

Synthesis of novel angularly fused pentacyclic heterocycles of pharmacological interest

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2-Substituted-4-oxo-naphtho[2,1-*b*]furo[3,2-*d*]pyrimidines **1a-c** on refluxing with phosphorous oxychloride result in the formation of 2-substituted-4-chloronaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines **2a-c**, which on nucleophilic substitution reaction with hydrazine hydrate in ethanol give the required 2-substituted-4-hydrazinonaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines **3a-c**. The compounds **3a-c** are converted into novel angularly fused pentacyclic heterocycles viz. tetrazolo[1,5-*c*]pyrimido[5,4-*b*]naphtho[2,1-*b*]furan derivatives **4a-c** and triazolo[4,3-*c*]pyrimido[5,4-*b*]naphtho[2,1-*b*]furan derivatives **5a-i** by reacting with appropriate reagents. Condensation of **3a-c** with typical aldehydes afford a series of 4-arylidine-hydrazinonaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines **6a-o**. All the newly synthesized compounds have been characterized by elemental analysis and spectroscopic data and have been evaluated for antimicrobial, anthelmintic, anticonvulsant and antipyretic activities.

Keywords: Pentacyclic heterocycles, pyrimidines, phosphorus oxychloride, nucleophilic substitution reaction, hydrazine hydrate, furan derivatives, antimicrobial activity, anthelmintic activity, anticonvulsant activity, antipyretic activity

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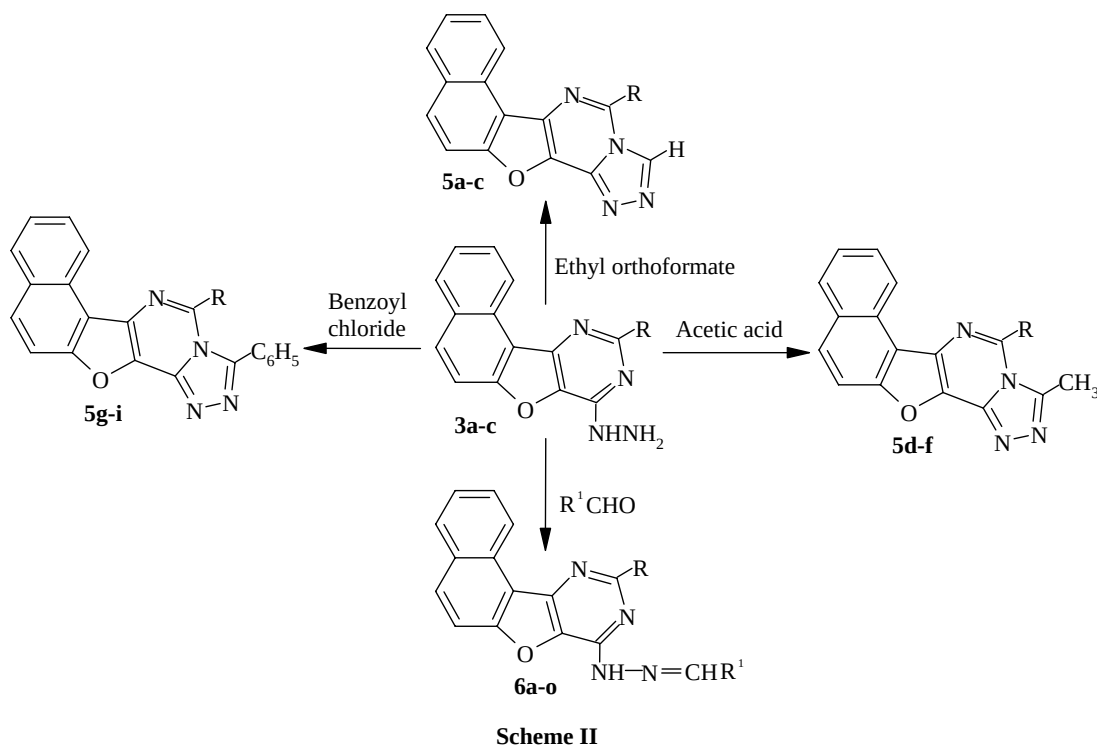
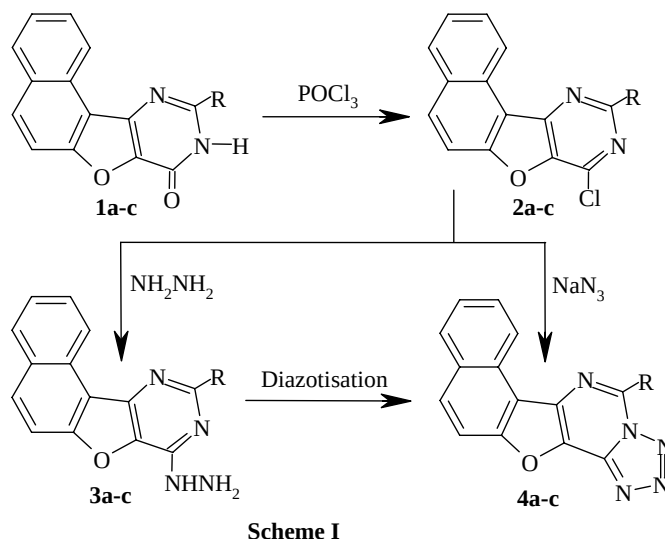
Historically, a wide range of biological activities have been attributed to fused triazoles and tetrazoles¹⁻⁴. It is observed that antifungal agents encompassing 1,2,4-triazole moiety inhibit the biosynthesis of the cell membrane in fungi⁵. However, such compounds were not effective against aspergillosis because of their low bioviability and poor solubility. Hence, more effective and safer drugs with wider biological spectrum have been synthesized and many 1,2,4-triazole antifungals containing heterocyclic moiety were developed^{6,7}. Similarly, the fused tetrazoles have been found to be active as superoxide scavengers, psychotropic and antiinflammatory agents^{8,9}. 1-[(Benzofuran-2-yl)-phenylmethyl]triazoles and tetrazoles have been tested for human placental aromatase inhibition *in vitro*, using [1 β -3H]-androstenedione as the substrate for the aromatase enzyme¹⁰.

