Synthesis and Antibacterial Activity of Some Novel Triazolothienopyrimidines

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A novel series of some novel 5-substituted-1,2,4-triazolo[4,3-*c*]8,9,10-trihydrocyclopenta/8,9,10,11,12-pentahydrocyclohepta[*b*]thieno[3,2-*e*]pyrimidin-3-thiones has been synthesized. The intermediates 4-chloro-2-substituted-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidines were prepared by warming 2-substituted-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-ones with oxalyl chloride. Thieno[2,3-*d*]pyrimidin-4[3*H*]-ones were prepared by a novel, microwave assisted, solvent free, synthetic route under basic conditions hitherto unreported in the literature from *ortho* amino ester of thiophene. The chloro derivatives, without further purification, were hydrazinated to yield 2-substituted-4-hydrazino-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidines. These compounds were cyclized with carbon disulphide to give the title compounds in quantitative yields. The final compounds were screened for antibacterial activity by Kirby Bauer's method using ampicillin as the standard against various gram positive and gram negative bacteria. All the compounds showed antibacterial activity comparable with the standard.

Key words triazolothienopyrimidine; antibacterial agent; Kirby Bauer's method; bioisosteres; microwave assisted synthesis

Antibiotics have revolutionized the medical care in the 20th century. With the discovery of antibiotics people were convinced that infectious diseases might some day be wiped out. Diseases that were once life threatening, such as pneumonia, had become curable. The success of antibiotics in therapy related fields has made them one of the most important products of the drug industry today.[1)] However, the emergence of super bugs ie. bacteria that resists the effects of the most powerful antibiotics are posing a great challenge to the field of medicines. Thus scientists are working to find new ways to defeat bacteria that are increasingly resistant to the antibiotics already available.[2)]

Literature survey shows that several fused pyrimidines and pyridines like triazolo quinazolines and triazoloquinolines[3)] have shown good antibacterial activity. Further condensed triazoles have been reported to possess large number of pharmacological activities like fungicidal, pesticidal *etc*.[4—7)] Thienopyrimidines has been reported to exhibit antimicrobial activities too.[8)] Based on the concept of bioisosterism and all the above observations have led us to the proposal to incorporate triazole ring system into thienopyrimidines leading to the synthesis of novel class of triazolothienopyrimidines as bioisosteres of triazoloquinolines and quinazolines and to test for its efficacy as antibacterial agents. Herewith we are reporting the synthesis of some novel 5-substiuted-1,2,4-triazolo[4,3-*c*]8,9,10,11,12-pentahydrocyclohepta/8,9,10-trihydrocyclopenta[*b*]thieno[3,2-*e*]pyrimidin-3-thiones as possible antibacterial agents.

Experimental

Analytical TLC was performed on Silica Gel F_{254} plates (Merck) with visualisation by UV or iodine vapours. Melting points were determined in open capillaries on a Gallenkemp Melting point apparatus and are uncorrected. The IR spectra (KBr, νMax, cm^{-1}) were run on Perkin Elmer FTIR Spectrophotometer. ^{1}H-NMR (δ ppm, $CDCl_3$/DMSO-d_6) spectra were recorded using AMX-400 with TMS as internal standard. MS spectra were recorded on Autospec. Elemental analyses were performed on Carlo Erba 1108 elemental analyzer and were within±0.4% of theoretical values. All the chemicals used were of analytical grade.

2-Substituted-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-ones (2a—h). General Procedure *Ortho* amino ester of thiophenes **1a**, **b** (0.0083 mol), potassium salt of tertiary butoxide (0.089 g, 0.0008 mol) and various nitriles (0.016 mol) were taken in a 5 ml microwave reaction vial equipped with a magnetic stir bar. The reaction mixture was capped and irradiated in the microwave oven (CEM, Discover) at 120 °C for 45—150 s. To the reaction mixture at room temperature, crushed ice was added and neutralized using dilute hydrochloric acid. The precipitate obtained was filtered, dried and recrystalized from ethylacetate to give the target compounds in 50—80% yields.

2-Methyl-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-one (**2a**): Reacn time: 40 s. Yield=68%, mp 217 °C; IR (KBr) cm^{-1}: 3421, 2856, 1674. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (3H, s), 2.43—2.49 (2H, pentet, J=7.1 Hz), 2.93—2.97 (2H, t, J=7.0 Hz), 3.04—3.08 (2H, t, J=7.0 Hz), 11.84—12.05 (1H, s). MS *m/z*: 206 (M^+). *Anal.* Calcd for $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.85; N, 13.59. Found: C, 58.50; H, 5.05; N, 13.79.

