Synthesis and Characterization of Nitrogen containing Heterocycles

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Abstract : This study has been undertaken to investigate the reaction mechanism in chemistry a one-pot synthesis. It is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor. This is much desired by chemists because avoiding a lengthy separation process and purification of the intermediate chemical compounds would save time and resources while increasing chemical yield. We have synthesized series of Nitrogen heterocycles of potentially important organic compounds which will show diverse biological activity. All compounds were synthesized characterized using UV, IR and NMR spectroscopy and Melting points were noted.

Keywords **– one-pot synthesis, Multicomponent reaction, Pyrimidine, Nitrogen heterocycles**

I. INTRODUCTION

Nitrogen heterocycles are of special interest as they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities[1]. In Nitrogen containing heterocyclic compounds dihydropyrimidinone and their sulphur analogue have been reported to possess diverse range of pharmacological activity[2] such as anticancer,antiHIV,antibacterial,antimalarial,antihypertensive,sedative,hypnotics,anticant, antithyroid,antihistaminic agents and antibiotics[3].They are mostly used as calcium channel blockers[4] alpha-antagonista[5] and neuropeptide-antagonists. Alkaloids containing the dihydro pyrimidine structure have been isolated from various marine source have interesting biological properties[6] like batzelladine, which was found to be potent HIV-gp-120-CD4 inhibitors[7]. Because of these efficient applications of the above compound our interest in synthesis of Dihydropyrimidinone and their thioanalogue is increasing tremendously

Pyrimidinones or Dihydropyrimidinones (DHPMs) are well known for their wide range of bioactivities and their applications in the field of drug research have stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations. Out of the five major bases in Nucleic acids three are pyrimidine derivatives

Aryl-substituted 3, 4-dihydropyrimidin-2(*1H*)-one and their derivatives are an important class of substances in organic and medicinal chemistry. Several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties[8]. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors.

The scope of this pharmacophore has been further widening with their identification of 4-(3-hydroxyphenyl)-2-thione derivative 4 called monastrol[9] as a novel cell-permeable molecule for the development of new anticancer drugs. Monastrol (4) has been identified as a compound that specifically affects the cell-division (mitosis) by a new mechanism which does not involve tubulin targeting. It has been established that the activity of 4 consists of the specific and reversible inhibition of the motility of the mitotic kinesis, a motor protein required for spindle bipolarity.

Trimethoprim is a type of drug with a pyrimidine core which attacks the folic acid metabolism of bacteria and is often used as antibacterial agents[10]. 4-aryl-1,4 dihydropyridines (DHPs) of the nifedipine type [11] were first introduced into clinical medicine in

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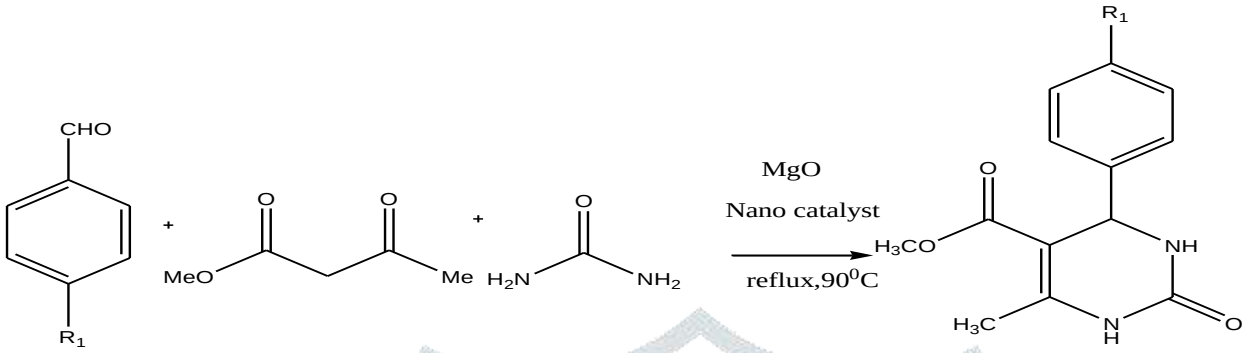
1975 and are still the most potent group of calcium channel modulators available for the treatment of cardiovascular diseases.[12] Dihydropyrimidines of type 7 show a very similar pharmacological profile, and in recent years, several related compounds were developed (e.g 7) that are equal in potency and duration of antihypertensive activity to classical and second-generation dihydropyridine drugs.[13]

