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Molecular Docking, Toxicity Study and Antimicrobial Assessment of Novel Synthesized 1,3-(Disubstituted)-thiazol-2-amines

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In current study, a novel analogous of substituted-2-aminothiazoles (**3a-o**) were synthesized through a multi-step synthetic process. Structural elucidation of these newly synthesized substituted-2-aminothiazoles were achieved using combination of analytical techniques, comprising proton nuclear magnetic resonance (PNMR), mass spectrometry and FTIR. An *in vitro* investigation was performed to measure the efficacy of antibacterial and antimycotic characteristics of these novel compounds (**3a-o**). Specifically, the growth-inhibiting action against the test fungal strains, including *A. niger*, *M. purpureos* and *A. flavus* was examined. Additionally, their inhibitory antibacterial activity against key bacterial strains, including *P. aeruginosa*, *S. aureus* and *E. coli* was ascertained employing the agar diffusion technique. The results of antibacterial screening disclosed that maximum number of the thiazole derivatives *viz.* **3a**, **3d**, **3e**, **3i**, **3k**, **3l** and **3n** displayed minimum inhibitory concentration of 12.5 µg/mL for *E. coli*. While compounds **3k** and **3n** displayed minimum inhibitory concentration of 12.5 µg/mL for *S. aureus*. A minimum inhibitory concentration of 25 µg/mL was exhibited by compounds **3i**, **3l** and **3n** against *P. aeruginosa*. None of the 2-aminothiazole derivative disclosed promising action against the fungal strains. Screening for *in silico* ADME and toxicity studies revealed that compounds are fairly compatible and were devoid of potential toxicity except compounds **3j** and **3m**. The docking studies on DNA gyrase (PDB ID; 1KZN) shows favourable binding interaction comparable to the pre-occupied ligand clorobiocin.

Keywords: 2-Chloroquinoline, Thiazole, Antibacterial, Antifungal, ADME, Clorobiocin.

INTRODUCTION

Bacterial infections arising from numerous types of microorganism, including Gram-positive, Gram-negative and mycobacterial species, contribute significantly to hospital acquired infections, resulting in substantial mortality rates and placing a substantial load world widely on healthcare and economic systems [1-3]. The emergence and widespread prevalence of drug resistant microorganisms, such as drug-resistant tuberculosis, *E. coli* producing extended spectrum β-lactamase, vancomycin resistant *S. aureus*, methicillin resistant *S. aureus* and methicillin resistant *S. epidermidis* have reached alarming levels in recent decades, leading to significant associated mortality rates [4-6].

Antibiotics have played a pivotal role in combating bacterial infections by significantly reducing mortality rates [7,8]. However, the unwarranted utilization of antimicrobials has forced to the gradual evolution of bacterial resistance [9,10]. Without intervention, projections indicate that drug-resistant infections may account for about 10 millions individuals' deaths yearly by 2050 [11]. Moreover, the quest for new antibiotics is driven by the aim to minimize their inherent toxicity and associated side effects [12].

Hence, there exists a pressing need to create innovative antimicrobial substances that can effectively combat both drug-sensitive and drug-resistant bacterial infections. The pursuit of discovering novel and more potent antimicrobial drugs holds significant importance, prompting numerous research endeavours dedicated to devising fresh agents [13,14]. Among these are synthetic antibacterial compounds like ofloxacin, norfloxacin, nalidixic acid, ciprofloxacin and cinoxacin, all belonging to the fluoroquinolone class, which is characterized by a common quinoline-based ring structure. The fluoroquinolone category

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of antibacterials have demonstrated remarkable success and still continuing to shape the landscape of potentials antibacterial therapeutics significantly. Consequently, the advancement of fluoroquinolone-derived new chemical entity (NCE) as potential antibacterials stands to enrich the arsenal of antibiotics available to counteract the challenge of drug resistance [15-17].

Moreover, the investigation into substituted quinoline compounds has garnered significant attention due to the pivotal role played by halogen atoms in conferring diverse biological activities [18], encompassing anticancer [19], anti-inflammatory [20], antioxidant [21] and antimicrobial properties [22]. The historical significance of penicillins as the inaugural efficacious antibiotics for microbial treatment is no coincidence, given their inclusion of a thiazole moiety [23]. This thiazole heterocycle is one of the components featuring a potent and electron-rich fragment (SCN). The presence of the thiazole moiety holds paramount importance within organic and natural molecule like thiamine (vitamin B), bacitracin, as well as antibiotics such as β-lactam penicillin's and thiopeptide micrococcin [24]. Early studies have indicated that thiazole has the capability to impede bacterial growth through its inhibition of specific bacterial lipid biosynthesis, including compounds like sulphathiazole [25]. This mechanism aligns with a broad category of antibiotics recognized as β-lactam penicillin's antibiotics, which exert effectiveness against various bacterial infections instigated by *Staphylococci* and *Streptococci*, exemplified by agents like benzylpenicillin, amoxicillin and phenoxymethylpenicillin [26,27]. The importance of this versatile nucleus thiazole is further appreciated, by the fact that several drug encompasses this nucleus as integral part of scaffold (Fig. 1).

Building upon the previously presented information and in extension of our endeavours related to the creation of small bioactive novel heterocyclic compounds, this study's rationale revolves around the creation of fresh therapeutically potent entities. This involves the synthesis of 2-chloroquinolines and their combination with thiazole derivatives. The aim is to enhance lipophilicity and incorporate multiple pharmacophoric components within a single molecular structure. The ultimate goal is to generate novel 2-chloroquinoline hybrids with robust antimicrobial properties. The designed derivatives underwent assessment against few microbes, encompassing three fungal and three bacterial strains.

EXPERIMENTAL

An electrical heating melting point device was used to determine the melting point using glass capillary tubes and are uncorrected. The FT-IR spectra was measured using Perkin-Elmer FT-IR device using KBr (pellet) and the ^{1}H NMR scans were developed on a Bruker NMR instrument 300 MHz using deuterated dimethyl sulphoxide or deuterated chloroform as solvents. Mass spectrometry was recorded on Agilent G6530AA instrument. Silica gel was employed as solid stationary component in a thin layer chromatograph (TLC), the advancement of the reaction and purity of the chemicals were examined. The Vilsmeyer-Haack reaction was used to obtain the key starting material 2-chloroquinoline-3-carbaldehyde (**2**) following a literature method [28].

