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Synthesis, characterisation and antimicrobial activity of some pyrimidine derivatives from chalcones.

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ABSTRACT

Pyrimidine derivatives were synthesized by the reaction of chalcone and urea using KOH in ethanol as solvent. The corresponding pyrimidine derivatives were obtained in good yield. All the new compounds obtained were characterized by IR, ^{1}HNMR and MS. The antibacterial activity of synthesised compound was tested *in vitro* by the disc diffusion method against two gram +ve and two gram –ve bacteria. The result showed that some of the pyrimidine derivatives is moderate to good activity.

Keywords: Chalcone, pyrimidine, urea, antimicrobial activity.

INTRODUCTION

Pyrimidines are heterocyclic compound, contain two nitrogen atoms at position 1 and 3 of the six member ring. pyrimidine ring system has wide occurrence in nature as substituted and ring fused compounds and derivatives including the nucleotides, cytosine, thymine, uracil, thiamine and alloxan. pyrimidines are the most important class of heterocyclic compounds having their broad spectrum of applications in biological, pharmaceutical as well as agrochemical fields. pyrimidine derivative are found to exhibit good anticancer [1], antidepressant [2], antibacterial [3], antihelmintic [4], anticonvulsant [5], antitumor [6], antifungal [7], anti-tubercular [8], antonoceptive [9], anti-inflammatory [10], analgesic [11],

antiamoebic [12], antimycobacterial [13], herbicidal [14], anti-malerial [15], antihistamic [16] activities. derivatives of pyrimidine have played crucial role in the history of heterocyclic chemistry as important pharmacophore and starting material in the field of organic chemistry and medicinal chemistry.

The purpose of present studies is to synthesize the iodo/bromo/chloro substituted *o*-hydroxy substituted pyrimidines and study their antimicrobial activities.

METHODOLOGY

Material

The substituted chalcones [17, 18] were used for synthesis. The chemicals Urea (99.9%), ethanol and potassium hydroxide were obtained from SD Fine chemical Ltd and were used as such without further purification. The solvent was purified as per the standard procedure. Reflux method was used for synthesis of pyramidine derivatives **7(a-e)** and **8(a-e)**

All the synthesized compounds were characterized by spectral data (IR, ^{1}H-NMR, and Mass) which is consistent with the proposed structures. IR spectra of compounds were scanned on Schimadzu spectrophotometer (in KBr palletes). ^{1}H NMR spectra were recorded (in $CDCl_3$) on a Brucker instrument at 400 MHz using TMS as an internal standard. The mass spectra were recorded on EI-SHIMADZU-GC-MS spectrometer.

Experimental Section

Melting points were determined in open capillary tube using melting point apparatus and are uncorrected. The synthesized compounds were characterized by spectral data (IR, ^{1}H-NMR, and Mass) which is consistent with the proposed structures. IR spectra of compounds were scaned on Schimadzu spectrophotometer (in KBr palletes). ^{1}H NMR spectra were recorded (in $CDCl_3$) on a Brucker instrument at 400 MHz using TMS as an internal standard. The mass spectra were recorded on EI-SHIMADZU-GC-MS spectrometer. Reaction was monitored by TLC using silica gel plate and pet ether, ethyl acetate (7:3) as a eluent system. The spots were visualized in an ultraviolet light at δλ= 254-266nm.

Procedure for synthesis *of* 6-(2-bromo/4-hydroxy-3-methoxyphenyl)-4-(2-hydroxy-3,5-substituted-phenyl)pyrimidin-2(1*H*)-one *(7a)*.

A mixture of chalcone **(1a**) (0.001mol) and urea (0.002mol) in ethanol 20 ml and KOH 1gm was refluxed for 4-6hrs. Reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled at room temperature, and transferred in ice cold water (100 ml). Filtered washed and after drying recrystallized from ethanol.

RESULTS AND DISCUSSION

In the present work, newly synthesized pyrimidine derivative were prepared from different substituted chalcone **(1a-e) (2a-e)** react with urea in presence of ethanol. Reflux method was used for synthesis of pyramidine derivatives **7(a-e)** and **8(a-e).** Substitution pattern and yield for compounds **7(a-e)** and **8(a-e)** showed in **table 1**. The synthesized compounds were characterized by spectral data IR, ^{1}H-NMR, and Mass.

Spectral data of Synthesised Compounds

7a.6-(2-bromophenyl)-4-(5-chloro-2-hydroxy-3-iodophenyl) pyrimidin-2(1*H*)-one

IR(KBr, cm^{-1}): 3421(OH), 3303(N-H), 1696(C=O), 1456(C=C), 1656 (C=N); ^{1}H-NMR($CDCl_3$): δ 13.04(s, 1H, OH), δ 9.72(s, 1H, NH), δ 7.48-7.82 (m, 6H , Ar-H), δ 7.94(s, 1H, CH of pyrimidine); Mass: (M^+): *m/z* 503.

7b.4-(3-bromo-5-chloro-2-hydroxyphenyl)-6-(2-bromophenyl)pyrimidin-2(1*H*)-one

IR(KBr, cm^{-1}): 3441(OH), 3340(N-H), 1695(C=O), 1645 (C=N), 1456(C=C); ^{1}H-NMR($CDCl_3$): δ 13.10(s, 1H, OH), δ 9.50(s, 1H, NH), δ 7.35-7.76 (m, 6H , Ar-H), δ 7.78(s, 1H, CH of pyrimidine); Mass: (M^+): *m/z* 456.

8a.4-(3-bromo-2-hydroxy-5-methylphenyl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2(1*H*) one

IR(KBr, cm^{-1}): 3421(OH), 3332(N-H), 1697(C=O), 1651 (C=N), 1467(C=C); ^{1}H-NMR($CDCl_3$): δ 13.10(s, 1H, OH), δ 12.51(s, 1H, OH), δ 9.50(s, 1H, NH), δ 7.41-7.71 (m, 5H , Ar-H), δ 7.95(s, 1H, CH of pyrimidine), δ 2.66 (s, 3H, CH_3), δ 4.20(s, 3H, OCH_3); Mass: (M^+): *m/z* 403.

8b.4-(3-bromo-5-chloro-2-hydroxyphenyl)-6-(2-bromophenyl)pyrimidin-2(1*H*)-one
IR(KBr, cm^{-1}): 3458(OH), 3340(N-H), 1698(C=O), 1645 (C=N), 1460(C=C); ^{1}H-NMR($CDCl_3$): δ 13.10(s, 1H, OH), δ 12.68(s, 1H, OH), δ 9.29(s, 1H, NH), δ 7.50-7.76 (m, 5H , Ar-H), δ 7.75(s, 1H, CH of pyrimidine), δ 4.01(s, 3H, OCH_3); Mass: (M^+): *m/z* 423.

