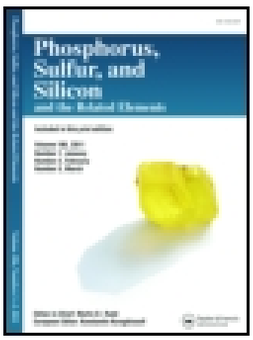

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Quinazoline clubbed thiazole and 1,3,4-oxadiazole heterocycles: synthesis, characterization, antibacterial evaluation, and molecular docking studies

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ABSTRACT

In search of potent antibacterial agents, a series of novel quinazolines, bearing thiazole and 1,3,4-oxadiazole heterocycles **6a–j** (3-(4-methyl-5-(4-((arylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3*H*)-ones) were synthesized and the structures of the compounds were elucidated by standard spectroscopic techniques. In order to evaluate their antibacterial potential, the antibacterial assay of synthesized compounds **6a–j** was performed against MTCC strains, wherein compounds **6d** (3-(4-methyl-5-(4-(((4-nitrophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3*H*)-one) (*Escherichia coli*, MIC = 100 μg mL^{-1}) and **6e** (3-(5-(4-(((2-chlorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3*H*)-one) (*E. coli*, MIC = 62.5 μg mL^{-1}) were most active against Gram-negative bacteria while compound **6f** (3-(5-(4-(((4-chlorophenyl)amino)-methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3*H*)-one) (*Staphylococcus aureus*, MIC = 50 μg mL^{-1}) was most active against Gram-positive bacteria. Furthermore, molecular docking simulation was performed to determine the probable binding mode and affinity of the synthesized compounds toward bacterial DNA *gyrase*. The preliminary results pave the way for further designing the thiazole based 1,3,4-oxadiazoles heterocycles for enhancing their potency as antibacterial agents.

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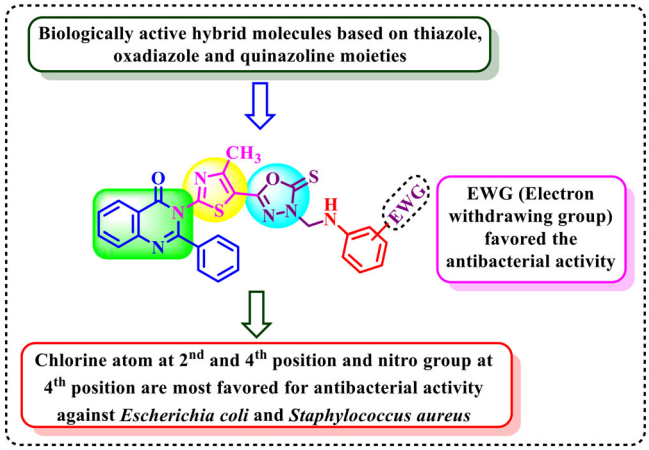
1,3,4-oxadiazole; antibacterial activity; molecular docking; quinazoline; thiazole

GRAPHICAL ABSTRACT



Introduction

Recently, the study of common scaffolds through a strategic design of their heterocyclic components has gained major attention in medicinal chemistry. Heterocycles containing several heteroatoms such as oxygen, nitrogen, and sulfur have a critical importance for medicinal chemists.[1] Infectious diseases caused by bacteria and viruses are life-threatening and are increasing in many countries.[2] Overcoming resistance to existing drugs designed to kill microorganisms is an additional challenge for those working in this synthetic chemistry field. There is a pressing need for the discovery of new and potent antimicrobial drugs.[3] The deterioration of the human population due to the high prevalence of infectious diseases is becoming a worldwide problem.[4] Thiazole, quinazoline, and 1,3,4-oxadiazole scaffolds and their compounds display a wide range of biological activities such as antimicrobial,[5–7] antifungal,[8,9] anticancer,[10]

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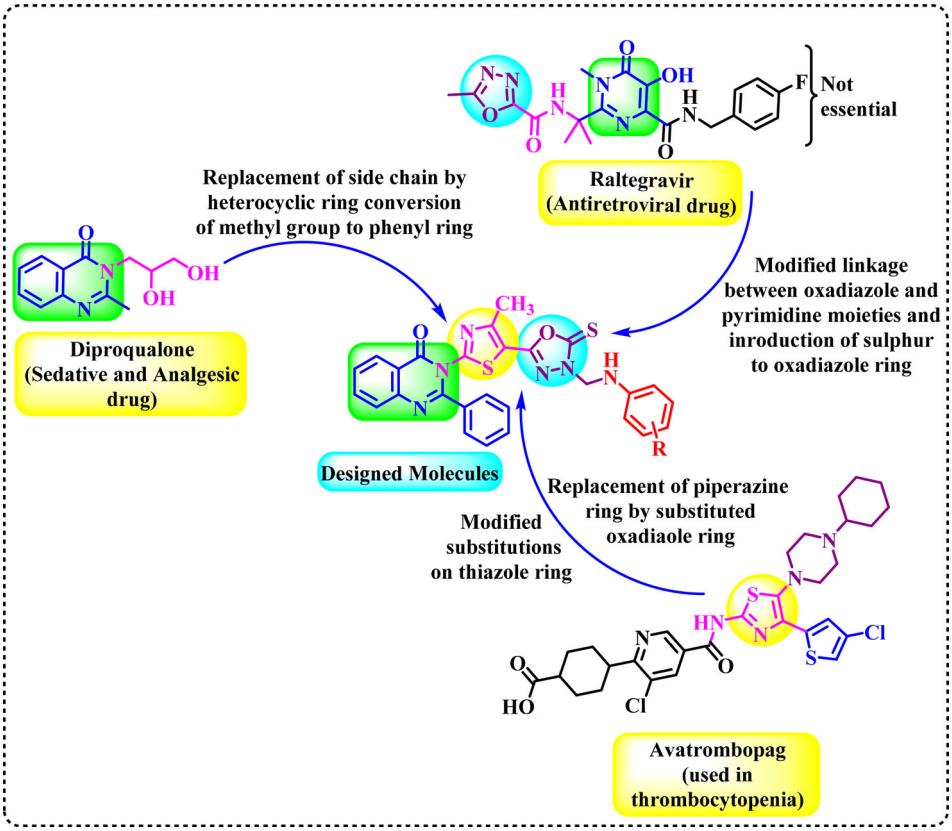


Figure 1. Concept of design based on clinical drugs containing the quinazoline, thiazole or 1,3,4-oxadiazole moieties.

