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Synthesis, spectral studies and biological activity of novel 1*H*-1,4-diazepine derivatives

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Sulphonation of 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*) pyrimidin-7-one **1** with chlorosulphonic acid affords 5-[(5-chlorosulphonyl-2-ethoxy) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*] pyrimidin-7-one **2**. Further, compound **2** is condensed with different β-diketones/β-ketoesters **3a-e,** to obtain new β-diketones/β-ketoesters **4a-e**. The synthesized new β-diketones/β-ketoesters and ethylenediamine (EDA) gives biologically active 1*H*-1,4-diazepines **5a-e**. All the newly synthesized compounds are characterized by elemental analysis and spectral studies. The compounds **5a-e** have been screened for antimicrobial, antifungal and anthelmintic activity.

Keywords: 1,4-Diazepines, β-diketones, β-ketoesters, pyrimidin-7-one, lanthanum (III) nitrate hexahydrate, ethylenediamine

1,4-Diazepines have been the object of intense studies since the early 1960s because of their biological activities such as anticancer[1,2], antibacterial[3], psychotopics[4], anticonvulsant[5] and antiviral[6]. Various diazepines have been reported as fungicidal and herbicidal[7]. Substituted 1,4-diazepine and their derivatives possess anti-HIV[8] activity which is lesser than that of zidovudine (3′-azidothymidine = AZT). They also show platelet activating factor (PAF) antagonistic[9] and serotoninergic S_3 antagonistic[10,11] activity.

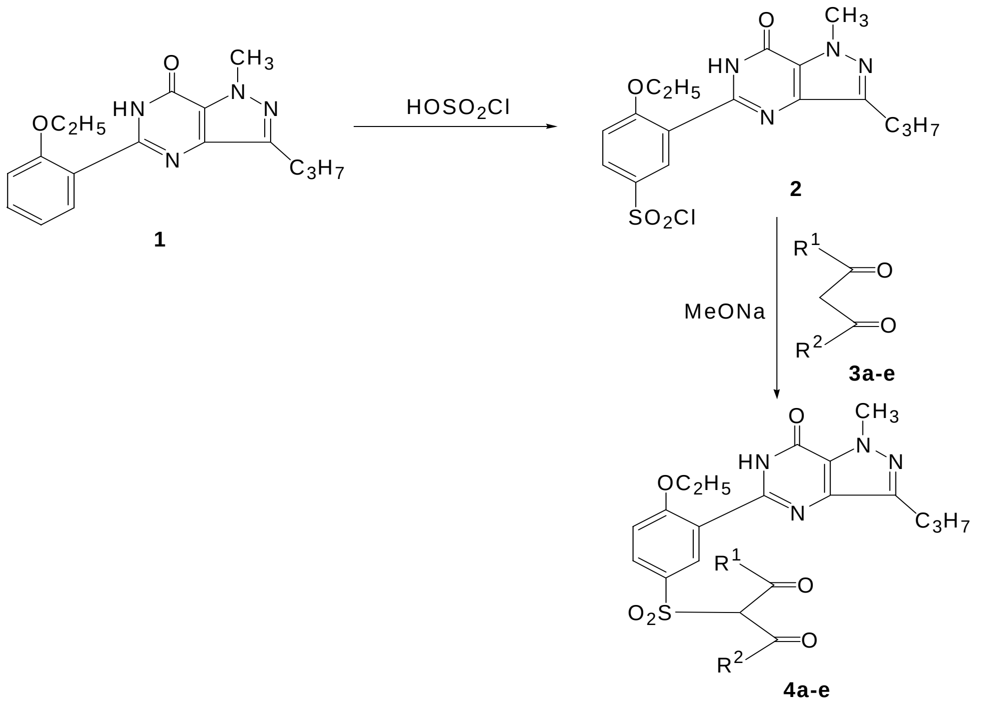
The target of the present work was the synthesis of pyrazolo[4,3-*d*] pyrimidin-7-one containing 1,4-diazepines due to their importance in medicinal chemistry[12-15]. To achieve this target, β-diketones/β-ketoesters **4a-e** were synthesized which were condensed with ethylenediamine (EDA) to the corresponding substituted 1*H*-1,4-diazepines **5a-e** with high yields. Various methods are reported in literature for the synthesis 1*H*-1,4-diazepines[16]. However, these methods are associated with several drawbacks such as harsh reaction condition, complex and tedious experimental procedures and low yields. Herein, has been developed a method for the synthesis of 1,4-diazepines from the reaction of β-diketones/β-ketoesters and ethylenediamine in the presence of lanthanum (III) nitrate hexahydrate. Lanthanum (III) nitrate hexahydrate was used as a catalyst for the deprotection of acetonides[17] and in selective deprotection of primary alcohols[18].