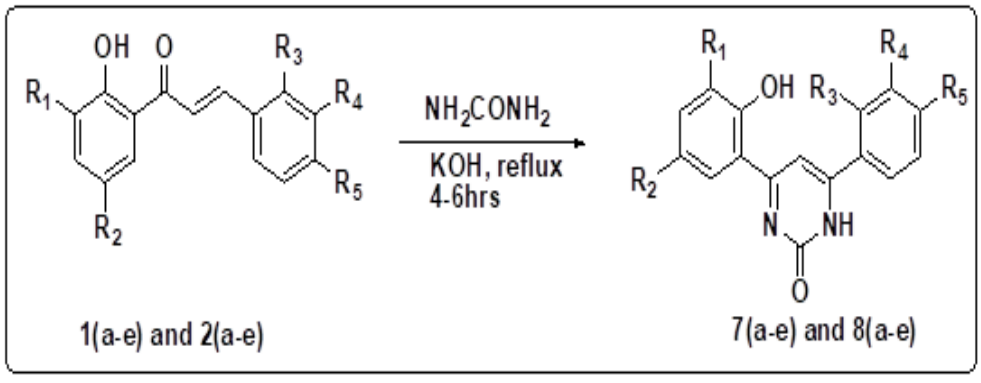
Table1: Substitution pattern and yield for compounds 7(a-e) and 8(a-e**)**

Entry	Product code	R_1	R_2	R_3	R_4	R_5
1.	**7a**	I	Cl	Br	H	H
2	**7b**	Br	Cl	Br	H	H
3	**7c**	I	I	Br	H	H
4	**7d**	Br	Br	Br	H	H
5	**7e**	Br	CH_3	Br	H	H
6	**8a**	Br	CH_3	H	OCH_3	OH
7	**8b**	Br	Cl	H	OCH_3	OH
8	**8c**	I	I	H	OCH_3	OH
9	**8d**	I	CH_3	H	OCH_3	OH
10	**8e**	I	Cl	H	OCH_3	OH

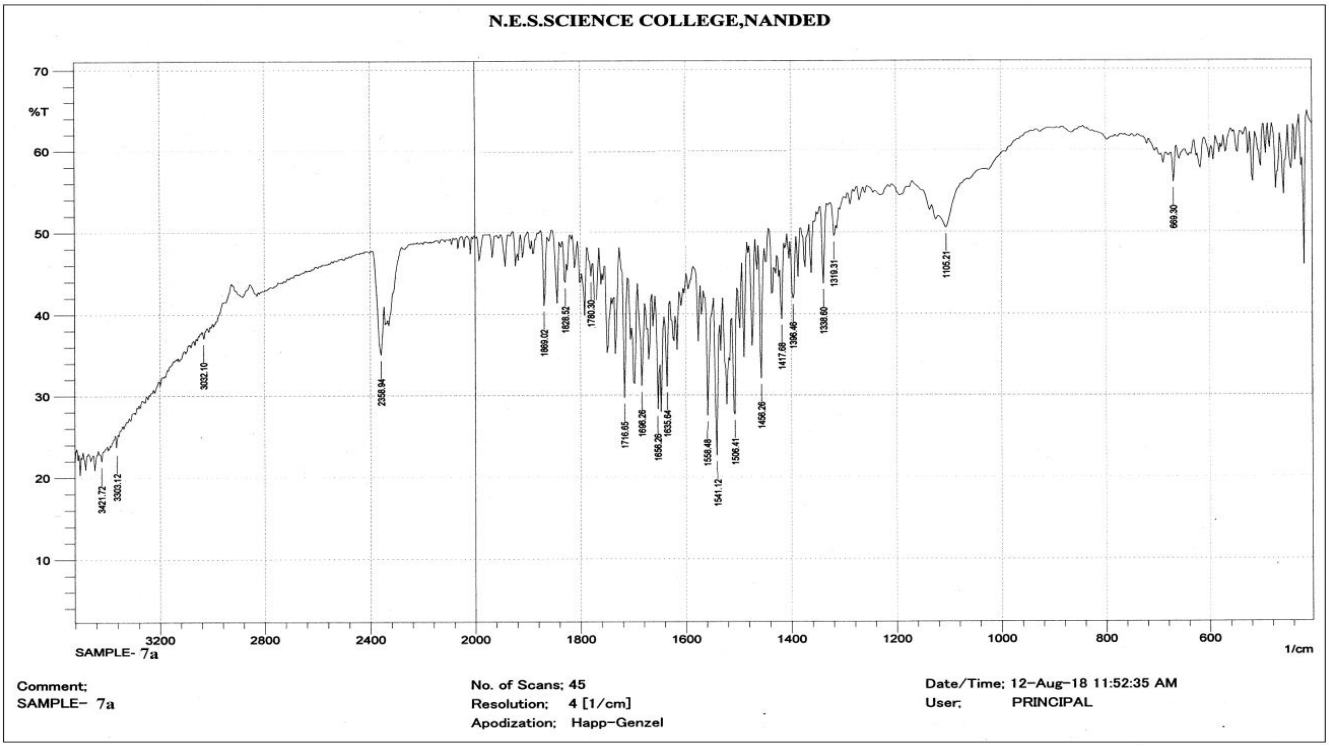
Table 2.: Antimicrobial activity

Sample	**Zone of inhibition (mm)**			
	Gram +ve		**Gram –ve**	
	B.subtilis	***S. aureus***	***E.coli***	***S.typhi***
Penicilline	**28mm**	**26mm**	**30 mm**	**28 mm**
7a	**19**	**16**	**14**	**17**
7b	**17**	**13**	**15**	**09**
7c	--	--	06	--
7d	**20**	**18**	**16**	**18**
7e	03	--	05	--
8a	06	08	06	09
8b	05	07	09	08
8c	06	09	20	--
8d	04	--	05	--
8e	05	--	--	--

