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

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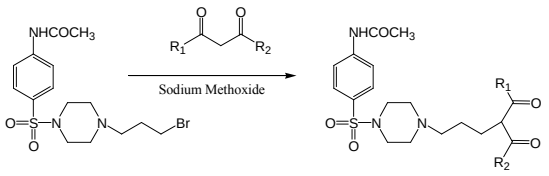
Abstract: **A series of novel β-diketones/β-ketoesters have been synthesized from 4-acetylaminobenzene sulphonyl chloride. Desired compounds were prepared by the reaction of [N^4-(4-acetylamino) benzene sulphonyl piperazinyl-N^1-1-bromopropane] (III) with β-diketone/β-ketoester to synthesize novel β-diketone/β-ketoester derivatives of [N^4-(4-acetylamino) benzene sulphonyl piperazinyl-N^1-1-bromopropane] (5a-d). All the newly synthesized compounds were characterized with IR and ^{1}HNMR studies.**

***Keywords*:** **β-diketone, β-ketoester, 4-acetylaminobenzene sulphonyl chloride.**

Graphical Abstract:



I. INTRODUCTION

The quest for a more reliable and suitable drug is always a fascinating and challenging task. A number of medicines containing simple heterocycles or combination of different heterocyclic moieties have been used these days. 4-acetyleaminobenzene sulphonyl chloride nucleus is well known for its antibacterial [1], antifungal [2], antitumer [3], neuroprotective and antiproliferative properties [4].

Various derivatives of piperazine have been found useful as brain protecting [5], in the diagnosis of schizophrenia [6], neurokinine [7-8], serotonin antagonist receptor [9-11], heart muscle receptor [12], and cholesterol reducing agents [13], HIV-I inhibitors [14-15], dopamine transporter [16-18], and sorbitol dehydrogenase inhibitor [19-21]. 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 [22], antibiotic [23], anticancer [24], and in the treatment of Erectile Dysfunction [25].

β-diketones and β-ketoesters posses many biological properties such as anticarcinogenic properties [26], antioxidant [27-29], antihistaminic [30], anticoagulant [31]. 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 4-Acetyleaminobenzene Sulphonyl Piperazine (II):

Piperazine (2g. 0.023 M) was taken in pyridine (4

ml) and acetic anhydride (20 ml) was added. To this 4-acetyleamino benzene sulphonyl chloride (2.5 g. 0.001M) was added and the mixture was kept on a water bath for two hours. After the completion of the reaction, the reaction mixture was poured into ice cold water, the solid obtained was filtered and recrystallized from ethanol-water mixture to obtain pure compound.

General Method of Synthesis of [N^4-(4-Acetylamino) Benzene Sulphonyl Piperazinyl-N^1-1-Bromopropane] (III):

4-acetylamino benzene sulphonyl piperazine (II) (2g, 0.007 M) and absolute alcohol (10 ml) was taken in a round-bottomed flask. 1,3-dibromopropane (2ml, 0.02 M) was added, the reaction mixture was refluxed for three hours, kept overnight in refrigerator. A solid was separated out. The reaction mixture was filtered; the crude solid so obtained was recrystallized from ethanol: ethyl acetate mixture (2:8) afforded as light green crystals.

General Method of Preparation of β-Diketone/β-Ketoester Derivatives of [N^4-(4-Acetylamino) Benzene Sulphonyl Piperazinyl-N^1-1-Bromopropane] (5 a-d):

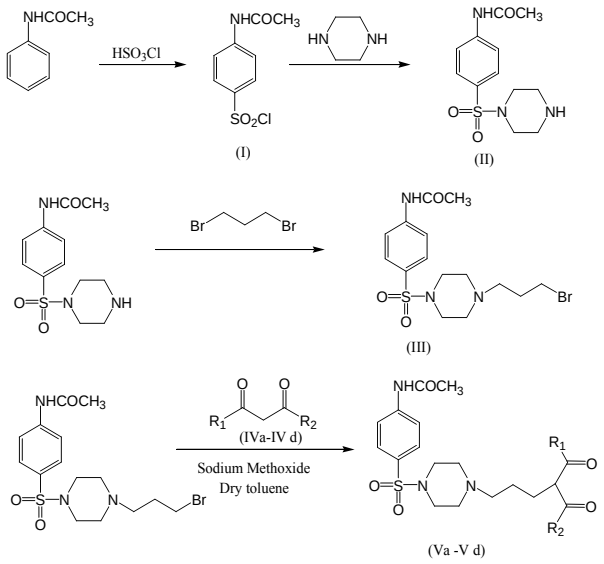
A mixture of β-diketone/β-ketoester (0.02 M) and sodium methoxide (1.0 g, 0.02 M) in dry toluene (10 ml) was stirred at 50°C for 2 h. The compound (III) (1 g., 0.0025 M) was added in small portion. The mixture was refluxed for 20 h at 100°C. Volatiles were removed under reduced pressure and the residue was partitioned between chloroform/water. The organic layer was separated, washed with water, dried over MgSO4, concentrated under reduced pressure, purified by column chromatography and recrystallized from absolute alcohol. Purity of compound was checked through TLC using benzene: ethanol: ammonia (7:2:1) upper layer as mobile phase.

