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Der Pharma Chemica, 2009, 1(2): 239-248
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Design & Synthesis of some novel 1, 2, 4-Thiadiazoline derivatives and their Biological activity

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Abstract

A series of 1, 2, 4 - thiadiazole derivatives were synthesized. The structures of these compounds were established by means of IR, ^{1}H-NMR, ^{13}C-NMR, Mass and Elemental analysis. All the compounds were evaluated for antimicrobial activities. Most of the compounds have shown significant antimicrobial activities when compared with standard drug.

Key words*:* 1, 2, 4 - thiadiazole, antimicrobial activity.

Introduction

1,2,4-Thiadiazole derivatives possess interesting biological activity probably conferred to them by the strong aromaticity of this ring system, which leads to great in vivo stability and generally, a lack of toxicity for higher vertebrates, including humans. When diverse functional groups that interact with biological receptors are attached to this ring, compounds possessing outstanding properties are obtained. 1, 2, 4-Thiadiazole are associated with diverse antimicrobial activities[1-7].

Result & Discussion

Methyl {[(5-imino-4-aryl-4, 5-dihydro-1, 2, 4-thiadiazol-3-yl) carbamoyl] amino} acetate were prepared according to method reported in the section-A synthetic scheme. These compounds are synthesized by the reaction between 3-aryl amino/amino-4-aryl-5-imino-Δ^{2}-1, 2, 4-thiadiazoline and ester of amino acid. In this reaction different substituted aryl anilines were used. These Methyl-{[(5-imino-4-aryl-4,5-dihydro-1,2,4-thiadiazol-3-yl) carbamoyl] amino} acetate were

then characterized by the elemental analysis, IR spectral studies and ^{1}H-NMR, ^{13}C-NMR and Mass spectral studies.

The screening results indicate that some of the compounds exhibit the antimicrobial activity. It was found that compounds NMC-6, NMC-7, NMC-8, NMC-9, NMC-12 and NMC-13 showed the moderate antimicrobial activity against all the strain used. Compound NMC-7, NMC-8, NMC-9 and NMC-12 show very good activity against the *Sachromyces cerviceae.*

Material and methods

All the chemicals used during the practical work were obtained from the Merck India (Pvt.) ltd, CDH, Sd fine limited and Himeddia. The chemicals and solvent used are of synthetic and AR grade respectively.

The compound synthesized were identified and characterized by following methods such as:

Melting Point Determination: The melting point of the organic compound was determined by Thiel's melting point tube using liquid paraffin by open capillary method. The melting point of all derivative taken are remains uncorrected.

Thin Layer Chromatography: TLC of the compound was taken by using silica gel G as a spreading agent. The solvent system used was BENZENE: ETHANOL (9:1)

Infra Red Spectroscopy: All the IR- spectra were carried out from the IIT Delhi. The IR spectra were recorded using the KBr pellets. The instrument used was PERKIN ELMER.

*Nuclear Magnetic Resonance Spectroscopy (HNMR & CNMR)***:** The NMR spectra of the compounds were carried out using Bruker Advanced II-400 spectrometer at IIT Delhi. The solvent used was $CDCl_3$ and DMSO.

Mass Spectroscopy: Mass- spectra was carried out from the IIT Delhi.

Elemental Analysis: Elemental Analysis was carried out from the CDRI Lucknow.

Experimental:
There are three steps involved in the synthesis of final product:
Step1: Synthesis of 3-aryl amino/amino-4-aryl-5-imino-Δ^2-1, 2, 4-thiadiazoline
Step2: Synthesis ester of 3-aryl amino/amino-4-aryl-5-imino-Δ^2-1, 2, 4-thiadiazoline
Step3: Reaction of esterifies amino acid with ester of 3-aryl amino/amino-4-aryl-5-imino-Δ^2-1, 2, 4-thiadiazoline

Synthetic Scheme:

