International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.5, No.1, pp 142-155, Jan-Mar 2013

Synthesis ,Characterization And Biological Evaluation Of Some New Thieno[2,3-d]Pyrimidine Derivatives

Vikunjana K. Akbari,Pragnesh D. Patel and Keshav C. Patel*

Department of Chemistry, Veer Narmad South Gujarat University, Surat-395007, Gujarat, India.

***Corres.author: akbarivk@yahoo.co.in**
Phone no: (+91) 9979735497

Abstract: Several new thieno[2,3-*d*]pyrimidine derivatives 2-{[3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amino}-*N*-(thieno[2,3-*d*]pyrimidin-4-yl)acetamide **6(a-j)**, 4-[(2*E*)-2-(substitutedbenzylidene)hydrazinyl]-2-[(2*Z*)-2-(2,4-dichlorobenzylidene) hydrazinyl] thieno[2,3-*d*]pyrimidine **9(a-j)** and 3-chloro-4-(substituted phenyl)-1-(thieno[2,3-*d*]pyrimidin-4-ylamino)azetidin-2-one **14(a-j)** were synthesized starting from 2-aminothiophene-3-carbonitrile **1**. The characterization of the newly synthesized compounds was established by IR, ^{1}H NMR, ^{13}C NMR and Elemental analysis. The final compounds were screened for their antibacterial activity against *Staphylococcus aureus* and *Streptococcus pyogenes* from Gram positive group of bacteria and *Escherichia coli* and *Pseudomonas aeruginosa* from Gram negative group of bacteria and antifungal activity against *Aspergillus niger*.
Key words: Thieno[2,3-*d*]pyrimidine, antimicrobial activity, schiff's base, azetidinone.

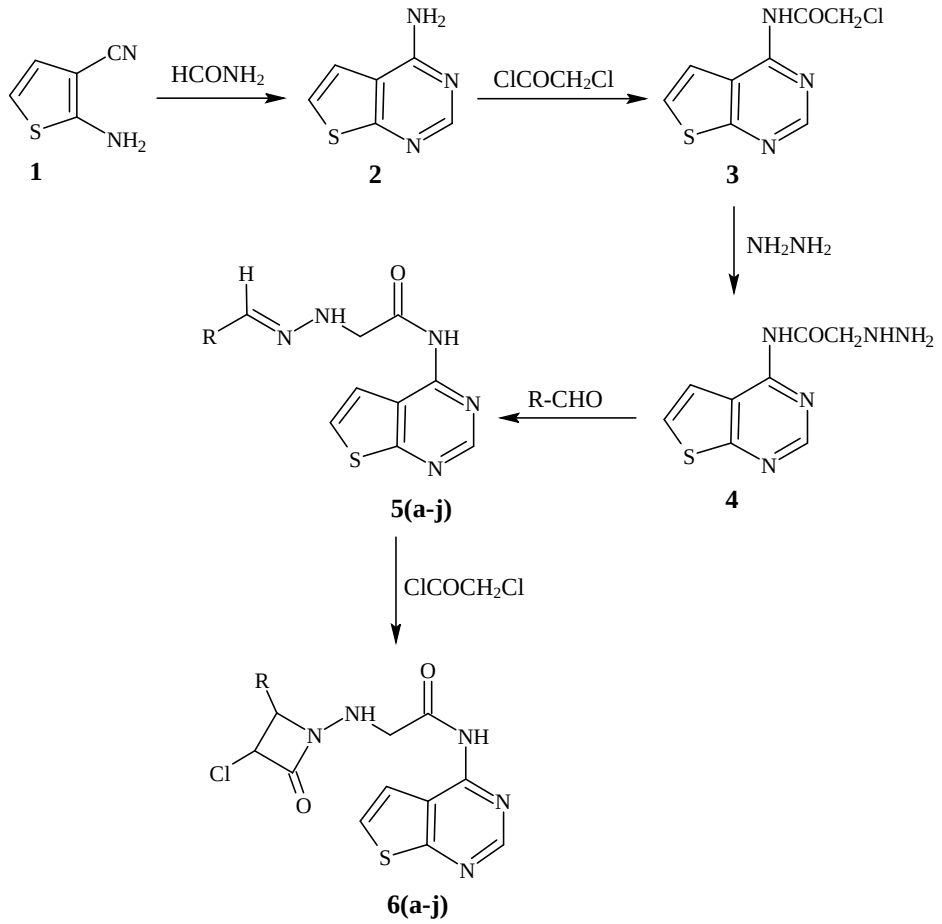
INTRODUCTION

Thienopyrimidine derivatives, which are structure analogues of purines, have been focus of great interest because of their large range of pharmacological activities[1] as antibacterial,[2,3] antifungal,[4] analgesic,[5-7] antipyretic,[8,9] antiinflammatory,[10] antihistaminic,[11,12] anticancer,[13-15] radioprotective.[16,17] Many thieno[2,3-*d*]pyrimidine derivatives were reported as phosphodiesterase inhibitors,[18] also exhibited good H_1 receptor antagonistic activities,[19] 4-amino derivatives showed insecticidal, pesticidal and acaricidal activities,[20] Numerous thieno[2,3-*d*]pyrimidines have been proved to use in case of cerebral ischemia, malaria, tuberculosis, Alzheimer's and Parkinson's diseases.[21] This work aimed to synthesize some new thieno[2,3-*d*]pyrimdine derivatives starting with 2-aminothiophene-3-carbonitrile and to evaluate their biological activities.

EXPERIMENTAL

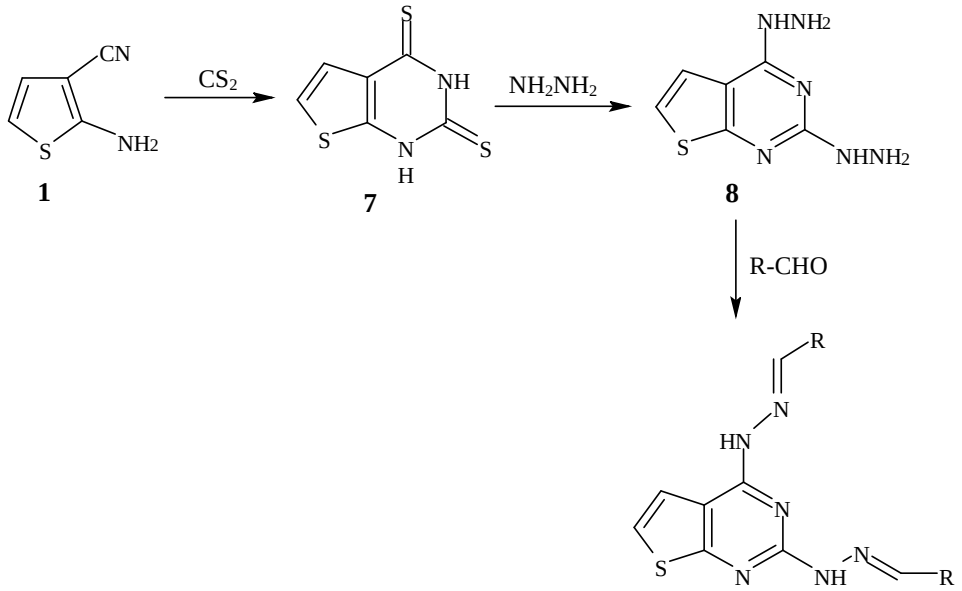
General Procedures:
Melting points were determined by open capillary method and are uncorrected. The structures of the compounds were confirmed by ^{1}H and ^{13}C nuclear magnetic resonance and Fourier transform infrared. ^{1}H NMR spectra were recorded with Bruker Avance II 400 MHz NMR spectrometer at SAIF, Chandigarh, in $CDCl_3$ or DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm. ^{13}C NMR spectra of the compounds were recorded with a Bruker Avance II 400 MHz NMR spectrometer at SAIF (Sophisticated Analytical Instrument Facilities), Chandigarh. The IR spectra were recorded with a Thermo Scientific Nicolet iS10 FTIR specrophotometer at the Deparetment of Chemistry, Veer Narmad South Gujarat University. Elemental analysis (C, H, N) were performed on Thermo Scientific FLASH 2000 at G.N.F.C.

(Gujarat Narmada Valley Fertilizer Company Ltd., Bharuch). The progress of reactions and the purity of synthesized compounds were checked by TLC on E-Merck precoated 60 F_{254} plates and the spotes were examined under short-wave UV light. The synthesis of 2-{[3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl]amino}-*N*-(thieno[2,3-*d*]pyrimidin-4-yl)acetamide **6(a-j)** are showm in Scheme 1, 4-[(2*E*)-2-(substitutedbenzylidene)hydrazinyl]-2-[(2*Z*)-2-(2,4-dichlorobenzylidene) hydrazinyl] thieno[2,3-*d*]pyrimidine **9(a-j)** are showm in Scheme 2 and 3-chloro-4-(substitutedphenyl)-1-(thieno[2,3-*d*]pyrimidin-4-ylamino)azetidin-2-one **14(a-j)** are showm in Scheme 3.



