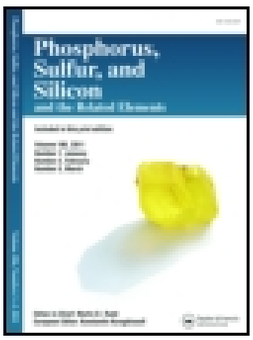

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Synthesis of 2-substituted-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline as a new heterocyclic system

Marzieh Akbarzadeh[a], Mehdi Bakavoli [a]*, Hossein Eshghi[a], Ali Shiri[a], Hamid Azizollahi[a], Joel T. Mague[b]

[a] Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, 91775-1436 Mashhad, Iran.

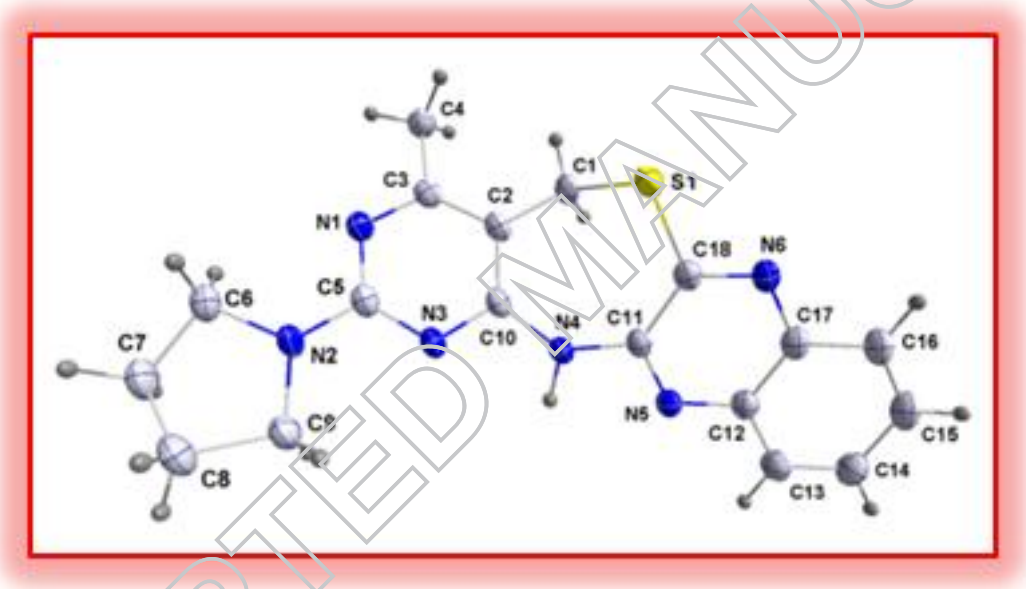
[b] *Department of Chemistry, Tulane University, New Orleans, LA 70118, USA.*

E-mail: mbakavoli@um.ac.ir, mbakavoli@yahoo.com

Abstract

2-Substituted-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxalines (**7a-g**), derivatives of a new heterocyclic system were synthesized through cyclocondensation of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine (**3**) with 3-aminoquinoxaline-2-thiol (**4**) and subsequent substitution by various secondary amines. Regioselective heterocyclization was confirmed by X-ray crystallographic analysis for 4-

methyl-2-(pyrrolidin-1-yl)-5,13-dihydropyrimido[4',5':5,6] [1,4]thiazepino[2,3-*b*]quinoxaline (**7a**).



Keywords 1,4-thiazepine, pyrimidothiazepine, quinoxaline-2,3-dithiol, intramolecular S_NAr reaction.

Introduction

The 1,4-thiazepine-containing aryl- and heteroaryl-fused structures play a vital role in natural and synthetic biologically active compounds [1-2]. They are recognized as antiviral [3], antitumor [4], and antiulcer agents [5] as well as inhibitors of HIV-1 integrase and reverse transcriptase [6]. Some of these compounds also show interesting pharmacological properties such as angiogenic [7] antispasmodic [8] and antiarrhythmic [9] activities.

Examples of synthetic methods to prepare 1,4-thiazepine-containing compounds include the condensation of dichloropyrimidine with 3,4-dimethoxythiophenol under basic conditions followed by cyclization in the presence of paraformaldehyde [10], cyclization of *N*-acyl derivatives of 2-arylthioethylbenzamide under Bischler-Napieralski conditions [11], reductive cyclization of 2-((3-nitropyrid in-4-yl)thio)benzaldehyde under catalytic hydrogen conditions [12] and Sonogashira coupling of electron poor (hetero)aryl halides and 1-phenyl propynol in the presence of 2-amino thiophenols [13].

