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 namelyE_{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'sactive gouge of the receptor. Compound E, tert Butyl 4-(((1-(4-methylbenzyl)-1H-1,2,3-triazol-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 have increasingly focused on the anticancer activities of 1,2,3-triazole containing drug molecules. A number of compounds with potentantitumor activity have been synthesized by combining 1,2,3-triazole with other pharmacophores[22-24].

Moreover, dithiocarbamates are a class oforganic molecules that form mono and bi-dentate 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 compoundsby 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].

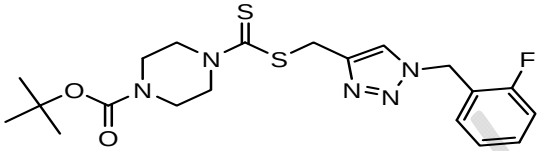
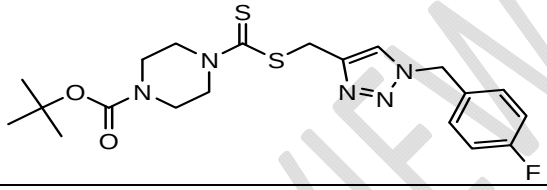
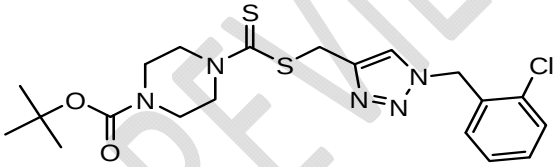
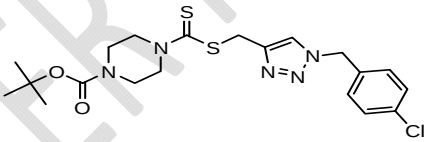
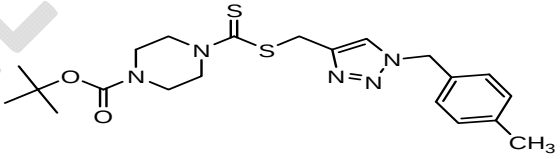
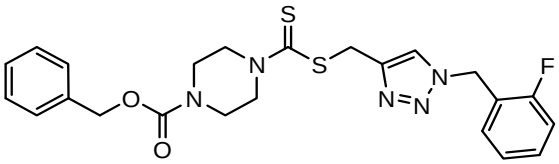
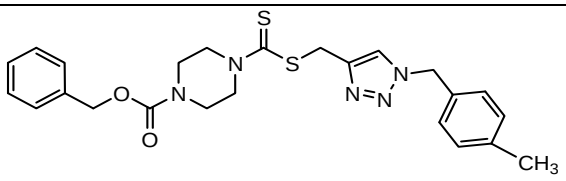
The aim of this study is to calculate and discuss the molecular parameters of some of the 1,2,3-TDHs synthesized by Ying-Chao et al [28]using DFT method, to develop a QSAR model for investigation of bioactivity of chosen molecules and finally to investigate the ligand–protein intermolecular interactions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

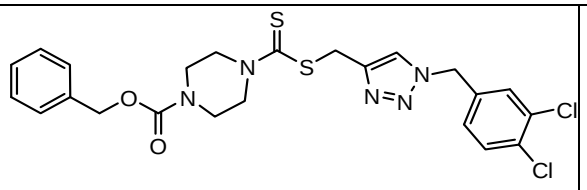
2. THEORETICAL METHODS

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 fromliterature reported by Ying-Chao et al (2013).

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

	IUPAC NAME	CHEMICAL STRUCTURE	Expt $IC_{50}(\mu M)$
A	tertButyl4-(((1-(2-fluorobenzyl)-1H1,2,3triazol-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 wavefunctionInc[34]. Chemical structures of the selected compounds (A-H) were drawn using Spartan software and initially geometrically optimized atthe molecular mechanics (MM) Merck molecular force field (MMFF) level. This was followed by DFT calculations using the Becke's gradient exchangecorrection[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.

