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Synthesis, Biological Evaluation and Molecular Modeling of Novel Ethyl 2′-Amino-5′-oxo-1′-(4-phenylthiazol-2-yl)-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate Derivatives and their Computational Quantum Mechanical Modelling

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A new series of biquinoline-phenylthiazole hybrids were designed and synthesized by a base-catalyzed cyclocondensation through one-pot multicomponent reaction. All compounds were tested for *in vitro* antimicrobial and anticancer activities. Enzyme inhibitory activities of all compounds were carried out against FabH and EGFR. Majority of the synthesized compounds displayed promising antimicrobial as well as anticancer activity against used strains and cancer cell lines, respectively. All the compounds were tested for *in vitro* anticancer activities against two cancer cell lines A549 and Hep G2. Compound **9n** (IC_{50} = 0.09 μM) against EGFR and (IC_{50} = 1.03 μM) against A549 kinase displayed the most potent inhibitory activity as compared to other member of the series. In the molecular modelling study, compound **9p** was bound in to the active pocket of EGFR with two hydrogen bonds and one π-cation interactions having minimum binding energy ΔG_b = -8.5626 kcal/mol. For FabH molecule **9u** was found to be binding in the active pocket with minimum binding energy of -8.4033 kcal/mol.

Keywords: Biquinoline-phenylthiazole hybrid, Enzyme inhibitory activity, One pot multicomponent, Anticancer activity.

INTRODUCTION

Studies suggest that the cancer mortality rate has been declining since 1991 with an overall drop of 31% leading to fewer deaths caused by cancer [1]. Healthy life styles, early detection and improved medical management is the reason behind it. But still the survival rate of small cell lung cancer remained at 14% to 15% [1]. One reason experts suggest is the emergence of resistance against commonly used antibiotics in almost all bacterial pathogens [2,3]. This calls for an extensive search for new pharmacophores in the drug designing to overcome this problem of resistance.

Various studies also show that the growth and spread of multi drug-resistant Gram-negative bacteria (MDR-GNB) has been a big challenge for physicians in recent years [4]. Nitrogen containing heterocyclic compounds have been known to be of great importance because of their abundance as well as their biological and chemical behaviour [5]. Almost 75% of the drugs present in the market today belong to N-containing heterocyclic compounds [6]. Quinoline and its derivatives are known to be an excellent and multipurpose motif in the medicinal chemistry [7]. Quinoline is known to play an important role in the drug designing and as a major part of anticancer drugs [8,9]. Quinoline is a versatile pharmacophore which plays an important role in the field of pharmaceutical and medicinal chemistry. They exhibit various properties like anticancer [10], anti-tuberculosis [11], anti-inflammatory [12], antiviral [13], antibacterial [14] and antimalarial [15-20]. Also, thiazole scaffold plays a vital role in many known drugs nowadays [21], whereas substituted thiazoles are known to possess excellent antimicrobial [22], anticancer [23], anti-inflammatory [24], anti-diabetic [25], analgesic properties [26], *etc*.

The SAR studies and chemical structure of substituted thiazole proves that they can be of great importance in designing pharmacophores to the concerned activities [27]. In light of the broad biological significance of quinoline and phenylthiazole, we have attempted to synthesize a new antimicrobial agent by combining phenylthiazole and biquinoline moieties

with thiophenol to investigate if this results in an apparent alteration of the biological activities of quinoline derivatives. We, therefore, report herein the synthesis, biological evaluation and molecular modeling of novel ethyl 2′-amino-5′-oxo-1′-(4-phenylthiazol-2-yl)-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro[3,4'-biquinoline]-3′-carboxylate derivatives by MCR approach.

EXPERIMENTAL

All the chemicals *viz.* acetanilide and its derivatives, thiophenol and its derivatives, ethyl cyanoacetate, phenylthiazole-2-amino-cyclohex-2-en-1-one and its derivatives, phosphorous oxychlorides were purchased commercially and used without further purification. Solvents like DMF and ethanol used were of analytical grade. The synthesis also involved the use of potassium carbonate and pyridine as catalyst. All the steps were closely checked and monitored by carrying out TLC by aluminum plates coated with silica gel 60 F_{254}, 0.25 mm thickness, Merck. Melting point (uncorrected) were taken in open capillaries. Thermo-Fischer LCMS spectrometer was used for mass spectra. Elemental analysis (% C, H, N) for all synthesized compounds was carried out using CHN/S/O Elemental Analyzer 2400 Series II, Perkin-Elmer and FTIR, Perkin Elmer Spectrum-GX spectrophotometer was used for detection of IR spectra using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400 MHz spectrometer using solvent peak as the internal standard.

Synthesis of 2-chloro-3-formylquinolines (3a-d): The starting material 2-chloro-3-formylquinolines **3a-d** was prepared *in situ* by adding $POCl_3$ (12 mol) to an ice-cold solution of DMF (3 mol) dropwise with continuous stirring using a magnetic stirrer. The addition was completed in almost 30 min and stirring was carried for further 30 min keeping the reaction mixture at 0 ºC. The reaction mixture was then brought to room temperature and calculated quantity of acetanilide (1 mol) was added to it. It was then refluxed at 90 ºC on a water bath for 6-7 h. The resultant mixture was then brought to room temperature and finally poured on crushed ice when yellow precipitates of the starting material 2-chloro-3-formylquinolines (**3a-d**) separated out in good to moderate yield. The crude product was filtered, washed with distilled water several times to remove any acidic impurities, dried and finally purified by recrystallization from ethyl acetate with an overall yield of 64-68%.

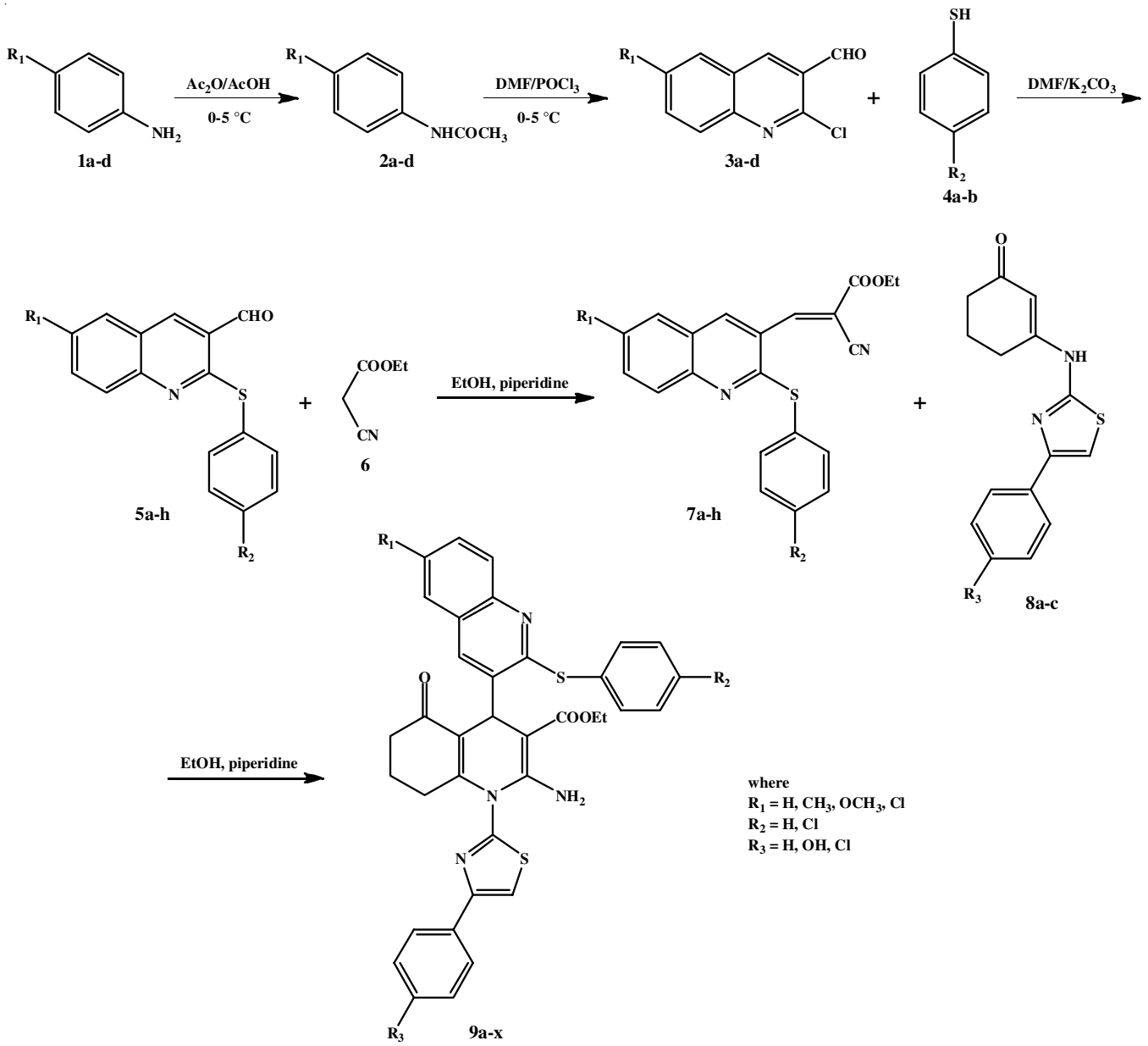
Synthesis of 2-phenylthioquinoline-3-carbaldehyde (5a-h): Nucleophilic substitution of chloro group with thiophenol **4a-b** at C2 position of the starting material 2-chloro-3-formylquinolines (**3a-d**) was carried out by taking in a round bottom flask (RBF) equimolar amount of each compound and refluxing on a water bath at 85 ºC for 1.5 h using K_2CO_3 as base. The cooled reaction mixture was then poured on crushed ice with vigorous stirring. The mixture on neutralization with 1.5 N HCl resulted in excellent yield of 2-phenylthioquinoline-3-carbaldehyde (**5a-h**). The crude product was filtered, washed with distilled water, dried and crystallized using hot ethanol.

Synthesis of ethyl 2′-amino-5′-oxo-1′-(4-substituted phenylthiazol-2-yl)-2-(4-substituted phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9a-x): One pot MCR process was utilized for the synthesis of the target compounds ethyl 2′-amino-5′-oxo-1′-(4-substituted phenylthiazol-2-yl)-2-(4-substituted phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro[3,4′-biquinoline]-3′-carboxylate (**9a-x**). For this, equimolar amount of 2-phenylthioquinoline-3-carbaldehyde (**5a-h**) (5 mmol) was added to ethyl cyanoacetate (**6**, 5 mmol) and 3-((4-phenylthiazol-2-yl)amino)cyclohex-2-en-1-one (**8**, 5 mmol) in a RBF using ethanol (10 mL) as solvent and adding a catalytic amount of piperidine to it. The mixture was stirred and refluxed for about 4 h and TLC (ethyl acetate:hexane = 1:1) was carried out to monitor the same. The solid separated out on completion of reaction and was washed with ethanol to get pure solid product (**Scheme-I**). In this Knoevenagel condensation of compounds **5a-h** and **6** in the presence of base gives an intermediate heterylidenenitrile, which is then followed by Michael type addition of 3-((4-phenylthiazol-2-yl)amino)cyclohex-2-en-1-one (**8**) along with cyclization and tautomerization to give the target molecules **9a-x**.