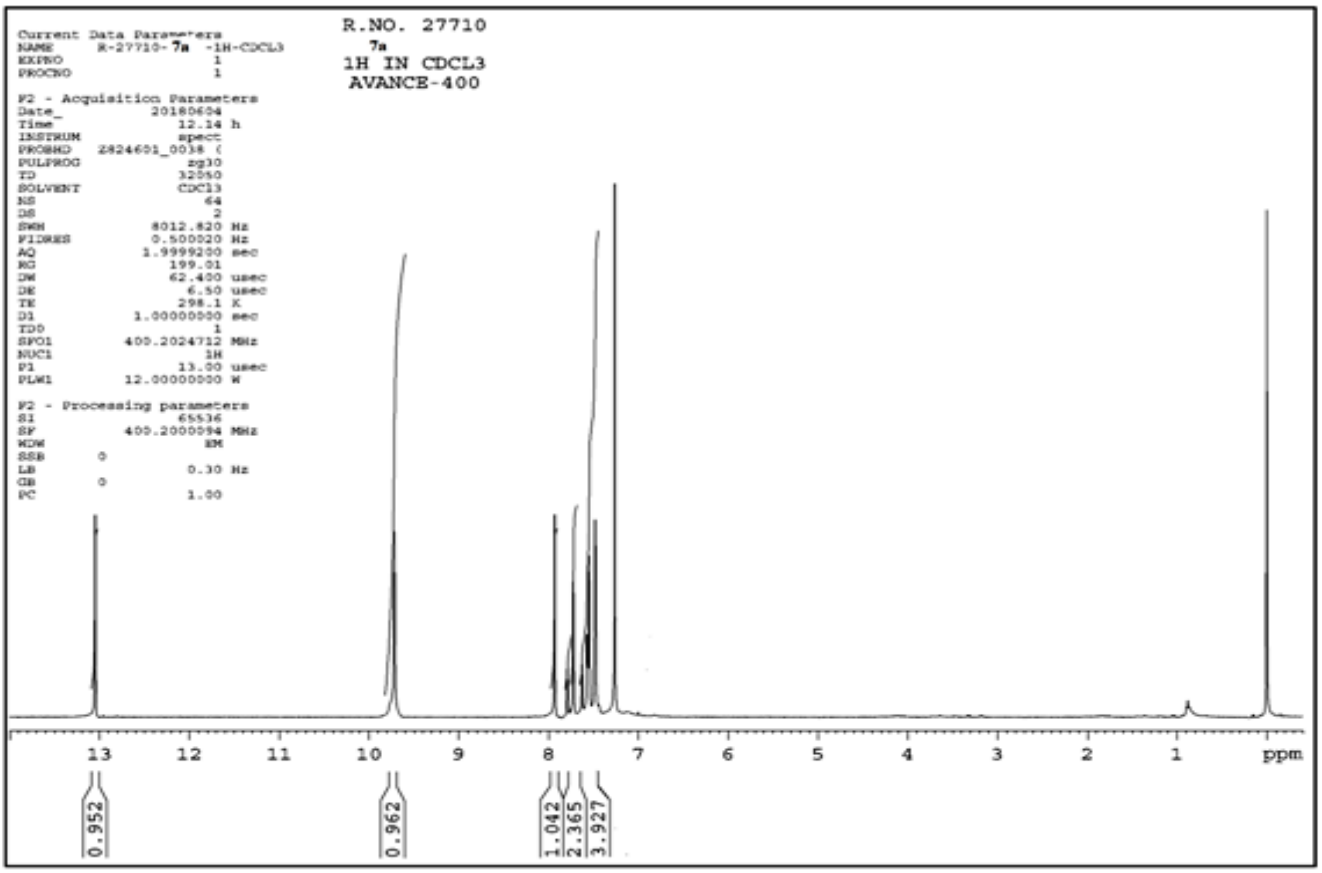
Scheme



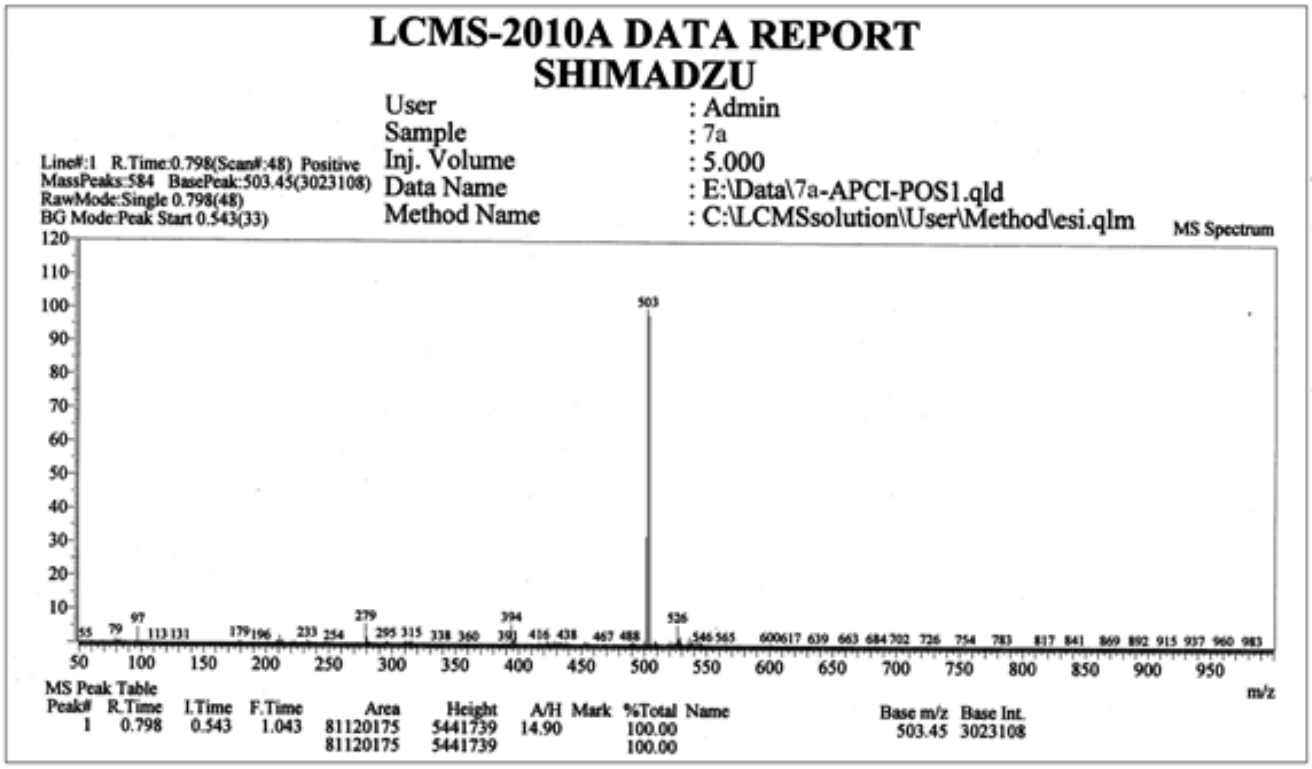
Spectra of synthesised Compounds
Sample : 7a (IR)



