Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(9):670-675

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and antibacterial activity of novel hydrazides containing thienopyrimidine

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ABSTRACT

A series of novel thieno pyrimidine-4yl-pyrrolidine-2-carboxylic acid hydrazide derivatives were prepared by a facile six step procedure that afford mild reaction conditions, simple protocol and good yields. Synthesized compounds were test for the antibacterial activities. The structure of the prepared compounds was confirmed by ES-MS, ^{1}H NMR and elemental analysis.

Keywords: thieno pyrimidine, proline, Gewald reaction, hydrazides, antibacterial activity

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INTRODUCTION

In an era of increasing bacterial resistance to classical antibacterial agents. It has been postulated that the development of resistance to known antibiotics could be overcome by identifying new drug targets via genomics, improving existing antibiotics and most importantly by identifying new antibacterial agents with novel structures and mode of action. [1] Pyrimidine derivatives play an imperative role in many transformation and biochemical processes. Pyrimidine and its fused ring system is present in Cytosine, adenine, guanine and thiamine, which form a part of ribonucleic acid (RNA), deoxyribonucleic acid (DNA), vitamins and co-enzymes and other purines. Fused pyrimidine nucleus is used in the discovery of bioactive molecules. [2] Hydrazide and their hetero-cyclic products show evidence of diverse biological activities including antibacterial, antifungicidal, analgesic, antituberculosis, anticancer, anti-inflammatory properties [3-17].

In continuation of our research work on synthesis of thieno pyrimidines, we prepared new thieno [2, 3-d] pyrimidines by introducing a secondary nitrogen containing amino acid L- proline at C-4 position and synthesized structurally different hydrazides to explore the potential of thieno[2,3-d] pyrimidine as antibacterial agents. The synthesized compounds were screened for their antibacterial activities.

EXPERIMENTAL SECTION

All the raw material were obtained commercially and used without further purification. ^{1}H NMR spectra were recorded using $CDCl_3$ and DMSO-D_6 as solvent with tetramethylsilane (TMS) as an internal standard on Varian 400-MHz instruments. Electron spray ionization-mass spectra were recorded on Shimadzu LC-MS-2010A instrument.

Ethyl 2-Amino-5, 6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate (2a)
Yield =96%. Mp 90 °C **^{1}H NMR** ($CDCl_3$) δ 5.83 (s, 2H), 4.25 (q, 2H, J = 7.1 Hz), 2.85-2.80 (m, 2H), 2.74-2.69 (m, 2H), 2.36-2.26 (m, 2H), 1.33 (t, 3H, J = 7.1 Hz); MS m/z (%) 211.3

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (2b)
In to a mixture of cyclohexanone (49 gm, 0.5 mol), ethyl 2-cyanoacetate (56gm, 0.5mol,) and sulphur (16gm, 0.5mol) in 150ml of ethanol was added morpholine (44gm, 0.5mol). The mixture was stirred for 8 hr at room temperature. The reaction mixture was diluted with water and the precipitate was collected by filtration and recrystallized from ethanol. **2b** as yellow solid (62gm, 55%) Mp= 115^0C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.94(s, 2H), 4.25(q, 2H), 2.69-2.60(m, 2H), 2.49-2.43(m, 2H), 1.76-1.66(m, 4H), 1.33(t, 3H).

3,5,6,7-Tetrahydro-4H-cyclopenta[4,5]thieno[2,3-d]pyrimidin-4-one (3a).
Yield=83%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.47 (dddd, 2H), 2.95-2.98 (m, 2H), 3.05-3.09 (m, 2H), 8.03 (s, 1H). LCMS (ESI): m/z 193.0 $[M + H]^+$.

5, 6, 7, 8-Tetrahydrobenzo [4, 5] thieno [2, 3-d] pyrimidin-4(3H)-one (3b)
The mixture of compound **2b** (35g, 0.16 mol) in 150ml of formamide was heated at 180^0C for 4 h and cooled down. The mixture was poured into 200 ml water and filtered. The solid was collected and recrystallized from ethanol. Compound **3b** as yellow solid (25 g, 75%); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 12.31 (br s, 1H), 8.00(s, 1H), 2.85-2.88 (m, 2H), 2.72-2.75(m, 2H), 1.75-1.82(m, 4H). ES-MS: m/z 207.2 $(M+H)^+$

4-Chloro-6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidine (4a)
Yield =88%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.48-2.56 (m, 2H), 3.04-3.08 (m, 2H), 3.13-3.17 (m, 2H), 8.70 (s, 1H). LCMS (ESI): m/z 210.9 $[M + H]^+$.

