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ARTICLE

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Synthesis, antimicrobial, and antioxidant activities of new pyridyl- and thiazolyl-bearing carbohydrazides

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Abstract

A series of novel substituted (*E*)-*N*′-benzylidene-4-methyl-2-(2-propylpyridin-4-yl) thiazole-5-carbohydrazide derivatives (**6a-l**) have been synthesized by following the multistep synthetic route starting from prothionamide. The resulting compounds were characterized via ^{1}H, ^{13}C NMR, and HRMS spectral data. The synthesized carbohydrazides were evaluated for their in vitro antimicrobial and antioxidant activities. Tested molecules have displayed moderate to good growth inhibition activity. Among the screened compounds, **6b**, **6e**, **6j**, and **6k** are found to be the more promising antimicrobial agents. A 2,2-diphenyl-1-picrylhydrazyl assay was used to test the antioxidant activity of the carbohydrazides. The carbohydrazide derivatives **6b** and **6i** have shown better free-radical scavenging ability than the other investigated compounds.

KEYWORDS

antimicrobial activity, antioxidant activity, carbohydrazides, hydrazones, molecular docking study, thiazoles

1 | INTRODUCTION

An antioxidant is a substance that reduces damage due to oxygen, such as that caused by free radicals. It acts as a radical scavenger, hydrogen donor, electron donor, peroxide decomposer, singlet oxygen quencher, enzyme inhibitor, synergist, and metal-chelating agent. It protects the liver from toxins and helps to repair damaged liver cells. Antioxidants include enzymes and other constituents, such as vitamin C, vitamin E, lycopene, β-carotene, and lutein, which are capable of countering the damaging effects of oxidation. They are also commonly added to food products such as vegetable oils and prepared foods to prevent or delay their deterioration from the action of air. Antioxidant deficiency causes neurodegenerative disorders, rheumatoid arthritis, cancer, cardiovascular diseases, respiratory diseases, immune deficiency, emphysema, Parkinson's disease, macular degeneration, and other inflammatory or ischemic conditions. Thus, the search of new nonsteroidal antioxidant agents is of prime importance.[1] A steady increase in various infectious microbial diseases has been observed in day-to-day life. This has become more complicated by the evolution of various microbial strains resistant to some single or combinations of drugs.[2] This causes an instant concern regarding the discovery of peculiar chemical substances of significant biological potential with different modes of action to get rid of the drug-resistant microbes.[3]

Thiazoles are five-membered heterocyclic compounds bearing sulfur and nitrogen in the ring and plays an essential role in medicinal and pharmaceutical chemistry. Thiazoles are endowed with potential biological activities such as anticancer,[4] antitubercular,[5] α-glucosidase inhibitor,[6] antioxidant,[7] antibacterial,[8] antiplatelet,[9] anti-inflammatory,[10] anti-Candida activity,[11] and antifungal properties.[12] In addition, thiamine or vitamin B_1 is one of the most important natural thiazoles. Besides, many commercial drugs contain the thiazole skeleton and have numerous clinical applications, such as the nonsteroidal anti-inflammatory drugs fentizac and meloxicam, the anticancer drug tiazofurin, the anti-HIV drug ritonavir, and the immune-regulating drug fanetizole.[13] The pyridine ring is essential to the structure of many biologically active compounds.[14] Functionalized pyridines are found to be accompanied by many biological activities, such as antioxidant, antimicrobial,[15] β-glucuronidase,[16] and cytotoxicity activities against several human cancer cell lines.[17] Pyridine-thiazole-fused heterocyclic systems are common structural designs with substantial applications in medicinal chemistry.[18]

The carbohydrazides and their derivatives are an interesting class of organic compounds with anticancer, antimicrobial, antioxidant, antitubercular, anti-inflammatory, and analgesic activities.[19] In addition to this, hydrazones are involved in numerous biological activities, such as anthelmintic and antimicrobial activities, as a cyclooxygenase inhibitor, as an antioxidant, and anti-HIV and antitubercular activities.[20] Some antimicrobial and antioxidant agents containing carbohydrazide moiety have been shown in Figure 1. Continuing our efforts of the synthesis of biologically active target molecules,[21] here, we have reported the synthesis and antimicrobial and antioxidant activities of some novel substituted (*E*)-*N*′-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide derivatives starting from prothionamide (**1**).

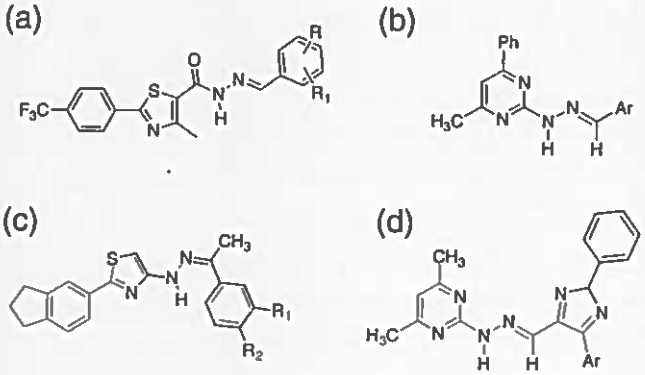


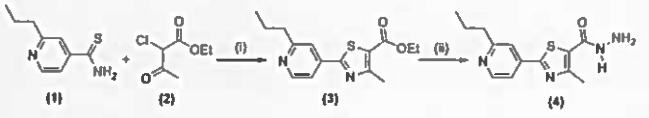
FIGURE 1 Representative of some antimicrobial and antioxidant agents containing carbohydrazide moiety. (a) antimicrobial and antioxidant, (b) antimicrobial and antihelmintic, (c) antitubercular, and (d) antimicrobial

