Synthesis, Characterization and Biological Screening of Schiff Bases Derived From 2-Amino-4´-Bromo Benzophenone

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Abstract: Schiff bases are the most extensively studied compounds because of their attractive chemical properties and wide range of applications. Generally they are synthesized by the condensation reaction between aldehyde or ketonic carbonyl compounds and amines. New Schiff bases derived from 2-Amino-4´-Bromo benzophenone with different aldehydes like p-chloro benzaldehyde, Salicylaldehyde and 3,4,5-trimethoxy benzaldehyde *namely (4-bromophenyl)(2-((4-chlorobenzylidene)amino)phenyl)methanone i.e. BCBAPM ; (4-bromophenyl)(2-((2-hydroxybenzylidene)amino)phenyl)methanone i.e. BHBAPM ; (4-bromophenyl)(2-((3,4,5-trimethoxybenzylidene)amino)phenyl)methanone i.e. BTBAPM* have been synthesized and characterized . The physical and structural data of these compounds have been derived by elemental analysis, IR spectra and ^{1}H NMR spectral studies. The biological activity of these new Schiff bases has been carried out with MIC determination for *Bacillus megaterium, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger* and *Aspergillus flavus.*

Keywords: Schiff bases, benzophenone derivative, Physical and Chemical characterization, Biological Screening, MIC determination

1. Introduction

Schiff bases are typically synthesized by the condensation of a primary amine and aldehyde in organic solvents like methanol, ethanol, THF etc. They are named so after a German chemist Hugo Schiff (1), Nobel Prize winner in 1864. These compounds are also known as azomethine or imine and their general structural formula is $R_1CH=N-R_2$ where R_1 and R_2 are alkyl, aryl or heterocyclic group having different substituents. Schiff bases are characterized by the presence of imine or azomethine group –CH=N-, which helps to explain the mechanism of racemization and transamination reaction occurred in biological systems (2).

Schiff bases are widely studied compounds as they have been playing very important and versatile role in industrial and biological field. Mainly these compounds show antifungal and antimicrobial activity (3,4). Too much interest in imines or azomethines is the fact as they are widely distributed in many biological systems and they are used in organic synthesis, chemical catalysis, medicine, pharmacy and chemical analysis as well as new technologies (5). Schiff bases are interesting compounds, which could be a part of antimalarial drugs (6). Schiff base is involved in a multi-stage reaction for the treatment of Malaria using Cryptolepine (7). Schiff bases have shown very effectiveness on Cucumber mosaic virus (8). Schiff bases of salicylaldehyde and 1-amino-3-hydroxy guanidine tosylate are very useful material for designing new antiviral agents (6). Anti-HIV activity of Isatin Schiff bases is very well known (9).
The development and research in the field of bioinorganic chemistry has increased the interest in Schiff base as well as their transition metal complexes also. Metal complexes of Schiff base derived from 2-thiophene carboxaldehyde and 2-amino benzoic acid with Fe(III), Cu(II), Co(II) and Ni(II) exhibiting biological activity were reported (10). The Schiff bases of 3-(2-hydroxy-3-ethoxy benzylidene amino)-5-methyl isoxazole and 3-(2-hydroxy-5-nitro benzylidene amino)-5 methyl isoxazole were screened against

Aspergillus niger and Rhizoctonia solani (11a, 11b). Anticancer activity on MDA-MB-231 breast cancer cells was observed in the Schiff base complexes of Cu (II), Cd (II), and Zn (II) derived from 2-acetyl pyridine and L- tryptophan (12).

