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Synthesis, antimicrobial and antifungal activities of novel 1H-1,4-diazepines containing pyrazolopyrimidinone moiety

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Abstract. Acylation of 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo [4,3-d) pyrimidin-7-one **1** with chloroacetylchloride in the presence of anyhydrous aluminium chloride affords 5-[(5-chloroacetyl-2-ethoxy)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo [4,3-d] pyrimidin-7-one **2**. The compound **2** condensed with various β-diketones/β-ketoesters compound, to obtain new β-diketones/β-ketoesters **4a–i** treated with ethylenediamine (EDA) gives 1H-1,4-diazepines. The compounds **5a–i** has been screened for antimicrobial, antifungal and anthelmintic activities.

Keywords. 1,4-Diazepines; β-diketones/β-ketoesters; *p*-toluenesulfonic acid; pyrazolo pyrimidinones.

1. Introduction

The development of new approaches for the construction of number of heterocycle continues to be essential for accessing natural products and their structural analogues. Among them, 1*H*-1,4-diazepines derivatives scaffolds over the years have gained an ongoing interest for biological activities as anti-cancer,[1,2] anti-bacterial,[3] psychotropics,[4] anti-convulsant,[5] anti-viral,[6] and herbicidal.[7] Substituted 1,4-diazepines and their derivatives possess anti-HIV activity.[8] They also showed platelet activating factor (PAF) antagonistic[9] and serotoninergic S_3 antagonistic[10,11] activities.

A variety of reagent such as $NaBH_4$, Al_2O_3–P_2O_5, MgO–$POCl_3$, $Yb(OTf)_3$ and glacial acetic acid[12,13] and SiO_2-Cl/wet SiO_2[14] and microwave irradiation[15] are used for the synthesis of 1*H*-1,4-diazepines. However, many of these methods involve the use of strong acids, high temperature conditions and extended reaction time and also entail several side reactions resulting in low yield in products. One to their wide range of biological, industrial and synthetic applications, the synthesis of 1*H*-1,4-diazepines has recently received renewed interest of researchers for the discovery of improved protocols and still awaits further development towards high yielding approaches.

We reckoned that *p*-toluene sulphonic acid/celite might promote the synthesis of diazepines as well. In the course of our investigations we found that *p*-toluene sulphonic acid/celite was used for the synthesis of 1,5-benzodiazepines[16] and phosphonates.[17]

We are interested to synthesis pyrazolo [4,3-d] pyrimidine-7-one containing 1,4-diazepines due to pyrazolopyrimidinones are potent and selective inhibitors of type 5 cyclic gaunosine-3′,5′-monophosphate phosphodiesterase (CGMP) PDE-5[18,19] which have utility in the treatment of male erectile dysfunction (MED)[20] and female sexual dysfuction (FSD). They also find use in the treatment of impotence, one of male sexual dysfunction with the reduced side effects.[21]

2. Experimental

2.1 *General*

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 spectro-meter 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 $CDCl_3$ using as solvent and TMS as an internal standard and mass spectra on a LCMS instrument. The purity of the newly synthesized compounds was checked by TLC. Satisfactory C, H, N analyses were obtained for all the compounds.

*For correspondence

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

To a solution of 5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo [4,3-d] pyrimidin-7-one (3·12 g, 0·01 m) in carbon tetrachloride (150 ml) was added anhydrous aluminium chloride (3·50 g, 0·03 m) under stirring. Chloroacetyl chloride (7·9 ml, 0·1 m) was added drop-wise at such a rate that the temperature was maintained below 5°C. After refluxing for 4 h, the mixture was poured into 1M hydrochloric acid (200 ml) and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$. To the water layer was added hydrochloric acid until the solution showed neutral and then extracted with CH_2Cl_2. The combined organic layer were dried (Mg_2SO_4) and concentrated in vacuo. A solid compound was obtained which was crystallized from benzene. Purity of the compound was checked with TLC using 7 : 2 : 1 (benzene : ethanol : ammonia) upper layer as mobile phase. (yield 3·9 g, 78%).

