Journal of the Indian Chemical Society 101 (2024) 101163

Contents lists available at ScienceDirect

Journal of the Indian Chemical Society

journal homepage: www.journals.elsevier.com/journal-of-the-indian-chemical-society

Quinoxaline clubbed thiazole: Molecular docking, synthesis and antimicrobial evaluation

Sagar Ramdas Shrimandilkar [a,b], Pravin Tatyaram Tryambake [a], Keshao Abasaheb Mahale [b], Dnyaneshwar Daulatrao Lokhande [b,*]

[a] Department of Chemistry and Research Centre, Sangamner Nagarpalika Arts, D. J. Malpani Commerce and B. N. Sarda Science College (Affiliated to Savitribai Phule Pune University, Pune), Sangamner, 422605, M.S., India
[b] Department of Chemistry and Research Centre, K. R. T. Arts, B. H. Commerce and A. M. Science College (Affiliated to Savitribai Phule Pune University, Pune), Nashik, 422002, M.S., India

ARTICLE INFO

Keywords:
Thiazole
Quinoxaline
Molecular docking
Anti-microbial activity
MIC

ABSTRACT

Novel hybrid molecules of thiazole with quinoxaline have been designed, synthesized and characterised by FT-IR, Mass, ^{1}H and ^{13}C NMR spectroscopic techniques. The pharmacological potential of synthesized compounds was checked for bacterial and fungal strains by the Broth microdilution method. All molecules exhibited significant antibacterial and antifungal activities. The compound (*E*)-4-(4-chlorophenyl)-2-(2-(1-(3-methylquinoxalin-2-yl)ethylidene)hydrazinyl)thiazole (**3b**) displayed (MIC = 12.5 μg/mL) excellent biological potential against *Staphylococcus aureus* [MTCC96] gram-positive bacterial strain. The molecular docking of thiazole derivatives was performed with *S. aureus* DNA gyrase (2XCT). The docked molecules displayed significant interactions with the active cavity of *S. aureus* DNA gyrase. The (*E*)-4-(4-chlorophenyl)-2-(2-(1-(3-methylquinoxalin-2-yl)ethylidene)hydrazinyl)thiazole (**3b**) molecule displayed the most stable conformation at the highest binding affinity (−10.9 kcal/mol) among the docked molecules with protein.

1. Introduction

Nitrogen and sulfur-based heterocycles are key pharmacophores of copious biologically active molecules [1–4]. Thiazole is one of the essential pharmacophores. It is 1,3-azole containing nitrogen and sulfur atoms in the aromatic five-membered heterocyclic ring. Many groups of researchers are working on thiazole due to its pharmacological potential such as anti-bacterial [5–7], anti-fungal [8–10], anti-viral [11–14], anti-tuberculosis [15–17], anti-cancer [18–21], anti-inflammatory [22–25], anti-malarial [26] and anti-HIV [27] activities. Most of the commercially available drugs possessed 2,4-disubstituted thiazole hybrids like cefpodoxime [28](anti-bacterial), ceftaroline fosamil [29] (anti-bacterial), cobicistat [30] (anti-HIV), ritonavir [31] (anti-HIV), meloxicam (anti-inflammatory) and fentiazac (anti-inflammatory) are shown in Fig. 1. Literature survey of thiazole derivatives with the substituents at 2 and 4 positions have proven their pharmacological potential like anti-microbial [32,33], anti-inflammatory [34,35], anti-viral [36,37], anti-oxidant [38,39] and anti-cancer [40,41] activities. These lead biologically potent 2,4-disubstituted thiazole hybrids are shown in Fig. 2.

4-methoxy-*N*-(4-(4-nitrophenyl)thiazol-2-yl)benzamide **I** exhibited potent antimicrobial activity (pMIC = 4.60) against *E. coli* and *S. aureus* due to the methoxy and nitro groups on terminal phenyl rings [32]. Coumarin thiazole derivative **II** showed an excellent inhibitory action against *F. moniliforme* with an inhibition rate of 74 %. The trifluoromethyl and methoxy groups amplify the antifungal activity of coumarin thiazole derivative **II** [33]. 2-(3-(2-methoxyphenyl)-5-(o-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-4-methylthiazole **III** appeared a significant inhibitor of cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS) by blocking mitogen-activated protein kinases (MAPK) pathway [35]. 1,3-thiazole derivative **IV** was observed as a potent anti-inflammatory agent in the *in vivo* screening by the paw edema method [34]. The scaffold A containing thiazole pharmacophore **V** becomes a potent inhibitor of HIV-1, which inhibits the binding of HIV to the protein of CD4 cells [37]. Thiazole hybrid **VI** displayed potent anti-viral activity against the Hepatitis C virus (EC_{50} = 0.56 μM) [36]. The *in vitro* antioxidant screening of **VII** revealed that it displayed more potent nitric oxide free radical scavenging activities (IC_{50} = 28 ± 0.01

* Corresponding author.
E-mail address: ddlokhande@kthmcollege.ac.in (D.D. Lokhande).

https://doi.org/10.1016/j.jics.2024.101163
Received 18 December 2023; Received in revised form 25 April 2024; Accepted 26 April 2024
Available online 30 April 2024

μg/mL) than reference ascorbic acid (IC_{50} = 32 ± 0.09) [39]. The Schiff base of thiazole **VIII** exhibited better anti-oxidant activity (IC_{50} = 3.6, 80.89 % inhibition) due to the electron donating –OH groups on both phenyl rings [38]. Pyrazolyl-thiazole **IX** exhibited anti-cancer activity, it exhibited potent cytotoxicity (IC_{50} = 0.97 μM) in comparison with Lapatinib (IC_{50} = 7.45 μM). Moreover, it exhibited better EGFR/HER2 inhibitory action (IC_{50} = 4.98, 9.85 μM respectively) compared with lapatinib (IC_{50} = 6.1, 17.2 μM) [41]. Thiazole-pyrimidine hybrid **X** appeared as a potent anticancer agent against various human cell lines like A2780, A549, Colo-205 and MCF-7 with IC_{50} values 0.33 ± 0.071 μM, 0.043 ± 0.006 μM, 0.12 ± 0.038 μM, 0.87 ± 0.045 μM respectively [40].

Quinoxaline is another important pharmacophore that gives biological activities like anti-microbial [42,43], anti-inflammatory [44,45], anti-cancer [46–48], anti-viral [49], anti-HIV [50,51], anti-bacterial [52,53], anti-tubercular [54,55], anti-oxidant [56,57], anti-malarial [58], etc. Some commercially available drugs possess quinoxaline pharmacophore like clofazimine [59](anti-mycobacterial), brimonidine (to treat Glaucoma), varenicline [60] (used for smoking cessation), *etc*. are shown in Fig. 3. Based on the literature, the structures of some lead biologically active agents that possessed quinoxaline moiety are shown in Fig. 4.

1,3-oxazole-quinoline hybrid **XI** exhibited good anti-bacterial activity (MIC = 62.5 μg/mL) against *M. luteus* (gram-positive) in comparison with tetracycline (MIC = 62.5 μg/mL) as a reference drug [61]. The quinoxaline-thiazole derivative **XII** displayed significant anti-bacterial activity against *P. aeruginosa* (MIC = 12.5 μg/mL) when compared to levofloxacin (MIC = 12.5 μg/mL) [62]. Quinoxaline derivative **XIII** exhibited good inhibition against *S. aureus* (MIC = 13.3 μM), *E. coli* (MIC = 7.9 μM) and *B. subtilis* (MIC = 7.9 μM) [63]. Quinoxaline derivative **XIV** on anti-microbial screening displayed potent inhibitory action against *S. aureus* (MIC = 0.92 mg/mL), *S. pyogenes* (MIC = 0.97 mg/mL), *P. aeruginosa* (MIC = 0.98 mg/mL) and *E. coli* (MIC = 0.93 mg/mL) as compared to ciprofloxacin (MIC = 0.89–0.97 mg/mL) [64]. Quinoxaline derivative **XV** displayed significant anti-proliferative property (IC_{50} = 22.11 μM) against the human breast adenocarcinoma cells (MCF7) as compared to standard suppressor XL147 (IC_{50} = 11.77 μM) [65]. The compound **XVI** exhibited excellent inhibitory activity against the c-Met kinase enzyme (IC_{50} = 6 nM) as compared to crizotinib (IC_{50} = 0.9–12.8 nM) as a reference inhibitor. Compound **XVI** also showed an excellent tumour growth inhibitor (IC_{50} = 175 nM) of MKN-45 mouse gastric cancer cells [66]. Quinoxaline-oxadiazole derivative **XVII** exhibited notable anti-inflammatory activity (% inhibition = 40.95), which is close to the % inhibition (52.79 %) by celecoxib [67]. Quinoxaline derivative **XVIII** exhibited good inhibition data (IC_{50} = 11.78 μg/mL, CC_{50} = 11.78 μg/mL) against strain IIIB of HIV-1 as compared to Didanosine (IC_{50} = 17.95 μg/mL, CC_{50} = 50 μg/mL) as a standard reference [68].

Molecular hybridization is a leading rationale and versatile approach for enriching the therapeutic potential of two distinct heterocycles by clubbing them into a single hybrid molecule. Some groups of researchers have reported quinoxaline-linked thiazole derivatives (Fig. 5). M. E. Salem et al. [69] have synthesized bis-thiazole derivatives (**XIX** and **XX**) in which they clubbed C-2 and C-3 of quinoxaline with C-4 or C-2 of thiazole. They synthesized the hybrids (**XIX** and **XX)** by reacting corresponding thiosemicarbazones and α-halo ketones in ethanol with triethyl amine. The methyl-substituted derivative of **XIX** exhibited 11 mm zone of inhibition against *S. aureus*.

A. M. Abdallah et al. [70] have adopted a greener route for the synthesis of indenoquinoxaline-thiazole derivatives (**XXI**) by reacting indenoquinoxaline thiosemicarbazone with α-halo ketones or hydrazononyl chlorides in the presence of 1,4-Diazabicyclo[2.2.2]octane as a catalyst.

M. E. Salem et al. [71] have synthesized bis-thiazole linked quinoxaline hybrids (**XXII and XXIII**) by using 1,1'-((quinoxaline-2, 3-diylbis(oxy))bis(4,1-phenylene))diethanone as a key precursor. Derivatives (**XXII**) synthesized by treating (2*E*,2′*E*)-2,2'-(((quinoxaline-2, 3-diylbis(oxy))bis(4,1-phenylene))bis(ethan-1-yl-1-ylidene))bis(hydrazinecarbothioamide) with various α-bromo ketones or α-keto-hydrazononyl chlorides in ethanol with triethyl amine. The hybrid molecules (**XXIII**) synthesized by reacting 2,3-Bis(4-(1-(2-(4-phenylthiazol-2-yl)hydrazono)ethyl)phenoxy)quinoxaline with thioamides or thiosemicarbazones in ethanol and triethyl amine. They have prepared quinoxaline-thiazole hybrids in which C-2 and C-3 of quinoxaline are linked with C-2 of thiazole (**XXII**) or C-4 of thiazole (**XXIII**).

Therefore, motivated by literature regarding the biological potential of thiazole and quinoxaline pharmacophores as well as the efficient routes for the synthesis of quinoxaline-thiazole hybrids, we designed the hybrid molecules containing thiazole and quinoxaline moieties to enrich the biological potential of both pharmacophores.

Most of the groups of researchers have reported bis(heterocycles) of quinoxaline-thiazole derivatives (Fig. 5). However, we planned to synthesize the novel hybrids with asymmetrically substituted quinoxaline at C-2 and C-3 positions. The hydrophobic methyl group and ethylidene-hydrazine linkage incorporated at C-3 and C-2 of quinoxaline respectively. In the proposed work, the substituted thiazole and quinoxaline

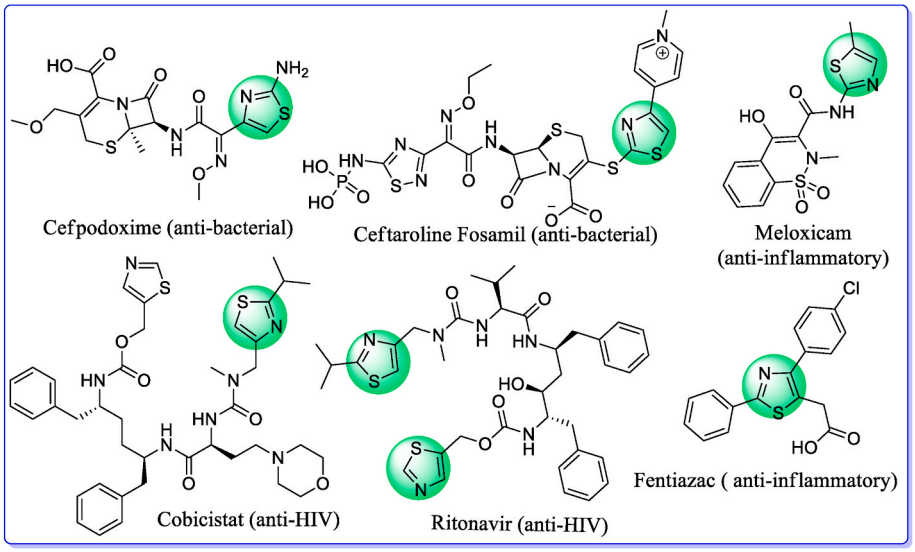


Fig. 1. Commercially available 2, 4-substituted thiazole-possessed drugs.

were clubbed through ethylidene-hydrazine linkage.