Ethyl 2′-amino-5′-oxo-1′-(4-phenylthiazol-2-yl)-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9a): Yield: 78%, IR (KBr, ν_{max}, cm^{-1}): 3440 and 3290 (asym. and sym. stretching of -NH_2), 3006 (arom. C-H *str.*), 1671 (C=O *str.*), 1720 (COO ester *str.*), 1542 and 1470 (C=C *str.* of aromatic ring), 1205 (C-S-C thioether *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.11 (t, 3H, CH_3), 1.70-2.21 (m, 6H, 3×CH_2), 3.91 (q, 2H, OCH_2), 4.53 (s, 1H, H4), 7.46-7.68 (m, 16H, Ar-H), 7.98 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.7 (CH_3), 18.7, 21.4, 36.4 (CH_2), 36.6 (C4), 61.7 (CH_2-O), 80.0, 111.9, 147.3, 154.3 (C=C), 105.1, 125.2, 125.3, 126.3, 126.8, 127.5, 127.7, 128.4, 128.6, 128.9, 129.0, 129.2, 129.3, 131.5, 133.1, 135.7, 144.8, 150.3, 173.1, 182 (Ar-C) 167.5, 198.4 (C=O). Anal. calcd. (found) % for $C_{36}H_{30}N_4O_3S_2$ (630.8 g/mol): C, 68.55 (68.56); H, 4.79 (4.78); O, 7.61 (7.60); S, 10.17 (10.16); N, 8.88 (8.89). MS (*m/z*): 630 (M^+).

Ethyl 2′-amino-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro[3,4′-biquinoline]-3′-carboxylate (9b): Yield: 80%, IR (KBr, ν_{max}, cm^{-1}): 3442 and 3291 (asym. and sym. stretching of -NH_2), 3370 (OH *str.*), 3004 (arom. C-H *str.*), 1673 (C=O *str.*), 1721 (COO ester *str.*), 1541 and 1471 (C=C *str.* of aromatic ring), 1207 (C-S-C thioether *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.13 (t, 3H, CH_3), 1.68-2.22 (m, 6H, 3×CH_2), 3.89 (q, 2H, OCH_2), 4.61 (s, 1H, H4), 7.42-7.69 (m, 15H, Ar-H), 7.95 (s, 2H, NH_2) 9.60 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.6 (CH_3), 18.5, 21.5, 36.3 (CH_2), 36.4 (C4), 61.8 (CH_2-O), 80.1, 111.8, 147.2, 154.4 (C=C), 105.1, 125.2, 125.6, 126.6, 126.7, 127.6, 127.8, 128.5, 128.7, 129, 129.1, 129.3, 129.5, 131.5, 132.7, 135.6, 144.8, 150.1, 173.1, 180.1 (Ar-C), 167.3, 198.7 (C=O). Anal. calcd. (found) % for $C_{36}H_{30}N_4O_4S_2$ (646.8 g/mol): C, 66.85 (66.86); H, 4.68 (4.67); O, 9.89 (9.88); S, 9.92 (9.91); N, 8.66 (8.67); MS (*m/z*): 646 (M^+).

Ethyl 2′-amino-1′-(4-(4-chlorophenyl)thiazol-2-yl)-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9c): Yield: 78%, IR (KBr, ν_{max}, cm^{-1}): 3438 and 3295 (asym. and sym. stretching of -NH_2), 3014 (arom. C-H *str.*), 1682 (C=O *str.*), 1724 (COO ester *str.*), 1543



Scheme-I: Synthesis of compound **9a-x**

and 1474 (C=C *str.* of aromatic ring), 1212 (C-S-C thioether *str.*) 747 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.12 (t, 3H, CH_3), 1.65-2.26 (m, 6H, 3×CH_2), 3.86 (q, 2H, OCH_2), 4.65 (s, 1H, H4), 7.41-7.67 (m, 15H, Ar-H), 7.93 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.2 (CH_3), 18.2, 21.8, 36.2 (CH_2), 36.7 (C4), 61.6 (CH_2-O), 80.3, 111.2, 147.1, 154.1 (C=C), 105.2, 125.3, 125.2, 126.3, 126.5, 127.3, 127.7, 128.2, 128.5, 128.9, 129.3, 129.4, 129.7, 131.3, 132.4, 135.4, 144.2, 150.4, 173.6, 180.5 (Ar-C) 167.2, 198.7 (C=O). Anal. calcd. (found) % for $C_{36}H_{29}N_4O_3S_2Cl$ (*m.w.* 665.2 g/mol): C, 65.00 (65.10); H, 4.39 (4.38); O, 7.22 (7.23); S, 9.64 (9.65); N, 8.42 (8.43); Cl, 5.33 (5.32). MS (*m/z*): 665 (M^+).

Ethyl 2′-amino-2-((4-chlorophenyl)thio)-5′-oxo-1′-(4-phenylthiazol-2-yl)-1′,4′,5′,6′,7′,8′-hexahydro[3,4′-biquinoline]-3′-carboxylate (9d): Yield: 76%, IR (KBr, ν_{max}, cm^{-1}): 3436 and 3294 (asym. and sym. stretching of -NH_2), 3012 (arom. C-H *str.*), 1681 (C=O *str.*), 1723 (COO ester *str.*), 1542 and 1471 (C=C *str.* of aromatic ring), 1211 (C-S-C thioether *str.*) 741 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.15 (t, 3H, CH_3), 1.69-2.28 (m, 6H, 3×CH_2), 3.84 (q, 2H, OCH_2), 4.67 (s, 1H, H4), 7.42-7.69 (m, 15H, Ar-H), 7.91 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.5 (CH_3), 18.4, 21.5, 36.3 (CH_2), 36.5 (C4), 61.3 (CH_2-O), 80.1, 111.4, 147.2, 154.2 (C=C), 105.1, 125.4, 125.8, 126.1, 126.2, 127.0, 127.5, 128.3, 128.5, 128.8, 129.1, 129.5, 129.9, 131.4, 132.1, 135.3, 144.4, 150.5, 173.7, 180.1 (Ar-C) 167.1, 198.9 (C=O). Anal. calcd. (found) % for $C_{36}H_{29}N_4O_3S_2Cl$ (*m.w.* 665.2 g/mol): C, 65.00 (65.10); H, 4.39 (4.36); O, 7.22 (7.24); S, 9.64 (9.65); N, 8.42 (8.46); Cl, 5.33 (5.30). MS (*m/z*): 665 (M^+).

Ethyl 2′-amino-2-((4-chlorophenyl)thio)-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-5′-oxo-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9e): Yield: 78%, IR

(KBr, ν_{max}, cm^{-1}): 3437 and 3292 (asym. and sym. stretching of -NH_2), 3372 (OH *str.*), 3013 (arom. C-H *str.*), 1683 (C=O *str.*), 1724 (COO ester *str.*), 1541 and 1472 (C=C *str.* of aromatic ring), 1210 (C-S-C thioether *str.*) 740 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.16 (t, 3H, CH_3), 1.68-2.29 (m, 6H, 3×CH_2), 3.83 (q, 2H, OCH_2), 4.66 (s, 1H, H4), 7.41-7.71 (m, 14H, Ar-H), 7.90 (s, 2H, NH_2) 9.62 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.4 (CH_3), 18.3, 21.4, 36.4 (CH_2), 36.7 (C4), 61.1 (CH_2-O), 80.2, 111.2, 147.1, 154.1 (C=C), 105.1, 125.4, 125.8, 126.1, 126.2, 127.0, 127.5, 128.3, 128.6, 128.8, 129.1, 129.5, 129.9, 131.4, 132.1, 135.3, 148.4, 152.5, 173.7, 180.1 (Ar-C) 167.1, 198.9 (C=O). Anal. calcd. (found) % for $C_{36}H_{29}N_4O_4S_2Cl$ (*m.w.* 681.2 g/mol): C, 63.47 (63.45); H, 4.29 (4.28); O, 9.39 (9.38); S, 9.41 (9.42); N, 8.22 (8.23); Cl, 5.20 (5.24). MS (*m/z*): 681 (M^+).

Ethyl 2′-amino-1′-(4-(4-chlorophenyl)thiazol-2-yl)-2-((4-chlorophenyl)thio)-5′-oxo-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9f): Yield: 78%, IR (KBr, ν_{max}, cm^{-1}): 3435 and 3292 (asym. and sym. stretching of -NH_2), 3010 (arom. C-H *str.*), 1680 (C=O *str.*), 1720 (COO ester *str.*), 1541 and 1473 (C=C *str.* of aromatic ring), 1210 (C-S-C thioether *str.*) 740 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.21 (t, 3H, CH_3), 1.65-2.29 (m, 6H, 3×CH_2), 3.83 (q, 2H, OCH_2), 4.68 (s, 1H, H4), 7.41-7.68 (m, 14H, Ar-H), 7.94 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3 (CH_3), 18.3, 21.6, 36.2 (CH_2), 36.4 (C4), 61.4 (CH_2-O), 80, 111.2, 147.1, 154 (C=C), 105, 125.2, 125.7, 126, 126.2, 127.1, 127.3, 128.2, 128.4, 128.6, 129, 129.2, 129.8, 131.2, 132, 135.2, 144.1, 150.1, 173.5, 180.5 (Ar-C) 167.6, 198.7 (C=O). Anal. calcd. (found) % for $C_{36}H_{28}N_4O_3S_2Cl_2$ (*m.w.* 699.7 g/mol): C, 61.80 (61.81); H, 4.03 (4.02); O, 6.86 (6.85); S, 9.17 (9.16); N, 8.01 (8.02); Cl, 10.13 (10.14). MS (*m/z*): 699 (M^+).

Ethyl 2′-amino-6-methyl-5′-oxo-1′-(4-phenylthiazol-2-yl)-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9g): Yield: 81%, IR (KBr, ν_{max}, cm^{-1}): 3442 and 3293 (asym. and sym. stretching of -NH_2), 3002 (arom. C-H *str.*), 1669 (C=O *str.*), 1719 (COO ester *str.*), 1541 and 1473 (C=C *str.* of aromatic ring), 1207 (C-S-C thioether *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.17 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 1.73-2.24 (m, 6H, 3×CH_2), 3.90 (q, 2H, OCH_2), 4.51 (s, 1H, H4), 7.45-7.71 (m, 15H, Ar-H), 7.97 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.2, 20.3 (CH_3), 18.4, 21.2, 36.3 (CH_2), 36.5 (C4), 61.5 (CH_2-O), 80.2, 111.7, 147.1, 154.4 (C=C), 105.3, 125.1, 125.2, 126.4, 126.7, 127.4, 127.6, 128.2, 128.3, 128.6, 129.2, 129.4, 129.5, 131.2, 133.2, 135.4, 144.6, 150.6, 173.4, 182.5 (Ar-C) 167.9, 198.2 (C=O). Anal. calcd. (found) (%) for $C_{37}H_{32}N_4O_3S_2$ (*m.w.* 644.8 g/mol): C, 68.92 (68.93); H, 5.00 (5.01); O, 7.44 (7.42); S, 9.95 (9.96); N, 8.69 (8.68). MS (*m/z*): 644 (M^+).

