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In vitro Antibacterial, ADME and Toxicity Screening of Newly Synthesized 4-(Substituted phenyl)-2-(2-chloroquinolin-3-yl)thiazoles

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A series of novel thiazole (**Va-o**) compounds were synthesized following multi-step synthetic process. Using analytical methods like nuclear magnetic resonance, mass spectrometry and FTIR, the elucidation of the structure of the synthesized compounds was performed. All the 15 novel thiazoles were assessed for their antibacterial activity. The synthesized thiazoles were examined for inhibitory antibacterial activity against a panel Gram-positive strain *viz*. *Staphylococcus aureus* (NCTC 65710), *Streptococcus pyogenes* (MTCC-442), *Bacillus subtilis* (NCIM 2250) and Gram-negative bacteria *Pseudomonas aeruginosa* (NCTC 10662) and *Escherichia coli* (NCTC 10418) by agar well diffusion technique. It was observed that some of the compounds, particularly those having substitution groups like chloro, fluoro and bromo in the phenyl ring bonded to thiazole nucleus, had moderate to good antibacterial activity. Quinoline clubbed thiazoles compounds **Vk**, **Vl**, **Vn** and **Vo** showed significant antibacterial against all bacterial strains having values of minimum inhibitory concentration (MIC) from 12.5 to 25 µg/mL. The results of antimicrobial investigation suggest that 2-chloroquinoline incorporated thiazole scaffold appears to more promising for developing potent antibacterial agents. Genome gyrase docking experiments (PDB ID: 1KZN) revealed a favourable binding relationship similar to that of the pre-occupied ligand clorobiocin. The study also provides *in silico* ADME and toxicity studies evaluation which revealed that compounds are impartially compatible and were devoid of potential toxicity except the hepatotoxicity.

Keywords: 2-Chloroquinoline, Thiazole, Antimicrobial activity, Antibacterial activity.

INTRODUCTION

Methicilin-resistant strains of *Staphylococcus aureus* (MRSA) and other *Candida albican*s species are two examples of the bacteria and fungus that have become increasingly common and pose a great threat to mankind owing to their ability to develop resistance to many antimicrobial drugs [1-4]. Because the method by which dangerous bacteria are getting resistant to commonly used antibiotics is becoming more complex, the creation of effective and cutting-edge antimicrobial drugs remains the best solution to this problem.

In our quest to identified novel compounds, herein we focused on thiazole and their congeners during our search for potential structures/pharmacophores that might have biological effects because they have diverse possibilities of potent pharmacological properties, including antibacterial, antimalarial, anticancer, anticonvulsant, anti-inflammatory, anti-tubercular, antifungal, antiviral and antidepressant properties [5-8]. Likewise, 2-chloroquinoline moiety has also being reported to exhibit potential antifungal and antibacterial activity [9-12]. In the current investigation, a few new phenyl thiazole derivatives covalently linked to 2-chloroquinoline moiety were prepared and evaluated antimicrobial properties comprising antibacterial and antifungal activities in light of the aforementioned pharmacophores.

EXPERIMENTAL

The glass capillary tubes and electrical heating apparatus were used to ascertain the melting point and are uncorrected. The ^{1}H NMR scans were conducted on a Bruker NMR apparatus at 300 MHz using deuterated DMSO-d_6 or deuterated $CDCl_3$ as the NMR solvent and the FT-IR spectra was acquired using a Perkin-Elmer FT-IR device with KBr (pellet). An Agilent G6530AA equipment was used to record the mass spectrometry results. A thin-layer chromatography (TLC) experiment

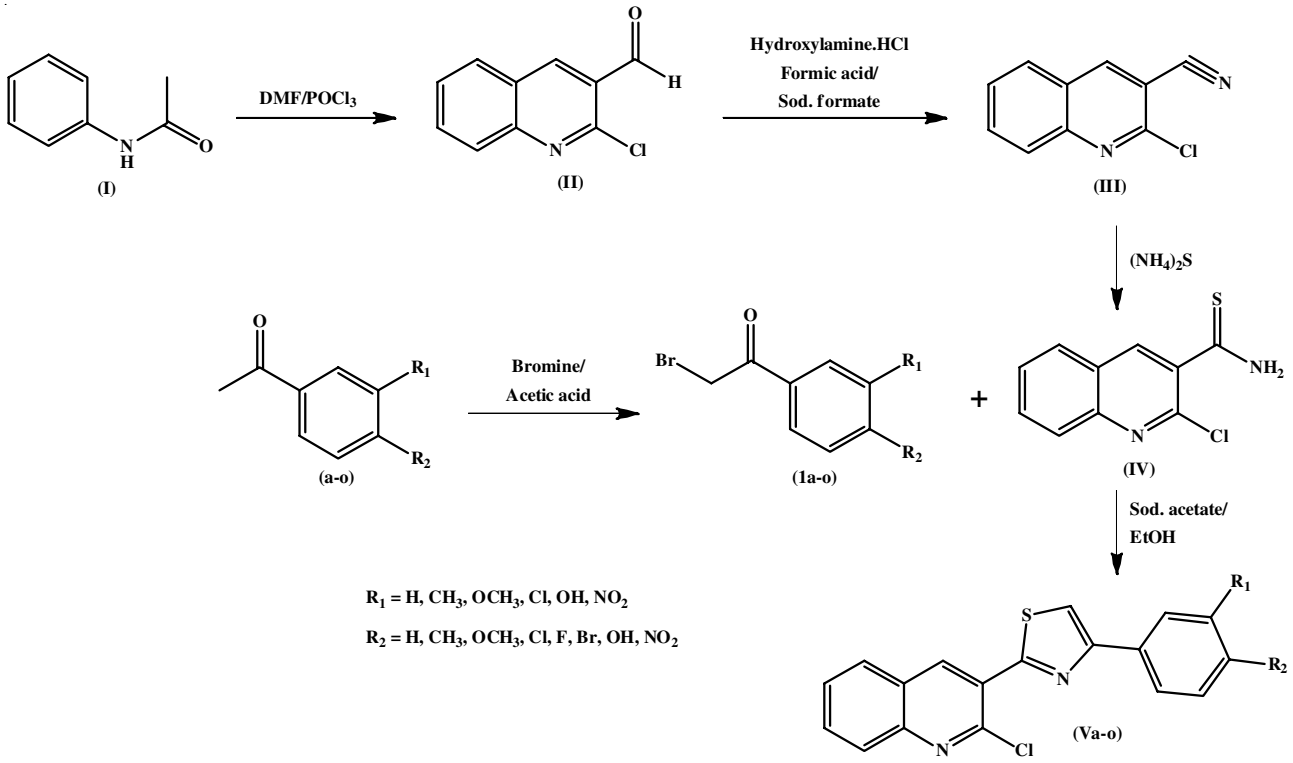
was conducted to assess the reaction progress and chemical purity. Silica gel (G) was utilized as the solid stationary phase. The Vilsmeyer-Haack reaction was used to synthesize 2-chloroquinoline-3-carbaldehyde (**2**), the primary building block, in accordance with a literature based technique.