2 | RESULTS AND DISCUSSION

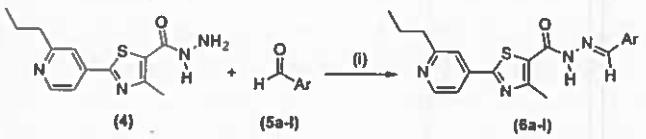
2.1 | Chemistry

The reaction sequence used for the synthesis of the carbohydrazide derivatives is shown in Schemes 1 and 2. In the first step, 2-propylpyridine-4-carbothioamide (**1**) and ethyl 2-chloro-3-oxobutanoate (**2**) were refluxed in ethanol for 5 hr to obtain ethyl 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carboxylate (**3**) with 92% yield. The obtained 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carboxylate (**3**) and excess of hydrazine hydrate were refluxed in ethanol for 4 hr to furnish a key intermediate, 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (**4**), with 78% yield. The condensations of aromatic aldehydes (**5a-l**) and 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (**4**) were performed in diisopropylethylammonium acetate (DIPEAc)[22] to obtain the corresponding substituted (*E*)-*N*′-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (**6a-l**) with 80–90% yields. The products obtained were purified by recrystallization in ethanol.

The structures of synthesized (*E*)-*N*′-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (**6a-l**) were established on the basis of their ^{1}H and ^{13}C NMR spectral data and satisfactory high resolution mass spectrometry (HRMS) analysis. The ^{1}H NMR, ^{13}C NMR and HRMS spectrums (Figures S_1 - S_{24}) is given in supplementary file. The characteristic peak of amido N–H of compound **6c** was observed at δ 12.23 ppm. The singlet at δ 2.79 (^{1}H NMR) and the peak at δ 17.73 ppm (^{13}C NMR) indicate the presence of methyl attached to thiazole ring. The triplet-sextet-triplet pattern was observed in ^{1}H NMR spectrum at δ 0.94, 1.75, and 2.83 ppm, respectively, indicating the presence of *n*-propyl substituent attached to the pyridine ring. The imine (–C=N–) proton was observed at δ 8.82 ppm as a singlet. The remaining protons were observed at their expected aromatic region. The peak at δ 166.79 ppm in ^{13}C NMR is due to carbonyl of carbohydrazides. The HRMS



SCHEME 1 *Reaction conditions*: (i) EtOH, reflux, 5 hr; (ii) H_2N-NH_2.H_2O; EtOH, reflux, 4 hr



SCHEME 2 *Reaction conditions*: (i) DIPEAc, rt, 30 min

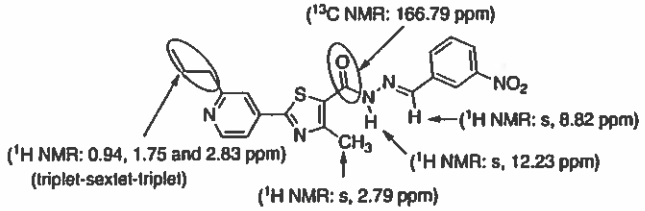


FIGURE 2 Spectral interpretation of (*E*)-4-methyl-*N*′-(3-nitrobenzylidene)-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (**6c**)

TABLE 1 Physical data of synthesized carbohydrazide derivatives (**6a-l**)

Entry	Ar	M.P. (°C)	Yield (%)
6a	4-(Br)C_6H_4	240–242	86
6b	1-Furyl	212–215	82
6c	3-(NO_2)C_6H_4	208–210	85
6d	4-(CH_3)C_6H_4	205–208	90
6e	4-(cl)C_6H_4	233–236	83
6f	2-(Br)C_6H_4	240–242	87
6g	4-(OCH_3)C_6H_4	218–220	90
6h	3-(cl)C_6H_4	210–212	84
6i	3-(OCH_3)C_6H_4	189–191	89
6j	4-(NO_2)C_6H_4	244–246	80
6k	C_6H_5	170–175	87
6l	3-(Br)C_6H_4	238–240	88

analysis of compound **6c** displays a $(M + H)^+$ peak at 410.1287 for its molecular formula $C_{20}H_{19}N_5O_3S$ (Figure 2). The physical data of all synthesized compounds is given in (Table 1).

2.2 | Antimicrobial activity

The in vitro antimicrobial activity of newly synthesized compounds (**6a-l**) was assessed by using the agar well diffusion method.[23] The Gram-positive pathogens *Staphylococcus aureus* ATCC6538, *Bacillus cereus* ATCC14579, *Bacillus megaterium* ATCC2326, *Micrococcus glutamicus* ATCC13032, and *Bacillus subtilis* ATCC6633 and the Gram-negative pathogens *Escherichia coli* ATCC8739, *Salmonella typhi* ATCC9207, *Shigella boydii* ATCC12034, *Enterobacter aerogenes* ATCC13048, *Pseudomonas aerogenosa* ATCC9027, and *Salmonella abony* NCTC6017 were used in this study. Antifungal activity of the synthesized compounds was determined against *Aspergillus niger* ATCC16404, *Saccharomyces cereviseae* ATCC9763, and *Candida albicans* ATCC10231 fungal pathogens. Fluconazole and tetracycline were used as antifungal and antibacterial standard reference compounds, respectively. The synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mg/mL. Each bacterium and fungi were inoculated in a sterile nutrient broth medium and maintained at 37°C for 24 hr to develop inoculums, 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. Diluted suspension of 200 μL 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, and 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 a positive result. After complete incubation, the antimicrobial activities of the synthesized compounds were measured. The zones were measured and recorded by using a scale in millimeter (mm). The compounds **6j** and **6k** showed good antibacterial and antifungal activities. Compound **6e** showed considerable activity against Gram-negative pathogens (Table 2).

