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Research Article

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Synthesis, spectral studies and antimicrobial studies of 7-[phenylamino]-5-methyl-1,4-diazepines and its derivatives

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ABSTRACT

A novel series of substituted 1,4-Diazepines were synthesised in good to excellent yield via cyclocondensation of 1-N (substituted phenyl carboxamido) propane-2-one with ethylene Diamine. This method is easy, rapid, user friendly and without use of any catalyst. Synthesised compounds were ecofriendly and completion of reactions was monitored by thin layer chromatography. The structure of these compounds were characterised by FT- IR, 1H-NMR, Mass spectroscopic technique and Elemental analysis. All newly synthesised compounds were screened for antimicrobial activities using gram positive and gram negative strains by Disk diffusion method. The main objective to synthesise substituted 1,4-Diazepines is because of its remarkable pharmacological and therapeutic activities.

Key words: Heterocyclic, 1, 4 Diazepines, Nitroso and benzoyl derivatives, antimicrobial activity, Gram positive and Gram negative strains

INTRODUCTION

Heterocyclic compound analogues and its derivatives have attracted strong interest due to their useful biological and pharmacological properties [1]. Now a days researcher also concentrated towards the synthesis of new and safe therapeutic agents of clinical importance [2]. Nitrogen containing heterocyclic compounds is found prominent place and considerable utility in drug design [3]. Nitrogen containing five or six membered rings is always of great importance in the pharmaceutical sector because of having bioisosteric factor [4]. Similarly, seven membered ring with two nitrogen at different position also plays important role in medicinal chemistry.

In concern with this, heterocyclic compound containing Diazepines moiety have attracted attention as a anticonvulsant, anti-anxiety, analgesic, antimicrobial [5], anti-HIV [6], herbicidal [7], psychotropic [8] and anticancer [9] activities, sedative, antidepressive\ [10] , safe chemotherapeutic agents [11], central nervous system depressants [12] and hypnotic agents, as well as anti-inflammatory agents. Other than their biological importance, diazepines derivatives are also commercially used as dyes for acrylic fibers [13].

Because of the wide range of pharmacological activity, industrial and synthetic applications, the synthesis of 1, 4diazepines has received increasing attention. 1, 4-Diazepines play prominent roles in the field of medicinal chemistry because it is the core moiety used for the synthesis of various drug molecules like, dibenzepine, clozapine, brotizolam and zometapine [14]. In view of above said importance, 1, 4-diazepine derivatives were synthesized using simple condensation of primary amine, ethyl acetoacetate and ethylene diamine stepwise and its nitroso and benzoyl derivatives also synthesised.

EXPERIMENTAL SECTION

All chemicals used for the synthesis were of analytical grade. H NMR spectra were recorded on BRUKER AVANCE II 400 NMR Spectrometer. IR spectra were recorded by using AFFINITY-1 FTIR

SPECTROPHOTOMETER. Melting points were determined by using INDO Melting Point M-AB-92 apparatus and were uncorrected. Purity of compounds and completion of reactions were checked by thin layer chromatography (TLC). The crude compounds were purified by recrystallization from ethanol. Mass spectra were also recorded.

General procedure for synthesis of 4-[amino phenyl]-5-methyl 1, 4 Diazepines:
Formerly prepared 1-(N-phenyl-carboxamido)-propan-2-one (Ia) (0.01M) was refluxed with ethylene diamine (0.01M) in methanol as a solvent for 2-3 hrs. After refluxing the reaction mixture was allowed to cool and poured it onto crushed ice. Crystals of 1, 4 Diazepines (IIa) were obtained. These were recrystallised with ethanol. Similarly compounds (IIb - IIe) were synthesised.

7-[2-Methoxy Phenyl amino] 5-Methyl 1,4 Diazepines **(IIa)** : $C_{12}H_{12}N_3O$, 175^{0}C, 81%, C= 62.48 (67.28), H= 5.31(5.60), N=17.34(19.62), O= 6.75(7.47) NMR: Ar-H=δ(6.90 to 7.97ppm), NH=δ(9.18 ppm), -CH_2= δ(4.74ppm), -CH_3=δ(2.50ppm), -OCH_3=δ(3.35ppm), CH_2-CH_2 = δ(3.33ppm); IR: N-H Str.=3282.02 cm^{-1}, C=N Str. =1532.51 cm^{-1}, C-N Str. =1329.01 cm^{-1}, Ar-OCH_3Str = 1174 cm^{-1}