Predicted $IC_{50} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots\ldots + \beta_n X_n$----------(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.$CV.R^2$andR_a^2 werecalculated 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 = Correlation coefficient

2.4 Molecular Docking Study

The MGC-803 receptor (PDB: 2UVL) was downloaded from protein data bank[37]. The quality of the downloaded residue was confirmed through ramachandran analysis (figure 1). In this, it was observed that almost all the residues were in favourable and allowed region. Also, there were no outliers observed. Thus, in order to obtain the desired chains, water molecules, multiple ligands and non-protein parts were removed from the downloaded residue using Discovery Studio 4.1 visualizer. The ligands (1,2,3-TDHs) were optimized using Density Functional Theory (DFT) with the standard 6-31G*(d,p) basis set via 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 AutoDockVina[38]. Biovia Discovery Studio[39]was used to analyze the output of docking process.

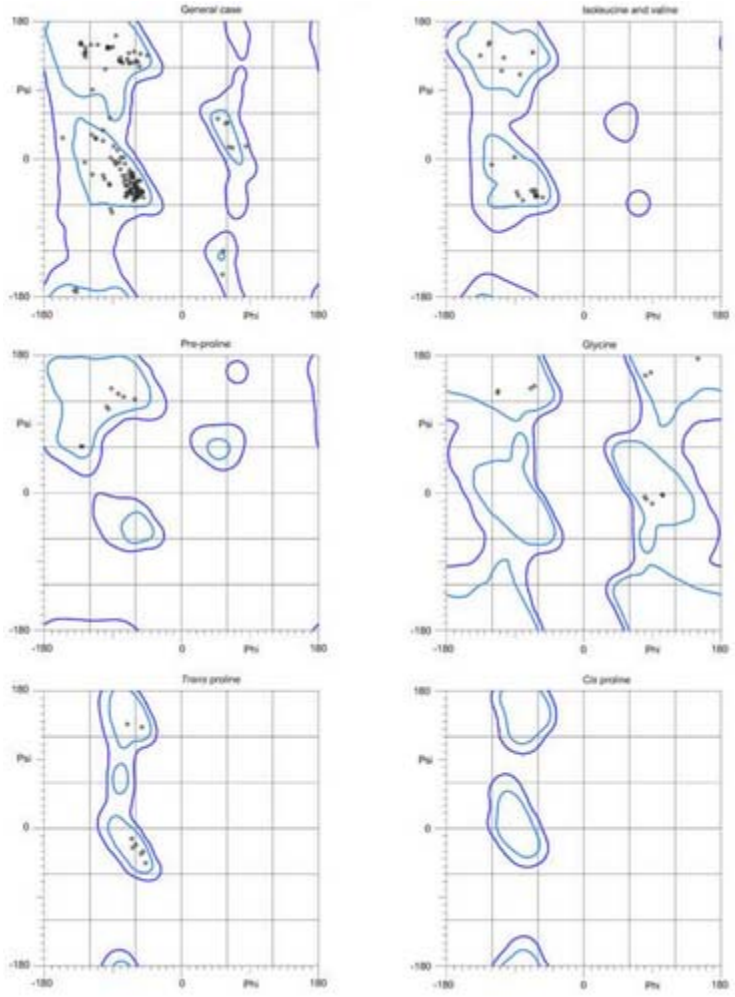


Figure 1: Ramachandran plot for the studied Residue (2UVL)

3.0 RESULTS AND DISCUSSION

3.1 Quantitative Structural Activity Relationship Modelling

In this work, several calculated molecular descriptors were obtained and used in the development of QSAR model. The calculated descriptors were used as independent variables while inhibition concentration (IC_{50}) were used as dependent variable. The calculateddescriptors are: 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

orbitalenergy),Dipole moment (DM), Band gap (BG), hydrogen bond donor (HBD), and hydrogen bond acceptor (HBA) (Table 2).

Moreover,in developing QSAR model, two (2) molecular descriptors were selected and this was done in order to avoid multi-collinearity.As shown in equation 4, increase LUMO brings about decrease in biological activity of 1,2,3-Triazole-Dithiocarbamate hybrid and decrease in dipole moment (DM) will lead to increase in biological activity.

