Synthesis, Characterization, and Antimicrobial Evaluation of Novel 4-Pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5] Thieno[2,3-d]pyrimidine Derivatives

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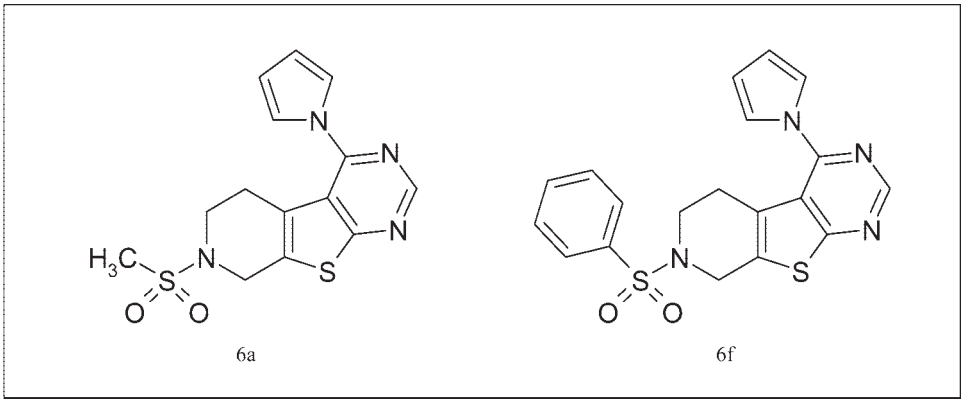

A series of novel 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d] pyrimidine **6** were synthesized for evaluation of their antibacterial and antifungal activity. The structures were determined by IR, NMR, mass spectroscopy, and elemental analysis. They were screened for activities against bacterial and fungal strains.

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INTRODUCTION

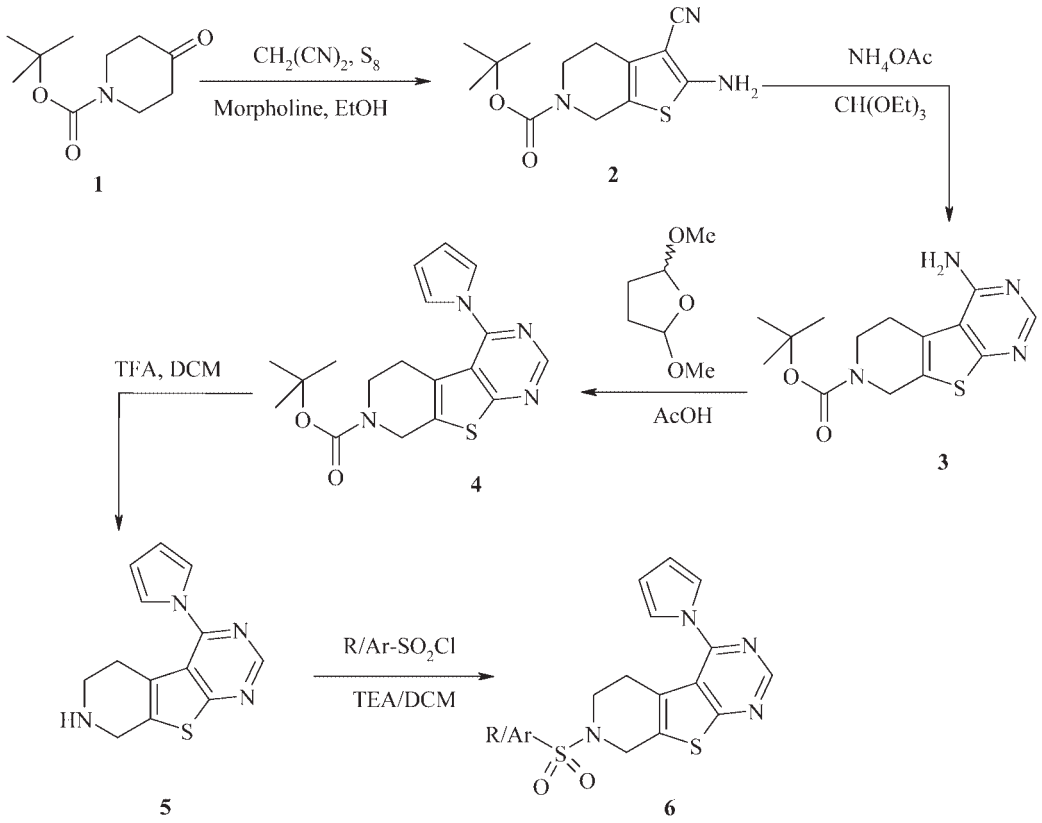
Fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily, due to a very wide spectrum of biological activities. This is evident, in particular, from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to various heterocycles, such as, purines [1], pteridines [2], quinazolines [3], pyridopyrimidines [4,5], triazolopyrimidines [6], pyrazolopyrimidines [7], pyrimidoazepines [8], furopyrimidines, and pyrrolopyrimidines. Thienopyrimidines occupy a special position among these compounds. Along with some other pyrimidine systems containing an annulated five-membered heteroaromatic ring, thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Earlier, various aspects of the chemistry and biology of isomeric thienopyrimidines have been reviewed [9,10]. The chemistry of pyrimidines and its derivatives has been studied over a century due to their diverse biological activities [11–14]. Thienopyrimidine possess various physiological and biological properties, and thus, find important use in medicine. According to recent literature survey, thienopyrimidine have been found to have antibacterial [15], antiviral [16], anticancer [17–19], analgesic [20], and antimalarial [21] activities. Though many synthetic strategies have been reported for the preparation of thienopyrimidine derivatives, most of them include use of expensive, commercially nonavailable or hazardous reagents, drastic reaction conditions, longer reaction time and difficult work-up [22–27]. In the view of biological importance of thienopyrimidine, we aimed the synthesis of a series of novel 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno [2,3-d]pyrimidine **6**.

