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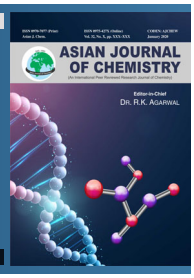

Design, Synthesis and Biological Evaluation of Novel Benzothiazole Based [1,2,4]Triazolo[4,3-*c*]quinazoline Derivatives

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A new series of *N*-(benzo[*d*]thiazol-2-yl)-[1,2,4]triazolo[4,3-*c*]quinazoline-5-carboxamide derivatives were synthesized by condensation of [1,2,4]triazolo[4,3-*c*]quinazoline-5-carboxylate derivatives with substituted benzothiazoles. The chemical structures of the synthesized compounds were confirmed by FT-IR, MS and ^{1}H NMR spectra. Designed triazoloquinazoline derivatives were docked with oxido-reductase enzyme (PDB Code 4h1j) and DNA gyrase enzyme (PDB Code 3g75). Based on high binding affinity score, the best compound were selected for synthesis and subjected to *in vitro* antioxidant and antibacterial activity. Compounds **7a** and **7d** were found to be most active compounds as antioxidant agent among this series when compared with ascorbic acid. Compounds **7a**, **7d** and **7f** were found to be most active compounds as an antibacterial agents among this series when compared with ciprofloxacin against bacterial strains such as *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853). Study revealed that the most active compounds after structural modifications can be exploited as lead molecules for other pharmacological activities such as anti-inflammatory, anticancer and antidepressant activities.

Keywords: Triazoloquinazoline, Benzothiazole, Molecular docking, Antioxidant activity, Antibacterial activity.

INTRODUCTION

In the family of heterocyclic chemistry, derivatives of quinazole, triazole and benzothiazole played significant role because they forms a part of structure of many different category drugs. Quinazole derivatives possess biological activities like anticancer [1], antidepressant [2], antiviral [3], antileishmanial [4], antitubercular [5], antimalarial [6], antimicrobial [7], analgesic [7], antiinflammatory [7,8], antiamoebic [9], *etc*. Triazole derivatives found to be active as anticonvulsant [10], antioxidant [11], urease inhibitor [11], antitubercular [12], anticancer [13] and antimicrobial [14] agent. Benzothiazole derivatives reported to have biological activities like antifungal [15], antimicrobial [16], antiviral [17], anticancer [17], and antioxidant [18], *etc*. The condensation products of these heterocycles exhibit biological activities like antihypertensive [19], antioxidant [20] and antimicrobial [21]. Various biological activities associated with quinazole, triazole and benzothiazole derivatives attracted the attention of many researchers.

Reactive oxygen species generated due to excessive oxidative stress or poor scavenging by antioxidants causes cellular damage. Antioxidants prevent progression of related chronic diseases like cancer, alzheimer, parkinson, inflammation, depression and cataract [22]. *in vitro* Study of heterocyclic derivatives by DPPH and H_2O_2 scavenging method revealed their antioxidant potential. The frequent use of antibacterial agents leads to increase in incidences of drug resistance. The development of resistant strains of bacteria leads to additional urgency for development of novel antibacterial agents. In view of above stated facts it is very much essential to design and develop antibacterial agents against pathogenic strains of microorganisms. The inhibition of bacterial growth under standardized condition may be utilized for demonstration of the therapeutic efficacy of antibacterial agents. The present work is extension of efforts for design and development of benzothiazole based triazoloquinazoline derivatives as a potential lead for antioxidant and antibacterial activity.

EXPERIMENTAL

All the reported organic compounds were synthesized using laboratory grade chemicals. All reactions were monitored by TLC and melting point. TLC (Type 60 GF254, Merck) was

used to check purity of compounds and visualization was done by iodine vapours and UV-Lamp. Melting points determined by VEEGO (Model: VMP-D) and temperatures were expressed in ºC. IR spectral study was carried out by Jasco FT/IR-4600 using KBr pellet technique. Mass spectra recorded on Impact HD QTOF Mass Spectrophotometer (Bruker-GmbH) with resolution 40,000 (*m/z* 1522). ^{1}H NMR spectral study by Bruker Advance III HD 500 MHz NMR Spectrometer (DMSO-d_6, TMS). Elemental analysis carried out on Bruker Electron Microscope Analyzer. Absorbance was measured using UV-VIS Spectrophotometer (Varian Carry100).

Molecular docking studies: Molecular docking study of logically designed novel benzothiazole based triazoloquinazoline derivatives was carried out using Autodock Vina docker in order to determine probable binding ligand for active site of target enzymes [23,24]. The X-ray crystal structure of oxidoreductase enzyme (PDB Code:4h1j) for antioxidant study and DNA gyrase enzyme (PDB Code: 3g75) for antibacterial study was used. Target enzymes were retrieved from the protein data bank by elimination of cocrystalized ligand and water molecules. All designed compounds were docked and lowest binding energy poses were analyzed for various intermolecular interactions. The residues phe568A, Leu556A, asp567A, glu474A and met478A of target PDB: 4h1j and residues Ile51A, Asp81A, Ile86A, Arg84A, Pro87A, Ser55A, Glu58A, Asn54A, Ile75A, Gly85A, Asp57A and Thr173A of target PDB:3g75 were recognized for interacting with antioxidant and antibacterial molecules, respectively.

Synthesis of ethyl 3,4-dihydro-4-oxoquinazoline-2-carboxylate (1): Mixed ethyl anthranilate (0.03 mol) and ethyl cyanoformate (0.04 mol) in 30 mL 1,4-dioxane, dry HCl was passed and refluxed for 8 h, cooled, filtered to give product.