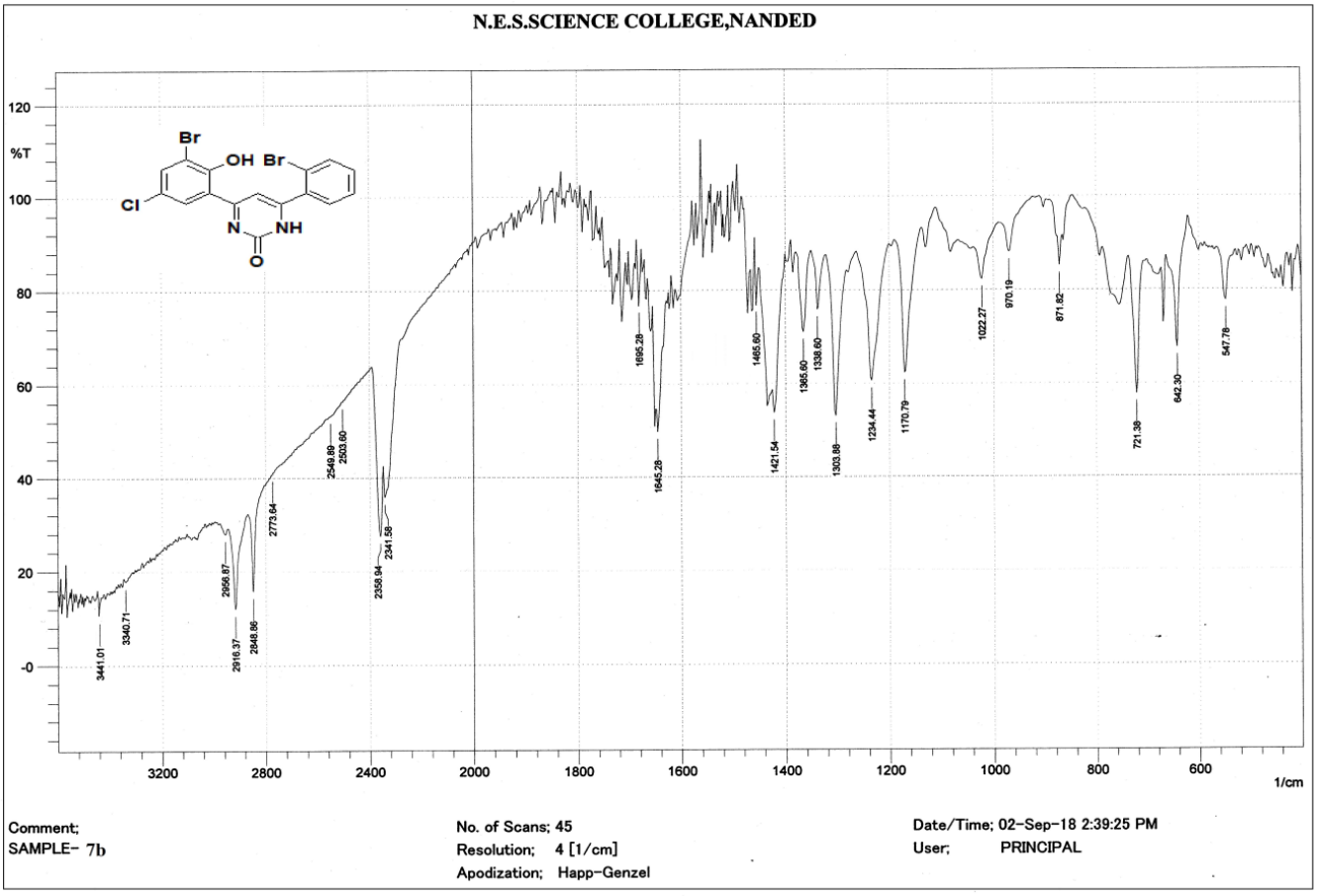
sample : 7a (IHNMR)



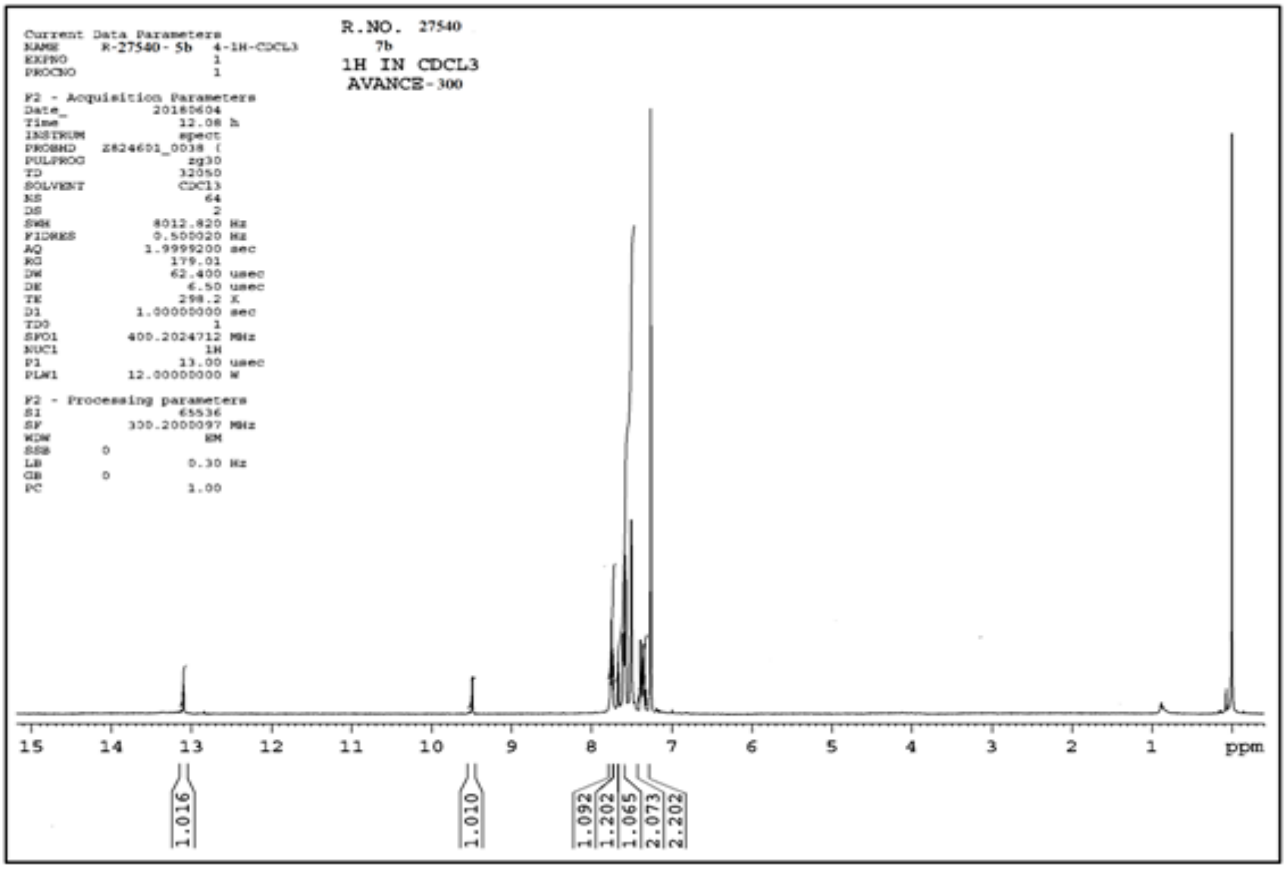
sample: 7a(MASS)



