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SYNTHESIS AND SPECTRAL CHARACTERISATION OF IMIDAZO [1,2A] PYRAZINE DERIVATIVES

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ABSTRACT
New pyrazine derivatives are synthesized in this work. 5-methyl 2-amino pyrazine reacted with 3-methyl 4-chloro phenyl acyl chloride to obtain 2- (4'-chloro 3' – methy1 pheny1) 6-methy1 imidazo [1,2a] pyrazine (1) which on reacting with NBS yielded 3-bromo 2- (4'-chloro 3' – methy1 pheny1) 6- methy1 imidazo [1,2 a] pyrazine (2). Compound 1 reacts with sodium acetate and formaldehyde in presence of AcOH gave (2 – (4' chloro 3' – methy1 phenyl) 6- methyl imidazo [1, 2 a] pyrazine – 3 – yl) methanol (3).This compound reacts with PBr_3 to produce 3-bromomethyl – 2-(4-chloro-3' methyl phenyl) 6-methyl imidazo [1, 2a] pyrazine (4). The same compound 3 reacts with thiophenol to produce 2 – (4'- chloro 3' – methyl phenyl) 6 – methyl 3 – ((phenylthio) methyl) imidazo [1, 2 a] pyrazine compound (5). 5-methyl 2-amino pyrazine dissolved in ethyl alcohol reacts with t-butyl bromomethyl ketone to produce 2-tert – butyl 6-methyl imidazo [1, 2a] pyrazine compound (6). Compound 6 reacts with NBS to give 2-tert – butyl 3- bromo 6- methyl imidazo [1, 2a] pyrazine compound (7). Compound 6 on reacting with formaldehyde in sodium acetate and acetic acid gave the compound (2 – tert – butyl 6 – methyl imidazo [1, 2a] pyrazine -3 –yl) methanol compound (8). The same compound 6 on reacting with thiophenol and acetic acid produced compound 2- tert – butyl 6 – methyl – ((phenylthio) methyl) imidazo [1,2a] pyrazine compound (9). Al these compounds (1-9) structure was confirmed with the help of IR, ^{1}H NMR and Mass spectral data.

KEYWORDS: Pyrazine derivatives, 5-methyl 2-amino pyrazine, 3-methyl 4-chloro phenyl acyl chloride, t-butyl bromomethyl ketone, IR, ^{1}H NMR and Mass spectra.

INTRODUCTION
Several structural analogues of the purines, pyridines pyrazines and pyrimidines are synthesized as potential chemotherapeutic and pharmacologically active agents.[1-3] Deazauridine, deazacytidine, azacytidine, azathymkidine and azauridine are the analogues of pyrazines and pyramidines and they show significant activity on different tumors. [4-11] An antibiotic emimycin 1, 2 dihydro-2-oxopyrazine 4- oxide structurally resembles with uracil.[12,13] Imidazo pyrazine and pyrimidines exhibit various pharmacological properties such as anti-inflammatory activity and β blocking activity[14-17] and show a wide variety of applications due to their biological activity and pharmacological activity [18,19] particularly as antiulcer agents,[20] congestive heart failure drugs,[21] and antiarrhythmic agents etc.[22]

Pyrazolo pyridines and imidazo pyridines were selective to inhibition against herpesvirus family which is highly disseminated in nature. The discovery of acyclovir [23] was the milestone in development of antiviral drugs and this was followed by a number of other nucleoside analogs – valacyclovir,[24] famciclovir[25] etc. Johns et al.[26] synthesised a series of pyrazo [1,5a] pyridines and they showed selective inhibition of HSV-1 and HSV-2. Gudmundsson and Johns [27] and Gudmundsson et al. [28] reported the synthesis of imidazo pyridine and its derivatives and their anti-HSV activity was studied. Gueiffer et al.[29-30] showed that 7, 8-dimethyl 3-phenyl methyl thiomethylimidazo [1,2a] pyridines are potent inhibitors of HCMV and VZV. Methyl substituted imidazo [1,2-a] pyrazine derivative were synthesised by Rimoli et al[31] and were reported to possess anti-inflammatory activity. Veron et al[32] synthesized several compounds analogous of the above compound. When biological evaluation was carried out on those compounds, it was found to be most potent against HCMV and VZV. Zimmermann et al.[33] synthesised a series of novel 6-substituted imidazo [1,2-a] pyrazines and reported the anti-secretary activity of gastric mucosa. Shailaja et al.[34] designed novel imidazo [1,2-a] pyrazine based inhibitors by condensing α – aminopyrazines with α – halocarbonyl compounds and their cytotoxic effects were evaluated. Therefore it is proposed to synthesize few more compounds with analogous structure and

elucidate their structure with help of spectral studies viz. IR, NMR and Mass.

