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RESEARCH ARTICLE

Insightful Bio-Evaluation of 1,2,4-Thiadiazole-1,2,4-Triazole derivatives as Anti-ubiquitin Ligase Down-regulating Human Lung Cancer.

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ABSTRACT

Human lung cancer still remains one of the dangerous diseases among human being worldwide. The danger of this disease in medical world remains colossal and this has drawn the attention of seasoned researcher to find lasting solution to this menace. Thus, eight 1,2,4-thiadiazole-1,2,4-triazole derivatives were investigated to observe their anti-ubiquitin ligase thereby reducing human lung cancer. The software used to achieve this work were Spartan 14 (optimization), PANDEL (for generating 2D descriptors), Pymol (for treating downloaded protein), Autodock Tool (for locating binding site in the downloaded protein and for converting ligand and receptor to .pdbqt format from .pdb format), Auto dock vina (for docking calculation) and discovery studio (for viewing the non-bonding interaction between the docked complexes). Ten 2D descriptors were selected from the entire descriptors in order to describe anti-ubiquitin ligase properties of 1,2,4-thiadiazole-1,2,4-triazole derivatives. Also, the developed QSAR model was observed to be predictive using the closeness the experimental IC50 to the predicted IC50 as well as the correlation coefficient (0.990) and adjusted correlation coefficient (0.976). More so, the calculated binding showed that compound **h** (-6.9 kcal/mol) possess ability to inhibit ubiquitin ligase than other studied compounds as well as Etoposide (Standard).

Keywords: 1,2,4-Thiadiazole, ubiquitin ligase, 1,2,4-Triazole, cancer, QSAR, Molecular docking

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INTRODUCTION

One of the most challenging health problems amidst human being globally is still cancer [1]. Its position among other dangerous diseases causing death remains the second [2-4]. As reported by many researchers, lung, colon and prostate cancer exists in men, breast, lung, rectum cancer can also be found in women [5, 6]. According to Georgios et al., (2019) and Wu et al., (2104), more than 70% of the cancer related death in the world could be linked to under-developed and developing countries [7, 8]. Also, Molina et al., (2008) reported that early detection of cancer in human being and apt treatment via surgery or radiation or chemotherapy could cure cancer [9].

The role of ubiquitin ligase right from the time it was discovered by a scientist in 1975 in maintaining cell homeostasis and determining the magnitude and worth of several proteins cannot be overemphasized [10]. According to Zheng et al., 2016 malfunction of ubiquitin result to several illnesses in human being [11]. The control of ubiquitin in human cell has several faces and it role cut across transcriptional level, posttranslational levels and protein level [12,13].

Moreover, the role of Nitrogen in heterocycles in drug development can never be overemphasize. According to investigation by Kaur *et al*., (2017) and Kapron *et al* (2019), the Nitrogen present in Triazole possesses the ability to form hydrogen bond targeting suitable site thereby improving its toxicological and pharmacological features [14,15]. Relationship between triazole and its derivatives have been liked with therapeutic features by many researchers such as antioxidant [16], anti-inflammatory [17, 18], tubulin inhibitors [19], analgesics [20, 21], anticancer [22], diuretics [23], antimicrobial [24, 25]. More so, thiadiazole has drawn the attention of many scientists due to its immense therapeutic features [26]. It has been investigated to have the many biological activities like antioxidant, anti-inflammatory, central nervous system (CNS) depressant, anti-bacterial, analgesic, anti-cancer, anti-diabetic, anti-hypertensive, and anti-tubercular activities, diuretic [27–36].

The non-bonding interactions such as conventional hydrogen bond, carbon hydrogen bond, Pi-Sigma, Pi-Pi stacked, Pi-Pi T-shaped, Pi-Alkyl, Pi-anion and Pi-cation are imperative in observing biological properties (such as enzyme inhibition) between the ligand-protein complex [37-39]. According to Oladipo 2021, docking expose facts about drug-protein relationship by detecting the active gouge in the protein and calculation of binding affinity [40].

