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Synthesis of novel triazolothione, thiadiazole, triazole functionalized furo/thieno [2,3-*b*] pyridine derivatives and their antimicrobial activity

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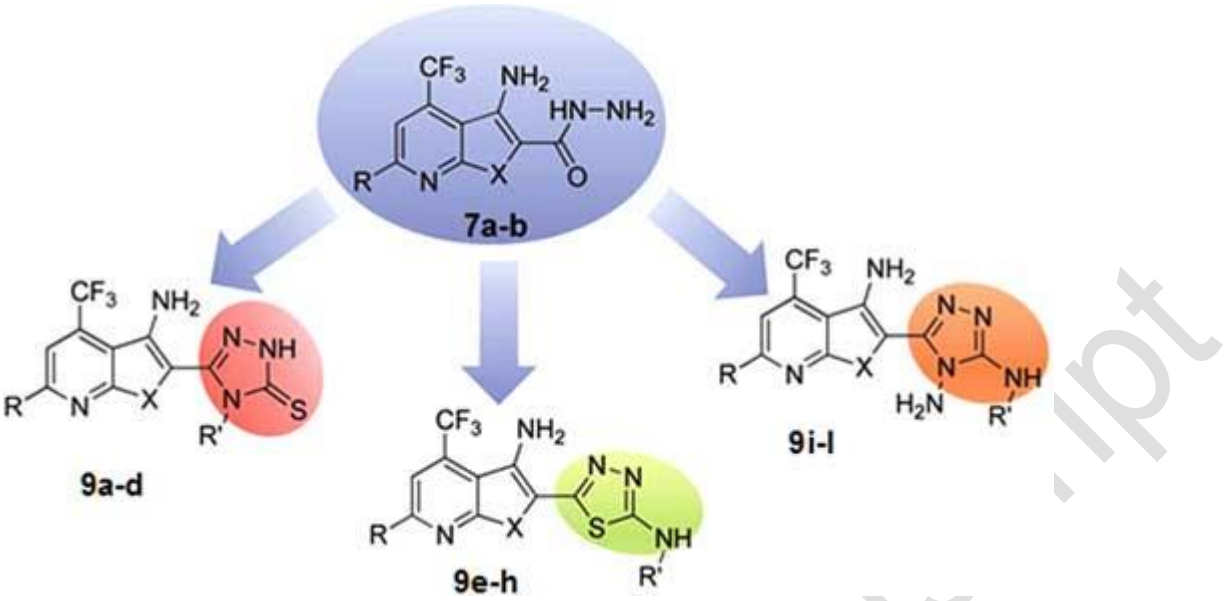
ABSTRACT

A series of novel triazolothione, thiadiazole, triazole functionalized furo/thieno [2,3-*b*] pyridine derivatives **9a-l** respectively were prepared starting from 2 (1*H*) pyridone **3** via selective O/S-alkylation followed by Thorpe-Ziegler cyclization to form furo/thieno [2,3-*b*] pyridine derivatives **6**. Compounds **6** on reaction with hydrazine hydrate resulted carbohydrazide derivatives **7** further reacted with diverse substituted phenyl isothiocyanates to form phenyl hydrazine carbothiamide derivatives **8**. Each compound **8** is independently reacted in presence of NaOH, H_2SO_4 and $N_2H_4.H_2O$ to form triazolothione, thiadiazole, triazole functionalized furo/thieno [2,3-*b*] pyridine derivatives **9a-l** respectively. All the products **9a-l** were screened against Gram +ve, Gram –ve bacteria and fungal strains. Compounds **9c-h** showed high activity against *Bacillus Subtilis* MTCC121 at < 8.0 micro molar concentration. Promising compounds further screened for minimum bactericidal concentration against *Bacillus Subtilis* MTCC 121 using ciprofloxacin as standard and found to show very good activity. These compounds also screened for bio-film inhibition activity against *Bacillus Subtilis* MTCC 121 using Erythromycin as standard and confirmed the high activity.

