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Note

Synthesis, spectral studies and antimicrobial activity of 7-chloro-2-alkyl/aryl-4-alkyl/aryl-3-arylidene-3*H*-1,5-benzodiazepines

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Condensation of various β-diketones **2** with appropriate araldehydes **1** in the presence of piperidene has afforded 2-arylidene-1,3-diketones **3** which in turn on condensation with 4-chloro-1,2-phenylene diamine in acidic medium give a series of 7-chloro-2-alkyl / aryl-4-alkyl / aryl-3-arylidene-3*H*-1,5-benzodiazepines **5a-j**. All the newly synthesized compounds are characterized on the basis of their spectral (IR, ^{1}H NMR, Mass) and analytical data. Representative compounds have been screened for their antibacterial and antifungal activities. Some of the compounds have been found to exhibit promising antibacterial and antifungal activities.

Keywords: Antimicrobial, benzodiazepines, araldehydes, piperidene, β-diketones

Since the discovery of flurazepam, flunitrazepam, quazepam, halazepam and triflubazam, the chemistry of benzodiazepines and allied compounds continues to draw attention of synthetic organic chemists due to their varied biological activities[1,2]. A large number of benzodiazepine derivatives have been synthesized as sedative[3], tranquillizer[3], anticonvulsant[3], antidepressant[4], anxiolytic[4,5] and antihypertensive[6,7] drugs. Some benzodiazepines and allied derivatives are known to exhibit muscle relaxant[3], anticoagulant[8], antiobesity[9], antiulcer[10], calcium channel blocking[11], cholecystokinin antagonists[12], thrombopoietin receptor agonist[13], endothelin antagonist[14], vasopressin receptor antagonist[15,16] activity.

From a structure activity stand point[2], generally electron withdrawing substituents at the 7-position of benzodiazepine moiety impart a high degree of activity and a rough rank order is: $NO_2 \approx CF_3 > Br > Cl \geq CH_3 \geq F > H$.

It has been observed that introduction of Cl at 7-position of benzodiazepine moiety enhances the CNS activity greatly, for example, chlorodiazepoxide, oxazepam, quazepam and fletazepam are well known CNS drugs. Keeping these observations a comprehensive programme of developing some new halogenated benzodiazepine and allied derivatives have been undertaken and as a part of this the synthesis and antimicrobial activity of some 7-fluoroaryl-1*H*-1,4-diazepine[17], 3-arylazo-1*H*-1,5-benzodiazepine[18] and 6-arylazo-2,3-dihydro-1*H*-1,4-diazepines[19] have been already reported.

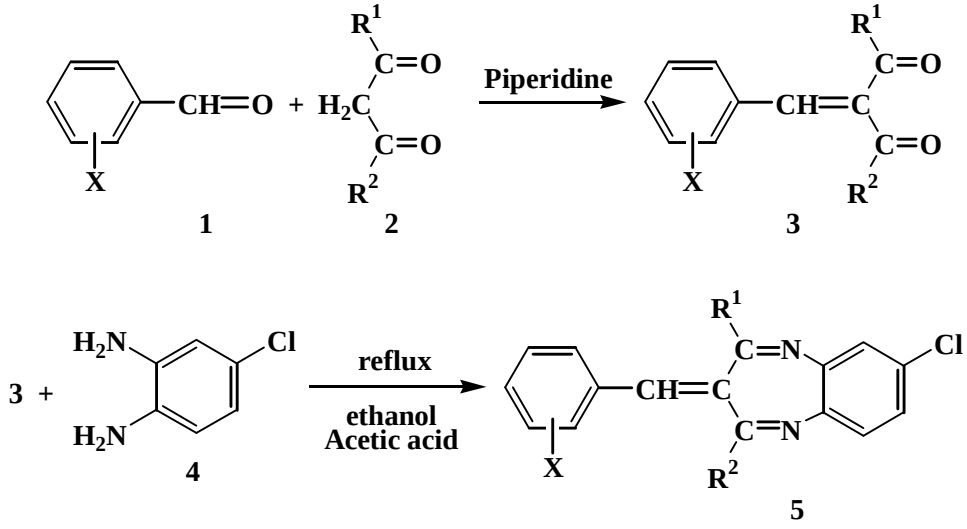
Now in the present communication the synthesis, spectral studies and antimicrobial activity of 7-chloro-2-alkyl /aryl-4-alkyl/aryl-3-arylidene-3*H*-1,5-benzodiazepines have been reported.