2-Phenyl-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-one (**2b**): Reacn time: 45 s. Yield=72%, mp 210 °C; IR (KBr) cm^{-1}: 3368, 2932, 1670. ^{1}H-NMR ($CDCl_3$) δ: 2.48—2.54 (2H, pentet, J=7.2 Hz), 2.98—3.01 (2H, t, J=7.1 Hz), 3.10—3.14 (2H, t, J=7.2 Hz), 7.44—8.09 (5H, m), 10.47—10.52 (1H, s). MS *m/z*: 268 (M^+). *Anal.* Calcd for $C_{15}H_{12}N_2OS$: C, 67.16; H, 4.47; N, 10.44. Found: C, 67.50; H, 4.59; N, 10.65.

2-Pyridyl-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-one (**2c**): Reacn time: 45 s. Yield=65%, mp 214 °C; IR (KBr) cm^{-1}: 3420, 3100, 1650. ^{1}H-NMR ($CDCl_3$) δ: 2.52—2.56 (2H, pentet, J=7.4 Hz), 3.01—3.05 (2H, t, J=7.4 Hz), 3.13—3.17 (2H, t, J=7.3 Hz), 8.10—8.12 (2H, d, J=5.7 Hz), 8.82—8.83 (2H, d, J=5.6 Hz), 11.92 (1H, s). MS *m/z*: 269 (M^+). *Anal.* Calcd for $C_{14}H_{11}N_3OS$: C, 62.45; H, 4.08; N, 15.61. Found: C, 62.55; H, 4.25; N, 15.75.

2-[*p*-Chloro-phenyl]-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-one (**2c**): Reacn time: 45 s. Yield=76%, mp 254 °C; IR (KBr) cm^{-1}: 3411, 3200, 1651. ^{1}H-NMR ($CDCl_3$) δ: 2.30—2.38 (2H, m), 2.95—3.00 (2H, t, J=7.0 Hz), 3.05—3.10 (2H, t, J=7.1 Hz), 7.23—7.25 (2H, d, J=5.3 Hz), 7.33—7.35 (2H, d, J=5.3 Hz), 10.55 (1H, s). MS *m/z*: 302 (M^+). *Anal.* Calcd for $C_{15}H_{11}ClN_2OS$: C, 59.60; H, 3.64; N, 9.27. Found: C, 59.78; H, 3.78; N, 9.35.

2-Methyl-5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-one (**2e**) Reacn time: 45 s. Yield=75%, mp 196 °C; IR (KBr) cm^{-1}: 3375.96, 2970, 750. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s), 1.67—1.74 (4H, m), 1.87—1.90 (2H, pentet, J=5.6 Hz), 2.82—2.85 (2H, t, J=5.7 Hz), 3.30—3.33 (2H, t, J=5.6 Hz), 11.12 (1H, s). MS *m/z*: 234 (M^+). *Anal.* Calcd for $C_{12}H_{14}N_2OS$: C, 61.53; H, 5.98; N, 11.96. Found: C, 61.80; H, 6.20; N, 12.15.

2-Phenyl-5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-one (**2f**): Yield=48%, mp 214 °C; IR (KBr) cm^{-1}: 3346.96, 2950. ^{1}H-NMR ($CDCl_3$) δ: 1.74—1.75 (4H, m), 1.94—2.16 (2H, m), 2.87—2.90 (2H, t, J=5.2 Hz), 3.40—3.42 (2H, t, J=5.2 Hz), 7.35—7.53 (3H, m), 8.16—8.17 (2H, d, J=5.8 Hz), 11.37 (1H, s). MS *m/z*: 296 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2OS$: C, 68.91; H, 5.40; N, 9.45. Found: C, 69.15; H, 5.65;

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N, 9.75.

2-Pyridyl-5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidin-4[3*H*]-one (**2g**): Reacn time: 45 s. Yield=66%, mp 182 °C; IR (KBr) cm^{-1}: 3397.96, 2920. ^{1}H-NMR ($CDCl_3$) δ: 1.75—1.80 (4H, m), 1.95—2.00 (2H, m), 2.95—2.98 (2H, t, *J*=5.4 Hz), 3.41—3.44 (2H, t, *J*=5.3 Hz), 8.08—8.09 (3H, d, *J*=5.4 Hz), 8.80—8.81 (2H, d, *J*=5.4 Hz), 11.65 (1H, s). MS *m/z*: 297 (M^+). *Anal.* Calcd for $C_{16}H_{15}N_3OS$: C, 64.64; H, 5.05; N, 14.14. Found: C, 64.75; H, 5.25; N, 14.28.

