to synthetic (from 1 (very easy) to 10 (very difficult)).

Table 7. Lipinski's properties of newly designed compounds.

Compounds	Property						
	Log P	HBD	HBA	TPSA	nrotb	MW	SA
Compound **Y1**	5.27	0	5	91.22	6	356.491	3.87
Compound **Y2**	5.00	0	5	91.22	6	342.464	4.22

3.9. ADMET Analysis Results

Prediction of ADMET properties is a more in-depth study used to decide if the new proposed molecules are viable medications or not. To do that, the pkCSM [23] and SwissADME [24] online tools were applied in order to determine the ADMET properties of the new 2,4,5-trisubstituted thiazoles molecules and their outcomes are shown in Table 8.

Table 8. In silico ADMET analysis of newly proposed molecules.

	Absorption (**A**)		Distribution (**D**)	Metabolism (**M**)						Excretion (**E**)		Toxicity (**T**)
N°	Water solubility	Intestinal absorption	BBB permeant	CYP					CYP	Clearance		Ames toxicity
	(log mol/l)	(human) Numeric (% absorbed)	(logBB)	1A2	2C19	2C9	2D6	3A4	2D6	3A4		
				Inhibitor					Substrate			Yes/No
				Categorical (Yes/No)						Numeric (log ml/min/kg)		
Y1	−5.874	93.881	0.013	Yes	Yes	Yes	No	No	No	Yes	0.325	No
Y2	-5.363	94.085	0.091	Yes	Yes	Yes	No	No	No	Yes	0.222	No

The trip of a medication from the point of administration to the point of effect is named absorption [27]. In fact, a medication must be absorbed before any therapeutic benefits can occur. Thus, the absorption is a major emphasis in drug development and medicinal chemistry. Results of table 8 demonstrate that the two 2,4,5-trisubstituted thiazoles molecules present high absorption (good absorption is translated with an absorption value higher than 30%). Blood brain barrier (BBB) is the

interface that segregates between central nervous system (CNS) and the blood circulation [28]. It is a crucial property used to control if a drug can pass the BBB or not. So, the brain/blood partition coefficient of molecules **Y1** and **Y2** was determined, and they exhibited little chance to traverse the BBB.

Continuously, Cytochrome P450s is deemed as a cardinal enzyme system for drugs metabolism in liver. The CYP3A4 enzyme regarded as the most crucial of the CYP family of enzymes, metabolizing 50% of all medications by itself [29]. The molecules **Y1** and **Y2** are substrates and not Inhibitors of CYP3A4. In a similar vein, the new molecules are not inhibitors for CYP2D6 substrate and inhibitor; exhibiting that the new compounds **Y1** and **Y2** can be effortlessly metabolized in the liver. Furthermore, clearance is a parameter that defines the relationship between medication concentration in the human body and the degree of medication elimination [13]. Indeed, a lower value of the clearance index leads to a greater persistence of drugs in the body. The results appear in Table 8 showed that all studied molecules present lower value of the clearance index. The study of the toxicity of a molecule is regarded as a crucial step that enables to determine whether a compound is toxic or not and therefore identify its capability to be a drug or not. For that, the new proposed 2,4,5-trisubstituted thiazoles molecules were assessed for their toxicity using the Ames test. Outcomes of Table 8 demonstrate that the molecules **Y1** and **Y2** are non-mutagenic; respecting Ames test data. As conclusion, the molecules **Y1** and **Y2** have more favorable properties and respect all drug likeness rules as shown in Table 9. Therefore, they can be adopted as a future drug for tuberculosis illness.

Table 9. Drug-likeness prediction of the molecules **Y1** and **Y2**.

Compound	Lipinski	Egan	Ghose	Veber
Y1	Yes	Yes	Yes	Yes
Y2	Yes	Yes	Yes	Yes

4. Conclusion

In this research, 3D-QSAR and molecular docking approaches were put into effect on set of eighteen 2,4,5-trisubstituted thiazoles derivatives. CoMFA and CoMSIA models afforded good internal and external outcomes with interesting statistical capability R^2 (0.995 and 0.982, respectively) and Q^2 (0.533 and 0.601, respectively). The generated CoMFA and CoMSIA contour maps were directed us to identify the key moieties that impacting the activity and therefore to propose new and potential molecules with high antituberculosis activities. Molecular docking was executed to examine the interactions between 2,4,5-trisubstituted thiazoles entities and the INHA receptor (PDB ID: 1ZID). Outcomes of molecular docking clearly showed the pivotal role of Ile194 (3.27Å) residue in the stability of compound **Y1** to the potential interactions in the INHA receptor pocket. In silico ADMET prediction was put into practice to define the pharmacokinetics properties of newly suggested molecules; it points out good oral bioavailability and no toxicity for new molecules **Y1** and **Y2**. Therefore, these outcomes would be of great importance to solve the biggest challenge associated with TB.

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Authors' Contributions

Soukaina Bouamrane and Reda El-mernissi designed the structure. Hamid Maghat and Mohammed Aziz Ajana grew the sample according to the specifications. Ayoub Khaldan fabricated the device, carried out the theoretical calculations, in collaboration with Abdelouahid Sbai, Mohammed Bouachrine and Tahar Lakhlifi, and wrote up the article. Abdelouahid Sbai and Tahar Lakhlifi are the inventor of the original device and the overall supervisor of the project. Both authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

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