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Synthesis and Antibacterial Activity of Some Novel 1,4-Diazepines from β-Diketones/ β -Ketoesters of 4-Acetylaminobenzene Sulphonyl Chloride

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***Abstract*- A series of novel 1,4- diazepines have been synthesized from β-diketones / β-ketoesters of 4-acetylaminobenzene sulphonyl chloride. Desired compounds were prepared by the reaction of novel β-diketone / β-ketoester derivatives of [N4-(4-acetylamino) benzene sulphonyl piperazinyl- N1-1-bromopropane] with ethylenediamine to get 1, 4-dizapines. All the newly synthesized compounds were characterized with IR and 1H NMR studies.**

***Keywords*- β-diketone, β-ketoester, diazepines, ethylenediamine, antibacterial activities**

I. INTRODUCTION

The quest for a more reliable and suitable drug is always fascinating and challenging. A number of drugs containing heterocyclic and a combinations of different heterocyclic have been used in now a day. 4-acetyleaminobenzene sulphonyl chloride nucleus is well known for its antibacterial [1], antifungal [2], antitumer [3], neuroprotective and antiproliferative properties [4]. Sulfonamide derivatives have possessed pharmacological properties such as antibacterial & antifungal [5], antitumor [6] and antiviral [7,8] activities and other benzene sulfonamide derivative such as sildenafil 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1Hpyrazolo[4,3-d] pyrimidin-5-yl] phenylsulf onyl]-4-methylpiperazine is used for the treatment of sexual dysfunction. Various derivatives of piperazine have been found useful as brain protecting [9], in the diagnosis of schizophrenia [10], neurokinine [11,12], serotonin antagonist receptor [13-15], heart muscle receptor [16], and cholesterol reducing agents [17], HIV-I inhibitors [18-19], dopamine transporter [20-22] and sorbitol dehydrogenase inhibitor [23-25]. By the condensation of 4-acetylamino benzenesulphonyl chloride with piperazine a large number of molecules were obtained, which possess various biological properties like anti-inflammatory [26], antibiotic [27], anticancer [28], and in the treatment of Erectile Dysfunction [29]. β-diketones have also been shown to have a wide assortment of pharmacological activities like antibacterial [30], antiviral [31], systematic insecticidal [32], antioxidant [33] and prophylactic antitumor [34]. In addition, β-diketones have also been used as an antisunscreen agent that filters U.V rays to protect skin [35]. Nevertheless, β-diketones have examined as breast cancer chemopreventive blocking agent [36], antiestrogenic [37] and anticarcinogenic [38] agent. Further β-diketones are well known to have a keto-enol tautomerism [39] and recently it is reported that β-keto-enols are the important pharmacophore for the HIV-I integrase (IN) inhibitor [40]. The medicinal properties of the above mentioned compounds encourage us to synthesize various novel substituted β-diketone and β-ketoesters as precursors with arylsulphonyl chloride of piperazine derivative.

II. EXPERMENTAL

All the recorded melting points are uncorrected. Purity of the compounds was checked by thin layer chromatography using silica gel 'G' as stationary phase and benzene: ethanol: ammonia (7:2:1) upper layer as mobile phase. IR spectra were recorded on Perkin-Elmer infrared spectrometer by using KBr pellets. ^{1}HNMR spectra were recorded on model DRX-300 at 300.13 MHz spectrometer, using TMS as an internal standard. The chemical shifts were

reported in δ ppm.

General method of preparation of novel 1,4-diazepines from novel β-Diketones/ β -Ketoesters of 4-acetylaminobenzene sulphonyl chloride(2a-2d)

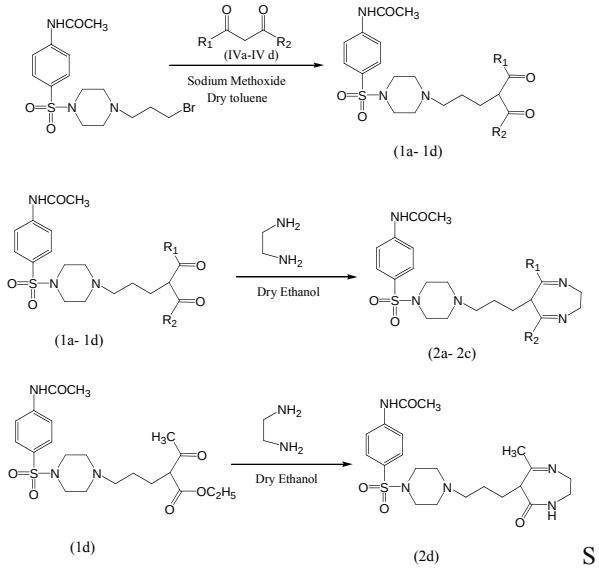
β- Diketone/ β-ketoester derivatives [41] (1 a-d) (0.01M) was dissolved in 10 ml of ethanol, to this glacial acetic acid (2.5 ml) was added followed by drop wise addition of ethylenediamine (0.01M) using a dropping funnel. Reaction mixture was refluxed for 8 h at 100 ^{0}C. Volatiles were removed under reduced pressure; viscous mass so obtained was thoroughly washed with dry ether to removed unreacted β-diketone/ β-ketoester. The crude product was recrystallized from acetone. Purity of the compounds was checked through TLC using benzene: ethanol: ammonia (7:2:1) upper layer as mobile phase.

