Original Research Article

DFT-QSAR and Molecular Docking Studies on 1,2,3-Triazole-Dithiocarbamate Hybrids as Potential Anticancer Agents

Abstract

Recently, considerable attention has been drawn on the search for novel anticancer drugs in order to improve survival rates and wellbeing of cancer patients. 1,2,3-triazole is an attractive scaffold possessing diverse biological activities. The quantitative structure–activity relationship (QSAR) is a powerful computational tool which has widened the scope of rational drug design, as well as the search for the mechanisms of drug actions.

A series of novel 1,2,3-triazole-dithiocarbamate hybrids (1,2,3-TDHs) were studied for anticancer activity against human gastric cancer cell line (MGC-803) using Density Functional Theory (DFT), Quantitative Structure Activity Relation (QSAR) and Docking approaches. QSAR models were successfully constructed with acceptable predictive performance. The QSAR analysis indicated that certain molecular descriptors namely E_{HOMO}, E_{LUMO}, Log P, Area, the total electronic charges on the heteroatom (H), and the average electronic charge on the heteroatoms (H_HET4r) are important factors for the observed biological activity. The results from docking study predicted stable conformations of the ligands within the enzyme's active gouge of the receptor. Compound E, tert Butyl 4-(((1-(4-methylbenzyl)-1H-1,2,3-tria zol-4-yl)methylthio)carbonothioyl)-piperazine-1-arboxylate, formed the most stable complex with the protein receptor.

Keywords: 1,2,3-Triazoles, Anticancer, Drug Design, DFT, QSAR, Molecular Docking.

1. Introduction

Cancer is a major public health burden in both developed and developing countries, and are estimated to be one of main causes of death [1,2]. The growing incidence of drug resistance to cancer chemotherapeutic agent represents a serious medical problem [3]. Besides the exploitation of new targets, the development of hybrid structures, that is combination of two or more pharmacophores into a single molecule, with each pharmacophore having different mode of action, could be beneficial for the treatment of cancer [4].This may offer the possibility to overcome drug resistance, reduce the appearance of new resistant strains, reduce unwanted side effects, and may also enhance biological potency [5,6]. Therefore, there is an urgent need to develop new classes of chemotherapeutic agent to treat cancer in order to improve survival rates and wellbeing of cancer patients.

Triazoles are heterocyclic organic compounds containing five member ring with three nitrogen and two carbon atoms. They are stable to metabolic degradation, highly selective, capable of hydrogen bonding and have less adverse effects [7]. 1,2,3-triazole and 1,2,4-triazole are the isomeric forms of triazoles [8]. 1,2,3-Triazoles have been well exploited for the generation of many medicinal scaffolds exhibiting diverse biological activities [9-11] such as anti-HIV [12], anticancer [13,14], antifungal [15], antimicrobial [16,17], antiviral, anti-inflammatory, analgelsic [18], anti-tubercular [19], anti-allergic [20] and antibacterial [21] activities. The 1,2,3-triazole moiety also serves as key synthetic intermediates in many industrial applications such as agrochemicals, corrosion inhibitors, additives, super-molecular chemistry, dendrimers, polymers, liquid crystals, photostabilizers, pigments and metal chelators [11]. Recently, researchers are increasingly focused on the anticancer activities of 1,2,3-triazole containing drug molecules. A number of compounds with potent antitumor activity have been synthesized by combining 1,2,3-triazole with other pharmacophores [22-24].

On the other hand, dithiocarbamates are a common class of organic molecules that form mono and bidentate coordination with transition metals. They possess diverse biological activities such as antifungal, anti-bacterial, and carbonic anhydrases inhibitor [25]. There is also an increasing interest on these compounds because of their applications in the treatment of cancer [26,27]. The biological importance of 1,2,3-triazoles and dithiocarbamates as anticancer agents inspired the

interest of Ying-Chao et al (2013) [28] to synthesize novel 1,2,3-triazole-dithiocarbamates hybrids, and study their anticancer activity.

