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Synthesis, characterization and antimicrobial study of N-Mannich base and its complex

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ABSTRACT

In this study, we have synthesized Mannich base of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide from acetamide solution with phenol and pyridine caboxaldehyde. A complex of the above compound also prepared with Nickel(II) chloride in methanol. Structures of the newly synthesized compounds were confirmed by elemental analyses, IR, UV-VIS & NMR. These compounds are characterized by physical and chemical methods. All the newly synthesized compounds were screened for their antimicrobial activity against gram positive Staphylococcus aureus, Bacillus subtilis, gram negative Escherichia coli, Pseudomonas aeruginosa, and Fungi Candida albicans. Both of the compounds showed a marked activity against the selected microorganisms. Metal complex has been found to possess more activity than the free ligand.

Keywords: mannich base, antibacterial activity, antifungal activity, metal complexes

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INTRODUCTION

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound is known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered as Mannich reactions because these imines form between amines and aldehydes.In the past few decades, Mannichbases[1] of heterocyclic molecules have been grabbing the attention of the synthetic chemists for their wide range of antimicrobial properties[2,3]. They possess many interesting pharmacological properties. Mannich bases have several biological activities such as anti microbial, cytotoxic, anticancer, analgesic and diuretic activities[4-9].In the recent past, it was estimated that nearly 35% of Mannich bases related articles were published in pharmaceutical journals[10]. Semicarbazides and thiosemicarbazides are found to be associated with antibacterial and antifungal activities. It is well known from the literature that the compounds containing amide moiety revealed an extensive range of biological behavior[11]. It has been clearly revealed from the literature that there were limited researches have been carried out using acetamide with 2-pyridine carboxaldehydeand its derivatives for the synthesis of Mannich bases. All the synthesized compounds were tested for antibacterial activities against certain pathogenic bacteria and antifungal activities against fungus *Candida albicans*.

The Cu (II), Ni (II), Co (II) and Zn (II) complexes of Mannich base, N-(1-morpholinobenzyl) semicarbazide have been synthesized and studied its antimicrobial properties by Raman et al[12]. Reddy et al[13] reported a novel Mannich ligand 1-phenyl-1,2-propanedione-2-oxime thiosemicarbazone and its Cu (II), Ni (II), Co (II), Fe (II) complexes. The chemical literature provides information on the complexation of such ligand with Nickel to form coordination compound. The synthesized ligand acts as an excellent bidentate ligand with H and/or O as donor atoms. A number of complexes of synthesized ligand with transition metals are known[14,15]. The variants in the structural geometry can be related with different transitions on the ligand molecules. The structural diagnosis of different transition metal complex can be evaluated from spectral properties[16].

MATERIALS AND METHODS

All the reagents and chemicals were used after purification. Melting points of the compounds were determined in open capillaries method and are uncorrected. The purity of the compoundswas checked by thin layer chromatography (TLC). Compound was dissolved in methanol and mixture of chloroform and methanol in 3:1 ratio was used as eluting solvent. The UV-Visible Spectrum was recorded by Lamda 35 spectrometer. The IR spectrum was recorded as KBr pellets using a Perkin - Elmer RXI spectrometer. The proton NMR Spectrum was recorded using 300MHz NMR spectrometer (BRUKER).

2.1. Synthesis of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide

It was prepared by reacting acetamide solution (14.75 g, 0.25 M) in 5 ml of water. To this solution 2.5 ml (0.25 M) phenol was added drop wise with constant stirring followed by 25 ml (0.25 M) of 2-pyridine carboxaldehyde was added and stirred well for 10 minutes using magnetic stirrer. The colorless solid formed, and it was filtered and recrystalized from methanol (Scheme 1).

2.2. Synthesis of Complex

A solution of Nickel(II) chloride in methanol and N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide in acetone were added to a round bottom flask and stirred well using magnetic stirrer for half an hour. The green coloured solid formed, and it was filtered, washed with diethylether and dried (Scheme 2).

RESULTS AND DISCUSSION

3.1. Characterization of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide

The purity of synthesized compound was confirmed by TLC. Compound was dissolved in methanol and the mixture of chloroform and methanol in 3:1 ratio is used as eluting solvent.

