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SYNTHESIS, ANTICANCER ACTIVITY AND MOLECULAR DOCKING STUDY OF SOME NOVEL THIAZOLE INCORPORATED SEMICARBAZONE DERIVATIVES

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Abstract
Thiazole-based semicarbazone derivatives have garnered significant attention in medicinal chemistry due to their diverse pharmacological properties, particularly anticancer potential. In this study, we report the synthesis, characterization, and biological evaluation of novel thiazole-incorporated semicarbazone derivatives. The synthesized compounds were characterized using spectroscopic techniques such as NMR, and mass spectrometry. Their anticancer activity was evaluated against selected cancer cell lines using MTT assay, revealing promising cytotoxic effects in comparison to standard anticancer drugs. Molecular docking studies were conducted to investigate the binding interactions of these derivatives with key oncogenic targets, providing insights into their mechanism of action. Additionally, drug-likeness properties were analyzed to assess their pharmacokinetic feasibility. The findings suggest that these novel derivatives exhibit potent anticancer activity and favorable drug-like properties, making them promising candidates for further development in cancer therapeutics.

Keywords Thiazole, Semicarbazone, Synthesis, Anticancer, Molecular docking

Introduction

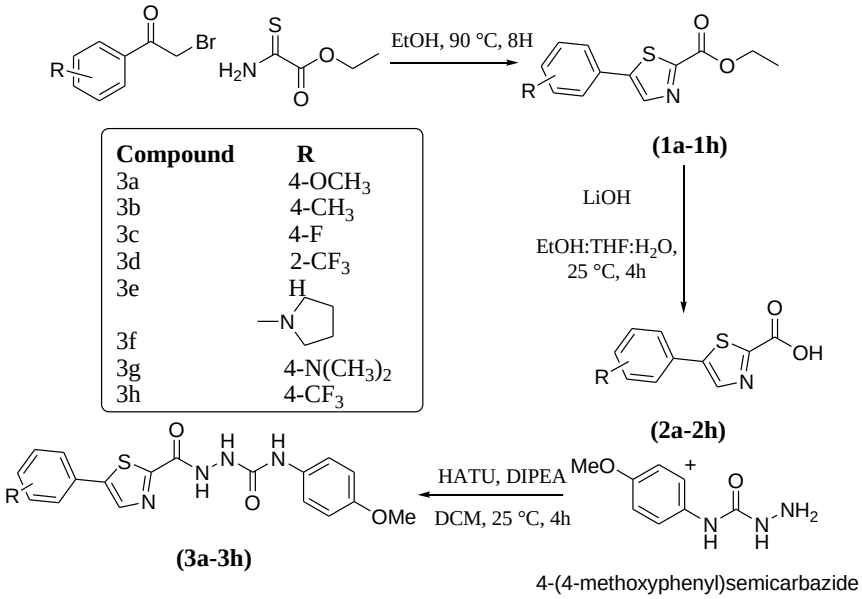
Cancer remains one of the leading causes of morbidity and mortality worldwide, necessitating the continuous development of novel therapeutic agents with enhanced efficacy and reduced toxicity [1-3]. Chemotherapeutic drug resistance, adverse side effects, and limited selectivity of conventional anticancer drugs further underscore the need for new

molecular entities with improved pharmacological profiles [3-7]. Heterocyclic compounds have played a pivotal role in drug discovery, with thiazole derivatives being particularly significant due to their wide-ranging biological activities, including anticancer, antimicrobial, anti-inflammatory, and antiviral properties [8-13].

Among heterocyclic frameworks, thiazole has been extensively studied for its ability to interact with various biological targets, including enzymes, receptors, and DNA [14-16]. Its presence in FDA-approved anticancer drugs such as tiazofurin and bleomycin highlights its therapeutic potential [17-18]. The introduction of a semicarbazone moiety, known for its strong hydrogen-bonding capability and metal-chelating properties, further enhances the biological activity of thiazole derivatives [19-21]. Semicarbazones have demonstrated promising anticancer effects by inhibiting key enzymes involved in tumor progression, such as topoisomerases, tyrosine kinases, and matrix metalloproteinases [22-24].

In recent years, computational approaches such as molecular docking and drug-likeness predictions have emerged as essential tools in drug discovery, enabling the rational design of novel compounds with improved pharmacokinetic and pharmacodynamic profiles. Molecular docking provides valuable insights into the binding interactions of drug candidates with specific oncogenic targets, while drug-likeness studies evaluate their pharmacokinetic properties, including absorption, distribution, metabolism, excretion, and toxicity (ADMET) [25-26].

This study aims to synthesize and characterize a series of novel thiazole-incorporated semicarbazone derivatives (Scheme 1), evaluate their anticancer potential against selected cancer cell lines, and explore their molecular interactions through docking studies. Furthermore, drug-likeness was performed to assess their suitability as potential anticancer agents. The findings from this study will contribute to the ongoing efforts in the development of novel heterocyclic compounds with potent anticancer activity and favorable drug-like properties.