IC_{50}= 66.0031 + 15.6382(LUMO) - 10.0612(DM)----------(4)

As shown by correlation coefficient (R^2), the developed model replicated the observed inhibition concentration. The analysis was validated by observing some statistical fact, like, cross validation (CVR^2), adjusted correlation coefficient (R^2_{adj}) and mean square error.The calculated $CV.R^2$ was 0.907 and this greater than 0.5 which is the standard as well as the adjusted R^2 which is greater than 0.6 (Standard) (Table 4). This show the effectiveness of the developed model and it ascertain the model to be predictive as displayed in Table 3.

Table 2: The calculated molecular descriptors for the studied compounds

Mol	E_{Homo}(eV)	E_{Lumo}(eV)	BG (eV)	DM (Debye)	MW (amu)	Log P	PSA Å^2	HBD	HBA	Pol	IC_{50}(µM)
A	-5.82	-1.08	4.74	4.85	451.6	4.0	43.8	0	8	75.50	0.73
B	-5.85	-1.21	4.64	4.53	451.6	4.0	44.0	0	8	75.53	1.93
C	-5.86	-1.11	4.75	4.63	468.1	4.4	43.7	0	8	76.25	0.49
D	-5.96	-0.95	5.01	4.13	468.1	4.4	43.2	0	8	76.26	9.79
E	-5.74	-1.26	4.48	4.36	447.6	4.4	43.7	0	8	76.69	3.49
F	-5.57	-1.34	4.23	3.81	485.6	4.9	45.7	0	8	78.01	5.06
G	-5.56	-1.34	4.22	3.69	481.7	5.2	46.0	0	8	79.13	9.37
H	-5.73	-1.46	4.27	3.55	536.5	5.8	45.4	0	8	79.84	7.14

Table 3: Experimental and Predicted IC_{50} Values

Compounds	Observed IC_{50}	Predicted IC_{50}	Residual
A	0.73	0.32	0.41
B	1.93	1.50	0.43
C	0.49	2.06	-1.57
D	9.79	9.59	0.20
E	3.49	2.43	1.06
F	5.06	6.71	-1.65
G	9.37	7.92	1.45
H	7.14	7.45	-0.31

Table 4: Statistical parameters for validation of QSAR model

N	P	R^2	$CV.R^2$	R_a^2
8	2	0.907	0.907	0.870

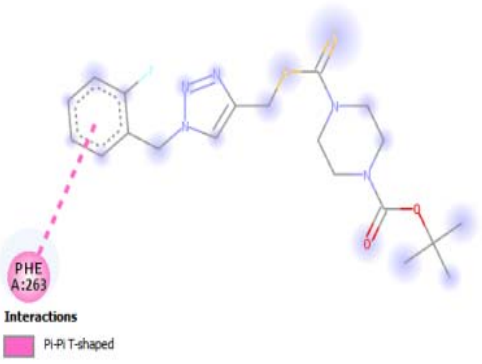
Docking and Scoring

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. CompoundE formed the most stable complex with the protein receptor. The interactions between the ligand and the receptor arealso 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

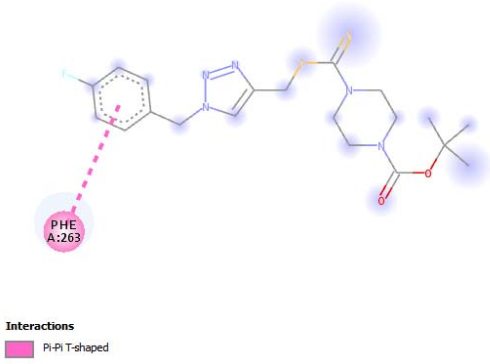
complexes formed by E and H. For complex formed by G only van der waal coordination was observed between the PHE-263 of the receptor and the ligand.