The advances in Quantitative Structure Activity Relationship (QSAR) studies have widened the scope of rational drug design as well as the search for the mechanisms of drug actions. QSAR is a technique used for predicting the biological activities such as environmental toxicology or drug activity of compounds by utilizing experimental data and molecular structures [29]. The advantage of using QSAR over other modeling techniques is that it takes into account the full complexity of the biological system without requiring any information about the binding site. QSAR is very useful for determining general criteria for activity, but it does not readily yield detailed structural predictions [30]. Obtaining a good quality QSAR model depends on the quality of biological data, the choice of descriptors, and statistical methods used [31]. Computational predictions of potential targets of bioactive small molecules have also received considerable interest during the last few decades. As part of this, docking is frequently used to predict the binding modes of small molecules to their targeted proteins; hence, it plays an important role in rational drug design [32,33].

Ying-Chao et al (2013) synthesized a series of novel 1,2,3-triazole-dithiocarbamate hybrids (1,2,3-TDHs), and evaluated them for anticancer activity against four selected human tumor cell lines (MGC-803, MCF-7, PC-3, EC-109). They reported that majority of the synthesized 1,2,3-TDHs exhibited moderate to potent activity against MGC-803 and MCF-7 [28].

The aim of this study is to calculate and discuss the molecular parameters of some of the 1,2,3-TDHs synthesized by Ying-Chao et al [28] using DFT method, to develop a QSAR model for investigation of bioactivity of chosen molecules and finally to investigate the ligand–protein intermolecular interactions between 1,2,3-TDHs and receptor proteins.

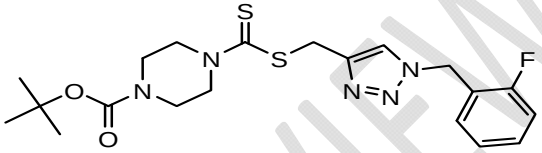
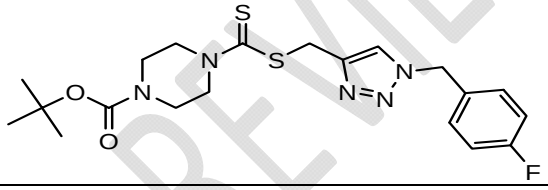
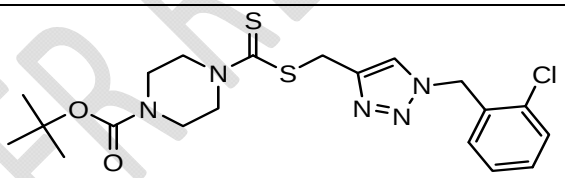
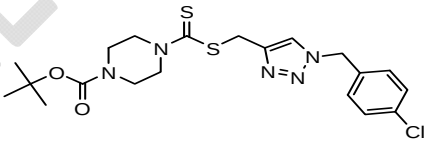
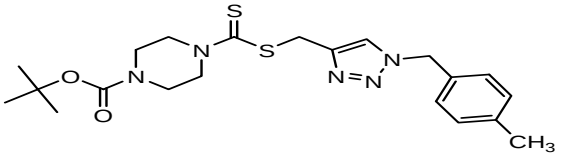
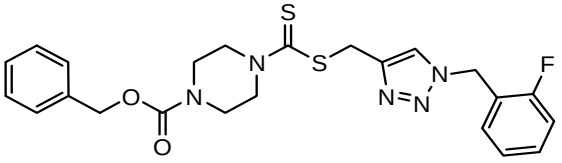
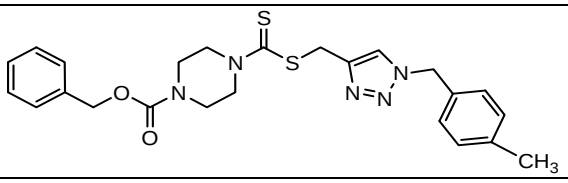
2. THEORETICAL METHODS

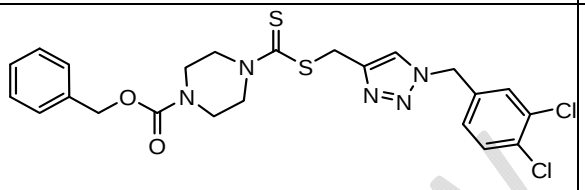
2.1 Data sets

A set of 1,2,3-TDHs and their experimental IC_{50} (concentration required to inhibit tumor cell proliferation by 50%) values against human gastric cancer cell line (MGC-803) were obtained from literature reported by Ying-Chao et al (2013). Eight compounds (Table 1) with IC_{50} values

≤ 10 μM (i.e., highly active to moderately active) were selected, while the compounds with IC_{50} values >10 μM (weakly active) were excluded from this study.