Scheme 1: Synthesis of some novel thiazole incorporated semicarbazone derivatives

Material and Methods

All the melting points reported in the dissertation progress report were determined by open capillary tube method and are uncorrected. The synthesis and analytical studies of the compounds were carried out using laboratory grade and analytical grade reagents as the case may be standard procedure or reported method were followed with or without modification appropriately as and when required. Elemental analysis (C, H and N) was undertaken with a Perkin-Elmer model 240C analyzer, and all analyses were consistent with theoretical values (within 0.4 %) unless indicated. ^{1}H NMR spectra were recorded on the Bruker DPX-400 instrument at 400 MHz. The ^{1}H chemical shifts are reported as parts per million (ppm) downfield from TMS (Me_4Si). The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer. The homogeneity of the compounds was monitored by ascending thin-layer chromatography (TLC) on silica gel G (Merck)-coated aluminum plates, visualized by iodine vapor.

General synthetic procedure for compound 1a-1h

In a 100 mL round-bottom flask, dissolve substituted ethyl 2-amino-2-thioxoacetate (1 eq.) in ethanol. Added 2-bromo-1-phenylethanone (1.2 eq.) to the reaction mixture. Stir the mixture thoroughly to ensure homogeneity. Heat the reaction mixture to 90°C under reflux for 8 hours. Stir continuously to allow the thiazole ring to form via nucleophilic substitution and cyclization. Monitor the reaction progress using thin-layer chromatography (TLC). After completion, of the reaction. Add the reaction mixture to cold water to precipitate the crude product extract the organic layer with ethyl acetate and wash with water and evaporate under vacuum.

General synthetic procedure for compound 2a-2h

The synthesis of substituted 5-phenylthiazole-2-carboxylic acid from ethyl 5-phenylthiazole-2-carboxylate involves the hydrolysis of the ester group using LiOH in a mixed solvent system. In a 100 mL round-bottom flask, dissolve ethyl 5-phenylthiazole-2-carboxylate (1 eq.) in a mixture of EtOH:THF:H_2O in a 2:1:1 ratio (v/v/v). Add $LiOH \cdot H_2O$ (3 eq.) to the solution under stirring. Stir the reaction mixture at 25°C for 4 hours. Monitor the progress of the reaction using thin-layer chromatography (TLC). After completion of reaction the reaction mixture was evaporated and quenching with water and neutralize the reaction mixture by dilute hydrochloric acid (HCl) dropwise until the pH reaches around 3-4. This will precipitate the carboxylic acid product and filter the precipitate and wash it with cold water to remove any soluble impurities, dry the product under vacuum.

5-(4-methoxyphenyl)thiazole-2-carboxylic acid (**2a**): yield: 73%; M.P.: 123-125 °C; R_f: 0.45 (silica gel, 50% EtOAc/Hexane).

5-p-tolylthiazole-2-carboxylic acid (**2b**): yield: 67%; M.P.: 132-135 °C; R_f: 0.47 (silica gel, 50% EtOAc/Hexane).

5-(4-fluorophenyl)thiazole-2-carboxylic acid (**2c**): yield: 62%; M.P.: 127-130 °C; R_f: 0.72 (silica gel, 50% EtOAc/Hexane).

5-(2-(trifluoromethyl)phenyl)thiazole-2-carboxylic acid (**2d**): yield: 71%; M.P.: 131-134 °C; R_f: 0.43 (silica gel, 50% EtOAc/Hexane).

5-phenylthiazole-2-carboxylic acid (**2e**): yield: 66%; M.P.: 126-129 °C; R_f: 0.65 (silica gel, 50% EtOAc/Hexane).

5-(4-(pyrrolidin-1-yl)phenyl)thiazole-2-carboxylic acid (**2f**): yield: 61%; M.P.: 123-126 °C; R_f: 0.51 (silica gel, 50% EtOAc/Hexane).
5-(4-(dimethylamino)phenyl)thiazole-2-carboxylic acid (**2g**): yield: 68%; M.P.: 137-139 °C; R_f: 0.59 (silica gel, 50% EtOAc/Hexane).
5-(4-(trifluoromethyl)phenyl)thiazole-2-carboxylic acid (**2h**): yield: 62%; M.P.: 124-127 °C; R_f: 0.58 (silica gel, 50% EtOAc/Hexane).

General synthetic procedure for compound 3a-3h

in Step 3 involves the coupling of compound 2(a-h) and compound 4-(4-methoxyphenyl)semicarbazide, using HATU and DIPEA in DCM at room temperature. In a clean, dry round-bottom flask, dissolve compound 9(a-l) (1.0 eq.) in DCM. Add HATU (2 eq.) to the solution and stir for 5 minutes to activate the carboxylic acid. Add DIPEA (3 eq.) to the reaction mixture and added dissolved compound 3 (1.1 eq.) in a small amount of DCM and add it dropwise to the reaction mixture under stirring. Stir the reaction mixture at 25°C for 4 hours. Monitor the progress using thin-layer chromatography (TLC) and after completion, quench the reaction by adding water. Extract the organic layer with DCM (3×20 mL). Combine the organic layers, wash with brine, and dry over anhydrous sodium sulphate. Concentrate the organic layer under reduced pressure to obtain the crude product. Purify the product by column chromatography using an appropriate solvent system (e.g., hexane/ethyl acetate). Confirm the structure of compound **3a**-**3h** using spectroscopic techniques such as FTIR, ^{1}H NMR and mass spectrometry.

