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Synthesis, characterization, anticancer, and antioxidant studies of new azo-Schiff compounds derived from 2-naphthol

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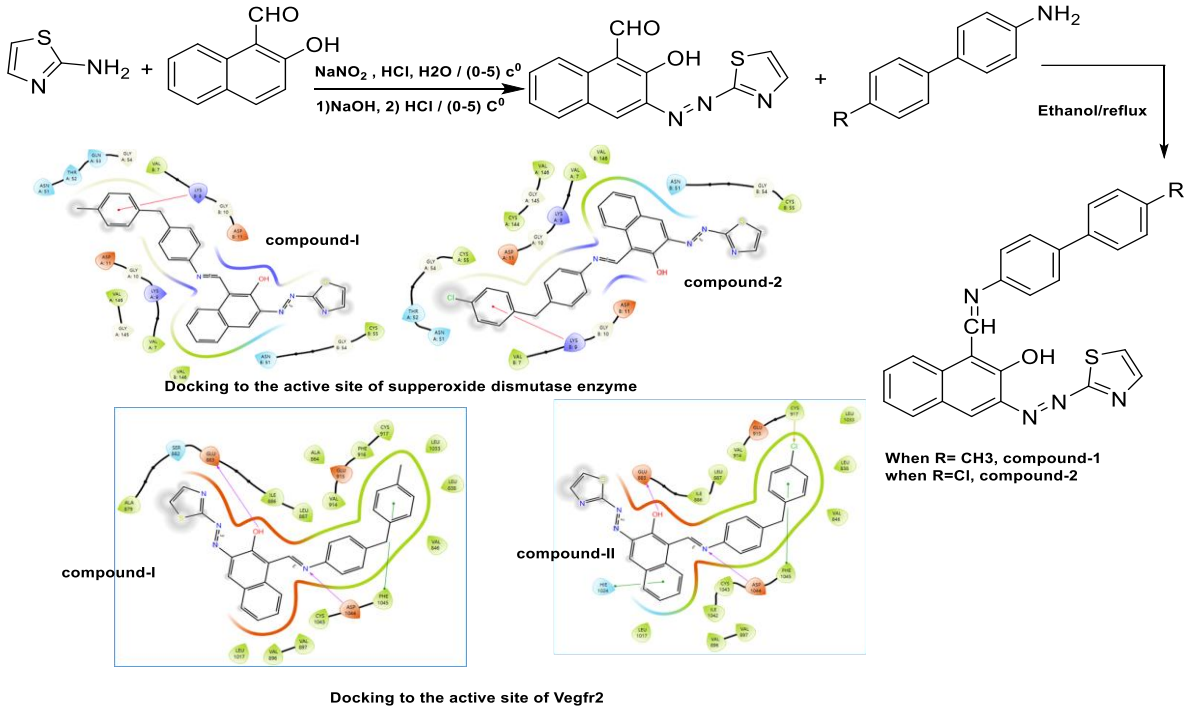
ABSTRACT

Two new 2-naphthol-thiazole-azo compound Schiff bases of potential antitumor and/or antioxidant influences were chemically synthesized. The synthesized Schiff bases structures were identified using elemental analysis (CHN), mass spectroscopy, Fourier transform infrared FTIR & 1HNMR spectral techniques. The geometrical optimization as well as electronic structure predications of our compounds were obtained using quantum chemical calculations through DFT/B3LYP/6-31+G (d). The computational analysis had demonstrated a close interaction between both theoretical and experimental data. Finally, compound (1) had been evaluated for its anticancer activity against MCF-7 and WRL68 cell lines, which had shown a good anticancer effect. However, the antioxidant activity of both compounds (1&2) is evaluated using DPPH scavenger and had demonstrated a good antioxidant activity. In conclusion, the inclusion of C3-*α*-naphthyl-azo-thiazinyl nucleus was essential for exploiting both in vitro anticancer as well as antioxidant influences. Docking study had revealed that compound 2 had more binding affinity to Vegfr2 than compound 1 due to the additional binding interactions of compound 2 as compared to compound 1, however, both had shared hydrogen bonding interactions with the same amino acid, Glu 883 and Asp 1044 of sorafenib. Meanwhile, compound 2 had some of priority in binding affinity than compound 1 to the active site superoxide dismutase enzyme although interactions was weaker than that of ascorbic acid. In conclusion, the inclusion of C3-*α*-naphthyl-azo-thiazinyl nucleus in the azo-Schiff base scaffold structure was essential for exploiting both in vitro anticancer as well as antioxidant influences.

Keywords: Schiff base, 2-naphthol, Azo, 2-amino-1,3-thiazole, antioxidant, anticancer.

Graphical Abstract:



1.INTRODUCTION

Heteroaromatic amines azo compounds and their metal complexes have gained a great deal of attention of diverse research groups owing to their biological activities such as antibacterial effect Kandil, (1988), analytical Eltaboni et al., (2022), and others on one hand. On the other hand, Schiff base, imine or also known as azomethine (C=N) functionality, is also of outstanding extensively diverse significant biological influences Hussain et al., (2014), Al-Amiery et al., (2012) including implications in biochemical investigations Pradhan et al., (2015), Bravo et al., (2017), antibacterial Login et al., (2019), Ceramella et al., (2022), antifungal Ceramella et al., (2022), Bharti et al., (2010), antimalarial Harpstrite et al., (2008), antiviral Linda et al., (2021), anti-proliferative Sharma et al., (2020), anti-cancer Sharma et al., (2020); De-Santana et al., (2018), antioxidant Taha et al., (2013), anti-inflammatory Geronikaki et al., (2003), as well as properties.

These multiple influences are attributed to the Schiff bases remarkable electronic distribution, charge density, mechanical, molecular shapes/sizes, redox potential as well as biological properties Patel, (2010), Abdulhadi et al., (2020), hence, contributing to drug evolution (Kaushik et al., 2023; Elsadek et al., 2021). Furthermore, thiazole, is a characteristically famous pharmacophoric moiety in modern drug design as well as lead molecule development as their compounds are reported to exploit broad spectrum of biological influences such as antibacterial Kubba and Rahim, (2018), Chen et al., (2017), anti-mycobacterial Al-Balas et al., (2009), antifungal Yadlapalli et al., (2013), Ejaz et al., (2019), antiviral Décor et al., (2013), Bhattacharya et al., (2005) especially anti-HIV Sadeek et al., (2023), antiprotozoal Jadav et al., (2020), anthelmintic De-Oliveira et al., (2018), antitumor Suresh et al., (2018), Zhang et al., (2018) via various modes of action including kinases inhibition Li et al., (2010), anti-inflammatory Sinha et al., (2018), Gouda et al., (2014), analgesic Gouda et al., (2014) , antioxidant Al-Thakafy et al., (2024), Khan et al., (2020), anti-thrombotic via non fibrinogen receptor antagonism Badorc et al., (1997), adenosine receptor antagonists (Pandya et al., 2015), ...etc.

In fact, some thiazol pharmacophore containing tyrosine kinase inhibitor anticancer drugs such as Dabrafenib and Dasatinib have been approved by the FDA and marketed. Moreover, thiazole pharmacophore Schiff bases are extensively reported to exhibit various biological significant influences such as enzymes inhibitor, antibacterial against gram positive and gram negative bacteria like

Pseudomonas aeruginosa especially those with p-electron donating group substituted phenyl substituent Azam et al., (2007), Lemilemu et al., (2021), antifungal such as against various *Candida* and *Aspergillus* species Lemilemu et al., (2021), Bhuiyan and Rahman, (2010), Vinusha et al., (2015), anthelmintic Amnerkar et al., (2015), antioxidant in both in vitro as well as Insilco molecular docking studies Lemilemu et al., (2021), anti-inflammatory Lemilemu et al., (2021), Chandak et al., (2014), Karabasannavar et al., (2017), as well as antitumor Lemilemu et al., (2021) influences.

In fact, 2-benzylideneaminonaphthothiazoles of very suitable physicochemical properties of drug candidate action since these schiff base compounds of thiazole pharmacophore, and imine functionality, the naphthyl group granted lipophilicity has contributed to the penetration power of the principally different bacterial bio-membranes especially those with 2` hydroxyl group (Azam et al., 2007; Palanimurugan and Kulandaisamy, 2018). One of the proposed mode of action for thiazole pharmacophore Schiff bases antimicrobial/anticancer influences is via microbial cells critical active centres-azomethine functionality H-bonding, hence, interfering with their cellular viability and growth (Palanimurugan and Kulandaisamy, 2018). The aim of our study is to investigate the in vitro biological as well as in silco antitumor and antioxidant influences of two new C3-*α*-naphthyl-azo-thiazinyl Schiff bases besides in silco investigation of their physicochemical parameters.

2. MATERIALS AND METHODS

Experimental

Chemicals and reagents used are of analytical grade, purchased from (Sigma-Aldrich). 2-Aminobenzyleamine 98%, Ortho vaniline, Vaniline, Salicylaldehyde, Diphenyle Picryl Hydrazyl, CuCl2.2H2O. SMP31 melting point apparatus is used for melting points measurements, and affinity (Shimadzu) spectrophotometer using KBr pellets was used for FTIR spectral analysis of the synthesized compounds. DMSO-d6 on the Bruker 500MHZ instrument, using TMS as internal standard were used for 1H NMR and 13C NMR spectral analysis. Perkin_Elmer_automatical instruments, and selective Detector 5973 were used for both elemental microanalysis and mass spectral analysis respectively. Electronic spectral inform were accomplished depending on GERMANY-BG(T60UV).

General procedure for the preparation of azo compound:

The azo compounds were prepared as reported Ali et al., (2023) through mixing (0.1g, 0.01 mol) of 2-aminothiazole in (10 ml) of 36% HCl in (10 ml) distilled water while solution temperature was kept between 0-5°C. Then, to that acidic solution, 8 ml of (0. 69 g, 0.01 mol) NaNO2 aqueous solution was added drop wise to produce diazonium chloride solution. The resulted diazonium chloride solution, was added to a cold ethanolic solution of (1.72 g, 01 mmol) 2-hydroxy-1-naphthaldehyde dissolved in 10% NaOH. The resulted mixture is kept under constant stirring for 2h then acidified with 1 mL of conc. HCl in (pH = 2-4). The resulted orange color precipitated product was filtered, washed several times with distilled water till the filtrate was neutral, and recrystallized from a hydroethanolic solution and dried.

Synthesis Schiff base

Schiff base was synthesized as reported Al-Redha et al., (2022) where a (15 ml) ethanolic solution (0.3 g, 5 mmol) of the azo compound was added to a 15 ml ethanolic solution of (5mmol of the corresponding aldehyde: 4-(4-methylbenzyl) aniline for compound (1) or 4-(4-chlorobenzyl) aniline for compound (2) acidified with 3 drops of glacial acetic acid. The obtained mixture was refluxed for 3hr with constant stirring to produce an orange color precipitate. The precipitated product was filtered then washed with cold EtOH several times. The scheme of synthesis is illustrated in Figure (1), structure elucidation is based on CHN elemental analysis besides, FTIR, 1HNMR and Mass spectral analysis.

