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

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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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 EHOMO,

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ELUMO, 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-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, photo-stabilizers, 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 potent antitumor activity have been synthesized by combining 1,2,3-triazole with other pharmacophores [22-24].

Moreover, dithiocarbamates are a class of organic 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. [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. 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].

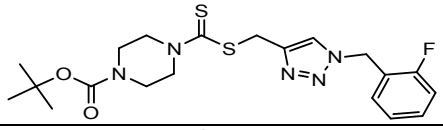
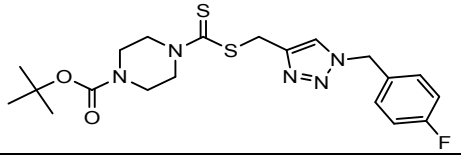
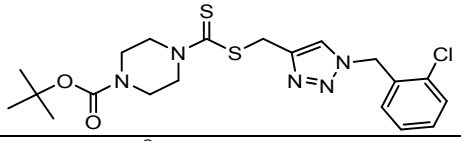
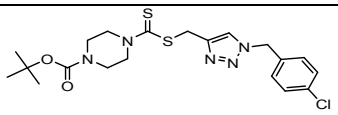
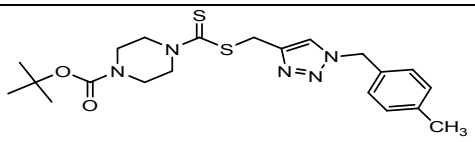
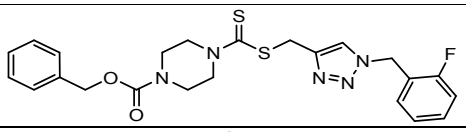
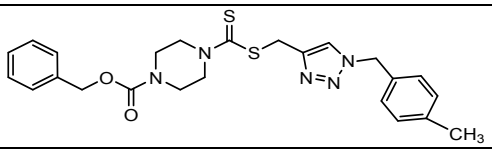
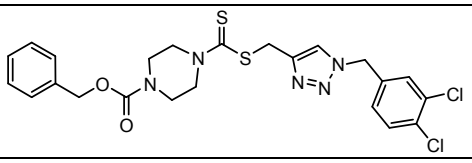
The aim of this study is to calculate and discuss the molecular parameters of some of the 1,2,3-TDHs synthesized by Ying-Chao et al [28] using DFT method, to develop a QSAR model for investigation of bioactivity of chosen molecules and finally to investigate the ligand–protein intermolecular interactions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

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)-1H1,2,3triazol-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