Ethyl 2′-amino-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-6-methyl-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4'-biquinoline]-3′-carboxylate (9h): Yield: 79%, IR (KBr, ν_{max}, cm^{-1}): 3440 and 3294 (asym. and sym. stretching of -NH_2), 3376 (OH *str.*), 3010 (arom. C-H *str.*), 1687 (C=O *str.*), 1726 (COO ester *str.*), 1542 and 1471 (C=C *str.* of aromatic ring), 1211 (C-S-C thioether *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.16 (t, 3H, CH_3), 2.33 (s, 3H, CH_3) 1.66-2.28 (m, 6H, 3×CH_2), 3.81 (q, 2H, OCH_2), 4.67 (s, 1H, H4), 7.38-7.70 (m, 14H, Ar-H), 7.92 (s, 2H, NH_2) 9.61 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.5, 21.1 (CH_3), 18.2, 21.3, 36.3 (CH_2), 36.6 (C4), 61.3 (CH_2-O), 80.4, 111.1, 147.2, 154.2 (C=C), 105.3, 125.1, 125.6, 126.2, 126.5, 127.2, 127.4, 128.1, 128.4, 128.7, 129.3, 129.4, 129.8, 131.5, 132.3, 135.2, 148.2, 152.2, 173.6, 180.4 (Ar-C) 167.4, 198.7 (C=O). Anal. calcd. (found) (%) for $C_{37}H_{32}N_4O_4S_2$ (*m.w.* 660.8 g/mol): C, 67.25 (67.24); H, 4.88 (4.87); O, 9.68 (9.69); S, 9.70 (9.71); N, 8.48 (8.49). MS (*m/z*): 660 (M^+).

Ethyl 2′-amino-1′-(4-(4-chlorophenyl)thiazol-2-yl)-6-methyl-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9i): Yield: 80%, IR (KBr, ν_{max}, cm^{-1}): 3442 and 3292 (asym. and sym. stretching of -NH_2), 3011 (arom. C-H *str.*), 1686 (C=O *str.*), 1727 (COO ester *str.*), 1540 and 1472 (C=C *str.* of aromatic ring), 1209 (C-S-C thioether *str.*), 740 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.19 (t, 3H, CH_3), 2.35 (s, 3H, CH_3) 1.64-2.29 (m, 6H, 3×CH_2), 3.82 (q, 2H, OCH_2), 4.66 (s, 1H, H4), 7.36-7.78 (m, 14H, Ar-H), 7.94 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.4, 21.2 (CH_3), 18.1, 21.2, 36.3 (CH_2), 36.7 (C4), 61.1 (CH_2-O), 80.2, 111, 147.1, 154.3 (C=C), 105.1, 125.3, 125.5, 126.3, 126.6, 127.1, 127.3, 128, 128.3, 128.6, 129.5, 129.7, 129.9, 131.1, 132.4, 135.3, 148.1, 152.1, 173.5, 180.7 (Ar-C) 167.2, 198.6 (C=O). Anal. calcd. (found) % for $C_{37}H_{31}N_4O_3S_2Cl$ (*m.w.* 679.3 g/mol): C, 65.42 (65.41); H, 4.60 (4.61); O, 7.07 (7.08); S, 9.44 (9.43); N, 8.25 (8.26), Cl, 5.22 (5.21). MS (*m/z*): 679 (M^+).

Ethyl 2′-amino-2-((4-chlorophenyl)thio)-6-methyl-5′-oxo-1′-(4-phenylthiazol-2-yl)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9j): Yield: 78%, IR (KBr, ν_{max}, cm^{-1}): 3440 and 3289 (asym. and sym. stretching of -NH_2), 3011 (arom. C-H *str.*), 1685 (C=O *str.*), 1726 (COO ester *str.*), 1543 and 1471 (C=C *str.* of aromatic ring), 1213 (C-S-C thioether *str.*), 742 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.21 (t, 3H, CH_3), 2.34 (s, 3H, CH_3) 1.61-2.28 (m, 6H, 3×CH_2), 3.81 (q, 2H, OCH_2), 4.67 (s, 1H, H4), 7.34-7.79 (m, 14H, Ar-H), 7.97 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3, 21.3 (CH_3), 18.2, 21.3, 36.4 (CH_2), 36.8 (C4), 61.2 (CH_2-O), 80.3, 111.2, 147.2, 154.1 (C=C), 105.2, 125.1, 125.4, 126.4, 126.7, 127.3, 127.4, 128.2, 128.4, 128.7, 129.6, 129.8, 129.9, 131.3, 132.5, 135.4, 148.2, 152.4, 173.7, 180.6 (Ar-C) 167.3, 198.5 (C=O). Anal. calcd. (found) % for $C_{37}H_{31}N_4O_3S_2Cl$ (*m.w.* 679.3 g/mol): C, 65.42 (65.43); H, 4.60 (4.61); O, 7.07 (7.06); S, 9.44 (9.43), N 8.25 (8.26); Cl, 5.22 (5.21). MS (*m/z*): 679 (M^+).

Ethyl 2′-amino-2-((4-chlorophenyl)thio)-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-6-methyl-5′-oxo-1′,4′,5′,6′,7′,8′-hexahydro[3,4′-biquinoline]-3′-carboxylate (9k): Yield: 77%, IR (KBr, ν_{max}, cm^{-1}): 3443 and 3292 (asym. and sym. stretching of -NH_2), 3377 (OH *str.*), 3014 (arom. C-H *str.*), 1685 (C=O *str.*), 1728 (COO ester *str.*), 1545 and 1473 (C=C *str.* of aromatic ring), 1212 (C-S-C thioether *str.*) 743 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.18 (t, 3H, CH_3), 2.32 (s, 3H, CH_3) 1.68-2.29 (m, 6H, 3×CH_2), 3.82 (q, 2H, OCH_2), 4.68 (s, 1H, H4), 7.36-7.72 (m, 13H, Ar-H), 7.94 (s, 2H, NH_2) 9.62 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3, 21.2 (CH_3),

18.1, 21.2, 36.2 (CH_2), 36.4 (C4), 61.4 (CH_2-O), 80.2, 111.3, 147.1, 154.3 (C=C), 105.2, 125.3, 125.4, 126.1, 126.4, 127.3, 127.3, 128.2, 128.3, 128.5, 129.4, 129.6, 129.7, 131.2, 132.6, 135.5, 148.1, 152.2, 173.5, 180.3 (Ar-C) 167.5, 198.6 (C=O). Anal. calcd. (%) for $C_{37}H_{31}N_4O_4S_2Cl$ (*m.w.* 695.2 g/mol): C, 63.92 (63.93); H, 4.49 (4.48); O, 9.20 (9.21); S, 9.22 (9.23); N, 8.06 (8.05); Cl, 5.11 (5.10); MS (*m/z*): 695 (M^+).

Ethyl 2′-amino-1′-(4-(4-chlorophenyl)thiazol-2-yl)-2-((4-chlorophenyl)thio)-6-methyl-5'-oxo-1′,4′,5′,6′,7′,8′-hexahydro[3,4′-biquinoline]-3′-carboxylate (9l): Yield: 78%, IR (KBr, ν_{max}, cm^{-1}): 3444 and 3293 (asym. and sym. stretching of -NH_2), 3012 (arom. C-H *str.*), 1688 (C=O *str.*), 1724 (COO ester *str.*), 1542 and 1471 (C=C *str.* of aromatic ring), 1211 (C-S-C thioether *str.*), 741 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.20 (t, 3H, CH_3), 2.36 (s, 3H, CH_3) 1.63-2.28 (m, 6H, 3×CH_2), 3.81 (q, 2H, OCH_2), 4.69 (s, 1H, H4), 7.35-7.78 (m, 13H, Ar-H), 7.93 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3, 21.3 (CH_3), 18.4, 21.3, 36.2 (CH_2), 36.5 (C4), 61.2 (CH_2-O), 80.3, 111.3, 147.4, 154.5 (C=C), 105.2, 125.4, 125.5, 126.1, 126.5, 127.3, 127.5, 128.2, 128.4, 128.8, 129.7, 129.8, 129.9, 131.2, 132.3, 135.5, 148.2, 152.4, 173.8, 180.9 (Ar-C) 167.4, 198.6 (C=O). Anal. calcd. (found) % for $C_{37}H_{30}N_4O_3S_2Cl_2$ (*m.w.* 713.7 g/mol): C, 62.27 (62.28); H, 4.24 (4.23); O, 6.73 (6.74); S, 8.99 (8.98); N, 7.85 (7.84); Cl, 9.94 (9.93); MS (*m/z*): 713 (M^+).

Ethyl 2′-amino-6-methoxy-5'-oxo-1′-(4-phenylthiazol-2-yl)-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9m): Yield: 76%, IR (KBr, ν_{max}, cm^{-1}): 3442 and 3290 (asym. and sym. stretching of -NH_2), 3009 (arom. C-H *str.*), 1676 (C=O *str.*), 1726 (COO ester *str.*), 1541 and 1471 (C=C *str.* of aromatic ring), (C-O-C asym and sym *str.* of-OCH_3), 1205 (C-S-C thioether *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.14 (t, 3H, CH_3), 1.72-2.21 (m, 6H, 3×CH_2), 3.89 (s, 3H, OCH_3), 3.94 (q, 2H, OCH_2), 4.52 (s, 1H, H4), 7.45-7.68 (m, 15H, Ar-H), 7.99 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.9 (CH_3), 18.6, 21.3, 36.2 (CH_2), 36.6 (C4), 55.4 (OCH_3), 61.4 (CH_2-O), 80.1, 111.7, 147.2, 154.1 (C=C), 105.3, 125.4, 125.6, 126.2, 126.8, 127.7, 127.8, 128.3, 128.7, 128.8, 129.1, 129.3, 129.6, 131.5, 133.2, 135.6, 144.6, 150.7, 173.2, 182.1 (Ar-C) 167.2, 198.6 (C=O). Anal. calcd. (found) % for $C_{37}H_{32}N_4O_4S_2$ (*m.w.* 660.8 g/mol): C, 67.25 (67.26); H, 4.88 (4.87); O, 9.68 (9.69); S, 9.70 (9.71); N, 8.48 (8.47). MS (*m/z*): 660 (M^+).

Ethyl 2′-amino-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-6-methoxy-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9n): Yield: 79%, IR (KBr, ν_{max}, cm^{-1}): 3442 and 3297 (asym. and sym. stretching of -NH_2), 3378 (OH *str.*), 3011 (arom. C-H *str.*), 1689 (C=O *str.*), 1728 (COO ester *str.*), 1544 and 1473 (C=C *str.* of aromatic ring), 1218 and 1024 (C-O-C asym and sym *str.* of-OCH_3), 1213 (C-S-C thioether *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.19 (t, 3H, CH_3), 1.62-2.28 (m, 6H, 3×CH_2), 3.83 (q, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 4.68 (s, 1H, H4), 7.34-7.72 (m, 14H, Ar-H), 7.94 (s, 2H, NH_2) 9.62 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.7 (CH_3), 18.1, 21.5, 36.3 (CH_2), 36.7 (C4), 55.3 (OCH_3), 61.4 (CH_2-O), 80.2, 111.4, 147.5, 154.3 (C=C), 105.6, 125.2, 125.4, 126.3, 126.8, 127.3, 127.5, 128.2, 128.3, 128.5, 129.1, 129.4, 129.7, 131.7, 132.5, 135.7, 148.4, 152.4, 173.5, 180.2 (Ar-C) 167.7, 198.9 (C=O). Anal. calcd. (found) % for $C_{37}H_{32}N_4O_5S_2$ (*m.w.* 676.8 g/mol): C, 65.66 (65.67); H, 4.77 (4.76); O, 11.82 (11.81); S, 9.48 (9.47); N, 8.28 (8.29). MS (*m/z*): 676 (M^+).