We report herein the designing, molecular docking and synthesis of 2,4-disubstituted thiazole derivatives containing quinoxaline moiety. All the hybrids were characterized by nuclear magnetic resonance (^{1}H and ^{13}C), FT-IR and mass spectroscopic techniques. Further, the prepared compounds were screened for antibacterial and antifungal activity. We found that they are significantly biologically active against some bacterial and fungal strains.

2. Materials and methods

All reagents, precursors and solvents used for synthesis were acquired from Sigma-Aldrich. The melting point of compounds was determined by the open capillary method and is uncorrected. The synthesized products were purified by column chromatography with the help of an appropriate solvent system. The characterization of hybrids was performed in SAIF, Panjab University, Panjab, India with the help of the Brucker-Advance Neo 500 MHz spectrometer for ^{1}H and ^{13}C NMR spectrum. The chemical shifts were reported in ppm relative to tetramethyl silane (TMS). The mass and FT-IR spectral analysis were taken by Waters Micromass Q-Tof Micro and Brucker FT-IR spectrometer respectively. The anti-microbial activity was examined in the Microcare Laboratory & Tuberculosis Research Centre, Surat, India.

2.1. Synthesis

2.1.1. General procedure for synthesis of 1-(3-methylquinoxalin-2-yl) ethanone (1a and 1b)

The compounds **1a** and **1b** were prepared by the reported procedure [72]. In this report, 2, 5-pentandione (1 mmol) was heated with *N*-bromosuccinimide (1.2 mmol) in water for 20 min at 70 °C to obtain 3-bromo-2,5-pentandione. To this reaction mixture, 1,2-phenylenediamine or 4,5-dimethyl-1,2-phenylenediamine was added and stirred at 70 °C for 4 h to obtain product **1a** or **1b** respectively. The TLC was performed to identify the completion of the reaction. Further, the product was extracted with ethyl acetate. The *n*-hexane-ethyl acetate (7:3 ratio) solvent system was used for the purification of products by the column chromatographic technique.

2.1.2. General procedure for synthesis of (E)-2-(1-hydrazonoethyl)-3-methylquinoxaline (QH)

The hydrazine hydrate (1 mmol) refluxed with compound **1a** (1 mmol) in ethanol with a catalytic amount of glacial acetic acid for 30 min. The formation of the product was confirmed by TLC. The solid product was obtained after the removal of solvent by vacuum evaporation. The *n*-hexane-ethyl acetate (7:3 ratio) solvent system was used in column chromatography for the purification of the product.

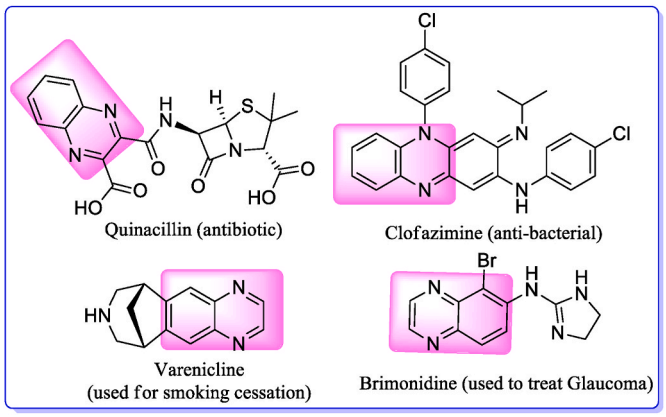


Fig. 3. Commercially available drugs included quinoxaline.

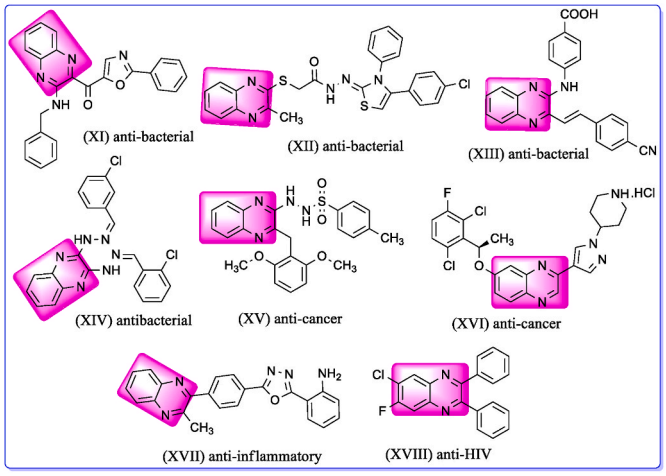


Fig. 4. Some biologically potent quinoxaline derivatives.

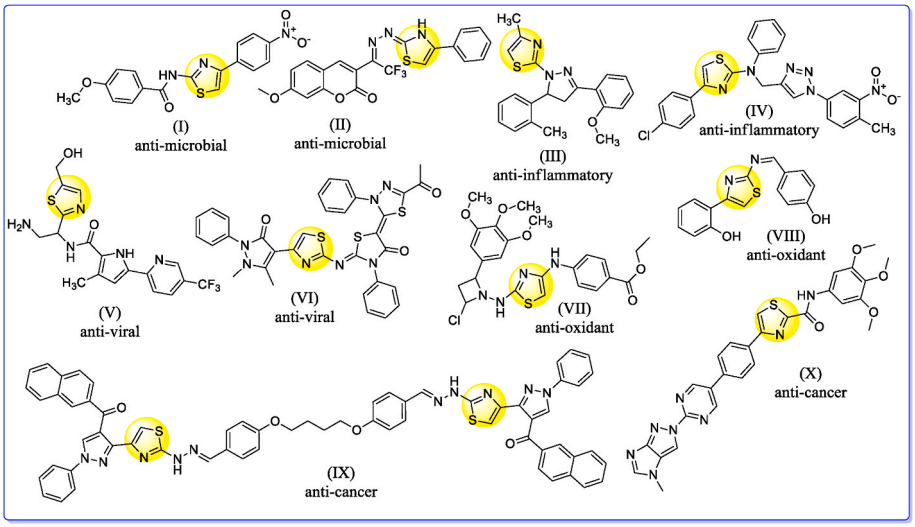


Fig. 2. Lead biologically active 2, 4-disubstituted thiazole derivatives.

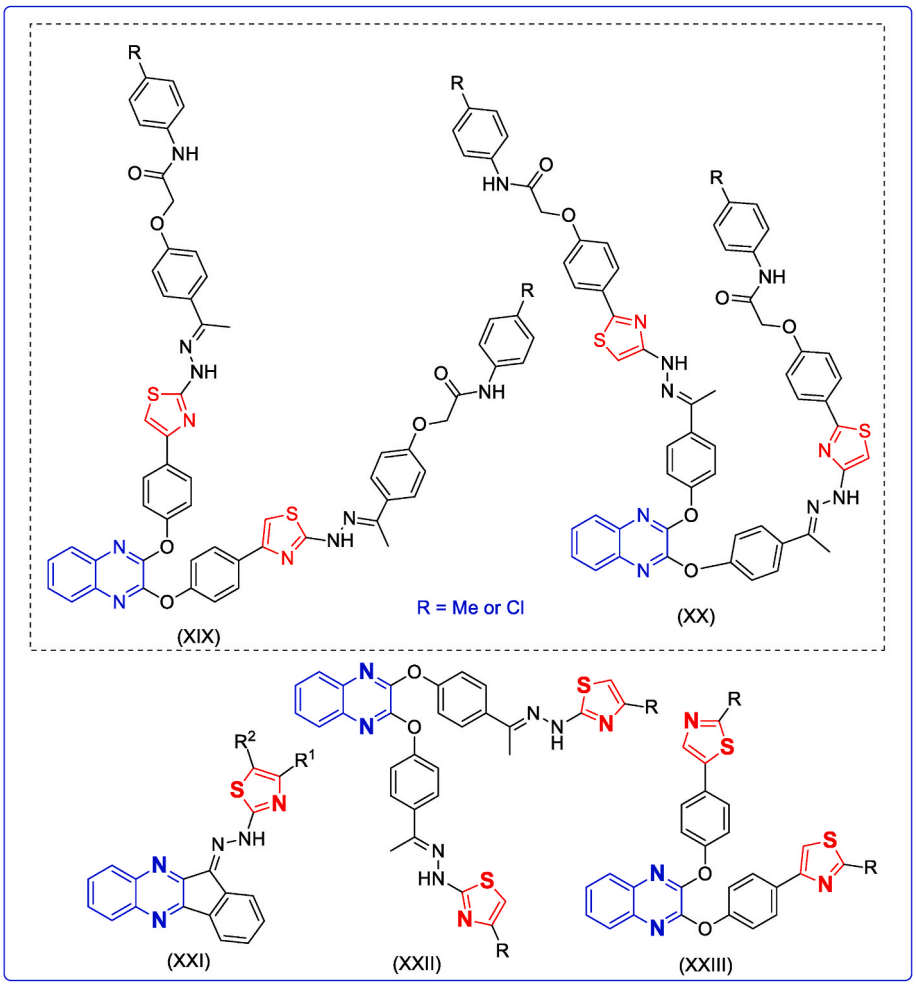


Fig. 5. Reported quinoxaline-thiazole derivatives.

2.1.3. General procedure for synthesis of (E)-2-(1-(3-methylquinoxalin-2-yl)ethylidene)hydrazinecarbothioamide derivatives (2a and 2b)

The compound **1a** or **1b** (1 mmol), thiosemicarbazide (1.1 mmol) and a few 2–3 drops of glacial acetic acid were dissolved in ethanol and refluxed for 4–5 h. The formation of the product was monitored by TLC. The product was separated after the addition of the reaction mixture in cold water. The filtered product was washed with water and the impure product was refined by column chromatographic technique.

2.1.4. General procedure for synthesis of (E)-2-(2-(1-(3-methylquinoxalin-2-yl)ethylidene)hydrazinyl)thiazole derivatives (3a-3j)

The compound **2a** or **2b** (1 mmol) was stirred in ethyl alcohol with 2-bromo-1-phenylethanone derivative (1 mmol) at room temperature for 4–5 h. Later on, the reaction mixture was poured on crushed ice to separate the product, which was filtered and the impure product was refined by column chromatographic technique. The details of synthesized molecules with substituents, yield and physical constant (m. p.) are given in Table 1. The route of synthesis of molecules **3a-3j** and **QH** is represented in Scheme 1.

2.2. Spectral analysis

2.2.1. (E)-2-(1-hydrazonoethyl)-3-methylquinoxaline (QH)

White solid; ^{1}H NMR (500 MHz, DMSO-d_6), δ(ppm): 2.24 (3H, s, –CH_3 C═N), 2.85 (3H, s, –CH_3 quinoxaline ring C-3), 7.99–7.91 (2H, m, quinoxaline), 7.74–7.70 (2H, m, quinoxaline), 7.10 (2H, s, –NH_2). M. W. = 200.2398, LCMS (*m/z*): 201.1229 (M^+).

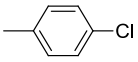
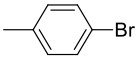
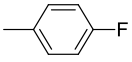
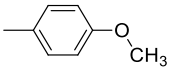
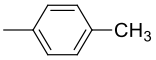
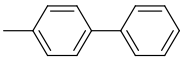
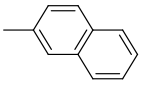
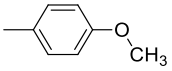
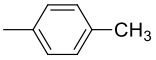
2.2.2. (E)-2-(2-(1-(3-methylquinoxalin-2-yl)ethylidene)hydrazinyl)-4-phenylthiazole (3a)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.50 (3H, s, –CH_3 C═N), 3.10 (3H, s, CH_3 quinoxaline ring C-3), 6.93 (1H, s, thiazole C-5), 7.30 (1H, t, J = 7.3 Hz, phenyl C-5), 7.40 (2H, t, J = 7.5 Hz, J = 7.7 Hz, phenyl C-3, C-5), 7.66–7.72 (2H, m, quinoxaline C-6, C-7), 7.81 (2H, d, J = 7.45 Hz, phenyl C-2, C-6), 8.00 (1H, dd, J = 1.1 Hz, J = 7 Hz, quinoxaline C-8), 8.02 (1H, dd, J = 1.1 Hz, J = 6.7 Hz, quinoxaline C-5), 9.28 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.93 (CH_3, C═N), 27.11 (CH_3, quinoxaline), 104.26 (CH, thiazole C-5), 127.96, 125.96, 128.20, 128.97, 129.11, 130.09, 134.40, 140.18, 140.57, 146.99 (C, thiazole C-4), 149.27 (C, C═N), 151.74, 153.28, 168.23 (C, thiazole C-2); IR, cm^{-1}: 3418.80 (N–H), 1566.60 (C═N), 1057 (N–N), 761.38 (C–S); M.W. = 359.45, LCMS (*m/z*): 360.0955 (M+).

