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Preliminary communication

Synthesis of some new bioactive 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives

B.V. Ashalatha [a], B. Narayana [a,*], K.K. Vijaya Raj [a], N. Suchetha Kumari [b]

[a] *Department of Post-Graduate Studies and Research in Chemistry, Mangalore University, Mangalagangothri 574 199, Mangalore, Karnataka, India*
[b] *Department of Biochemistry, K.S. Hegde Medical Academy, Deralakatte 574 162, India*

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Abstract

Nine new 2-(substituted phenyl)/alkyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-ones, six new 3-amino-2-[(2-oxo-2-(aryl)ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones, one 2-mercapto[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one and one 2-chloromethyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)-thieno[3,2-*e*]pyrimidin-5(4*H*)-one were synthesized from 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one. The newly synthesized compounds were characterized by analytical and spectral data. Compounds were screened for anti-inflammatory, CNS depressant and antimicrobial activities. Some of the compounds exhibited promising biological activities.

Keywords: Synthesis; Bioactive; Tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one

1. Introduction

A large number of thienopyrimidines were reported in literature as virucides, bactericides, fungicides, acaricides and insecticides [1,2]. Condensed thienopyrimidines exhibit interesting biological activities like antibacterial [3], antihistaminic [4], analgesic and anti-inflammatory [5] and antimalarial [6]. Various condensed quinazoline and thienopyrimidine systems were studied for their biological activities [7]. Large number of tetrahydrobenzothieno derivatives were reported as anticancer, antibacterial and antifungal agents [8]. Several thienopyrimidones were also synthesized and evaluated for their anticonvulsant activity [9]. As a continuation of our research program to find out bioactive thienopyrimidines [10], we aimed at the synthesis and characterization of some new tetrahydrobenzothieno pyrimidinone derivatives and evaluate these compounds for their various biological activities.

2. Results and discussion

2.1. Chemistry

The starting material 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**1**) was prepared from 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(*b*)thiophene in three steps as per the reported literature [8]. The compound 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**1**) was condensed with aromatic and aliphatic carboxylic acids in presence of phosphorous oxychloride to yield 2-(substituted phenyl)/alkyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-ones (**2a–i**). The compound **1** was also treated with aromatic acyl bromides in presence of anhydrous sodium acetate in methanol to yield 3-amino-2-[(2-oxo-2-(aryl)ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**3a–f**). Actual attempt was made to synthesize pyrimido thiadiazinone derivative (**6**) by the cyclocondensation of **1** with acyl bromides. But the reaction ended in the formation of uncyclised **3a–f**, which could be isolated

* Corresponding author. Tel.: +91 8242287262; fax: +91 8242287367.
E-mail address: nbadiadka@yahoo.co.uk (B. Narayana).

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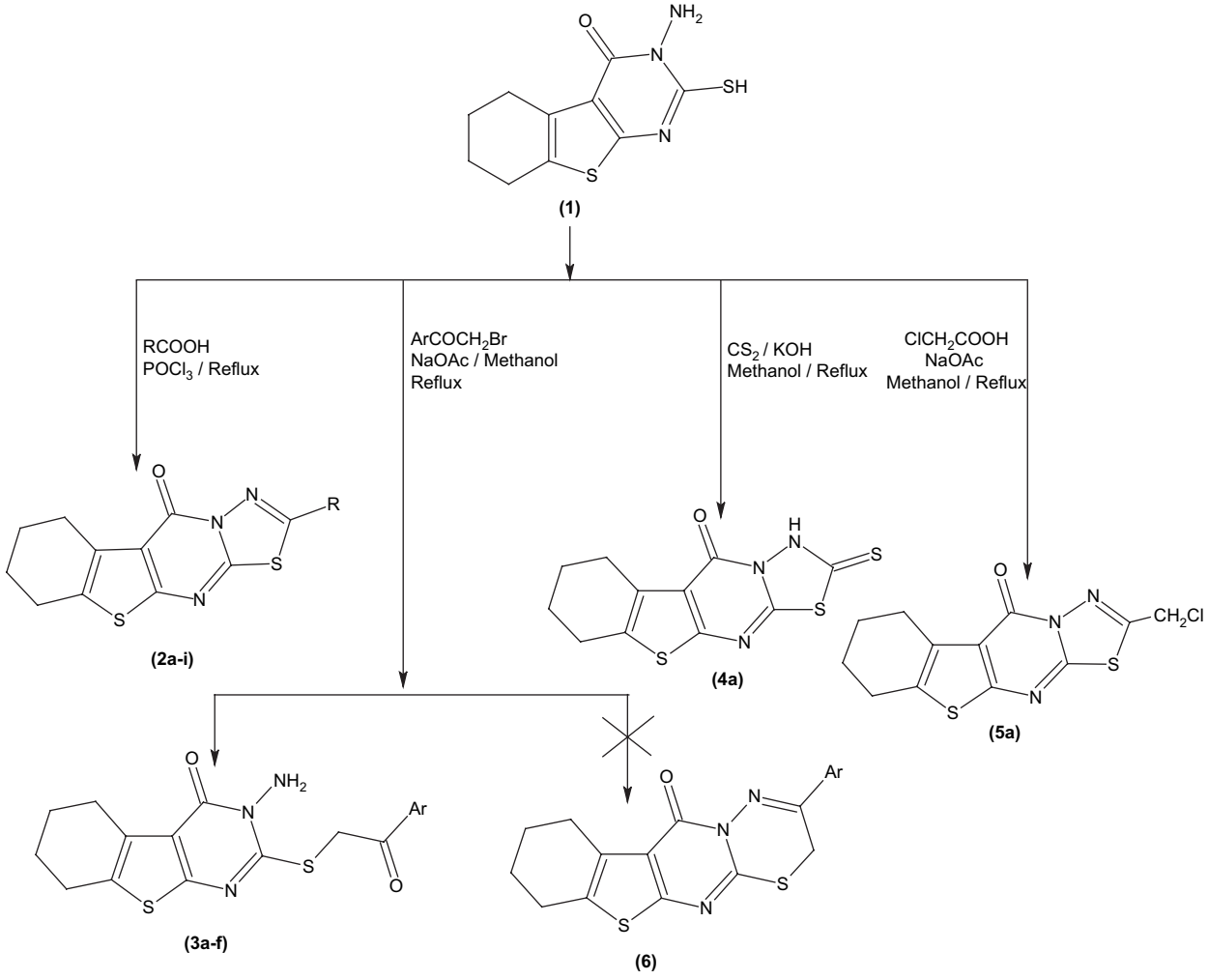
in good yield and purity. The structures of the newly synthesized compounds **2a–i** and **3a–f** were confirmed by analytical and spectral data. Scheme 1 illustrates the reaction pathway. Characterization data and spectral data of the selected compounds are given in Section 3.