2-[*p*-Chloro-phenyl]-5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]-pyrimidin-4[3*H*]-one (**2h**): Reacn time: 45 s. Yield=60%, mp 236 °C; IR (KBr) cm^{-1}: 3350.96, 2925, 750. ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.72 (4H, m), 1.89—1.94 (2H, pentet, *J*=5.5 Hz), 2.83—2.86 (2H, t, *J*=5.4 Hz), 3.35—3.38 (2H, t, *J*=5.4 Hz), 7.27—7.28 (2H, d, *J*=5.3 Hz), 7.36—7.37 (2H, d, *J*=5.3 Hz), 11.23 (1H, s). MS *m/z*: 330.8 (M^+). *Anal.* Calcd for $C_{17}H_{15}ClN_2OS$: C, 61.66; H, 4.53; N, 8.46. Found: C, 61.75; H, 4.75; N, 8.55.

2-Substituted-4-chloro-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidines (3a—h). General Procedure 2-Substituted-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]-thieno[2,3-*d*]pyrimidin-4[3*H*]-ones [0.01 mol] [**2a**—**h**] and oxalyl chloride [10.0 ml] were taken in a round bottomed flask and heated to reflux for 3 h. The excess of oxalyl chloride was removed from the reaction mixture by rotoevoporator and the resulting free flowing solid (yield 75—85%) was taken to next step without any further purification.

2-Alkyl/Aryl-4-hydrazino-5,6,7-trihydrocyclopenta/ 5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidines (4a—h). General Procedure To a warm solution of 2-alkyl/aryl-4-chloro-5,6,7-trihydrocyclopenta/ 5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidines [0.01 mol] [**4a**—**h**] in ethanol (95%, 20 ml) was added a solution of hydrazine hydrate [99%, 4.3 g, 0.1 mol] drop-wise and heated under reflux for 2 h. Then the reaction mixture was cooled and poured onto crushed ice. The solid precipitate obtained was filtered, dried and recrystallized from 95% ethanol.

2-Methyl-4-hydrazino-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidine (**4a**): Yield=78%, mp 260 °C; IR (KBr) cm^{-1}: 3421, 3210, 2856. ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, s), 2.45—2.50 (2H, pentet, *J*=6.9 Hz), 2.95—2.98 (2H, t, *J*=6.9 Hz), 3.05—3.09 (2H, t, *J*=6.9 Hz), 4.6—4.8 (2H, d, *J*=4.7 Hz), 11.92 (1H, t, *J*=4.8 Hz). MS *m/z*: 220 (M^+). *Anal.* Calcd for $C_{10}H_{12}N_4S$: C, 54.54; H, 5.45; N, 25.45. Found: C, 54.66; H, 5.76; N, 25.35.

2-Phenyl-4-hydrazino-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidine (**4b**): Yield=65%, mp 191 °C; IR (KBr) cm^{-1}: 3425, 3225, 2856. ^{1}H-NMR ($CDCl_3$) δ: 2.46—2.52 (2H, pentet, *J*=7.0 Hz), 2.97—3.00 (2H, t, *J*=7.0 Hz), 3.07—3.12 (2H, t, *J*=7.0 Hz), 4.65—4.85 (2H, d, *J*=4.8 Hz), 7.45—8.10 (5H, m), 11.85 (1H, t, *J*=4.8 Hz). MS *m/z*: 282 (M^+). *Anal.* Calcd for $C_{15}H_{14}N_4S$: C, 63.82; H, 4.96; N, 19.85. Found: C, 63.96; H, 5.06; N, 20.05.

2-Pyridyl-4-hydrazino-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidine (**4c**): Yield=65%, mp 230 °C; IR (KBr) cm^{-1}: 3321, 3230, 2856. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.54 (2H, pentet, *J*=7.3 Hz), 2.99—3.03 (2H, t, *J*=7.3 Hz), 3.15—3.19 (2H, t, *J*=7.3 Hz), 4.62—4.82 (2H, d, *J*=4.9 Hz), 8.13—8.15 (2H, d, *J*=5.5 Hz), 8.83—8.85 (2H, d, *J*=5.5 Hz), 12.20 (1H, t, *J*=4.9 Hz). MS *m/z*: 283 (M^+). *Anal.* Calcd for $C_{14}H_{13}N_5S$: C, 59.36; H, 4.59; N, 24.73. Found: C, 59.45; H, 4.65; N, 24.89.