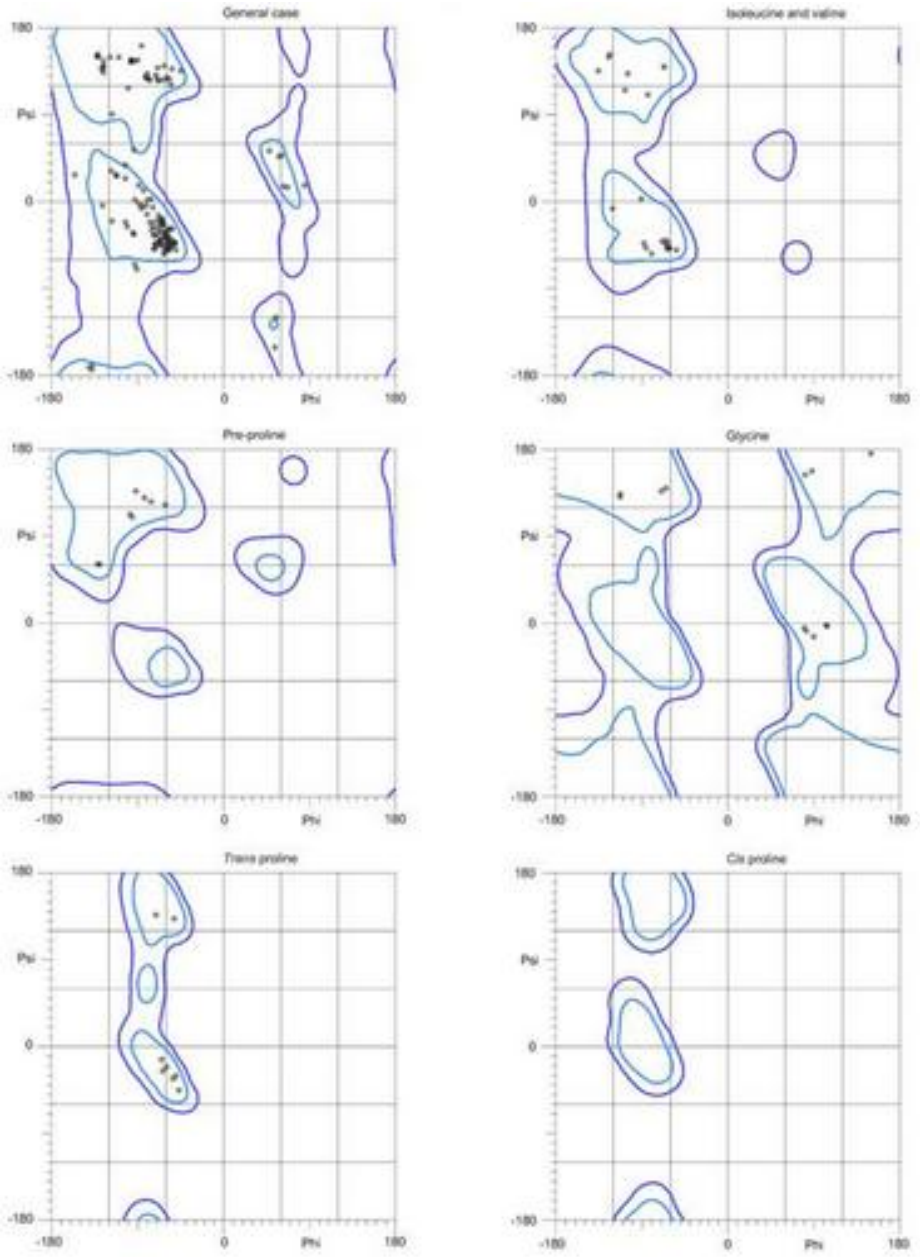


Fig. 1. Ramachandran plot for the studied Residue (2UVL)

2.2 Quantum Chemical Methods

All quantum chemical calculations were performed using Spartan ’14 by wave function 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.

Predicted $IC_{50} = \alpha + \beta_1X_1 + \beta_2X_2 + \ldots\ldots\ldots + \beta_nX_n$----------(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. $CV.R^2$ and R_a^2 werecalculated using equations (2) and (3)

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

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

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

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 (Fig. 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.

3. 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 calculated descriptors 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 orbital energy), 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_{adj}^2) 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.

3.2 Docking and Scoring

The result of the Molecular docking performed to evaluate the binding modalities of the 1,2,3-TDHs against 2UVL suggested that all the 1,2,3-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 interactions between the ligand and the receptor are also shown in Table 5 and Fig. 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 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

