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ARTICLE

Synthesis, antimicrobial screening, and docking study of new 2-(2-ethylpyridin-4-yl)-4-methyl-*N*-phenylthiazole-5-carboxamide derivatives

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Abstract

A series of new 2-(2-ethylpyridin-4-yl)-4-methyl-*N*-phenylthiazole-5-carboxamide derivatives (**5a-l**) were synthesized and evaluated for their in vitro antimicrobial activities. Among the screened compounds, **5b**, **5d**, **5e**, **5f,** and **5j** have shown promising antimicrobial activities against both bacterial and fungal pathogens. A molecular docking study was conducted to know the probable mode of action of synthesized derivatives for antimicrobial activity. The active compounds have shown excellent binding affinity toward *DNA gyrase* and *lumazine synthase* enzymes. The physicochemical properties of the synthesized thiazole-carboxamide derivatives were calculated. It has displayed the potential to be a reasonable oral bioavailability drug as determined by Lipinski's rule.

KEYWORDS

ADME prediction, antimicrobial activity, carboxamide, docking study, thiazole

1 | INTRODUCTION

Antimicrobial resistance has become the most challenging issue for worldwide researchers.[1] According to the World Health Organization, every day, thousands of peoples are dying due to microbial infections.[2] Hence, it has become a serious problem for human health. There are many reasons for antimicrobial resistance. Of the reasons, mutation in genetic material, transfer of drug-resistant genes from one microbe to another, replication and spreading of survivor-resistant strains,[3] improper use of antibiotics in viral infection, improper diagnosis referring broad-spectrum antibiotic over a narrow-spectrum antibiotic, not finishing the complete course, overuse of antibiotics,[4] and insanitary environment[5] have enhanced the increase in resistance.[6] The use of broad-spectrum antibiotics can leads to undesirable disturbances to the microbiota, which has important roles in various features of human biology.[7] The innovation of antimicrobial agents with a unique model of action is essential for the clinical management of bacterial infections.[8]

Thiazoles are sulfur- and nitrogen-containing five-membered heterocyclic compounds. Their derivatives have played an important role in medicinal and pharmaceutical chemistry. They have potential biological

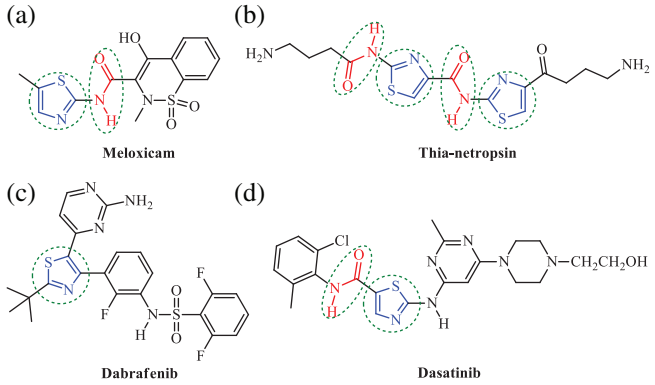
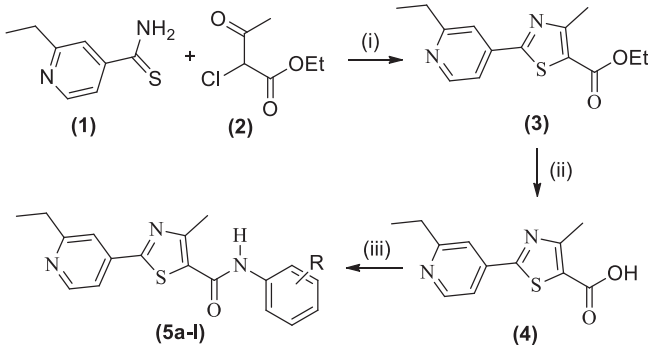


FIGURE 1 Representative drugs containing thiazole and carboxamide moiety



SCHEME 1 *Reaction Conditions*: (a) EtOH, reflux, 5 hr (90%); (b) LiOH·H_2O, THF + MeOH, rt, 3 hr (95%); (c) Amines, EDC·HCl, HOBt, DMF, 0-rt, 10–12 hr (82–90%)

activities such as anticancer,[9] antitubercular,[10] α-glucosidase inhibitor,[11] antioxidant,[12] antibacterial,[13] anti-inflammatory,[14] anti-Candida activity[15] and photo protection[16] and antifungal[17] and antiviral activities.[18] Thiamine is one of the most essential natural thiazole. Many commercial drugs containing thiazole moiety have several clinical uses, such as the nonsteroidal anti-inflammatory drugs fentiazac and meloxicam, the anticancer drug tiazofurin, the anti-HIV drug ritonavir, and the immune-regulating drug fanetizole.[19] Pyridine derivatives are found to have many biological activities, such as antioxidant, antimicrobial,[20] β-glucuronidase[21] and cytotoxicity activities against several human cancer cell lines.[22] Pyridine–thiazole clubbed conjugates are common structural designs with extensive applications in drug discovery.[23] Representative drugs containing thiazole and carboxamide moiety are shown in Figure 1.