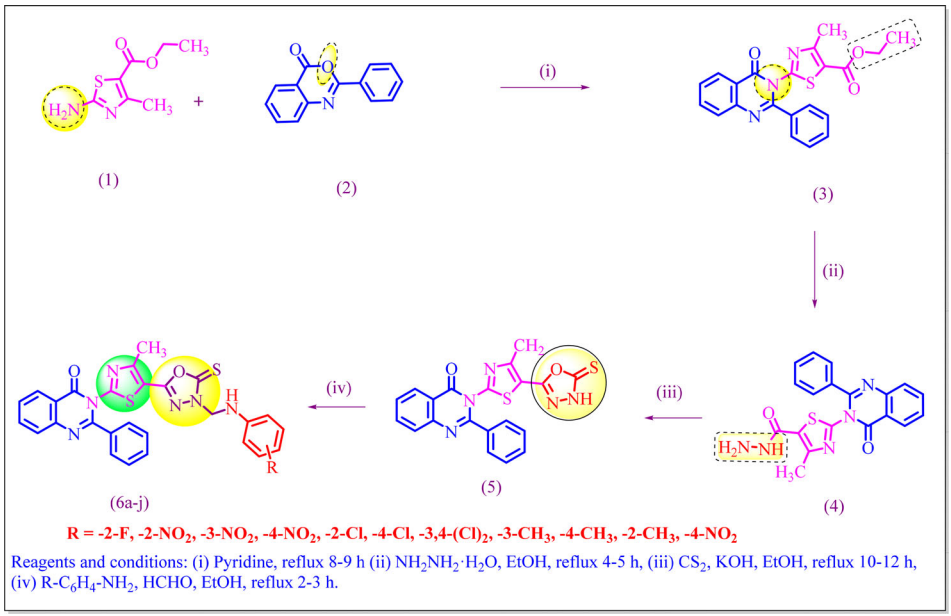
antitubercular,[11–14] antimalarial,[15] analgesic,[16] anticonvulsant,[17] hypoglycemic,[18] antioxidant,[19] and other biological properties such as genotoxic potential and lipid peroxidation inhibition.[20,21] On further conjugating, 1,3,4-oxadiazole and thiazole are proven to demonstrate antimicrobial properties and to restrain bacteria by blocking their biosynthesis through certain bacterial lipids by additional mechanisms.[22] In the present study, we report the scientific rationale in designing hybrid heterocycles by conjugating 1,3,4-oxadiazoles with different thiazole nuclei to form novel heterocyclic compounds exhibiting better potency toward established microbes. The synthesized compounds are equally promising for medicinal chemists when compared with commercially available drugs containing quinazoline, thiazole, and 1,3,4-oxadiazole scaffolds. The structural similarities of these compounds are shown in Figure 1. The most prominent examples of established agents containing quinazoline, thiazole and 1,3,4-oxadiazoles nuclei include the Diproqualone, Avantrombopag, and Lusutrombopag.[23–25]

These research findings motivated us to explore thiazole based 1,3,4-oxadiazole heterocycles as potential antibacterial agents. The objective of our study was to explore the combination of three heterocycles which may exhibit synergistic effect while improving their antibacterial activity. The present study reports, (1) novel hybrid heterocyclic molecules consisting of quinazoline based thiazole, 1,3,4-oxadiazoles; (2) evaluation of their antibacterial potency; (3) and investigation of their active inhibitor's interaction with bacterial DNA gyrase by docking study. In order to strategically develop and establish novel promising antimicrobial agents, the concept of design thinking was applied in this manuscript which is as depicted in Figure 1. DNA gyrase subunit b is a target to be inhibited by multiple scaffolds and also being a target situated in the bacterial cell. It is the most vulnerable target for the molecules approaching the bacteria. This motivated us to evaluate the binding affinity of the title class of molecules against this crucial bacterial enzyme.

Results and discussion

Chemistry

The reaction conditions employed in the synthesis of strategically designed compounds **6a–j** are explained in Scheme 1. The nucleophilic attack of compound **3** with $NH_2NH_2{\cdot}H_2O$ afforded compound **4** in EtOH at reflux temperature. Compound **4** was further characterized by the presence of three strong IR bands showing functional presence at 3131 (>NH), 3311, and 3255 cm^{-1} (-NH_2) in the IR spectrum. In compound **4**, presence of -NH-NH_2 functional group was recorded in the ^{1}H NMR spectrum at 4.2 (-NH_2) and 8.94 (>NH) ppm. Further, the mass fragmentation and elemental analysis results were also consistent with the assigned structure. The condensation of compound **4**, with KOH, CS_2 using EtOH at reflux temperature for 12 h, yielded the corresponding oxadiazole **5.** The final compounds **6a–j** were derived by coupling reaction of compound **5**, with various substituted aniline and HCHO under reflux using EtOH for 3 h. The structural characterization of newly synthesized compounds **6a–j** was done by spectral



Scheme 1. Synthetic pathway of the reported compounds **6a–j**.

analysis. The IR spectrum of compound **6a,** as an example, exhibited the characteristic absorption band of the carbonyl group exhibited at 1713 cm^{-1}. The vibrations appeared at 3109, 2940 cm^{-1} corresponding to C-H stretching, aromatic ring, -CH_3 stretching, and –CH_2 stretching, respectively. Characteristic absorption observed at 1227 cm^{-1} was due to C-O-C stretching vibration of 1,3,4-oxadiazole ring. A strong absorption band observed at 3233 cm^{-1} is the distinctive peak of (-NH). In ^{1}H NMR spectra, the emergence of singlet peaks at $\delta = 2.49$ and 5.82 ppm were due to three protons of methyl groups and proton of –NH respectively. In the ^{13}C NMR spectrum, synthetic product **6a** displayed a signal at $\delta = 177.5$ ppm arising from the C = O group, and the signal obtained in the region of $\delta = 17.4$ ppm confirmed the presence of carbon of methyl group. The molecular ion peak is observed at $m/z = 542.10$ which is in confirmative evidence of the suggested molecular weight and elemental analysis. [For detailed information see Supporting Information].