Promising anti inflammatory activity was observed in the Schiff bases derived from 4-amino antipyrine (4-amino-1,5-dimethyl-2-phenylpyrazole-3-one) and benzaldehyde (13). A very rapid increase in multi drug resistant bacteria and fungi has made it mandate for scientists to research new anti microbial compounds as well as coordination compounds of biologically important molecules (14,15,16). Anticancer potential of benzophenone-Bis-Schiff base was studied on Human Pancreatic Cancer cell line by Khalid Mohammed Khan et al. (17). Tetradentate Schiff base ligands of 3, 4-diamino benzophenone were synthesized and studied by Mozaffar Asadi et al. (18). Antioxidant potential of Schiff bases containing benzophenone was studied by Ghulam Fareed et al. (19).

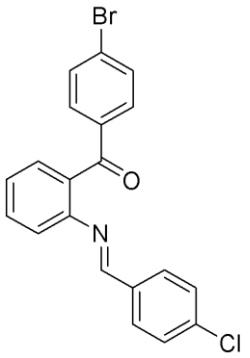
Looking to the importance of Schiff base in various field of chemical and biological science, the objective of this work was to synthesize, characterize and determine the antimicrobial activities of derived Schiff bases from 2-amino-4´-bromo benzophenone.

2. Experimental

All necessary chemicals were of A.R. Grade and purchased from Sigma Aldrich and E. Merck. They all were used as such. Solvents were used also of AR Grade and were purified by distillation. Melting points of all solid samples are uncorrected. They were determined using capillary and Thiels tube filled with paraffin oil. The IR spectra were recorded in cm^{-1} using Shimadzu-435-IR spectrophotometer by KBr pellets techniques. The ^1H NMR were recorded on Bruker spectrophotometer (300 MHz) using TMS as an internal standard and $CDCl_3$ as solvent at ambient temperature. Biological screening of Schiff bases R_1, R_2 and R_3 were carried out with MIC determination.

2.1 Synthesis of Schiff bases

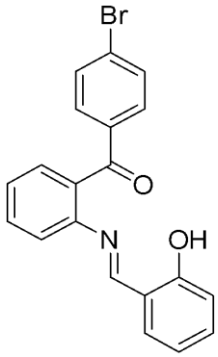
An equimolar methanolic solution of 2-Amino-4´-Bromo benzophenone and *p*-chloro benzaldehyde were mixed and heated for 5 to 6 hours with constant stirring at 60 °C-70 °C. The characteristic pale yellow coloured compound obtained was distinguished in colour from amine. Slow evaporation method was used to obtain Schiff base. It was frequently washed with sodium bisulphite solution to remove excess aldehyde and then methanol to remove impurities if any then dried by ether. The product was recrystallized from hot methanol and dried. Structural formula of R_1,R_2 and R_3 are given as *figure 1, figure 2 and figure 3*.



(4-bromophenyl)(2-((4-chlorobenzylidene)amino)phenyl)methanone

R_1 [BCBAPM]

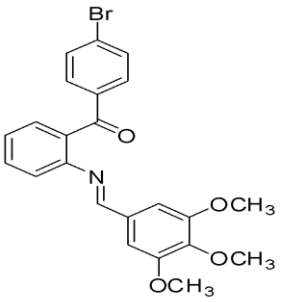
Figure 1:- Schiff base R_1



(4-bromophenyl)(2-((2-hydroxybenzylidene)amino)phenyl)methanone

R_2 [BHBAPM]

Figure 2:- Schiff base R_2



(4-bromophenyl)(2-((3,4,5-trimethoxybenzylidene)amino)phenyl)methanone

R_3 [BTBAPM]

Figure 3:- Schiff base R_3

Like *p*-chloro benzaldehyde, another aldehydes i.e. salicylaldehyde and 3,4,5- trimethoxy benzaldehyde also reacts with 2-amino-4´-bromo benzophenone to yield corresponding Schiff base in the same manner.

