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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological activity of novel 1*H*-1,4-diazepines containing benzene sulfonyl piperazine moiety

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Abstract The synthesis of biologically active 1*H*-1,4-diazepines **6a–e** in good yield, from the heterocyclization reaction of [N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl]-1,3-dialkyl/aryl propane-1,3-dione **5a–e** and ethylenediamine (EDA) in the presence of silica sulphuric acid (SSA) is described. The novel β-diketones/β-ketoesters **5a–e** were synthesized by the condensation reaction of [N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-1-bromopropane with various β-diketones/β-ketoesters **4a–e**. All structures of the newly synthesized compounds were elucidated by elemental analysis and spectral studies. The compounds **6a–e** have been screened for antimicrobial, antifungal and anthelmintic activity.

Keywords 1*H*-1,4-diazepines · β-Diketones/β-ketoesters · Piperazine · Silica sulphuric acid · Ethylenediamine · Biological activities

Introduction

The diverse biological activities of various derivatives of 1*H*-1,4-diazepine are well known. Some of the 1*H*-1,4-diazepine derivatives show interesting biological activities such as anticancer (Krezel *et al.*, 1999), antibacterial (Kumar and Joshi, 2009), psychotropics (Childress and Gluckman, 1964), anticonvulsant (Fiakpui *et al.*, 1993), antihistaminic (Guryn *et al.*, 1980), antiproliferative (Ramajayam *et al.*, 2007), anti-inflammatory (Stochla *et al.*, 1984), fungicidal and herbicidal (Tandon *et al.*, 2009). The anti-HIV activity of substituted 1*H*-1,4-diazepine and their derivatives is comparable to that of zidovuline (3′-azidothymidine, AZT), the well known anti-HIV drug (Görlitzer *et al.*, 1995). They also exhibit platelet-activating factor (PAF) antagonistic and serotoninergic S_3 antagonistic (Casals and Tenzel 1991; Fray *et al.*, 1995) activities.

1*H*-1,4-diazepine nucleus has been proved as a versatile system in medicinal chemistry. Furthermore, a number of established drug molecules like Brotizolam, Bunazosin, Dilazep, Etizolam, Homofenazine, Zometapine, Clotiazepam, Clozapine and Dibenzepine are accessible starting from the corresponding 1*H*-1,4-diazepines (Sternbach *et al.*, 1968). Research in this area is still very active and is directed towards the synthesis of potential bioactive 1*H*-1,4-diazepine with enhanced pharmacology activity.

Various methods are reported in literature for the synthesis *1H*-1,4-diazepines (El-Kashef *et al.*, 2007; Insuasty *et al.*, 2008; Lee and Kim, 2009; Mibu *et al.*, 2003; Raboisson *et al.*, 2005). However, these methods are associated with several drawbacks such as harsh reaction conditions, complex and tedious experimental procedures and low yields. In recent years, the use of organic–inorganic hybrid-immobilized solid support reagents have received great interest. Such reagents not only simplify the purification process, but also provide help in preventing the release of reaction residues into the environment (Wight and Davis, 2002). Furthermore, from the synthetic point of view, these reagents significantly reduce reaction time and make the workup easier. Recently, silica and sulphuric acid in dichloromethane have been reported for the oxathioacetalyzation of carbonyl compounds (Shirini *et al.*, 2009).

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The efficiency of silica sulphuric acid (SSA), under operationally simple conditions, has prompted us to explore the possibility of using this reagent for the synthesis of 1*H*-1,4-diazepines from the reaction of *β*-diketones/*β*-ketoesters and ethylenediamine (EDA).

In continuation of our ongoing research program to develop new reagents and synthetic procedure for the synthesis of novel heterocyclic compounds (Kumar and Joshi, 2007a, b, c, 2010), we report here a new convenient method for the synthesis of N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl containing 1*H*-1,4-diazepines due to their importance in medicinal chemistry (Lavecchia *et al.*, 2005; Kerns *et al.*, 2003a, b; Zhao *et al.*, 2006). To achieve this target, we had synthesized *β*-diketones/*β*-ketoesters **5a–e** which were condensed with EDA in presence of SSA, to obtain the corresponding substituted 1*H*-1,4-diazepines **6a–e** with high yields.