Antibacterial assay

The *in vitro* antibacterial activity of newly synthesized targeted compounds **6a–j** was screened against pathogenic bacterial strains for two Gram-positive bacterial strains like *Staphylococcus aureus* (MTCC-96), and *Streptococcus pyogenes* (MTCC-442) while two Gram-negative bacterial strains like *Escherichia coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC-1688) were also used in the biological screening. The antibacterial potency of the strategically designed compounds was investigated by minimum inhibitory concentration (MIC) applying conventional broth microdilution method using gentamycin as a reference drug.[26] The results of antibacterial activity are tabulated in [Table S1 (Supporting Information)]. Based on the results presented in this research article and to further design and synthesize active molecules for the future, the molecular modeling was also performed showing the potency of these scaffolds in the heterocyclic research for scouting novel antibacterial agent. Among the synthesized compounds, (*3-(5-(4-(((4-chlorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3H)-one*) **(Compound 6f)** possessed excellent activity at MIC of 50 μg mL^{-1} and good activity at MIC of 150 μg mL^{-1} against *S. aureus* and *E. coli* respectively [See Figure S28 (Supporting Information)]. (*3-(5-(4-(((2-chlorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3H)-one*) **(Compound 6e)** exhibited very good activity at MIC of 62.5 μg mL^{-1} and good activity at MIC of 150 μg mL^{-1} against *E. coli* and *P. aeruginosa* respectively. This may be attributed to the presence of lipophilic H-bond acceptor type of group like 2-chloro and 4-chloro present on benzene ring of oxadiazole functionality. (*3-(4-methyl-5-(4-(((4-nitrophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one*) **(Compound 6d)** shown a good activity with MIC of 100 μg mL^{-1} against *E. coli.*

Experimental

Materials and methods

Melting points were determined via in open capillary method. The reactions were monitored using thin-layer chromatography (TLC) on silica gel plates (Merck, 60, F_{254}) was used to check purity and reaction monitoring and completion. Percentage of carbon, hydrogen, and nitrogen were checked via Perkin-Elmer 2400 CHN analyzer. IR spectra of the synthesized compounds were recorded on Shimadzu IR Prestige-21 (CE) Fourier transform infrared spectrophotometer using KBr; the frequencies were reported in cm^{-1}. ^{1}H NMR spectra were recorded on Varian Gemini at 400 MHz and ^{13}C NMR spectra on a Varian Mercury at 100 MHz

using dimethyl sulfoxide (DMSO)-d_6 as a solvent and tetramethylsilane as an internal standard. ^{1}H NMR data were given in multiplicity (s, singlet; d, doublet; t, triplet; m, multiple) and chemical shifts were in δ ppm unit. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. The reactions were carried out in oven-dried glass wares under a nitrogen atmosphere and Büchi rotavapor was used for the distillation.[27] The progress of the reaction and the purity of the synthesized compound was checked on TLC [Aluminium sheet silica gel 60 F_{254} (E. Merck)] using n-hexane: ethyl acetate (7:3) as an irrigator and the plates were developed in an iodine chamber or observed under UV light. The Supporting Information contains sample IR, ^{1}H, and ^{13}C NMR spectra of the products 6 (Supporting Information Figures S10–S27).

Synthesis of ethyl 4-methyl-2-(4-oxo-2-phenyl (3-hydroquinazolin-3-yl))-1,3-thiazole-5-carboxylate (compound 3)

In a round bottom flask, a mixture of ethyl-2-amino-4-methyl-1,3-thiazole-5-carboxylate **(Compound 1)** (0.012 mol) and 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (0.01 mol) **(Compound 2)** (prepared as per the reported literature method[28]) were added in pyridine (50 mL) and the reaction mixture was refluxed for 8–9 h. The progress of the reaction was monitored periodically and on completion of the reaction, the reaction mixture was poured over ice-cold water. The reaction mixture was acidified using dilute hydrochloric acid (10% v/v) to remove unreacted compound **1**. The obtained solid was filtered and washed using cold water. The resulting solid was crystallized using ethanol. Yield: 77%; m.p. 173–175 °C; IR (KBr, cm^{-1}): 3031, 2827 (C-H, -CH = CH-), 2759 (C-H), 1733 (>C = O), 1694, 1663, 1619 (C = C, -COO-, C = N), 1147 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.21 - 7.48$ (m, 9H, Ar-H), 4.2 (m, 2H, -O-CH_2), 2.3 (m, 3H, Het-CH_3), 1.3 (m, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.9$ (C_2 of thiazole ring), 163.8 (-C = O), 162.5 (C_4 of quinazoline ring), 155.3 (C_4 of thiazole ring), 154.8 (C_2 of quinazoline ring), 148.7 (C_9 of quinazoline ring),135.3 (C_7 of quinazoline ring),130.3 (C_4 of phenyl ring), 128.8(2) (C_3 and C_5 of phenyl ring), 128.7 (C_1 of phenyl ring), 128.4(2) (C_2 and C_6 of phenyl ring), 127.9 (C_8 of quinazoline ring), 126.3 (C_6 of quinazoline ring), 120.1 (C_{10} of quinazoline ring), 117.1 (C_5 of quinazoline ring), 115.2 (C_5 of thiazole ring), 62.5 (O-CH_2), 16.1 (CH_3), 15.2 (CH_3), MS (*m/z*): 391.10 (M^+); Anal. Calcd. for:$C_{21}H_{17}N_3O_3S$: C, 64.44%; H, 4.38%; N, 10.73%. Found: C, 64.47%; H, 4.41%; N, 10.80%.