2.3 *Synthesis of 5-[2-Ethoxy-5-(1,3-dimethyl/1,3-diphenyl/1-phenyl-3-methyl,1-ethoxy-3-methyl,1,3-diethoxy,1-ethoxy-3-propyl,1-ethoxy-3-isopropyl, 1-ethoxy-3-furnyl, 1-ethoxy-3-(2-methylbenzene) propane-1,3-dione-2-acetyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one* **(4a–i)**

Sodium methoxide (0·54 g, 0·01 mol) and 1,3-diketones/1,3-ketoesters (0·01 mol) were placed in a dry round bottom flask and stirred for 1 h on a magnetic stirrer at a temperature of 50°C, to obtain the sodium salt of 1,3-diketones/1,3-ketoesters. The acetyl chloride derivative **2** (3·885 g, 0·01 mol) was added followed by dry toluene sufficient as solvent to effect proper stirring of the reaction mass. The reaction mixture was heated for 18 h at 80°C with stirring. The progress of the reaction was monitored through TLC. After the reaction was complete, the reaction mixture was cooled and toluene was removed under reduced pressure. The reaction mixture was extracted with chloroform (4 × 50 ml). The chloroform layer was washed with water and dried with anhydrous sodium sulphate. Chloroform was evaporated to get solid compound. The crude residue was purified through column chromatography. It was crystallized with chloroform and ethyl acetate. Purity of the compound was checked through TLC using 7 : 2 : 1 (benzene: ethanol: ammonia) upper layer as mobile phase (yield 62·5–78·3%).

2.4 *Synthesis of 1H-1,4-diazepines* **(5a–i)**

1,3-Diketones/1,3-ketoesters **4a–i** (0·01 mol) and *p*-toluenesulfonic acid/celite (prepared by adding *p*-toluenesulfonic acid (2 g) and celite (2 g) in acetone, stirred for 0·5 h on magnetic stirrer and then acetone was removed by vacuum) mixed in mortar for 10 min. To the aforesaid mixture taken in conical flask and ethylenediamine (0·01 mol), heated on water bath at 60°C for 30 min. The reaction mixture was washed with dichloromethane (200 mL), dried over (Na_2SO_4), and the solvent was evaporated to give the crude products. The crude products washed with ether to remove unreacted dicarbonyl compounds. The crude product was recrystallized from pet ether: ethyl acetate (1 : 1). Purity of the compound was checked through TLC using 7 : 2 : 1 (benzene : ethanol : ammonia) upper layer as mobile phase.

2.5 *Spectral data*

2.5a *5-[2-Ethoxy-5-(5,7-dimethyl-2,3-dihydro-1H-1,4-diazepine-6-acetyl)-phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one* **(5a)**: Crystalline solid, m.p.: 152°C; yield: 80·8%; IR (KBr) ν_{max}: 3320, 3130, 3050, 2915, 1730, 1600, 1245, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1·02 (*t*, *J* = 7·97, 3H), 1·55–1·60 (*m*, 2H), 1·64 (*t*, *J* = 6·95, 3H), 2·50 (*s*, 6H), 2·65 (*t*, *J* = 7·58, 2H), 3·23 (*d*, *J* = 7·79, 2H), 3·80 (*s*, 3H), 4·42 (*q*, *J* = 8·05, 2H), 5·25 (*t*, *J* = 7·85, 1H), 8·73 (*s*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160·65, 149·93, 75·37, 67·88, 53·26, 40·39, 15·87, 14·72; Anal. Calcd. for $C_{26}H_{32}N_6O_3$: C, 65·53; H, 6·77; N, 17·63%. Found: C, 65·55; H, 6·73; N, 17·60%. MS (APCI): 477·25 ($M + H^+$).

2.5b *5-2-Ethoxy-5-[5,7-diphenyl-2,3-dihydro-1H-1,4-diazepine-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one* **(5b)**: m.p.: 155°C; yield: 75%; IR (KBr) ν_{max}: 3310, 3100, 3020, 2960, 1710, 1605, 1250, 1025 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$): δ 1·02 (*t*, *J* = 7·93, 3H), 1·55–1·60 (*m*, 2H), 1·57 (*t*, *J* = 7·56, 3H), 2·65 (*t*, *J* = 8·51, 2H), 3·44 (*d*, *J* = 7·48, 2H), 3·80 (*s*, 3H), 4·42 (*q*, *J* = 7·58, 2H), 5·25 (*t*, *J* = 8·02, 1H), 8·80 (*s*, 3H); ^{13}C NMR(75 MHz, $CDCl_3$): δ

160·64, 149·95, 75·37, 67·84, 53·25, 40·34, 15·82, 14·76; Anal. Calcd. for $C_{36}H_{36}N_6O_3$: C, 71·98; H, 6·04; N, 13·99%. Found: C, 71·96; H, 6·01; N, 13·95%; MS (APCI): 601·28 ($M + H^+$).

