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Synthesis and Antimicrobial Activity of Novel N-{[(5-chloro-1,3-benzoxazol-2-yl)thio]methyl}aniline derivatives

*[1]N. D.Jayanna, [1]K. M. Achuthananda,[1]Magdum.Prashant, [1]Madalagi. Kiran & [2]T. Manjuraj

*[1]Assistant professor Department of Chemistry, S. S. M. S. College, Belgaum, Karnataka, INDIA
[1]Assistant professor Department of Chemistry, S. S. M. S. College, Belgaum, Karnataka, INDIA
[2]Assistant professor, Department of Chemistry, DRM Science College, Davangere. INDIA.

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***Corresponding Author**

Email: jayanna007@gmail.com

ABSTRACT

Abstract: In the present study, series of benzoxazole mannich base derivatives containing substituted amine moiety were synthesized by single step reaction. The compounds (2-8) were synthesized by reacting 2 mercapto benzoxazole with amine derivatives in presence of formaldehyde. The newly synthesized molecules were characterized by IR, 1H NMR and mass spectral analysis. To all the compounds, the antimicrobial activity was evaluated. The compounds 3, 6 and 7 shows very good microbial activity

1. Introduction

Benzoxazoles belong to biologically very active skeletons1.Various benzoxazole derivatives were extensively studied for their antibacterial and antifungal activity4–5 anticancer activity6,7also as new non-nucleoside topoisomerase I poisons8and HIV-1 reverse transcriptase inhibitors9,10.Benzoxazoles are also interesting fluorescent probes which show high Stokes shift and present thermal and photophysical stability due to an excited state intramolecular proton transfer mechanism11,12.Since they interfere with biosynthesis of colored carotenoids by inhibiting the enzyme phytoenedesaturase, they are studied as potential bleaching herbicides13.Benzoxazoles can be considered as structural bioisosters of naturally occurring nucleotides such as adenine and guanine, which allow them to interact easily with the biopolymers of a living system. They have shown low toxicity in warm-blooded animals14.

The Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. tropinone). Other applications are in agro chemicals such as plant growth regulators,15 paint- and polymer chemistry, catalysts and main mechanism of formalin tissue crosslinking.TheMannich reaction is also used in the synthesis of medicinal compounds e.g. rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant), tramadol, and tolmetin (anti-inflammatory drug)and azacyclophanes,16-17

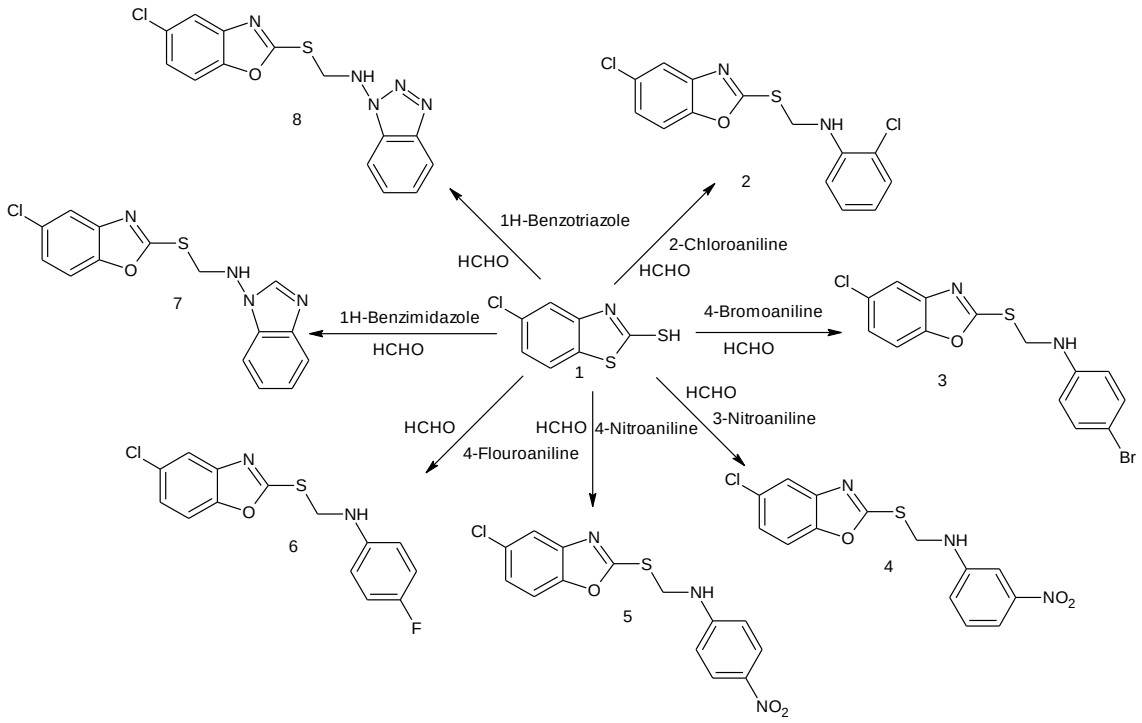
Considering these literatures we are plan to synthesize novel compounds which contains mannich derivatives of benzoxazole moiety.