Synthesis and characterization of N-amino[4-methyl-2-(4-oxo-2-phenyl(3-hydroquinazolin-3-yl))(1,3-thiazol-5-yl)]carboxamide (compound 4)

Compound **3** (0.01 mol) and $NH_2NH_2{\cdot}H_2O$ (99%, 0.015 mol) were taken in a round bottom flask and the reaction mixture was refluxed for 10 min. EtOH (95%) was added till both the layers were miscible and refluxing was continued for 5 h. The excess EtOH and unreacted $NH_2NH_2{\cdot}H_2O$ were distilled out. The reaction mass was poured into a beaker containing water (100 mL). The solid was crystallized using ethanol to obtain a pure white crystalline product. Yield: 65%; m.p. 130–132 °C; IR (KBr, cm^{-1}): 3311, 3255 (N-H, primary amine), 3131 (N-H, primary amine),3031, 2827 (C-H, -CH = CH-), 2759 (C-H), 1733 (>C = O), 1694, 1619(C = C, C = N), 1234 (C-O-C), 1147 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.9$ (m, 1H, -NH-NH_2), $8.2 - 7.3$ (m, 9H, Ar-H), 4.2 (m, 2H, -NH-NH_2), 2.4 (m, 3H, Het-CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 166.7$ (C_2 of thiazole ring), 160.3(2) (C_4 of quinazoline ring and C-C = O-N), 156.8 (C_4 of thiazole ring), 155.1 (C_2 of quinazoline ring), 147.6 (C_{10} quinazoline ring), 133.8 (C_8 of quinazoline ring), 132.6 (C_5 of thiazole ring), 130.3 (C_4 of phenyl ring), 128.9(2) (C_3 and C_5 of phenyl ring), 128.4 (C_1 of phenyl ring), 128.3(2) (C_2 and C_6 of phenyl ring), 127.5 (C_7 of quinazoline ring), 126.5 (C_6 of quinazoline ring), 126.1 (C_9 of quinazoline ring), 120.6 (C_5 of quinazoline ring), 16.5 (CH_3), MS (*m/z*): 377.09 (M^+); Anal. Calcd. for: $C_{19}H_{15}N_5O_2S$: C, 60.41%; H, 4.08%; N, 18.50% Found: C, 60.46%; H, 4.01%; N, 18.56%.

Synthesis and characterization of 3-(4-methyl-5-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one (compound 5)

A mixture of compound **4** (0.01 mol), KOH (0.01 mol), CS_2 (0.02 mol), and EtOH (95%, 100 mL) was refluxed for 12 h. The excess solvent was removed by vacuum evaporation and the residue was dissolved in water and acidified with CH_3COOH (40% v/v) to get a solid product. It was filtered, dried, and crystallized using H_2O:EtOH (60:40). Yield: 63%; m.p. 178–181 °C; IR (KBr, cm^{-1}): 3037, 2835 (C-H, -CH = CH-), 2761 (C-H), 1737 (>C = O), 1686, 1630 (C = C, C = N), 1239 (C-O-C), 1152 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 13.2$ (s, 1H, N-NH), 8.2–7.3 (m, 9H, Ar-H), 2.2 (m, 3H, Het-CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 189.7$ (C_5 of oxadiazole ring), 166.4 (C_2 of thiazole ring), 160.4 (C_4 of quinazoline ring), 157.8 (C_2 of oxadiazole ring), 156.6 (C_4 of thiazole ring), 156.1 (C_2 of quinazoline ring), 148.6 (C_{10} of quinazoline ring), 133.7 (C_8 of quinazoline ring), 132.1(C_5 of thiazole ring), 130.5 (C_4 of phenyl ring), 128.9 (C_1 of phenyl ring), 128.6(2) (C_3 and C_5 of phenyl ring), 128.5(2) (C_2 and C_6 of phenyl ring), 127.3 (C_7 of quinazoline ring), 126.8 (C_9 of quinazoline ring), 126.3 (C_6 of quinazoline ring), 120.1 (C_5 of quinazoline ring), 17.5 (CH_3), MS (*m/z*): 419.05 (M^+); Anal. Calcd. for: $C_{20}H_{13}N_5O_2S_2$:C, 57.21%; H, 3.18%; N, 16.75%. Found: C, 57.26%; H, 3.12%; N, 16.70%.

General preparation of 3-(4-methyl-5-(4-((phenylamino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-ones, (compounds 6a–j)

Compound **5** was mixed with aromatic amines and the mixture was applied heat under controlled conditions using

ethanol (95%, 50 mL) with formaldehyde (36%, 0.02 mol) for 3 h. The resulting solid was poured into water (100 mL) and crystallized using methanol.

Physical constant and characterization of 3-(5-(4-(((2-fluorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3H)-one (compound 6a)

Gray (Yield 62%) m.p. 212–214 °C; IR (KBr, cm^{-1}): 3233 (N-H), 3109, 2940 (C-H, -CH = CH-), 1713 (>C = O), 1651 (C = C, C = N), 1228 (C-O-C), 1018 (C = S), 779 (C-F), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.28–6.49 (m, 13H, Ar-H), 5.82 (s, 1H, Het –CH_2-NH-), 4.93 (s, 2H, CH_2), 2.49 (s, 3H,-CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.5 (C_5 of oxadiazole ring), 166.3 (C_2 of thiazole ring), 160.9 (C_4 of quinazoline ring), 157.4 (C_2 of oxadiazole ring), 155.8 (C_4 of thiazole ring), 155.6 (C_2 of quinazoline ring), 154.2 (C_2 of phenyl ring), 148.7 (C_{10} of quinazoline ring), 133.4 (C_1 of phenyl ring), 132.4 (C_5 of thiazole ring), 130.5 (Ar-C), 130.2 (Ar-C), 128.8(2) (Ar-C), 128.4 (Ar-C), 128.1(2), 127.6 (Ar-C), 126.8 (Ar-C), 126.4 (Ar-C), 125.7 (Ar-C), 124.7 (Ar-C), 121.5 (C_5 of quinazoline ring), 116.3 (Ar-C), 112.8 (Ar-C), 70.7 (-CH_2-NH), 17.4 (C_6 of thiazole ring), MS (*m/z*): 542.6 (M^+); Anal. Calcd. for: $C_{27}H_{19}FN_6O_2S_2$: C, 59.77; H, 3.53; N, 15.49; Found: C, 59.56; H, 3.90; N, 15.41%

