DESIGN, CHARACTERISATION, MOLECULAR DOCKING, AND CYTOTOXICITY STUDY OF NEW 5-PHENYL-4*H*-1,2,4-TRIAZOLE-3-THIOL SCHIFF BASES DERIVATIVES

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Received 15.12.2024
Accepted 11.02.2025

***Abstract**: A sequence of 5-phenyl-4H-1,2,4-triazole-3-thiol Schiff base derivatives ([3a], [3b], [3c], and [3d]) has been synthesized. The spectral analyses validated the synthesis of novel 1,2,4-triazole Schiff bases, which were examined using IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. The results obtained were corroborated by 2D and 3D molecular modeling. Their docking scores vary from -3.472 to -4.389 kCal/mol, in contrast to the normal Xalkori value of -3.22 kCal/mol. The newly synthesized compounds were assessed for their in vitro cytotoxic activities against the hepatocyte carcinoma cell line (HCAM). Synthesized compounds exhibited significant cytotoxic activity against the tested HCAM cell line compared to Xalkori. The study demonstrated a strong agreement between molecular docking analysis and in vitro outcomes for manufactured drugs targeting the EGFR tyrosine kinase receptor protein.*

***Keywords:** Anticancer, Characterization, Docking, Schiff base, Design, and Triazole*
DOI: 10.65382/2221-8688-2026-4-570-581

1. Introduction

Currently, heterocyclic chemistry has emerged as a distinct discipline within contemporary culture and scientific horizons since nitrogen, oxygen, and sulfur are the most recognized heteroatoms with crucial functions in biological systems. Heterocyclic compounds are considered a significant class of organic molecules due to their relevance in pharmaceuticals and industrial research [1-4]. The most important category of heterocyclic compounds is five-membered triazoles, including three nitrogen and two carbon atoms.

Schiff bases are recognized as adjustable compounds characterized by azomethine linkages and are gaining prominence in chemical and medicinal chemistry due to their unique attributes and diverse biological activities [5-7].

Due to their extensive range of biological uses, Schiff bases, particularly hydrazone derivatives, amines, and thione-substituted triazoles, have been investigated and are regarded as intriguing medicinal compounds for novel drug development [8]. Numerous studies have thoroughly examined them for their antibacterial, antiviral, antimalarial, anti-inflammatory, antioxidant, and anticancer properties [9-16].

This study seeks to enhance the bioactivities of 1,2,4-triazole Schiff base and derive related derivatives with superior curing effects and improved bioavailability through the design of 1,2,4-triazole Schiff base heterocyclic compounds, followed by molecular docking studies comparing these compounds with the Xalkori drug. The synthesis of 1,2,4-triazole Schiff base heterocyclic molecules is examined. Correlation of molecular docking results with in vitro results for synthesized 1,2,4-triazole Schiff base chemicals targeting the EGFR tyrosine kinase receptor [17-19].

Conventional chemotherapy employs antineoplastic agents to eradicate rapidly

proliferating neoplastic cells throughout the organism. Cytotoxic anticancer medications cannot differentiate between cancer cells and naturally quickly dividing normal cells, potentially resulting in one or more adverse effects [18-21]. Targeted anticancer agents preferentially attach to cancer cells, leading to reduced side effects compared to cytotoxic medications that seek to selectively target chemicals or proteins involved in the proliferation and spread of cancer cells [20-25].