Based on these findings,[24] the objective of this study was to combine the pyridyl and thiazolyl group with the carboxamide moiety to form a new skeleton that has the potential to act as an antimicrobial agent. In continuation of our efforts toward the synthesis of antimicrobial agents[25] here, we have designed and synthesized a series of new pyridyl and thiazolyl clubbed with carboxamide derivatives. All the synthesized compounds were evaluated for their in vitro antimicrobial activity, and a molecular docking study was performed to identify the possible mode of action of synthesized derivatives.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthetic sequence followed for the synthesis of the target compounds is as shown in Scheme 1. In the first step, 2-ethylpyridine-4-carbothioamide (**1**) and ethyl 2-chloro-3-oxobutanoate (**2**) were refluxed in ethanol for 5 hr to furnish 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxylate (**3**) with 90% yield.[26] The base-catalyzed hydrolysis of 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxylate (**3**) gave 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxylic acid (**4**) with 95% yield.[27] The target compounds (**5a-l**) were synthesized by the reaction of 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxylic acid (**4**) and substituted amines in the presence of EDC-HOBt in DMF.[28]

TABLE 1 Physical data of thiazole–carboxamide derivatives (**5a-l**)

Entry	R	M.P. (°C)	Yield (%)
5a	2-Cl	90–92	86
5b	4-OCH_3	128–130	90
5c	4-Br	145–147	85
5d	4-CH_3	110–112	88
5e	2-CH_3, 4-NO_2	150–152	82
5f	2-OCH_3	135–137	88
5g	4-F	140–142	84
5h	2-F	108–110	86
5i	H	86–90	85
5j	2-CH_3, 4-CH_3	111–113	88
5k	3-Cl	120–122	85
5l	4-Cl	116–118	87

The synthesized compounds were purified by recrystallization with ethanol. The physical data of these newly synthesized thiazole–carboxamide derivatives are summarized in Table 1. The structures of synthesized compounds (5a-l) were assigned on the basis of their ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectra (HRMS) spectral data analysis.

2.2 | Antimicrobial activity

The in vitro antimicrobial activity of newly synthesized compounds (**5a-l**) was assessed by using the agar well diffusion method.[29] The Gram-positive pathogens *Staphylococcus aureus* ATCC6538, *Bacillus cereus* ATCC14579, and *Bacillus subtilis* ATCC6633 and the Gram-negative pathogens *Escherichia coli* ATCC8739, *Salmonella typhi* ATCC9207, *Shigella boydii* ATCC12034, *Enterobacter aerogenes* ATCC13048, *Pseudomonas aeruginosa* ATCC9027, and *Salmonella abony* NCTC6017 were used. The antifungal activity of synthesized compounds was determined against *Saccharomyces cerevisiae* ATCC9763 and *Candida albicans* ATCC10231 fungal pathogens. Tetracycline and fluconazole were used as antibacterial and antifungal standard reference compounds, respectively. The synthesized compounds were dissolved in dimethylsulfoxide (DMSO) at a concentration of 1 mg/ml. Each bacterium and fungus was inoculated into sterile nutrient broth medium and stored at 37°C for 24 hr to develop inoculum, and then, this broth was used for the study. Using sterile saline, the bacterial suspension was diluted to adjust the turbidity to the 0.5 McFarland standards. A total of 200 µl of diluted suspension of each pathogen was inoculated on sterile Mueller Hinton agar plates. Wells were punched in the agar medium. Using a micropipette, 100 µl of each compound solution was put in a separate well. A total of 100 µl of DMSO solution without any compound was also placed in a well to check its activity against the pathogenic culture. All Petri dishes were incubated for 24 hr at 37°C. A clear zone around the well was considered to demonstrate positive results. After complete incubation, the antimicrobial activity of the synthesized compounds was measured. The zones were measured and recorded by using scale in millimeter (mm). The five compounds have shown good antibacterial and antifungal activities against almost all pathogens. It has been observed that the compounds having electron-donating substituents, such as **5b** (4-OCH_3), **5d** (4-CH_3), **5e** (2-CH_3), **5f** (2-OCH_3), and **5j** (2, 4-CH_3), displayed better activities (Table 2).