(a) R = 2,4-$(Cl)_2C_6H_3$ (b) R = 3,4-$(OH)_2C_6H_3$ (c) R = 3-$OCH_3C_6H_4$ (d) R = 4-ClC_6H_4
(e) R = 4-FC_6H_4 (f) R = 4-OHC_6H_4 (g) R = 4-$OCH_3C_6H_4$ (h) R = 4-$CH_3C_6H_4$
(i) R = 4-$NO_2C_6H_4$ (j) R = 4-$CH_2CH_2CH_2CH_3C_6H_4$

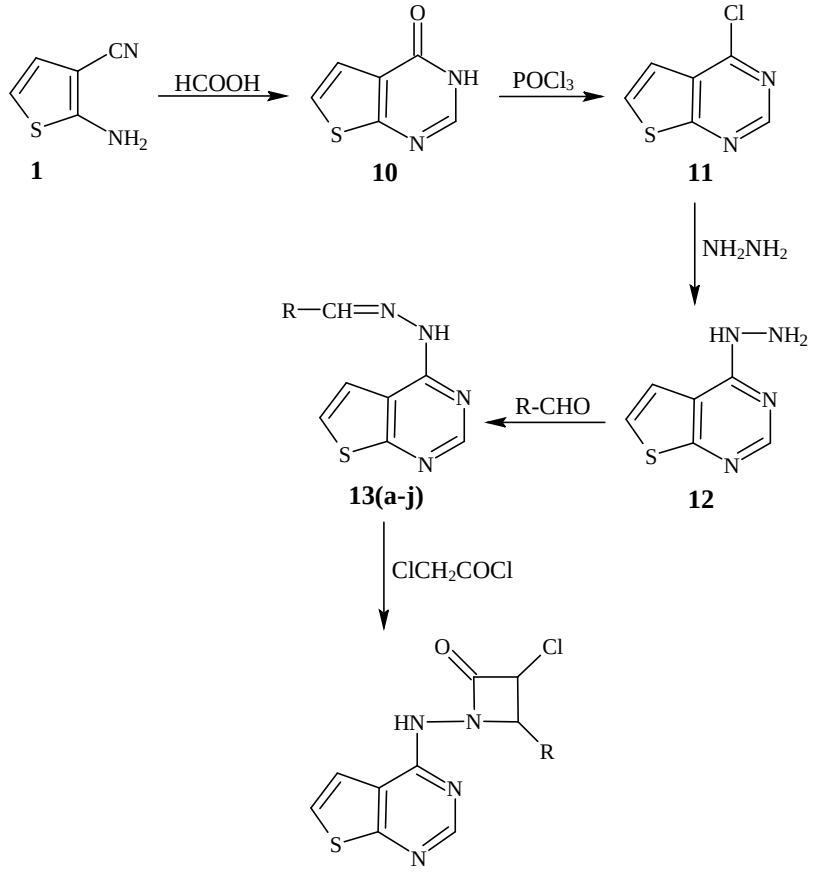
Scheme-1



1 **7** **8** **9(a-j)**

(a) R = 2,4-$(Cl)_2C_6H_3$ (b) R = 3,4-$(OH)_2C_6H_3$ (c) R = 3-$OCH_3C_6H_4$ (d) R = 4-ClC_6H_4
(e) R = 4-FC_6H_4 (f) R = 4-OHC_6H_4 (g) R = 4-$OCH_3C_6H_4$ (h) R = 4-$CH_3C_6H_4$
(i) R = 4-$NO_2C_6H_4$ (j) R = 4-$CH_2CH_2CH_2CH_3C_6H_4$

Scheme-2



1 **10** **11** **12** **13(a-j)** **14(a-j)**

(a) R = 2,4-$(Cl)_2C_6H_3$ (b) R = 3,4-$(OH)_2C_6H_3$ (c) R = 3-$OCH_3C_6H_4$ (d) R = 4-ClC_6H_4
(e) R = 4-FC_6H_4 (f) R = 4-OHC_6H_4 (g) R = 4-$OCH_3C_6H_4$ (h) R = 4-$CH_3C_6H_4$
(i) R = 4-$NO_2C_6H_4$ (j) R = 4-$CH_2CH_2CH_2CH_3C_6H_4$

Scheme-3

Thieno[2,3-d]pyrimdin-4-amine (2)

A mixture of compound **1** (0.01 mol) and formamide (10 mL) was heated under reflux for 4 h. After cooling, the reaction mixture was poured into ice cold water. The separated product was collected by filtration, dried and recrystallised from dioxane to give compound **2** (0.95g, 63.00%); mp 214-219˚C. IR spectrum (KBr, ν, cm^{-1}): 3420-3313 (NH_2); ^{1}NMR spectrum ($CDCl_3$, δ ppm): 7.49 (d, 1H, CH), 7.71 (d, 1H, CH), 6.85 (s, 2H, NH_2), 8.47 (s, 1H, CH). Anal. calcd. for $C_6H_5N_3S$: C, 47.66; H, 3.33; N, 27.79; S, 21.21; found: C, 47.55; H, 3.42; N, 27.70; S, 21.32.

2-Chloro-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (3)

To a solution of compound **2** (0.01 mol) in chloroform (10 mL) and chloroacetyl chloride (0.01 mol) were refluxed in presence of K_2CO_3 (0.01 mol) for 9-10 h. The solvent was distilled on vaccum and residue was treated with 5% $NaHCO_3$ (10 mL) and then with water (15 mL). The product was collected, dried and recrystallised from methanol to furnish compound **3** (1.64g, 72.00%); mp 243-248˚C. IR spectrum (KBr, ν, cm^{-1}): 3435 (NH), 1636 (CONH); ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 4.31 (s, 2H, CH_2), 7.50 (d, 1H, CH), 7.70 (d, 1H, CH), 7.98 (s, 1H, CONH), 8.45 (s, 1H, CH). Anal. calcd. for $C_8H_6ClN_3OS$: C, 42.20; H, 2.66; N, 18.46; S, 14.08; found: C, 42.11; H, 2.75; N, 18.34; S, 14.19.

2-Hydrazinyl-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (4)

A mixture of compound **3** (0.01 mol) and hydrazine hydrate (99%) (5 mL) in methanol (10 mL) was refluxed for 8h and then held for ~16h at room temperature. The separated product was filtered off, dried and recrystallised from ethanol to give compound **4** (1.49g, 67.00%); mp 177-182˚C. IR spectrum (KBr, ν, cm^{-1}): 3455 (NH), 3350 ($NHNH_2$), 2888 (CH_2), 1648 (CONH); ^{1}H NMR ($CDCl_3$, δ ppm): 2.01 (brs, 2H, NH_2, D_2O exchangeable), 2.21 (brs, 1H, NH, D_2O exchangeable), 3.60 (s, 2H, CH_2), 7.52 (d, 1H, CH), 7.73 (d, 1H, CH), 8.01 (s, 1H, CONH), 8.51 (s, 1H, CH). Anal. calcd. for $C_8H_9N_5OS$: C, 43.04; H, 4.06; N, 31.37; S, 14.36; found: C, 43.16; H, 4.18; N, 31.25; S, 14.24.

Synthesis of compounds 5(a-j)

A solution of compound **4** (0.005 mol) in methanol (10 mL) and appropriate aromatic aldehyde (0.005 mol) containing 2-3 drops of glacial acetic acid, was boiled under reflux on a water bath for 8-9 h. The product that separated on cooling was filtered off, dried and recrystallized from ethanol to give **5(a-j)**.

2-[(2E)-2-(2,4-dichlorobenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5a)

Yield: 2.47g (65%); mp 219-224 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3265 (NH), 1648 (CONH), 1548 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 2.05 (s, 1H, NH), 3.54 (s, 2H, CH_2), 7.28-7.40 (m, 3H, Ar-H), 7.51 (d, 1H, CH), 7.77 (d, 1H, CH), 7.94 (s, 1H, CH), 8.2 (s, 1H, N=CH), 8.52 (s, 1H, CONH). Anal. calcd. for $C_{15}H_{11}Cl_2N_5OS$: C, 47.38; H, 2.92; N, 18.42; S, 8.43; found: C, 47.31; H, 3.01; N, 18.36; S, 8.39.

2-[(2E)-2-(3,4-dihydroxybenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5b)

Yield: 2.44g (71%); mp 197-202 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3495 (OH), 3264 (NH), 1651 (CONH), 1554 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 2.10 (s, 1H, NH), 3.56 (s, 2H, CH_2), 6.40-6.84 (m, 3H, Ar-H), 7.50 (d, 1H, CH), 7.76 (d, 1H, CH), 7.96 (s, 1H, N=CH), 8.18 (s, 1H, CH), 8.45 (s, 1H, CONH), 9.13, 9.39 (2brs, 2H, 2OH). Anal. calcd. for $C_{15}H_{13}N_5O_3S$: C, 52.47; H, 3.82; N, 20.40; S, 9.34; found: C, 52.39; H, 3.92; N, 20.46; S, 9.43.

2-[(2E)-2-(3-methoxybenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5c)

Yield: 2.39g (70%); mp 214-219 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3277 (NH), 1649 (CONH), 1551 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 2.12 (s, 1H, NH), 3.54 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 6.65-7.09 (m, 4H, Ar-H), 7.56 (d, 1H, CH), 7.72 (d, 1H, CH), 7.96 (s, 1H, N=CH), 8.21 (s, 1H, CH), 8.51 (s, 1H, CONH). Anal. calcd. for $C_{16}H_{15}N_5O_2S$: C, 56.29; H, 4.43; N, 20.51; S, 9.39; found: C, 56.32; H, 4.38; N, 20.60; S, 9.31.