Biological studies

Antioxidant effect

Ascorbic acid was used as a positive reference to investigate the antioxidant activity of the azo Schiff compounds. A series of standards different concentrations (200, 100,50 ,25 and 12.5 µg/ml) of ascorbic acid solution were prepared in water. A 6 ml amount of (45 µg/ml) DPPH solution was added to 100 µl of each of the normal solutions of the compounds. The mixed solutions were incubated for 30 minutes at room temperature in the dark place. Then, the reaction mixture absorbance was taken at 517 nm. 100 µl of each sample

solution was mixed with 6 ml (45 μg/ml) DPPH dissolved in ethanol. The change in the DPPH concentration was determined through measuring the solution absorbance at 517 nm. The DPPH radical scavenging activity of compounds is visually observed as a change in the color of the solution as DPPH• from violet to yellow as a result of its reduction to the non-radical state by mean of a proton or electron donor (Kareem et al., 2021; Borah et al., 2019). The percentage of DPPH radical scavenger was calculated using the following equation:

$$\text{DPPH scavenging ability (\%)} = [\text{A control} - \text{A sample} / \text{A control}] \times 100$$

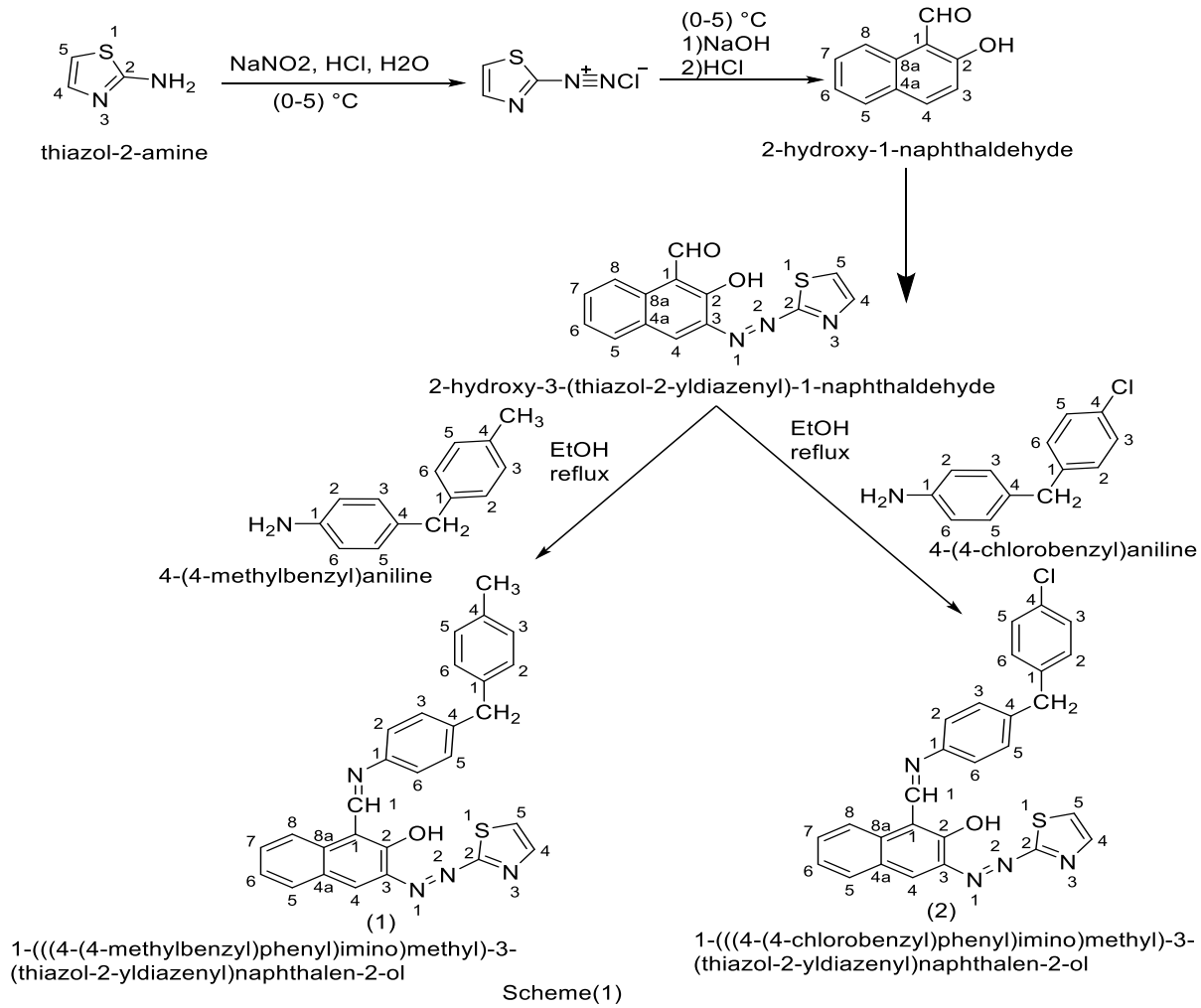


Figure 1 The Scheme of synthesis of the two new C3-*α*-naphthyl-azo-thiazinyl Schiff bases.

Assays for cell viability and cytotoxicity

The MTT assay was used to determine the viability of cells (Al-Adilee and Hasan, 2021). The synthesized Azo Schiff (compound 1) cytotoxicity was screened against MCF-7 and WRL68 cell lines (breast cancer cells). Therefore, the synthesized compounds were studied against a single dose concentration (100 μg/ml) of the MCF-7 cell line.

Insilco studies

Theoretical study

Calculations using DFT were utilized to determine the minimum geometrical structure at cam-b3lyp/6-31g (d) level of theory through applying Gaussian 09 programs (Rayati et al., 2010). The theoretical parameters were used in order to aid the describe molecular structure of the compounds under investigation molecular structure. Theoretically estimated, highest molecular occupied orbital (HOMO), the lowest molecular unoccupied orbital (LUMO), and some chemical quantum descriptors (CQDs) were used to study their properties.

Docking study

Molecular docking evaluation study and molecular modeling drug design were carried out by Glide software (Maestro 13.5) under Schrodinger software Schrodinger, (2023) running on Windows 10 operating system on workstation (Intel(R) Core(TM) i7-10750 @ 2.60 GHz, 16.00 GB). The crystal structure of the vascular endothelial growth factor receptor-2 (Vegfr2) with a benzimidazole-urea inhibitor were obtained from protein data bank under the PDB code: 2OH4 with 2.05 crystallographic resolution. Suitable programs were used for receptor preparation and optimization.

While, Ligprep program (prior to docking) was used for ligand structure preparation to determine and add of hydrogens for attaining optimal orientation and ionization position with low energy conformations of all ligands based on OPLS4 force field. The grid box was set through setting the atom of the ligand with keeping the default settings besides keeping the best docking orientation, then processing docking using glide and analysis. The result depends on docking score and interaction between our ligand and references drugs with amino acid residues. Types of interactions is shown in (Figure 1).

However, the superoxide dismutase enzyme (SOD) protein crystal structure (PDB: 1CB4) was retrieved from the protein data bank in Europe. (https://www.rcsb.org). After visualizing in Maestro Tool developed by the schrodinger. According to the active site exists in each CuZnSOD subunit posse a single copper ion linked to three histidine residues, projecting side chains for all reside. Docking processing has been done using glide and analysis. The result depends on docking score and interaction between our ligand and references drugs with amino acid residues. Types of interactions is shown in (Figure 2).

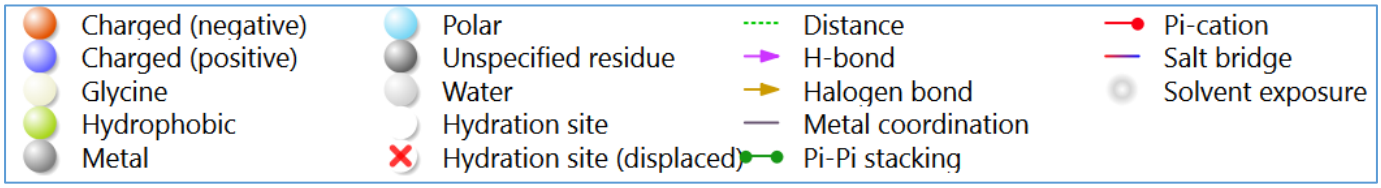


Figure 2 Represent the map for clarify bond interactions in 2D mode.

3. RESULTS AND DISCUSSION

Elemental Analysis

The elemental analysis results obtained for the synthesized Schiff bases were in accordance with those calculated for the proposed formula as shown in (Table 1). All compounds were stable at room temperature.

Table 1 The elemental analysis and physical properties

Compound	%found (calcul)			Color	m.p °C	%yield
	C	H	N			
C28H22N4OS	71.86(72.7)	5.35(4.79)	13.79(12.11)	brown	184-186	73%
C27H19ClN4OS	68.25(67.14)	2,79(3.97)	12.92(11.60)	red	212-215	69%

FTIR Spectrum

The FTIR spectra of the synthesized Schiff base compounds has given remarkable peaks reflecting a successful synthesis of compounds. The spectrum has shown a strong band at (3442- 3474) cm−1 which assigned to the stretching band of ν(OH) group Ali et al., (2015), a

weak band at (3042-3061) cm-1 corresponding to the (C-H) aromatic group, a sharp band has appeared at (1643-1645) cm-1 characteristic to the ν(C=N) imine linkage, indicating the Schiff bases formation. The two bands occur at (1592-1609) and (1588-1593) cm-1 indicate correspondece to the ν(C=C) and ν(N=N) functionalities respectively Al-Adilee and Hasan, (2021), Mahmoud et al., (2018) as shown in (Figures 3 and 4).

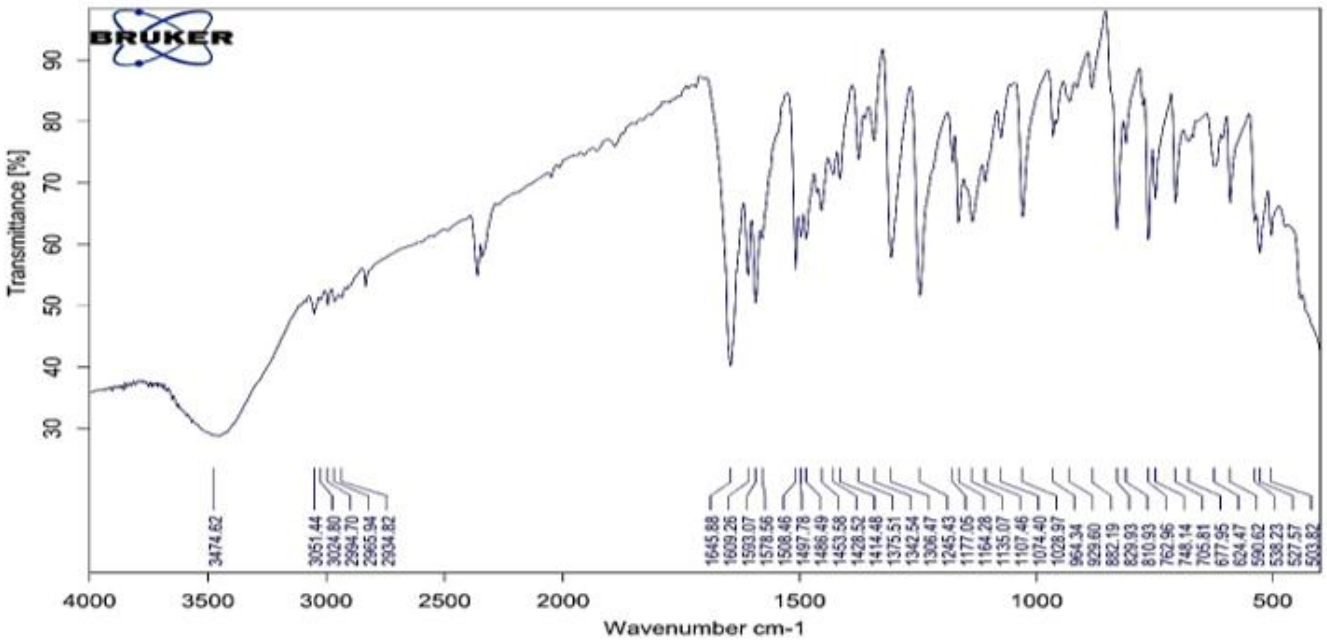


Figure 3 FTIR spectrum of the compounds (1)