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

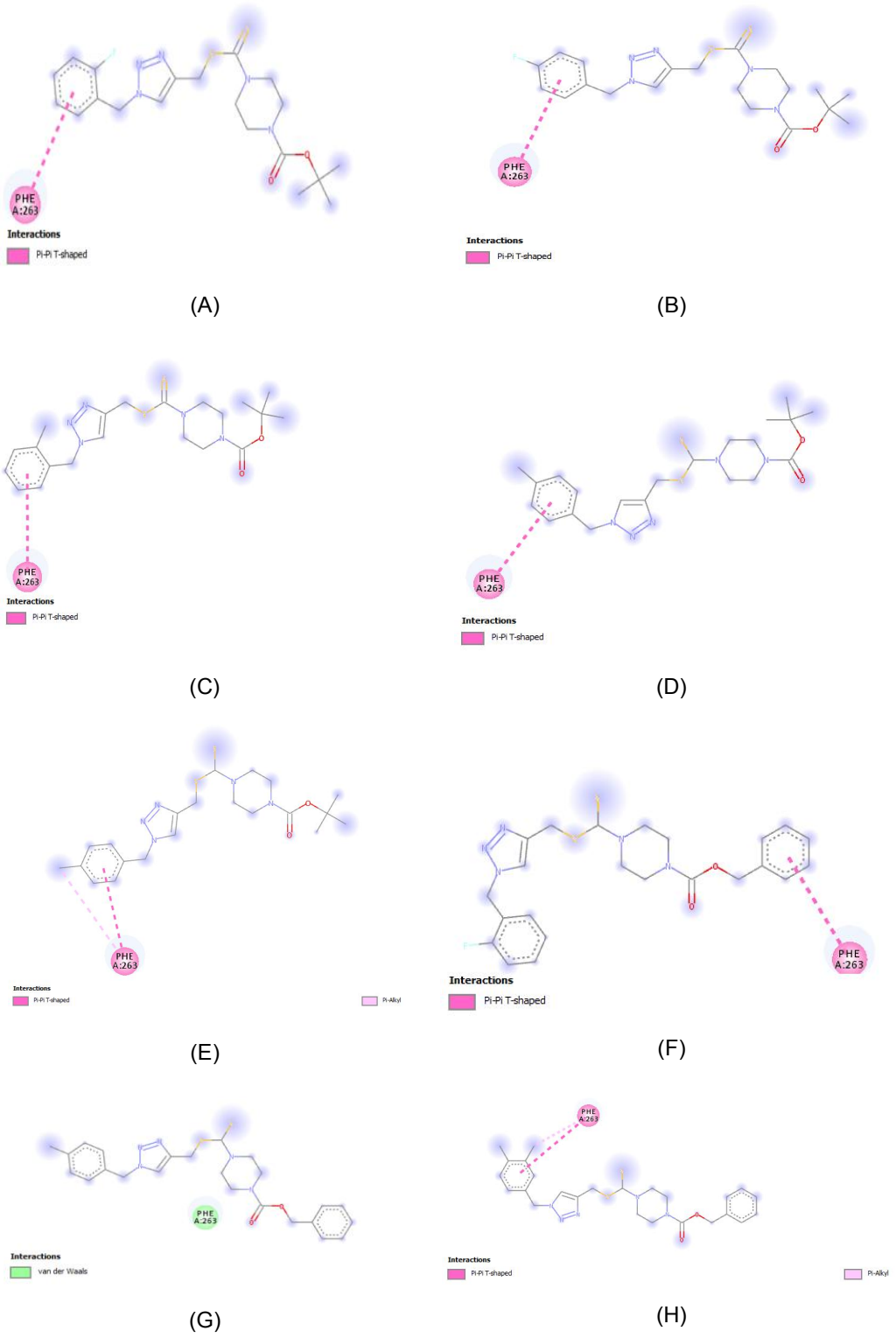


Fig. 2. Binding interactions between the studied1,2,3-TDHs and 2UVL.

