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Synthesis and Biological Evaluation of Bioactive 5-Bromo-2-Hydroxy-4-Chloro Substituted Ketimines

[1]Ganesh Andhale[*], [2] Sanghapal Paden, [3] Prabhakar Kute & [4]Satyanarayan Arde
[1]Department of Chemistry Shri Shivaji Arts, Commerce & Science College Akot. Dist. Akola Maharashtra 444101
[2]Rajarshi Shau Science College Chandur Railway, Dist Amravati Maharashtra 444101
[3]Department of Chemistry, Pratishthan Mahavidylaya, Paithan, Dist. Sambhaji Nagar (M.S.) 431107
[4]Department of Chemistry Y.C. Warana Mahavidyalaya, Warananagar (M.S.) 416113 India.
ganeshandhale005@gmail.com

ABSTRACT:
Ketimines exhibit a wide range of biological activities such as antibacterial, antifungal, anti-inflammatory, antiviral and antipyretics. Ketimines or azomethine which are analogue of aldehyde or ketone in which carbonyl group (C=O) replaced by azomethine (C=N) group. This class of organic compounds has great importance in the field of coordination chemistry because of potentially capable of forming stable complexes with metal ions. Fast and very rapid procedure is reported for the synthesis of 2-hydroxy-5-bromo-n-(substituted-phenyl)-ketimines from substituted 2-hydroxychalcone and different substituted aromatic amines under 10% ethanol suspension. The study of imine metal complexes is very interesting because of their unusual stability, sensitivity, selectivity, chemical and magnetic properties. The chemical and biological importance of azomethine (C=N) group is due to presence of lone pair in sp^2 hybridized orbital which make them a good chelating agents. Generally the bi and tri dentate ligands are more capable of forming stable complexes with S and D block elements. Therefore imine metal complexes were significantly investigated for their antifungal, antibacterial, antimicrobial, antitumor and enzymatic activities.

INTRODUCTION:
In 1864 German Chemist Hugo Schiff's first synthesized condensation product of primary amine and aldehyde or ketone called as Schiff's base[1]. These are also called imines or azomethine which are analogue of aldehyde or ketone in which carbonyl group (C=O) replaced by azomethine (C=N) group[2]. This class of organic compounds has great importance in the field of coordination chemistry because of potentially capable of forming stable complexes with metal ions[3].

Recently the study of chemistry of imines continuously is increasing because of their applicability in various biological systems, polymer stabilizer, homogeneous and heterogeneous catalysis, medicine, pharmacy and other technologies[4]. Schiff's bases exhibit a wide range of biological activities such as antibacterial, antifungal, anti-inflammatory, antiviral and antipyretics[5-6].

The complexing properties of imines with metals have led to the formation of various complexes in which imines act as a ligand. Imines can be a good ligand if they bear –OH group closer to the azomethine (C=N) group. The study of imine metal complexes is very interesting because of their unusual stability, sensitivity, selectivity, chemical and magnetic properties. The chemical and biological importance of azomethine (C=N) group is due to presence of lone pair in sp^2 hybridized orbital which make them a good chelating agents. Generally the bi and tri dentate ligands are more capable of forming stable complexes with S and D block elements. Therefore imine metal complexes were significantly investigated for their antifungal, antibacterial, antimicrobial, antitumor and enzymatic activities[7-11].

Literature survey shows that many researchers have made their attempt to synthesize imine derivatives by condensation of substituted 2-hydroxy acetophenone with substituted aromatic amines and evaluated their biological properties. Patil et.al.[12] synthesized imine derivatives from substituted 2-hydroxy acetophenone with substituted aromatic amines and evaluated their antibacterial and antifungal properties. But however there has been less information about the study of binary and ternary metal complexes of imine derived from substituted 2-hydroxy acetophenone and substituted aromatic amines.

So keeping these views in consideration to understand the chelating nature of imines towards alkaline earth and transition metal ions, present work is undertaken. The behavior of these metal complexes is studied in binary Dichloro methane (DCM) Water mixture. The stability constants of binary complexes of metal ion with imines has been determined pH metrically in 75% DCM-Water mixture at 0.1M (KNO_3) ionic strength.