A literature survey revealed that various methods are reported for the synthesis of fused thiazepines including cyclocondensation of 5-amino-6-methylpyrimidine-4-thiols and 2-chloroquinoline-3-carbaldehydes in the presence of K_2CO_3 in DMF [14], reaction of 6-methyl-4-phenyl-N-(pyridin-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide with 2-(benzo[*d*]thiazol-2-yl)-4-chloro-3-oxobutannitrile [15], treatment of 6-chloro-1-methyluracil with 2-aminothiophenol followed by heating with appropriate aromatic aldehydes [16] and treatment of 4-methoxy-5-amino-6-mercaptopyrimidine with 4,6-dichloro-5-formylpyrimidine in methanolic KOH medium [17].

Prompted by these findings and as part of our ongoing studies towards the synthesis of various fused pyrimidines [18-24], herein, we wish to report the synthesis of 2-substituted-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxalines (**7a-g**) as a new

heterocyclic system and a possible candidate in designing new biologically active compounds.

Results and discussion

Initially, the reaction of 6-methylpyrimidine-2,4-(1*H*,3*H*)-dione **(1)** with formaldehyde in aqueous NaOH solution at room temperature gave 5-(hydroxymethyl)-6-methylpyrimidine-2,4-(1*H*,3*H*)-dione **(2)** which was subsequently treated with $POCl_3$ to give 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine **(3)** [25]. Alternatively, 3-aminoquinoxaline-2-thiol **(4)** was prepared in quantitative yield according to the previously published method [26]. The reaction of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine **(3)** with compound **(4)** in $CHCl_3$ at -15 ºC gave compound (**5)** in good yield. (**Scheme 1**)

[Insert Scheme 1]

The evidence which confirms that the chlorine atom of chloromethyl group on the pyrimidine core of compound **(3)** was initially substituted by sulfur atom of 3-aminoquinoxaline-2-thiol **(4)** and produces compound **(5)** was gathered from the previously published method [27].

The ^{1}H NMR spectrum of compound **(5)** showed two singlet signals at δ 2.76 and 4.82 ppm, attributed to methyl and thiomethylene group, respectively. The presence of a broad singlet signal at δ 5.02 ppm due to the NH_2 group as well as the multiplet signal at δ 7.45-7.85 ppm

corresponding to the hydrogens of aromatic moieties clearly confirms the depicted structure. The ^{13}C NMR spectrum demonstrates fourteen signals for the corresponding carbons of the desired compound **(5)**. Two signals at δ 22.9 and 27.5 ppm assigned to the carbons of the methyl and methylene group and twelve signals at δ 125.7, 125.9, 126.5, 127.0, 129.0, 137.9, 139.5, 143.7, 148.8, 158.4, 162.8, 171.1 ppm are attributed to the unsaturated carbons. The IR spectrum of **(5)** revealed the existence of two absorption bands at 3455 and 3297 cm^{-1} attributed to the NH_2 group and the mercaptan absorption was omitted. The mass spectrum also showed the molecular ion peak at *m/z* 308 (M^+) corresponding to the molecular formula of $C_{14}H_{11}Cl_2N_5S$.

The subsequent cyclization reaction of the compound **(5)** in an intramolecular S_NAr type reaction in the presence of K_2CO_3 in DMF at 90 ºC provided pyrimidothiazepinoquinoxaline as a new heterocyclic system. The structure of the product was assessed by IR, ^1H NMR, ^{13}C NMR and mass spectra. The IR spectrum of this compound revealed the absence of NH_2 signals and the presence of characteristic absorption NH stretching vibration band at 3346 cm^{-1}. In the ^1H NMR spectrum, the addition of a new signal at δ 10.96 ppm to the other signals of the precursor confirmed the heterocylization but we found a challenge as to whether the reaction proceeded via path (I) or (II) and provided pyrimidothiazepinoquinoxaline **(6)** or **(6')** according to Scheme 2.

[Insert Scheme 2]

Some of our previous studies [28-29] shows the occurrence of the Smiles rearrangement [30-31] on similar heterocyclic systems. In order to answer this ambiguity, we decided to prepare a single crystal of this compound to confirm the structure by X-ray analysis. Since no

acceptable crystal was obtained, we decided to displace the remaining chlorine atom in compound **(6)** or **(6')** with the appropriate secondary amines in ethanol under reflux condition to furnish the corresponding **(7a-g)** or **(7'a-g)**.

The attempt to prepare a suitable single crystal for X-ray diffraction studies was accomplished for **(7a)**. **(Figures 1, 2)** The single crystal X-ray crystallographic data (Table 1) of this compound showed that the sulfur atom of thiazepine ring is linked to the methylene group and the nitrogen atom is bonded to C4 of pyrimidine ring and no Smiles rearrangement had occurred. Therefore, the products have the depicted structures (**7a-g)** in Scheme 2. The crystallographic data for the structure reported here has been deposited with the Cambridge Crystallographic Data Centre (deposition No. CCDC 1576194).