The minimum inhibitory concentration (MIC) value was determined for the five most potent antimicrobial compounds **5b**, **5d**, **5e**, **5f**, and **5j**. It was determined against *S. aureus* ATCC6538, *B. cereus* ATCC14579, and *B. subtilis* ATCC6633 by following the method and guidelines of the Clinical and Laboratory Standard Institute (CLSI). All experiments were performed in triplicate. The results were expressed as mean ± *SD* in µg/ml (Table 3).

2.3 | Molecular docking study

A molecular docking was performed to investigate the probable mode of action of synthesized derivatives for anti-infective potential. The structure of the S.aureus *DNA gyrase* (PDB ID: 6QX1) was used for the docking analysis.[30] The compound **5b** has shown a hydrogen bonding interaction with ARG630 and hydrophobic interactions with GLU634, MET27, VAL31, ARG342, and PRO343 (Figure 2). The compound **5d** has shown a hydrogen bond interaction with ARG630 and

TABLE 2 Results of antimicrobial activity of thiazole–carboxamide derivatives (**5a-l**)

Entry →													
Pathogens ↓	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**	**5k**	**5l**	**Standard[a]**
Staphylococcus aureus ATCC6538	13	11	11	14	10	12	22	20	—	12	20	—	29
Bacillus cereus ATCC14579	—	11	12	14	11	11	14	10	08	06	11	08	33
Bacillus subtilis ATCC6633	—	09	—	16	15	18	10	—	—	11	14	11	32
Escherichia coli ATCC8739	—		—	07	09	10	10	—	07	07	—	—	29
Salmonella typhi ATCC9207	—	08	—	10	11	09	07	—	—	10	—	06	33
Shigella boydii ATCC12034	—	13	—	12	13	13	06	—	—	—	—	07	34
Enterobacter aerogenes ATCC13048	—	07	—	—	14	06	—	—	—	06	—	—	33
Pseudomonas aeruginosa ATCC9027	—	06	—	09	—	06	06	—	03	11	10	—	32
Salmonella abony NCTC6017	—	10	09	09	09	—	06	—	—	08	—	10	32
Saccharomyces cerevisiae ATCC9763	—	08	—	06	—	08	—	—	—	12	—	—	30
Candida albicans ATCC10231	14	—	10	10	13	11	—	14	—	07	—	08	30

Note: "—" denotes inactive.

[a]Tetracycline and fluconazole were used as antibacterial and antifungal standard reference compounds, respectively.

TABLE 3 MIC determinations of most potent antimicrobial compounds

Entry →						
Pathogens ↓	**5b**	**5d**	**5e**	**5f**	**5j**	**Tetracycline**
Staphylococcus aureus	120	200	150	170	210	30
Bacillus cereus	270	150	170	200	250	30
Bacillus subtilis	280	220	210	130	230	25