Results and discussion

Acetanilide was sulfonated with chlorosulfonic acid, to obtain 4-(acetylamino) benzene sulfonyl chloride **1**. This compound **1**, on condensation with piperazine in presence of pyridine and acetic anhydride yielded *N*-[4-(1-piperazinyl sulfonyl) phenyl] acetamide **2**. The condensation had an important role in this reaction. Pyridine, a weak base when used as a solvent for condensation was not sufficiently strong enough to cause the removal of proton as HCl. On the contrary when acetic anhydride and pyridine were used as solvent mixture it formed (*N*-acetyl pyridinium) complex, an electrophilic complex which facilitated the condensation to give desired product by removal of HCl. This is because acetate ion in this complex being a comparatively strong base helped in the removal of proton easily than pyridine alone. Then compound **2** on bromination with 1,3-dibromopropane in presence of ethanol, afforded [N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-1-bromopropane **3**. The condensation reaction of compound **3** with various *β*-diketones/*β*-ketoesters **4a–e** in the presence of sodium methoxide yielded corresponding substituted *β*-diketones/*β*-ketoesters **5a–e**. The compounds **5a–e** were characterized by elemental analysis and spectral studies (Tables 1, 2). Compounds **5a–e** on the reaction with EDA in the presence of SSA underwent dehydrative annulation to afford novel substituted 1*H*-1,4-diazepines **6a–e** (Scheme 1). SSA was prepared by reported method (Salehi *et al.*, 2006).

Antimicrobial, antifungal and anthelmintic activities of compounds 6a–e

The newly synthesized diazepine compounds **6a–e** have been screened for the antibacterial activity against *Staphylococcus aureus* and *Klebsiella pneumoniae* and antifungal activity against *Aspergillus niger* and *Candia albicans* by the cup-plate method (Saundane *et al.*, 1998). 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 as described by Bagavant *et al.* (1994) with slight modification. Piperazine citrate was used as standard drug. The values of antimicrobial and anthelmintic activity are terms of mean ± SEM of results done in triplicate, reported in Table 3. The compounds **6a–e** were exhibited normal antimicrobial and antifungal activities but showed significant anthelmintic activity due to presence of piperazine moiety.

From these results, it is apparent that attempts to introduce functionality methyl/phenyl at position 5 and 7 resulted in significantly increased antibacterial and antifungal activities due to its electron donating character but steric hindrance also played a major important role. The diazepine-5,7-dione showed more anthelmintic activity than others due to more electronegativity of oxygen. This result implies that the presence of electron withdrawing groups at position 5 and 7 of diazepines can increase anthelmintic activity.

Table 1 Physical and analytical data of compounds **5a–e**

Compd.	R^1	R^2	Melting point (°C)	Yield (%)	Molecular formula
5a	CH_3	CH_3	155	81.3	$C_{20}H_{29}N_3O_5S$
5b	C_6H_5	C_6H_5	183	76.2	$C_{30}H_{33}N_3O_5S$
5c	CH_3	C_6H_5	159	69.6	$C_{25}H_{31}N_3O_5S$
5d	CH_3	OC_2H_5	146	72.4	$C_{21}H_{31}N_3O_6S$
5e	OC_2H_5	OC_2H_5	152	67.7	$C_{22}H_{33}N_3O_7S$

Experimental section

General procedures

All the melting points were determined in open capillary tubes and are uncorrected. The purity of the newly synthesized compounds was checked by TLC on aluminium oxide 60 F_{254} plates (Merck) and spots were visualized by exposing the dry plates in iodine vapour. The IR spectra were recorded on a Nicolet-Magna-FT-IR-550 spectrometer in using KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were run on model DRX 300 at 300.13 and 75 MHz, respectively in $CDCl_3$ and mass spectra on a LCMS instrument. The elemental analysis (C, H, N) of compounds was performed on Carlo Erba-1108 element analyzer. Their