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

Mol	Affinity (Kcal/Mol)	Residue that re involved in the 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)



(B)

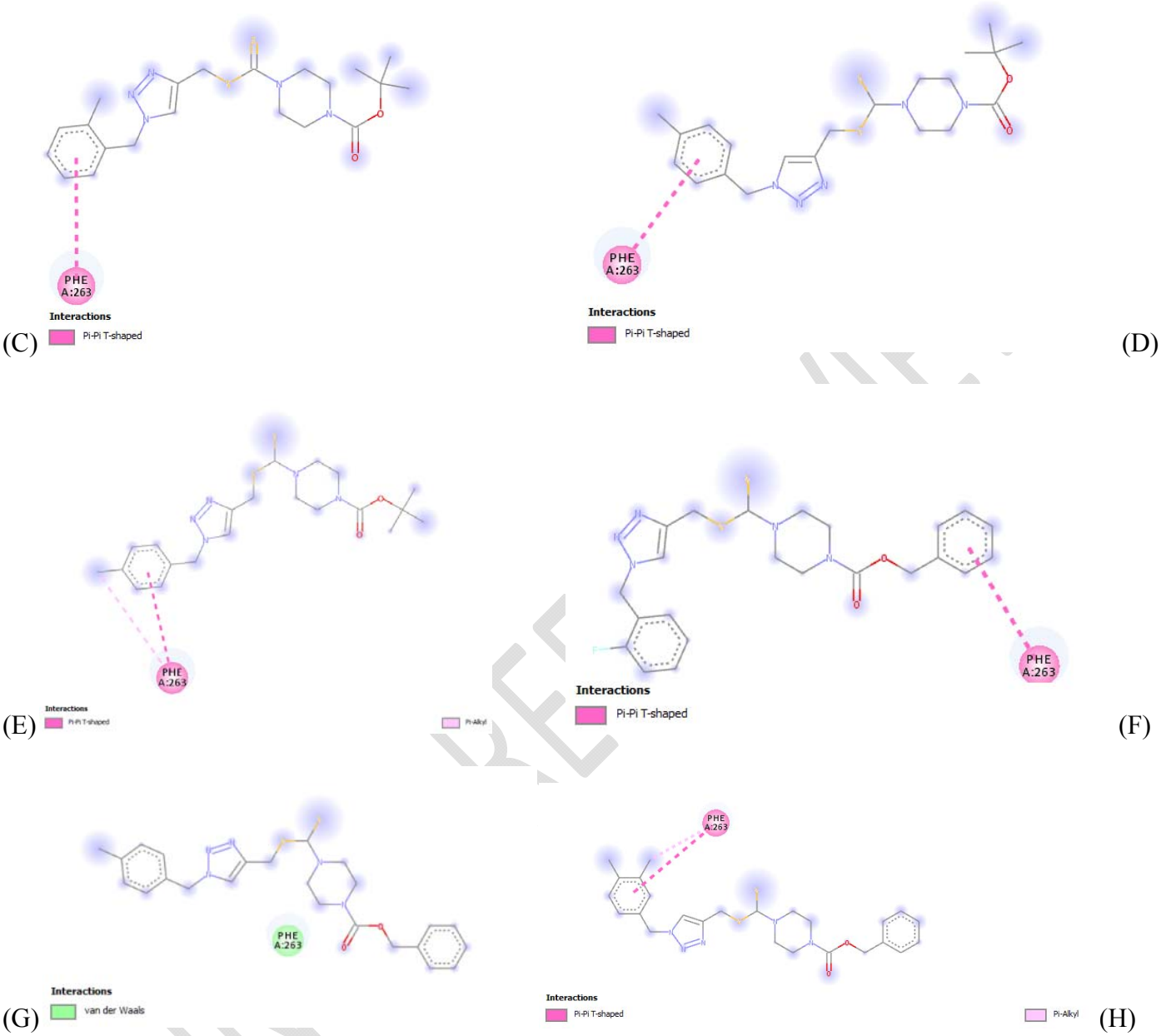


Figure2: Binding interactions between the studied1,2,3-TDHs and 2UVL.

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'sactive gouge. The free energy of interactions whichwere also obtained from the docking process showed that compound E formed the most stable complex with the protein receptor.

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