2. Results and Discussions

Encouraged by the literature reports and to further assess the pharmacological profile of such a class of compounds, it was thought worthwhile to construct the benzoxazole nucleus, which subjected to Mannich base reaction to yield Mannich bases, which may impart enhanced biological activity to the resulting compounds and that we have to be check.

The synthetic strategy involved the following steps

- Synthesis of 5-chloro-1,3-benzoxazole-2-thiol1
- Synthesis of N-{[(5-chloro-1,3-benzoxazol-2-yl)thio]methyl}aniline(2-8)



Scheme-1: Synthetic route for the compounds (2-8)

The 2-mercapto benzoxazole was synthesized by refluxing the 5-choro aminophenol with carbon disulfide in ethanol. The obtained product was confirmed by spectral data and further used for the preparation of mannich base of different derivatives using formaldehyde. The target molecules were further confirmed by I R, NMR and Mass spectra. In IR spectra the peak for thiol group was absent in target molecules by not showing peak at 2225 cm-1. And also it again confirmed by absent of broad peak at 12 in target molecule followed by supporting Mass spectra by showing exact molecular ion peak. The amine derivatives after reacting with mercapto benzoxazole, there is lack of data for hydrogen in primary amines. A these evidence support the formation of mannich base by the reaction of 2-mercapto benzoxazole with amine derivatives to form mannich bases. The physical data of the synthesized compounds were tabulated in the Table-1

Table-1.
Physical data of synthesized compounds

Compound	R	Mol. Formula	Mol. Weight	M.P.	% Yield
1	--	C_7H_4ClNOS	185.6307	198^0C	92
2	-Cl	$C_{14}H_{10}ClN_2OS$	325.213	120^0C	89
3	-Br	$C_{14}H_{10}BrClN_2OS$	369.664	210^0C	90
4	$-NO_2$	$C_{14}H_{10}ClN_3O_3S$	335.766	178-179^0C	85
5	$-NO_2$	$C_{14}H_{10}ClN_3O_3S$	335.766	202^0C	87
6	-F	$C_{14}H_{10}ClFN_2OS$	308.758	192-193^0C	91
7	1*H*-Benzimidazole	$C_{15}H_{10}ClN_3OS$	315.777	208-210^0C	89
8	1*H*-Benzotriazole	$C_{14}H_9ClN_4OS$	316.765	245-251^0C	89