Graphical Abstract



A series of novel triazolothione, thiadiazole, triazole functionalized furo/thieno [2,3-*b*] pyridine derivatives **9a-l** respectively were prepared. All the products **9a-l** were screened against Gram +ve, Gram –ve bacteria and fungal strains. Compounds **9c-h** showed promising activity against *Bacillus subtilis* MTCC121 at < 8.0 micro molar concentration, promising compounds further screened for minimum bactericidal concentration against *Bacillus Subtilis* MTCC 121 using ciprofloxacin as standard and found to show very good activity. These compounds also screened for bio-film inhibition activity against *Bacillus Subtilis* MTCC 121 using Erythromycin as standard and confirmed the high activity.

KEY WORDS: 2(1H) pyridone, antimicrobial activity, O/S-alkylation, thiadiazole, thorpe-ziegler cyclization, triazole, triazolothione

1. Introduction

Among all classes of biologically active compounds, the 5,6 fused ring systems such as furopyridines and thienopyridines attracts important position in the development of new

pharmaceutical agents which are structurally analogues to indoles and pyrrolopyridines, and play a significant role in promoting activity.[1], [2] Pyridyl, furopyridine and thienopyridine ring system also considered as a prominent scaffold present in many of bioactive molecules, played a vital role in the development of different medicinal agents.[3] However, this core structures have shown activity against HIV,[4] CNS disorders,[5] skin diseases[6] and hyperglycemia.[7] Azoles, especially the bio-isosteric 1,2,4-triazolothione, 1,2,4-triazoles and 1,3,4-thiadiazoles, are important molecules known to interact with particular receptors on enzyme receptor sites.[8] During recent years, there has been intense investigation of different classes of thiadiazole compounds and many of which known to possess interesting biological activity such as antimicrobial,[9–11] antituberculosis,[12] antiinflammatory,[13–15] anticonvulsant,[16], [17] antihyper tensive,[18], [19] local anesthetic,[20] anticancer,[21], [22] and hypoglycemic activities.[23] Recently, it was found that the trifluoromethyl group[24], [25] at a strategic position of an organic molecule, dramatically alters the properties of molecule in terms of lipid solubility, oxidative thermal stability, permeability and oral bio-availability. Moreover, in our earlier reports, we have reported the synthesis of different oxadiazole derivatives and found that the combination of these derivatives with furo/thieno [2,3-*b*] pyridine fused ring exhibited promising antimicrobial activities. Encouraged by these reports, some azole derivatives bearing a furo/thieno [2,3-*b*] pyridine moiety were synthesized with an aim to achieve the compounds having better antimicrobial activity. Keeping in view of earlier findings on the importance of azoles, here we have synthesized a series of novel 1,2,4-triazolothione, 1,3,4-thiadiazole and 1,2,4-triazole functionalized furo/thieno [2,3-*b*] pyridine derivatives, screened for antimicrobial activity and compounds **9c-h** which showed promising activity have been identified.

2. Chemistry

The 3-cyano-4-trifluoromethyl-6-(thiophen-2-yl)-pyridine 2(1*H*) one/ pyridine 2(1*H*) thione[26]

3 was reacted with 2-bromoethyl acetate and obtained selectively 2-O/S-ethylacetoxy-3-cyano-4-trifluoromethyl-6-(thiophen-2-yl) pyridine **5** and **6**. Compound **5** was cyclized in DMF using potassium carbonate as base and obtained furo/thieno pyridine derivatives **6**. The sequence of reactions is mainly an abstraction of proton from active methylene followed by cyclization onto nitrile carbon. This type of cyclization is also known as Thorpe-Ziegler cyclization. Compound **6** on reaction with hydrazine hydrate followed by reaction with diverse substituted phenylisocyanate in the presence of ethanol as a solvent resulted phenylhydrazinecarbothio amide derivatives **7**. Compound **7** was on reaction with phenylisothiocyante to form thiourea containing derivatives **8** on further reaction under different conditions with different reagents obtained different azole substituted furo/thieno [2,3-*b*] pyridine derivatives **9**. The synthetic pathway leading to the title compounds is given in Scheme 1, Scheme 2 and products are tabulated in **Table 1**.