Results and Discussion

5-(2-Ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*] pyrimidin-7-one was sulphonated with chlorosulphonic acid, to obtain compound **2**. Compound **2** was condensed with different β-diketones/β-ketoesters **3a-e** in the presence of sodium methoxide (**Scheme I**). Newly synthesized β-diketone/β-ketoesters **4a-e** were condensed with ethylenediamine under microwave irradiation, to obtain novel substituted 1*H*-1,4-diazepines **5a-e** (**Scheme II**).

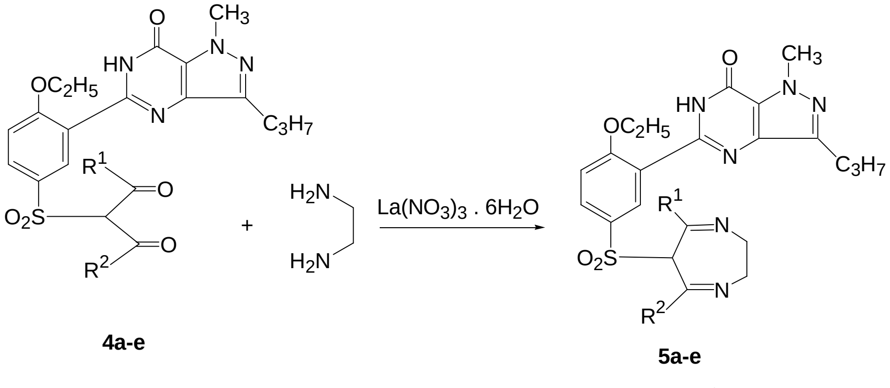
Antimicrobial, antifungal and anthelmintic activities of compounds 5a-e

The newly synthesized diazepine compounds **5a-e** have been screened for antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae* and antifungal activity against *Aspergillus niger* and *Candida albicans* by the cup-plate method[19,20]. Ciprofloxin and ciclopiroxolamine were used as standards for comparison of antibacterial and antifungal activities, respectively. The results indicate that these compounds were active against all the four organisms. The anthelmintic activity was carried out on earth worms *Pherituma posthuma*, by a technique described by Bagavant *et al.*[21] with slight modification. Piperazine citrate was used as standard drug. The result of antimicrobial and anthelmintic



3a/4a $R^1 = R^2 = CH_3$
3b/4b $R^1 = R^2 = C_6H_5$
3c/4c $R^1 = CH_3$ $R^2 = C_6H_5$
3d/4d $R^1 = CH_3$, $R^2 = OC_2H_5$
3e/4e $R^1 = R^2 = OC_2H_5$

Scheme I



5a $R^1 = R^2 = -CH_3$
5b $R^1 = R^2 = C_6H_5$
5c $R^1 = CH_3$ $R^2 = C_6H_5$
5d $R^1 = CH_3$, $R^2 = =O$
5e $R^1 = R^2 = =O$

Scheme II

Table I — Antimicrobial, antifungal and anthelmintic activities of compounds **5a-e**

Compd	Antibacterial activity zone of inhibition in mm		Antifungal activity zone of inhibition in mm		Anthelmintic activity in min	
	A. aureus	*K. pneumoniae*	*A. niger*	*C. albicans*	Paralysis	Death
5a	12	09	17	18	90	90
5b	08	10	15	16	90	125
5c	24	24	23	24	102	122
5d	27	28	23	26	100	115
5e	14	07	08	19	102	129
Std	24	26	22	24	100	125

activity is reported in **Table I**. The compound **5c** exhibited antimicrobial and antifungal activities higher than the standard drug but compounds **5d** and **5e** showed significant anthelmintic activity.

Experimental Section

All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Nicolet-Megna-FT-IR-550 spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were run on model DRX 300 at 300.13 MHz and 75 MHz respectively in $CDCl_3$ and mass spectra on a LCMS instrument. The homogeneity of the newly synthesized compounds was checked by TLC. Satisfactory CHN analyses were obtained for all the compounds.