Synthesis of ethyl 4-chloro-3,4-dihydroquinazoline-2-carboxylate (2): Refluxed compound **1** (0.04 mol) and $POCl_3$ (0.24 mol) for 5 h, cooled and poured on ice. The precipitate was filtered to obtain desired product.

Synthesis of ethyl 4-hydrazinyl-3,4-dihydroquinazoline-2-carboxylate (3): Compound **2** (0.03 mol) and hydrazine hydrate (0.053 mol) was dissolved in 60 mL ethanol and the heated solution at 65 ºC with constant stirring for 6 h. Cooled the reaction and obtained precipitate was filtered.

Synthesis of substituted triazoloquinazoline-5-carboxylate (4a-c): Mixed compound **3** (0.02 mol) and substituted benzoyl chloride (0.05 mol) in 50 mL of 1,4-dioxane. Potassium carbonate (0.025 mol) was added, stirred and heated at 50 ºC for 4-6 h. Precipitate obtained was filtered to obtain products.

Synthesis of substituted triazoloquinazoline-5-carboxylic acid (5a-c): Compound **4** (0.01 mol) in 10 % alcoholic NaOH solution (0.02 mol) was refluxed for 3-5 h. Cooled and acidified to get precipitate and then filtered the product.

Synthesis of substituted triazoloquinazoline-5-carbonyl chloride (6a-c): Dissolved compound **5a** (0.01 mol) in thionyl chloride (0.06 mol) and refluxed for 4-6 h. Excess thionyl chloride was distilled off by vacuum distillation and residue was collected as product.

Synthesis of substituted benzothiazole based [1,2,4]triazolo[4,3-*c*]quinazoline (7a-g): Mixed compound **6a** (0.01 mol), substituted 2-aminobenzothiazole (0.1mol) and K_2CO_3 (0.02 mol) in 1,4-dioxane. Refluxed reaction mixture for 8-13 h, cooled, poured on ice and extracted with ethyl acetate. Distilled off ethyl acetate by vacuum distillation and residue was collected (**Scheme-I**).

***N*-(6-Ethoxybenzo[*d*]thiazol-2-yl)-3-phenyl-[1,2,4]-triazolo[4,3-c]quinazoline-5-carboxamide (7a):** Yield: 71 %, m.p.: 168 ºC and R_f: 0.64 (ethyl acetate); IR (KBr, cm^{-1}): 3432 (N-H, 2º), 3012 (C-H, Ar), 1680 (C=O, amide), 1676 (C=N, Ar), 1257 (C-O-C, ether); MS: $[M]^+$ 466.12, $[M+1]^+$ 467.12; Fragments: 274.08, 273.08, 246.09, 245.08, 193.04, 179.04, 178.03; ^{1}H NMR: 7.58-8.01 (m, 4H, quinazoline), 6.94-7.38 (m, 5H, phenyl), 4.64 (s, 1H, amide -NH), 7.22-8.03 (m, 3H, benzothiazole), 1.14-3.48 (s, 5H, ethoxy); Elemental analysis % for $C_{25}H_{18}N_6O_2S$: C, 64.34; H, 3.90; N, 18.01; S, 6.87.