3. Results & Discussion:

Antimicrobial activity &structure activity relationship

Compounds **9a-l** were screened for antimicrobial activity against seven bacterial organisms such as *Micrococcus luteus* MTCC 2470, *Staphylococcus aureus* MTCC96, *Staphylococcus aureus* MLS-16 MTCC 2940, *Bacillus subtilis* MTCC 121, *Escherichia coli* MTCC 739, *Pseudomonas aeruginosa* MTCC 2453, *Klebsiellaplanticola* MTCC 530 and one fungal strain *Candida albicans* MTCC 3017. Out of twelve compounds screened, six compounds **9c**, **9d**, **9e**, **9f**, **9g** and **9h** showed promising activity against Gram +ve *Bacillus subtilis* MTCC

121. Structure verses activity relationship revealed that, specific variation in structure showed enhanced activity. If we consider compound **9a-d** series of 1,2,4-triazolothione derivatives, compounds **9a** and **9b** (furopyridine derivatives) showed moderate activity MIC 15.6 µg/mL and compounds **9c** and **9d** (thienopyridine derivatives) showed promising activity MIC 7.8 µg/mL. It may be due to the presence of sulphur in place of oxygen. Compounds **9e-l** (1,3,4-thiadiazole derivatives) plays a crucial role to promote antibacterial activity against Gram +ve *Bacillus subtilis* MTCC 121. Among all the derivatives, compound **9h** showed high activity *i.e.* MIC is 3.9 µg/mL. It may be attributed to the presence of thiophene and methoxyphenyl group. However, compounds **9a-b** and **9i-l** could not show activity upto the concentration of 125 µg/mL against all the organisms. The details of activity data is outlined in **Tables 2–4**.

Experimental section

Melting points were recorded on Casia-Siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Bruker AV 300MHz in $CDCl_3$ & DMSO-d_6 using TMS as internal standard. Electron impact (EI) and chemical ionization mass spectra were recorded on a VG 7070 H instrument at 70 eV. All high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, USA) under Electrospray ionization.All the reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F_{254} (mesh); spots were visualized with UV light. Merck silica gel (60-120 mesh) was used for column chromatography. CHN analysis was recorded on a Vario EL analyser.

Antibacterial assay

The antimicrobial activity of the synthesized compounds was determined using well diffusion method[27] against different pathogenic bacterial and *Candida* strains procured from the Microbial Type Culture Collection and Gene Bank (MTCC), CSIR-Institute of Microbial Technology, Chandigarh, India. The pathogenic reference strains were seeded on the surface of the media petri plates, containing Muller-Hinton agar with 0.1 ml of previously prepared microbial suspensions individually containing 1.5×10^8cfu ml^{-1} (equal to 0.5 McFarland). Wells of 6.0 mm diameter were prepared in the media plates using a cork borer and the synthesized compounds dissolved in 10% DMSO at a dose range of 125-0.97 µg were added in each well under sterile conditions in a laminar air flow chamber. Standard antibiotic solutions of neomycin (bacterial strains) and miconazole (*Candida* strains) at a dose range of 125-0.97 µg $well^{-1}$, served as positive controls, while the well containing DMSO served as negative control. The plates were incubated for 24 h at 30°C and the well containing the least concentration showing the inhibition zone is considered as the minimum inhibitory concentration. All experiments were carried out in duplicates and mean values are represented.

Minimum bactericidal concentration (MBC) assay

Bactericidal assay[28] (NCCLS, 2000) was performed in sterile 2.0 mL micro fuge tubes against a panel of pathogenic bacterial strains, including *Micrococcus luteus* MTCC 2470, *Staphylococcus aureus* MTCC 96, *Staphylococcus aureus* MLS-16 MTCC 2940, *Bacillus subtilis* MTCC 121, *Escherichia coli* MTCC 739, *Pseudomonas aeruginosa* MTCC 2453 and *Klebsiella planticola* MTCC 530, cultured overnight in Mueller Hinton broth. Serial dilutions of test compounds were prepared in Mueller Hinton broth with different concentrations ranging from 0 to150 µg mL^{-1}. To the test compounds, 100 µL of overnight cultured bacterial suspensions were added to reach a final concentration of 1.5×10^8cfu mL^{-1} (equal to 0.5

McFarland) and incubated at 37 ºC for 24 h. After 24 h of incubation, the Minimum Bactericidal Concentration (MBC) was determined by sampling 10 µL of suspension from the tubes onto Mueller Hinton agar plates and were incubated for 24 h at 37 ºC to observe the growth of test organisms. MBC are the lowest concentration of test compound required to kill a particular bacterium strain. All the experiments were carried in duplicates.