Thus, the aim of this work is identifying the descriptors describing anti- ubiquitin ligase down regulating lung cancer and developing efficient quantitative structural activities relationship (QSAR) model using selected descriptor as well as observing non-bonding interaction existing between 1,2,4-thiadiazole-1,2,4-triazole derivatives and ubiquitin ligase (PDB ID:2oo9) [41]

COMPUTATIONAL DETAILS

Quantum Chemical Calculations

The studied 1,2,4-thiadiazole-1,2,4-triazole derivatives were optimized via density functional theory using 6-31G* as basis set. In density functional theory method, three-parameter density functional which includes Becke's gradient exchange correction [42] and the Lee, Yang, Parr correlation functional. According to Semire *et al.,* (2017), it was reported that the accuracy of density functional theory (DFT) calculations is a function of the chosen basis set [43]; thus, 6-31G* was used for optimization of the studied compounds. The studied compounds were (5-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1*H*-1,2,4-Triazol-1-yl)(Phenyl)Methanone (**a**), (3,4,5-Trimethoxyphenyl)(5-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1*H*-1,2,4-Triazol-1-yl)Methanone (**b**), (3,5-Dimethoxyphenyl)(5-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1*H*-1,2,4-Triazol-1-yl)Methanone (**c**), (4-Methoxyphenyl)(5-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1*H*-1,2,4-Triazol-1-yl)Methanone (**d**), (5-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1*H*-1,2,4-Triazol-1-yl)(4-Nitrophenyl)Methanone (**e**), (4-Chlorophenyl)(5-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1*H*-1,2,4-Triazol-1-yl)Methanone (**f**), 4-[(5-(3,4,5-Trimethoxyphenyl)-3-4-[3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl]Phenyl-1*H*-1,2,4-Triazol-1-yl)Carbonyl]Benzonitrile (**g**), (5-

(3,4,5-Trimethoxyphenyl)-3-(4-(3-(3,4,5-Trimethoxyphenyl)-1,2,4-Thiadiazol-5-yl)Phenyl)-1*H*-1,2,4-Triazol-1-yl)(*p*-Tolyl)Methanone (**h**) (Figure 1) [44].

Quantitative Structure-Activity Relationship Study

Experimental data set division

The optimised compounds were divided into two divisions "training set (80%) and test set (20%)" by using Kennard stone algorithm approach via Dataset Division GUI 1.2 software [45, 46]. The selected compounds for training set were used for developing reliable QSAR model while the compounds for test set were used to validate the predictability of the developed QSAR model (Eqn 1).

IC_{50} = 2.249935730(AMR) - 0.072798159(ATS0V) + 0.030197911(ATS2V) + 253.444092170----------(1)

R^2= 0.990, Adj R^2= 0.976, F-value = 21.78, P-value ≤0.001, CV.R^2=0.772

Validation of Developed QSAR Model

The use of correlation coefficient in ascertaining the efficiency of develop model in QSAR study is not enough; this need validation of QSAR model where dependability and predicting ability of developed QSAR model can be confirmed [47]; therefore, internal and external validation via training set and the test set were studied respectively.

Docking Study

The docking study was investigated on 1,2,4-Thiadiazole-1,2,4-Triazole and epidermal growth factor receptor kinase with PDB ID: 2oo9 downloaded from protein data bank (www.rcsb.org). The receptor was treated using EduPyMOL-v1.7.4.4-Win32 and the treated receptor was subjected to Autodock tool 1.5.6 so as to locate binding site and then converted to .pdbqt format in preparation for docking calculation using autodock vina 1.1.2. The observed grid box was as follows: center (X = 39.092, Y = 11.874, Z = -7.241) and size (X = 40, Y = 40, Z = 40) as well as the spacing was set to be 1.00Å.

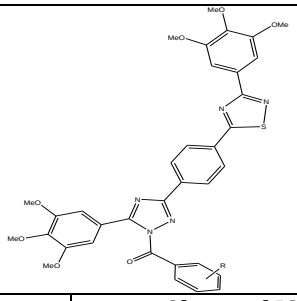
RESULT AND DISCUSSION

Optimization and QSAR Study

The obtained calculated 2D descriptors were divided into two sets (Training and Test Sets) and were screened in order to identify the descriptors that describe anti-ubiquitin ligase activities of the studied compounds. The observed IC_{50} served as the dependent variable while the selected 2D descriptors (AMR, ATS0V and ATS2V) served as independent variables which were further used to develop QSAR model using Material studio software. As shown in the developed model (Eqn 1), it was observed that increment in AMR and ATS2V led to a reliable inhibition concentration (IC_{50}) for individual studied compound and decrease in ATS0V also resulted to a reliable inhibition concentration (IC_{50}) for each of the ligand investigated in this work.

