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Synthesis and Docking Studies of Novel *Bis*(2-(Substituted(methyl)amino)-4-phenylthiazol-5-yl)methanone

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A new series of novel synthesis of *bis*(2-(substituted(methyl)amino)-4-phenylthiazol-5-yl)methanone (**PVS 1-9**) is reported. The carbonyl isothiocyanate (**3**) was synthesized by a *para*-cleavage of C–Cl bond of benzoyl chloride (**1**) with ammonium thiocyanate (**2**). The presence of carbonyl group in acyl isothiocyanates enhance the reactivity of acyl isothiocyanates upon reaction with substituted secondary amine (**4**) give *n*-alkylated adduct (**5**), which upon the reaction with dichloro acetone give target compound **7**. Substituted derivatives as inhibitors against lungs, breast and EJFR assist cancer based on virtual screening cellular evaluations with NSCLC H1975 harboring EGFR L858R/T790M double mutations indicated that the most active compound **PVS-7** could inhibit the proliferation of two cell lines in one digital micromolar scale. The enzymatically results indicated that the compounds **PVS-2**, **PVS-4** and **PVS-9** were the most active inhibitor against EGFR T790M and above cancer activity with ~82%. All compounds were well characterized by spectroscopic techniques and their purity was confirmed by UV-HPLC.

Keywords: *Bis*-thiazole, Substituted secondary amine, Virtual computational study.

INTRODUCTION

Lung cancer is the predominant disease and the second leading cause of death after heart disease. Globally, one of 20th century's most popular malignancies, in which 85% of lung cancer is in non-small cell lung cancer (NSCLC) [1]. Epidermal growth factor receptor (EGFR) play an indispensable role in cell proliferation, survival, migration, adhesion and differentiation, while its over expression or dysregulation is responsible for the development and growth of various solid tumors [2]. Therefore, EGFR is a highly promising drug target in the clinical management of NSCLC. FDA approved first-generation EGFR tyrosine kinase inhibitors (TKIs) *e.g.* gefitinib and erlotinib containing 4-anilinoquinazolines for the treatment of del19 and L858R mutations, which resulted in rapid tumor volume shrinkage [3,4]. However, drug resistance through the acquired secondary EGFR (T790M) mutation is commonly observed after 10-16 months treatment of these inhibitors [5].

Heterocycles such as thiazole (azole) have significant importance in current medicinal chemistry due to their wide range of applications. Thiazoles are the backbone of medicinal chemistry because of their synthesis feasibility [6-8]. Thiazole and its derivatives are the most active classes of compounds which are known for their broad spectrum of activities [9,10]. Thiazole attracts researchers to focus their efforts to synthesize novel molecules bearing the thiazole and *bis* thiazole ring [8]. Few of them are represented in Fig. 1.

Zaharia *et al.* [11] synthesized several *bis*-thiazoles derivatives and studied their biological activity against the most common type of cancers, such as prostate and liver. Turan-Zitouni *et al.* [12] compared the biological activity of compounds and its analog to measure the effect of the presence of thiazole ring in the anticancer agent, it was found that the insertion of thiazole fragment into a *bis*-thiourea derivative made it more active against A549 (human lung adenocarcinoma) and C6 (rat glioma) cell lines.

A literature survey reported several synthetic methods for *bis*-thiazoles [13-21]. However, there is no reports on the synthesis of *bis*(2-(substituted (methyl)-amino)-4-phenylthiazol-5-yl)methanone and its derivatives in a single molecular frame work. Keeping in the view of substituted thiazole medicinal applications of our interest in designing and synthesizing a