4-Chloro-5,6,7,8-Tetrahydrobenzo-[4,5]thieno[2,3-d]pyrimidin-4(3H)-one (4b)
A suspension of compound **3b** (25g, 0.12 mol) in 150 ml of $POCl_3$ was heated at reflux for 2h. $POCl_3$ was removed at reduced pressure and the residue was poured onto ice and filtered. The solid was washed with water and dried. Compound **4b** as brown solid (23g, 85%); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.72(s, 1H), 3.10-3.12 (m, 2H), 2.88-2.90 (m, 2H), 1.75-1.92-1.95(m, 4H). ES-MS: m/z 225.3 $(M+H)^+$

1-(2, 3-Dihydro-1H-8-thia-5,7-diaza-cyclopenta[a] indene-4yl)-pyrrolidine-2-carboxylic acid ethyl ester (5a) Yield =80 %, Yellowish gel (25 g) ES-MS: m/z 346.3 $(M+H)^+$

1-(5,6,7,8-tetrehydrobenzo-[4,5]thieno[2,3-d]pyrimidine-4-yl)-pyrolidine-2-carboxylic acid ethyl ester (5b) To a clear solution of compound **4b** (20 g, 0.089 mol) in Methanol 200ml was added L-Proline Ethyl ester hydrochloride (16g, 0.089 mol) and Triethylamine (27 ml, 0.267 mol) , stirred the reaction mixture for 3h. Methanol was removed under reduced pressure and residue was taken in EtOAc, washed with water, 1N HCl solution in water and saturated $NaHCO_3$ solution in water. Collected Organic layer was dried over Na_2SO_4 and removed under reduced pressure to yield Ester intermediate **5b** as a yellowish gel (25 g, 84%) **5.** This was used for without further purification. ES-MS: m/z 332.3 $(M+H)^+$

1-(2,3-Dihydro-1H-8-thia-5,7-diaza-cyclopenta[a] indene-4yl)-pyrrolidine-2-carboxylic acid (6a) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.49-1.50 (m, 1H). 1.75-1.98(m, 6H), 2.80-2.86 (m, 2H), 3.81-3.84 (m, 2H), 4.78 (t, 1H), 8.23(s, 1H), ES-MS: m/z 388.3 $(M+H)^+$

1-(5,6,7,8-tetrehydro-benzo[4,5]thieno[2,3-d]pyrimidine-4-yl)-pyrolidine-2-carboxylic acid (6b) A suspension of ester compound **5b** (25g, 0.075 mol) in 225 ml THF and 25 ml water was added Lithium hydroxide monohydrate (4.2 g, 0.11 mol) at 0^0C, and the reaction mixture for 12 h. Distilled out THF under vacuum and to the remaining aqueous residue was added 1N HCl solution in water to adjusted the solution PH = 4, solid was precipitates out. Filtered the solid and dried Compound **6b** as yellowish solid (16g, 70%); **^{1}H NMR** (DMSO-d6, 400 MHz) δ 8.23(s, 1H), 4.80(t, 1H), 3.82-3.89 (m, 2H), 2.80-2.86 (m, 4H), 1.75-1.98(m, 6H), 1.49-1.50 (m, 1H). ES-MS: m/z 302.2 $(M+H)^-$