II EXPERIMENT

2.1 REACTION SCHEME:



1 2 3 4

Table 1.1

ENTRY	R_1	PRODUCT	TIME(min)	YIELD%	MELTINGPOINT(^{0}c)
1	H	4a	45	97	201
2	Cl	4b	30	94	213
3	OH	4c	35	90	227
4	OMe	4d	40	93	200
5	Me	4e	30	86	215

1, Ethyl 6-methyl-2-oxo-4-phenyl-1, 2,3,4,-tetrahydropyrimidine-5-carboxylate:

0.11g of Benzaldehyde (0.1molar), 0.07g of Urea (0.1molar), 0.13g of Methyl acetoacetate (0.1molar), is weighed accurately. The precursors were finely powdered and mixed together and allowed to mechanically stirring for 15 minutes at ambient temperature by using MgO as Nano catalyst. The resulting reaction mixture was refluxed for 1 hour at 90^0 using reflux condenser with periodically stirring the reaction mixture until the reaction was competed. The completion of reaction as indicated by Thin layer Chromatography. The contents of the reaction mixture were cooled to room temperature and the crude reaction mixture was crushed and washed twice with cold water. The crude product was washed with ethyl acetate filtered using germen filter paper and his product was purified by recrystallization from ethanol. Let it for the growth of crystal and the yield of product is 89-92%. Then a Sharp melting point was noted.

2, Ethyl4-(4-chlorophenyl)- 6-methhyl-2-oxo-4-phenyl-1,2,3,4,-tetrahydropyrimidine-5-carboxylate:

0.14g of chloroBenzaldehyde (0.1molar), 0.07g of Urea (0.1molar), 0.13g of Methyl acetoacetate (0.1molar), is weighed accurately. The precursors were finely powdered and mixed together and allowed to mechanically stirring for 15 minutes at ambient temperature by using MgO as Nano catalyst.. The resulting reaction mixture was refluxed for 1 hour at 90^0 C using reflux condenser with periodically stirring the reaction mixture until the reaction was competed. The completion of reaction as indicated by Thin layer Chromatography. The contents of the reaction mixture were cooled to room temperature and the crude

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reaction mixture was crushed and washed twice with cold water. The crude product was washed with ethyl acetate filtered using germen filter paper and his product was purified by recrystallization from ethanol. Let it for the growth of crystal and the yield of product is 89-92%. Then a Sharp melting point was noted.

3, Ethyl4-(4-hydroxyphenyl) - 6-methhyl-2-oxo-4-phenyl-1,2,3,4,-tetrahydropyrimidine-5-carboxylate:

0.12g of hydroxyphenylBenzaldehyde (0.1molar), 0.07g of Urea (0.1molar), 0.13g of Methyl acetoacetate (0.1molar), is weighed accurately. The precursors were finely powdered and mixed together and allowed to mechanically stirring for 15 minutes at ambient temperature by using MgO as Nano catalyst.. The resulting reaction mixture was refluxed for 1 hour at 90^0 C using reflux condenser with periodically stirring the reaction mixture until the reaction was competed. The completion of reaction as indicated by Thin layer Chromatography. The contents of the reaction mixture were cooled to room temperature and the crude reaction mixture was crushed and washed twice with cold water. The crude product was washed with ethyl acetate filtered using germen filter paper and his product was purified by recrystallization from ethanol. Let it for the growth of crystal and the yield of product is 89-92%. Then a Sharp melting point was noted.

4, Ethyl4-(4-methoxyphenyl)- 6-methhyl-2-oxo-4-phenyl-1,2,3,4,-tetrahydropyrimidine-5-carboxylate:

0.35g of methoxy Benzaldehyde (0.1molar), 0.07g of Urea (0.1molar), 0.13g of Methyl acetoacetate (0.1molar), are weighed accurately. The precursors were finely powdered and mixed together and allowed to mechanically stirring for 15 minutes at ambient temperature by using MgO as Nano catalyst.. The resulting reaction mixture was refluxed for 1 hour at 90^0 C using reflux condenser with periodically stirring the reaction mixture until the reaction was competed. The completion of reaction as indicated by Thin layer Chromatography. The contents of the reaction mixture were cooled to room temperature and the crude reaction mixture was crushed and washed twice with cold water. The crude product was washed with ethyl acetate filtered using germen filter paper and his product was purified by recrystallization from ethanol. Let it for the growth of crystal and the yield of product is 89-92%. Then a Sharp melting point was noted.