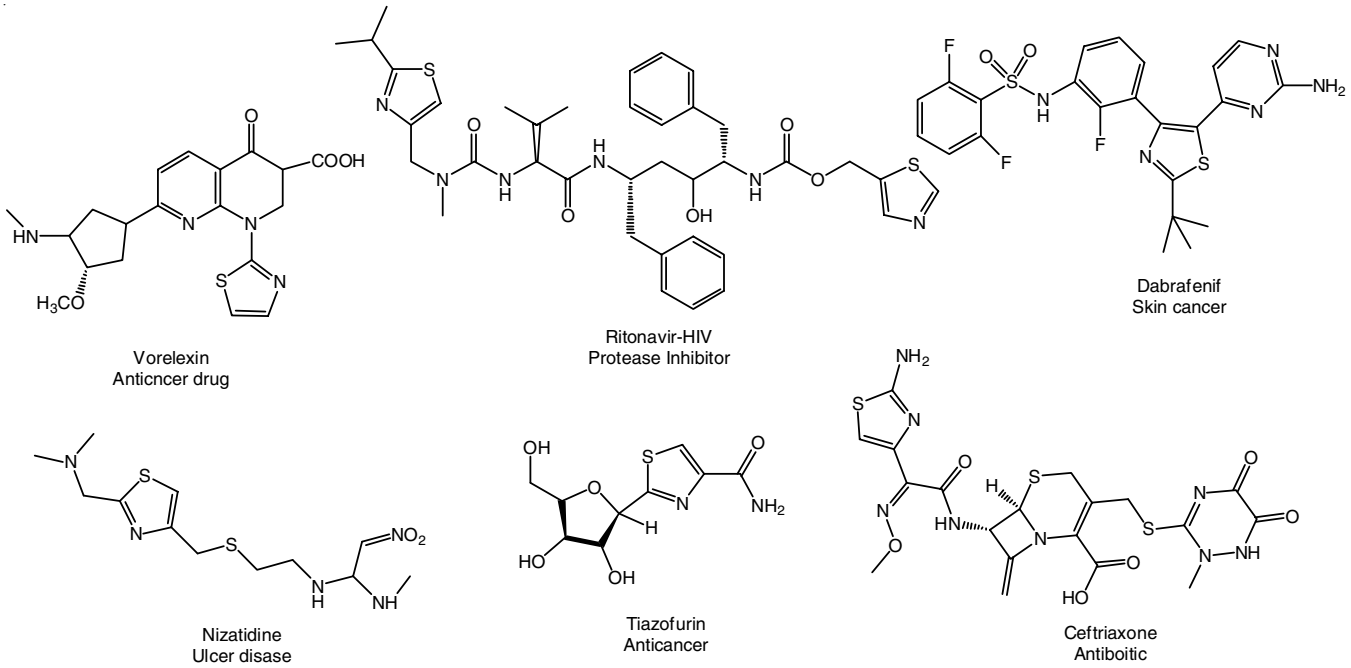


Fig. 1. Drug containing one or two rings of thiazole

bioactive heterocycles, a novel series of *bis*(2-(substituted)-methylamino)-4-phenylthiazol-5-yl)methanone moiety as a pharmacophore is proposed. Therefore, herein, we report a synthesis, characterization, docking and ADME studies of *bis*-(2-(substituted)methylamino)-4-phenyl-thiazol-5-yl)methanone moiety.