2.2.3. (E)-4-(4-chlorophenyl)-2-(2-(1-(3-methylquinoxalin-2-yl) ethylidene)hydrazinyl)thiazole (3b)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.56 (3H, s, CH_3 C═N), 3.10 (3H, s, CH_3 quinoxaline C-3), 6.92(1H, s, thiazole C-5), 7.37 (2H, d, J = 8.5 Hz, phenyl C-3, C-5), 7.68–7.73(2H, m, quinoxaline C-6, C-7), 7.74 (2H, d, J = 8.5 Hz, phenyl C-2, C-6), 8.02 (1H, dd, J = 1.2 Hz, J = 9.1 Hz, quinoxaline C-8), 8.04 (1H, dd, J = 1.3 Hz, J = 9.2 Hz, quinoxaline C-5), 9.10(1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.90 (CH_3,C═N), 27.08 (CH_3 quinoxaline), 104.56 (CH, thiazole C-5), 127.20, 128.86, 128.21, 130, 128.98, 129.15, 133.15, 133.66, 140.17, 140.60, 147.10 (C, thiazole C-4), 153.25, 150.67, 149.17 (C, C═N), 168.24 (C, thiazole C-2); IR, cm^{-1}: 3335.95 (N–H),

Table 1
Yield and physical constant of QH and 3a-3j.

Entry	R^1	R^2	-Ar	Yield (%)	M. P. (°C)
QH	-H	-H	—	91	192–193
3a	-H	-H		85	221–223
3b	-H	-H		86	226–228
3c	-H	-H		84	215–217
3d	-H	-H		88	222–224
3e	-H	-H		91	218–219
3f	-H	-H		87	227–229
3g	-H	-H		84	228–230
3h	-H	-H		89	225–226
3i	$-CH_3$	$-CH_3$		88	252–254
3j	$-CH_3$	$-CH_3$		86	246–248

1552.45 (C═N), 1472, 1055 (N–N), 833.09 (C–Cl benzene), 750.31 (C–S thiazole); M.W. = 393.89, LCMS (*m/z*): 393.9734 (M+).

2.2.4. (E)-4-(4-bromophenyl)-2-(2-(1-(3-methylquinoxalin-2-yl) ethylidene)hydrazinyl)thiazole (3c)

Pale yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 3.07 (3H, s, CH_3, C═N), 3.17 (3H, s, CH_3 quinoxaline C-3), 6.93 (1H, s, thiazole C-5), 7.52 (2H, d, J = 8.5Hz, phenyl C-3, C-5), 7.69 (2H, d, J = 8.45Hz, phenyl C-2, C-6), 7.71–7.74 (2H, m, quinoxaline C-6, C-7), 8.0 (1H, dd, 1.05 Hz, J = 8.4 Hz, quinoxaline C-8), 8.04 (1H, dd, J = 1.0 Hz, J = 8.2 Hz, quinoxaline C-5), 8.875 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.96 (CH_3, C═N), 27.09 (CH_3 quinoxaline), 104.77 (CH, thiazole C-5), 131.93, 131.81, 133.59, 127.50, 128.21, 121.84, 128.99, 129.15, 131.93, 131.81, 140.18, 140.60, 147.14 (C, thiazole C-4), 149.18, 150.70, 153.23, 168.3 (C, thiazole C-2); IR, cm^{-1}: 3418.41 (N–H), 1555.53 (C═N), 1059 (N–N), 723.70 (C–Br), 765.37 (C–S); M. W. = 438.34, LCMS (*m/z*): 439.9812 (M+).

2.2.5. (E)-4-(4-fluorophenyl)-2-(2-(1-(3-methylquinoxalin-2-yl) ethylidene)hydrazinyl)thiazole (3d)

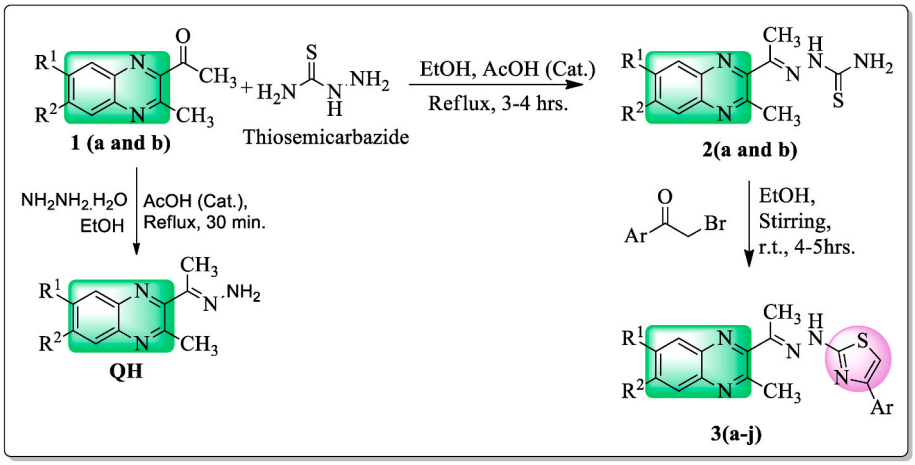
Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.54 (3H, s, CH_3 C═N), 3.10 (3H, s, CH_3 quinoxaline C-3), 6.86 (1H, s, thiazole C-5), 7.09 (2H, dd, J = 1.95 Hz, J = 8.4 Hz, phenyl C-3, C-5), 7.67–7.72 (2H, m, quinoxaline C-6, C-7), 7.78 (2H, dd, J = 2 Hz, J = 8.5 Hz, phenyl C-2, C-6), 8.01 (1H, dd, J = 1.15 Hz, J = 8.2 Hz, quinoxaline C-8), 8.03 (1H, dd, J = 1.2 Hz, J = 8.3 Hz, quinoxaline C-5), 9.11 (1H, s, N–H); ^{13}C NMR (500 MHz, CDCl3), δ(ppm): 12.94 (CH_3, C═N), 27.10 (CH_3, quinoxaline), 103.83 (CH, thiazole C-5), 115.51, 115.68, 127.63, 127.69, 128.19, 128.97, 129.13, 130.15, 130.93, 130.95, 140.16, 140.57, 147.09 (C, thiazole C-4), 149.20 (C═N), 150.80, 153.24, 163.59 (C–F, phenyl), 163.55 (C–F, Phenyl), 168.36 (C, thiazole C-2); IR, cm^{-1}: 3427.94 (N–H), 1561.72 (C═N), 1056 (N–N), 760.43 (C–S), 726.75 (C–F); M. W. = 377.44, LCMS (*m/z*): 378.0548 (M+).

2.2.6. (E)-4-(4-methoxyphenyl)-2-(2-(1-(3-methylquinoxalin-2-yl) ethylidene)hydrazinyl)thiazole (3e)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.48 (3H, s, CH_3, C═N), 3.10 (3H, s, CH_3 quinoxaline C-3), 3.81 (3H, s, OCH_3, phenyl), 6.92 (2H, d, J = 9.7 Hz, phenyl C-3, C-5), 6.79 (1H, s, thiazole C-5), 7.66–7.71 (2H, m, quinoxaline C-6, C-7), 7.74 (2H,d, J = 9.7 Hz, phenyl C-2, C-6), 7.99 (1H, dd, J = 1.15 Hz, J = 7.5 Hz, quinoxaline C-8), 8.02 (1H, dd, J = 1.2 Hz, J = 7.8 Hz, quinoxaline C-5), 9.32 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.94 (CH_3 C═N), 27.15 (CH_3, quinoxaline), 55 (-OCH_3 phenyl), 102.42 (CH, thiazole C-5), 114.06, 127.24, 127.63, 128.95, 129.06, 130.03, 140.16, 140.51, 146.30 (C, thiazole C-4), 149.94 (C, C═N), 151.53, 153.30, 159.46 (C–OCH_3), 168.36 (C, thiazole C-2); IR, cm^{-1}: 3364.21 (N–H), 1549.41 (C═N), 1243.11 (C–O), 1147.81 (O–CH3), 1058 (N–N), 759.76 (C–S); M. W. = 389.47, LCMS (*m/z*): 390.0885 (M+).

2.2.7. (E)-2-(2-(1-(3-methylquinoxalin-2-yl)ethylidene)hydrazinyl)-4-(p-tolyl)thiazole (3f)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.36 (3H, s, CH_3 phenyl C-4), 2.52 (3H, s, CH_3, C═N), 3.11 (3H, s, CH_3, quinoxaline C-3), 6.88 (1H, s, thiazole C-5), 7.21 (2H, d, J = 7.21 Hz, phenyl C-3, C-5),



Scheme 1. Synthesis of thiazole-quinoxaline derivatives (**3a-3j**) and **QH**.

7.68–7.72 (2H, m, quinoxaline C-6, C-7), 7.70 (2H, d, $J = 7.9$ Hz, phenyl C-2, C-6), 8.01 (1H, dd, $J = 1.1$ Hz, $J = 7.7$ Hz, quinoxaline C-8), 8.03 (1H, dd, $J = 1.2$ Hz, $J = 7.75$ Hz, quinoxaline C-4), 9.14 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.92 (CH_3, C═N), 21.25(CH_3, phenyl C-4), 27.14 (CH_3, quinoxaline), 103.44 (CH, thiazole C-5), 125.85, 128.18, 128.95, 129.07, 129.38, 130.04, 131.92, 137.78, 140.17, 140.53, 146.92 (C, thiazole C-4), 149.90 (C, C═N), 151.82, 153.30, 168.25 (C, thiazole C-2); IR, cm-1: 3369.96 (N–H), 1567.04 (C═N), 1057 (N–N), 757.85 (C–S); M. W. = 373.47, LCMS (*m/z*): 374.0600 (M+).

2.2.8. (E)-4-([1,1′-biphenyl]-4-yl)-2-(2-(1-(3-methylquinoxalin-2-yl) ethylidene)hydrazinyl)thiazole (3g)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.55 (3H, s, CH_3, C═N), 3.12 (3H, s, CH_3, quinoxaline C-3), 6.98 (1H, s, thiazole C-5), 7.34 (1H, t, $J = 7.4$ Hz, biphenyl C-8), 7.44 (2H, t, $J = 7.4$ Hz, $J = 7.8$ Hz, C-7, biphenyl C-9), 7.63 (2H, d, $J = 8.3$ Hz, biphenyl C-3, C-11), 7.67–7.74 (2H, m, quinoxaline C-6, C-7), 7.64 (2H, d, $J = 7.8$ Hz, biphenyl C-6, C-10), 7.88 (2H, d, $J = 8.3$ Hz, biphenyl C-2, C-12), 8.01 (1H, dd, $J = 1.45$ Hz, $J = 7.6$ Hz, quinoxaline C-8), 8.03 (1H, dd, $J = 1.15$ Hz, $J = 7.74$ Hz, quinoxaline C-5), 9.14 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.93 (CH_3, C═N), 27.12 (CH_3, quinoxaline), 104.34 (CH, thiazole C-5), 126.35, 126.99, 127.39, 128.22, 128.81, 128.99, 129.13, 130.12, 133.58, 140.19, 140.60, 140.65, 147.02 (C, thiazole C-4), 149.25 (C, C═N), 151.41, 153.29, 168.17 (C, thiazole C-2); IR, cm^{-1}: 3438.22 (N–H), 1568.50 (C═N), 1059 (N–N), 753.90 (C–S); M. W. = 435.54, LCMS (*m/z*): 436.2437 (M+).