[Insert Figure 1]

[Insert Figure 2]

[Insert Table 1]

The formation of the seven-membered ring differs from all other similar compounds here. The thiazepine ring fragment is in a boat conformation in most compounds while in this structure, the ring is folded along C10---S1 and consequently a 55.61° angle is formed. The resonance within the adjacent rings leads to this phenomenon which can also inhibit the extra bending of the thiazepine ring. This folding causes the pyrimidine and quinoxaline planar rings to form a dihedral angle equals of 33.63° so that the structure become twisted. Since the similar compound (ref. No. TASBEX) has just one saturated ring with no suitable resonance, that structure forms the boat conformation, therefore, the resonance resulted from adjacent unsaturated rings in compound (**7a**) is very significant. The C18-S1 bond

length (1.754(2) Å) due to resonance with the adjacent ring is shorter than C1-S1 bond (1.827(2) Å). (**Table 2**)

[Insert Table 2]

All physical, chemical and spectral data were in agreement with the newly synthesized compounds **(7a-g)**. For example, the ^{1}H NMR spectrum of **(7a)** showed two triplet signals at δ 1.91 ppm and 3.48 ppm corresponding to the hydrogens of the pyrrolidine moiety, two singlet signals at δ 2.38 ppm and 4.27 ppm assigned to the hydrogens of the CH_3 of pyrimidine and CH_2 of thiazepine ring, respectively. Two triplet-doublet signals at δ 7.59 and 7.69 ppm, two doublet signals at δ 7.75 ppm and 7.84 ppm due to aryl hydrogens and D_2O exchangeable broad peak of NH moiety was also appeared at δ 9.39 ppm. The ^{13}C NMR spectrum reveals four signals at δ 22.2, 25.4, 27.3 and 46.7 ppm for the aliphatic carbons and twelve distinct signals for unsaturated carbons at δ 108.3, 125.6, 126.6, 127.9, 130.5,137.5, 139.3, 148.4, 159.2 and 164.4 ppm.

Experimental

Melting points were recorded on an Electrothermal type 9200 melting point apparatus. The IR spectra were obtained on Avatar 370 FT-IR Thermo Nicolet and only noteworthy absorptions were listed. The ^{1}H NMR (300 and 400 MHz) and the ^{13}C NMR (75 and 100 MHz) spectra were recorded on Bruker DRX-300 Avance spectrometers, Bruker DRX-400 Avance spectrometers. Chemical shifts were reported in ppm downfield from TMS as internal

standard. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer.

Synthesis of 3-(((2,4-dichloro-6-methylpyrimidin-5-yl)methyl)thio)quinoxalin-2-amine (5) To a stirred solution of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine **(3)** (1 mmol, 0.211 g) and triethylamine (1.2 mmol, 0.12 g) in $CHCl_3$ (2 mL), 3-aminoquinoxaline-2-thiol **(4)** (1 mmol, 0.177 g) in DMSO (2 mL) was added dropwise with vigorous stirring at -15 ºC. After 2 hours, the solvent was evaporated under reduced pressure. The formed precipitate washed with water (5 mL) and crystallized from ethanol. This compound was obtained in 80% yield as a yellow powder. mp 240-242 ^{o}C; IR (KBr) *ν*: 3456, 3297, 3105, 3064, 3019, 2946, 2745, 1645, 1597, 1547, 1523, 1426, 1377, 1332, 1249, 1219, 1123, 1062 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 2.76 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 5.02 (br s, 2H, NH_2, D_2O exchangeable), 7.45 (t, 1H, *J* = 7.3 Hz, Ar-H), 7.55 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.66 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.85 (d, 1H, *J* = 7.8 Hz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 22.9, 27.5, 125.7, 125.9, 126.5, 127.0, 129.0, 137.9, 139.5, 143.7, 148.8, 158.4, 162.8, 171.1; MS *m/z:* 350 (M^+), 351, 352, 316 (M^+- Cl), 176 (M^+- $C_6H_5Cl_2N_2$); Anal. Calcd. For $C_{14}H_{11}Cl_2N_5S$: C, 47.74; H, 3.15; N, 19.88; S, 9.10. Found: C, 47.79; H, 3.18; N, 19.98; S, 9.02.