III. RESULT AND DISCUSSION

A series 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 as shown in Table-I, II and III. [N^4-(4-acetylamino) benzene sulphonyl piperazinyl-N^1-1-bromopropane] was treated with various β-diketone/β-ketoester (4 a-d), in presence of mild base ($NaHCO_3$) in dry toluene to give of β-diketone/β-ketoester derivatives of [N^4-(4-acetylamino) benzene sulphonyl piperazinyl-N^1-1-bromopropane] (5a-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, (5a-d)

Comp no.	R_1	R_2	M.P.	Yield
5a	CH3	CH3	175	55
5b	CH3	C6H5	180	65
5c	C6H5	C6H5	185	70
5d	CH3	OC2H5	170	50

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

Comp no.	Molecular Formula	Elemental analysis Calculated (Found) %		
		C	H	N
5a	C20H29N3O5S	56.737 (56.532)	6.856 (6.432)	9.929 (9.725)
5b	C25H31N3O5	61.983 (61.632)	6.198 (6.024)	8.677 (8.432)
5c	C30H33N3O5S	65.813 (65.432)	6.032 (6.011)	7.678 (7.532)
5d	C21H31N3O6S	55.629 (55.417)	6.843 (6.425)	9.271 (9.019)

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

Comp. No.	**IR Spectra (KBr) cm^{-1}**	**^{1}HNMR Spectra ($CDCl_3$/DMSO-d_6) (δ ppm)**
5a	3310 (N-H), 3020 (Ar-H), 2850(C-H), 1700 (C=O), 1320 (-SO_2), 1150 (-SO_2)	1.10 (2H, q, CH_2-$\underline{CH_2}$-CH_2), 1.40 (2H, t, CH_2-CH_2-$\underline{CH_2}$), 1.90 (6H, s, CO$\underline{CH_3}$), 2.10 (3H, s $\underline{CH_3}$CO), 2.30 (2H, t, $\underline{CH_2}$-CH_2-CH_2), 2.80-2.36 (8H, m, -CH_2 Piperazin), 7.12 (1H, s, -CH=), 7.60-7.80 (4H, dd, Ar-H), 10.38 (1H, s, NH)
5b	3320 (N-H), 3050 (Ar-H), 2940(C-H), 1735 (C=O), 1325 (-SO_2), 1175 (-SO_2)	1.12 (2H, q, CH_2-$\underline{CH_2}$-CH_2), 1.39 (2H, t, CH_2-CH_2-$\underline{CH_2}$), 1.91 (6H, s, CO$\underline{CH_3}$), 2.11 (3H, s $\underline{CH_3}$CO), 2.32 (2H, t, $\underline{CH_2}$-CH_2-CH_2), 2.79-2.36 (8H, m, -CH_2 Piperazin), 7.18 (1H, s, -CH=), 7.40-7.79 (9H, m, Ar-H), 10.34 (1H, s, NH)
5c	3330 (N-H), 3040 (Ar-H) 2900(C-H), 1750 (C=O), 1351 (-SO_2), 1176 (-SO_2)	1.09 (2H, q, CH_2-$\underline{CH_2}$-CH_2), 1.38 (2H, t, CH_2-CH_2-$\underline{CH_2}$), 2.12 (3H, s, CO$\underline{CH_3}$), 2.30 (2H, t, $\underline{CH_2}$-CH_2-CH_2), 2.81-2.40 (8H, m, -CH_2 Piperazin), 7.15 (1H, s, -CH=), 7.31-7.80 (14H, m, Ar-H), 10.35 (1H, s, NH)
5d	3350 (N-H), 3010 (Ar-H), 2860(C-H), 1760 (C=O), 1350 (-SO_2), 1130 (-SO_2),	1.10 (2H, q, CH_2-$\underline{CH_2}$-CH_2), 1.41 (2H, t, CH_2-CH_2-$\underline{CH_2}$), 1.63 (3H, t, -OCH_2-

Comp. No.	IR Spectra (KBr) cm^{-1}	^{1}HNMR Spectra ($CDCl_3$/DMSO-d_6) (δ ppm)
	1100 (C-O- C), 1245 (C-O-C)	CH_3), 2.15 (3H, s, $CO\underline{CH_3}$), 1.92 (3H, s $\underline{CH_3}CO$), 2.29 (2H, t, $\underline{CH_2}$-CH_2-CH_2), 2.85-2.41 (8H, m, -CH_2 Piperazin), 4.28 (2H, q, OCH_2-CH_3), 7.22 (1H, s, -CH=), 7.40-7.98 (4H, dd, Ar-H), 10.41 (1H, s, NH)

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

CompNo.	Zone of inhibition (mm)			
	Staphylococcus aureus	Staphylococcus epidermidis	Escherichia coli	Klebsiella pneumonia
5 a	15	12	18	12
5 b	17	13	17	11
5 c	16	14	18	12
5 d	14	13	13	13
[a]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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