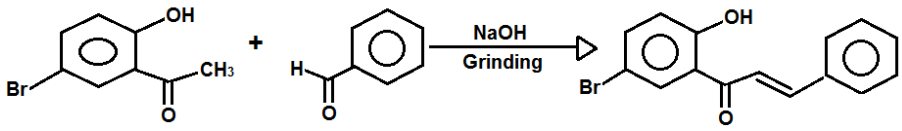
EXPERIMENTAL

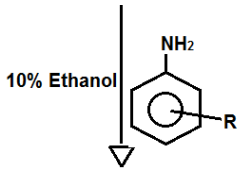
Procedure for Synthesis of Chalcone

A solution of 2-hydroxy-5-bromoacetophenone (0.01 moles) and benzaldehyde (0.01 mol) were dissolved in ethanol (10 ml), under stirring and aqueous NaOH (40%) was added drop wise. Orange colour solid was separate out. The reaction mixture was stirred at room temperature and kept overnight.The reaction mixture was acidified with HCl (50%). The separated solid was filtered and wash with 1% sodium bicarbonate solution again followed by water. Product was crystallized from ethanol and glacial acetic acid (1:1) to give yellow colour solid [1]. Yellow solid; Yield: 78%; m.p:150-155°C

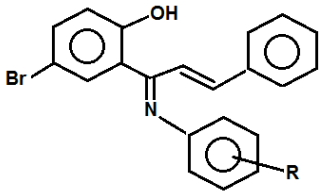
Procedure for the Synthesis of Ketimines

2-hydroxy-5-bromochalcone [1] (0.01mol) and substituted aniline (0.01 mol) was dissolved in ethanol (20 ml). To this mixture 2-3 drops of conc. H2SO4 was added and it was refluxed for 3 hrs. On cooling and dilution with ice cold water, a solid mass separated out. It was recrystallized from ethanol. Dark yellow solid; Yield: 70 %; m.p:100-102 °C





R = -H, ortho -NO $_2$, meta -NO $_2$, para -NO $_2$,
ortho -OH, meta -OH, para -OH,
ortho -CH $_3$, meta -CH $_3$, para -CH $_3$,



Biological Evaluation

Anti-bacterial activity of Ketimines: The study has been conducted according to the method adopted by Cruickshank et al**.** Nutrient agar broth was melted in a water bath and cooked to 45 °C with gentle shaking to bring about uniform cooling. It was inoculated with 0.5-0.6 ml of 24 hour old culture especially and mixed well by gentle shaking before pouring on the sterilized Petri dish (25 ml each). The poured material was allowed to set (1.5 hour) and there after the "cups" was made by punching into the agar surface with a sterile cork borer and soaping out the punched part of agar. Into this "cups" 0.1 ml of test solution (prepared by dissolving 10 mg of sample in 1 ml DMF) was added by sterile micropipette. The plates were noted. The antibacterial activities of all compounds are compared against standard drug.

Antifungal activity of Ketimines: The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *C. albicans* and *A. clavatus*. The antifungal activity of all the compounds was measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium such a PDA medium contained potato 200 gm., dextrose 20 gm., agar 20 gm., and water 1 liter. Five days old cultures were employed. The compounds to be tested were suspended (1000 ppm) in a PDA medium and autoclaved at 120°C for 15 min and at 15 atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates.

RESULTS AND DISCUSSION:

The aromatic substituted ketimines have been synthesized by the reaction of 2-hydroxy-5-bromo-Chalcone (2) and substituted aniline at reflux temperature using ethanol as solvent in presence of conc. H2SO4 in 78-85 % yield. The antimicrobial activity of all the compounds were tested for against the microorganism S. aureus, E. coli, P. aeruginosa, S. pyogenes, C. albicans and A. clavatus. The results were compared with the standard antibacterial drug Amplicilline, Chloramphenicol, Ciprofloxacin, Norfloxacin and standard antifungal drug Greseofulvin and Nystatin.

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