Synthesis of 2-chloroquinoline-3-carbaldehyde (II): In a flask fitted with a drying tube, solvent DMF (0.125 mol, 9.13 g) was chilled to 0 ºC, then phosphoryl chloride (0.35 mol, 57.3 g) was added dropwise while stirring. Acetanilide (**I**) (0.05 mol, 6.75 g,) was added into reaction mixture and after 10 min, the temperature of solution was raised to 75 ºC for about 16 h. When reaction completes, 300 mL of ice water was added and agitated for 30 min between 0-10 ºC. At this point, solid separates out, which was filtered and washed with ice-cold water. The solid was then dried and recrystallized using ethylacetate solvent, as creamy-yellowish, glossy needle-shaped crystals [13]. Schiff's test indicated that the obtained solid appears to contain carbonyl group. TLC was used to verify the purity of the compound, with toluene:ethylacetate:formic acid (5:4:1) serving as mobile phase. Yield: 63 %, m.p.: 145-147 ºC. FT-IR (ν_{max}, KBr, cm^{-1}): 760 (C–Cl), 1597 (C=N), 1624 (C=C), 1698 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.68 (1H, t, C_6-H, *J* = 7.6 Hz), 7.90 (1H, t, C_7-H, *J* = 7.2 Hz), 8.01 (1H, d, C_5-H, *J* = 7.80 Hz), 8.09 (1H, d, C_8-H, *J* = 8.0 Hz), 8.78 (1H, s, C_4-H), 10.56 (1H, s, CHO). ESI-MS: *m/z* 191.6314 $[M]^+$, 193.6342 $[M+2]^+$.

Synthesis of 2-chloroquinoline-3-carbonitrile (III): A solution of compound **II** (0.015 mol) in anhydrous formic acid (10 mL) was added and the reaction mixture was warmed to a temperature of about 100 ºC for ~ 8 h. Hydroxylamine hydrochloride (1.9 g, 0.02 mol) and sodium formate (2.5 g, 0.035 mol) were then added. Once reaction was finished, the temperature of reaction mass was lowered to around 40 ºC and then water was added. After stirring for about 1 h, the reaction mass was again cooled to 25 ºC. The resulting product solid was filtered, washed with water, dried and recrystallized from alcohol. Yield: 74%, m.p.: 165-167 ºC. FT-IR (ν_{max}, KBr, cm^{-1}): 758 (C–Cl), 1595 (C=N), 1629 (C=C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 7.67-7.71 (t, 1H, C6-H, *J* = 7.4 Hz), 7.92 (t, 1H, C7-H, *J* = 7.2 Hz), 8.02 (d, 1H, C_5-H, *J* = 8.2 Hz), 8.08 (d,1H, C_8-H, *J* = 8.0 Hz), 8.82 (s, 1H, C_4-H).ESI-MS: *m/z* 188.5932 $[M]^+$, 190.6031 $[M+2]^+$.

Synthesis of 2-chloroquinoline-3-carbothioamides (IV): A solution of 2-chloroquinoline-3-carbothioamides (**III**) (0.005 mol) and ammonium sulphide (0.075 mol) in methanol (10 mL) was stirred at room temperature for 18 h. After the reaction complete, the mixture was evaporated under vacuum and then split between 10 mL of ethyl acetate and 10 mL of water. After a second ethylacetate extraction of the aqueous layer, the organic extracts were combined, washed with brine (10 mL), dried over sodium sulphate and evaporated *in vacuo* to yield thioamide **IV** [14]. Yield: 76%, m.p.: 189-191 ºC. FT-IR (ν_{max}, KBr, cm^{-1}): 754 (C–Cl), 1590 (C=N), 1628 (C=C), 1605 (C=S). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 6.87 (bs, 2H, NH), 7.67 (t, 1H, C_6-H, *J* = 7.6 Hz), 7.94 (t, 1H, C_7-H, *J* = 7.0 Hz), 8.00 (d, 1H, C_5-H, *J* = 8.4 Hz), 8.11 (d, 1H, C_8-H, *J* = 7.8 Hz), 8.79 (s, 1H, C_4-H). ESI-MS: *m/z* 222.6014 $[M]^+$, 224.6054 $[M+2]^+$.

General synthesis of title compounds: Equimolar amounts of the appropriate haloketones (**1a-o**) were added, along with sodium acetate (10 mmol), to a solution of carbothioamide (**IV**) (5 mmol) dissolved in absolute ethanol (20 mL). The reaction mixture was then refluxed for 6-8 h [14]. The precipitate that emerged was vacuum-filtered, rinsed in water and then dried (**Scheme-I**).



Scheme-I: Synthetic route of novel thiazole (**Va-o**) compounds

2-(2-Chloroquinolin-3-yl)-4-phenylthiazole (Va): Yield: 41%, m.p.: 156-158 ºC. Anal. calcd. (found) % for $C_{18}H_{11}N_2SCl$: C, 66.97 (66.79); H, 3.43 (3.40); N, 8.68 (N, 8.74). FT-IR (ν_{max}, KBr, cm^{-1}): 1624 (C=C), 1597 (C=N), 1027 (C-N), 757 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.91 (2H, d, Ar-H, *J* = 7.2 Hz), 7.03-7.6 (m, 1H, Ar-H), 7.28 (d, 2H, Ar-H, *J* = 7.0 Hz), 7.51 (t, 1H, C_6-H, *J* = 7.0 Hz), 7.66-7.78 (m, 3H, C5-H, C7-H & C′$_5$-H), 8.04 (d, 1H, C8-H, *J* = 7.6 Hz), 8.20 (s, 1H, C_4-H). Mass (*m.w.* 322.81): *m/z* 322.8032 $[M]^+$, 324.7910 $[M+2]^+$.