Ethyl 2′-amino-1′-(4-(4-chlorophenyl) thiazol-2-yl)-6-methoxy-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9o): Yield: 76%, IR (KBr, ν_{max}, cm^{-1}): 3447 and 3295 (asym. and sym. stretching of -NH_2), 3008 (arom. C-H *str.*), 1687 (C=O *str.*), 1726 (COO ester *str.*), 1541 and 1473 (C=C *str.* of aromatic ring), 1217 and 1027 (C-O-C asym and sym *str.* of-OCH_3), 1214 (C-S-C thioether *str.*), 745 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.21 (t, 3H, CH_3), 1.62-2.26 (m, 6H, 3×CH_2), 3.83 (q, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 4.66 (s, 1H, H4), 7.35-7.79 (m, 14H, Ar-H), 7.97 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.5 (CH_3), 18.5, 21.2, 36.1 (CH_2), 36.7 (C4), 55.4 (OCH_3), 61.4 (CH_2-O), 80.1, 111.2, 147.1, 154.4 (C=C), 105.4, 125.1, 125.3, 126.2, 126.4, 127.4, 127.6, 128.1, 128.3, 128.7, 129.5, 129.6, 129.7, 131.1, 132.4, 135.6, 148.2, 152.3, 173.9, 180.8 (Ar-C) 167.7, 198.7 (C=O). Anal. calcd. (found) % for $C_{37}H_{31}N_4O_4S_2Cl$ (*m.w.* 695.2 g/mol): C, 63.92 (63.91); H, 4.49 (4.48); O, 9.20 (9.21); S, 9.22 (9.23); N, 8.06 (8.07); Cl, 5.10 (5.09). MS (*m/z*): 695 (M^+).

Ethyl 2′-amino-2-((4-chlorophenyl)thio)-6-methoxy-5′-oxo-1′-(4-phenylthiazol-2-yl)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9p): Yield: 74%, IR (KBr, ν_{max}, cm^{-1}): 3446 and 3296 (asym. and sym. stretching of -NH_2), 3009 (arom. C-H *str.*), 1685 (C=O *str.*), 1725 (COO ester *str.*), 1542 and 1472 (C=C *str.* of aromatic ring), 1219 and 1027 (C-O-C asym and sym *str.* of-OCH_3), 1212 (C-S-C thioether *str.*), 747 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.22 (t, 3H, CH_3), 1.61-2.26 (m, 6H, 3×CH_2), 3.85 (q, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 4.67 (s, 1H, H4), 7.32-7.79 (m, 14H, Ar-H), 7.96 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3 (CH_3), 18.2, 21.3, 36.2 (CH_2), 36.6 (C4), 55.5 (OCH_3), 61.6 (CH_2-O), 80.1, 111, 147.2, 154.3 (C=C), 105.1, 125.2, 125.5, 126.3, 126.4, 127.3, 127.4, 128.2, 128.5, 128.8, 129.4, 129.7, 129.9, 131.2, 132.6, 135.1, 148.3, 152.2, 173.7, 180.9 (Ar-C) 167.5, 198.6 (C=O). Anal. calcd. (found) % for $C_{37}H_{31}N_4O_4S_2Cl$ (*m.w.* 695.2 g/mol): C 63.92 (63.93); H, 4.49 (4.48); O, 9.20 (9.22); S, 9.22 (9.21); N, 8.06 (8.05); Cl, 5.10 (5.10). MS (*m/z*): 695 (M^+).

Ethyl 2′-amino-2-((4-chlorophenyl)thio)-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-6-methoxy-5′-oxo-1′,4′,5′,6′,7′,8′-hexahydro[3,4′-biquinoline]-3′-carboxylate (9q): Yield: 79%, IR (KBr, ν_{max}, cm^{-1}): 3445 and 3293 (asym. and sym. stretching of -NH_2), 3381 (OH *str.*), 3008 (arom. C-H *str.*), 1685 (C=O *str.*), 1724 (COO ester *str.*), 1543 and 1470 (C=C *str.* of aromatic ring), 1220 and 1023 (C-O-C asym and sym *str.* of-OCH_3), 1211 (C-S-C thioether *str.*) 745 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.20 (t, 3H, CH_3), 1.64-2.29 (m, 6H, 3×CH_2), 3.82 (q, 2H, OCH_2), 3.89 (s, 3H, OCH_3), 4.69 (s, 1H, H4), 7.31-7.76 (m, 13H, Ar-H), 7.91 (s, 2H, NH_2) 9.61 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.4 (CH_3), 18.6, 21.8, 36.4 (CH_2), 36.6 (C4), 55.6 (OCH_3), 61.2 (CH_2-O), 80.3, 111.1, 147.3, 154.5 (C=C), 105.3, 125.2, 125.6, 126.2, 126.6, 127.2,

127.6, 128.1, 128.4, 128.6, 129.2, 129.5, 129.8, 131.5, 132.7, 135.8, 148.6, 152.1, 173.2, 180.6 (Ar-C) 167.4, 198.3 (C=O). Anal. calcd. (found) % for $C_{37}H_{31}N_4O_5S_2Cl$ (*m.w.* 711.2 g/mol): C, 62.48 (62.47); H, 4.39 (4.38); O, 11.25 (11.26); S, 9.02 (9.03); N, 7.88 (7.87); Cl, 4.98 (4.99). MS (*m/z*): 711 (M^+).

Ethyl 2′-amino-1′-(4-(4-chlorophenyl)thiazol-2-yl)-2-((4-chlorophenyl)thio)-6-methoxy-5′-oxo-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9r): Yield: 78%, IR (KBr, ν_{max}, cm^{-1}): 3442 and 3293 (asym. and sym. stretching of -NH_2), 3007(arom. C-H str.), C-H *str.*), 1682 (C=O *str.*), 1728 (COO ester *str.*), 1541 and 1471 (C=C *str.* of aromatic ring), 1211 and 1025 (C-O-C asym and sym *str.* of-OCH_3), 1210 (C-S-C thioether *str.*), 748 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.19 (t, 3H, CH_3), 1.64-2.29 (m, 6H, 3×CH_2), 3.82 (q, 2H, OCH_2), 3.91 (s, 3H, OCH_3), 4.69 (s, 1H, H4), 7.31-7.79 (m, 13H, Ar-H), 7.99 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.1 (CH_3), 18.2, 21.7, 36.4 (CH_2), 36.7 (C4), 55.6 (OCH_3), 61.7 (CH_2-O), 80.5, 111.1, 147.1, 154.4 (C=C), 105.6, 125.2, 125.4, 126.3, 126.6, 127.1, 127.5, 128.2, 128.4, 128.8, 129.1, 129.7, 129.8, 131.6, 132.7, 135.4, 148.5, 152.1, 173.5, 180.7 (Ar-C) 167.1, 198.5 (C=O). Anal. calcd. (found) % for $C_{37}H_{30}N_4O_4S_2Cl_2$ (*m.w.* 729.7 g/mol): C, 60.90 (60.91); H, 4.14 (4.13); O, 8.77 (8.78); S, 8.79 (8.78); N, 7.68 (7.67); Cl, 9.72 (9.73). MS (*m/z*): 729 (M^+).

Ethyl 2′-amino-6-chloro-5′-oxo-1′-(4-phenylthiazol-2-yl)-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro[3,4′-biquinoline]-3′-carboxylate (9s): Yield: 77%, IR (KBr, ν_{max}, cm^{-1}): 3433 and 3293 (asym. and sym. stretching of -NH_2), 3011 (arom. C-H *str.*), 1685 (C=O *str.*), 1726 (COO ester *str.*), 1541 and 1472 (C=C *str.* of aromatic ring), 1210 (C-S-C thioether *str.*) 746 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.14 (t, 3H, CH_3), 1.62-2.24 (m, 6H, 3×CH_2), 3.84 (q, 2H, OCH_2), 4.66 (s, 1H, H4), 7.41-7.65 (m, 15H, Ar-H), 7.97 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3 (CH_3), 18.5, 21.7, 36.4 (CH_2), 36.6 (C4), 61.4 (CH_2-O), 80.1, 111.5, 147.3, 154.3 (C=C), 105.1, 125.1, 125.4, 126.2, 126.6, 127.4, 127.5, 128.5, 128.3, 128.9, 129.2, 129.3, 129.7, 131.1, 132.3, 135.6, 144.1, 150.3, 173.4, 180.6 (Ar-C) 167.4, 198.6 (C=O). Anal. calcd. (found) % for $C_{36}H_{29}N_4O_3S_2Cl$ (*m.w.* 665.2 g/mol): C, 65.00 (65.01); H, 4.39 (4.38); O, 7.22 (7.23); S, 9.64 (9.63); N, 8.42 (8.41); Cl, 5.33 (5.34); MS (*m/z*): 665 (M^+).

Ethyl 2′-amino-6-chloro-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9t): Yield: 76%, IR (KBr, ν_{max}, cm^{-1}): 3436 and 3294 (asym. and sym. stretching of -NH_2), 3374 (OH *str.*), 3011 (arom. C-H *str.*), 1685 (C=O *str.*), 1722 (COO ester *str.*), 1543 and 1471 (C=C *str.* of aromatic ring), 1212 (C-S-C thioether *str.*) 743 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.16 (t, 3H, CH_3), 1.64-2.28 (m, 6H, 3×CH_2), 3.81 (q, 2H, OCH_2), 4.67 (s, 1H, H4), 7.42-7.76 (m, 14H, Ar-H), 7.91 (s, 2H, NH_2) 9.60 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.7 (CH_3), 18.2, 21.4, 36.3 (CH_2), 36.5 (C4), 61.2 (CH_2-O), 80.1, 111.2, 147.3, 154.2 (C=C), 105.2, 125.2, 125.6, 126.1, 126.4, 127.2, 127.7, 128.4, 128.7, 128.8, 129.2, 129.6, 129.9, 131.5, 132.1, 135.2, 148.6, 152.1, 173.5, 180.1 (Ar-C) 167.2, 198.7 (C=O). Anal. calcd. (found) % for $C_{36}H_{29}N_4O_4S_2Cl$ (*m.w.* 681.2 g/mol): C, 63.47 (63.48); H, 4.29 (4.28); O, 9.39 (9.38); S, 9.41 (9.42); N, 8.22 (8.23); Cl, 5.20 (5.21). MS (*m/z*): 681 (M^+).