Synthesis of 2-chloroquinoline-3-carbaldehyde (2): A flask containing DMF (0.189 mol) and locked with a guard tube was cooled to 0 ºC, then $POCl_3$ (0.53 mol) was poured portion wise with stirring. To this Vilsmeyer-Haack reagent acetanilide (**1**) (0.075 mol) was added into reaction mass and after 10 min and then the reaction mixture warmed to 78-80 ºC for about 15 h. When reaction completed, as supervised by TLC, the flask content temperature was lowered 0-5 ºC. Later about 300 mL of chilled water was added and agitated for 30 min. Herein, a yellow precipitate appeared, which was separated using ice-cold water. The yellow mass was then dried and recrystallized from ethyl acetate solvent, as creamy-yellowish, shiny crystals. TLC was used to verify the compound's purity, using toluene/ethyl acetate/formic acid, 5:4:1 as an eluent. Yield: 67 %; m.p.: 145-147 ºC; FT-IR (ν_{max}, cm^{-1}): 1695, 1622, 1595, 753; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.66 (t, 1H, C_6-$H_{quinoline}$, J = 7.4 Hz), 7.90 (t, 1H, C_7-$H_{quinoline}$, J = 7.2 Hz), 8.02 (d, 1H, C_5-$H_{quinoline}$, J = 8.2 Hz), 8.11 (d,1H, C_8-$H_{quinoline}$, J = 8.4 Hz), 8.78 (s, 1H, C_4-$H_{quinoline}$), 10.58 (s, 1H, CHO); HRMS: m/z 191.6314 $[M]^+$, 193.6342 $[M+2]^+$.

Synthesis of *N*-[(2-chloroquinolin-3-yl)methyl]-4-(substituted phenyl-1,3-thiazol-2-amine (3a): A mixture of 2-chloroquinoline-3-carbaldehyde (**2**, 0.01 M) in methanol (10 mL) was added to a stirred solution 0.012 mol of 2-amine-thiazole intermediate **(IIIa)** at room temperature followed by the addition of I_2 (50 mg) and stirring was continued further, till I_2 dissolve completely. Then solid $NaBH_4$ (0.02 M) was introduced slowly in parts with agitation and progressed was checked by TLC for completion of reaction. Upon completion, a precipitate separates out and the final product was crystallized using alcohol to yield compounds**3a** (**Scheme-I**) [29]. The remaining compounds **3b** to **3n** were synthesized according to the process mentioned above.

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-phenyl-1,3-thiazol-2-amine (3a):** Yield: 49%; m.p.: 141-142 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1635, 1597, 1045, 763; ^{1}H NMR δ_H (ppm): 4.81 (s, 2H, CH_2), 5.08 (bs, 1H, NH), 7.01 (2H, d, Ar-H, J = 7.0 Hz), 7.18-7.26 (m, 3H, Ar-H), 7.51 (t, 1H, C_6-$H_{quinoline}$, J = 7.0 Hz), 7.66-7.78 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.04 (d, 1H, C_8-$H_{quinoline}$, J = 7.6 Hz), 8.20 (s, 1H, C_4-$H_{quinoline}$); HRMS: 351.0671 (M^+), 353.0649 (M+2); Elemental analysis of $C_{19}H_{14}N_3SCl$ calcd. (found) %: C, 64.86 (64.70); H, 4.01 (4.05); N, 11.94 (11.99).

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(4-methylphenyl)-1,3-thiazol-2-amine (3b):** Yield: 37%; m.p.: 163-165 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1640, 1592, 1028, 761; ^{1}H NMR δ_H (ppm): 2.28 (s, 3H, CH_3), 4.77 (s, 2H, CH_2), 5.15 (bs, 1H, NH), 6.93 (2H, d, Ar-H, J = 7.4 Hz), 7.22-7.28 (m, 2H, Ar-H), 7.55 (t, 1H, C_6-$H_{quinoline}$, J = 7.3 Hz), 7.69-7.79 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.07 (d, 1H, C_8-$H_{quinoline}$, J = 7.4 Hz), 8.17 (s, 1H, C_4-$H_{quinoline}$); HRMS: 365.0809 (M^+), 367.0818 (M+2); Elemental analysis of $C_{20}H_{16}N_3SCl$ calcd. (found) %: C, 65.65 (65.78); H, 4.41 (4.43); N, 11.48 (11.53).

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(4-methoxyphenyl)-1,3-thiazol-2-amine (3c):** Yield: 44%; m.p.: 129-131 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1640, 1603, 1081, 757; ^{1}H NMR δ_H (ppm): 3.42 (s, 3H, OCH_3), 4.84 (s, 2H, CH_2), 5.09 (s, 1H,