2-(2-Chloroquinolin-3-yl)-4-(*p*-tolyl)thiazole (Vb): Yield: 55%, m.p.: 171-173 ºC. Anal. calcd. (found) % for $C_{19}H_{13}N_2SCl$: C, 67.75 (67.84); H, 3.89 (3.88); N, 8.32 (8.39). FT-IR (ν_{max}, KBr, cm^{-1}): 1619 (C=C), 1593 (C=N), 1024 (C-N), 752 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 2.23 (s, 3H, CH_3), 6.81 (d, 2H, Ar-H, *J* = 6.8 Hz), 6.98 (d, 2H, Ar-H, *J* = 6.8 Hz), 7.55 (t, 1H, C6-H, *J* = 7.2 Hz), 7.70-7.81 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.01 (d, 1H, C_8-H, *J* = 7.8 Hz), 8.16 (s, 1H, C_4-H). Mass (*m.w.* 336.84): *m/z* 336.0923 $[M^+]$, 338.1032 $[M+2]^+$.

2-(2-Chloroquinolin-3-yl)-4-(4-methoxyphenyl)thiazole (Vc): Yield: 48%, m.p.: 140-141 ºC. Anal. calcd. (found) % for $C_{19}H_{13}N_2OSCl$: C, 64.68 (64.47); H, 3.71 (3.74); N, 7.94 (7.99). FT-IR (ν_{max}, KBr, cm^{-1}): 1618 (C=C), 1599 (C=N), 1020 (C-N), 759 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 3.37 (s, 3H, OCH_3), 6.76 (d, 2H, Ar-H, *J* = 7.8 Hz), 6.86 (d, 2H, Ar-H, *J* = 7.8 Hz), 7.52 (t, 1H, C6-H, *J* = 7.0 Hz), 7.67-7.79 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.07 (d, 1H, C_8-H, *J* = 8.0 Hz), 8.16 (s, 1H, C_8-H). Mass (*m.w.* 352.84): *m/z* 352.0724 $[M]^+$.

4-(4-Chlorophenyl)-2-(2-chloroquinolin-3-yl)thiazole (Vd): Yield: 30%, m.p.: 189-191 ºC. Anal. calcd. (found) % for $C_{18}H_{10}N_2SCl_2$: C, 60.51 (60.73); H, 2.82 (2.85); N, 7.84 (7.95). FT-IR (ν_{max}, KBr, cm^{-1}): 1618 (C=C), 1588 (C=N), 1031 (C-N), 729 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.89 (d, 2H, Ar-H, *J* = 8.6 Hz), 7.10 (d, 2H, Ar-H, J = 8.2 Hz), 7.68-7.80 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.02 (d, 1H, C_8-H, *J* = 8.2 Hz), 8.09 (s, 1H, C_4-H). Mass (*m.w.* 357.25): *m/z* 356.0625 $[M^+]$, 358.0702 [M+2].

2-(2-Chloroquinolin-3-yl)-4-(4-fluorophenyl)thiazole (Ve): Yield: 42%, m.p.: 159-161 ºC. Anal. calcd. (found) % for $C_{18}H_{10}N_2SClF$: C, 63.44 (63.71); H, 2.96 (2.93); N, 8.22 (8.32). FT-IR (ν_{max}, KBr, cm^{-1}): 1635 (C=C), 1596 (C=N), 1034 (C-N), 728 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.82 (d, 2H, Ar-H, *J* = 7.6 Hz), 7.07 (d, 2H, Ar-H, *J* = 7.4 Hz), 7.54 (t, 1H, C_6-H, *J* = 7.2 Hz), 7.71-7.82 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.04 (d, 1H, C_8-H, *J* = 7.97 Hz), 8.12 (s, 1H, C_4-H). Mass (*m.w.* 340.80): *m/z* 340.0487 $[M^+]$.

4-(4-Bromophenyl)-2-(2-chloroquinolin-3-yl)thiazole (Vf): Yield: 50%, m.p.: 190-193 ºC. Anal. calcd. (found) % for $C_{18}H_{10}N_2SBrCl$: C, 53.82 (53.70); H, 2.51 (2.54); N, 6.97 (6.90); FT-IR (ν_{max}, KBr, cm^{-1}): 1633 (C=C), 1594 (C=N), 1036 (C-N), 744 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.81 (d, 2H, Ar-H, *J* = 7.8 Hz), 7.05 (d, 2H, Ar-H, *J* = 7.6 Hz), 7.53 (t, 1H, C_6-H, *J* = 7.0 Hz), 7.68-7.82 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.02 (d, 1H, C_8-H, *J* = 8.2 Hz), 8.15 (s, 1H, C_8-H). Mass (*m.w.* 401.71): *m/z* 400.1024 $[M^+]$.

2-(2-Chloroquinolin-3-yl)-4-(4-nitrophenyl)thiazole (Vg): Yield: 48%, m.p.: 171-173 ºC. Anal. calcd. (found) % for $C_{18}H_{10}N_3O_2SCl$; C, 58.78 (58.61); H, 2.74 (2.77); N, 11.42 (11.49); FT-IR (ν_{max}, KBr, cm^{-1}): 1632 (C=C), 1601 (C=N), 1039 (C-N), 765 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.78 (d, 2H, Ar-H, *J* = 7.8 Hz), 7.05 (d, 2H, Ar-H, *J* = 8.2 Hz), 7.51 (t, 1H, C_6-H, *J* = 7.0 Hz), 7.69-7.79 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.01 (d, 1H, C_8-H, *J* = 8.0 Hz), 8.10 (s, 1H, C_4-H). Mass (*m.w.* 367.81): *m/z* 367.1207 $[M^+]$.