Results and Discussion

β-Diketones **2** were prepared by condensation of different substituted acetophenones with appropriate ester according to the method of Joshi *et al*[20]. β-Diketones **2** were treated with appropriate araldehydes **1** in the presence of piperidine to give 2-arylidene-1,3-diketones **3**. Condensation of 2-arylidene-1,3-diketones **3** with 4-chloro-1,2-phenylene diamine in the presence of gl. acetic acid afforded 7-chloro-2-alkyl/aryl-4-alkyl/aryl-3-arylidene-3*H*-1,5-benzodiazepines **5a-j**. The reaction sequence is depicted in **Scheme I**.

The synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral data. The IR spectra of **3a-j** showed absorption bands in the region of 1680-1700 (>C=O str.) and 1640-1655 cm^{-1} (-CH=C< str.). The IR spectra of **5a-j** exhibited absorption band in the region of 1589-1600 cm^{-1} (>C=N str.). The ^{1}H NMR ($CDCl_3$) spectra of compounds **5a-j** exhibited resonance signal at δ 6.68-8.24 ppm as multiplet for the aromatic protons and at 3.60-4.30 ppm as singlet for the =CH proton. Compounds **5a-e** showed singlet at δ 2.35-2.83 ppm for the methyl protons. Compound **5d** exhibited a resonance signal at δ 3.89 for the methoxy and =CH proton. Finally, the structure of compounds was confirmed by high resolution mass spectra. Mass spectra of compounds **5a-j** showed molecular ion peak M^+.

The mass fragmentation pathways of compound **5j** are given in **Scheme II**. Compound **5j** exhibited a molecular ion peak (M^+) **I** at *m*/*z* 392.8 corresponding to the molecular formula $C_{23}H_{15}ClF_2N_2$ and M^++1 peak



Compd	X	R^1	R^2	Compd	X	R^1	R^2
5a	4-Cl	Me	Me	**5f**	4-Cl	Ph	4-ClC_6H_4
5b	2-Cl	Me	Me	**5g**	4-F	Ph	4-ClC_6H_4
5c	2-OCH_3	Me	Me	**5h**	4-Cl	Me	4-ClC_6H_4
5d	3,4,5-tri OCH_3	Me	Me	**5i**	4-F	Me	Ph
5e	3-F	Me	Me	**5j**	3,4-diF	Me	Ph