3-Chloro-benzoic acid N'-[1-(2,3-dihydro-1H-8-thia-5,7-diaza-cyclopenta[a]inden-4-yl)-pyrrolidine-2-carbonyl]-hydrazide (7a) To a solution of 1-(2,3-Dihydro-1H-8-thia-5,7-diaza-cyclopenta[a] indene-4yl)-pyrrolidine-2-carboxylic acid (1g, 3.31 mmol) in DMF (5ml) was added EDC.HCl (950 mg, 4.96 mmol) and 3-Chloro-benzoic acid hydrazide (331 mg, 3.31mmol) followed by the HOBt (443mg, 3.31mmol). Stirred the reaction mixture for 6h. Quenched the reaction mixture with water (50ml), solid was comes out was filtered, dried and washed with diethyl ether to gave compound **7a (**800mg, 62%).**^{1}H NMR** (DMSO-d6, 400 MHz) δ 2.04-2.18 (m,2H), 2.25-2.44 (m, 3H), 2.89-2.99 (m, 3H), 3.08-3.16 (m, 2H), 3.72-3.77 (m,1H), 3.88-3.92 (m, 1H), 4.84-4.87 (m, 1H, N-CH-CO), 7.50-7.54 (m, 1H, Ar-H), 7.62-7.64 (m, 1H, Ar-H), 7.82-7.90 (m, 2H, Ar-H), 8.24 (s, 1H, Ar-H), 9.99 (s, 1H, -NH-NH-), 10.47 (s, 1H, -NH-NH-), ES-MS: m/z 442.4 $(M+H)^+$, Mp= 122-124^{0}C, Anal. Calcd. for $C_{21}H_{20}ClN_5O_2S$: C, 57.07; H, 4.56; N, 15.85; S, 7.26. Found: C, 57.04; H, 4.53; N, 15.83; S, 7.22

4-Methoxy-benzoic acid N'-[1-(2, 3-dihydro-1H-8-thia-5, 7-diaza-cyclopenta[a]inden-4yl)-pyrrolidine-2-carbonyl]-hydrazide (8a) ^{1}H NMR (DMSO-d6, 400 MHz) δ 2.73 (s, 1H), 2.10-2.42 (m, 6H), 2.89-2.98 (m, 3H, -OC<u>H</u>$_3$), 3.10-3.16 (m, 2H), 3.73-3.74 (m,1H), 3.80 (s, 1H), 3.90-3.92 (m, 1H), 4.85-4.88 (t, 1H, -N-C<u>H</u>-CO), 6.98-7.00 (d, 2H, Ar-<u>H</u>), 7.84-7.86 (d, 2H, Ar-<u>H</u>), 8.23 (s, 1H, Ar-<u>H</u>), 9.85 (s, 1H, -NH-N<u>H</u>), 10.18 (s, 1H, -N<u>H</u>-NH), ES-MS: m/z 397.3 (M+H) $^+$ Mp= 131-133^{0}C. Anal. Calcd. for $C_{22}H_{23}N_5O_3S$: C, 60.40; H, 5.30; N, 16.01; S, 7.33. Found: C, 60.38; H, 4.28; N, 15.09; S, 7.30

1-(2, 3-dihydro-1H-8-thia-5, 7-diaza-cyclopenta[a]inden-4yl)-pyrrolidine-2-carboxylic acid N' (3-Phenyl-propionyl)-hydrazide (9a) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.93-2.03 (m,3H), 2.07-2.12 (m, 1H), 2.32-2.42 (m,4H), 2.67-2.83 (m,2H), 2.89-2.98 (m, 2H), 3.09-3.14 (m, 2H), 3.71-3.75 (m, 1H), 3.84-3.89 (m, 1H), 4.75-4.78 (m, 1H, N-C<u>H</u>-CO), 7.13-7.28 (m, 5H, Ar-<u>H</u>), 8.19 (s, 1H, Pyrimidine-H), 9.77-9.79 (d, 2H, -N<u>H</u>-N<u>H</u>-), ES-MS: m/z 435.3 (M+H) $^+$ Mp= 126-128^{0}C. Anal. Calcd. for $C_{23}H_{25}N_5O_2S$: C, 63.43; H, 5.79; N, 16.08; S, 7.36. Found: C, 63.39; H, 5.75; N, 16.04; S, 7.33