4-(4-methoxyphenyl)-1-(5-(4-methoxyphenyl)thiazole-2-carbonyl)semicarbazide (**3a**): yield: 66%; M.P.: 201-205 °C; R_f: 0.46 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.81 (s, 6H, 2OCH3), 5.92 (s, 1H, NH), 7.21 (s, 1H, NH), 8.04 (s, 1H, NH), 6.50-8.59 (m, 9H, Ar-H); LCMS (ESI): calcd. for $C_{19}H_{18}N_4O_4S$ $[M+H]^+$: 398.4451, found: 399.1121. Elemental analysis: C, 57.27; H, 4.55; N, 14.06.

4-(4-methoxyphenyl)-1-(5-p-tolylthiazole-2-carbonyl)semicarbazide (**3b**): yield: 63%; M.P.: 196-199 °C; R_f: 0.47 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.82 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3), 6.30 (s, 1H, NH), 7.47 (s, 1H, NH), 7.96 (s, 1H, NH), 6.50-8.59 (m, 9H, Ar-H); LCMS (ESI): calcd. for $C_{19}H_{18}N_4O_3S$ $[M+H]^+$: 382.4415, found: 383.1165. Elemental analysis: C, 59.67; H, 4.74; N, 14.65.

1-(5-(4-fluorophenyl)thiazole-2-carbonyl)-4-(4-methoxyphenyl)semicarbazide (**3c**): yield: 68%; M.P.: 202-207 °C; R_f: 0.53 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.82 (s, 3H, OCH_3), 6.95 (s, 1H, NH), 7.36 (s, 1H, NH), 7.90 (s, 1H, NH), 6.50-8.59 (m, 9H, Ar-H); LCMS (ESI): calcd. for $C_{18}H_{15}FN_4O_3S$ $[M+H]^+$: 386.4056, found: 387.0934. Elemental analysis: C, 55.95; H, 3.91; N, 14.50.

4-(4-methoxyphenyl)-1-(5-(2-(trifluoromethyl)phenyl)thiazole-2-carbonyl)semicarbazide (**3d**): yield: 71%; M.P.: 184-188 °C; R_f: 0.49 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.81 (s, 3H, OCH_3), 6.95 (s, 1H, NH), 7.23 (s, 1H, NH), 7.41 (s, 1H, NH), 6.50-8.59 (m, 9H, Ar-H); LCMS (ESI): calcd. for $C_{19}H_{15}F_3N_4O_3S$ $[M+H]^+$: 436.4132, found: 437.0941. Elemental analysis: C, 52.29; H, 3.46; N, 12.84.

4-(4-methoxyphenyl)-1-(5-phenylthiazole-2-carbonyl)semicarbazide (**3e**): yield: 62%; M.P.: 188-191 °C; R_f: 0.47 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.82 (s, 3H, OCH_3), 6.94 (s, 1H, NH), 7.27 (s, 1H, NH), 7.57 (s, 1H, NH), 6.50-

8.59 (m, 10H, Ar-H); LCMS (ESI): calcd. for $C_{18}H_{16}N_4O_3S$ $[M+H]^+$: 368.4162, found: 369.1081. Elemental analysis: C, 58.68; H, 4.38; N, 15.21.
4-(4-methoxyphenyl)-1-(5-(4-(pyrrolidin-1-yl)phenyl)thiazole-2-carbonyl)semicarbazide (**3f**): yield: 74%; M.P.: 204-209 °C; R_f: 0.51 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.81 (s, 3H, OCH_3), 6.37 (s, 1H, NH), 6.93 (s, 1H, NH), 7.63 (s, 1H, NH), 6.50-8.59 (m, 9H, Ar-H), 1.00-4.00 (m, 8H, Al-H); LCMS (ESI): calcd. for $C_{22}H_{23}N_5O_3S$ $[M+H]^+$: 437.5165, found: 438.1641. Elemental analysis: C, 60.39; H, 5.30; N, 16.01.
1-(5-(4-(dimethylamino)phenyl)thiazole-2-carbonyl)-4-(4-methoxyphenyl)semicarbazide (**3g**): yield: 69%; M.P.: 177-181 °C; R_f: 0.44 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.82 (s, 3H, OCH_3), 2.93 (s, 6H, $2CH_3$), 6.97 (s, 1H, NH), 7.51 (s, 1H, NH), 7.94 (s, 1H, NH), 6.50-8.59 (m, 9H, Ar-H); LCMS (ESI): calcd. for $C_{20}H_{21}N_5O_3S$ $[M+H]^+$: 411.4819, found: 412.1441. Elemental analysis: C, 58.38; H, 5.14; N, 17.02.
4-(4-methoxyphenyl)-1-(5-(4-(trifluoromethyl)phenyl)thiazole-2-carbonyl)semicarbazide (**3h**): yield: 66%; M.P.: 205-209 °C; R_f: 0.48 (silica gel, 50% EtOAc/Hexane); ^{1}H-NMR (400 MHz, DMSO-d_6, TMS): δ 3.81 (s, 3H, OCH_3), 6.06 (s, 1H, NH), 7.47 (s, 1H, NH), 8.31 (s, 1H, NH), 6.00-9.00 (m, 9H, Ar-H); LCMS (ESI): calcd. for $C_{19}H_{15}F_3N_4O_3S$ $[M+H]^+$: 436.41, found: 437.0961. Elemental analysis: C, 52.29; H, 3.46; N, 12.84.