5, Ethyl4-(4-methylphenyl) - 6-methhyl-2-oxo-4-phenyl-1,2,3,4,-tetrahydropyrimidine-5-carboxylate:

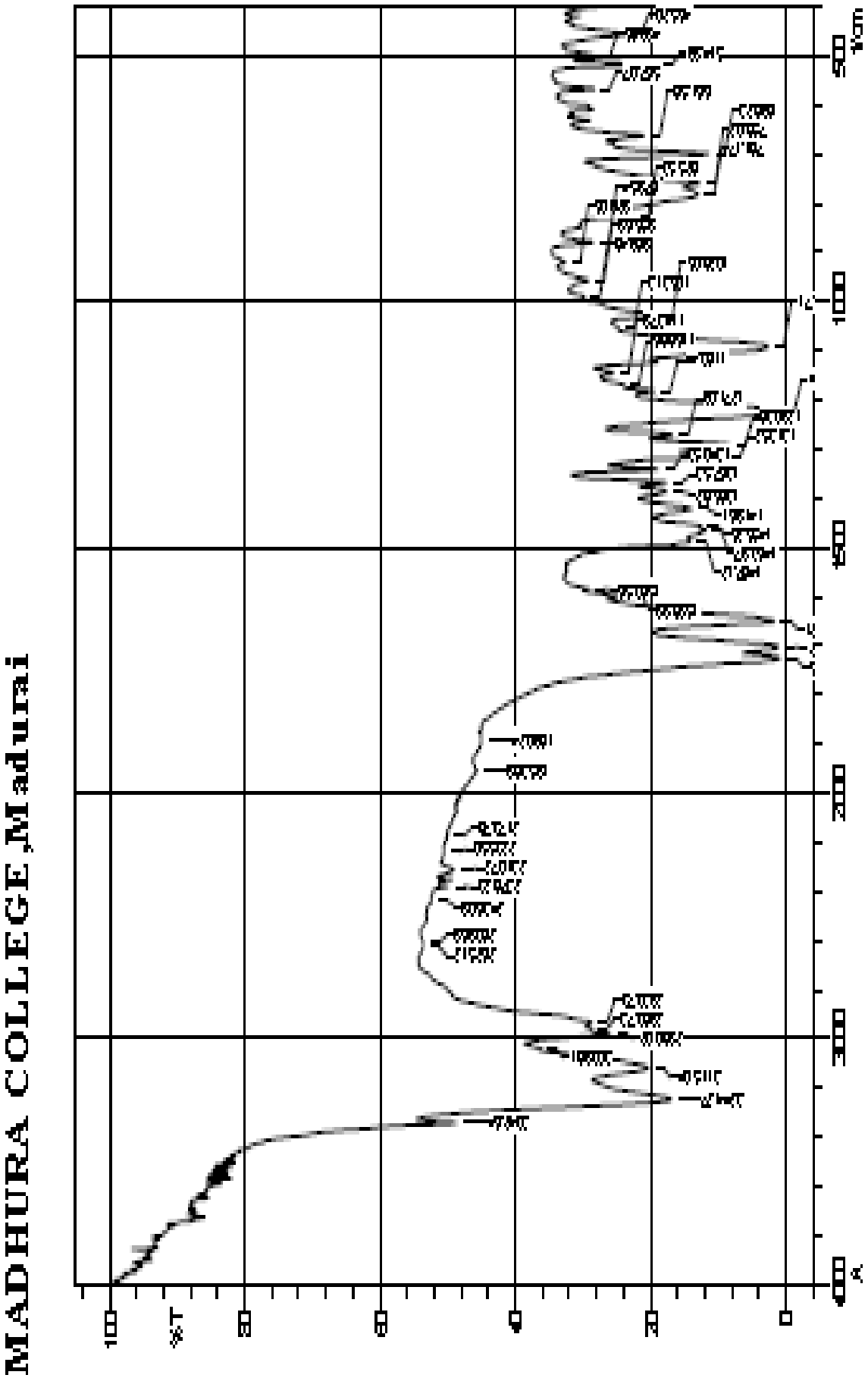
0.12g of Methyl phenylBenzaldehyde (0.1molar), 0.07g of Urea (0.1molar), 0.13g of Methyl acetoacetate (0.1molar), are weighed accurately. The precursors were finely powdered and mixed together and allowed to mechanically stirring for 15 minutes at ambient temperature by using MgO as Nano catalyst. The resulting reaction mixture was refluxed for 1 hour at 90^0 using reflux condenser with periodically stirring the reaction mixture until the reaction was competed. The completion of reaction as indicated by Thin layer Chromatography. The contents of the reaction mixture were cooled to room temperature and the crude reaction mixture was crushed and washed twice with cold water. The crude product was washed with ethyl acetate filtered using germen filter paper and his product was purified by recrystallization from ethanol. Let it for the growth of crystal and the yield of product is 89-92%. Then a Sharp melting point was noted.