Nicotinic acid N'-[1-(2, 3-dihydro-1H-8-thia-5, 7-diaza-cyclopenta[a]inden-4yl)-pyrrolidine-2-carbonyl]-hydrazide (10a) ^{1}H NMR (DMSO-d6, 400 MHz) δ 2.07-2.18 (m,2H), 2.26-2.44 (m, 3H), 2.95-2.99 (m, 3H), 3.09-3.14 (m, 1H), 3.72-3.74 (m,2H), 3.89-3.93 (m, 1H), 4.85-4.88 (m, 1H, N-C<u>H</u>-CO), 7.50-7.54 (m, 1H, Ar-H), 8.19-8.24 (m, 2H, Ar-H), 8.72-8.74 (m, 1H, Ar-H), 9.01 (s, 1H, Ar-H), 10.01 (s, 1H, -N<u>H</u>-NH-), 10.56 (s, 1H, -NH-N<u>H</u>-), ES-MS: m/z 409.1 (M+H) $^+$ Mp= 112-114^{0}C, Anal. Calcd. for $C_{20}H_{20}N_6O_2S$: C, 58.81; H, 4.94; N, 20.57; S, 7.85. Found: C, 58.83; H, 4.91; N, 20.53; S, 7.83

Furan-2-carboxylic acid N'-[1-(2, 3-dihydro-1H-8-thia-5, 7-diaza-cyclopenta[a]inden-4yl)-pyrrolidine-2-carbonyl]-hydrazide (11a) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.95-2.15 (m,3H) 2.25-2.45 (m,3H), 2.95-2.98 (m, 2H), 3.10-3.15 (m, 2H), 3.73-3.76 (m, 1H), 3.87-3.90 (m,1H), 4.82-4.85 (m, 1H, N-C<u>H</u>-CO), 6.62 (br s, 1H, Ar-<u>H</u>), 7.20-7.21 (d, 1H, Ar-<u>H</u>), 7.86 (s, 1H, Ar-<u>H</u>), 8.22 (s, 1H, Ar-<u>H</u>), 9.89 (s, 1H, -NH-N<u>H</u>), 10.22 (s, 1H, -N<u>H</u>-NH-), ES-MS: m/z 397.1 (M+H) $^+$ Mp= 112-114^{0}C. Anal. Calcd. for $C_{19}H_{19}N_5O_3S$: C, 57.42; H, 4.82; N, 17.62; S, 8.07. Found: C, 57.39; H, 4.80; N, 17.60; S, 8.03

3-Chloro-benzoic acid N'-[1-(5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-pyrrolidine-2-carbonyl]-hydrazide (7b) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.74-1.79 (m, 4H), 1.95-2.02 (m, 4H), 2.33-2.40 (m, 2H), 3.11-3.15 (m, 2H), 3.65-3.69 (m,1H), 3.90-3.94 (m, 1H), 4.93-4.97 (m, 1H, N-C<u>H</u>-CO), 7.50-7.54 (m, 1H, Ar-<u>H</u>), 7.62-7.64 (m, 1H, Ar-<u>H</u>), 7.81-7.89 (m, 2H, Ar-<u>H</u>), 8.26 (s, 1H), 10.05 (s, 1H, -NH-N<u>H</u>-), 10.45 (s, 1H, -N<u>H</u>-NH-), ES-MS: m/z 455.3 (M+H) $^+$ Mp= 115-117^{0}C. Anal. Calcd. for $C_{22}H_{22}ClN_5O_2S$: C, 57.95; H, 4.86; N, 15.36; S, 7.03. Found: C, 57.93; H, 4.84; N, 15.33; S, 7.01

4-Methoxy-benzoic acid N'-[1-(5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-pyrrolidine-2-carbonyl]-hydrazide (8b) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.77-2.03 (m, 6H) 2.40 (br s, 1H), 2.87 (br s, 3H), 3.06-3.10 (m, 2H), 3.77-3.78 (m,1H), 3.80 (s, 3H), 3.95 (br s, 1H), 4.93-4.97 (t, 1H, -N-C<u>H</u>-CO), 6.99-7.01 (d, 2H, Ar-H), 7.84-7.86 (d, 2H, Ar-H), 8.14 (s, 1H, Ar-H), 9.95 (s, 1H, -NH-N<u>H</u>), 10.20 (s, 1H, -N<u>H</u>-NH-), ES-MS: m/z 451.3 (M+H) $^+$ Mp= 89-91^{0}C Anal. Calcd. for $C_{23}H_{25}N_5O_3S$: C, 61.18; H, 5.58; N, 15.51; S, 7.10. Found: C, 61.15; H, 5.55; N, 15.49; S, 7.08