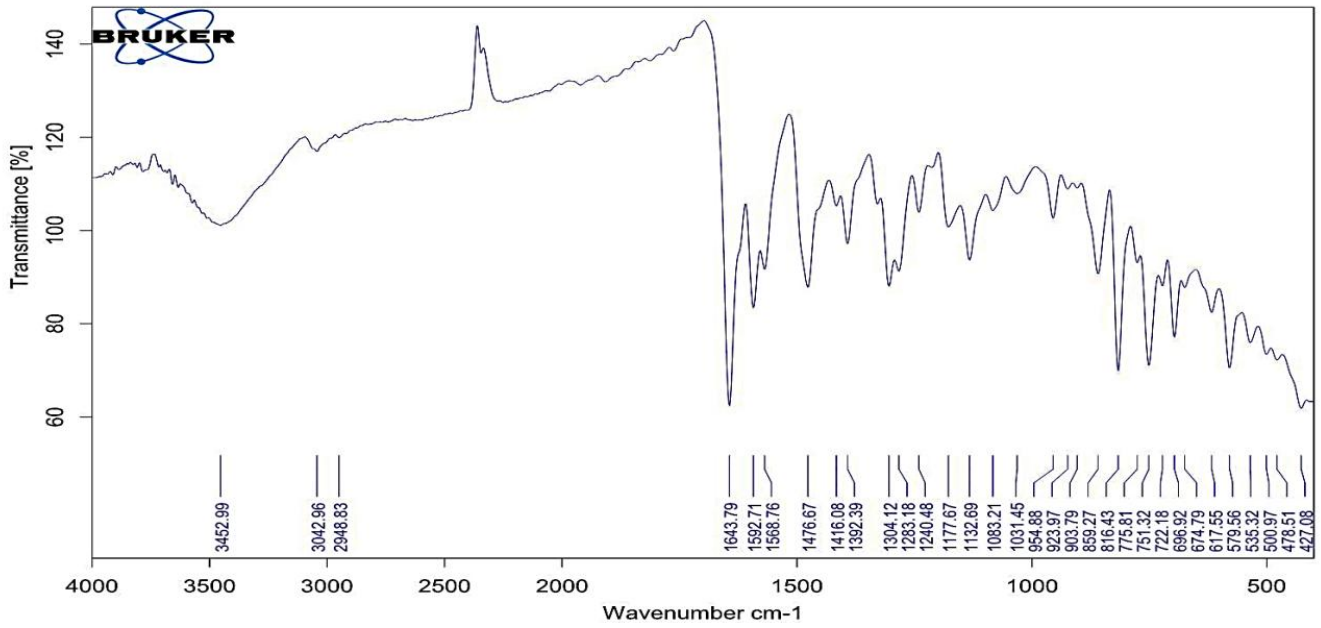


Figure 4 FTIR spectrum of the compounds (2)

HNMR Spectrum

The 1HNMR spectrum of the compound (1) has shown a peak perceived at δ (2.50) ppm, attributed to the chemical shifts of CH3. The peaks located at δ (4.06) ppm and multiple peaks at δ (6.62-8.48) ppm are assigned to the chemical shift of (CH2) protons and those of the aromatic rings respectively. The singlet signal located at δ (9.64) ppm is attributed to the azomethine functionality N=C–H proton. However, the singlet peak located at δ (15.86) ppm is correspondent to the phenolic (OH) proton Shaker et al., (2010), Al-Zoubi and Ko, (2020) as shown in (Figure 5).

The 1HNMR spectrum of the compound (2) has shown a peak perceived at δ (4.05) ppm assigned to the chemical shift of (CH2) protons, multiple peaks at δ (6.97-8.49) ppm assigned to the aromatic rings protons, and singlet signal located at δ (9.65) ppm attributed to the of the azomethine functionality N=C–H proton. However, the peak of singlet signal located at δ (15.86) ppm was attributed to the phenolic (OH) proton as shown in (Figure 6).

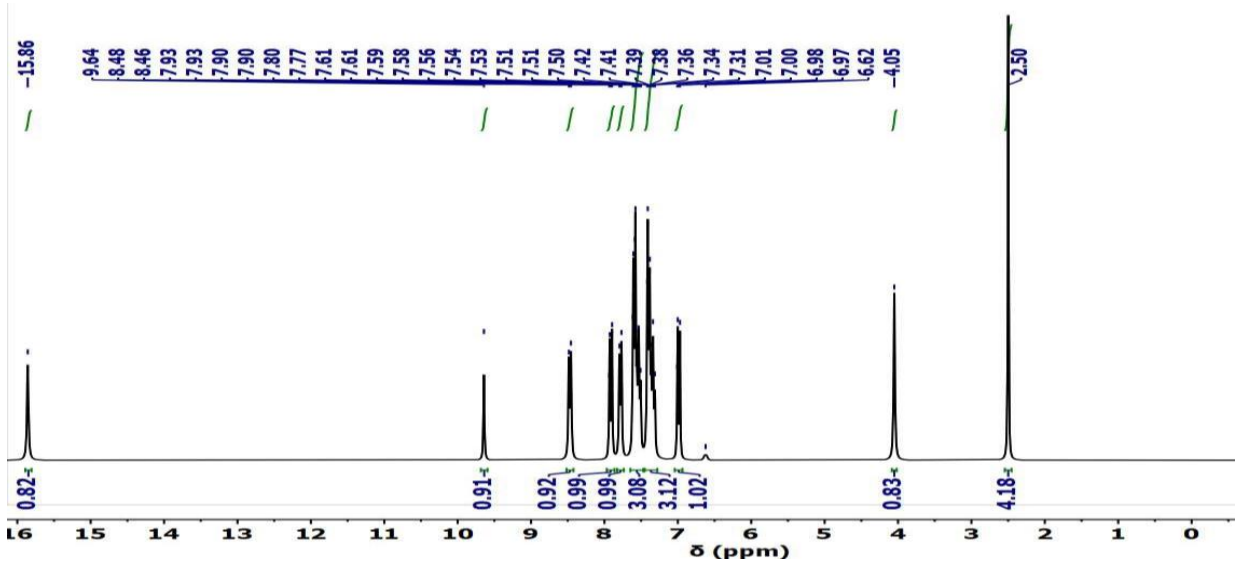


Figure 5 1HNMR of the compound (1)

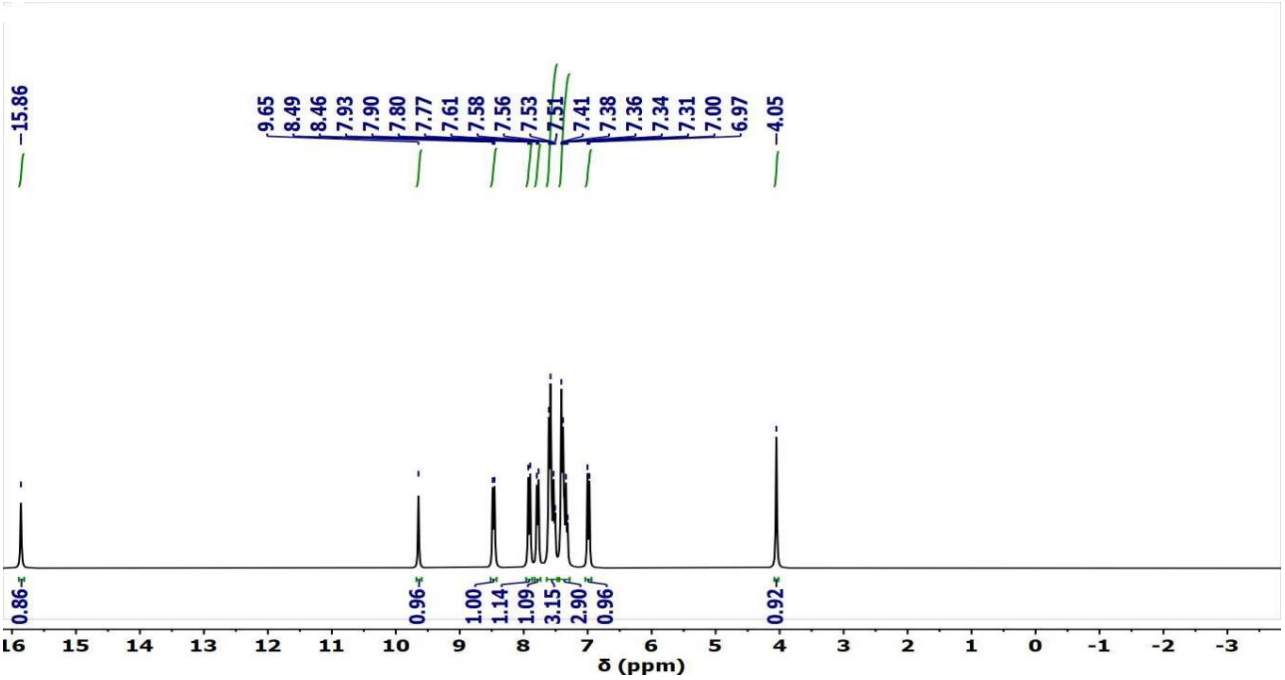


Figure 6 1HNMR of the compound (2)

Mass spectrum of the compounds (1) and (2)

The mass spectrum of the compound (1) exhibits a molecular ion peak [M]+ 462 m/z, 425 m/z for the base peak [C28H21N4S], and other fragments at (378,350, 254, 237, 195, 142, 112 and 77) m/z due to [C25H20N3O]+, [C25H8N3OS]+, [C13H16NO]+, [C13H7N3S]+, [C14H13N]+, [C10H6O]+, [C3H2N3S]+ and [C6H5]+ respectively as shown in (Figures 7 and 9). The mass spectrum of the compound (2) exhibits a molecular ion peak [M]+ 482 m/z, 57 m/z for the base peak [C2HS], and other fragments at (370,320, 200, 150, 83 and 57) m/z due to [C24H18ClNO]+, [C20H15ClNOS]+, [C13H9Cl]+, [C9H7Cl]+ and [C3HNS]+ respectively as shown in (Figures 8 and 10).The intensity of these peaks gives the idea of the stability of fragments (Mohan et al., 2018).

Biological studies

Antioxidant activity

It has been observed that the free radical scavenging activity is concentration dependent to the synthesized phenolic azo Schiff base compounds as shown in (Table 2). Compound (1) has exploited the highest DPPH radical scavenging activity, yet, lower than vitamin C on one hand. On the other hand, compounds (2) also has demonstrated moderate DPPH scavenging activity as shown in (Figure 11). It can be proposed that the Schiff base of thiazole compound pharmacophore antioxidant influence lies behind their capability to donate proton to the DPPH radical, besides, presumably being capable to counteract reversibly with the biological system redox enzymes, hence, even possibly deactivate these enzymes as Al-Amiery et al., (2012), Chen et al., (2017) especially Schiff bases of aromatic aldehydes with proton donating group or even on the aromatic ring next to the imine functionality (Kumar et al., 2021; Saqib et al., 2016).

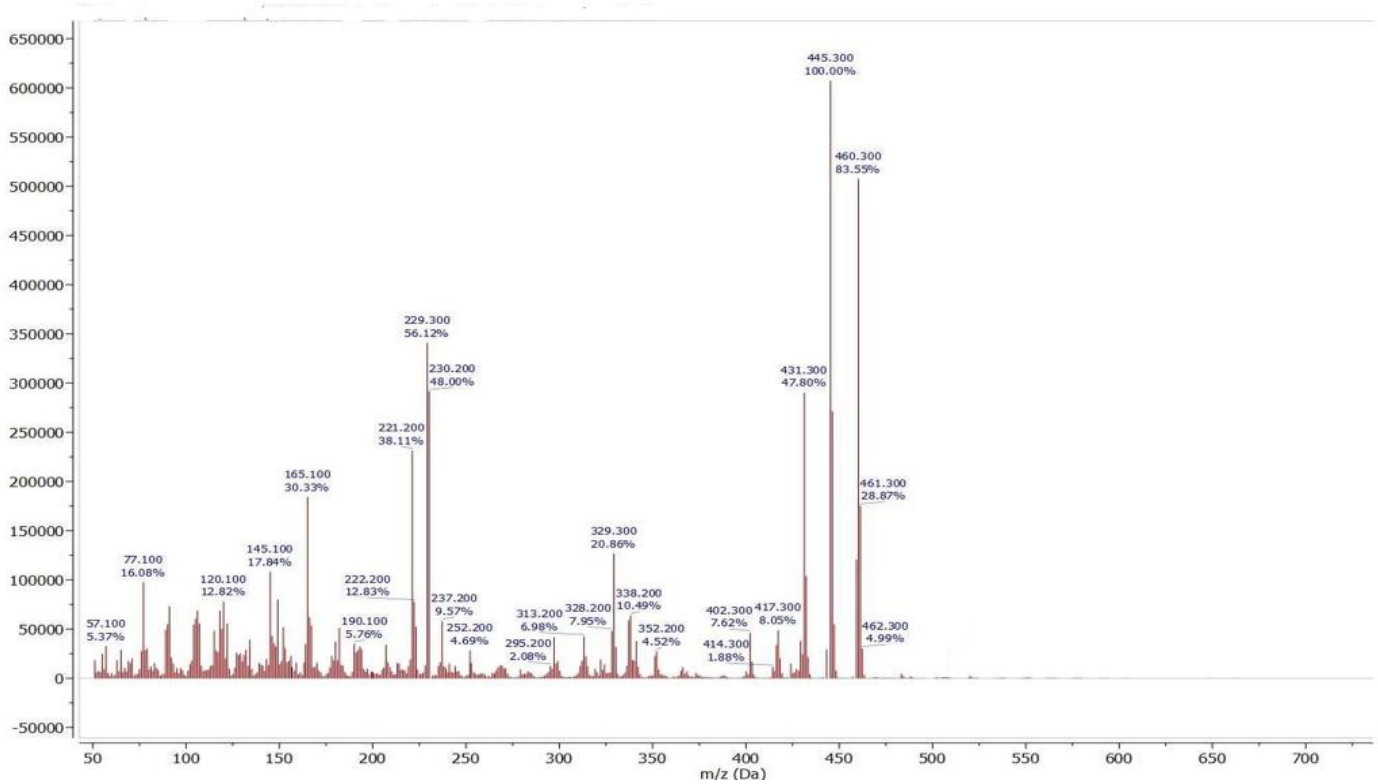


Figure 7 Mass spectrum of compound (1)