2-[4-Chloro-phenyl]-4-hydrazino-5,6,7-trihydrocyclopenta[*b*]thieno[2,3-*d*]pyrimidine (**4d**): Yield=76%, mp 215 °C; IR (KBr) cm^{-1}: 3356, 3245, 2856. ^{1}H-NMR ($CDCl_3$) δ: 2.35—2.40 (2H, pentet, *J*=6.9 Hz), 2.97—3.02 (2H, t, *J*=6.9 Hz), 3.02—3.07 (2H, t, *J*=6.9 Hz), 4.63—4.84 (2H, d, *J*=5.0 Hz), 7.24—7.26 (2H, d, *J*=5.1 Hz), 7.34—1.36 (2H, d, *J*=5.1 Hz), 11.95 (1H, t, *J*=5.0 Hz). MS *m/z*: 317 (M^+). *Anal.* Calcd for $C_{15}H_{13}ClN_4S$: C, 56.78; H, 4.10; N, 17.66. Found: C, 56.89; H, 4.20; N, 17.82.

2-Methyl-4-hydrazino-5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]-pyrimidine (**4e**): Yield=75%, mp 182 °C; IR (KBr) cm^{-1}: 3370.96, 2820. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, s), 1.67—1.71 (4H, m), 1.82—1.85 (2H, pentet, *J*=5.1 Hz), 2.80—2.82 (2H, t, *J*=5.1 Hz), 3.34—3.36 (2H, t, *J*=5.1 Hz), 4.8—4.0 (2H, d, *J*=4.8 Hz), 11.20 (1H, t, *J*=4.8 Hz). MS *m/z*: 250.4 (M^+). *Anal.* Calcd for $C_{12}H_{18}N_4S$: C, 57.50; H, 7.18; N, 22.36. Found: C, 57.62; H, 7.30; N, 22.45.

2-Phenyl-4-hydrazino-5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]-pyrimidine (**4f**): Yield=70%, mp 191 °C; IR (KBr) cm^{-1}: 3340, 3250, 2970. ^{1}H-NMR ($CDCl_3$) δ: 1.75—1.78 (4H, m), 1.95—2.20 (2H, m), 2.90—2.92 (2H, t, *J*=5.2 Hz), 3.44—3.46 (2H, t, *J*=5.2 Hz), 4.62—4.85 (2H, d, *J*=4.4 Hz), 7.51—7.52 (3H, m), 8.16—8.17 (2H, d, *J*=5.9 Hz), 11.26 (1H, t, *J*=4.4 Hz). MS *m/z*: 312.4 (M^+). *Anal.* Calcd for $C_{17}H_{20}N_4S$: C, 65.30; H, 6.40; N, 17.92. Found: C, 65.44; H, 6.72; N, 18.08.

2-Pyridyl-4-hydrazino-5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]-pyrimidine (**4g**): Yield=61%, mp 216 °C; IR (KBr) cm^{-1}: 3450, 3295, 3108.^{1}H-NMR ($CDCl_3$) δ: 1.54—1.72 (4H, m), 1.93—2.12 (2H, m), 2.81—2.84 (2H, t, *J*=5.7 Hz), 3.42—3.44 (2H, t, *J*=5.7 Hz), 4.68—4.88 (2H, d, *J*=4.1 Hz), 8.14—8.16 (2H, d, *J*=4.8 Hz), 8.82—8.84 (2H, d, *J*=4.4 Hz), 12.36 (1H, t, *J*=4.1 Hz). MS *m/z*: 313.4 (M^+). *Anal.* Calcd for $C_{16}H_{19}N_5S$: C, 61.26; H, 6.06; N, 22.33. Found: C, 61.35; H, 6.20; N, 22.45.