Ethyl 2′-amino-6-chloro-1′-(4-(4-chlorophenyl)thiazol-2-yl)-5′-oxo-2-(phenylthio)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9u): Yield: 79%, IR (KBr, ν_{max}, cm^{-1}): 3433 and 3294 (asym. and sym. stretching of -NH_2), 3011 (arom. C-H *str.*), 1685 (C=O *str.*), 1723 (COO ester *str.*), 1541 and 1471 (C=C *str.* of aromatic ring), 1213 (C-S-C thioether *str.*) 743 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.13 (t, 3H, CH_3), 1.63-2.26 (m, 6H, 3×CH_2), 3.85 (q, 2H, OCH_2), 4.67 (s, 1H, H4), 7.41-7.68 (m, 14H, Ar-H), 7.95 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.4 (CH_3), 18.2, 21.7, 36.5 (CH_2), 36.6 (C4), 61.5 (CH_2-O), 80.1, 111.3, 147.1, 154.4 (C=C), 105, 125.1, 125.4, 126.2, 126.4, 127.6, 127.8, 128.1, 128.5, 128.7, 129.4, 129.7, 129.8, 131.4, 132.3, 135.2, 144.1, 150.4, 173.4, 180.6 (Ar-C) 167.5, 198.3 (C=O). Anal. calcd. (found) % for $C_{36}H_{28}N_4O_3S_2Cl_2$ (*m.w.* 699.7 g/mol): C, 61.80 (61.81); H, 4.03 (4.04); O, 6.86 (6.87); S, 9.17 (9.18); N, 8.01 (8.02); Cl, 10.13 (10.10). MS (*m/z*): 699 (M^+).

Ethyl 2′-amino-6-chloro-2-((4-chlorophenyl)thio)-5′-oxo-1′-(4-phenylthiazol-2-yl)-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9v): Yield: 81%, IR (KBr, ν_{max}, cm^{-1}): 3437 and 3295 (asym. and sym. stretching of -NH_2), 3010 (arom. C-H *str.*), 1686 (C=O *str.*), 1721 (COO ester *str.*), 1542 and 1471 (C=C *str.* of aromatic ring), 1210 (C-S-C thioether *str.*) 746 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.13 (t, 3H, CH_3), 1.62-2.28 (m, 6H, 3×CH_2), 3.88 (q, 2H, OCH_2), 4.68 (s, 1H, H4), 7.43-7.67 (m, 14H, Ar-H), 7.94 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3 (CH_3), 18.3, 21.8, 36.7 (CH_2), 36.8 (C4), 61.9 (CH_2-O), 80.2, 111.1, 147.2, 154.3 (C=C), 105.1, 125.1, 125.4, 126.5, 126.7, 127.3, 127.5, 128.2, 128.4, 128.9, 129.1, 129.2, 129.6, 131.2, 132.5, 135.5, 144.1, 150.2, 173.3, 180.6 (Ar-C) 167.4, 198.6 (C=O). Anal. calcd. (found) % for $C_{36}H_{28}Cl_2N_4O_3S_2$ (*m.w.* 699.7 g/mol): C, 61.80 (61.81); H, 4.03 (4.04); O, 6.86 (6.87); S, 9.17 (9.16); N, 8.01 (8.02); Cl, 10.13 (10.12). MS (*m/z*): 699 (M^+).

Ethyl 2′-amino-6-chloro-2-((4-chlorophenyl)thio)-1′-(4-(4-hydroxyphenyl)thiazol-2-yl)-5′-oxo-1′,4′,5′,6′,7′,8′-hexahydro-[3,4′-biquinoline]-3′-carboxylate (9w): Yield: 80%, IR (KBr, ν_{max}, cm^{-1}): 3433 and 3291 (asym. and sym. stretching of -NH_2), 3370 (OH *str.*), 3012 (arom. C-H *str.*), 1681 (C=O *str.*), 1726 (COO ester *str.*), 1544 and 1471 (C=C *str.* of aromatic ring), 1211 (C-S-C thioether *str.*) 743 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.18 (t, 3H, CH_3), 1.63-2.29 (m, 6H, 3×CH_2), 3.82 (q, 2H, OCH_2), 4.67 (s, 1H, H4), 7.42-7.77 (m, 13H, Ar-H), 7.95 (s, 2H, NH_2) 9.61 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.3 (CH_3), 18.2, 21.4, 36.2 (CH_2), 36.8 (C4), 61.2 (CH_2-O), 80.3, 111.3, 147.1, 154.3 (C=C), 105.1, 125.3, 125.6, 126.1, 126.4, 127.1, 127.5, 128.4, 128.5, 128.8, 129.3, 129.5, 129.7, 131.4, 132.3, 135.6, 148.5, 152.7, 173.6, 180.4 (Ar-C) 167.1, 198.2 (C=O). Anal. calcd. (found) % for $C_{36}H_{28}N_4O_4S_2Cl_2$ (*m.w.* 715.7 g/mol): C, 60.42 (60.43); H, 3.94 (3.93); O, 8.94 (8.95); S, 8.96 (8.95); N, 7.83 (7.84); Cl, 9.91 (9.92); MS (*m/z*): 715 (M^+).

Ethyl 2′-amino-6-chloro-1′-(4-(4-chlorophenyl)thiazol-2-yl)-2-((4-chlorophenyl)thio)-5′-oxo-1′,4′,5′,6′,7′,8′-

hexahydro-[3,4′-biquinoline]-3′-carboxylate (9x): Yield: 79%, IR (KBr, ν_{max}, cm^{-1}): 3435 and 3297 (asym. and sym. stretching of -NH_2), 3012 (arom. C-H *str.*), 1687 (C=O *str.*), 1726 (COO ester *str.*), 1542 and 1477 (C=C *str.* of aromatic ring), 1209 (C-S-C thioether *str.*) 749 (C-Cl *str.*). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.14 (t, 3H, CH_3), 1.64-2.27 (m, 6H, 3×CH_2), 3.88 (q, 2H, OCH_2), 4.67 (s, 1H, H4), 7.42-7.69 (m, 13H, Ar-H), 7.94 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.4 (CH_3), 18.5, 21.3, 36.1 (CH_2), 36.4 (C4), 61.5 (CH_2-O), 80.1, 111.5, 147.1, 154.2 (C=C), 105.1, 125.3, 125.1, 126.3, 126.4, 127.3, 127.6, 128.1, 128.4, 128.9, 129.2, 129.5, 129.8, 131.2, 132.5, 135.2, 144.1, 150.5, 173.4, 180.6 (Ar-C) 167.6, 198.8 (C=O). Anal. calcd. (found) % for $C_{36}H_{27}N_4O_3S_2Cl_3$ (*m.w.* 734.1 g/mol): C, 58.90 (58.91); H, 3.71 (3.70); O, 6.54 (6.53); S, 8.74 (8.75); N, 7.63 (7.64); Cl, 14.49 (14.48). MS (*m/z*): 734 (M^+).

Biological assay: EGFR inhibitory assay was performed as per the method used by Tsou *et al*. [28], the FabH inhibitory assay was performed as per the method of Lv *et al*. [29] where all the requirement was purchased locally.

RESULTS AND DISCUSSION

In order to confirm the functional groups, present in all the 24 synthesized compounds, the infrared spectral analysis was carried out. The asymmetric and symmetric stretching bands of the primary amine (-NH_2) were observed in regions of 3443-3347 cm^{-1} and 3297-3289 cm^{-1} for all compounds. The stretching vibration of carbonyl ester (-COO-) was observed in the region of 1728-1719 cm^{-1} for compounds **9a-x**. The strong stretching accounting for the carbon and oxygen of the carbonyl group (-CO-) for all the compounds appeared in the region of 1689-1669 cm^{-1}. A broad band for the phenolic (-OH) was observed for compounds **9b**, **9e**, **9h**, **9k**, **9n**, **9q**, **9r** and **9w** in the region of 3381-3370 cm^{-1}. Thioether linkage (-C-S-C-) for all compounds appeared in the region of 1214-1205 cm^{-1}. A carbon and chlorine stretching was also observed for compounds **9c**, **9f**, **9i**, **9l**, **9o**, **9r**, **9u** and **9x** appeared in the 749-740 cm^{-1} region. Asymmetric and symmetric bands for C-O-C for methoxy group in compounds **9m-9r** is observed in the range of 1220-1214 and 1027-1023 cm^{-1}.

Three protons of the methyl group appeared as a triplet in the region of δ 1.11-1.22 ppm and two protons of –OCH_2 resonated in the region of δ 3.83-3.94 ppm for **9a-x**. A singlet for three protons of the methyl group as R_1 substitution in compounds **9g-l** was observed in the region of δ 2.32-2.36 ppm. A multiplet for six protons of three methylene protons appeared at δ 1.61-2.29 ppm, while an aromatic chiral proton for all synthesized compounds appeared in the region δ 4.51-4.69 ppm as a singlet. A multiplet for aromatic protons ranging from 13 to 16 in all the synthesized compounds was observed at δ 7.31-7.79 ppm. A singlet for proton of the phenolic group for compounds **9b**, **9e**, **9h**, **9k**, **9n**, **9q**, **9r** and **9w** appeared in the range of δ 9.60-9.62 ppm. A singlet for three protons of methoxy group as R_1 substituent in compounds **9m-r** is observed in the range of δ 2.32-2.36 ppm.

Similarly, ^{13}C NMR analysis was also carried out for all the synthesized compounds. The methyl and oxymethylene carbon showed signals in the range of δ 14.1-14.9 and δ 61.1-61.9 ppm for compounds **9a-x**. The R_1 substitution containing methyl carbon in compounds **9g-l** showed a straight line in the range of δ 20.3-21.3 ppm while the R_1 substitution having methoxy group in compounds **9m-r** showed a single line in the range of δ 55.4-55.6 ppm. Active methylene (C_1) carbon showed a single line in the range of δ 36.2-36.8 ppm for **9a-x**. The presence of ester carbon atom and a carbonyl carbon atom was confirmed by a single line in the range of δ 167.1-167.9 and 198.2-198.9 ppm for compounds **9a-x**. The aromatic carbon atoms present in the biquinoline, phenyl thiazole and thiophenol showed a multiple line in the range of δ 105-182 ppm for all the 24 compounds.

Biological evaluation

Antiproliferation and EGFR inhibitory activity: All the synthesized compounds (**9a-x**) were tested against EGFR kinase as well as against cancer cell A549 (adenocarcinoma human alveolar basal epithelial cell line) and Hep G2 (liver cancer cell line) having quinoline and phenyl thiazole core. The EGFR tyrosine kinase inhibition mode of action is well known, which works by inhibiting the signal transferring between the two EGFR molecules. It has been observed that compounds **9n** (IC_{50} = 1.03 ± 0.05 μM) and **9c** (IC_{50} = 1.51 ± 0.15 μM) against A549 as well as compounds **9c** (IC_{50} = 1.10 ± 0.05 μM) and **9r** (IC_{50} = 1.25 ± 0.10 μM) against Hep G2 showed most effective activity as compared to other compounds. As shown in Table-1, compounds **9n** (IC_{50} = 0.09 ± 0.14 μM), displayed the most potent inhibitory activity against EGFR as compared to other compounds and less comparable to the positive control Erlotinib (IC_{50} = 0.032 ± 0.02 μM).

***E. coli* FabH inhibitory activity:** The *E. coli* FabH inhibitory potency of the synthetic **9a-x** derivatives was examined and the results are summarized in Table-1. Most of the tested compounds showed potent *E. coli* FabH inhibitory activity. Among them, compound **9c**, **9n**, **9s** and **9u** showed the most potent inhibitory with IC_{50} of 3.1, 3.2, 3.9 and 3.3 μM, respectively. This result provides the basis to the overall activity of compounds **9c** and **9n** among the synthesized compounds.