Physical constant and characterization of 3-(4-methyl-5-(4-(((2-nitrophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6b)

Pale yellow (Yield 59%) m.p. 215–218 °C; IR (KBr, cm^{-1}): 3518 (N-H), 3078, 2932 (C-H, -CH = CH-), 1690 (>C = O), 1589, 1512 (C = C, C = N), 1342 (-NO_2), 1258 (C-O-C), 1057 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32–6.91 (m, 13H, Ar-H), 5.84 (s, 1H, Het –CH_2-NH-), 4.91 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.2 (C_5 of oxadiazole ring), 167.5 (C_2 of thiazole ring), 160.5 (C_4 of quinazoline ring), 156.9 (C_2 of oxadiazole ring), 156.2 (C_4 of thiazole ring), 148.4 (C_2 of quinazoline ring), 146.2 (C_{10} of quinazoline ring), 135.5 (C_2 of phenyl ring), 132.6 ($C_1$of phenyl ring), 131.8 (C_5 of thiazole ring), 130.1 (Ar-C), 128.5(2) (Ar-C), 128.4 (Ar-C), 128.3(2) (Ar-C), 127.4 (Ar-C), 126.8 (Ar-C), 126.6 (Ar-C), 125.7 (Ar-C), 118.6 (Ar-C), 117.7 (C_5 of quinazoline ring), 116.4 (Ar-C), 115.6 (Ar-C), 114.2 (Ar-C), 69.4 (-CH_2-NH), 17.7 (C_6 of thiazole ring), MS (*m/z*): 569.6 (M^+); Anal. Calcd. for: $C_{27}H_{19}N_7O_4S_2$: C, 56.93; H, 3.36; N, 17.21; Found: C, 56.91; H, 3.37; N, 17.24%

Physical constant and characterization of 3-(4-methyl-5-(4-(((3-nitrophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6c)

Gray (Yield 60%) m.p. 206–209 °C; IR (KBr, cm^{-1}): 3317 (N-H), 3037, 2834 (C-H, -CH = CH-), 2756 (C-H), 1727 (>C = O), 1694, 1614 (C = C, C = N), 1557 (C-NO_2), 1227 (C-O-C), 1153 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.35–6.88 (m, 13H, Ar-H), 6.19 (s, 2H, Het –CH_2-NH-), 4.93 (s, 2H, -CH_2), 2.48 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.1 (C_5 of oxadiazole ring), 166.9 (C_2 of thiazole ring), 160.6 (C_4 of quinazoline ring), 156.8 (C_2 of oxadiazole ring), 156.2 (C_4 of thiazole ring), 148.5 (C_2 of quinazoline ring), 146.8 (C_3 of phenyl ring), 133.2 (C_1 of phenyl ring), 132.8 (C_5 of thiazole ring), 131.3 (Ar-C), 130.8 (Ar-C), 128.8(2) (Ar-C), 128.5 (Ar-C), 128.1(2) (Ar-C), 127.6 (Ar-C), 126.4 (Ar-C), 126.8 (Ar-C), 125.5 (Ar-C), 120.2 (C_5 of quinazoline ring), 118.1 (Ar-C), 117.4 (Ar-C), 116.7 (Ar-C), 115.8 (Ar-C), 70.9 (-CH_2-NH), 17.8 (C_6 of thiazole ring), MS (*m/z*): 569.0 (M^+); Anal. Calcd. for: $C_{27}H_{19}N_7O_4S_2$: C, 56.93; H, 3.36; N, 17.21; Found: C, 56.92; H, 3.34; N, 17.27%

Physical constant and characterization of 3-(4-methyl-5-(4-(((4-nitrophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6d)

Dark yellow (Yield 64%) m.p. 210–212 °C; IR (KBr, cm^{-1}): 3217 (N-H), 3025, 2839 (C-H, -CH = CH-), 2761 (C-H), 1735 (>C = O), 1692, 1611 (C = C, C = N), 1559 (C-NO_2), 1224 (C-O-C), 1155 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33–6.92 (m, 13H, Ar-H), 6.29 (s, 1H, Het –CH_2-NH-), 4.93 (s, 2H, CH_2), 2.52 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.6 (C_5 of oxadiazole ring), 167.9 (C_2 of thiazole ring), 160.3 (C_4 of quinazoline ring), 156.6 (C_2 of oxadiazole ring), 156.5 (C_4 of thiazole ring), 148.7 (C_2 of quinazoline ring), 146.4 (C_4 of phenyl ring), 135.6 (C_1 of phenyl ring), 134.1 (C_5 of thiazole ring), 131.7 (Ar-C), 129.2 (Ar-C), 128.9(2) (Ar-C), 128.8 (Ar-C), 128.5(2) (Ar-C), 127.2 (Ar-C), 126.3 (Ar-C), 126.1 (Ar-C), 125.5 (Ar-C), 119.8 (C_5 of quinazoline ring), 118.7 (Ar-C), 117.4 (Ar-C), 116.9 (Ar-C), 115.5 (Ar-C), 70.7 (-CH_2-NH), 17.9 (C_6ofthiazole ring), MS (*m/z*): 569.0 (M^+); Anal. Calcd. for: $C_{27}H_{19}N_7O_4S_2$: C, 62.44; H, 4.12; N, 15.60; Found: C, 62.45; H, 4.14; N, 15.62%

Physical constant and characterization of 3-(5-(4-(((2-chlorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6e)

White (Yield 61%) m.p. 216–218 °C; IR (KBr, cm^{-1}): 3311 (N-H), 2975, 2833 (C-H, -CH = CH-), 2753 (C-H), 1725 (>C = O), 1689, 1619 (C = C, C = N), 1227 (C-O-C), 1156 (C = S), 755 (C-Cl), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27–6.89 (m, 13H, Ar-H), 6.29 (s, 1H, Het –CH_2-NH-), 4.91 (s, 2H,-CH_2), 2.47 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.2 (C_5 of oxadiazole ring), 167.9 (C_2 of thiazole ring), 160.5 (C_4 of quinazoline ring), 156.2 (C_2 of oxadiazole ring), 156.1 (C_4 of thiazole ring), 148.3 (C_2 of quinazoline ring), 146.4 ($C_2$of phenyl ring), 135.4 (C_1 of phenyl ring), 134.8 (C_5 of thiazole ring), 133.1 (Ar-C), 129.4 (Ar-C), 128.7(2) (Ar-C), 128.6 (Ar-C), 128.4(2) (Ar-C),