7-[3-Methoxy Phenyl amino] 5-Methyl 1,4 Diazepines **(IIb)** : $C_{12}H_{12}N_3O$, 160^{0}C, 76%, C= 65.05 (67.28), H= 4.21(5.60), N=18.87(19.62), O= 7.51(7.47) NMR: Ar-H=δ(7.03 to 7.32ppm), NH=δ(9.05 ppm), -CH_2= δ(4.54ppm), -CH_3=δ(1.91ppm), -OCH_3=δ(3.70ppm), CH_2-CH_2 = δ(3.31 – 3.45ppm); IR: N-H Str.=3274.42 cm^{-1}, C=N Str. =1509.84 cm^{-1}, C-N Str. =1310.51 cm^{-1}, Ar-OCH_3Str = 1116 cm^{-1}

7-[4-Methoxy Phenyl amino] 5-Methyl 1,4 Diazepines **(IIc)** : $C_{12}H_{12}N_3O$, 210^{0}C, 86%, C= 63.45 (67.28), H= 6.04(5.60), N=17.98(19.62), O= 6.23(7.47) NMR: Ar-H=δ (7.14 to 7.85ppm), NH=δ(9.11 ppm), -CH_2= δ(4.32ppm), -CH_3=δ(2.37pm), -OCH_3=δ(3.46ppm), CH_2-CH_2 = δ(3.12ppm); IR: N-H Str. =3304.20 cm^{-1}, C=N Str. =1497.21 cm^{-1}, C-N Str. =1304.11 cm^{-1}, Ar-OCH_3Str = 1204 cm^{-1}

7-[2-hydroxy Phenyl amino] 5-Methyl 1,4 Diazepines **(IId)** : $C_{11}H_{10}N_3O$, 134^{0}C, 60%, C= 64.55 (66.00), H= 4.57(5.00), N=19.65(21.00), O= 7.42(8.00) NMR: Ar-H=δ(7.14 to 7.72ppm), NH=δ(9.82ppm), -CH_2= δ(3.87ppm),-CH_3=δ(2.84ppm), -OH=δ(11.23ppm) CH_2-CH_2=(3.14ppm) IR: N-H Str. =3180.90 cm^{-1}, C=N Str. =1650.80 cm^{-1}, C-N Str. =1285.41 cm^{-1}, Ar-OCH_3Str = 1198 cm^{-1}.

7-[3-hydroxy Phenyl amino] 5-Methyl 1,4 Diazepines **(IIe)** : $C_{11}H_{10}N_3O$, >300^{0}C, 82%, C= 65.67 (66.00), H= 6.48(5.00), N=19.45(21.00), O= 7.03(8.00) NMR: Ar-H=δ(6.12 to 7.16ppm), NH=δ(9.81ppm), -CH_2= δ(3.33ppm),-CH_3=δ(2.62ppm), -OH=δ(11.24ppm) CH_2-CH_2=(2.37ppm) IR: N-H Str. =3234.20 cm^{-1}, C=N Str. =1577.80 cm^{-1}, C-N Str. =1322.41 cm^{-1}, Ar-OCH_3Str = 1212 cm^{-1}.

7-[4-hydroxy Phenyl amino] 5-Methyl 1,4 Diazepines **(IIf)** : $C_{11}H_{10}N_3O$, 110^{0}C, 78%, C= 64.05 (66.00), H= 5.83(5.00), N=20.49(21.00), O= 8.50(8.00) NMR: Ar-H=δ(6.92 to 7.32ppm), NH=δ(9.45ppm), -CH_2= δ(3.92ppm),-CH_3=δ(2.42ppm), -OH=δ(11.47ppm) CH_2-CH_2=(2.98ppm) IR: N-H Str. =3374.12cm^{-1}, C=N Str. =1457.87 cm^{-1}, C-N Str. =1298.45 cm^{-1}, Ar-OCH_3Str = 1204 cm^{-1}.

Derivatives of 1, 4 Diazepines
Nitroso derivative of 1,4 Diazepines:-
IIa, IIb, IIc, (0.01 M) was made into solution with conc. HCl. Cool this solution at 0-5° C. To this acidic solution 5ml of 20% sodium nitrite was added with continuous stirring. The reaction mixture was allowed to stand for half an hrs for completion of reaction. It was filtered through Buchner funnel and washed with water [15 – 16].

4-N-Nitroso 5-methyl 7- [2-methoxy Phenyl amino] 1, 4 Diazepines **(IIIa):** $C_{13}H_{14}N_4O_2$, 126^{0}C, C= 58.88 (60.46), H= 4.67(5.42), N=22.74(21.70), O= 11.05(12.40).