Synthesis of 2-chloro-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (6) A mixture of 3-(((2,4-dichloro-6-methylpyrimidin-5-yl)methyl)thio)quinoxalin-2-amine **(5)** (1 mmol, 0.35 g) and potassium carbonate (3 mmol,

0.42 g) in DMF (5 mL) was heated at 100 ^{o}C for 9 h. After the completion of the reaction which was monitored by TLC using chloroform: methanol (9:1), the solvent was removed in vacuum. Water (5 mL) was added to the resulting residue and extracted with EtOAc (3×5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated to provide a brown solid. The desired products were purified by column chromatography eluting with a 9:1 mixture of $CHCl_3$/MeOH. mp 243-245 ^{o}C; IR (KBr) *v*: 3346, 2962, 2922, 2848, 1522, 1529, 1396, 1374, 1294, 1220, 1175, 1135, 1033 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.52 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 7.67 (td, *J* = 1.2 Hz, 1H, *J* = 6.8 Hz, Ar-H), 7.75 (td, 1H, *J* = 6.8 Hz, *J* = 1.2 Hz, Ar-H), 7.82 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.90 (d, 1H, *J* = 8.0 Hz, Ar-H), 10.96 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.9, 27.6, 117.2, 127.1, 127.8, 128.8, 130.9, 137.2, 139.4, 147.9, 148.3, 157.0, 160.7, 166.7; MS *m/z:* 315 (M^+), 316, 317, 280 (M^+-Cl), 239 (M^+-C_6H_4); Anal. Calcd. For $C_{14}H_{10}ClN_5S$: C, 53.25; H, 3.19; N, 22.18; S, 10.15. Found: C, 53.20; H, 3.15; N, 22.29; S, 10.06.

General procedure for the synthesis of 2-substituted-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (7a-g) A mixture of 2-chloro-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline **(6)** (1 mmol, 0.31 g) and appropriate secondary amine (3 mmol) in EtOH (5 mL) was refluxed for 8 h. After being cooled to r.t, the resulting precipitate was filtered off, washed with water (5 mL) and recrystallized from EtOH.

4-Methyl-2-(pyrrolidin-1-yl)-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (7a) yield 65%; yellow powder; mp 234-236 ^{o}C; IR (KBr) *v*: 3358, 2954, 2919, 1844, 1597, 1535, 1523, 1474, 1398, 1376, 1332, 1303, 1249, 1176, 1127 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.91 (t, 4H, *J* = 6.8 Hz, CH_2), 2.38 (s, 3H, CH_3), 3.48 (t, 4H, *J* = 6.8 Hz,

CH_2-N), 4.27 (s, 2H, CH_2), 7.59 (td, 1H, *J* = 7.6 Hz, *J* = 1.2 Hz, Ar-H), 7.69 (td, 1H, *J* = 8.2 Hz, *J* = 1.2 Hz, Ar-H), 7.75 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.84 (d, 1H, *J* = 7.2 Hz, Ar-H), 9.39 (s, 1H, NH, D_2O exchangeable);^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.2, 25.4, 27.3, 46.7, 108.3, 126.6, 127.5, 127.9, 130.5, 136.9, 139.3, 148.2, 148.4, 159.2; MS *m/z:* 350 (M^+), 280 (M^+- C_4H_8N); Anal. Calcd. For $C_{18}H_{18}N_6S$: C, 61.69; H, 5.18; N, 23.98; S, 9.15. Found: C, 61.60; H, 5.14; N, 23.87; S, 9.11.

4-(4-Methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxalin-2-yl)morpholine (7b) yield 78%; yellow powder; mp 245-246 ^{o}C; IR (KBr) *v*: 3367, 2956, 2919, 2852, 1597, 1524, 1474, 1395, 1360, 1302, 1255, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (s, 3H, CH_3), 3.75-3.83 (m, 8H, morpholine), 4.12 (s, 2H, CH_2), 7.59 (t, 1H, *J* =7.2 Hz, Ar-H), 7.68 (t, 1H, *J* = 6.8 Hz, Ar-H), 7.78 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.94 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.12 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 28.0, 44.2, 66.9, 106.9, 126.5, 127.7, 127.8, 130.2, 137.7, 139.5, 147.0, 147.4, 158.7, 159.9, 164.4; MS *m/z:* 366 (M^+); Anal. Calcd. For $C_{18}H_{18}N_6OS$: C, 59.00; H, 4.95; N, 22.93; S, 8.75. Found: C, 58.92; H, 4.91; N, 22.85; S, 8.80.