As shown in Table 1, the predicted IC_{50} values were closer to the experimental IC_{50} which was also confirmed via correlation coefficient (R_2) (0.990), since the correlation coefficient (R^2) cannot be greater than 1, and the closer the calculated R^2 to 1, the closer the predicted IC_{50} to the experimental IC_{50} thereby revealing the efficiency and reliability of the developed model (Figure 1). The experimental IC_{50} and the predicted IC_{50} were 2.98, 2.44; 0.17, 1.69; 1.79, 0.41; 2.10, 2.21; 1.64, 154; 169, 1.65; 1.90,-1.55; 11.50, 11.35 for compound **a** to compound **h.** The descriptors involved in the developed model were AMR, ATS0V and ATS2V (Table 2). More so, as reported by Oyebamiji and Semire 2020, [39], correlation coefficient (R^2) is not enough to ascertain the dependability of any developed model which therefore called for validation of the developed model by considering adjusted correlation coefficient (Adj R^2) (≥0.6) and cross validation (CV.R^2) (≥0.5); thus, the value for the calculated adjusted R^2 and the cross validation (CV.R^2) confirm the predicting ability of the developed model.

Table 1: Schematic structures of 1,2,4-Thiadiazole-1,2,4-Triazole derivatives



	R	Observed IC_{50}	Predicted IC_{50}
a*	H	2.98	2.44
b	3,4,5-trimethoxy	0.17	1.69
c	3,5-dimethoxy	1.79	0.41
d	4-methoxy	2.10	2.21
e	4-nitro	1.64	1.54
f	4-chloro	1.69	1.65
g*	4-cyano	1.90	-1.55
h	4-methyl	11.50	11.35
Etoposide	-	3.08	-

**denote Test set*

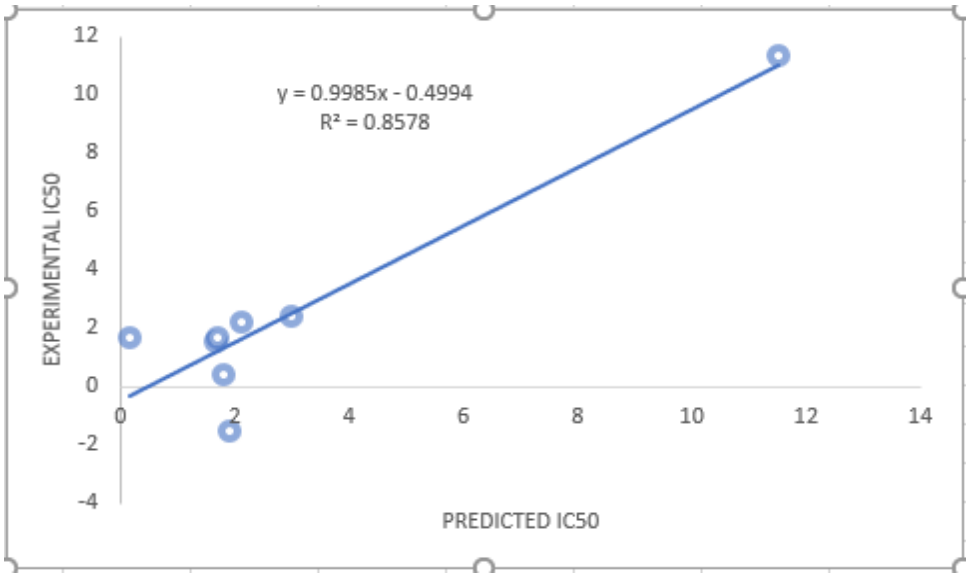


Figure 1: Correlation between the Experimental IC_{50} and Predicted IC_{50}

Table 2: Calculated Descriptors from optimized 1,2,4-Thiadiazole-1,2,4-Triazole derivatives