Encouraged by the pharmacological efficacy of triazoles and tetrazoles, guided by the observation that many a times the combination of one or more heterocyclic nuclei in a molecule enhances the biological profile many-folds and in continuation of our search for biologically potent naphthofuran derivatives¹¹⁻¹³, we report in this paper, the synthesis and pharma-

cological investigation of tetrazolo[1,5-*c*]pyrimido-[4,5-*b*]naphtho[2,1-*b*]furans **4a-c** and 2-substituted-s-triazolo[4,3-*c*]pyrimido[4,5-*b*]naphtho[2,1-*b*]furans **5a-i**. The sequence of reactions is shown in **Scheme I** and **Scheme II**.

The required starting materials, 2-methyl/phenyl-4-oxo-pyrimido[3,2-*d*]naphtho[2,1-*b*]furans **1b,c** were synthesized from 2-hydroxy-1-naphthaldehyde by series of reactions already reported from our laboratory¹³. The compound 4-oxo-pyrimido[3,2-*d*]naphtho[2,1-*b*]furan **1a** was synthesized by treating 3-aminonaphtho[2,1-*b*]furan-2-carboxamide with formamide in ethanol.

The IR spectrum of compound **1a** exhibited absorption band at 1677 cm⁻¹ due to carbonyl stretching frequency. ¹H NMR spectrum of this compound showed a multiplet at δ 7.2-8.2 integrating for six aromatic protons. The NH proton appeared at δ 9.1 as a singlet, which was exchangeable with D₂O. The proton at C-2 position, which is flanked by two nitrogen atoms, appeared as singlet at a downfield of δ 10.2. The structure of 2-methyl-4-oxo-naphtho[2,1-*b*]furo[3,2-*d*]pyrimidine **1b** has already been established by IR and ¹H NMR data and already



reported¹³. As an additional proof, the mass spectrum of **1b** was recorded. The mass spectrum showed a molecular ion peak at m/z 250 corresponding to its molecular weight. The peaks of fragment ions appearing at m/z 209, 181, 153 and 127 gave further evidence in support of the structure assigned.