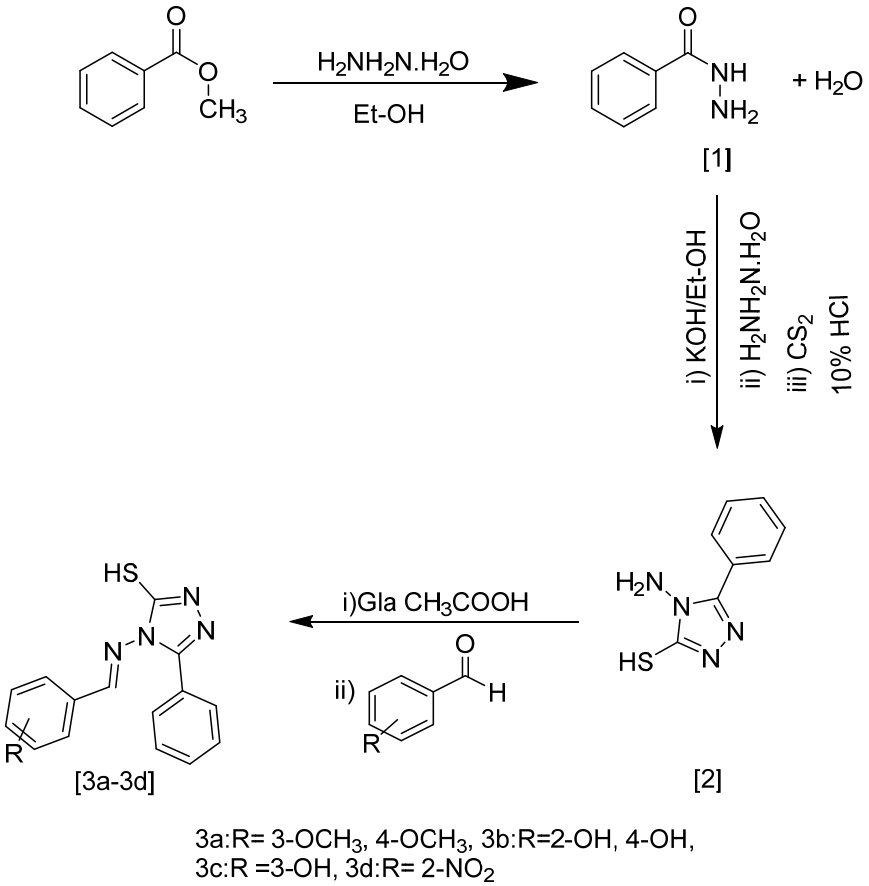
2. Experimental part

The materials used were methyl benzoate (Merck, ≥98%), carbon disulfide (Aldrich, ≥99.9%), pyridine (Merck, ≥99.5%), 3,4-dimethoxybenzaldehyde (Aldrich, 99%), 2,4-dihydroxybenzaldehyde (Aldrich), 4-hydroxybenzaldehyde (Aldrich, 97%), 2-nitrobenzaldehyde (Aldrich, 99%), 2,4-dihydroxybenzaldehyde (Aldrich, 98%), and deionized water.

Instrumentations used in this research are infrared spectroscopy (FT-IR), Perkin Elmer toner 27 (Bruker, Germany),
Nuclear magnetic resonance spectrometer (1H-NMR,^{13}C-NMR) BioSpin GmbH 400,100 MHz (Bruker, Germany), and Mass Spectrometer U3500(Mass Spectrometer), Mass Selective Detector(5973) (Agilent Technologies, USA).

Synthesis of 5-phenyl-4H-1,2,4-triazole-3-thiol Schiff bases derivatives [3a-3d]

In a round-bottom flask, a mixture of different aromatic aldehydes (0.01 mole) and 1,2,4-triazole (1 g, 0.005 moles) was combined in 100 mL of ethanol with two drops of glacial acetic acid. The mixture was then allowed to reflux for two hours. The resultant solid product was then filtered, refined by crystallizing it from ethanol, cleaned with diethyl ether, and vacuum-dried over anhydrous calcium chloride. The physiochemical data of synthesized new Schiff base 1,2,4-triazole derivatives [3a-3d] are illustrated in Scheme 1 and Table 1 [26-30].



Scheme 1. Preparation of 5-phenyl-4H-1,2,4-triazole-3-thiol Schiff bases derivatives

Table 1. Physical properties of synthesized compounds

Comp. No	Molecular formula	M.Wt	M.P., °C.	% Yield	R_f 70% hexane 30% ethyl acetate	Color
1	$C_7H_8N_2O$	136	138-140	94%	0.86	white
3	$C_8H_8N_4S$	192	190-192	88 %	0.70	pink
3a	$C_{17}H_{16}N_4O_2S$	340	261-263	73%	0.71	yellow
3b	$C_{15}H_{12}N_4O_2S$	312	267-269	75%	0.75	yellow
3c	$C_{15}H_{12}N_4OS$	296	254-256	75%	0.73	yellow
3d	$C_{15}H_{11}N_5O_2S$	325	256-258	74%	0.74	brown

3. Results and discussion

3.1. Characterization of 4-((2,3-dimethoxybenzyli -dene)amino)-5-phenyl-4H-1,2,4-triazol-3-thiol [3a]

FT-IR data (cm^{-1}): 3093 (C-H Ar), 2945 (C-H Ali), 2750 (S-H),1610(C=N), 1446(C=C), 1184 (C-S).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 14.22 (s, 1H), 9.48 (s, 1H), 8.63 (s, 1H), 7.88 (dd, J = 6.7, 3.0 Hz, 2H), 7.53 (d, J = 2.3 Hz, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.09 (dd, J = 26.4, 8.2 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H). ^{13}C-NMR (101 MHz): δ 166.97, 162.35 ppm (C=N-SH, C=N-Ar) of triazole ring, 160.80 ppm (CH=N-), 152.96, 151.58, 148.97, 148.37, 130.66, 128.72, 128.19, 126.67, 124.38, 123.52, 111.63, 108.99 ppm of aromatic carbon 55.79, 55.40 ppm (O-CH3) (Fig. 1-3).

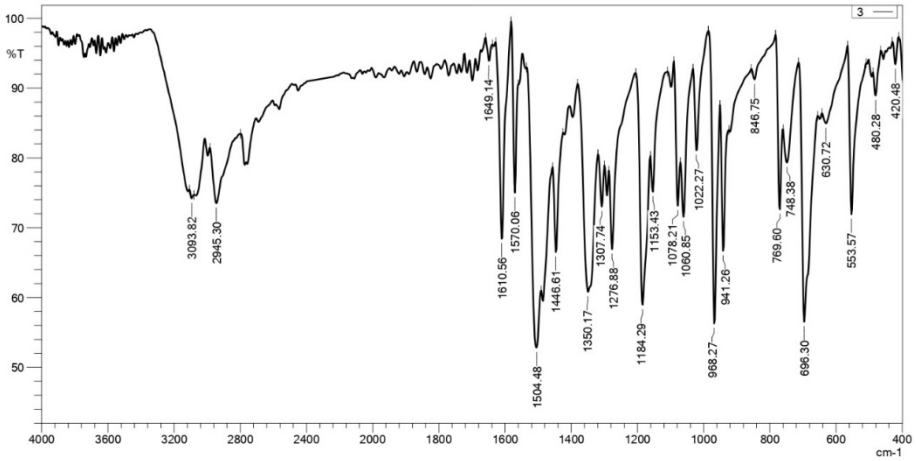


Fig. 1. FT-IR spectrum of compound 3a.