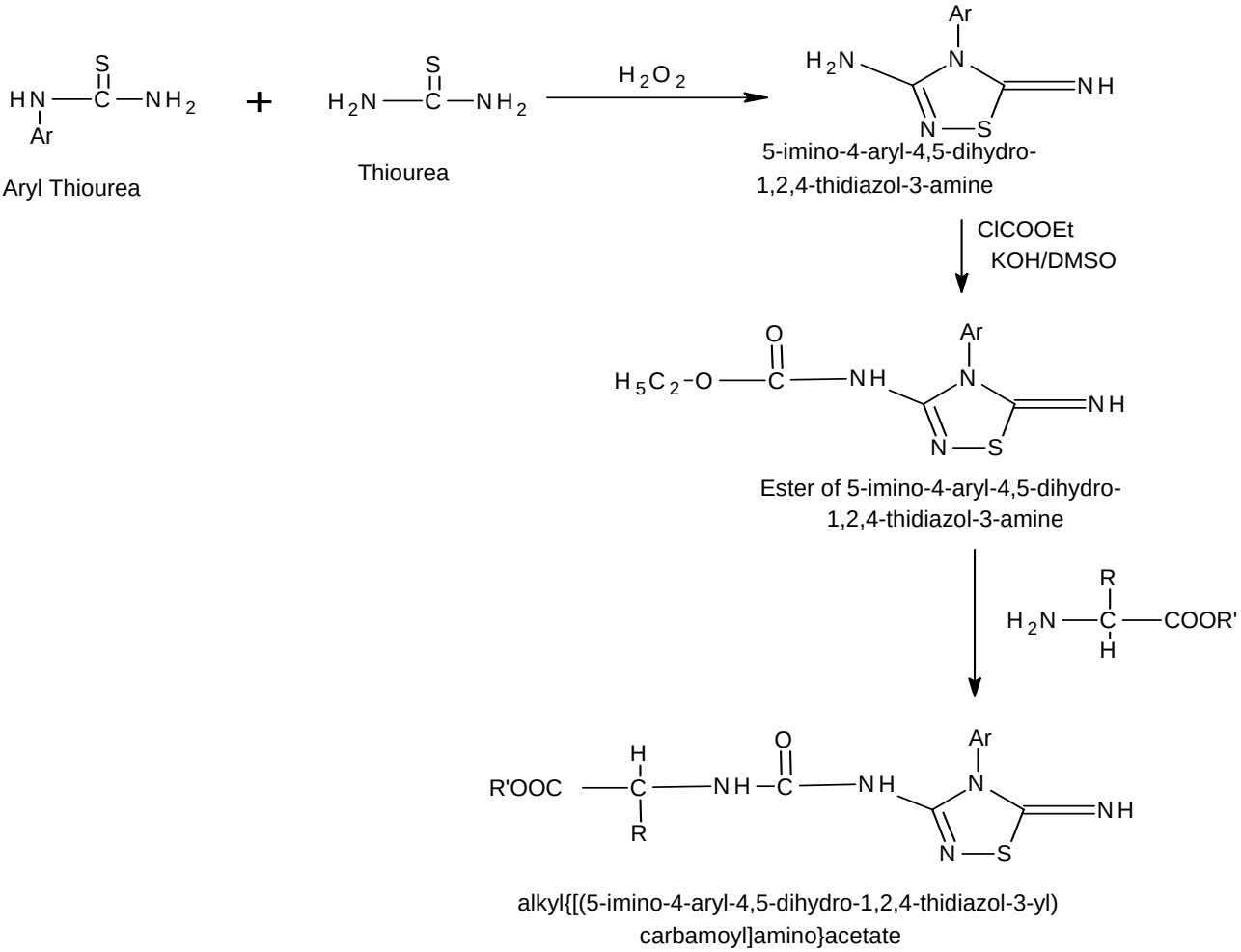


Table 1:

Ar	R	R’
$C_6H_5NH_2$	CH_3	CH_3
p-Cl-C_6H_4-NH_2	CH_3	CH_3
p-NO_2-C_6H_4-NH_2	CH_3	CH_3
p-CH_3-C_6H_4-NH_2	CH_3	CH_3

Step1: Synthesis of 3-aryl amino/amino-4-aryl-5-imino-Δ^2-1, 2, 4-thiadiazoline:

Corresponding aryl thiourea (0.5 mol) was taken in a conical flask equipped with separating funnel and condenser and was dissolved in a warm 10 ml of HCl. Hydrogen peroxide (60-70ml) was added drop wise from the separating funnel with continuous stirring. The mixture was kept aside for 2hr.The oxidized mixture was then diluted with water and neutralized with dilute ammonia. The precipitate thus obtained was collected and recrystallised from ethanol (95%). Then synthesized compound was analyzed by TLC, with using Benzene: ethanol (9:1) ratio as a solvent system.[8]

Step2: Synthesis ester of 3-aryl amino/amino-4-aryl-5-imino-Δ^2-1, 2, 4-thiadiazoline:
Corresponding Step1 compound (0.1mol) and equimolar amount of ethylchloroformate was taken in a round bottom flask. Then added DMSO and KOH solution. Reaction mixture was reflux for 30 minutes which was recrystallised by ethanol 95%. The reaction mixture was vaporized & solid crystal was obtained. Then synthesized compound was analyzed by TLC, with using Benzene: ethanol (9:1) ratio as a solvent system.[9]

Esterification of Amino acid:
Esterifies amino acid was synthesized by Fischer-Speier method. In this method a mixture of methanol and organic acid was boiled under reflux whilst a steam of dry hydrogen chloride gas is passed, a high yield of the ester being obtained.
The formation of hydrogen chloride is protonating and catalytic, since Fischer found that 5% hydrogen chloride in the reaction mixture gave efficient esterification.