2.2.9. (E)-2-(2-(1-(3-methylquinoxalin-2-yl)ethylidene)hydrazinyl)-4-(naphthalen-2-yl)thiazole (3h)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.53 (3H, s, CH_3 C═N), 3.12 (3H, s, CH_3 quinoxaline C-3), 7.05(1H, s, thiazole C-5), 7.43–7.47 (2H, m, naphthyl C-6, C-7), 7.67–7.73 (2H, m, quinoxaline C-6, C-7), 7.80 (1H, d, $J = 8.7$ Hz, naphthyl C-3), 7.85 (1H, d, $J = 8.7$ Hz, naphthyl C-4), 7.87–7.89 (2H, m, naphthyl C-5, C-8), 8.0 (1H, dd, $J = 1.9$ Hz, $J = 7.2$ Hz, quinoxaline C-8), 8.02 (1H, dd, $J = 1.6$ Hz, $J = 6.9$ Hz, quinoxaline C-5), 8.32 (1H, s, naphthyl C-1), 9.20 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.97 (CH_3, C═N), 27 (CH_3, quinoxaline), 104.81 (CH, thiazole C-5), 123.93, 124.9126.06 126.36, 127.68, 128.20, 128.36, 128.99, 129.11, 130.11, 131.87, 133.08, 133.63, 140.17, 140.57, 147.17 (C, thiazole C-4), 149.21 (C, C═N), 151.70, 153.23, 168.35 (C, thiazole C-2); IR, cm^{-1}: 3293.98 (N–H), 1563.43 (C═N), 1055 (N–N), 750.39 (C–S); M. W. = 409.51, LCMS (*m/z*): 410.2076 (M+).

2.2.10. (E)-4-(4-methoxyphenyl)-2-(2-(1-(3,6,7-trimethylquinoxalin-2-yl)ethylidene)hydrazinyl)thiazole (3i)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.4819 (3H, s, CH_3, quinoxaline C-7), 2.4899 (3H, s, CH_3, quinoxaline C-6), 2.54 (3H, s, CH_3 C═N), 3.06 (3H, s,CH_3, quinoxaline C-3), 3.84 (3H, s, –OCH_3, phenyl), 6.78 (1H, s, thiazole C-5), 6.93 (1H, s, quinoxaline C-8), 6.95 (1H, s, quinoxaline C-5), 7.74 (2H, d, $J = 9.2$ Hz, phenyl C-3, C-5), 7.77 (2H, d, $J = 9.2$ Hz, phenyl C-2, C-6), 8.9 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.91 (CH_3, C═N), 20.22 (-CH_3, quinoxaline C-7), 20.46 (CH_3, quinoxaline C-6), 26.95 (CH_3 quinoxaline C-4), 55.34 (OCH_3, Phenyl), 102.40 (CH, thiazole C-5), 114.06, 127.23, 127.38, 127.66, 128.03, 139.13, 139.46, 139.54, 140.72 (C, thiazole C-4), 148.42 (C, C═N), 152.25, 159.47, 168.18 (C, thiazole C-2); IR, cm^{-1}: 3399.44 (N–H), 1564.92 (C═N), 722.75 (C–S), 1060 (N–N); M. W. = 417.53, LCMS (*m/z*): 418.2182 (M+).

2.2.11. (E)-4-(p-tolyl)-2-(2-(1-(3,6,7-trimethylquinoxalin-2-yl) ethylidene)hydrazinyl)thiazole (3j)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 2.37 (3H, s), 2.4758 (3H, s, CH_3, quinoxaline C-7), 2.4841 (3H, s, CH_3, quinoxaline C-6), 2.52 (3H, s, CH_3, C═N), 3.06 (3H, s, CH_3, quinoxaline C-3), 6.8 (1H, s, thiazole C-5), 7.20 (1H, s, quinoxaline C-8), 7.21 (1H, s, quinoxaline C-5), 7.70 (2H, d, $J = 8.5$ Hz, C-3, phenyl C-5), 7.76 (2H, d, $J = 8.5$ Hz, phenyl C-2, C-6), 9.07 (1H, s, N–H); ^{13}C NMR (500 MHz, $CDCl_3$), δ(ppm): 12.93 (CH_3, C═N), 20.22 (CH_3, quinoxaline C-7), 20.45 (CH_3, quinoxaline C-7), 21.26 (CH_3, phenyl C-4), 26.96 (CH_3, quinoxaline C-4), 103.38 (CH, thiazole C-5), 125.84, 127.03, 128.37, 129.38, 131.96, 137.75, 139.12, 139.46, 139.53, 140.71, 147.13 (C═N), 148.41 (C, thiazole C-4), 151.76, 152.25, 168.21 (C, thiazole C-2); IR, cm^{-1}: 3399.44 (N–H), 1564.92 (C═N), 1060 (N–N), 722.75 (C–S); M. W. = 401.53, LCMS (*m/z*): 402.2121 (M+).

2.3. Antimicrobial activity assay

The *in vitro* antibacterial activity of **AT**, **QH** and **3a-3j** compounds was checked against *S. pyogenus* (MTCC442), *S. aureus* (MTCC96), *E. coli* (MTCC443) and *P. aeruginosa* (MTCC1688) bacterial strains using broth microdilution method [73] along with varied reference standards chloramphenicol, ciprofloxacin and norfloxacin. However, **AT**, **QH** and **3a-3j** molecules were examined for antifungal activity against *A. niger* (MTCC 282), *C. albicans* (MTCC 227) and *A. clavatus* (MTCC 1323) with reference standards griseofulvin and nystatin. The stock solution (2000 μg/mL) of each compound was prepared in dimethyl sulphoxide. Mueller Hinton Broth was used as a nutrient medium for the test bacteria. Ciprofloxacin, chloramphenicol, norfloxacin, griseofulvin and nystatin were used as a standard reference for positive control. The primary screening was carried out with 1000, 500 and 250 μg/mL diluted solutions. After primary screening, only active molecules were used for the secondary screening. The secondary screening was performed with diluted solutions with concentrations of 200, 100, 50, 25, 12.5 and 6.25 μg/mL. The minimal inhibitory concentration (MIC in μg/mL) for each synthesized molecule was measured by using the results of primary screening and secondary screening data.

2.4. Molecular docking

The molecular docking of molecules (ligands) and protein (PDB ID: 2XCT) was computed in AutoDock Vina software [74]. The twined 3.35A structure of *S. aureus* gyrase complex with ciprofloxacin and DNA (2XCT) [75] was downloaded from https://www.rcsb.org. in PDB file format. The structures of all molecules were drawn in Chem Draw ultra-software version 12.0.2 and further converted into PDB format by using open Babel software. The preparation of the protein and the ligand molecules with a grid box was carried out by using a standard protocol [76]. All prepared PDBQT format files were run in AutoDock Vina software to obtain binding affinity values for different stable conformations of the docked molecule (ligand) with the protein in the log file and output files in PDBQT format. All PDBQT format results obtained in AutoDock Vina software were visualized in Biovia Discovery Studio 2021 software for the interpretation of the ligand-protein interactions. All 3D and 2D images were saved in PNG format.

3. Results and discussion

3.1. Chemistry

The synthesis of proposed molecules **3a-3j** was performed in two steps (**Scheme-1**). In the first step, thiosemicarbazone (**2a-2b**) was obtained by refluxing ketone (**1a-1b**) with thiosemicarbazide in ethanol. Further, in the second step targeted molecules **3a-3j** were obtained by condensation and cyclisation of thiosemicarbazone (**2a-2b**) with 2-bromo-1-phenylethanone derivatives in ethanol at room temperature. (*E*)-2-(1-hydrazonoethyl)-3-methylquinoxaline (**QH**) was prepared by condensation of **1a** with hydrazine hydrate in ethanol (**Scheme-1**) further 4-(4-chlorophenyl)thiazol-2-amine (**AT**) was purchased from Sigma-Aldrich for the anti-microbial evaluation.

Synthesized hybrids (**3a-3j**) were confirmed by analysing the

spectral data produced by ^{1}H NMR, ^{13}C NMR, LCMS and FT-IR spectroscopic techniques. In ^{1}H NMR analysis, the methyl group attached to C-3 of electron-withdrawing quinoxaline ring appeared as a singlet in the range of δ 3.06–3.17 ppm while the other methyl group attached to C═N exhibited a singlet in the lower region of δ 2.36–3.07 ppm due to the conjugation of hydrazine group. The characteristic singlet signal of a proton at C-5 of the thiazole ring appeared in the range of δ 6.78–7.05 ppm. The proton of N–H in molecules showed a characteristic singlet signal in the region of δ 8.87–9.32 ppm. Aryl protons appeared between δ 6.68–8.02 ppm.

The ^{13}C NMR spectrum of molecules **3a-3j** revealed that $-CH_3$ of the hydrazone group exhibited a signal in the range of δ 12.90–12.98 ppm. The other $-CH_3$ attached to C-3 of the quinoxaline ring appeared in the range of δ 26.94–27.40 ppm. The carbon C-2 of the thiazole ring bonded to sulfur and two nitrogen atoms displayed a signal between δ 168.21–168.36 ppm. The peak of carbon C-4 of the thiazole appeared in the range of δ 146–147 ppm. The characteristic signal of –CH (C-5) of the thiazole ring displayed between δ 102.40–104.81 ppm while the carbon of the imine group which attached to C-2 of the quinoxaline ring and nitrogen exhibited a signal in the range of δ 147.13–149.94 ppm. The C═N stretching was detected in the FT-IR spectrum in the range of 1552.15–1567.04 cm^{-1}. The characteristic absorption band for N–H appeared in the range of 3293.98–3438.22 cm^{-1}. The structure of all products (**3a-3j**) was also supported by molecular ion peaks in mass spectroscopy.

3.2. Antimicrobial activity

The *in vitro* anti-bacterial and anti-fungal potential of newly synthesized molecules **AT**, **QH** and **3a-3j** were checked against bacterial strains (*S. pyogenus*, *S. aureus*, *E. coli* and *P. aeruginosa*) and fungal strains (*A. niger*, *C. albicans* and *A. clavatus*) by using broth microdilution method. The results of the anti-bacterial activity of the compounds (**AT**, **QH** and **3a-3j**) were evaluated using minimal inhibitory concentration (MIC) as shown in Table 2. The compounds (**AT**, **QH** and **3a-3j**) exhibited moderate to potent inhibition against all the tested bacterial strains. Compound **3b** showed the highest anti-bacterial activity (MIC = 12.5 μg/mL) against *S. aureus* than ciprofloxacin (MIC = 50 μg/mL) and chloramphenicol (MIC = 50 μg/mL), while exhibiting good anti-bacterial activity compared to with norfloxacin (MIC = 10 μg/mL). The molecules **3f** and **3i** exhibited good anti-bacterial activity (MIC = 50 μg/mL) against *S. aureus*. The anti-bacterial activity was decreased in the sequence of **3d**, **3a**, **3c**, **3e**, **3h**, **3g** and **3j** respectively. Similarly, molecule **3b** displayed good anti-bacterial activity (MIC = 25 μg/mL) against *P. aeruginosa* bacterial strain compared with reference drugs. The compounds **3c**, **3d**, **3f**, **3h** and **3i** showed moderate anti-bacterial activities against *P. aeruginosa*. The decreasing anti-bacterial potential order against *E. coli* strain was found that **3b**, **3d**, **3c**, **3i**, **3e**, **3g**, **3a**, **3h** and **3j** respectively. The molecule **3f** exhibited the highest anti-bacterial activity (MIC = 25 μg/mL) against *S. pyogenus* compared to ciprofloxacin (MIC = 50 μg/mL) and chloramphenicol (MIC = 50 μg/mL) as well as molecules **3a**, **3b** and **3i** exhibited good anti-bacterial potential against *S. pyogenus* bacterial strain. The MIC values for anti-bacterial activities elucidated that compound **3b** is a good antibacterial agent against *S. aureus, S. pyogenus, E. coli* and *P. aeruginosa* bacterial strains.

The MIC values of anti-fungal activity (shown in Table 3) displayed that compounds **3f** and **3g** exhibited good activity (MIC = 250 μg/mL) against C. albicans when compared to Griseofulvin (MIC = 500 μg/mL). The molecules **3g** and **3c** exhibited moderate anti-fungal activity (MIC = 500 μg/mL) against *A. clavatus* and *A. niger* but the rest of the compounds are not active for screened fungal strains.

4-(4-chlorophenyl)thiazol-2-amine (**AT**) and (*E*)-2-(1-hydrazonoethyl)-3-methylquinoxaline (**QH**) are two logical fragments of highly potent antibacterial compound **3b** (MIC = 12.5 μg/mL). Compound **AT** exhibited anti-bacterial activity in the range of MIC = 100–200 μg/mL, while compound **QH** displayed anti-bacterial activity in the range of MIC = 62.5–125 μg/mL against the tested bacterial strains (Table 2). This study revealed that the anti-bacterial activity of both fragments was boosted after the clubbing of thiazole and quinoxaline pharmacophores in the targeted molecule (**3b**).