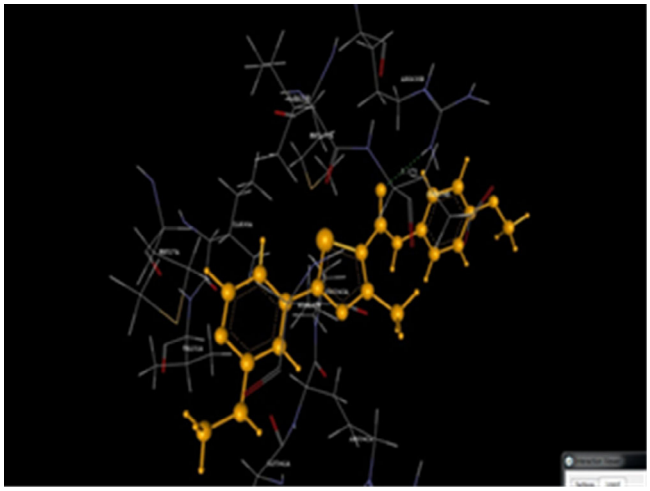


FIGURE 2 Docking interactions of **5b** with DNA gyrase

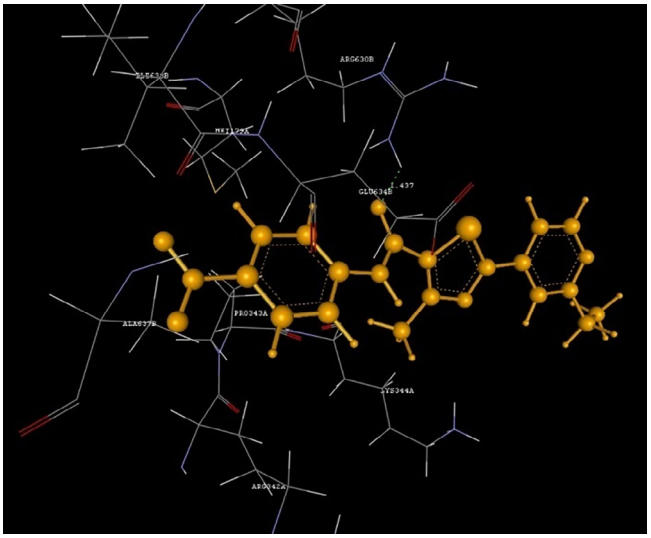


FIGURE 4 Docking interactions of **5e** with DNA gyrase

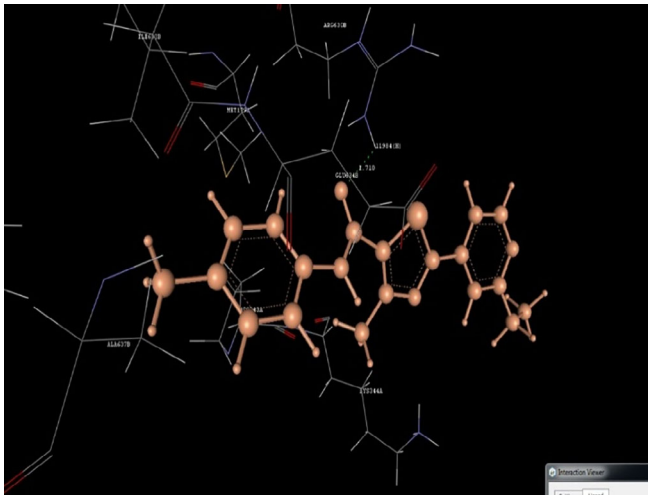


FIGURE 3 Docking interactions of **5d** with DNA gyrase

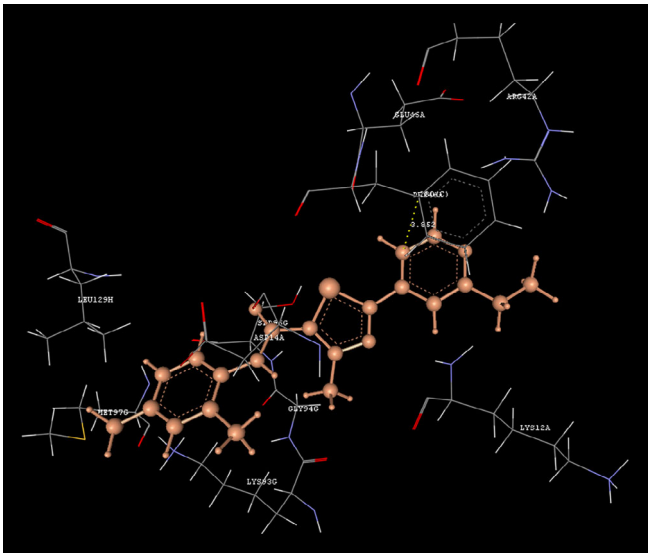


FIGURE 5 Docking interactions of **5f** with DNA gyrase

hydrophobic interactions with ILE633, GLU634, ALA637, MET27, and LYS344 (Figure 3). The compound **5e** was found to interact with DNA gyrase via the formation of a hydrogen bond interaction with ARG630 and a hydrophobic interaction with LYS344 (Figure 4). The compound **5f** has shown a hydrogen bond interaction with ARG630 and hydrophobic interactions with GLU634, MET27, VAL31, ARG342, and LYS344 (Figure 5). The compound **5J** has displayed a hydrogen bond interaction with ARG630 and hydrophobic interactions with ILE633, GLU634, ALA637, ARG342, PRO343, and LYS344 (Figure 6).

The *lumazine synthase* is an enzyme involved in the vitamin regulations is and nonhomologous to the mammalian system.[31] The structure of the *lumazine synthase*