3. Experimental section

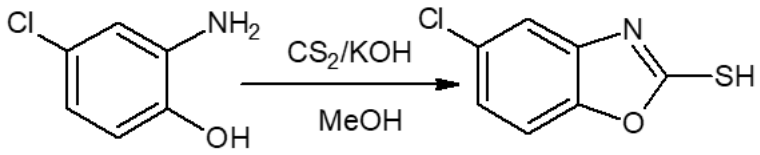
Chemistry

Melting points were recorded on electro thermal melting point apparatus and are uncorrected. ^{1}HNMR spectra were recorded on Bruker 400 MHz spectrometer. Chemical shifts were shown in □ values (ppm) with tetramethylsilane (TMS) as an internal standard. LC-MS were obtained using C18 column on Shimadzu, LCMS 2010A, Japan. The FT-IR spectra of compounds were taken in KBr pellets (100 mg) using Shimadzu Fourier transformed infrared (FT-IR)

spectrophotometer. The chemicals were purchased from Sigma Aldrich Co. and solvents for column chromatography were of reagent grade and purchased from commercial source.

3.1. Preparation of 5-chloro-1,3-benzoxazole-2-thiol 1

To a solution of methanol (50 mL), KOH (1.1eq) was added and stirred for 10 min followed by slow addition of CS_2 at room temperature. To the reaction mass2-amino-4, 6-dichlorophenol was addedon stirring. The reaction mass was refluxed for 6 h on water bath. Completion of reaction was confirmed by TLC. The reaction mass was poured onto ice cold water and acidified with glacial acetic acid (P^H6). The obtained solid was filtered, dried and recrystallized using ethanol.Yield (95%), M.P. 198°C.



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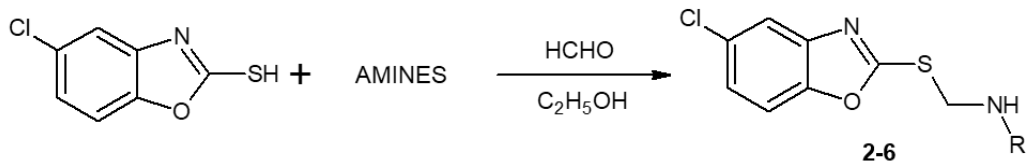
3.2. Synthesis of N-{[(5-chloro-1,3-benzoxazol-2-yl)thio]methyl}aniline (2-6)

A mixture of 6-chloro-1,3-benzoxazole-2-thiol (1g; 0.0053 mol), compounds of a to e and ethanol (30ml) was taken in a round bottom flask and 3-4 drops of hydrogen chloride was added drop wise to the reaction mixture with continuous stirring. After 15 minutes add formaldehyde (0.161g; 0.0053 mol) drop wise to the reaction mixture, and stirred for 30 minutes. The reaction mixture was refluxed for four hours. TLC was performed for the completion of the reaction. The product obtained was filtered, dried and recrystallized from ethanol.

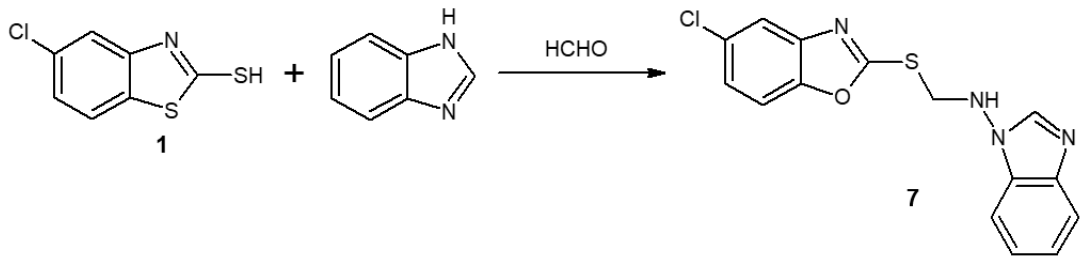


2-6

R= 2-Chloroaniline, 4-Bromoaniline, 3-Nitroaniline, 4-nitroaniline, 4-Fluoroaniline

3.3. Synthesis of 2-[(1H-benzimidazol-1-ylmethyl)sulfanyl]-5-chloro-1,3-benzoxazole7

A mixture of 6-chloro-1,3-benzoxazole-2-thiol (1g; 0.0053 mol), Benzimidazole (0.65g; 0.0053 mol) and ethanol (30ml) was taken in a round bottom flask and 3-4 drops of hydrogen chloride was added drop wise to the reaction mixture with continuous stirring. After 15 minutes add formaldehyde (0.161g; 0.0053 mol) drop wise to the reaction mixture, and stirred for 30 minutes. The reaction mixture was refluxed for four hours. TLC was performed for the completion of the reaction. The product obtained was filtered, dried and recrystallized from ethanol.