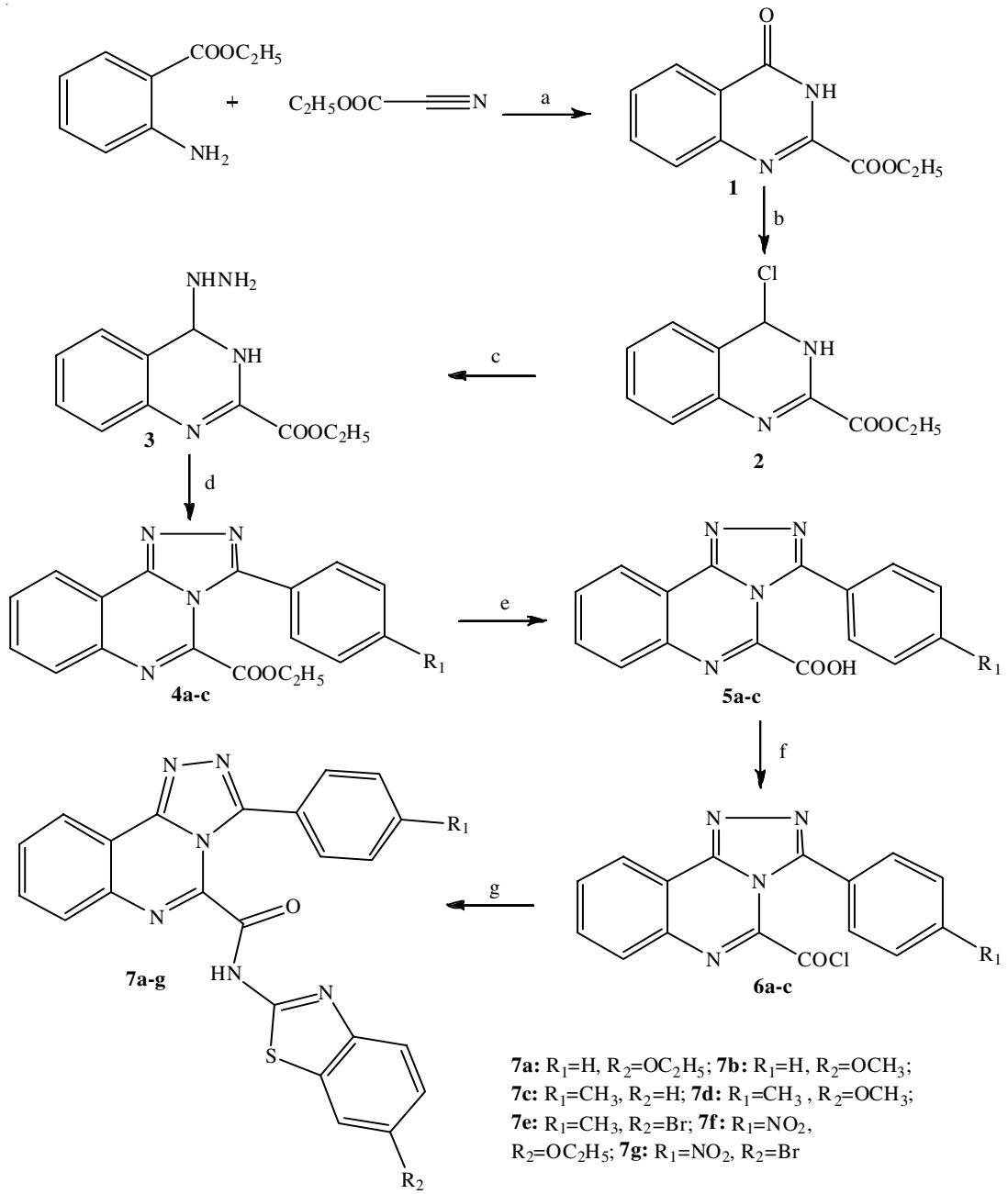
***N*-(6-Methoxybenzo[*d*]thiazol-2-yl)-3-phenyl-[1,2,4]-triazolo[4,3-c]quinazoline-5-carboxamide (7b):** Yield: 68 %, m.p.: 212 ºC and R_f: 0.60 (ethyl acetate); IR (KBr, cm^{-1}): 3458 (N-H, 2º), 3024 (C-H, Ar), 1674 (C=O, amide), 1666 (C=N, Ar), 1226 (C-O-C, ether); MS: $[M]^+$ 452.11, $[M+1]^+$ 453.11; Fragments: 245.08, 246.09, 273.08, 274.08, 179.03, 180.03, 207.02, 208.03; ^{1}H NMR: 7.27-8.10 (m, 4H, quinazoline), 7.02-7.53 (m, 5H, phenyl), 4.56 (s, 1H, amide-NH), 7.14-7.84 (m, 3H, benzothiazole), 3.36 (s, 3H, methoxy); Elemental analysis % for $C_{24}H_{16}N_6O_2S$: C, 63.69; H, 3.56; N, 18.58; S, 7.09.

***N*-(Benzo[*d*]thiazol-2-yl)-3-*p*-tolyl-[1,2,4]triazolo[4,3-*c*]-quinazoline-5-carboxamide (7c):** Yield: 66 %, m.p.: 186 ºC and R_f: 0.48 (ethyl acetate); IR (KBr, cm^{-1}): 3445 (N-H, 2º), 3018 (C-H, Ar), 2924 (C-H, alkyl), 1687 (C=O, amide), 1661 (C=N, Ar); MS: $[M]^+$ 436.11, $[M+1]^+$ 437.11; Fragments: 303.12, 288.10, 287.09, 149.02, 177.01, 178.02; ^{1}H NMR: 7.76-8.12 (m, 4H, quinazoline), 7.10-7.46 (m, 4H, phenyl), 2.23 (s, 3H, methyl), 5.11 (s, 1H, amide-NH), 7.36-7.93 (m, 4H, benzothiazole); Elemental analysis % for $C_{24}H_{16}N_6OS$: C, 66.02; H, 3.69; N, 19.25; S, 7.36.

***N*-(6-Methoxybenzo[*d*]thiazol-2-yl)-3-*p*-tolyl-[1,2,4]-triazolo[4,3-c]quinazoline-5-carboxamide (7d):** Yield: 71 %, m.p.: 204 ºC and R_f: 0.72 (ethyl acetate:methanol) (9:1); IR (KBr, cm^{-1}): 3462 (N-H, 2º), 3030 (C-H, Ar), 2906 (C-H, alkyl), 1673 (C=O, amide), 1617 (C=N, Ar), 1238 (C-O-C, ether); MS: $[M]^+$ 466.12, $[M+1]^+$ 467.12; Fragments: 302.11, 303.12, 288.10, 287.09, 179.09, 180.10, 165.02; ^{1}H NMR: 7.27-7.87 (m, 4H, quinazoline), 6.68-7.27 (m, 4H, phenyl), 2.04 (s, 3H, methyl), 4.44 (s, 1H, amide-NH), 7.02-7.76 (m, 3H, benzothiazole), 3.38 (s, 3H, methoxy); Elemental analysis % for $C_{25}H_{18}N_6O_2S$: C, 64.38; H, 3.88; N, 18.02; S, 6.87.