4-Methyl-2-(piperidin-1-yl)-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (7c) yield 58%; yellow powder; mp 212-214 ^{o}C; IR (KBr) *v*: 3370, 3047, 2998, 2922, 2850, 1598, 1522, 1474, 1441, 1394, 1302, 1257, 1178, 1091, 1023 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.61-1.69 (m, 6H, CH_2), 2.43 (s, 3H, CH_3), 3.79 (t, 4H, *J* = 5.4 Hz, CH_2-N), 4.11 (s, 2H, CH_2), 7.54 (td, 1H, *J* = 7.5 Hz, *J* =1.2 Hz, Ar-H), 7.64 (td, 1H, *J* = 8.2 Hz, *J* = 1.2 Hz, Ar-H), 7.75 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.90 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.05 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.2, 24.9, 25.8, 28.0, 44.7, 105.9, 126.5, 127.5, 127.8, 130.0, 137.7, 139.6, 147.2, 147.6, 158.8, 159.9, 164.2; MS *m/z:* 364 (M^+), 280 (M^+-

$C_5H_{10}N$); Anal. Calcd. For $C_{19}H_{20}N_6S$: C, 62.61; H, 5.53; N, 23.06; S, 8.80. Found: C, 62.73; H, 5.58; N, 23.13; S, 8.85.

4-Methyl-2-(4-methylpiperidin-1-yl)-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (7d) yield 60%; yellow powder; mp 198-200 ^{o}C; IR (KBr) *v*: 3367, 3056, 3007, 2942, 2917, 2868, 2835, 1598, 1525, 1474, 1394, 1366, 1319, 1252, 1205, 1135, 1082 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 0.99 (d, 3H, *J* = 6.0 Hz, CH_3), 1.10-1.24 (m, 2H, axial hydrogens of CH_2), 1.60-1.74 (m, 3H, equatorial hydrogens of CH_2, CH), 2.43 (s, 3H, CH_3), 2.84 (td, 2H, *J* = 13.5 Hz, *J* = 1.8 Hz, axial hydrogens of CH_2-N), 4.12 (s, 2H, CH_2), 4.69-4.76 (m, 2H, equatorial hydrogens of CH_2-N), 7.56 (td, 1H, *J* = 8.2 Hz, *J* = 1.2 Hz, Ar-H), 7.65 (td, 1H, *J* = 9.2 Hz, *J* = 1.5 Hz, Ar-H), 7.76 (dd, 1H, *J* = 8.2 Hz, *J* = 1.2 Hz, Ar-H), 7.90 (dd, 1H, *J* = 8.1 Hz, *J* = 0.9 Hz, Ar-H), 8.04 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 22.2, 28.0, 43.3, 46.0, 54.8, 106.7, 126.5, 127.7, 127.8, 130.2, 137.7, 139.5, 147.0, 147.4, 158.7, 159.7, 164.4; MS *m/z:* 378 (M^+), 280 (M^+- $C_6H_{12}N$); Anal. Calcd. For $C_{20}H_{22}N_6S$: C, 63.47; H, 5.86; N, 22.20; S, 8.47. Found: C, 63.55; H, 5.89; N, 22.31; S, 8.52.

4-Methyl-2-(4-methylpiperazin-1-yl)-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (7e) yield 73%; yellow powder; mp 209-211 ^{o}C; IR (KBr) *v*: 3367, 2958, 2926, 2935, 2793, 2758, 1600, 1560, 1524, 1473, 1445, 1396, 1363, 1305, 1250, 1207, 1146, 1005 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 2.46 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.84 (t, 4H, CH_2), 4.12 (m, 6H, CH_2-N, CH_2), 7.59 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.68 (t, 1H, *J* = 6.8 Hz, Ar-H), 7.78 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.93 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.08 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 22.5, 31.4, 32.9, 34.1, 44.1, 104.9, 120.9, 121.6, 126.9, 128.2, 133.1, 142.4, 158.9, 159.6, 163.5; MS *m/z:* 379 (M^+), 294 (M^+- $C_5H_{11}N_2$), 364 (M^+-CH_3); Anal. Calcd. For $C_{19}H_{21}N_7S$: C, 60.14; H, 5.58; N, 25.84; S, 8.45. Found: C, 60.07; H, 5.53; N, 25.72; S, 8.38.

2-(4-Ethylpiperazin-1-yl)-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (7f) yield 75%; yellow powder; mp 200-202 ^{o}C; IR (KBr) *v*: 3366, 2970, 2934 2808, 2766, 1598, 1527, 1473, 1396, 1363, 1306, 1252, 1135, 1013 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.16 (t, 3H, *J* = 7.2 Hz, CH_3), 2.44 (s, 3H, CH_3), 2.50-2.53 (m, 6H, CH_2 of piperazine, CH_2 of ethyl), 3.86 (t, 4H, *J* = 5.1 Hz, CH_2-N), 4.11 (s, 2H, CH_2), 7.56 (td, 1H, *J* = 7.5 Hz , *J* = 1.2 Hz, Ar-H), 7.65 (td, 1H, *J* = 8.2 Hz, *J* = 1.2 Hz, Ar-H), 7.75 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.90 (d, 1H, *J* = 8.1 Hz, Ar-H), 8.08 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 12.0, 22.2, 28.0, 43.7, 52.5, 52.8, 106.5, 126.5, 127.6, 127.8, 130.1, 137.7, 139.6, 147.1, 147.5, 158.8, 159.8, 164.3; MS *m/z:* 393 (M^+), 280 (M^+- $C_6H_{13}N_2$); Anal. Calcd. For $C_{20}H_{23}N_7S$: C, 61.04; H, 5.89; N, 24.92; S, 8.15. Found: C, 60.91; H, 5.85; N, 24.81; S, 8.07.