RESULTS AND DISCUSSION

Chemistry. As shown in synthetic Scheme 1, the synthetic route involves the Gewald reaction [28] of boc-piperidone **1** with malononitrile and sulfur in presence of morpholine in refluxing ethanol to obtain 2-amino thiophene derivative **2**. The formation of 2-amino thiophene **2** was evident from the ^{1}H NMR spectra and mass spectrometry.

The cyclization of 2-amino thiophene **2** with triethyl orthoformate and ammonium acetate at 120°C led to formation of thienopyrimidine derivative **3.** In

Scheme 1



the ^{1}H NMR spectra of **3**, one aromatic proton resonance of pyrimidine ring was observed at 8.85 δδas a singlet, in addition molecular ion peak (M+, 90%) in mass spectrum was also observed. The compound **3** was further reacted with 2,5-dimethoxy-tetrahydrofuran in refluxing acetic acid furnished pyrrole derivative **4**. The identity of pyrrole **4** was established by mass spectrometry and ^{1}H NMR spectra, the aromatic protons resonance of pyrrole ring were observed at 6.32 δ, J = 2.1 and 7.34 δ, J = 2.0 as two doublet. The hydrolysis of carbamate group by TFA furnished secondary amine derivative **5**, which was supported by molecular ion peak in mass spectrum and ^{1}H NMR spectra, where a singlet at 1.38 δ for nine protons of boc group was not present. The target compounds 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine **6a–j** were obtained with excellent yield, by reacting secondary amine **5** with various aryl or alkyl sulfonyl chloride in presence of TEA as base.

The structure of all newly synthesized compounds **6a–j** were established on the basis of elemental analysis and spectral (IR, ^{1}H NMR, and mass) data. The physical characterization data are listed in Table 1.

The ^{1}H NMR spectral data of compound **6a** revealed a singlet of CH_3SO_2 group at 2.97 δ, a singlet of pyrimidine ring at 8.95 δ and two doublet of pyrrole ring at 6.36 δ, J = 2.0 Hz and 7.35 δ„J = 2.0 Hz. The IR spectra of **6a** revealed —SO_2 absorptions at 1334 cm^{-1} and 1159 cm^{-1}. In addition, the EI-MS spectra of **6a** showed a molecular ion peak (M+, 90%).

In conclusion, we have developed a facile and efficient synthetic method for the preparation of novel 7-alkyl/aryl sulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5] thieno[2,3-d]pyrimidine **6**.

Biological activities.