Step3: Reaction of esterifies amino acid with ester of 3-aryl amino/amino-4-aryl-5-imino-Δ^2-1, 2, 4-thiadiazoline:
Equimolar quantity of corresponding step 2 compounds and glycine ester taken in a r.b.f. and dissolved in methanol then this reaction mixture was reflux for 2 hours. Then after completion of reaction, the mixture was filtered off & after cooling the filtrate solid crystal was obtained. This was recrystallised by ethanol. Then synthesized compound was analyzed by TLC, with using ethanol: water (7:3) ratio as a solvent system.

Table-2: Synthesized compound: Derivatives of 3-aryl amino/amino-4-aryl-5-imino-Δ^2-1, 2, 4-thiadiazoline with amino acid ester

S.N.	Code	Mol. Formula	Mol. Wt.	m.p. (^{0}C)	Rf. Value	% Yeild
1.	**NMC-6**	$C_8H_8N_4S$	192.24	65	0.69	64.85
2.	**NMC-7**	$C_8H_7N_5O_2S$	237.24	138	0.52	74.53
3.	**NMC-8**	$C_8H_7ClN_4S$	226.69	120	0.42	82.03
4.	**NMC-9**	$C_9H_{10}N_4S$	206.26	180	0.48	61.35
5.	**NMC-10**	$C_{10}H_{11}N_5OS$	249.29	165	0.27	52.83
6.	**NMC-11**	$C_{12}H_{13}N_5O_3S$	307.33	148	0.33	68.02
7.	**NMC-12**	$C_{12}H_{12}ClN_5O_3S$	341.77	160	0.68	65.32
8.	**NMC-13**	$C_{12}H_{12}N_6O_5S$	352.33	80	0.86	72.80

Analytical Data:
Generalized IR spectra studies of synthesized compound:
Figure-1: IR-spectra of NMC-6