EXPERIMENTAL

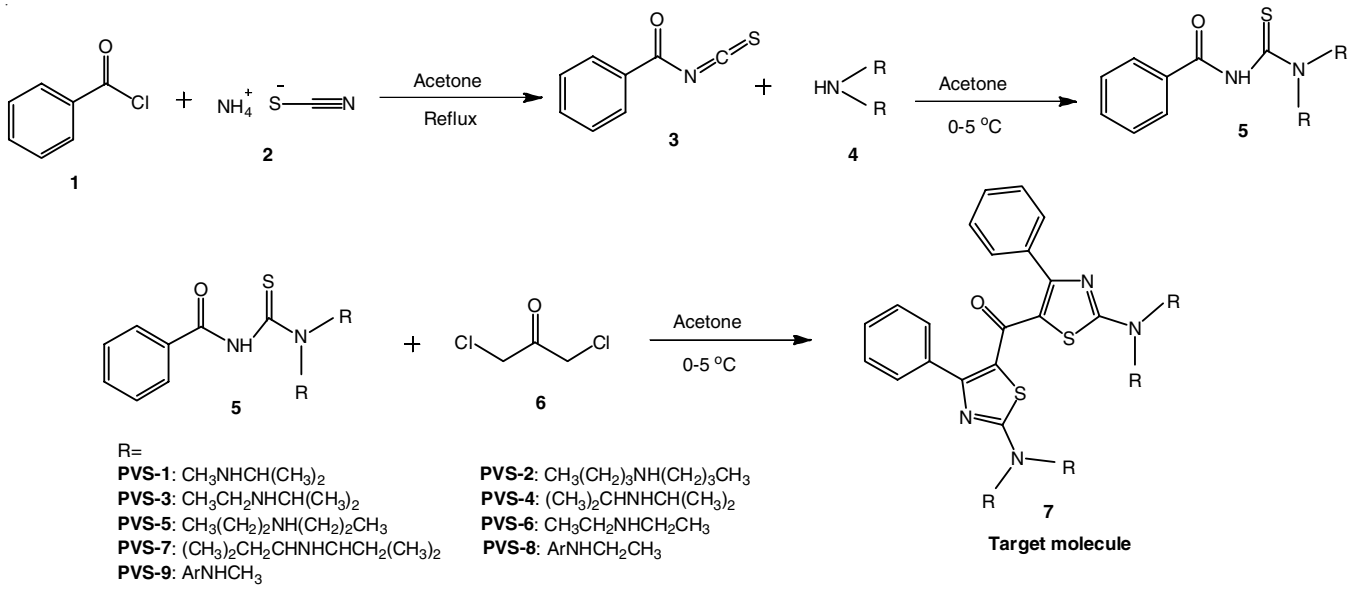
All reagents and solvents were purchased from Merck and Spectrochem and used without further purification. ^{1}H NMR spectra were recorded on a Bruker DRX-400 MHz NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) ESI-HRMS instrument and LC-MS spectrometer. The purity of each of the compounds was checked by thin-layer chromatography (TLC) using silica-gel (60 F_{254}) and the visualization was accomplished by iodine/ ultraviolet light. Furthermore, the purity of all the samples was confirmed by UV-HPLC at 254 nm by photodiode-array detection (PDA) using column Zorbax SB C18 5µ (4.6 × 150), diluent (80:20) acetonitrile:water, the mobile phase was dipotassium hydrogen orthophosphate and the pH 6.5 was adjusted using formic acid.

Synthetic route of *bis*(2-(isopropyl(methyl) substituted amino)-4-phenylthiazol-5-yl)methanone (PVS 1-9): Charged ammonium thiocyanate (**2**, 0.071 mol) in round bottom flask having acetone (4 v/w), stirred to get the homogenous solution and then cooled the reaction mass to 0-5 ºC followed by the addition of benzyl chloride (**1**) over a period of 30-60 min, raise the temperature to reflux and continued the refluxation for 60 min. The reaction progress was monitored by TLC (mobile phase 95:5 hexane:ethyl acetate). At the end of reaction, the yellow colour suspension was observed and the precipitated ammonium chloride (byproduct) was separated by filtration. Filtrate MLR upon distillation gave yellow oily liquid benzoyl isothiocyanate (**3**) with a yield 95%.

To benzoyl isothiocyanate (**3**), acetone (4 v/w) was added and cool the reaction mass to 0-5 ºC. Then substituted 2º amine (0.071 mol) (adduct) was slowly added over a period of 60-90 min by maintaining the same temperature (0-5 ºC) and again stirred for 2-3 h. The reaction progress was monitored by TLC (mobile phase: 95:5 MDC:MeOH & two drops of acetic acid). At the end of reaction, the precipitated product was collected and washed thoroughly with acetone to get pure compound benzamidine derivatives (**5**) with yield 90-95% after drying at 35-45 ºC under vacuum.

To benzamidines (**5**, 0.6288 mol), acetonitrile (4 v/w) was added and cool the reaction mass to 10-15 ºC. Now added triethylamine (1.2 mol) over a period of 60-120 min and then raise the temperature to reflux and maintain for 60-120 min to give *bis*(2-(substituted(methyl)amino)-4-phenylthiazol-5-yl)methanone (**PVS 1-9**). The progress of the reaction was monitored by TLC (mobile phase: 95:5 MDC:MeOH & two drops of acetic acid). After completion of reaction mass cool to 20-25 ºC and added water to precipitate the product, which was collected by filtration. All the derivatives were purified by column (mobile phase hexane:ethyl acetate 85:15) (**Scheme-I**).