Antibacterial and antifungal activities. The newly synthesized derivatives were evaluated for their *in vitro* antibacterial activity against Gram-positive *Staphylococcus aureus* and *Streptococcus pyogenes*, Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*, and antifungal activity against *Candida albicans* and *Aspergillus niger* by micro broth dilution methods [29–31]. The standard strains used for screening antibacterial and antifungal activities were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. The MIC values are given in Table 2. The standard drugs used for antibacterial activity were ampicillin and ciprofloxacin,

Table 1

Physical characterization data.

Compound	R/Ar	Physical state	Time (h)	Mp (°C)	Yield (%)	Molecular formula/M.W.	Analysis (%) Calcd./found C	H	N
6a	Me	White crystals	3	112–115	93	$C_{14}H_{14}N_4O_2S_2$	50.28	4.22	16.75
						334	50.14	4.31	16.68
6b	Et	White crystals	4	74–75	90	$C_{15}H_{16}N_4O_2S_2$	51.71	4.63	16.08
						348	51.54	4.27	16.21
6c	iso-Pr	Off white crystals	5	77–79	89	$C_{16}H_{18}N_4O_2S_2$	53.02	5.01	15.46
						362	53.23	4.86	15.51
6d	*n*-Pr	White crystals	4	91–93	91	$C_{16}H_{18}N_4O_2S_2$	53.02	5.01	15.46
						362	53.23	5.12	16.31
6e	*n*-Bu	Off white crystals	5	113–115	93	$C_{17}H_{20}N_4O_2S_2$	54.23	5.35	14.88
						376	54.11	5.43	14.72
6f	C_6H_5	White crystals	4	194–196	86	$C_{19}H_{16}N_4O_2S_2$	57.56	4.07	14.13
						396	57.41	4.22	14.01
6g	*p*-$CH_3C_6H_4$	Pale yellow crystals	5	185–187	91	$C_{20}H_{18}N_4O_2S_2$	58.52	4.42	13.65
						410	58.61	4.30	13.71
6h	*p*-F-C_6H_4	Pale yellow crystals	3	269–271	89	$C_{19}H_{15}FN_4O_2S_2$	55.06	3.65	13.52
						414	55.17	3.49	13.64
6i	*p*-CH_3O-C_6H_4	Off white crystals	4	139–141	85	$C_{20}H_{18}N_4O_3S_2$	56.32	4.25	13.14
						426	56.47	4.11	13.34
6j	*p*-NO_2-C_6H_4	Yellow crystals	3	131–133	88	$C_{19}H_{15}N_5O_4S_2$	51.69	3.42	15.86
						441	51.55	3.23	15.98

and nystatin for antifungal activity. Mueller Hinton Broth was used as nutrient medium for bacteria and Sabouraud Dextrose Broth for fungal to grow. Inoculums size for test strain was adjusted to 10^8 CFU/mL by comparing the turbidity. The serial dilutions were prepared in primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO-water at a concentration of 2.0 mg/mL. In primary screening, 500 μg/mL, 250 μg/mL, and 125 μg/mL concentrations of the synthesized drugs were taken. Data were not taken for the initial solution because of the high DMSO concentration (10%). The actively synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100 μg/mL, 50 μg/mL, 25 μg/mL, 12.5 μg/mL, and 6.250 μg/mL concentrations. The inoculated wells were incubated overnight at 37°C in a humid atmosphere overnight. The highest dilution showing at least 99% inhibition zone is taken as MIC.

The MIC values revealed that some of the newly synthesized compounds showed moderate to good

Table 2

Antibacterial and antifungal activity of compound **6a–j**.

Compounds	Antibacterial MIC (μg/mL) *E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	Antifungal MIC (μg/mL) *C. albicans* MTCC 227	*A. niger* MTCC 282
Ampicillin	100	100	250	100	–	–
Ciprofloxacin	25	25	50	50	–	–
Nystatin	–	–	–	–	100	100
6a	62.5	62.5	62.5	62.5	100	500
6b	125	250	25	500	500	500
6c	200	200	125	250	1000	500
6d	25	250	50	100	1000	1000
6e	50	500	62.5	500	1000	500
6f	62.5	500	250	250	500	>1000
6g	100	250	125	500	1000	1000
6h	100	125	100	500	500	1000
6i	200	100	250	500	1000	1000
6j	62.5	62.5	500	250	200	500

inhibition. Compounds **6a**, **6d**, and **6j** exhibited good activity against all the four bacterial strains. Compounds **6d**, **6e**, **6h**, and **6f** showed good activity against *E .coli* and *S. aureus* bacterial strains. The MIC values of antifungal activity revealed that compound **6a** exhibited good activity against *C. albicans* fungal strain. Rest of all compounds did not exhibit comparable activity against both the fungal strains.