***N*-(6-Bromobenzo[*d*]thiazol-2-yl)-3-*p*-tolyl-[1,2,4]-triazolo[4,3-c]quinazoline-5-carboxamide (7e):** Yield: 57 %, m.p.: 242 ºC and R_f: 0.22 (ethyl acetate); IR (KBr, cm^{-1}): 3394 (N-H, 2º), 3016 (C-H, Ar), 2920 (C-H, alkyl), 1682 (C=O, amide), 1656 (C=N, Ar), 671 (C-Br); MS: $[M]^+$ 514.12, $[M+1]^+$ 516.12; Fragments: 302.11, 303.12, 288.10, 287.09, 228.93, 226.93, 179.09, 180.10, 165.02, 148.01; ^{1}H NMR: 7.69-8.24 (m, 4H, quinazoline), 7.17-7.52 (m, 4H, phenyl), 2.86 (s, 3H, methyl), 4.38 (s, 1H, amide-NH), 7.47-8.06 (m, 3H, benzothiazole); Elemental analysis % for $C_{24}H_{15}N_6OSBr$: C, 55.94; H, 2.93; N, 16.30; S, 6.22.

***N*-(6-Ethoxybenzo[*d*]thiazol-2-yl)-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-c]quinazoline-5-carboxamide (7f):** Yield:



7a: R_1=H, R_2=OC_2H_5; **7b:** R_1=H, R_2=OCH_3;
7c: R_1=CH_3, R_2=H; **7d:** R_1=CH_3 , R_2=OCH_3;
7e: R_1=CH_3, R_2=Br; **7f:** R_1=NO_2,
R_2=OC_2H_5; **7g:** R_1=NO_2, R_2=Br

Reaction conditions: (a) Dry HCl, dioxane; (b) $POCl_3$, 5 h; (c) NH_2-NH_2·H_2O, 65 °C, 6 h; (d) Sub. benzoyl chloride, 50 °C, 4-6 h; (e) 10 % NaOH, 3-5 h; (f) $SOCl_2$, 1-3 h; (g) K_2CO_3, Sub. benzothiazole, 8-13 h

Scheme-I: General scheme for synthesis of compounds

61 %, m.p.: 152 ºC and R_f: 0.44 (ethyl acetate:toluene) (4:1); IR (KBr, cm^{-1}): 3403 (N-H, 2º), 3031 (C-H, Ar), 1680 (C=O, amide), 1676 (C=N, Ar), 1541 (N-O, nitro), 1246 (C-O-C, ether); MS: $[M]^+$ 511.11, $[M+1]^+$ 512.11; Fragments: 319.07, 318.06, 290.07, 221.04, 194.05, 193.04, 164.01; ^{1}H NMR: 7.48-7.91 (m, 4H, quinazoline), 7.29-8.25 (m, 4H, phenyl), 4.82 (s, 1H, amide -NH), 7.02-7.67(m, 3H, benzothiazole), 1.02-3.21 (s, 5H, ethyl); Elemental analysis % for $C_{25}H_{17}N_7O_4S$: C, 58.71; H, 3.35; N, 19.18; S, 6.27.

***N*-(6-bromobenzo[*d*]thiazol-2-yl)-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-c]quinazoline-5-carboxamide (7g):** Yield 65 %, m.p.: 174 ºC and R_f: 0.40 (ethyl acetate:toluene) (4:1); IR (KBr, cm^{-1}): 3448 (N-H, 2º), 2996 (C-H, Ar), 1669 (C=O, amide), 1662 (C=N, Ar), 1524 (N-O, nitro), 658 (C-Br); MS: $[M]^+$ 546.99, $[M+1]^+$ 548.00; Fragments: 319.07, 318.06, 290.07, 228.93, 226.93, 149.01, 148.01; ^{1}H NMR: 7.64-8.12 (m, 4H, quinazoline), 7.48-8.31 (m, 4H, phenyl), 4.77 (s, 1H, amide-NH), 7.23-7.72 (m, 3H, benzothiazole); Elemental analysis % for $C_{23}H_{12}N_7O_3SBr$: C, 50.55; H, 2.21; N, 17.96; S, 5.87.

Antioxidant activity

DPPH Scavenging method: The antioxidant activity was carried out as per method of Venkatachalam *et al*. [25] and Stefania-Felicia *et al*. [26] with slight modifications. A DPPH solution (2 mL, 400 µM) mixed with test compound solutions 50, 100, 150, 200, 250 and 500 µM in methanol. The samples incubated for 20 min and absorbance measured at 517 nm.

Ascorbic acid was used as standard. The IC_{50} values were calculated from a plot between sample concentration and % scavenging.

Hydrogen peroxide scavenging method: Hydrogen peroxide scavenging activity evaluated as per method of Ruch *et al*. [27] with slight modifications. A 3.4 mL of test compound (50, 100, 150, 200, 250 and 500 µM) was mixed with H_2O_2 solution (0.6 mL, 40 µM) in phosphate buffer (pH 7.4). Absorbance measured after 10 min at 230 nm. Ascorbic acid was used as standard for comparison.

Antibacterial activity: Synthesized derivatives were screened for antibacterial activity against microbial strains such as *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853) using well-diffusion method [28]. Test samples (5, 10, 25 and 50 µg/mL) were prepared in dimethyl sulphoxide. The wells, seeded with bacterial culture, were impregnated with test solutions. Zone of inhibition measured after incubation at 37 ºC for 24 h. DMSO and ciprofloxacin were used as control and reference standard, respectively.