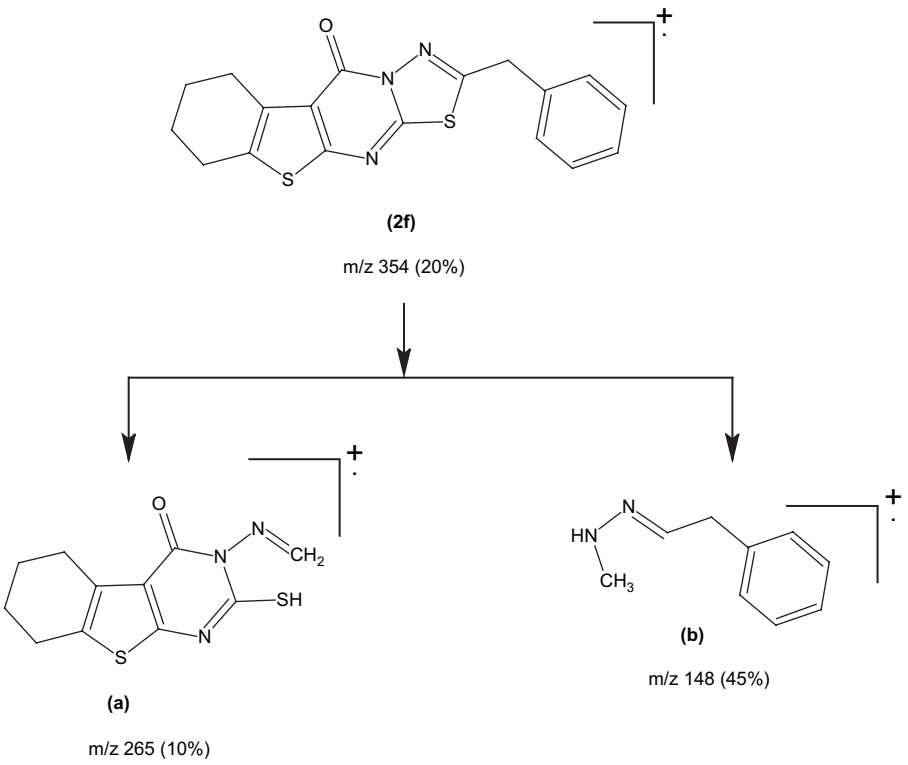
Further, the treatment of 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**1**) with carbon disulphide and alcoholic potassium hydroxide resulted in the formation of 2-mercapto[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**4a**) and the treatment with 2-chloroacetic acid in methanol and sodium acetate resulted in the cyclised product 2-chloromethyl[1,3,4] thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**5a**) (Scheme 1). The compounds were isolated in 52–92% yield after crystallising from methanol–DMF mixture. The structures of **4a** and **5a** were confirmed by the analytical and spectral data. Characterization data and the spectral data of the compounds are given in Section 3.

The formation of 2-(substituted phenyl)[1,3,4]thiadiazolo [2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-ones (**2a–i**) from 3-amino-2-mercapto-5,6,7,8-tetrahydro [1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one was confirmed by recording ^{1}H NMR, ^{13}C NMR and mass spectra. The ^{1}H NMR spectrum of 2-(benzyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2f**) displayed a multiplet at δ 2.57–3.51 accounts for eight protons of CH_2 group of tetrahydrobenzo(*b*)thieno group. A singlet signal seen at δ 4.37 accounts for CH_2 of the benzyl group that proves the cyclisation. Another multiplet appeared at δ 7.19–7.38 accounts for five aromatic protons of the phenyl ring. The ^{13}C NMR also displayed peaks at δ 21.52 (CH_2), 22.21 (CH_2), 24.48 (CH_2), 25.01 (CH_2), 36.92 (CH_2), 117.82, 126.07, 127.47, 127.75, 128.54, 128.61, 128.64, 130.75, 131.77, 134.35, 152.79, 156.03 and 160.27 (C=O), which exactly account for 18 carbon atoms in the molecule. The FAB mass spectrum of **2f** displayed a protonated molecular ion peak at *m*/*z* 354 (20%), which is in agreement with its molecular formula $C_{18}H_{15}N_3OS_2$. Peaks at *m*/*z* 265 (10%) and 148 (45%) are due to the radical cations 2-mercapto-3-(methylene amino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*) -one (**a**) and phenylacetaldehyde methylhydrazone (**b**), respectively, as shown in Scheme 2.

The IR spectrum of 3-amino-2-[(2-oxo-2-(phenyl) ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**3c**) displayed bands at 3315 and 1678 cm^{-1} due to $-NH_2$ and $-C=O$ stretching frequencies, respectively, which



Scheme 1.



Scheme 2. Mass fragmentation pattern of 2-(benzyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2f**).

confirms the uncyclisation. The ^{1}H NMR spectrum of **3c** displayed a mutliplet at δ 1.64–2.92 accounts for eight protons of CH_2 group of tetrahydrobenzo(*b*)thieno group and two singlets appeared at δ 4.57 and 4.79 are due to two protons each on the CH_2 and NH_2 protons. Aromatic protons resonated as a multiplet at δ 7.41–7.65 and a doublet at δ 8.05 ($J = 6.9$ Hz). The ^{13}C NMR displayed peaks at δ 22.16 (CH_2), 22.88 (CH_2), 25.04 (CH_2), 25.27 (CH_2), 38.97 (CH_2), 118.34, 127.50, 128.49 (2C), 128.69 (2C), 128.98, 130.92, 132.11, 133.50, 136.37, 157.27, 158.06, 194.19 (C=O) exactly accounts for 18 carbon atoms. The FAB mass spectrum of **3c** gave molecular ion peak at *m/z* 371 (90%) and protonated molecular ion peak at *m/z* 372 (100%) which are in agreement with its molecular formula $C_{18}H_{17}N_3O_2S$. Other prominent fragment ions at *m/z* 192 (10%) and 154 (75%) are shown in Scheme 3.