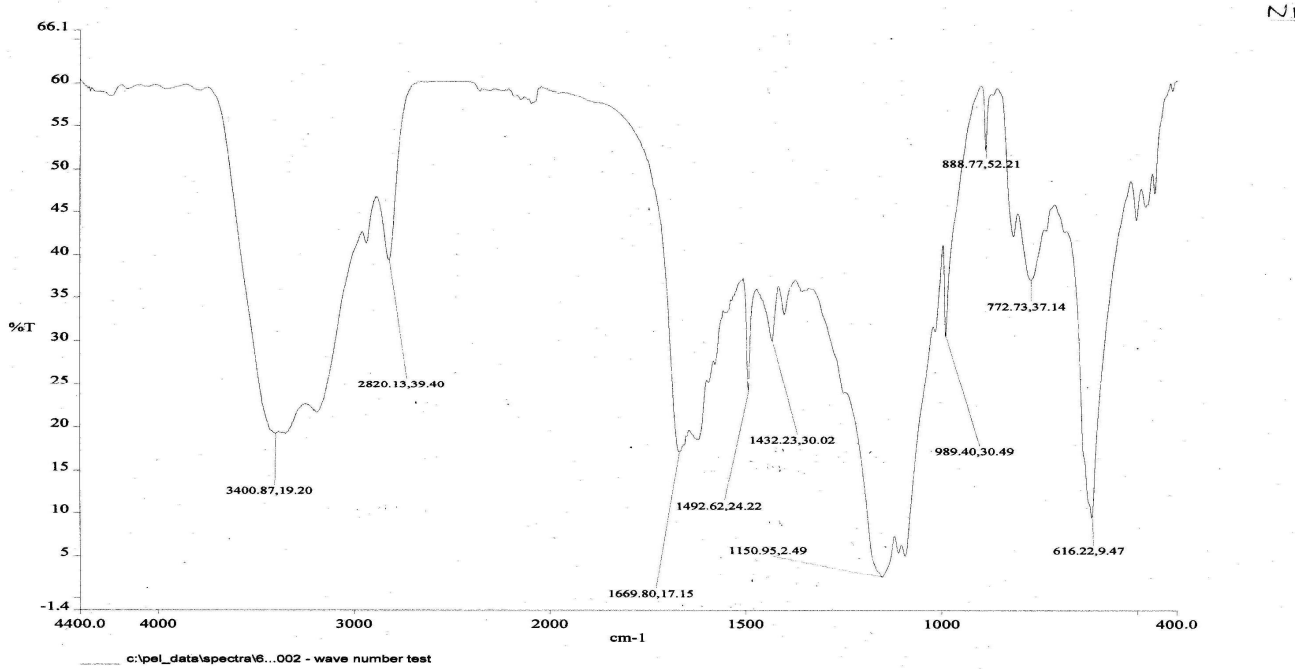


Figure-2: IR-spectra of NMC-7

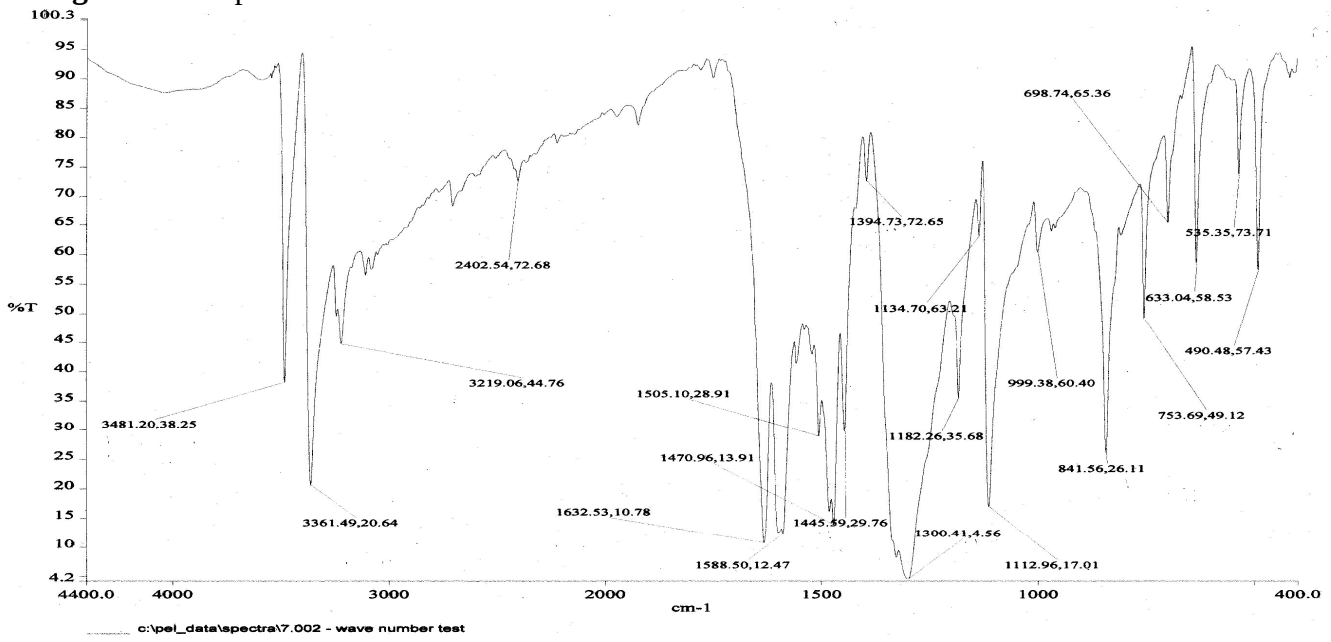


Figure-3: IR-spectra of NMC-11