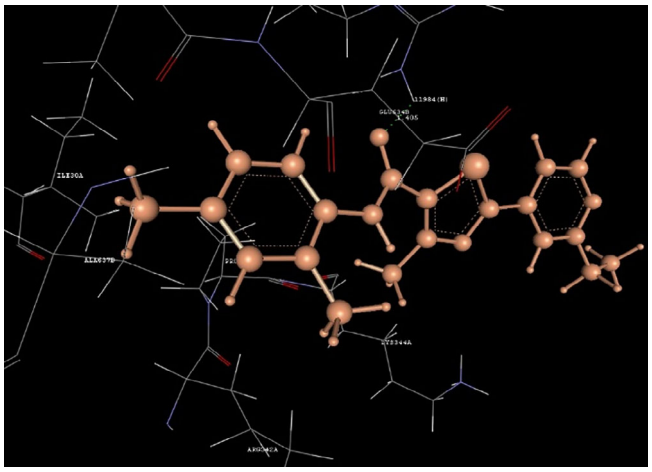


FIGURE 6 Docking interactions of **5j** with DNA gyrase

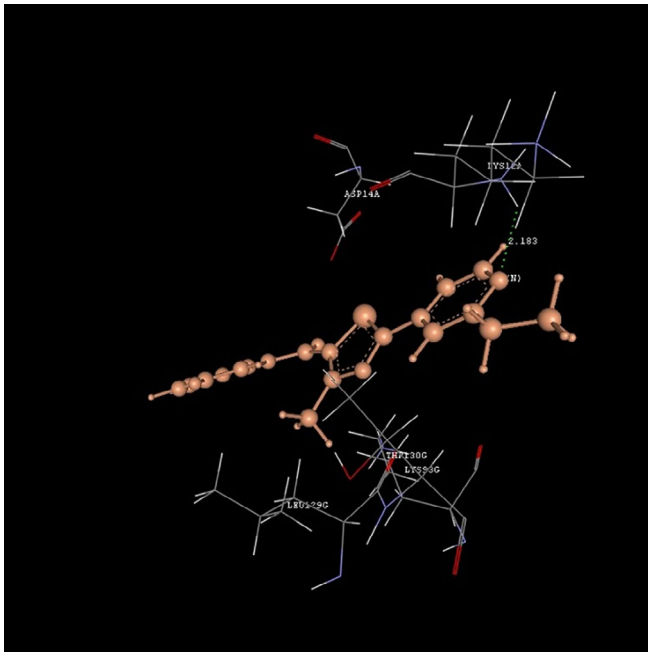


FIGURE 7 Docking interactions of **5f** with lumazine synthase

(PDB ID 2JFB) was downloaded from the free protein database www.rscb.org. The compound **5f** has shown a hydrogen bond interaction with LYS12 and hydrophobic interactions with LYS12, LYS93, LEU129, and THR130 (Figure 7). The compound **5j** has displayed an aromatic interaction with PHE46 and hydrophobic interactions with LYS12, ASP14, LYS93, GLY94, SER95, and MET97 (Figure 8).

2.4 | ADME prediction

The absorption, distribution, metabolism and excretion (ADME) predictions of synthesized molecules were carried out using the online portal www.swiss.adme.ch. All the synthesized molecules have shown desired ADME properties, which indicates their suitability as drug-like candidates (Table 4).

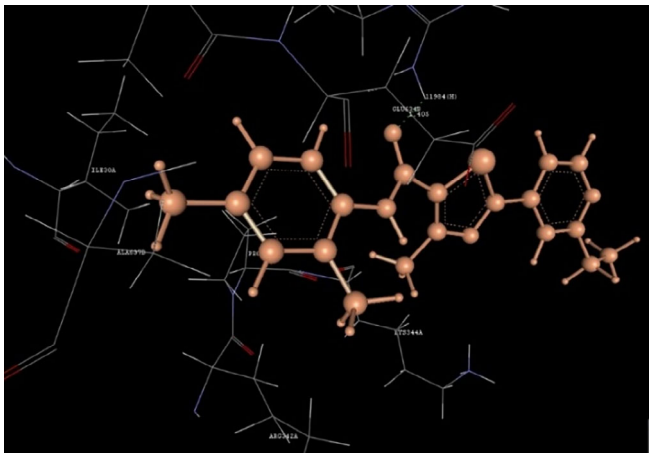


FIGURE 8 Docking interactions of **5j** with lumazine synthase

3 | EXPERIMENTAL

3.1 | General

All the chemicals were obtained from commercial suppliers and used without further purification. The melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on Bruker FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard. HRMS were obtained using the XEVO G_2-XS QTOF (TOF MS ES^{+}) instrument.

3.2 | General procedure for the synthesis of 2-(2-ethylpyridin-4-yl)-4-methyl-*N*-phenylthiazole-5-carboxamide derivatives (5a-l)

A mixture of 2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxylic acid (**4**) (1 mol), DIPEA (2 mol), and HOBt (1 mol) in DMF was cooled to 0°C. To this reaction mixture, various amines (1 mol) were added followed by EDC·HCl (1 mol) at 0°C and stirred overnight at room temperature. After completion of reactions, cold water was added to the reaction mixture. The solids obtained were filtered, washed with water, and crystallized with ethanol to furnish the corresponding 2-(2-ethylpyridin-4-

TABLE 4 ADME predictions of thiazole–carboxamide derivatives (**5a-l**)