The ^{1}H NMR spectrum of 2-mercapto[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**4a**) exhibited a singlet at δ 1.77, a multiplet at δ 2.50–2.87 and another singlet at δ 3.45 which accounts for eight methylene protons. The ^{13}C NMR displayed peaks at δ 21.82 (CH_2), 22.47 (CH_2), 24.51 (CH_2), 25.45 (CH_2), 129.68, 130.65, 151.93 (2C), 159.42 and 160.27 (C=O), which accounts for all the carbon atoms in the molecule. The FAB mass spectrum of **4a** exhibited peaks at *m/z* 296 (10%, M^+) and 318 (100%, M + Na), which is in accordance with its molecular formula $C_{11}H_9N_3OS_3$. Other prominent peaks at *m/z* 206 (5%), 207 (5%), 176 (65%), 154 (100%) and 413 (75%) are shown in Scheme 4.

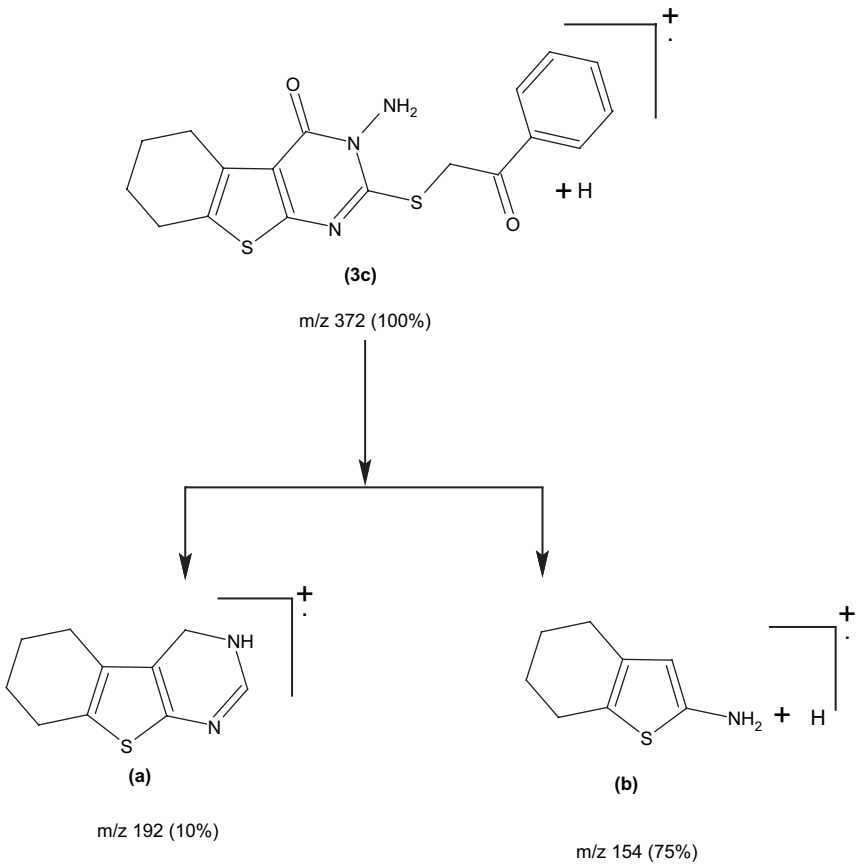
The compound 2-chloromethyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**5a**) was confirmed by recording FABMS. The FAB mass spectrum of **5a** displayed a molecular ion peak at *m/z* 312 (20%, M^+) and 321 (60%, M + H_2O) in accordance with its molecular formula $C_{12}H_{10}ClN_3OS_2$.

2.2. Biological evaluation

2.2.1. Anti-inflammatory activity

Wister albino rats of either sex weighing 180–250 g were used for the experiment. They were housed in clean polypropylene cages and kept under room temperature (25 ± 2 °C), relative humidity (60–70%) in a 12 h light–dark cycle. The animals were given standard laboratory diet and water ad libitum. Food was withdrawn 12 h before and during the experimental hours. The institutional ethical committee approved all experiments.

The rats were divided into twelve groups of one each as shown in Table 1. Group-1 received 10 ml/kg of 2% gum acacia, group-2 received indomethacin at a dose of 1.5 mg/kg; 3rd, 4th, 5th, 6th, 7th, 8th, 9th, 10th, 11th and 12th groups were administered with the test compounds **2a**, **2b**, **2d**, **2e**, **2g**, **2h**, **2i**, **3c**, **3e**, and **4a**, respectively, at a dose of 50 mg/kg suspended in 10 ml/kg of 2% gum acacia orally by gavage feeding. Acute inflammation was produced by subplantar injection of 0.1 ml of 1% suspension of carrageenan with gum acacia in normal saline in the left hind paw of the rats, one hour after the oral administration of the drugs [11]. The paw



Scheme 3. Mass fragmentation pattern of 3-amino-2-[(2-oxo-2-(phenyl)ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**3c**).

volume was measured plethysmometrically (Ugo Basile, Italy) at 0 h and 3 h after carrageenan injection. The difference between the two readings was taken as the volume of edema and the percentage of anti-inflammatory activity was calculated. Indomethacin (1.5 mg/kg) was used as the standard drug.

The percentage of inhibition by the drugs was calculated using the formula,

$$\%\ \text{Of edema inhibition} = 100 - (V_{\text{test}}/V_{\text{control}}) \times 100$$

where, V_{control} = volume of paw edema in control group; V_{test} = volume of paw edema in drug treated group