3.2. Characterization of 4-(((3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl)imino)methyl)benzene-1,3-diol [3b]

FT-IR data (cm^{-1}): 3348 (O-H), 3068 (C-H Ar), 2939 (C-H Ali), 2746 (S-H),1610(C=N), 1452(C=C), 1184 (C-S). ^{1}H-NMR (400 MHz, DMSO-d6): δ 14.13 (s, 1H), 10.47 (s, 1H), 10.31 (s, 1H), 9.51 (s, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H), 7.52 (s, 2H), 7.43 (s, 1H), 7.40(s, 1H). ^{13}C-NMR (101 MHz): δ 164.58, 162.15, ppm (C=N-SH, C=N-Ar) of triazole ring, 160.6 ppm (CH=N), 148.34, 132.89, 130.57, 129.44, 128.71, 128.17, 125.69 110.26, 109.76, 108.26, 102.51 ppm of aromatic carbon (Fig. 4-6).

3.3. Characterization of 4-(((3-mercapto-5-phenyl-4H-1,2,4-triazole-4-yl)imino)methyl)phenol [3c]

FT-IR data (cm^{-1}): 3317 (O-H), 3010 (C-H Ar), 2831 (C-H Ali), 2733 (S-H), 1647(C=N), 1485 (C=C), 1176 (C-S). ^{1}H-NMR (400 MHz, DMSO-d6) δ 14.19 (s, 1H), 10.43 (s, 1H), 9.37 (s, 1H), 8.02 – 7.79 (m, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 6.9 Hz, 2H), 6.86 (s, 1H). ^{13}C-NMR (101 MHz): δ 167.65, 162.04 ppm (C=N-SH, C=N-Ar) of triazole ring, 160.45 ppm (CH=N), 148.34, 130.19, 128.74, 128.14, 122.77, 116.14, 115.79, 102.45 ppm of aromatic

carbon) (Fig. 7-9).

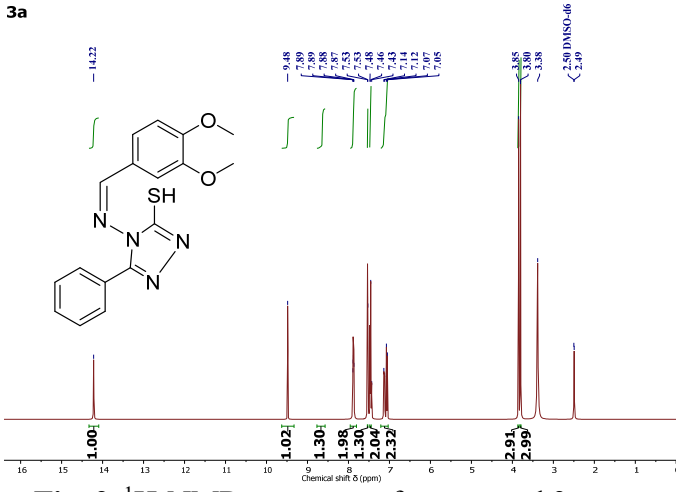


Fig. 2. ^{1}H-NMR spectrum of compound 3a.