2.5c *5-[2-Ethoxy-5-(5-phenyl-7-methyl-2,3-dihydro-1H-1,4-diazepine-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one* (**5c**): m.p.: 175°C, yield: 73%; IR (KBr) ν_{max}: 3325, 3130, 3050, 2930, 1655, 1610, 1245, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1·02 (*t*, J = 7·55, 3H), 1·55–1·60 (*m*, 2H), 1·57 (*t*, J = 7·98, 3H), 2·65 (*t*, J = 8·11, 2H), 4·42 (*q*, J = 7·85, 2H), 3·43 (*d*, J = 7·56, 2H), 3·80 (*s*, 3H), 5·25 (*t*, J = 8·58, 1H), 8·70 (*s*, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164·6, 160·690, 65·11, 33·74, 24·95, 23·39, 15·65, 13·67; Anal. Calcd. for $C_{31}H_{34}N_6O_3$: C, 69·12; H, 6·36; N, 15·60%. Found: C, 69·10; H, 6·33; N, 15·64%. MS (APCI): 539·50 ($M + H^+$).

2.5d *5-[2-Ethoxy-5-(5-methyl-2,3-dihydro-1H-1,4-diazepine-7-one-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo {4,3-d}pyrimidin-7-one* (**5d**): m.p.: 145°C; yield: 71·3%; IR (KBr) ν_{max}: cm^{-1} 3300, 3120, 3030, 2950, 1720, 1580, 1260, 1020 ^1H NMR (300 MHz, $CDCl_3$): δ 1·02 (*t*, J = 7·45, 3H), 1·55–1·62 (*m*, 2H), 2H), 1·57 (*t*, J = 7·47, 3H), 2·65 (*t*, J = 7·48, 2·40 (*s*, 3H), 3·25 (*d*, J = 8·45, 2H), 3·80 (*s*, 3H), 4·42 (*q*, J = 7·95, 2H), 5·30 (*t*, J = 8·06, 1H), 8·75 (*s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157·23, 149·95, 75·32, 68·39, 54·34, 40·37, 29·50, 15·84, 14·67. Anal. Calcd. for $C_{25}H_{30}N_6O_4$: C, 62·75; H, 6·32; N, 17·56%. Found: C, 62·71; H, 6·30; N, 17·53%. MS (APCI): 479·23 ($M + H^+$).

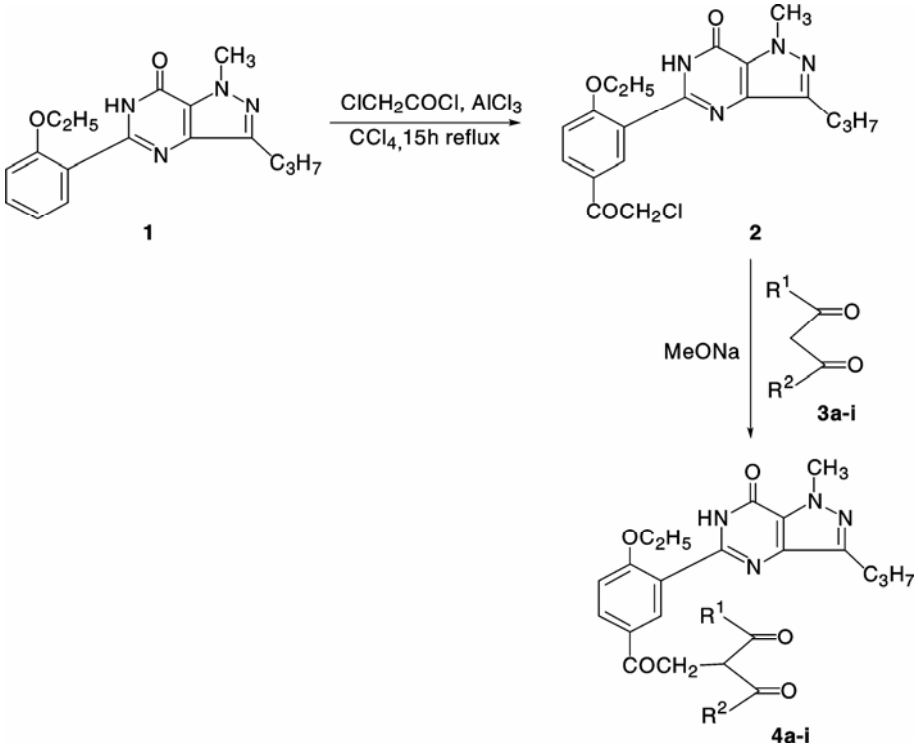
2.5e *5-[2-Ethoxy-5-(1,2,3,4-tetrahydro-1H-1,4-diazepine-5,7-dione-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo {4,3-d}pyrimidin-7-one* (**5e**): m.p.: 164°C, yield: 79·4%; IR (KBr) ν_{max}: 3300, 3120, 3060, 2930, 1720, 1600, 1240, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1·02 (*t*, J = 7·48, 3H), 1·55–1·61 (*m*, 2H), 1·62 (*t*, J = 7·32, 3H), 2·65 (*t*, J = 8·23, 2H), 3·25 (*d*, J = 7·15, 2H), 3·80 (*s*, 3H), 4·44 (*q*, J = 8·58, 2H), 5·30 (*t*, J = 7·86, 1H) 8·75 (*s*, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165·51, 157·12, 149·84, 75·35, 68·38, 54·88, 40·34, 15·87, 14·67. Anal. Calcd. for $C_{24}H_{28}N_6O_5$: C, 59·99; H, 5·87; N, 17·49%. Found: C, 59·95; H, 5·85; N, 17·50%. MS (APCI): 481·12 ($M + H^+$).