2.3 | Minimum inhibitory concentration

Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial (compounds) drug that will inhibit the visible growth of a microorganism after overnight incubation. The MIC was determined for the four most potent antimicrobial compounds **6b**, **6e**, **6j**, and **6k**. The MIC was determined against *S. typhi* ATCC9207, *B. subtilis* ATCC6633, and *E. coli* ATCC8739 pathogens. It was determined by following the method and guidelines of the Clinical and Laboratory Standard Institute (CLSI). Compound **6b** was found to inhibit the visible growth of *S. typhi* ATCC9207 at a low concentration with MIC of 18 μg/mL. The *E. coli* ATCC8739 was inhibited by the compounds **6b**, **6e**, **6j**, and **6k** at concentration of 26, 38, 25, and 21 μg/mL, respectively. All experiments were performed in triplicate, and results are expressed as mean ± SD in μg/mL (Table 3).

2.4 | DPPH-based free radical scavenging activity

2,2-Diphenyl-1-picrylhydrazyl (DPPH) is a widely accepted in vitro method to govern the antioxidant strength of the compounds. DPPH is a stable free radical. The deep violet color of the DPPH reagent solution is due to the presence of an odd electron. When an antioxidant is present in the surrounding, it donates an electron to the DPPH molecule and gives rise to its reduced form, and this results in the disappearance of the deep violet color.

TABLE 2 Results of antimicrobial assay of synthesized carbohydrazide derivatives (6a-l)[a]

Pathogens	Compounds												
	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Std[b]
S. typhi	—	20	—	10	13	—	—	—	—	11	13	—	27
E. aerogenes	—	10	11	—	08	—	—	—	—	12	08	13	33
B. subtilis	—	13	—	—	12	—	10	—	—	14	11	—	34
C. albicans	—	—	—	—	—	—	—	—	—	09	10	—	25
P. aerogenosa	—	11	—	—	10	—	—	—	—	13	09	—	30
S. abony	—	09	—	—	11	—	11	—	—	13	12	—	30
B. megaterium	—	10	—	—	11	—	10	—	—	12	13	—	27
E. coli	—	12	—	—	09	—	—	—	—	12	14	—	29
S. aureus	—	12	—	—	08	14	09	—	—	12	13	12	25
S. boydii	—	11	—	—	10	11	—	—	—	08	13	—	27
S. cerevisiae	—	08	—	—	—	—	—	—	—	12	10	—	24
A. niger	—	—	—	09	10	—	—	—	—	13	12	—	26
B. cereus	—	12	—	—	—	—	10	—	—	14	13	08	33
M. glutamicus	—	11	—	—	—	—		—	—	13	10	—	31

[a]Diameter of the zone of inhibition is given in millimeter (mm).
[b]Standard used for antibacterial and antifungal activity was tetracycline and fluconazole, respectively.

TABLE 3 MIC determinations of the most potent antimicrobial compounds

Pathogens	Compounds				
	6b	6e	6j	6k	Tetracycline
S. typhi	18 ± 2.3	28 ± 1.5	25 ± 1.8	26 ± 2.3	3.0 ± 1 .2
B. subtilis	22 ± 1.7	25 ± 2.1	20 ± 1.1	25 ± 1.9	3.5 ± 0.8
E. coli	26 ± 2.4	38 ± 2.6	25 ± 1.4	21 ± 1.8	4.5 ± 0.5

The antioxidant activity of all the newly synthesized compounds (6a-l) was tested and quantified by DPPH assay (Figure 3). The method described by Chang et al.[24] was followed with some minor modifications. Stock solutions of all compounds with a 10 mg/mL concentration were prepared in DMSO. By using a stock solution, several concentrations, that is, 20, 40, 60, 80, 100, 120, and 140 µg/mL, were prepared and used in the assay. Ascorbic acid was used as a positive control, and the same concentrations, 20–140 µg/mL, of ascorbic acid were prepared. Two mL of 0.2 mM DPPH solution was prepared in DMSO. It was added to each test tube containing each concentration of the compounds. In one test tube, instead of the compounds, 2 mL of distilled water was added, and this test tube was used as the negative control (Blank). For positive control, 2 mL of each concentration of ascorbic acid was added to a tube containing 2 mL of DPPH. The contents of each test tube were stirred vigorously and were stored for incubation at room temperature for 30 min. After incubation, spectrophotometric readings (Elico UV–Visible double beam spectrophotometer) of all positive control and test pigment extracts were recorded against a Blank at 517 nm. The percentage of DPPH radical scavenging

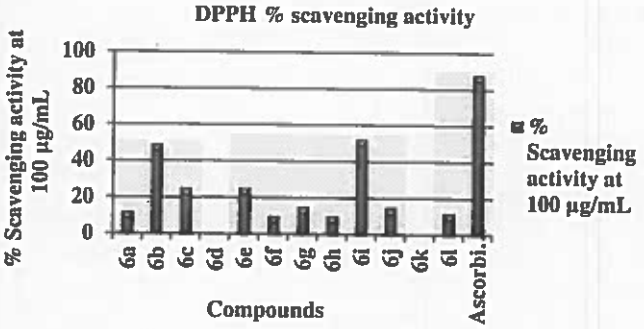


FIGURE 3 Percent DPPH scavenging activity of synthesized carbohydrazide derivatives (6a-l)

activity was calculated by using the below-mentioned formula. A decrease in absorbance indicates the DPPH radical scavenging activity.

$$\text{DPPH radical scavenging activity [Inhibition } (I_0)] = [(A_0 - A)/A_0] \times 100,$$

where A_0 is the absorbance of negative control solution containing all reagents except test compounds, and A is theabsorbance of test compounds.