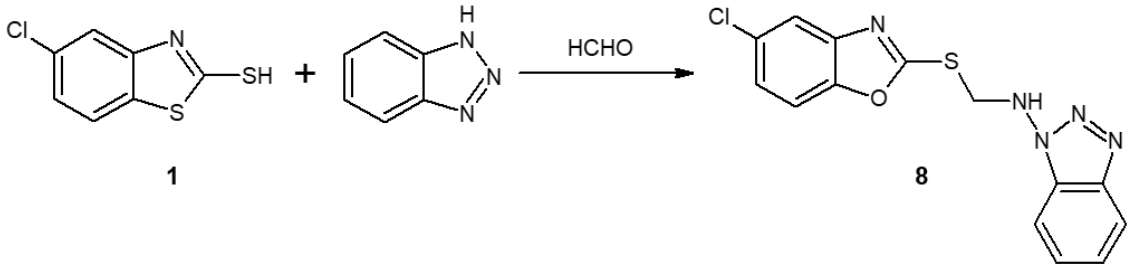


1 **7**

3.4 Synthesis of 1-{[(5-chloro-1,3-benzoxazol-2-yl)sulfanyl]methyl}-1H-benzotriazole

A mixture of 6-chloro-1,3-benzoxazole-2-thiol (1g; 0.0053 mol), Benzotriazole (0.64g; 0.0053 mol)and ethanol (30ml) was taken in a round bottom flask and 3-4 drops of hydrogen chloride was added drop wise to the reaction mixture with continuous stirring. After 15 minutes add formaldehyde (0.161g; 0.0053 mol) drop wise to the reaction

mixture, and stirred for 30 minutes. The reaction mixture was refluxed for four hours. TLC was performed for the completion of the reaction. The product obtained was filtered, dried and recrystallized from ethanol.



The obtained compounds characterized using I R, H NMR, and Mass Spectral analysis. The peak appeared at the region of 3.1 □□value corresponds for the methyle proton and the singlet at 9.3 □□value supports the presence of NH proton and the range between 7.6-7.8 regions respected to aromatic protons. The mass spectra exactly match with molecular weight of compounds **4** and **7**.