***Bis*(2-(isopropyl(methyl)amino)-4-phenylthiazol-5-yl)methanone (PVS-1):** Yield: 95%, HPLC purity: 99.04%, m.p.: 220-222 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3052.48 (arom. C-H *str.*), 2970 (alkyl C-H *str.*), 1612.24, 1528.93, 1482.23, 1408.46 (arom. C=C *str.* in-ring), 1674.83 (C=O *str.*), 701.94 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.75 (m, 4H of 2-phenyl ring), 7.54-7.51 (m, 2H of 2-phenyl ring), 7.46-7.43 (m, 4H of 2-phenyl ring), 4.68 (m, 2H of CH $(CH_3)_2$), 2.98 (s, 6H of -N-CH_3), 1.25-1.23 (d, 12H, CH $(CH_3)_2$) HRMS: *m/z* 491.2 $(M+H)^+$.



Scheme-I: Synthetic route for *bis*(2-(isopropyl(methyl)amino adduct)-4-phenylthiazol-5-yl)methanone (**PVS 1-9**)

***Bis*(2-(dibutylamino)-4-phenylthiazol-5-yl)methanone (PVS-2):** Yield: 92%, HPLC purity: 95.28%, m.p.: 188-190 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 2948.77 (alkyl C-H *str.*), 1605.17, 1531.22, 1445.81 (arom. C=C *str.* in-ring), 692.16 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.17 (m, 8H of 2-phenyl ring), 7.11-7.07 (m, 2H of 2-phenyl ring), 3.48 (t, 4H), 3.32 (m, 4H), 1.70-1.55 (m, 8H) 1.41-1.28 (m, 8H), 0.96 (t, 12H). HRMS: *m/z* 603.2 $(M+H)^+$.

***Bis*(2-(ethyl(isopropyl)amino)-4-phenylthiazol-5-yl) methanone (PVS-3):** Yield: 94%, HPLC purity: 96.14%, m.p.: 204-206 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3073.57 (arom. C-H *str.*), 2978.51 (alkyl C-H *str.*), 1620.11, 1495.10, 1411.89, (arom. C=C *str.* in-ring), 1708.08 (C=O *str.*), 701.34 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78-7.76 (m, 4H of 2-phenyl ring), 7.56-7.51 (m, 2H of 2-phenyl ring), 7.47-7.44 (m, 4H of 2-phenyl ring) 4.67 (d, 2H), 3.46-3.43 (m, 4H), 1.29-1.26 (d, 18H). HRMS: *m/z* 519.2 $(M+H)^+$.

***Bis*(2-(diisopropylamino)-4-phenylthiazol-5-yl)-methanone (PVS-4):** Yield: 90%, HPLC purity: 90.10%, m.p.: 302-304 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3072.90 (arom. C-H *str.*), 2944.13 (alkyl C-H *str.*),1609.17, 1523.44, 1477.40, (arom. C=C *str.* in-ring), 1681.44 (C=O *str.*), 696.67 (C=C bending out-of-plane ring).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.28 (m, 4H of 2-phenyl ring), 7.18-7.17 (m, 4H of 2-phenyl ring), 7.08-7.06 (m, 2H of 2-phenyl ring) 4.00-3.94 (m, 2H), 3.75-3.65 (m, 2H), 1.41-1.40 (d, 12H),1.32-1.31 (d, 12H). HRMS: *m/z* 547.2 $(M+H)^+$.