2-[*p*-Chloro-phenyl]-4-hydrazino-5,6,7,8,9-pentahydrocyclohepta[*b*]-thieno[2,3-*d*]pyrimidine (**4h**): Yield=79%, mp 201 °C; IR (KBr) cm^{-1}: 3440, 3293, 3008, 750. ^{1}H-NMR ($CDCl_3$) δ: 1.72—1.77 (4H, m), 1.95—2.12 (2H, m), 2.85—2.87 (2H, t, *J*=5.6 Hz), 3.35—3.37 (2H, t, *J*=5.6 Hz), 4.72—4.82 (2H, d, *J*=5.0 Hz), 7.25—7.27 (2H, d, *J*=4.3 Hz), 7.35—7.36 (2H, d, *J*=4.3 Hz), 10.25 (1H, t, *J*=5.0 Hz). MS *m/z*: 346.8 (M^+). *Anal.* Calcd for $C_{17}H_{19}ClN_4S$: C, 58.82; H, 5.47; N, 16.14. Found: C, 58.95; H, 5.55; N, 16.20.

5-Alkyl/Aryl-1,2,4-triazolo[4,3-*c*]-8,9,10,11,12-pentahydrocyclohepta/ 8,9,10-trihydrocyclopenta[*b*]thieno[3,2-*e*]pyrimidin-3-thiones (5a—h). General Procedure A mixture of 2-alkyl-4-hydrazino-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidines [**4a**—**h**] [0.01 mmol] and carbondisulphide [0.1 mol, 7.6 g, 10 ml] in 10% alcoholic potassium hydroxide (20 ml) solution was heated under reflux for 9 h. The reaction mixture was cooled and added onto crushed ice. The solid product obtained was filtered, dried and recrystallized from DMF–water (1 : 1) mixture.

5-Methyl-1,2,4-triazolo[4,3-*c*]-8,9,10-trihydrocyclopenta[*b*]thieno[3,2-*e*]pyrimidin-3-thione (**5a**): Yield=62%, mp 242 °C; IR (KBr) cm^{-1}: 3442, 2854. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (3H, s), 2.43—2.48 (2H, pentet, *J*=7.1 Hz), 2.93—2.97 (2H, t, *J*=6.9 Hz), 3.04—3.08 (2H, t, *J*=6.9 Hz), 11.86 (1H, br s). MS *m/z*: 262 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_4S_2$: C, 50.38; H, 3.81; N, 21.37. Found: C, 50.58; H, 3.95; N, 21.48.

5-Phenyl-1,2,4-triazolo[4,3-*c*]-8,9,10-trihydrocyclopenta[*b*]thieno[3,2-*e*]-pyrimidin-3-thione (**5b**): Yield=64%, mp 228 °C; IR (KBr) cm^{-1}: 3426, 2924. ^{1}H-NMR ($CDCl_3$) δ: 2.25—2.28 (2H, pentet, *J*=7.3 Hz), 2.95—2.97 (2H, t, *J*=7.3 Hz), 3.12—3.16 (2H, t, *J*=7.3 Hz), 7.45—8.10 (5H, m), 10.37—10.42 (1H, br s). MS *m/z*: 324 (M^+). *Anal.* Calcd for $C_{16}H_{12}N_4S_2$: C, 59.25; H, 3.70; N, 17.28. Found: C, 59.45; H, 3.88; N, 17.45.

5-Pyridyl-1,2,4-triazolo[4,3-*c*]-8,9,10-trihydrocyclopenta[*b*]thieno[3,2-*e*]-pyrimidin-3-thione (**5c**): Yield=60%, mp 240 °C; IR (KBr) cm^{-1}: 3448, 3381. ^{1}H-NMR ($CDCl_3$) δ: 2.49—2.53 (2H, pentet, *J*=7.2 Hz), 3.02—3.07 (2H, t, *J*=7.2 Hz), 3.14—3.17 (2H, t, *J*=7.2 Hz), 8.12—8.14 (2H, d, *J*=5.5 Hz), 8.84—8.85 (2H, d, *J*=5.5 Hz), 11.90 (1H, br s). MS *m/z*: 325 (M^+). *Anal.* Calcd for $C_{15}H_{11}N_5S_2$: C, 55.38; H, 3.38; N, 21.53. Found: C, 55.54; H, 3.56; N, 21.77.