4-Methyl-2-(4-phenylpiperazin-1-yl)-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (7g) yield 68%; yellow powder; mp 246-247 ^{o}C; IR (KBr) v: 3358, 3052, 2974, 2921, 2856, 2803, 1594, 1558, 1527, 1472, 1443, 1395, 1367, 1338, 1232, 1204, 1046, 1005 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 2.47 (s, 3H, CH_3), 3.27 (t, 4H, *J* = 5.2 Hz, CH_2), 4.00 (t, 4H, *J* = 5.2 Hz, CH_2N), 4.14 (s, 2H, CH_2), 6.93 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.02 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.33 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.58 (td, 1H, *J* = 6.9 Hz, *J* = 1.2 Hz, Ar-H), 7.67 (td, 1H, *J* = 6.9 Hz, *J* = 1.2 Hz, Ar-H), 7.78 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.93 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.08 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 22.2, 28.0, 43.7, 49.4, 106.8, 116.6, 120.1, 126.5, 127.7, 127.8, 129.2, 130.2, 137.7, 139.6, 147.1, 145.5, 151.4, 158.8, 159.8,

164.4; MS *m/z:* 441 (M^+), 280 (M^+- $C_{10}H_{13}N_2$), 322 (M^+- C_8H_9N); Anal. Calcd. For $C_{24}H_{23}N_7S$: C, 65.28; H, 5.25; N, 22.21; S, 7.26. Found: C, 65.37; H, 5.5.29; N, 22.32; S, 7.31.

Conclusions

We have successfully synthesized new four cyclic 2-substituted-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino[2,3-*b*]quinoxaline (**7a-g**) through the initial treatment of 2,4-dichloro-5-(chloromethyl)-6-methylpyrimidine (**3**) with 3-aminoquinoxaline-2-thiol (**4**) to produce compound (**5**). The cyclocondensation of this compound in the presence of K_2CO_3 gave 2-chloro-4-methyl-5,13-dihydropyrimido[4',5':5,6][1,4]thiazepino [2,3-*b*]quinoxaline which was further substituted with various *sec*-amines to obtain compounds (**7a-g**). Compound (**7a**) as one of the synthesized compounds was conducted to study its true regiochemistry *via* X-ray crystallographic data and the results showed that no Smiles rearrangement occurred.