In vitro Anticancer activity
The anticancer activity of the synthesized compounds was evaluated against four cancerous cell lines; human breast (MCF-7), cervical cancer (C33A), oral (KB) and prostrate (DU-145) using (SRB) colorimetric assay. Erlotinib was included in the experiments as reference cytotoxic compounds for all the tested cell lines. The results were expressed as median growth inhibitory concentration (IC_{50}) values, which represent the concentration of a drug that is required for 50% inhibition of cell growth after 48 h of incubation, compared to untreated controls [27-28].

In Silico Likeness
In-silico study of synthesized compounds (3a-3h) was performed for prediction of ADME properties. Polar surface area (TPSA) and molecular volume were calculated online using Swiss ADME tool [29-30].

Molecular Docking Study
The molecular docking studies of the synthesized peptides was performed on Windows 10(64-bit) operating systems with 64 GB RAM and AMD Ryzen 9 5950X 16-Core Processor3.40 GHz. Autodock tools, Autodock Vina, PyRx, Pymol and Maestro Visualiser tools were used.
The crystallographic 3D structure of E. coli thymidylate Synthase complexed with an anticancer drug ZD1694 (PDB ID: 2KCE) was accessed from Protein Data Bank. The resolution of the XRD structure of pdb (2KCE) is 2.20 Å. The structure of PDB complexes was downloaded from RCSB database and protein preparation was carried out using the Autodock Wizard by deleting attached water molecules, bound heteroatoms/ligand, adding polar hydrogens, kollman charges, spreading charge equally over all atoms and checking

for missing atoms on residues. The PDB files were then converted to the PDBQT format for executing the next step [31-35].
The 2D structures were drawn by Chemdraw and converted into 3D format. The ligands were minimized by MMFF94 Force Field and converted to PDBQT format by openbabel in PyRx tool.
For carrying out docking between prepared receptors and ligands, grid was generating by taking the center on attached ligand. The grid dimensions for PDB ID: 2KCE was number of points as 25, 25, 25 in X,Y,Z direction 14.1, 13.6, 34.4 with default spacing.

Results and Discussion

In step 1 performed the thiazole cyclization followed by reflux of ethyl 2-amino-2-thioxoacetate and 2-bromo-1-phenylethanone to get the desire, in step 2 get the desired acid followed by hydrolysis using LiOH, final step amide coupling we prepared compound **2a-2h** and compound **3a-3h**, using HATU and DIPEA in DCM at room temperature.
The reaction was monitored by TLC and melting point. The structures of the compounds were confirmed by IR, NMR and Mass spectrometry. The purity of compounds was established by elemental analysis.
The synthesized thiazole-incorporated semicarbazone derivatives (**3a–3h**) were screened for their anticancer activity against four different human cancer cell lines are DU 145 (Prostate cancer), MCF7 (Breast cancer), C33A (Cervical cancer) and KB (Oral cancer). The IC_{50} values (µg/ml) for each compound were determined using the MTT assay, and the results were compared with the standard anticancer drug Erlotinib. The data are presented in the table 1 and figure 1.
Among all synthesized derivatives, compound 3h exhibited the most potent anticancer activity, with IC_{50} values of 0.7 µg/ml (DU 145), 1.4 µg/ml (MCF7), 2.5 µg/ml (C33A), and 1.8 µg/ml (KB). The activity of **3h** was comparable to the standard drug Erlotinib, suggesting its potential as a promising anticancer lead compound.
Compounds **3a** and **3d** displayed moderate anticancer activity, with IC_{50} values below 10 µg/ml for most cell lines. Compound 3d (IC_{50}= 2.1 µg/ml for DU 145, 3.5 µg/ml for MCF7, 2.9 µg/ml for C33A, and 4.5 µg/ml for KB) showed particularly good activity across all tested cancer cell. The significantly lower IC_{50} of compound **3h** suggests the presence of trifluoromethyl group at 4^{th} postion enhancing its anticancer activity. Compounds **3d** and **3a**, with moderately low IC_{50} values, substitution of 2-CF_3 and 4-OCH_3 respectively that contribute to their cytotoxicity.