EXPERIMENTAL

Melting points are determined on a Mel Temp apparatus and are uncorrected. The infrared absorption spectra were recorded on a Thermo Nicolet Nexus 670 Spectrometer and Perkin Elmer Infrared spectrophotometer as KBr pellet at Indian Institute of Chemical Technology (IICT), Hyderabad. Proton NMR spectra and ^{13}C NMR are recorded on AVANCS 300 Mez (Hz), GMINI 200 Mez (Hz) at IICT, Hyderabad. All spectra are taken in $CDCl_3$ or DMSO d_6. Mass Spectra are recorded on V G 7070 Hz micro mass spectrometer using CI low-resolution mode at IICT, Hyderabad.

PREPARATION OF 2 – (4'- CHLORO 3' – METHYL PHENYL) 6 – METHYL IMIDAZO [1,2a] PYRAZINE (1): 1.26 g (0.01 mole) 5 – Methyl 2 – amino pyrazine was dissolved in 5 ml of ethanol in a two necked round bottomed flask fitted with reflux condenser and 3.90 g (0.04mol) sodium bicarbonate was added to it at room temperature, then 2.3 g (0.01 mole) 3-Methyl 4 – chloro phenyl acyl chloride was also added at room temperature. This mixture was refluxed for about three hours. The progress of the reaction was monitored with the help of TLC. After the reaction was completed the reaction mixture was cooled to room temperature and sodium bicarbonate was filtered off. Ethanol was removed on rotovapour and washed with water. The product obtained was dried with anhydrous sodium sulphate and filtered. The filtrate was concentrated and purified by neutral alumina column chromatography by taking n-hexane and ethyl acetate (7:3) and (1:1). A colorless power was obtained.

^{13}C NMR data in δ ppm from TMS as internal standard: 19.0, 25.4, 106.5 (C_2), 139.2 (C_3) 142.2 (C_5), 155.1 (C_7), 117.1 (C_8), 133.4 (C_9), 124.5, 129.0, 130.7, 132.4, 135.6, 136.9 (aromatic)

PREPARATION OF 3 – BROMO 2 – (4'- CHLORO 3' – METHYL PHENYL) 6 – METHYL IMIDAZO [1,2 a] PYRAZINE (2): 250 mg (0.01 m mol) of 2.(4'-chloro-3'-methyl)6-methyl imidezo(1,2a) pyrazine dissolved in 5 ml of EtOH was taken in a two necked round bottomed flask with a $CaCl_2$ guard tube and 319.36 mg (0.01 m mol) N – bromosuccinamide (NBS) was added and stirred at room temperature for 24 hours. The progress of the reaction was monitored with by TLC. Once the reaction was complete, ethanol was removed by rotovapour. The remaining material was dissolved in ethyl acetate washed with water in a separating funnel. The organic layer was obtained as a gummy material. This gum material was dissolved in n-hexane and scratched for three hours. Brown colour powder was obtained.

PREPARATION of (2 – (4' CHLORO 3 – METHYL PHENYL) 6 – METHYL IMIDAZO [1, 2 a] PYRAZINE -3 – YL) METHANOL (3) : 2 – (4' – chloro 3' – methyl phenyl) 6- methyl imidazo [1,2 a] pyrazine 1 g (0.003mol) was dissolved in 1.6 ml (0.02mol) acetic acid. To this mixture 1.78g (0.01 mol) sodium acetate was added and dissolved with stirring. Then 0.94ml (0.03 mol) formaldehyde solution was added with the help of separating funnel and refluxed at 50^0 C for 24 hours in paraffin liquid oil bath. The progress of the reaction mixture was monitored with the help of TLC. The reaction mixture was cooled to room temperature and saturated solution of sodium bicarbonate was added and filtered. The organic layer separated was dried with anhydrous sodium sulphate and filtered. Organic layer was concentrated on rotovapour and purified by neutral alumina column chromatography by taking n-hexane and ethyl acetate (7:3) and (1:1).