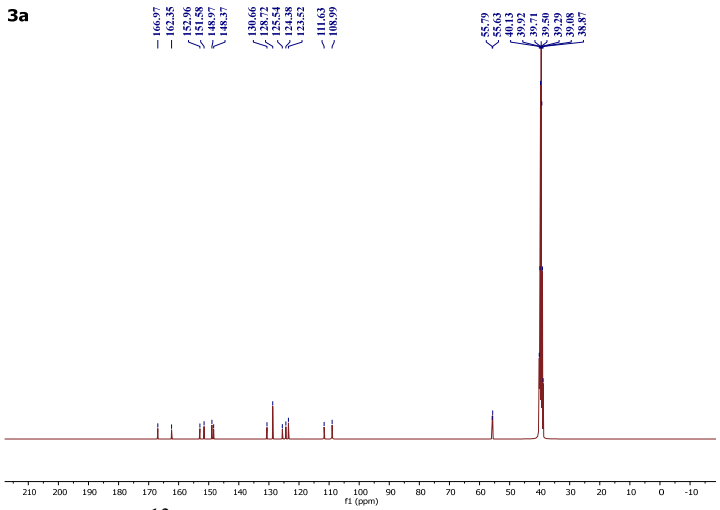


Fig. 3. ^{13}C-NMR spectrum of compound 3a

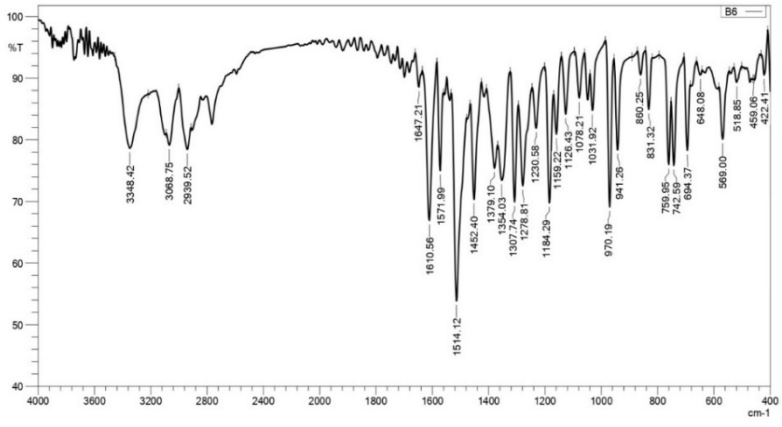


Fig. 4. FT-IR spectrum of compound 3b.

3.4. Characterization of 4-((2-nitrobenzylidene) amino)-5-phenyl-4H-1,2,4-triazole-3-thiol [3d].

FT-IR data (cm^{-1}): 3009 (C-H Ar), 2941 (C-H Ali), 2740 (S-H),1633 (C=N), 1477 (C=C), 1170 (C-S). ^{1}H-NMR (400 MHz, DMSO-d6): δ 14.37 (s, 1H), 10.48 (s, 1H), 8.97 (s, 1H), 8.22 – 8.12 (m, 4H), 7.87 (d, J = 8.7 Hz, 3H), 7.55 (s, 2H).

^{13}C-NMR (101 MHz): δ 162.27, 160.66 ppm (C=N-SH, C=N-Ar) of triazole ring, 158.77 ppm (CH=N-), 148,88, 134.21, 132.21, 129.44, 128.73, 128.57, 125.25, 125.00, 124.81 ppm of aromatic carbon (Fig. 10-12).

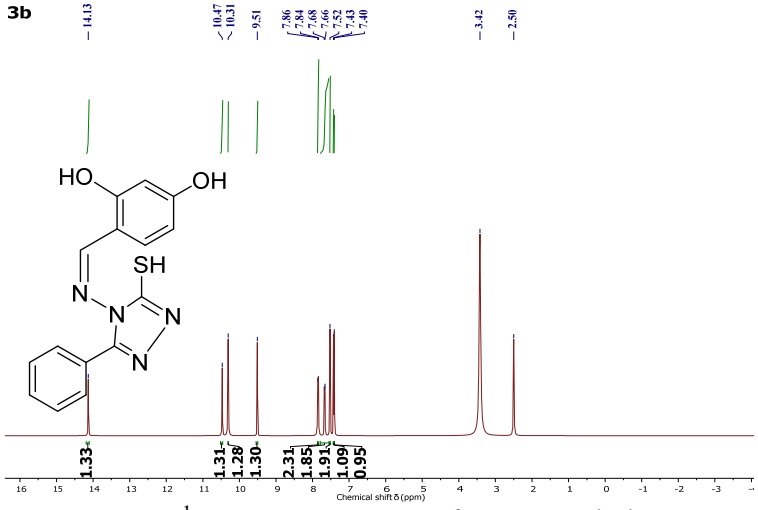


Fig. 5. ^{1}H-NMR spectrum of compound 3b.