2.2 Antimicrobial activity

New synthesized Schiff bases R_1, R_2, R_3 *i.e.* BCBAPM, BHBAPM and BTBAPM respectively were tested for antibacterial and antifungal activities and MIC determination by Microtitre Broth dilution method. The Bacterial strains used were *Bacillus megaterium, Staphylococcus aureus, Escherichia coli, pseudomonas aeruginosa* and fungal strains were *Aspergillus niger* and *Aspergillus flavus*. MIC was determined by the comparision between the amount of growth in the tubes/wells containing antimicrobial agents and the growth in the growth-control wells/tubes (without anti bacterial agents) in each sets of tests. The lowest concentration at which the isolate is completely inhibited is recorded as the minimal inhibitory concentration and it is evidenced by the absence of visible bacterial growth.

3. Result and Discussion

3.1 Physical and structural data

All Schiff bases R_1,R_2 and R_3 have characteristic yellow colour and they are soluble in methanol, ethanol, acetone, chloroform, 1,4-dioxane, ether etc. organic solvents. Elemental analysis data are in accordance with the theoretically calculated percentage of C, H, and N. Percentage of C, H, N were derived using CHN/S/O Analyser, Perkin Elmer, series11, 2400. Characterization data of all the three Schiff bases are as given in the table-1.

Table-1: Physical and Analytical Structural Data of R_1, R_2 and R_3

Sr. No.	Molecular Formula	Molecular Weight gm mol^{-1}	Melting point	Yield (%)	Colour	% of C,H,N Calculated (found)		
						%C	%H	%N
1.	$C_{20}H_{13}ONClBr$ R_1,[BCBAPM]	398	110 °C	81.66%	Yellow	60.30 (60.62)	3.27 (3.33)	3.52 (3.60)
2.	$C_{20}H_{14}O_2NBr$ R_2,[BHBAPM]	380	108 °C	76.5%	Light Brown	63.16 (63.20)	3.68 (3.73)	3.68 (3.80)
3.	$C_{23}H_{20}O_4NBr$ R_3,[BTBAPM]	454	80 °C	60.12%	Light Yellow	60.79 (60.75)	4.40 (4.42)	3.08 (3.15)

3.2 IR spectra

FTIR spectra of Schiff bases were recorded in the range 4000-400 cm^{-1} on a Perkin Elmer 16 FPC FT-IR using KBr Pellet technique. Information regarding the nature of functional groups present in the molecule can be derived from the Infrared Spectra. The spectrum of unknown compound can be interpreted and identified by comparision to a library of known compounds. Some characteristic IR stretching band frequencies of all the three Schiff bases are as given in Table-2

Table-2: IR Frequencies of Schiff base R_1, R_2 and R_3

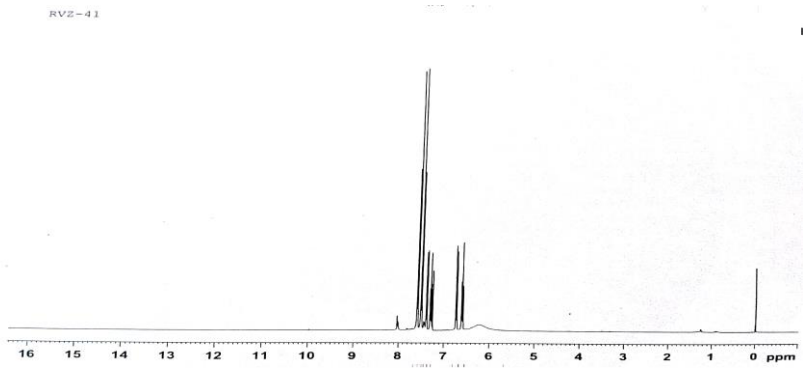
Compound	ν (C=N) cm^{-1} azomethine	ν(OH) cm^{-1}	ν(C-N) cm^{-1} str.	Aromatic ν(C=C) cm^{-1} str.	ν(>C=O) cm^{-1} str.
$C_{20}H_{13}ONClBr$ R_1,[BCBAPM]	1640.42	-	1295.36	1565	1683
$C_{20}H_{14}O_2NBr$ R_2,[BHBAPM]	1640.25	3476.44	1294.31	1547.96	1665
$C_{23}H_{20}O_4NBr$ R_2,[BTBAPM]	1640.05	-	1303.48	1547.37	1684