4-Cyano-benzoic acid N'-[1-(5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-pyrrolidine-2-carbonyl]-hydrazide (9b) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.71-2.02 (m, 6H), 2.32-2.40 (m, 1H), 2.67-2.74 (m, 1H), 2.85 (br s, 3H), 3.11-3.14 (m, 1H), 3.65-3.70 (m, 1H), 3.90-3.96 (m, 1H), 4.93-4.97 (t, 1H, N-C<u>H</u>-CO), 7.96-8.08 (m, 4H, Ar-H), 8.26 (s, 1H, Ar-<u>H</u>), 10.02 (s, 1H, -NH-N<u>H</u>-), 10.59 (s, 1H, -N<u>H</u>-NH-), ES-MS: m/z 446.2 (M+H) $^+$ Mp= 117-119^{0}C. Anal. Calcd. for $C_{23}H_{22}N_6O_2S$: C, 61.87; H, 4.97; N, 18.82; S, 7.18. Found: C, 61.83; H, 4.94; N, 18.81; S, 7.16

Furan-2-carboxylic acid N'-[1-(5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-d]pyrimidin-4-yl)-pyrrolidine-2-carbonyl]-hydrazide (10b) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.85-2.05 (m,3H), 2.25-2.45 (m,3H), 2.58-2.62 (m,2H), 2.95-2.98 (m, 2H), 3.13-3.17 (m, 2H), 3.73-3.76 (m, 1H), 3.91-3.93 (m,1H), 4.83-4.85 (m, 1H, N-C<u>H</u>-CO), 6.68 (br s, 1H, Ar-<u>H</u>), 7.23-7.225 (d, 1H, Ar-<u>H</u>), 7.86 (s, 1H, Ar-<u>H</u>), 8.22 (s, 1H, Ar-<u>H</u>), 9.89 (s, 1H, -NH-N<u>H</u>), 10.22 (s, 1H, -N<u>H</u>-NH-), ES-MS: m/z 412.2 (M+H) $^+$ Mp= 118-120^{0}C. Anal. Calcd. for $C_{20}H_{21}N_5O_3S$: C, 58.38; H, 5.14; N, 17.02; S, 7.79. Found: C, 57.34; H, 5.12; N, 17.01; S, 7.77

Thiophene-2-carboxylic acid N'-[1-(5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-]pyrimidin-4-yl)-pyrrolidine-2-carbonyl]-hydrazide (11b) ^{1}H NMR (DMSO-d6, 400 MHz) δ 1.89-2.03 (m,3H), 2.25-2.46 (m,3H), 2.58-2.62 (m,2H), 2.95-2.98 (m, 2H), 3.15-3.18 (m, 2H), 3.73-3.76 (m, 1H), 3.91-3.93 (m,1H), 4.81-4.83 (m, 1H, N-C<u>H</u>-CO), 6.70 (br s, 1H, Ar-<u>H</u>), 7.27-7.29 (d, 1H, Ar-<u>H</u>), 7.66 (s, 1H, Ar-<u>H</u>), 8.22 (s, 1H, Ar-<u>H</u>), 9.85 (s, 1H, -NH-N<u>H</u>),