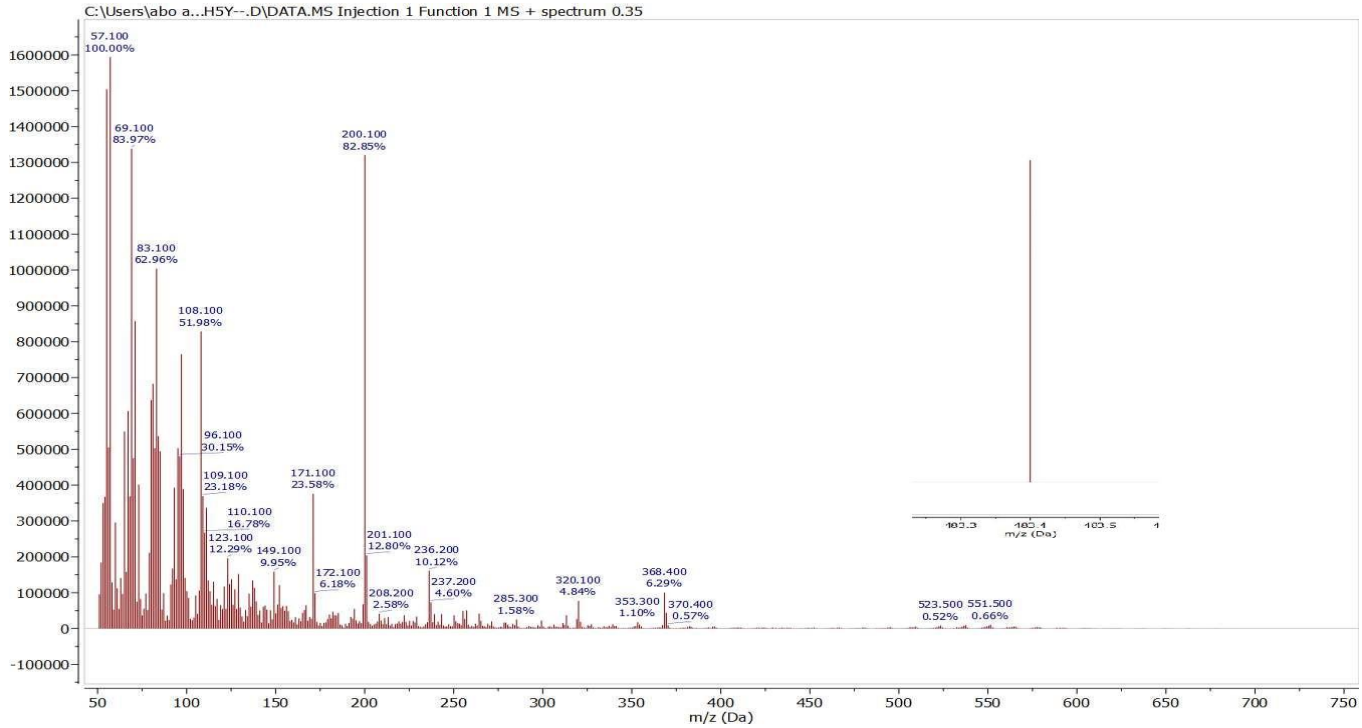


Figure 8 Mass spectrum of compound (2)

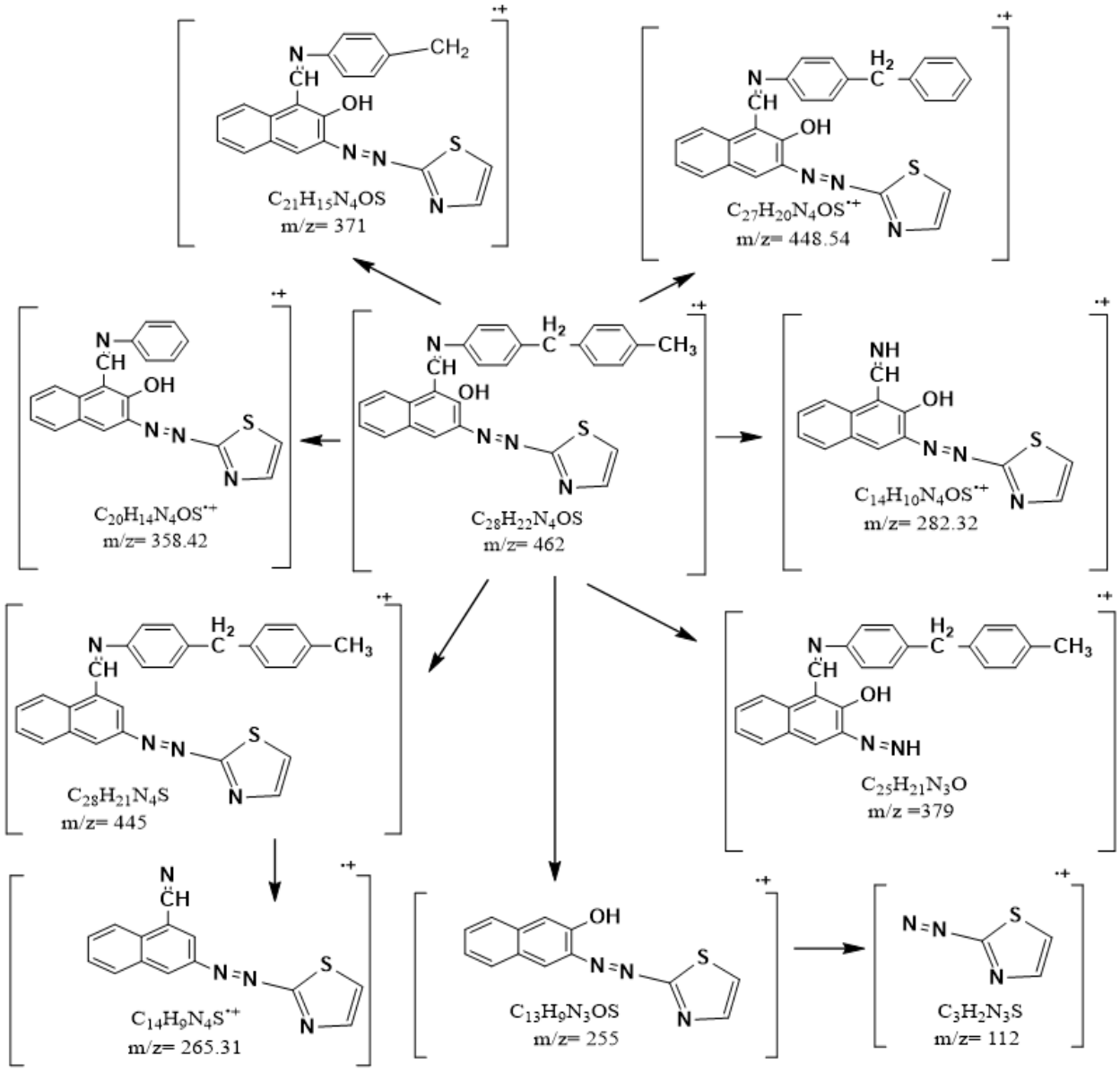


Figure 9 Fragments of the compound (1)

In fact, the amino-thiazole pharmacophore as a characteristic heterocylic system is an integral part in many reported diverse biological activity including antioxidant and cytotoxic effects as earlier reported (Saqib et al., 2016). However, regarding the cytotoxic influence, the in-vitro screening of the compounds showed that the azo-Schiff bases have exerted considerable anticancer activity, using various concentrations (5, 12.5, 25 and 50 μg/ml), whereas, the IC50 is 113 μg mL-1, as shown in (Figure 12). The data obtained are shown in (Table 3).

We propose that the aminothiazole pharmacophoric moiety contribute to the antitumor as well as cytotoxic influence, as earlier reported for their derivatives (Kaushik et al., 2023). We also presume that our compounds' cytotoxicity is related to the incorporated heteroatoms as reported for that of sulphur and nitrogen atoms containing heterocycle including thiazoles are known to exploit cytotoxicity against the tumours DU145, HCT116, and MCF7 (Yakdhan et al., 2024; Nofal et al., 2014).

Similar to what is earlier reported for cytotoxic influence of p-flourophenyl aldehyde Schiff bases of thiazole against hepatocellular carcinoma (Arshad et al., 2022); that the similar molecular target as well as mode of action to our compounds are expected against WRL68 cell lines. In addition, our compounds, like 2-hydroxybenzylidene-4-(4-substituted phenyl)-2-amino-thiazole Schiff base has

been reported to exploit powerful antioxidant as well as antitumor influence against human breast cancer cell line (MCF-7). Aldelfy et al., (2019) exploit their antitumor effect probably by the same mode of action, based on the assumption that, substituted-aryl-amino-thiazole Schiff base of different substitution are reported to exploit potent effects (Zhou et al., 2007), particularly those of p-electron donating groups as they enhance the H-bonding capability of these Schiff bases to the target biomolecules as demonstrated by docking studies (Shruthy and Ahammed, 2014; Al-Musawi and Al-Mudhafar, 2024).