127.5 (Ar-C), 126.8 (Ar-C), 126.2 (Ar-C), 125.9 (Ar-C), 119.4(C_5 of quinazoline ring), 118.1 (Ar-C), 117.5 (Ar-C), 116.7 (Ar-C), 115.6 (Ar-C), 72.4 (-CH_2-NH), 17.3 (C_6 of thiazole ring), MS (*m/z*): 559.0 (M^+); Anal. Calcd. for: $C_{27}H_{19}ClN_6O_2S_2$: C, 58.01; H, 3.43; N, 15.03; Found: C, 57.82; H, 3.79; N, 14.97%

Physical constant and characterization of 3-(5-(4-(((4-chlorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6f)

Off-white (Yield 60%) m.p. 212–215 °C; IR (KBr, cm^{-1}): 3313 (N-H), 3033, 2830 (C-H, -CH = CH-), 2755 (C-H), 1727 (>C = O), 1691, 1617 (C = C, C = N), 1229 (C-O-C), 1155 (C = S), 759 (C-Cl), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.32–6.92 (m, 13H, Ar-H), 6.37 (s, 1H, Het –CH_2-NH-), 4.91 (s, 2H, CH_2-NH-Ar), 2.46 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.2 (C_5 of oxadiazole ring), 167.7 (C_2 of thiazole ring), 160.9 (C_4 of quinazoline ring), 156.5 (C_2 of oxadiazole ring), 156.2 (C_4 of thiazole ring), 148.5 (C_2 of quinazoline ring), 146.7 (C_4 of phenyl ring), 133.8 (C_1 of phenyl ring), 132.3 (C_5 of thiazole ring), 131.7 (Ar-C), 130.7 (Ar-C), 128.8(2) (Ar-C), 128.5 (Ar-C), 128.2(2) (Ar-C), 127.9 (Ar-C), 126.6 (Ar-C), 126.2 (Ar-C), 125.6 (Ar-C), 120.7 (C_5 of quinazoline ring), 117.1 (Ar-C), 116.4 (Ar-C), 115.9 (Ar-C), 114.1 (Ar-C), 72.7 (-CH_2-NH), 17.9 (C_6 of thiazole ring), MS (*m/z*): 559.0(M^+); Anal. Calcd. for: $C_{27}H_{19}ClN_6O_2S_2$: C, 58.01; H, 3.43; N, 15.03; Found: C, 58.02 H, 3.45; N, 15.01%

Physical constant and characterization of 3-(5-(4-(((3,4-dichlorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6g)

White (Yield 63%) m.p. 219–222 °C; IR (KBr, cm^{-1}): 3315 (N-H), 3029, 2833 (C-H, -CH = CH-), 2755 (C-H), 1724 (>C = O), 1692, 1619 (C = C, C = N), 1228 (C-O-C), 1158 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.82–6.33 (m, 12H, Ar-H), 6.3 (s, 1H, Het –CH_2-NH-), 4.92 (s, 2H, CH_2), 2.48 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.7 (C_5 of oxadiazole ring), 166.9 (C_2 of thiazole ring), 160.1 (C_4 of quinazoline ring), 157.5 (C_2 of oxadiazole ring), 156.5 (C_4 of thiazole ring), 156.3 (C_2 of quinazoline ring), 148.9 (C_3 of in phenyl ring), 147.7 (C_4 of phenyl ring), 133.5 (C_1 of phenyl ring), 132.7 (C_5 of thiazole ring), 131.1 (Ar-C), 130.4 (Ar-C),129.5 (Ar-C), 128.5(2) (Ar-C), 128.4 (Ar-C), 128.1(2) (Ar-C), 127.5 (Ar-C), 126.9 (Ar-C), 126.4 (Ar-C), 121.6 (Ar-C), 120.4 (C_5 of quinazoline ring), 115.9 (Ar-C), 113.4 (Ar-C), 70.7 (-CH_2-NH), 17.3 (C_6 of thiazole ring), MS (*m/z*): 593.5 (M^+); Anal. Calcd. for: $C_{27}H_{18}Cl_2N_6O_2S_2$: C, 54.64; H, 3.06; N, 14.16; Found: C, 54.61; H, 3.04; N, 14.20%

Physical constant and characterization of 3-(4-methyl-5-(5-thioxo-4-((m-tolylamino)methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6h)

Brown, (Yield 58%) m.p. 220–223 °C; IR (KBr, cm^{-1}): 3313 (N-H), 3032, 2837 (C-H, -CH = CH-), 2756 (C-H), 1724 (>C = O), 1692, 1614 (C = C, C = N), 1226 (C-O-C), 1152 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27–6.58 (m, 13H, Ar-H), 6.35 (s, 1H, Het –CH_2-NH-), 4.9 (s, 2H, CH_2), 2.48 (s, 3H, -CH_3), 2.34 (s, 3H, Het-CH_3) , ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.1 (C_5 of oxadiazole ring), 166.6 (C_2 of thiazole ring), 160.3 (C_4 of quinazoline ring), 157.7 (C_2 of oxadiazole ring), 156.9 (C_4 of thiazole ring), 156.5 (C_2 of quinazoline ring), 148.7 (C_3 of phenyl ring), 144.3 (C_1 of phenyl ring), 133.6 (C_5 of thiazole ring), 132.3 (Ar-C), 130.6 (Ar-C), 129.8(2) (Ar-C), 129.4 (Ar-C), 128.9(2) (Ar-C), 128.7 (Ar-C), 128.3(2) (Ar-C), 127.3 (Ar-C), 126.6 (Ar-C), 126.7 (Ar-C), 120.2 (C_5 of quinazoline ring), 117.1 (Ar-C), 114.4(2) (Ar-C), 70.2 (-CH_2-NH), 21.4 (C_7 in phenyl ring), 17.6 (C_6 of thiazole ring), MS (*m/z*): 538.6 (M^+); Anal. Calcd. for: $C_{28}H_{22}N_6O_2S_2$: C, 62.44; H, 4.12; N, 15.60; Found: C, 62.48; H, 4.15; N, 15.63%