4-(2-(2-Chloroquinolin-3-yl)thiazol-4-yl)phenol (Vh): Yield: 52%, m.p.: 138-139 ºC. Anal. calcd. (found) % for $C_{18}H_{11}N_2OSCl$: C, 63.81 (63.62); H, 3.27 (3.30); N, 8.27 (8.33); FT-IR (ν_{max}, KBr, cm^{-1}): 1614 (C=C), 1589 (C=N), 1027 (C-N), 756 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.77 (d, 2H, Ar-H, *J* = 7.8 Hz), 6.86 (d, 2H, Ar-H, *J* = 8.0 Hz), 8.52 (bs, H, OH), 7.53 (t, 1H, C_6-H, *J* = 7.2 Hz), 7.67-7.79 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.02 (d, 1H, C_8-H, *J* = 8.0 Hz), 8.16 (s, 1H, C_4-H). Mass (*m.w.* 338.81): *m/z* 338.1050 $[M^+]$.

4-(3-Chlorophenyl)-2-(2-chloroquinolin-3-yl)thiazole (Vi): Yield: 47%, m.p.: 166-167 ºC. Anal. calcd. (found) % for $C_{18}H_{10}N_2SCl_2$: C, 60.52 (60.74); H, 2.82 (2.86); N, 7.84 (7.93); FT-IR (ν_{max}, KBr, cm^{-1}): 1619 (C=C), 1603 (C=N), 1024 (C-N), 755 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.73 (d, 1H, Ar-H, *J* = 7.2 Hz), 6.79 (s, 1H, Ar-H), 6.95 (d, 1H, Ar-H, *J* = 7.0 Hz) 7.58 (t, 1H, Ar-H, *J* = 7.1 Hz), 7.09 (t, 1H, C_6-H, *J* = 7.4 Hz), 7.73-7.80 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.03 (d, 1H, C_8-H, *J* = 7.8 Hz), 8.13 (s, 1H, C_4-H). Mass (*m.w.* 357.25): *m/z* 356.0841 $[M^+]$.

2-(2-Chloroquinolin-3-yl)-4-(3,4-dimethoxyphenyl)-thiazole (Vj): Yield: 56%, m.p.: 130-131 ºC. Anal. calcd. (found) % for $C_{20}H_{15}N_2O_2Cl$: C, 62.74 (62.86); H, 3.95 (3.98); N, 7.32 (7.30); FT-IR (ν_{max}, KBr, cm^{-1}): 1617 (C=C), 1597 (C=N), 1022 (C-N), 760 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 3.39 (bs, 3H, OCH3), 3.54 (s, 3H, OCH_3), 6.76 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.55-7.60 (m, 1H, Ar-H), 7.55-7.60 (m, 2H, C_6-H), 7.70-7.79 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.04 (d, 1H, C_8-H, *J* = 8.0 Hz), 8.14 (s, 1H, C_4-H). Mass (*m.w.* 382.86): *m/z* 382.1092 $[M^+]$.

2-Chloro-4-(2-(2-chloroquinolin-3-yl)thiazol-4-yl)phenol (Vk): Yield: 47%, m.p.: 177-179 ºC. Anal. calcd. (found) % for $C_{18}H_{10}N_2OSCl_2$: C, 57.92 (57.79); H, 2.70 (2.74); N, 7.51 (7.58); FT-IR (ν_{max}, KBr, cm^{-1}): 1616 (C=C), 1593 (C=N), 1030 (C-N), 751 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.86 (s, 1H, Ar-H), 7.95-7.90 (m, 2H, Ar-H), 7.95-7.90 (m, 2H, C_6-H), 7.72-7.81 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.01 (d, 1H, C_8-H, *J* = 8.0 Hz), 8.10 (s, 1H, C_4-H). Mass (*m.w.* 373.25): *m/z* 371.9805 $[M^+]$.

4-(2-(2-Chloroquinolin-3-yl)thiazol-4-yl)-2-nitrophenol (Vl): Yield: 44%, m.p.: 184-185 ºC. Anal. calcd. (found) % for $C_{18}H_{10}N_3O_3SCl$: C, 56.33 (56.52); H, 2.63 (2.66); N, 10.95 (10.99); FT-IR (ν_{max}, KBr, cm^{-1}): 1621 (C=C), 1593 (C=N), 1029 (C-N), 754 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 7.15-7.21 (m, 2H, Ar-H), 8.67 (s, 1H, OH). 7.58-7.61 (m, 2H, Ar-H), 7.58-7.61 (m, 2H, C6-H), 7.75-7.82 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.03 (d, 1H, C_8-H, *J* = 8.2 Hz), 8.12 (s, 1H, C_4-H). Mass (*m.w.* 383.81): *m/z* 383.2410 $[M^+]$.

2-(2-Chloroquinolin-3-yl)-4-(4-methoxy-3-methyl-phenyl)thiazole (Vm): Yield: 55%, m.p.: 148-149 ºC. Anal. calcd. (found) % for $C_{20}H_{15}N_2OSCl$: C, 65.48 (65.67); H, 4.12 (4.16); N, 7.64 (7.69); FT-IR (ν_{max}, KBr, cm^{-1}): 1615 (C=C), 1593 (C=N), 1025 (C-N), 752 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 2.31 (s, 3H, CH_3), 3.34 (s, 3H, OCH_3), 6.79-6.82 (m, 2H, Ar-H), 7.54-7.60 (m, 2H, C_6-H), 7.72-7.81 (m, 3H, C_5-H, C_7-H & C′$_5$-H),

8.05 (d, 1H, C_8-H, *J* = 8.0 Hz), 8.16 (s, 1H, C_4-H). Mass (*m.w.* 366.86): *m/z* 366.0825 [M^+].

2-(2-Chloroquinolin-3-yl)-4-(3,4-dichlorophenyl)thiazole (Vn): Yield: 45%, m.p.: 150-152 ºC. Anal. calcd. (found) % for $C_{18}H_9N_2SCl_3$: C, 55.19 (55.36); H, 2.32 (2.35); N, 7.15 (7.22); FT-IR (ν_{max}, KBr, cm^{-1}): 1623 (C=C), 1596 (C=N), 1029 (C-N), 754 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 6.85 (d, 1H, Ar-H, *J* = 8.2 Hz), 6.71 (s, 1H, Ar-H), 7.18 (d, 1H, Ar-H, *J* = 8.2 Hz), 7.57 (t, 1H, C_6-H, *J* = 7.0 Hz), 7.72-7.80 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.01 (d, 1H, C_8-H, *J* = 8.2 Hz), 8.08 (s, 1H, C_4-H). Mass (*m.w.* 391.69): *m/z* 390.1250 [M^+].