	AMR	ATS0m	ATS1m	ATS0v	ATS1v	ATS2v	ATS3p	ATS4p	AATS4p	AATS5p
A1	59.12	8881.34	9433.34	19114.77	23469.5	33363.67	255.93	279.82	1.5632	1.44
A2	81.07	10088.13	10658.98	21221	25974.3	36780.06	284.62	325.69	1.55	1.39
A3	82.34	9978.463	10587.39	21490.29	26445.35	37292.23	286.92	323.27	1.57	1.42
A4	66.44	9283.606	9841.89	19816.85	24304.43	34502.47	265.48	294.71	1.55	1.41
A5	63.01	9588.458	10037.68	19759.78	24134.69	34598.07	263.31	288.61	1.54	1.43
A6	64.74	10137.03	9847.03	19587.66	23816.76	34058.19	263.00	284.36	1.58	1.46
A7	65.32	9220.786	9733.74	19750.52	24099.29	34302.24	264.29	287.97	1.57	1.45
A8	64.63	9027.638	9601.82	19600.46	24122.49	34418.69	267.30	292.18	1.52	1.42

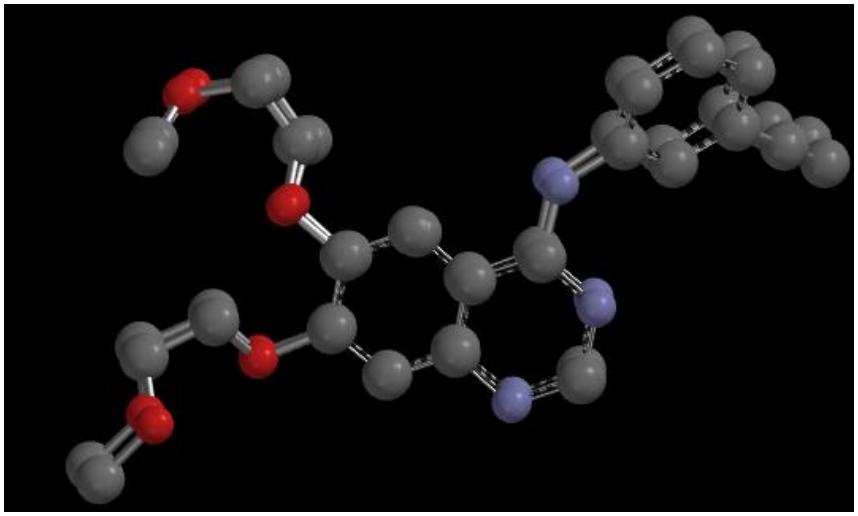


Figure 2: Overlay of native drug-like compounds over re-docked drug compound

Molecular Docking Study

In this work, the employed docking method was validated by re-docking the native ligand into the active gouge of ubiquitin ligase (PDB ID: 2oo9) in order to observe the similarity between the re-docked ligand with the best conformation to the posture of the native molecule (Figure 2). Therefore, the observed similarity and the root mean square deviation (RMSD) between the re-docked native molecule and the native ligand were nearer to 1; hence, this proved the dependability of the molecular docking method used. Therefore, this docking method was employed to study the non-bonding interaction between the studied 1,2,4-thiadiazole-1,2,4-triazole derivatives and ubiquitin ligase (PDB ID: 2oo9) as well as to calculate the binding affinity between the complex. The calculated binding affinity for compound **a** – **h** is -6.6kcal/mol, -6.1kcal/mol, -6.7 kcal/mol, -6.6 kcal/mol, -6.5 kcal/mol, -6.8 kcal/mol, -6.7 kcal/mol and -6.9 kcal/mol respectively. It was observed that the calculated binding affinity for the studied compounds were higher (in term of negativity) than etoposide (Standard) except for compound **b**. More so, compound **h** (-6.9kcal/mol) proved to inhibit well than other studied compounds (Figure 3). The residue involve in the interaction were displayed in figure 3.

More so, three sets of compound which were designed by adding new derivatives to the parent compound were proposed in this work. The proposed compounds were docked against ubiquitin Ligase and the calculated binding affinity were -6.3 kcal/mol, -6.2 kcal/mol, -6.1 kcal/mol (Table 4). It was observed that **PC1** and **PC2** have the ability to inhibit ubiquitin ligase than the referenced drug.