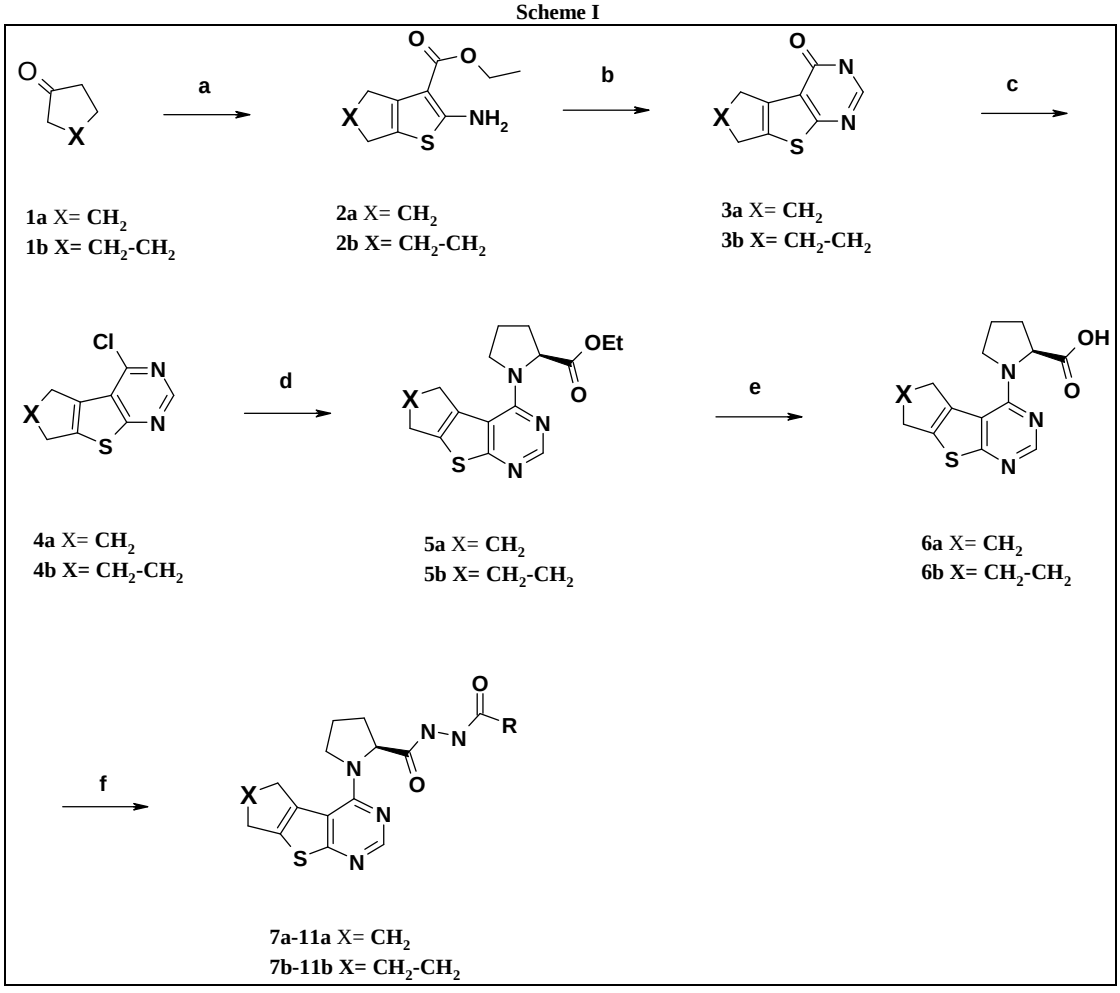
10.18(s, 1H, -NH-NH-), ES-MS: m/z 428.2 $(M+H)^+$ Mp= 122-124^{0}C. Anal. Calcd. for $C_{20}H_{21}N_5O_2S_2$: C, 56.19; H, 4.95; N, 16.38; S, 15.00. Found: C, 56.16; H, 4.94; N, 16.35; S, 14.8.

RESULTS AND DISCUSSION

3.1. Chemistry

The target compounds were prepared as outlined in **Scheme 1**. The starting material Ethyl 2-Amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate **2a** and Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate **2b** was prepared following the method of Gewald[18] [19] via the reaction of Cyclohexanone **1a** and Cyclopentanone **1b** and sulfur with ethyl cynoacetate in the presence of morpholine. Cyclization of **2a** to **3a** and **2b** to **3b** is adopted using the reported reaction condition by refluxing it in formamide [20] The desired 4-chloro derivative **4a** and **4b** was obtained via the reaction **3a** and **3b** with phosphorous oxychloride in reflux [21] L-Proline ethyl ester was introduced by replacing Chloro group of thieno [2, 3-d] pyrimidine **4a** and **4b** in Methanol to obtained the Ester intermediate **5a** and **5b.** Tetrahydrobenzo [4, 5] thieno [2, 3-d] pyrimidine-4yl-pyrrolidine-2-carboxylic acid **6a** and **6b** was after the alkaline hydrolysis of ester intermediate **5a** and **5b** by using lithium hydroxide in Water-THF mixture

Scheme I



Scheme1. Reagents and solvents: a. Ethyl cynoacetate, sulphur, morpholine, EtOH; b. Formamide; c. POCl3 d. L-proline ethyl ester hydrochloride, Et_3N, MeOH e. $LiOH.H_2O$, THF: H_2O f. R-Hydrazide, EDC.HCl/HOBt, DMF