PREPARATION OF 3 – BROMOMETHYL 2 – (4' – CHLORO 3' – METHYL PHENYL) 6 – METHYL IMIDAZO [1,2 a] PYRAZINE (4): 220 mg (0.9 m mol) (2 – (4' chloro 3 – methyl phenyl) 6 – methyl imidazo [1,2 a] pyrazine – 3 – yl) methanol was dissolved in ether (86.3 ml). The solution was kept at – 5^oC with the help of dry ice and closed with a septum and then 0.08 ml (0.9 m mol) phosphorus tribromide was added very slowly for half hour with stirring at the lower temperature by using a syringe. After the addition was completed, the temperature was slowly increased to room temperature and stirred for 12 hours. The progress of the reaction was monitored with TLC. The product was quenched with potassium bromide and then ether was added. The reaction mixture was concentrated to get a light brown powder.

PREPARATION OF 2 – (4'- CHILORO 3' – METHYL PHENYL) 6 – METHYL 3 – ((PHENYLTHIO) METHYL) IMIDAZO [1,2 a] PYRAZINE (5): 200mg (06m mol) (2-(4' Chloro 3- methyl phenyl) 6 – methyl Imidazo [1, 2a] pyrazine – 3 – yl) methanol was dissolved in 5 – 7 ml acetic acid and 0.06 ml (0.6 m mol) of thiophenol was added very slowly with the help of a syringe and stirred at room temperature for 24 hours. The progress of the reaction was monitored with TLC. The reaction mixture was cooled to room temperature and a saturated solution of sodium bicarbonate was added. It was extracted with ethyl acetate and washed with water. The organic layer separated was dried with anhydrous sodium sulphate and filtered. It was concentrated on rotovapour. It was purified by neutral alumina column chromatography by taking n-hexane and ethyl acetate (7:3) and (1:1).

PREPARATION OF 2 – tert – BUTYL 6 METHYL IMIDAZO [1,2 a] PYRAZINE (6): 4.07 g (0.03 mol) 5 – Methyl 2 – amino pyrazine was dissolved in 14 ml ethanol in a two necked round bottomed flask fitted with reflux condenser and 9.40 g (0.11 mol) sodium bicarbonate was added. To this t-butyl bromomethyl

ketone 5.0 ml (0.03 mol) was added at room temperature and the mixture was refluxed for three hours. The progress of the reaction was monitored by TLC. When the reaction was complete, reaction mixture was cooled to room temperature sodium bicarbonate was filtered off. From the filtrate the solvent ethanol was removed on rotovapour and washed with water. The product obtained was dried with anhydrous sodium sulphate and filtered. The filtrate was concentrated and purified by neutral alumina column chromatography by taking n-hexane and ethyl acetate (7:3) and (1:1).

^{13} C NMR data in δ ppm from TMS as internal standard: 25.7, 30.7, 37.3, 108.5 (C_2), 133.2 (C_3) 142.7 (C_5), 152.1 (C_7), 117.1 (C_8), 135.4 (C_9).

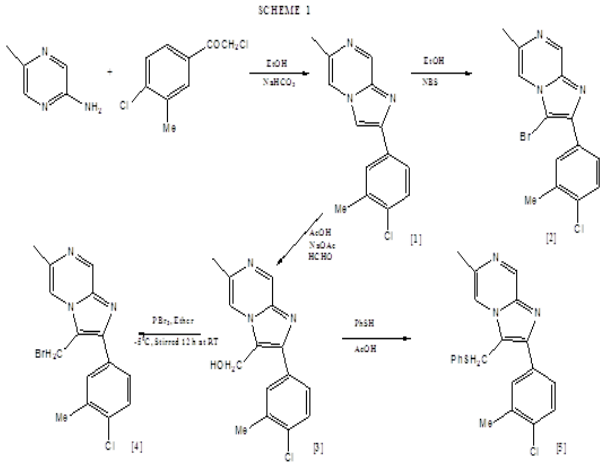
PREPARATION OF 2 – tert – BUTYL 3 – BROMO 6 METHYL IMIDAZO [1,2 a] PYRAZINE (7): In a two necked round bottomed flask fitted with a calcium chloride guard tube 2 – t – butyl 6 – methyl imidazo [1,2 a] pyrazine 1.0 g (0.005 mol) was dissolved in 5 ml ethanol and 1.40 g (0.007 mol) N – bromosuccinamide was added and stirred at room temperature for 24 hours. The progress of the reaction was monitored with the help of TLC. Once the reaction was completed, ethanol was removed on rotovapour. The remaining material was dissolved in ethyl acetate and washed with water in a separating funnel. The organic layer was separated as a gummy material. This gum was dissolved in n-hexane and scratched for three hours. Brown colour powder was obtained.