RESULTS AND DISCUSSION

In designing of synthetic protocol for target molecules, it was envisaged that 2-carbethoxy-3,4-dihydro-quinazolin-4-one (**1**) was synthesized by passing the HCl gas through solution of ethyl anthranilate and ethyl cyanoformate in 1,4-dioxane, compound **1** was refluxed with $POCl_3$ to get 4-chlorodihydroquinazoline derivative (**2**), compound **2** was treated first with hydrazine hydrate to form 4-hydrazino dihydro-quinazoline derivative (**3**) and then treated with substituted benzoyl chloride to obtain substituted [1,2,4]triazolo[4,3-*c*]-quinazoline-5-carboxylate (**4a-c**). Compounds **4a-c** after alkaline hydrolysis converted to corresponding carboxylic acid (**5a-c**), which was then treated with thionyl chloride to obtain triazoloquinazoline carbonyl chlorides (**6a-c**). Compounds **6a-c** was condensed with substituted benzothiazoles to obtain desired title compounds (**7a-g**) (**Scheme-I**) [29,30].

The structural elucidation of the synthesized compounds was done by using FTIR, NMR and MS spectral analysis. The IR spectra showed peaks at 1687-1669 cm^{-1} (C=O, 2º amide) and 3462-3394 cm^{-1} (N-H, 2° amide) gives confirmation of CONH-bridge between benzothiazole and quinazoline in addition to other characteristic peaks for functional groups. Mass spectra showed $[M]^+$ and $[M+1]^+$ peaks, characteristic base peaks and other fragments. ^1H NMR spectra showed peaks at 7.27-8.24 ppm assigned to aromatic 4H of quinazoline, 7.02-8.06 ppm for 3H (or 4H) of benzothiazole, 4.44-5.11 ppm for N-H bridge between benzothiazole and quinazoline and characteristic alkyl peak between 1-3 ppm are assigned to CH_3 and CH_2 present as alkoxy substituents on ring.

Molecular docking: Molecular docking using oxidoreductase enzyme (PDB Code 4h1j) and DNA gyrase enzyme (PDB Code 3g75) recognizes the amino residues to be interacting with ligand molecule. The amino acid residues phe568A, Leu556A, asp567A, glu474A and met478A for antioxidant ligand and Ile51A, Asp81A, Ile86A, Arg84A, Pro87A, Ser55A, Glu58A, Asn54A, Ile75A, Gly85A, Asp57A and Thr173A were recognized for interacting with antibacterial molecules. Docking results (Table-1) revealed that designed triazoloquinazoline derivatives exhibit good docking scores when compared with the reference standards ascorbic acid and ciprofloxacin for antioxidant and antibacterial activities, respectively. The molecules were ranked according to their docking score and lowest binding energy poses are selected and analyzed for various intermolecular interactions. Interestingly compounds **7a** and **7f** showed better score as antioxidant and **7a**, **7d** and **7f** as antibacterial compound. Antioxidant target residues asp-567A, Lys457A showed hydrogen bond interaction with N-H bridge between quinazoline and thiazole and also with imine nitrogen of benzothiazole. Residue His547A and Arg572A showed π-π staking and π-cation interactions respectively with triazoloquinazoline aromatic rings. Glu474A forms salt bridge with nitro substituent on phenyl group. Phe568A residue interacts with benzothiazole by hydrophobic interactions. Antibacterial target residues Asp81A, Ile86, Asn54A and Glu58A showed H-bond interaction with N-H bridge between quinazoline and thiazole ring and also with ethoxy oxygen on benzothiazole (Figs. 1-5).

Antioxidant activity: The results of antioxidant activity by DPPH and H_2O_2 scavenging method are expressed as IC_{50} in µM (Fig. 6). In DPPH scavenging method, compounds **7a**, **7d** and ascorbic acid showed IC_{50} at 112.42, 91.57 and 74.12 µM, respectively. However, In H_2O_2 scavenging method, **7a**, **7d** and ascorbic acid showed IC_{50} at 135.52, 125.62 and 102.41 µM, respectively. The binding interaction showed in docking study may be the reason for the better antioxidant activity. But, in contrast to docking score compound **7d** showed better antioxidant activity as compared to compound **7f**. Methyl substitution at *para*-position gives more active compound than the *para*-nitro analog of this series.

Antibacterial activity: The antibacterial activity results revealed that compounds **7a** and **7f** were moderately active against *S. aureus* (ATCC 25923), while compounds **7a** and **7d** were moderately active against *E. coli* (ATCC 25922). Similarly, compounds **7b** and **7d** were moderately active against *Pseudomonas aeruginosa* (ATCC 27853) (Fig. 7). The binding interaction showed in docking study may be the reason for the better antibacterial activity. But, in contrast to docking results *in vitro* activity results showed compound **7b** had more antibacterial activity which is comparable to compounds **7a**, **7d** and **7f**.

Conclusion

In this work, benzothiazole based [1,2,4]triazolo[4,3-*c*]-quinazoline derivatives were synthesized and characterized. The synthesized compounds displayed remarkable antioxidant and antibacterial activities. Compounds **7a** and **7d** have been

TABLE-I
BINDING ENERGY (kcal/mol) OF LIGANDS WITH PROTEIN CRYSTAL STRUCTURE (PDB CODE: 4h1j AND 3g75)

PDB code	7a	7b	7c	7d	7e	7f	7g	Standard drug
4h1j	-8.557	-8.452	-8.453	-7.455	-6.535	-8.892	-7.412	-7.288
3g75	-3.686	-3.143	-3.476	-3.624	-3.246	-3.792	-3.553	-4.969

Standard drug for 4h1j = ascorbic acid; Standard drug for 3g75 = ciprofloxacin.