2-[(2E)-2-(4-chlorobenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5d)

Yield: 2.35g (68%); mp 229-234 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3262 (NH), 1645 (CONH), 1551 (N=CH); ^{1}H NMR ($CDCl_3$, δ ppm): 2.05 (s, 1H, NH), 3.52 (s, 2H, CH_2), 7.18-7.40 (m, 4H, Ar-H), 7.55 (d, 1H, CH), 7.75 (d, 1H, CH), 7.89 (s, 1H, N=CH), 8.10 (s, 1H, CH), 8.50 (s, 1H, CONH). Anal. calcd. for $C_{15}H_{12}ClN_5OS$: C, 52.10; H, 3.50; N, 20.25; S, 9.27; found: C, 52.20; H, 3.55; N, 20.18; S, 9.32.

2-[(2E)-2-(4-fluorobenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5e)

Yield: 2.17g (66%); mp 270-275 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3271 (NH), 1639 (CONH), 1550 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 2.11 (s, 1H, NH), 3.59 (s, 2H, CH_2), 7.07-7.13 (m, 4H, Ar-H), 7.50 (d, 1H, CH), 7.71 (d, 1H, CH), 7.94 (s, 1H, N=CH), 8.18 (s, 1H, CH), 8.47 (s, 1H, CONH).

Anal. calcd. for $C_{15}H_{12}FN_5OS$: C, 54.70; H, 3.67; N, 21.26; S, 9.74; found: C, 54.62; H, 3.73; N, 21.32; S, 9.67.

2-[(2E)-2-(4-hydroxybenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5f)

Yield: 2.39g (73%); mp 256-261 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3489 (OH), 3263 (NH), 1647 (CONH), 1554 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 2.08 (s, 1H, NH), 3.48 (s, 2H, CH_2), 6.70-7.12 (m, 4H, Ar-H), 7.51 (d, 1H, CH), 7.73 (d, 1H, CH), 7.92 (s, 1H, N=CH), 8.14 (s, 1H, CH), 8.52 (s, 1H, CONH), 9.75 (s, 1H, OH). Anal. calcd. for $C_{15}H_{13}N_5O_2S$: C, 55.03; H, 4.00; N, 21.39; S, 9.79; found: C, 55.08; H, 4.10; N, 21.31; S, 9.86.

2-[(2E)-2-(4-methoxybenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5g)

Yield: 2.28g (67%); mp 211-216 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3269 (NH), 1643 (CONH), 1548 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 2.14 (s, 1H, NH), 3.57 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 6.70-6.84 (m, 4H, Ar-H), 7.54 (d, 1H, CH), 7.76 (d, 1H, CH), 7.96 (s, 1H, N=CH), 8.20 (s, 1H, CH), 8.51 (s, 1H, CONH). Anal. calcd. for $C_{16}H_{15}N_5O_2S$: C, 56.29; H, 4.43; N, 20.51; S, 9.39; found: C, 56.36; H, 4.36; N, 20.45; S, 9.31

2-[(2E)-2-(4-methylbenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5h)

Yield: 2.34g (72%); mp 262-267 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3259 (NH), 1654 (CONH), 1544 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 2.09 (s, 1H, NH), 2.33 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 7.00-7.35 (m, 4H, Ar-H), 7.59 (d, 1H, CH), 7.80 (d, 1H, CH), 7.90 (s, 1H, N=CH), 8.08 (s, 1H, CH), 8.49 (s, 1H, CONH). Anal. calcd. for $C_{16}H_{15}N_5OS$: C, 59.06; H, 4.65; N, 21.52; S, 9.85; found: C, 59.16; H, 4.60; N, 21.49; S, 9.82.

2-[(2E)-2-(4-nitrobenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5i)

Yield: 2.31g (65%); mp 259-264 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3263 (NH), 1651 (CONH), 1549 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 2.04 (s, 1H, NH), 3.52 (s, 2H, CH_2), 7.07-7.45 (m, 4H, Ar-H), 7.51 (d, 1H, CH), 7.77 (d, 1H, CH), 7.91 (s, 1H, N=CH), 8.19 (s, 1H, CH), 8.44 (s, 1H, CONH). Anal. calcd. for $C_{15}H_{12}N_6O_3S$: C, 50.56; H, 3.39; N, 23.58; S, 9.00; found: C, C, 50.45; H, 3.45; N, 23.52; S, 9.06

2-[(2E)-2-(4-butylbenzylidene)hydrazinyl]-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (5j)

Yield: 2.24g (61%); mp 271-276 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3265 (NH), 1656 (CONH), 1543 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 1.01 (t, 3H, CH_3), 1.26-1.45 (m, 6H, $3CH_2$), 2.10 (s, 1H, NH), 3.53 (s, 2H, CH_2), 7.07-7.45 (m, 4H, Ar-H), 7.55 (d, 1H, CH), 7.75 (d, 1H, CH), 7.97 (s, 1H, N=CH), 8.18 (s, 1H, CH), 8.49 (s, 1H, CONH). Anal. calcd. for $C_{19}H_{21}N_5OS$: C, 62.10; H, 5.76; N, 19.06; S, 8.73; found: C, .18; H, 5.70; N, 19.16; S, 8.69.

Synthesis of compounds 6(a-j)

Chloroacetyl chloride (0.005 mol) was added drop wise to a solution of Schiff's base **5(a-j)** (0.005 mol) and triethylamine (2-3 drops) in dry dioxane (10 mL) at 5-10˚C. The reaction mixture was stirred for 3 hrs and then refluxed for 4-5 h. On cooling, the precipitate was obtained which was filtered, dried and recrystallised from dimethylformamide to produce **6(a-j).**

2-{[3-chloro-2-(2,4-dichlorophenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6a)

Yield: 3.06g (67%); mp 213-218 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3259 (NH), 1657 (CONH), 1751 (CO, β-lactum); ^1H NMR (DMSO-d_6, δ ppm): 3.04 (s, 1H, NH), 3.56 (s, 2H, CH_2), 5.12 (d, 1H, CH-Ar), 5.46 (d, 1H, CH-Cl), 7.23-7.40 (m, 3H, Ar-H), 7.50 (d, 1H, CH), 7.71 (d, 1H, CH), 8.12 (s, 1H, CH), 8.45 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.4 (CH_2), 62.5 (CH), 63.5 (CH-Cl), 110.1-170.3 (thienopyrimidine aromatic carbon atoms), 163.7 (CO, β-lactam), 168.8 (CONH). Anal. calcd. for $C_{17}H_{12}Cl_3N_5O_2S$: C, 44.70; H, 2.65; N, 15.33; S, 7.02; found: C, 44.76; H, 2.61; N, 15.39; S, 7.10.

2-{[3-chloro-2-(3,4-dihydroxyphenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6b)

Yield: 2.18g (52%); mp 198-203 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3495 (OH), 3249 (NH), 1652 (CONH), 1745 (CO, β-lactum); ^1H NMR (DMSO-d_6, δ ppm): 3.08 (s, 1H, NH), 3.60 (s, 2H, CH_2), 5.06 (d, 1H, CH-Ar), 5.44 (d, 1H, CH-Cl), 6.61-6.77 (m, 3H, Ar-H), 7.50 (d, 1H, CH), 7.71 (d, 1H, CH), 8.08 (s, 1H, CH), 8.41 (s, 1H, CONH), 9.14, 9.34 (2brs, 2H, 2OH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.3 (CH_2), 62.9 (CH), 63.3 (CH-Cl), 110.3-170.1 (thienopyrimidine aromatic carbon atoms), 163.3 (CO, β-lactam), 169.1 (CONH). Anal. calcd. for $C_{17}H_{14}ClN_5O_4S$: C, 48.63; H, 3.36; N, 16.68; S, 7.64; found: C, 48.70; H, 3.42; N, 16.59; S, 7.58.

2-{[3-chloro-2-(3-methoxyphenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6c)

Yield: 2.76g (66%); mp 244-249 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3253 (NH), 1659 (CONH), 1754

(CO, β-lactum); ^{1}H NMR (DMSO-d_6, δ ppm): 3.10 (s, 1H, NH), 3.53 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 5.09 (d, 1H, CH-Ar), 5.45 (d, 1H, CH-Cl), 7.32-7.48 (m, 4H, Ar-H), 7.50 (d, 1H, CH), 7.73 (d, 1H, CH), 8.02 (s, 1H, CH), 8.52 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.1 (CH_2), 62.9 (CH), 63.3 (CH-Cl), 110.6-170.8 (thienopyrimidine aromatic carbon atoms), 163.3 (CO, β-lactam), 168.7 (CONH). Anal. calcd. for $C_{18}H_{16}ClN_5O_3S$: C, 51.74; H, 3.86; N, 16.76; S, 7.67; found: C, 51.68; H, 3.81; N, 16.71; S, 7.72.