4-(3-Chloro-4-methoxyphenyl)-2-(2-chloroquinolin-3-yl)thiazole (Vo): Yield: 49%, m.p.: 189-191 ºC. Anal. calcd. (found) % for $C_{19}H_{12}N_2OSCl_2$: C, 58.93 (58.83); H, 3.12 (3.15); N, 7.23 (7.29); FT-IR (ν_{max}, KBr, cm^{-1}): 1610 (C=C), 1599 (C=N), 1027 (C-N), 755 (C-Cl). ^{1}H NMR (300 MHz) δ ppm: 3.61 (s, 3H, OCH_3), 6.83 (d, 1H, Ar-H, *J* = 7.6 Hz), 7.61-7.68 (m, 1H, Ar-H), 7.61-7.68 (m, 3H, C_6-H), 7.73-7.80 (m, 3H, C_5-H, C_7-H & C′$_5$-H), 8.03 (d, 1H, C_8-H, *J* = 8.0 Hz), 8.12 (s, 1H, C_4-H). Mass (*m.w.* 405.61): *m/z* 406.0521 [M^+].

***In silico* toxicity and ADME evaluation:** The two main requirements for any new chemical entity (NCE) to become a marketable product are an acceptable ADME profile and minimal toxicity. The prediction of compound toxicities is an important part of the drug design development process. The computational toxicity estimations are not only faster than the determination of toxic doses in animals, but can also help to reduce the amount of animal experiments In this study, we used the Swiss ADME online software [15] to perform ADME prediction studies and the ProTox II online software [16] to predict *in silico* toxicity.

Molecular docking: A Windows 11-based system with a 64-bit configuration and an Intel(R) Core TM i3-CPU @ 2.21 GHz processor, along with 8 GB of RAM, was used as a workstation for conducting molecular docking studies. The ligand and protein preparation followed the reported method [17]. The PyRx virtual screening program's AutoDock Vina wizard was used to complete the molecular docking of each ligand with the generated protein. The results of docking for various structures were analyzed further using BIOVIA Discovery Studio Visualizer 2020.

Antimicrobial screening: A variety of bacterial strains, including against Gram-positive strain *viz*. *Staphylococcus aureus* (NCTC 65710), *Streptococcus pyogenes* (MTCC-442), *Bacillus subtilis* (NCIM 2250) and Gram-negative bacteria *Pseudomonas aeruginosa* (NCTC 10662) and *Escherichia coli* (NCTC 10418), were used to screen the antibacterial activity on nutrient agar. A suspension of bacterial spores was prepared for grass planting using normal saline that included 0.01% Tween 80. Each petri dish had a diameter of 15 cm and was filled with 0.5 mL of PDA medium. Before the plates were dried 37 ºC for 1 h using incubator, 5 mL of spore suspension were added to the solid agar medium. Test chemical solutions in DMSO at concentrations of 6.25, 12.5, 25, 50, 100, 200 µg/mL were added to the previously labelled wells of these seeded agar plates using an agar punch. A control group that was treated with DMSO was also included. The Petri plates were placed in an incubator set at 37 ºC for 24 h [18]. The minimal inhibitory concentration (MIC) was found by measuring the inhibition zone, which allowed to identify the lowest concentration of the test medication at which no significant growth was detected.

RESULTS AND DISCUSSION

Scheme-I outlines the synthetic process utilized to synthesize the target compounds (**Va-o**). By reacting with hydroxylamine hydrochloride in the presence of formic acid and sodium formate, the key intermediate 2-chloro-3-formyl-quinoline **(II)** was transformed into 2-chloroquinoline-3-carbonitrile **(III)**, which was then converted into 2-chloroquinoline-3-carbothioamides (**IV**) by the addition of ammonium sulphide in methanol. Then the title molecules (thiazole analogues) were synthesized by reacting 2-bromo-1-(substituted phenyl)ethan-1-one (**1a-o**) with 2-chloroquinoline-3-carbothioamides (**IV**) in ethanolic medium in the presence of sodium acetate as base to yield the title compounds (**Va-o**).

On the basis of FT-IR, ^{1}H NMR and mass spectral data of the synthesized compounds (**Va-o**), the structure of the compounds were established. The stretching band with respect to (C-N) and (C-Cl) was detected at 1027 and 757 cm^{-1}, respectively, whereas the absorption bands for compound **Va** were observed at 1624 and 1597 cm^{-1} corresponding to (C=C) and (C=N). Similar to this, the distinctive proton peaks of the phenyl ring, thaizole and 2-chloroquinoline were also found at their prescribed values. The ESI-MS spectrometry at 322.8032 as (M^+) and 324.7910 for (M+2) peaks due to the presence of a halogen atom further proved the formation of compound **Va**.

Antibacterial activity: The synthesized compounds (**Va-o**) showed the antibacterial activity against the studied bacteria which was ranging from fair to very good. According to the antibacterial screening findings presented in Table-1, as ZI (MIC) most of the compounds exhibits prominent anti *E. coli* growth inhibiting activity at 12.5 and 25 µg/mL specially thiazoles **Ve**, **Vk**, **Vl**, **Vn** and **Vd**, **Vf**, **Vi**, **Vm**, **Vo** at 12.5 and 25 µg/mL, respectively. The following thiazoles **Ve**, **Vk**, **Vl**, **Vn** and **Vo** showed highest growth inhibiting activity against the *S. aureus* bacteria as revealed by zone of inhibition. The lowest MIC values at 50 µg/mL as anti-*P. auroginosa* activity was observed by compounds **Vd**, **Ve**, **Vf**, **Vi**, **Vk**, **Vl**, **Vn**, **Vo** with varied zone of inhibition (08.5 to 12.0 mm) and among them compound **Vn** exhibits the highest ZOI of 12.0 mm at 25 µg/mL. The thiazoles which were exhibiting the lowest MIC values as anti-*B. subtilis* includes **Ve**, **Vk** and **Vn** and among them compound **Vn** was found to be having MIC of 12.5 µg/mL (ZI = 8.5 mm). Rest of the compounds showed moderate to poor activity against the *B. subtilis*. The anti-*S. pyrogen* screening of all the thiazoles revealed that compounds **Vk**, **Vl**, **Vn** and **Ve**, **Vm** and **Vo** exhibit MIC of 25 and 50 µg/mL, respectively. Rest of the compounds exhibit moderate to poor MIC against the studied bacterial strains which was in the range of 100 to 200 µg/mL.