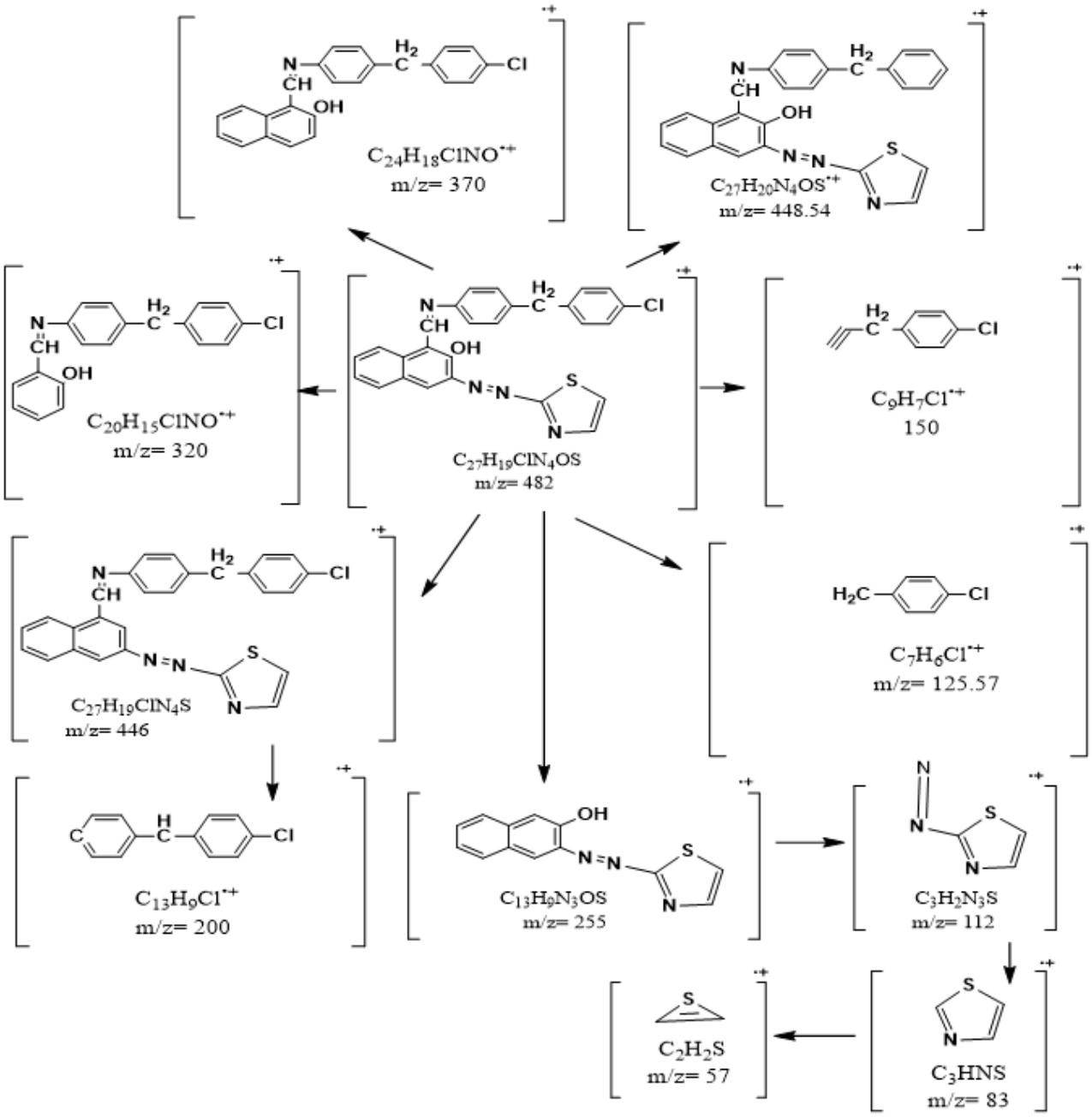


Figure 10 Fragments of the compound (2)

We also propose that as previously reported, the azomethine (-C=N-) functionality H-bonding forming functionality with the cellular critical biomolecules Bravo et al., (2017), Orvig and Abrams, (1999) as well as chelation complex formation capability of thiazole

pharmacophore Schiff bases with the central enzyme metal co-enzymes Login et al., (2019) lies behinds the observed multiple antioxidant, antitumor as well as other potential unstudied influences.

Table 3 Anticancer activity of compound (1) against breast cancer cell lines.

Conc.(µg/ml)	Mean viability (%) ± SD	
	WRL68	MCF-7
400	73.248±1.14	39.8 ±2.6
200	84.01 ± 1.2	49.6± 6.5
100	92.1± 0.98	70.6± 5.1
50	96.2 ±	89.6±4.7
25	96.1±0.6	94.2 ±0.5

Table 2 DPPH scavenging activity of Compounds (1&2) versus Ascorbic acid.

Concentration µg mL-1	Scavenging % (Mean±SD)		
	Ascorbic acid	comp.(1)	Comp.(2)
200	82.7±2.7	77.77±3.19	51.582±2.8
100	74.80±1.5	71.142±3.70	44.791±4.158
50	67.09±1.6	65.702±1.4	35.10±6.58
25	53.74±1.26	52.70±2.82	24.34±2.64
12.5	23.03±13.43	42.55±1.7	14.96±1.3

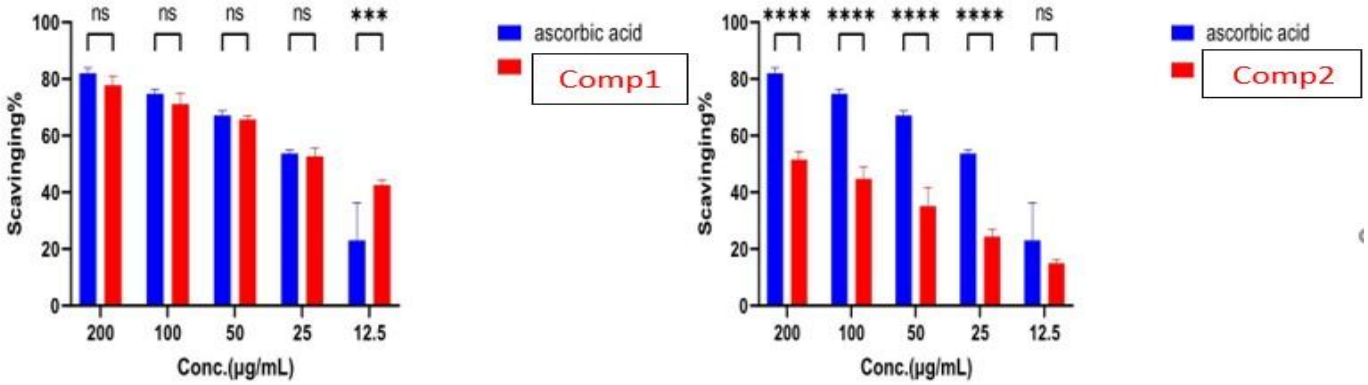


Figure 11 Radical scavenging activities of Schiff base compounds (1) and (2).

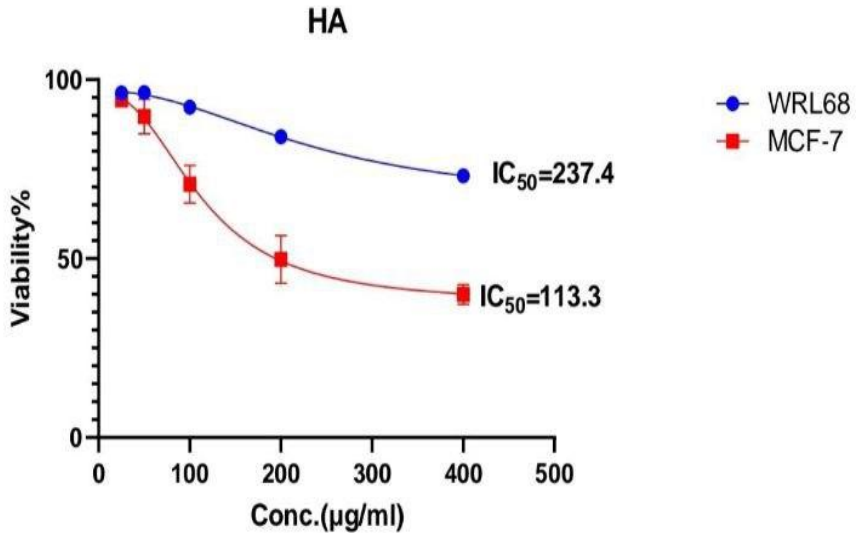


Figure 12 Effective of the compound (1) on cell line of MCF-7 and WRL68.

In silco studies

Computational analysis has shown the computed properties using the same technique as the geometry optimization. In addition, the estimated information has helped in further describing the molecular characteristics of the compounds as shown in (Table 4 and Figure 13). The values of the electronic properties of the compounds are displayed in Table (4) and Figure (14) HOMO and LUMO energies: The ability of a molecule to interact with other molecules is generally represented by the values of the highest and the lowest occupied molecular orbital energies (EHOMO and ELUMO), respectively. The electron-donating capability of a molecule is represented by the term EHOMO.

A molecule with a high EHOMO value has a strong ability to donate electrons to a lower energy molecule (an empty orbital). The ability of a molecule to receive electrons from an energetic molecule is greatest when it has a low ELUMO value (an occupied orbital) (Décor et al., 2013; Bhattacharya et al., 2005). Energy gap (ΔE): The HOMO-LUMO energy separation has been a basic indicator of kinetic stability. A chemically-reactive molecule has a low HOMO-LUMO gap (Sadeek et al., 2023). Absolute electronegativities, χ, chemical potentials, Pi, absolute hardness, η, absolute softness, σ, global electrophilicity, ω and global softness, S, have been estimated for the compound (C1and C2) by the following equations:

$\Delta E = ELUMO–EHOMO$ …….. (1) **$\sigma = 1/\eta$ ……(4)**

$\chi = -(EHOMO + ELUMO)/2$ ……(2) **$S = 1/2\eta$ ……...(5)**

$\eta = (ELUMO - EHOMO)/2$ …….(3) **$Pi = -\chi$ …….(6)**

$\omega = Pi/2\eta$ ……..…..(7)

Table 4 Quantum chemical parameters.

Parameters	L1	L2
EHOMO (eV)	-6.7511	-6.6422
ELUMO (eV)	-5.6493	-5.7500
Δ E (eV)	1.0018	0.8922
χ (eV)	6.2002	6.1961
η (eV)	0.5009	0.4461
σ (eV)−1	1.996	2.242
Pi (eV)	-6.2002	-6.1961
S (eV)−1	0.9982	1.1208
ω (eV)	-6.1890	-6.9447

Docking study

The docking scores of the synthesized compounds (1 and 2) as compared to the positive standard to the most abundant antioxidant enzyme superoxide dismutase enzyme is listed in (Table 5). Yet through comparing our compounds with the reference drug, vitamin C, we have noticed that both shared hydrogen bond interactions with the two amino acids along with multiple bonding in both enzyme active site chains A and B, VAL 7 and VAL 146. Docking poses and interactions of vitamin C are shown in (Figures 15, 16). While, our compounds (1 & 2) had exhibited only one main interaction by pi-cation bond with LYS 9 without hydrogen bond interactions. In addition, we have noticed that the same glide score between compounds (1 & 2), besides, some advantage of compound 2 as reflected by the glide E-model score.

E-model has also exploited a more convenient weighing mean to the force field components (electrostatic and van der Waals energies), which makes it well-suited for comparing conformers, but much less so for comparing chemically-distinct species. Therefore, Glide uses E-model to pick the "best" pose of a ligand (pose selection), hence, ranks these best poses against one another with Glide score. In fact, with respect of Glide XP, the pose-selection procedure is a bit more complicated, though it still involves Emodel and Glide Score. Poses produced by Glide XP have an "XP Pose Rank" property that shows how Glide XP has ranked the poses of a given ligand. Docking poses and interactions of compounds 1 and 2 are shown in (Figures 16-20). These interesting findings encourage us to go forward to in vitro biochemical investigations about our final compounds. Our docking study on the targeted enzyme revealed that compound 2 has some of priority in binding affinity than compound 1.