2.5f *5-[2-Ethoxy-5-(5-propyl-2,3-dihydro-1H-1,4-diazepine-7-one-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo {4,3-d}pyrimidin-7-one* (**5f**): m.p.: 168°C; yield: 72·5%; IR (KBr) ν_{max}: cm^{-1} 3305, 3115, 3025, 2930, 1725, 1585, 1255, 1025 ^1H NMR (300 MHz, $CDCl_3$): δ 0·96 (*t*, J = 7·30, 3H), 1·02 (*t*, J = 7·15, 3H), 1·55–1·62 (*m*, 4H), 2H), 1·73 (*t*, J = 7·47, 3H), 2·60 (*t*, J = 7·50, 2H) 2·45 (*s*, 3H), 3·20 (*d*, J = 8·40, 2H), 3·85 (*s*, 3H), 4·42 (*q*, J = 7·90, 2H), 5·30 (*t*, J = 8·05, 1H), 8·75 (*s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164·50, 158·23, 147·65, 74·50, 68·39, 54·34, 40·37, 29·50, 23·70 15·84, 14·67; Anal. Calcd. for $C_{27}H_{34}N_6O_4$: C, 67·13; H, 6·18; N, 15·15%. Found: C, 62·11; H, 6·20; N, 17·19%. MS (APCI): 506·60 ($M + H^+$).

2.5g *5-[2-Ethoxy-5-(5-isopropyl-2,3-dihydro-1H-1,4-diazepine-7-one-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo {4,3-d}pyrimidin-7-one* (**5g**): m.p.: 160°C; yield: 68·70%; IR (KBr) ν_{max}: cm^{-1} 3320, 3125, 3040, 2955, 1725, 1580, 1260, 1020 ^1H NMR (300 MHz, $CDCl_3$): δ 0·96 (*t*, J = 7.30, 6H), 1·05 (*t*, J = 7·40, 3H), 1·55–1·60 (*m*, 2H), 1·57 (*t*, J = 7·47, 3H), 1·72 (*m*, 1H), 2·60 (*t*, J = 7·40, 2H), 2·45 (*s*, 3H), 3·20 (*d*, J = 8·50, 2H), 3·85 (*s*, 3H), 4·42 (*q*, J = 7·66, 2H), 5·30 (*t*, J = 8·05, 1H), 8·65 (*s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157·25, 149·87, 75·90, 68·20, 54·23, 47·56, 40·37, 29·50, 15·84, 14·67; Anal. Calcd. for $C_{27}H_{34}N_6O_4$: C, 67·13; H, 6·18; N, 15·15%. Found: C, 62·11; H, 6·20; N, 17·19%. MS (APCI): 506·60 ($M + H^+$). MS (APCI): 506·60 ($M + H^+$).