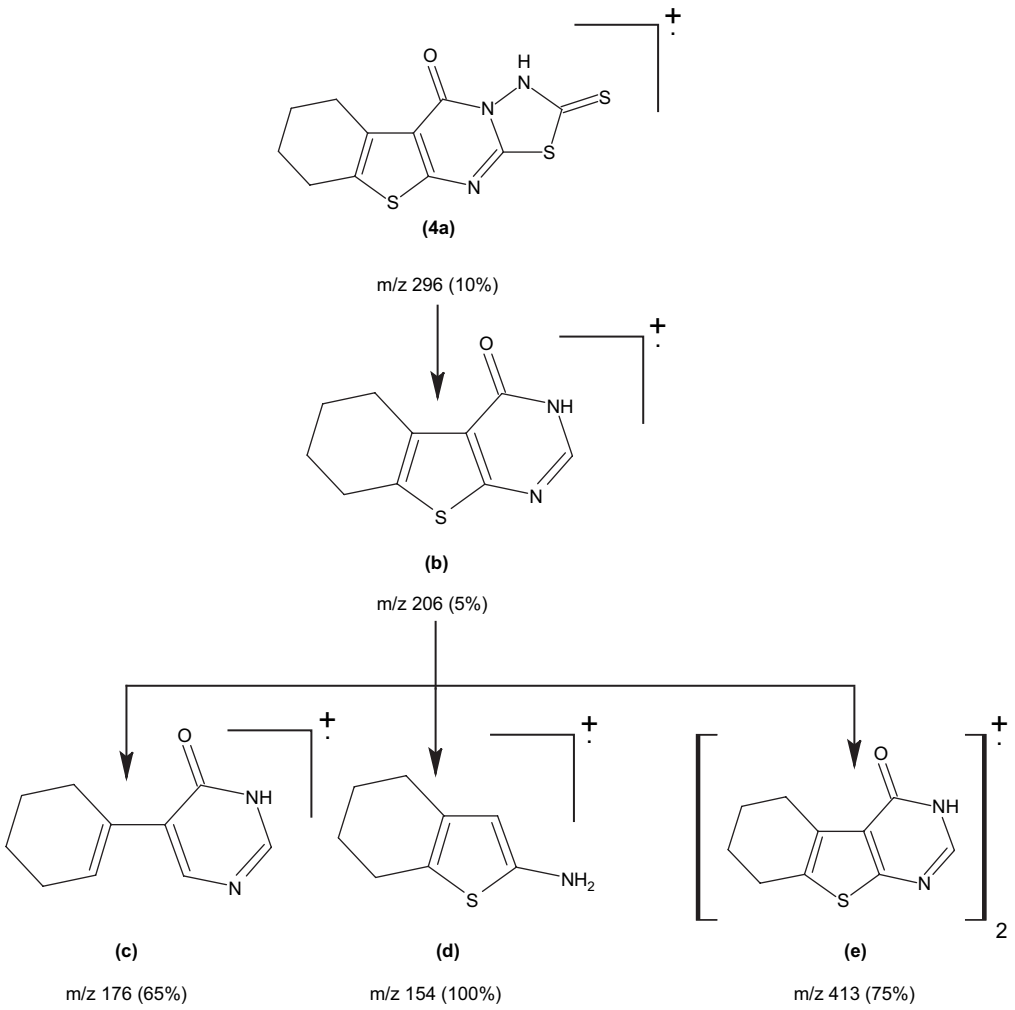
The anti-inflammatory study reveals that the compound 2-(3-methylphenyl) [1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2a**) bearing 3-methylphenyl moiety and 2-ethyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2g**) bearing ethyl moiety exhibited highest activity at a dose of 50 mg/kg in comparison with indomethacin at a dose of 1.5 mg/kg. The compound 2-(4-nitrophenyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2e**) exhibited moderate activity. All the other compounds did not show any considerable activity. It can be concluded that thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*) thieno[3,2-*e*]pyrimidin-5(4*H*)-one derivatives exhibited promising anti-inflammatory activity in comparison with other series. These inferences are based on the findings in a pilot study only. Further studies using larger samples have to be done for obtaining conclusive evidence.

2.2.2. Antibacterial activity

We investigated the newly synthesized compounds (**2a–i**) and (**3a–f**) for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853), and *Klebsiella pneumoniae* (recultured) bacterial strains by disc diffusion method [12,13]. Streptomycin was used as standard drug. Solvent and growth controls were kept and the zone of inhibition in mm and MIC in μg/ml were noted. The results of such studies are given in Table 2. The compounds 2-propyl[1,3,4] thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2h**) and 2-methyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2i**) exhibited the highest inhibition among the tested compounds. It can be seen from the studies that the compounds with alkyl substitution exhibited more inhibition than the compounds with aryl substitution.

2.2.3. Antifungal activity

Newly synthesized compounds (**2a–i**) and (**3a–f**) were screened for their antifungal activity against *Aspergillus flavus*



Scheme 4. Mass fragmentation pattern of 2-mercapto[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**4a**).

(NCIM No.524), *Aspergillus fumigatus* (NCIM No.902), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [12,13]. Antifungal activity was determined by measuring the diameter of the inhibition zone and MIC values in μg/ml. The results of such studies are given in Table 3. Activity of each compound was compared with fluconazole as standard drug. The study reveals that most of the compounds possess less inhibition against the fungal strains. The compounds 2-propyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)-thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2h**) and 2-methyl[1,3,4]-thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]-pyrimidin-5(4*H*)-one (**2i**) exhibited highest activity in comparison with other tested compounds. All other compounds exhibited least activity or no activity. As seen in the case of antibacterial activity compounds with alkyl substitution exhibited more activity than aryl substitution. The compound 2-propyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydroben zo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2h**) can be considered as a promising antibacterial and antifungal agent.

Table 1
Anti-inflammatory activity of the newly synthesized compounds (**2a–i**), (**3a–f**), and (**4a**)

Group	Compound	Dose mg/kg p.o.	Increase in paw volume in ml	% Inhibition of paw edema
1	2% Gum acacia (control)	10 ml/kg	0.45	–
2	Indomethacin	1.5	0.21	53.33
3	**2a**	50	0.22	51.11
4	**2b**	50	0.31	31.11
5	**2d**	50	0.34	24.44
6	**2e**	50	0.23	48.89
7	**2g**	50	0.22	51.11
8	**2h**	50	0.36	30.77
9	**2i**	50	0.34	34.61
10	**3c**	50	0.43	4.44
11	**3e**	50	0.42	6.67
12	**4a**	50	0.48	7.69

2.2.4. Anticonvulsant activity (PTZ induced seizure test) [14]

Inbred male albino mice (Swiss strain) weighing between 25 and 30 g were used in the study. They were housed in colony rooms with 12/12 light/dark cycle at 21 ± 2 °C and had

Table 2
Antibacterial activity of the compounds (**2a–i**) and (**3a–f**) – zone of inhibition in mm and MIC values in μg/ml