III RESULT AND DISCUSSION:

This one pot Nano catalysed protocol was then applied to the century old Biginelli reaction involving the interaction of various aldehyde, Ethyl acetoacetate, urea and an acid catalyst (such as p-toluene sulfonic acid). The test was successful with this multi component reaction mixture on a near good scale with 92% yield of the desired product. For instance, the urea is react with 4-methyl benzaldehyde and ethyl acetoacetate it forms 5-Pyrimidinecarboxylic acid,1,2,3,4-tetrahydro-6-methyl-4-(4-mthylphenyl)-2-oxo-,ethyl ester.

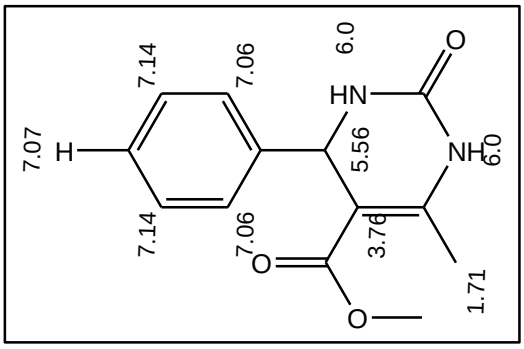
IR Spectroscopy:

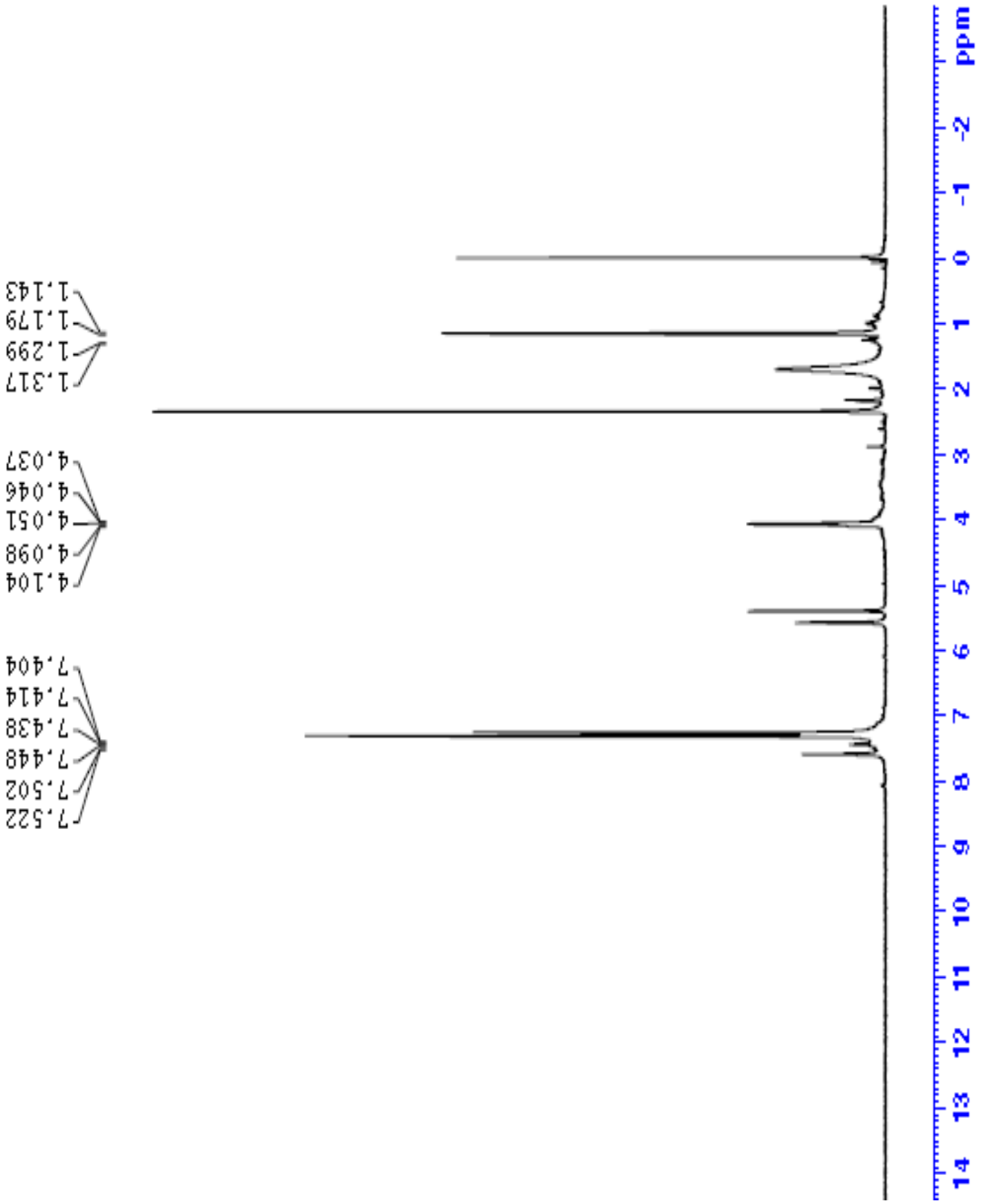
The IR spectral values(Instrument; Shimadzu FT-IR-8400,Sample technique:KBr pellet) of the product is the stretching vibration of secondary amine(>NH) appears around 3100-3200cm^{-1} The carbonyl (>C=O) stretching vibration of ester group is observed around 1700 cm^{-1}.The stretching vibration at 1463cm^{-1} shows the presence of C-C in the system which connects the two phenyl ring system. The ring skeleton vibration is observed between 1500-1600cm^{-1} due to the presence of phenyl ring system.