The solubility of N-[(2-hydroxyphenyl)(pyridine-2-yl)-methyl]acetamidewas tested. It is soluble in Methanol, Ethanol, Acetone, DMSO, THF and Acetic acid whereasit is insoluble in Water, Diethyl ether, Petroleum ether, Chloroform, CCl_4 and Benzene. Melting point was determined using melting point apparatus and is about 232°C. The molecular mass of the ligand was determined by Rast method using biphenyl as the solvent. The molecular weight determination using biphenyl as solvent gave the value of 240, which is very close to expected value of 242.
The UV-Visible spectrum of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide was recorded on Lamda 35 spectrometer. The synthesized compound is freely soluble in DMSO and it was observed from the spectrum,an intense broad band at 319 nm which may be due to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, $n \rightarrow \sigma^*$ transition of the carbonyl group.

The IR spectrum of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide was recorded as KBr pellets using a Perkin - Elmer RXI spectrometer. The IR spectrum of the compound showed bands in the region of 3415 cm^{-1} assigned to ע(O-H) and ע(N-H). The bands located in the regions of 2931 and 2372 cm^{-1}were attributed to the aromatic and aliphatic C-H stretching vibration. The absorption band in the region of 1608 $cm^{-1}$was assigned to ע(C=O). The split bands from 1380-1272 cm^{-1}were due to the mixed ע(N-H) and ע(C-N) vibrations. The band in the region of 1114 $cm^{-1}$was due to ע(C-N-C) of pyridine. The presence of absorption bands in the regionsof 957-612 cm^{-1}were due to out of plane bending vibrations of aromatic C-H.

The proton NMR Spectrum of N-[(2-hydroxyphenyl)-(Pyridine-2-yl)methyl]acetamide was recorded using 300MHz NMR spectrometer (BRUKER). The spectrum showed the multiplets in the regions of 7.0 and 8.0 ppm were due to aromatic protons. A singlet peak appeared at 2.6 ppm was assigned to methyl proton. Splitting of signal appeared at 3.3 and 3.7 ppm was assigned to C-H and N-H protons.

Based on the above physical and spectral data, the structure of the synthesized compound was confirmed as N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide.

N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide (1a)
IR (ν cm-1): 3415 (O-H and N-H), 1608 (C=O Str.), 2931 and 2372 (Ar C-H Str. and C-H Str.), 1114 (C-N-C of pyridine); ^{1}H NMR(300 MHz, DMSO) δ: 7.0 – 8.0 (m, Ar C-H), 2.6 (s, 1H, CH), 3.3(d,N-H), 3.7 (d, C-H).

3.2. Characterization of Dichloro-N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide-nickel(II)
A known amount of the complex was decomposed with con.HNO_3 and diluted to 25 mL in a graduated flask. It was made alkaline by the addition of aqueous ammonia, and dimethylglyoxime (DMG) was added to the above solution. The rosy red precipitate was obtained and filtered through sintered crucible, and then dried in an air oven at 120ºC for 1 h.It was weighed as nickel(II)dimethylglyoximate. The % of Ni ion was 9.4 and calculated value is 8.86.

The estimation of chloride was determined by Volhard's method. In a clean conical flask 20 ml of complex solution was pipette and about 5 ml of 6 M nitric acid was added followed by 40 ml of standard silver nitrate solution (N/20). The mixture was then slightly warmed and thoroughly shaken so that all chlorides coagulated as silver chloride. It is cooled and the filtrate was collected in a conical flask and washed with cold water until free from silver nitrate. About 1 ml of ferric alum indicator was added to the solution and titrated against standardized ammonium thiocyanate solution. Appearance of faint reddish brown colour in the solution was taken as end point. From the titer values, the volume of ammonium thiocyanate equivalent to the silver nitrate reacted with chloride was determined, which in turn gives the weight of chloride in the whole of the given solution. The % of chloride ion was 12.2 and the calculated value was 11.23.

The molar conductance of 10^{-3} M solution of the complex in DMF was measured. The molar conductance was shown to 32 ohm^{-1} cm^2 mol^{-1}, which indicates the non electrolyticbehaviour of the complex. That is the anions are present inside the coordination sphere.