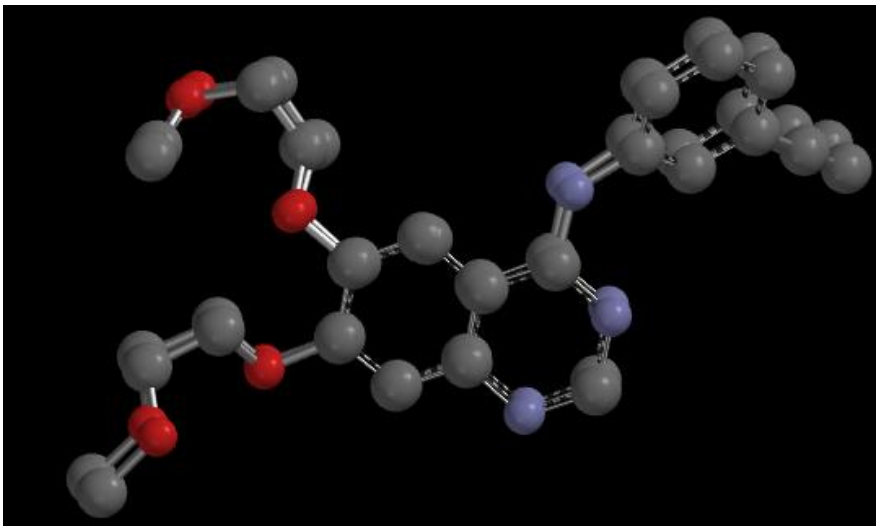
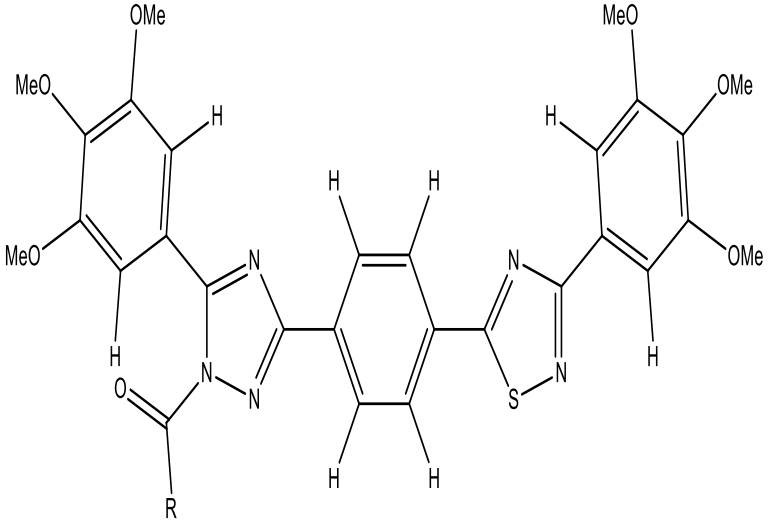


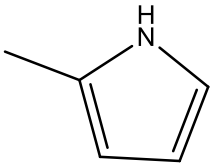
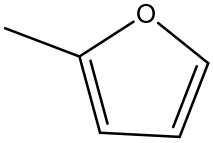
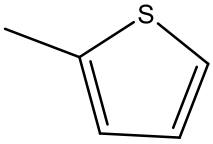
Figure 2: Overlay of native drug-like compounds over re-docked drug compound

Table 3: Calculated binding affinity and residues involved in the interaction

	Binding Affinity (kcal/mol)	Residues involved in the interactions	Types of Non-bonding interaction involved
a	-6.6	Ile861, Tyr871, Ser866, Glu862, Leu857	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Pi T-Shaped, Pi-Alkyl
b	-6.1	Arg893, Asn863, Gln867, Lys889, Ile885	Conventional hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Alkyl
c	-6.7	Lys876, Asp873, Ala896, Ile891, Phe895, Ala888, Asn890	Van der waals, Conventional Hydrogen bond, carbon hydrogen bond, Pi-Pi Stacked, Amide-Pi Stacked, Pi-Alkyl
d	-6.6	Ser855, Tyr871, Glu862, Ser866, Ile861, Leu857	Conventional Hydrogen bond, carbon hydrogen bond, Pi-Pi T-shaped, Pi-Alkyl
e	-6.5	Ser866, Ile861, Ser855	Conventional Hydrogen bond, Unfavourable Donor-Donor, Pi-Alkyl
f	-6.8	Asp-873, Ala896, Phe895, Ile891, Ile880, Ala881	Conventional Hydrogen bond, Carbon hydrogen bond, Pi-Anion, Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl
g	-6.7	Lys876, Phe895, Ile891, Ile880, Ala881, Ala 896	Carbon Hydrogen Bond, Unfavorable Donor- Donor, Pi-Sigma, Pi-Pi Stacked, Pi-Pi T-Shaped, Pi-Alkyl
h	-6.9	Ile861, Tyr869, Ser866, Glu862, Tyr871, Gln872, Gln875	Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavorable Acceptor-Acceptor, Pi-Pi Stacked, Pi-Akyl
Etoposide	-6.1	Phe895, Ile891, Ala888, Asn884, Asn890	Conventional Hydrogen Bond, Pi-Pi Stacked, Amide-Pi Stacked, Akyl, Pi-Akyl