EXPERIMENTAL

Melting points were determined with Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer PE-1600 FTIR spectrometer in KBr disk. ^{1}H NMR spectra were recorded on a Varian 400 spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. EI-MS spectra were measured on a Waters Mass Spectrometer. All of the solvents and materials were reagent grade and purified as required.

2-Amino-3-cyano-4,7-dihydro-5H-thieno[2,3-c]pyridine-6-carboxylic acid tert-butyl ester (2). To a stirred solution of (10.0 g, 0.050 mol) of 1-Boc-4-piperidone (**1**), malononitrile (3.97 g, 0.060 mol) and sulfur (1.92 g, 0.060 mol) in ethanol (70 mL), morpholine (5.71 mL, 0.065 mol) was added over period of 15 min at room temperature. The reaction mixture was heated at 82°C with stirring for 1 h and cooled at room temperature. Water (200 mL) was charged to a reaction mixture and stirred at room temperature for 30 min. Product was separated by filtration and washed with water (50 mL), hexane (50 mL), and dried. Recrystallization from ethanol gave compound **2** as pale yellow solid, 11.2 g (80%), mp 193–195°C; ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9H), 2.62 (t, 2H, J = 5.6 Hz), 3.02 (t, 2H, J = 5.7 Hz), 4.21 (s, 2H), 5.84 (bs, 2H); ms: *m/z* 280 (M + 1). Anal. Calcd. for $C_{13}H_{17}N_3O_2S$: C, 55.89; H, 6.13; N, 15.04. Found: C, 55.92; H, 6.10; N, 15.06.

4-Amino-5,8-dihydro-6H-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid tert-butyl ester (3). A solution of compound **2** (11.0 g, 0.039 mol), ammonium acetate (9.1 g, 0.118 mol) in triethyl orthoformate (50 mL) was heated at 120°C with stirring for 6 h and cooled at room temperature. Water (150 mL) was added to reaction mixture and stirred at room temperature for 15 min. Solid product was filtered, washed with water (50 mL), hexane (50 mL), and dried. Solid was recrystallized from ethanol gave compound **3** as off white solid, 7.6 g (63%), ^{1}H NMR (DMSO-d_6): δ 1.40 (s, 9H), 2.64 (t, 2H, J = 5.7 Hz), 2.99 (t, 2H, J = 5.8 Hz), 4.24 (s, 2H), 5.75 (bs, 2H), 8.85 (s, 1H); ms: *m/z* 307 (M + 1). Anal. Calcd. for $C_{14}H_{18}N_4O_2S$: C, 54.88; H, 5.92; N, 18.29. Found: C, 54.91; H, 5.89; N, 18.32.

4-Pyrrol-1-yl-5,8-dihydro-6H-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylic acid tert-butyl ester (4). A solution of compound **3** (7.5 g, 0.025 mol), 2,5-dimethoxy-tetrahydrofuran (3.5 mL, 0.027 mol) in acetic acid (50 mL) was heated at 100°C with stirring for 3 h and cooled at room temperature. Reaction mixture was charged in ice water (100 mL) and stirred for 15 min. Product was extracted with ethyl acetate (2 × 100 mL), combined ethyl acetate layer was washed with water (2 × 50 mL), dried on anhydrous sodium sulfate and evaporated to dryness. The residue was purified on a silica gel column, packed in hexane. Elution of the column with hexane: ethyl acetate (80:20 v/v) gave the pure compound **4** as off white solid, 4.88 g (56%), ^{1}H NMR (DMSO-d_6): δ 1.38 (s, 9H), 2.61 (t, 2H, J = 5.6 Hz), 2.98 (t, 2H, 5.6 Hz), 4.19 (s, 2H), 6.32 (d, 2H, J = 2.1 Hz), 7.34 (d, 2H, J = 2.0 Hz), 8.86 (s, 2H); ms: *m/z* 357 (M + 1). Anal. Calcd. for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.66; N, 15.72. Found: C, 60.68; H, 5.63; N, 15.69.