From the obtained results, the IC_{50} value was determined. It was the concentration of the sample required to scavenge 50% DPPH free radicals. The IC_{50} value was determined by plotting inhibition data against test compound concentrations by regression analysis. DPPH radical scavenging activity was evaluated in terms of percentage inhibition and IC_{50} value. The compounds **6b** and **6i** have shown good antioxidant activity. The compounds **6c** and **6e** also showed moderate DPPH radical scavenging activity. The DPPH radical scavenging activity of compounds **6b** and **6i** was comparable with ascorbic acid. The compounds **6b** and **6i** scavenged 49.45 ± 0.006 and 52.14 ± 0.02 of DPPH radicals at a concentration of 100 μg/mL, respectively. These two compounds could scavenge 100% of the DPPH radicals when the concentration is close to 200 μg/mL. This indicates the efficient antioxidant activity of the synthesized compounds. At low concentrations, they can scavenge the DPPH radicals completely. The IC_{50} values of ascorbic acid and compounds **6b** and **6i** were calculated using linear regression analysis as shown in Figures 4–6, respectively. The lowest IC_{50} value was observed for ascorbic acid, which was 32.43 ± 0.8 μg/mL, followed by **6i** (96.80 ± 0.2 μg/mL) and **6b** (109.66 ± 0.8 μg/mL).

2.5 | Molecular docking

A molecular docking study was performed to ascertain the mode of action of the substituted (*E*)-*N*′-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (**6a-l**) for antibacterial and antifungal potential. Gyrase is a critical enzyme in the life cycle of bacteria. It is present almost in all the bacteria, playing a vital role in the replication of the genetic material. Another advantage of the *gyrase* is that it served as targets for the broad-spectrum fluroquinolone type of synthetic antibacterial compounds. The docking studies of compounds **6a–l** were performed in addition to cocrystallized ligand CPF. The compound **6b** was found to interact with gyrase via the formation of a hydrogen bond with ASN1334, THR1236, ARG1232, and ALA1180 and demonstrated hydrophobic interactions with LEU1345, PRO1343, ILE1336, ARG1238, MET1179, and LEU1035 (Figure 7). The compound **6e** was found to interact through the formation of a hydrogen bond with ASN1334, THR1236, and ALA1180 and demonstrated hydrophobic interactions with LEU1345, PRO1343, ILE1336, THR1236, ARG1238, ALA1180, MET1179, LEU1035, and ARG630 (Figure 8). The compound **6j** was found to interact via the formation of a hydrogen bond with THR1236, ARG1232, and ALA1180 and demonstrated hydrophobic interactions with LEU1345, PRO1343, ILE1336, ARG1238, THR1181,

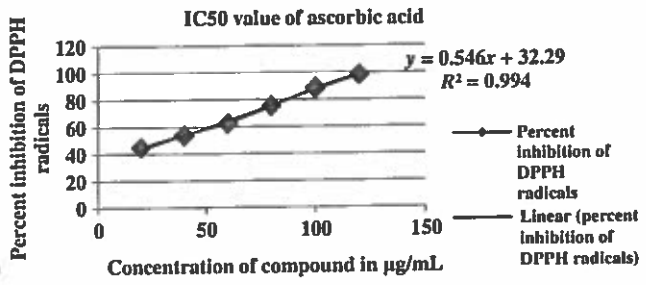


FIGURE 4 Percent inhibition of ascorbic acid

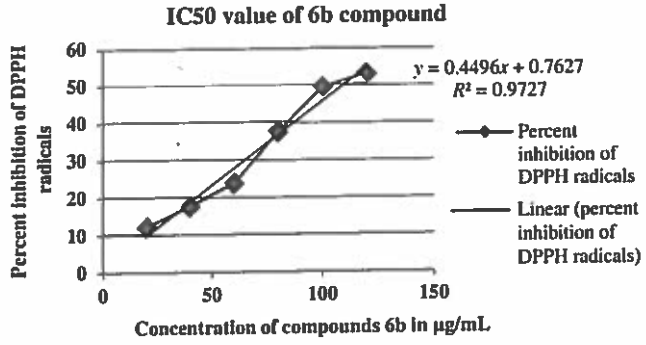


FIGURE 5 Percent inhibition of compound (6b)

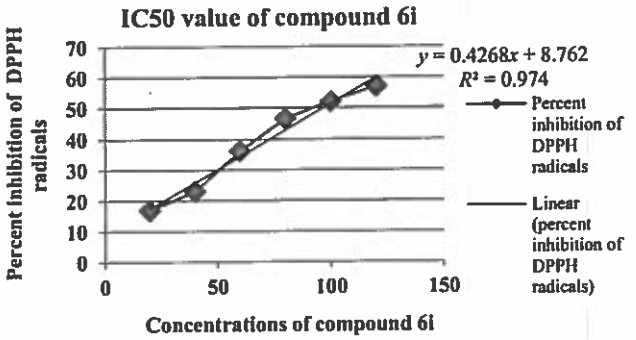


FIGURE 6 Percent inhibition of compound (6i)