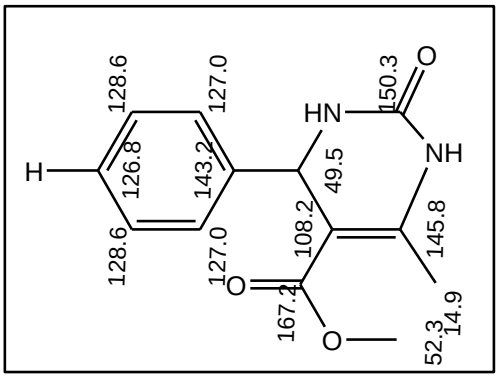

MADHURA COLLEGE,Madurai
100
%T
80
60
40
20
0
4000
3000
2000
1500
1000
500
cm-1

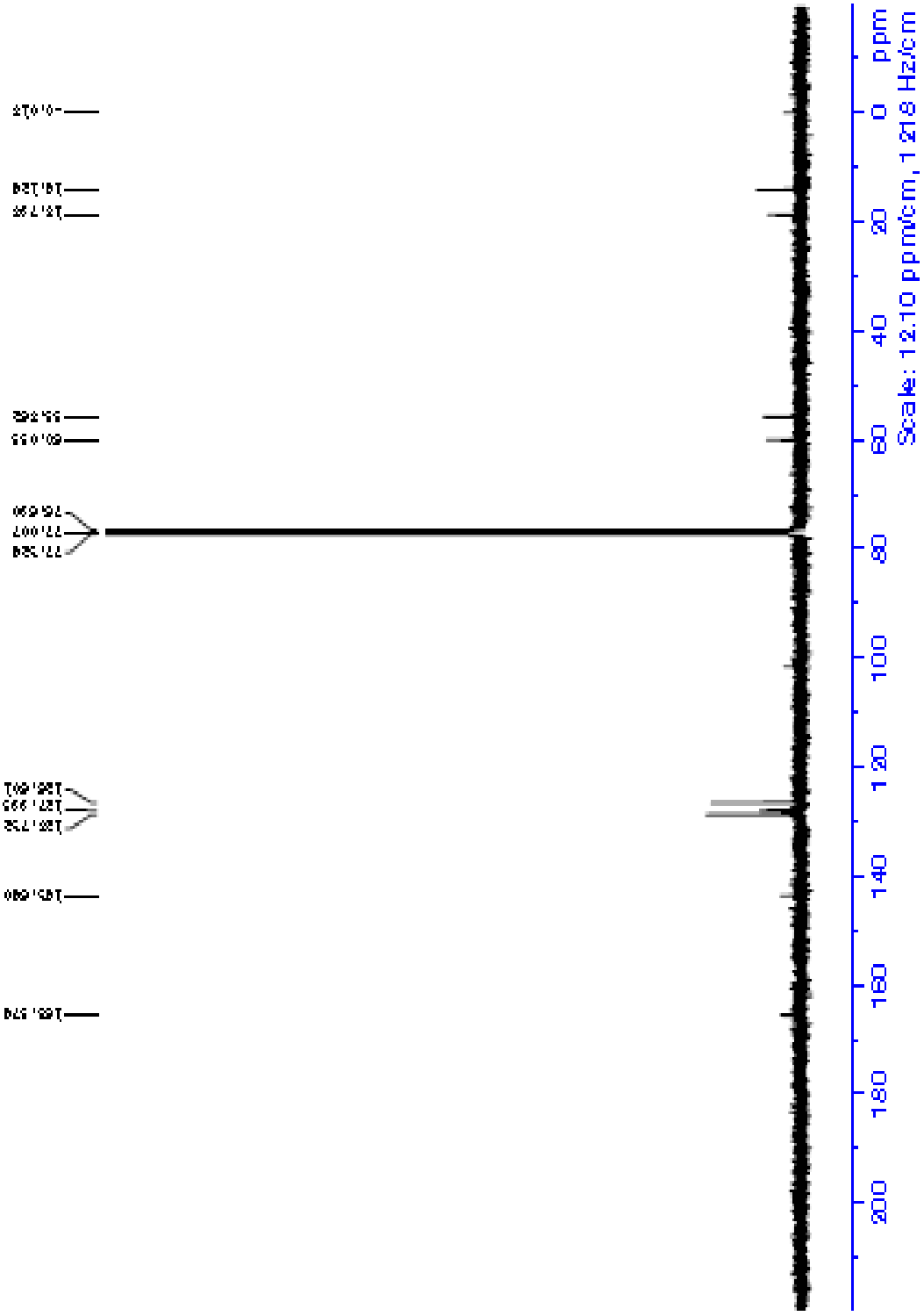
NMR Spectroscopy:

All NMR spectral values are taken in the instrument: BRUKER AC 400 MHz FT-NMR, Solvent :$CDCl_3$.The spectral values 1.14 is quartet of Methyl group containing three protons on $–CH_3$ with respect to neighbouring carbon atom, 2.35 is singlet of the two primary $–CH_3$ of which one $–CH_3$ group containing $–CH_3$,4.04 is quartet may be present in DHP'S ring in sixth position and other on the fourth position of phenyl group containing one proton (J=24) 7.26-7.33 is multiplet of aromatic ring containing four protons,7.71 is singlet of one –NH group .Finally the spectrum of ^{1}H, ^{13}C and DEPT are shown below