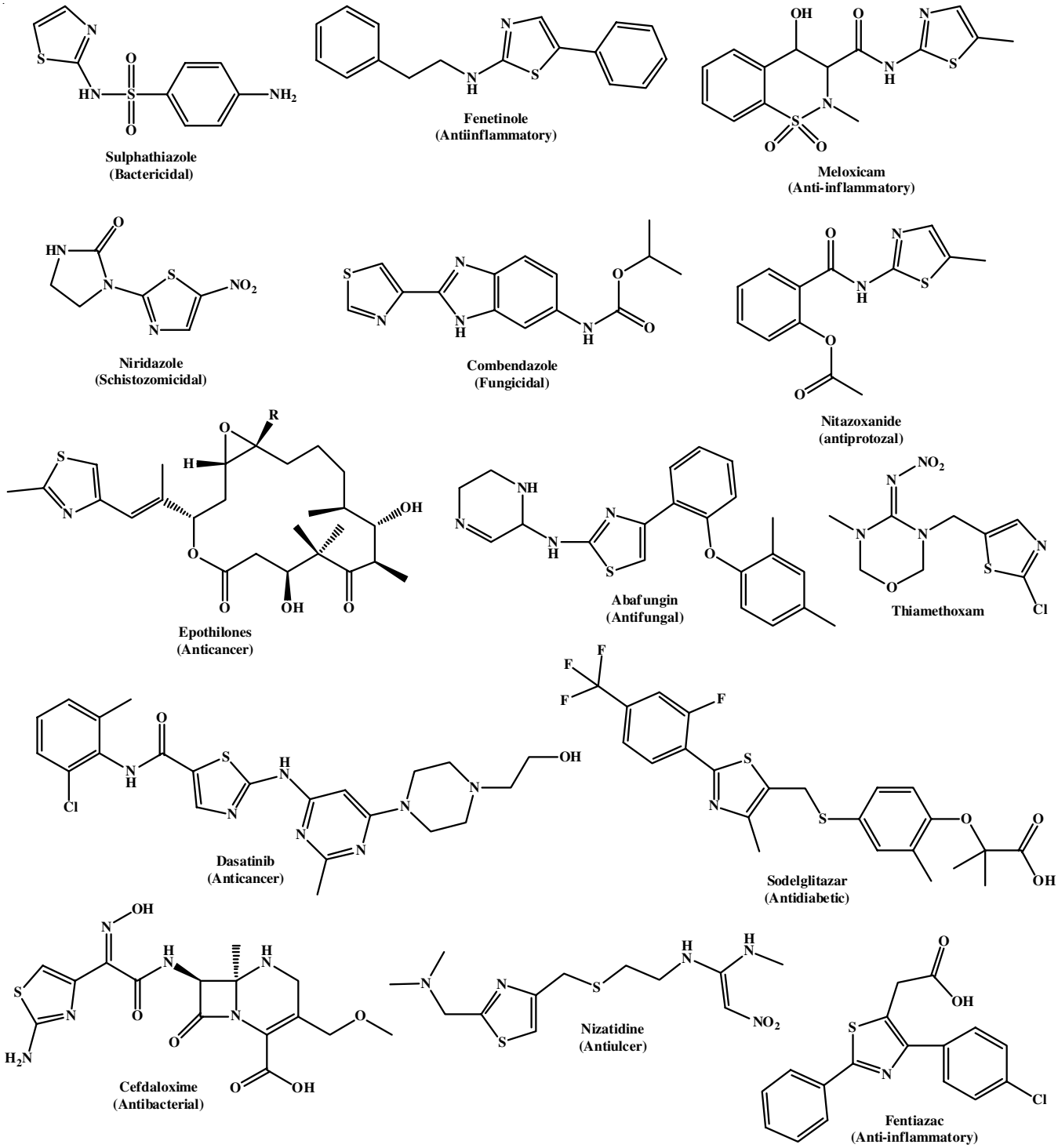
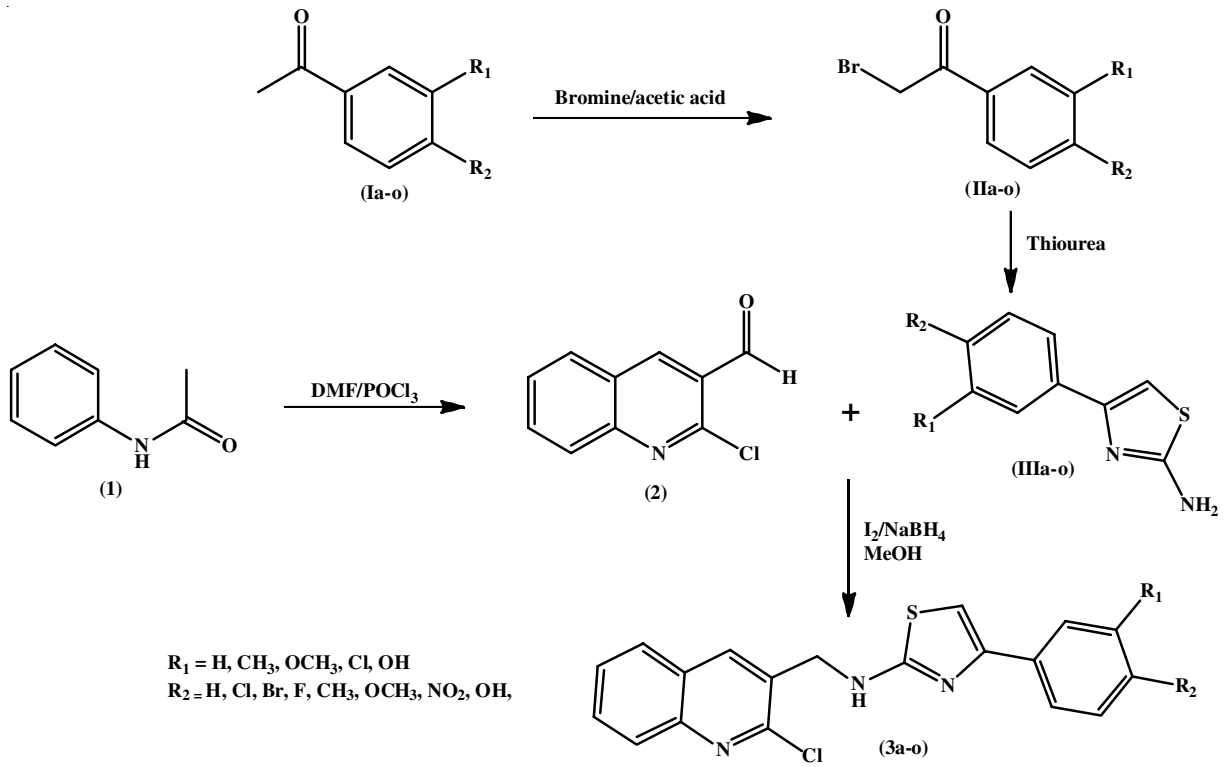


Fig. 1. Structure of various class of medicinal drugs having thiazole nucleus as an integral part of their structure

NH), 6.98 (2H, d, Ar-H, J = 7.0 Hz), 7.29 (d, 2H, Ar-H, J = 7.4 Hz), 7.59 (t, 1H, C_6-$H_{quinoline}$, J = 7.0 Hz), 7.65-7.74 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.10 (d, 1H, C_8-$H_{quinoline}$, J = 7.2 Hz), 8.19 (s, 1H, C_4-$H_{quinoline}$); HRMS: 381.1083 (M^+), 383.1092 (M+2); Elemental analysis of $C_{20}H_{16}N_3OSCl$ calcd. (found) %: C, 62.90 (62.78); H, 4.22 (4.26); N, 11.00 (11.08).

4-(4-Chlorophenyl)-*N*-[(2-chloroquinolin-3-yl)methyl]-1,3-thiazol-2-amine (3d): Yield: 38%; m.p.: 160-162 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1650, 1601, 1051, 760; ^1H NMR δ_H (ppm): 4.80 (s, 2H, CH_2), 5.12 (s, 1H, NH), 7.05 (2H, d, Ar-H, J = 7.4 Hz), 7.38 (d, 2H, Ar-H, J = 7.2 Hz), 7.58 (t, 1H, C_6-$H_{quinoline}$, J = 7.0 Hz), 7.68-7.75 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.08 (d, 1H, C_8-$H_{quinoline}$, J = 7.2 Hz), 8.21 (s, 1H, C_4-$H_{quinoline}$); HRMS: 385.0412 (M^+), 387.0409 (M+2); Elemental analysis of $C_{19}H_{13}N_3SCl_2$ calcd. (found) %: C, 59.07 (59.30); H, 3.39 (3.43); N, 10.88 (10.97).