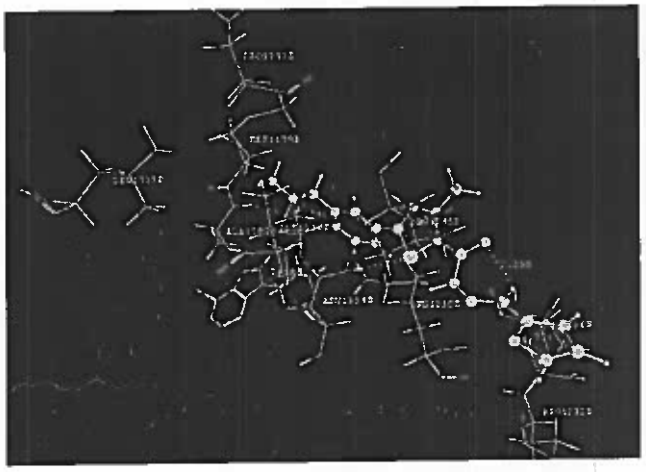


FIGURE 7 Docking interactions of compound (6b)

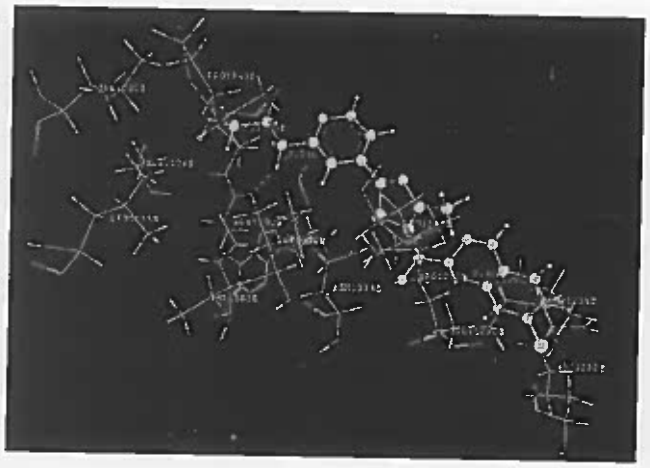


FIGURE 8 Docking interactions of compound (6e)

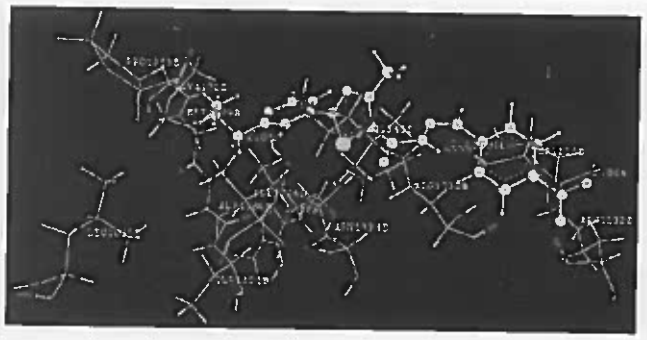


FIGURE 9 Docking interactions of compound (6j)

ALA1180, and MET1179, LEU1035 (Figure 9). The compound 6k found to interact via the formation of hydrogen bond with ASN1334, THR1236, ARG1238, and ALA1180 and through hydrophobic interactions with LEU1345, PRO1343, ILE1336, MET1179, and LEU1035 (Figure 10). The docking interaction also demonstrated the importance of the pyridine and thiazole nucleus on which hydrogen bond interactions are prominently observed. The amino groups bearing carbonyl moiety were also found to be important for biological activities as they interact with gyrase through the formation of hydrogen bond interactions.

Lumazine synthase is also known as 5-amino-6-uracil butanedione transferase and is an important enzyme involved in the biosynthesis of the riboflavin in fungi. The fungi are not capable of utilizing vitamins, which are supplied from external sources, such as mammalian cells. They are dependent on the enzyme-like *Lumazine synthase* for generation of vitamins for cell growth and development. Hence, inhibition of *Lumazine synthase* will be an attractive way of development of antifungal agents. The docking studies of compounds **6a–l** were performed in addition to cocrystallized ligand INJ. The most active molecule, **6j**,

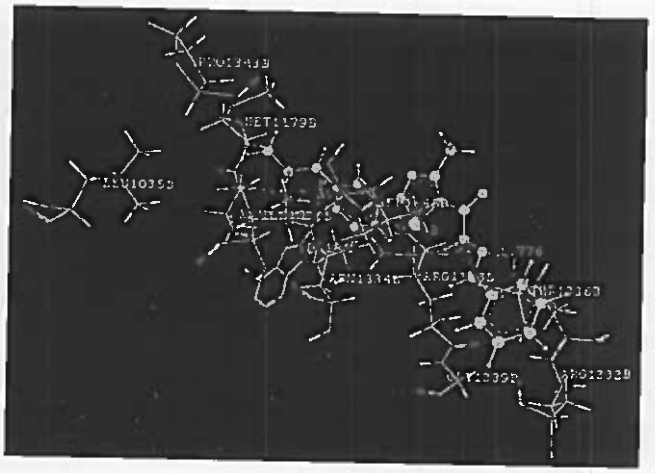


FIGURE 10 Docking interactions of compound (6k)