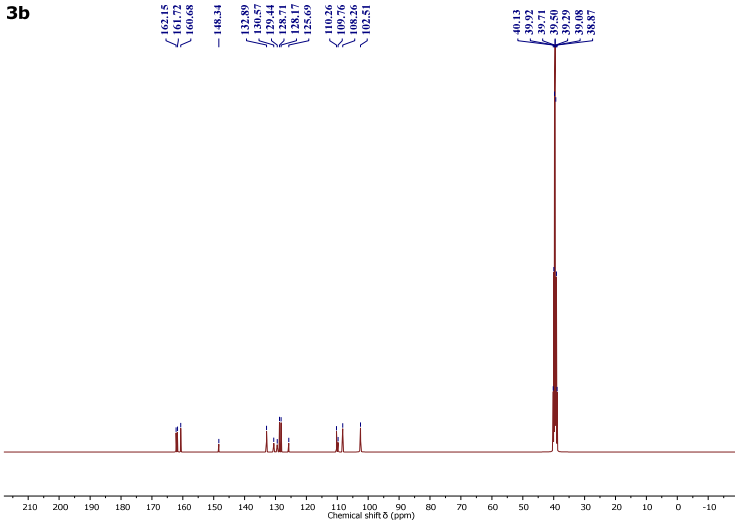


Fig. 6. ^{13}C-NMR spectrum of compound 3b

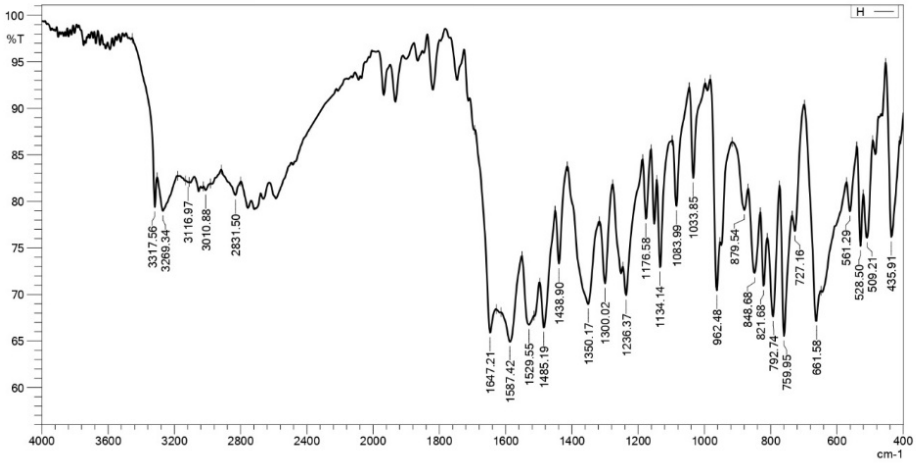


Fig. 7. FT-IR spectrum of compound 3c.

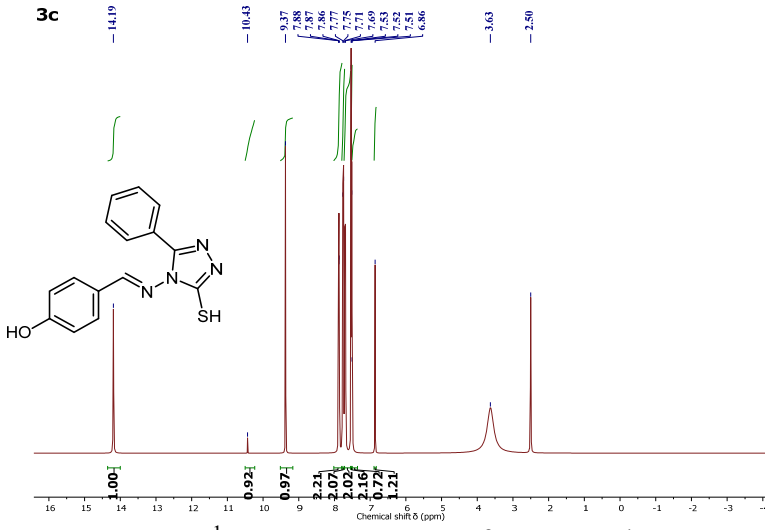


Fig. 8. ^{1}H-NMR spectrum of compound 3c.

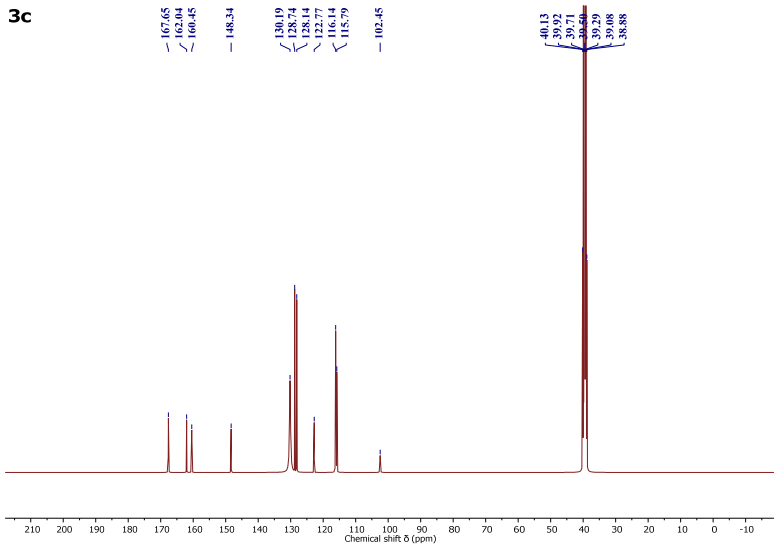


Fig. 9. ^{13}C-NMR spectrum of compound 3c

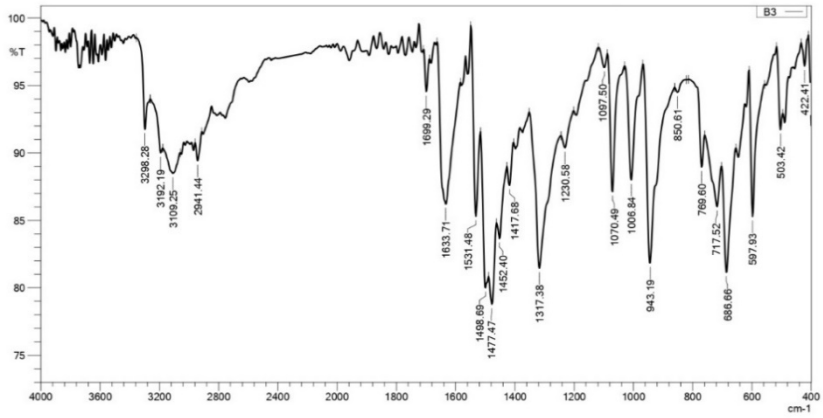


Fig. 10. FT-IR spectrum of compound 3d.