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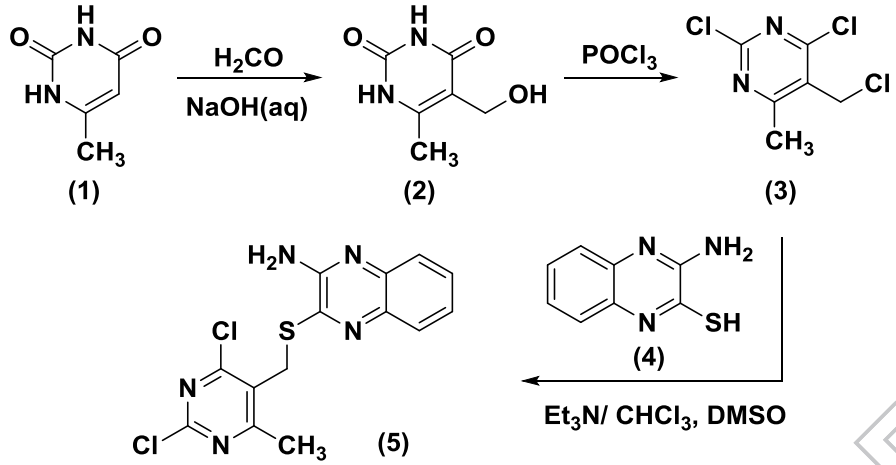
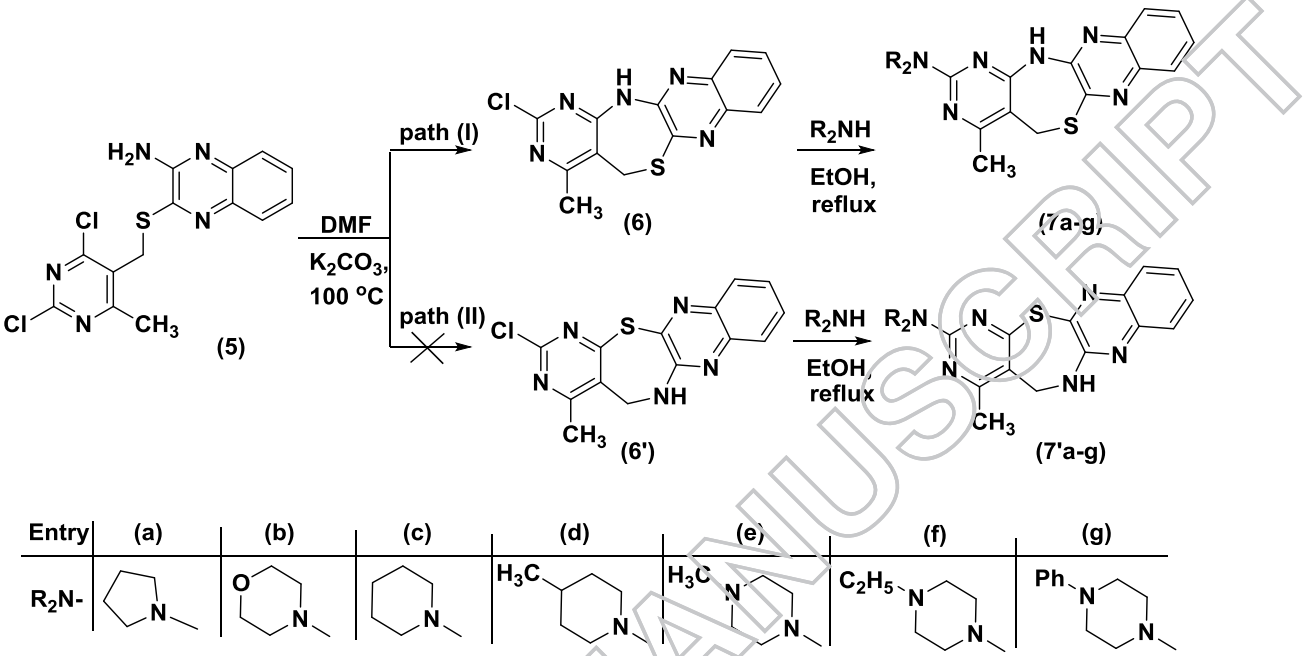


Scheme 1. Preparation of compound **(5)**.