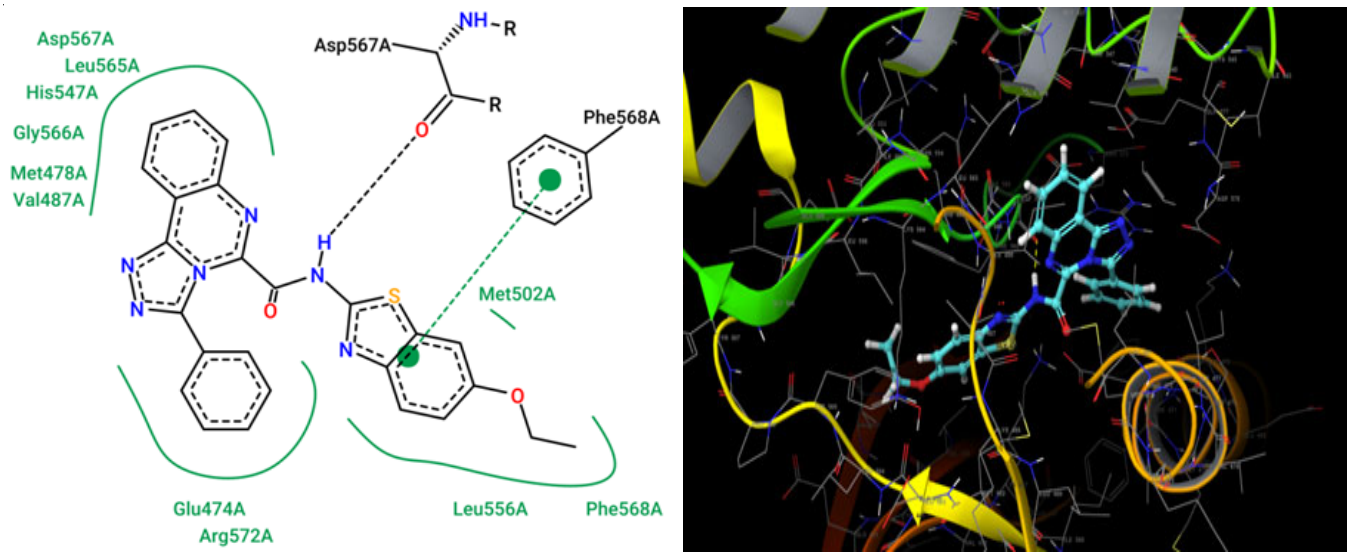


Fig. 1. 2D and 3D image for compound **7a** docked with protein crystal structure (PDBCode: 4h1j)

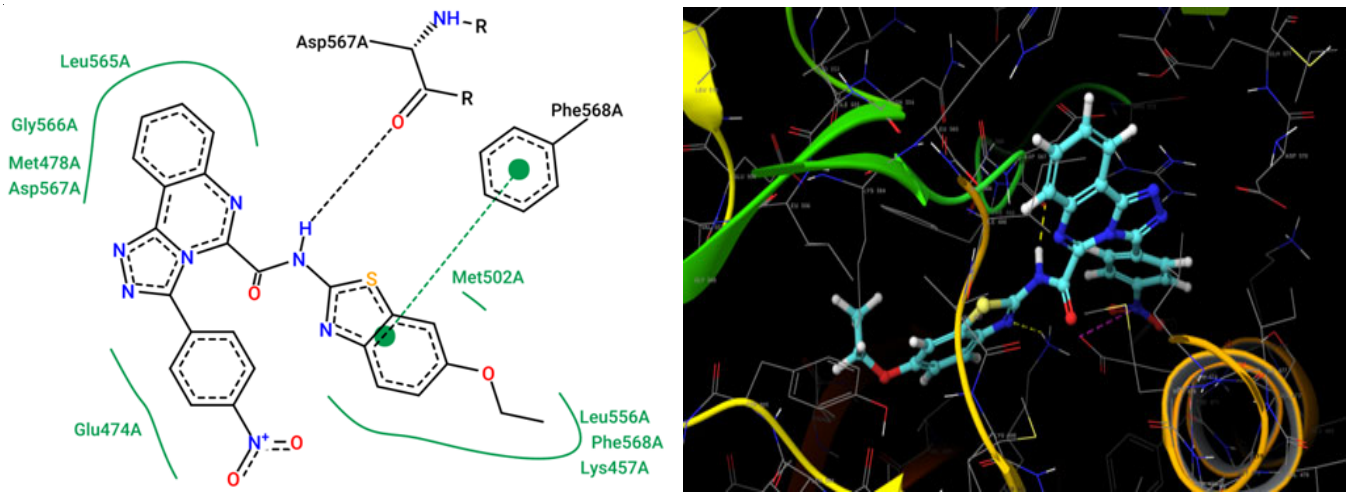


Fig. 2. 2D and 3D image for compound **7f** docked with protein crystal structure (PDBCode: 4h1j)