Compound	*Escherichia coli*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*
2a	8 (>100)	20 (10)	20 (10)	10 (80)
2b	16 (60)	8 (>100)	18 (60)	20 (10)
2c	8 (>100)	8 (>100)	8 (>100)	6 (>100)
2d	9 (100)	18 (60)	18 (60)	16 (60)
2e	8 (>100)	8 (>100)	9 (100)	20 (10)
2f	10 (80)	8 (>100)	10 (80)	8 (>100)
2g	10 (80)	8 (>100)	18 (10)	22 (10)
2h	18 (10)	20 (10)	22 (10)	26 (6.25)
2i	18 (10)	20 (10)	22 (6.25)	20 (10)
3a	10 (80)	16 (60)	16 (60)	10 (80)
3b	8 (>100)	10 (80)	8 (>100)	10 (80)
3c	8 (>100)	18 (12.5)	8 (>100)	8 (>100)
3d	8 (>100)	8 (>100)	18 (12.5)	6 (>100)
3e	18 (12.5)	22 (6.25)	8 (>100)	22 (<6.25)
3f	8 (>100)	8 (>100)	8 (>100)	18 (12.5)
Standard (streptomycin)	20 (<6.25)	21 (<6.25)	24 (<6.25)	24 (<6.25)

Table 4
Anticonvulsant activity of the tested compounds (PTZ induced seizure test)

Group	Drug	Dose (mg/kg)	Latency (s)	Duration of seizure (s)	Mortality
1	Diazepam	2.0	3600	0	Alive
2	**2a**	50	51	220	Died
3	**2b**	50	68	0	Alive
4	**2d**	50	58	65	Died
5	**2e**	50	56	40	Died
6	**2g**	50	110	185	Died
7	**2h**	50	73	75	Died
8	**2i**	50	3600	0	Alive
9	**3a**	50	62	270	Died
10	**3d**	50	400	255	Died
11	**3e**	50	56	30	Died
12	**3f**	50	41	450	Died
13	**4a**	50	56	39	Died
14	**5a**	50	70	450	Died
15	2% Gum acacia (control)	0.1 ml/10 g	120	312	Died

free access to food and water. Pentylene tetrazole (PTZ, Sigma Chemicals, USA) was used as convulsant and diazepam (Ranbaxy Laboratories, India) was used as standard drug.

Mice were divided into groups as shown in Table 4. Diazepam (2 mg/kg) and the test compounds (50 mg/kg) were suspended in 2% gum acacia. Normal control received 2% gum acacia. All drugs were administered orally by gavage feeding 1 h before injecting PTZ. (i.p. 90 mg/kg). The onset of a general clonus was used as the end point. The general clonus was characterized by forelimb clonus followed by full clonus of the body. The time taken before the onset of clonic convulsions, the durations of clonic convulsion, and mortality protection were recorded. Seizure free interval of 1 h was considered as protection.

In the present model, the standard drug diazepam protected the animals from developing seizures. The compounds 2-(3,5-dimethylphenyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2b**) and 2-methyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2i**) protected the animals from developing seizures. The results of the present study prompted us to investigate these compounds for their neuropsychobehavioural effects also.

Table 3
Antifungal activity of the compounds (**2a–i**) and (**3a–f**) – zone of inhibition in mm and MIC values in μg/ml

Compound	*Penicillium marneffei*	*Aspergillus flavus*	*Aspergillus fumigatus*	*Trichophyton mentagrophytes*
2a	18 (12.5)	6 (>100)	18 (12.5)	4 (>100)
2b	18 (12.5)	7 (>100)	18 (12.5)	9 (80)
2c	5 (>100)	6 (>100)	5 (>100)	6 (>100)
2d	16 (12.5)	7 (>100)	18 (12.5)	7 (>100)
2e	6 (>100)	10 (80)	5 (>100)	6 (>100)
2f	6 (>100)	10 (80)	6 (>100)	6 (>100)
2g	6 (>100)	8 (>100)	6 (>100)	6 (>100)
2h	19 (12.5)	28 (<6.25)	26 (<6.25)	6 (>100)
2i	16 (12.5)	12 (80)	16 (12.5)	7 (>100)
3a	6 (>100)	6 (>100)	8 (>100)	8 (>100)
3b	6 (>100)	6 (>100)	10 (80)	8 (>100)
3c	6 (>100)	10 (80)	8 (>100)	8 (>100)
3d	6 (>100)	6 (>100)	8 (>100)	8 (>100)
3e	6 (>100)	12 (80)	8 (>100)	8 (>100)
3f	8 (>100)	12 (80)	16 (12.5)	4 (>100)
Standard (fluconazole)	21 (<6.25)	18 (<6.25)	21 (<6.25)	19 (<6.25)

2.2.5. Neuropsychobehavioural effects [15–18]

Anticonvulsant study reveals that two compounds such as 2-(3,5-dimethylphenyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2b**) and 2-methyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)-thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2i**) exhibited promising activity. It is in this background we decided to carryout the continuation of our studies. Antianxiety properties were carried out by elevated plus maze model and effect on coordination by rotarod test and effect of learning and memory by transfer latency method.

Diazepam was used as standard drug. Swiss albino mice of either sex weighing around 25–30 g were used for the study. The test compounds (50 mg/kg) and standard drugs (2 mg/kg) were suspended in 2% gum acacia and were administered in a volume of 10 ml/kg.

2.2.5.1. Elevated plus maze model of anxiety. The plus maze apparatus consisting of two open arms (16 × 5 cm) and two closed arms (16 × 5 × 12 cm) having an open roof, with the plus maze elevated (25 cm) from the floor used to observe anxiolytic behaviour in mice. Each mouse was placed at the center of the elevated plus maze with its head facing the open arm. During the 5 min experiment, the behaviour was recorded as number of entries in open and closed arms, time spent in open and closed arms, number of rears in open and closed arms. The rationale is that, open arms are more fear provoking and the ratio of either time spent in open arms to closed arms

reflects the relative fearfulness of the open arms. Anxiolytic drugs are expected to increase the proportion of entries and the time spent on open arms. The results are given in Table 5.

2.2.5.2. Effect on coordination – rotarod test. Motor coordination and balance were tested using accelerating rotarod (TSE rotarod system). Mice were placed on a horizontal metal coated rod with rubber (3 cm diameter) rotating at an initial speed of 10 rpm/min. Rotational velocity of the rod was linearly increased from 10 to 20 rpm within 20 s. The time each animal was able to maintain its balance walking on the top of the rod was measured. Mice were given two trials with a maximum time of 300 s and a 30 to 60 min intertribal rest interval. Before the beginning of all the experiments, the riding ability of the animals in the rotarod was checked. Thus, the mice were initially put on a rotating rod, and the mice that immediately dropped off (within 30 s) were removed from the experiment.