***Bis*(2-(dipropylamino)-4-phenylthiazol-5-yl)methanone (PVS-5):** Yield: 95%, HPLC purity: 98.89%, m.p.: 186-188 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3094.45 (arom. C-H *str.*), 2892.90 (alkyl C-H *str.*), 1596.78, 1510.79, 1421.48 (arom. C=C *str.* in-ring), 1698.80 (C=O *str.*), 676.40 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24-7.21 (m, 4H of 2-phenyl ring),7.18-7.17(m, 4H of 2-phenyl ring), 7.12-7.08 (m, 2H of 2-phenyl ring), 3.44 (t, 4H),3.30, (t, 4H), 1.74-1.68 (m, 4H) 1.65-1.58 (m, 4H), 0.96-0.89 (m, 12H). HRMS: *m/z* 547.2 $(M+H)^+$.

***Bis*(2-(diethylamino)-4-phenylthiazol-5-yl)methanone (PVS-6):** Yield: 94%, HPLC purity: 98.07%, m.p.: 250-252 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3162.65.45 (arom. C-H *str.*), 2958.98 (alkyl C-H *str.*), 1598.30, 1531.98, 1472.59 (arom. C=C *str.* in-ring), 691.00 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.08 (m, 10H of 2-phenyl ring), 3.59-3.54 (m, 4H), 3.43-3.48 (m, 4H), 1.28 (t, 6H) 1.84 (t, 6H). HRMS: *m/z* 491.19 $(M+H)^+$.

***Bis*(2-(diisobutylamino)-4-phenylthiazol-5-yl)methanone (PVS-7):** Yield: 95%, HPLC purity: 98.80%, m.p.: 190-192 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3061.45 (arom. C-H *str.*), 2956.14 (alkyl C-H *str.*), 1601.73, 1528.63, 1447.18 (arom. C=C *str.* in-ring), 1653.24 (C=O *str.*), 689.60 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.04 (m, 10H of 2-phenyl ring), 3.34 (d, 4H), 3.13, (d, 4H), 2.21-2.06 (m, 4H) 0.94-0.88 (d, 24H), HRMS: *m/z* 603.2 $(M+H)^+$.

***Bis*(2-(ethyl(phenyl)amino)-4-phenylthiazol-5-yl)-methanone (PVS-8):** Yield: 92%, HPLC purity: 93.20%, m.p.: 308-310 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3077.00 (arom. C-H *str.*), 2996.75 (alkyl C-H *str.*), 1619.10, 1500.41 (arom. C=C *str.* in-ring), 1682.59 (C=O *str.*), 689.29 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.16 (m, 20H of 2-phenyl ring), 4.06-4.00 (m, 2H),3.96-3.90, (m, 2H), 1.26-1.94 (m, 6H). HRMS: *m/z* 587.2 $(M+H)^+$.

***Bis*(2-(methyl(phenyl)amino)-4-phenylthiazol-5-yl)-methanone (PVS-9):** Yield: 94%, HPLC purity: 99.28%, m.p.: 288-290 °C. FT-IR (KBr, ν_{max}, cm^{-1}): 3014.96 (arom. C-H *str.*), 2996.93 (alkyl C-H *str.*), 1614.50, 1511.41, 1400.89 (arom. C=C *str.* in-ring), 1734.11 (C=O *str.*), 694.16 (C=C bending out-of-plane ring). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.17 (m, 20H of 2-phenyl ring), 3.56 (s, 3H), 3.47 (s,3H). HRMS: *m/z* 559.2 $(M+H)^+$.

RESULTS AND DISCUSSION

Ammonium thiocyanate (**2**) upon reaction with benzoyl chloride (**1**) in the presence of acetone at reflux conditions to give arylisothiocynate (**3**), which upon reaction with 2º amine

adduct (**4**) in acetone at lower temperature to give substituted benzamide (**5**). The dried substituted product upon reaction with dichloroacetone in acetonitrile using triethylamine base at reflux condition to give *bis*(2-(substituted(methyl)amino adduct)-4-phenylthiazol-5-yl)methanone (**PVS 1-9**).