Scheme I

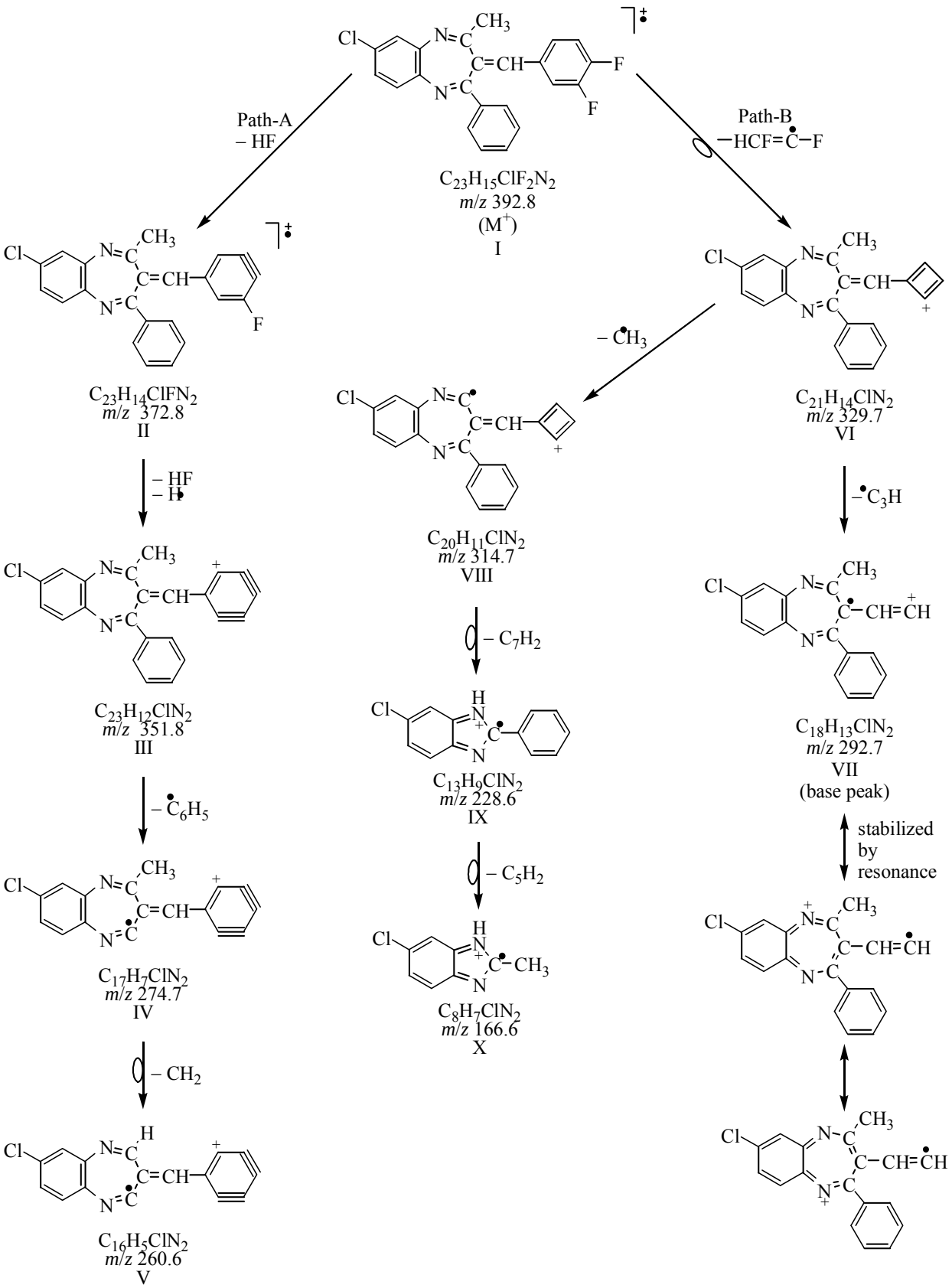
at *m*/*z* 393.8 due to isotopic carbon and hydrogen atoms. The molecular ion **I** further fragmented by two pathways A and B. In pathway-A, molecular ion **I** eliminated HF molecule to afford cation radical **II** at *m*/*z* 372.8 (8.0%). The successive elimination of HF molecule and hydrogen radical from cation radical **II** gave a cation **III** at *m*/*z* 351.8 (9.4 %) which in turn eliminated phenyl radical to afford cation radical **IV** at *m*/*z* 274.7 (6.5%). Cation radical **IV** extruded CH_2 moiety followed by scrambling of hydrogen to give cation radical **V** at *m*/*z* 260.6 (18.9 %). In pathway-B, molecular ion **I** eliminated C_2HF_2 radical to give cation **VI** at *m*/*z* 329.7 (20.2 %). The loss of C_3H radical from cation **VI** afforded cation radical **VII** at *m*/*z* 292.7 (100.0 %) corresponding to the base peak, which was stabilized by resonance. The elimination of methyl radical from cation **VI** gave cation radical **VIII** at *m*/*z* 314.7 (5.0%) which in turn lost a C_7H_2 moiety to give cation radical **IX** at *m*/*z* 228.6 (66.1 %). Cation radical **IX** eliminated C_5H_2 moiety to give cation **X** at *m*/*z* 166.6 (71.5 %).

Antimicrobial activity

Representative compounds were screened for their antibacterial activity against gram-negative bacteria *Escherichia coli* and gram-positive bacteria *Staphyllococcus aureus* at 200, 400 and 800 ppm concentration. Antifungal activity was done against *Candida albicans* and *Aspergillus niger* at 200, 400 and 800 ppm concentration. Streptomycin and Ketoconazole were used as standard drugs for antibacterial and antifungal evaluations, respectively. The compounds were screened for their biological activity by using inhibition zone technique[21].