2.2.5.3. Effects on learning and memory. The elevated plus maze is used to measure the anxiety state in animals, however, transfer latency that is, the time elapsed between the movement of the animal from an open to enclosed arm was markedly shortened if the animal had previously experienced entering open and closed arms, and this shortened transfer latency has been shown to be related with memory processes.

In EPM, acquisition (learning) can be considered as transfer latency on first day trials and the retention/consolidation (memory) is examined 24 h later.

On the first day, each mouse was placed at the end of an open arm, facing away from central platform. Transfer latency (TL) is the time taken by the mouse with all its four legs to move into one of the closed arms. TL was recorded on the first day. If the animal did not enter into one of the enclosed arms within 90 s, it was gently pushed into one of the enclosed arms and the TL was assigned as 90 s the mouse was allowed to explore the maze for 10 s and then returned to its home cage. Retention was examined 24 h after the first day trial.

In the present study, the standard drug diazepam (2 mg/kg) increased the number of entries to open arms, time spent and rearing in open arms. The percentile ratio of open arm to the total arm entries was also increased by diazepam. The compound 2-(3,5-dimethylphenyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2b**) increased the time spent and rearing in open arms. Both 2-(3,5-dimethylphenyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2b**) and 2-methyl [1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2i**) did not show a decline in motor function significantly as given in Table 6. Also both the compounds did not have any significant effect on latent periods on both the days (Table 7).

Among the tested compounds, 2-(3,5-dimethylphenyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-e]pyrimidin-5(4*H*)-one (**2b**) seems to have some antianxiety property but both the compounds did not have any effect on neuromuscular coordination, learning and memory.

3. Experimental

Melting points were taken in open capillary tubes and are uncorrected. The purity of compounds was confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates. IR spectra were recorded on Shimadzu-FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Varian (300 MHz) spectrometer using TMS as internal standard and ^{13}C NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Varian (75 MHz) spectrometer. FABMS spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas.

The starting material 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**1**) was prepared from ethyl-2-amino-4,5,6,7-tetrahydro-1-benzo thiophene-3-carboxylate as per reported procedure [8]. IR (KBr, ν in cm^{-1}): 3292, 3138 (−NH_2), 1668 (−C═O), 960 (C═S); FABMS: *m/z* 254 (100%, M + H).

*3.1. General procedure for the synthesis of 2-(substituted phenyl)/alkyl[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5(4H)-ones (**2a–i**)*

3-Amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**1**) (0.5 g, 2 mmol) and appropriate aromatic/aliphatic carboxylic acid (2 mmol) in phosphorus oxychloride (5 mL) was refluxed for 5–6 h. Progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was slowly poured in to crushed ice. The solid separated was filtered and washed with water followed by 5% sodium bicarbonate solution. The products were purified by crystallization from 10% methanol in dimethylformamide.

Table 5
Antianxiety studies (elevated plus maze model)

	No. of entries			Percentage of open/total	Time spent (s)		No. of rears	
	Open	Close	Total		Open	Close	Open	Close
Control	1	17	18	5.56	5	290	0	19
Diazepam	2	17	19	10.53	36	260	0	24
2b	1	13	14	7.14	56	231	0	29
2i	1	5	6	16.67	4	285	0	11

Table 6
Effects on coordination by accelerod test

Treatment	First trial	Second trial
Control	300	300
Diazepam	11.4	30.2
2b	256	300
2i	284	300

Table 7
Effects on learning and memory

Treatment	Latent period (1st day) (s)	Latent period (2nd day) (s)
Control	32	20
2b	34	18
2i	39	25

*3.1.1. 2-(3-Methylphenyl)[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5(4H)-one (**2a**)*

The compound was obtained as cream micro-crystals with an yield of 60%, m.p. > 250 °C; FABMS: *m/z* 354 (100%, M + H), 353 (50%, M^+), 338 (10%), 251 (12%), 154 (20%), 119 (25%); Anal. Calcd. for $C_{18}H_{15}N_3OS_2$: C, 61.16; H, 4.28; N, 11.89; S, 18.14. Found: C, 61.10; H, 4.22; N, 11.82; S, 18.10.

*3.1.2. 2-(3,5-Dimethylphenyl)[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5-(4H)-one (**2b**)*

The compound was obtained as brown crystals with an yield of 68%, m.p. 216 °C; Anal. Calcd. for $C_{19}H_{17}N_3OS_2$: C, 62.10; H, 4.66; N, 11.43; S, 17.45. Found: C, 62.04; H, 4.60; N, 11.43; S, 17.40.

*3.1.3. 2-(3,5-Dichlorophenyl)[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5-(4H)-one (**2c**)*

The compound was obtained as reddish brown micro-crystals with an yield of 87%, m.p. 205 °C; FABMS: *m/z* 408 (45%, M^+), 410 (30%, M + 2), 426 (10%, M + H_2O), 307 (30%), 289 (20%), 154 (100%), 136 (80%); Anal. Calcd. for $C_{17}H_{11}Cl_2N_3OS_2$: C, 50.00; H, 2.72; N, 10.29; S, 15.71. Found: C, 49.08; H, 2.68; N, 10.22; S, 14.65.

*3.1.4. 2-Phenyl[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydro-benzo(b)thieno[3,2-e]pyrimidin-5(4H)-one (**2d**)*

The compound was obtained as yellow micro-crystals with an yield of 65%, m.p. 244 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.90–2.95 (m, 8H, $-CH_2$), 7.46 (t (J = 7.3 Hz), 1H, ArH), 7.52–7.70 (m, 3H, ArH), 7.92–7.99 (m, 1H, ArH); FABMS: *m/z* 337 (20%, M − 2), 175 (20%), 776 (100%, dimerised product); Anal. Calcd. for $C_{17}H_{13}N_3OS_2$: C, 60.15; H, 3.86; N, 12.38; S, 18.89. Found: C, 60.10; H, 3.82; N, 12.32; S, 18.79.