2-{[3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6d)

Yield: 3.08g (73%); mp 229-234 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3252 (NH), 1656 (CONH), 1751 (CO, β-lactum); ^{1}H NMR (DMSO-d_6, δ ppm): 3.08 (s, 1H, NH), 3.60 (s, 2H, CH_2), 5.05 (d, 1H, CH-Ar), 5.44 (d, 1H, CH-Cl), 7.27-7.48 (m, 4H, Ar-H), 7.56 (d, 1H, CH), 7.78 (d, 1H, CH), 8.06 (s, 1H, CH), 8.49 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.3 (CH_2), 62.4 (CH), 63.7 (CH-Cl), 110.6-170.9 (thienopyrimidine aromatic carbon atoms), 163.7 (CO, β-lactam), 168.2 (CONH). Anal. calcd. for $C_{17}H_{13}Cl_2N_5O_2S$: C, 48.35; H, 3.10; N, 16.58; S, 7.59; found: C, 48.30; H, 3.17; N, 16.63; S, 7.62.

2-{[3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6e)

Yield: 2.72g (67%); mp 214-219 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3252 (NH), 1657 (CONH), 1756 (CO, β-lactum); ^{1}H NMR (DMSO-d_6, δ ppm): 3.10 (s, 1H, NH), 3.55 (s, 2H, CH_2), 5.12 (d, 1H, CH-Ar), 5.48 (d, 1H, CH-Cl), 7.13-7.43 (m, 4H, Ar-H), 7.59 (d, 1H, CH), 7.80 (d, 1H, CH), 8.09 (s, 1H, CH), 8.47 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.7 (CH_2), 62.5 (CH), 63.2 (CH-Cl), 110.6-170.5 (thienopyrimidine aromatic carbon atoms), 164.3 (CO, β-lactam), 168.8 (CONH). Anal. calcd. for $C_{17}H_{13}ClFN_5O_2S$: C, 50.31; H, 3.23; N, 17.26; S, 7.90; found: C, 50.37; H, 3.28; N, 17.16; S, 7.95.

2-{[3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6f)

Yield: 2.42g (60%); mp 204-209 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3291 (OH), 3246 (NH), 1659 (CONH), 1760 (CO, β-lactum); ^{1}H NMR (DMSO-d_6, δ ppm): 3.15 (s, 1H, NH), 3.58 (s, 2H, CH_2), 4.93 (s, 1H, OH), 5.16 (d, 1H, CH-Ar), 5.46 (d, 1H, CH-Cl), 7.08-7.41 (m, 4H, Ar-H), 7.52 (d, 1H, CH), 7.74 (d, 1H, CH), 8.04 (s, 1H, CH), 8.51 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.8 (CH_2), 62.4 (CH), 63.6 (CH-Cl), 110.3-170.6 (thienopyrimidine aromatic carbon atoms), 164.4 (CO, β-lactam), 168.4 (CONH). Anal. calcd. for $C_{17}H_{14}ClN_5O_3S$: C, 50.56; H, 3.49; N, 17.34; S, 7.94; found: C, 50.50; H, 3.54; N, 17.29; S, 7.90

2-{[3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6g)

Yield: 3.00g (72%); mp 244-249 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3259 (NH), 1657 (CONH), 1751 (CO, β-lactum); ^{1}H NMR (DMSO-d_6, δ ppm): 3.08 (s, 1H, NH), 3.59 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 5.11 (d, 1H, CH-Ar), 5.50 (d, 1H, CH-Cl), 7.30-7.51 (m, 4H, Ar-H), 7.55 (d, 1H, CH), 7.76 (d, 1H, CH), 8.12 (s, 1H, CH), 8.54 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.5 (CH_2), 62.7 (CH), 63.9 (CH-Cl), 110.2-170.8 (thienopyrimidine aromatic carbon atoms), 163.7 (CO, β-lactam), 168.5 (CONH). Anal. calcd. for $C_{18}H_{16}ClN_5O_3S$: C, 51.74; H, 3.86; N, 16.76; S, 7.67; found: C, 51.69; H, 3.79; N, 16.82; S, 7.70.

2-{[3-chloro-2-(4-methylphenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6h)

Yield: 2.77g (69%); mp 250-255 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3252 (NH), 1658 (CONH), 1745 (CO, β-lactum); ^{1}H NMR (DMSO-d_6, δ ppm): 2.34 (s, 3H, CH_3), 3.01 (s, 1H, NH), 3.56 (s, 2H, CH_2), 5.24 (d, 1H, CH-Ar), 5.49 (d, 1H, CH-Cl), 7.25-7.44 (m, 4H, Ar-H), 7.54 (d, 1H, CH), 7.75 (d, 1H, CH), 8.05 (s, 1H, CH), 8.53 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.1 (CH_2), 62.8 (CH), 63.3 (CH-Cl), 110.9-170.5 (thienopyrimidine aromatic carbon atoms), 163.8 (CO, β-lactam), 168.8 (CONH). Anal. calcd. for $C_{18}H_{16}ClN_5O_2S$: C, 53.80; H, 4.01; N, 17.43; S, 7.98; found: C, 53.86; H, 4.09; N, 17.34; S, 7.91

2-{[3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6i)

Yield: 3.07g (71%); mp 263-268 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3257 (NH), 1651 (CONH), 1753 (CO, β-lactum); ^{1}H NMR (DMSO-d_6, δ ppm): 3.09 (s, 1H, NH), 3.57 (s, 2H, CH_2), 5.21 (d, 1H, CH-Ar), 5.52 (d, 1H, CH-Cl), 7.12-7.49 (m, 4H, Ar-H), 7.53 (d, 1H, CH), 7.75 (d, 1H, CH), 8.01 (s, 1H, CH), 8.50 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.3 (CH_2), 62.6 (CH), 63.7 (CH-Cl), 110.4-170.3 (thienopyrimidine aromatic carbon atoms), 164.2 (CO, β-lactam), 168.3 (CONH). Anal. calcd. for $C_{17}H_{13}ClN_6O_4S$: C, 47.17; H, 3.03; N, 19.42; S, 7.41; found: C, 47.09; H, 3.11; N, 19.37; S, 7.48.

2-{[3-chloro-2-(4-butylphenyl)-4-oxoazetidin-1-yl]amino}-N-(thieno[2,3-d]pyrimidin-4-yl)acetamide (6i)

Yield: 3.20g (72%); mp 297-302 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3262 (NH), 1656 (CONH), 1758 (CO, β-lactum); ^1H NMR (DMSO-d_6, δ ppm): 1.05 (t, 3H, CH_3), 1.31-1.72 (m, 6H, $3CH_2$), 3.04 (s, 1H, NH), 3.60 (s, 2H, CH_2), 5.19 (d, 1H, CH-Ar), 5.45 (d, 1H, CH-Cl), 6.61-6.77 (m, 4H, Ar-H), 7.50 (d, 1H, CH), 7.72 (d, 1H, CH), 8.06 (s, 1H, CH), 8.54 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, δ ppm): 53.6 (CH_2), 62.4 (CH), 63.1 (CH-Cl), 110.1-170.4 (thienopyrimidine aromatic carbon atoms), 163.9 (CO, β-lactam), 168.9 (CONH). Anal. calcd. for $C_{21}H_{22}ClN_5O_2S$: C, 56.81; H, 4.99; N, 15.78; S, 7.22; found: C, 56.87; H, 5.05; N, 15.72; S, 7.18.

Thieno[2,3-d]pyrimidine-2,4(1H,3H)-dithione (7)

A mixture of compound **1** (0.01 mol) and carbon disulphide (0.01 mol) in pyridine (10 mL) were heated under reflux for 8 h. After completion of reaction, the reaction mixture was cooled at room temperature then poured into ice cold water (50 mL) and neutralized with hydrochloric acid. The separated product was collected by filtration, washed with water, dried and recrystallised from ethanol to give compound **7**. Yield 1.28 g (64%); mp 198-203˚C; IR spectrum (KBr, ν, cm^{-1}): 3342, 3215 (2NH), 1360, 1348 (2C=S); ^{1}NMR ($CDCl_3$, δ ppm): 7.50 (d, 1H, CH), 7.76 (d, 1H, CH), 8.76 (brs, 1H, NH, D_2O exchangeable), 12.45 (brs, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_6H_4N_2S_3$: C, 35.98; H, 2.01; N, 13.99; S, 48.02; found: C, 36.09; H, 2.17; N, 13.88; S, 47.91.

2,4-dihydrazinylthieno[2,3-d]pyrimidine (8)

A solution of compound **7** (0.01 mol) in ethanol (20 mL) was treated with hydrazine hydrate (99%) (20 mL) and refluxed on water bath for 8 h and then held for ~16 h at room temperature. The separated product was fitered off, dried and recrystallised from dioxane to give compound **8**. Yield 1.37 g (70%); mp 173-178˚C; IR spectrum (KBr, ν, cm^{-1}): 3434-3243 ($2NH_2$, 2NH); ^{1}NMR ($CDCl_3$, δ ppm): 4.17 (brs, 2H, NH_2, D_2O exchangeable), 4.66 (brs, 2H, NH_2, D_2O exchangeable), 5.73 (brs, 1H, NH, D_2O exchangeable), 6.52 (brs, 2H, NH, D_2O exchangeable), 7.48 (d, 1H, CH), 7.72 (d, 1H, CH). Anal. calcd. for $C_6H_8N_6S$: C, 36.72; H, 4.11; N, 42.83; S, 16.34; found: C, 36.65; H, 4.24; N, 42.74; S, 16.41.