3.3. Molecular docking

The DNA gyrase is an important enzyme for the replication of bacterial species [77]. The designing and synthesis of good inhibitors of *S. aureus* DNA gyrase are vital targets of many researchers [53,78–83]. The molecules **3b**, **3d**, **3f** and **3i** exhibited significant MIC values in the antibacterial evaluation, therefore the molecular docking of these molecules was performed with *S. aureus* DNA gyrase (PDB ID: 2XCT) by using AutoDock Vina software. The twined 3.35A structure of *S. aureus* gyrase complex with ciprofloxacin and DNA (2xct) is shown in Fig. 6. All images were visualized in Biovia Discovery Studio 2021 software. The result obtained by molecular docking of molecules **3b**, **3i**, **3f** and **3d** with *S. aureus* DNA gyrase is summarised in Table 4 and also represented in 3D and 2D images in Fig. 7.

In the molecular docking analysis of molecule **3b**, the most stable conformation was observed at the highest binding affinity −10.9 kcal/mol (Table 4). The methyl group attached to quinoxaline moiety displayed hydrophobic pi-sigma interaction in which C–H bonds of the methyl group interacted with pi-orbitals of adenine-H13 of DNA nucleotide by distance 3.71 Å. The pi orbital of sulfur of thiazole moiety interacted with pi orbitals of threonine-E8 and guanine-G9 of DNA by distances of 4.07 and 4.23 Å respectively. The pi orbital of the chlorine

Table 2
Antibacterial activities of synthesized compounds.

Entry	Bacterial Pathogens and their MIC values in μg/mL			
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*
AT	100	125	200	100
QH	62.5	100	100	125
3a	250	250	125	62.5
3b	50	25	12.5	62.5
3c	100	62.5	125	125
3d	62.5	125	100	250
3e	100	250	125	100
3f	125	100	50	25
3g	125	250	250	100
3h	250	100	125	100
3i	100	125	50	62.5
3j	250	500	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

Table 3
Antifungal activities of synthesized compounds.

Entry	Fungal Pathogens and their MIC values in μg/mL		
	C. albicans	*A. niger*	*A. clavatus*
AT	1000	1000	1000
QH	500	1000	1000
3a	1000	1000	1000
3b	1000	1000	1000
3c	500	500	1000
3d	500	1000	1000
3e	1000	1000	1000
3f	250	1000	1000
3g	250	500	500
3h	1000	1000	1000
3i	1000	1000	>1000
3j	500	1000	>1000
Nystatin	100	100	100
Griseofulvin	500	100	100

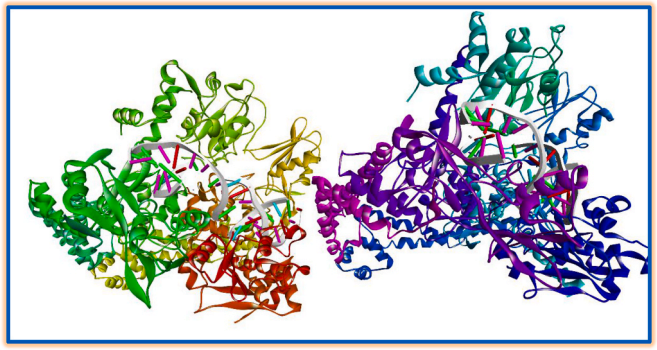


Fig. 6. Structure of twined 3.35A structure of *S. aureus* gyrase complex with ciprofloxacin and DNA (PDB: 2XCT).

atom of molecule 3b interacted with the alkyl group of phenylalanine-1123 residue of protein by a distance of 4.72 Å. The pi orbitals of quinoxaline moiety displayed hydrophobic pi-alkyl interactions with the alkyl group of arginine-458 by distances 4.33 and 4.81 Å. The hydrophobic pi-pi stacked interactions exhibited between pi-orbitals of thiazole moiety and pi orbitals of thymine-E8 of DNA with a distance of 3.82 Å.

In the molecular docking analysis of molecule **3i**, the most stable conformation was observed at the highest binding affinity −10.6 kcal/mol (Table 4). The pi-orbitals of quinoxaline moiety interacted with C–H of arginine 458 by distance 3.48 Å, while C–H bonds of methyl group attached to quinoxaline moiety (C-3) interacted with pi-orbitals of adenine-H13 of DNA by distance 3.66 Å. The pi-pi stacked type of interactions observed between pi-orbitals of quinoxaline and thiazole moieties with guanine-G9 of DNA by distance 4.97 and 5.37 Å, while thiazole moiety interacted with threonine-E8 by distance 3.95 Å. The pi-alkyl interactions established between the pi-orbitals of phenylalanine-1123 and the methyl group (C–H bond) of methoxy substituent by distance 4.95 Å and also between pi- orbitals of quinoxaline moiety and arginine-458 by distance 4.35 Å.

In the molecular docking analysis of molecule **3f**, the most stable docking conformation was observed at the highest binding affinity −10.4 kcal/mol (Table 4). In hydrophobic pi-alkyl interactions, pi-orbitals of phenylalanine-1123 and quinoxaline moiety interacted with the methyl group of the phenyl ring and the alkyl group of arginine-458 respectively by distance 4.76 and 4.34 Å. The hydrophobic pi-pi stacked interactions established between pi-orbitals thiazole moiety and thymine-E8 of DNA by a distance of 3.91 Å as well as between pi-orbitals of quinoxaline moiety and guanine-G9 of DNA by a distance 4.98 Å. The methyl group (C–H bonds) attached to quinoxaline moiety displayed pi-sigma hydrophobic interaction with pi-orbitals of adenine-H13 of DNA by a distance of 3.67 Å.

In the molecular docking analysis of molecule **3d**, the most stable conformation was observed at the highest binding affinity −10.3 kcal/mol (Table 4). The pi-orbitals of quinoxaline moiety displayed hydrophobic pi-alkyl interaction with the alkyl group of arginine-458 by a distance of 4.44 Å. The methyl group attached to quinoxaline moiety (C-3) displayed the pi-sigma hydrophobic interaction with pi-orbitals of adenine-H13 of DNA by a distance of 3.88 Å. The pi-orbital sulfur of thiazole moiety interacted with the pi-orbital of guanine-G9 of DNA by a distance of 3.93 Å. The hydrophobic pi-pi stacked interactions observed between the pi-orbital of thiazole moiety and pi-orbital of thymine-E8 of DNA (3.68 Å) as well as between the pi-orbital of thymine-E8 of DNA and pi-orbitals of phenyl ring (5.81 Å).

Both *in silico* and antibacterial studies of synthesized molecules confirmed the efficacy of our novel compound **3b**. The *in silico* data about the binding affinity between the ligand (compound **3b**) and target (DNA gyrase) was generated using the AutoDock vina docking platform. The docking analysis depicted a higher negative value for the binding affinity between the ligand and DNA complex, indicative of the stronger binding between the two. The binding affinity of compound **3b** (−10.9 kcal/mol) against various nitrogenous bases of DNA like adenine, thymine and guanine, is more profound for adenine-H13 (3.71 Å) and least for guanine-G9 (4.23 Å). The affinity and interactions of compound **3b** with various DNA bases suggest that the compound may bind to some of these and inhibit the replication process by creating topological changes in the DNA molecule. Also, the *in silico* analysis exhibited the affinity of compound **3b** for DNA gyrase, an ATP-dependent important bacterial enzyme (topoisomerase) that controls DNA topological transitions by catalysing negative super-coiling of double-stranded closed-circular DNA.

The strong inhibition of growth or doubling of *S. aureus* was evident

Table 4
Molecular docking analysis of 3b, 3i, 3f and 3d with *S. aureus* DNA gyrase.

Entry	Binding affinity (kcal/mol)	Type of interactions	Binding sites	Interaction Distance (Å)
3b	−10.9	pi-sigma	methyl group of quinoxaline (sigma) →Adenine- H13 (DNA) (pi)	3.71
		pi-sulfur	sulfur of thiazole → thymine-E8 (DNA) (pi)	4.07
			sulfur of thiazole → guanine-G9 (DNA) (pi)	4.23
		pi-pi stacked	thiazole (pi) → thymine-E8 (DNA) (pi)	3.82
		pi-alkyl	Cl atom (pi) → phenylalanine-1123 (alkyl)	4.72
			quinoxaline (pi) → arginine-458 (alkyl)	4.33, 4.81
3i	−10.6	pi-sigma	C–H bond of Argenine-458 (sigma) → quinoxaline (pi)	3.48
			methyl group of quinoxaline (sigma) → adenine-H13 (DNA) (pi)	3.66
		pi-pi stacked	guanine-G9 (DNA) (pi) → thiazole (pi)	5.37
			guanine-G9 (DNA) (pi) → quinoxaline (pi)	4.97
			thiazole (pi) → thymine-E8 (DNA) (pi)	3.95
		pi-alkyl	phenylalanine-1123 (pi)→ methyl of methoxy (alkyl)	4.95
			quinoxaline (pi) → Argentine-458 (alkyl)	4.35
3f	−10.4	pi-sigma	methyl group of quinoxaline (sigma) → Adenine-H13 (DNA) (pi)	3.67
		pi-pi stacked	thiazole (pi) → thymine-E8 (DNA) (pi)	3.91
			guanine-G9 (DNA) (pi) → quinoxaline (pi)	4.98
		pi-alkyl	phenylalanine-1123 (pi) → methyl group of phenyl ring (alkyl)	4.76
			quinoxaline (pi) → arginine-458 (alkyl)	4.34
3d	−10.3	pi-sigma	methyl group of quinoxaline (sigma) → adenine-H13 (DNA) (pi)	3.88
		pi-sulfur	sulfur of thiazole → guanine-G9 (DNA) (pi)	3.93
		pi-pi stacked	thiazole (pi) → thymine-E8 (DNA) (pi)	3.68
			thymine-E8 (DNA) (pi) → phenyl ring (pi)	5.81
		pi-alkyl	quinoxaline (pi) → arginine-458 (alkyl)	4.44

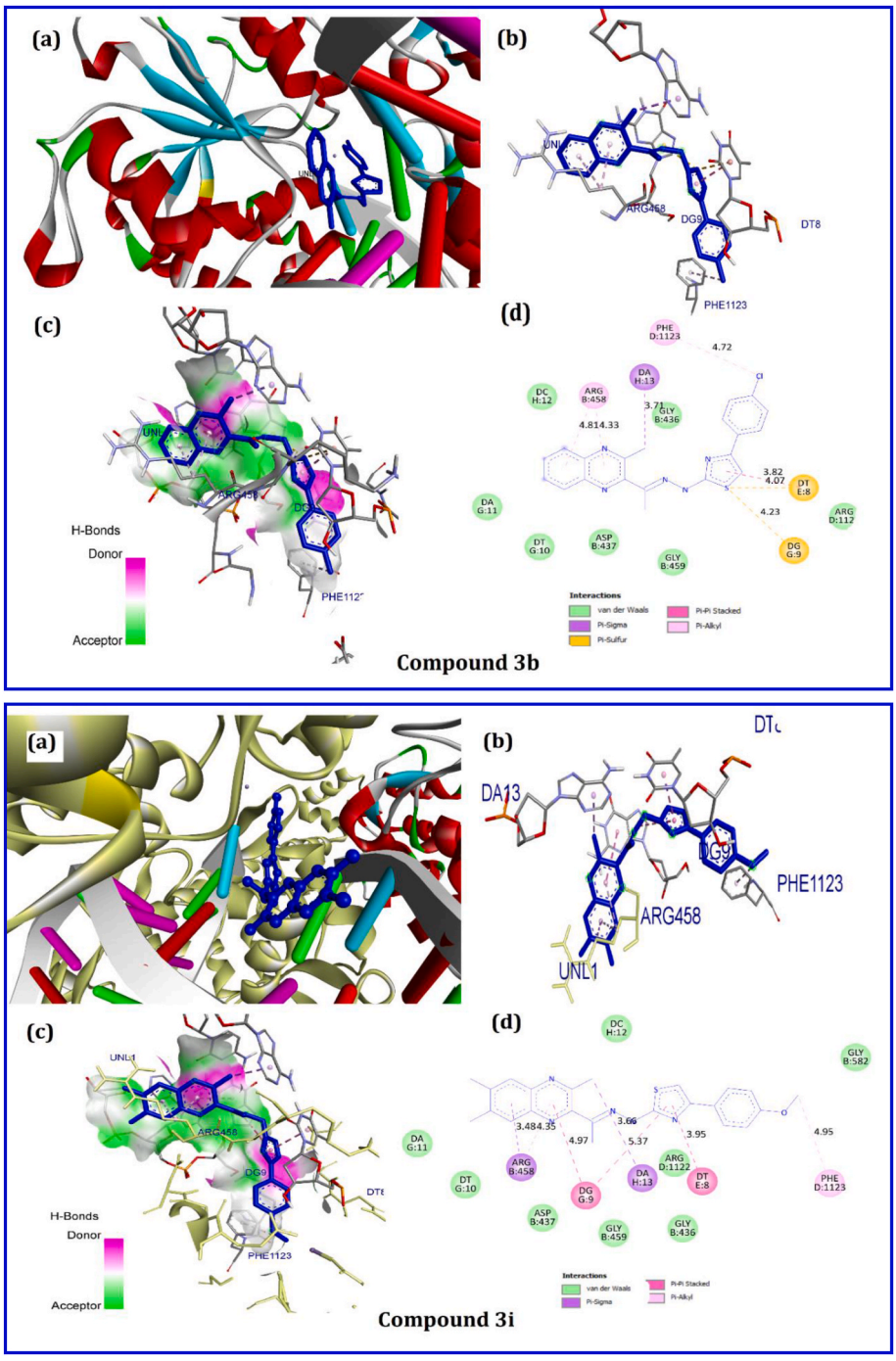


Fig. 7. Interactions showing in molecular docking of **3b**, **3i**, **3f** and **3d** with *S. aureus* DNA gyrase in 3D and 2D representation respectively **(a)** 3D ribbon-stick structure, **(b)** 3D stick structure, **(c)** 3D H-bond donor-acceptor structure and **(d)** 2D structure with interaction distance.

in the presence of **3b** (Table 2) as compared to the same bacterium without the compound, suggesting interference of compound **3b** in the replication process. In this way, the work proposes compound **3b** as a potent inhibitor of DNA replication either by binding to DNA bases directly or through blocking DNA gyrase.