2-Substituted-4-chloronaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines **2a-c** were obtained by refluxing **1a-c** with POCl_3 by a reported method¹³. The key intermediates 4-hydrazinopyrimido[3,2-*d*]naphtho[2,1-*b*]furans **3a-c** were synthesized by reacting the

corresponding chloro compounds **2a-c** with hydrazine hydrate in ethanol under reflux condition. The IR spectra of the compounds **3a-c** exhibited absorption bands in the region of $3056\text{--}2849\text{ cm}^{-1}$ due to --NHNH_2 group, which were found to be absent in the precursors. To obtain further evidence to the proposed structure, the ^1H NMR spectrum of **3a** was recorded. It showed a broad singlet at δ 6.0 (D_2O exchangeable) attributed to --NH_2 protons. Other protons appeared as multiplet at δ 7.2-8.8. The ^1H NMR spectrum of **3b** exhibited a singlet at δ 2.6 due to --CH_3 protons, a

broad singlet at δ 6.0 (D_2O exchangeable) due to $-NH_2$ protons and a multiplet in the region δ 7.2- δ 8.2 for six aromatic protons and $-NH$ proton. The mass spectrum of **3a** showed a molecular ion peak at m/z 250 corresponding to its molecular weight. The peaks of fragment ions appearing at m/z 219, 192, 165 and 136 confirmed the structure.

The synthesis of tetrazolo[1,5-*c*]pyrimido[4,5-*b*]naphtho[2,1-*b*]furans **4a-c** was accomplished by the diazotization of 4-hydrazino compounds **3a-c**. The structure assigned to **4a** is in well agreement with its ^1H NMR spectrum, which exhibited only a multiplet at δ 7.2- δ 8.5 due to six aromatic protons including a proton of pyrimidine ring. The mass spectrum of **4a** showed a molecular ion peak at m/z 261 and peaks of fragment ions appeared at m/z 233, 207, 193, 166 and 138. The compounds **4a-c** were also obtained by an alternative route, in which chloro compounds **2a-c** were reacted with sodium azide in ethanol. These compounds were found to be identical with the compounds obtained by other method as indicated by superimposable IR and ^1H NMR spectra and also by the determination of mixed melting points.

The compounds **3a-c** on refluxing with ethyl orthoformate afforded anticipated fused *s*-triazolo compounds i.e. 2-substituted-*s*-triazolo[4,3-*c*]pyrimido[4,5-*b*]naphtho[2,1-*b*]furans **5a-c** in good yield. The IR spectrum of compound **5a** exhibited absorption band at 1578 cm^{-1} due to $C=N$ stretching frequency. The ^1H NMR spectrum of **5a** exhibited a multiplet at δ 7.1-8.3 integrating for six aromatic protons and protons of the pyrimidine ring and the triazole ring resonated as a

singlet at δ 9.2 integrating for two protons. The IR spectrum of compound **5b** exhibited absorption band at 1582 cm^{-1} due to $C=N$ stretching frequency. The ^1H NMR spectrum of **5b** exhibited a singlet at δ 2.6 integrating for three protons of methyl group, a multiplet at δ 7.1- δ 8.3 integrating for six aromatic protons, whereas the proton of triazole ring appeared as singlet at δ 9.4 integrating for one proton. The mass spectrum of **5d** showed a molecular ion peak at m/z 288 and peaks of fragment ions appeared at m/z 273, 247, 221, 207, 166 and 138. The structures of tetrazoles were further confirmed by recording mass spectrum of **5g**, which showed a molecular ion peak at m/z 336 and peaks of fragment ions appeared at m/z 259, 233, 207, 193, 166 and 138.

Similar reaction of **3a-c** with acetic acid resulted in the formation of 2-substituted-5'-methyl-*s*-triazolo[4,3-*c*]pyrimido[4,5-*b*]naphtho[2,1-*b*]furans **5d-f** and with benzoyl chloride afforded 2-substituted-5'-phenyl-*s*-triazolo[4,3-*c*]pyrimido[4,5-*b*]naphtho[2,1-*b*]furans derivatives **5g-i** in moderate yield. The IR spectrum of compound **5c** exhibited absorption band at 1582 cm^{-1} due to $C=N$ stretching frequency.

It has been established that antibacterial and antiparasitic activities of nitrofur derivatives are due to the presence of $-NH-N=CH-$ group¹⁴. Hence it was thought of to synthesize some arylidenehydrazino derivatives making use of corresponding 4-hydrazino compounds. The treatment of 4-hydrazino compounds **3a-c** with various aromatic aldehydes in ethanol produced the desired 4-arylidenehydrazinonaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines **6a-o** (Table I).