PREPARATION OF (2 – tert – BUTYL 6 – METHYL IMIDAZO [1,2 a] PYRAZINE – 3 – YL) METHANOL (8): 2 –t-butyl 6 – methyl imidazo [1,2 a] pyrazine 1.65 g (0.008 mol) was dissolved in 17 ml acetic acid. To this mixture 4.06 g (0.03 mol) sodium acetate was added and stirred. Then 2.14 ml (0.07 mol) formaldehyde solution was added with the help of separating funnel and refluxed at 50 ^{0}C for 24 hours in paraffin liquid oil bath. The progress of the reaction mixture was monitored with TLC. The reaction mixture was cooled to room temperature and saturated solution of sodium bicarbonate was added filtered. The filtrate was extracted with ethyl acetate and washed with water. The organic layer separated was dried with anhydrous sodium sulphate and filtered. The filtrate was concentrated on rotovapour. It was purified by neutral alumina column chromatography by taking n-hexane and ethyl acetate (7:3) and (1:1).

PREPARATION OF 2 – tert – BUTYL 6 – METHYL 3 – ((PHYNYLTHIO) METHYL) IMIDAZO [1,2 a] PYRAZINE (9): 200 mg 0.9 m mol) (2 – tert – buty 1, 8a – dihydro 6 – methyl imidazo [1,2 a] pyrazine – 3 – yl) methanol was dissolved in 3 – 4 ml acetic acid. To it 0.08 ml (0.8 m mol) of thiophenol was added very slowly with the help of a syringe and stirred at room temperature for 24 hours. The progress of the reaction was monitored with TLC. The reaction mixture was cooled to room temperature and saturated solution of sodium bicarbonate was added and filtered. It was extracted with ethyl acetate and washed with water. The organic layer separated was dried with anhydrous sodium sulphate and filtered. Organic layer was concentrated on rotovapour. It was purified by neutral alumina column chromatography by taking n-hexane and ethyl acetate (7:3) and (1:1).

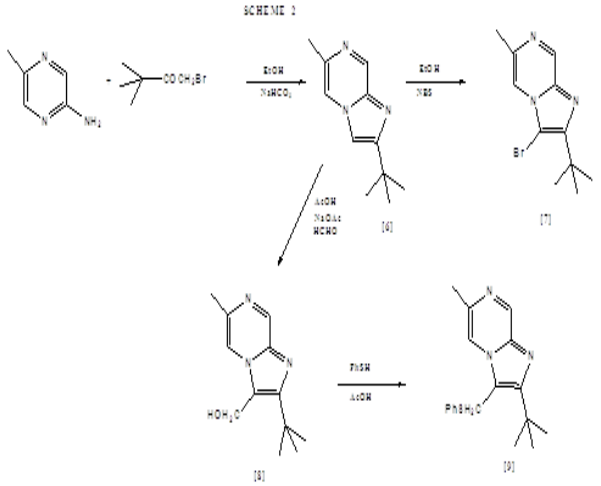
RESULTS AND DISCUSSION

New pyrazine derivatives were synthesized in the present work. The first series of five compounds were synthesised by reacting 5-methy1 2-amino pyrazine dissolved in ethanol with 3-methy1 4-chloro pheny1 acy1 chloride in presence of sodium hydrogen carbonate at room temperature and then refluxed for three hours. The product 2- (4'-chloro 3' – methy1 pheny1) 6-methy1 imidazo [1,2a] pyrazine (1) was so obtained on further reaction with N-bromosuccinimide in ethanol gave a 3-bromo 2- (4'-chloro 3' – methy1 pheny1) 6- methy1 imidazo [1, 2 a] pyrazine (2). Compound 1 on reaction with sodium acetate and formaldehyde in presence of acetic acid gave (2 – (4' chloro 3' – methy1 phenyl) 6-methyl imidazo [1, 2 a] pyrazine – 3 – yl) methanol (3). To the compound (3) prosphorous tribromide was added at - 5^0 C and stirred for 12 hours at room temperature to obtain the product 3-bromomethyl – 2-(4-chloro-3' methyl phenyl) 6-methyl imidazo [1, 2a] pyrazine (4). The compound 3 on further reaction with thiophenol in acetic acid gave 2 – (4'- chloro 3' – methyl phenyl) 6 – methyl 3 – ((phenylthio) methyl) imidazo [1, 2 a] pyrazine compound (5). These compounds synthesis are presented in scheme 1.