Table 1: IUPAC Name, Chemical Structures and Experimental IC_{50} values of the Studied Compounds.

	IUPAC NAME	CHEMICAL STRUCTURE	Expt IC_{50}(μM)
A	tertButyl4-(((1-(2-fluorobenzyl)-1H1,2,3 triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate		0.73
B	tertButyl4-(((1-(4-fluorobenzyl)-1H-1,2,3 triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate		1.93
C	tertButyl4-(((1-(2-chlorobenzyl)-1H-1,2,3 triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate		0.49
D	tertButyl4-(((1-(4-chlorobenzyl)-1H1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate		9.79
E	tertButyl4-(((1-(4-methylbenzyl)-1H-1,2, 3- triazol-4-yl)methylthio)carbonothioyl) -piperazine-1-carboxylate		3.49
F	Benzyl 4-(((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate		5.06
G	Benzyl4-(((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate		9.37

H	Benzyl4-(((1-(3,4-dichlorobenzyl)-1H-1, 2,3triazol-4-yl)methylthio)carbonothioyl)-piperazine-1-carboxylate		7.14

2.2 Quantum Chemical Methods

All quantum chemical calculations were performed using Spartan '14 by wavefunction Inc [34]. Chemical structures of the selected compounds (A-H) were drawn using Spartan software and initially geometrically optimized at the molecular mechanics (MM) Merck molecular force field (MMFF) level. This was followed by DFT calculations using the Becke's gradient exchange correction [35] with the Lee–Yang–Parr correlation functional (B3LYP) [36], together with the 6-31G*(d,p) basic set.

2.3 QSAR Modeling

Multiple linear regression method was used to build QSAR model for biological investigation of the selected molecules. Six selected descriptors from the calculated molecular parameters served as the independent variable and the experimental IC_{50} values were used as the dependent variable. The model was constructed according to the following linear equation.

$$\text{Predicted } IC_{50} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots + \beta_n X_n \quad \text{----------(1)}$$

Where α and β are constants i.e regression coefficients determined through regression analysis, X_1, X_2.... X_n are quantum chemical indices characteristic of the molecule.

The QSAR model was validated using statistical equations by considering cross validation R^2 ($CV.R^2$) and Adjusted R^2 (R_a^2). Cross validation governs how reliable a QSAR model can be used for a particular set of data. It is also used as an analytic instrument to estimate the prognostic control of an equation. $CV.R^2$and R_a^2 were calculated using equations (2) and (3)

$$CV.R^2 = 1 - \frac{\sum(Yobs-Ycal)^2}{\sum(Yobs-\bar{Y}obs^2)}$$ ---------- (2)

Where $Yobs$ = experimentally observed IC_{50}, $Ycal$ = calculated IC_{50} and $\bar{Y}obs$ = average of the experimentally observed IC50

$$R_a^2 = \frac{(N-1)\times R^2-P}{N-1-P}$$ ----------(3)

Where N = no of compounds observed, P = no of molecular descriptors used in the QSAR model and R^2 = R- squared value obtained from the QSAR model

2.4 Molecular Docking Study

The MGC-803 receptor (PDB: 2UVL) was downloaded from protein data bank [37] and to obtain the desired chains, water molecules, multiple ligands and non-protein parts were deleted from the pdb files using Discovery Studio 4.1 visualizer. The ligands (1,2,3-TDHs) were optimized at Density Functional Theory (DFT) with the standard 6-31G*(d,p) basis set using Spartan 14 version. Autodock tool was used to convert the ligands and the receptor to pdbqt format, and the docking process was carried out using AutoDock Vina[38]. Biovia Discovery Studio [39] was used to analyze the output of docking process.

3 RESULTS AND DISCUSSION

3.1 Molecular Descriptors

Calculated molecular descriptors of the 1,2,3-TDHs in Table 1, namely; molecular weight (MW), partition coefficient (Log P), volume (V), Area, polar surface area (PSA), E_{HOMO} (highest occupied molecular orbital energy), E_{LUMO} (lowest unoccupied molecular orbital energy),dipole moment (DM), Band gap (BG), global nucleophilicity (ω), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), the total electronic charges on the heteroatom (H) and the average electronic charge on the heteroatoms (H_HET4r) are given in Table 2.