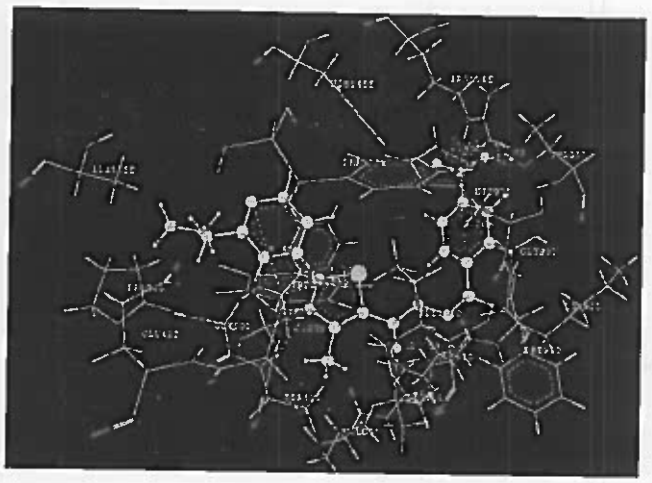


FIGURE 11 Docking interactions of compound (6j) with lumazine synthase

was found to interact with *Lumazine synthase* via the formation of hydrogen bond with ARG136, THR95, ILE91, and SER60 and showed aromatic interactions with TRP26 and HIS97 and hydrophobic interactions with ALA155, LEU90, VAL89, GLU62, TYR61, SER60, GLY59, PRO58, and TRP26 (Figure 11). The compound **6l** was found to interact via the formation of hydrogen bond with GLY93 and showed aromatic interactions with TRP152, PHE98, and TRP26 and hydrophobic interactions with ILE101, GLY93, LYS92 LEU90, SER60, and TRP26 (Figure 12).

2.6 | Docking analysis

The Biopredicta module of the V life MDS 4.3 was utilized for molecular docking analysis.[25] Crystal structure of the *S. aureus* gyrase complex with ciprofloxacin (PDB ID 2XCT) and *Lumazine synthase* from *Saccharomyces*

cerevisiae (PDB ID 1EJB) was utilized for docking analysis. Grip-based docking analysis was performed, keeping the protein structure in rigid conformation and ligands in flexible conformation. The crystal structure of both proteins was downloaded from the free protein database www.rcsb.org. Downloaded crystal structures were refined via removal of the water and addition of the hydrogen atoms so that native geometry of the protein is achieved. Ligands were prepared in the Vlife engine module and optimized via the Merck molecular force field.

2.7 | ADME prediction

ADME predictions of all the synthesized compounds (6a-l) were predicted using the Swiss ADME portal.[26] (http://www.swissadme.ch.) All the synthesized compounds showed excellent physicochemical parameters with low Lipinski violation, which is desirable for the oral absorption of drug candidates (Table 4).

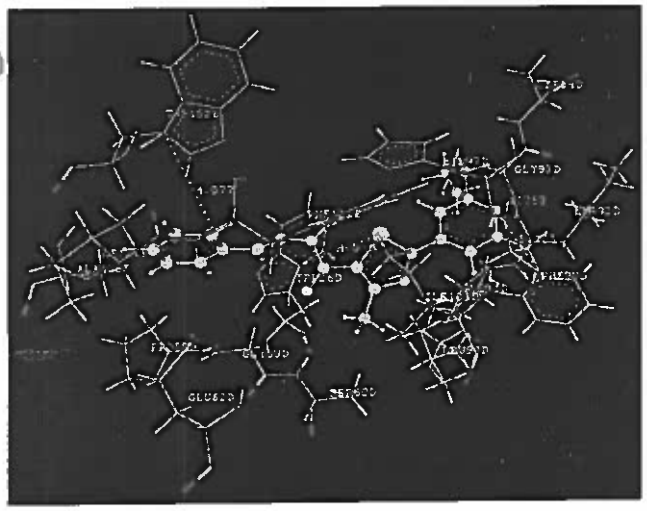


FIGURE 12 Docking interactions of compound (6k) with lumazine synthase

3 | EXPERIMENTAL

3.1 | General

Commercially available chemicals and reagents were used directly without further purification. The synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR spectral, and HRMS data. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker NMR (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm). Trimethylsilane (TMS) is used as a reference. Coupling constants (*J*) are reported in hertz (Hz).

3.2 | Procedure for the synthesis of ethyl 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carboxylate (3)

A mixture of 2-propylpyridine-4-carbothioamide (1) (1.0 mmol) and ethyl 2-chloro-3-oxobutanoate (2) (1.3 mmol) was refluxed in ethanol. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction in 5 hr, the ethanol was evaporated under vacuum. The residue obtained was dissolved in ethyl acetate (50 mL) and neutralized by ammonia solution. The organic layer was washed with brine and dried over anhydrous sodium sulphate. The ethyl acetate was evaporated under vacuum, and the obtained product was purified by column chromatography using ethyl acetate and petroleum ether to furnish ethyl 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carboxylate (3) with 92% yield.

TABLE 4 ADME predictions of synthesized carbohydrazides (6a-l)

Entry	Mol. wt.	Rotatable bonds	H-bond acceptors	H-bond donors	LOGP	Bioavailability score
6a	443.36	7	4	1	3.62	0.55
6b	354.43	7	5	1	2.77	0.55
6c	409.46	8	6	1	2.74	0.55
6d	378.49	7	4	1	3.49	0.55
6e	398.91	7	4	1	3.46	0.55
6f	443.36	7	4	1	3.65	0.55
6g	394.49	8	5	1	3.54	0.55
6h	398.91	7	4	1	3.44	0.55
6i	394.49	8	5	1	3.52	0.55
6j	409.46	8	6	1	2.93	0.55
6k	364.46	7	4	1	3.21	0.55
6l	443.36	7	4	1	3.55	0.55

3.2.1 | Ethyl 4-methyl-2-(2-propylpyridin-4-yl) thiazole-5-carboxylate (3)

Yield: 95%; M.P.: Thick oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 0.99 (t, J = 8 Hz, 3H), 1.41 (t, J = 8 Hz, 3H), 1.80 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.84 (t, J = 8 Hz, 2H), 4.36 (q, J = 8 Hz, 2H), 7.59 (dd, J = 8 & 4 Hz, 1H), 7.68 (s, 1H), 8.61 (d, J = 4 Hz, 1H).