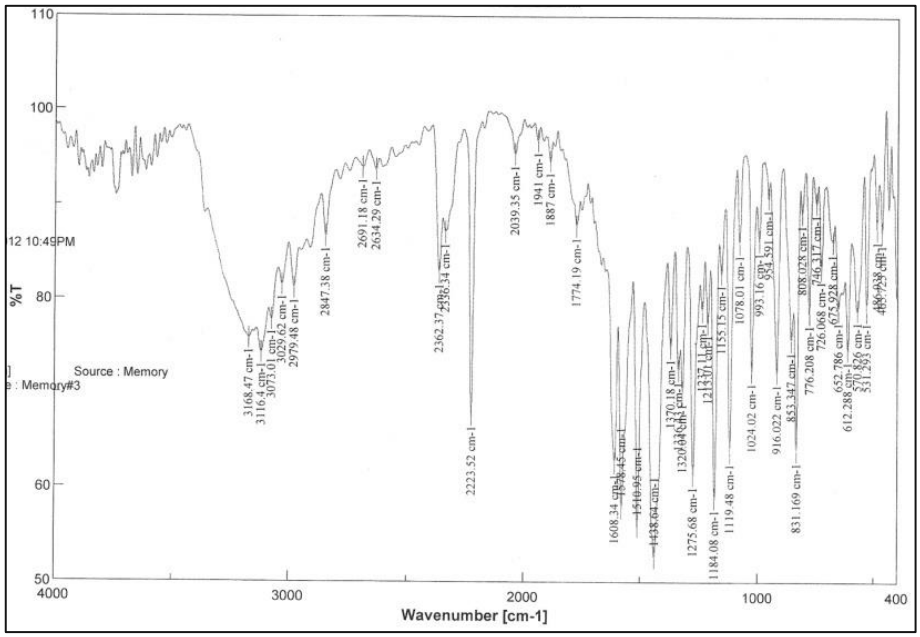


Fig 1. IR spectra of Copmound 4

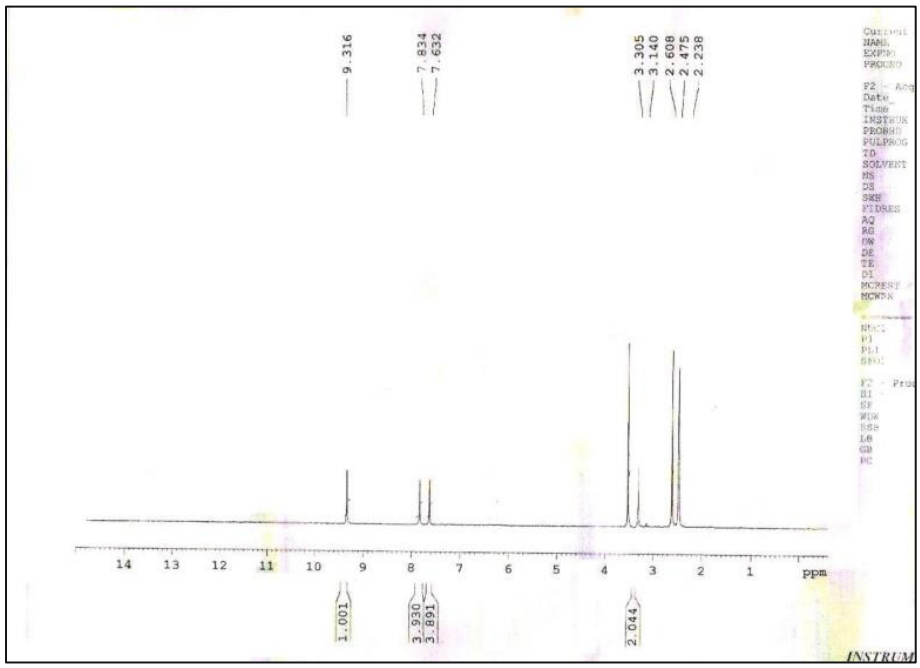


Fig 2. H NMR spectra of Compound 4

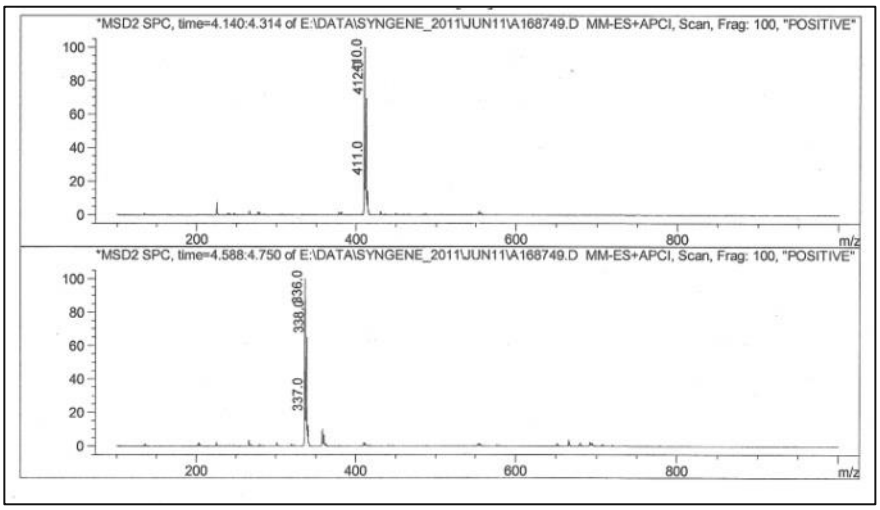


Fig 3. LCMS spectra of Compound 4

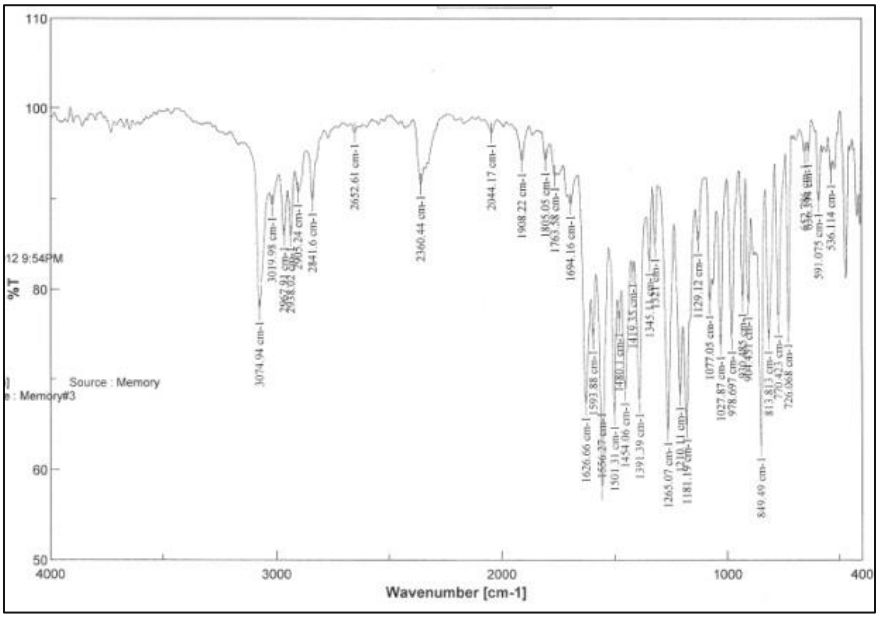


Fig 4. I R spectra of *Compound 7*

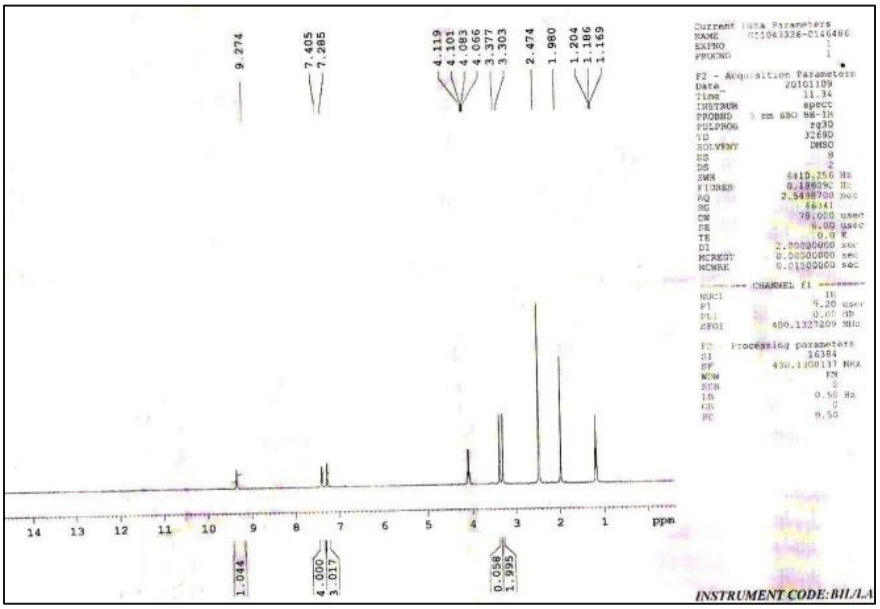


Fig 5. H NMR spectra of Compound 7

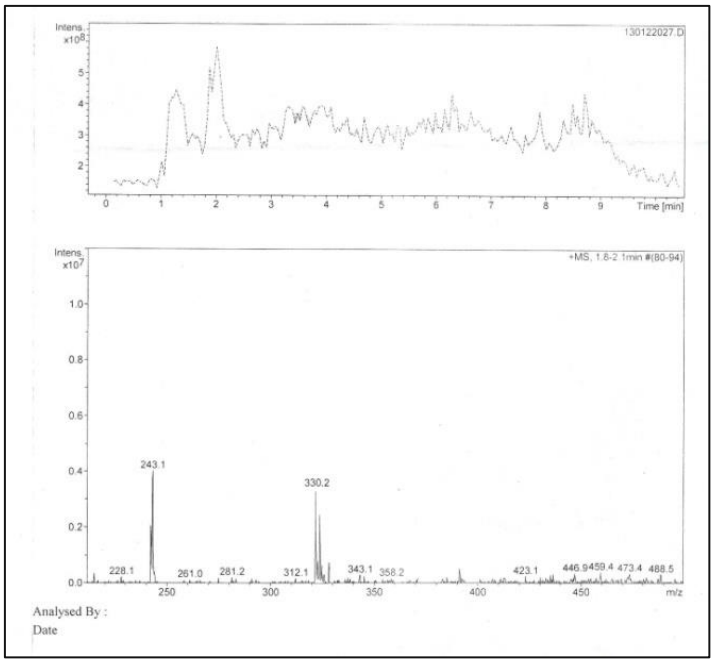


Fig 6. LCMS spectra of Compound 7

4. Biological activities

4.1 Antibacterial activity

The antibacterial efficacy of compounds was tested against two Gram positive bacteria namely Staphylococcus aureus and Bacillus cereus and Gram negative bacteria namely Pseudomonas aeruginosaand Escherichia coli by agar well diffusion method16.Twenty four old Muller-Hinton broth cultures of test bacteria were