Entry	Mol. Wt.	Rotatable bonds	H-bond acceptors	H-bond donors	LOGP	Bioavailability score
5a	357.86	5	3	1	3.64	0.55
5b	353.44	6	4	1	3.55	0.55
5c	402.31	5	3	1	3.54	0.55
5d	337.44	5	3	1	3.49	0.55
5e	382.44	6	5	1	3.19	0.55
5f	353.44	6	4	1	3.63	0.55
5g	341.40	5	4	1	3.28	0.55
5h	341.40	5	4	1	3.48	0.55
5i	323.41	5	3	1	3.22	0.55
5j	351.47	5	3	1	3.74	0.55
5k	357.86	5	3	1	3.47	0.55
5l	357.86	5	3	1	3.62	0.55

yl)-4-methyl-*N*-phenylthiazole-5-carboxamide derivatives (**5a-l**) with 82–90% yields.

3.3 | *N*-(2-Chlorophenyl)-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxamide (5a)

Yield: 86%; M.P.: 90–92°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.38 (t, J = 7.6 Hz, 3H, CH_3), 2.90 (s, 3H, Thiazolyl-CH_3), 2.92 (q, J = 7.6 Hz, 2H, CH_2), 7.11–7.7.15 (m, 1H, Ar-H), 7.33–7.37 (m, 1H, Ar-H), 7.44 (dd, J = 1.6 and 8 Hz, 1H, Ar-H), 7.63 (dd, J = 1.6 and 5.2 Hz, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 8.20 (s, 1H, N-H), 8.49 (dd, J = 1.6 and 8.4 Hz, 1H, Ar-H), 8.66 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.83, 17.84, 31.46, 117.88, 118.71, 121.52, 122.87, 125.25, 127.99, 128.28, 129.15, 134.26, 139.75, 150.27, 156.76, 159.26, 164.99, 165.81; HRMS (ESI)$^+$ calcd. for $C_{18}H_{16}ClN_3OS$ $[M + H]^+$: 358.0736 and found 358.0784.

3.4 | 2-(2-Ethylpyridin-4-yl)-*N*-(4-methoxyphenyl)-4-methylthiazole-5-carboxamide (5b)

Yield: 90%; M.P.: 128–130°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.35 (t, J = 7.6 Hz, 3H, CH_3), 2.80 (s, 3H, Thiazolyl-CH_3), 2.90 (q, J = 7.6 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 6.90 (d, J = 6.8 Hz, 2H, Ar-H), 7.48 (d, J = 8.8 Hz, 2H, Ar-H), 7.56 (dd, J = 1.6 and 5.2 Hz, 1H, Ar-H), 7.68 (s, 2H, Ar-H and N-H), 8.61 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.80, 17.48, 31.38, 55.49, 114.29, 117.84, 118.65, 122.46, 127.47, 130.20, 139.88, 150.12, 156.92, 157.04, 159.60, 164.79, 164.89; HRMS (ESI)$^+$ calcd. for $C_{19}H_{19}N_3O_2S$ $[M + H]^+$: 354.1232 and found 354.1274.

3.5 | *N*-(4-Bromophenyl)-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxamide (5c)

Yield: 85%; M.P.: 145–147°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.33 (t, J = 7.6 Hz, 3H, CH_3), 2.76 (s, 3H, Thiazolyl-CH_3), 2.88 (q, J = 7.6 Hz, 2H, CH_2), 7.44 (d, J = 8 Hz, 2H, Ar-H), 7.54 (d, J = 8 Hz, 2H, Ar-H), 7.57 (s, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 8.60 (d, J = 4.8 Hz, 1H, Ar-H), 8.72 (s, 1H, N-H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ = 13.80, 17.46, 31.36, 117.37, 117.81, 118.62, 122.15, 127.36, 131.90, 136.99, 139.90, 150.13, 157.39, 159.92, 164.88 (2-carbons merged); HRMS (ESI)$^+$ calcd. for $C_{18}H_{16}BrN_3OS$ $[M + H]^+$: 404.0211 and found 404.0259.

3.6 | 2-(2-Ethylpyridin-4-yl)-4-methyl-*N*-(*p*-tolyl)thiazole-5-carboxamide (5d)

Yield: 88%; M.P.: 110–112°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.33 (t, J = 7.6 Hz, 3H, CH_3), 2.32 (s, 3H, Ar-CH_3), 2.76 (s, 3H, Thiazolyl-CH_3), 2.87 (q, J = 7.6 Hz, 2H, CH_2), 7.14 (d, J = 8.4 Hz, 2H, Ar-H), 7.45 (d, J = 8.4 Hz, 2H, Ar-H), 7.51 (d, J = 4 Hz, 1H, Ar-H), 7.64 (s, 1H, Ar-H), 7.89 (s, 1H, N-H), 8.57 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.81, 17.45, 20.94, 31.35, 117.84, 118.65, 120.57, 127.63, 129.66, 134.69, 134.93, 139.88, 150.06, 156.86, 159.62, 164.79, 164.85.