Scheme-I: Route of synthesis of substituted 2-aminothiazole derivatives **(3a-o)**

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(4-fluorophenyl)-1,3-thiazol-2-amine (3e):** Yield: 46%; m.p.: 172-173 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1647, 1608, 1055, 748; ^1H NMR δ_H (ppm): 4.85 (s, 2H, CH_2), 5.08 (s, 1H, NH), 7.03 (2H, d, Ar-H, *J* = 7.2 Hz), 7.41 (d, 2H, Ar-H, *J* = 7.2 Hz), 7.60 (t, 1H, C_6-$H_{quinoline}$, *J* = 7.2 Hz), 7.68-7.79 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.06 (d, 1H, C_8-$H_{quinoline}$, *J* = 7.2 Hz), 8.17 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{19}H_{13}N_3SClF$ calcd. (found) %: C, 61.70 (61.88); H, 3.54 (3.59); N, 11.36 (11.42).

4-(4-Bromophenyl)-*N*-[(2-chloroquinolin-3-yl)methyl]-1,3-thiazol-2-amine (3f): Yield: 51%; m.p.: 195 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1652, 1604, 1044, 752; ^1H NMR δ_H (ppm): 4.80 (s, 2H, CH_2), 5.13 (s, 1H, NH), 7.00 (2H, d, Ar-H, *J* = 7.4 Hz), 7.34 (d, 2H, Ar-H, *J* = 7.2 Hz), 7.57 (t, 1H, C_6-$H_{quinoline}$, *J* = 7.0 Hz), 7.69-7.78 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.09 (d, 1H, C_8-$H_{quinoline}$, *J* = 7.2 Hz), 8.16 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{19}H_{13}N_3SBrCl$ calcd. (found) %: C, 52.98 (52.82); H, 3.04 (3.08); N, 9.76 (9.83).

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(4-nitrophenyl)-1,3-thiazol-2-amine (3g):** Yield: 55%; m.p.: 169-170 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1533, 1352, 1659, 1601, 1039, 755; ^1H NMR δ_H (ppm): 4.78 (s, 2H, CH_2), 5.19 (s, 1H, NH), 6.90 (2H, d, Ar-H, *J* = 7.4 Hz), 7.28-7.31 (m, 2H, Ar-H), 7.60 (t, 1H, C_6-$H_{quinoline}$, *J* = 7.2 Hz), 7.70-7.79 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.10 (d, 1H, C_8-$H_{quinoline}$, *J* = 7.2 Hz), 8.19 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{19}H_{13}N_4O_2SCl$ calcd. (found) %: C, 57.50 (57.72); H, 3.30 (3.36); N, 14.12 (14.22).

4-(2-{[(2-Chloroquinolin-3-yl)methyl]amino}-1,3-thiazol-4-yl)phenol (3h): Yield: 58%; m.p.: 139-141 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3409, 1648, 1603, 1035, 750; ^1H NMR δ_H (ppm): 4.80 (s, 2H, CH_2), 5.14 (s, 1H, NH), 6.92 (2H, d, Ar-H, *J* = 7.4 Hz), 7.30-7.36 (m, 2H, Ar-H), 7.58 (t, 1H, C_6-$H_{quinoline}$, *J* = 7.0 Hz), 7.71-7.80 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.07 (d, 1H, C_8-$H_{quinoline}$, *J* = 7.2 Hz), 8.16 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{19}H_{14}N_3OSCl$ calcd. (found) %: C, 62.04 (62.28); H, 3.84 (3.88); N, 11.42 (11.49).

4-(3-Chlorophenyl)-*N*-[(2-chloroquinolin-3-yl)methyl]-1,3-thiazol-2-amine (3i): Yield: 40%; m.p.: 148-149 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3245, 1642, 1598, 1039, 756; ^1H NMR δ_H (ppm): 4.83 (s, 2H, CH_2), 5.09 (s, 1H, NH), 7.01 (1H, s, Ar-H), 7.25-7.31 (m, 3H, Ar-H), 7.56 (t, 1H, C_6-$H_{quinoline}$, *J* = 7.4 Hz), 7.71-7.82 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.10 (d, 1H, C_8-$H_{quinoline}$, *J* = 7.2 Hz), 8.19 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{19}H_{13}N_3SCl_2$ calcd. (found) %: C, 59.07 (59.30); H, 3.39 (3.43); N, 10.88 (10.97).

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(3,4-dimethoxyphenyl)-1,3-thiazol-2-amine (3j):** Yield: 52%; m.p.: 144 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1646, 1606, 1080, 755; ^1H NMR δ_H (ppm): 3.38 (s, 6H, 2×OCH_3), 4.83 (s, 2H, CH_2), 5.09 (bs, 1H, NH), 6.93 (1H, s, Ar-H), 7.23-7.33 (m, 3H, Ar-H), 7.58 (t, 1H, C_6-$H_{quinoline}$, *J* = 7.2 Hz), 7.68-7.77 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.08 (d, 1H, C_8-$H_{quinoline}$, *J* = 7.2 Hz), 8.16 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{21}H_{18}N_3O_2SCl$ calcd. (found) %: C, 61.23 (61.48); H, 4.40 (4.45); N, 10.20 (10.28).

2-Chloro-4-(2-{[(2-chloroquinolin-3-yl)methyl]amino}-1,3-thiazol-4-yl)phenol (3k): Yield: 43%; m.p.: 180 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3389, 1645, 1604, 1039, 758; ^1H NMR δ_H (ppm): 4.87 (s, 2H, CH_2), 5.11 (s, 1H, NH), 6.98 (1H, s, Ar-H), 7.33-7.38 (m, 2H, Ar-H), 7.55 (t, 1H, C_6-$H_{quinoline}$, *J* = 7.4 Hz), 7.68-7.77 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.09 (d, 1H, C_8-$H_{quinoline}$, *J* = 7.2 Hz), 8.18 (s, 1H, C_4-$H_{quinoline}$).