swabbed on sterile Muller-Hinton agar plates using sterile cotton swab followed by punching wells of 6mm with the help of sterile cork borer. The standard drug (Chloramphenicol, 1mg/ml of sterile distilled water), compounds 2(a-j) (20mg/ml in 10% DMSO) and control (10% DMSO) were added to respectively labeled wells. The plates are allowed to stand for 30 minutes and were incubated at 37oC for 24 h in upright position and the zone of inhibition was recorded. The compounds 3, 6 and 7 shows very good microbial activity and the results were tabulated in the Table-2.

Table-2

Antimicrobial Activities of the compounds (2-8)

Compound	**Zone of inhibition in (mm), concentration (µg/mL)**							
	S. aureus		***B. substillus***		***E. coli***		***P .aeruginosa***	
	20	**10**	**20**	**10**	**20**	**10**	**20**	**10**
2	14	12	15	12	12	---	14	11
3	**18**	**15**	**14**	**10**	**10**	**---**	**14**	**10**
4	14	11	13	10	10	---	11	---
5	13	10	12	---	10	---	11	---
6	**16**	**12**	**16**	**10**	**14**	**---**	**10**	**---**
7	**16**	**13**	**17**	**10**	**14**	**---**	**10**	**---**
8	13	11	11	10	10	---	09	---
DMSO	00	00	00	00	00	00	00	00
Standard	34	34	35	35	32	32	30	30

5. Conclusion

A series of benzoxazole mannich base derivatives containing substituted amine moiety were synthesized by single step reaction. . The newly synthesized molecules were characterized by IR, 1H NMR and mass spectral analysis. To all the compounds, the antimicrobial activity was evaluated. The compounds 3, 6 and 7 shows very good microbial activity and Remaining compounds also exhibit moderate activity has supported by docking studies.

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