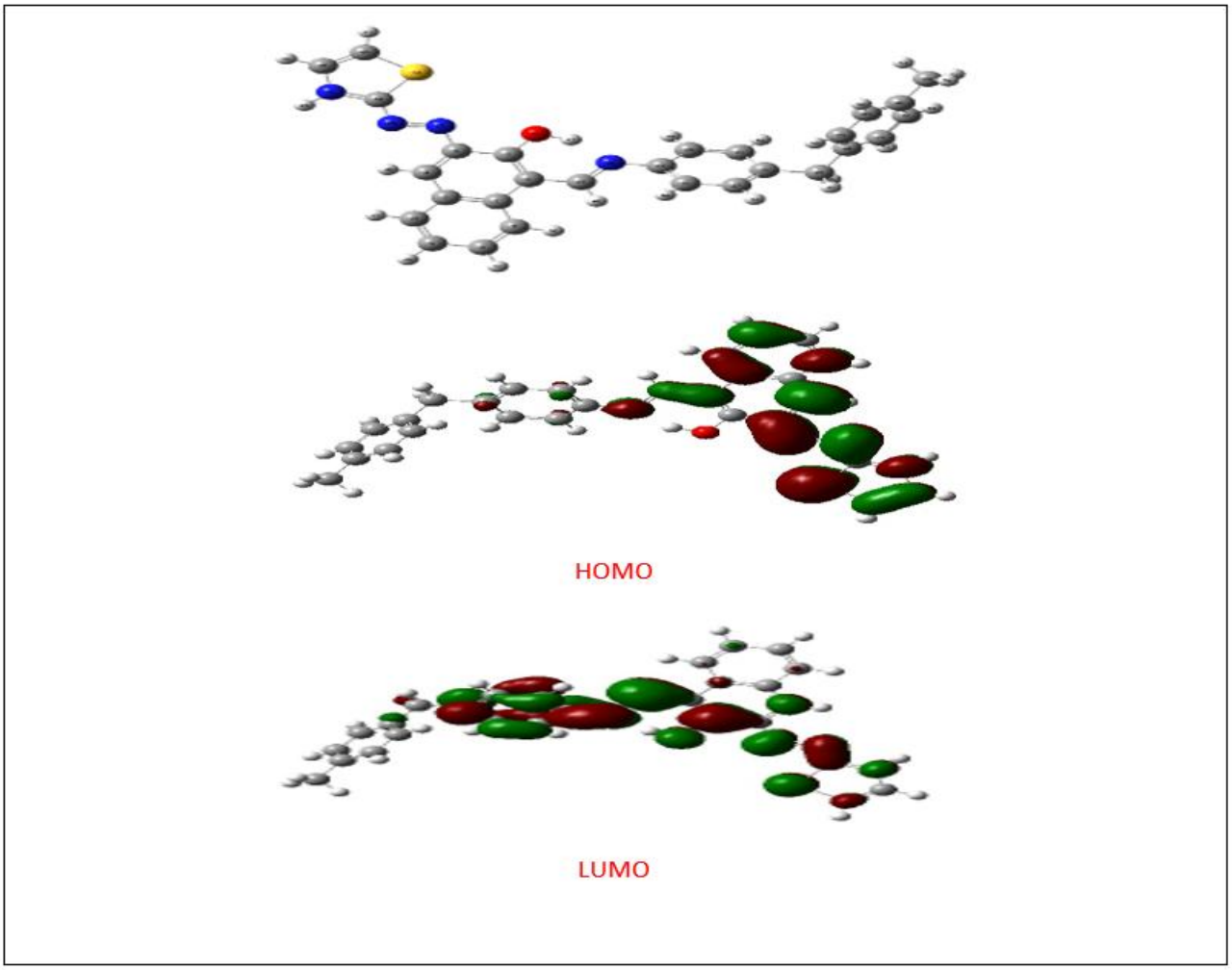


Figure 13 Geometry optimization and molecular orbitals (LUMO-HOMO) of comp (1)

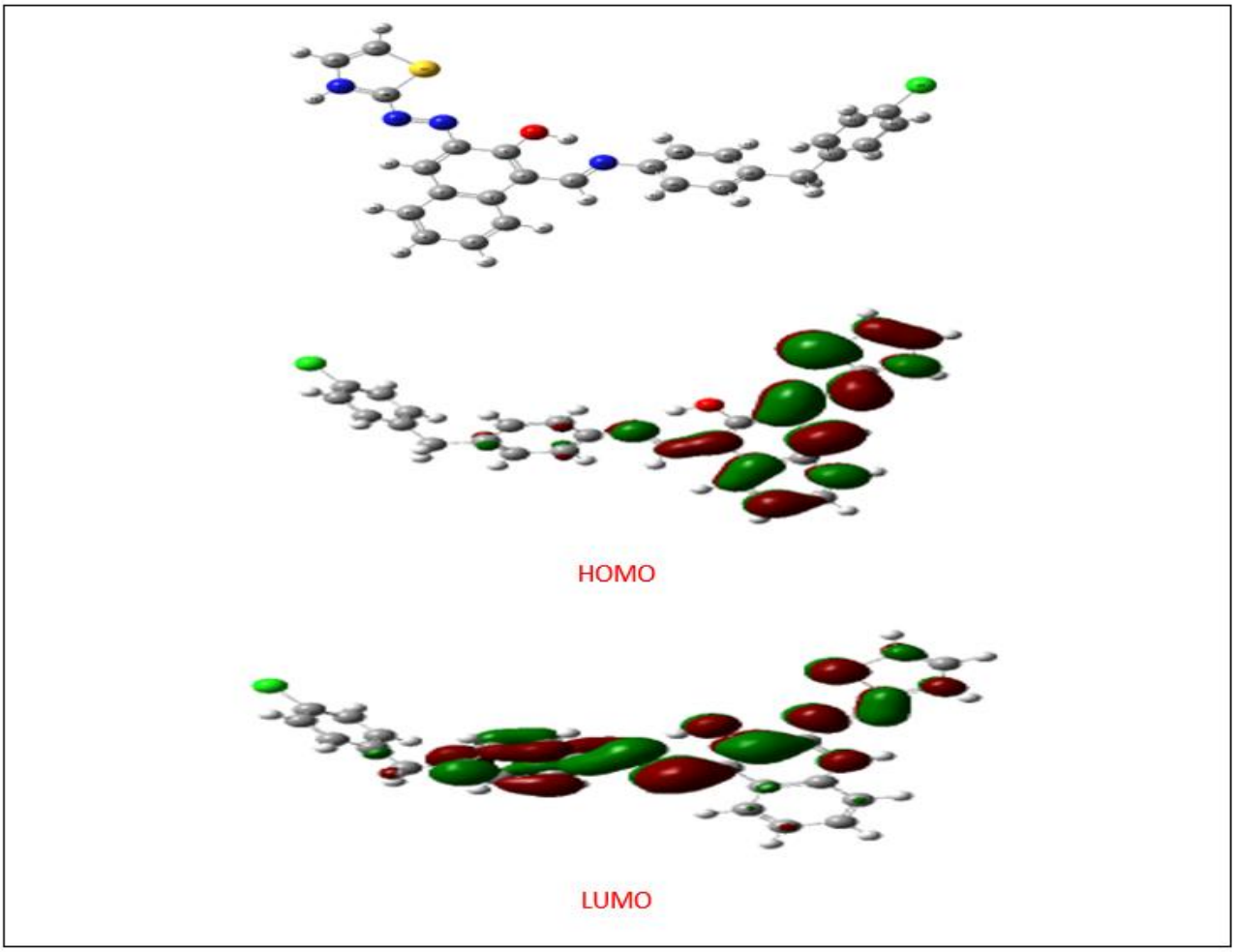


Figure 14 Geometry optimization and molecular orbitals (LUMO-HOMO) of comp (2)

Table 5 Docking score with binding interaction of compounds (1 & 2) with Vit C to the active site of supperoxide dismutase enzyme active site.

Compound	Docking score (Glide emodel)	Hydrogen bond		Other bonds	
		No. of bonds	A.A. Residues	No. of bonds	A.A. Residues
1	-4.61 (-58.21)	0	-	1	LYS 9 (B)
2	-4.61 (-62.75)	0	-	1	LYS 9 (B)
Vit C. (reference drug)	-6.48	5	VAL 7 (B) VAL 146 (B) VAL 7 (A) (2) VAL 146 (A)	0	-

Moreover, the docking scores of the synthesized compounds (1 and 2) as compared to the positive standard to the crystal structure of Vegfr2, as compared to the potent benzimidazole-urea inhibitor; sorafenib is listed in (Table 6). However, through comparing our compounds (1 & 2) with the reference drug, sorafenib, we have noticed that both have shared hydrogen bonding interactions with the same amino acid, Glu 883 and Asp 1044, with additional bond interactions with four amino acids in compound 2 as shown in the

docking poses and interactions of sorafenib in Figures (21, 22), as well as the docking poses and interactions of compounds 1 and 2 are shown in (Figures 23-26).

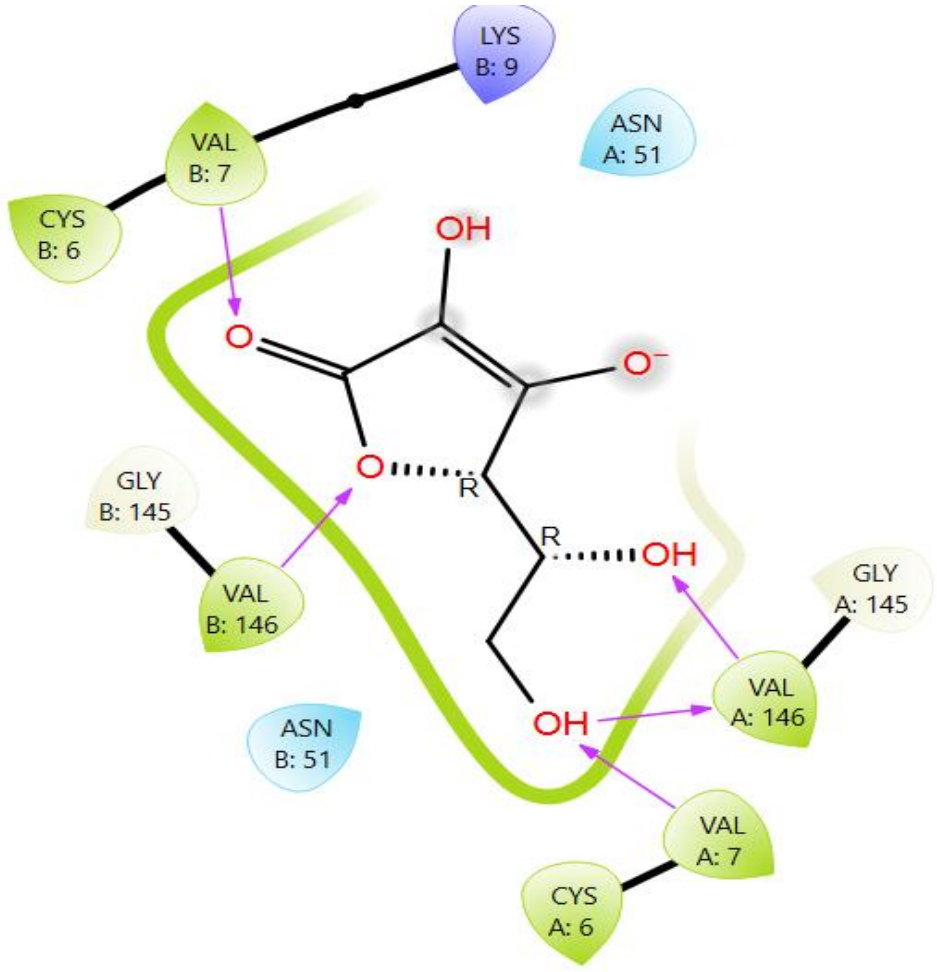


Figure 15 2D shape of interaction mode of Vit C.

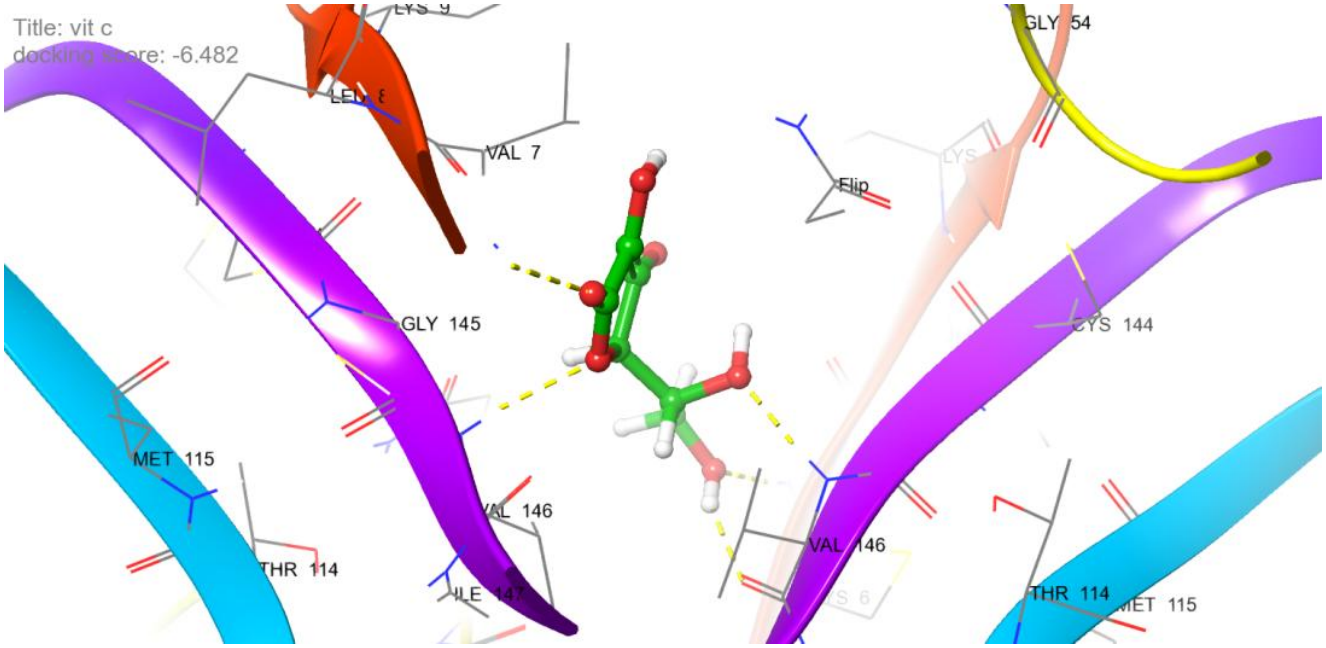


Figure 16 3D shape of interaction mode of Vit C (H bond: yellow, bad contact: Orange, Halogen bond: Purple, salt bridges: violet).