Elemental analysis of $C_{19}H_{13}N_3OSCl_2$ calcd. (found) %: C, 56.73 (56.88); H, 3.26 (3.30); N, 10.45 (10.55).

5-(2-{[(2-Chloroquinolin-3-yl)methyl]amino}-1,3-thiazol-4-yl)-2-nitrophenol (3l): Yield: 48%; m.p.: 178-180 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3422, 1652, 1601, 1533, 1352, 1042, 765; ^1H NMR δ_H (ppm): 4.83 (s, 2H, CH_2), 5.15 (s, 1H, NH), 6.94 (1H, s, Ar-H), 7.36-7.42 (m, 2H, Ar-H), 7.59 (t, 1H, C_6-$H_{quinoline}$, J = 7.4 Hz), 7.70-7.79 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.05 (d, 1H, C_8-$H_{quinoline}$, J = 7.2 Hz), 8.14 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{19}H_{13}N_4O_3SCl$ calcd. (found) %: C, 55.28 (55.49); H, 3.17 (3.23); N, 13.57 (13.65).

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(4-methoxy-3-methylphenyl)-1,3-thiazol-2-amine (3m):** Yield: 53%; m.p.: 155 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1648, 1605, 1042, 762; ^1H NMR δ_H (ppm): 2.26 (s, 3H, CH_3), 3.35 (s, 3H, OCH_3), 4.80 (s, 2H, CH_2), 5.07 (s, 1H, NH), 6.90 (1H, s, Ar-H), 7.29-7.35 (m, 2H, Ar-H), 7.60 (t, 1H, C_6-$H_{quinoline}$, J = 7.2 Hz), 7.71-7.79 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.07 (d, 1H, C_8-$H_{quinoline}$, J = 7.2 Hz), 8.13 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{21}H_{18}N_3OSCl$ calcd. (found) %: C, 63.71 (63.88); H, 4.58 (4.59); N, 10.61 (10.69).

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(3,4-dichlorophenyl)-1,3-thiazol-2-amine (3n):** Yield: 43%; m.p.: 174-175 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1643, 1600, 1046, 755; ^1H NMR δ_H (ppm): 4.84 (s, 2H, CH_2), 5.10 (s, 1H, NH), 7.05 (1H, s, Ar-H), 7.36-7.41 (m, 2H, Ar-H), 7.58 (t, 1H, C_6-$H_{quinoline}$, J = 7.0 Hz), 7.69-7.78 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.04 (d, 1H, C_8-$H_{quinoline}$, J = 7.2 Hz), 8.15 (s, 1H, C_4-$H_{quinoline}$). Elemental analysis of $C_{19}H_{12}N_3SCl_3$ calcd. (found) %: C, 54.24 (54.41); H, 2.87 (2.92); Cl, 25.28 (25.30); N, 9.99 (10.05).

***N*-[(2-Chloroquinolin-3-yl)methyl]-4-(3-methoxyphenyl)-1,3-thiazol-2-amine (3o):** Yield: 40%; m.p.: 121-123 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 1643, 1605, 1088, 754; ^1H NMR δ_H (ppm): 3.43 (s, 3H, OCH_3), 4.81 (s, 2H, CH_2), 5.08 (s, 1H, NH), 6.97 (1H, s, Ar-H), 7.18-7.25 (m, 3H, Ar-H), 7.58 (t, 1H, C_6-$H_{quinoline}$, J = 7.2 Hz), 7.70-7.81 (m, 3H, C_5-$H_{quinoline}$, C_7-$H_{quinoline}$ and C_5-$H_{thiazole}$), 8.08 (d, 1H, C_8-$H_{quinoline}$, J = 7.0 Hz), 8.14 (s, 1H, C_4-$H_{quinoline}$); Elemental analysis of $C_{20}H_{16}N_3OSCl$ calcd. (found) %: C, 62.90 (62.83); H, 4.22 (4.20); N, 11.00 (11.06).

Antimicrobial screening: Screening for antibacterial activity was performed on nutrient agar using strains of bacteria including *P. aeruginosa* (NCTC, 10662), *S. aureus* (NCTC, 65710) and *E. coli* (NCTC, 10418). *M. purpureos* (MTCC 369), *A. niger* (MTCC, 281) and *A. flavus* (MTCC, 277) were employed to examine the antifungal action on potato dextrose agar (PDA) cup-plate method [30,31]. Saline solution containing Tween-80 (0.01%) was employed for preparing a dispersion of fungi and bacteria spore meant for lawn seeding. The potato agar dextrose culture medium (5 mL) was transferred every culture plate. Five millilitre of spore dispersion was poured and distributed on surface of agar medium and the petri-dishes were dehydrated in an incubator for about 1 h at 37 ºC. These seeded agar plates were converted into wells with an agar punch and the previously labelled wells were filled with test chemical solutions in DMSO at concentrations of 3, 12, 6, 25, 50, 100, 200 and 500 µg/mL. In addition, a DMSO-treated control group was included. The pairs of petri dishes were incubated for 24 h at 37 ºC and 30 ºC for bacteria and fungi, respectively. The minimum inhibitory concentration (MIC) was determined by measuring the inhibition zone at the lowest concentration of the test drugs at which no significant growth was detected. The activity of each compounds was measured against that of two commonly used drugs, miconazole and ciprofloxacin.

***In silico* ADME and toxicity prediction studies:** Two principal requirements for any NCE for marketable product, are acceptable ADME profile and free from or minimum toxicity. In present study, the ADME prediction studies was performed by online software *viz.* Swiss ADME [32]. While *in silico* toxicity studies were predicted by online ProTox II software [33].

Molecular docking: Windows 11 based system, configuration with 64-bit and processor of Intel(R) Core TM i3-CPU @2.21 GHz with 8GB RAM was employed as a work station for performing the molecular docking studies. The preparation of ligand for docking and preparation of protein was carried out as per the method reported in teh literature [34]. The Auto-Dock Vina wizard in the PyRx virtual screening program, the molecular docking of each ligand with the generated protein was completed. The docking results for various structures were further scrutinized using BIOVIA Discovery Studio Visualizer 2020.