Bio-film inhibition assay

The test compounds were screened in sterile 96 well polystyrene micro titer plates using the modified bio-film inhibition assay,[29] against a panel of pathogenic bacterial strains including *Staphylococcus aureus* MTCC 96, *Staphylococcus aureus* MLS16 MTCC 2940, *Bacillus subtilis* MTCC121, *Pseudomonas aeruginosa* MTCC 2453, and *Klebsiella planticola* MTCC 530, which were cultured overnight in tryptone soy broth (supplemented with 0.5% glucose). The test compounds of predetermined concentrations ranging from 0 to 250 µgmL^{-1} were mixed with the bacterial suspensions having an initial inoculum concentration of 5×10^5 cfu mL^{-1}. Aliquots of 100 µL were distributed in each well and then incubated at 37 ºC for 24 h under static conditions. The medium was then discarded and washed with phosphate buffered saline to remove the non-adherent bacteria. Each well of the micro titer plate was stained with 100 µL of 0.1% crystal violet solution followed by 30 min., incubation at room temperature. Later, the crystal violet solution from the plates was discarded, thoroughly washed with distilled water for 3 to 4 times and air dried at room temperature. The crystal violet stained bio-film was solubilized in 95% ethanol (100 µL) and the absorbance was recorded at 540 nm using TRIAD multimode reader (Dynex Technologies, Inc, Chantilly, VA, USA). Blank wells were employed as background check. The inhibition data were interpreted from the dose-response curves, where IC_{50} value is defined as the concentration of inhibitor required to inhibit 50% of bio-film

formation under the above assay conditions. All the experiments were carried out in triplicates and the values are indicated as mean ± S.D.

4. Conclusion

In conclusion, we have successfully prepared a series of novel triazolothione, thiadiazole, triazole functionalized furo/thieno [2,3-*b*] pyridine derivatives **9a-l**, screened against Gram +ve, Gram –ve bacteria and fungal strains. Compounds **9c-h** showed high activity against *Bacillus subtilis* MTCC121 at < 8.0 micro molar concentration. Promising compounds further screened for minimum bactericidal concentration against *Bacillus Subtilis* MTCC 121 using ciprofloxacin as standard and found to show moderate to very good activity.

General procedure for the synthesis of 3-(3-Amino-6-(thiophen-2-yl)-4-(trifluoromethyl) furo[2,3-b]pyridin-2-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione derivatives (9a-d)

2-(3-Amino-6-(thiophen-2-yl)-4-(trifluoromethyl)furo[2,3-b]pyridine-2-carbonyl)-N-phenyl hydrazinecarbothioamide (**8a**) (0.01 mol) in 2 N NaOH was allowed to reflux for 4-6 h. The resulting solution was cooled to room temperature and acidified to pH 3-4 with 37% hydrochloric acid. The precipitate formed was filtered and washed with distilled water, dried to afford compound **9a**.

3-(3-Amino-6-(thiophen-2-yl)-4-(trifluoromethyl)furo[2,3-b]pyridin-2-yl)-4-phenyl-1H-1,2,4-triazole-5(4H)-thione (9a):

White solid; mp181-183^{o}C;IR (KBr, cm^{-1}): 3380, 3310 (-NH_2) 1223 (-NHCS-); ^{1}H NMR (DMSO-d_6, 300 MHz): δ ppm 6.22 (br, s, 2H, NH_2), 7.12-7.18 (m, 2H, Ar-H), 7.41-7.48 (m, 4H,

Ar-H), 7.60 (dd, *J* = 4.90, 1H, Ar-H), 7.78 (dd, *J* = 3.76, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 13.28 (br, s, 1H, -NHCS-); ^{13}C NMR (DMSO-d_6, 75 MHz): δ ppm 123.0, 123.1, 123.7, 125.2, 126.0, 128.0, 129.0, 129.8, 129.9, 131.3, 133.4, 133.8, 134.6, 142.1, 146.6, 150.4, 157.0, 162.3;MS (ESI): m/z [$(M+H)^+$]: 460. HRMS m/z Calcd.for $C_{20}H_{12}F_3N_5OS_2$ [$(M+H)^+$]: 460.0469 Found: 460.0472.