Pharmacokinetic and toxicity prediction: Swiss ADME software was used to estimate the pharmacokinetic (ADME) features of thiazole derivatives. Based on many computed parameters, including the molecular weight (mw), the partition

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

Compd.	R^1	R^1	MIC (µg/mL)				
			E. coli	*S. aureus*	*P. auroginosa*	*B. subtilis*	*S. pyogenes*
Va	H	H	08.0 (50)	09.5 (100)	08.0 (200)	08.5 (50)	10.0 (200)
Vb	H	CH_3	10.0 (100)	11.0 (100)	10.0 (200)	10.0 (100)	08.5 (100)
Vc	H	OCH_3	09.5 (50)	08.5 (50)	10.5 (100)	09.0 (100)	9.5 (100)
Vd	H	Cl	12.0 (25)	10.0 (50)	10.5 (50)	08.0 (50)	09.0 (100)
Ve	H	F	10.5 (12.5)	08.5 (25)	09.5 (50)	10.5 (25)	08.5 (50)
Vf	H	Br	09.0 (25)	10.0 (50)	10.5 (50)	12.5 (100)	11.5 (100)
Vg	H	NO_2	11.5 (50)	12.5 (100)	12.5 (100)	09.5 (100)	12.0 (100)
Vh	H	OH	08.5 (50)	09.5 (100)	09.5 (100)	12.0 (200)	08.0 (100)
Vi	Cl	H	12.0 (25)	08.0 (50)	08.5 (50)	10.0 (50)	10.0 (100)
Vj	OCH_3	OCH_3	08.5 (50)	09.0 (50)	09.5 (200)	11.0 (100)	09.5 (200)
Vk	Cl	OH	11.0 (12.5)	10.0 (25)	09.0 (25)	08.0 (25)	09.0 (25)
Vl	NO_2	OH	10.5 (12.5)	08.5 (25)	08.0 (25)	08.5 (50)	08.5 (25)
Vm	CH_3	OCH_3	09.0 (25)	11.0 (50)	10.0 (100)	09.0 (50)	08.0 (50)
Vn	Cl	Cl	13.0 (12.5)	10.0 (12.5)	12.0 (25)	08.5 (12.5)	10.0 (25)
Vo	Cl	OCH_3	14.5 (25)	09.5 (25)	11.5 (50)	10.5 (50)	11.5 (50)
Ciprofloxacin	–	–	14.5 (6.25)	13.5 (6.25)	12.0 (6.25)	13.0 (6.25)	14.0 (6.25)

TABLE-2
SWISS ADME TOOL ONLINE SOFTWARE WAS USED TO PREDICT THE ADME PROPERTIES OF COMPOUNDS (**Va-o**)

Compd.	%ABS = 109 – 0.345 PSA	Solubility	TPSA (Å²)	NROTB	HBA	HBD	Log $P_{o/w}$ (iLOGP)	BBB	GI absorption	Lipinski violation	Bioavailability score
Va	108.65	Poorly soluble	54.02	2	2	0	3.41	No	High	0	0.55
Vb	108.65	Poorly soluble	54.02	2	2	0	3.45	No	High	0	0.55
Vc	87.17	Moderately soluble	63.25	3	3	0	3.47	No	High	0	0.55
Vd	87.17	Moderately soluble	63.25	3	3	0	3.47	No	High	0	0.55
Ve	108.65	Poorly soluble	54.02	2	3	0	3.38	No	High	0	0.55
Vf	108.65	Poorly soluble	54.02	2	2	0	3.60	No	High	0	0.55
Vg	74.55	Moderately soluble	99.84	3	4	0	2.65	No	High	0	0.55
Vh	83.38	Moderately soluble	74.25	2	3	1	2.85	No	High	0	0.55
Vi	108.65	Poorly soluble	54.02	2	2	0	3.49	No	High	0	0.55
Vj	83.99	Moderately soluble	72.48	4	4	0	3.68	No	High	0	0.55
Vk	83.38	Poorly soluble	74.25	2	3	1	3.39	No	High	0	0.55
Vl	67.57	Poorly soluble	120.07	3	5	1	2.29	No	Low	0	0.55
Vm	87.17	Poorly soluble	63.25	3	3	0	3.74	No	Low	0	0.55
Vn	108.65	Poorly soluble	54.02	2	2	0	3.75	No	Low	1	0.55
Va	87.17	Poorly soluble	63.25	3	3	0	3.73	No	High	0	0.55
11o	87.17	Poorly soluble	63.25	2	2	0	3.75	No	High	0	0.55

coefficient [log P (o/w)], the number of hydrogen-bond acceptors (HBA) and the number of hydrogen-bond donors (HBD), the forecast was made. Upon examining Table-2, it is evident that NROTB are (2-4) and no. HBA are (2-5) for all the thiazole derivatives (**Va-o**) and these no. were lower than maximum permitted value of 10. Additionally, no. HBD were (0-1) for all the synthesized thiazoles which is again less than five. The assessed clog P values were deemed acceptable, falling below 5 and the molecular weights of thiazoles (**Va-o**) were below 500. Since none of the thiazoles (**Va-o**) seem to defy Lipinski's rule of five, these results suggest that they are orally bioactive compounds with good G.I. absorption. Further, the percentage of absorption was computed from TPSA value using the formula %Abs = 109 ± [0.345 × Topological polar surface area]. The topological polar surface area varied between 54.02 and 120.07. According to Table-2, not a single one of the compounds would be able to pass the BBB. The results for the synthesized thiazoles (**Va-o**) in the ADME profile seem to be satisfactory.

The synthesized compounds underwent *in silico* toxicity screening using the web-based prediction tool Pro-Tox-II and the results are presented in Table-3. The study predicated that all the compounds appear to be hepatotoxic while compound **Vl** found to be toxic in all the toxicity predictions and compound **Vg** was shown to toxic in all prediction except the immunotoxicity predictions. All thiazole compounds were classified as class IV and compounds **Va**, **Vb**, **Vd**, **Ve**, **Vf**, **Vh**, **Vi**, **Vk**, **Vm**, **Vn** and **Vo** were found to be non-toxic except the hepatotoxicity. However, compounds **Vc** and **Vj** exhibited hepatotoxicity and immunotoxicity.