Synthesis of compounds 9(a-j)

A mixture of compound **8** (0.005 mol) and appropriate aromatic aldehyde (0.005 mol) in 10 mL ethanol containing 2-3 drops of glacial acetic acid, was boiled under reflux on a water bath for 10-12 h. The product that separated on cooling was filtered off, dried and recrystallized from ethanol to give **9(a-j)**.

4-[(2E)-2-(2,4-dichlorobenzylidene)hydrazinyl]-2-[(2Z)-2-(2,4-dichlorobenzylidene) hydrazinyl]thieno[2,3-d]pyrimidine (9a)

Yield: 3.62g (71%); mp 236-241˚C; IR spectrum (KBr, ν, cm^{-1}): 3252 (NH), 1590 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 7.25-7.42 (m, 6H, Ar-H), 7.51 (d, 1H, CH), 7.73 (d, 1H, CH), 8.25 (s, 1H, N=CH), 9.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.2-167.8 (thienopyrimidine aromatic carbon atoms), 144.7 (CH), 151.2 (CH). Anal. calcd. for $C_{20}H_{12}Cl_4N_6S$: C, 47.08; H, 2.37; N, 16.47; S, 6.28; found: C, 47.17; H, 2.43; N, 16.36; S, 6.19.

4-[(E)-(2-{2-[(2Z)-2-(3,4-dihydroxybenzylidene) hydrazinyl]thieno[2,3-d]pyrimidin-4-yl }hydrazinylidene)methyl]benzene-1,2-diol (9b)

Yield: 2.18g (50%); mp 232-237˚C; IR spectrum (KBr, ν, cm^{-1}): 3437 (OH), 3247 (NH), 1596 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 3.63 (brs, 4H, 4OH), 6.87-7.12 (m, 6H, Ar-H), 7.54 (d, 1H, CH), 7.77 (d, 1H, CH), 8.23 (s, 1H, N=CH), 9.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.8-167.6 (thienopyrimidine aromatic carbon atoms), 144.7 (CH), 151.6 (CH). Anal. calcd. for $C_{20}H_{16}N_6O_4S$: C, 55.04; H, 3.70; N, 19.26; S, 7.35; found: C, 55.11; H, 3.62; N, 19.19; S, 7.42.

4-[(2E)-2-(3-methoxybenzylidene)hydrazinyl]-2-[(2Z)-2-(2,4-dichlorobenzylidene) hydrazinyl]thieno[2,3-d]pyrimidine (9c)

Yield: 3.41g (79%); mp 245-250˚C; IR spectrum (KBr, ν, cm^{-1}): 3246 (NH), 1602 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 3.75 (s, 6H, $2OCH_3$), 6.98-7.36 (m, 8H, Ar-H), 7.50 (d, 1H, CH), 7.73 (d, 1H, CH), 8.28 (s, 1H, N=CH), 9.09 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.8-167.6 (thienopyrimidine aromatic carbon atoms), 145.4 (CH), 151.9 (CH). Anal. calcd. for $C_{22}H_{20}N_6O_2S$: C, 61.10; H, 4.66; N, 19.43; S, 7.41; found: C, 61.21; H, 4.58; N, 19.52; S, 7.34.

4-[(2E)-2-(4-chlorobenzylidene)hydrazinyl]-2-[(2Z)-2-(4-chlorobenzylidene)hydrazinyl] thieno[2,3-d]pyrimidine (9d)

Yield: 3.18g (72%); mp 271-276˚C; IR spectrum (KBr, ν, cm^{-1}): 3250 (NH), 1595 (N=CH); ^1H NMR (DMSO-d_6, δ ppm): 7.24-7.48 (m, 8H, Ar-H), 7.49 (d, 1H, CH), 7.71 (d, 1H, CH), 8.30 (s, 1H, N=CH), 9.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.2-167.0 (thienopyrimidine aromatic carbon atoms), 144.7 (CH), 151.4 (CH). Anal. calcd. for

$C_{20}H_{14}Cl_2N_6S$: C, 54.43; H, 3.20; N, 19.04; S, 7.27; found: C, 54.35; H, 3.29; N, 18.93; S, 7.35.

4-[(2E)-2-(4-fluorobenzylidene)hydrazinyl]-2-[(2Z)-2-(4-fluorobenzylidene)hydrazinyl] thieno[2,3-d]pyrimidine (9e)

Yield: 2.82g (69%); mp 252-257˚C; IR spectrum (KBr, ν, cm^{-1}): 3254 (NH), 1599 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): .20-7.41 (m, 8H, Ar-H), 7.51 (d, 1H, CH), 7.72 (d, 1H, CH), 8.23 (s, 1H, N=CH), 9.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.2-167.8 (thienopyrimidine aromatic carbon atoms), 145.5 (CH), 151.6 (CH). Anal. calcd. for $C_{20}H_{14}F_2N_6S$: C, 58.81; H, 3.46; N, 20.58; S, 7.85; found: C, 58.76; H, 3.52; N, 20.50; S, 7.92.

4-[(E)-(2-{2-[(2Z)-2-(4-hydroxybenzylidene) hydrazinyl]thieno[2,3-d]pyrimidin-4-yl} hydrazinylidene)methyl]phenol (9f)

Yield: 3.03g (75%); mp 209-214˚C; IR spectrum (KBr, ν, cm^{-1}): 3445 (OH), 3251 (NH), 1594 (N=CH);^{1}H NMR (DMSO-d_6, δ ppm):): 4.55 (s, 2H, 2OH), 6.94-7.21 (m, 8H, Ar-H), 7.48 (d, 1H, CH), 7.70 (d, 1H, CH), 8.23 (s, 1H, N=CH), 9.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.9-167.2 (thienopyrimidine aromatic carbon atoms), 144.9 (CH), 151.9 (CH). Anal. calcd. for $C_{20}H_{16}N_6O_4S$: C, 59.39; H, 3.99; N, 20.78; S, 7.93; found: C, 59.30; H, 4.09; N, 20.69; S, 8.01.

4-[(2E)-2-(4-methoxybenzylidene)hydrazinyl]-2-[(2Z)-2-(4-methylbenzylidene)hydrazinyl] thieno[2,3-d]pyrimidine (9g)

Yield: 3.28g (76%); mp 245-250˚C; IR spectrum (KBr, ν, cm^{-1}): 3245 (NH), 1603 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.78 (s, 6H, $2OCH_3$), 7.33-7.48 (m, 8H, Ar-H), 7.50 (d, 1H, CH), 7.72 (d, 1H, CH), 8.25 (s, 1H, N=CH), 9.10 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.2-167.5 (thienopyrimidine aromatic carbon atoms), 145.2 (CH), 151.8 (CH). Anal. calcd. for $C_{22}H_{20}N_6O_2S$: C, 61.10; H, 4.66; N, 19.43; S, 7.41; found: C, 61.01; H, 4.59; N, 19.54; S, 7.48.

4-[(2E)-2-(4-methylbenzylidene)hydrazinyl]-2-[(2Z)-2-(4-methylbenzylidene) hydrazinyl]thieno[2,3-d]pyrimidine (9h)

Yield: 3.24g (81%); mp 248-253˚C; IR spectrum (KBr, ν, cm^{-1}): 3256 (NH), 1598 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 2.25 (s, 6H, $2CH_3$), 7.26-7.42 (m, 8H, Ar-H), 7.52 (d, 1H, CH), 7.71 (d, 1H, CH), 8.23 (s, 1H, N=CH), 9.07 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.6-167.7 (thienopyrimidine aromatic carbon atoms), 145.1 (CH), 151.5 (CH). Anal. calcd. for $C_{22}H_{20}N_6S$: C, 65.98; H, 5.03; N, 20.98; S, 8.01; found: C, 66.08; H, 5.11; N, 20.88; S, 7.94.

4-[(2E)-2-(4-nitrobenzylidene)hydrazinyl]-2-[(2Z)-2-(4-nitrobenzylidene)hydrazinyl] thieno[2,3-d]pyrimidine (9i)

Yield: 3.28g (71%); mp 278-283˚C; IR spectrum (KBr, ν, cm^{-1}): 3259 (NH), 1593 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 7.33-7.45 (m, 8H, Ar-H), 7.48 (d, 1H, CH), 7.70 (d, 1H, CH), 8.29 (s, 1H, N=CH), 9.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.3-167.6 (thienopyrimidine aromatic carbon atoms), 144.6 (CH), 151.1 (CH). Anal. calcd. for $C_{20}H_{14}N_8O_4S$: C, 51.94; H, 3.05; N, 24.23; S, 6.93; found: C, 51.86; H, 3.15; N, 24.12; S, 7.01.

4-[(2E)-2-(4-butylbenzylidene)hydrazinyl]-2-[(2Z)-2-(4-nitrobenzylidene)hydrazinyl] thieno[2,3-d]pyrimidine (9j)

Yield: 3.54g (73%); mp 291-296˚C; IR spectrum (KBr, ν, cm^{-1}): 3251 (NH), 1601 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 1.02 (t, 6H, $2CH_3$), 1.31-1.72 (m, 12H, $6CH_2$), 7.26-7.40 (m, 6H, Ar-H), 7.52 (d, 1H, CH), 7.75 (d, 1H, CH), 8.30 (s, 1H, N=CH), 9.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 109.1-167.0 (thienopyrimidine aromatic carbon atoms), 144.8 (CH), 151.3 (CH). Anal. calcd. for $C_{28}H_{32}N_6S$: C, 69.39; H, 6.66; N, 17.34; S, 6.62; found: C, 69.30; H, 6.59; N, 17.43; S, 6.72.