Table 2 Spectral data of synthesized compounds **5a–e**

Compd.	IR (λ_{max}/cm^{-1})	^{1}HNMR (δ/ppm)	^{13}CNMR (δ/ppm)
5a	3350, 3025, 2918, 1730, 1682, 1370, 1155	1.09 (q, 2H), 1.37 (t, 2H), 1.86 (s, 6H), 2.15 (s, 3H), 2.35 (t, 2H), 2.42–2.75 (complicate, 8H) 4.12 (m, 1H), 7.62–7.85 (m, 4H), 10. 38 (s, 1H)	17.5 (CH_3), 19.3, 24.9, 49.7 (CH_2–CH_2–CH_2–), 22.6 (CH_3), 47.5, 53.8 (N–CH_2–CH_2–N), 68.5 (CH), 120–125 (Ar–C), 169.7 (CONH), 193.7 (C=O)
5b	3345, 3017, 2915, 1735, 1680, 1370, 1145	1.10 (q, 2H), 1.42 (t, 2H), 2.13 (s, 3H), 2.40 (t, 2H), 2.38–2.73 (complicate, 8H) 4.14 (m, 1H), 7.62–7.85 (m, 14H), 10. 40 (s, 1H)	17.8 (CH_3), 19.4, 24.9, 49.5 (CH_2–CH_2–CH_2–), 47.4, 53.7 (N–CH_2–CH_2–N), 68.5 (CH), 120–129 (Ar–C), 168.9 (CONH), 194.3 (C=O)
5c	3350, 3020, 2915, 1736, 1680, 1370, 1155	1.13 (q, 2H), 1.38 (t, 2H), 1.95 (s, 3H), 2.18 (s, 3H), 2.35 (t, 2H), 2.42-2.75 (Complicate, 8H) 4.13 (m, 1H), 7.60-7.83 (m, 9H), 10. 42 (s, 1H)	18.3 (CH_3), 19.3, 24.9, 49.8 (CH_2-CH_2-CH_2-), 24.7 (CH_3), 47.5, 53.8 (N-CH_2-CH_2-N), 169.7 (CONH), 68.3 (CH), 121-129 (Ar–C), 193.5 (C=O)
5d	3350, 3025, 2907, 1730, 1680, 1370, 1150, 1105, 1245	1.15 (q, 2H), 1.36 (t, 3H), 1.49 (t, 2H), 2.07 (s, 3H), 2.15 (s, 3H), 2.36 (t, 2H), 2.40-2.78 (complicate, 8H), 4.05 (q, 2H), 4.15 (m, 1H), 7.62–7.85 (m, 4H), 10. 23 (s, 1H)	17.5 (CH_3), 19.3, 24.9, 49.7 (CH_2–CH_2–CH_2–), 22.6 (CH_3), 47.5, 53.8 (N–CH_2–CH_2–N), 59.5 (O–CH2–), 68.5(CH), 168.9 (CONH), 122–128 (Ar–C), 194.3 (C=O)
5e	3350, 3020, 2915, 1780, 1660, 1370, 1150, 1120, 1245	1.10 (q, 2H), 1.30 (t, 6H), 1.40 (t, 2H), 2.10 (s, 3H), 2.35 (t, 2H), 2.42–2.75 (complicate, 8H), 3.85 (q, 4H), 4.12 (m, 1H), 7.62-7.85 (m, 4H), 10. 38 (s, 1H)	17.5 (CH_3), 19.3, 24.9, 49.7 (CH_2–CH_2–CH_2–), 47.5, 53.8 (N–CH_2–CH_2–N), 59.3 (O–CH2–), 68.5 (CH), 169.4 (CONH), 124–129 (Ar–C), 194.8 (C=O)

results were found to be in good agreement with the calculated values.

Synthesis of [N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl]-1,3-dimethyl/1-methyl-3-phenyl/1,3-diphenyl/1-methyl-3-ethoxy/1,3-diethoxy propane-1,3-dione **5a–e**

Sodium methoxide (0.54 g, 0.01 mol) and β-diketones/β-ketoester (0.01 mol) were placed in a dried round-bottom flask and stirred for 1 h on a magnetic stirrer at 50°C, after which a creamy mass was obtained. The N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-1-bromopropane **3** (3.9 g, 0.01 mol) was taken in dry toluene and added drop by drop in above said reaction mass. The reaction mixture was heated for 7 h at 80°C with stirring. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and toluene was removed. The reaction mixture was extracted using chloroform and washed with water.

The chloroform layer was dried using anhydrous sodium sulphate and distilled to yields the 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. Purity of the compound was checked by TLC on aluminium oxide 60 F_{254} plates (Merck) in a 7:2:1 (benzene:ethanol:ammonia) upper layer using as a mobile phase (Table 2).

Synthesis of 1*H*-1,4-diazepine derivatives **6a–e**: general procedure

An equimolar ratio of β-diketones/β-ketoesters (0.01 M) **5a–e**, and EDA (0.01 M) in ethyl acetate (50 ml) in the presence of SSA (0.01 M) was stirred 50°C for 2 h. The progress of reaction was monitored by TLC using 7:2:1 (benzene:ethanol:ammonia) upper layer as mobile phase. Upon completion of reaction, the mixture was extracted with ethyl acetate (2 × 25 ml), and the solvent was removed. The crude product was washed with dry ether and 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.