Table 1: *In vitro* anticancer activity of Compound

Compound	**IC_{50} (µg/ml)**			
	DU 145	**MCF7**	**C33A**	**KB**
3a	3.8	6.4	8.2	7.9
3b	14.4	19.2	21.8	22.3
3c	21.1	24.9	19.8	16.7
3d	2.1	3.5	2.9	4.5
3e	7.6	11.9	14.3	17.8
3f	24.7	28.1	32.1	21.9

3g	8.2	6.9	11.3	17.4
3h	0.7	1.4	2.5	1.8
Erlotinib	2.6	1.3	1.5	1.2

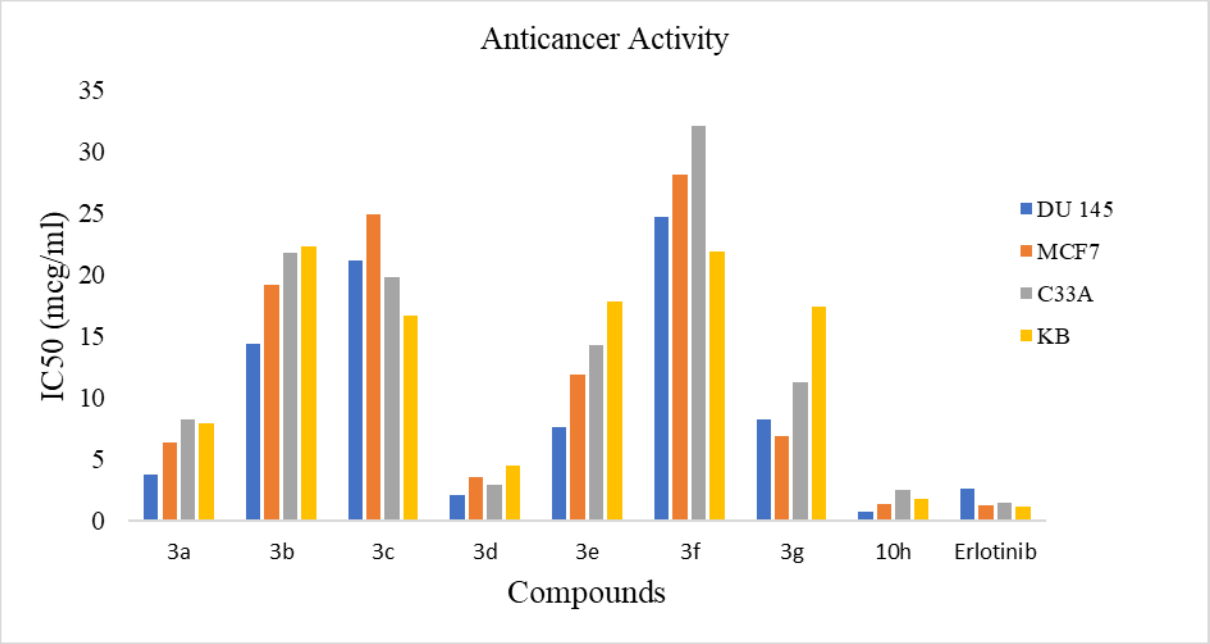


Figure 1: In vitro Anticancer activity

All derivatives followed Lipinski's rule of five, indicating good drug-likeness properties. Compounds **3a, 3b, 3c, 3e, 3f,** and **3g** exhibited high gastrointestinal (GI) absorption, making them promising candidates for oral bioavailability. However, compounds **3d** and **3h** showed low GI absorption, which may require further optimization to improve their pharmacokinetic profiles (Table 2).

Table 2: In silico Drug Likeness and absorption

Comp	**Molecular weight (g/mol)**	**Num. rotatable bonds**	**Num. H-bond acceptors**	**Num. H-bond donors**	**TPSA (Å^2)**	**Log Po/w (iLOGP)**	**GI Absorption**	**Lipinski**
3a	398.44	9	5	3	129.82	3.01	High	0
3b	382.44	8	4	3	120.59	2.96	High	0
3c	386.40	8	5	3	120.59	2.70	High	0
3d	436.41	9	7	3	120.59	2.87	Low	0
3e	368.41	8	4	3	120.59	2.72	High	0
3f	437.51	9	4	3	123.83	3.30	High	0
3g	411.48	9	4	3	123.83	3.02	High	0
3h	436.4	9	7	3	120.59	2.93	Low	0