3.5. Molecular docking study. Molecular docking is becoming increasingly vital in the targeted drug discovery and development process since it conserves time, decreases costs, minimizes research efforts, and lessens the adverse effects of anticancer medications. Molecular docking is increasingly vital for pharmaceutical development.

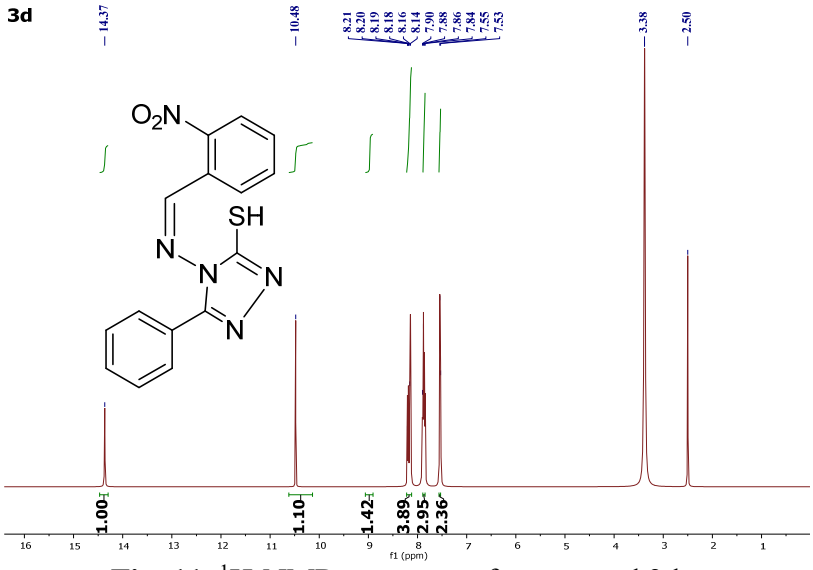


Fig. 11. ^{1}H-NMR spectrum of compound 3d.

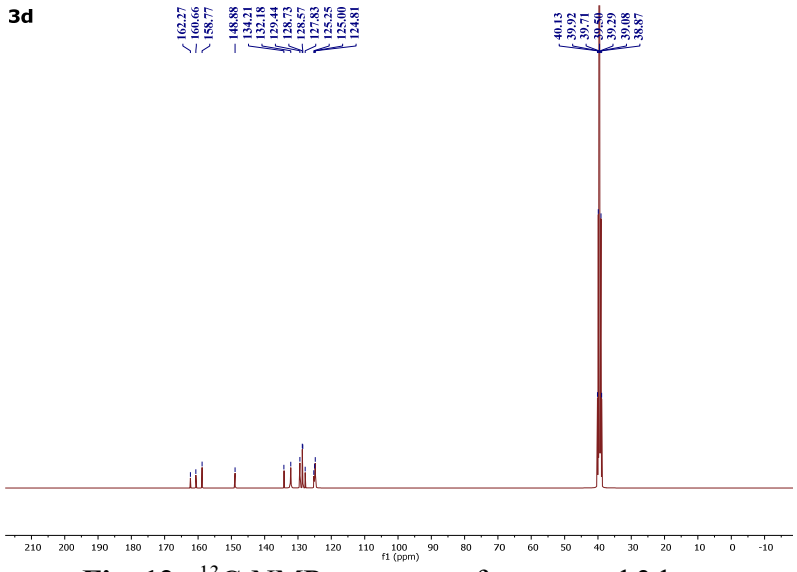


Fig. 12. ^{13}C-NMR spectrum of compound 3d

The main objectives are to assess ligand-protein affinity and to attain a ligand-receptor complex with an optimum shape and reduced binding free energy. The molecular docking investigation indicates that the newly synthesized chemicals demonstrated an anticancer impact. The anticancer properties of these drugs target the EGFR tyrosine kinase receptor, exhibiting diverse efficacy ratings. Their docking scores vary from -3.472 to -4.389 kcal/mol, while the binding affinity of Xalkori is -3.23 kcal/mol. Moreover, compound 4b had the highest binding affinity, with a value of -4.389 kcal/mol. Upon introduction into the EGFR tyrosine kinase receptor, several compounds demonstrate anticancer activity with differing binding affinities, as illustrated in Table 2. Hydrogen bonds (H-bonds) form with amino acid residues in the protein receptor's active site, accompanied by other transient interactions that enhance the association. Molecular docking is becoming increasingly vital in the targeted drug discovery and development process as it conserves time, decreases costs, minimizes research efforts, and mitigates the negative effects of anticancer medications. Molecular docking is increasingly vital for pharmaceutical development. The main objectives are to evaluate ligand-protein affinity and to attain a ligand-receptor complex with an optimum shape and reduced binding free energy. The molecular docking investigation indicates that the newly synthesized chemicals demonstrated an anticancer impact. The anticancer properties of

these drugs target the EGFR tyrosine kinase receptor, exhibiting diverse efficacy ratings. Their docking scores vary from -3.472 to -4.389 kcal/mol, while the binding affinity of Xalkori is -3.23 kcal/mol. Moreover, compound 4b had the highest binding affinity with a value of -4.389 kcal/mol. These compounds demonstrate anticancer activity with differing binding affinities when introduced to the EGFR tyrosine kinase receptor, as illustrated in Table 2. Hydrogen bonds (H-bonds) are formed with amino acid residues in the active site of the protein receptor, accompanied by additional transient interactions that enhance the binding affinity.