3.3 | Procedure for the synthesis of 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (4)

Ethyl 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carboxylate (3) (1.0 mmol) and excess of hydrazine hydrate (3.0 mmol) were refluxed in ethanol. The progress of the reaction was monitored by TLC. After completion of the reaction, the ethanol was removed under reduced pressure. The obtained residue was poured in ice-cold water. The solid obtained was filtered, washed with water, and recrystallized from ethanol to obtain 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (4) with 78% yield.

3.3.1 | 4-Methyl-2-(2-propylpyridin-4-yl) thiazole-5-carbohydrazide (4)

Yield: 78%; M.P.: 161–163°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 0.99 (t, J = 8 Hz, 3H), 1.80 (sextet, J = 8 Hz, 2H), 2.77 (s, 3H), 2.83 (q, J = 8 Hz, 2H), 4.13 (bs, 2H), 7.15 (s, 1H), 7.57 (dd, J = 8 & 4 Hz, 1H), 7.66 (s, 1H), 8.62 (d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 13.88, 17.51, 23.06, 40.35, 117.84, 119.31, 124.73, 139.62, 150.22, 157.19,.162.96, 163.77, 165.34.

3.4 | General procedure for the synthesis of substituted (*E*)-*N*′-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (6a-l)

A mixture of aromatic aldehydes (**5a-l**) (1.0 mmol) and 4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (4) (1.0 mmol) was dissolved in DIPEAc (5 mL) and stirred at room temperature for 30 min. Then, the reaction mixture was poured in cold water. The solid obtained was filtered and washed with saturated $NaHCO_3$ and cold water. The products obtained were recrystallized from ethanol to obtain the corresponding substituted (*E*)-*N*′-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides (**6a-l**) with 80–90% yields.

3.4.1 | (*E*)-*N*′-(4-bromobenzylidene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6a)

Yield: 86%; M.P.: 240–242°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.94 (t, J = 8 Hz, 3H), 1.75 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.83 (t, J = 8 Hz, 2H), 7.70–7.77 (m, 5H), 7.82 (d, J = 4 Hz, 1H), 8.12 (s, 1H), 8.65 (d, J = 4 Hz, 1H), 12.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 14.46, 17.66, 23.10, 40.12, 118.00, 119.28, 122.18, 123.30, 124.78, 130.87, 135.13, 138.23, 140.31, 142.80, 143.39, 162.85, 163.90, 167.08.

3.4.2 | (*E*)-*N*′-(furan-2-ylmethylene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6b)

Yield: 82%; M.P.: 212–215°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 0.82 (t, J = 8 Hz, 3H), 1.63 (sextet, J = 8 Hz, 2H), 2.55 (s, 3H), 2.65 (t, J = 8 Hz, 2H), 7.40–7.46 (m, 1H), 7.52–7.59 (m, 1H), 7.68–7.74 (m, 2H), 7.92–7.97 (m, 1H), 8.03–8.12 (m, 2H), 8.41–8.48 (m, 1H), 11.67 (s, 1H); HRMS (ESI)$^+$ calcd. for $C_{18}H_{18}N_4O_2S$ [M + H]$^+$: 354.1150 and found to be 355.1228.

3.4.3 | (*E*)-4-methyl-*N*′-(3-nitrobenzylidene)-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6c)

Yield: 85%; M.P.: 208–210°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.94 (t, J = 8 Hz, 3H), 1.75 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.83 (t, J = 8 Hz, 2H), 7.76–7.81 (m, 3H), 8.12 (d, J = 8 Hz, 1H), 8.22 (s, 1H), 8.27 (d, J = 8 Hz, 1H), 8.64 (d, J = 8 Hz, 1H), 8.82 (s, 1H), 12.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.50, 17.73, 21.61, 38.63, 116.11, 117.71, 118.17, 119.41, 122.37, 128.84, 132.62, 134.81, 138.48, 139.50, 147.06, 148.60, 160.95, 161.31, 162.02, 166.79; HRMS (ESI)$^+$ calcd. for $C_{20}H_{19}N_5O_3S$ [M + H]$^+$: 409.1209 and found to be 410.1287.

3.4.4 | (*E*)-4-methyl-*N*′-(4-methylbenzylidene)-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6d)

Yield: 90%; M.P.: 205–208°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.90 (t, J = 8 Hz, 3H), 1.72 (sextet, J = 8 Hz, 2H), 2.31 (s, 3H), 2.74 (s, 3H), 2.78 (t, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 7.62–7.75 (m, 4H), 8.06 (s, 1H), 8.60 (d, J = 4 Hz, 1H), 11.88 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 13.66, 21.08, 22.31, 36.48, 118.75, 120.39, 127.10, 127.25, 127.39, 129.58, 129.69, 140.03, 147.39, 150.36, 155.77, 158.10, 160.35, 168.05;

HRMS (ESI)$^+$ calcd. for $C_{21}H_{22}N_4OS$ $[M + H]^+$: 378.1514 and found to be 379.1592.

3.4.5 | (*E*)-*N'*-(4-chlorobenzylidene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6e)

Yield: 83%; M.P.: 233–236°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.94 (t, J = 8 Hz, 3H), 1.75 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.83 (t, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H), 7.76–7.82 (m, 4H), 8.14 (s, 1H) 8.65 (d, J = 4 Hz, 1H), 12.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm = 14.33, 17.56, 22.15, 39.12, 118.20, 119.08, 122.78, 123.42, 125.08, 131.17, 134.22, 137.29, 141.01, 142.10, 143.40, 161.15, 162.70, 166.17.