3.3 ^{1}H NMR:-

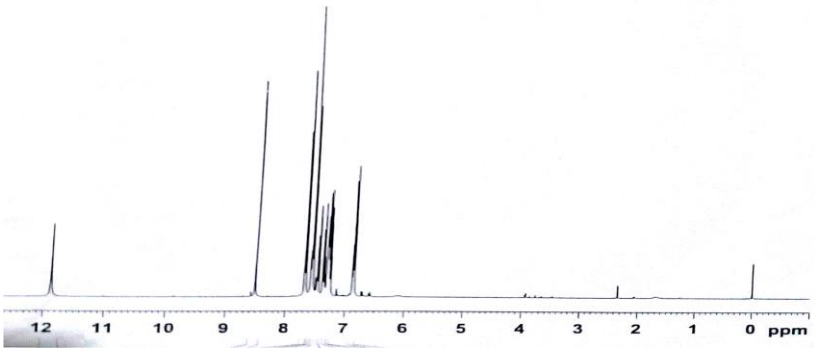
The ^{1}H NMR Spectrum of R_1, R_2 and R_3 Schiff bases show following signals as given in Table- 3. In R_1, R_2 and R_3, proton of azomethine (-CH=N-) group appears at 8.1 ppm, 8.52ppm and 9.873ppm(20) respectively and the multiplets of aromatic (phenylic) hydrogen are observed in the range from 6.1 to 7.8 δppm. In R_2 Schiff base the ^{1}H resonance of the salicyldehydic –OH group is present at 11.88 δppm. In R_3 schiff base -OCH_3 group gives singlet at 3.935 δppm.

Table-3: ^{1}H NMR Spectrum data of R_1, R_2 and R_3

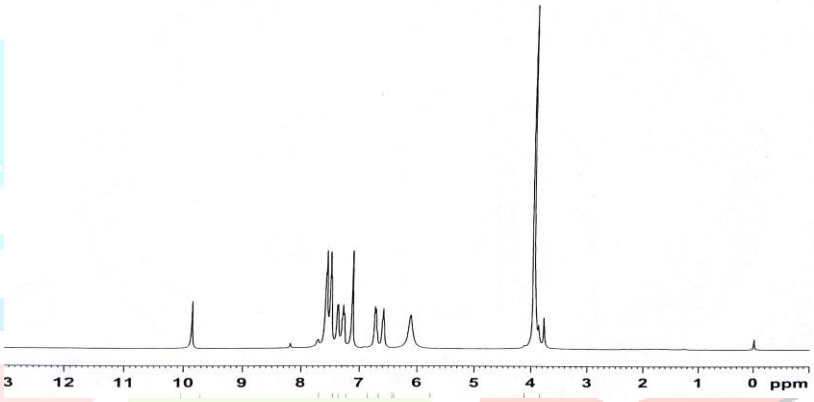
Compound	δ(-CH=N-)ppm	δ(Ar-H)ppm	δ (ppm)
$C_{20}H_{13}ONClBr$ R_1, [BCBAPM]	8.1	6.58- 7.66	_
$C_{20}H_{14}O_2NBr$ R_2,[BHBAPM]	8.52	6.85 – 7.7	11.88 (-OH of salicylaldehyde)
$C_{23}H_{20}O_4NBr$ R_3,[BTBAPM]	9.873	6.1 - 7.6	3.935 (-OCH_3)



^{1}H NMR Spectrum of R_1



^{1}H NMR Spectrum of R_2



^{1}H NMR Spectrum of R_3

3.4 Antimicrobial activity

MIC can be helpful in establishing the level of resistance of a particular bacterial strain. For present study, antibiotics used were i) Streptomycin as antibacterial against gram negative bacteria , ii) Ampicillin as antibacterial against gram positive bacteria and iii) Nystatin as antibacterial against fungi. Gram negative test cultures were Escherichia coli and *Pseudomonas Aeruginosa; Staphylococcus aureus* and *Bacillus megaterium* as gram positive test cultures and fungi used were *Aspergillus niger* and *Aspergillus flavus*. Different dilution prepared were 1000,500,200,125 and 62.5 µg/ml for test compounds.