The magnetic susceptibility of the Nickel (II) complex of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide was determined using Gouy's balance. The magnetic susceptibility value was 3.52 B.M.

The Electronic spectrum of the Ni(II) chloro complex of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide in DMSO solution showed a broad band at 14960 and 15350 cm^{-1} along with 8400 and 9250 cm^{-1} in the visible region which are assignable to 3T1(F) - 3T1(P) and 3T1(F) - 3A2(F) transitions corresponding to distorted tetrahedral geometry.

The IR spectrum of Ni (II) chloro complex of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide was recorded. In order to study the binding mode of the ligand to the metal ion in the complex, the IR spectrum of the free ligand was compared with the spectra of complex. The band due to ע(C=O) at 1608 cm^{-1}was shifted to 1595 cm^{-1} in the spectrum of the complex indicating coordination of carbonyl oxygen to central metal ion. The band at 3431 cm^{-1}observed in the free ligand was shifted to 3415 cm^{-1} in the complex, suggesting the coordination of pyridine nitrogen to metal ion. On this basis, it is concluded that the ligand base acted as a bidentate donor.

The TG curve shows (Fig. 1) an endothermic peak at 200°C, which is corresponding to the elimination of chlorine that coordinated to the metal ion. The organic part decomposes at 460°C. Above 580°C there is no change in weight, the plateau observed is corresponds to the oxide of copper.

Based on the above physical and spectral data, the structure of the synthesized complex was confirmed as Dichloro-N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamidenickel(II).

4. Biological activity
4.1. Antibacterial activity
The compound 1a and 2b were evaluated for their *in vitro* antibacterial activity against the test microorganisms of gram positive *S. aureus, B. subtilis*, gram negative *E. coli, P. aeruginosa*, by disc diffusion method[17]. All the bacterial and fungal species were obtained from National Chemical Laboratory (NCL), Pune and maintained by periodical sub culturing. Nutrient agar was used for bacterial screening. DMSO (0.5 mL) was used as solvent and

Ciprofloxacin (1µg/disk) as control.The effect produced by the sample was compared with the effect produced by the positive control (Plate 1 (b) – (e)).

4.2. Antifungal activity

The compounds 1a and 2b were evaluated for their *in vitro* antifungal activity such as *C. albicans*, using a disc diffusion method[18]with potato dextrose agar (PDA). The zone of inhibition values are given in the Table 4 and Plate 1 (a).

Table 1: Antimicrobial activity of synthesized compound and its metal complex

Compound	Zone of inhibition (mm)				
	Tested Microbes				
	*B. subtils*MTCC-441	*S. aureus*ATCC 25923	*E. coli*ATCC 25922	*P.aeruginosa*ATCC 27853	*C. albicans* MTCC 227
1a	-	06	07	09	-
2b	14	16	17	16	09
Ciproloxacin (1µg)	20	25	20	19	12
DMSO	-	-	-	-	-

Tested compounds 1a: N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide,; 2b: Dichloro N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamidenickel(II); (-): No Inhibitory effect; Ciprofloxacin: Standard control; DMSO: negative control