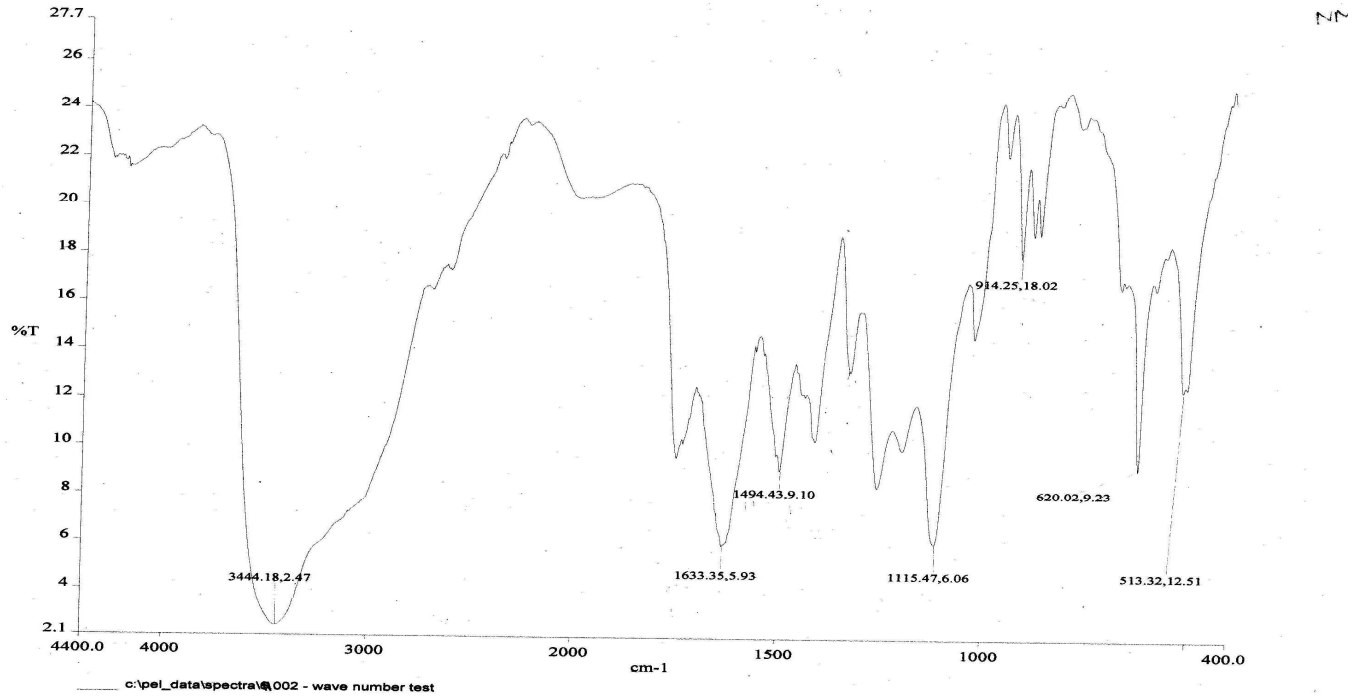
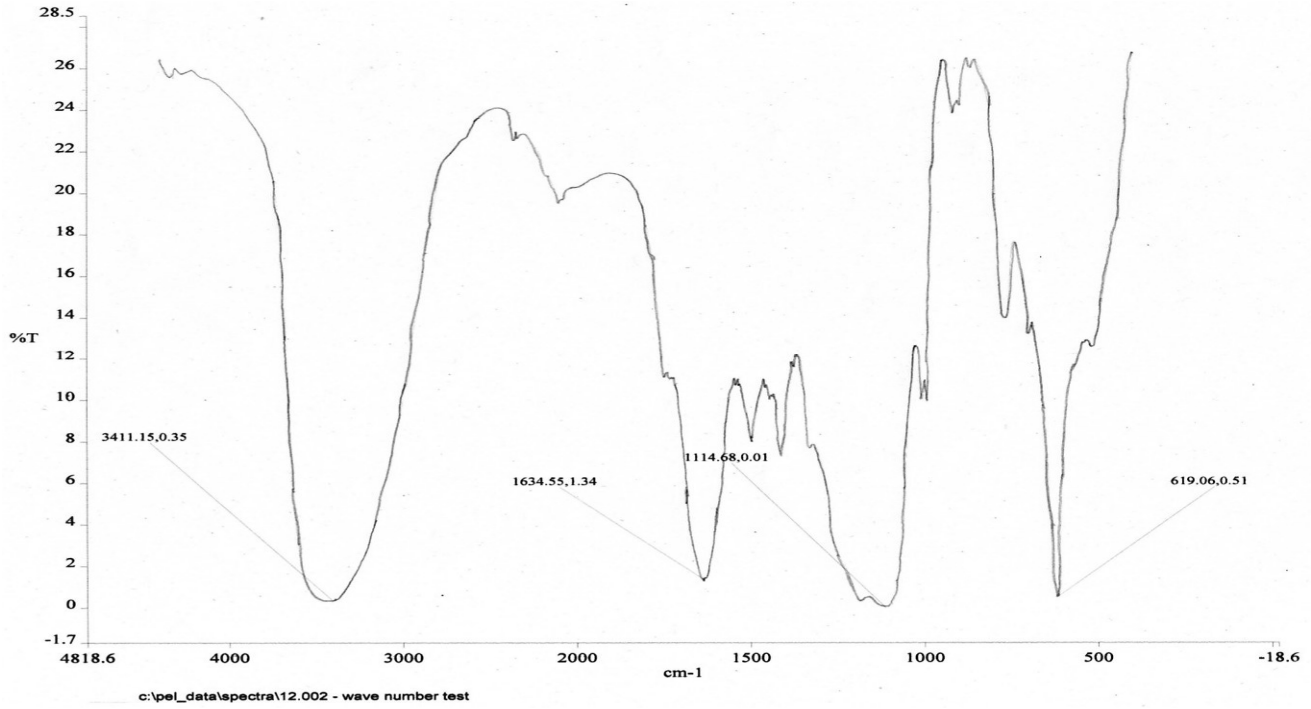
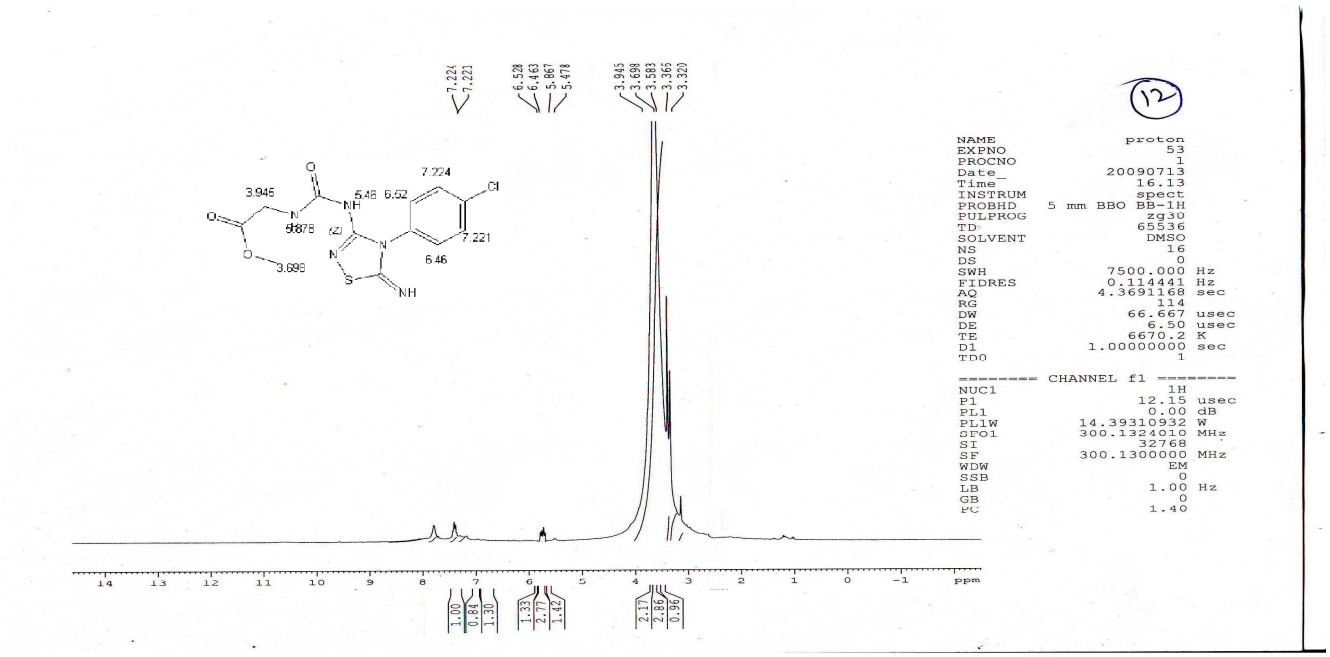