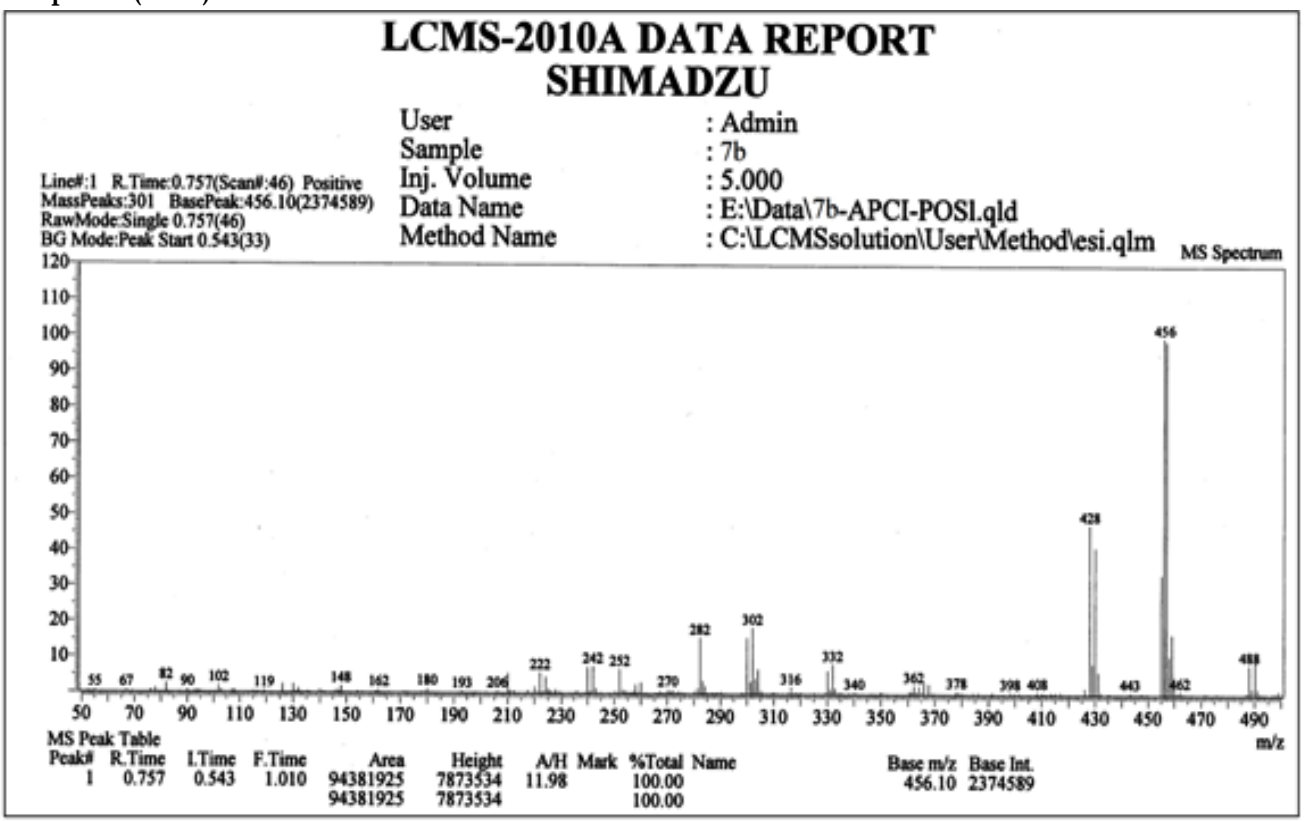
Sample: 7b (IR)



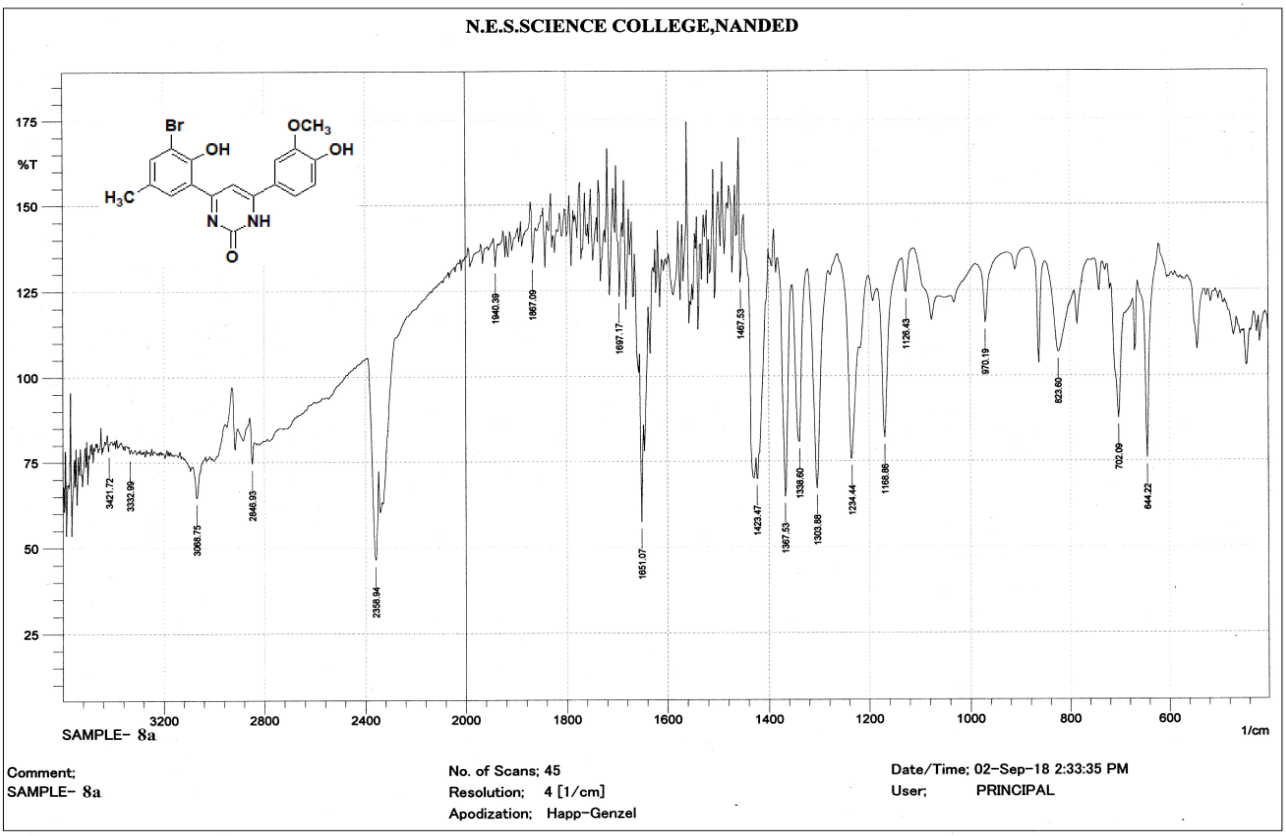
sample: 7b (IHNMR)