Table I — Characterization data of compounds 1-6

Compd	R	R ¹	Mol. formula	Yield (%)	m.p. °C	Found % (Cald)		
						C	H	N
1a	H	-	C ₁₄ H ₈ N ₂ O	72	164	76.36 (76.38)	3.63 3.61	2.72 12.70)
2a	H	-	C ₁₄ H ₇ N ₂ OCl	78	170	66.04 (66.01)	2.75 2.71	10.96 11.00)
2b	CH ₃	-	C ₁₅ H ₉ N ₂ OCl	76	168	67.05 (67.03)	3.38 3.35	10.28 10.42)
2c	C ₆ H ₅	-	C ₂₀ H ₁₁ N ₂ OCl	72	122	72.61 (72.61)	3.34 3.32	08.34 08.47)
3a	H	-	C ₁₄ H ₁₀ N ₄ O	76	164	67.0 (67.20)	3.98 4.00	22.42 22.40)
3b	CH ₃	-	C ₁₅ H ₁₂ N ₄ O	68	144	68.14 (68.18)	4.52 4.54	19.98 20.00)
3c	C ₆ H ₅	-	C ₂₀ H ₁₄ N ₄ O	67	168	73.60 (73.61) (73.61)	4.27 4.29 4.29	17.12 17.17) 17.17)

contd

Table I — Characterization data of compounds **1-6** — *contd*

Compd	R	R ¹	Mol. formula	Yield (%)	m.p. °C	Found % (Cald)		
						C	H	N
4a	H	-	C ₁₄ H ₇ N ₅ O	69	227	71.19 (71.21)	2.63 2.68	26.56 26.61
4b	CH ₃	-	C ₁₅ H ₉ N ₅ O	65	217	65.41 (65.45)	3.25 3.27	25.38 25.45
4c	C ₆ H ₅	-	C ₂₀ H ₁₁ N ₅ O	69	243	71.19 (71.21)	3.20 3.26	20.72 20.77
5a	H	-	C ₁₅ H ₈ N ₄ O	67	214	69.21 (69.23)	3.06 3.07	21.48 21.53
5b	CH ₃	-	C ₁₆ H ₁₀ N ₄ O	69	189	70.08 (70.07)	3.62 3.64	20.38 20.43
5c	C ₆ H ₅	-	C ₂₁ H ₁₂ N ₄ O	68	201	74.97 (75.00)	3.55 3.57	16.60 16.66
5d	H	-	C ₁₆ H ₁₀ N ₄ O	82	226	70.04 (70.07)	3.62 3.64	20.40 20.43
5e	CH ₃	-	C ₁₇ H ₁₂ N ₄ O	74	234	70.81 (70.83)	4.13 4.16	19.36 19.44
5f	C ₆ H ₅	-	C ₂₂ H ₁₄ N ₄ O	68	198	75.40 (75.42)	3.98 4.00	15.96 16.00
5g	H	-	C ₂₁ H ₁₂ N ₄ O	70	194	74.99 (75.00)	3.54 3.57	16.68 16.66
5h	CH ₃	-	C ₂₂ H ₁₄ N ₄ O	75	209	75.40 (75.42)	3.98 4.00	15.94 16.00
5i	C ₆ H ₅	-	C ₂₇ H ₁₆ N ₄ O	65	233	78.62 (78.64)	3.85 3.88	13.52 13.59
6a	H	C ₆ H ₅	C ₂₁ H ₁₄ N ₄ O	75	122	74.54 (74.55)	4.12 4.14	16.49 16.56
6b	H	C ₆ H ₄ -2-OH	C ₂₁ H ₁₄ N ₄ O ₂	73	139	71.16 (71.18)	3.93 3.95	15.76 15.81
6c	H	C ₆ H ₄ -3-NO ₂	C ₂₁ H ₁₃ N ₅ O ₃	78	143	65.77 (65.79)	3.37 3.39	18.22 18.27
6d	H	C ₆ H ₄ -4-NH ₂	C ₂₁ H ₁₅ N ₅ O	81	150	71.36 (71.38)	4.22 4.24	19.80 19.83
6e	H	2-Furyl	C ₁₉ H ₁₂ N ₄ O ₂	69	187	69.50 (69.51)	3.63 3.65	17.02 17.07
6f	CH ₃	C ₆ H ₅	C ₂₂ H ₁₆ N ₄ O	69	210	74.97 (75.00)	4.52 4.54	15.89 15.90
6g	CH ₃	C ₆ H ₄ -2-OH	C ₂₂ H ₁₆ N ₄ O ₂	74	180	71.71 (71.73)	4.32 4.34	15.19 15.21
6h	CH ₃	C ₆ H ₄ -3-NO ₂	C ₂₂ H ₁₅ N ₅ O ₃	75	178	66.47 (66.49)	3.75 3.77	17.60 17.63
6i	CH ₃	C ₆ H ₄ -4-NH ₂	C ₂₂ H ₁₇ N ₅ O	67	197	71.91 (71.93)	4.61 4.63	19.00 19.07
6j	CH ₃	2-Furyl	C ₂₀ H ₁₄ N ₄ O ₂	70	215	70.16 (70.17)	4.06 4.09	16.30 16.37
6k	C ₆ H ₅	C ₆ H ₅	C ₂₇ H ₁₈ N ₄ O	82	187	78.24 (78.26)	4.32 4.34	13.47 13.52
6l	C ₆ H ₅	C ₆ H ₄ -2-OH	C ₂₇ H ₁₈ N ₄ O ₂	66	203	75.32 (75.34)	4.13 4.18	12.98 13.02
6m	C ₆ H ₅	C ₆ H ₄ -3-NO ₂	C ₂₇ H ₁₇ N ₅ O ₃	72	227	70.54 (70.58)	3.69 3.70	15.21 15.25
6n	C ₆ H ₅	C ₆ H ₄ -4-NH ₂	C ₂₇ H ₁₉ N ₅ O	74	213	75.50 (75.52)	4.41 4.42	16.27 16.31
6o	C ₆ H ₅	2-Furyl	C ₂₅ H ₁₆ N ₄ O ₂	71	234	74.23 (74.25)	3.95 3.96	13.80 13.86