The results obtained for antibacterial and antifungal evaluations are recorded in **Table I** and **Table II**, respectively. The perusal of our results revealed that compounds possessing *o*-methoxy and *m*-fluoro substituents in the arylidene moiety of the synthesized compounds **5c**, **5e**, *p*-chloro, p-fluoro substituent in the arylidene moiety in combination with 4-chlorophenyl ring at 2-position of the synthesized compounds **5f**, **5g** and *p*-fluoro, 3,4-difluoro substituents in the arylidene moiety in combination with phenyl ring at 2-position of the synthesized compounds **5i**, **5j** showed higher degree of activity as compared to rest of the compounds against *S.aureus* at 200,400 and 800 ppm concentration.

The compounds possessing *o*-methoxy and *p*-fluoro substituents in the arylidene moiety of the synthesized compounds **5c**, **5i** and *p*-chloro, *p*-fluoro substituent in the arylidene moiety in combination with *p*-chloro-phenyl ring at 2-position of the synthesized



Scheme II — Mass fragmentation pattern of 7-chloro-2-phenyl-4-methyl-3-(3,4-difluorbenzylidene)-3*H*-1,5-benzodiazepine, **5j**

Table I — Antibacterial activity data of compounds **5a-j**

Compd	Mean value of area of inhibition in mm (800 ppm) IZ (AI)		Mean value of area of inhibition in mm (400 ppm) IZ (AI)		Mean value of area of inhibition in mm (200 ppm) IZ (AI)	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*	*S. aureus*	*E. coli*
Streptomycin	12.5	12.0	10.3	9.8	8.0	6.2
5a	8.0 (0.64)	9.5 (0.79)	6.0 (0.58)	7.0 (0.71)	4.5 (0.56)	4.1 (0.66)
5b	7.5 (0.60)	10.0 (0.83)	5.2 (0.50)	7.5 (0.76)	3.4 (0.42)	4.2 (0.68)
5c	15.0 (1.20)	12.5 (1.04)	12.0 (1.16)	10.2 (1.04)	9.0 (1.12)	6.4 (1.03)
5d	8.0 (0.64)	12.0 (1.0)	5.0 (0.48)	9.7 (0.99)	3.4 (0.42)	5.9 (0.95)
5e	13.0 (1.04)	8.0 (0.67)	10.6 (1.03)	5.1 (0.52)	8.2 (1.02)	3.0 (0.48)
5f	13.5 (1.08)	13.0 (1.08)	10.9 (1.06)	10.4 (1.06)	8.4 (1.05)	6.5 (1.04)
5g	14.0 (1.12)	13.2 (1.10)	11.0 (1.07)	10.4 (1.06)	8.3 (1.03)	6.5 (1.04)
5h	12.5 (1.0)	13.0 (1.08)	10.0 (0.97)	10.3 (1.05)	6.1 (0.76)	6.4 (1.03)
5i	13.0 (1.04)	14.0 (1.16)	10.7 (1.04)	11.0 (1.12)	8.2 (1.02)	6.6 (1.06)
5j	13.5 (1.08)	12.0 (1.0)	11.0 (1.07)	9.6 (0.98)	8.6 (1.07)	5.9 (0.95)

IZ = Inhibition area (zone) excluding diameter of disc
AI (Activity Index) = Inhibition area of sample/inhibition area of standard