Thieno[2,3-d]pyrimidin-4(3H)-one (10)

A mixture of compound **1** (0.01 mol) and formic acid (20 mL) was refluxed for 10 h. After the completion of reaction, the reaction mixture was allowed to cool and then poured into ice cold water. The solid thus obtained was filtered, washed with water, dried and crystallized from ethanol to give compound **10**. Yield 0.86g (57%); mp 192-197˚C; IR spectrum (KBr, ν, cm^{-1}): 3160 (NH), 1684 (C=O); ^{1}NMR ($CDCl_3$, δ ppm): 7.57 (d, 1H, CH), 7.81 (d, 1H, CH), 8.15 (s, 1H, CH), 10.46 (brs, 1H, NH, D_2O exchangeable). Anal. calcd. for $C_{18}H_{13}ClN_8OS_3$: C, 47.36; H, 2.65; N, 18.41; S, 21.07; found: C, 36.09; H, 2.17; N, 13.88; S, 47.91.

4-chlorothieno[2,3-d]pyrimidine (11)

A mixture of compound **10** (0.01 mol) and phosphorus oxychloride (20 mL) was refluxed for 12 h. The excess of phosphorus oxychloride was distilled off under reduced pressure and the residue thus obtained was treated with sodium bicarbonate solution (10%). The resulting solid was collected, washed with water, dried and recrystallized from ethanol to give compound **11**. Yield 1.14g (67%); mp 259-264˚C; ^{1}NMR ($CDCl_3$, δ ppm): 7.50 (d, 1H, CH), 7.73 (d, 1H, CH), 8.23 (s, 1H, CH). Anal.

calcd. for $C_6H_3ClN_2S$: C, 42.24; H, 1.77; N, 16.42; S, 18.79; found: C, 36.09; H, 2.17; N, 13.88; S, 47.91.

4-hydrazinylthieno[2,3-d]pyrimidine (12)

A mixture of compound **11** (0.01 mol) in hydrazine hydrate (99%) (10 mL) and ethanol were refluxed for 6 h. After cooling the separated product was filtered off, washed with water, dried and recrystallized from dioxane to give compound **12**. Yield 1.12g (68%); mp 177-182˚C; IR spectrum (KBr, ν, cm^{-1}): 3416-3206 (NH, NH_2); ^{1}NMR ($CDCl_3$, δ ppm): 4.06 (brs, 2H, NH_2, D_2O exchangeable), 6.52 (brs, 1H, NH, D_2O exchangeable), 7.55 (d, 1H, CH), 7.79 (d, 1H, CH), 8.29 (s, 1H, CH). Anal. calcd. for $C_6H_6N_4S$: C, 43.36; H, 3.64; N, 33.71; S, 19.29; found: C, 36.09; H, 2.17; N, 13.88; S, 47.91.

Synthesis of compounds 13(a-j)

A solution of compound **12** (0.005 mol) in ethanol (10 mL) and appropriate aromatic aldehyde (0.005 mol) containing 2-3 drops of glacial acetic acid, was boiled under reflux on a water bath for 8-9 h. The product that separated on cooling was filtered off, washed with water, dried and recrystallized from dioxane to give **13(a-j)**.

4-[2-(2,4-dichlorobenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13a)

Yield: 2.23g (69%); mp 168-173 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3268 (NH), 1549 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 7.32-7.50 (m, 3H, Ar-H), 7.55 (d, 1H, CH), 7.79 (d, 1H, CH), 8.05 (s, 1H, N=CH), 8.29 (s, 1H, CH), 8.92 (s, 1H, NH). Anal. calcd. for $C_{13}H_8Cl_2N_4S$: C, 48.31; H, 2.49; N, 17.34; S, 9.9; found: C, 48.25; H, 2.55; N, 17.40; S, 9.82.

4-{[2-(thieno[2,3-d]pyrimidin-4-yl)hydrazinylidene]methyl}benzene-1,2-diol (13b)

Yield: 1.49g (52%); mp 201-206 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3486 (OH), 3260 (NH), 1543 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.54 (s, 2H, 2OH), 6.88-7.22 (m, 3H, Ar-H), 7.51 (d, 1H, CH), 7.73 (d, 1H, CH), 8.06 (s, 1H, N=CH), 8.27 (s, 1H, CH), 8.99 (s, 1H, NH). Anal. calcd. for $C_{13}H_{10}N_4O_2S$: C, 54.54; H, 3.52; N, 19.57; S, 11.20; found: C, 54.59; H, 3.60; N, 19.51; S, 11.11.

4-[2-(3-methoxybenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13c)

Yield: 2.22g (78%); mp 213-218 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3272 (NH), 1540 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.80 (s, 3H, OCH_3), 7.23-7.35 (m, 4H, Ar-H), 7.53 (d, 1H, CH), 7.72 (d, 1H, CH), 8.09 (s, 1H, N=CH), 8.23 (s, 1H, CH), 8.93 (s, 1H, NH). Anal. calcd. for $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70; S, 11.28; found: C, 59.07; H, 4.32; N, 19.61; S, 11.35.

4-[2-(4-chlorobenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13d)

Yield: 2.11g (73%); mp 225-230 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3276 (NH), 1551 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 7.30-7.45 (m, 4H, Ar-H), 7.53 (d, 1H, CH), 7.75 (d, 1H, CH), 7.99 (s, 1H, N=CH), 8.29 (s, 1H, CH), 8.95 (s, 1H, NH). Anal. calcd. for $C_{13}H_9ClN_4S$: C, 54.07; H, 3.14; N, 19.40; S, 11.10; found: C, 54.17; H, 3.19; N, 19.34; S, 11.01.

4-[2-(4-fluorobenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13e)

Yield: 1.77g (65%); mp 206-211 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3275 (NH), 1549 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 7.23-7.49 (m, 4H, Ar-H), 7.59 (d, 1H, CH), 7.81 (d, 1H, CH), 8.05 (s, 1H, N=CH), 8.30 (s, 1H, CH), 8.95 (s, 1H, NH). Anal. calcd. for $C_{13}H_9FN_4S$: C, 57.34; H, 3.33; N, 20.58; S, 11.78; found: C, 57.29; H, 3.28; N, 20.65; S, 11.83.

4-{[2-(thieno[2,3-d]pyrimidin-4-yl)hydrazinylidene]methyl}phenol (13f)

Yield: 1.89g (70%); mp 217-222 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3282 (NH), 1554 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.94 (s, 1H, OH), 7.27-7.47 (m, 4H, Ar-H), 7.56 (d, 1H, CH), 7.80 (d, 1H, CH), 8.05 (s, 1H, N=CH), 8.28 (s, 1H, CH), 8.91 (s, 1H, NH). Anal. calcd. for $C_{13}H_{10}N_4OS$: C, 57.76; H, 3.73; N, 20.73; S, 11.86; found: C, 57.65; H, 3.65; N, 20.83; S, 11.93.

4-[2-(4-methoxybenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13g)

Yield: 2.10g (74%); mp 168-173 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3276 (NH), 1556 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 3.85 (s, 3H, OCH_3), 7.23-7.44 (m, 4H, Ar-H), 7.54 (d, 1H, CH), 7.77 (d, 1H, CH), 8.01 (s, 1H, N=CH), 8.28 (s, 1H, CH), 8.92 (s, 1H, NH). Anal. calcd. for $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70; S, 11.28; found: C, 59.23; H, 4.31; N, 19.63; S, 11.19.

4-[2-(4-methylbenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13h)

Yield: 2.04g (76%); mp 225-230 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3280(NH), 1559 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 2.27 (s, 3H, CH_3), 7.33-7.49 (m, 4H, Ar-H), 7.59 (d, 1H, CH), 7.81 (d, 1H, CH), 7.98 (s, 1H, N=CH), 8.25 (s, 1H, CH), 8.99 (s, 1H, NH). Anal. calcd. for $C_{14}H_{12}N_4S$: C, 62.66; H, 4.51; N, 20.88; S, 11.95; found: C, 62.60; H, 4.57; N, 20.80; S, 12.04.

4-[2-(4-nitrobenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13i)

Yield: 2.09g (70%); mp 202-207 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3275 (NH), 1562 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 7.28-7.47 (m, 4H, Ar-H), 7.52 (d, 1H, CH), 7.76 (d, 1H, CH), 7.99 (s, 1H, N=CH), 8.27 (s, 1H, CH), 8.92 (s, 1H, NH). Anal. calcd. for $C_{13}H_9N_5O_2S$: C, 52.17; H, 3.03; N, 23.40; S, 10.71; found: C, 52.26; H, 3.11; N, 23.34; S, 10.66.

4-[2-(4-butylbenzylidene)hydrazinyl]thieno[2,3-d]pyrimidine (13j)

Yield: 2.20g (71%); mp 217-222 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3281 (NH), 1557 (N=CH); ^{1}H NMR (DMSO-d_6, δ ppm): 1.09 (t, 3H, CH_3), 1.34-1.77 (m, 6H, $3CH_2$), 7.30-7.45 (m, 4H, Ar-H), 7.53 (d, 1H, CH), 7.74 (d, 1H, CH), 8.03 (s, 1H, N=CH), 8.25 (s, 1H, CH), 8.95 (s, 1H, NH). Anal. calcd. for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.84; N, 18.05; S, 10.33; found: C, 65.72; H, 5.91; N, 17.95; S, 10.27.