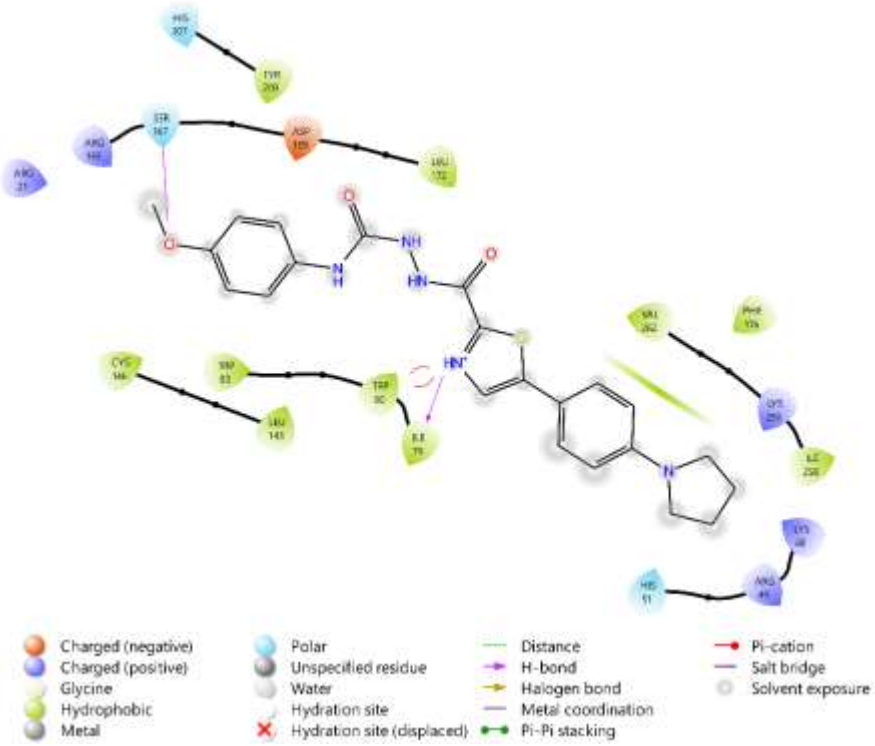
The molecular docking analysis of the thiazole-incorporated semicarbazone derivatives was conducted to evaluate their binding affinity and interactions with the target protein. The docking scores (binding energies) ranged from -8.6 to -9.4 kcal/mol, with compound **3h** and **3f** exhibiting the most favorable docking scores (-9.4 kcal/mol), surpassing the reference drug Erlotinib (-8.4 kcal/mol) (Table 3).

All compounds demonstrated strong hydrophobic interactions with critical residues such as PHE176, TYR209, ILE79, TRP80, and CYS146, which are known to be crucial for ligand binding and stability.

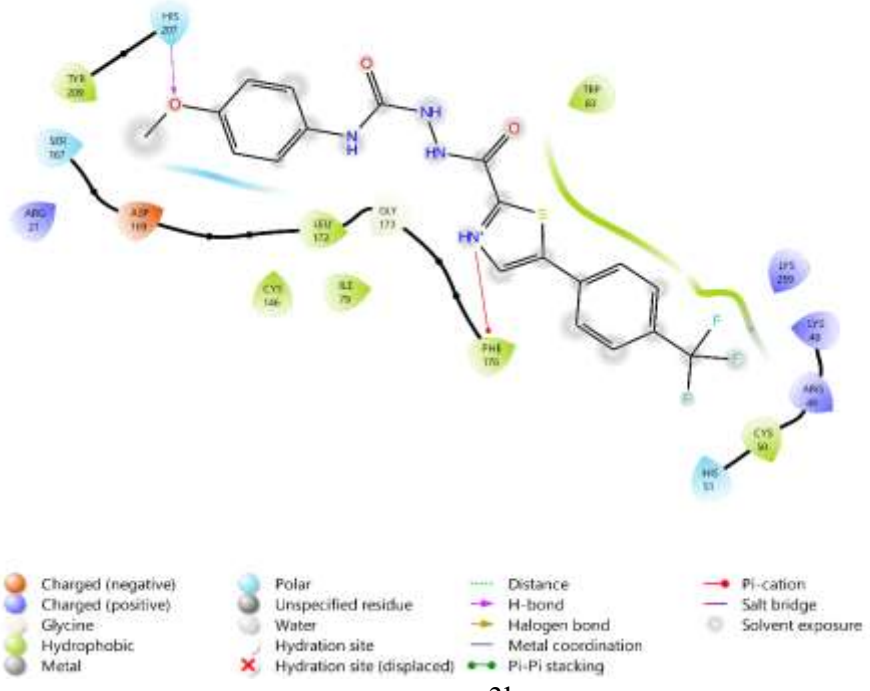
Most compounds exhibited at least one hydrogen bond, with HIS207, ASP169, and SER167 being the most frequently involved residues. Compound **3d** showed an additional interaction with ASP169, which might contribute to its slightly higher binding affinity.