Figure-4: IR-spectra of NMC-12



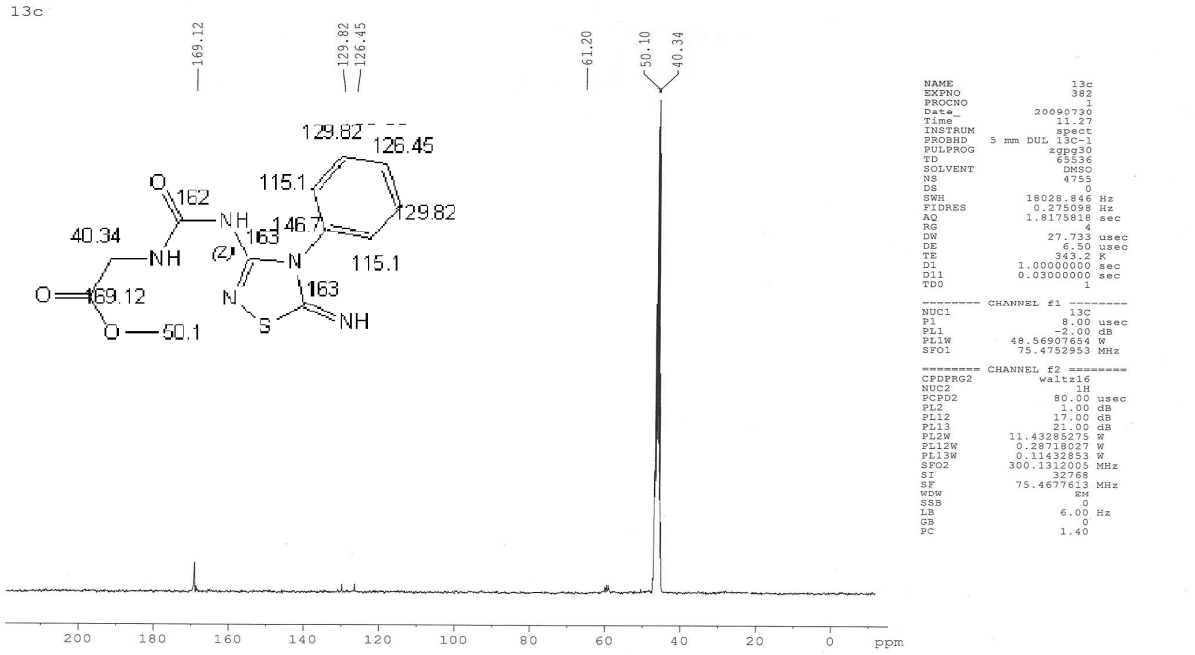
N-$H_{(s)}$(3444.18 cm^{-1}), C=$O_{(s)}$(1750 cm^{-1}), C=$C_{(s)}$ in Ar(1633.35 cm^{-1}), N-$H_{(d)}$ in amide(1494.43 cm^{-1}), C-$N_{(s)}$ in amide(1400 cm^{-1}), C-$N_{(s)}$ in Ar amide(1350 cm^{-1}), C-N $_{(d)}$ in Ar(914.25 cm^{-1}), C-H $_{(d)}$ in Ar(753.69 cm^{-1}), N=$O_{(s)}$(1300.4cm^{-1}), C=$N_{(s)}$in ring (1445.59 cm^{-1}), N=$O_{(s)}$(1505.10 cm^{-1}), Ar-$H_{(s)}$(3219.06 cm^{-1}), N-$H_{(s)}$ in sec. amine(3362.49 cm^{-1}), N-$H_{(s)}$ in pri. Amine(3481.20 cm^{-1}), C-H $_{(d)}$ disubstituted p- Ar ring (841.56 cm^{-1}).