Molecular docking study

With EGFR: To gain better understanding on the potency of all compounds and guide further SAR studies, we proceeded to examine the interaction of those with EGFR (PDB code: 1M17) by molecular docking, which was performed by simulation of compounds into the ATP binding site in EGFR. The binding energy of all the compounds is mentioned in Table-2. Of the compounds studied, compound **9p** was nicely bound into the active site of EGFR with minimum binding energy ΔG_b = -8.5626 kcal/mol. The binding model of compound **9p** and EGFR was depicted in Fig. 1. The amino acid residues within the active site radius which had interacted with EGFR were labeled. In the binding mode, compound **9p** was well bound to the ATP binding site of EGFR through hydrophobic interaction and the binding was stabilized by two hydrogen bonds and one π-cation arene-arene interaction. Among them one hydrogen bond forms between O atom of ester carbonyl oxygen group and LYS721 (distance: 3.32 Å), second one

TABLE-1
INHIBITION OF EGFR KINASE, ANTIPROLIFERATIVE AND *E. coli* FabH INHIBITORY ACTIVITY IC_{50} (μM) OF COMPOUNDS **9a-x**

Compound	R_1	R_2	R_3	EGFR	A549	Hep G2	*E. coli* FabH IC_{50} (μM)	Hemolysis LC_{30}[a] (mg/mL)
				18.05 ± 0.03	9.35 ± 0.01	10.15 ± 0.04	32.1	> 10
9b	H	H	OH	1.29 ± 0.02	7.11 ± 0.04	9.32 ± 0.10	8.6	> 10
9c	H	H	Cl	0.13 ± 0.02	1.51 ± 0.15	1.10 ± 0.05	3.1	> 10
9d	H	Cl	H	12.70 ± 0.12	6.08 ± 0.05	2.65 ± 0.20	12.6	> 10
9e	H	Cl	OH	36.23 ± 0.13	15.21 ± 0.15	13.01 ± 0.05	5.8	> 10
9f	H	Cl	Cl	11.10 ± 0.15	5.20 ± 0.32	9.65 ± 0.02	5.1	> 10
9g	CH_3	H	H	8.23 ± 0.16	4.11 ± 0.11	5.03 ± 0.01	4.2	> 10
9h	CH_3	H	OH	2.03 ± 0.14	8.12 ± 0.10	10.03 ± 0.03	4.6	> 10
9i	CH_3	H	Cl	6.13 ± 0.10	3.12 ± 0.10	7.24 ± 0.02	6.1	> 10
9j	CH_3	Cl	H	3.45 ± 0.15	9.32 ± 0.05	13.21 ± 0.05	7.8	> 10
9k	CH_3	Cl	OH	18.27 ± 0.13	7.15 ± 0.10	14.12 ± 0.10	5.3	> 10
9l	CH_3	Cl	Cl	21.17 ± 0.13	8.10 ± 0.14	11.60 ± 0.10	6.1	> 10
9m	OCH_3	H	H	3.42 ± 0.10	5.08 ± 0.05	4.36 ± 0.12	4.6	> 10
9n	OCH_3	H	OH	0.09 ± 0.14	1.03 ± 0.05	1.38 ± 0.15	3.2	> 10
9o	OCH_3	H	Cl	11.25 ± 0.05	11.07 ± 0.15	21.23 ± 0.05	4.1	> 10
9p	OCH_3	Cl	H	2.03 ± 0.14	2.53 ± 0.10	3.12 ± 0.01	5.9	> 10
9q	OCH_3	Cl	OH	5.01 ± 0.12	9.35 ± 0.06	22.30 ± 0.10	3.9	> 10
9r	OCH_3	Cl	Cl	0.15 ± 0.05	2.10 ± 0.17	1.25 ± 0.10	7.2	> 10
9s	Cl	H	H	5.31 ± 0.02	2.12 ± 0.14	4.56 ± 0.12	3.9	> 10
9t	Cl	H	OH	7.02 ± 0.15	10.02 ± 0.05	4.22 ± 0.05	4.1	> 10
9u	Cl	H	Cl	6.82 ± 0.15	3.32 ± 0.10	1.11 ± 0.05	6.8	> 10
9v	Cl	Cl	H	6.15 ± 0.17	3.21 ± 0.10	5.80 ± 0.10	7.8	> 10
9w	Cl	Cl	OH	11.01 ± 0.10	13.30 ± 0.10	21.11 ± 0.10	8.5	> 10
9x	Cl	Cl	Cl	7.68 ± 0.05	21.13 ± 0.12	8.08 ± 0.15	9.1	> 10
Erlotinib	–	–	–	0.032 ± 0.02	0.13 ± 0.01	0.12	Lytic concentration 30%	

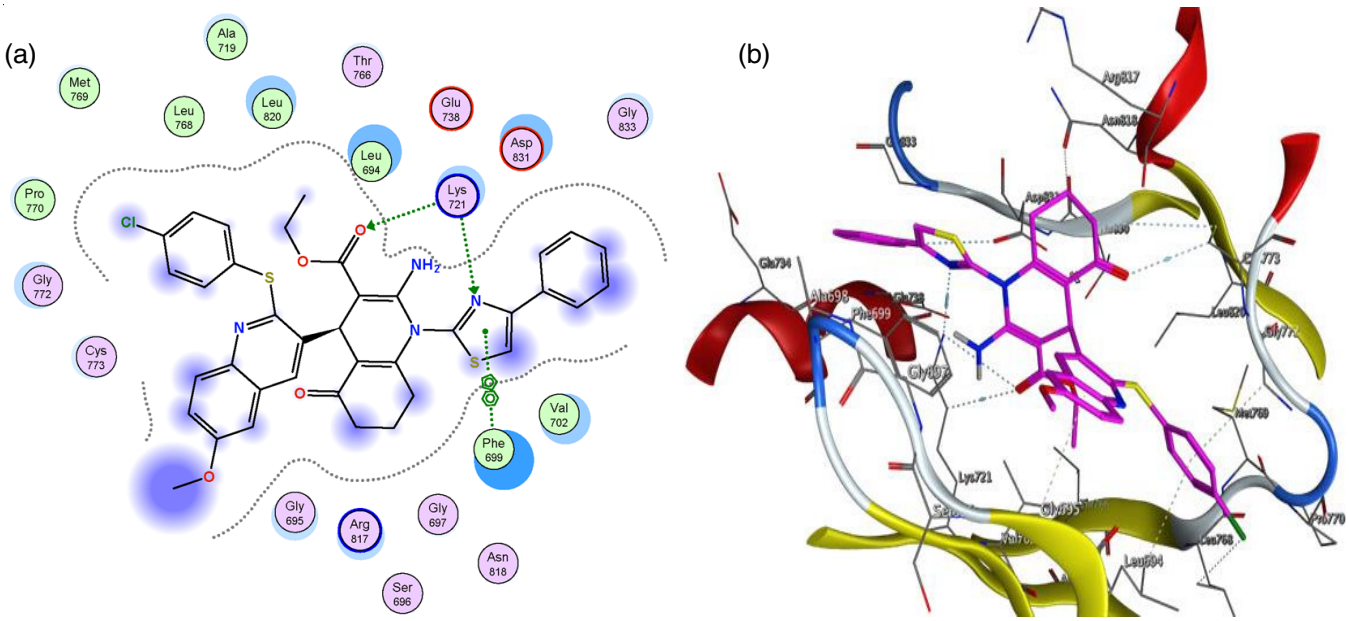


Fig. 1. (a) 2D and (b) 3D binding model of compound **9p** into the active pocket of EGFR

between N atom of thiazole and LYS721 (distance: 3.61 Å) One π-cation bond forms between thiazole ring and PHE699. From this binding model, it could be concluded that these two hydrogen bonds and one π-cation interaction from the thiazole ring and the pocket are responsible for the effective EGFR inhibitory of compound **9p**.

With FabH: Similarly, to gain better understanding on the potency of all compounds and guide further SAR studies, molecular docking of compounds and *E. coli* FabH was performed on the binding model based on the *E. coli* FabH-CoA complex structure (PDB code: 1HNJ). The FabH active site generally contains a catalytic triad tunnel consisting of Cys-His-Asn, which is conserved in various bacteria. This catalytic triad plays an important role in the regulation of chain elongation and substrate binding. Since the alkyl chain of CoA is broken by Cys of the catalytic triad of FabH, interactions between Cys and substrate appear to play an important role in substrate binding. Of the compounds studied, compound **9u**

TABLE-2
BINDING ENERGY OF COMPOUNDS **9a-x** AND ERLOTINIB WITH EGFR AND MALONYL CoA WITH FabH

Compound	Binding energy ΔG_b	
	Erlotinib with EGFR	Malonyl CoA with FabH
9a	-7.6730	-7.1557
9b	-7.8623	-7.9109
9c	-7.9387	-8.2965
9d	-7.4787	-7.3454
9e	-7.5273	-7.7012
9f	-7.7777	-7.7965
9g	-7.5102	-7.4785
9h	-7.5824	-7.7342
9i	-7.3696	-7.6746
9j	-7.2184	-7.7074
9k	-7.4894	-8.0743
9l	-7.5994	-7.5439
9m	-7.5672	-7.8728
9n	-8.0227	-8.1727
9o	-7.7833	-7.7753
9p	-8.5626	-7.9143
9q	-7.4671	-8.2955
9r	-7.8631	-8.0331
9s	-7.3736	-8.3225
9t	-7.6625	-7.8391
9u	-7.4760	-8.4033
9v	-7.3248	-7.2221
9w	-7.2938	-7.9179
9x	-7.7775	-7.6217
Erlotinib	-8.2033	–
Malonyl CoA	–	-10.3895

was nicely bound to active site of FabH with hydrogen bonds with minimum binding energy ΔG_b = -8.4033 kcal/mol. The binding energy of all the compounds is mentioned in Table-2. The binding model of compound **9u** and FabH is depicted in Fig. 2. Among them hydrogen bonds formed with sulphur atom between the phenyl and of quinoline ring and LEU189 (distance: 3.82 Å), where as two π-cation arene hydrogen interactions were formed between the thiazole ring and THR81 and second interaction between nitrogen bearing quinoline ring and GLY-307. From this binding model, it could be concluded that hydrogen bond interaction with sulphur atom and the arene interaction with thiazole ring as well as quinoline ring are responsible for the effective FabH inhibitory of compound **9u**.