RESULTS AND DISCUSSION

A novel analogous of substituted-2-aminothiazoles, N-[(2-chloroquinolin-3-yl)methyl]-4-(substituted-phenyl-1,3-thiazol-2-amines (**3a-o**) were synthesized as shown in **Scheme-I**. The primary intermediate 2-chloroquinoline-3-carbaldehyde (**2**) was synthesized form acetanilide (**1**) by the action of DMF/$POCl_3$ following a Vilsmeyer-Haack reaction. The subsequent, one-pot reaction of **2** (1.0 equiv.) with 4-(substituted) phenyl-thiazol-2-amines (**3a-o**) (1.2 equiv.) by slowly stirring in methyl alcohol along with I_2 and $NaBH_4$. In this single step, reductive amination reaction, I_2 catalyzed the *in situ* generation of an imine intermediate at room temperature, which was subsequently reduced to methylene amine by the action of $NaBH_4$.

All synthesized compounds **3a-o** structure were elucidated by one or more combination of techniques comprising FT-IR, ^1H NMR and MS. The spectral data for all compounds was in agreement with the presumed structures. In IR spectra of compounds **3a** and **3b**, the presence of carbonyl function of carbaldehyde in compound **2** which was appeared at 1695 cm^{-1}, subsequently disappeared in IR spectra of compounds **3a** and **3b** and a new C-N stretching band appeared at 1045 cm^{-1} and 1028 cm^{-1} respectively for compounds **3a** and **3b**. Similarly, in ^1H NMR spectral analysis of compounds **3a** and **3b**, the carbonyl proton of intermediate **2** resonated as a sharp singlet at 10.58 ppm, which vanished in the spectrum of compounds **3a** and **3b**. Further, a new peak of methylene group of-CH_2NH-emerged as wide singlet at δ 4.81 and 4.77 ppm for compound **3a** and **3b** respectively, while the amine proton appeared at δ 5.08 and 5.15 ppm as broad singlet for compounds **3a** and **3b**, respectively. The aforementioned observation of IR and H NMR data reflect the successful conversion of carbaldehyde group

to methylene amine function. The remaining 2-chloroquinoline and thiazole phenyl ring aromatic protons were resonated at their designated values as mentioned in the spectral data of each compound. The fact was further affirmed by the HRMS spectrometry of compounds **3a** and **3b**, which recorded the M+ and (M+2) ion peak at 351.0671 and 353.0649 for compound **3a** and 365.0809 and 367.0818 for compound **3b**, respectively.

Antibacterial activity: The outcomes of the antibacterial screening are shown in Table-1. 2-Aminothiazole derivatives **3a-o** against the bacterial strains *viz. P. aeruginosa* (NCTC, 10662), *S. aureus* and *E. coli* altogether derivatives disclosed moderate to respectable antibacterial activity, having MIC ranging from 12.5 to 200 µg/mL. Among the test compounds, compounds **3a**, **3d**, **3e**, **3i**, **3k**, **3l** and **3n** displayed low MIC value of 12.5 µg/mL *vs*. *E. coli*, while lowest MIC of 12.5 µg/mL against *S. aureus* was shown by compounds **3k** and **3n**. The lowest MIC *P. aeruginosa* was exhibited by compounds **3i**, **3l** and **3n** at 25 µg/mL.

Antifungal activity: The synthesized 2-aminothiazole derivatives **3a-o** were also tested against fungi *viz. A. niger*, *M. purpureos* and *A. flavus* (Table-1) were found to be moderate to poorly active. Many compounds unveiled MIC in the range of 50 to 100 µg/mL against *A. niger* and *A. flavus* strains.

ADME and toxicity prediction: Swiss ADME software was employed to predict the ADME properties of 2-aminothiazole derivatives and their predicted values are provided in Table-2. The *in silico* predication is based on serval calculated properties such no. rotatable bonds (NROTB), no. of hydrogen-bond acceptor (HBA), no. of hydrogen-bond donor (HBD), partition coefficient [log P (o/w)] and molecular weights (MW), *etc*. A thorough examination of Table-2, exhibit that NROTB (4-6) and HBA (2-4) for all compounds **3a-o** were less than

TABLE-1
In vitro ANTIMICROBIAL ACTIVITY DATA OF COMPOUNDS (**3a-o**)

Compd. No	R_1	R_2	MIC (µg/mL)					
			Antibacterial activity			Antifungal activity		
			E. coli	*S. aureus*	*P. auroginosa*	*M. purpureos*	*A. flavus*	*A. niger*
3a	H	H	12.5	50	50	200	100	100
3b	H	CH_3	50	50	100	200	100	50
3c	H	OCH_3	100	100	100	–	100	100
3d	H	Cl	12.5	25	50	100	50	50
3e	H	F	12.5	50	50	100	50	50
3f	H	Br	25	50	50	200	100	50
3g	H	NO_2	25	25	50	–	100	100
3h	H	OH	50	100	200	200	50	50
3i	Cl	H	12.5	25	25	100	50	50
3j	OCH_3	OCH_3	25	25	100	200	100	100
3k	Cl	OH	12.5	12.5	50	200	50	50
3l	NO_2	OH	12.5	25	25	–	–	200
3m	CH_3	OCH_3	25	50	100	200	200	100
3n	Cl	Cl	12.5	12.5	25	100	25	25
3o	OCH_3	H	25	50	50	200	100	50
Miconazole				NT	NT	6.25	6.25	6.25
Ciprofloxacin				6.25	6.25	NT	NT	NT

(–) Indicate no activity; (NT) indicate not tested

TABLE-2
PREDICTED ADME PROPERTIES OF COMPOUNDS (**3a-o**) USING THE TOOL SwissADME ONLINE SOFTWARE

Compd. No.	% ABS	Solubility	TPSA (Å²)	NROTB	HBA	HBD	Log $P_{o/w}$ (iLOGP)	BBB	GI absorption	Lipinski violation	Bioavailability score	MR
3a	86.21	Poorly sol.	66.05	4	2	1	3.43	No	High	0	0.55	101.65
3b	86.21	Poorly sol.	66.05	4	2	1	3.74	No	High	0	0.55	106.62
3c	83.02	Poorly sol.	75.28	5	3	1	3.77	No	High	0	0.55	108.15
3d	86.21	Poorly sol.	66.05	4	2	1	3.76	No	High	0	0.55	106.66
3e	86.21	Poorly sol.	66.05	4	3	1	3.42	No	High	0	0.55	–
3f	86.21	Poorly sol.	66.05	4	2	1	3.76	No	High	0	0.55	109.35
3g	70.40	Poorly sol.	111.87	5	4	1	2.51	No	Low	0	0.55	110.48
3h	79.23	Poorly sol.	86.28	4	3	2	3.17	No	High	0	0.55	103.68
3i	86.21	Poorly sol.	66.05	4	2	1	3.58	No	High	0	0.55	106.66
3j	79.84	Poorly sol.	84.51	6	4	1	3.99	No	High	0	0.55	114.64
3k	79.23	Poorly sol.	86.28	4	3	2	3.41	No	High	0	0.55	108.69
3l	63.46	Poorly sol.	132.10	5	4	1	3.16	No	low	0	0.55	115.49
3m	83.02	Poorly sol.	75.28	5	3	1	4.02	No	High	0	0.55	113.11
3n	86.21	Poorly sol.	66.05	4	2	1	3.77	No	High	1	0.55	111.67
3o	86.21	Poorly sol.	66.05	4	2	1	3.71	No	High	1	0.55	119.16