All the synthesized compounds' structures conformed by a spectroscopic techniques such as FT-IR, ^{1}H NMR and HRMS. As a representative **PVS-1** in ^{1}H NMR, the multiplate at δ 7.77-7.75 ppm integrated for four protons of two phenyl rings attached to *ortho* to thialozole ring, four protons show the multiplicity at δ 7.46-7.43 ppm of two phenyl rings attached to *meta* to thiazole ring, two proton shows multiplicity at δ 7.54-7.51 ppm, two phenyl rings attached to *para* to thiazole ring, the signal at δ 4.68 shows the multiplicity of isopropyl group attached to a substituted amine group. the signal at δ 2.98 singlets of 6H two methyl group attached to amine group & two hydrogen double observed at δ 1.25-1.23 ppm, which shows the presence of four methyl groups. The structure of compound **6a** was confirmed by HRMS at molecular ion peaks *m/z* = 391.2 $(M+H)^+$. The 99.04 % AUC purity was confirmed by HPLC.

Docking study: The protein crystal structure of EGFR T790M kinase domain co-crystallized with AEE788 (PDB: 2JIU) was obtained from the Protein Data Bank. Protein preparation was carried out with the protein preparation wizard in Maestro. The protein was prepared after confirming chemical correctness, assigning bond orders, eliminating water molecules, hydrogens added for pH 7.0 using Epik, Prime was used to complete missing side chains and loops and termini were capped. Using the default constraint of 0.30 Å RMSD and the OPLS 2005 force field, a restrained minimization of the protein structure was performed to complete protein preparation. The binding site was defined around the co-crystalized AEE788 and the receptor grid was prepared based on this entry using receptor grid generation. Molecular docking was performed using the glide ligand docking module in standard precision mode, where the receptor grid defined in the receptor grid generation folder was selected for the docking of ligands prepared by using LigPrep. The binding conformations were examined to identify critical interactions.

Prime MM-GBSA binding free energy analysis: Molecular mechanics with generalized born surface area (MM/GBSA) is the most popular method to calculate the ligand binding energies, which include the OPLS3 force field and VSGB solvent model. The Prime MM-GBSA simulation was carried out by using the Glide pose viewer file to calculate the total binding free energy. These poses were taken as inputs for the energy minimization of the protein-ligand complexes ($E_{complex}$), the free protein ($E_{protein}$) and the free ligands (E_{ligand}). The binding free energy ΔG_{bind} was determined according to the following equation:

$$\Delta G_{bind} = E_{Complex\ (minimized)} - E_{Ligand\ (minimized)} - E_{Receptor\ (minimized)}$$

The MM/GBSA calculations were used to estimate relative binding affinity of ligands to the receptor (kcal/mol). As the MM/GBSA binding energies are approximate free energies of binding, a more negative value indicates stronger binding [22,23].

Drug likeness and *in silico* ADME study: The drug likeliness of novel *bis*(2-(substituted amino-4-phenylthiazol-5-yl)-methanone (**PVS 1-9**) was calculated according to Lipinski's rule of five and the Jorgensen's rule of three using QikProp module of Maestro [24]. In general, the studied parameters were allow to ascertain a poor oral absorption or membrane permeability, which occurs when the evaluated molecules present values higher than 5 H-bond donors (HBD), 10 H-bond acceptors (HBA), molecular weight (MW) greater than 500 Da and greater octanol/water partition coefficient Log P (log Po/w). The docking study data (Table-1), ADME properties (Table-2) and *in silico* pharmacokinetic (Table-3).

TABLE-1
DOCKING RESULTS OF NOVEL SYNTHESIZED *BIS*(2-(SUBSTITUTED(METHYL)AMINO)-4-PHENYLTHIAZOL-5-YL)METHANONE (**PVS 1-9**)

Compd.	Docking score	Glide evdw	Glide emodel	Glide energy
PVS-1	-5.66904	-50.7841	-66.1413	-51.8628
PVS-2	-5.87236	-47.5589	-65.1008	-50.3867
PVS-3	-5.6088	-48.2663	-67.4794	-51.4997
PVS-4	-6.34164	-52.252549	-73.2867	-55.2305
PVS-5	-7.92431	-56.405	-90.5082	-61.2401
PVS-6	-62987	-35.5844	-52.1614	-37.2154
PVS-7	-6.34039	-38.0783	-52.3018	-38.2258
PVS-8	-6.17377	-38.7282	-51.6541	-38.0763
PVS-9	-6.24889	-39.1426	-53.9118	-40.1772