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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3:442.
   DOI:10.1371/journal.pmed.0030442
2. Soerjomataram I, Lortet-Tieulent J, Ferlay J, Forman D, Mathers C, Parkin D, Bray F. Estimating and validating disability-adjusted life years at the global level: A methodological framework for cancer. BMC Med Res. 2012;12:125.
   DOI:10.1186/1471-2288-12-125
3. Szakacs G, Paterson JK, Ludwig JA, Booth-Genthe C, Gottesman MM. Nat. Rev. Drug Disc. 2006;5:219.
4. Mayur YC, Peters G J, Prasad VV, Lemo C, Sathish NK. Curr. Cancer Drug Targets. 2009;9:298.
5. Bektas H, Demirbas A, Demirbas N, Karaoglu SA. Synthesis and biological activity studies of new hybrid molecules containing tryptamine moiety. Med Chem Res. 2012;21:212–223.
6. Solomon VR, Hua C, Lee Pingaew HR, Design and synthesis of anti-breast cancer agents from 4-piperazinylquinoline: A hybrid pharmacophore approach. Bioorganic & Medicinal Chemistry. 2010; 18:1563–1572.
7. Vatmurge NS, Hazra BG, Pore VS, Shirazi F, Chavan PS, Deshpande MV. Synthesis and antimicrobial activity of β-lactam–bile acid conjugates linked via triazole. Bioorg. Med. Chem. Lett. 2008;18:2043–2047.
   DOI:10.1016/j.bmcl.2008.01.102
8. Praveena KSS, Murthy NYS, Pal S. Synthesis and biological activities of 1,4-disubstituted-1,2,3-triazoles. J. Chem. Pharm. Res. 2015;7:506–522.
9. Agalave SG, Maujan SR, Pore VS. Click chemistry: 1,2,3-triazoles as pharmacophores. Chem. Asian J. 2011;6:2696–2718.
10. Bębenek E, Kadela-Tomanek M, Chrobak E, Latocha M, Boryczka S. Novel triazoles of 3 acetylbetulin and betulone as anticancer agents Medicinal Chemistry Research; 2018.
    Available:https://doi.org/10.1007/s00044-018-2213-x
11. Dheer D, Singh V, Shankar R. Medicinal attributes of 1,2,3-triazoles: Current developments. Bioorg Chem. 2017;71:30–54.
12. Silva MC, De Souza BV, Frugulhetti IIP, Castro HC, Souza SLDO, De Souza TML, Rodrigues DQ, Souza AMT, Abreu PA, Passamani F, Rodrigues CR, Ferreira VF. Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. Eur. J. Med. Chem. 2009;44:373–383.
13. Holla BS, Poojary KN, Rao BS, Shivananda MK. New bis-aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents. Eur J Med Chem. 2002;37:511–517.
    DOI:10.1016/S0223-5234(02)01358-2
14. Pingaew R, Mandi P, Nantasenamat C, Prachayasittikul S, Ruchirawat S, Prachayasittikul V. Design, synthesis and molecular docking studies of novel N-benzenesulfonyl-1,2,3,4-tetrahydro isoquinoline - based triazoles with potential anticancer activity. Eur J Med Chem. 2014;81:192–203.
    DOI:10.1016/j.ejmech.2014.05.019
15. Aher NG, Pore VS, Mishra NN, Kumar A, Shukla PK, Sharma A, Bhat MK, Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues. Bioorg. Med. Chem. Lett. 2009;19:759-763.
16. Fichtali M, Chraibi FE, Aroussi A, Ben-Tama EME, Hadrami KF, Benbrahim SE,

Stiriba, Synthesis of some 1,2,3-triazoles derivatives and evaluation of their antimicrobial activity. Der. Pharma. Chem. 2016;8:236-242.