Synthesis of 5-[(5-chlorosulphonyl-2-ethoxy) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo-[4,3-*d*] pyrimidin-7-one, 2

5-(2-Ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*] pyrimidin-7-one (3.12 g, 0.01 mole) was placed into a two neck round bottom flask, diluted with dichloromethane and chlorosulphonic acid (1.17 g, 0.01 mole) added dropwise at 0°C. After complete addition, the reaction-mixture was stirred on a magnetic stirrer at 50°C for 2 hr. The progress of reaction was monitored by TLC using 7:2:1 (benzene: ethanol:ammonia) upper layer as mobile phase. After completion of reaction, the reaction mass was poured into ice and extracted with dichloromethane (2 × 50 mL). The dichloromethane layer was evaporated to get a white solid compound. The product was purified by column chromatography over silica gel using pet ether:ethyl acetate (50:50) as eluent. It was purified by recrystallization from methanol. Homogeneity of the compound was checked by TLC using 7:2:1 (benzene:ethanol:ammonia) upper layer as mobile phase (m.p. 195°C, yield 2.8 g, 65%).

Synthesis of 5-[2-ethoxy-5-(1,3-dimethyl/1,3-diphenyl/1-phenyl-3-methyl/1-methyl-3-ethoxy/1,3-diethoxypropane-1,3-dione-2-sulphonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*] pyrimidin-7-one, 4a-e

Sodium methoxide (0.54 g, 0.01 mole) and β-diketones / β-ketoester (0.01 mole) were placed in a dry round bottom flask and the mixture stirred for 1 hr on a magnetic stirrer at 50°C, after which a creamy mass was obtained. The sulphonyl chloride derivative **2** (3.885 g, 0.01 mole) was then added and dry toluene added as solvent to effect proper stirring of the reaction mass. The reaction-mixture was heated for 7 hr at 80°C with stirring. The progress of the reaction was monitored by TLC. On completion of the reaction, the reaction mass was cooled to RT and toluene was removed. The reaction-mixture was extracted using chloroform and washed with water to remove salt.

The chloroform layer was dried using anhydrous sodium sulphate. Chloroform was evaporated to get solid compound. The product was purified by column chromatography over silica gel using pet ether:ethyl acetate (50:50) as eluent. It was purified by recrystallization from chloroform and ethyl acetate. Homogeneity of the compound was checked by TLC using 7:2:1 (benzene:ethanol:ammonia) upper layer as mobile phase.

General method for preparation of diazepine derivatives 5a-e

To a stirred mixture of β-diketones / β-ketoesters (0.01 mole) **2a-e,** ethylenediamine (0.01 mole) and lanthanum (III) nitrate hexahydrate (0.01 mole) were added in dichloromethane (50 mL). The reaction-mixture was stirred at 50°C for 60 min. The progress of reaction was monitored by TLC using 7:2:1 (benzene:ethanol:ammonia) upper layer as mobile phase. The mixture was extracted with CH_2Cl_2 (2×25 mL) and the solvent was removed to obtain the crude product. The crude product was washed with dry ether to remove unreacted β-diketones/β-ketoesters. The crude product was then recrystallized from pet ether:ethyl acetate (1:1). The product was purified by column chromatography over silica gel using pet ether:ethyl acetate (40:60) as eluent.

5-[2-Ethoxy)-5-(5,7-dimethyl-2,3-dihydro-*1H*-1,4-diazepine-6-sulphonyl)-phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5a. m.p.148°C, yield 77.5%; IR (KBr): 3330, 3040, 2950, 1250, 1020, 1345, 1125, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.02 (t, *J* = 8.46, 3H), 1.66 (m, *J* = 7.65, 2H), 1.69 (t, *J* = 8.23, 3H), 2.07 (s, 6H), 2.50 (s, 4H,), 2.55 (t, *J* = 7.98, 2H), 3.45 (s,1H), 3.80 (s,3H), 3.95 (q, *J* = 7.56, 2H), 7.2-7.8 (m, *J* = 7.85, 4H), 8.50 (s,1H); ^{13}C NMR ($CDCl_3$): δ 168.52, 162.23, 133.50, 124-128, 65.12, 48.55, 33.70, 32.35, 24.92, 14.30, 13.65; MS: *m/z* 499 ($M+H^+$). Anal. Calcd for $C_{24}H_{30}N_6O_4S$: C, 57.81; H, 6.06; N, 16.86. Found: C, 57.85; H, 6.01; N, 16.83%.