Table II —Antifungal activity data of compounds **5a-j**

Compd	Mean value of area of inhibition in mm (800 ppm) IZ (AI)		Mean value of area of inhibition in mm (400 ppm) IZ (AI)		Mean value of area of inhibition in mm (200 ppm) IZ (AI)	
	C. albicans	*A. niger*	*C. albicans*	*A. niger*	*C. albicans*	*A. niger*
Ketoconazole	15	12	12.1	10.0	10.2	7.6
5a	12 (0.80)	9 (0.75)	9.2 (0.76)	6.7 (0.67)	7.3 (0.71)	4.2 (0.55)
5b	13.5 (0.90)	09 (0.75)	10.2 (0.84)	6.9 (0.69)	8.1 (0.79)	4.3 (0.56)
5c	15.0 (1.0)	15.5 (1.29)	12.0 (0.99)	12.0 (1.20)	10.1 (0.99)	8.9 (1.17)
5d	8.5 (0.57)	8.0 (0.67)	5.1 (0.42)	6.0 (0.60)	3.2 (0.31)	03 (0.39)
5e	15.5 (1.03)	12.0 (1.0)	12.3 (1.02)	10.0 (1.0)	10.3 (1.01)	7.5 (0.99)
5f	6.0 (0.40)	7.0 (0.58)	4.1 (0.34)	05 (0.50)	3.3 (0.32)	3.5 (0.46)
5g	7.0 (0.46)	9.2 (0.76)	5.4 (0.45)	7.0 (0.70)	3.8 (0.37)	4.1 (0.53)
5h	8.2 (0.54)	7.3 (0.61)	6.4 (0.53)	5.5 (0.55)	5.3 (0.51)	4.1 (0.53)
5i	10.5 (0.70)	11.0 (0.92)	6.8 (0.56)	8.9 (0.89)	5.1 (0.50)	6.2 (0.81)
5j	12.5 (0.83)	13.0 (1.08)	9.1 (0.75)	10.7 (1.07)	7.0 (0.69)	7.9 (1.04)

IZ = Inhibition area (zone) excluding diameter of disc
AI (Activity Index) = Inhibition area of sample/inhibition area of standard

compound **5f**, **5g**, **5h** showed higher degree of activity as compared to rest of the compounds against *E.coli* at 200, 400 and 800 ppm concentration. Compound possessing *m*-fluoro substituent in the arylidene moiety of the synthesized compound **5e** showed higher degree of activity as compared to rest of the compounds against *C.albicans* and the compounds possessing *o*-methoxy and 3,4-difluoro substituents in the arylidene moiety showed higher degree of activity against *A.niger* at 200, 400 and 800 ppm concentration.

Experimental Section

Melting points were determined in open glass capillary tubes and are uncorrected. The IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 557 grating infrared spectrophotometer in KBr pellets; ^1H NMR spectra in $CDCl_3$ (chemical shift in δ, ppm) on a Bruker spectrometer (200 MHz) using TMS as internal standard and mass spectra on a Esquire 3000 Bruker make spectrometer. The purity of the synthesized compounds was checked by TLC on silica gel G in

various nonaqueous solvent systems. All the compounds gave satisfactory elemental analyses.

Synthesis of 3-(4-chlorobenzylidene) pentane-2,4-dione 3a: A homogeneous mixture of 4-chlorobenzaldehyde (2.81 g, 20 mmoles), acetylacetone (2.0 g, 20 mmoles) and piperidine (0.02 mL) in chloroform (20 mL) was stirred at room temperature for about 50 hr. The mixture was diluted with chloroform and the piperidene was removed by washing with dilute hydrochloric acid followed by water. The chloroform layer was dried over $MgSO_4$. The solvent was removed and the solid residue was recrystallized from ethanol. Molecular formula $C_{12}H_{11}ClO_2$, yield 62%, m.p. 170°C; IR (KBr): 3055 (aromatic C-H str.), 2830 (aliphatic C-H str.), 1690 (>C=O str.), 1640 (>C=C< str.); ^{1}H NMR ($CDCl_3$): δ 2.90 (s, 6H, CH_3), 4.35 (s, 1H, CH), 7.21-7.40 (m, 4H, ArH). All other compounds **3b-j** were prepared similarly.

3-(2-chlorobenzylidene) pentane-2,4-dione 3b: Mol. formula $C_{12}H_{11}ClO_2$, yield 61%, m.p. 41°C; IR (KBr, cm^{-1}): 3054 (aromatic C-H str.), 2828 (aliphatic C-H str.), 1690 (>C=O str.), 1640 (>C=C str.).

3-(2-Methoxybenzylidene) pentane-2,4-dione 3c: Mol. formula: $C_{13}H_{14}O_3$, yield 65%, m.p. 98°C; IR (KBr, cm^{-1}): 3055 (aromatic C-H str.), 2835 (aliphatic C-H str.), 1692 (>C=O str.), 1640 (>C=C< str.).