3.7 | 2-(2-Ethylpyridin-4-yl)-4-methyl-*N*-(2-methyl-4-nitrophenyl)thiazole-5-carboxamide (5e)

Yield: 82%; M.P.: 150–152°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.36 (t, J = 7.6 Hz, 3H, CH_3), 2.44 (s, 3H, Ar-CH_3) 2.85 (s, 3H, Thiazolyl-CH_3), 2.91 (q, J = 7.6 Hz, 2H, CH_2), 7.39 (d, J = 8.4 Hz, 1H, Ar-H), 7.59 (dd, J = 1.6 and 5.2 Hz, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 7.70 (s, 1H, N-H), 7.97 (dd, J = 2.4 and 8.4 Hz, 1H, Ar-H), 8.61 (d, J = 5.2 Hz, 1H, Ar-H), 8.86 (d, J = 2.4 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.81, 17.75, 18.25, 31.41, 117.76, 117.88, 118.72, 120.23, 126.71, 131.19, 136.08, 136.17, 139.62, 146.84, 150.23, 157.89, 159.60, 165.02, 165.62.

3.8 | 2-(2-Ethylpyridin-4-yl)-*N*-(2-methoxyphenyl)-4-methylthiazole-5-carboxamide (5f)

Yield: 88%; M.P.: 135–137°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, J = 7.6 Hz, 3H, CH_3), 2.85 (s, 3H, Thiazolyl-CH_3), 2.91 (q, J = 7.6 Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 6.93 (dd, J = 1.2 and 8.4 Hz, 1H, Ar-H), 7.02 (td, J = 8 and 1.2 Hz, 1H, Ar-H), 7.11 (td, J = 7.6 and 1.6 Hz, 1H, Ar-H), 7.61 (dd, J = 1.6 and 5.2 Hz, 1H, Ar-H), 7.71 (s, 1H, Ar-H), 8.34 (s, 1H, N-H), 8.43 (dd, J = 1.6 and 8 Hz, 1H, Ar-H), 8.63 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.84, 17.55, 31.45, 55.93, 109.98, 117.86, 118.66, 119.84, 121.28, 124.43, 127.19, 129.21, 139.94, 147.93, 150.20, 155.79, 159.07, 164.90, 165.31; HRMS $(ESI)^+$ calcd. for $C_{19}H_{19}N_3O_2S$ $[M + H]^+$: 354.1232 and found 354.1274.

3.9 | 2-(2-Ethylpyridin-4-yl)-*N*-(4-fluorophenyl)-4-methylthiazole-5-carboxamide (5g)

Yield: 84%; M.P.: 140–142°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, J = 7.6 Hz, 3H, CH_3), 2.83 (s, 3H, Thiazolyl-CH_3), 2.92 (q, J = 7.6 Hz, 2H, CH_2), 7.10 (d, J = 8 Hz, 2H, Ar-H), 7.54–7.70 (m, 4H, Ar-H), 7.71 (s, 1H, N-H), 8.64 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.80, 17.55, 31.41, 115.84, 116.07, 117.86, 118.70, 122.37, 126.99, 133.15, 139.78, 150.21, 157.42, 159.59, 164.97, 165.08; HRMS $(ESI)^+$ calcd. for $C_{18}H_{16}FN_3OS$ $[M + H]^+$: 342.1032 and found 342.1086.

3.10 | 2-(2-Ethylpyridin-4-yl)-*N*-(2-fluorophenyl)-4-methylthiazole-5-carboxamide (5h)

Yield: 86%; M.P.: 108–110°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.36 (t, J = 7.6 Hz, 3H, CH_3), 2.84 (s, 3H, Thiazolyl-CH_3), 2.91 (q, J = 7.6 Hz, 2H, CH_2), 7.08–7.20 (m, 3H, Ar-H), 7.60 (dd, J = 2 and 5.2 Hz, 1H, Ar-H), 7.69 (s, 1H, Ar-H), 7.84 (s, 1H, N-H), 8.35 (td, J = 8.4 and 1.2 Hz, 1H, Ar-H), 8.63 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.82, 17.60, 31.42, 114.88, 115.07, 117.86, 118.70, 121.85, 125.82, 125.92, 127.76, 139.75, 150.21, 153.80, 156.96, 159.29, 164.95, 165.59; HRMS $(ESI)^+$ calcd. for $C_{18}H_{16}FN_3OS$ $[M + H]^+$: 342.1032 and found 342.1086.