2.5h *5-[2-Ethoxy-5-(5-furyl-2,3-dihydro-1H-1,4-diazepine-7-one-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo {4,3-d}pyrimidin-7-one* (**5h**): m.p.: 175°C; yield: 75·5%; IR (KBr) ν_{max}: cm^{-1} 3300, 3120, 3030, 2950, 1720, 1580, 1260, 1020 ^1H NMR (300 MHz, $CDCl_3$): δ 1·05 (*t*, J = 7·25, 3H), 1·55–1·62 (*m*, 2H), 1·57 (*t*, J = 7·15, 3H), 2·60 (*t*, J = 7·25, 2H), 2·40 (*s*, 3H), 3·25 (*d*, J = 8·45, 2H), 3·80 (*s*, 3H), 4·42 (*q*, J = 7·95, 2H), 5·30 (*t*, J = 8·06, 1H), 8·75 (*s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164·70, 158·25, 150·65, 143·67, 110·54, 75·32, 67·35, 55·40, 40·37, 30·90, 29·50, 15·84, 14·67; Anal. Calcd. for $C_{28}H_{30}N_6O_5$: C, 63·38; H, 5·70; N, 15·84%. Found: C, 63·40; H, 5·75; N, 15·85%. MS (APCI): 530·58 ($M + H^+$).

2.5i *5-[2-Ethoxy-5-(5-(2-methylbenzene)-2,3-dihydro-1H-1,4-diazepine-7-one-6-acetyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo {4,3-d}*



Scheme 1.

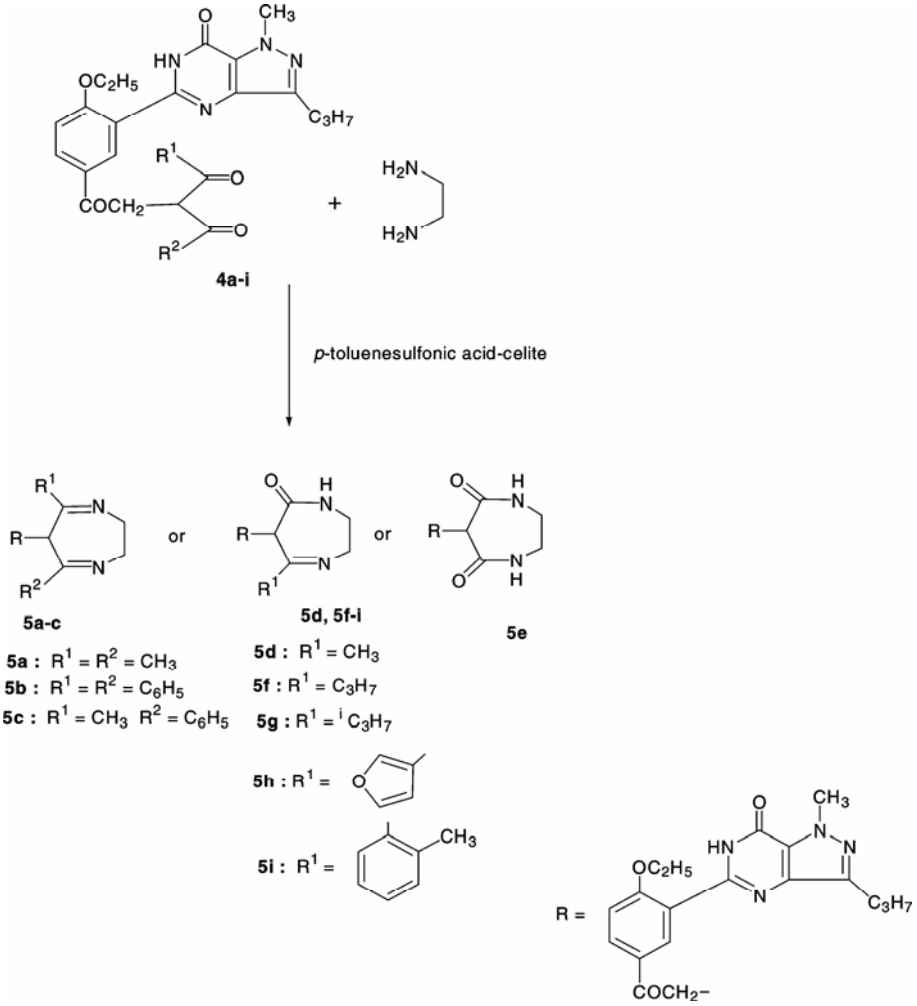
Table 1. Physical and analytical data of compounds **4a–i**.