10, while HBD was less than 05 (1-2). The calculated clog P values was found to be less than 05 (2.51-4.02) and the molecular weights of 2-aminothiazoles **3a-o** were lower than 500. The 2-aminothiazoles (**3a-o**) were foreseen as orally bioactive substances with good gastrointestinal (G.I.) absorption as none of them appeared to violate the Lipinski's rule of five. Further, by employing the calculation %Abs = 109 ± [0.345 × Topological polar surface area] a percent absorption was calculated using TPSA values and the % absorption were found to be between 63.46 and 86.21. From Table-2, it is projected that none of the compound would cross the blood-brain barrier (BBB). Hence, the ADME profile for synthesized compounds **3a-o** appears to be respectable.

The compounds were also examined *in silico* for their toxicity screening using a web based prediction tool Pro-Tox-II and computed in Table-3. All the synthesized compounds were anticipated as class IV compounds and their toxicity screening revealed that compounds **3a**, **3b** and **3c** were devoid of any toxicity, while compounds **3d**, **3e**, **3f**, **3n**, **3o** were immunotoxicity and cytotoxicity. Compounds **3g**, **3j**, **3l**, **3m** were shown to have toxicity against most of model of toxicity and compounds **3j** and **3m** were found to be toxic against all models of toxicity study.

Molecular docking studies: The AutoDock Vina program was employed to study the docking of synthesized substituted 2-aminothiazoles (**3a-o**) into the active site of the DNA gyrase enzyme (PDBID: 1KZN). Present investigation focused on exploring the potential binding interactions of 15 derivatives at the clorobiocin binding site through molecular docking. The purpose of molecular docking was to analyze the binding affinity and potential intermolecular interactions of thiazole derivatives with the DNA gyrase enzyme.

Table-4 presents an overview of the binding profiles of substituted-2-aminothiazoles (**3a-o**) with DNA gyrase (PDBID: 1KZN). The selection of poses from the docking procedure was based on their favourable binding energy, ranging from approximately -7.6 to -8.6 kcal/mol. As presented in Table-4 compounds **3e**, **3k** and **3n** appears to be most fit compounds

TABLE-3
PREDICTED TOXICITIES PROPERTY OF COMPOUNDS (**3a-o**) USING THE TOOL Pro-toxII ONLINE SOFTWARE

Compd. No.	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	LD_{50} (mg/Kg)	Class	Average similarity	Prediction accuracy
3a	–	–	–	–	–	1000	IV	69.3	68.07
3b	–	–	–	–	–	1000	IV	68.45	68.07
3c	–	–	–	–	–	1000	IV	65.69	68.07
3d	–	–	+	–	+	1000	IV	70.06	69.26
3e	+	–	+	–	+	1000	IV	66.32	68.07
3f	–	–	+	–	+	1000	IV	66.02	68.07
3g	+	+	+	+	-	1000	IV	63.33	68.07
3h	+	–	+	–	+	1000	IV	66.61	68.07
3i	–	–	–	–	+	1000	IV	67.21	68.07
3j	+	+	+	+	+	1000	IV	61.78	68.07
3k	+	–	+	–	+	1000	IV	64.33	68.07
3l	+	+	+	+	+	1000	IV	58.03	67.38
3m	+	+	+	+	+	1000	IV	63.5	68.07
3n	–	–	+	–	+	1000	IV	67.96	68.07
3o	–	–	+	–	+	1000	IV	67.96	68.07

TABLE-4
CALCULATED FREE ENERGY OF BINDING (kcal/mol) AND AMNIO ACIDS OF THIAZOLE DERIVATIVES DOCKED INTO DNA GYRASE (PDB ID; 1KZN)

Compd. No	Calculated free energy of binding (kcal/mol)	Amino acids residues involved in Hydrogen bond, Pi-alkyl, Pi-sigma, Pi-anion, Pi-cation interaction
3a	-8.2	Glu-42, Asp-49, Asn-46, Glu-50, Ala-47, Thr-165
3b	-8.4	Val-43, Ala-47, Glu-50, Val-71, Arg-76, Ala-86, Ile-78, Arg-136, Val-167
3c	-8.1	Val-43, Ala-47, Arg-76, Ala-86, Ile-78, Ile-90, Val-167
3d	-8.4	Val-43, Ala-47, Val-71, Ala-96, Ile-78, Ile-90, Val-167
3e	-8.5	Ala-47, Asn-46, Val-71, Ala-96, Ile-78, Ile-90, Thr-165, Val-167
3f	-8.4	Val-43, Ala-47, Ala-86, Ile-78, Ile-90, Thr-195, Val-167
3g	-8.3	Ala-47, Asn-46, Ile-90, Ala-96, Gly-119
3h	-8.3	Ala-47, Asn-46, Asp-49, Glu-50, Gly-117, Gly-119, Thr-165, Val-167
3i	-8.4	Ala-47, Asn-46, Asp-49, Glu-50, Val-167
3j	-8.1	Val-43, Glu-42, Asp-45, Ala-47, Asn-46, Asp-49, Glu-50, Gly-117, Thr-165, Val-167
3k	-8.6	Val-43, Ala-47, Asp-49, Glu-50, Gly-117, Gly-119
3l	-7.6	Ala-47, Asn-46, Asp-49, Glu-50, Gly-117, Gly-119
3m	-8.4	Val-43, Ala-47, Asn-46, Asp-49, Glu-50, Thr-165, Val-167
3n	-8.6	Val-43, Ala-47, Ala-86, Ile-78, Ile-90, Thr-165, Val-167
3o	-8.2	Val-43, Arg-76, Ala-86, Ile-78, Ile-90, Thr-165, Val-167
Chlorobiocin	-8.2	Asn-46, Ala-47, Glu-50, Val-71, Asp-73, Arg-76, Gly-77, Pro-79, Ile-90, Arg-136, Thr-165

with binding energy, -8.5, -8.6 and 8.6 kcal/mol, respectively. In Fig. 2, the 2D and 3D schematic representations illustrate the interactions of compounds **3e**, **3k** and **3n** resides within the chlorobiocin binding site, demonstrating their well-fitted placement in the binding pocket. The hydrophobic sites and hydrogen bond interactions observed in these derivatives are consistently preserved across the majority of synthesized compounds. The docking results revealed that compounds **3e**, **3k** and **3n**, establish the robust hydrophobic interactions and form hydrogen bonds with Asn46, Glu50, Gly117, Gly119