3.11 | 2-(2-Ethylpyridin-4-yl)-4-methyl-*N*-phenylthiazole-5-carboxamide (5i)

Yield: 85%; M.P.: 86–90°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.36 (t, J = 7.6 Hz, 3H, CH_3), 2.82 (s, 3H, Thiazolyl-CH_3), 2.91 (q, J = 7.6 Hz, 2H, CH_2), 7.08 (t, J = 8 Hz, 2H, Ar-H), 7.53–7.59 (m, 5H, Ar-H), 7.69 (s, 1H, Ar-H), 8.64 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.81, 17.58, 31.43, 115.20, 116.11, 117.40, 118.52, 121.60, 125.27, 126.79, 127.14, 139.75, 150.17, 159.43, 164.68, 165.12.

3.12 | *N*-(2,4-Dimethylphenyl)-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxamide (5j)

Yield: 88%; M.P.: 111–113°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.35 (t, J = 7.6 Hz, 3H, CH_3), 2.27 (s, 3H, Ar-CH_3), 2.30 (s, 3H, Ar-CH_3), 2.80 (s, 3H, Thiazolyl-CH_3), 2.91 (q, J = 7.6 Hz, 2H, CH_2), 7.02 (s, 1H, Ar-H), 7.04 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.57 (dd, J = 1.6 and 5.2 Hz, 1H, Ar-H), 7.61 (d, J = 8 Hz, 1H, Ar-H), 7.68 (s, 1H, N-H), 8.60 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.83, 17.58, 17.91, 20.94, 31.37, 117.86, 118.67, 123.78, 127.46, 128.42, 130.06, 131.36, 132.51, 135.88, 139.92, 150.11, 156.77, 159.59, 164.86, 164.92

3.13 | *N*-(3-Chlorophenyl)-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxamide (5k)

Yield: 85%; M.P.: 120–122°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, J = 7.6 Hz, 3H, CH_3), 2.86 (s, 3H, Thiazolyl-

CH_3), 2.92 (q, J = 7.6 Hz, 2H, CH_2), 7.11–7.7.22 (m, 3H, Ar-H), 7.61 (dd, J = 1.6 and 5.2 Hz, 1H, Ar-H), 7.71 (s, 1H, N-H), 7.82 (d, J = 4 Hz, 1H, Ar-H), 8.38 (td, J = 8 and 1.6 Hz, 1H, Ar-H), 8.65 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.81, 17.85, 31.42, 117.21, 118.35, 121.48, 122.60, 126.18, 127.78, 128.10, 129.33, 134.30, 139.55, 150.21, 156.17, 159.79, 164.67, 165.27.

3.14 | *N*-(4-Chlorophenyl)-2-(2-ethylpyridin-4-yl)-4-methylthiazole-5-carboxamide (5l)

Yield: 87%; M.P.: 116–118°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.37 (t, J = 7.6 Hz, 3H, CH_3), 2.82 (s, 3H, Thiazolyl-CH_3), 2.91 (q, J = 7.6 Hz, 2H, CH_2), 7.35 (d, J = 8.8 Hz, 2H, Ar-H), 7.54–7.58 (m, 3H, Ar-H), 7.69 (s, 2H, Ar-H and N-H), 8.63 (d, J = 5.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ = 13.78, 17.45, 31.37, 117.79, 118.60, 121.83, 127.35, 128.96, 129.71, 136.46, 139.88, 150.14, 157.34, 159.92, 164.88 (2-carbons merged); HRMS (ESI)$^+$ calcd. for $C_{18}H_{16}ClN_3OS$ $[M + H]^+$: 358.0736 and found 358.0784.

4 | CONCLUSIONS

In conclusion, a series of new pyridyl–thiazolyl clubbed carboxamide derivatives (**5a-l**) were synthesized starting from the clinically used antitubercular drug ethionamide. The synthesized compounds were characterized with the help of ^{1}H NMR, ^{13}C NMR, and HRMS spectral analysis. The *in vitro* antimicrobial activity of all the synthesized carboxamide derivatives were evaluated by using the diffusion method. Among the series, compounds **5b**, **5d**, **5e**, **5f**, and **5j** were found to possess encouraging antimicrobial activities. A molecular docking study was performed to identify the possible mode of action of synthesized derivatives. The compounds have shown excellent binding affinity toward *DNA gyrase* and *lumazine synthase* enzymes. We believe that these newly synthesized thiazole–carboxamide derivatives with antimicrobial properties will be helpful for identification of new potential antimicrobial agents

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