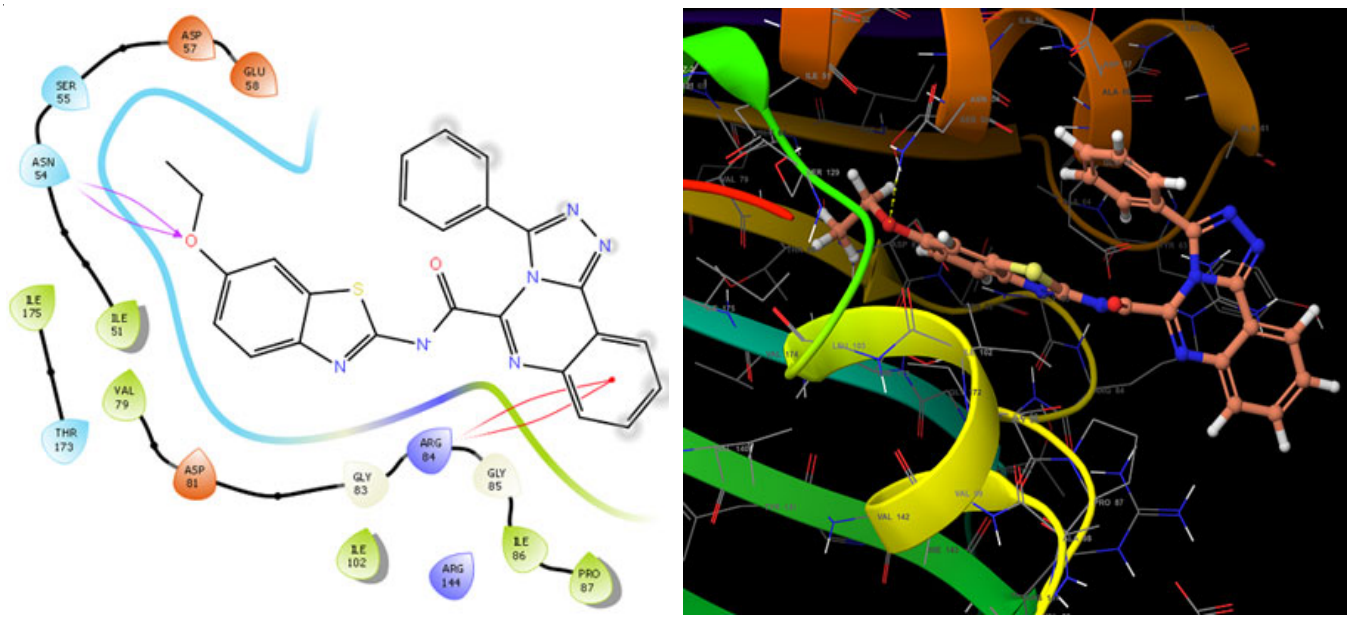


Fig. 3. 2D and 3D image for compound **7a** docked with protein crystal structure (PDBCode: 3g75)

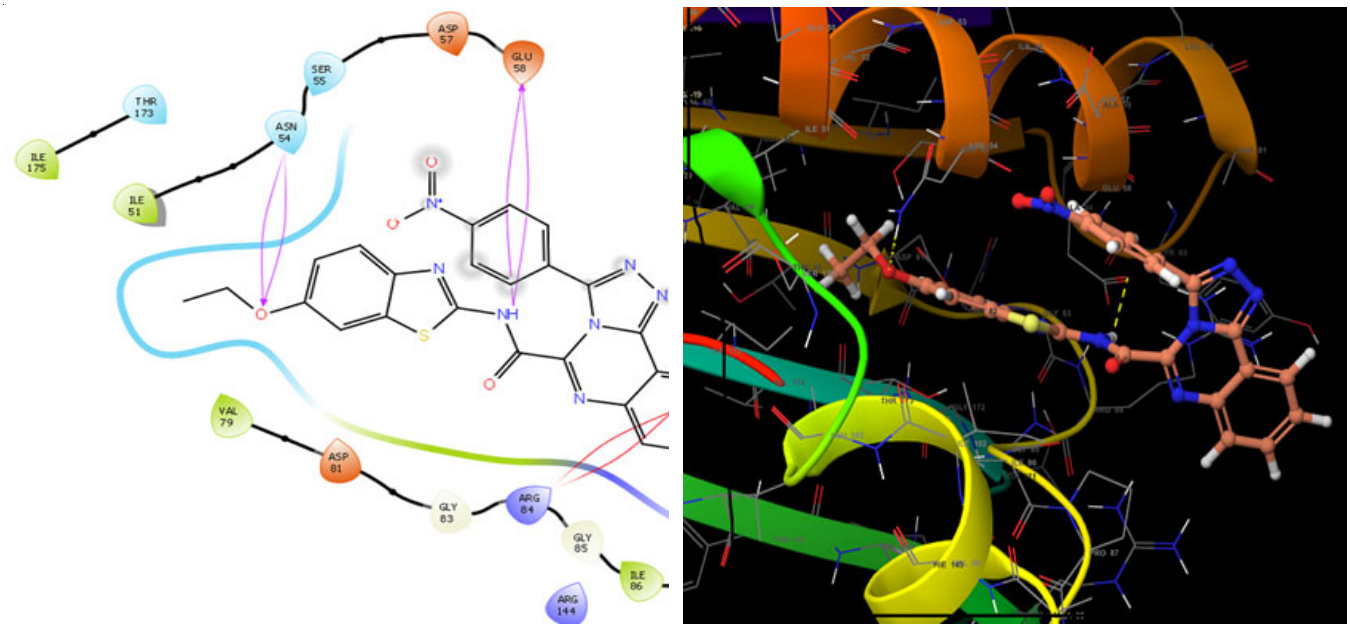


Fig. 4. 2D and 3D image for compound **7f** docked with protein crystal structure (PDBCode: 3g75)