4-Pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (5). A solution of compound **4** (4.8 g, 0.013 mol) and TFA (3.2 mL, 0.040 mol) in DCM (20 mL) was stirred at 10°C for 1.5 h. Reaction mixture was charged into saturated $NaHCO_3$ (50 mL) and DCM layer was separated, aqueous layer was washed with DCM (100 mL). Combined DCM layer was washed with water (2 × 50 mL), dried on anhydrous sodium sulfate and evaporated to dryness gave compound **5** as off white solid, 2.05 g (59%), ^{1}H NMR (DMSO-d_6): δ 2.65 (t, 2H, J = 5.7 Hz), 3.01 (t, 2H, J = 5.8 Hz), 4.19 (s, 2H), 5.56–5.58 (m, 1H), 6.33 (d, 2H, J = 2.0 Hz), 7.36 (d, 2H, J = 2.1 Hz), 8.89 (s, 2H); ms: *m/z* 257 (M + 1). Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.90; H, 4.75; N, 21.83.

General procedure for preparation of 7-alkyl/aryl sulf onyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno [2,3-d]pyrimidine (6). All of these reactions were carried out under a nitrogen atmosphere. To a stirred and cooled (5°C) solution of Compound **5** (0.781 mmol), dimethyl amino pyridine (0.0781 mmol) and triethylamine (1.56 mmol) in dry THF (15 mL), alkyl/aryl sulfonyl chloride (0.859 mmol) was added and the reaction mixture was allowed to warm at room temperature and stirred at room temperature for 3–5 h. Reaction mixture was evaporated under vacuum gave an oily residue. The residue was dissolved in ethyl acetate (50 mL) and washed with 5% aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and water (50 mL). Ethyl acetate layer was dried and evaporated under vacuum gave solid residue which was washed with hexane (10 mL) and dried, gave **6a–j**. The yield, reaction time, and physical properties are reported in Table 1.

7-Methanesulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido [4′,3′:4,5]thieno[2,3-d]pyrimidine (6a). IR: —SO_2 1334, 1159 cm^{-1}; ^{1}H NMR: δ 2.64 (t, 2H, J = 5.4 Hz), 2.97 (s, 3H), 2.98 (t, 2H, J = 6.0 Hz), 4.66 (s, 2H), 6.36 (d, 2H, J = 2.0 Hz), 7.35 (d, 2H, J = 2.0 Hz), 8.95 (s, 1H); ms: *m/z* 335 (M^+).

7-Ethanesulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido [4′,3′:4,5]thieno[2,3-d]pyrimidine (6b). IR: —SO_2 1336, 1163 cm^{-1}; ^{1}H NMR: δ 1.31 (t, 3H, J = 6.5), 2.61 (t, 2H, J = 6.0 Hz), 3.01 (t, 2H, J = 6.2 Hz), 3.01 (q, 2H, J = 6.0 Hz), 4.63 (s, 2H), 6.32 (d, 2H, J = 1.9 Hz), 7.32 (d, 2H, J = 2.0 Hz), 8.89 (s, 1H); ms: *m/z* 349 (M^+).

7-(Propane-2-sulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6c). IR: —SO_2 1332, 1160 cm^{-1}; ^{1}H NMR: δ 1.13 (d, 6H, J = 6.4 Hz), 2.63 (t, 2H, J = 6.1 Hz), 2.99 (t, 2H, J = 5.9 Hz), 3.32 (m, 1H, J = 6.1 Hz), 4.67 (s, 2H), 6.32 (d, 2H, J = 2.0 Hz), 7.34 (d, 2H, J = 2.0 Hz), 8.91 (s, H); ms: *m/z* 363 (M^+).

7-(Propane-1-sulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6d). IR: —SO_2 1330, 1152 cm^{-1}; ^{1}H NMR: δ 1.01 (t, 3H, J = 6.3 Hz), 1.93 (m, 2H, J

= 5.7 Hz), 2.67 (t, 2H, J = 6.1 Hz), 2.92 (t, 2H, J = 6.1 Hz), 3.10 (t, 2H, J = 6.1 Hz), 4.68 (s, 2H), 6.38 (d, 2H, J = 2.1 Hz), 7.37 (d, 2H, J = 2.1 Hz), 8.90 (s, 1H); ms: m/z 363 (M^+).