Compound	R^1	R^2	Melting point (°C)	Yield (%)	Molecular formula
4a	CH_3	CH_3	142	78·3	$C_{24}H_{28}N_4O_5$
4b	C_6H_5	C_6H_5	165	72·1	$C_{34}H_{32}N_4O_5$
4c	CH_3	C_6H_5	158	70·3	$C_{29}H_{30}N_4O_5$
4d	CH_3	OC_2H_5	146	73·8	$C_{25}H_{30}N_4O_6$
4e	OC_2H_5	OC_2H_5	152	74·9	$C_{26}H_{32}N_4O_7$
4f	C_3H_7	OC_2H_5	160	73·4	$C_{27}H_{34}N_4O_6$
4g	$^iC_3H_7$	OC_2H_5	154	62·5	$C_{27}H_{34}N_4O_6$
4h		OC_2H_5	167	68·5	$C_{28}H_{30}N_4O_7$
4i		OC_2H_5	172	72·6	$C_{31}H_{34}N_4O_6$

pyrimidin-7-one (**5i**)*:* m.p.: 183°C; yield: 65·8%; IR (KBr) ν_{max}: cm^{-1} 3305, 3090, 3015, 2890, 1710, 1580, 1260, 1025 ^1H NMR (300 MHz, $CDCl_3$): δ 1·02 (*t*, $J = 7·23$, 3H), 1·55–1·62 (*m*, 2H), 1·60 (*t*, $J = 7·47$, 3H), 2·45 (*t*, $J = 6·90$, 2H), 2·40 (*s*, 3H), 3·20 (*d*, $J = 7·60$, 2H), 3·80 (*s*, 3H), 4·45 (*q*, $J = 8·05$, 2H), 5·35 (*t*, $J = 6·80$, 1H), 7·17–7·58 (*m*, 5H), 8·70 (*s*, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157·23, 149·95, 125–138, 76·43, 67·90, 55·87, 41·47, 28·60, 15·85, 14·65; Anal. Calcd. for $C_{31}H_{34}N_6O_4$: C, 67·13; H, 6·18; N, 15·15%. Found: C, 67·15; H, 6·20; N, 15·20%. MS (APCI): 554·64 ($M + H^+$).

3. Antimicrobial and anthelmintic activities of compounds 5a–i

The newly synthesized diazepine compounds 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.[22,23] Crofloxin 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



Scheme 2.

Table 2. Antimicrobial and anthelmintic activities of compounds **5a–i**.

	Antibacterial activity zone of inhibition (in mm)		Antifungal activity zone of inhibition (in mm)		Anthelmintic activity (in min)	
Compd.	*S. aureus*	*K. pneumoniae*	*A. niger*	*C. albicans*	Paralysis	Death
5a	14	17	15	13	91	96
5b	16	19	11	20	85	113
5c	23	26	21	25	89	117
5d	11	15	16	12	102	124
5e	16	13	14	18	100	126
5f	09	07	10	15	93	112
5g	17	13	11	09	78	106
5h	15	10	17	13	98	122
5i	21	19	19	16	93	94
Std	24	26	22	24	100	125

on earthworms *Pherituma posthuma*, by a technique as described by Bagavant *et al*[24] with modification. Piperazine citrate was used as standard drug. The results of antimicrobial and anthelmintic activity are reported in table 2. The compound **5c** exhibited antimicrobial and antifungal activities more than the standard drug but compounds **5d**, **5e** and **5h** showed significant anthelmintic activity.

From these results it is apparent that attempts to introduce functionality at R^1 and R^2, the group

resulted in significant increased antibacterial and antifungal activity due to its electron donating character but steric hindrance also play important role. Whereas diazepine-5,7-dione shows more anthelmintic activity than others due to more electronegativity of oxygen. Present studies have been carried out with an objective to prove the increased anthelmintic activity of diazepines with electron withdrawing group position at 5 and 7.

4. Results and discussion

5-(2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-d]pyrimidin-7-one was acylated with chloroacetyl chloride in the presence of anhydrous $AlCl_3$. This position more reaction than simple pyrazolopyrimin-7-one. Compound **2** was condensed with different β-diketones/β-ketoesters in the presence of sodium methoxide (scheme 1). The condensation of newly synthesized β-diketones/β-ketoesters **4a–i** with ethylene-diamine (EDA) in the presence of *p*-toluenesulfonic acid/celite, to obtain *1H*-1,4-diazepines **5a–i**.

5. Conclusion

In conclusion, we have synthesized various 1*H*-1,4-diazepines with good yields. The main advantage of this method is that reactions were found clean and had operational simplicity. Among the synthesized compounds evaluated **(5a–5i)**, compound **5c** exhibited antimicrobial and antifungal activities more than the standard drug but compounds **5d**, **5e** and **5h** showed significant anthelmintic activity. The results obtained from this study suggested that the above said compounds could be useful for searching newer antimicrobial, antifungal and anthelmintic molecules from synthesis methods.

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