Molecular docking studies: An investigation of the docking of new thiazole compounds **Va-o** into the DNA gyrase enzyme's active site (PDBID: 1KZN) was conducted using the AutoDock Vina tool. Using molecular docking, we investigated all fifteen different derivatives for their possible binding interactions with the clorobiocin binding site.

TABLE-3
TOOL Pro-toxII ONLINE SOFTWARE USED TO PREDICT TOXICITIES PROPERTY OF COMPOUNDS (**Va-o**)

Compd.	Hepatotoxicity	Carcinogenicity	Immune toxicity	Mutagenicity	Cytotoxicity	LD_{50} (mg/Kg)	Class	Average similarity	Prediction accuracy
Va	+	–	–	–	–	681	IV	59.51	67.38
Vb	+	–	–	–	–	681	IV	59.11	67.38
Vc	+	–	+	–	–		IV	56.10	67.38
Vd	+	–	–	–	–	681	IV	59.46	67.38
Ve	+	–	–	–	–	681	IV	56.27	67.38
Vf	+	–	–	–	–	681	IV	56.66	67.38
Vg	+	+	–	+	+	681	IV	55.85	67.38
Vh	+	–	–	–	–	681	IV	56.99	67.38
Vi	+	–	–	–	–	681	IV	57.96	67.38
Vj	+	–	+	–	–	681	IV	52.45	67.38
Vk	+	–	–	–	–	681	IV	55.27	67.38
Vl	+	+	+	+	+	681	IV	51.92	67.38
Vm	+	–	–	–	–	681	IV	56.36	67.38
Vn	+	–	–	–	–	681	IV	57.93	67.38
Vo	+	–	–	–	–	681	IV	54.16	67.38

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

Compd.	Free energy of binding (kcal/mol)	Amino acids residues involved in Hydrogen bond, Pi-alkyl, Pi-sigma, Pi-anion, Pi-cation interaction
Va	-6.3	Asn-46, Glu-50, Val-71, Ile-78, Pro-79, Ile-90, Val-93, Ala-96 and Ser-121
Vb	-7.4	Val-43, Glu-50, Val-71, Ile-78, Arg-136, Ile-90, Ala-96 and Ser-121, Thr-165
Vc	-6.8	Ala-47, Glu-50, Ile-78, Pro-79, Ala-86 Ile-90, Ala-96 and Ser-121
Vd	-5.1	Val-43, Glu-50, Val-71, Ile-78, Pro-79, Ile-90, Val-93 and Ser-121
Ve	-7.7	Asn-46, Glu-50, Val-71, Arg-76, Ile-78, Pro-79, Ile-90 and Ser-121
Vf	-6.7	Val-43, Asp-45, Asp-49, Asn-46, Glu-42, Ile-90, Val-167
Vg	-7.8	Ala-47, Asn-46, Glu-50, Pro-79, Ile-90, Val-93, Ala-96 and Gly-119
Vh	-8.5	Asn-46, Asp-49, Glu-50, Ile-78, Ile-90, Val-93, Ala-96 and Ser-121
Vi	-7.4	Asn-46, Asp-49, Arg-76, Ile-78, Pro-79, Ile-90 and Val-167
Vj	-7.6	Val-43, Glu-42, Asp-45, Asp-49, Asn-46, Glu-42, Ile-90, Gly-117
Vk	8.0	Val-43, Ala-47, Glu-50, Arg-76, Ile-78, Ile-90, Gly-119 and Ser-121
Vl	-7.9	Ala-47, Asn-46, Asp-49, Glu-50, Gly-117, Gly-119
Vm	-7.3	Ala-47, Asn-46, Asp-49, Asn-46, Glu-42, Ile-90 and Gly-117
Vn	-7.5	Val-43, Ala-47, Glu-50, Ile-90, Val-93, Ala-96 and Ser-121
Vo	-7.3	Asp-45, Asp-49, Asn-46, Glu-42, Ile-90
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 DNA gyrase (PDBID: 1KZN) as the target, Table-4 shows the binding patterns of several thiazole compounds (**Va-o**). Docking method postures were chosen according to their favourable binding energies, which ranged from around -5.1 to -8.5 kcal/mol. The two compounds with the lowest binding energies (-8.5 and -8.0 kcal/mol, respectively) are **Vh** and **Vk**. The interactions of compounds **Vh** and **Vk** inside the chlorobiocin binding site are shown in Figs. 1 and 2, where the 2D schematic representations show their well-fitted arrangement in the binding pocket. Figs. 1 and 2 show that compounds maintain the hydrophobic sites and hydrogen bond interactions found in these derivatives. Docking studies showed that compounds **Vh** and **Vk** form strong hydrophobic interactions and hydrogen bonds with the following amino acids: Glu-50, Ile-78, Ile-90, Val-93 and Ser-121. It is proposed that the differences in activity are due to hydrophobic contacts, even though no comparable interactions were found in other derivatives.

Conclusion

A series of thiazole compounds containing 2-chloroquinoline was successfully synthesized from 2-chloro-3-formylquinoline with moderate to excellent yields. Novel thiazole structures were elucidated by analyzing mass, ^{1}H NMR and FT-IR data. The newly compounds were screened for their antibacterial activity against Gram-positive and Gram-negative bacteria. Most of the compounds exhibited moderate to significant growth inhibiting activity, but compound **Ve**, **Vk**, **Vl** and **Vn** had the lowest minimum inhibitory concentration (MIC) of 12.5 µg/mL against *E. coli*, while activity against *S. aureus* and *B. subtilis* compound **Vn** was only effective at (MIC) of 12.5 µg/mL. Remaining compounds were able to inhibit the growth of bacteria only at concentration higher than 12.5 µg/mL. Additionally, docking screening revealed strong binding interactions, which may indicate their antibacterial mechanism of action.