Table 2: The calculated molecular descriptors for the studied compounds

Mol	E_{Homo} (eV)	E_{Lumo} (eV)	BG (eV)	DM (Debye)	ω	MW (amu)	Log P	Area (A^2)	Vol (A^3)	PSA $Å^2$	HBD	HBA	H	Pol	H Het4r	IC_{50} (μM)
A	-5.82	-1.08	4.74	4.85	2.51	451.6	4.0	462.80	434.54	43.8	0	8	-1.18	75.50	-0.294	0.73
B	-5.85	-1.21	4.64	4.53	2.69	451.6	4.0	463.73	434.55	44.0	0	8	-1.16	75.53	-0.30	1.93
C	-5.86	-1.11	4.75	4.63	2.56	468.1	4.4	473.22	443.74	43.7	0	8	-0.90	76.25	-0.22	0.49
D	-5.96	-0.95	5.01	4.13	2.38	468.1	4.4	477.36	443.87	43.2	0	8	-0.90	76.26	-0.23	9.79
E	-5.74	-1.26	4.48	4.36	2.73	447.6	4.4	479.90	448.43	43.7	0	8	-0.87	76.69	-0.29	3.49
F	-5.57	-1.34	4.23	3.81	2.82	485.6	4.9	485.12	463.94	45.7	0	8	-1.15	78.01	-0.29	5.06
G	-5.56	-1.34	4.22	3.69	2.82	481.7	5.2	502.73	477.78	46.0	0	8	-0.84	79.13	-0.28	9.37
H	-5.73	-1.46	4.27	3.55	3.03	536.5	5.8	511.73	486.64	45.4	0	8	-0.82	79.84	-0.20	7.14

HOMO and LUMO are the main orbitals taking part in chemical reactions. E_{HOMO} and E_{LUMO} represent the ability to donate electron and the ability to obtain an electron respectively. The higher the E_{HOMO}, the greater is the tendency of a molecule to donate its electrons to the electron poor species and vice versa [40]. The calculated E_{HOMO} for compounds A to H are -5.82, -5.85,-5.86, -5.96, -5.74, -5.57, -5.56 and -5.73eV respectively. While E_{LUMO} for compounds A to H are -1.08, -1.21, -1.11, -0.95, -1.26, -1.34, -1.34 and -1.46eV respectively. The energy difference between the HOMO and the LUMO (band gap) is a measure of electron conductivity [41] and reactivity. It makes an important contribution to the energy for charge transfer processes to occur and, consequently, is of relevance to drug-receptor interactions. Molecules with narrower energy gap have higher chemical reactivity, lower stability and better ability to donate electrons to the neighboring molecule [42,43]. For the studied compounds the order of reactivity is G>F>H>E>B>A>C>D based on the band gap values.

The magnitude of the dipole moment is a description of the degree of polarity of the molecule and, as such, is an important quantity in intermolecular interactions, including those associated with hydrogen-bond formation and other related dipole-dipole and ion-dipole interactions [44]. Compounds A to H have moderate values of dipole moment which range from 3.55 to 4.85debye. Compound A showed highest dipole moment which suggests that it has the highest polarity and would have better protein-ligand interactions, while compound H has the lowest polarity.

Polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties and biological activities [45]. Highly polarizable molecules are expected to have strong attractions with other molecules. Larger molecules in which electrons are far from the positively charged

nucleus are more polarizable than smaller molecules hence polarizability increases with increase in volume and area of the molecule. From the results the Polarizabilty is observed to be in the order H>G>F>E>D>C>B>A. This order is the same for volume and area (Table 2). The most polarizable molecule H has two chlorine atoms in the structure while the molecules containing fluorine substituent are least polarizable.

Log P is a measure of the distribution of a molecule between aqueous and non-aqueous phase. It estimates a molecule's overall lipophilicity. Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as the biological activity of ligands [45,46]. For a molecule to be used as drug it should have a low or moderate lipophilicity. A molecule with high lipophilicity will partition into the lipid interior of membranes and be retained there [47]. Log p, molecular weight, H-bond donors (HBD) and H-bond acceptors (HBA) are globally associated with solubility and permeability of a molecule. Based on the Lipinski's rule, for a drug to have good absorption or permeation, the drug must have molecular weight value ≤ 500, Hydrogen Bond Donor ≤ 5, Hydrogen Bond Acceptor ≤ 10 and partition coefficient (LogP) value ≤ 5 [48]. From the results (Table 2) compounds A-F obeyed the Lipinski's rule. Compound G have lop P value > 5 (5.2), also compound H have log P value > 5(5.8), and molecular weight > 500 hence they do not obey the rule and will both have poor absorption when used as drugs.