Further, this study revealed that all docked molecules significantly interacted with adenine, thymine and guanine bases of DNA gyrase of *S. aureus* bacterial protein. The molecules **3i**, **3f** and **3d** showed −10.6, −10.4 and −10.3 kcal/mol (Table 4) binding affinities respectively. Therefore, molecules **3i**, **3f** and **3d** are also good inhibitors of *S. aureus* DNA gyrase.

4. Conclusion

A series of novel thiazole-quinoxaline hybrids were designed and synthesized efficiently. These newly synthesized molecules were characterized by spectroscopic techniques and evaluated for antibacterial as well as antifungal activities. Some derivatives show moderate to excellent activities against bacteria and fungi. Compound **3b** exhibited higher anti-bacterial activity such as MIC = 12.5, 25, 50 and 62.5 μg/mL against *S. aureus*, *P. aeruginosa, E. coli* and *S. pyogenus* respectively. The excellent anti-bacterial activity of compound **3b** makes it an attractive anti-bacterial candidate. The result showed that all reported hybrid

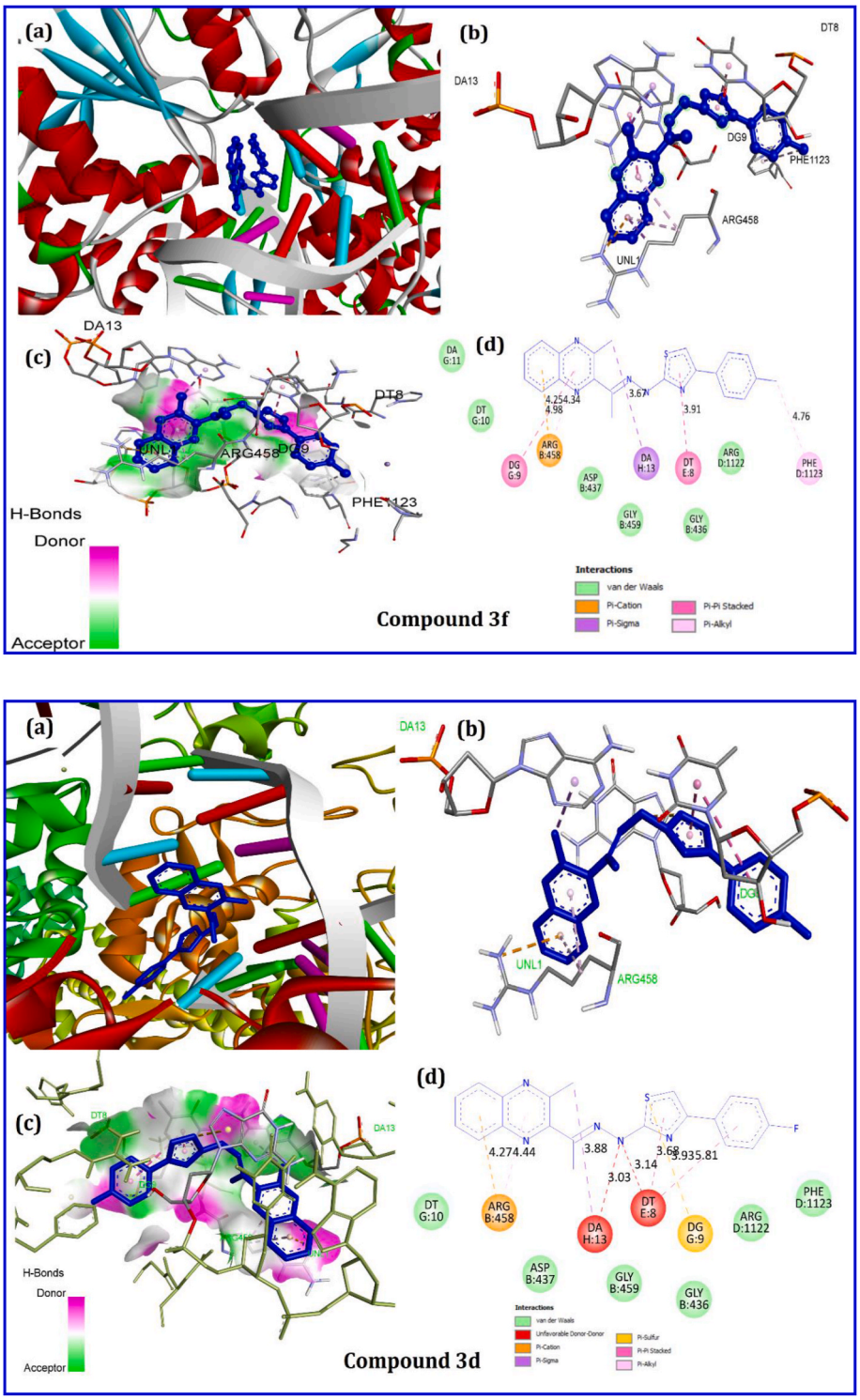


Fig. 7. (*continued*).

molecules are potentially active against *C. albicans*. Compounds **3c**, **3d**, and **3j** are equally potent (MIC = 500 μg/mL) while **3f** and **3g** are highly potent (MIC = 250 μg/mL) against *C. albicans* as compared to Griseofulvin (MIC = 500 μg/mL). The molecular docking study revealed that some synthesized derivatives significantly interacted with *S. aureus* DNA gyrase. The most stable conformation of compound **3b** showed higher binding affinity (−10.9 kcal/mol) with *S. aureus* DNA gyrase than that of **3i** (−10.6 kcal/mol), **3f** (−10.4 kcal/mol) and **3d** (−10.3 kcal/mol) compounds.

Availability of data and materials

The data supporting the findings of the article is available on www.figshare.com at https://figshare.com/s/37e533be4873553fa03c.

CRediT authorship contribution statement

Sagar Ramdas Shrimandilkar: Software, Methodology, Formal analysis. **Pravin Tatyaram Tryambake:** Writing – review & editing,

Supervision, Methodology. **Keshao Abasaheb Mahale:** Formal analysis, Data curation. **Dnyaneshwar Daulatrao Lokhande:** Writing – review & editing, Writing – original draft, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are thankful to the Principal of K. T. H. M. College, Nashik and the Principal of S. N. Arts, D. J. M. Commerce and B. N. S. Science College, Sangamner for providing facilities to conduct research. We are also thankful to the Director, SAIF, Panjab University, Chandigarh, India for providing a spectral analysis facility.