3.4.6 | (*E*)-*N'*-(2-bromobenzylidene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6f)

Yield: 87%; M.P.: 240–242°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.94 (t, J = 8 Hz, 3H), 1.75 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.83(t, J = 8 Hz, 2H), 7.71–7.82 (m, 6H), 8.13(s, 1H), 8.65 (d, J = 4 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 12.84, 17.62, 22.94, 34.82, 116.87, 120.12, 125.17, 127.35, 131.15, 133.57, 138.52, 144.64, 146.53, 151.70, 153.12, 157.60, 158.25, 159.82, 162.38, 166.16.

3.4.7 | (*E*)-*N'*-(4-methoxybenzylidene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6g)

Yield: 90%; M.P.: 218–220°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.93 (t, J = 8 Hz, 3H), 1.75 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.87 (t, J = 8 Hz, 2H), 3.87 (s, 3H), 7.02 (d, J = 8 Hz, 2H), 7.65–7.77 (m, 4H), 8.08 (s, 1H), 8.66 (d, J = 4 Hz, 1H), 11.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.95, 17.78, 22.18, 39.35, 56.67, 112.67, 116.19, 116.70, 119.18, 124.76, 127.06, 138.35, 142.33, 148.40, 159.12, 159.77, 160.22, 162.14, 166.27.

3.4.8 | (*E*)-*N'*-(3-chlorobenzylidene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6h)

Yield: 84%; M.P.: 210–212°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.92 (t, J = 8 Hz, 3H), 174 (sextet, J = 8 Hz, 2H), 2.78 (s, 3H), 2.80 (t, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 7.69–7.76 (m, 4H), 7.90 (s, 1H), 8.11 (s, 1H), 8.64 (d, J = 4 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm = 13.77, 20.36, 21.38, 36.40, 118.47, 118.90, 124.10, 126.54, 129.15, 131.21, 133.82, 140.77, 142.43, 146.95, 147.99, 150.46, 152.30, 163.87, 164.59, 166.20.

3.4.9 | (*E*)-*N'*-(3-methoxybenzylidene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6i)

Yield: 89%; M.P.: 189–191°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.92 (t, J = 8 Hz, 3H), 1.74 (sextet, J = 8 Hz, 2H), 2.77 (s, 3H), 2.79 (t, J = 8 Hz, 2H), 3.82 (s, 3H), 7.40 (t, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 7.65–7.78 (m, 3H), 8.05 (d, J = 8 Hz, 2H), 8.62 (d, J = 8 Hz, 1H), 11.65 (s, 1H).

3.4.10 | (*E*)-4-methyl-*N'*-(4-nitrobenzylidene)-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6j)

Yield: 80%; M.P.: 244–246°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.94 (t, J = 8 Hz, 3H), 1.75 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.83 (t, J = 8 Hz, 2H), 6.80–6.95 (m, 4H), 7.53–7.64 (m, 1H), 7.66–7.77 (m, 1H), 8.56–8.78 (m, 1H), 11.05 (s, 1H). HRMS (ESI)$^+$ calcd. for $C_{20}H_{19}N_5O_3S$ $[M + H]^+$: 409.1209 and found to be 410.1287.

3.4.11 | (*E*)-*N'*-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6k)

Yield: 87%; M.P.: 170–175°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.93 (t, J = 8 Hz, 3H), 1.75 (sextet, 2H), 2.76 (s, 3H), 2.97 (t, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H), 7.53–7.68 (m, 5H), 8.02 (s, 1H), 8.55 (d, J = 4 Hz, 1H), 11.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 13.31, 18.42, 22.29, 39.66, 117.25, 118.61, 125.53, 126.88, 128.26, 129.43, 133.63, 143.57, 145.18, 149.51, 161.59, 162.09, 162.78, 167.51; HRMS (ESI)$^+$ calcd. for $C_{20}H_{20}N_4OS$ $[M + H]^+$: 364.1358 and found to be 365.1439.

3.4.12 | (*E*)-*N'*-(3-bromobenzylidene)-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazide (6l)

Yield: 88%; M.P.: 238–240°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm = 0.94 (t, J = 8 Hz, 3H), 1.75 (sextet, J = 8 Hz, 2H), 2.79 (s, 3H), 2.80 (t, J = 8 Hz, 2H), 7.43 (t, J = 8 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 7.70–7.75 (m, 3H), 8.08 (d, J = 8 Hz, 2H), 8.63 (d, J = 8 Hz, 1H), 12.07 (s,

1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ ppm = 12.07, 17.19, 20.96, 38.68, 115.73, 117.13, 120.66, 125.12, 127.61, 129.21, 130.68, 134.59, 134.80, 140.33, 148.24, 148.44, 160.27, 161.24, 161.38, 166.11; HRMS $(ESI)^+$ calcd. for $C_{20}H_{19}N_4OSBr$ $[M + H]^+$: 442.0463 and found to be 443,0537.

4 | CONCLUSIONS

In conclusion, we have reported the synthesis of new substituted (*E*)-*N'*-benzylidene-4-methyl-2-(2-propylpyridin-4-yl)thiazole-5-carbohydrazides starting from the clinically used antitubercular drug prothionamide. The synthesized compounds were characterized with the help of ^1H, ^{13}C NMR, and HRMS spectral analyses. The in vitro antimicrobial activities of all the synthesized carbohydrazides (**6a-l**) were investigated by using the diffusion method. Among the series, compounds **6b**, **6e**, **6j**, and **6k** are found to possess encouraging antimicrobial activities. Good DPPH scavenging activity was demonstrated by carbohydrazides **6b** and **6i** compared to ascorbic acid. The obtained results imply that the new pyridinyl- and thiazolyl-bearing carbohydrazide framework may be considered for further investigation and optimization when designing antimicrobial and antioxidant agents.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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