Table 4: Proposed 1,2,4-thiadiazole-1,2,4-triazole based compounds



	R	Binding Affinity (kcal/mol)
PC1		-6.3
PC2		-6.2
PC3		-6.1

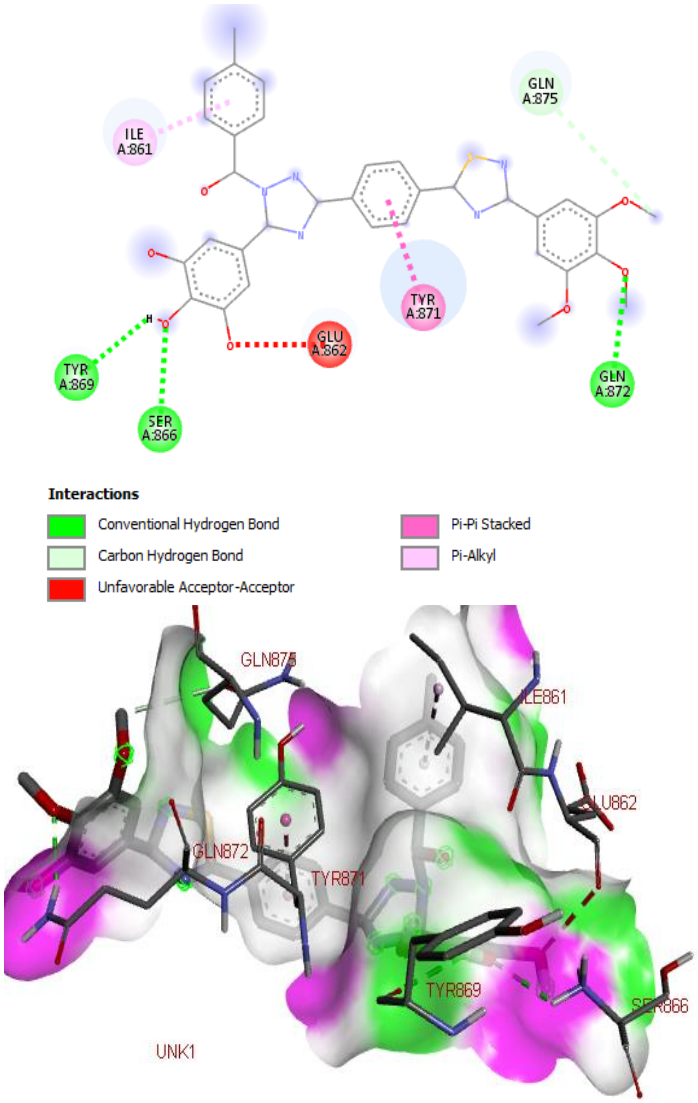


Figure 4: Residual interactions between compound h and ubiquitin Ligase (PDB ID: 2oo9)

CONCLUSION

Human lung cancer still remains a dangerous disease affecting both female and male globally. Also, the role played by 1,2,4-thiadiazole-1,2,4-triazole derivatives in drug design cannot be overemphasized. Thus, anti-ubiquitin ligase properties of 1,2,4-thiadiazole-1,2,4-triazole derivatives was investigated using quantum chemical method, and docking software (Pymol, Autodock Tool, Auto dock vina and discovery studio). It was discovered that the calculated descriptors described the anti-ubiquitin Ligase and the developed QSAR model was confirmed to be predictive via correlation coefficient, adjusted correlation coefficient, p-value and mean square error. The predicted IC_{50} was observed to be closer to the experimental IC_{50} and this also revealed the dependability of the developed QSAR model which therefore helped in designing five set of new compounds and predicting their biological activities. Also, compound "**a**" proved to inhibit better than other studied compounds as well as the standard used. It was discovered that the effect of substituents attached to the studied parent compound played a major role in the interaction between the studied compounds and the receptor. Hence, the developed QSAR model will assist in designing and developing more efficient drug like compounds.

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Declarations

All authors contributed equally

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Competing interest statement

The authors declare no conflict of interest.

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