References

[1] N. Kerru, L. Gummidi, S. Maddila, K.K. Gangu, S.B. Jonnalagadda, A review on recent advances in nitrogen-containing molecules and their biological applications, Molecules 25 (2020), https://doi.org/10.3390/molecules25081909.
[2] M.M. Heravi, V. Zadsirjan, Prescribed drugs containing nitrogen heterocycles: an overview, RSC Adv. 10 (2020) 44247–44311, https://doi.org/10.1039/d0ra09198g.
[3] E. Kabir, M. Uzzaman, A review on biological and medicinal impact of heterocyclic compounds, Results Chem. 4 (2022), https://doi.org/10.1016/j.rechem.2022.100606.
[4] P.K. Sharma, A. Amin, M. Kumar, A review: medicinally important nitrogen sulphur containing heterocycles, Open Med. Chem. J. 14 (2020) 49–64, https://doi.org/10.2174/1874104502014010049.
[5] M.T. Sayed, S.A. Elsharabasy, A. Abdel-Aziem, Synthesis and antimicrobial activity of new series of thiazoles, pyridines and pyrazoles based on coumarin moiety, Sci. Rep. 13 (2023) 1–9, https://doi.org/10.1038/s41598-023-36705-0.
[6] S.I. Eissa, A.M. Farrag, S.Y. Abbas, M.F. El Shehry, A. Ragab, E.A. Fayed, Y. A. Ammar, Novel structural hybrids of quinoline and thiazole moieties: synthesis and evaluation of antibacterial and antifungal activities with molecular modeling studies, Bioorg. Chem. 110 (2021) 104803, https://doi.org/10.1016/j.bioorg.2021.104803.
[7] S.A. Ibrahim, H.F. Rizk, D.S. Aboul-Magd, A. Ragab, Design, synthesis of new magenta dyestuffs based on thiazole azomethine disperse reactive dyes with antibacterial potential on both dyes and gamma-irradiated dyed fabric, Dyes Pigments 193 (2021) 109504, https://doi.org/10.1016/j.dyepig.2021.109504.
[8] G. Yang, L. Shi, Z. Pan, L. Wu, L. Fan, C. Wang, C. Xu, J. Liang, The synthesis of coumarin thiazoles containing a trifluoromethyl group and their antifungal activities, Arab. J. Chem. 14 (2021) 102880, https://doi.org/10.1016/j.arabjc.2020.10.027.
[9] M.A. Kumar, T.N. Minh An, I.J. Lee, S. Park, K.D. Lee, Synthesis and bioactivity of novel phenothiazine-based thiazole derivatives, Phosphorus, Sulfur, Silicon Relat. Elem. 190 (2015) 1160–1168, https://doi.org/10.1080/10426507.2014.978324.
[10] N.D. Amnerkar, B.A. Bhongade, K.P. Bhusari, Synthesis and biological evaluation of some 4-(6-substituted-1,3-benzothiazol-2-yl)amino-1,3-thiazole-2-amines and their Schiff bases, Arab. J. Chem. 8 (2015) 545–552, https://doi.org/10.1016/j.arabjc.2014.11.034.
[11] S.J. Takate, A.D. Shinde, B.K. Karale, H. Akolkar, L. Nawale, D. Sarkar, P. C. Mhaske, Thiazolyl-pyrazole derivatives as potential antimycobacterial agents, Bioorg. Med. Chem. Lett 29 (2019) 1199–1202, https://doi.org/10.1016/j.bmcl.2019.03.020.
[12] K.M. Dawood, T.M.A. Eldebss, H.S.A. El-Zahabi, M.H. Yousef, Synthesis and antiviral activity of some new bis-1,3-thiazole derivatives, Eur. J. Med. Chem. 102 (2015) 266–276, https://doi.org/10.1016/j.ejmech.2015.08.005.
[13] A. Lamut, M. Gjorgjieva, L. Naesens, S. Liekens, K.E. Lillsunde, P. Tammela, D. Kikelj, T. Tomašič, Anti-influenza virus activity of benzo[d]thiazoles that target heat shock protein 90, Bioorg. Chem. 98 (2020) 103733, https://doi.org/10.1016/j.bioorg.2020.103733.
[14] E. Gürsoy, E.D. Dincel, L. Naesens, N. Ulusoy Güzeldemirci, Design and synthesis of novel Imidazo[2,1-b]thiazole derivatives as potent antiviral and antimycobacterial agents, Bioorg. Chem. 95 (2020) 103496, https://doi.org/10.1016/j.bioorg.2019.103496.
[15] S. Belveren, H. Ali Dondas, M. Ülger, S. Poyraz, E. García-Mingüens, M. Ferrándiz-Saperas, J.M. Sansano, Synthesis of highly functionalized 2-(pyrrolidin-1-yl) thiazole frameworks with interesting antibacterial and antimycobacterial activity, Tetrahedron 73 (2017) 6718–6727, https://doi.org/10.1016/j.tet.2017.10.007.
[16] X. Lu, X. Liu, B. Wan, S.G. Franzblau, L. Chen, C. Zhou, Q. You, Synthesis and evaluation of anti-tubercular and antibacterial activities of new 4-(2,6-dichlorobenzyloxy)phenyl thiazole, oxazole and imidazole derivatives. Part 2, Eur. J. Med. Chem. 49 (2012) 164–171, https://doi.org/10.1016/j.ejmech.2012.01.007.
[17] C.B. Scarim, F.R. Pavan, Thiazole, triazole, thio- and semicarbazone derivatives - promising moieties for drug development for the treatment of tuberculosis, Eur. J. Med. Chem. Rep. 1 (2021) 100002, https://doi.org/10.1016/j.ejmcr.2021.100002.
[18] M.E. Salem, E.M. Mahrous, E.A. Ragab, M.S. Nafie, K.M. Dawood, Synthesis of novel mono- and bis-pyrazolylthiazole derivatives as anti-liver cancer agents through EGFR/HER2 target inhibition, BMC Chem. 17 (2023) 1–17, https://doi.org/10.1186/s13065-023-00921-6.
[19] S.A. Audat, N.A. Al-Shar'i, B.A. Al-Oudat, S. Alnabulsi, Design, synthesis, and biological evaluation of SMYD3 inhibitors possessing N-thiazole benzenesulfonamide moiety as potential anti-cancer agents, J. Saudi Chem. Soc. 26 (2022) 101482, https://doi.org/10.1016/j.jscs.2022.101482.
[20] C.M. Bandaru, N. Poojith, S.S. Jadav, M.V. Basaveswara Rao, K.S. Babu, R. Sreenivasulu, R. Alluri, Design, synthesis, anticancer evaluation, and molecular docking studies of thiazole–pyrimidine linked amide derivatives, Polycycl. Aromat. Compd. 42 (2022) 5368–5384, https://doi.org/10.1080/10406638.2021.1939067.
[21] A.R. Oliveira, F.A. dos Santos, L.P. de L. Ferreira, M.G. da R. Pitta, M.V. de O. Silva, M.V. de O. Cardoso, A.F. Pinto, P. Marchand, M.J.B. de Melo Rêgo, A.C.L. Leite, Synthesis, anticancer activity and mechanism of action of new phthalimido-1,3-thiazole derivatives, Chem. Biol. Interact. 347 (2021), https://doi.org/10.1016/j.cbi.2021.109597.
[22] M. Modrić, M. Božičević, I. Faraho, M. Bosnar, I. Škorić, Design, synthesis and biological evaluation of new 1,3-thiazole derivatives as potential anti-inflammatory agents, J. Mol. Struct. 1239 (2021), https://doi.org/10.1016/j.molstruc.2021.130526.
[23] K.N. Ankali, J. Rangaswamy, M. Shalavadi, N. Naik, G. naik Krishnamurthy, Synthesis and molecular docking of novel 1,3-thiazole derived 1,2,3-triazoles and in vivo biological evaluation for their anti anxiety and anti inflammatory activity, J. Mol. Struct. 1236 (2021) 130357, https://doi.org/10.1016/j.molstruc.2021.130357.
[24] Z. Zhang, P. Cao, M. Fang, T. Zou, J. Han, Y. Duan, H. Xu, X. Yang, Q.S. Li, Design, synthesis, and SAR study of novel 4,5-dihydropyrazole-Thiazole derivatives with anti-inflammatory activities for the treatment of sepsis, Eur. J. Med. Chem. 225 (2021) 113743, https://doi.org/10.1016/j.ejmech.2021.113743.
[25] C.M. Moldovan, O. Oniga, A. Pârvu, B. Tiperciuc, P. Verite, A. Pîrnău, O. Crişan, M. Bojiţă, R. Pop, Synthesis and anti-inflammatory evaluation of some new acyl-hydrazones bearing 2-aryl-thiazole, Eur. J. Med. Chem. 46 (2011) 526–534, https://doi.org/10.1016/j.ejmech.2010.11.032.
[26] J.M. Bueno, M. Carda, B. Crespo, A.C. Cuñat, C. de Cozar, M.L. León, J.A. Marco, N. Roda, J.F. Sanz-Cervera, Design, synthesis and antimalarial evaluation of novel thiazole derivatives, Bioorg. Med. Chem. Lett 26 (2016) 3938–3944, https://doi.org/10.1016/j.bmcl.2016.07.010.
[27] C. Deng, H. Yan, J. Wang, B. shan Liu, K. Liu, Y. min Shi, The anti-HIV potential of imidazole, oxazole and thiazole hybrids: a mini-review, Arab. J. Chem. 15 (2022) 104242, https://doi.org/10.1016/j.arabjc.2022.104242.
[28] J.E. Frampton, R.N. Brogden, H.D. Langtry, M.M. Buckley, Cefpodoxime proxetil therapeutic potential, Drugs 44 (1992) 889–917.
[29] T. Welte, M. Kantecki, G.G. Stone, J. Hammond, Ceftaroline fosamil as a potential treatment option for Staphylococcus aureus community-acquired pneumonia in adults, Int. J. Antimicrob. Agents 54 (2019) 410–422, https://doi.org/10.1016/j.ijantimicag.2019.08.012.
[30] L. Xu, H. Liu, B.P. Murray, C. Callebaut, M.S. Lee, A. Hong, R.G. Strickley, L.K. Tsai, K.M. Stray, Y. Wang, G.R. Rhodes, M.C. Desai, Cobicistat (GS-9350): a potent and selective inhibitor of human CYP3A as a novel pharmacoenhancer, ACS Med. Chem. Lett. 1 (2010) 209–213, https://doi.org/10.1021/ml1000257.
[31] A.P. Lea, D. Faulds, Ritonavir: new drug profile, Drugs 52 (1996) 541–546.
[32] P. Arora, R. Narang, S. Bhatia, S.K. Nayak, S.K. Singh, B. Narasimhan, Synthesis, molecular docking and QSAR studies of 2, 4-disubstituted thiazoles as antimicrobial agents, J. Appl. Pharmaceut. Sci. 5 (2015) 28–42, https://doi.org/10.7324/JAPS.2015.50206.
[33] G. Yang, L. Shi, Z. Pan, L. Wu, L. Fan, C. Wang, C. Xu, J. Liang, The synthesis of coumarin thiazoles containing a trifluoromethyl group and their antifungal activities, Arab. J. Chem. 14 (2021), https://doi.org/10.1016/j.arabjc.2020.10.027.
[34] K.N. Ankali, J. Rangaswamy, M. Shalavadi, N. Naik, G. naik Krishnamurthy, Synthesis and molecular docking of novel 1,3-thiazole derived 1,2,3-triazoles and in vivo biological evaluation for their anti anxiety and anti inflammatory activity, J. Mol. Struct. 1236 (2021), https://doi.org/10.1016/j.molstruc.2021.130357.
[35] Z. Zhang, P. Cao, M. Fang, T. Zou, J. Han, Y. Duan, H. Xu, X. Yang, Q.S. Li, Design, synthesis, and SAR study of novel 4,5-dihydropyrazole-Thiazole derivatives with anti-inflammatory activities for the treatment of sepsis, Eur. J. Med. Chem. 225 (2021), https://doi.org/10.1016/j.ejmech.2021.113743.
[36] K.M. Dawood, T.M.A. Eldebss, H.S.A. El-Zahabi, M.H. Yousef, Synthesis and antiviral activity of some new bis-1,3-thiazole derivatives, Eur. J. Med. Chem. 102 (2015) 266–276, https://doi.org/10.1016/j.ejmech.2015.08.005.
[37] A.V. Kurkin, F. Curreli, I.R. Iusupov, E.A. Spiridonov, S. Ahmed, P.O. Markov, E. V. Manasova, A. Altieri, A.K. Debnath, Design, synthesis, and antiviral activity of the thiazole positional isomers of a potent HIV-1 entry inhibitor NBD-14270, ChemMedChem 17 (2022), https://doi.org/10.1002/cmdc.202200344.
[38] F. Lemilemu, M. Bitew, T.B. Demissie, R. Eswaramoorthy, M. Endale, Synthesis, antibacterial and antioxidant activities of Thiazole-based Schiff base derivatives: a combined experimental and computational study, BMC Chem. 15 (2021), https://doi.org/10.1186/s13065-021-00791-w.
[39] V. Jaishree, N. Ramdas, J. Sachin, B. Ramesh, In vitro antioxidant properties of new thiazole derivatives, J. Saudi Chem. Soc. 16 (2012) 371–376, https://doi.org/10.1016/j.jscs.2011.02.007.

[40] C.M. Bandaru, N. Poojith, S.S. Jadav, M.V. Basaveswara Rao, K.S. Babu, R. Sreenivasulu, R. Alluri, Design, synthesis, anticancer evaluation, and molecular docking studies of thiazole–pyrimidine linked amide derivatives, Polycycl. Aromat. Compd. 42 (2022) 5368–5384, https://doi.org/10.1080/10406638.2021.1939067.

[41] M.E. Salem, E.M. Mahrous, E.A. Ragab, M.S. Nafie, K.M. Dawood, Synthesis of novel mono- and bis-pyrazolylthiazole derivatives as anti-liver cancer agents through EGFR/HER2 target inhibition, BMC Chem. 17 (2023), https://doi.org/10.1186/s13065-023-00921-6.

[42] D. Dewangan, K. Nakhate, A. Mishra, A.S. Thakur, H. Rajak, J. Dwivedi, S. Sharma, S. Paliwal, Design, synthesis, and characterization of quinoxaline derivatives as a potent antimicrobial agent, J. Heterocycl. Chem. 56 (2019) 566–578, https://doi.org/10.1002/jhet.3431.

[43] A.M. Omar, M. Alswah, H.E.A. Ahmed, A.H. Bayoumi, K.M. El-Gamal, A. El-Morsy, A. Ghiaty, T.H. Afifi, F.F. Sherbiny, A.S. Mohammed, B.A. Mansour, Antimicrobial screening and pharmacokinetic profiling of novel phenyl-[1,2,4]triazolo[4,3-a] quinoxaline analogues targeting DHFR and E. coli DNA gyrase B, Bioorg. Chem. 96 (2020) 103656, https://doi.org/10.1016/j.bioorg.2020.103656.

[44] D. Dewangan, K.T. Nakhate, V.S. Verma, K. Nagori, H. Badwaik, N. Nair, D. K. Tripathi, A. Mishra, Synthesis and molecular docking study of novel hybrids of 1,3,4-oxadiazoles and quinoxaline as a potential analgesic and anti-inflammatory agents, J. Heterocycl. Chem. 55 (2018) 2901–2910, https://doi.org/10.1002/jhet.3363.

[45] S. Tariq, O. Alam, M. Amir, Synthesis, anti-inflammatory, p38α MAP kinase inhibitory activities and molecular docking studies of quinoxaline derivatives containing triazole moiety, Bioorg. Chem. 76 (2018) 343–358, https://doi.org/10.1016/j.bioorg.2017.12.003.

[46] N.A. Alsaif, M.S. Taghour, M.M. Alanazi, A.J. Obaidullah, W.A. Alanazi, A. Alasmari, H. Albassam, M.A. Dahab, H.A. Mahdy, Identification of new [1,2,4] triazolo[4,3-a]quinoxalines as potent VEGFR-2 tyrosine kinase inhibitors: design, synthesis, anticancer evaluation, and in silico studies, Bioorg. Med. Chem. 46 (2021) 116384, https://doi.org/10.1016/j.bmc.2021.116384.

[47] N.A. Alsaif, M.A. Dahab, M.M. Alanazi, A.J. Obaidullah, A.A. Al-Mehizia, M. M. Alanazi, S. Aldawas, H.A. Mahdy, H. Elkady, New quinoxaline derivatives as VEGFR-2 inhibitors with anticancer and apoptotic activity: design, molecular modeling, and synthesis, Bioorg. Chem. 110 (2021) 104807, https://doi.org/10.1016/j.bioorg.2021.104807.

[48] K. El-Adl, H.M. Sakr, R.G. Yousef, A.B.M. Mehany, A.M. Metwaly, M.A. Elhendawy, M.M. Radwan, M.A. ElSohly, H.S. Abulkhair, I.H. Eissa, Discovery of new quinoxaline-2(1H)-one-based anticancer agents targeting VEGFR-2 as inhibitors: design, synthesis, and anti-proliferative evaluation, Bioorg. Chem. 114 (2021) 105105, https://doi.org/10.1016/j.bioorg.2021.105105.

[49] L.M. Wilhelmsson, N. Kingi, J. Bergman, Interactions of antiviral indolo[2,3-b] quinoxaline derivatives with DNA, J. Med. Chem. 51 (2008) 7744–7750, https://doi.org/10.1021/jm800787b.

[50] E. De Clercq, Toward improved anti-HIV chemotherapy: therapeutic strategies for intervention with HIV infections, J. Med. Chem. 38 (1995) 2491–2517, https://doi.org/10.1021/jm00014a001.

[51] S.B. Patel, B.D. Patel, C. Pannecouque, H.G. Bhatt, Design, synthesis and anti-HIV activity of novel quinoxaline derivatives, Eur. J. Med. Chem. 117 (2016) 230–240, https://doi.org/10.1016/j.ejmech.2016.04.019.