The second series of four compounds were synthesised by reacting 5-methyl 2-amino pyrazine dissolved in ethyl alcohol with t-butyl bromomethyl ketone in presence of sodium hydrogen carbonate at room temperature. The reaction mixture was refluxed for three hours. The product 2-tert – butyl 6-methyl imidazo [1, 2a] pyrazine compound (6) was worked up from the reaction mixture after bringing it to room temperature. This compound on reacting with N-bromosuccinimide in ethanol produced the compound 2-tert – butyl 3- bromo 6- methyl imidazo [1, 2a] pyrazine compound (7). Compound 6 on reacting

with formaldehyde, sodium acetate and acetic acid gave the compound (2 – tert – butyl 6 – methyl imidazo [1, 2a] pyrazine -3 –yl) methanol compound (8). The same compound 6 on reacting with thiophenol and acetic acid produced compound 2- tert – butyl 6 – methyl – (phenylthio) methyl) imidazo [1,2a] pyrazine (9) and all these reactions are shown in scheme 2.



The synthetic and physical data of **1-9** are presented Table 1. The infrared spectral study of all the title compounds **(1-9)** was made with a view to confirm to functional group present in them. The infrared spectral data of the compound **1-9** are presented in Table 1. All these compounds **(1-9)** exhibited characteristic absorption bands for C=N group in the region of 1654.4 - 1617.9 cm^{-1}.[35] These compounds exhibited characteristic infrared absorption bands in region of 2926.3-2923.5 for C-H stretching frequencies. [35] The compounds **[2, 4, 7]** exhibited characteristic infrared absorption bands in region of 649.4 – 618.5 cm^{-1} for C-Br stretching frequencies.[36] The compounds **[5, 9]** exhibited characteristic infrared absorption bands in region of 698.5 – 692.9 cm^{-1} for C-S stretching frequencies.[37] The compounds **[3, 8]** exhibited characteristic infrared absorption bands in region of 3383.6 – 3256.2 cm^{-1} for –OH stretching frequencies.[36]

The proton NMR chemical shifts of the compounds **[1-4 & 6-8]** are presented in Table 2**.** Aromatic protons of the title compounds display a complex multiplet in the range of (δ 7.3 - 7.4). In compounds **1-5** there are two methyl protons of CH_3 – one on the aromatic ring at 3' position and the other in the heterocycle at C-6 position. In the synthesized

Table – 1 Synthesis, Physical and IR data of 6 - Methyl Imidazo [1, 2a] Pyrazine Derivatives

Comp. No	Compound Name	Yield %	M.P. ^oC	IR frequencies in cm^{-1}				
				C = N	C - H	C -Br	C – S	-OH
1	2-(4'-Chloro 3'- methyl phenyl)-6-methylimidazo [1,2a] pyrazine	40	110 -120	1653.8	2923.8	-	-	-
2	3-Bromo-2-(4'-Chloro 3'-methyl phenyl)-6-methyl imidazo [1,2a] pyrazine	50	130 - 135	1654.4	2924.4	633.3	-	-
3	(2-(4'-Chloro 3'- methyl phenyl)-6-methylimidazo [1,2a] pyrazine-3yl) methanol	63	162-171	1649.9	2923.5	-	-	3256.2
4	3-(Bromomethyl)-2-(4'-chloro 3'- methyl phenyl)-6-methylimidazo [1,2a] pyrazine	61	110-120	1641.7	2925.2	649.4	-	-
5	2-(4'-Chloro 3'- methyl phenyl)-6-methyl 3-((phenylthio) methyl) imidazo [1,2a] pyrazine	46	-	1653.9	2924.4	-	692.9	-
6	2-t-Butyl 6-methyl imidazo [1,2a] pyrazine	53	72 - 75	1632.0	2925.1	-	-	-
7	2-t-Butyl 6-methyl imidazo [1,2a] pyrazine	45	75 - 80	1618.2	2926.1	618.9	-	-
8	2-t-Butyl 6-methyl imidazo [1,2a] pyrazine	73	70 - 75	1621.7	2926.3	-	-	3383.6
9	2-t-Butyl 6-methyl imidazo [1,2a] pyrazine	46	-	1617.9	2925.1	-	698.5	-