TABLE-2
ADME PROPERTIES OF NOVEL SYNTHESIZED *BIS*(2-(SUBSTITUTED(METHYL)AMINO)-4-PHENYLTHIAZOL-5-YL)METHANONE (**PVS 1-9**)

Compd.	Lipinski's rule				
	m.w.	Donor HB	Acceptor HB	QPlog Po/w[a]	Rule of five
Rule	< 500	≤ 5	< 10	< 5	–
PVS-1	391.2	0	6	6.752	2
PVS-2	603.2	0	5	5.785	2
PVS-3	519.2	0	7	6.5	2
PVS-4	574.2	0	6	8.368	2
PVS-5	547.2	0	6	7.781	2
PVS-6	491.19	0	8	9.043	2
PVS-7	603.2	0	5.7	2.533	0
PVS-8	587.2	0	4	3.794	0
PVS-9	559.2	0	4.5	3.776	0

Using cellular evaluations with NSCLC H1975 harboring EGFR L858R/T790M double mutations indicated that the most active compound **PVS-7** could inhibit the proliferation of two cell lines in one digital micro-molar scale. The enzymatically biological results indicated that compounds with **PVS-2**, **PVS-4** and **PVS-9** were the most active inhibitor against EGFR T790M and above cancer with a ~82% (Fig. 2). These three compounds were less active against wild type EGFR type 2, demonstrating its high selectivity value against EGFR T790M over WT EGFR. Compound **PVS-7** demonstrated a favourable docking score, binding free energy, interacted with key amino acid residue (Met793) necessary for T790M EGFR inhibition and also showed significant moderation for parameters investigated for druglikness and ADME properties (Tables 1-3).