5-[2-Ethoxy)-5-(5,7-diphenyl-2,3-dihydro-1*H*-1,4-diazepine-6-sulphonyl)-phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5b. m.p.165°C, yield 72.3%; IR (KBr): 3320, 3045, 2945, 1255, 1020, 1340, 1125, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.02 (t, *J* = 8.26,3H), 1.60 (t, *J* = 8.25,3H), 1.65 (m, *J* = 7.56,2H), 2.55 (s, 4H), 2.60 (t, *J* = 7.23, 2H), 3.50 (s,1H), 3.80 (s,3H), 4.05 (q, *J* = 8.12, 2H), 7.2-7.8 (m, *J* = 7.92,14H), 8.25 (s,1H); ^{13}C NMR ($CDCl_3$): δ 168.45, 162.56, 133.23, 124-128, 65.19, 48.59, 33.73, 32.36, 24.97, 14.38, 13.67; MS: *m/z* 623 ($M+H^+$). Anal. Calcd. for $C_{34}H_{34}N_6O_4S$: C, 65.58; H, 5.50; N, 13.80. Found: C, 65.54; H, 5.52; N, 13.83%.

5-[2-Ethoxy)-5-(5-methyl-7-phenyl-2,3-dihydro-*1H*-1,4-diazepine-6-sulphonyl)-phenyl]-1-methyl-3-propyl-1, 6-dihydro-7*H*-pyrazolo[4,3-*d*] pyrimidin-7-one, 5c. m.p.157°C, yield 81%; IR (KBr): 3323, 3025, 2945, 1260, 1029, 1348, 1126, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.05 (t, *J* = 8.45,3H), 1.60 (t, *J* = 7.56,3H), 1.68 (m, *J* = 7.26,2H), 2.15 (s, 3H), 2.50 (t, *J* = 8.46, 2H), 2.65 (s, 4H), 3.55 (s,1H), 3.80 (s,3H), 3.95 (q, *J* = 8.15,2H), 7.2-7.8 (m, *J* = 7.85,9H), 8.65 (s,1H); ^{13}C NMR ($CDCl_3$): δ 166.55, 163.45, 133.56, 124-128, 65.17, 48.58, 34.05, 31.36, 24.98, 14.89,14.65; MS: *m/z* 561($M+H^+$). Anal. Calcd for $C_{29}H_{32}N_6O_4S$: C, 62.12; H, 5.75; N, 14.99. Found: C, 62.10; H, 5.73; N, 14.95%.

5-[2-Ethoxy)-5-(7-methyl-2,3,4, 6-tetrahydro-*1H*-1,4-diazepine-5-one-6-sulphonyl)-phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5d. m.p. 145°C, yield 69%; IR (KBr): 3330, 3040, 2950, 1725,1250, 1020, 1345, 1125, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.02 (t, *J* = 8.23,3H), 1.66 (m, *J* = 7.56, 2H), 1.68 (t, *J* = 7.89, 3H), 2.07(s, 3H), 2.60 (s, 4H) 2.55 (t, *J* = 8.15, 2H), 3.45 (s, 1H), 3.80 (s, 3H), 3.95 (q, *J* = 7.36, 2H), 7.2-7.8 (m, *J* = 7.86, 4H), 8.50 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 168.52, 164.23, 132.74, 122-128.70, 68.12, 48.56, 33.78, 25.04, 33.12,13.98,12.56; MS: *m/z* 501($M+H^+$). Anal. Calcd for $C_{23}H_{28}N_6O_5S$: C, 55.19; H, 5.64; N, 16.79. Found: C, 55.17; H, 5.65; N, 16.75%.

5-[2-Ethoxy)-5-(1, 2, 3, 4,-tetrahydro-1*H*-1, 4-diazepine-5,7-dione-6-sulphonyl)-phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5e. m.p. 137°C, yield 78%; IR (KBr): 3265, 3015, 2895, 1265, 1035, 1355, 1125, 1698, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.05 (t, *J* = 8.25, 3H), 1.62 (m, *J* = 7.88, 2H), 1.80 (t, *J* = 7.45, 3H), 2.54 (t, *J* = 7.85, 2H), 2.80 (s, 4H), 3.40 (s, 1H), 3.80 (s, 3H), 4.05 (q, *J* = 8.25, 2H), 7.2-7.8 (m, *J* =7.98, 4H), 8.55 (s,1H); ^{13}C NMR ($CDCl_3$): δ 168.56, 163.52, 132.36, 123-127.50,65.15, 48.25, 33.94, 31.59, 24.90, 13.56, 12.98; MS: *m/z* 503($M+H^+$). Anal. Calcd for $C_{22}H_{26}N_6O_6S$: C, 52.59; H, 5.21; N, 16.72. Found: C, 52.55; H, 5.23; N, 16.74%.

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