Physical constant and characterization of 3-(4-methyl-5-(5-thioxo-4-((p-tolylamino)methyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6i)

White (Yield 62%) m.p. 207–209 °C; IR (KBr, cm^{-1}): 3320 (N-H), 3029, 2829 (C-H, -CH = CH-), 2757 (C-H), 1721 (>C = O), 1690, 1617 (C = C, C = N), 1222 (C-O-C), 1157 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.34–6.44 (m, 13H, Ar-H),6.31 (s, 1H, Het –CH_2-NH-), 4.92 (s, 2H, CH_2), 2.48 (s, 3H Het -CH_3), 2.33 (s, 3H, -CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.6 (C_5 of oxadiazole ring), 166.9 (C_2 of thiazole ring), 160.7 (C_4 of quinazoline ring), 157.6 (C_2 of oxadiazole ring), 156.4 (C_4 of thiazole ring), 156.1 (C_2 of quinazoline ring), 148.1 (C_4 of phenyl ring), 144.4, (C_1 of phenyl ring), 135.8 (C_5 of thiazole ring), 133.7 (Ar-C), 130.7 (Ar-C), 129.2 (2) (Ar-C), 129.1 (Ar-C), 128.6(2) (Ar-C),128.5 (Ar-C), 128.1(2) (Ar-C),127.7 (Ar-C), 126.8 (Ar-C), 124.4 (Ar-C), 118.6 (C_5 of quinazoline ring), 114.4(2) (Ar-C), 70.7 (-CH_2-NH), 21.9 (C_7 in phenyl ring), 17.9 (C_6 of thiazole ring), MS (*m/z*): 538.6 (M^+); Anal. Calcd. for: $C_{28}H_{22}N_6O_2S_2$: C, 62.44; H, 4.12; N, 15.60; Found: C, 62.45; H, 4.18; N, 15.65%

Physical constant and characterization of 3-(4-methyl-5-(4-(((2-methyl-4-nitrophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-2-phenylquinazolin-4(3H)-one (6j)

White (Yield 63%) m.p. 211–214 °C; IR (KBr, cm^{-1}): 3329 (N-H), 3028, 2825 (C-H, -CH = CH-), 2752 (C-H), 1724 (>C = O), 1692, 1616 (C = C, C = N), 1552 (C-NO_2), 1225 (C-O-C), 1152 (C = S), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.27–6.93 (m, 12H, Ar-H), 5.83 (s, 1H, Het –CH_2-NH-),

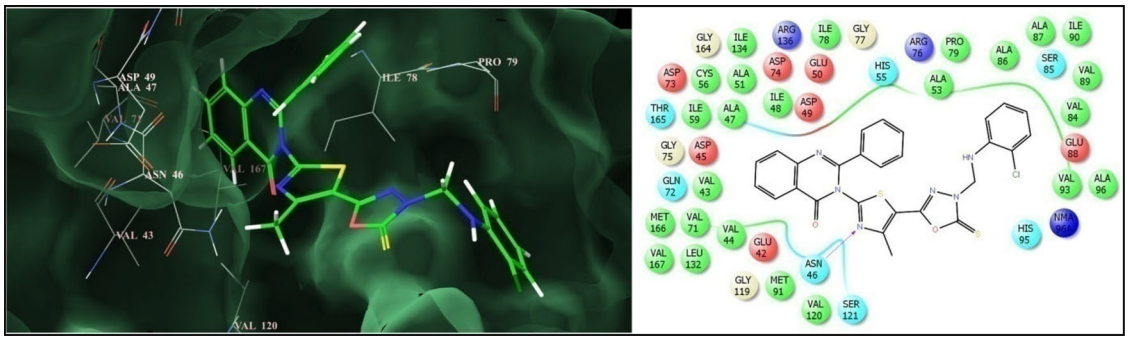


Figure 2. Binding mode of **6e** into the active site of DNA gyrase *subunit*.

4.81 (s, 2H, CH_2), 2.51 (s, 3H, Het-CH_3), 2.15 (s, 3H, CH_3), ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 177.5$ (C_5 of oxadiazole ring), 166.7 (C_2 of thiazole ring), 160.9 (C_4 of quinazoline ring), 157.5 (C_2 of oxadiazole ring), 156.9 (C_4 of thiazole ring), 156.8 (C_2 of quinazoline ring), 152.6, (C_2 of phenyl ring), 148.9 (C_4 of phenyl ring), 136.7 (C_1 of phenyl ring), 133.5 (C_5 of thiazole ring), 132.8 (Ar-C), 130.4 (Ar-C), 128.9(2) (Ar-C), 128.6 (Ar-C), 128.4(2) (Ar-C), 127.7 (Ar-C), 127.4 (Ar-C), 126.9 (Ar-C), 126.6 (Ar-C), 126.2 (Ar-C), 121.7 (C_5 of quinazoline ring), 120.6 (Ar-C), 114.4 (Ar-C), 71.7 (-CH_2-NH), 17.7 (C_7 phenyl ring), 16.6 (C_6 of thiazole ring), MS (*m/z*): 583.6 (M^+); Anal. Calcd. for: $C_{28}H_{21}N_7O_4S_2$: C, 57.62; H, 3.63; N, 16.80; Found: C, 57.67; H, 3.64; N, 16.85%

Molecular docking

DNA gyrase is a well-studied drug target present in almost all bacteria and is known to play essential roles in bacterial DNA replication.[29] It is a heterotetrameric protein consisting of two GyrA subunits and two GyrB subunits (A_2B_2) encoded by the *gyrA* and *gyrB* genes, respectively. While the GyrA subunit mediates the enzyme-catalyzed DNA breakage-reunion reaction, the GyrB subunit contains an ATPase activity which facilitates the DNA strand-passing reaction of DNA gyrase. The low structural homology exhibited by these enzymes with human topoisomerases and being critical for the survival of the microorganism make them attractive drug targets for antibacterial therapy. The B-subunit of DNA gyrase (GyrB) consist of ATP binding pocket and small molecules inhibition of this pocket is plausible which has resulted in several lead compounds.[30,31]