5-[*p*-Chloro-phenyl]-1,2,4-triazolo[4,3-*c*]-8,9,10-trihydrocyclopenta[*b*]-thieno[3,2-*e*]pyrimidin-3-thione (**5d**): Yield=72%, mp 230 °C; IR (KBr) cm^{-1}: 3432, 3012, 750. ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.27 (2H, pentet, *J*=7.2 Hz), 2.98—3.02 (2H, t, *J*=7.1 Hz), 3.07—3.12 (2H, t, *J*=7.2 Hz) 7.22—7.24 (2H, d, *J*=5.4 Hz), 7.30—7.33 (2H, d, *J*=5.3 Hz), 10.89 (1H, s). MS *m/z*: 358 (M^+). *Anal.* Calcd for $C_{16}H_{11}ClN_4S_2$: C, 53.63; H, 3.07; N, 15.64. Found: C, 53.78; H, 3.29; N, 15.73.

5-Methyl-1,2,4-triazolo[4,3-*c*]-8,9,10,11,12-pentahydrocyclohepta[*b*]-thieno[3,2-*e*]pyrimidin-3-thione (**5e**): Yield=61%, mp 232 °C; IR (KBr) cm^{-1}: 3300, 2900. ^{1}H-NMR ($CDCl_3$) 1.60 (3H, s), 1.65—1.70 (4H, m), 1.85—1.87 (2H, pentet, *J*=5.3 Hz), 2.80—2.82 (2H, t, *J*=5.3 Hz), 3.32—3.34 (2H, t, *J*=5.3 Hz), 11.14 (1H, s). MS *m/z*: 290.4 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_4S_2$: C, 53.71; H, 4.82; N, 19.28. Found: C, 53.84; H, 4.97; N, 19.43.

5-Phenyl-1,2,4-triazolo[4,3-*c*]-8,9,10,11,12-pentahydrocyclohepta[*b*]-thieno[3,2-*e*]pyrimidin-3-thione (**5f**): Yield=56%, mp 248 °C; IR (KBr) cm^{-1}: 3300, 2900, 2850. ^{1}H-NMR ($CDCl_3$) δ: 1.74—1.75 (4H, m), 1.94—2.17 (2H, m), 2.88—2.90 (2H, t, *J*=5.3 Hz), 3.40—3.42 (2H, t, *J*=5.2 Hz), 7.52—7.54 (3H, m), 8.15—8.17 (2H, d, *J*=5.9 Hz), 11.36 (1H, s). MS *m/z*: 352.5 (M^+). *Anal.* Calcd for $C_{18}H_{16}N_4S_2$: C, 61.10; H, 4.53; N, 15.88. Found: C, 61.25; H, 4.68; N, 15.97.

5-Pyridyl-1,2,4-triazolo[4,3-*c*]-8,9,10,11,12-pentahydrocyclohepta[*b*]-thieno[3,2-*e*]pyrimidin-3-thione (**5g**): Yield=57%, mp 238 °C; IR (KBr) cm^{-1}: 3050, 2900, 2850. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.77 (4H, m), 1.97—2.17 (2H, m), 2.91—2.94 (2H, t, *J*=5.4 Hz), 3.43—3.46 (2H, t, *J*=5.4 Hz), 8.15—8.17 (2H, d, *J*=4.4 Hz), 8.80—8.81 (2H, d, *J*=4.4 Hz), 12.36 (1H, s). MS *m/z*: 353.5 (M^+). *Anal.* Calcd for $C_{17}H_{15}N_5S$: C, 57.70; H, 4.24; N, 19.80. Found: C, 57.88; H, 4.57; N, 19.98.

5-[*p*-Chloro-phenyl]-1,2,4-triazolo[4,3-*c*]-8,9,10,11,12-pentahydrocyclohepta[*b*]thieno[3,2-*e*]pyrimidin-3-thione (**5h**): Yield=78%, mp 255 °C; IR (KBr) cm^{-1}: 3440, 3012, 750. ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.73 (4H, m), 1.96—2.15 (2H, m), 2.80—2.83 (2H, t, *J*=5.4 Hz), 3.32—3.36 (2H, t, *J*=5.4 Hz), 7.25—7.27 (2H, d, *J*=4.2 Hz), 7.35—7.36 (2H, d, *J*=4.2 Hz),

10.25 (1H, s). MS *m/z*: 387 (M^+). *Anal.* Calcd for $C_{18}H_{15}ClN_4S_2$: C, 55.81; H, 3.87; N, 14.47. Found: C, 55.94; H, 3.96; N, 14.55.