7-(Butane-1-sulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido [4′,3′:4,5]thieno[2,3-d]pyrimidine (6e). IR: —SO_2 1334, 1159 cm^{-1}; ^{1}H NMR: δ 0.97 (t, 3H, J = 6.2 Hz), 1.45 (m, 2H, J = 5.7 Hz), 2.13 (q, 2H, J = 6.0 Hz), 2.64 (t, 2H, J = 5.8 Hz), 2.98 (t, 2H, J = 6.0 Hz), 3.55 (t, 2H, J = 6.1 Hz), 4.66 (s, 2H), 6.35 (d, 2H, J = 2.1 Hz), 7.36 (d, 2H, J = 2.0 Hz), 8.95 (s, 1H); ms: m/z 377 (M^+).

7-Benzenesulfonyl-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido [4′,3′:4,5]thieno[2,3-d]pyrimidine (6f). IR: —SO_2 1342, 1168 cm^{-1}; ^{1}H NMR: δ 2.50 (t, 2H, J = 5.6 Hz), 3.29 (t, 2H, J = 5.1 Hz), 4.55 (s, 2H), 6.33 (d, 2H, J = 2.1 Hz), 7.20 (d, 2H, J = 2.1 Hz), 7.60–7.71 (m, 3H), 7.83–7.85 (m, 2H), 8.92 (s, 1H); ms: m/z 397 (M^+).

4-Pyrrol-1-yl-7-(toluene-4-sulfonyl)-5,6,7,8-tetrahydro-pyrido [4′,3′:4,5]thieno[2,3-d]pyrimidine (6g). IR: —SO_2 1345, 1171 cm^{-1}; ^{1}H NMR: δ 2.35 (s, 3H), 2.60 (t, 2H, J = 5.4 Hz), 3.33 (t, 2H, J = 5.3 Hz), 4.61 (s, 2H), 6.36 (d, 2H, J = 2.0 Hz), 7.25 (d, 2H, J = 2.0 Hz), 7.35 (d, 2H, J = 7.5 Hz), 7.87 (d, 2H, J = 7.6 Hz), 8.89 (s, 1H); ms: m/z 411 (M^+).

7-(4-Fluoro-benzenesulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro -pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6h). IR: —SO_2 1341, 1161 cm^{-1}; ^{1}H NMR: δ 2.62 (t, 2H, J = 5.4 Hz), 3.37 (t, 2H, J = 5.3 Hz), 4.64 (s, 2H), 6.33 (d, 2H, J = 2.0 Hz), 7.31 (d, 2H, J = 2.0 Hz), 7.25 (d, 2H, J = 7.7 Hz), 7.82 (d, 2H, J = 7.8 Hz), 8.91 (s, 1H); ms: m/z 415 (M^+).

7-(4-Methoxy-benzenesulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetra-hydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6i). IR: —SO_2 1352, 1167 cm^{-1}; ^{1}H NMR: δ 2.63 (t, 2H, J = 5.2 Hz), 3.40 (t, 2H, J = 5.6 Hz), 3.78 (s, 3H), 4.61 (s, 2H), 6.34 (d, 2H, J = 2.0 Hz), 7.23 (d, 2H, J = 2.1 Hz), 7.05 (d, 2H, J = 7.7 Hz), 7.81 (d, 2H, J = 7.6 Hz), 8.90 (s, 1H); ms: m/z 427 (M^+).

7-(4-Nitro-benzenesulfonyl)-4-pyrrol-1-yl-5,6,7,8-tetrahydro-pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine (6j). IR: —SO_2 1345, 1171 cm^{-1}, NO_2 1540, 1361 cm^{-1}; ^{1}H NMR: δ 2.63 (t, 2H, J = 5.8 Hz), 3.38 (t, 2H, J = 5.6 Hz), 4.64 (s, 2H), 6.38 (d, 2H, J = 2.0 Hz), 7.26 (d, 2H, J = 2.0 Hz), 8.20 (d, 2H, J = 7.8 Hz), 8.46 (d, 2H, J = 7.7 Hz), 8.93 (s, 1H); ms: m/z 442 (M^+).

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