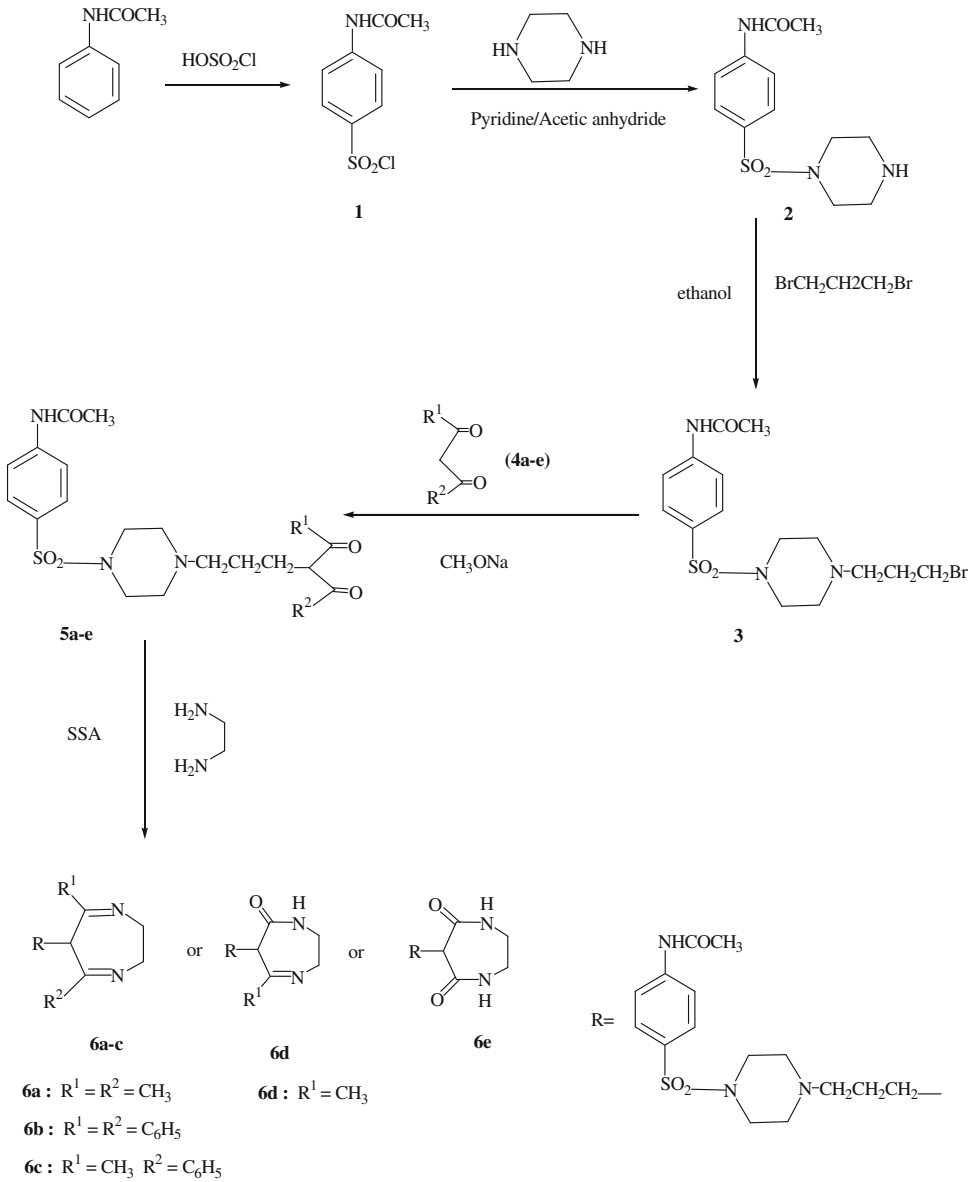
6-[N^4-(4-Acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl]-5,7-dimethyl-2,3-dihydro-1H-1,4-diazepine ***6a***