*3.1.5. 2-(4-Nitrophenyl)[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5(4H)-one (**2e**)*

The compound was obtained as reddish orange micro-crystals with an yield of 57%, m.p. > 250 °C; Anal. Calcd. for $C_{17}H_{12}N_4O_3S_2$: C, 53.11; H, 3.15; N, 14.57; S, 16.68. Found: C, 53.52; H, 3.10; N, 14.51; S, 16.58.

*3.1.6. 2-(Benzyl)[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5(4H)-one (**2f**)*

The compound was obtained as cream crystals with an yield of 52%, m.p. 164–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 2.57–3.51 (m, 8H, CH_2), 4.37 (s, 2H, CH_2), 7.19–7.38 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 21.52 (CH_2), 22.21 (CH_2), 24.48 (CH_2), 25.01 (CH_2), 36.92 (CH_2), 117.82, 126.07, 12747, 127.75, 128.54, 128.61, 128.64, 130.75, 131.77, 134.35, 152.79, 156.03, 160.27; FABMS: *m/z* 354 (20%, M + H), 265 (10%), 148 (40%); Anal. Calcd. for $C_{18}H_{15}N_3OS_2$: C, 61.16; H, 4.28; N, 11.89; S, 18.14. Found: C, 60.04; H, 4.18; N, 11.68; S, 18.06.

*3.1.7. 2-Ethyl[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5 (4H)-one (**2g**)*

The compound was obtained as beige crystals with an yield of 81%, m.p. 174–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (t (J = 6.0 Hz), 3H, $-CH_3$), 3.08 (q, 2H, CH_2), 1.62–2.77 (m, 8H, 4 × $-CH_2$); FABMS: *m/z* 291 (75%, M^+), 292 (100%, M + H), 176 (15%), 154 (30%), 136 (25%); Anal. Calcd. for $C_{13}H_{13}N_3OS_2$: C, 53.58; H, 4.50; N, 14.42; S, 22.01. Found: C, 53.43; H, 4.37; N, 14.39; S, 21.92.

*3.1.8. 2-Propyl[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5(4H)-one (**2h**)*

The compound was obtained as brown crystals with an yield of 88%, m.p. > 250 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (t (J = 6.0 Hz), 3H, $-CH_3$), 1.81–1.92 (m, 6H, CH_2), 2.78 (q, 2H, CH_2), 3.0 (t (J = 8.0 Hz), 2H, CH_2), 3.07 (q, 2H, CH_2); FABMS: *m/z* 305 (75%, M^+), 306 (100%, M + H), 289 (30%); Anal. Calcd. for $C_{14}H_{15}N_3OS_2$: C, 55.06; H,4.95; N, 13.76; S, 21.00. Found: C, 55.01; H, 4.65; N, 13.59; S, 20.80.

*3.1.9. 2-Methyl[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5 (4H)-one (**2i**)*

The compound was obtained as dark brown crystals with an yield of 78%, m.p. 196 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79 (s, 3H, $-CH_3$), 2.55–2.89 (m, 8H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 17.16 (CH_3), 21.68 (CH_2), 22.36 (CH_2), 24.5 (CH_2), 25.32 (CH_2), 117.70, 130.78, 131.42, 152.66, 157.15, 157.67, 161.18; FABMS: *m/z* 277 (75%, M^+), 278 (100%, M + H); Anal. Calcd. for $C_{12}H_{11}N_3OS_2$: C, 51.96; H, 4.00; N, 15.15; S, 23.12. Found: C, 51.85; H, 3.85; N, 15.11; S, 23.01.

*3.2. General procedure for the synthesis of 3-amino-2-[(2-oxo-2-(aryl)ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]-pyrimidin-4(3H)-ones (**3a–f**)*

3-Amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*] pyrimidin-4(3*H*)-one (**1**) (0.5 g, 2 mmol), appropriate aromatic acyl bromide (2 mmol) and anhydrous sodium acetate (2.5 mmol) were refluxed in methanol (5 mL) for 6–8 h. Progress of the reaction was monitored by TLC. The reaction mixture was then kept overnight. The solid separated was filtered and then re-crystallized in 10% ethanol in dimethylformamide.

*3.2.1. 3-Amino-2-[(2-oxo-2-(3,4-dihydroxyphenyl)ethyl)-thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**3a**)*

The compound was obtained as buff coloured crystals with an yield of 80%, m.p. 185–186 °C; IR (KBr, ν in cm^{-1}): 3400 (−OH), 3219 (NH_2), 2929 (−CH), 1664 (−C═O); FABMS: *m/z* 403 (48%, M^+), 404 (100%, M + 1), 380 (10%), 289 (10%), 222 (10%), 205 (10%), 192 (10%), 176 (10%), 154 (20%); Anal. Calcd. for $C_{18}H_{17}N_3O_4S_2$: C, 53.58; H, 4.25; N, 10.41; S, 15.89. Found: C, 53.62; H, 4.21; N, 10.29; S, 15.78.

*3.2.2. 3-Amino-2-[(2-oxo-2-(2-chloro-4-pyridinyl)ethyl)-thio]-5,6,7,8-tetrahydro[1]benzothieno-[2,3-d]pyrimidin-4(3H)-one (**3b**)*

The compound was obtained as light orange crystals with an yield of 65%, m.p. 244–245 °C; IR (KBr, ν in cm^{-1}): 3313 (NH_2), 2937 (−CH), 1695 (−C═O); FABMS: *m/z* 388 (40%, M − H_2O), 389 (50% (M + H) − H_2O), 355 (5%), 353 (20%), 308 (10%), 307 (30%), 292 (22%), 289 (20%), 232 (25%), 154 (100%), 136 (70%); Anal. Calcd. for $C_{17}H_{15}ClN_4O_2S_2$: C, 50.18; H, 3.72; N, 10.41; S, 15.76. Found: C, 50.01; H, 3.68; N, 13.65; S, 15.61.