4-N-Nitroso 5-methyl 7- [3-methoxy Phenyl amino] 1, 4 Diazepines **(IIIb):** $C_{13}H_{14}N_4O_2$, 154^{0}C, C= 56.65 (60.46), H= 5.12(5.42), N=24.03(21.70), O= 10.85(12.40).

4-N-Nitroso 5-methyl 7- [4-methoxy Phenyl amino] 1, 4 Diazepines **(IIIc):** $C_{13}H_{14}N_4O_2$, 210^{0}C, C= 57.93 (60.46), H= 4.88(5.42), N=23.54(21.70), O= 11.65(12.40).

4-N-Nitroso 5-methyl 7- [2-hydroxy Phenyl amino] 1, 4 Diazepines **(IIId):** $C_{12}H_{12}N_4O_2$, 174^{0}C, C= 58.25 (59.01), H= 3.27(4.91), N=22.08(22.95), O= 12.41(13.11).

4-N-Nitroso 5-methyl 7- [3-hydroxy Phenyl amino] 1, 4 Diazepines **(IIIe):** $C_{12}H_{12}N_4O_2$, 212^{0}C, C= 57.87 (59.01), H= 4.22(4.91), N=22.74(22.95), O= 13.78(13.11).

4-N-Nitroso 5-methyl 7- [4-hydroxy Phenyl amino] 1, 4 Diazepines **(IIIf):** $C_{12}H_{12}N_4O_2$, 94^{0}C, C= 59.18 (59.01), H= 4.58(4.91), N=22.18(22.95), O= 12.88(13.11).

Benzoyl derivative of 1,4 Diazepines

Ia, IIb, IIc (0.01 M) of compound was mixed with NaOH solution .The reaction mixture was cooled on ice bath. Approximately 2ml Benzoyl Chloride was added drop wise and shake. Allow the reaction mixture to settle down. Filter the mixture [17-18]. Recrystallised with ethanol to form **IVa – IVc**. Physical data were shown below.

4-N-Benzoyl 5-methyl 7- [2-methoxy Phenyl amino] 1, 4 Diazepines **(IVa):** $C_{19}H_{19}N_3O_2$, 120^{0}C, C= 68.98 (71.02), H= 5.71(5.91), N=12.24(13.08), O= 9.75(9.96).

4-N-Benzoyl 5-methyl 7- [3-methoxy Phenyl amino] 1, 4 Diazepines **(IVb):** $C_{19}H_{19}N_3O_2$, 116^{0}C, C= 69.18 (71.02), H= 4.76(5.91), N=12.65(13.08), O= 8.67(9.96).

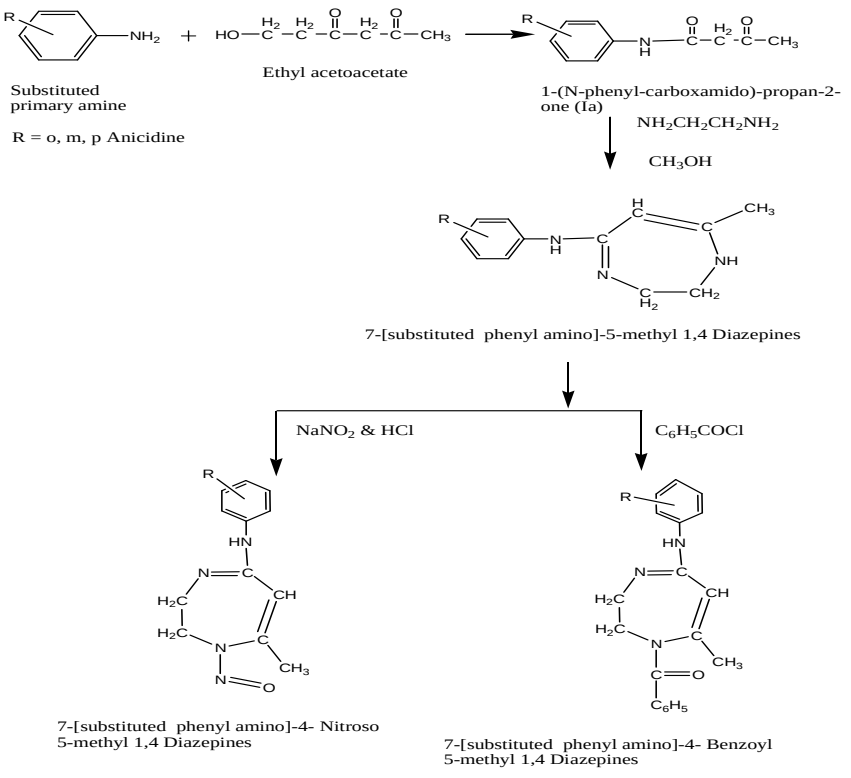
4-N-Benzoyl 5-methyl 7- [4-methoxy Phenyl amino] 1, 4 Diazepines **(IVc):** $C_{19}H_{19}N_3O_2$, 110^{0}C, C= 61.98 (71.02), H= 6.21(5.91), N=12.88(13.08), O= 9.70(9.96).