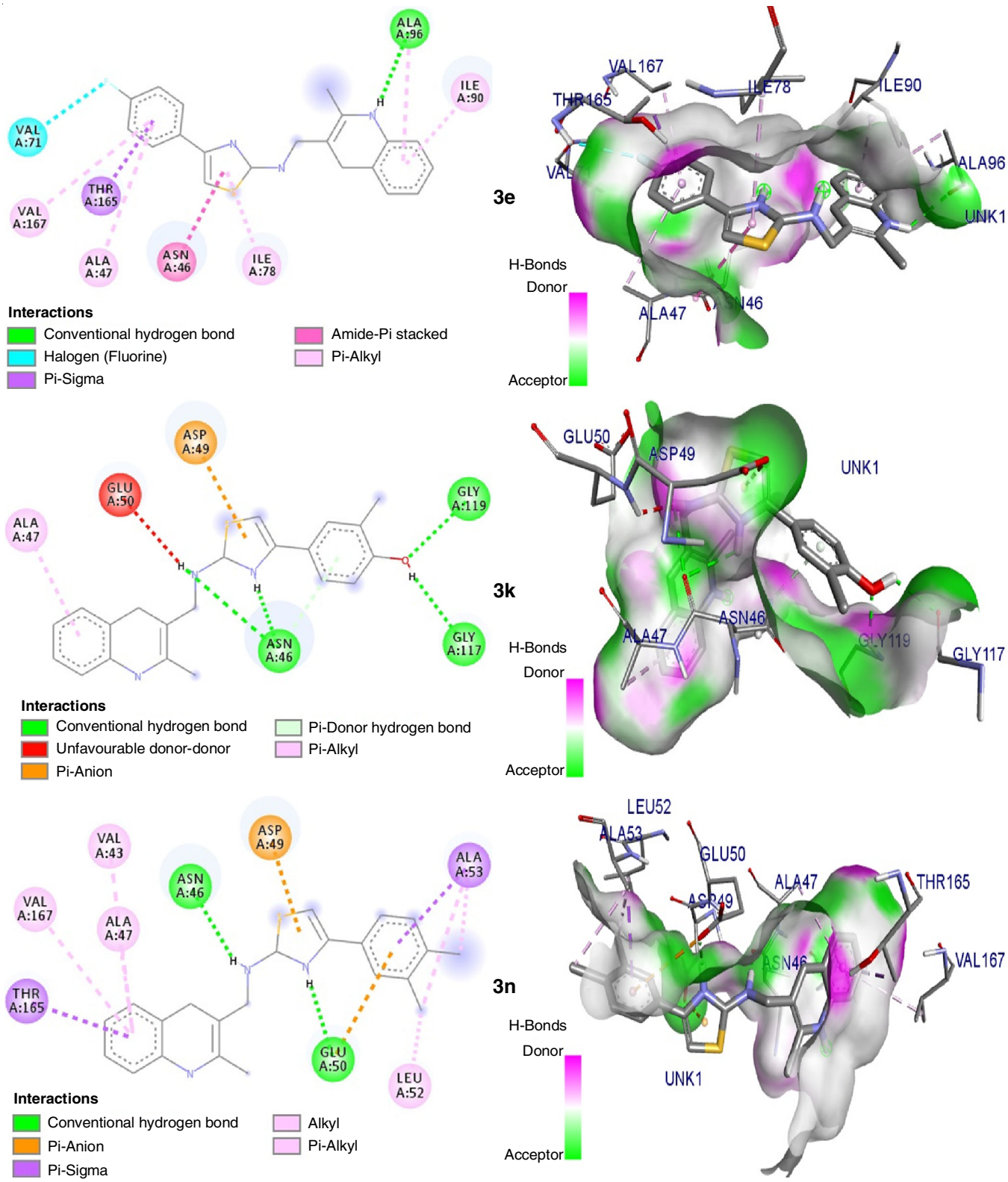


Fig. 2. The binding interaction of compounds **3e**, **3k** and **3n** with the DNA gyrase binding site

and Ala96 in the binding site. Although similar interactions were observed in other derivatives too, it is believed that the differences in activity can be ascribed to the hydrophobic interactions.

Conclusion

A new series of 2-chloroquinoline incorporated thiazole derivatives (**3a-o**) was synthesized, in moderate to good yields, using 2-chloroquinoline-3-carbaldehyde intermediate as an penultimate compound. This vital intermediate was obtained in good yield from easily accessible acetanilide following Vilsmeyer-Haack reaction. The structures of novel substituted-2-amino-thiazoles were characterized by analytical techniques such as mass spectrometry and ^{1}H NMR and FTIR spectroscopy data. The results of antibacterial screening disclosed that the most of the thiazole derivatives such **3a**, **3d**, **3e**, **3i**, **3k**, **3l** and **3n** unveiled the minimum inhibitory concentration of 12.5 µg/mL against *E. coli*, while compounds **3k** and **3n** displayed the lowest minimum inhibitory concentration against *S. aureus*. At 25 µg/mL, compounds **3i**, **3l** and **3n** exhibited the lowest minimum inhibitory conc. against *P. aeruginosa*. The thiazole compounds were also examined against three fungi *viz. M. purpureos, A. niger* and *A. flavus* and found to be moderate to poorly active. None of the derivatives displayed promising antifungal property against the test fungi. The findings of the antimicrobial study, indicates that 2-chloroquinoline-incorporated thiazole system is a more fruitful scaffold for creating novel antibacterial rather than antifungal active molecules. Antimicrobial research indicates that a thiazole scaffold incorporating 2-chloroquinoline has a potential to further enhance into effective antibacterial drugs. Further, the molecular docking interaction of thiazole derivatives into the active site DNA gyrase (PDBID: 1KZN) suggest their possible mode of antimicrobial activity.

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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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