Also Polar surface area (PSA) is a sum of surfaces of polar atoms (usually oxygen, nitrogen and attached hydrogen) in a molecule [49]. This parameter has been shown to correlate very well with the human intestinal absorption, Caco-2 monolayer permeability, and blood-brain barrier penetration. PSA is an indicator of the ligand hydrophilicity. It plays an important role in shaping the protein-ligand interaction by affecting the non-bonded contribution to the binding energy. Molecules with a PSA greater than 140 $Å^2$ are usually believed to be poor at permeating cell membranes. For molecules to penetrate the blood-brain barrier, PSA should be less than 60 $Å^2$ [50,51]. PSA for the studied compounds range from 43.2-46.0$Å^2$, hence they will effectively penetrate the blood-brain barrier and hence can be used as Drugs targeted to the central nervous system.

3.2 QSAR STUDIES

In this study the biological activities of eight experimental molecules were probed into and six descriptors were selected among the calculated molecular descriptors (Table 2) in order to avoid multi collinearity. The developed model (equation 4) replicated the experimental IC_{50} values well as shown in Table 3 and Figure 1.

IC_{50}= -793.228 + 17.809 (E_{HOMO}) + 4.55552 (E_{LUMO}) – 63.7412 (Log P) + 2.504 (Area) - 67.357 (H) + 269.729(H_HET4r) ----------(4)

The result of the predicted IC_{50} showed that certain descriptors namely E_{HOMO}, E_{LUMO}, Log P, Area, the total electronic charges on the heteroatom (H) and the average electronic charge on the heteroatoms (H_HET4r) were critical factors for the observed biological activity.

Furthermore, Cross Validation ($CV.R^2$) and adjusted R^2 values were calculated (Table 4) to statistically validate the developed QSAR model. The value for calculated $CV.R^2$ was greater than 0.5 (standard) which showed the reliability, acceptability and appropriateness of the developed model. The calculated R_a^2 was greater than 0.6 (standard), therefore, the QSAR model would be predictive.

Table 3: Experimental and Predicted IC_{50} Values

Compounds	Observed IC_{50}	Predicted	Residual
A	0.73	0.73	0.00
B	1.93	1.92	0.01
C	0.49	0.49	0.00
D	9.79	9.79	0.00
E	3.49	3.50	-0.01
F	5.06	5.07	-0.01
G	9.37	9.36	0.01
H	7.14	7.14	0.00

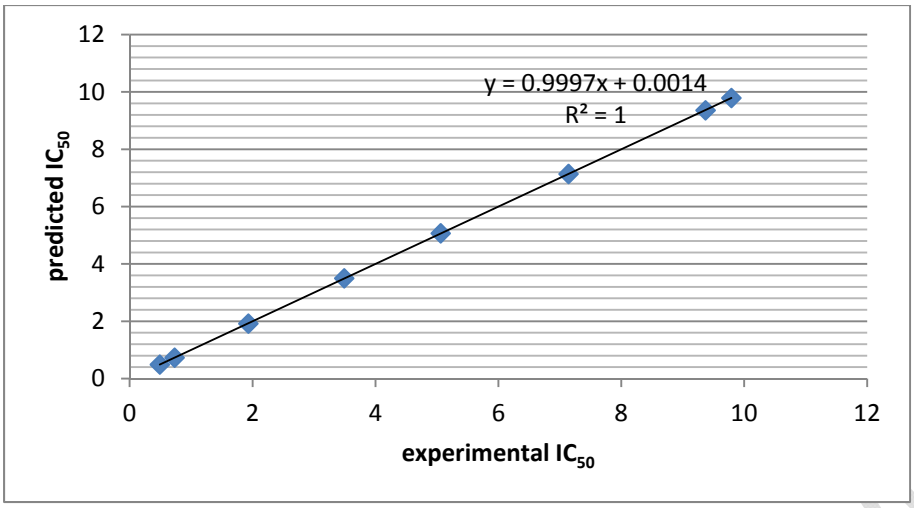


Figure 1: The calculated predicted IC_{50} against the experimentally observed IC_{50}