These interesting findings encourage us to go forward to in vitro investigations about our final compounds as the MTT investigation has also demonstrated a promising outcomes against the two elected cell lines. Thus, our docking study on the targeted enzyme has revealed that compound 2 has more binding affinity than compound 1 due to the additional binding interactions of compound 2 as compared to compound 1.

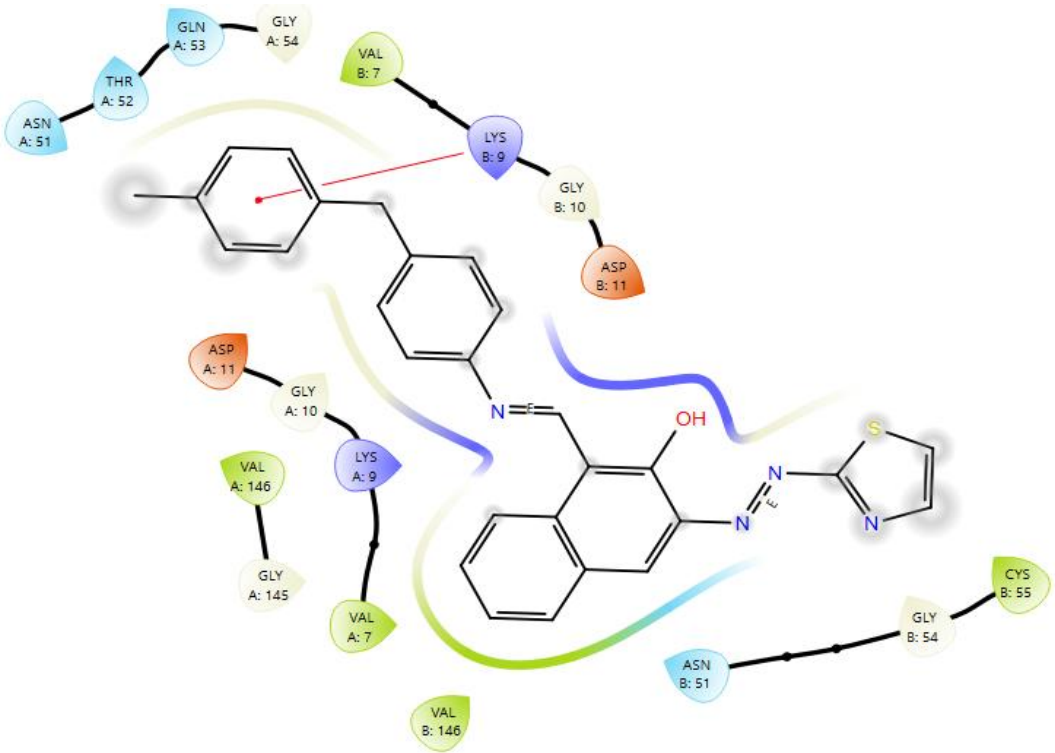


Figure 17 2D shape of interaction mode of compound (1)

Figure 18 3D shape of interaction mode of Compound 1 (H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking).

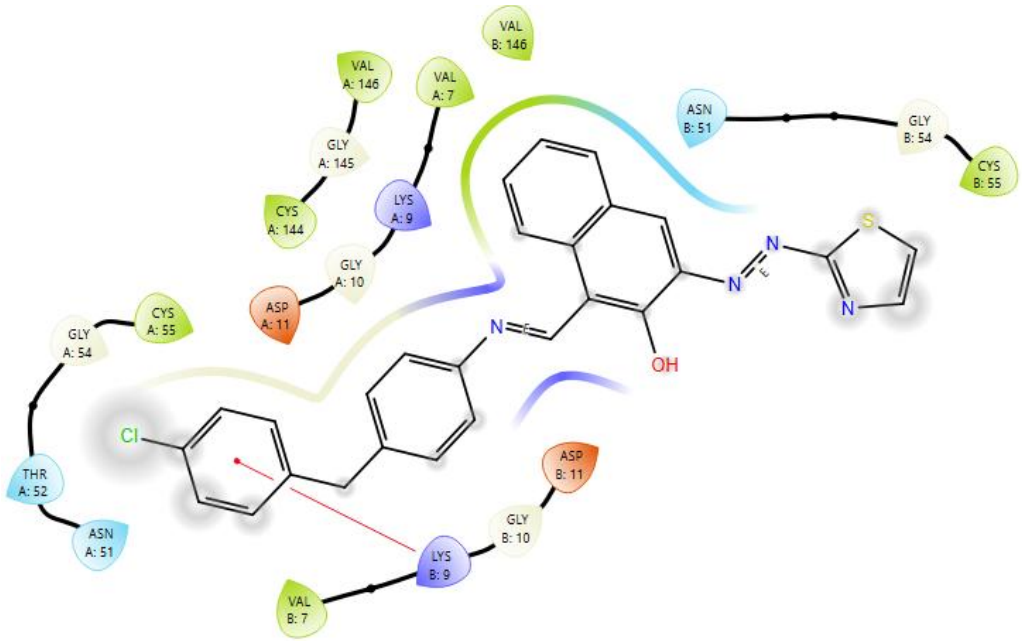


Figure 19 2D shape of interaction mode of compound (2).

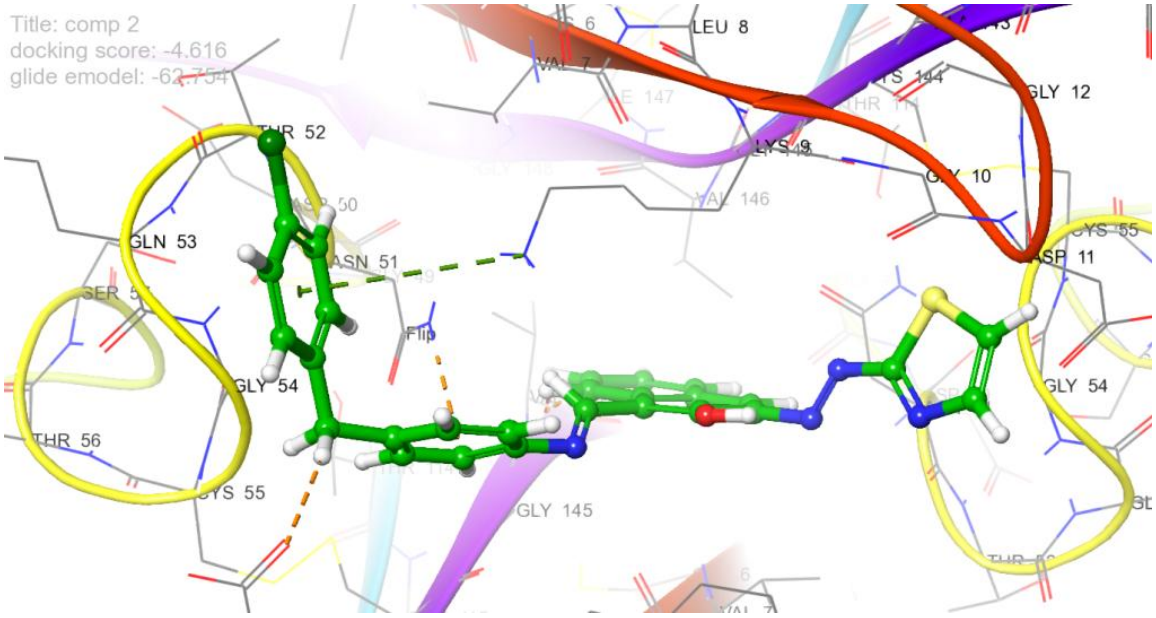


Figure 20 3D shape of interaction mode of Compound 2 (H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking).

Table 6 Docking score with binding interaction of compounds (1 & 2) with sorafenib with the active site of Vegfr2.

Compound	Docking score	Hydrogen bond		Other bonds	
		No. of bonds	A.A. Residues	No. of bonds	A.A. Residues
1	-8.62	2	GLU 883 ASP 1044	2	LYS 866 PHE 1045
2	-9.19	2	GLU 883 ASP 1044	4	HIE 1024 CYS 917 PHE 1045 LYS 866
Sorafenib (Reference drug)	-11.96	3	ASP 1044 GLY 883 CYS 917	0	-

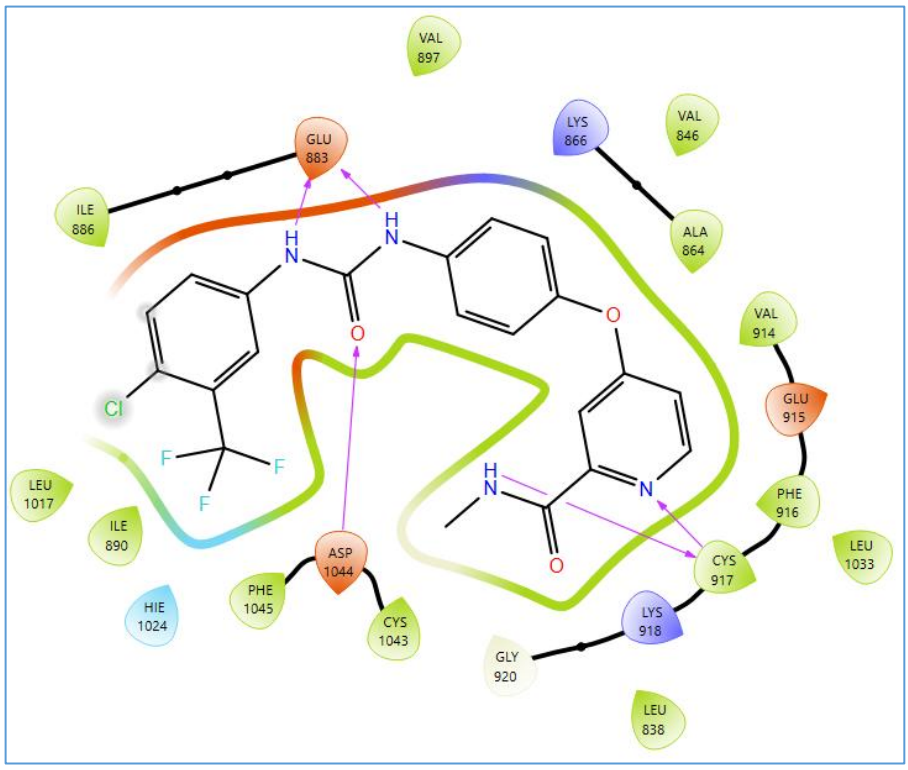


Figure 21 2D shape of interaction mode of sorafenib.