^{1}H-NMR studies: (Solvent $CDCl_3$ + DMSO)
Figure-5: ^{1}HNMR Spectra of NMC-12



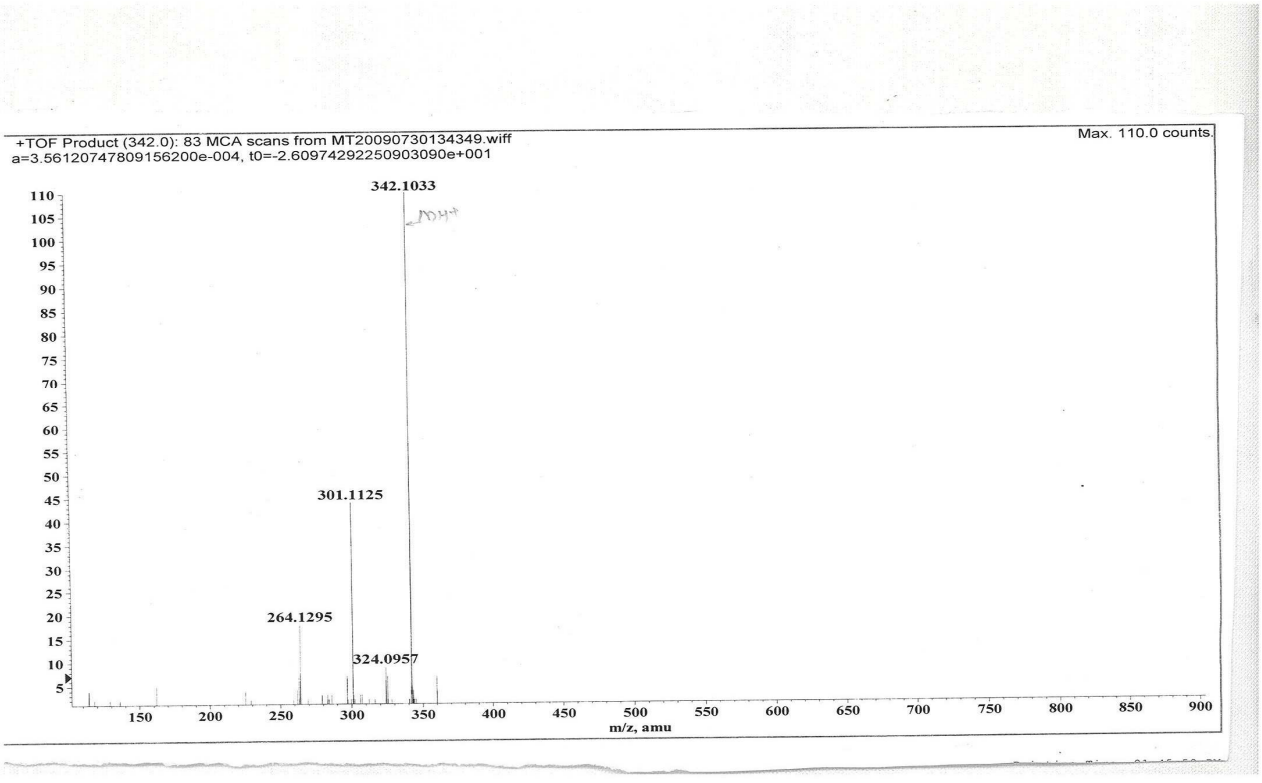
CH_2 (δ=3.545 ppm, 2H, triplet), NH (δ=7.787 ppm, sec amide, 1H, Singlet), CH (δ=6.468 ppm, 1H, *o* -Ar-H, Multiplet), CH (δ=7.239 ppm, 1H, *m*-Ar-H, Multiplet), CH (δ=6.468 ppm, 1H, *p* -Ar-H, Triplet), NH_2 (δ=2.058 ppm, amine, 2H, Triplet) NH (δ= 5.478 ppm, urea, 1H, Triplet), NH (δ=5.478 ppm, urea, 1H, Singlet), CH (δ=6.78 ppm, 1H, *p* -Ar-H, Doublet), CH_3 (δ=3.362 ppm, methyl, 3H, Singlet), CH (δ=7.27 ppm, 1H *o*-chloro Ar-H , Doublet), CH (δ=6.46 ppm, 1H, *o* -Ar-H to 1, 2, 4- thiadiazole group, Doublet).