General procedure for the synthesis of 2-(5-(Phenylamino)-1,3,4-thiadiazol-2-yl)-6-(thiophen-2-yl)-4-(trifluoromethyl)furo[2,3-b]pyridin-3-amine derivatives (9e-h)

A mixture of 0.001 mol of 2-(5-(phenylamino)-1,3,4-thiadiazol-2-yl)-6-(thiophen-2-yl)-4-(trifluoromethyl)furo[2,3-b]pyridin-3-amine (**8a**) and concentrated H_2SO_4 (1 mL) was stirred at room temperature for 1 h. Then the reaction mixture was poured over crushed ice. The precipitated solid was washed with sodium carbonate solution followed by water to afford compound (**9e**).

2-(5-(Phenylamino)-1,3,4-thiadiazol-2-yl)-6-(thiophen-2-yl)-4-(trifluoromethyl)furo[2,3-b]pyridin-3-amine (9e):

Light yellow solid; mp 236-238 ^oC; IR (KBr, cm^{-1}): 3386, 3313 (-NH_2); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz): δ ppm 6.23 (br. s, 2H, -NH_2), 7.32-7.36 (m, 2H, Ar-H), 7.53 (dd, *J* = 4.78, 2H, Ar-H), 7.59-7.62 (m2H, Ar-H), 7.71 (dd, *J* = 4.75, 1H, Ar-H), 8.86 (dd, *J* = 3.71, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 10.14 (br. s, 1H, -NH-),;^{13}C NMR (DMSO-d_6, 75 MHz): δ ppm 121.2, 122.8, 123.9, 125.7, 127.0, 128.4, 129.1, 130.1, 131.5, 133.5, 134.9, 136.6, 139.7, 140.7, 142.6, 143.8, 152.5, 153.7; MS (ESI): m/z [$(M+H)^+$]: 460. HRMS m/z Calcd.for $C_{20}H_{12}F_3N_5OS_2$ [$(M+H)^+$]: 460.0460, Found 460.0464.

General procedure for the synthesis of 5-(3-Amino-6-(thiophen-2-yl)-4-(trifluoromethyl) furo[2,3-b]pyridin-2-yl)-N3-phenyl-4H-1,2,4-triazole-3,4-diamine(9i-l)

2-(3-Amino-6-(thiophen-2-yl)-4-(trifluoromethyl)furo[2,3-b]pyridine-2-carbonyl)-N-phenyl hydrazinecarbothioamide (**8a**) (0.01 mol) was mixed with $N_2H_4.H_2O$ (0.01 mol) and MeOH (1mL). The solution was refluxed for 5-6 h. After cooling to room temperature, ice water (10mL) was added to the reaction mixture, which was then neutralized with 3N HCl to form a precipitate. The precipitate was isolated by filtration to afford the Triazole derivatives **9i-l**.

5-(3-Amino-6-(thiophen-2-yl)-4-(trifluoromethyl)furo[2,3-b]pyridin-2-yl)-N3-phenyl-4H-1,2,4-triazole-3,4-diamine (9i):

White solid; mp 222-224 ºC; IR (KBr, cm^{-1}): 3482, 3420 (-NH_2),3378, 3318 (-NH_2); ^{1}H NMR ($CDCl_3$+DMSO-d_6, 300 MHz): δ ppm 5.21(br. s, 2H, -NH_2), 6.26 (br. s, 2H, -NH_2), 7.01 (br. s, 1H, -NH-), 7.29-7.33 (m, 2H, Ar-H), 7.50 (dd, *J* = 4.71, 1H, Ar-H), 7.58-7.62 (m, 3H, Ar-H), 7.68(dd, *J* = 4.71, 1H, Ar-H), 7.79 (dd, *J* = 3.71, 1H, Ar-H), 7.91 (s, 1H, Ar-H);^{13}C NMR (DMSO-d_6, 75 MHz): δ ppm 119.9, 120.8, 123.0, 123.4, 124.6, 125.6, 126.4, 127.9, 129.6, 131.4, 133.9, 134.2, 135.6, 137.3, 139.5, 141.8, 147.9, 149.8 121.7, 123.4, 123.9, 124.6, 125.1, 126.2, 126.8, 128.4, 130.3, 131.7, 132.7, 134.7, 136.9, 139.2, 140.7, 142.6, 143.7, 146.4, 149.7, 154.4;MS (ESI): m/z [$(M+H)^+$]: 458. HRMS m/z Calcd. for $C_{20}H_{14}F_3N_7OS$ [$(M+H)^+$]: 458.1023, Found 458.1026.