Antibacterial Activity—Kirby Bauer's Method Peptone water was prepared and autoclaved. Four broth cultures were prepared using peptone water containing one type of organism each from stock cultures. A sterile cotton swab was dipped into one of the broth cultures and used to inoculate a Mueller Hinton agar plate. Inoculation of the plate in this way ensured a lawn of bacterial growth after incubation. Repeated this inoculation procedure for four plates from four different broth cultures and the plates were labeled. After inoculation the plates were allowed to dry for 15 min before proceeding to the next step. 70% ethanol was poured into a 250 ml beaker. The forceps was dipped into the alcohol and then passed the forceps over the Bunsen burner flame to sterilize it. The standard antibiotic disk (ampicillin) was picked up and placed it in the centre of the plate. The Whatman filter paper disc impregnated with newly synthesized drugs (0.005 ml, 50 μg) was picked and placed it in the corners. This procedure was repeated for the four plates for four newly synthesized drugs and incubated for 18 h at 35 °C. The plates were examined for zones of inhibition. They were measured with millimeter ruler across the disk. The diameter of the zone to the nearest whole millimeter was recorded. The disk impregnated with solvent (DMSO) and evaporated to dryness was used as negative control.

Results and Discussion

The *ortho* amino ester of thiophenes (**1a**, **b**) were prepared by following the reported procedures.[9,10] Although various synthetic procedures are available for the synthesis of thieno[2,3-*d*]pyrimidines,[11—19] no efforts were made to synthesize this moiety utilizing microwaves. Hence we are herewith reporting the synthesis of 2-substituted 5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]thieno[2,3-*d*]pyrimidines (**2a**—**h**) by a novel, microwave assisted solvent free, synthetic route in which starting material **1a**, **b** was irradiated with various equimolar quantities of aryl/alkyl nitriles in presence 10% potassium tertiary butoxide in a microwave oven at 120 °C (CEM, Discover) for 40 to 45 s. The resulting reaction mixture was added onto crushed ice and neutralized with 5% hydrochloric acid to yield the target compounds **2a**—**h** in good yields. The disappearance of two peaks of primary amino group and appearance of secondary amino peak in the range of 3200 to 3400 cm^{-1} and shift of carbonyl peak from 1724 cm^{-1} to 1650—1680 cm^{-1} indicated the cyclization of *ortho* amino ester of thiophene. The ^{1}H-NMR spectra showed D_2O exchangeable secondary amino signals as broad singlet at around δ 11.9 ppm and mass spectra exhibited molecular ion peaks (as base peaks) corresponding to the molecular weight of the compounds. This further confirmed the formation of the product. The details of reaction time and physical data are given in Experimental.

Compounds **2a**—**h** were taken in excess amount of oxalyl chloride and warmed for 3 h to replace the hydroxyl group at 4th position by chloro group. The excess of oxalyl chloride was removed by warming in a roto evaporator to get the compounds in good yields (75—85%). The chlorination was also tried out using phosphorus oxychloride as per the reported procedures[20] but it took long time (12 h), high temperatures (120 °C) and tedious workup procedures resulting in lower yields (40—50%). Thus oxalyl chloride was used for the chlorination of thienopyrimidines. The compounds **3a**—**h** were taken to next step immediately without any purification as they were unstable.

The chloro group in compounds **3a**—**h** was replaced by hydrazine by heating them with hydrazine hydrate 99% in presence of ethanol to yield the 2-substituted-4-hydrazino-5,6,7-trihydrocyclopenta/5,6,7,8,9-pentahydrocyclohepta[*b*]-thieno[2,3-*d*]pyrimidines (**4a**—**h**) in good yields.[20] The IR spectra of the compounds showed the presence of primary and secondary amino peaks at 3200—3400 cm^{-1} respectively which indicated the formation of the product. The NMR spectra showed the NH and NH_2 peaks at around δ 11.92 and 4.80 ppm respectively which confirmed the formation of the product. Further the mass spectra revealed the molecular ion peak as base peak with characteristic fragmentation pattern.