M.p. 145°C, yield 75%; IR (KBr): 3315 (N–H), 3010 (Ar–H), 2930 (C–H), 1700 (C=O), 1570 (C=N), 1345, 1140 ($-SO_2$) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.09 (quintet, $J = 7.46$, 2H, $CH_2\mathbf{CH_2}CH_2$), 1.15 (triplet, $J = 7.50$, 2H, $\mathbf{CH_2}CH_2CH_2$), 2.07 (s, 6H,CH_3–C=N), 2.16 (s, 3H, CH_3), 2.30 (triplet, $J = 7.45$, 2H, $CH_2CH_2\mathbf{CH_2}$–N), 3.14 (complicated s, 4H,N–CH_2–CH_2–N), 3.45 (s, 1H, =CH–), 7.65–7.80 (m, 4H, Ar–H), 8.50 (s,1H, N–H); ^{13}C NMR ($CDCl_3$): δ 10.45, 16.45, 17.63, 28.20, 47.30, 48.55, 53.40, 124–128, 134.90, 164.60, 168.20; MS (m/z): 448 ($M + H^+$); Anal. Calcd for $C_{22}H_{33}N_5O_3S$: C, 59.06; H, 7.38; N, 15.66. Found: C 58.95, H 7.13, N, 15.45.

6-[N^4-(4-Acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl]-5,7-diphenyl-2,3-dihydro-1H-1,4-diazepine ***6b***

M.p. 167°C, yield 73%; IR (KBr): 3325 (N–H), 3010 (Ar–H), 2915 (C–H), 1705 (C=O), 1580 (C=N), 1355, 1145 ($-SO_2$) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.10(quintet, $J = 7.03$, 2H, $CH_2\mathbf{CH_2}CH_2$), 1.13 (triplet, $J = 7.25$, 2H, $\mathbf{CH_2}CH_2CH_2$), 2.15 (s, 3H, CH_3), 2.32 (triplet, $J = 6.85$, 2H, $CH_2CH_2\mathbf{CH_2}$–N), 3.15 (complicated s, 4H,N–CH_2–

Scheme 1 Synthesis of 1*H*-1, 4-diazepines **6a–e**



CH_2–N), 3.43 (s, 1H, =CH–), 7.65–7.80 (m, 14H, Ar–H), 8.52 (s, 1H, N–H); ^{13}C NMR ($CDCl_3$): δ 10.65, 17.05, 17.79, 29.10, 47.35, 48.50, 52.93, 124–128, 134.96, 166.73, 168.85; MS (m/z): 572 ($M + H^+$); Anal. Calcd for $C_{32}H_{37}N_5O_3S$: C, 67.22; H, 6.52; N, 12.25. Found: C, 67.14; H, 6.50; N, 12.30.

6-[N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl]-5-methyl-7-phenyl-2,3-dihydro-1H-1,4-diazepine ***6c***

M.p. 147°C, yield 69%; IR (KBr): 3320 (N–H), 3010 (Ar–H), 2935 (C–H), 1709 (C=O), 1585 (C=N), 1345, 1125 ($-SO_2$) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.09 (quintet, $J = 6.86$, 2H, $CH_2\mathbf{CH_2}CH_2$), 1.12 (triplet, $J = 7.05$, 2H, $\mathbf{CH_2}CH_2CH_2$), 2.07 (s, 3H, CH_3–C=N), 2.10 (s, 3H, CH_3), 2.30 (triplet, $J = 6.85$, 2H, $CH_2CH_2\mathbf{CH_2}$–N), 3.13 (complicated s, 4H, N–CH_2–CH_2–N), 3.44 (s, 1H, =CH–), 7.61–7.80 (m, 9H, Ar–H), 8.55 (s, 1H, N–H); ^{13}C NMR ($CDCl_3$): δ 11.37, 17.85, 18.53, 28.55, 46.85, 49.05, 55.60, 123–129, 135.70, 169.45, 168.20; MS (m/z): 510($M + H^+$); Anal. Calcd for $C_{27}H_{35}N_5O_3S$: C, 63.63; H, 6.92; N, 13.74. Found: C, 63.65; H, 6.87; N, 13.70.