All three Schiff bases were found biologically active but R_1 [BCBAPM] and R_2 [BHBAPM] were found broad spectrum drug which inhibit the gram positive and the gram negative bacteria. R_1 [BCBAPM] is more potent and active against gram negative bacteria. R_1 [BCBAPM] also exhibited antifungal activity thus all the strains show potentiality as antibacterial compound. The graph of MIC with test organisms in fig- 4 gives Antibacterial and antifungal activities of Schiff bases R_1, R_2 and R_3 *i.e*. BCBAPM, BHBAPM and BTBAPM respectively.

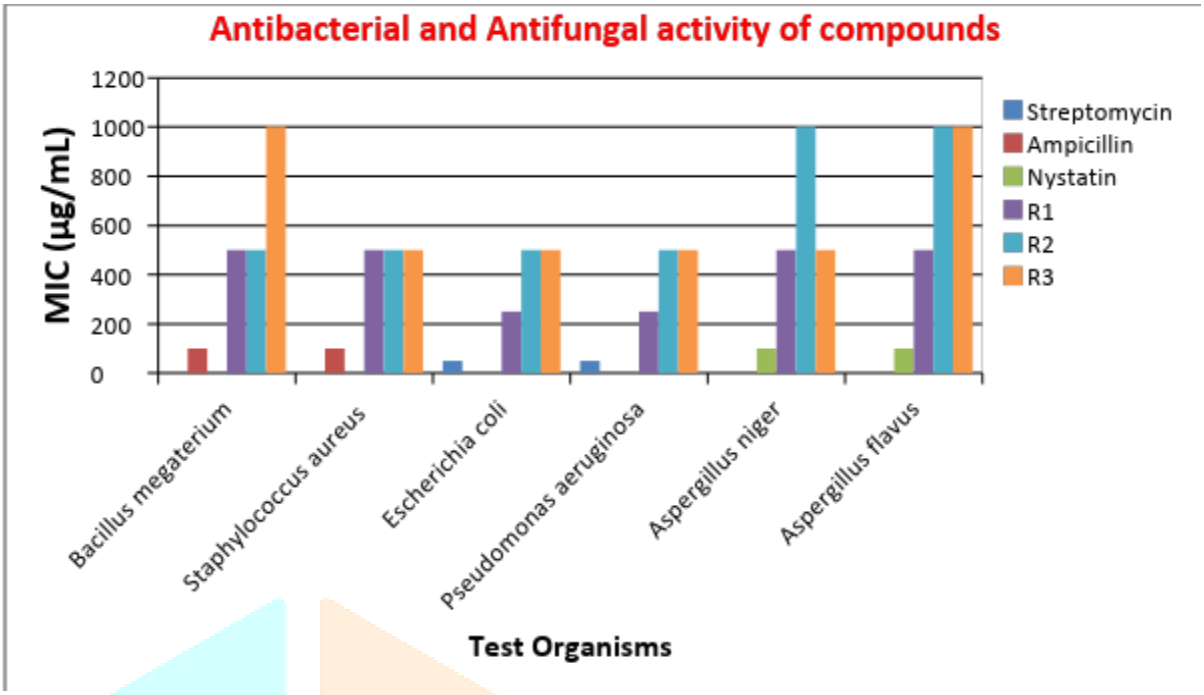


Figure 4: Antibacterial and Antifungal activity of R_1[BCBAPM], R_2[BHBAPM] and R_3[BTBAPM]

4. Acknowledgement

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