The hydrazinated products **4a**—**h** was heated to reflux with carbon disulphide in an alkaline medium for 9 h. The white precipitate obtained on neutralization was recrystallised using DMF–water mixture to give the target compounds 5-substiuted-1,2,4-triazolo[4,3-*c*]8,9,10,11,12-pentahydrocyclohepta/8,9,10-trihydrocyclopenta[*b*]thieno[3,2-*e*]-pyrimidin-3-thiones (**5a**—**h**) in pure form. The IR spectra of the compounds showed a single peak at 3050 to 3300 cm^{-1} for secondary amino group and weak C=S peak around 1200 cm^{-1} indicating the formation of the product. The NMR spectra showed the NH peak at δ 11.9—12.1 ppm and the disappearance of primary amino signal at around δ 4.60—4.90 ppm confirmed the formation of the product. The mass spectra showed the molecular ion peak corresponding to its molecular weight which further gave the confirmation for product formation. The elemental analyses showed that all the newly synthesized compounds were having purity

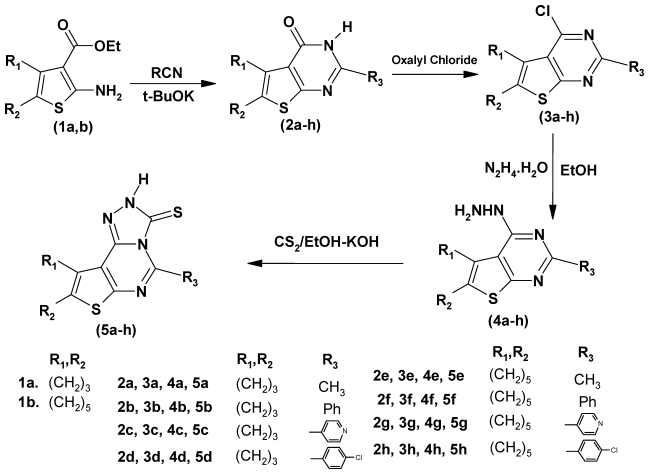

Chart 1. 5-Substituted-1,2,4-triazolo[4,3-*c*]8,9,10-trihydrocyclopenta/8,9,10,11,12-pentahydrocyclohepta[*b*]thieno[3,2-*e*]pyrimidin-3-thiones (**5a**—**h**)

Table 1. Antibacterial Activity of 5-Substituted-1,2,4-triazolo[4,3-*c*]-8,9,10-trihydrocyclopenta/8,9,10,11,12-pentahydrocyclohepta[*b*]thieno[3,2-*e*]pyrimidin-3-thiones (**5a**—**h**)

Compd. code	Concn.	Zones of inhibition (in mm)±S.E.M.		
		S. coag+	*E. coli*	*K. pneumoniae*
5a	50 μg	7.0±0.48	8.0±0.12	8.0±0.14
5b	50 μg	7.0±0.37	9.0±0.34	7.0±0.13
5c	50 μg	10.0±0.44	8.0±0.31	7.0±0.28
5d	50 μg	9.0±0.24	8.0±0.44	6.0±0.31
5e	50 μg	7.0±0.31	7.0±0.24	6.0±0.31
5f	50 μg	8.0±0.30	10.0±0.24	7.0±0.30
5g	50 μg	9.0±0.31	9.0±0.30	7.0±0.24
5h	50 μg	6.0±0.31	6.0±0.30	6.0±0.37
Ampicillin	50 μg	15.5±0.32	9.0±0.30	11.1±0.30

within±0.4% of theoretical values.

The synthesized compounds were evaluated for antimicrobial activity against various gram-positive and gram-negative bacteria like *Klebsiella*, *E. coli*, *Staphylococcus coagulase* and Pneumococci using Kirby Bauer's Method.[21] The negative control did not show any zone of inhibition in all the bacterial strains used for the study. Pneumococcus was found to be resistant and *E. coli* was the most susceptible organism. *Klebsiella* and *Staphylococcus coagulase* showed intermediate activity.

Activity of **5c** (9±0.34), **5f** (10±0.24) and **5g** (9±0.30) was comparable with the activity of ampicillin (9±0.30) against *E. coli*. Compound **5h** showed less activity against *E. coli*.

Compound **5c** (10.0±0.44) **5d** (9.0±0.24) and **5g** (9.0±0.31) showed better activity than other compounds against *Staphylococcus coagulase positive*. However the activity of the compounds was not comparable with the standard drug ampicillin (15.5±0.32).

Compound **5a** (8.0±0.14) was the most active against *Klebsiella* among the other compound in the series although not comparable with ampicillin (11.1±0.30).

As all the compounds showed antibacterial activity against the bacteria tested, it indicates that this basic moiety can be a potential scaffold for antibacterial drugs. Further the activity of these compounds was comparable with ampicillin against *E. coli* only. None of the compounds were having activity comparable with standard drug against *Staphylococcus coagulase positive* and *Klebsiella* respectively. Thus it shows that further lead optimization should be carried out for the better antibacterial activity.

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