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Supporting Information

Full experimental detail, ^{1}H and ^{13}C NMR spectra, ESI MS and HRMS. This material can be found via the "Supplementary Content" section of this article's webpage.

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Table 1. Preparation of 1,3,4-oxadiazole substituted furo/thieno [2,3-*b*] pyridine derivatives **9a-l.**

Entry	Compound	R	X	R′	Yield(%)
1.	**9a**	Thien-2-yl	O	C_6H_5	81
2.	**9b**	Thien-2-yl	O	4-$OCH_3C_6H_4$	82
3.	**9c**	Thien-2-yl	S	C_6H_5	79
4.	**9d**	Thien-2-yl	S	4-$OCH_3C_6H_4$	80
5.	**9e**	Thien-2-yl	O	C_6H_5	88
6.	**9f**	Thien-2-yl	O	4-$OCH_3C_6H_4$	85
7.	**9g**	Thien-2-yl	S	C_6H_5	70
8.	**9h**	Thien-2-yl	S	4-$OCH_3C_6H_4$	72
9.	**9i**	Thien-2-yl	O	C_6H_5	85
10.	**9j**	Thien-2-yl	O	4-$OCH_3C_6H_4$	82
11.	**9k**	Thien-2-yl	S	C_6H_5	80
12.	**9l**	Thien-2-yl	S	4-$OCH_3C_6H_4$	78

Table 2. Antibacterial and antifungal activity.

Entry	Compds.	Minimum Inhibitory Concentration (MIC) (µg/ml)							
		Micrococcus luteus MTCC 2470	Staphylococcus aureus MTCC 96	Staphylococcus aureus MLS-16 MTCC 2940	Bacillus subtilis MTCC 121	Escherichia coli MTCC 739	Pseudomonas aeruginosa MTCC 2453	Klebsiellapl anticola MTCC 530	Candida albicans MTCC 3017
1	**9a**	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0
2	**9b**	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0
3	**9c**	>125.0	>125.0	>125.0	15.6	>125.0	>125.0	>125.0	>125.0
4	**9d**	>125.0	>125.0	>125.0	15.6	>125.0	>125.0	>125.0	>125.0
5	**9e**	>125.0	>125.0	>125.0	7.8	>125.0	>125.0	>125.0	>125.0
6	**9f**	>125.0	>125.0	>125.0	7.8	>125.0	>125.0	>125.0	>125.0
7	**9g**	>125.0	>125.0	>125.0	7.8	>125.0	>125.0	>125.0	>125.0
8	**9h**	>125.0	>125.0	>125.0	3.9	>125.0	>125.0	>125.0	>125.0
9	**9i**	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0
10	**9j**	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0

11	**9k**	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0
12	**9l**	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0	>125.0
Ciprofloxacin		0.9	0.9	0.9	0.9	0.9	0.9	0.9	–
Miconazole (Standard)		–	–	–	–	–	–	–	7.8