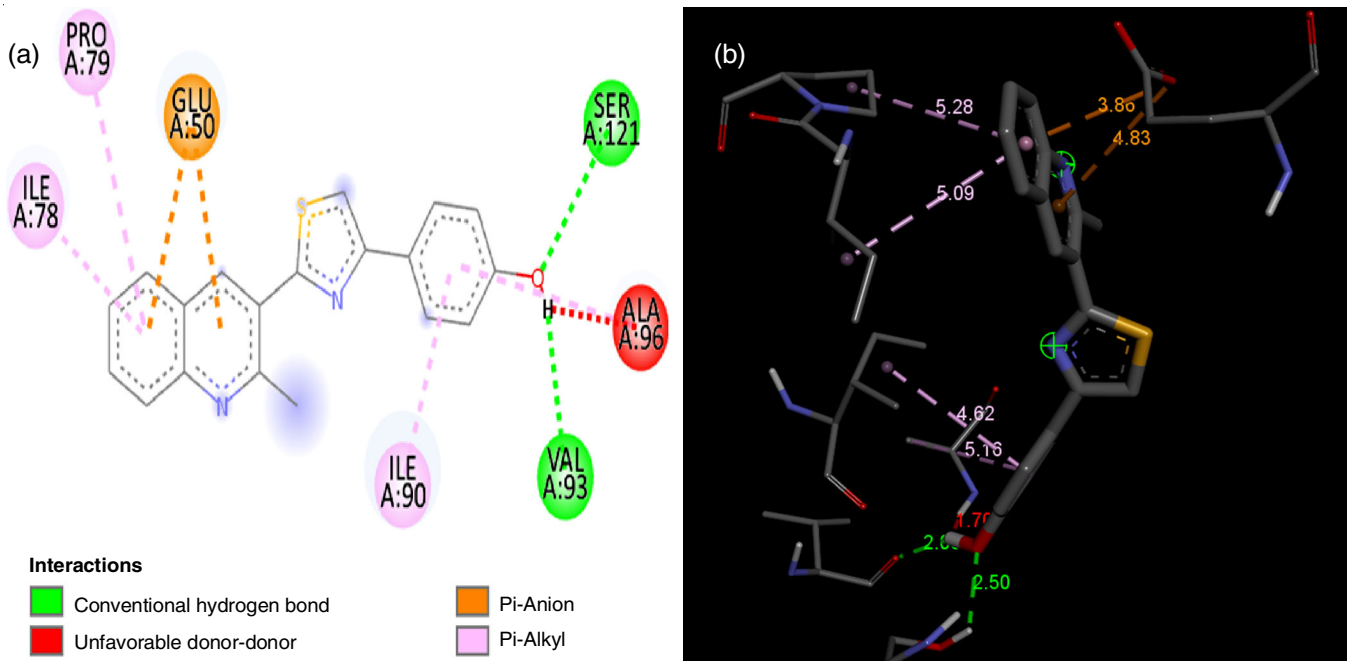


Fig. 1. 2D Molecular docking binding interaction of compound **Vh** in the (a) binding site of DNA-gyrase (PDB ID; 1KZN) and (b) amino acid residue interaction distance (Å)

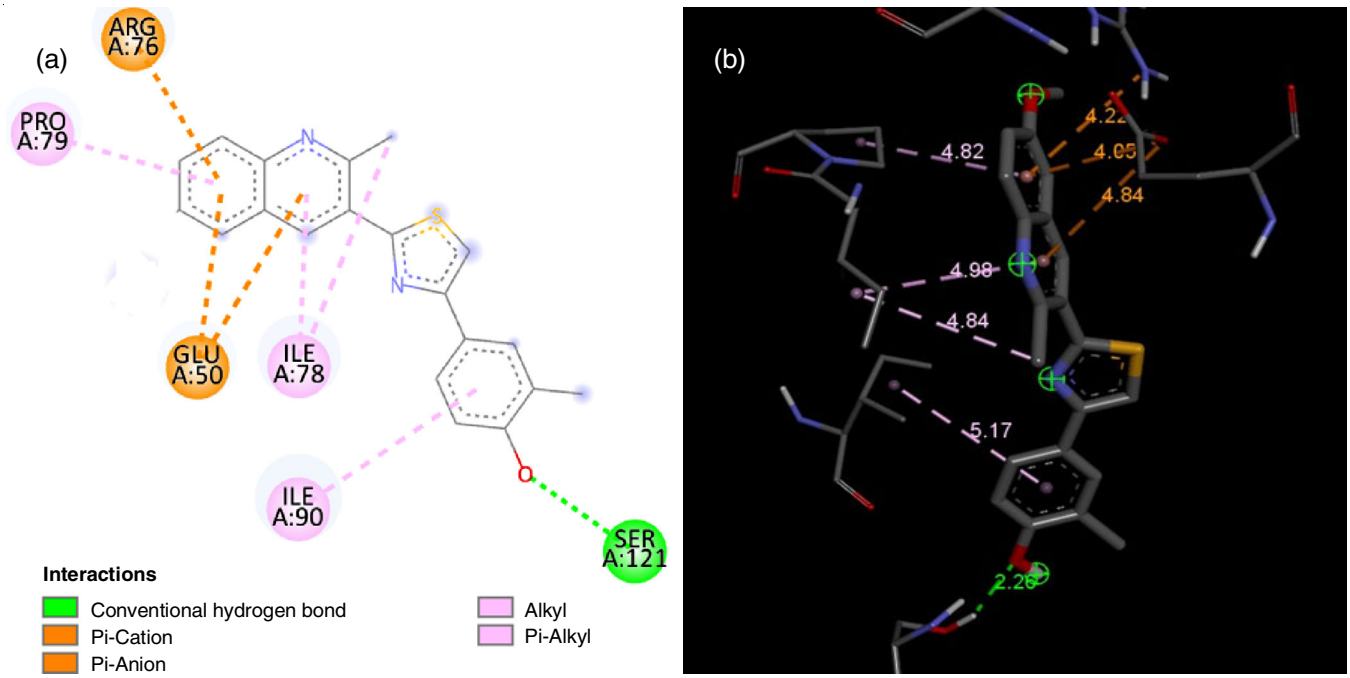


Fig. 2. 2D Molecular docking binding interaction of compound **Vk** in the (a) binding site of DNA-gyrase (PDB ID; 1KZN) and (b) amino acid residue interaction distance (Å)

The ADME and toxicity predication of the all the synthesized compounds (**Va-o**) suggest that good druggable properties except that hepatoxicity which limit their future development.

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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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