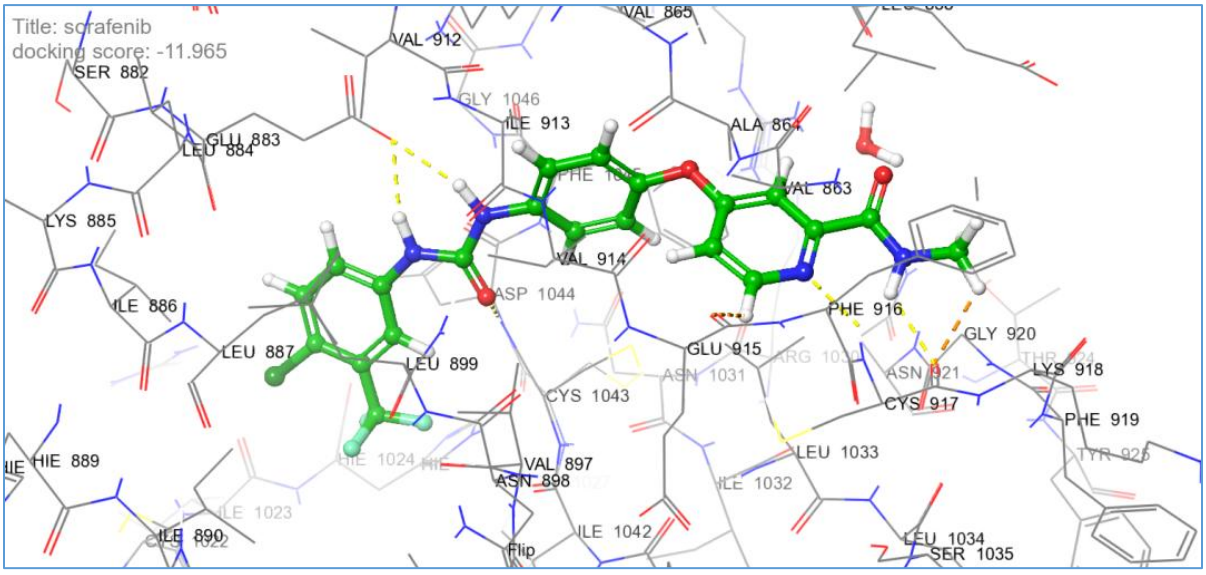


Figure 22 3D shape of interaction mode of sorafenib (H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking).

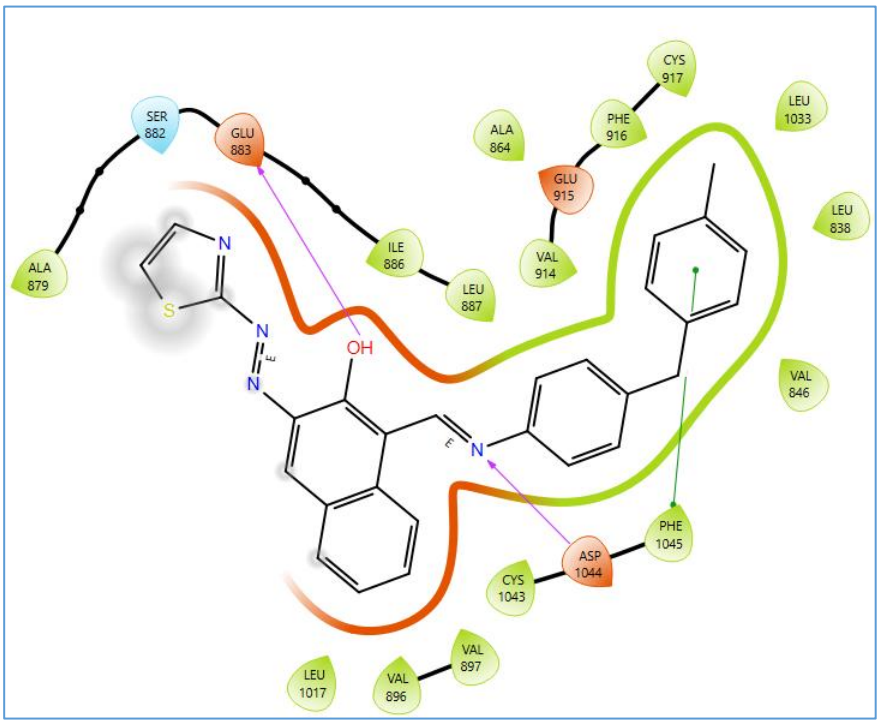


Figure 23 2D shape of interaction mode of compound (1).

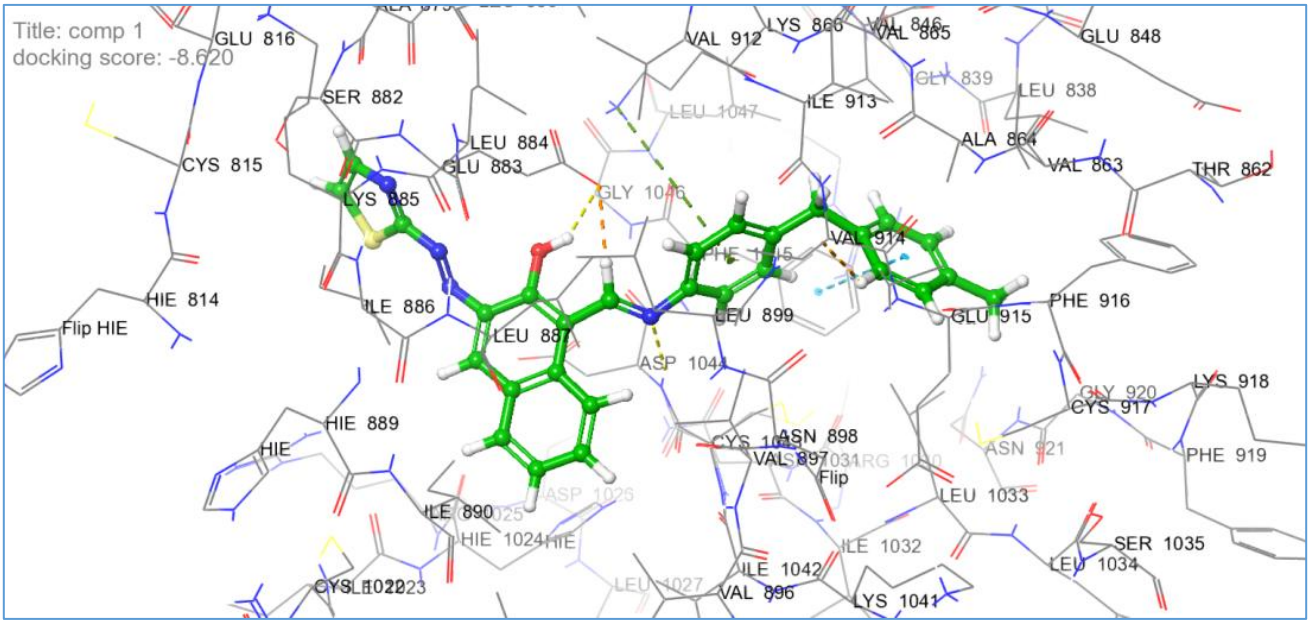


Figure 24 3D shape of interaction mode of Compound 1 (H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking).

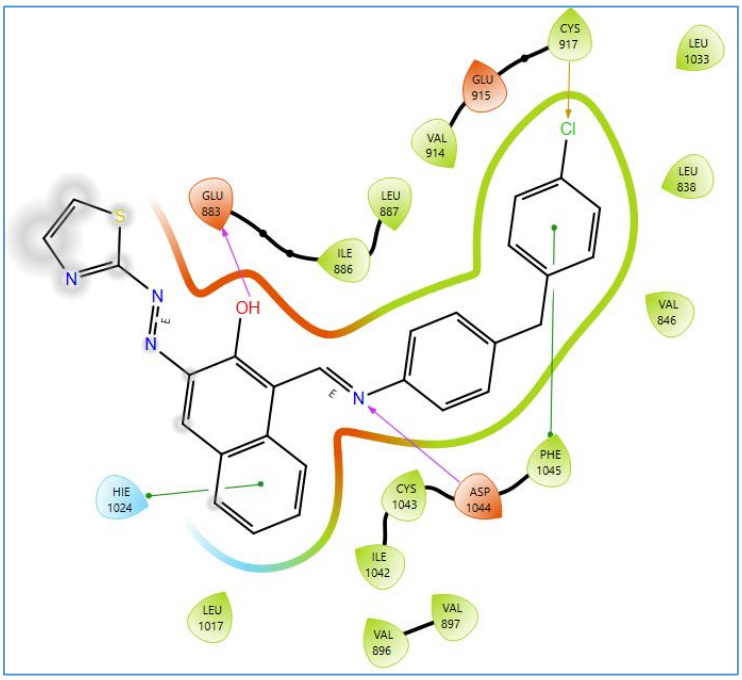


Figure 25 2D shape of interaction mode of compound (2)

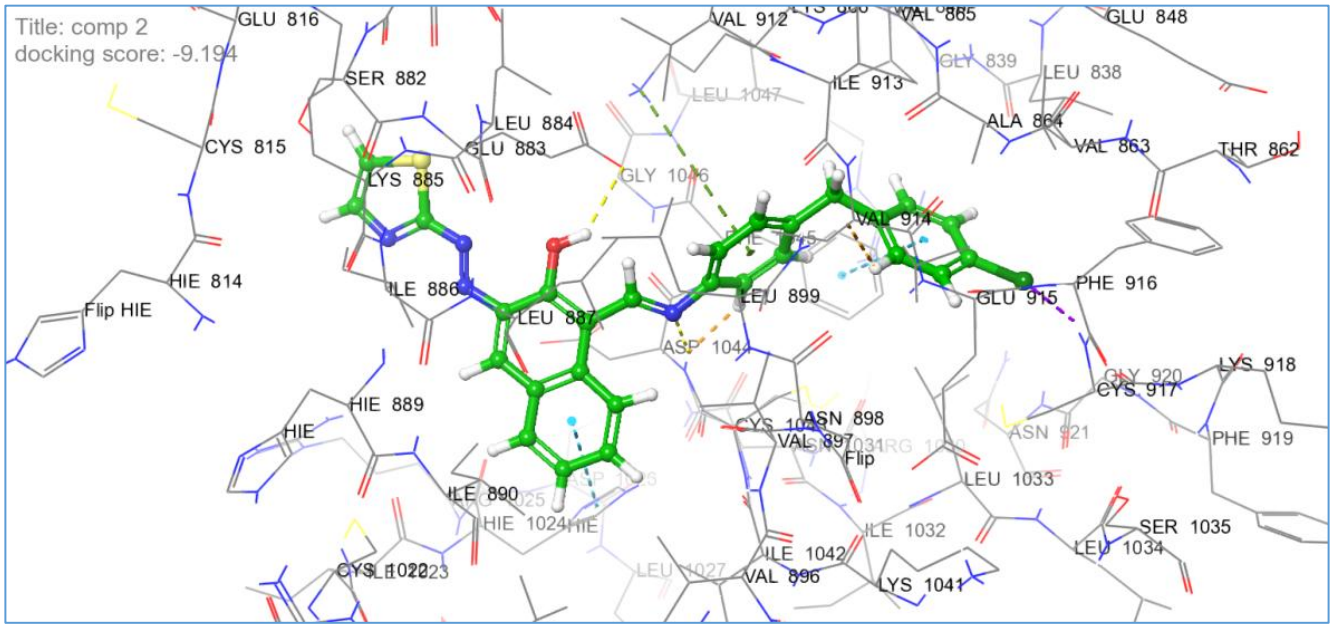


Figure 26 3D shape of interaction mode of Compound 2 (H bond: yellow, bad contact: Orange, Halogen bond: Purple, Green: pi-cation, Sky blue: Pi-Pi Stacking).

4. CONCLUSION

The two new 2-naphthol-thiazole-azo compound Schiff bases are synthesized and found to have a considerable antioxidant as well as anticancer influences. Compound (1) has shown a good anticancer effects against MCF-7 and WRL68 cell lines. However, both of compounds (1&2) have shown a good antioxidant influences. Docking study has revealed that compound 2 has more binding affinity to Vegfr2 than compound 1 due to the additional binding interactions of compound 2 as compared to compound 1, yet, both have shared hydrogen bonding interactions with the same amino acid, Glu 883 and Asp 1044 of sorafenib. Meanwhile, compound 2 has

some of priority in binding affinity than compound 1 to the active site superoxide dismutase enzyme although interactions was weaker than that of ascorbic acid. In conclusion, the inclusion of C3-α-naphthyl-azo-thiazinyl nucleus in the azo-Schiff base scaffold structure is essential for exploiting both in vitro anticancer as well as antioxidant influences.

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Authors Contribution
This work was carried out in collaboration between all authors. All author designed and performed the study, write, read and approved the final manuscript.

Ethical Approval
All the study was *in vitro* & *in sillico*, the ethical guidelines of Thi-Qar university are followed in the study for experimentation. No animals are included in the study.

Informed consent
Not applicable.

Conflicts of interests
The authors declare that there are no conflicts of interests.

Funding
The study has not received any external funding.

Data and materials availability
All data associated with this study are present in the paper.

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