Table 3: Molecular Docking Study Results of PDB Id: 2KCE

Compound No.	**Hydrophobic Interactions**	**H-bond**	**Energy**
3a	LEU143, CYS146, PHE176, ILE79, TRP80, LEU172, TYR209	HIS207	-8.7
3b	TYR209, LEU172, PHE176, ILE79, TRP80, CYS146, LEU143	HIS207	-8.9
3c	TYR209, PHE176, ILE79, CYS146, LEU172	HIS207	-8.6
3d	PHE176, CYS146, TRY209, CYS168, TRP83, TRP80, ILE79	ASP169	-9.3
3e	LEU143, CYS146, TYR209, PHE176, ILE79, TRP80, LEU172	HIS207	-8.7
3f	TRY209, LEU172, VAL262, PHE176, ILE258, ILE79, TRP80, TRP83, LEU143, CYS146	ILE79, SER167	-9.4
3g	ALA263, VAL262, PHE176, ILE79, LEU172, TRP83, CYS146, LEU143	-	-8.8
3h	TRY209, TRP83, CYS50, PHE176, LEU172, ILE79, CYS146	HIS207	-9.4
Erlotinib	GLU58, TRP80, ILE79, TYR94, VAL262, PHE176, ALA263, LEU143, CYS146, TYR209, HIS207, SER167, ASP169, CYS168, GLY173, ASN177, HIS147,		-8.4



3f



3h

Figure 2: Binding Pattern of Synthesized compounds (3f and 3h) against 2KCE

Conclusion

Overall, the study highlights compound **3h** as the most potent anticancer agent, with favorable molecular properties, strong cytotoxic effects, and promising drug-likeness characteristics. Future research should focus on further structural modifications, mechanistic studies, *and in vivo* evaluations to enhance the therapeutic potential of these derivatives in cancer treatment.

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References

[1]. Thun MJ, DeLancey JO, Center MM, Jemal A, Ward EM. The global burden of cancer: priorities for prevention. Carcinogenesis. 2010 Jan 1;31(1):100-10.
[2]. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021 May;71(3):209-49.
[3]. Shah SC, Kayamba V, Peek Jr RM, Heimburger D. Cancer control in low-and middle-income countries: is it time to consider screening?. Journal of global oncology. 2019 Mar;5:1-8.
[4]. Luqmani YA. Mechanisms of drug resistance in cancer chemotherapy. Medical principles and practice. 2005;14(Suppl. 1):35-48.
[5]. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nature Reviews Cancer. 2013 Oct;13(10):714-26.
[6]. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The different mechanisms of cancer drug resistance: a brief review. Advanced pharmaceutical bulletin. 2017 Sep;7(3):339.
[7]. Ward RA, Fawell S, Floc'h N, Flemington V, McKerrecher D, Smith PD. Challenges and opportunities in cancer drug resistance. Chemical Reviews. 2020 Jul 21;121(6):3297-351.
[8]. Pathania, S., Narang, R. K., & Rawal, R. K. (2019). Role of sulphur-heterocycles in medicinal chemistry: An update. *European journal of medicinal chemistry*, *180*, 486-508.
[9]. Sahil, Kaur, K., & Jaitak, V. (2022). Thiazole and related heterocyclic systems as anticancer agents: A review on synthetic strategies, mechanisms of action and SAR studies. *Current medicinal chemistry*, *29*(29), 4958-5009.
[10]. Mishra CB, Kumari S, Tiwari M. Thiazole: A promising heterocycle for the development of potent CNS active agents. European journal of medicinal chemistry. 2015 Mar 6;92:1-34.
[11]. Arshad MF, Alam A, Alshammari AA, Alhazza MB, Alzimam IM, Alam MA, Mustafa G, Ansari MS, Alotaibi AM, Alotaibi AA, Kumar S. Thiazole: A versatile standalone moiety contributing to the development of various drugs and biologically active agents. Molecules. 2022 Jun 21;27(13):3994.