3-(3,4,5-Trimethoxybenzylidene) pentane-2,4-dione 3d: Mol. formula: $C_{15}H_{18}O_5$, yield 60%, m.p. 85°C; IR (KBr, cm^{-1}); 3050 (aromatic C-H str.), 2845 (aliphatic C-H str.), 1680 (>C=O str.), 1648 (>C=C< str.), 1238 (C-O str.).

3-(3-Fluorobenzylidene) pentane-2,4-dione 3e: Mol. formula: $C_{12}H_{11}FO_2$, yield 59%, m.p. 100°C; IR (KBr, cm^{-1}): 3055 (aromatic C-H str.), 2830 (aliphatic C-H str,.), 1700 (>C=O str.), 1650 (>C=C< str.), 1265 (C-F str.).

1-(4-Chlorophenyl)-3-phenyl-2-(4-chlorobenzylidene) propane-1,3-dione 3f: Mol. formula: $C_{22}H_{14}Cl_2O_2$, yield 60%, m.p. 90°C, IR (KBr, cm^{-1}); 3055 (aromatic C-H str.), 1685 (>C=O str.), 1655 (>C=C< str.), 700 (C-Cl str.).

1-(4-Chlorophenyl)-3-phenyl-2-(4-fluorobenzylidene)propane-1,3-dione 3g: Molecular formula: $C_{22}H_{14}ClFO_2$, yield 55%, m.p. 165°C, IR (KBr, cm^{-1}): 3055 (aromatic C-H str.), 1690 (>C=O str.), 1645 (>C=C< str.), 1270 (C-F str.), 700 (C-Cl str.).

1-(4-Chlorophenyl)-2-(4-chlorobenzylidene) butane-1,3-dione 3h: Mol. formula: $C_{17}H_{12}Cl_2O_2$, yield 53%, m.p. 86°C, IR (KBr, cm^{-1}): 3051 (aromatic C-H str.), 2845 (aliphatic C-H str.), 1685 (>C=O str.), 1650 (>C=C< str.), 727 (C-Cl str.).

1-Phenyl-2-(4-fluorobenzylidene)butane-1,3-dione 3i: Mol. formula: $C_{17}H_{13}FO_2$, yield 64%, m.p. 96°C, IR (KBr, cm^{-1}): 3055 (aromatic C-H str.), 2830 (aliphatic C-H str.), 1686 (>C=O str.), 1640 (>C=C< str.), 1275 (C-F str.).

1-Phenyl-2-(3,4-difluorobenzylidene)butane-1,3-dione 3j: Mol. formula: $C_{17}H_{12}F_2O_2$, yield 61%, m.p. 88°C, IR (KBr, cm^{-1}): 3060 (aromatic C-H str.), 2830 (aliphatic C-H str.), 1685 (>C=O str.), 1650 (>C=C< str.), 1275 (C-F str.).

7-Chloro-2,4-dimethyl-3-(4-chlorobenzylidene)-3*H*-1,5-benzodiazepine 5a: A mixture of 4-chloro-1,2-phenylene diamine (1.42 g, 10 mmoles), 3-(4-chlorobenzylidene) pentane-2,4-dione (2.22 g, 10 mmoles) and gl. acetic acid (1.0 mL) in ethanol (25 mL) was refluxed for 7 to 8 hr. The reaction mixture was cooled, hydrochloric acid (12*N*, 10 mL) was added to it and the whole mixture was kept overnight at 0°C. The crystals of benzodiazepinium hydrochloride were filtered off, washed successively with cold ethanol, ether and dried. The crystals were recrystallized from ethanol. Treatment of 50% aqueous ethanolic solution of this hydrochloride with ammonia solution afforded the benzodiazepine free base. Mol. Formula: $C_{18}H_{14}Cl_2N_2$, Yield 45%, m.p. 140°C; IR (KBr): 3050 (aromatic C-H str.), 2838 (aliphatic C-H str.), 1651 (C=C str.), 1592 (>C=N str.), 1492 (aromatic C=C str.), 762 cm^{-1} (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ 2.83 (s, 6H, CH_3), 4.30 (s, 1H, CH), 7.28-8.15 (m, 7H, ArH); Mass (*m*/*z*) (%): M^+ 329.2 (11), 285.6 (44.5), 232.5 (100), 196.6 (13.5), 166.4 (82.3), 115.6 (2.7); Anal. Calcd for $C_{18}H_{14}Cl_2N_2$ (329): C, 65.65; H, 4.25; N, 8.51. Found: C, 65.55; H, 4.27; N, 8.49%.