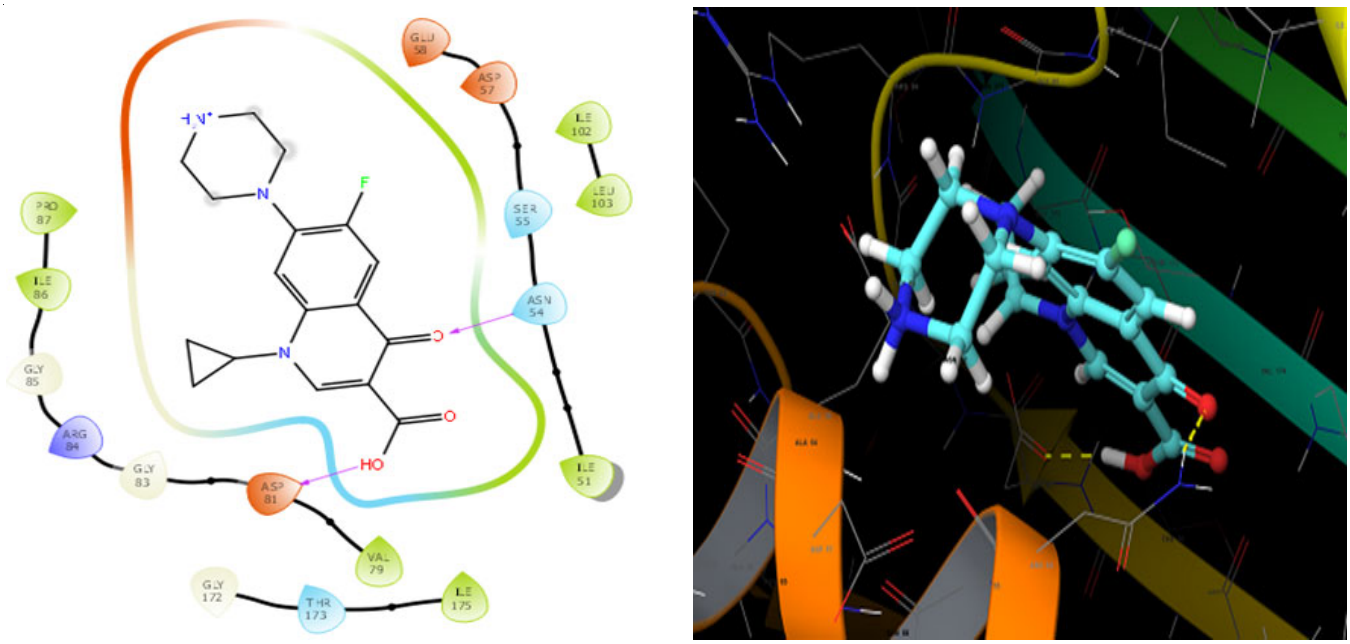


Fig. 5. 2D and 3D image for ciprofloxacin docked with protein crystal structure (PDBCode: 3g75)

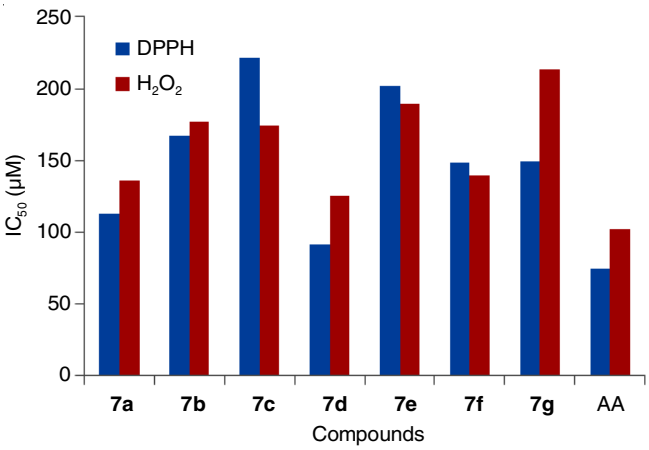


Fig. 6. Antioxidant activity by DPPH and H_2O_2 scavenging method

determined as good antioxidants whereas other compounds showed moderate to less antioxidant activities. Compounds **7a**, **7b**, **7d** and **7f** showed good antibacterial activity.

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CONFLICT OF INTEREST

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

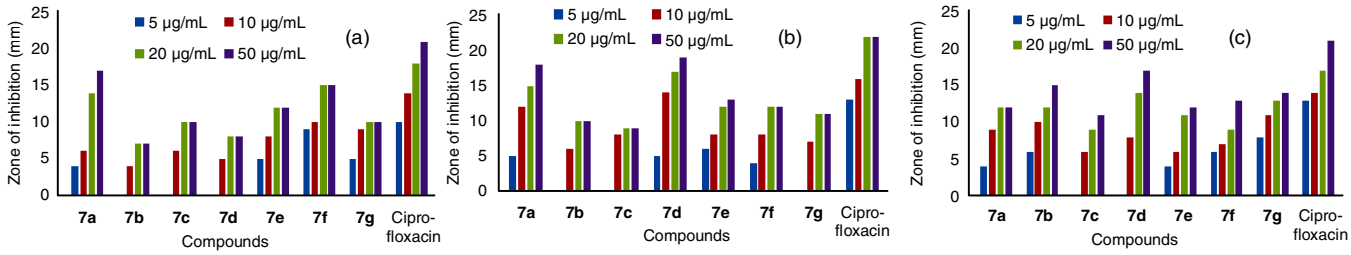

Fig. 7. Antibacterial activity against different bacterial strains [(a) *S. aureus*, (b) *E. coli* and (c) *P. aeruginosa*]

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