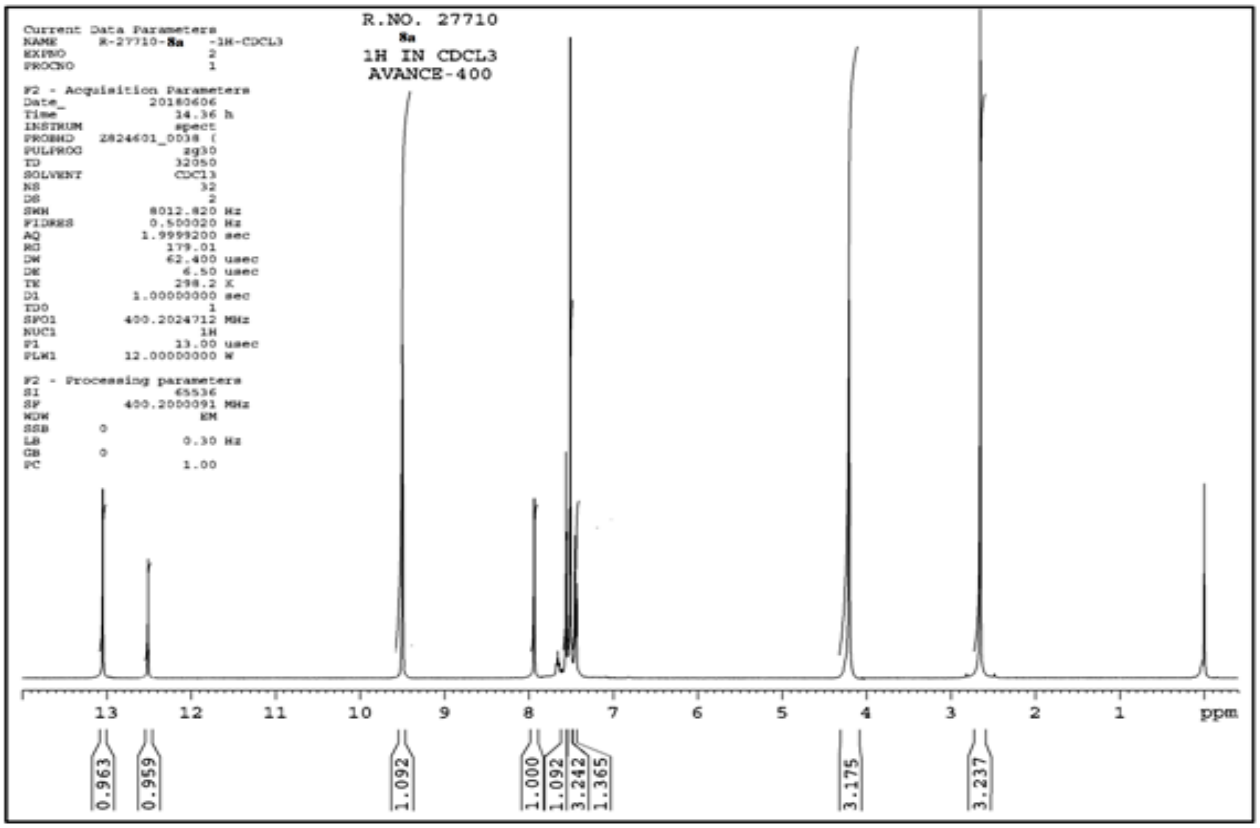
Sample:7b (mass)



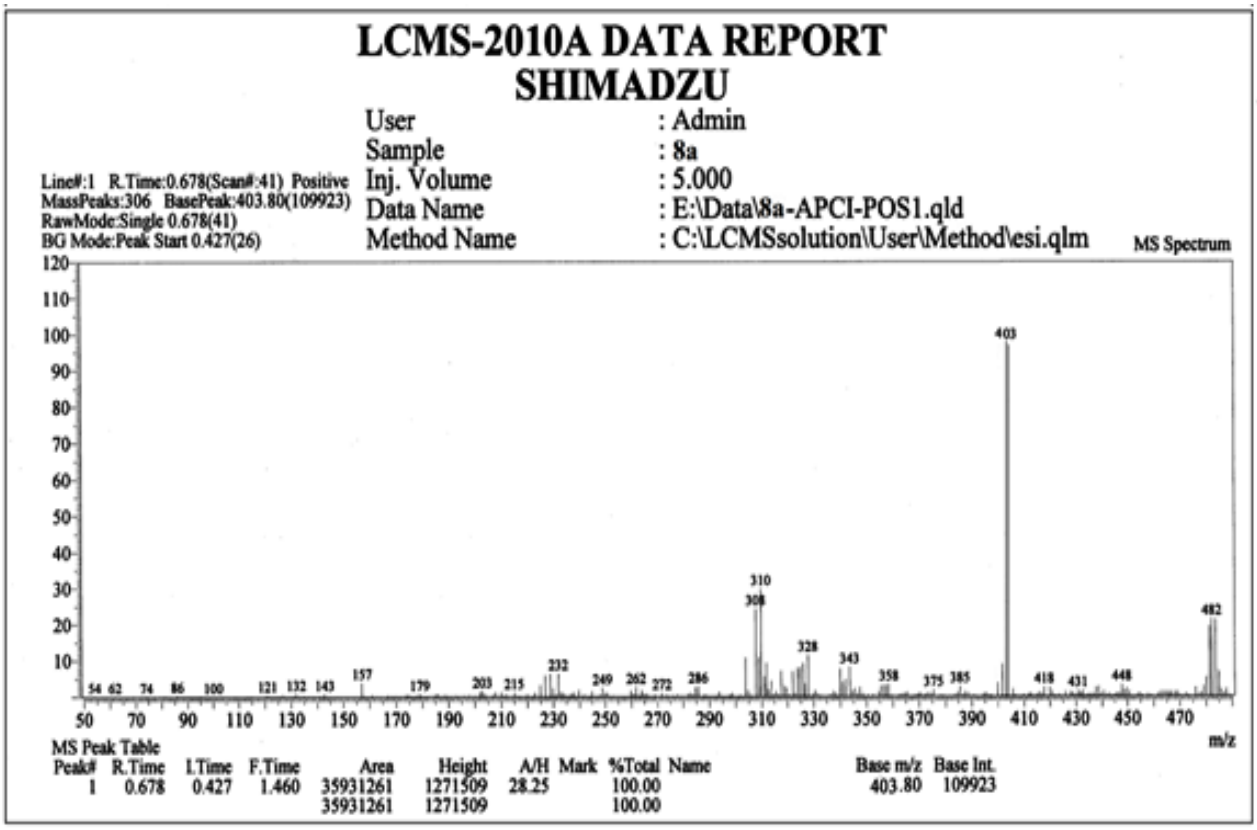
Sample: 8a (IR)