Table 4: Statistical parameters for validation of QSAR model

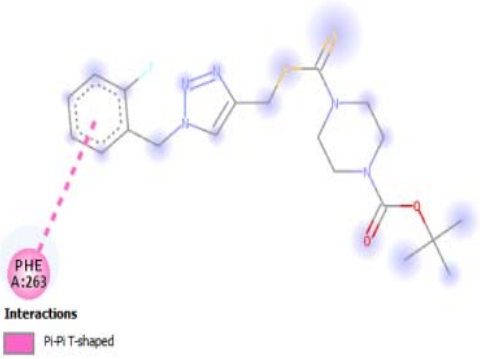
N	P	R^2	CV.R^2	R_a^2
8	6	0.999996	0.999998	0.999972

Docking and Scoring

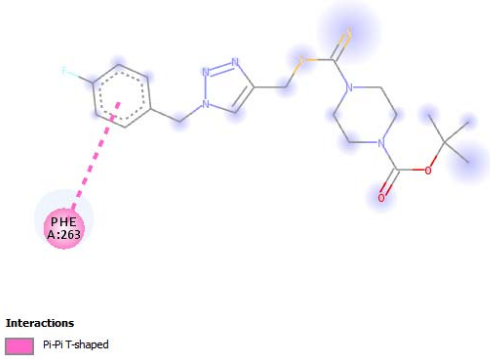
The result of the Molecular docking performed to evaluate the binding modalities of the1,2,3-TDHs against 2UVL suggested that all the1,2,3-TDHs could snugly occupy the active site of the protein. The docking simulation of each compound (ligand) produced nine conformations and the best conformation is assumed to be the conformation with the most negative binding energy in each docking. The free energies of the interactions also known as binding energies for compounds A-H are displayed in Table 5. The calculated free binding energies are -0.9kcal/mol for A, B, C, D, and F, -1.0kcal/mol for E, -0.7kcal/mol for G, and -0.6kcal/mol for H. compound E formed the most stable complex with the protein receptor. The interaction between the ligand and the receptor are also shown in Table 5 and Figure 2. Only hydrophobic interactions were observed in the complexes. For complexes formed by A, B, C, D and F PHE-263 of the receptor form Pi-Pi T shaped coordination with the ligand. Pi-Pi T shaped and Pi alkyl coordination was observed between PHE-263 of the receptor and the ligands in complexes formed by E and H. For complex formed by G only van der waal coordination was observed between the PHE-263 of the receptor and the ligand.

Table 5: Binding Energy, Interactions between Ligands and 2UVL receptor.

Mol	Affinity (Kcal/Mol)	Interaction between Ligands and 2UVL receptor
A	-0.9	PHE-263
B	-0.9	PHE-263
C	-0.9	PHE-263
D	-0.9	PHE-263
E	-1.0	PHE-263
F	-0.9	PHE-263
G	-0.7	PHE-263
H	-0.6	PHE-263



(A)



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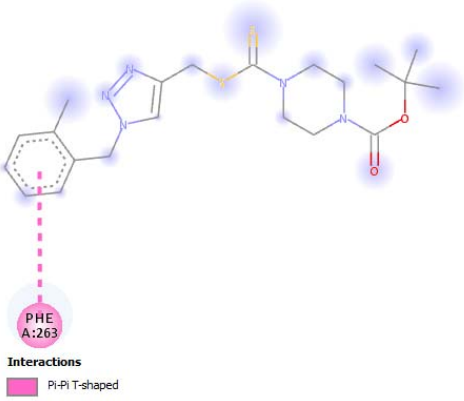
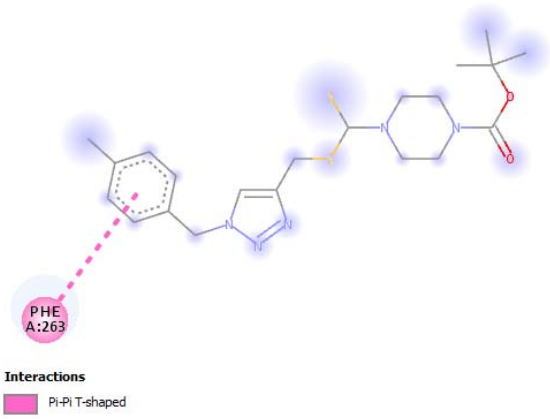