All other compounds **5b-j** were prepared by same procedure.

7-Chloro-2,4-dimethyl-3-(2-chlorobenzylidene)-3*H*-1,5-benzodiazepine 5b: Yield 48%, m.p. 172°C; IR (KBr): 3055 (aromatic C-H str.), 2828 (aliphatic C-H str.), 1640 (C=C str.), 1597 (>C=N str.), 1468 (aromatic C=C str.), 756 cm^{-1} (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ 2.82 (s, 6H, CH_3), 3.79 (s, 1H, CH), 7.36-8.06 (m, 7H, ArH); Mass (*m*/*z*) (%): M^+ 329.3 (13), 272.4 (100), 193.6 (44.4), 180.1 (17.0), 164.6 (16.3), 136.8 (38.0), 134.8 (12.8), 132.6 (12.3); Anal. Calcd for $C_{18}H_{14}Cl_2N_2$ (329): C, 65.65; H, 4.25; N, 8.51. Found: C, 65.54; H, 4.26; N, 8.49%.

7-Chloro-2,4-dimethyl-3-(2-methoxybenzylidene)-3*H*-1,5-benzodiazepine 5c: Yield 47%, m.p. 176°C; IR (KBr): 3056 (aromatic C-H str.), 2838 (aliphatic C-H str), 1639 (C=C str.) 1597 (>C=N str.), 1463 (aromatic C=C str.), 1238 (C-O str.) 722 cm^{-1} (C-Cl

str.); Anal. Calcd for $C_{19}H_{17}ClN_2O$ (324.5): C, 70.26; H, 5.24; N, 8.63. Found: C, 70.14; H, 5.23; N, 8.61%.

7-Chloro-2,4-dimethyl-3-(3,4,5-trimethoxybenzylidene)-3*H*-1,5-benzodiazepine 5d: Yield 49%, m.p. 160°C; IR (KBr): 3050 (aromatic C-H str.), 2849 (aliphatic C-H str.), 1639 (C=C str.), 1590 (>C=N str.), 1238 (C-O str.), 725 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 2.35 (s, 6H, CH_3), 3.89 (s, 10H, OCH_3 + C*H*), 7.28-8.24 (m, 5H, ArH); Mass (*m*/*z*) (%): M^+ 384.8 (15), 351.8 (9.5), 318.5 (34.5), 288.5 (20.2), 257.6 (13.1), 230.4 (100), 195.5 (45.2), 180.5 (19.0), 151.6 (7.1), 63.4 (2.3); Anal. Calcd for $C_{21}H_{21}ClN_2O_3$ (384.5): C, 65.54; H, 5.46; N, 7.28. Found: C, 65.44; H, 5.44; N, 7.26%.

7-Chloro-2,4-dimethyl-3-(3-fluorobenzylidene)-*3H*-1,5-benzodiazepine 5e: Yield 46%, m.p. 145°C; IR (KBr): 3055 (aromatic C-H str.), 2829 (aliphatic C-H str.), 1638 (C=C str.), 1597 (>C=N str.), 1465 (aromatic C=C str.), 1270 (C-F str.), 757 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 2.40 (s, 6H, CH_3), 3.78 (s, 1H, CH), 7.35-8.06 (m, 7H, ArH); Mass (*m*/*z*) (%): M^+ 312.7 (15), 307.5 (63.4), 288.4 (28.3), 230.5 (82.3), 200.5 (100), 166.4 (21.6), 134.5 (24.3), 107.5 (4.0); Anal. Calcd for $C_{18}H_{14}ClFN_2$ (312.5): C, 69.12; H, 4.48; N, 8.96. Found: C, 69.01; H, 4.49; N, 8.94%.