III. RESULT AND DISCUSSION

A series of 1,4-diazepin of β-diketone/ β-ketoester derivatives of [N^4-(4-acetylamino) benzene sulphonyl piperazinyl-N^1-1-bromopropane] (5 a-d)derivatives were synthesized in moderate yields using the synthetic route outlined in Scheme I. Structures of the synthesized compounds were established on the basis of IR and ^{1}HNMR and elemental analysis. (Table-I, II & III). β-diketone/ β-ketoester derivatives of [N^4-(4-acetylamino) benzene sulphonyl piperazinyl-N^1-1-bromopropane] was treated with ethylenediamine and refluxed for 8 h at 100 ^{0}C to give 1,4-diazepin derivatives of β-diketone/β-ketoester of [N^4-(4-acetylamino) benzene sulphonyl piperazinyl-N^1-1-bromopropane] (5 a-d).

Antibacterial Activity

The in vitro antibacterial activities of the compound in this study were determined by conventional agar dilution method. The in vitro antibacterial activity of quinolone against several gram-positive bacteria (Staphylococcusaureus ATCC 6538, and Staphylococcus epidermidis ATCC 12228) and gram-negative bacteria (Escherichia coli ATTC 8739 and Klebsiella pneumonia ATTC 10031) are summarized in Table IV. The data of ciprofloxacin was included for comparison.



Scheme-I

Table I

Substitution Pattern and Physical Properties for Novel β-Diketone/β-Ketoester, (5 a-d)

Comp no.	R_1	R_2	M.P.	Yield
2a	CH_3	CH_3	145	40
2b	CH_3	C_6H_5	160	35
2c	C_6H_5	C_6H_5	140	45
2d	-	-	145	40

Table II

Molecular Formula and Elemental analysis for Novel β-Diketone/β-Ketoester, (5 a-d)

Comp no.	Molecular Formula	Elemental analysis Calculated (Found) %		
		C	H	N
2a	$C_{22}H_{33}N_5O_3S$	59.06 (58.82)	7.38 (7.12)	15.65 (15.32)

2b	$C_{27}H_{35}N_5O_3S$	67.25 (67.02)	6.47 (6.21)	12.25 (12.01)
2c	$C_{32}H_{37}N_5O_3S$	57.86 (57.42)	7.33 (7.11)	14.675 (14.32)
2d	$C_{21}H_{31}N_5O_4S$	63.65 (63.65)	6.87 (6.43)	13.752 (13.41)

Table III

Spectral Details of Synthesized Novel β-Diketone/β-Ketoester, (5 a-d)

Comp. No.	IR Spectra (KBr) cm^{-1}	^{1}HNMR Spectra ($CDCl_3$/DMSO-d_6) (δ ppm)
2a	3313 (N-H), 3010 (Ar-H), 2900 (C-H),1700 (C=O), 1570 (C=N), 1310,1140 (-SO2)	1.09 (2H, q, CH_2-CH_2-CH_2), 1.12 (2H, t,CH_2-CH_2-CH_2), 2.02 (6H, s, CH_3-C=N), 2.10 (3H, s, CH_3-C=N), 2.30 (2H, t, CH_2-CH_2- CH_2), 2.81-2.36 (8H, m, -CH_2 Piperazin), 3.10 (4H, t, -N-CH_2-CH_2-N -), 7.60-7.80 (4H, m, Ar-H), 8.20 (1H, s, -NH-), 10.31 (1H, s, - NH – of Anilide group)
2b	3322 (N-H), 3040 (Ar-H), 2845 (C-H), 1720 (C=O), 1590 (C=N), 1320,1170 (-SO2)	1.10 (2H, q, CH_2-CH_2-CH_2), 1.11 (2H, t, CH_2-CH_2-CH_2), 2.08 (3H, s, CH_3-C=N), 2.02 (3H, s, CH_3-C=N), 2.32 (2H, t, CH_2-CH_2- CH_2), 2.79-2.35 (8H, m, -CH_2 Piperazin), 3.10 (4H, t, -N-CH_2-CH_2-N -), 7.55-7.65 (9H, m, Ar-H), 8.20 (1H, s, -NH-), 10.34 (1H, s, - NH – of Anilide group)
2c	3340 (N-H), 3060 (Ar-H), 2900 (C-H),1730(C=O), 1600) (C=N), 1350,1120 (-SO2)	1.01 (2H, q, CH_2-CH_2-CH_2), 1.12 (2H, t, (CH_2-CH_2-CH_2), 2.09 (3H, s, CH_3-C=N), 2.35(2H, t, CH_2-CH_2-CH_2), 2.79-2.39 (8H, m, -CH_2 Piperazin), 3.11 (4H, t, -N-CH_2-CH_2-N), 7.60-7.85 (14H, m, Ar-H), 8.21 (1H, s, - NH-), 10.35 (1H, s, - NH – of Anilide group)
2d	3370 (N-H), 3030 (Ar-H), 2870 (C-H),1735 (C=O),1620 (C=N), 1350,1120 (-SO2)	1.04 (2H, q, CH_2-CH_2-CH_2), 1.40 (2H, t, CH_2-CH_2-CH_2), 2.05 (3H, s, CH_3-C=N), 2.11 (3H, s, CH_3-C=N), 2.31 (2H, t, CH_2-CH_2- CH_2), 2.75-2.35 (8H, m, -CH_2 Piperazin), 3.08 (4H, t, -N-CH_2-CH_2-N -), 7.60-7.81 (4H, m, Ar-H), 8.19 (1H, s, -NH-),8.21 (1H, s, - NH-) 10.36 (1H, s, - NH – of Anilide group)

Table IV

The in Vitro Antibacterial Activities of Novel β-Diketone/β-Ketoester, (5 a- d)

Comp. No.	Zone of inhibition (mm)			
	Staphylococcus aureus	Staphylococcus epidermidis	Escherichia coli	Klebsiella pneumonia
2a	12	13	12	12
2b	13	12	12	12
2c	12	12	13	10
2d	13	12	12	12
Cipro	25	23	21	17

[a]The zone of inhibition values by the conventional agar dilution, a Ciprofloxacin used as reference drug.

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