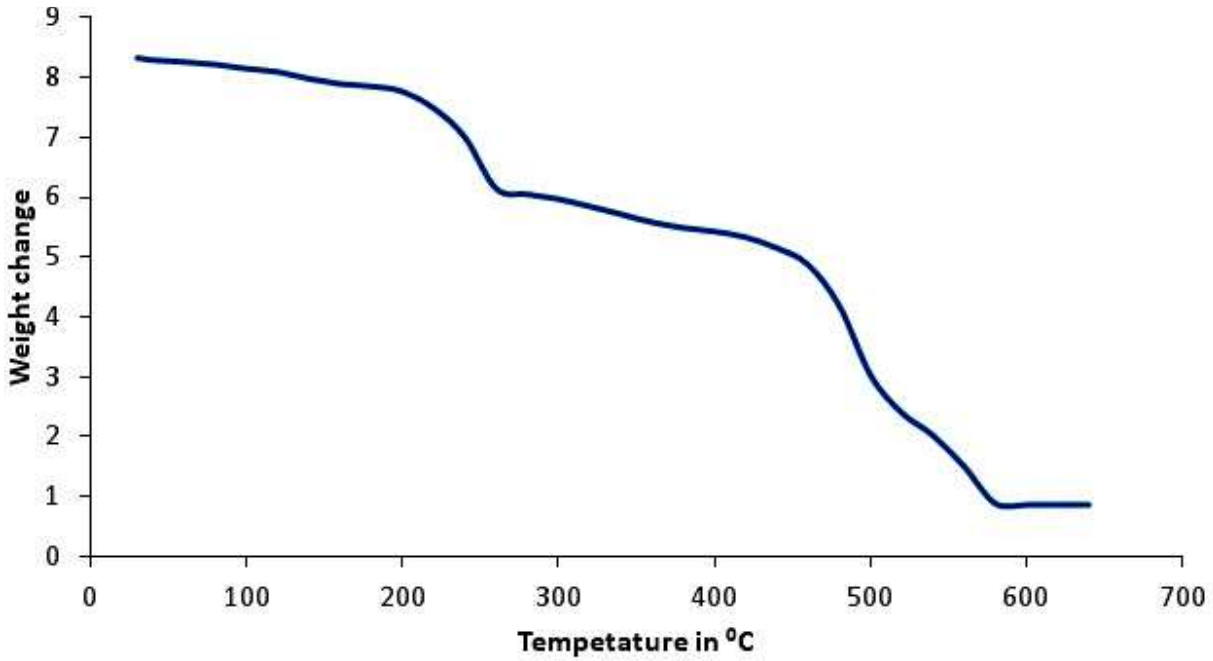


Figure 1. Thermo Gravimetric Analysis (TGA) curve for of Dichloro-N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamidenickel(II).