Table 2. Results of molecular interaction between EGFR tyrosine inhibitor, compounds **3a, 3b, 3c**, **3d** and reference Xalkori drug

Title	Docking score on ER – (kcal/mol)	H-bond	Others bonds
3a	-3.894	ARG 134 (2), LYS 170	ARG 134, LYS 170
3b	-4.260	ASN 77, ARG 134, LYS 34	LYS 170
3c	-4.389	----	ARG 134, LYS 170, LYS 137
3d	-3.472	ARG 73	LYS 78, ARG 76, ARG 73
Xalkori	-3.222	ASP 123, ASN 77	Salt bridge with ASP 123

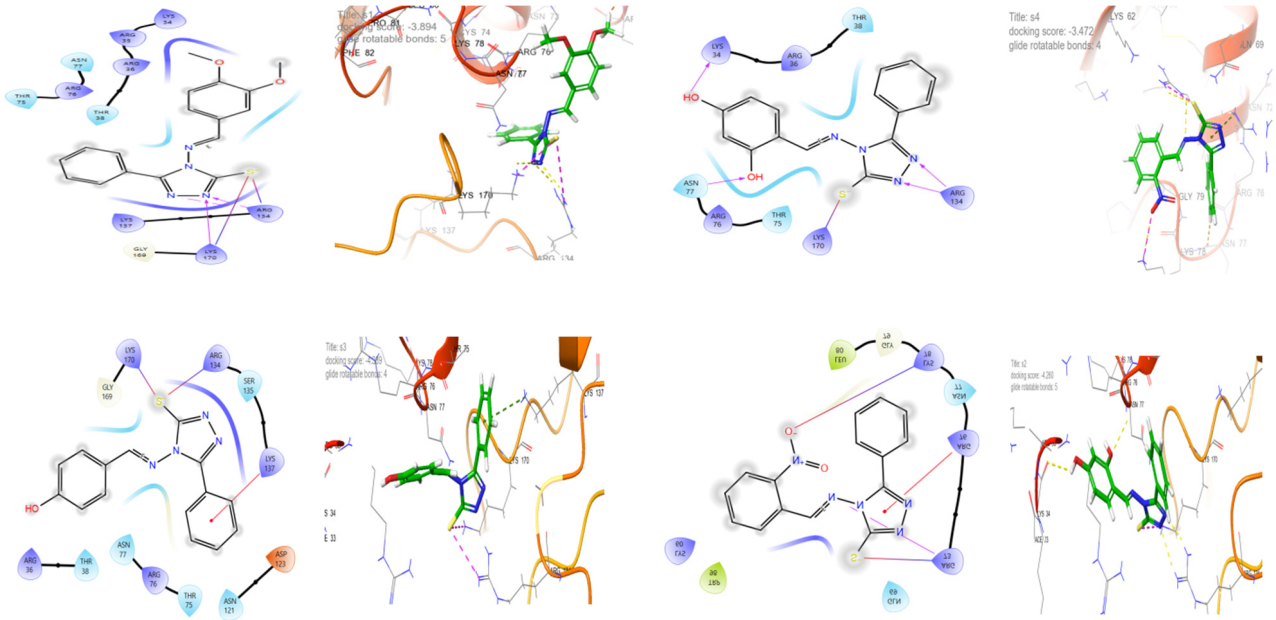


Fig. 13. 2D, 3D interaction diagrams between 3a, 3b, 3c, and 3d compounds and EGFR tyrosine kinase receptor protein

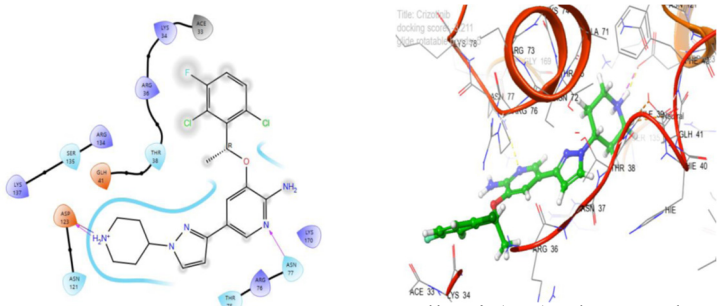


Fig. 14. 2D and 3D interaction diagrams between Xalkori (Xa) drug and EGFR tyrosine kinase receptor protein.