[12]. Kabir E, Uzzaman M. A review on biological and medicinal impact of heterocyclic compounds. Results in Chemistry. 2022 Jan 1;4:100606.
[13]. Kumar N, Goel N. Heterocyclic compounds: importance in anticancer drug discovery. Anti-Cancer Agents in Medicinal Chemistry-Anti-Cancer Agents). 2022 Nov 1;22(19):3196-207.
[14]. Sahil, Kaur K, Jaitak V. Thiazole and related heterocyclic systems as anticancer agents: A review on synthetic strategies, mechanisms of action and SAR studies. Current medicinal chemistry. 2022 Sep 1;29(29):4958-5009.
[15]. Jadhav PM, Kantevari S, Tekale AB, Bhosale SV, Pawar RP, Tekale SU. A review on biological and medicinal significance of thiazoles. Phosphorus, Sulfur, and Silicon and the Related Elements. 2021 Oct 3;196(10):879-95.
[16]. Seboletswe P, Cele N, Singh P. Thiazolidinone-Heterocycle Frameworks: A Concise Review of Their Pharmacological Significance. ChemMedChem. 2023 Apr 3;18(7):e202200618.
[17]. Wang J, Long S, Liu Z, Rakesh KP, Verma R, Verma SK, Kumar KS. Structure-activity relationship studies of thiazole agents with potential anti methicillin-resistance Staphylococcus aureus (MRSA) activity. Process Biochemistry. 2023 Sep 1;132:13-29.
[18]. O'Neill EC, Schorn M, Larson CB, Millán-Aguiñaga N. Targeted antibiotic discovery through biosynthesis-associated resistance determinants: Target directed genome mining. Critical reviews in microbiology. 2019 May 4;45(3):255-77.
[19]. El-Masry RM, Kadry HH, Taher AT, Abou-Seri SM. Comparative study of the synthetic approaches and biological activities of the bioisosteres of 1, 3, 4-oxadiazoles and 1, 3, 4-thiadiazoles over the past decade. Molecules. 2022 Apr 22;27(9):2709.
[20]. Malik MA, Dar OA, Gull P, Wani MY, Hashmi AA. Heterocyclic Schiff base transition metal complexes in antimicrobial and anticancer chemotherapy. MedChemComm. 2018;9(3):409-36.
[21]. Shahin AI, Zaib S, Zaraei SO, Kedia RA, Anbar HS, Younas MT, Al-Tel TH, Khoder G, El-Gamal MI. Design and synthesis of novel anti-urease imidazothiazole derivatives with promising antibacterial activity against Helicobacter pylori. PLoS One. 2023 Jun 2;18(6):e0286684.
[22]. Tolomeo M, Simoni D. Drug resistance and apoptosis in cancer treatment: development of new apoptosis-inducing agents active in drug resistant malignancies. Current Medicinal Chemistry-Anti-Cancer Agents. 2002 May 1;2(3):387-401.
[23]. Santini C, Pellei M, Gandin V, Porchia M, Tisato F, Marzano C. Advances in copper complexes as anticancer agents. Chemical reviews. 2014 Jan 8;114(1):815-62.
[24]. Pinto C, Cidade H, Pinto M, Tiritan ME. Chiral flavonoids as antitumor agents. Pharmaceuticals. 2021 Dec 5;14(12):1267.
[25]. Leelananda SP, Lindert S. Computational methods in drug discovery. Beilstein journal of organic chemistry. 2016 Dec 12;12(1):2694-718.
[26]. Wu F, Zhou Y, Li L, Shen X, Chen G, Wang X, Liang X, Tan M, Huang Z. Computational approaches in preclinical studies on drug discovery and development. Frontiers in chemistry. 2020 Sep 11;8:726.

[27]. Ismail PS, Khan I, Kumar Kashyap V, Verma VP, Shukla M, Dhasmana A, Pandey S, Singh GP, Khan S, Singh J. Synthesis and biological evaluation of 2, 4-diaminopyrimidine-5-carbonitrile and N-(2-amino-5-cyanopyrimidin-4-yl) benzamide derivatives as EGFR inhibitors. Chemistry & Biology Interface. 2019:148.
[28]. Valenti C, Billi M, Pancrazi GL, Calabria E, Armogida NG, Tortora G, Pagano S, Barnaba P, Marinucci L. Biological effects of cannabidiol on human cancer cells: Systematic review of the literature. Pharmacological Research. 2022 Jul 1;181:106267.
[29]. Korkmaz A, Kurtay G, Kaya E, Bursal E. Design, synthesis, spectroscopic characterizations, in vitro pancreatic lipase as well as tyrosinase inhibition evaluations and in silico analysis of novel aryl sulfonate-naphthalene hybrids. Journal of Biomolecular Structure and Dynamics. 2023 Oct 13;41(15):7128-43.
[30]. da Silva Filho FA, de Freitas Souza T, Ribeiro AG, Alves JE, de Oliveira JF, de Lima Souza TR, de Moura RO, de Lima MD, de Carvalho Junior LB, de Almeida SM. Topoisomerase inhibition and albumin interaction studies of acridine-thiosemicarbazone derivatives. International journal of biological macromolecules. 2019 Oct 1;138:582-9.
[31]. Yadav T, Brahmachari G, Karmakar I, Saha S, Chowdhury J, Pathak A, Kumar R, Sharma R, Bento RR, Yadav NP. Spectroscopic Investigation of Electron-Releasing Functional Groups Substituted N-Iso-Butyl, S-2-Nitro-1-Phenylethyl Dithiocarbamate–A DFT Approach. Polycyclic Aromatic Compounds. 2022 Nov 26;42(10):6917-31.
[32]. Wei BQ, Weaver LH, Ferrari AM, Matthews BW, Shoichet BK. Testing a flexible-receptor docking algorithm in a model binding site. Journal of molecular biology. 2004 Apr 9;337(5):1161-82.
[33]. Suwitono MR, Lizki AC. Docking study of Cyclomulberrin, Cyclomorusin and Engeletin into p50 NF-kÎ² Transcription Factor with AutoDock Vina. InJournal of International Scholars Conference-SCIENCE & ENGINEERING 2016 Jan 1 (Vol. 1, No. 4).
[34]. Kumar P, Alpana A, Dinesh C, Abhinav B. In silico screening and molecular docking of bioactive agents towards human coronavirus receptor. GSC Biological and Pharmaceutical Sciences. 2020;11(1):132-40.
[35]. Ferrari IV, Ravagnan G. Computational study on Polydatin with the Human Alpha-Defensins and the Human Beta Defensins evaluated by Blind Molecular Docking method. Int. J. Sci. Res. in Biological Sciences Vol. 2023 Dec;10(6).