compounds these protons appear as singlets in the range of 2.1 – 2.6 δ ppm values.[38] For compounds 6, 7 & 8 tert-butyl methyl protons appear at 1.4 & 1.5 δ ppm, which are slightly low values and this may be due to the attachment to heterocycle causing slight deshielding.[38] The compounds **3, 4 & 8** with CH_2 protons appear at 4.7, 4.9 and 5.0 δ ppm.[39] Compounds **1 & 6** have C – H protons and they are recorded at 7.6 & 7.5 as singlets. These protons are part of the 5 membered heterocyle containing two nitrogen atoms. Hence, there is much deshielding effect on these protons and the same values are predicted by Chem. Draw Ultra 8.0 (2003) Cambridge soft ware corporation, Cambridge.

Table – 2 ^{1}H NMR Spectra of 6 – Methyl Imidazo [1, 2a] Pyrazine Derivatives in δ ppm (from TMS)

S.No.	Comp. No.	Ar-H	CH_3	CH_3	C_5	C_8	CH_2	CH	OH
1	1	7.3 (m)	2.1 (s)	2.5 (s)	8.9 (s)	8.1 (s)	-	7.6 (s)	-
2	2	7.3 (m)	2.4 (s)	2.6 (s)	9.0 (s)	8.1 (s)	-	-	-
3	3	7.4 (m)	2.4 (s)	2.6 (s)	8.9 (s)	8.4 (s)	4.7 (s)	-	2.7 (s)
4	4	7.4 (m)	2.4 (s)	2.6 (s)	8.8 (s)	8.2 (s)	4.9 (s)	-	-
5	6	-	1.4 (s)	3.0 (s)	8.8 (s)	8.0 (s)	-	7.5 (s)	-
6	7	-	1.5 (s)	2.6 (s)	8.9 (s)	7.8 (s)	-	-	-
7	8	-	1.4 (s)	2.5 (s)	8.9 (s)	8.1 (s)	5.0 (s)		2.5 (s)

Table -3: Mass Spectra of 6- Methyl Imidazo [1, 2a] Pyrazine Derivatives

Comp. No.	m/z (Relative abundance) %
1.	321 (15), 260 (20), 258 (50) ($M^{\cdot}$+), 217 (15), 187 (5), 173 (16), 151 (6), 143 (6), 129(3), 110(100).
2.	415 (32), 377 (25), 340 (25), 338 (100) ($M^{\cdot}$+), 336 (80), 238 (26), 142 (27), 129 (28).
3.	402 (20), 380 (22), 379 (22), 287 (25) ($M^{\cdot+}$), 260 (12), 237 (30), 231 (19), 213 (36), 189 (45), 190 (100)
4.	380 (39), 367 (100), 342 (31), 326 (89), 351 (25) ($M^{\cdot}$+), 310 (25), 289 (25), 142 (29), 122 (30).
5.	378 (11) ($M^{\cdot}$+), 364 (11), 342 (20), 319 (20), 305 (11), 289 (12), 275 (12), 142 (100), 101 (40).
6.	245 (19), 231 (45), 220 (100), 217 (42), 190 (32) ($M^{\cdot}$+), 187 (19), 173 (31).
7	285 (100), 283 (98), 270 (29), 268 (29) ($M^{\cdot}$+), 247(11), 245 (11).
8	220 (100) ($M^{\cdot+}$), 219 (40), 190(49), 102 (10).
9	312 (100) ($M^{\cdot+}$), 301 (8), 190 (55).

In these compounds C_5 & C_8 of pyrazine ring contains protons and are much deshielded due to high electronegative nitrogen atoms and π –electron cloud in the ring. The values recorded for these compounds as singlet for C_5 are in the range of 8.8 – 8.9 and for C_8 are in the range of 7.8 – 8.4 δ ppm.[39] Only two compounds 1 and 6 ^{13}C NMR was obtained. All the carbon atoms in these two compounds show values appropriate to the position of the carbon atoms. The C I mass spectral data of the compounds **(1-9)** are presented in Table 3. In compounds **(2, 8 and 9)** molecular Ion peak is the base peek, 338(100) ($M^{\cdot+}$), 220 (100) ($M^{\cdot+}$), 312 (100) ($M^{\cdot+}$). All other compounds showed the molecular ion peaks with good to moderate intensity.

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