Computational studies

Density functional theory: The structure of the prepared compounds at the lowest energy level was obtained by quantum computational using density functional theory at the B3LYP level of theory and def-2SVP basis set using ORCA 5.0.3 computational chemistry tool [30]. The geometry of all the synthesized 24 compounds were optimized using above stated parameters, the resultant geometry with the global minima was then checked for any imaginary IR frequency, where no presence of such frequency confirmed the correct geometry of compound at lowest energy level. To understand the influence of the various substitutions on the core component of the molecule, the angle between rigid ring part was calculated for this purpose. Where the angle between the thiazole ring and quinoline ring was observed as twist angle θ_1, the angle between quinoline ring and hydroquinone ring was noted as twist angle θ_2 and the angle between thiazole ring and hydroquinone ring was noted as θ_3. Distribution of the charge on the individual atom as well as molecular orbitals are responsible for the electronic properties of the molecule, using which the UV-Vis properties of the compound can be predicted, the value of which is based on solvent system. It is well known that smaller the molecular orbital energy gap ΔE, the more grater the activity of the material [31], which also represents the reactivity and stability of the respective compound. The values of the molecular orbitals and their energy gap obtained from the DFT study is recorded in Table-3. The iso-identity surface plot of highest occupied molecular orbital and lowest occupied molecular orbital for molecules **9a**, **9c**, **9e**, **9n**, **9r** and **9s** are shown in Fig. 3. It can be observed that the orbital delocalization is composed of fewer nodal planes, which allows stronger orbital overlap.

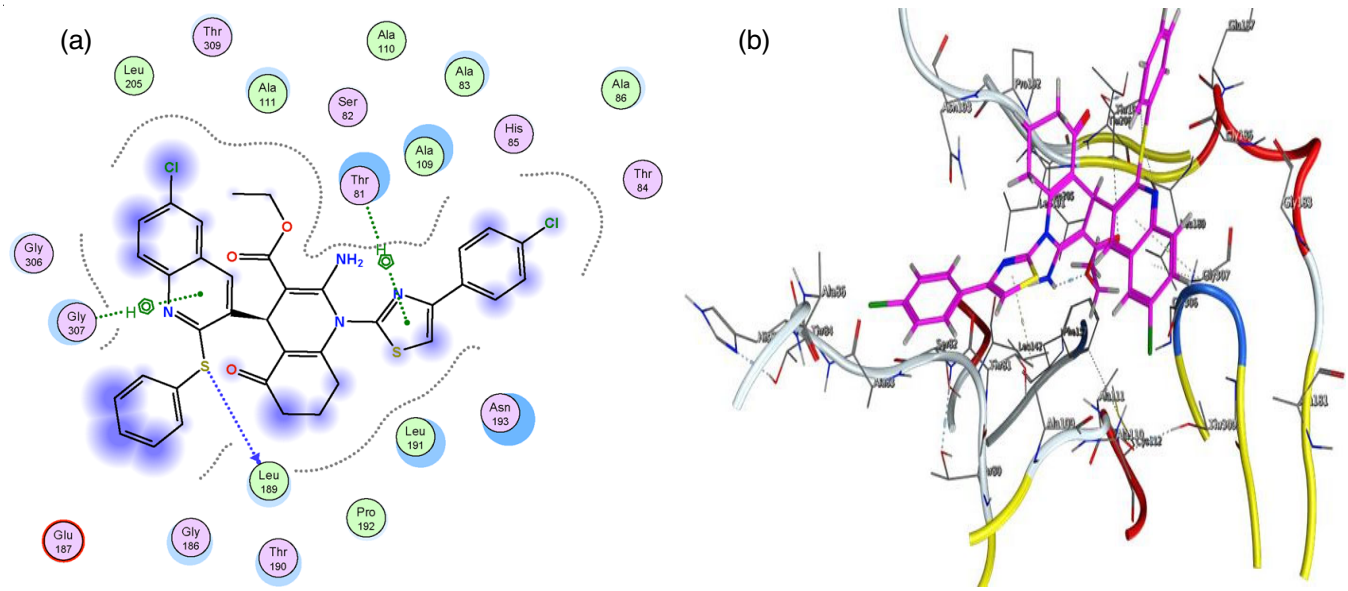


Fig. 2. (a) 2D and (b) 3D binding model of compound **9u** into the active pocket of FabH

TABLE-3
FACTORS CALCULATED FROM THE QUANTUM COMPUTATIONAL DFT STUDY OF MOST AND LEAST ACTIVE MOLECULES

Element		9a	9c	9e	9n	9r	9s
E_{HOMO} (eV)		-8.860	-8.644	-8.485	-8.543	-8.397	-8.540
E_{LUMO} (eV)		-3.710	-3.611	-3.608	-3.501	-3.507	-3.429
$I = - E_{HOMO}$		8.860	8.644	8.485	8.543	8.397	8.540
$A = - E_{LUMO}$		3.710	3.611	3.608	3.501	3.507	3.429
$\Delta E = I - A$ (eV)		5.150	5.033	4.877	5.042	4.890	5.111
Dipole moment (Debye)		5.385	6.905	9.677	7.530	7.457	8.103
Energy (a.u)		-2628.227	-3087.630	-3162.767	-2817.741	-3661.412	-3087.630
Twist angle (θ)	θ_1	16.59	18.470	19.08	23.520	16.040	18.540
	θ_2	89.12	87.670	87.68	84.510	87.580	87.660
	θ_3	72.64	73.920	73.32	72.460	76.380	73.930
$\eta = (I - A)/2$		2.575	2.517	2.438	2.521	2.445	2.556
$\chi = (I + A)/2$		6.285	6.128	6.046	6.022	5.952	5.985
$\sigma = 1/\eta$		0.388	0.397	0.410	0.397	0.409	0.391
$S = 1/2\eta$		0.194	0.199	0.205	0.198	0.204	0.196
$Pi = -\chi$		-6.285	-6.128	-6.046	-6.022	-5.952	-5.985
$\omega = (Pi)^2/2\eta$		7.670	7.460	7.496	7.192	7.245	7.007
$\Delta N_{max} = \chi/\eta$		2.440	2.435	2.479	2.389	2.434	2.342

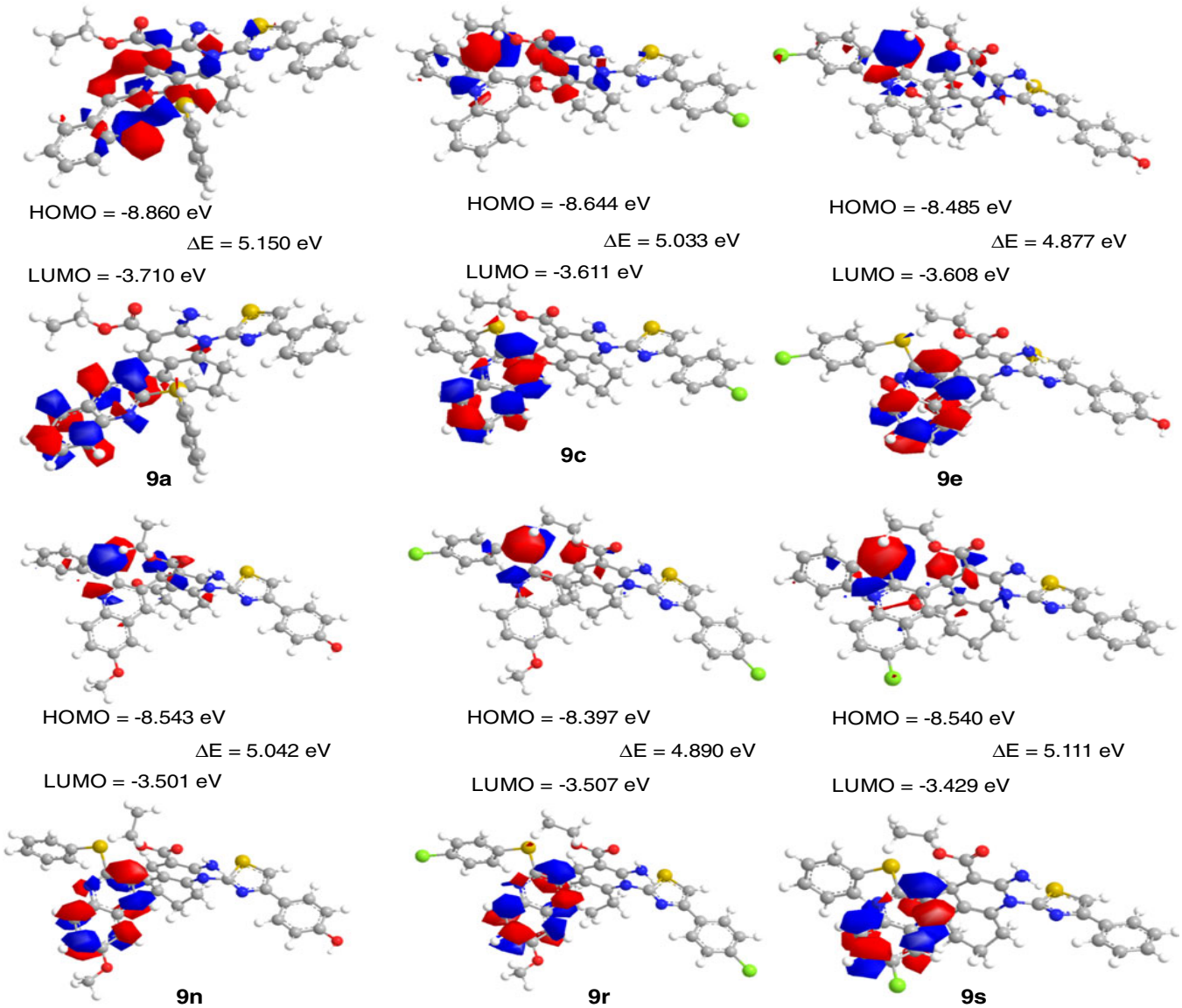
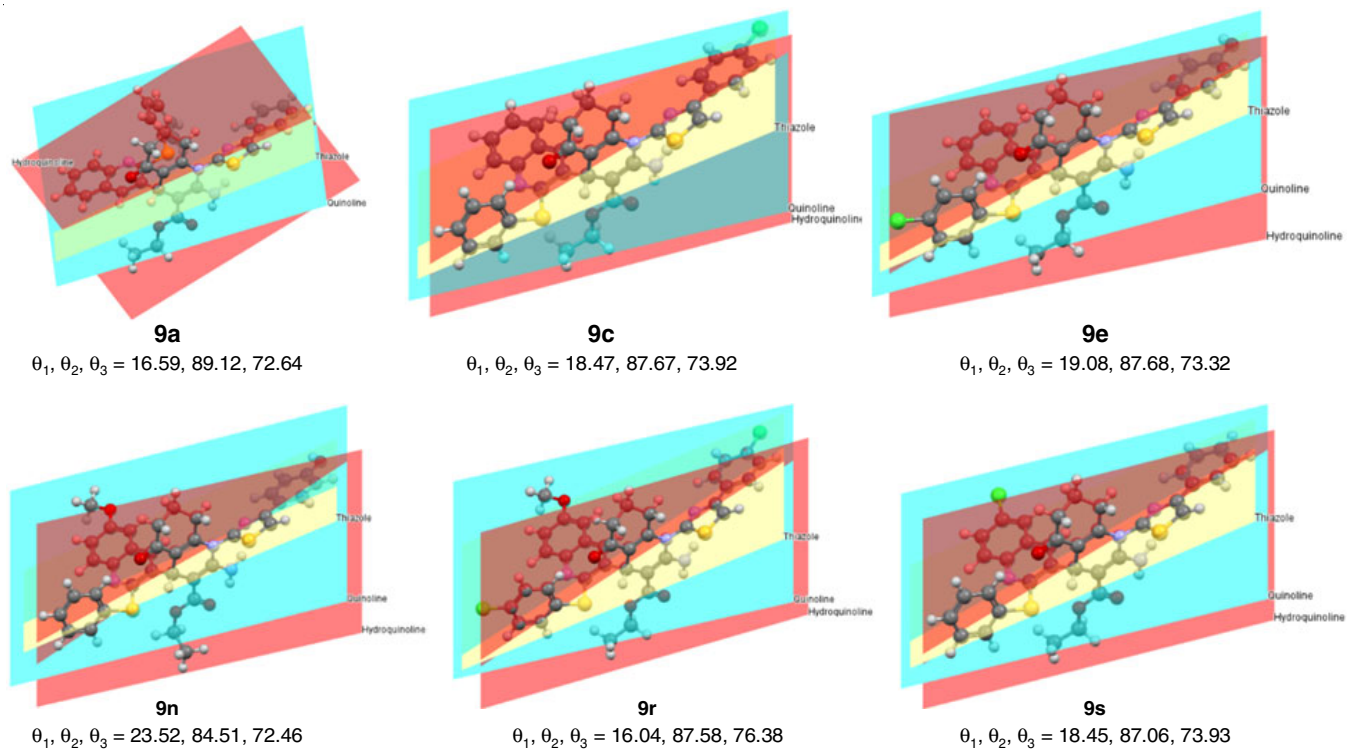


Fig. 3. Frontier molecular orbitals diagram of **9a, 9c, 9e**, **9n, 9r** and **9s**.