Synthesis of compounds 14(a-j)

Chloroacetyl chloride (0.005 mol) was added drop wise to a solution of Schiff's base **13(a-j)** (0.005 mol) and triethylamine (2-3 drops) in dry benzene (15 mL) at 5-10˚C. The reaction mixture was stirred for 3 h and then refluxed for 4-5 h. On cooling, the precipitate was obtained which was filtered, washed with water, dried and recrystallised from dimethylformamide to produce **14(a-j)**.

3-chloro-4-(2,4-dichlorophenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14a)

Yield: 2.20g (55%); mp 199-204 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3262 (NH), 1748 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 4.46 (s, 1H, NH), 5.01 (d, 1H, CH-Ar), 5.49 (d, 1H, CH-Cl), 7.21-7.43 (m, 3H, Ar-H), 7.54 (d, 1H, CH), 7.75 (d, 1H, CH), 8.14 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.9 (CH-Cl), 67.4 (CH), 110.4-167.3 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{15}H_9Cl_3N_4OS$: C, 45.08; H, 2.27; N, 14.02; S, 8.02; found: C, 45.15; H, 2.32; N, 13.98; S, 7.91.

3-chloro-4-(3,4-dihydroxyphenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14b)

Yield: 1.48g (41%); mp 188-193 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3446 (OH), 3268 (NH), 1752 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 3.69 (s, 2H, 2OH), 4.41 (s, 1H, NH), 5.01 (d, 1H, CH-Ar), 5.52 (d, 1H, CH-Cl), 6.78-7.19 (m, 3H, Ar-H), 7.50 (d, 1H, CH), 7.72 (d, 1H, CH), 8.13 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.8 (CH-Cl), 67.3 (CH), 111.1-167.5 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{15}H_{11}ClN_4O_3S$: C, 49.66; H, 3.06; N, 15.44; S, 8.84; found: C, 49.61; H, 3.14; N, 15.39; S, 8.93.

3-chloro-4-(3-methoxyphenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14c)

Yield: 2.02g (56%); mp 198-203 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3271 (NH), 1759 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 3.72 (s, 3H, OCH_3), 4.43 (s, 1H, NH), 4.99 (d, 1H, CH-Ar), 5.45 (d, 1H, CH-Cl), 7.34-7.49 (m, 4H, Ar-H), 7.58 (d, 1H, CH), 7.79 (d, 1H, CH), 8.13 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.9 (CH-Cl), 67.4 (CH), 110.8-167.3 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{16}H_{13}ClN_4O_2S$: C, 53.26; H, 3.63; N, 15.53; S, 8.89; found: C, 53.17; H, 3.56; N, 15.57; S, 8.95.

3-chloro-4-(4-chlorophenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14d)

Yield: 2.19g (60%); mp 207-212 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3262 (NH), 1748 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 4.49 (s, 1H, NH), 5.03 (d, 1H, CH-Ar), 5.45 (d, 1H, CH-Cl), 7.08-7.17 (m, 4H, Ar-H), 7.52 (d, 1H, CH), 7.74 (d, 1H, CH), 8.09 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.7 (CH-Cl), 67.3 (CH), 110.3-166.9 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. For $C_{15}H_{10}Cl_2N_4OS$: C, 49.33; H, 2.76; N, 15.34; S, 8.78; found: C, 49.24; H, 2.69; N, 15.44; S, 8.83.

3-chloro-4-(4-fluorophenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14e)

Yield: 1.88g (54%); mp 216-221 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3273 (NH), 1753 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 4.45 (s, 1H, NH), 5.01 (d, 1H, CH-Ar), 5.50 (d, 1H, CH-Cl), 7.39-7.49 (m, 4H, Ar-H), 7.51 (d, 1H, CH), 7.75 (d, 1H, CH), 8.12 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.9 (CH-Cl), 67.5 (CH), 110.6-167.6 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{15}H_{10}ClFN_4OS$: C, 51.65; H, 2.89; N, 16.06; S, 9.19; found: C, 51.60; H, 2.93; N, 16.15; S, 9.08.

3-chloro-4-(4-hydroxyphenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14f)

Yield: 1.63g (47%); mp 192-197 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3465 (OH), 3263 (NH), 1745 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 4.46 (s, 1H, NH), 4.55 (s, 1H, OH), 5.06 (d, 1H, CH-Ar), 5.56 (d, 1H, CH-Cl), 7.27-7.43 (m, 4H, Ar-H), 7.53 (d, 1H, CH), 7.74 (d, 1H, CH), 8.14 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.3 (CH-Cl), 67.7 (CH), 111.2-167.4 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{15}H_{11}ClN_4O_2S$: C, 51.95; H, 3.20; N, 16.16; S, 9.25; found: C, 51.89; H, 3.12; N, 16.26; S, 9.33.

3-chloro-4-(4-methoxyphenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14g)

Yield: 2.24g (62%); mp 183-188 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3269 (NH), 1754 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 3.75(s, 3H, OCH_3), 4.48 (s, 1H, NH), 5.05 (d, 1H, CH-Ar), 5.50 (d, 1H, CH-Cl), 7.11-7.39 (m, 4H, Ar-H), 7.56 (d, 1H, CH), 7.78 (d, 1H, CH), 8.06 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, δ ppm): 63.8 (CH-Cl), 67.4 (CH), 110.5-167.7 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{18}H_{13}ClN_4O_2S$: C, 53.26; H, 3.63; N, 15.53; S, 8.89; found: C, 53.17; H, 3.56; N, 15.60; S, 8.97.

3-chloro-4-(4-methylphenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14h)

Yield: 2.24g (65%); mp 203-208 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3278 (NH), 1768 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.23 (s, 3H, CH_3), 4.47 (s, 1H, NH), 5.03 (d, 1H, CH-Ar), 5.53 (d, 1H, CH-Cl), 6.97-7.34 (m, 4H, Ar-H), 7.52 (d, 1H, CH), 7.73 (d, 1H, CH), 8.11 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.3 (CH-Cl), 67.4 (CH), 110.2-167.6 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{16}H_{13}ClN_4OS$: C, 55.73; H, 3.80; N, 16.25; S, 9.30; found: C, 55.67; H, 3.76; N, 16.31; S, 9.38.

3-chloro-4-(4-nitrophenyl)-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14i)

Yield: 2.03g (54%); mp 231-236 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3269 (NH), 1757 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 4.42 (s, 1H, NH), 4.96 (d, 1H, CH-Ar), 5.47 (d, 1H, CH-Cl), 7.22-7.44 (m, 4H, Ar-H), 7.50 (d, 1H, CH), 7.72 (d, 1H, CH), 8.08 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 64.4 (CH-Cl), 67.5 (CH), 110.4-167.7 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{15}H_{10}ClN_5O_3S$: C, 47.94; H, 2.68; N, 18.64; S, 8.53; found: C, 47.89; H, 2.61; N, 18.73; S, 8.61.

4-(4-butylphenyl)-3-chloro-1-(thieno[2,3-d]pyrimidin-4-ylamino)azetidin-2-one (14j)

Yield: 2.36g (61%); mp 245-250 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3266 (NH), 1759 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 1.04 (t, 3H, CH_3), 1.29-1.50 (m, 6H, $3CH_2$), 4.44 (s, 1H, NH), 5.02 (d, 1H, CH-Ar), 5.49 (d, 1H, CH-Cl), 7.19-7.32 (m, 4H, Ar-H), 7.51 (d, 1H, CH), 7.73 (d, 1H, CH), 8.15 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, δ ppm): 63.2 (CH-Cl), 67.9 (CH), 110.6-167.7 (thienopyrimidine aromatic carbon atoms), 166.7 (CO). Anal. calcd. for $C_{19}H_{19}ClN_4OS$: C, 58.98; H, 4.95; N, 14.48; S, 8.29; found: C, 59.03; H, 4.90; N, 14.54; S, 8.22.

BIOLOGICAL EVALUATION

Antimicrobial activity

The prepared compounds were tested against *S.aureus* (ATCC-96) and *S.pyogenes* (ATCC-443) as Gram positive and *E.coli* (ATCC-442) and *P.aeruginosa* (ATCC-441) as Gram negative bacterial strains. Antifungal activities of the compounds were tested against *A.niger* (ATCC-282) as fungal strain. All the newly synthesized compounds were screened *in vitro* for their antibacterial and antifungal activities by broth dilution method (Table-1). The lowest concentration inhibiting growth of the organism is recorded as the MIC. DMSO was used as diluent. The stock 1000 µg/ml was prepared. Serial dilutions were prepared in primary and secondary screening. Mueller Hinton Broth was used as nutrient medium to grow and dilute the drug suspension for the test bacteria, and sabaouraus dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to 10^8 CFU [Colony Forming Unit] per milliliter by comparing the turbidity. The control tube containing no antibiotic is immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37˚C overnight. The tubes are then incubated overnight. The MIC of the control organism is read to check the accuracy of the drug concentrations. The amount of growth from the control tube before incubation (which represents the original inoculum) is compared. Ampicillin and Chloramphenicol were used as standard antibacterial and Nystatin and Gresefulvin were used as standard antifungal drugs. Standard strains were procured from Institute of Microbial Technology, Chandigarh.