(C)



(D)

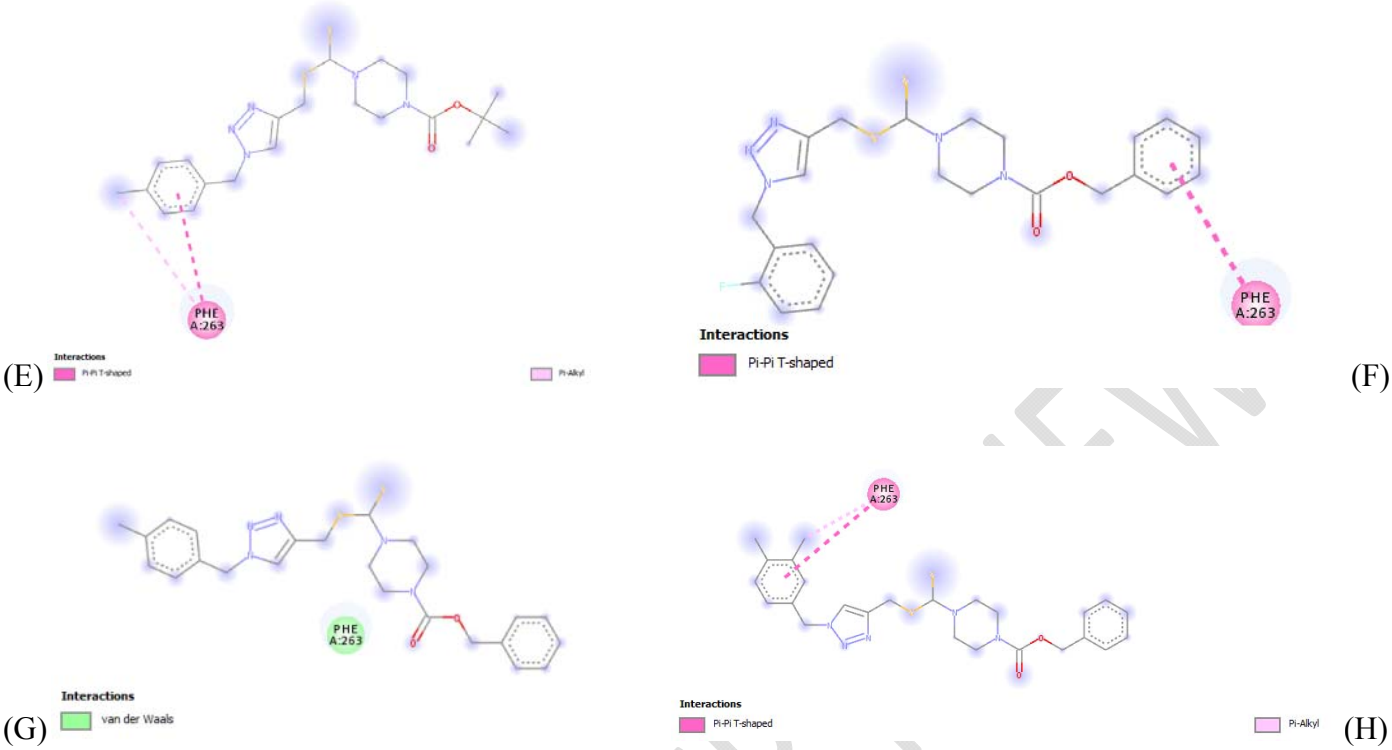


Figure 2: Binding interactions between the studied1,2,3-TDHs and 2UVL.

4 CONCLUSIONS

In this work eight compounds (1,2,3-triazole-dithiocarbamate hybrids) were studied using density functional theory (DFT) method, QSAR model and molecular docking. The QSAR models developed reproduced the experimental bioactivities of the compounds against MGC-803. The QSAR analysis indicated that E_{HOMO}, E_{LUMO}, Log P, Area, the total electronic charges on the heteroatom (H) and the average electronic charge on the heteroatoms (H_HET4r) were critical factors for the observed biological activity. The results obtained from docking study predicted stable conformations of the ligands within the enzyme's active gouge. The free energy of interactions which were also obtained from the docking process showed that compound E formed the most stable complex with the protein receptor.

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