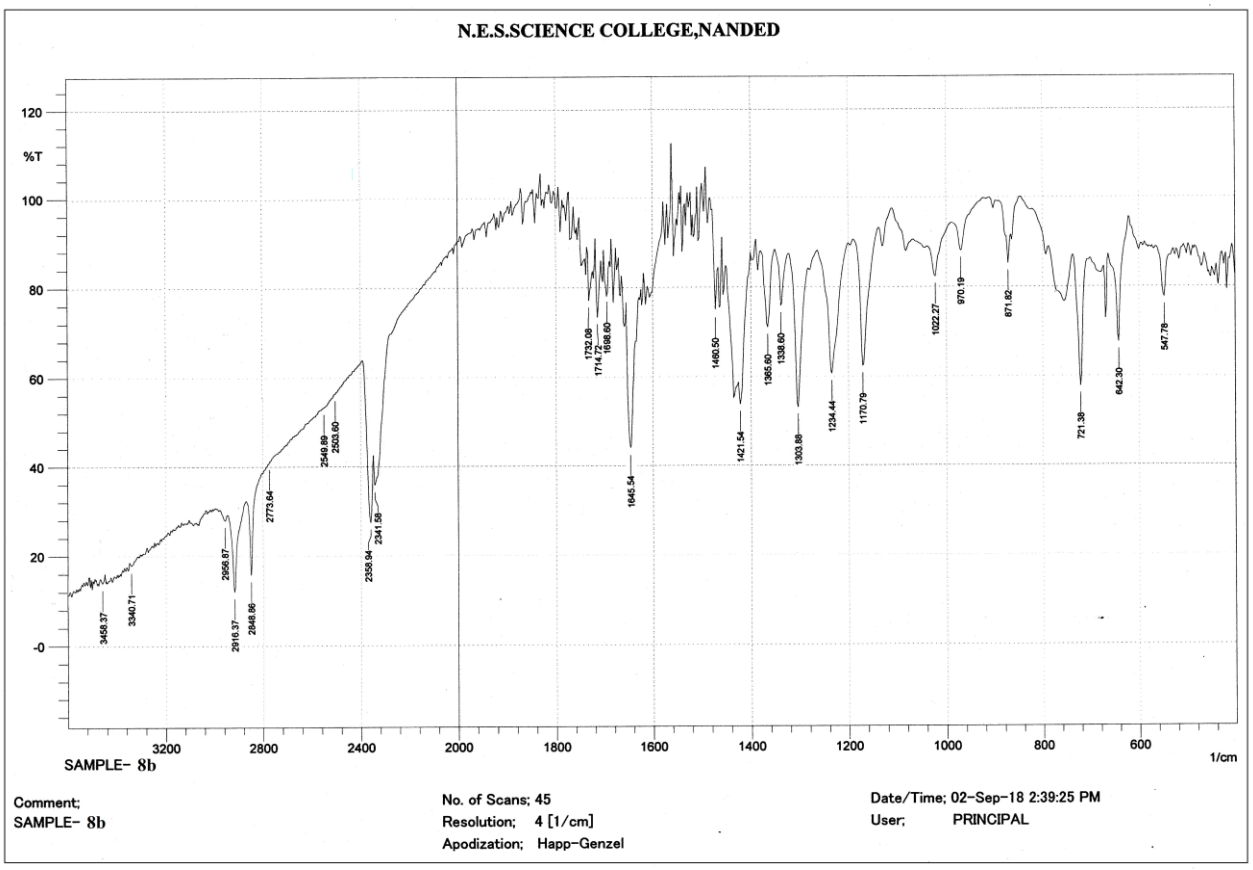
sample :8a (1HNMR)



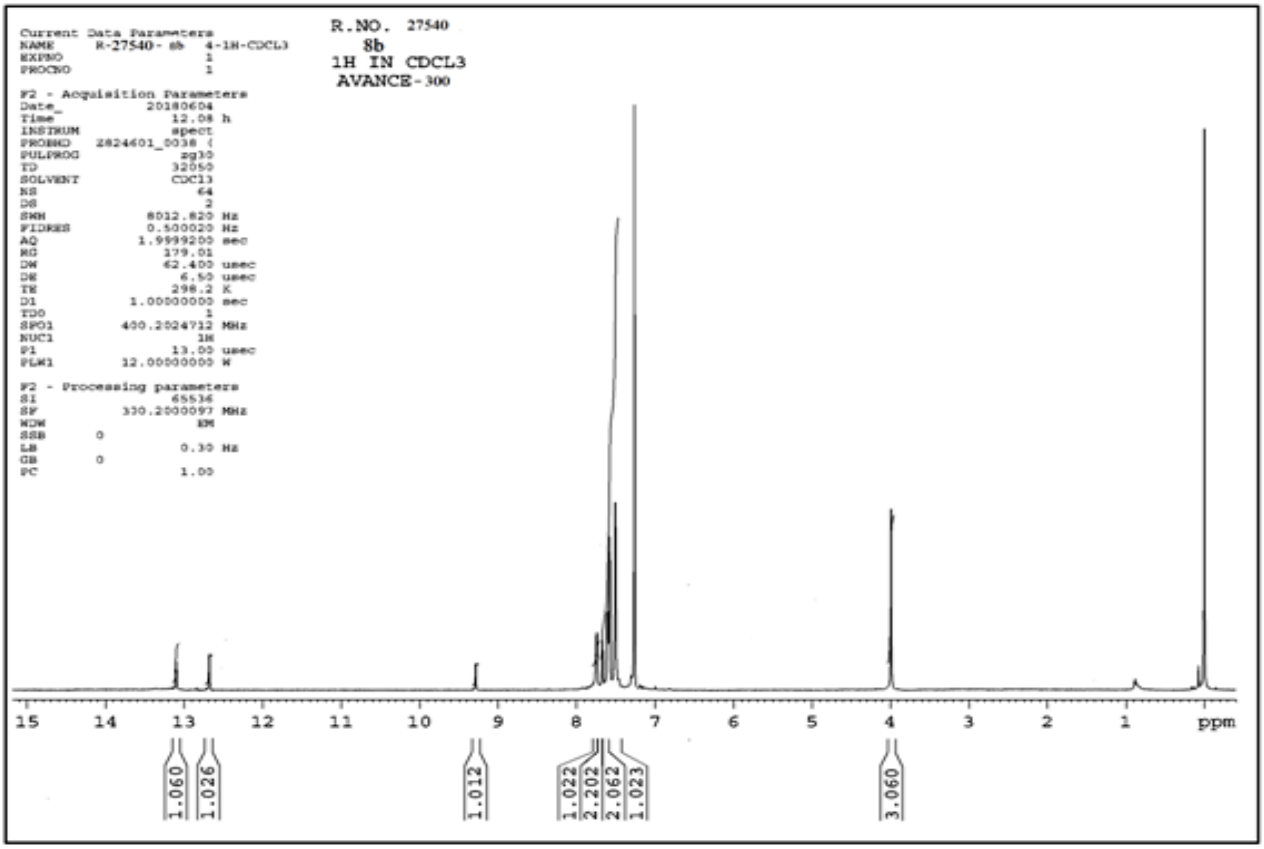
sample :8a (mass)