7-Chloro-2-(4-chlorophenyl)-4-phenyl-3-(4-chlorobenzylidene)-3*H*-1,5-benzodiazepine 5f: Yield 50%, m.p. 150°C (d); IR (KBr): 3055 (aromatic C-H str.), 1640 (C=C str.), 1593 (>C=N str.), 1490 (aromatic C=C str.), 700 cm^{-1} (C-Cl str.); ^1H NMR ($CDCl_3$): δ 3.68 (s, 1H, CH), 6.68-8.09 (m, 16H, ArH); Anal. Calcd for $C_{28}H_{17}Cl_3N_2$ (487.5): C, 68.92; H, 3.49; N, 5.74. Found: C, 68.80; H, 3.50; N, 5.72 %.

7-Chloro-2-(4-chlorophenyl)-4-phenyl-3-(4-fluorobenzylidene)-3*H*-1,5-benzodiazepine 5g: Yield 53%, m.p. 100°C; IR (KBr, cm^{-1}): 3056 (aromatic C-H str.), 1637 (C=C str.), 1595 (>C=N str.), 1480 (aromatic C=C str.), 1273 (C-F str.), 703 (C-Cl str.); ^1H NMR ($CDCl_3$): δ 3.60 (s, 1H, CH), 6.70-8.06 (m, 16H, ArH); Anal. Calcd for $C_{28}H_{17}Cl_2FN_2$ (471): C, 71.34; H, 3.61;, N, 5.94. Found: C, 71.20; H, 3.62; N, 5.93%.

7-Chloro-2-(4-chlorophenyl)-4-methyl-3-(4-chlorobenzylidene)-3*H*-1,5-benzodiazepine 5h: Yield 49%, m.p. 156°C; IR (KBr, cm^{-1}): 3055 (aromatic C-H str.), 2849 (aliphatic C-H str.), 1655 (C=C str.), 1589 (>C=N str.), 1490 (aromatic C=C str.), 727 (C-Cl str.); ^1H NMR ($CDCl_3$): δ 2.80 (s, 3H, CH_3), 3.61 (s, 1H, CH), 7.13-8.14 (m, 11H, ArH); Mass (*m*/*z*) (%): M^+ 425.7 (20%), 420.4 (4.0), 394.6 (8.1), 348.6 (8.1), 338.6 (42.1), 324.6 (55.7), 310.6 (46.2), 262.3 (100), 238.5 (4), 226.5 (80), 206.4 (2.7); Anal. Calcd for $C_{23}H_{15}Cl_3N_2$ (425.5): C, 64.86; H, 3.52; N, 6.58. Found: C, 64.71; H, 3.53; N, 6.57%.

7-Chloro-2-phenyl-4-methyl-3-(4-fluorobenzylidene)-3*H*-1,5-benzodiazepine 5i: Yield 53%, m.p. 79°C; IR (KBr, cm^{-1}): 3055 (aromatic C-H str.), 2828 (aliphatic C-H str.), 1639 (C=C str.), 1590 (>C=N str.), 1473 (aromatic C=C str.), 1275 (C-F str.), 721 (C-Cl str.); ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H, CH_3), 3.80 (s, 1H, CH), 7.10-8.16 (m, 12H, ArH); Anal. Calcd for $C_{23}H_{16}ClFN_2$ (374.5): C, 73.70; H, 4.27; N, 7.48. Found: C, 73.58; H, 4.29; N, 7.47%.

7-Chloro-2-phenyl-4-methyl-3-(3,4-difluorobenzylidene)-3*H*-1,5-benzodiazepine 5j: Yield 54%, m.p. 96°C (d); IR (KBr, cm^{-1}): 3061 (aromatic C-H str.), 2830 (aliphatic C-H str.), 1657 (C=C str.), 1600 (>C=N str.), 1448 (aromatic C=C str.), 1275 (C-F str.), 765 (C-Cl str.); ^1H NMR ($CDCl_3$): δ 2.85 (s, 3H, CH_3), 3.91 (s, 1H, CH), 6.81-8.03 (m, 11H, ArH); Mass (*m*/*z*) (%): M^+ 392.8 (21%), 372.8 (8.0%), 351.6 (9.4), 329.7 (20.2), 314.7 (5.0%), 292.7 (100), 274.7 (6.5%), 260.6 (18.9), 228.6 (66.1), 166.4 (71.5); Anal. Calcd for $C_{23}H_{15}ClF_2N_2$ (392.5): C, 70.32; H, 3.82; N, 7.13. Found C, 70.21; H, 3.82; N, 7.11%.

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