From the energy gap values of HOMO-LUMO (Table-3), the molecules having -Cl at R_1 and -H at R_2 substitution position shows higher energy gap value, while at the R_3 position if a bulky group is attached it lowers the energy gap value, compared to the other molecules which differ at only R_1 substitution. Softness, hardness and other factors based on the hardness and softness can also be calculated from the values of the HOMO-LUMO energy gap. It can be observed that the molecule having only one -Cl at the R_1 substitution position and no substitution on R_2 and R_3 position is the hardest one, compound **9s** with value of 2.556, while the molecule having Cl at the R_2 position were found to be the soft molecules among, which **9r** was the softest one with the value of 2.445. Other such factors which are dependent on the quantum chemical parameters are also included into Table-3, namely global softness (S), absolute soft-ness (σ), chemical potential (Pi), global electrophilicity (ω), electro negativity (χ), additional electronic charge (ΔN_{max}) as well as the dipole moment (D) and twist angle (θ) between the planes of the molecule. These values of the softness and hardness and the data of inhibition of EGFR kinase and *E. coli* FabH inhibitory activity suggest that the conventional relation between the softness and activity or stability of molecule does not stand true for all molecules and is not sufficient to explain activity of the molecules.

Molecular docking study: For all molecules **9a-x**, the data of EGFR kinase inhibition and antiproliferative activity it is found that molecule compound **9n** showed the most potent against EGFR as well as A549 cancer cell line with the IC_{50} concentration value of 0.09 ± 0.14 μM and 1.03 ± 0.05 μM, among which the EGFR activity is found to be much more promising when compared to the standard Erlotinib, which required minimum 0.032 ± 0.02 μM concentration to inhibit EGFR, whereas molecules **9e** and **9x** showed the least activity against EGFR and cancer cell line A549 with the IC_{50} concentration of 36.23 ± 0.13 μM and 21.13 ± 0.01 μM, this can be attributed to the variation at the R_1 and R_2 substitution group which exhibits behaviour opposite to that of an electron, both in terms of its presence and its ability to withdraw, also resulting in the twist angle between planes of the molecule as can be seen in Fig. 4. This change in the nature of substituents and twist angle formed a strong interaction of compound **9n** with the EGFR protein residue LYS721 and PHE699 with the binding energy of -8.0227 kcal/mol as shown in Fig. 5. Molecule **9c** showed the most potent activity against HepG2 among all the prepared molecules with the inhibition concentration IC_{50} of 1.10 ± 0.05 μM, while molecule **9q** found to be least active against HepG2, this behaviour is also found to be similar as found for molecule **9n** and **9e**, where the nature of the substituent groups at R_1 and R_2 positions are of opposite character.

In case of the inhibitory activity for *E. coli* FabH for all the compounds **9a-x** showed that compound **9c** found to be most active against *E. coli* with the IC_{50} concentration of 3.1 μM whereas compound **9a** found to be least active against it with the IC_{50} concentration of 32.1 μM. The substitutions at the R_1, R_2 and R_3 positions suggests that when there is only hydrogen at these positions it shows 16.59º, 89.12º and 72.64º angle between the planes of thiazole, quinoline and hydroquinoline, when the hydrogen of the R_3 substitution is changed to Cl atom the molecule shows the deviation in the angle of the planes of about 2º in the counter direction of θ_1 and θ_2 (Fig. 4) allowing **9c** to bind strongly to the ASP107, GLY186 and LEU191 residues of the FabH with binding energy of -8.2965 kcal/mol as shown in Fig. 6.



9a
$\theta_1, \theta_2, \theta_3$ = 16.59, 89.12, 72.64

9c
$\theta_1, \theta_2, \theta_3$ = 18.47, 87.67, 73.92

9e
$\theta_1, \theta_2, \theta_3$ = 19.08, 87.68, 73.32

9n
$\theta_1, \theta_2, \theta_3$ = 23.52, 84.51, 72.46

9r
$\theta_1, \theta_2, \theta_3$ = 16.04, 87.58, 76.38

9s
$\theta_1, \theta_2, \theta_3$ = 18.45, 87.06, 73.93

Fig. 4. Twist angle θ of **9a**, **9c, 9e**, **9n**, **9r** and **9s**

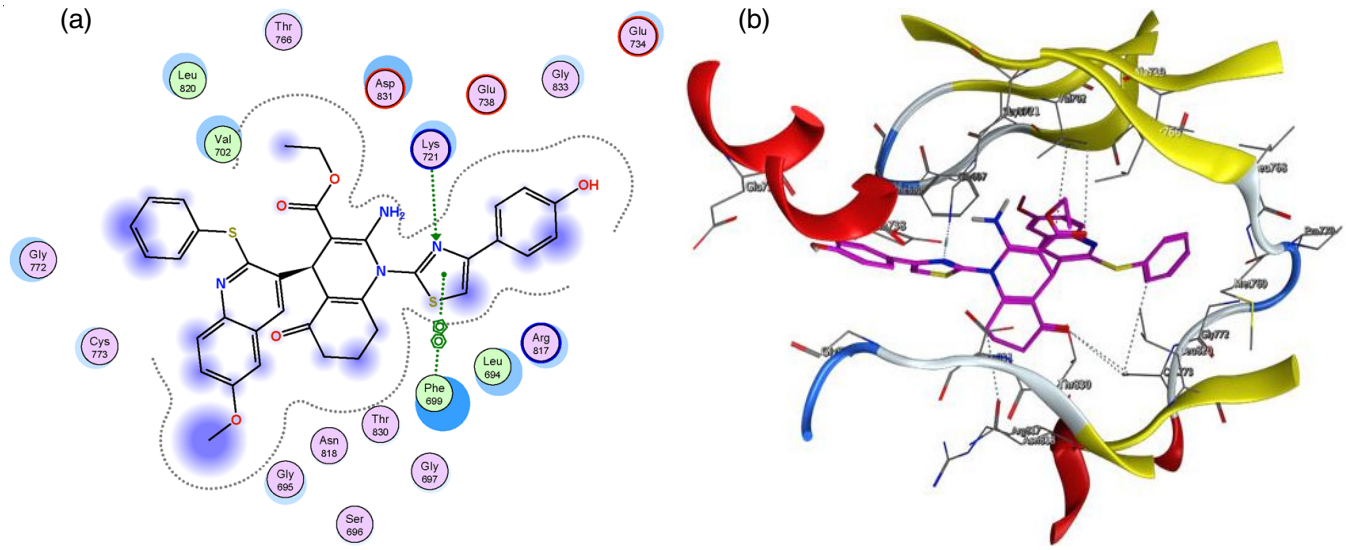


Fig. 5. (a) 2D and (b) 3D binding model of compound **9n** into the active pocket of EGFR

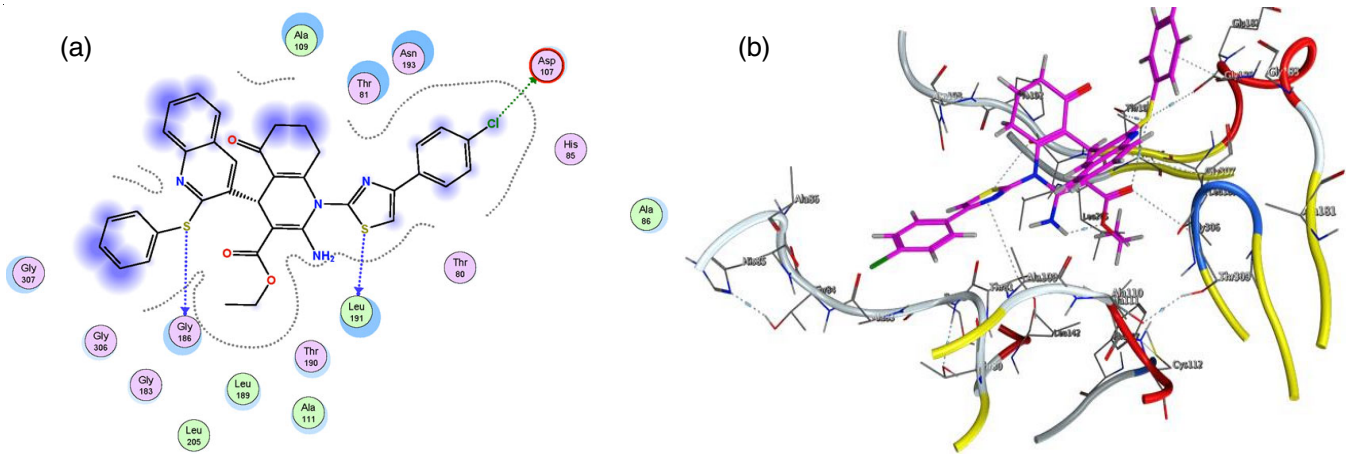


Fig. 6. (a) 2D and (b) 3D binding model of compound **9c** into the active pocket of FabH

Conclusion

A new series of molecules with biquinoline, phenylthiazole and thiophenyl with various potent substitutions were synthesized with the aim of establishing antimicrobial and anticancer activities of designed core. Biquinoline-thiazole hybridized scaffold, with majority of the prepared derivatives showed some admirable biological results. Compounds **9n** and **9c** showed most effective activity against the EGFR kinase inhibition and A549 lung cancer cell line, while compounds **9c** and **9u** showed the most effective activity against liver cancer cell line Hep G2. Against *E. coli* FabH, compounds **9c** and **9n** showed almost similar activity which has the highest among the synthesized derivatives. All these synthesized compounds were optimized with DFT to obtain their arrangement in space to evaluate plane angle on the basis of the substitutions, these plane angles were then related with their activity against EGFR and FabH in terms of binding efficiency, antibacterial as well as anticancer activities. Consequently, the biquinoline-thiazole hybrid core has potential for further development and serves as a template against which other complex substituent groups can be evaluated. Further, investigation can provide a greater scope as well as limitations for such templates as a potent antimicrobial and anticancer agents.

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CONFLICT OF INTEREST

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

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