^{13}C-NMR studies:
Figure-6: ^{13}CNMR Spectra of NMC-11
C (δ=169.12 ppm, 1-carboxyl carbon of ester), CH (δ=115.1 ppm, 1-benzene, ortho), CH_2 (δ=40.34 ppm, aliphatic),CH (δ=129.3 ppm, 1-benzene meta), C (δ=61.2 ppm, N-urea), CH (δ=118.5 ppm, 1-benzene, para), C (δ=162.8 ppm, 1-imine),CH (δ=129.3 ppm, 1-benzene, meta), C (δ=162.8 ppm, 1-imine), CH (δ=115.1 ppm, 1-benzene, ortho), C (δ=146.7 ppm, 1- enzene), CH_3 (δ=50.1 ppm, aliphatic).



Mass Spectra studies:

Figure-7: Mass Spectra of NMC-12



M^+ (parent peak) of the synthesized compound NMC-12 was found to be 342.1033 that is just equal to the molecular weight of NMC-12. On this basis synthesized compound NMC-12 chemical structure was confirmed.

Elemental Analysis:
Compound NMC-11 has (C 39.515%, N24.612%, H 10.96%, S 7.71%, O 15.62%, Cl nil)

Biological evaluation:
The antimicrobial activity of synthesized compound was determined by paper disc method. The organisms selected for antimicrobial activity were *Bacillus substilis, Escherichia coli, Sachromyces cerviceae, Staphylococcus aureus, Pseudomonas aeruginosa, Corynebacteriun diphtheriae, Bacillus megaterium.* The concentration of sample compound was 1mg/ml. Ampicillin was used as standard drug for antimicrobial activity. Control test with solvent was perform for every assay but showed no inhibition of the microbial growth. The results are reported in table.

Table 3: (Zone of inhibition in mm)

Comp. code	*B. substilis*	*E. coli*	*S. cerviceae*	*S. aureus*	*P. aeruginosa*	*C. diphtheriae*	*B. megaterium*
NMC-6	8.5 mm	7.0 mm	9.5 mm	7.5 mm	9.0 mm	9.0 mm	*10.0 mm*
NMC-7	8.5 mm	8.5 mm	27.0 mm	11.5 mm	8.0 mm	12.0 mm	*15.0 mm*
NMC-8	9.5 mm	9.0 mm	25.0 mm	7.0 mm	8.5 mm	10.0 mm	*11.5 mm*
NMC-9	8.5 mm	8.0 mm	20.0 mm	9.5 mm	12.5 mm	13.0 mm	*14.5 mm*
NMC-10	7.5 mm	7.5 mm	No	6.5 mm	No	7.0 mm	*6.5 mm*
NMC-11	7.0 mm	6.5 mm	No	8.0 mm	No	6.5 mm	*9.0 mm*
NMC-12	6.5 mm	No	21.0 mm	No	No	No	*7.0 mm*
NMC-13	8.5 mm	7.5 mm	12.5 mm	10.0 mm	10.5 mm	11.0 mm	*14.0 mm*
Ampicillin	25.0 mm	14.0 mm	23.0 mm	26.0 mm	21.0 mm	25.0 mm	*22.0 mm*
DMSO	*No*	*No*	*No*	*No*	*No*	*No*	*No*

Acknowledgement

Authors thank to Department of Pharmacy, Sroj Institute of Technology & Management, Lucknow, India, CDRI Lucknow, India and IIT Delhi, India for their support and provide analytical data.

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