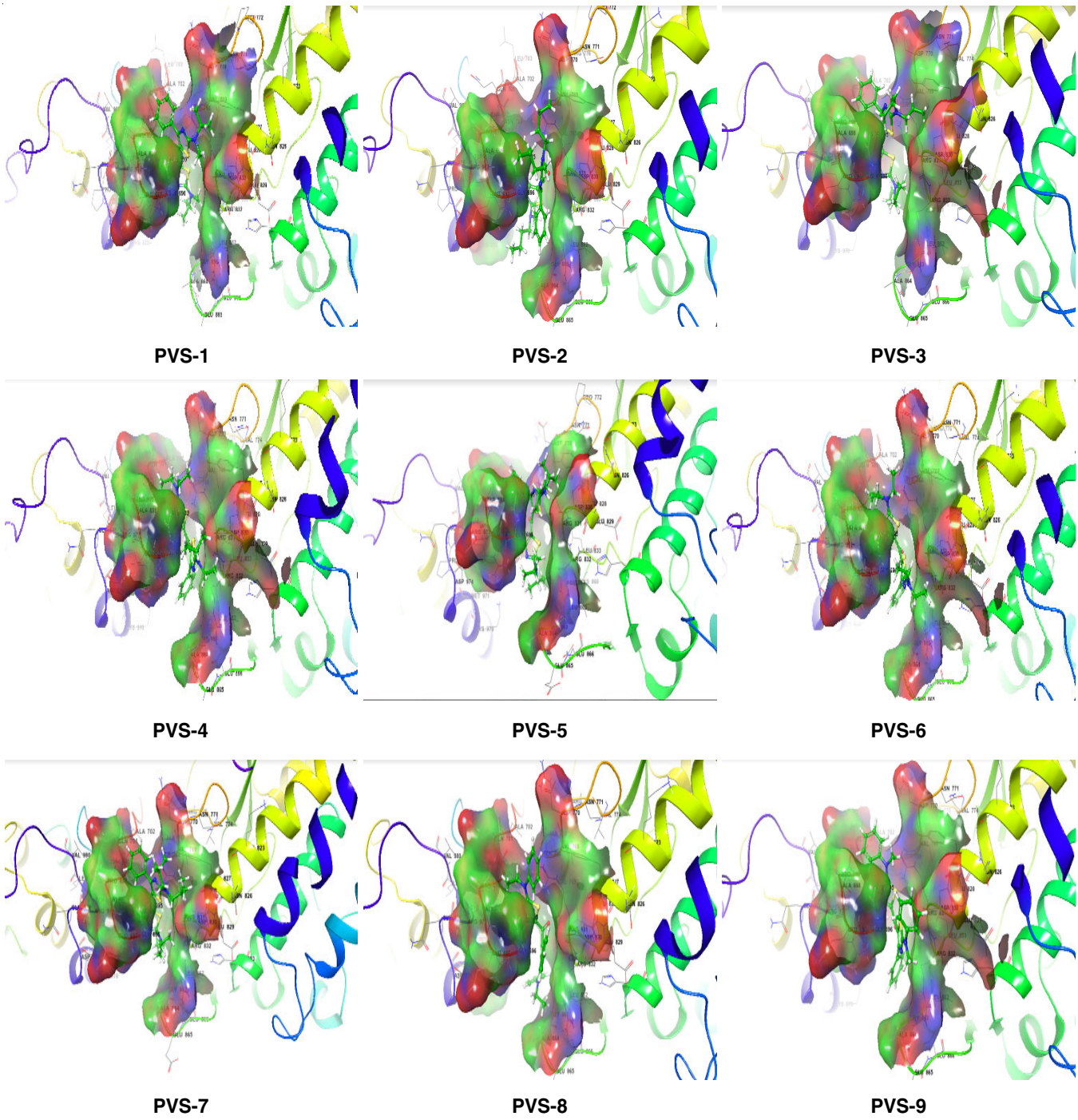


Fig. 2. 3D Molecular docking structures of synthesized *bis*(2-(substituted(methyl)amino)-4-phenylthiazol-5-yl)methanone (**PVS 1-9**) with EGFR L858R/T790M

Conclusion

A new series of *bis*(2-(substituted amino-4-phenylthiazol-5-yl)methanone (**PVS 1-9**) have been synthesized and structurally conformed by various spectroscope techniques. In a computational study of all synthesized compounds, cellular evaluations with NSCLC H1975 harboring EGFR L858R/T790M double mutations indicated that the most active compound **PVS-7** could inhibit the proliferation of two cell lines in one digital micromolar scale. The enzymatically biological results indicated that compounds **PVS-2**, **PVS-4** and **PVS-9** were the most active inhibitors against EGFR T790M whereas rest of the synthesized compounds showed the mild to moderate results.

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TABLE-3
In silico PHARMACOKINETIC STUDIES OF NOVEL SYNTHESIZED
BIS(2-(SUBSTITUTED(METHYL)AMINO)-4-PHENYLTHIAZOL-5-YL)METHANONE (**PVS 1-9**)

Compd.	QPlog S [b]	QPlog HERG[c]	QPPC aco[d]	QPP MDCK[e]	QPlog Khsa[f]	%Human oral absorption[g]
PVS-1	-8.379	-6.441	4636.867	4628.669	1.405	100
PVS-2	-7.827	-6.093	4936.722	10000	1.074	100
PVS-3	-12.91	-8.602	24303.41	1753.46	2.18	100
PVS-4	-9.552	-6.446	4621.076	10000	1.643	100
PVS-5	-5.606	-8.495	73.326	54.215	0.9	70.133
PVS-6	-11.87	-9.488	3450.129	2467.516	2.195	100
PVS-7	-3.372	-4.691	2507.412	3659.34	-0.317	100
PVS-8	-4.77	-4.899	3565.516	6214.096	0.26	100
PVS-9	-4.876	-5.067	361.364	10000	0.141	100

[b]Predicted aqueous solubility in mol/L (acceptable range: 6.5 to 0.5); [c]Predicted IC_{50} value for blockage of HERG K + channels (concerns below-5.0); [d]Predicted Caco-2-cell permeability in nm/s (acceptable range: < 25 is poor > 500 is grate); [e]Predicted apparent MDCK cell permeability in nm/s; [f]Prediction of binding to human serum albumin; [g]Predicted of human oral absorption (< 25% is poor and > 80% is high).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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