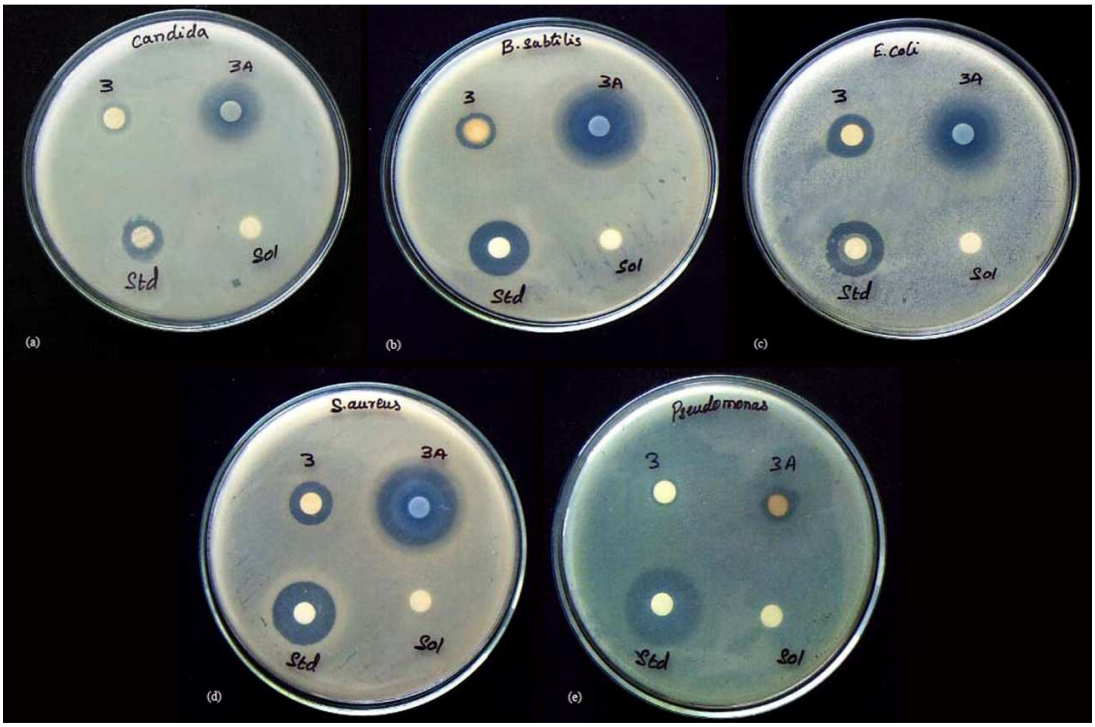
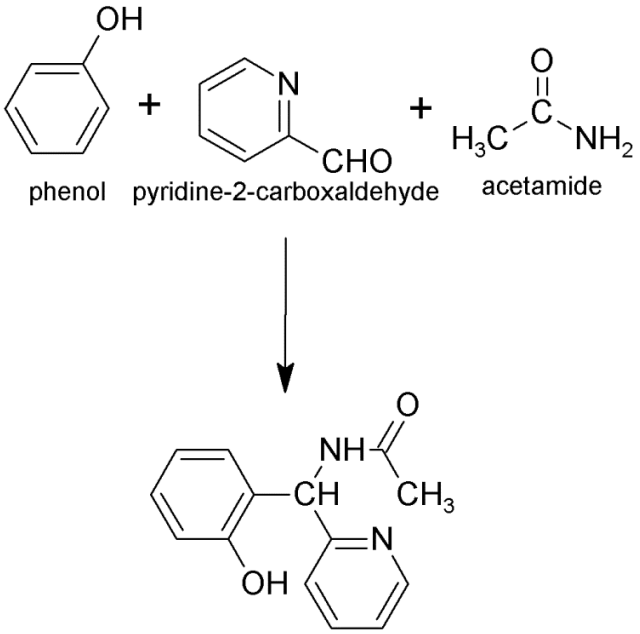
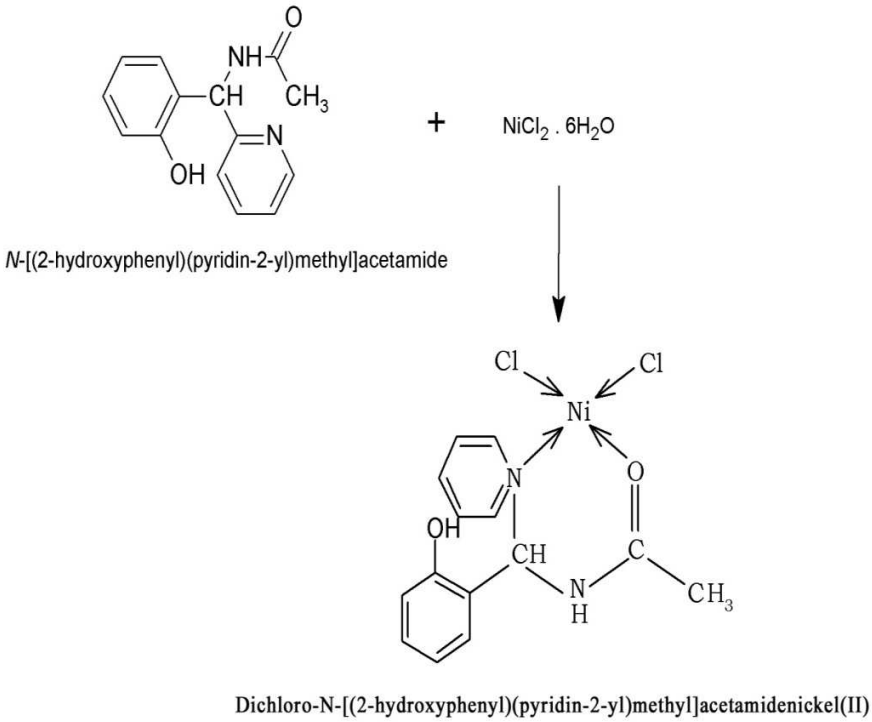


Plate 1.Antimicrobial activity of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide (3), Dichloro N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamidenickel(II) (3A)



N-[(2-hydroxyphenyl)(pyridin-2-yl)methyl]acetamide

Scheme 1: Preparation of N-[(2-hyroxyphenyl)(pyridine-2-yl)methyl]acetamide.