To gain better understanding on the potency of the studied compounds, to elucidate the plausible mechanism by which they can induce antimicrobial activity and guide further SAR studies, we proceeded to examine the interaction of these thiazole based 1,3,4-oxadiazoles heterocycles with DNA gyrase subunit b (PDB ID:1KZN). These calculations were performed using the standard protocol implemented in the GLIDE (Grid-Based Ligand Docking with Energetics) module of the Small Drug Discovery Suite (Schrödinger, LLC, New York, NY).[32–34] It was observed that all the synthesized molecules could dock nicely into the active site of DNA gyrase with good binding energies ranging from −45.222 to −40.057 kcal mol^{-1}with equally significant docking scores (–7.970 to –6.749) [See Table S1 (Supporting Information)]. Their docking scores and glide binding energies corroborated well with the observed antimicrobial activities.

The binding affinity exhibited by these molecules is attributed to significant bonded and non-bonded interactions with residues lining the active site of the enzyme. The per-residue interaction analysis for one of the most active analog **6e** (Figure 2) showed that the molecule is embedded into the active site through a series of significant van der Waals interactions observed with Val:A167(–1.400 kcal mol^{-1}), Thr:A165(–3.547 kcal mol^{-1}), Ser:A121(–1.104 kcal mol^{-1}), Val:A120(–2.628 kcal mol^{-1}), Gly:A119(–2.116 kcal mol^{-1}), Gly:A117(–2.503 kcal mol^{-1}), Ile:A78(–5.592 kcal mol^{-1}), Gly:A77(–1.753 kcal mol^{-1}), Arg:A76(–2.479 kcal mol^{-1}), Asp:A73(–1.155 kcal mol^{-1}), Val:A71(–1.639 kcal mol^{-1}), Glu:A50(–4.227 kcal mol^{-1}), Asp:A49(–1.605 kcal mol^{-1}), Ala:A47(–2.047 kcal mol^{-1}), Asn:A46(–4.635 kcal mol^{-1}), Asp:A45(–1.014 kcal mol^{-1}), Val:A43(–1.135 kcal mol^{-1}), and Glu:A42(–1.514 kcal mol^{-1}) through the 4-methylthiazol-2-yl-2-phenylquinazolin-4(3*H*)-one portion of the molecule while the 3-(5-(4-(((2-chlorophenyl)amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) component interacted similarly with Val:A118(–1.515 kcal mol^{-1}), Ala:A96(–3.08 kcal mol^{-1}), His:A95(–2.537 kcal mol^{-1}), Met:A91(–1.113 kcal mol^{-1}), Ile:A90(–4.986 kcal mol^{-1}), Val:A89(–1.954 kcal mol^{-1}), Ala:A86(–3.164 kcal mol^{-1}), and Pro:A79(–2.685 kcal mol^{-1}) residues of the active site. The enhanced binding of **6e** is also contributed by several significant electrostatic interactions through Arg:A136(–2.776), Ala:A96(–1.724), His:A95(–1.085), Arg:A76(–2.878), Asp:A74(–1.112), Asp:A73(–1.769), Asp:A49(–2.776), Asn:A46(–1.157), Glu:A42(–1.709) residues lining the active site of DNA gyrase. A very similar network of balanced steric, as well as electrostatic interactions, contributed to the binding affinity of all the synthesized molecules in the series (Supporting Information Figures S1–S9). Furthermore, these thiazole-based 1,3,4-oxadiazoles heterocycles were found to be engaged in a significant hydrogen bonding interaction with Asn46 residue which serves as an "anchor" that guides the orientation of these molecules into the 3D space of the active site and facilitate the non-bonded (steric and electrostatic) interactions. Overall, these results of the molecular docking study showed that these thiazole-based 1,3,4-oxadiazoles heterocycles could interact significantly with the DNA gyrase. In the absence of available resources to perform enzyme-based experiments, the *in silico* approach of

molecular docking provides a viable option to identify and optimize the leads targeting crucial antibacterial enzymes. The results obtained herein suggest that the quinazoline clubbed thiazole and 1,3,4-oxadiazoles could serve as promising leads for structure-based lead optimization to identify more potent analogs through iterative design, synthesis, and biological evaluation. The docking score of co-crystallized ligand-Chlorobiocin, an aminocoumarin antibacterial that inhibits the enzyme DNA gyrase, was found to be −9.902 Glide energy of −50.733 kcal mol^{-1}.[35]

Structure-activity relationship study

The result of antibacterial screening of compounds **6a–j** showed that the presence of electron- withdrawing group in screened compounds is responsible for the antibacterial activity. Among various functional groups with –I effect, the presence of −4-Cl showed excellent activity against bacterial strains. However, other electron-withdrawing group-2-Cl and electron-donating group −3-CH_3 showed moderate activity against *S. aureus, E. coli*, and *P. aeruginosa* species. These findings were found to be in harmony with the observed binding affinity data were the compound **6e** (-2Cl) showed the highest binding score (Glide score: −7.970, Glide energy: −45.222 kcal mol^{-1}) as compared to the compound of formulae **6f** (–4Cl) and **6 h** (-3-CH_3).

Conclusion

In the present research work, the authors have synthesized quinazoline clubbed thiazole and 1,3,4-oxadiazoles heterocycles and performed molecular docking studies. The molecular docking study could provide an insight into the binding affinity of these molecules toward DNA gyrase. The key structural elements and their interactions with the active site are now considered for further optimization of this scaffold to redesign them for increasing their potency as antimicrobial agents. Results of biological activities revealed that compound **6f,** furnished excellent antibacterial activity against *S. aureus*, whereas compounds of formulae **6e,** and **6d** furnished very good to prominent antibacterial activity against *E. coli*. Data reveals that electron-withdrawing groups were much effective for enhancing the antibacterial activity on different strains.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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