^{1}H NMR spectrum of **2b** revealed the presence of triplet signal at 1.33 ppm and quartet signal at 4.25 ppm corresponds to ethyl group of ester, and singlet of two protons at 5.94 ppm corresponds to amino group. Similarly ^{1}H NMR spectrum of **3b** can be identified by the broad singlet at 12.31 and singlet at 8.00 ppm of the pyrimidin-4(3H)-one. Chloro intermediate **4b** was assigned by the shifted single signal to 8.72 ppm. Crude ester intermediate **5b** was used directly for hydrolysis reaction its formation is confirmed by the ESMS spectrum showing ES^+ = 332.3 respectively. Acid intermediate **6b** shows a characteristic triplet signal at 4.80 ppm corresponds to chiral proton of L-proline and pyrimidine proton at 8.32 ppm. Novel hydrazide derivatives **7a-11a and 7b-11b**were prepared by coupling selected hydrazides with the acid core **6a** and **6b.** Substituted aromatic and heterocyclic aromatic hydrazides were selected to evaluate the structure activity relationship among the novel analogue.

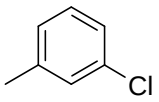
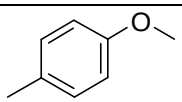
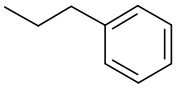
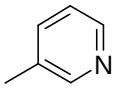
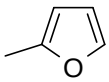
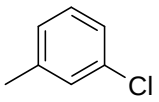
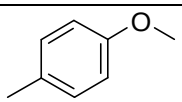
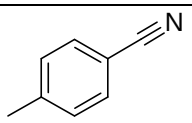
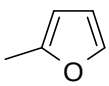
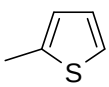
3.2. Antibacterial activity

The evaluation of the synthesized compounds **7a-11a** and **7b-11b** for antibacterial activity was carried out by standard literature procedure using agar diffusion method by finding the zone of inhibition of the drug sample against the standard drugs. The organisms employed in vitro testing of the compounds were *S. aureus* (Gram Positive), *S albus* (Gram Positive) *S. faecalis* (Gram Positive), *Bacillus sp.* (Gram Positive) *Pseudomonas aeruginosa* (Gram Negative), *sp. Proteus sp.* (Gram Negative) *Klebsiella sp.* (Gram Negative) *Escherichia coli* (Gram Negative). All the cultures were maintained on Nutrient agar (Microbiology) grade, Hi Media) medium by periodic sub culturing. Ciprofloxacin was used as reference compound for antibacterial activity. The compounds were tested at a concentration of a 100µg/ml were prepared in Dimethylsulphoxide.

Table 1

Code No	Gram Positive Bacteria	Code No	Gram Negative Bacteria
A	*Staphylococcus aureus*	**E**	*Pseudomonas sp.*
B	*Staphylococcus albus*	**F**	*Proteus sp.*
C	*Staphylococcus faecalis*	**G**	*Klebsiella sp.*
D	*Bacillus species*	**H**	*Escherichia coli*

Table 2

Entry	R	Inhibition Zone Diameter (mm) Gram Positive Bacteria				Inhibition Zone Diameter(mm) Gram Negative Bacteria			
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
7a		16	19	18	22	22	18	27	25
8a		18	24	22	24	20	19	30	28
9a		21	26	24	24	19	22	29	26
10a		23	31	19	21	25	22	28	27
11a		17	28	21	23	18	23	33	21
7b		13	24	17	19	26	25	27	29
8b		15	22	19	20	19	27	25	33
9b		18	19	18	23	22	16	25	25
10b		18	21	20	27	20	19	32	28
11b		19	20	14	13	17	17	20	22
Standard	***Ciprofloxacin***	***19***	***20***	***14***	***13***	***17***	***17***	***20***	***22***

CONCLUSION

A series of novel tetrahydrobenzo [4, 5] thieno [2, 3-d] pyrimidine-4yl-pyrrolidine-2-carboxamide derivatives were synthesized by a facile six step procedure. Their structures were characterized by ^{1}H NMR, ES-MS and elemental analysis. The preliminary bioassay results imply that some of the compounds exhibit excellent to moderate antibacterial activity against gram positive and gram negative bacteria. These compounds will be further studied for different biological properties in future research.

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