[52] Z. Ahmed, B. Munshi, M.H. Shaikh, Antibacterial Activity of Novel 1-Cyclopropyl-6 , 7-Difluoro-8-, 2023, pp. 1–12.

[53] R.H.H. Salih, A.H. Hasan, N.H. Hussen, F.E. Hawaiz, T. Ben Hadda, J. Jamalis, F. A. Almalki, A.S. Adeyinka, L.C.C. Coetzee, A.K. Oyebamiji, Thiazole-pyrazoline hybrids as potential antimicrobial agent: synthesis, biological evaluation, molecular docking, DFT studies and POM analysis, J. Mol. Struct. 1282 (2023), https://doi.org/10.1016/j.molstruc.2023.135191.

[54] Y. Pan, P. Li, S. Xie, Y. Tao, D. Chen, M. Dai, H. Hao, L. Huang, Y. Wang, L. Wang, Z. Liu, Z. Yuan, Synthesis, 3D-QSAR analysis and biological evaluation of quinoxaline 1,4-di-N-oxide derivatives as antituberculosis agents, Bioorg. Med. Chem. Lett 26 (2016) 4146–4153, https://doi.org/10.1016/j.bmcl.2016.01.066.

[55] R. Peraman, R. Kuppusamy, S.K. Killi, Y.P. Reddy, New conjugates of quinoxaline as potent antitubercular and antibacterial agents, Int J Med Chem 2016 (2016) 1–8, https://doi.org/10.1155/2016/6471352.

[56] M. Missioui, S. Mortada, W. Guerrab, G. Serdaroğlu, S. Kaya, J.T. Mague, E. M. Essassi, M.E.A. Faouzi, Y. Ramli, Novel antioxidant quinoxaline derivative: synthesis, crystal structure, theoretical studies, antidiabetic activity and molecular docking study, J. Mol. Struct. 1239 (2021), https://doi.org/10.1016/j.molstruc.2021.130484.

[57] M.V.K. Reddy, K.Y. Rao, G. Anusha, G.M. Kumar, A.G. Damu, K.R. Reddy, N. P. Shetti, T.M. Aminabhavi, P.V.G. Reddy, In-vitro evaluation of antioxidant and anticholinesterase activities of novel pyridine, quinoxaline and s-triazine derivatives, Environ. Res. 199 (2021) 111320, https://doi.org/10.1016/j.envres.2021.111320.

[58] L. Bonilla-Ramirez, A. Rios, M. Quiliano, G. Ramirez-Calderon, I. Beltrán-Hortelano, J.F. Franetich, L. Corcuera, M. Bordessoulles, A. Vettorazzi, A. López de Cerain, I. Aldana, D. Mazier, A. Pabón, S. Galiano, Novel antimalarial chloroquine- and primaquine-quinoxaline 1,4-di-N-oxide hybrids: design, synthesis, Plasmodium life cycle stage profile, and preliminary toxicity studies, Eur. J. Med. Chem. 158 (2018) 68–81, https://doi.org/10.1016/j.ejmech.2018.08.063.

[59] J.L. Arbiser, S.L. Moschella, Clofazimine: a review of its medical uses and mechanisms of action, J. Am. Acad. Dermatol. 32 (1995) 241–247, https://doi.org/10.1016/0190-9622(95)90134-5.

[60] P.M. Cinciripini, J.A. Minnix, C.E. Green, J.D. Robinson, J.M. Engelmann, F. Versace, D.W. Wetter, S. Shete, M. Karam-Hage, An RCT with the combination of varenicline and bupropion for smoking cessation: clinical implications for front line use, Addiction 113 (2018) 1673–1682, https://doi.org/10.1111/add.14250.

[61] A. Keivanloo, S. Abbaspour, S. Sepehri, M. Bakherad, Synthesis, antibacterial activity and molecular docking study of a series of 1,3-oxazole-quinoxaline amine hybrids, Polycycl. Aromat. Comp. 42 (2022) 2378–2391, https://doi.org/10.1080/10406638.2020.1833052.

[62] M.A.Z. El-Attar, R.Y. Elbayaa, O.G. Shaaban, N.S. Habib, A.E. Abdel Wahab, I. A. Abdelwahab, S.A.M. El-Hawash, Design, synthesis, antibacterial evaluation and molecular docking studies of some new quinoxaline derivatives targeting dihyropteroate synthase enzyme, Bioorg. Chem. 76 (2018) 437–448, https://doi.org/10.1016/j.bioorg.2017.12.017.

[63] H.M. Patel, V. Bhardwaj, P. Sharma, M.N. Noolvi, S. Lohan, S. Bansal, A. Sharma, Quinoxaline-PABA bipartite hybrid derivatization approach: design and search for antimicrobial agents, J. Mol. Struct. 1184 (2019) 562–568, https://doi.org/10.1016/j.molstruc.2019.02.074.

[64] D. Dewangan, K. Nakhate, A. Mishra, A.S. Thakur, H. Rajak, J. Dwivedi, S. Sharma, S. Paliwal, Design, synthesis, and characterization of quinoxaline derivatives as a potent antimicrobial agent, J. Heterocycl. Chem. 56 (2019) 566–578, https://doi.org/10.1002/jhet.3431.

[65] J. Lin, P. Wang, Z. Zhang, G. Xue, D. Zha, J. Wang, X. Xu, Z. Li, Facile synthesis and anti-proliferative activity evaluation of quinoxaline derivatives, Synth. Commun. 50 (2020) 823–830, https://doi.org/10.1080/00397911.2020.1714054.

[66] S.C. Kim, P.R. Boggu, H.N. Yu, S.Y. Kim, J.M. Jung, Y.S. Kim, G.M. Park, S.H. Ma, I. S. Kim, Y.H. Jung, Synthesis and biological evaluation of quinoxaline derivatives as specific c-Met kinase inhibitors, Bioorg. Med. Chem. Lett 30 (2020), https://doi.org/10.1016/j.bmcl.2020.127189.

[67] D. Dewangan, K.T. Nakhate, V.S. Verma, K. Nagori, H. Badwaik, N. Nair, D. K. Tripathi, A. Mishra, Synthesis and molecular docking study of novel hybrids of 1,3,4-oxadiazoles and quinoxaline as a potential analgesic and anti-inflammatory agents, J. Heterocycl. Chem. 55 (2018) 2901–2910, https://doi.org/10.1002/jhet.3363.

[68] S.B. Patel, B.D. Patel, C. Pannecouque, H.G. Bhatt, Design, synthesis and anti-HIV activity of novel quinoxaline derivatives, Eur. J. Med. Chem. 117 (2016) 230–240, https://doi.org/10.1016/j.ejmech.2016.04.019.

[69] M.E. Salem, A.H. Abdullah, N.S. Ibrahim, M.E.A. Zaki, A.H.M. Elwahy, I. A. Abdelhamid, Novel scaffolds based on bis-thiazole connected to quinoxaline or thienothiophene through 2-phenoxy- N -arylacetamide groups as new hybrid molecules: synthesis, antibacterial activity, and molecular docking investigations, ACS Omega (2023), https://doi.org/10.1021/acsomega.3c07125.

[70] A.M. Abdallah, S.M. Gomha, M.E.A. Zaki, T.Z. Abolibda, N.A. Kheder, A green synthesis, DFT calculations, and molecular docking study of some new indeno[2,1-b]quinoxalines containing thiazole moiety, J. Mol. Struct. 1292 (2023), https://doi.org/10.1016/j.molstruc.2023.136044.

[71] M.E. Salem, M.S. Qenawy, A.M. Farag, A.H.M. Elwahy, Synthesis of novel scaffolds based on bis-thiazole or bis-triazolothiadiazine linked to quinoxaline as new hybrid molecules, Synth. Commun. 53 (2023) 103–118, https://doi.org/10.1080/00397911.2022.2153338.

[72] B.S.P. Anil Kumar, B. Madhav, K. Harsha Vardhan Reddy, Y.V.D. Nageswar, Quinoxaline synthesis in novel tandem one-pot protocol, Tetrahedron Lett. 52 (2011) 2862–2865, https://doi.org/10.1016/j.tetlet.2011.03.110.

[73] D.C. Dieterich, J.J. Lee, A.J. Link, J. Graumann, D.A. Tirrell, E.M. Schuman, Labeling , Detection and Identification of Newly Synthesized Proteomes with Bioorthogonal Non-canonical Amino-Acid Tagging, 2007, pp. 2–10, https://doi.org/10.1038/nprot.2007.52.

[74] A. Allouche, Software news and updates gabedit — a graphical user interface for computational Chemistry softwares, J. Comput. Chem. 32 (2012) 174–182, https://doi.org/10.1002/jcc.

[75] B.D. Bax, P.F. Chan, D.S. Eggleston, A. Fosberry, D.R. Gentry, F. Gorrec, I. Giordano, M.M. Hann, A. Hennessy, M. Hibbs, J. Huang, E. Jones, J. Jones, K. K. Brown, C.J. Lewis, E.W. May, M.R. Saunders, O. Singh, C.E. Spitzfaden, C. Shen, A. Shillings, A.J. Theobald, A. Wohlkonig, N.D. Pearson, M.N. Gwynn, Type IIA topoisomerase inhibition by a new class of antibacterial agents, Nature 466 (2010) 935–940, https://doi.org/10.1038/nature09197.

[76] S. Forli, R. Huey, M.E. Pique, M.F. Sanner, D.S. Goodsell, A.J. Olson, Computational protein-ligand docking and virtual drug screening with the AutoDock suite, Nat. Protoc. 11 (2016) 905–919, https://doi.org/10.1038/nprot.2016.051.

[77] R.J. Reece, A. Maxwell, J.C. Wang, DNA gyrase: structure and function, Crit. Rev. Biochem. Mol. Biol. 26 (1991) 335–375, https://doi.org/10.3109/10409239109114072.

[78] P. Tiwari, S. Phadte, S. Chandavarkar, B. Biradar, S. Mamle Desai, Design, synthesis and characterization of a series of 6-substituted-4-hydroxy-1-(2-substitutedthiazol-4-yl)quinolin-2(1H)-one derivatives and evaluation of their in vitro anticancer and antibacterial activity, J. Indian Chem. Soc. 100 (2023), https://doi.org/10.1016/j.jics.2023.100951.

[79] G. Venkateswara Rao, T.R. Allaka, M.K. Gandla, P.K. Veera Venkata Nanda, S. R. Pindi, P.R.R. Vaddi, H.B. Bollikolla, Synthesis, antimicrobial activity, and in silico studies of fluoroquinolones bearing 1,3,4-oxadiazolyl-triazole derivatives, J. Heterocycl. Chem. (2023) 1666–1683, https://doi.org/10.1002/jhet.4700.

[80] H.H.H. Mohammed, D.M.E. Ali, M. Badr, A.G.K. Habib, A.M. Mahmoud, S. M. Farhan, S.S.H.A. El Gany, S.A. Mohamad, A.M. Hayallah, S.H. Abbas, G.E.D. A. Abuo-Rahma, Synthesis and molecular docking of new N4-piperazinyl ciprofloxacin hybrids as antimicrobial DNA gyrase inhibitors, Mol. Divers. 27 (2023) 1751–1765, https://doi.org/10.1007/s11030-022-10528-z.

[81] H.A. Mohamed, Y.A. Ammar, G.A.M. Elhagali, H.A. Eyada, D.S. Aboul-Magd, A. Ragab, Discovery a novel of thiazolo[3,2-a]pyridine and pyrazolo[3,4-d]

thiazole derivatives as DNA gyrase inhibitors; design, synthesis, antimicrobial activity, and some in-silico ADMET with molecular docking study, J. Mol. Struct. 1287 (2023), https://doi.org/10.1016/j.molstruc.2023.135671.

[82] I. Waziri, M.T. Kelani, M.O. Oyedeji-Amusa, A.K. Oyebamiji, L.C.C. Coetzee, A. S. Adeyinka, A.J. Muller, Synthesis and computational investigation of N,N-dimethyl-4-[(Z)-(phenylimino)methyl]aniline derivatives: biological and quantitative structural activity relationship studies, J. Mol. Struct. 1276 (2023), https://doi.org/10.1016/j.molstruc.2022.134756.

[83] A. Ragab, D.M. Elsisi, O.A. Abu Ali, M.S. Abusaif, A.A. Askar, A.A. Farag, Y. A. Ammar, Design, synthesis of new novel quinoxalin-2(1H)-one derivatives incorporating hydrazone, hydrazine, and pyrazole moieties as antimicrobial potential with in-silico ADME and molecular docking simulation, Arab. J. Chem. 15 (2022) 103497, https://doi.org/10.1016/j.arabjc.2021.103497.