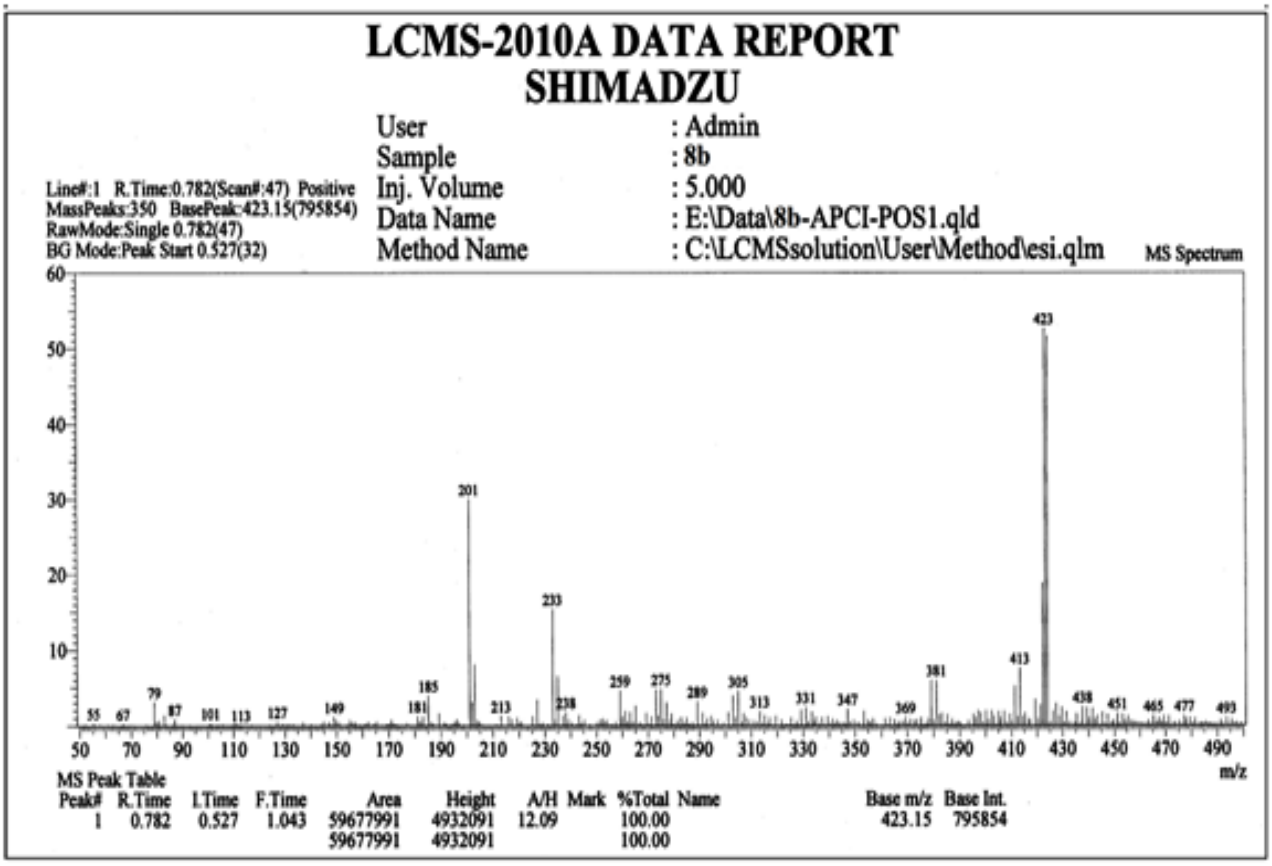
Sample:8b (IR)



Sample :8b(1HNMR)



Sample:8b (mass)



Antimicrobial activity

In present work Disc-diffusion method was used. Kirby-Bauer method was followed for disc diffusion assay. *In vitro* antimicrobial activity was screened by using Mueller Hinton Agar (MHA) obtained from Himedia (Mumbai). The MHA plates were prepared by pouring 15 ml of molten media into sterile Petri plates. The plates were allowed to solidify for 5 min and 0.1 % inoculums suspension was swabbed uniformly and the inoculums were allowed to dry for 5 min. The concentration of compounds were set at 10 µg/disc and were loaded on 5 mm sterile individual discs. The loaded discs were placed on the surface of medium and the compound was allowed to diffuse for 5 min and the plates were kept for incubation at 37°C for 24 h. Penicillin (10 µg/disc) was used as positive control. At the end of incubation, inhibition zones formed around the disc were measured with transparent ruler in millimeter. **(Table2)**

Newly synthesized compounds were screened for their antimicrobial activity against two gram positive *Bacillus Subtilis*, *Staphylococcus Aureus* and two gram negative bacteria *Escherichia Coli, Salmonella Typhi* using penicillin as standard drug. Compound **7d** showed good anti-bacterial activity against *B. subtilis*, and moderate activity against *E. coli* which good activity against *S.typhi.* Compound **7e** showed good activity against *S. subtilis*. Compound **8b** showed good antibacterial activity against *S. aureus.* Compound **8c** showed good activity against *E. coli*. Compound **8d** showed good activity against *B. subtilis*. Compounds **7a**, **7b**, **7c**, **8a**, **8e** show poor activity against all bacterial strain.

CONCLUSION

Herein, we reported some novel pyrimidine derivatives using substituted chalcones and urea with good yield. These pyrimidine derivatives were characterized by their physical constant and spectroscopic data. *In-vitro* antimicrobial activity was studied by disc diffusion method using *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella typhi.* Some of the compounds showed moderate activity. It can be concluded that the -I effect of halogen always enhance the activity as compared with the standard.

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Conflicts of interest: The authors stated that no conflicts of interest.

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