*3.2.3. 3-Amino-2-[(2-oxo-2-(phenyl)ethyl)thio]-5,6,7,8-tetra-hydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one (**3c**)*

The compound was obtained as yellowish crystals with an yield of 76%, m.p. 179–180 °C; IR (KBr, ν in cm^{-1}): 3315 ($-NH_2$), 1678 (−C═O); ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 1.64–2.92 (m, 8H, 4 × -CH_2), 4.57 (s, 2H, CH_2), 4.79 (s, 2H, NH_2), 7.41–7.65 (m, 3H, ArH), 8.05 (d (J = 6.9 Hz), 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6): 22.16 (CH_2), 22.88 (CH_2), 25.04 (CH_2), 25.27 (CH_2), 38.97 (CH_2), 118.34, 127.50, 128.49 (2C), 128.69 (2C), 128.98, 130.92, 132.11, 133.50, 136.37, 157.27, 158.06, 194.19 (C═O); FABMS: *m/z* 371 (90%, M^+), 372 (100%, M + H), 354 (25%), 353 (15%), 307 (30%), 289 (20%), 226 (10%), 154 (75%), 136 (50%); Anal. Calcd. for $C_{18}H_{17}N_3O_2S_2$: C, 58.20; H, 4.61; N, 11.31; S, 17.26. Found: C, 58.14; H, 4.56; N, 11.25; S, 17.12.

*3.2.4. 3-Amino-2-[(2-oxo-2-(4-chlorophenyl)ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]-pyrimidin-4(3H)-one (**3d**)*

The compound was obtained as cream crystals with an yield of 87%, m.p. 206–208 °C; IR (KBr, ν in cm^{-1}): 3325 ($-NH_2$), 1682 (−C═O), 1100 (Ar-Cl); Anal. Calcd. for $C_{18}H_{16}ClN_3O_2S_2$: C, 53.26; H, 3.97; N, 10.35; S, 15.80. Found: C, 53.15; H, 4.61; N, 10.25; S, 15.65.

*3.2.5. 3-Amino-2-[(2-oxo-2-(3-coumarinyl)ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]-pyrimidin-4(3H)-one (**3e**)*

The compound was obtained as yellow crystals with an yield of 64%, m.p. 226–228 °C; IR (KBr, ν in cm^{-1}): 3318 ($-NH_2$), 1680 and 1740 (−C═O); Anal. Calcd. for $C_{21}H_{17}N_3O_4S_2$: C, 57.39; H, 3.90; N, 9.56; S, 14.59. Found: C, 57.26; H, 3.84; N, 9.46; S, 14.49.

*3.2.6. 3-Amino-2-[(2-oxo-2-(4-methoxyphenyl)ethyl)thio]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]-pyrimidin-4(3H)-one (**3f**)*

The compound was obtained as cream crystals with an yield of 92%, m.p. 192–194 °C; IR (KBr, ν in cm^{-1}): 3315 ($-NH_2$), 2931 (CH_2), 1676 (−C═O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.74 (s, 4H, 2 × CH_2), 2.50–2.81 (m, 4H, 2 × CH_2), 3.86 (s, 3H, OCH_3), 5.81 (s, 2H, $-NH_2$), 7.08 (d (J = 8.7 Hz), 2H, ArH), 8.04 (d (J = 9.0 Hz), 2H, ArH); FABMS: *m/z* 401 (30%, M), 402 (70%, M + H), 307 (40%), 289 (20%), 154 (100%), 136 (75%); Anal. Calcd. for $C_{19}H_{19}N_3O_3S_2$: C, 56.84; H, 4.77; N, 10.47; S, 15.97. Found: C, 56.75; H, 4.69; N, 10.38; S, 15.89.

*3.3. Synthesis of 2-mercapto[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno[3,2-e]pyrimidin-5(4H)-one (**4a**)*

A mixture of 3-amino-2-mercapto-5,6,7,8-tetrahydro[1]-benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**1**) (0.5 g, 2 mmol) and potassium hydroxide (2 mmol) in methanol (10 mL) was refluxed for 6 h. Progress of the reaction was monitored by TLC. The reaction mixture was cooled and poured into crushed ice, acidified with dilute hydrochloric acid. The precipitate so obtained was filtered, washed with water, dried and recrystallized from aqueous ethanol. The compound was obtained as yellow crystals with an yield of 65%, m.p. > 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.77 (s, 2H, CH_2), 2.50–2.87 (m, 4H, CH_2), δ 3.45 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 21.82 (CH_2), 22.47 (CH_2), 24.51 (CH_2), 25.45 (CH_2), 129.68, 130.65, 151.93 (2C), 159.42, 160.27 (C═O); FABMS: *m/z* 296 (10%, M^+), 318 (100%, M + Na), 279 (8%), 232 (10%), 176 (60%), 154 (100%), 136 (60%); Anal. Calcd. for $C_{11}H_9N_3OS_3$: C, 44.72; H, 3.07; N, 14.22; S, 32.56. Found: C, 44.65; H, 2.95; N, 14.15; S, 32.38.

*3.4. Synthesis of 2-chloromethyl[1,3,4]thiadiazolo[2,3-b]-6,7,8,9-tetrahydrobenzo(b)thieno-[3,2-e]pyrimidin-5(4H)-one (**5a**)*

3-Amino-2-mercapto-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*] pyrimidin-4(3*H*)-one (**1**) (0.5 g, 2 mmol), chloroacetic acid (2 mmol) and anhydrous sodium acetate (2.5 mmol) in methanol (10 mL) was refluxed for 4–5 h. Progress of the reaction was monitored by TLC. The solid obtained on cooling was filtered and recrystallized from methanol. The compound was obtained as white crystals with an yield of 72%, m.p. 228–230 °C; FABMS: *m/z* 312 (20%, M^+), 321 (60%, M + H_2O), 299 (100%), 289 (20%), 225 (25%), 199 (30%), 154 (100%), 136 (80%); Anal. Calcd. for $C_{12}H_{10}ClN_3OS_2$: C, 46.22; H, 3.23; N, 13.48; S, 20.57. Found: C, 46.11; H, 3.15; N, 13.35; S, 20.43.

4. Conclusion

Seventeen new tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one derivatives were synthesized and evaluated for their biological activities such as antimicrobial, anti-inflammatory, anticonvulsant and neuropsychobehavioural effects. The compound 2-propyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2h**) was found to be promising antimicrobial agent and 2-ethyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2g**) was found to be promising anti-inflammatory agent. The compound 2-methyl[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2i**) protected the animals from developing seizures and the compound 2-(3,5-dimethylphenyl)[1,3,4]thiadiazolo[2,3-*b*]-6,7,8,9-tetrahydrobenzo(b) thieno[3,2-*e*]pyrimidin-5(4*H*)-one (**2b**) seems to have some antianxiety property.

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