Table 1. Antimicrobial activity (MIC µg/ml) of some selected synthesized compounds.

Compd.	Minimum Inhibitory Concentration (µg/ml)				
	Gram +ve		Gram -ve		Antifungal
	S.aureus ATCC-96	*S.pyogenes* ATCC-443	*E.coli* ATCC-442	*P.aeruginosa* ATCC-441	*A.niger* ATCC-282
6a	250	250	100	250	500
6b	500	1000	250	500	1000
6c	100	200	150	250	1000
6d	250	250	100	200	1000
6e	500	500	100	250	500
6f	62.5	100	500	500	250
6g	100	100	150	200	1000
6h	500	1000	250	250	1000
6i	500	500	500	500	1000
6j	250	250	1000	500	500
9a	500	250	500	1000	1000
9b	200	200	100	100	1000
9c	100	100	150	200	1000
9d	250	250	500	500	1000
9e	500	500	500	1000	1000
9f	500	500	500	500	1000
9g	250	250	500	500	1000
9h	250	250	1000	500	500
9i	250	250	100	100	1000
9j	100	200	200	100	500
14a	500	125	250	250	500
14b	1000	1000	500	1000	1000
14c	1000	500	250	1000	1000
14d	1000	500	500	500	250
14e	500	500	500	500	500
14f	100	100	62.5	100	1000
14g	500	500	500	500	1000
14h	100	250	500	500	1000
14i	500	500	200	200	500
14j	500	200	150	200	1000
Ampicillin	250	100	100	100	-
Chloramphenicol	50	50	50	50	-
Gresefulvin	-	-	-	-	100
Nystatin	-	-	-	-	100

From the screening results, it can be seen that compound 6f showed excellent activity against Gram positive bacteria *S.aureus* and compound 14f showed excellent activity against Gram negative bacteria *E.coli*. Rest of the compounds showed good to moderate activity against other bacteria compared with the standard drugs.

CONCLUSION

In this work, we have prepared some new thieno[2,3-*d*]pyrimidine derivatives 6(a-j), 9(a-j) and 14(a-j) which were screened for their antibacterial and antifungal activities. The structures of all new synthesized compounds are confirmed successfully by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. Antibacterial activity of title compounds showed that hydroxyl group present at 4th position of phenyl ring in compound 6f could be responsible for increase activity against *S.aureus*. Compound 14f also contain hydroxyl group at 4th position in phenyl ring to show highest activity against *E.coli*.

ACKNOWLEDGMENTS

The authors would like to acknowledge Professor and Head Dr. P. Bahadur, Department of Chemistry, Veer Narmad South Gujarat University, Surat for providing laboratory facilities and D. Rajani, Microcare Laboratory, Surat, for help in antimicrobial activity work. The authors also thank to SAIF, Chandigarh for analytical analysis.

REFERENCES

[1] Rashad A. E., Shamroukh A. H., Abdel-Megeid R. E. and El-Sayed W. A., Synthesis, reactions, and antimicrobial evaluation of some polycondensed thienopyrimidine derivatives, Synth Commun., 2010, 40, 1149-1160.

[2] Al-Taisan K. M., Al-Hazimi H. M. A. and Al-Shihry S. S., Synthesis, characterization and biological studies of some novel thieno[2,3-*d*]pyrimidines, Molecules, 2010, 15, 3932-3957.

[3] Salahuddin M., Kakad S. and Shantakumar S. M., Synthesis of some novel Thieno [2,3-*d*] pyrimidines and their antibacterial activity, E. J. Chem., 2009, 6, 801-808.

[4] Gaber H. M., Bagley M. C. and Sherif S. M., Antimicrobial investigations on synthetic *p*-tolylazo derivatives of thienopyrimidinone based on an ortho funtionalized thiophene nucleus, Eur. J. Chem., 2010, 1, 115-123.

[5] Alagarsamya V., Solomonb V. R., Meenac R., Ramaseshuc K. V., Thirumuruganc K. and Murugesan S., Design and synthesis of 2-methylthio-3-substituted-5,6-dimethylthieno [2,3-*d*] pyrimidin-4(3*H*)-ones as analgesic, anti-inflammatory and antibacterial agents, Med. Chem., 2007, 3, 67-73.

[6] Alagarsamya V., Meenab S., Ramseshub K. V., Solomonc V. R., Thirumuruganb D. K. and Murugana M., Synthesis, analgesic, anti-inflammatory, ulcerogenic index and antibacterial activities of novel 2-methylthio-3-substituted-5,6,7,8-tetrahydrobenzo (*b*) thieno[2,3-*d*]pyrimidin-4(3*H*)-ones, Eur. J. Med. Chem., 2006, 41, 1293-1300.

[7] El-Deana A. M. K. and Abdel-Moneama M. E., Synthesis of pyrimidines, thieno pyrimidines, and pyrazolopyrimidines, Phosphorus, Sulfur, Silicon Relat. Elem., 2002, 177, 2745-2751.

[8] Zadorozny A. V. and Kovtunenko V. A., Condensed isoquinolines. 34.* transformations of 4*H*-thieno-[3',2':5,6]- and 4*H*-thieno[2',3':5,6]pyrimido-[1,2-*b*]isoquinolines, Chem. Heterocycl. Comp., 2009, 45, 489-497.

[9] Ameena M. A., Ahmeda E. K. and Abdel-latifa F. F., A novel synthetic routes to new 3-substituted4-oxo-3,4,5,6,7,8-hexahydro pyrido[[4], [4], [5]] thieno[[2], [3]]pyrimidine-7-carboxylic acid ethyl ester derivatives, Phosphorus, Sulfur, Silicon Relat. Elem., 2005,180, 95-107.

[10] Panico A. M., Santagati A., Cardile V., Urso D., Gentile B. and Ronsisvalle G., Calorimetric study on the interaction of thienopyrimidine derivatives with phosphatidylcholine membranes, Colloids and Surfaces B: Biointerfaces., 2003, 28, 77-81.

[11] Dzhavakhishvili S. G., Gorobets N. Y., Shishkina S. V., Shishkin O. V., Desenko S. M. and Groth U. M., Diversification of a thieno[2,3-*d*]pyrimidin-4-one scaffold via regioselective alkylation reactions, J. Comb. Chem., 2009, 11, 508-514.

[12] Azaba M. E., Utility of the enaminonitrile moiety in the synthesis of some biologically active thienopyrimidine derivatives, Phosphorus, Sulfur, Silicon Relat. Elem., 2008, 183, 1766-1782.

[13] Moustafaa A. H., Saada H. A., Shehaba W. S. and El-Mobayeda M. M., Synthesis of some new pyrimidine derivatives of expected antimicrobial activity, Phosphorus, Sulfur, Silicon Relat. Elem., 2008, 183, 115-135.

[14] El-Gazzara A. B. A., Hussein H. A. R. and Alya A. S., Synthesis and reactions of polynuclear heterocycles: azolothieno pyrimidines and thienothiazolo pyrimidines. Phosphorus, Sulfur, Silicon Relat. Elem., 2006, 181, 2771-2784.

[15] El-Baih F. E. M., Al-Blowy A. S. and Al-Hazimi H. M., Synthesis of some thienopyrimidine derivatives, Molecules, 2006, 11, 498-513.

[16] Ghoraba M. M., Osmanb A. N., Noamanc E., Heibaa H. I. and Zahera N. H., The synthesis of some new sulfur heterocyclic compounds as potential radioprotective and anticancer agents, Phosphorus, Sulfur, Silicon Relat. Elem., 2006, 181, 1935-1950.

[17] Hossain M. I. and Bhuiyan M. M. H., Synthesis and antimicrobial acitivities of some new thieno and furopyrimidine derivatives, J. Sci. Res., 2009, 1, 317-325.

[18] Bogolubsky A. V., Ryabukhin S. V., Plaskon A. S., Stetsenko S. V., Volochnyuk D. M. and Tolmachev A. A., Dry HCl in parallel

synthesis of fused pyrimidin-4-ones, J. Comb. Chem., 2008, 10, 858-862.

[19] Bogolubsky A. V., Ryabukhin S. V., Stetsenko S. V., Chupryna A. A., Volochnyuk D. M. and Tolmachev A. A., Synthesis of thieno[2,3-*d*]pyrimidin-2-ylmethanamine combinatorial library with four diversity points, J. Comb. Chem., 2007, 9, 661-667.

[20] Alya A. S., El-Gazzara A. B. A. and Hussein H. A. R., The synthesis of some new derivatives derived from 1,2,3,4-tetrahydrocyclohepteno[4,5]thieno-[2,3-*d*]pyrimidine, Phosphorus, Sulfur, Silicon Relat. Elem., 2007, 182, 35-56.

[21] Chaykovsky M., Lin M., Rosowsky A. and Modest E. J., 2,4-Diaminothieno[2,3-*d*] pyrimidines as antifolates and antimalarials. 2. Synthesis of 2,4-diaminopyrido [4',3':4,5] thieno[2,3-*d*]pyrimidines and 2,4-diamino-8*H*-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidines, J. Med. Chem., 1973,16, 188-191.

[22] Rashmi P., Nargund L. G. and Hazra K., Thienopyrimidines as novel anti-inflammatory agents and antioxidants, Der Chemica Sinica., 2011, 2, 165-171.

*****