6-[N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl]-7-methyl-2,3,4,6-tetrahydro-1H-1,4-diazepine-5-one ***6d***

M.p. 155°C, yield 72%; IR (KBr): 3325 (N–H), 3028 (Ar–H), 2895 (C–H), 1735 (C=O), 1585 (C=N), 1335, 1120 ($-SO_2$) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.09 (quintet, $J = 6.46$, 2H, $CH_2\mathbf{CH_2}CH_2$), 1.12 (triplet, $J = 6.46$, 2H,

Table 3 Antimicrobial, antifungal and anthelmintic activities of compounds **6a–e**

Compd.	Antibacterial activity zone of inhibition in mm*		Antifungal activity zone of inhibition in mm*		Anthelmintic activity in min.*	
	S. aureus	*K. pneumoniae*	*A. niger*	*C. albicans*	Paralysis	Death
6a	19 ± 0.57	21 ± 0.65	19 ± 0.58	21 ± 0.58	92 ± 0.65	103 ± 0.48
6b	17 ± 0.48	19 ± 0.57	18 ± 0.54	19 ± 0.57	93 ± 0.69	110 ± 0.57
6c	20 ± 0.65	19 ± 0.85	20 ± 0.57	20 ± 0.54	91 ± 0.57	111 ± 0.54
6d	16 ± 0.75	17 ± 0.54	17 ± 0.55	16 ± 0.48	102 ± 0.85	119 ± 0.48
6e	13 ± 0.58	15 ± 0.59	15 ± 0.57	13 ± 0.80	103 ± 0.56	122 ± 0.65
Ciprofloxin	24 ± 0.57	26 ± 0.24	–	–	–	–
Ciclopirox	–	–	22 ± 0.44	24 ± 0.74	–	–
Olamine Piperazine citrate	–	–	–	–	100 ± 0.57	125 ± 0.57

* Values are in terms of mean ± SEM of results done in triplicate

CH_2 CH_2CH_2), 2.32 (triplet, $J = 6.46$, 2H, CH_2CH_2**CH_2**–N), 2.15 (s, 3H, CH_3), 2.07 (s, 3H, CH_3–C=N), 3.14 (complicated s, 4H, N–CH_2–CH_2–N), 3.43 (s, 1H, =CH–), 7.61–7.83 (m, 4H, Ar–H), 8.76 (s, 1H, N–H), 10.23 (s, 1H, N–H); ^{13}C NMR ($CDCl_3$): δ 10.55, 17.13, 18.75, 29.15, 46.83, 49.55, 57.60, 121–127, 135.68, 164.55, 169.10, 193.80; MS (m/z): 450 ($M + H^+$); Anal. Calcd for $C_{21}H_{31}N_5O_4S$: C, 56.10; H, 6.95; N, 15.58. Found: C, 56.15; H, 6.95; N, 15.60.

6-[N^4-(4-acetylamino) benzene sulfonyl) piperazinyl-N^1-propyl]-7-methyl-2,3,4,6-tetrahydro-1H-1,4-diazepine-5, 7-dione ***6e***

M.p. 167°C, yield 76%; IR (KBr): 3323 (N–H), 3015 (Ar–H), 2915 (C–H), 1735 (C=O), 1573 (C=N), 1355, 1123 ($-SO_2$) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.10 (quintet, $J = 6.76$, 2H, CH_2**CH_2**CH_2), 1.12 (triplet, $J = 7.33$, 2H, **CH_2**CH_2CH_2), 2.13 (s, 3H, CH_3), 2.32 (triplet, $J = 8.45$, 2H, CH_2CH_2**CH_2**–N), 3.15 (complicated s, 4H, N–CH_2–CH_2–N), 3.44 (s, 1H, =CH–), 7.50–7.75 (m, 4H, Ar–H), 8.53 (s, 1H, N–H), 10.71 (s, 2H, N–H); ^{13}C NMR ($CDCl_3$): δ 10.55, 15.95, 18.33, 28.15, 47.20, 48.65, 53.40, 125–128, 134.70, 164.45, 168.20, 198.10; MS (m/z): 452 ($M + H^+$); Anal. Calcd for $C_{20}H_{29}N_5O_5S$: C, 53.20; H, 6.47; N, 15.51. Found: C, 53.15; H, 6.50; N, 15.50.

Conclusion

In conclusion, this new method for the synthesis of 1*H*-1, 4-diazepine derivatives using SSA offers significant improvement over existing method. Also, this simple and reproducible method affords various 1*H*-1,4-diazepines with short reaction times, excellent yields and without the formation of undesirable by products. Among the synthesized compounds evaluated (**6a–e**), compounds **6a–c** exhibited antimicrobial and antifungal activities in comparison the standard drug, but compounds **6d** and **6e** showed significant anthelmintic activity. More extensive study is needed to confirm the preliminary results and mode of action studies are required to be able to optimize the effectiveness of this series of compounds **6a–e**.

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