Molecule 3a exhibits a docking score of -3.894 kcal/mol and is stabilized by three hydrogen bonds with ARG 134 (two bonds) and LYS 170, along with other interactions involving ARG 134 and LYS 170, as depicted in Figure 13 and Table 2. Molecule 3b exhibits a docking score of -4.260 kcal/mol and is stabilized by three hydrogen bonds with ASN 77, ARG 134, and LYS 34, in addition to other interactions with LYS 170, as depicted in Figure 13 and Table 2. The molecule 3d has a docking score of -4.389 kcal/mol and is associated with three additional bonds: ARG 134, LYS 170, and LYS 137, as depicted in Fig. 13 and Table 2. The molecule 3c exhibits a docking score of -3.472 kcal/mol and is associated with one hydrogen bond with ARG 73, along with further interactions involving LYS 78, ARG 76, and ARG 73, as depicted in Fig. 13 and Table 2, pertaining to the Xalkori medication. The docking score was -3.22 kcal/mol, signifying the formation of a single hydrogen bond with THR 75, as depicted in Table 2, Fig. 13 and 14 [31-33].

3.6. Anticancer study. The synthesized compounds 3a, 3b, 3c, 3d, and Xalkori (Xa) were evaluated for their cytotoxicity against HEPATOCYT CARCINOMA CELL LINE (HCAM) cell lines by using the MTT assay. This assay is based on the color change of tetrazoliumderivatives from yellow to purple when live cells undergo apoptosis.

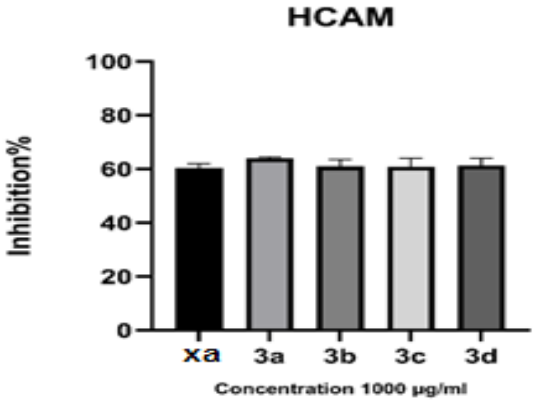


Fig. 15. Cytotoxic effects diagrams of 3a, 3b, 3c, 3d, and (Xa) against HCAM cell line

Table 3. Cytotoxic effects of 3a, 3b, 3c, 3d, and (Xa) against HCAM cell line

Compound	**Xalkori**	**3a**	**3b**	**3c**	**3d**
concentration µg/ml	1000	1000	1000	1000	1000
technical replicate	4	4	4	4	4
mean absorbance	0.05325	0.0485	0.0525	0.05275	0.052
mean inh%	60.48237477	64.00742115	61.03896104	60.85343228	61.41001855
SD±	1.52990704	0.42846318	2.46131952	3.22770291	2.64120758
IC_{50}		µg/ml			
control	0.13475				
R squared					
type of test	MTT assay				
Absorbances nm	620				
cell line		HCAM	HEPATOCYT CARCINOMA CELL LINE		

After incubating the plates at body temperature and in the presence of CO_2 for 24 hours, one concentration (1000 µg ml^{-1}) of the synthesized compounds 3a, 3b, 3c, 3d, and commercial anticancer drugs like Xalkori (Xa). The results of mean inhibition % of synthesized compounds

3a, 3b, 3c, and 3d are 64, 61, 60.8, and 61.4, respectively, while Xalkori (xa) 60.4, Which indicated that the synthesized compounds exhibit anticancer activity against the HCAM, and having higher significant cytotoxicity than Xalkori (Xa). However, the study proved a good correlation between molecular docking results and in vitro results for synthesized compounds towards the EGFR tyrosine kinase receptor, as illustrated in Fig. 15 and Table 3 [34-35].

Conclusion

This study examines derivatives of 5-phenyl-4H-1,2,4-triazole-3-thiol Schiff base derivatives. 4-((2,3-dimethoxybenzylidene)amino)-5-phenyl-4H-1,2,4-triazole-3-thiol [3a], 4-(((3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl)imino)methyl)benzene-1,3-diol [3b], 4-(((3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl)imino)methyl)phenol [3c], and 4-((2-nitrobenzylidene)amino)-5-phenyl-4H-1,2,4-triazole-3-thiol [3d]. The produced compounds were validated using various spectral techniques, including FT-IR, ^{1}H-NMR, and ^{13}C-NMR. The newly synthesized chemicals demonstrated an anticancer impact. These chemicals have docking scores ranging from -3.472 to -4.389 kcal/mol when associated with the EGFR tyrosine kinase receptor. Xalkori exhibits a binding affinity of -3.23 kcal/mol. The synthesized compound exhibited significant cytotoxic action against the tested HCAM cell line in comparison to Xalkori (Xa) (µg/ml). The research demonstrated a strong association between molecular docking and in vitro outcomes for manufactured drugs targeting the EGFR tyrosine kinase receptor. The characterization of these novel 1,2,4-triazole Schiff base compounds as potential anticancer drugs is feasible.

Acknowledgments

Collage of Shatraa technical, Southern Technical University, Basra, Iraq , College of Pharmacy of Thiqar University is under the Ministry of Higher Education and Scientific Research, Iraq.

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