Scheme 2. Synthetic route for the synthesis of compounds **(7a-g)**

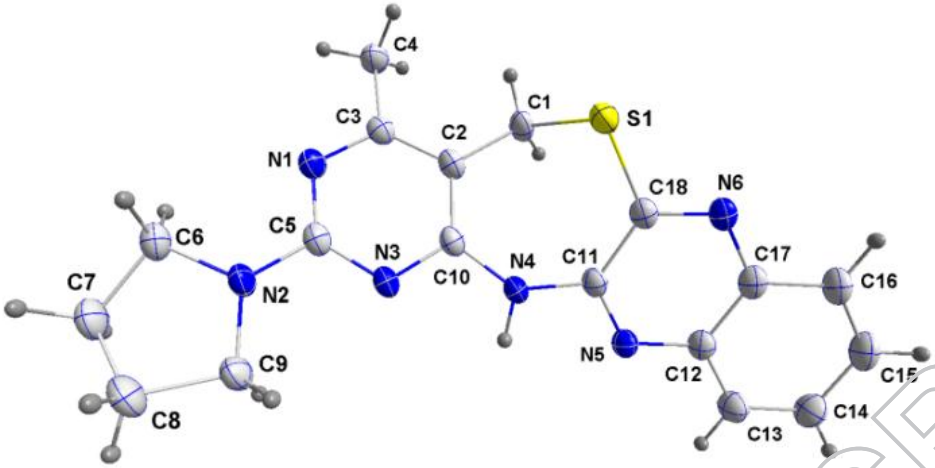


Figure 1. ORTEP view of compound (**7a**) in 50% probability ellipsoids

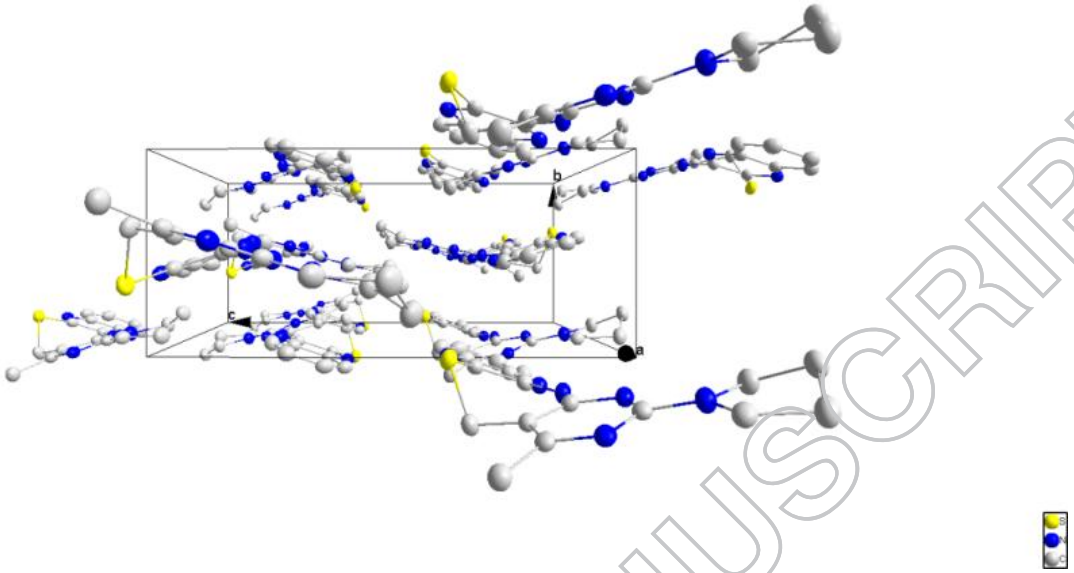


Figure 2. Packing viewed down the a axis for compound (**7a**).

Table 1: Sample, crystal data and structure refinement for JTM548.

Chemical formula	$C_{18}H_{18}N_6S$	
Formula weight	350.44 g/mol	
Temperature	150(2) K	
Wavelength	1.54178 Å	
Crystal size	0.066 x 0.141 x 0.266 mm	
Crystal habit	light yellow block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 13.5002(4) Å	α = 90°
	b = 7.1431(2) Å	β = 90.8160(10)°
	c = 16.8731(5) Å	γ = 90°
Volume	1626.96(8) $Å^3$	
Z	4	
Density (calculated)	1.431 g/cm^3	
Absorption coefficient	1.878 mm^{-1}	
F(000)	736	
Diffractometer	Bruker D8 VENTURE PHOTON 100 CMOS	
Radiation source	'INCOATEC IμS micro-focus source', Cu	
Theta range for data collection	3.27 to 72.44°	
Reflections collected	5926	
Independent reflections	5926 [R(int) = 0.0803]	
Coverage of independent reflections	98.6%	
Absorption correction	multi-scan	

Max. and min. transmission	0.8860 and 0.6350
Structure solution technique	direct methods
Structure solution program	*SHELXT* (Sheldrick, 2015)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5926 / 0 / 228
Goodness-of-fit on F^2	1.042
Final R indices	5028 data; $I>2\sigma(I)$ R1 = 0.0428, wR2 = 0.1057
	all data R1 = 0.0530, wR2 = 0.1123
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0561P)^2+0.4693P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	0.216 and -0.315 eÅ^{-3}
R.M.S. deviation from mean	0.051 eÅ^{-3}

Table 2: Selected bond lengths (Å) and angles for compound 7a

S1-C18	1.754(2)	S1-C1	1.827(2)
N1-C3	1.343(3)	N1-C5	1.350(3)
N2-C5	1.352(3)	N2-C6	1.460(3)
N2-C9	1.466(3)	N3-C10	1.338(3)
N3-C5	1.345(3)	N4-C11	1.384(3)
N4-C10	1.393(3)	N4-H4N	0.91
N5-C11	1.318(3)	N5-C12	1.365(3)
N6-C18	1.313(3)	N6-C17	1.366(3)
C1-C2	1.496(3)	C1-H1A	0.99
C1-H1B	0.99	C2-C3	1.386(3)
C2-C10	1.401(3)	C3-C4	1.505(3)
C4-H4A	0.98	C4-H4B	0.98
C4-H4C	0.98	C6-C7	1.530(3)
C6-H6A	0.99	C6-H6B	0.99
C7-C8	1.518(3)	C7-H7A	0.99
C7-H7B	0.99	C8-C9	1.528(3)
C8-H8A	0.99	C8-H8B	0.99
C9-H9A	0.99	C9-H9B	0.99
C11-C18	1.449(3)	C12-C13	1.413(3)
C12-C17	1.415(3)	C13-C14	1.374(3)
C13-H13	0.95	C14-C15	1.414(3)

C14-H14	0.95	C15-C16	1.365(3)
C15-H15	0.95	C16-C17	1.413(3)
C16-H16	0.95		