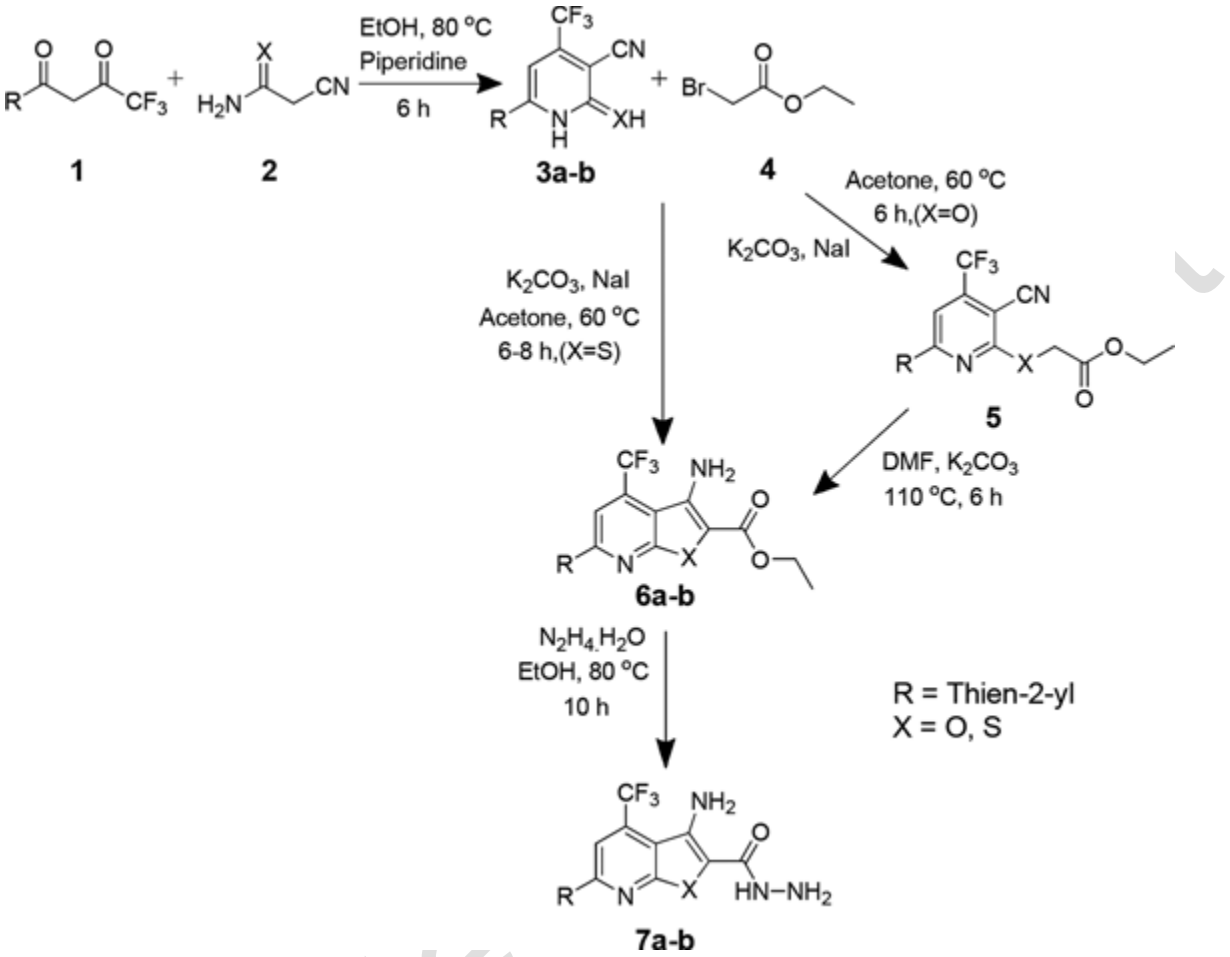
Table 3. Bactericidal activity results.

S. No.	Test compound	Minimum Bactericidal Concentration (µg/ml)
		Bacillus subtilis MTCC 121
1	**9c**	15.6
2	**9d**	15.6
3	**9e**	7.8
4	**9f**	7.8
5	**9g**	7.8
6	**9h**	3.9
Ciprofloxacin (Standard)		1.17

Table 4. Bio-film inhibition assay results.

S. No.	Test compound	IC_{50} values in (μg/ml)
		Bacillus subtilis MTCC 121
1	**9c**	4.2 ± 0.26
2	**9d**	16.4± 0.32
3	**9e**	6.1± 0.16
4	**9f**	3.6± 0.12
5	**9g**	6.8± 0.34
6	**9h**	1.9± 0.11
Erythromycin (Standard)		0.2± 0.09

Scheme 1.[Aq]



Scheme 2.[Aq]