^1H NMR spectrum of **6a** exhibited a singlet at a downfield of δ 9.3 assignable to methine proton and a multiplet between δ 7.2-8.2 integrating for 12 protons was attributed to 11 aromatic protons and one $-\text{NH}$ proton. It also exhibited a singlet at δ 8.8 assignable to proton of pyrimidine ring. The mass spectrum of **6a** showed a molecular ion peak at m/z 338 and peaks of fragment ions appeared at m/z 232, 219, 193, 166 and 138. ^1H NMR of **6f** exhibited a singlet at δ 2.6 due to methyl protons integrating for three protons. It also exhibited a multiplet in between δ 7.2-8.2 integrating for 12 protons, which was attributed to 11 aromatic protons and one $-\text{NH}$ proton. A peak appeared as a singlet at δ 9.3 was attributed to methine proton. The D_2O exchange studies supported the assignment of ^1H NMR peaks.

The newly synthesized compounds have been screened for antimicrobial, anthelmintic, anti-convulsant and antipyretic activities.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on FT-IR (Research spectrophotometer series) and Perkin-Elmer FT-IR (spectrum 1000); ^1H NMR spectra on a Jeol GSX 270 FT NMR spectrophotometer using $\text{DMSO}-d_6$ or CDCl_3 as solvent and TMS as an internal standard (chemical shifts in δ , ppm); and mass spectra on a Jeol JMS-D 300 mass spectrometer operating at 70 eV. Compounds were checked for their purity by TLC on silica gel G plates using carbon tetrachloride-methanol (v/v) of varying polarity and the spots were located by iodine vapours.

4-Oxo-naphtho[2,1-*b*]furo[3,2-*d*]pyrimidines 1a. 3-Aminonaphtho[2,1-*b*]furan-2-carboxamide (2 g, 0.001 mole) was refluxed with formamide (6 mL) in ethanol (40 mL) for 4 hr. The resulting mixture on pouring into ice cold water gave the product as solid, which was collected by filtration and recrystallized from aqueous ethanol.

2-Substituted-4-chloronaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines 2a-c. A mixture of compound **1a** (2 g, 0.001 mole) and freshly distilled phosphorus oxychloride (50 mL) was heated under reflux until a clear solution was obtained. The resulting solution was cooled and poured into crushed ice with stirring. The chloro compound **2a** thus separated was collected and recrystallized from aqueous ethanol.

Similarly, compounds **2b-c** were prepared from **1b-c**.

2-Substituted-4-hydrazinonaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines 3a-c. To a solution of **2a-c** (0.0015 mole) in methanol (80 mL), was added hydrazine hydrate (80%, 10 mL) and the mixture was heated under reflux on a water-bath for 4 hr. The yellow coloured hydrazino compounds **3a-c**, which separated on cooling, were collected and recrystallized from suitable solvent.

Tetrazolo[1,5-*c*]pyrimido[5,4-*b*]naphtho[2,1-*b*]furans 4a-c. Method (A)—A suspension of **3a-c** (0.002 mole) in acetic acid (1N, 5 mL) was treated with sodium nitrite (0.2 g) at 45°C for 2 hr. After cooling, the solid, which separated, was collected and recrystallized from appropriate solvents.