4-N-Benzoyl 5-methyl 7- [2-hydroxy Phenyl amino] 1, 4 Diazepines **(IVd):** $C_{18}H_{17}N_3O_2$, 122^{0}C, C= 69.21 (70.35), H= 4.52(5.53), N=12.84(13.68), O= 8.43(10.42).

4-N-Benzoyl 5-methyl 7- [2-hydroxy Phenyl amino] 1, 4 Diazepines **(IVe):** $C_{18}H_{17}N_3O_2$, 175^{0}C, C= 68.76 (70.35), H= 5.12(5.53), N=13.14(13.68), O= 9.18(10.42).

4-N-Benzoyl 5-methyl 7- [2-hydroxy Phenyl amino] 1, 4 Diazepines **(IVf):** $C_{18}H_{17}N_3O_2$, 118^{0}C, C= 69.08 (70.35), H= 5.11(5.53), N=12.96(13.68), O= 10.16(10.42).

Reaction Scheme



Biological evaluation:

Preparation of sample:

0.003 g/ 30 mg was taken and dissolved in 1 ml of DMSO.

Preparation of inoculums:
Stock cultures were maintained at 4^{o}C on slants of nutrient agar. Active cultures of experiment were prepared by transferring a loop full of cells from the stock cultures to test tube of Muller-Hinton broth (MHB) for bacteria that were incubated for 24 hrs at 37^{o}C .

Screening of Bacteria:
The disk diffusion method was used for antimicrobial activity. The nutrient agar were poured in Petri plates and allowed it to solidify. The above prepared microbial cultures were spread uniformly on the surface of the agar. The diffused disks of each sample are placed on the agar. Plates were then incubated at 37°C for 24hrs [19-21]. Antimicrobial results were shown in Table.

Organism	Conc. (mg/ml)	Zone of Inhibition						Zone of Inhibition for Ciprofloxacin (30mg/ml)	% Activity					
		IIa	IIb	IIc	IId	IIe	IIf		IIa	IIb	IIc	IId	IIe	IIf
P. vulgaris	30	18	12	20	20	16	20	20	90	60	100	100	80	100
S. typhi	30	16	.....	11	18	.....	22	38	42.1	-----	28.9	47.3	-----	57.8
S. aureous	30	16	.....	14	....	26	20	38	42.1	-----	36.8	----	68.4	52.6
B. subtilis	30	12	10	12	20	24	.....	35	34.2	28.5	34.2	57.1	68.5	-----
Kl. shegella	30	10	12	14	16	16	18	25	40	48	56	64	64	72

RESULTS AND DISCUSSION

Novel 1, 4 Diazepines were synthesised using ethylene diamine according to procedure explained above in experimental section. Structural conformations were carried out by H NMR, IR and Mass spectroscopic data. Simultaneously, Nitroso and benzoyl derivatives also prepared by simple techniques. Reaction scheme also accompanision synthesis of diazepines.

Antimicrobial activities of synthesised compounds were determined by Agar Plate disk diffusion technique against gram +ve and gram –ve strains. The diameter of inhibition zone around each disc was measured in mm. Results revels that compound IIa and IIc shows better antimicrobial activity against all strains of microorganism. Compounds IIb, IId, IIe and IIf gives moderate antimicrobial activity for selected gram +ve and gram –ve strains. Their % Activity also calculated by comparing with standard drug Ciprofloxacin. In feature these Diazepines and its derivatives shows grateful work in medicinal chemistry.

CONCLUSION

- Results of present study demonstrated that a new class of seven membered heterocyclic compound diazepines were synthesised more easily and efficiently using ethylene diamine.
- Formation of Nitroso and Benzoyl derivatives indicates the presence of free hydrogen on nitrogen. It forms high molecular weight heterocyclic compounds.
- In future antimicrobial activity of these derivatives also performed.
- Antimicrobial activity results show significant inhibition efficiency when compared with standard drug Ciprofloxacin.

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