17. Prasad DJ, Ashok M, Karegoudar P, Poojary B, Holla BS, Kumari NS. Synthesis and antimicrobial activities of some new triazolothiadiazoles bearing 4-methylthiobenzyl moiety. Eur J Med Chem. 2009;44:551–557. DOI:10.1016/j.ejmech.2008.03.025
18. Almasirad A, Tabatabai SA, Faizi M, Kebriaeezadeh A, Mehrabi N, Dalvandi A, Shafiee A. Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles. Bioorg Med; 2004.
19. Costa MS, Boechat N, Rangel EA, Silva FDCD, Souza AMTD, Rodrigues CR, Castro HC, Junior IN, Lourenc MCS, Wardell SMSV, Ferreirab VF, Synthesis, tuberculosis inhibitory activity, and SAR study of N-substituted-phenyl- 1,2,3-triazole derivatives. Bioorg. Med. Chem. 2006;14:8644-8653.
20. Buckle DR, Outred DJ, Rockell CJM, SmithV, Spicer BA. Studies on v-triazoles. 7. Antiallergic 9-oxo- 1H,9H-benzopyrano [2,3-d]-v-triazoles. J. Med. Chem. 1983; 26:251-254.
21. Wang XL, Wan K, Zhou CH. Synthesis of novel sulfanilamide-derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities. Eur. J. Med. Chem. 2010;45:4631-639.
22. Fray MJ, Bull DJ, Carr CL, Gautier ECL, Mowbray CE, Stobie A. Structure activity relationships of 1,4-dihydro-(1H,4H)-quinoxaline-2,3-dionesas N-methyl-D-aspartate (glycine site) receptor antagonists. 1. Heterocyclic substituted 5-alkyl derivatives. J. Med. Chem. 2001;24:1951-1962.
23. Vantikommu J, Palle S, Reddy PS, Ramanatham V, Khagga M, Pallapothula VR. Synthesis and cytotoxicity evaluation of nove 1,4-disubstituted 1,2,3-triazoles via CuIcatalysed 1,3-dipolar cycloaddition. Eur. J. Med. Chem. 2010;45:5044-5050.
24. Reddy DM, Srinivas J, Chashoo G, Saxena AK, Kumar HMS. 4b-[(4- Alkyl)-1,2,3-triazol-1-yl] podophyllotoxins as anticancer compounds: Design, synthesis and biological evaluation. Eur. J. Med. Chem. 2011;46:1983-1991.
25. Carta F, Aggarwal M, Maresca A, McKenna R, Masini E, Supuran CT. Dithiocarbamates strongly inhibit carbonic anhydrases and show antiglaucoma action *In vivo*. J. Med. Chem. 2012;55:1721-1730.
26. Wang XJ, Xu HW, Guo LL, Guo X, Zheng CX, Liu HM. Synthesis and *In vitro* antitumor activity of new butenolide-containing dithiocarbamates. Bioorg. Med. Chem. Lett. 2011;21:3074-3077.
27. Zheng YC, Wang LZ, Zhao LJ, Zhao LJ, Zhan QN, Ma JL, et al. 1,2,3-Triazole-dithiocarbamate hybrids, a group of novel cell active SIRT1 inhibitors. Cellular Physiology and Biochemistry. 2016;38(1): 185–193.
28. Ying-Chao D, Yong-Cheng M, En Zhang XS, Meng-Meng W, Xian-Wei Y, Hong-Min L. Design and synthesis of novel 1,2,3-triazole-dithiocarbamate hybrids as potential anticancer agents. European Journal of Medicinal Chemistry. 2013;62:11-19.
29. Pourbasheer E, Aalizadeh R, Ganjali MR, Norouzi P, Shadmanesh J. QSAR study of ACK1 inhibitors by genetic algorithm–multiple linear regression (GA–MLR). Journal of Saudi Chemical Society. 2014;18:681–688.
30. David CY. Computational chemistry: A Practical guide for applying techniques to real-world problems copyright. John Wiley & Sons, Inc. 2001. ISBNs: 0-471-33368-9 (Hardback); 0-471-22065-5 (Electronic).
31. Leonard JT, Roy K. On selection of training and test sets for the development of predictive QSAR models. QSAR & Combinatorial Science. 2006;25:235-251.
32. Gfeller D, Grosdidier A, Wirth M, Daina A, Michielin O, Zoete V. Swiss target prediction: A web server for target prediction of bioactive small molecules. Nucl. Acids Res. 2014;42:32-38.
33. Tewari AK, Singh VP, Yadav P, Gupta G, Singh A, Goel RK, Shinde P, Mohan CG. Synthesis, biological evaluation and molecular modeling study of pyrazole derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Bioorg. Chem. 2014;56:8–15.
34. Spartan 14, wavefunction, INC, Irvine CA 92612, USA.
35. Becke AD, Density-functional thermo-chemistry. III. The role of exact exchange. J. Chem. Phys. 1993;98:5648-5652.
36. Lee C, Yang W, Parr RG. Development of the colle-salvetti correlation-energy

formula into a functional of the electron density Phys. Rev, B. 1988;37:785-789.
37. Herman MD, Moche M, Flodin S, Welin M, Treasaugues L, Johansson I, Nilsson M, Nordlund P, Nyman T. Human BIR3 domain of Baculoviral. Inhibitor of Apoptosis Repeat- Containing 3 (BIRC3). Acta Crystallogr Sect F Struct Biol Cryst Commun. 2009;65:1091.
38. Trott O, Olson AJ. Auto Dock Vina: Improving the speed and accuracyof docking with a new scoring function, efficient optimization and multithreading. Journal of Computational Chemistry. 2010;31:455-461.
39. Biovia. Wateridge vista drive, San Diego, CA92121, USA; 2005.

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