Scheme 2: Preparation of Dichloro-N--[(2-hyroxyphenyl)(pyridine-2-yl)methyl]acetamide-nickel(II)

CONCLUSION

This paper describes the summary of Mannich reaction, mechanism and important properties, also discussed about the metal coordination and importance of coordination compounds. The literature survey states that the coordination occurs through oxygen and nitrogen. Experimental techniques employed in the synthesis and characterization of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide and its Ni (II) complex also discussed in detail. The IR spectrum of the complex shows a negative shift in absorption band frequencies of C = O and C-N of pyridine which are suggesting that carbonyl oxygen and nitrogen of pyridine involved in the coordination. The band in the Electronic spectrum of complex can be taken as indication of distorted tetrahedral geometry. Based on the analytical and spectral studies the structure of N-[(2-hydroxyphenyl)(pyridine-2-yl)methyl]acetamide as well as the complex Dichloro-N-[(2-hydroxy-phenyl)(pyridine-2-yl)methyl]acetamidenickel(II) are established. The analytical data reveals 1:1 (metal:ligand) ratio in the Ni (II) complex. The electrolytic conductivity data of the complex indicates its non-electrolytic nature. The magnetic susceptibility value indicates the magnetic property of the complex. The biological activity of synthesized compound and its Ni (II) complex shows a marked activity against the selected microorganisms. Metal complex has been found to possess more activity than the free ligand.

REFERENCES

[1] F.Aydoğan,Z. Turgut, N.Öcal,*Turk. J. Chem.***2002,**26, 159.
[2] C.R. Katica,D. Vesna,K. Vlado,G.M. Dora,B. Aleksandra,*Molecules*.**2001,**6, 815-824.
[3] R. Valarmathi, S. Akilandeswari, V.N.I. Latha, G. Umadevi, *Der ChemicaSinica*,**2011,** 2(5), 64-68
[4] P. Mittal, V. Uma, *Der ChemicaSinica*,**2010,** 1(3), 124-137.
[5] H.I. Gul, T. Ojanen, J. Vepsalainen, M. Gul, E. Erciyas, O. Hanninen, *Arzneimittelforschung*.**2001,**51(1), 72-5.
[6] H.I. Gul, M. Gul, O. Hänninen, *Arzneimittelforschung*. **2002,**52(11), 840-3.
[7] T. Siatra-Papastaikoudi, A. Tsotinis, I. Chinou, C. Roussakis,*Farmaco*. **1994,**49(3), 221-3.
[8] A. Sabastiyan, M.Y. Suvaikin, *Adv. in App. Sci. Res.*,**2012,** 3(1), 45-50
[9] D.A. Koechel, G.O. Rankin,*J Med Chem*. **1978,**21(8), 764-9.

[10] Po-Jung J. Huang, D. Youssef, T.S. Cameron, A. Jha,*ARKIVOC(XVI),***2008,** 16, 165.
[11] R.M. Silverstein, G.C. Bassier, T.C. Morrill,"*Spectrometric Identification of organic compounds"* (4th Ed.).John Wiley and sons.**1981.**
[12] N. Raman, S. Esther, C. Thangaraja,*J. Chem. Sci*. **2004,**116, 209-213.
[13] K.H. Reddy, M.S. Babu, P.S. BabuS. Dayananda, *Ind. J. Chem*. **2004,**43 A, 1233-1238.
[14] Y.T. Thahor, S.G. Patel, K.N. Patel, *Der ChemicaSinica*,**2011,** 2(1), 43-51
[15] E.M. Mosoarca, R. Tudose, R. Alexandrova, C. Otilia, *Chem. Bull. "POLITEHNICA" Univ. (Timişoara)*. **2005,**50(64), 1-2.
[16] A.A. Jameel, M. Palanisamy, M.S.A. Padusha, *Der ChemicaSinica*,**2012,** 3(4), 860-863
[17] S.H. Gillespie, Medical Microbiology-Illustrated. Butterworth Heinemann, London, **1994,**pp. 234‑237.
[18] R.S. Verma, I.K. Khan, A.P. Singh, (Eds.), *Antifungal Agents: Past, Present, Future Prospects. National Academy of Chemistry and Biology*, (pp. 55–128)Lucknow, India**(1998).**