Method (B)—A mixture of **2a-c** (0.0015 mole) and sodium azide (0.3 g) in ethanol (10 mL) was heated under reflux on a water-bath for 4 hr. The resulting solid, that separated after cooling the reaction mixture, was collected and recrystallized from suitable solvent. The compounds were identical with those obtained by Method (A).

2-Substituted-*s*-triazolo[4,3-*c*]pyrimido[5,4-*b*]naphtho[2,1-*b*]furans 5a-c. Compounds **3a-c** (0.002 mole) were heated in ethyl orthoformate (3 mL) at 80°C for 20 min. The solid cake formed in each case, after cooling, was triturated with pet. ether and recrystallized from suitable solvent.

2-Substituted-5'-methyl-*s*-triazolo[4,3-*c*]pyrimido[5,4-*b*]naphtho[2,1-*b*]furans 5d-f. Compounds **3a-c** (0.002 mole) were heated in acetic acid (4 mL) at 80°C for 20 min. The solid cake formed in each case, after cooling, was triturated with pet. ether and recrystallized from suitable solvent.

2-Substituted-5'-phenyl-*s*-triazolo[4,3-*c*]pyrimido[5,4-*b*]naphtho[2,1-*b*]furans 5g-i. Compounds **3a-c** (0.002 mole) were heated in benzoyl chloride (4 mL) at 80°C for 20 min. The solid cake formed in each case, after cooling, was triturated with pet. ether and recrystallized from suitable solvent.

4-Arylidinehydrazinonaphtho[2,1-*b*]furo[3,2-*d*]pyrimidines 6a-o. To a solution of **3a-c** (0.0025 mole) in methanol (50 mL), freshly distilled appropriate aldehyde (0.0025 mole) was added and the mixture stirred for about 2 hr at room temperature and left overnight. The solid, which separated, was collected and recrystallized from suitable solvent.

Antimicrobial activity

The antimicrobial activity of the selected compounds was determined by cup plate method¹⁵,

using bacteria *Proteus vulgaris* and *Pseudomonas aeruginosa* and fungi *Aspergillus niger* and *Candida albicans*. The compounds were tested at a concentration of 0.001 mole/mL in dimethyl formamide against all the four microorganisms. Ciprofloxacin (0.001 mole/mL) and Chlotrimazole (0.001 mole/mL) were used as standard to compare the zone of inhibition for antibacterial and antifungal activities, respectively. Amongst the tested compounds, **6a**, **6f** and **6k** were found to be moderately active against all the four microorganisms and their zone of inhibition was found to be in the range of 13-16 mm.

Anthelmintic activity

The activity was evaluated on earthworms *Pheretima posthuma* by reported method¹⁶. The compounds were tested at a dose of 0.001 mole/mL suspension in 0.1% Tween-80 solution. Solution of 0.1% Tween-80 in 6% dextrose, 6% dextrose solution and Piperazine citrate suspension (0.001 mole/mL) were poured into separate petridishes as a control, blank and standard, respectively. The time taken for paralysis and death of the worm was recorded. The compounds **4a** and **5c** were found to exhibit considerable anthelmintic activity against earthworms, which is comparable with that of standard drug.

Anticonvulsant activity

The maximal electroshock (MES) induced convulsion method was adopted to carryout anticonvulsant activity in rats¹⁷. Diazepam, at the dose of 25 mg/kg body weight was used as standard. The compounds were tested at the dose of 80 mg/kg body weight as determined by dose fixation studies. A current of 150 mA was applied to the rats for 0.2 seconds, through corneal electrodes and the time spent by the rats in different stages of convulsion were noted. The triazoles **5a** and **5c** were found to possess anticonvulsant activity since they reduced the extensor phase of the MES convulsions to a considerable extent, which is comparable with that of standard drug.

Antipyretic activity

The antipyretic activity was carried out on Wistar strain albino rats by adopting yeast induced hyperpyrexia method¹⁸. The hyperpyrexia was induced by subcutaneous injection of yeast (2.0 mL, 15%) suspension in saline solution. Then, test compounds were administered to each test group animals orally at the dose of 80 mg/kg body weight as determined by

dose fixation studies. Acetyl salicylic acid was used as standard. The rectal temperature was noted after 1, 3, 6 hr interval and compared with standard. The compounds **5a** and **5b** were found to exhibit equipotent antipyretic activity in comparison with the standard drug.

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