H
128.6
126.8
143.2
127.0
128.6
127.0
108.2
167.2
O
O
49.5
HN
150.3
O
NH
145.8
14.9
52.3


ppm
0
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120
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160
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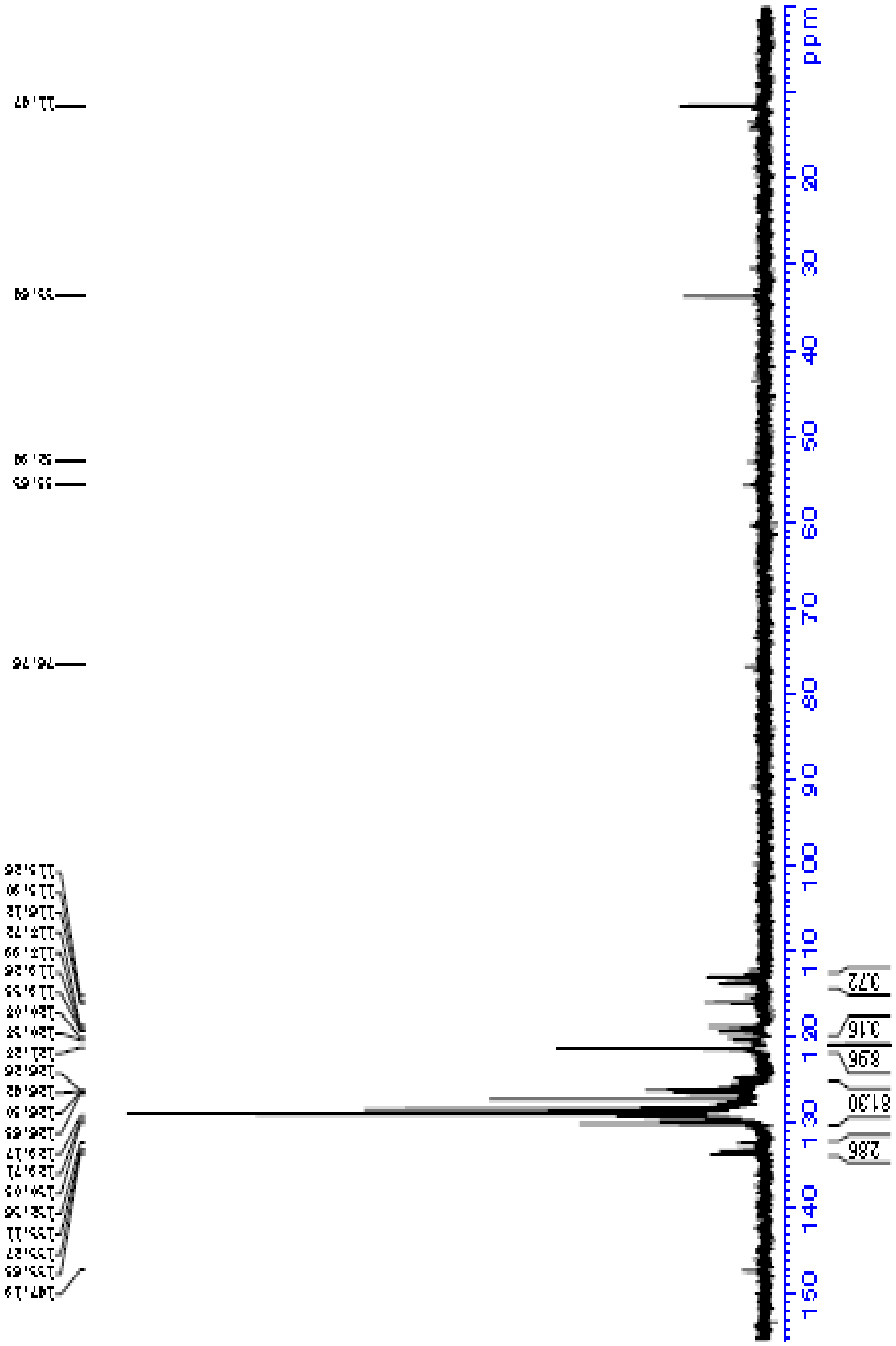
200
Scale: 12.10 ppm/cm, 1218 Hz/cm


ppm
372
316
896
8130
286

II. Conclusion:

Heterocycles are biologically active molecule, especially compounds containing nitrogen heterocycles. We choose pyrimidine-diones which has twoNitrogen in the ring system. Though pyrimidine-dione is being prepared by different methods under normal conditions our method is novel method of preparation as we choose MgO nanoparticles as Nano catalyst in organic synthesis. As expected the reaction time& the product yield is high when using Nano catalyst. There are no by-products. The reaction was 100% efficient as we also have reusable solvent. This is one of the best methods of greener reaction for the synthesis of Dihydropyrimidinone.